The relationship between cognition and mortality in a community sample of older adults

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A thesis submitted for the degree of Doctor of Philosophy of

The Australian National University

March 2011

Research contribution statement

The work presented is an accurate account of research performed during the academic program towards the degree of Doctor of Philosophy.

For each manuscript in the thesis, I selected and performed the analyses, performed literature reviews, wrote the manuscript, sought comments on the manuscript from Prof Helen Christensen and Prof Andrew Mackinnon and revised the manuscript accordingly, submitted the manuscript and addressed peer reviewer comments where necessary. I also wrote the remainder of the thesis (abstract, introduction and discussion), with minor revisions suggested by Profs Christensen and Mackinnon. While data collection had been completed at the start of the project and datasets had been cleaned previously, I was required to check, code, structure and format the data according to the requirements of each analysis. In addition to commenting on the manuscripts, Profs Christensen and Mackinnon provided ongoing feedback on the progress of each analysis. In particular, Prof Christensen provided guidance on theories of cognitive aging and suggested exploring the differentiation-dedifferentiation hypothesis, while Prof Mackinnon provided suggestions for types of statistical analyses (particularly for the cognitive change models), provided technical assistance and recommended the use of Mplus software. I also received brief feedback regarding the mental health and mortality paper from Prof Scott Hofer.

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Philip Batterham

Acknowledgements

First and foremost, I would like to thank my supervisors, Prof Helen Christensen and Prof Andrew Mackinnon for their support and guidance. I am very grateful for the opportunity to work with them and they both provided outstanding and inspiring mentorship, making the process as smooth as possible.

Thank you to the participants and project team of the Canberra Longitudinal Study.
Thank you to my colleagues at the Centre for Mental Health Research for your support and encouragement, particularly the students who were on their doctoral journeys with me.

Thank you to my family, Alellie, Nicholas and Catherine, and my parents, for their love and support and for keeping me focussed on the important things.

Abstract

Cognitive performance has previously been shown to be associated with time to death in a broad range of studies. There are multiple perspectives that have been used to better understand this relationship, including identifying the types of cognitive abilities that predict mortality, investigating potential mechanisms that might explain the relationship, examining whether level of ability or changes in ability are responsible for the association, assessing evidence of terminal decline and exploring patterns of late-life decline. It is also important to rule out the confounding of the relationship between cognition and time to death by other factors such as mental health. Five research articles investigated multiple aspects of the relationship between cognition and mortality using the Canberra Longitudinal Study cohort, a sample of 896 community-dwelling Australians aged 70 and older. Findings suggested that fluid intelligence was a better predictor of mortality than crystallised intelligence. While socioeconomic status, health behaviours and health status accounted for some of the variance in the relationship, certain domains of cognitive ability including processing speed and global ability had an independent effect on mortality. Using unbiased estimates of cognitive change, it was found that initial cognitive performance was a better predictor of mortality, particularly cardiovascular mortality, than the rate of change in ability. However, there was evidence of terminal decline in the sample, with decline accelerating two- to four-fold, beginning 6-8 years prior to death across various abilities. Although education modified the time course of terminal decline, the effects were not consistent with the predictions of the cognitive reserve hypothesis. Age-related decline in ability could not be attributed to common biological constraints, as little evidence was found for late-life dedifferentiation of abilities after accounting for dementia. Finally, depression and anxiety had no significant association with mortality after accounting for physical health, indicating that the cognition-mortality relationship

did not result from confounding by mental health status. Overall, late-life cognitive performance appears to be related to mortality partly because it reflects life-long outcomes from a range of health behaviours, disease states, educational experience and socioeconomic background. In addition, pathological events including dementia and cardiovascular changes may contribute to the decline of cognitive performance that occurs in proximity to death. However, beyond these influences, there is an aspect of cognitive ability that is independently predictive of mortality.

LIST OF PUBLICATIONS INCLUDED IN THE THESIS

1. Batterham PJ, Christensen H, Mackinnon AJ. (2009). Fluid intelligence is independently associated with all-cause mortality over 17 years in an elderly community sample: An investigation of potential mechanisms. *Intelligence, 37*, 551-560.
2. Batterham PJ, Mackinnon AJ, Christensen H. (in press). The association between change in cognitive ability and cause-specific mortality in a community sample of older adults. *Psychology and Aging*.
3. Batterham PJ, Mackinnon AJ, Christensen H. (2011). The effect of education on the onset and rate of terminal decline. *Psychology and Aging, 26*, 339-350
4. Batterham PJ, Christensen H, Mackinnon AJ. (in press). Comparison of age and time-to-death in the dedifferentiation of late-life cognitive abilities. *Psychology and Aging*.
5. Batterham PJ, Christensen H, Mackinnon AJ. (in press). Mental health symptoms associated with morbidity, not mortality, in an elderly community sample. *Social Psychiatry and Psychiatric Epidemiology.*

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INTEGRATED INTRODUCTION

Cognitive performance has previously been shown to be associated with time to death in a broad range of studies (Bäckman & MacDonald, 2006; Batty, Deary, & Gottfredson, 2007; Bosworth & Siegler, 2002; Deary, 2005; Ghisletta, McArdle, & Lindenberger, 2006; Pavlik et al., 2003; Portin et al., 2001; Shipley, Der, Taylor, & Deary, 2006; Sliwinski et al., 2006; Small & Bäckman, 1999). A variety of explanations have been proposed for this association. The theory of terminal decline suggests that pathological events in the few years prior to death hasten the rate of decline in cognitive performance (Kleemeier, 1962; Riegel & Riegel, 1972; Sliwinski et al., 2006; Thorvaldsson et al., 2008). Research has implicated a range of factors in the association between cognition and mortality, from developmental events, childhood intelligence, genes and environment, through lifetime health behaviours and health literacy, to physical disease or vitality and mental health status, in concert with normative neurological decline and dementia (Bäckman & MacDonald, 2006; Deary, 2005). Understanding why cognitive performance is associated with mortality may further distinguish the mechanisms that lead to cognitive decline, dementia and death. In addition, understanding patterns of cognitive decline prior to death provides further insight into of the reasons for the decline. As cognitive decline and mortality may both be driven by complex interactions between multiple factors, examining these outcomes using a range of methodologies that account for the diversity of the aging population is vital to understanding these processes.

The relationship between cognition and mortality has been examined from a number of perspectives. Many prospective studies have directly described the relationship between late-life cognitive performance and mortality, taking either cross-sectional or longitudinal measures of cognitive performance. In such studies, the

outcome is usually survival time, and methods such as survival analysis (primarily Cox proportional hazards regression) are used. This methodology has been extended to examine whether changes in cognitive performance over time are associated with mortality, using a variety of methods of estimating change including latent growth models (Johansson et al., 2004) and mixed effects models (Ghisletta et al., 2006). A converse perspective has investigated the effect of time-to-death on cognitive performance, to explain the phenomenon of terminal decline. The hastening of cognitive decline in proximity to death has been proposed to result from pathological processes that are distinct from normative age-related cognitive decline. Methods such as change point models (Sliwinski et al., 2006; Thorvaldsson et al., 2008) have been used to test the conditions in which terminal decline might occur.

Explaining the nature of cognitive change close to death may also be achieved by examining relationships between different cognitive domains in terms of developmental trajectories. Specifically, the differentiation-dedifferentiation hypothesis is the most prominent developmental theory of late-life cognitive decline (Baltes, Cornelius, Spiro, Nesselroade, & Willis, 1980; Garrett, 1946; Li & Lindenberger, 1999). The theory suggests that different cognitive abilities become more closely related in old age in response to biological constraints, much as they become differentiated in childhood and early adulthood due to motivation, interest and fluid ability (Tucker-Drob, 2009). Understanding relationships between different cognitive abilities may help to reveal the underlying bases for their decline in late life.

Finally, the investigation of a broad range of risk factors is important in identifying whether relationships between cognition and mortality are influenced by sociodemographic factors, health behaviours, physical health or mental health. Understanding the factors associated with individual differences in cognitive aging may provide greater insight into why cognitive decline occurs and how it may be related to

mortality. One area of particular importance involves the associations observed between late-life depression and declines in cognitive performance (Christensen, Griffiths, Mackinnon, & Jacomb, 1997; Jorm, 2000). Previous research has also found a consistent relationship between depression and mortality (Cole & Bellavance, 1997; Cuijpers & Schoevers, 2004; Harris & Barraclough, 1998; Saz & Dewey, 2001; Schulz, Drayer, & Rollman, 2002; Wulsin, Vaillant, & Wells, 1999), although only limited evidence for a relationship between anxiety and mortality (Dewey & Chen, 2004; Harris & Barraclough, 1998). Determining the role of mental health on late-life mortality is important for assessing whether the cognition-mortality relationship may be confounded.

This thesis examines the relationship between cognition and mortality from multiple perspectives using the Canberra Longitudinal Study cohort (Christensen et al., 2004). The study is a community-based cohort study that commenced in 1990 with a sample of 896 elderly participants from cities of Canberra and Queanbeyan in Australia. Participants in the study completed comprehensive surveys every four years for twelve years, assessing their cognitive performance, physical health, social interactions, background variables and a range of other measures. The final wave of interviews was completed in 2002. However, the study continued to collect vital status information beyond the interview period, finishing in mid-2007 with up to 17 years of vital status follow-up. These data have provided a new opportunity for studying relationships between cognition and mortality. The thesis presents five manuscripts each reporting a study addressing a facet of the issues above. The manuscripts have been published in (or submitted to) peer-reviewed journals. The topics covered are: (i) survival as a function of cognitive performance (Batterham, Christensen, & Mackinnon, 2009), (ii) a comparison of two methods to examine cause-specific mortality as a function of cognitive change (Batterham, Mackinnon, & Christensen, submitted), (iii) estimation of

the effects of education on terminal decline using change point models (Batterham, Mackinnon, & Christensen, in press), (iv) a comparison of age and time-to-death as indicators for cognitive dedifferentiation (Batterham, Christensen, & Mackinnon, in press-a), and, (v) an analysis of the relationship between mental health symptoms and mortality (Batterham, Christensen, & Mackinnon, in press-b). The following sections provide a background of research and theory for each of the studies and provide context for their inclusion in the thesis.

Research examining the relationship between cognitive performance and mortality

The bulk of the literature examining the relationship between cognition and mortality has used prospective or retrospective study designs to observe how initial performance on cognitive tasks might be associated with subsequent survival time or mortality rates. While most prospective studies examining the relationship find evidence that poorer cognitive performance is associated with shorter survival time, the relationship is dependent of the type of test administered, the age of the cohort and the length of the follow-up period. Much of the research has examined the effect using tests of general intelligence. A review of nine studies on the relationship between early-life intelligence (between the ages of 8 and 22) and later mortality risk (Batty et al., 2007) reported that all studies found an association between higher intelligence and lower mortality. Even long-term studies of intelligence and mortality have shown that better cognitive abilities predict lower all-cause mortality, even over extended periods. Whalley and Deary (2001) retrospectively traced the vital status of 2,230 participants of the Scottish Mental Survey of 1932 for 65 years until 1997 and found that the hazard of mortality over the 65 year follow-up period was decreased by 21% for each 15-point increase in scores on a test of general intelligence. Similarly, Deeg, Hofman, & van Zonneveld (1990) retrospectively examined a cohort of 211 elderly Dutch residents who

were administered the Wechsler Memory Scale in 1957. After 26 years of follow-up, both lower initial performance on the scale and decreases in performance over the first eight years of follow-up were significantly associated with survival time (Deeg et al., 1990).

Other research has examined whether specific domains of cognitive function are associated with mortality. Poor executive performance tends to be associated with higher mortality risk, even after adjustment for health and sociodemographic measures (Bassuk, Wypij, & Berkman, 2000; Blazer, Sachs-Ericsson, & Hybels, 2005; Dartigues et al., 2007; Liang, Bennett, Sugisawa, Kobayashi, & Fukaya, 2003; Schultz-Larsen, Rahmanfard, Kreiner, Avlund, & Holst, 2008). However the relationship is not always found to be significant (Ganguli, Dodge, & Mulsant, 2002; Ostbye et al., 2006) and may be attenuated over longer follow-up periods (Ganguli et al., 2002; van Gelder, Tijhuis, Kalmijn, Giampaoli, & Kromhout, 2007). Verbal ability tends to be robust to the effects of aging and is less likely to be associated with mortality after adjusting for health and social status (Abas, Hotopf, & Prince, 2002; Anstey, Luszcz, Giles, & Andrews, 2001; Rabbitt et al., 2002).

Poor performance on short-term memory tasks (Ghisletta et al., 2006; Portin et al., 2001; Shipley et al., 2006) or associative learning tasks (Abas et al., 2002; Ghisletta et al., 2006; Rabbitt et al., 2002; Royall, Chiodo, Mouton, & Polk, 2007) tends to be more strongly associated with increased mortality rates than performance on tests of general intelligence or tests of executive functioning. Likewise, tests of processing speed such as Digit-Symbol Substitution (Anstey et al., 2001; Ghisletta et al., 2006; Pavlik et al., 2003; Portin et al., 2001) have strong associations with mortality. As performance on such tests is often reliant on motor speed, it has been suggested that decline in these basic abilities may be driving the association with mortality (Deary & Der, 2005). Nevertheless, the effects are often strong even after accounting for health

status, and sensory and motor abilities (Ghisletta et al., 2006; Pavlik et al., 2003). In general, evidence suggests that tests with a fluid intelligence component tend to be more strongly predictive of mortality than crystallised intelligence tests.

To better understand why cognitive performance may be associated with mortality, it is necessary to examine a range of cognitive abilities and account for possible mediators or moderators that may explain the mechanism of the association. Deary (2005) has categorised possible mechanisms to explain the childhood intelligence and mortality connection into three general mechanisms, which are equally relevant to explaining the relationship between late-life cognitive ability and death. Firstly, socio-economic status may mediate the relationship between intelligence and mortality. Disadvantages in intelligence lead to burdens in occupation, which are linked to poorer health outcomes (Siegrist & Marmot, 2004). Secondly, the relationship may be mediated by health behaviours and knowledge. Many positive health behaviours that prevent disease, including health monitoring, screening, medication adherence and becoming health literate, require high levels of cognitive functioning (Gottfredson & Deary, 2004). Conversely, poor cognitive ability may be associated negative health behaviours, including substance use, poor diet, decreased physical activity and low healthcare utilization (Deary, 2005), leading to poorer health outcomes and greater risk of mortality.

Thirdly, the relationship between intelligence and mortality may be due to a common association with health status. Studies of the common cause hypothesis have linked sensory function, lung function, grip strength and other biological markers with performance on cognitive tests (Christensen, Mackinnon, Korten, & Jorm, 2001; Salthouse, Hancock, Meinz, & Hambrick, 1996). To a considerable extent, intelligence reflects core processing mechanisms such as reaction time, which may decline in direct response to biological deterioration (Deary & Der, 2005). Intelligence may therefore

serve as a marker of biological fitness (Deary, 2005). In addition, development in early life, influenced by foetal events, birth weight and early nutrition, shapes future patterns of health and disease and may confound the relationship between intelligence and mortality (Deary, 2005).

Few studies of the relationship between cognition and mortality have explicitly tested these potential mechanisms. Systematic adjustment for measures of socioeconomic status, health behaviours and health status enables estimation of the proportion of the variance in the relationship that may be explained by each of these mechanisms. Such investigation of the relationship is also necessary for furthering our understanding of why cognitive abilities such as processing speed are associated with mortality, while other abilities such as verbal performance are not. Previous studies have demonstrated that socioeconomic status and health factors may attenuate this relationship but that core processes such as processing speed and reaction time remain critical in predicting mortality (Deary & Der, 2005; Pavlik et al., 2003; Shipley et al., 2006; Shipley, Der, Taylor, & Deary, 2007). However, with few studies directly testing these mechanisms of the relationship in aging cohorts, further investigation across a range of cognitive abilities is warranted.

The first study in the present thesis systematically examined three potential mechanisms for the relationship between cognition and mortality in the Canberra Longitudinal Study cohort (Batterham et al., 2009). While this relationship has been widely studied using survival analysis, the first study took a hierarchical modelling approach to assess each of the three primary mechanisms detailed by Deary (2005). The association between tasks tapping fluid and crystallised intelligence and all-cause mortality was assessed, accounting for possible moderation by sociodemographic factors, health behaviours and health status. This study also examined whether fluid

intelligence was more strongly related to mortality than crystallised intelligence. The manuscript begins on page 43.

Research examining changes in cognitive performance with respect to mortality

There has been markedly less research examining how change in cognition, as opposed to levels of cognitive performance, might be associated with mortality. Bosworth and Siegler (2002) reviewed studies that examined change in cognition as a predictor of mortality. The review noted that while an established relationship exists between cognitive performance and risk of mortality, the relationship between rate of cognitive change and mortality is less clear. Only nine studies met the selection criteria for the review, which covered the period from 1975-2000. Among the included studies, methods used to assess cognitive change included the comparison of mean differences (Bosworth & Schaie, 1999; Mortensen & Kleven, 1993), categorizing participants as decliners or non-decliners based on the size of change scores (Anstey et al., 2001) or grouping the sample by time to death and comparing change in cognitive scores (Johansson & Berg, 1989). These methods only account for within-person change or rely on arbitrary characterizations of decline. The reviewed studies also tended not to adjust for the initial level of performance, which may confound the effects of change in performance. Bosworth and Siegler (2002) concluded that the relationship between cognitive change and mortality has not been clearly established, necessitating further analysis of existing and future population-based studies to provide a better understanding of the relationship.

More recent studies of the relationship between cognitive change and mortality have used more defensible and robust methods to characterise change. Johansson et al. (2004) and Ghisletta et al. (2006) used two related methods to obtain unbiased estimates of change in cognition to predict mortality. Johansson et al. (2004) used a latent growth

model, while Ghisletta et al. (2006) used a mixed model approach to obtain Best Linear Unbiased Predictors of linear change (BLUPs). Both studies found some effect of cognitive change on all-cause mortality. However the types of cognitive decline associated with mortality differed: Johansson et al. (2004) reported an association between declines in crystallised abilities and mortality, while Ghisletta et al. (2006) reported that declines in speed and fluency were significantly related to survival time. Given the disparate findings, a comparison of the two methods for investigating the effect of cognitive change on mortality would serve as an important development. Furthermore, these methods may also be extended to examine cause-specific mortality within a survival analysis framework, which has not previously been done using latent growth models. Specifically, Johansson et al. (2004) used time-to-death as a predictor of cognitive change within the latent growth model, rather than using time-to-death as an outcome and accounting for censored (surviving) observations. Given these omissions from past research and the divergence of findings, further examination of the relationship between cognitive change and both all-cause and cause-specific mortality using these two emerging methods would provide an important and innovative extension to the literature.

Recognising these deficits, the second study (Batterham et al., submitted) examined whether longitudinal within-person changes in cognitive performance were associated with mortality. As very little research has used defensible methods for assessing within-person cognitive change with respect to mortality, the study compared two unbiased methods for estimating cognitive change. Latent growth models (Johansson et al., 2004) and best linear unbiased predictors (Ghisletta et al., 2006) were used to generate within-person level and slope estimates of cognitive performance over time. The study extended previous research by examining whether these estimates of

change were associated with mortality from specific causes, including cardiovascular disease, respiratory disease and cancer. This manuscript is presented on page 73.

Research on changes in the rate of cognitive decline: the terminal decline theory

An alternative approach that directly tests the theory of terminal decline is to examine how the rate of cognitive decline changes in proximity to death. Change in cognition may not be strongly predictive of time-to-death because changes in cognitive performance may not accelerate continuously as death approaches (Sliwinski et al., 2006). The terminal decline theory originally proposed by Kleemeier (1962) and developed by Riegel and Riegel (1972) suggests that cognitive decline is initially gradual, resulting from normative age-related changes in cognition, then accelerates due to pathological events closer to death. This conceptualization of terminal decline suggests that instead of examining linear or quadratic changes in cognitive performance, decline in proximity to death might be better characterised as having two distinct phases – preterminal decline and terminal decline. The preterminal phase is proposed to represent normative changes, while the terminal phase occurs close to death when biological constraints increase resulting in more rapid decline in cognitive performance (Laukka, MacDonald, & Bäckman, 2008; Sliwinski et al., 2006). This hypothesis can be explicitly tested by partitioning longitudinal data to estimate the change point at which the terminal phase begins, and estimating the two rates of change before and after the change point. Only recently have researchers developed methods to formally model the time course of terminal decline. Hall, Lipton, Sliwinski and Stewart (2000) were the first to use the change point method for identifying the onset of cognitive decline prior to the diagnosis of Alzheimer's Disease. Wilson et al. (2003), Sliwinski et al. (2006), Wilson et al. (2007) and Thorvaldsson et al. (2008) have used the method to distinguish

terminal cognitive decline from preterminal cognitive decline with respect to time-to-death.

Change point models allow for two rates of change, with the time from a specified base point to death partitioned on the basis of a hypothesised change point. To account for within-person change, fixed and random effects of the two slopes are included in the models. A range of change points are tested, starting, for example, 20 years prior to death, then incrementing this point by monthly intervals. The fit of models using each of the potential change points across the range can then be compared using a fit statistic (usually -2 log likelihood) with the optimal change point being selected using this criterion. Using a likelihood function as the criterion also allows for a confidence interval to be calculated around the change point. Once a specific change point is selected, rates of terminal decline may be compared to rates of preterminal decline. Using the change point method, Wilson and colleagues (2003; 2007) identified change points around 3.5 years, while Sliwinski et al. (2006) and Thorvaldsson et al. (2008) generally identified change points between 5-9 years prior to death. The rate of terminal decline was generally 2-5 times greater than the rate of decline in the preterminal phase. Some of the variation in findings may be explained by methodological differences, such as Wilson et al. (2003; 2007) including survivors in their models using a slight variation of Hall et al.'s (2000) change point model. However, much of the variation appears likely to be due to the types of cognitive measures used to characterise decline. The four studies generally reported findings for single cognitive tests or global composite scores, with the exception of Thorvaldsson et al. (2008) who found marked differences across different domains of ability. Consequently, it is important to examine a range of cognitive abilities to determine the specificity of the terminal decline phenomenon.

The change point method may also be extended to examine the effects of specific risk factors on terminal decline. One specific risk factor of interest is poor education, as the theory of cognitive reserve suggests that education may increase the brain's ability to compensate for pathology (Stern, 2002). Education may be associated with a greater number of healthy synapses or neurons, more efficient circuits of synaptic connectivity or more efficient use of alternative brain networks (Scarmeas, Albert, Manly, & Stern, 2006). The functional effects of this reserve may be seen in research suggesting that increased education delays the onset of Alzheimer's disease, although, ultimately, rate of decline is more rapid among more highly educated individuals (Stern, Albert, Tang, & Tsai, 1999). Thus it may be expected that terminal decline may be altered similarly, with increased education hypothesised to delay the onset but be associated with an accelerated rate of terminal decline. Wilson et al. (2007) examined the effects of multiple risk factors on terminal decline, including education. While they found no effect of education on the rate of decline, they did not examine whether cognitive reserve may influence specific domains of cognitive decline, as they only examined a global cognition composite score.

Further examination of the effect of education on terminal decline is therefore warranted. Accordingly, the third study (Batterham, Mackinnon et al., in press) examined evidence for terminal decline in the Canberra Longitudinal Study cohort. The change point methodology (Hall et al., 2000) was used to describe the time course of terminal decline by estimating the point of onset of terminal decline and comparing rates of decline before and after this point. To test whether cognitive reserve impacted the onset or rate of terminal decline, the effect of education on terminal decline was assessed across three domains of cognitive performance: processing speed, global cognition and episodic memory. Analyses also accounted for dementia and other potential confounders. This manuscript begins on page 105.

Research examining the nature of late-life cognitive change: the differentiation-dedifferentiation hypothesis

While it is clear that some cognitive abilities decline earlier and more rapidly than others, the mechanisms driving these differences are not fully understood. The differentiation-dedifferentiation hypothesis proposes that different abilities become more strongly correlated in late life as a result of increasing biological constraints (Li & Lindenberger, 1999). These increasing correlations are proposed to be the reverse of the differentiation of abilities in early life (Lienert & Crott, 1964), which may be attributed to childhood intelligence and genetics interacting with environmental factors and motivation (Cattell, 1987). The theory is referred to as the differentiation-dedifferentiation hypothesis due to this rise and fall in the differentiation of abilities. However, evidence for dedifferentiation as a function of advanced age is mixed. Several studies have reported late-life increases in the correlation between cognitive abilities (Baltes & Lindenberger, 1997; Ghisletta & Lindenberger, 2003; Li et al., 2004) while other studies have found no systematic relationship (Anstey, Hofer, & Luszcz, 2003; Juan-Espinosa et al., 2002; Sims, Allaire, Gamaldo, Edwards, & Whitfield, 2009; Tucker-Drob & Salthouse, 2008; Zelinski & Lewis, 2003). Some of the differences in findings may be attributable to the broad array of methods used to examine the hypothesis.

In assessing the dedifferentiation hypothesis, there are three methodological issues that have rarely been addressed by previous research. Firstly, differentiation-dedifferentiation as a function of age occurs in a non-linear pattern by definition. According to the theory, the amount of variance accounted for by a general ability factor over the lifetime should be curvilinear, approximating an inverted-U. However, much of the research on dedifferentiation defines the general ability factor using linear factor analysis. Secondly, differentiation of cognitive abilities can also occur as a

function of ability, as the proportion of abilities accounted for by a general factor increases at lower ability levels (Deary, Egan, Gibson, Austin, & et al., 1996; Der & Deary, 2003; Tucker-Drob, 2009). In estimating the degree to which dedifferentiation occurs as a function of age, adjustment must be made for ability differentiation, otherwise the observed effects may simply be the result of poorer overall performance among older individuals. Again, not all dedifferentiation research accounts for potential ability differentiation effects. Recent analytical developments have enabled investigators to account for both the nonlinear nature of the hypothesis and the effects of level of ability. The statistical model used by Tucker-Drob (2009) allows assessment of the effects of age dedifferentiation using a structural equation model to simultaneously combine a nonlinear factor analysis to estimate a general ability factor with a regression that tests the effects of age dedifferentiation and ability differentiation. This methodology has only been used in one previous analysis, which found little support for the dedifferentiation of cognitive abilities as a function of age (Tucker-Drob, 2009).

Thirdly, there is limited research adequately assessing whether age dedifferentiation occurs in response to age-related biological constraints as proposed by the theory. In assessing this element of the theory, it is important to separate the effects of dementia from normative age-related neurological decline. Furthermore, a metric that better reflects biological deterioration could be used as a comparator for age. Chronological age may only be weakly associated with biological damage, as lifetime accumulation of biological damage and resulting cognitive health may vary widely (Lovden, Bergman, Adolfsson, Lindenberger, & Nilsson, 2005; Sliwinski, Hofer, & Hall, 2003). Instead, time-to-death is a stronger indicator of declines in both physical health and cognitive performance (Hassing et al., 2002; Small & Bäckman, 1999). Comparing age dedifferentiation to time-to-death dedifferentiation is an approach that

has not previously been used to assess this aspect of the dedifferentiation hypothesis. In addition, such an approach may further explain the changes in cognitive abilities that are observed in proximity to death.

To address these limitations of previous research, the fourth study (Batterham, Christensen et al., in press-a) investigated the differentiation-dedifferentiation hypothesis using the aforementioned methodology that accounts for non-linear relationships between cognitive measures and factors and adjusts for the effects of ability differentiation (Tucker-Drob, 2009). The study also contrasted age with time-to-death as the metric for dedifferentiation, to examine evidence that dedifferentiation could be attributed to biological constraints in late life. Such an analysis has not previously been presented. The evidence for dedifferentiation was further evaluated in a subgroup analysis that excluded participants with possible pre-clinical dementia. This manuscript is presented on page 139.

The role of mental health in the cognition-mortality relationship

There is extensive evidence for a relationship between late-life depression and reduced cognitive performance (Christensen et al., 1997; Jorm, 2000; Willner, 1984). People with depression perform more poorly than controls on every cognitive ability that has been examined, including intelligence, verbal ability, memory, attention, executive ability, conceptual ability and orientation (Christensen et al., 1997). Furthermore, there is evidence that depression may be a risk factor for subsequent dementia (Jorm, 2000). There is also some evidence suggesting that late-life depression is a risk factor for death. Evidence for this relationship has been summarised in six reviews, each of which has concluded that depression is associated with an increased all-cause mortality rate (Cole & Bellavance, 1997; Cuijpers & Schoevers, 2004; Harris & Barraclough, 1998; Saz & Dewey, 2001; Schulz et al., 2002; Wulsin et al., 1999). A

review of 57 studies published between 1966 and 1996 (Wulsin et al., 1999) found that 29 (51%) reported a positive relationship between depression and mortality. A later review of 61 articles subsequently published between 1996 and 2001 (Schulz et al., 2002) reported that 72% found a significant relationship between depression and mortality. A meta-analysis (Saz & Dewey, 2001) reported a combined odds ratio for mortality with depression of 1.73 (95% CI 1.53-1.95), while another recent review (Cuijpers & Schoevers, 2004) reported a relative risk for mortality in depressed subjects of 1.81 (95% CI 1.58-2.07) compared to non-depressed subjects. Given the relationships of depression with both cognition and mortality that have been previously observed, it is possible that some proportion of the relationship between cognition and mortality could be explained by depression.

However, before examining how depression may moderate the cognition-mortality relationship, there are some limitations to the depression-mortality relationship that require further investigation. Wulsin et al. (1999) cautioned against drawing strong conclusions about the nature of the relationship between depression and mortality due to a lack of adequate controlling for confounders, the potential of publication bias in favour of positive studies and the heterogeneity of samples and methods used in the studies. In particular, very few studies of this relationship have adequately controlled for the effect of physical health status. Physical health status was not controlled for in 25 of the 57 studies reported by Wulsin et al. (1999), 20 of the 61 studies reported by Schulz et al. (2002), and 31 of the 38 studies reported by Saz and Dewey (2001). Moreover, very few studies used objective measures of health status, with most using self-report measures such as presence/absence of chronic disease. Furthermore, the effect of depression on mortality is greatly attenuated over long follow-up periods (Saz & Dewey, 2001) and tends to be weak or non-existent in population samples (Wulsin et al., 1999). Given the methodological inadequacies of

some previous studies and the limited generalisability of the relationship, the association between depression and mortality may have been overstated and requires more refined evaluation.

Comparatively few studies have examined the effect of anxiety on mortality. In a review of six studies of the effect of anxiety disorders on mortality, Harris and Barraclough (1998) reported that the risk of all-cause mortality was significantly greater for neurosis or panic disorder but not for anxiety neurosis. However, Dewey and Chen (2004) reviewed seven studies of the effect of anxiety disorders on mortality in elderly cohorts and found that there was no significant relationship between either anxiety diagnosis or anxiety symptoms and mortality. While there is little evidence for an effect of anxiety on mortality, it is still worthwhile examining the relationship, as anxiety may also have effects on cognitive performance. Gallacher et al. (2009) found that anxiety was associated with significant declines in learning memory and increased risk of cognitive impairment and dementia. Bierman, Comijs, Jonker and Beekman (2005) reported a curvilinear association between anxiety and cognition, with severe anxiety symptoms associated with significantly poorer cognitive performance. Sinoff and Werner (2003) also found that anxiety was a significant predictor of cognitive decline, particularly memory loss. Consequently, this study sought to assess potential confounding of the relationship between cognition and mortality that might be attributable to anxiety.

The final study (Batterham, Christensen et al., in press-b) investigated the effects of depression and anxiety on mortality, as mental health may be closely related to cognitive performance. While other studies in this thesis adjusted for the effects of depression and anxiety (Batterham et al., 2009; Batterham, Mackinnon et al., in press; Batterham et al., submitted), previous research on interactions between mental health and cognition indicated a need to examine how mental health might influence mortality.

The mediating effect of physical health on the association between mental health symptoms and mortality was assessed using a novel methodology that incorporated a Cox Proportional Hazards regression into a structural equation model (Asparouhov, Masyn, & Muthen, 2006). This manuscript begins on page 163.

While published separately, the studies below represent an integrated attempt to carefully apply innovative methods to clarify and extend what is known about mechanisms associating cognition at the very latest phase of life and transition to the non-cognitive state.

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Fluid intelligence is independently associated with all-cause mortality over 17 years in an elderly community sample: An investigation of potential mechanisms

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Published in *Intelligence*, 2009, 37 (6), 551-560.

Abstract

The long-term relationship between lower intelligence and mortality risk in later life is well established, even when controlling for a range of health and sociodemographic measures. However, there is some evidence for differential effects in various domains of cognitive performance. Specifically, tests of fluid intelligence may have a stronger association with mortality than do tests of crystallized intelligence. The present study examines the relationship between intelligence and mortality in a sample of 896 Australian community-dwelling males and females, aged 70-97 at recruitment and followed for up to 17 years. There were 687 deaths during the follow-up period. Cox proportional hazard regression models examined whether the relationship between intelligence and mortality might be mediated by socioeconomic status, by health behaviors, by health status, or a combination of these. Higher fluid intelligence – as measured by the Symbol-Letters Modalities Test – was strongly associated with lower mortality rates (Hazard ratio = 0.80; 95% confidence interval = 0.72–0.88), even after accounting for any combination of potential mediators and confounders. A significant association between crystallized intelligence, as measured by the National Adult Reading Test, and mortality (HR = 0.89; 95% CI = 0.80–0.99) was attenuated by the inclusion of socioeconomic, health status measures, and health behavior measures and when deaths from the first four years of the study were excluded. The findings show little support for the hypothesized mechanisms of the intelligence-mortality relationship.

Long-term studies of intelligence and mortality demonstrate that higher intelligence is associated with lower all-cause mortality. A recent review (Batty, Deary, & Gottfredson, 2007) examined nine studies investigating the relationship between early-life intelligence and later mortality risk. The studies followed cohorts for between 17 and 69 years. All found that higher IQ was associated with lower mortality. For example, one of the reviewed studies retrospectively traced the vital status of 2,230 participants in the 1932 Scottish Mental Survey after 65 years (Whalley & Deary, 2001). The hazard of mortality over the 65 year follow-up period was decreased by 21% for each 15-point increase in intelligence as measured by the Moray House test. Studies reporting follow-up into old age have also reported consistent findings (Deeg, Hofman, & van Zonneveld, 1990; Rabbitt, Lunn, & Wong, 2006; Shipley, Der, Taylor, & Deary, 2006). However, the intelligence-mortality relationship may be dependent of the type of test administered, the age of the cohort and the length of the follow-up period.

Poor performance on *executive tests* such as the Mini-Mental State Exam (Bassuk, Wypij, & Berkman, 2000; Dartigues et al., 2007) or the Short Portable Mental Status Questionnaire (Blazer, Sachs-Ericsson, & Hybels, 2005; Liang, Bennett, Sugisawa, Kobayashi, & Fukaya, 2003) tends to be associated with higher mortality risk, however the relationship has not always been found to be significant (Ganguli, Dodge, & Mulsant, 2002; Ostbye et al., 2006) and may be dependent on the length of the follow-up period (Ganguli et al., 2002; van Gelder, Tijhuis, Kalmijn, Giampaoli, & Kromhout, 2007). Performance on tests of *crystallized intelligence*, such as the National Adult Reading Test (Abas, Hotopf, & Prince, 2002; Anstey, Luszcz, Giles, & Andrews, 2001) or Raven's Mill Hill Vocabulary Scale (Rabbitt et al., 2002) tends to be robust to the effects of aging and is less likely to exhibit an association with mortality after health and social status are taken into account.

Tests of *fluid intelligence*, such as Digit-Symbol Substitution (Anstey et al., 2001; Ghisletta, McArdle, & Lindenberger, 2006; Pavlik et al., 2003; Portin et al., 2001) or various learning tasks (Abas et al., 2002; Ghisletta et al., 2006; Rabbitt et al., 2002; Royall, Chiodo, Mouton, & Polk, 2007) tend to decline more with age and are more strongly associated with mortality than performance on tests of general intelligence or tests of executive functioning. However, the effect size may be greater for long-term (e.g., Ghisletta et al., 2006) rather than short-term (e.g., Bosworth, Schaie, & Willis, 1999) studies and for older rather than younger cohorts (Lyyra, Heikkinen, Lyyra, & Jylha, 2006; Shipley et al., 2006). The association between *short-term memory performance* and mortality among non-demented adults is also well documented (Ghisletta et al., 2006; Portin et al., 2001; Shipley et al., 2006). In addition, two reviews have reported an association between dementia or mild cognitive disorders and mortality (Dewey & Saz, 2001; Guehne et al., 2006; Guehne, Riedel-Heller, & Angermeyer, 2005). Indeed, it has been contended that the relationship between intelligence and mortality is largely mediated by dementia (Backman & MacDonald, 2006).

Given the evidence for the relationship between intelligence and mortality, potential mechanisms driving this association warrant further examination. In early research on the relationship between cognitive decline and mortality, Riegel and Riegel (1972) described the effect in terms of "terminal drop". While the relationship between childhood intelligence and mortality cannot be explained by terminal decline alone, two theories posited by Riegel and Riegel (1972) form the basis of contemporary understanding of the intelligence-mortality relationship. Firstly, a biological theory suggested that physiological mechanisms related to cell aging were responsible for the decline and also for death. Secondly, a sociological theory suggested that performance and chance of survival drops earlier in life for those who cope less well with their

environment due to disadvantages in, for example, education, income, nutrition and medical assistance.

More recently, three potential mechanisms for the relationship have been detailed by Whalley and Deary (2001) and Deary (2005) and tested by Kuh et al. (2004) and Shipley et al. (2006). First, socio-economic status (SES) may mediate the relationship between intelligence and mortality. This theory, advocated by Siegrist and Marmot (2004), is similar to the sociological theory of Riegel and Riegel (1972), suggesting that disadvantages in intelligence lead to burdens in occupation, which are linked to poorer health outcomes. Siegrist and Marmot (2004) elaborate on the relationship by taking into account the mediating effect of control on health outcomes. The demand-control model (Karasek, 1979) proposes that high work demands interact with low levels of perceived control to cause such outcomes as depression and exhaustion, which adversely effect health outcomes and consequent mortality. A second explanation is that the relationship between intelligence and mortality is mediated by health behaviors and knowledge, which include substance use, diet, physical activity, healthcare utilization, and accident and illness prevention (Deary, 2005). Gottfredson and Deary (2004) argued that a high level of cognitive resources are required to prevent disease and ameliorate illness through behaviors such as health monitoring, screening, medication adherence, understanding health information and becoming health literate. Failure to adequately undertake these health behaviors can lead to illness or more severe illness, resulting in hospitalization and health costs, and consequently, greater risk of mortality (Gottfredson & Deary, 2004).

A third explanation is that the relationship between intelligence and mortality may be due to a common association with health status. There are two possible explanations for an association between intelligence and health (Deary, 2005): (i) intelligence may be viewed as a marker of biological “fitness” or of system integrity, or

(ii) intelligence may be an indicator of developmental problems that impact on later health. The former explanation aligns with the biological theory proposed by Riegel and Riegel (1972), with evidence from studies of the common cause hypothesis linking sensory function, lung function, grip strength and other biological markers with performance on cognitive tests (Christensen et al., 2000; Christensen, Mackinnon, Korten, & Jorm, 2001; Salthouse, Hancock, Meinz, & Hambrick, 1996). The latter explanation suggests that development in early life, such as fetal events, birth weight and early nutrition, shape future patterns of health and disease, which confound the relationship between intelligence and mortality (Deary, 2005). A refinement of (i) is that intelligence is associated with mortality because it reflects basic or core information processing mechanisms reflected in measures such as RT and grip strength (Deary & Der, 2005; Shipley et al., 2006). These two studies demonstrated that SES and health factors affect the relationship but that core processes such as reaction time are critical in predicting mortality.

The three proposed explanations of the link between mortality and intelligence are testable. The first predicts that education, employment history and other measures of lifetime opportunity will be associated with both intelligence and mortality and will consequently reduce the effect of intelligence on mortality. The second predicts that health behaviors, such as substance use history and healthcare utilization measured both currently and retrospectively over the lifespan, will likewise mediate the association between intelligence and mortality. The third set of explanations is more complex but suggests that disease status and a range of health or biological markers may account for a large proportion of the variance in the relationship between intelligence and mortality. The refinement of the explanation proposed by Deary and Der (2005) is that after accounting for core biological processes (reflected in biological measures such as grip

strength, sensory processing and reaction time), the relationship between intelligence and mortality should be reduced or eliminated.

Two tests that capture the construct of intelligence are used in the present study. The Symbol-Letters Modalities Test (SLMT), a task similar to Smith's (1973) Symbol-Digit Modalities Test and Wechsler's (Wechsler, 1981) Digit-Symbol Substitution, is a perceptual speed test that provides a measure of fluid intelligence. SLMT measures the efficiency of visual search and memory for the symbols presented in the task (Gilmore, Spinks, & Thomas, 2006) and performance on the task is correlated with measures of general intelligence such as the Wechsler Adult Intelligence Scale (Waldmann, Dickson, Monahan, & Kazelskis, 1992). The National Adult Reading Test (NART; Nelson, 1982) is a test of vocabulary that provides a measure of crystallized intelligence. NART performance is also correlated with measures of general intelligence and, unlike SLMT, is resistant to the effects of dementia (Bright, Jaldow, & Kopelman, 2002). Having the two tests allowed us to formulate differential predictions of the effect of these cognitive variables on mortality. Based on past research, SLMT performance was hypothesized to be a better predictor of mortality than NART. We also predicted that the relationship between SLMT and mortality would be more strongly mediated by health status than the relationship between NART and mortality, since NART performance is more resistant to the effects of declining health.

Method

Participants

The Canberra Longitudinal Study (CLS) was a large epidemiological survey of mental health and cognitive functioning that began in 1990. The study design is more fully detailed by Christensen et al. (2004). Eight hundred and ninety-six participants

(456 men and 440 women) aged 70 or older at the time of the baseline assessment were recruited for the baseline assessment. All participants were initially living in the community in the cities of Canberra or Queanbeyan, Australia. Participants were sampled from the compulsory electoral roll, with 69% responding. Approval for the research was obtained from the Ethics in Human Experimentation Committee of The Australian National University.

Survey Procedure

Participants were interviewed up to four times over 12 years. Interviews were sought from both the participant and an informant, although the present study only examines participant data. Baseline interviews lasted approximately two hours, incorporating a survey measuring a wide range of risk factors including socio-demographics, physical health and disease status, mental health status, cognitive performance and social support. Interviews also included physical assessments of blood pressure, lung function, grip strength, vision and reaction time. Trained professional interviewers conducted the interviews.

Of the original sample of 896 participants, 185 (20.6%) were deceased by four years, 363 (40.5%) were deceased by eight years, and 544 (60.7%) were deceased by 12 years. At the end of vital status collection in June 2007, 687 (76.7%) of the participants were deceased. Of the participants who remained in the study, 14.1% (100/711) refused or were unable to complete the first follow-up interview, 21.1% (100/474) for the second follow-up and 21.1% (57/270) for the third follow-up.

Assessment of mortality

Mortality status and date of death were established by contacting relatives, searching the National Death Index, and from death notices in the local newspaper. The

National Death Index, a register of all deaths in Australia, was searched by name and date of birth. Missing death identifications from the National Death Index would most likely have been a rare occurrence, as the index provides nationwide coverage. The additional methods used for death reporting (contacting relatives, newspaper searches) provide further confidence in the mortality status data. Mortality status was followed for up to 17 years, from the start of baseline interviews in September, 1990 until June 30, 2007. Survival was calculated as the time from the baseline interview to death for deceased participants, or from baseline until June 30, 2007 for surviving (right-censored) participants. For six participants with unknown day of death, the day was set to the 15th of the month. For two participants with an unknown month of death, the month was set to June. Taking deaths into account, the mean follow-up time was 9.7 years – 16.4 years for surviving participants and 7.6 years for deceased participants.

Assessment of intelligence

Two tasks were used to assess different domains of intelligence. The Symbol Letter Modalities Test is a test of perceptual speed that has been used as a measure of fluid intelligence. This test is based on earlier tests of fluid intelligence such as Digit Symbol Substitution (Wechsler, 1981) and the Symbol Digit Modalities Test (Smith, 1973). Participants were provided with a key which linked 10 symbols with letters of the alphabet (A to I). They were given 90 seconds to call out to the examiner the letters of the alphabet that corresponded to symbols printed in rows on the page. The key to the symbol-letter pairings was printed above the array. The test measures both fluid intelligence and cognitive speed. However, it allows an oral response to be made by the participants, thereby limiting possible contamination from impaired psychomotor functioning. The number of correct symbol-letter pairs made in 90 seconds was summed and the scores were standardized to produce an IQ-type score (SLMT IQ).

The National Adult Reading Test (NART; Nelson, 1982) assessed crystallized intelligence by testing the vocabulary of participants. The NART is a list of 50 words that are not pronounceable phonetically. Participants read the words aloud and testing is discontinued whenever there were 14 failures out of 15 items. The number of correct pronunciations made was summed and the scores were standardized to produce an IQ-type score (NART IQ).

Control variables

All of the control variables were measured in the baseline interview, with the exception of subsequent dementia diagnosis which was made on each wave of measurement.

Socio-economic status: Educational status was based on responses to two questions regarding the number of years in school and the highest qualification obtained. These two questions were combined into a single measure representing the number of years it took participants to attain their highest educational qualification. Work history was asked as an open-ended question that was then given a standard job classification coding. From these codings, participants were classified into one of six categories: unskilled, semi-skilled, skilled, white collar, lower professional, managerial/professional. However, given the advanced age of the sample (the categorizations are based on a contemporary coding system) and a lack of predictive power provided by these categories, they were collapsed into a binary measure reflecting manual or non-manual employment. Participants who were involved in home duties were classified based on their spouse's occupational status.

Locus of control: A 14-item locus of control scale was administered, with participants rating items such as "I am confident of being able to deal successfully with future problems" on a six-point Likert scale from "Strongly disagree" to "Strongly agree".

The scale was based on the 17-item Locus of Control of Behavior scale (Craig, Franklin, & Andrews, 1984) with three symptom-related items removed. Eight items were negatively-worded and were reverse scored. The score was a mean of the ratings (range 1-6), with higher scores indicating that the participant saw themselves as the locus of control.

Health behaviors: Participants reported whether they were current smokers, past smokers who had quit, or had never smoked. Level of activity was based on a six-item scale asking participants how often they engaged in activities "these days", with possible scores ranging from 0-18. The activities were reading, some sort of physical activity, active involvement in interests or hobbies, sitting at home (inactivity, negatively scored), and planned activities such as household tasks and visiting people. (Christensen et al., 1996) While there is a relationship between the activity scale and the level of physical disability (r = -.44), participation in social and intellectual pursuits are not captured by measures of physical disability.

Physical health: A brief self-reported medical history for each participant was taken during the survey. Heart attack history, stroke history (combining strokes, mini-strokes and transient ischemic attacks) and hypertension history were measured as dichotomous variables. A disease count covering 14 other diseases (including diabetes and cancer) and a symptom count for 21 symptoms (including falls, dizziness and chest pain) were generated. To measure functional ability, eight Activities of Daily Living (ADLs) were rated for difficulty on a four-point scale (no difficulty, some difficulty but no help needed, need help, bedridden) and five Instrumental Activities of Daily Living (IADLs) were rated on a three-point scale (no help needed, need help, cannot do). Two scales of functional ability were generated from these items, with ADL scores ranging from 0 to 24 and IADL scores ranging from 0 to 8. Higher scores on these scales indicate greater

functional disability. Self-rated health was measured by asking participants to rate their general health on a four-point scale from "Excellent" (1) to "Poor" (4).

Sensory indicators of physical health included reaction time, grip strength, visual and auditory function. To measure choice reaction time, participants were asked to press a button with their left or right hand depending on which of two stimulus lights were illuminated (interstimulus intervals ranged from 0.5 to 2.0 seconds) (Christensen et al., 2000). The trials were performed mid-way through the survey, and choice reaction time was measured as the mean response time over 20 trials. Grip strength was taken using a Smedley hand dynamometer which measures the force exerted in kilograms (Christensen et al., 2000). Visual impairment was self-rated, with participants reporting "poor" eyesight or blindness classified as visually impaired. Hearing impairment was also self-rated, with participants who used a hearing aid or reported poor hearing classified as hearing impaired.

Mental health: Mental health ratings were included in the analysis as supplementary measures of health status. The Goldberg Depression Scale and Goldberg Anxiety Scale each consist of nine yes/no items measuring symptoms of depression and anxiety (Goldberg, Bridges, Duncan-Jones, & Grayson, 1988). Scores on these tests reflect a symptom count ranging from 0 to 9.

Dementia: To control for potential confounding by dementia, participants who were given an ICD-10 (World Health Organization, 1993) diagnosis of dementia or severe dementia later in the study (at waves 2-4, 4-12 years after baseline) were identified. Diagnoses were made using the Canberra Interview for the Elderly (CIE) (Social Psychiatry Research Unit, 1992), which provides information from which a diagnosis of dementia can be made according to ICD-10 (World Health Organization, 1993) and DSM-III-R (American Psychiatric Association, 1987) by means of a computer algorithm.

Analyses

Descriptive analyses compared living participants to deceased participants to investigate which predictors were associated with death during the follow-up time. Survival time was graphed using Kaplan Meier curves and modeled using Cox proportional hazards regression analyses. A series of six regression analyses included the intelligence measures with a combination of potential mediators or confounders, corresponding to the hypothesized mechanisms of the intelligence-mortality relationship. To facilitate interpretation of the Cox regression analyses, continuous variables (excluding age, years of education and disease and symptom counts) were standardized by subtracting the mean for the entire sample and dividing by the standard deviation. To account for potential confounding by end-of-life illness, specifically, sub-clinical disease states not captured by the health status measures, the analyses were repeated with the exclusion of participants who died in the first four years of the study. The analyses were also repeated separately by gender to investigate whether the intelligence-mortality relationship differed for males and females.

Incomplete data for the survival analyses were imputed using the *ICE* procedure in Stata. Ten imputed data sets were generated by simultaneously modeling all of the independent variables from the baseline survey that were used in the analyses. The imputation procedure used linear regression to impute continuous variables, logistic regression to impute dichotomous variables and multinomial logistic regression to impute the two categorical variables (smoking status and self-rated health). Survival was not imputed, as complete data were available. Among the variables used in the analysis, 13% of the sample had one missing value and a further 10% of the sample had two or more missing values. The imputed data sets were combined using the *micombine* procedure in Stata, in conjunction with the *stcox* procedure that was used for

the Cox proportional hazards regression models. SPSS version 15 was used for the descriptive analysis. Stata version 9 was used for the imputation and survival analyses.

Results

Descriptive statistics are shown in Table 1. These are based on the raw data, with p-values taken from Wald tests from univariate Cox regressions combined from analyses of the ten imputed data sets. Overall, the mean age was 76.6 years, with 11.4 years of education. With the exceptions of education, hypertension history, hearing impairment and Goldberg Anxiety score, all variables were significantly associated with mortality ($p < 0.05$).

The effects of SLMT (Figure 1a) and NART (Figure 1b) on survival time were plotted using Kaplan Meier curves. A median split was chosen to separate high and low performance on the two tasks. The figures show that the effect of SLMT on survival is much more pronounced than that of NART. There is a 20% difference in cumulative survival between high and low SLMT groups after approximately five years, and this difference is maintained until the end of the period of observation. The difference between high and low NART groups, however, is only apparent between approximately four and thirteen years after baseline.

Six models of mortality risk were tested using Cox proportional hazards regression models (Table 2). The univariate effect of SLMT was tested in Model 1, then age and gender were added to create Model 2. Model 3 built on Model 2, simultaneously testing the effect of SES (education and employment background) in conjunction with locus of control, a potential mediator of the effect of SES on mortality (Siegrist & Marmot, 2004). Health behaviors (smoking status and activity level) were entered into a separate model with SLMT, age and gender (Model 4). Health status, including physical health and mental health measures and dementia, was included

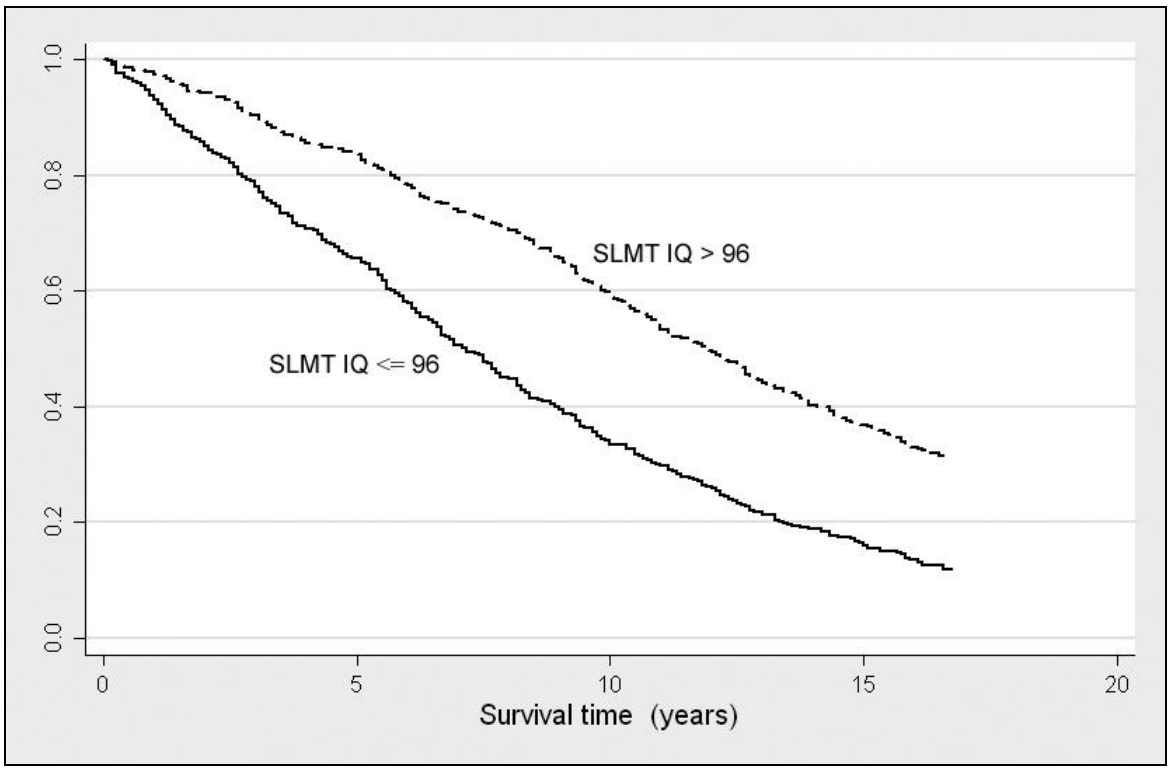
Table 1: Descriptive statistics for predictor variables by vital status after 17 years (n = 896)

		Survivors (n = 191-209)		Decedents (n = 566-687)		
	N	Mean (SD) or freq (%)		Mean (SD) or freq (%)		p value
SLMT IQ score	853	103.80	(14.10)	93.91	(16.97)	<0.001
NART IQ score	835	113.16	(8.35)	111.32	(10.08)	0.001
Age	896	74.09	(3.38)	77.30	(5.09)	<0.001
Gender: male	896	83	(39.7%)	373	(54.3%)	<0.001
Socio-economic status						
Years of education	894	11.17	(2.29)	11.41	(2.66)	0.275
Work history: manual work	896	141	(67.5%)	551	(59.7%)	0.039
Self as locus of control	759	4.36	(0.61)	4.21	(0.60)	<0.001
Health behaviors						
Smoking status	877					0.004
Never smoked		110	(52.9%)	391	(42.0%)	
Previously smoked		78	(37.5%)	383	(45.6%)	
Currently smoke		20	(9.6%)	103	(12.4%)	
Activity score	875	12.72	(2.43)	11.51	(3.17)	<0.001
Physical health						
Self-rated health	874					<0.001
Excellent		59	(28.5%)	160	(15.1%)	
Good		120	(58.0%)	478	(53.7%)	
Fair		27	(13.0%)	192	(24.7%)	
Poor		1	(0.5%)	44	(6.4%)	
Heart attack history	885	23	(11.1%)	157	(19.8%)	<0.001
Hypertension history	887	80	(38.5%)	371	(42.9%)	0.553
Stroke history	887	45	(78.4%)	269	(67.0%)	0.002
Disease count	896	1.69	(1.35)	2.12	(1.47)	<0.001
Symptom count	896	2.93	(2.74)	3.58	(2.87)	<0.001
ADL score	877	0.98	(1.31)	2.14	(2.78)	<0.001
IADL score	877	0.28	(0.67)	0.86	(1.61)	<0.001
Choice RT (sec)	798	0.46	(0.12)	0.48	(0.15)	<0.001
Grip strength (kg)	877	25.95	(9.91)	24.29	(9.44)	0.012
Visual impairment	887	163	(78.4%)	455	(67.0%)	<0.001
Hearing impairment	887	156	(75.0%)	475	(70.0%)	0.069
Subsequent dementia diagnosis	896	3	(1.4%)	41	(6.0%)	0.013
Mental health						
Goldberg depression score	865	1.71	(1.79)	2.13	(2.00)	<0.001
Goldberg anxiety score	870	2.49	(2.35)	2.46	(2.25)	0.761

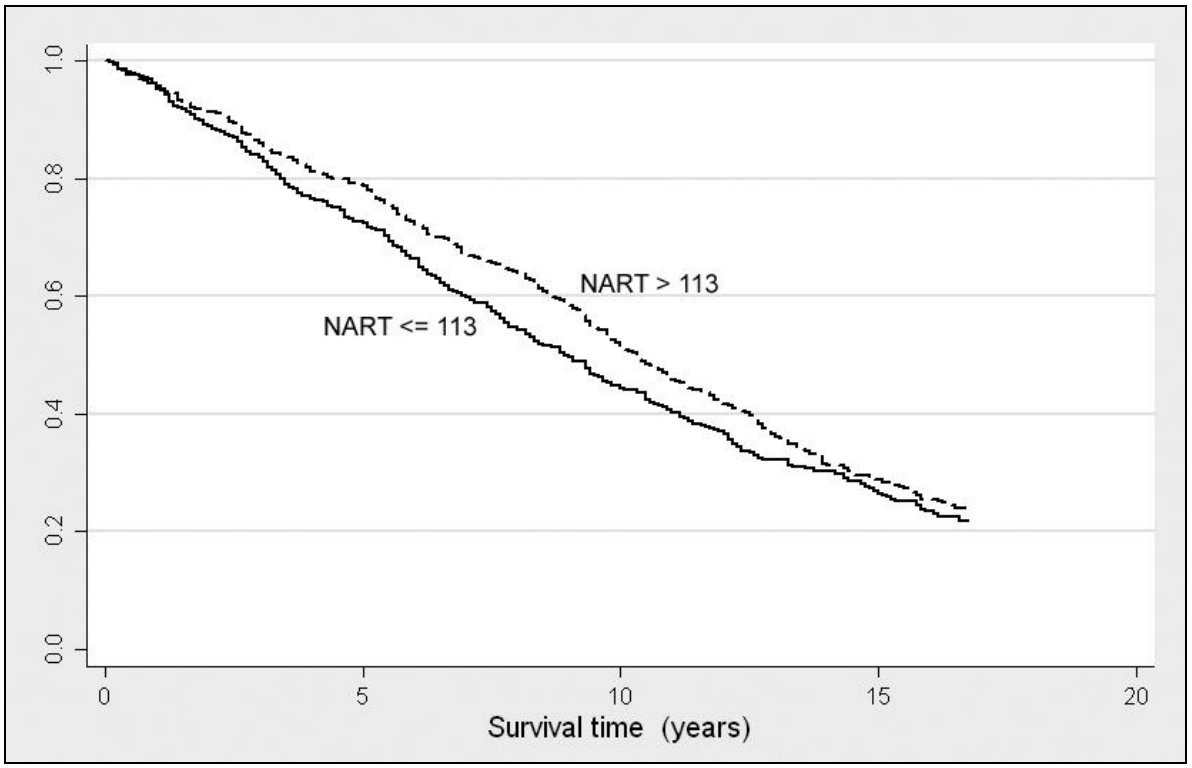
Notes: p values are from Z tests (binary and continuous variables) and χ^2 tests (categorical variables) from univariate Cox regressions using imputed data; SLMT IQ: Symbol-Letters Modalities Test IQ score; NART IQ: National Adult Reading Test IQ score; ADL: Activities of Daily Living; IADL: Instrumental Activities of Daily Living; RT: reaction time

simultaneously with SLMT, age and gender in Model 5. Finally, the significant predictors (at $p < .05$) from Models 2-5 were combined into a single model (Model 6). The six models were also fitted to the NART (Table 3).

SLMT IQ was significantly and substantially associated with mortality irrespective of which other variables were in the model. The effect of fluid intelligence on mortality was reduced but not fully accounted for when adjusting for age and gender, and including the 'competing' predictors measuring SES, health behavior, health status and sensory processing. A 15-point (one SD) disadvantage in SLMT IQ score was associated with between 23-45% increase in the risk of mortality (25% for the combined model), depending on which variables were included in the model. When age and gender were excluded from the models, attenuation of the SLMT hazard ratios from the inclusion of predictors representing the three proposed mechanisms ranged from 0-7%. In contrast, the effect of NART IQ on mortality was reduced when accounting for SES or health status and no longer significant after adjusting for health behaviors. A 15-point (one SD) disadvantage in NART IQ score was associated with between 8-14% increase in the risk of mortality, depending on the model. Attenuation for the NART hazard ratios ranged from 0-4%, after excluding the effects of age and gender. Subsequent dementia onset was not responsible for the association between intelligence and mortality.



a) Fluid intelligence: Symbol-letters Modalities Test



b) Crystallized intelligence: National Adult Reading Test

Figure 1: Kaplan-Meier curves of cumulative survival over 17 years plotted separately for participants with IQ above and below the sample median (n = 896)

Table 2: Cox proportional hazards regression models of mortality over 17 years using baseline fluid intelligence measure (n = 896; 687 decedents)

Model:	(1) Univariate	(2) With age & gender	(3) SES & locus of control	(4) Health behaviours	(5) System integrity	(6) Combined model
SLMT IQ score	0.69 (0.64, 0.75)***	0.76 (0.70, 0.82)***	0.74 (0.67, 0.81)***	0.81 (0.74, 0.89)***	0.81 (0.74, 0.89)***	0.80 (0.72, 0.88)***
Age		1.08 (1.07, 1.10)***	1.08 (1.06, 1.10)***	1.08 (1.06, 1.10)***	1.07 (1.05, 1.09)***	1.07 (1.05, 1.09)***
Gender = male		1.62 (1.39, 1.89)***	1.60 (1.37, 1.87)***	1.56 (1.31, 1.84)***	2.43 (1.87, 3.14)***	2.41 (1.89, 3.06)***
Yrs of education			1.06 (1.03, 1.10)***			1.06 (1.03, 1.09)***
Manual worker			1.02 (0.85, 1.22)			
Self as locus of control			0.91 (0.83, 1.00)*			0.93 (0.85, 1.02)
Smoking status						
Never				1.13 (0.95, 1.35)		
Previous				1.05 (0.81, 1.35)		
Current †				1.00		
Activity scale				0.83 (0.76, 0.90)***		0.91 (0.83, 1.00)*
Self-rated health						
Excellent					0.44 (0.27, 0.73)**	0.38 (0.24, 0.61)***
Good					0.53 (0.34, 0.83)**	0.46 (0.30, 0.69)***
Fair					0.71 (0.45, 1.13)	0.63 (0.41, 0.98)*
Poor †					1.00	1.00
Heart attack history					1.42 (1.16, 1.74)**	1.50 (1.24, 1.83)***
Hypertension history					1.24 (1.05, 1.45)*	1.28 (1.09, 1.51)**
Stroke history					1.13 (0.89, 1.43)	
Disease count					1.05 (0.99, 1.11)	
Symptom count					1.00 (0.97, 1.04)	
ADL score					1.11 (0.98, 1.25)	
IADL score					1.06 (0.94, 1.19)	
Choice RT					1.02 (0.90, 1.16)	
Grip strength					0.80 (0.70, 0.92)**	0.76 (0.67, 0.86)***
Visual impairment					1.12 (0.93, 1.34)	
Hearing impairment					0.99 (0.84, 1.18)	
Goldberg depression					1.03 (0.93, 1.14)	
Goldberg anxiety					0.89 (0.80, 0.99)*	0.91 (0.83, 0.99)*
Dementia diagnosis					1.14 (0.82, 1.58)	

† *Reference category*; * $p < .05$; ** $p < .01$; *** $p < .001$

Table 3: Cox proportional hazards regression models of mortality over 17 years using baseline crystallized intelligence measure (n = 896; 687 decedents)

Model:	(1) Univariate	(2) With age & gender	(3) SES & locus of control	(4) Health behaviours	(5) System integrity	(6) Combined model
NART IQ score	0.88 (0.81, 0.95)**	0.89 (0.82, 0.97)**	0.90 (0.81, 0.99)*	0.93 (0.85, 1.01)	0.90 (0.83, 0.98)*	0.89 (0.80, 0.99)*
Age		1.10 (1.08, 1.12)***	1.10 (1.08, 1.11)***	1.09 (1.07, 1.11)***	1.07 (1.05, 1.09)***	1.08 (1.06, 1.10)***
Gender = male		1.61 (1.38, 1.87)***	1.64 (1.40, 1.92)***	1.56 (1.32, 1.85)***	2.65 (2.05, 3.41)***	2.51 (1.97, 3.18)***
Yrs of education			1.05 (1.01, 1.08)*			1.05 (1.02, 1.09)**
Manual worker			1.09 (0.90, 1.31)			
Self as locus of control			0.87 (0.79, 0.95)**			0.92 (0.83, 1.01)
Smoking status						
Never				1.13 (0.94, 1.35)		
Previous				1.09 (0.85, 1.40)		
Current †				1.00		
Activity scale				0.78 (0.72, 0.85)***		0.86 (0.79, 0.94)**
Self-rated health						
Excellent					0.42 (0.26, 0.68)***	0.35 (0.23, 0.56)***
Good					0.51 (0.33, 0.80)**	0.43 (0.29, 0.64)***
Fair					0.69 (0.44, 1.10)	0.59 (0.38, 0.90)*
Poor †					1.00	1.00
Heart attack history					1.41 (1.15, 1.73)**	1.51 (1.24, 1.84)***
Hypertension history					1.22 (1.04, 1.44)*	1.27 (1.08, 1.50)**
Stroke history					1.14 (0.90, 1.44)	
Disease count					1.05 (0.99, 1.11)	
Symptom count					0.99 (0.96, 1.03)	
ADL score					1.12 (1.00, 1.27)	
IADL score					1.08 (0.96, 1.21)	
Choice RT					1.10 (0.97, 1.24)	
Grip strength					0.80 (0.70, 0.92)**	0.75 (0.66, 0.85)***
Visual impairment					1.09 (0.91, 1.31)	
Hearing impairment					1.02 (0.86, 1.21)	
Goldberg depression					1.04 (0.94, 1.16)	
Goldberg anxiety					0.89 (0.81, 0.99)*	0.91 (0.83, 0.99)*
Dementia diagnosis					1.16 (0.83, 1.61)	

† *Reference category*; * $p < .05$; ** $p < .01$; *** $p<.001$

Additional analyses were conducted to further account for potential confounding by baseline health status. Participants who died in the first four years of the study, prior to the first follow-up interview (n = 190 decedents), were excluded from the analysis. The effect of SLMT on mortality remained stable, as estimated by the six models presented in Tables 2 and 3. Hazard ratios remained between 0.72 and 0.84 with $p <$ .001 for all models. However, the effect of NART was further attenuated, with only the univariate effect of NART significantly associated with mortality status (HR = 0.89, p = .015). When age and gender (HR = 0.91, p = .055), socioeconomic status (HR = 0.90, p = .087), health behaviors (HR = 0.94, p = .223) and health status (HR = 0.93, p = .146) were entered, the effect of NART became non-significant. A second supplemental analysis investigated whether the intelligence-mortality relationship was different for men and women. The effect of SLMT on mortality was consistent across males and females, with $p < .01$ for all six models across both genders and hazard ratios ranging from 0.64 to 0.84. However, the effect of NART tended to be weaker among men than women when adjusting for age (HR_{female} = 0.86, p = .014; HR_{male} = 0.91, p = .078) and when adjusting for health behaviors (HR_{female} = 0.88, p = .039; HR_{male} = 0.95, p = .349). The univariate effect of NART was significant for both genders, but after adjusting for socioeconomic variables or health status, the effect of NART did not reach significance for either males or females (HRs ranging from 0.88 to 0.90).

Discussion

The present study examined the intelligence-mortality relationship using data collected from the Canberra Longitudinal Study (CLS) over 17 years in an older cohort of community dwellers. Better SLMT performance was found to be significantly associated with lower mortality risk. This effect persisted for 17 years of follow-up,

extending the findings of Korten et al. (1999) that examined the same cohort after four years. The relationship between SLMT and mortality remained when participants who died early in the study were omitted and was similar for men and women. NART performance was also significantly associated with mortality, although the effect was mitigated by controlling for health behaviors such as smoking status and activity level. Excluding participants who died in the first four years of the study diminished the effect of NART to non-significance. In addition, the effect of NART was stronger for women than men.

A set of six models tested three major proposed mechanisms for the relationship between intelligence and mortality. We tested for the effect of SES, as measured by education and type of employment. The effect of health behavior was tested using measures of smoking history and physical, mental and social activity. We tested for the effect of health status using measures of self-rated health, disease history, functional disability, grip strength and mental health status. In response to the findings of Deary and Der (2005), we controlled for sensory processing ability using measures of choice reaction time, visual impairment and hearing impairment. We also controlled for dementia diagnosis in response to the theory of Backman & MacDonald (2006) that the intelligence-mortality relationship is due largely to dementia-related deficits. The present study did not find strong support for any of the three explanations. Moreover, evidence for a particular explanation was contingent on the type of intelligence test used. For SLMT, although there was slight attenuation of the effect when controlling for SES, health behaviors or health status, the effect of SLMT remained significant, providing limited support for the three major mechanisms. The effect of intelligence on mortality when measured by the NART was also slightly attenuated by the effects of SES and health status. However, after adjusting for smoking status and activity level,

the attenuation was sufficient that NART was no longer significantly associated with mortality.

The divergence in findings suggests the mediation of the relationship between intelligence and mortality by SES, health behaviors and health status is marginally stronger for fluid intelligence performance than for tests of crystallized intelligence. Fluid intelligence tasks such as the SLMT may reflect any initial and early adulthood effects of intelligence on mortality, combined with the effects of physical health decline and ageing processes not due to physical health. NART performance, on the other hand, is likely to reflect initial intelligence, education across the lifespan and consistent implementation of health behaviors, but is less susceptible to effects of independent or systemic disease and biological ageing processes.

Choice reaction time was associated with mortality, however, there was no effect of reaction time when models also included SLMT or NART score. Grip strength was associated with mortality but accounted for little of the variance in the intelligence-mortality relationship. Sensory impairments were not associated with mortality. Manual occupation was also not associated with mortality after controlling for intelligence. This finding is not due to the collapsing of occupational categories into a binary measure, as a six-category version of the measure also had no association with mortality. Smoking status was not associated with mortality, a finding divergent from past research (Tessier et al., 2000) which may be explained by the advanced age and low smoking prevalence of this sample. In the final model, which included measures of SES, health behavior and health status, a one standard deviation decrement in SLMT performance was associated with a 25% increase in mortality, while a one standard deviation decrement in NART performance was associated with an 12% increase in mortality

In this cohort, the intelligence-mortality relationship appears to be based on more than lower-level processing efficiency. There was a strong independent effect of SLMT even after adjusting for the hypothesized mechanisms of the relationship together with reaction time and sensory impairment. In addition to mental speed, SLMT measures the efficiency of visual search and memory for the symbols presented in the task (Gilmore et al., 2006). Since reaction time was controlled for, the aspects of SLMT that are associated with mortality would appear to be a combination of processing speed with memory and attention performance. Further research into which constituents of the SLMT task best predict mortality could adapt the frameworks used by Gilmore et al. (2006) and Salthouse and Kersten (1993) to modify the SLMT task into components that separately measure the processing speed, memory and attentional aspects of the task.

While the present findings were often in accordance with previous research, there were some important differences. Previous research of the relationship between poor SLMT performance and mortality risk was supported (Anstey et al., 2001; Ghisletta et al., 2006; Pavlik et al., 2003; Portin et al., 2001). Previous investigations have found little evidence for a relationship between NART performance and mortality (Abas et al., 2002; Anstey et al., 2001). While NART performance was significantly associated with mortality risk in the present study, the effect was tenuous after controlling for measures of SES, health behavior and health status. However, contrary to previous findings (Deary & Der, 2005), reaction time did not explain the effect of either of the intelligence tasks. The differences in findings may be attributable to the age of the cohort in the present study. All of the participants were 70 or older at baseline, averaging over 75 years of age, and were followed until they were in their late-80s or beyond. Previous research has shown that the effect of intelligence on mortality is most pronounced in older age groups (Lyyra et al., 2006; Shipley et al., 2006).

Limitations of the findings and directions for future research

The present study examined vital status over 17 years using baseline measurements as predictors. However, intelligence was assessed at the start of the study, when participants were already advanced in age and potentially in poor health. Participants who were close to death at the time of the baseline may have been in a state of terminal decline, leading to an overestimation of the effect of poor cognitive performance on mortality. While the follow-up analysis omitted participants who died in the early stages of the study, the baseline intelligence measurement may still have been influenced by sub-clinical health problems. Additional research into temporal variations in the intelligence-mortality relationship would further delineate the influence of time-to-death on cognitive performance, as would modeling cognitive performance as an outcome, using time-to-death as a predictor. Another problem for the survival models is that there may have been cases where death occurred but was not recorded. Despite a thorough search protocol, the extent of missing death records could not be assessed in the present study, so all cases were treated as living if there was no evidence to the contrary. Having noted this, however, treating potential decedents as survivors would result in a more conservative estimate of the association between intelligence and mortality.

The models that were tested were operationalized using available measures from the baseline survey. Although it is difficult to articulate the models sufficiently well to test then more than in a general way, testing them is important, as it forces a theoretical articulation and reveals the difficulties of testing complex relationships among processes over long periods. Nevertheless, some of the measures that were used in this study could be further refined for the purposes of future research. Only a self-reported measure of vision impairment was included in the baseline interview, which may not

accurately reflect visual functioning. Sensory function, particularly visual acuity, can influence performance on tasks like SLMT (Gilmore et al., 2006). Self-report measures of health status (disease history, functional ability) may also have been inaccurate, although objective health measures (grip strength, reaction time) were also included as predictors in the models. Additional measures of health behaviors would also have strengthened the analysis – the baseline interview did not include measures of alcohol and other substance use, diet, healthcare utilization or medication adherence. Reflecting the constraints of a large in-home epidemiological survey, the tests available to measure intelligence assessed only specific domains of cognitive performance. General intelligence tests, such as the WAIS and AH4, cover a broader array of abilities. However, simply examining the construct of general intelligence is not sufficient in investigating what aspects of intelligence are most strongly associated with mortality. Further research on the intelligence-mortality relationship should continue to examine a broad range of cognitive abilities, including memory, attention, reasoning, knowledge and executive function, in a variety of domains, including episodic, verbal and visuospatial.

Finally, examining all-cause mortality is a starting point for investigating the relationship between intelligence and mortality. There is strong evidence for a relationship between intelligence and cardiovascular mortality but less for the relationship between intelligence and cancer mortality (Hart et al., 2003; Shipley, Der, Taylor, & Deary, 2007). Examining modifiable mediators of both mortality and cognitive performance has the potential to guide future health interventions. Continuing to research the associations between various domains of cognitive performance and mortality will advance our understanding into the nature of the intelligence-mortality relationship.

Acknowledgements

The Canberra Longitudinal Study was supported by NHMRC Unit Grants 973301 and 933301 and NHMRC Program Grant 179805. HC is supported by NHMRC Principal Research Fellowship 366781.

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Measuring longitudinal change in cognitive abilities to predict cause-specific mortality in an elderly community sample

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Psychology and Aging, in press (revised version), accepted 19/4/2011.

Abstract

While there is consistent evidence that initial levels of cognitive ability predict mortality, there is mixed evidence for a relationship between changes in cognition and mortality. There have been few studies that have examined whether the level and slope of cognitive performance is predictive of subsequent mortality from all causes or from cardiovascular disease, stroke, heart disease, respiratory disease or cancer. Moreover, the statistical methods used to assess change in mortality research are not always definitive and require greater scrutiny. This study aimed to assess whether the level and slope of cognitive ability were associated with all-cause or cause-specific mortality, using unbiased statistical estimates. A cohort of 896 community-based elderly people in Australia were interviewed four times over twelve years, with vital status followed for up to 17 years. Of these, 592 participants completed two or more interviews and were included in survival models of six mortality outcomes. Cognitive change in five domains of ability was estimated using both Best Linear Unbiased Predictors and latent growth models. Poorer initial processing speed, verbal fluency and global ability were significantly associated with greater all-cause and/or cardiovascular mortality. In addition, declines in global ability were associated greater all-cause, cardiovascular and heart disease mortality. Vocabulary and episodic memory were not associated with mortality and none of the cognitive tests predicted respiratory or cancer mortality. The two methods of estimating change showed strong agreement. Initial levels of cognitive ability tend to be better predictors of subsequent mortality than changes in ability. The results suggest that vascular events may be responsible for the overall relationship between cognition and mortality.

While prospective research has consistently shown that cognitive ability predicts mortality, there is mixed evidence for a relationship between changes in cognition and mortality. Few studies have definitively examined whether the level and slope of cognitive performance is associated with all-cause mortality and whether specific causes of mortality might explain the overall relationship. Furthermore, the use of appropriate methodologies for assessing change in cognition is critical for providing definitive evidence about relationships between cognitive change and mortality. The present study compared two methods of obtaining unbiased estimates of level and slope of cognitive ability, with the aim of assessing whether initial cognitive ability or changes in cognitive performance were associated with mortality from all causes, cardiovascular disease, cancer, respiratory disease, heart disease or stroke.

A review by Bosworth and Siegler (2002) reported that while there was consistent evidence that initial levels of cognitive performance were predictive of mortality, there was mixed evidence for a relationship between cognitive change and mortality. Declines in crystallized abilities were more consistently associated with increased mortality than declines in memory and fluid abilities. Bosworth & Siegler (2002) attributed this differential effect to the robustness of crystallized abilities to normal aging, suggesting that changes in these abilities may reflect the types of biological deterioration associated with mortality. Relationships between cognitive change and mortality may be partly explained by common associations of both cognition and mortality with psychomotor or sensory abilities, health behaviors, physical health or genetic factors (Bosworth & Siegler, 2002; Shipley, Der, Taylor, & Deary, 2008). However, studies of the cognition-mortality relationship often report little attenuation of the effect even after adjusting for such factors (Batterham, Christensen, & Mackinnon, 2009; Shipley et al., 2008). Bosworth and Siegler (2002) concluded that further population-based longitudinal research on the association

between cognitive change and cause-specific mortality was necessary to better characterize this relationship.

One of the primary problems in examining the effect of cognitive change on mortality is that there has been little consistency in the way that cognitive change has been assessed. Previous research has measured cognitive change by comparing mean differences (Bosworth & Schaie, 1999; Mortensen & Kleven, 1993), categorizing participants as decliners or non-decliners based on the size of change scores (Anstey et al., 2001) or grouping the sample by time to death and comparing change in cognitive scores (Johansson & Berg, 1989). These methods only account for within-person change, rely on arbitrary characterizations of decline or may confound the initial level of performance with the rate of change in performance. A more sophisticated method involves conducting individual linear regressions of cognitive test scores over time for each subject to obtain individual intercept and slope least squares estimates that can then be used to predict mortality (Deeg, Hofman, & van Zonneveld, 1990). However this method does not appropriately account for missing data, as a participant with few measurements is given the same weighting as one with many measurements, despite the increased variance of the estimate (Verbeke & Molenberghs, 2000). Consequently, a defensible method that takes into account group effects in estimating individual change might be considered to be more appropriate for estimating change.

Two methods of achieving unbiased estimates of within-person change are mixed effects models and latent growth models, both of which can accommodate incomplete data and unbalanced data structures (Lindenberger & Ghisletta, 2004). While these types of analytical methods have been available for several decades, their application to the longitudinal study of terminal decline processes has been somewhat limited (Bäckman & MacDonald, 2006). It is important to use analytical approaches such as these to accommodate missing data, adjust for unequal numbers of individual

observations, to account for dependencies among observations both between and within individuals and to account for individual differences in the rates of cognitive decline (Bäckman & MacDonald, 2006). A goal of the present study was to demonstrate whether a mixed model approach, which is widely available in statistical software, can provide comparable estimates of cognitive change on survival compared to a latent growth approach. The paucity of mortality research that has utilized these methods may be related to the complexity of implementing latent growth models or Bayesian single-stage joint mixed-survival models (Guo & Carlin, 2004) and their need for special software. We aimed to assess whether a simple two-stage mixed model and survival method could provide comparable results to a single-stage joint growth-survival model.

Mixed effects models can be used to create unbiased estimates of intercept and slope for each individual across repeated cognitive measures. When the mixed model estimates are used as independent predictors of an outcome, they are called the Best Linear Unbiased Predictors (BLUPs) (Robinson, 1991), as the mixed model minimizes the mean squared error across the entire sample although the estimate may not be optimal for a specific individual (Gould, Abramson, Galasko, & Salmon, 2001). Gould, et al. (2001) compared the use of BLUPs to change scores and least squares estimators, finding that change score and least squares estimates were unreliable when few observations were made, and BLUPs provides both an appropriate adjustment for limited observations and greater power for detecting differences. Likewise, Reynolds, Gatz, & Pedersen (2002) compared change scores, criterion-based methods, least squares and random effects (BLUPs) for assessing cognitive change. They concluded that the random effects method was an improvement over the other three methods as it showed the strongest relationships across domains of cognitive performance and stronger associations with demographic, health, and psychosocial predictors (Reynolds et al., 2002). In the present context, the BLUP estimates of intercept and slope

parameters provided by the mixed effects model were incorporated into a Cox Proportional Hazards model to assess the effects of cognitive performance and change on mortality.

Latent growth models are a class of structural equation models that represent individual level data in terms of an initial level of performance latent variable or factor (level), a rate of change factor (slope), and error (residual) parameters (Hofer et al., 2002). These structures are analogous to random intercept and slope terms in mixed models. While it is rare to do so, individual estimates of level and slope can be estimated as factor scores on these latent variables. Recent developments in SEM allow the incorporation of latent growth models into a survival model (or other type of regression model) (Asparouhov, Masyn, & Muthén, 2006). Such models are similar to mixed effects models, although latent growth-survival models are implemented in a single step that does not require the estimation of intercept and slope terms. No previous study of cognition and mortality has sought to demonstrate the implementation of both BLUP and LGM approaches to assess the comparability of these methods.

Latent growth models and BLUPs have each been used only once to examine the relationship between cognitive change and mortality. Johansson et al. (2004) used a latent growth model and found that declines in crystallized knowledge and verbal abilities were associated with increased risk of mortality. However, the latent growth model used by Johansson et al. (2004) did not incorporate survival analysis, warranting the extension of the latent growth methodology in the present analysis. Ghisletta, McArdle, & Lindenberger (2006) used a mixed model approach and reported significant associations of changes in both speed and fluency on survival. While there were commonalities among the findings of these two studies, the types of abilities that were predictive of mortality were divergent. Fluid and speed-based cognitive tasks decline more rapidly than crystallized intelligence as a consequence of normative aging

(Anstey, Stankov, & Lord, 1993; Compton, Bachman, Brand, & Avet, 2000), so declines in crystallized abilities may be more strongly associated with biological deterioration that leads to mortality, consistent with the findings of Johansson et al. (2004). However, among cohorts that are cognitively intact with dementia excluded at baseline or controlled for, rates of normative aging, as represented by declines in fluid abilities, may be a more dominant characteristic in predicting mortality, consistent with the findings of Ghisletta et al. (2006). Indeed, Ghisletta et al. (2006) concluded that the relationship between cognitive decline and mortality was not specific to any domain of functioning.

Nevertheless, both studies reported the common finding that the initial level of cognitive performance was more strongly and consistently associated with mortality than change in performance. Sliwinski et al. (2006) suggested that cognitive change may only weakly predict mortality because the change does not accelerate continuously. Instead, normative cognitive change begins at a gradual pace in the preterminal phase, then when biological constraints increase in proximity to death, cognitive decline increases more rapidly in the terminal phase (Sliwinski et al., 2006). Researchers have modeled the time course of terminal decline using change point models to distinguish two phases of decline (Batterham, Mackinnon et al., in press; Sliwinski et al., 2006; Thorvaldsson et al., 2008). However, this methodology does not directly assess whether declines in cognition are associated with increased risk of death. Since there have been so few studies of cognition and mortality that have used estimates of change, it is important to further explore this relationship directly using latent growth and mixed models approaches and compare the findings of the two methods.

An additional gap in the research on cognitive change and mortality is the examination of cause-specific mortality. Small, Fratiglioni, von Strauss, & Bäckman (2003) separated cardiovascular and non-cardiovascular causes of death, and found no

differences in the strength of the cognition-mortality associations for the two groups. However, Shipley, Der, Taylor, & Deary (2007; Shipley et al., 2008) reported that associations between cognition and mortality were strongest for cardiovascular mortality, slightly less consistent for respiratory mortality and non-significant for cancer mortality. These associations remained after adjusting for a range of sociodemographic, health behavior and health status measures and excluding participants who died in the first five years of follow-up (Shipley et al., 2008). The difference in findings may be due to the more specific types of mortality defined in the Shipley et al. (2007; 2008) studies, in contrast to the Small et al. (2003) study that combined cancer, respiratory and other causes of death due to small cell sizes. A review of studies examining the relationship between cognition and mortality in diseased populations found strong evidence for the association in patients with stroke and cancer, although the relationship was less clear for heart disease patients (Anstey, Mack, & von Sanden, 2006). Few of these studies, however, identified the cause of death. Identification of the circumstances in which mortality is best predicted by poor cognitive performance may lead to a better understanding of this association. Likewise, identifying the causes of death predicted by *changes* in cognitive abilities may further pinpoint the mechanisms behind such associations. To date, there has been no direct examination of the relationship between cognitive change and multiple causes of death.

The present study aimed to assess the relationship between level and slope of cognitive performance on cause-specific mortality in a cohort of 896 community-based Australian participants aged 70 and older. They were assessed over a 12-year period with up to four comprehensive interviews, and vital status information including cause of death was collected for up to 17 years. Consequently, it was possible to assess change in cognitive performance using both mixed model and latent growth approaches to examine associations with cause-specific mortality. Models were adjusted for

measures of physical and mental health to account for the roles of physical function (Prince et al., 2010; Rosano et al., 2005; Wang, Larson, Bowen, & van Belle, 2006), depression (Christensen et al., 1997) and anxiety (Beaudreau & O'Hara, 2008) on late-life cognitive ability. Such adjustment provides a stronger test of the hypothesized relationships between cognition and mortality. The second aim of the study was to assess whether latent growth models and BLUPs from mixed models yielded similar results. While very similar, the latent growth approach implemented in Mplus does not involve the estimation of individual estimates of level and slope. Based on previous findings (Ghisletta et al., 2006; Johansson et al., 2004), it was predicted that changes in cognitive performance would be less strongly associated with mortality than initial levels of performance.

Furthermore, in comparing the five cognitive domains that were assessed, it was hypothesized that there would be no clear patterns in the strengths of association between changes in these abilities and mortality, consistent with the findings of Ghisletta et al. (2006). It is difficult to disentangle normative age-graded effects from nonnormative or pathological effects, as most older adults without preclinical dementia have likely experienced some form of vascular pathology across the lifespan (M. J. Sliwinski, S. M. Hofer, C. Hall, H. Buschke, & R. B. Lipton, 2003a). However, examining the effects of changes in multiple cognitive domains on death from specific causes allows testing of the hypothesis proposed by White and Cunningham (1988). They suggested that declines in tasks which are resistant to the effects of pathology are more strongly predictive of impending death. Recent evidence from the Ghisletta et al. (2006) study and others (Batterham, Mackinnon et al., in press; Thorvaldsson et al., 2008) appears to refute the White and Cunningham (1988) hypothesis, with terminal decline in fluid abilities shown to be greater than in tasks of crystallized ability such as vocabulary tests. Consequently, performance in all cognitive domains except

vocabulary were expected to be associated with mortality. In examining cause-specific mortality, stronger relationships were hypothesized between cognitive performance and cardiovascular mortality than cancer or respiratory mortality, as reported by Shipley et al. (2007; 2008). Such findings would also be predicted by the strong links reported between cardiovascular disease and cognitive function (Laukka, Fratiglioni, & Bäckman, 2010; Spiro & Brady, 2008) and would suggest that vascular pathology may be a critical predictor of terminal decline. Finally, the results from the latent growth models were predicted to be comparable to the results from the BLUP models.

Method

Participants

The Canberra Longitudinal Study is an epidemiological survey of mental health and cognitive functioning in older people. The study design has previously been detailed by Christensen et al. (2004). Eight hundred and ninety-six participants (456 men and 440 women) aged 70-97 were recruited for the baseline assessment in 1990. All participants were initially living in the community in the cities of Canberra or Queanbeyan, Australia. Participants were sampled from the compulsory electoral roll, with 69% responding, and the sample was stratified by age and gender. Approval for the research was obtained from the Ethics in Human Experimentation Committee of The Australian National University.

Of the original sample of 896 participants, 185 (20.6%) were deceased by four years, 363 (40.5%) were deceased by eight years, and 544 (60.7%) were deceased by 12 years. At the end of vital status collection in June 2007, 687 (76.7%) of the participants were deceased. Of the surviving participants at each measurement occasion, 14.1% (100/711) refused or were unable to complete the first follow-up interview, 21.1%

(100/474) for the second follow-up and 21.1% (57/270) for the third follow-up. Only participants who had one or more follow-up interviews were included in the analyses, so that measures of cognitive change could be obtained. Nineteen participants were excluded on the basis of missing baseline data, resulting in a sample size of 592 for the analyses.

Survey Procedure

Participants were interviewed up to four times over 12 years by trained professional interviewers. Baseline interviews lasted approximately two hours, which included a survey that covered background characteristics, physical health and disease status, mental health status, cognitive performance and social support. Interviews also included physical assessments of blood pressure, lung function, grip strength, vision and reaction time.

Measures

A range of cognitive tests was administered at each interview. *Speed of processing* was measured by the Symbol-Letters Modalities Test (SLMT), a task similar to Smith's (1973) Symbol-Digit Modalities Test and Wechsler's (1981) Digit-Symbol Substitution. The number of correct symbol-letter pairs made in 90 seconds was summed. *Verbal ability* was measured using the National Adult Reading Test (Nelson, 1982), a test of vocabulary. The NART is a list of 50 words that are not pronounceable phonetically. The number of correct pronunciations made was summed. An *episodic memory* task consisted of four brief episodic memory tasks testing word, face, name and address recall and figure reproduction (Jorm, 1992). *Verbal fluency* was assessed as the number of animals named in 30 seconds. *Global function* was tested using the Mini-Mental State Examination (Folstein, Folstein, & McHugh, 1975), scored out of 30. To

facilitate comparisons between tests, all of the tests were standardized to a common metric across the full sample, with a mean of 100 and standard deviation of 10 for the full sample at baseline.

Mortality status and date of death were established by contacting relatives, searching the National Death Index, and from death notices in the local newspaper. The National Death Index is a register of all deaths in Australia maintained by a Government instrumentality, the Australian Institute of Health and Welfare and based on data collected by the Registrars of Births, Deaths and Marriages in each State and Territory in Australia, so failure to identify deaths occurring in Australia would be an unusual occurrence. The additional methods used for death reporting (contacting relatives, newspaper searches) provide further confidence in the mortality status data. Mortality status was followed for up to 17 years, from the start of baseline interviews in September, 1990 until June 30, 2007. For six participants with unknown day of death, the day was set to the 15th of the month. For two participants with an unknown month of death, the month was set to June. *Cause of death* was based on the primary cause of death provided by the National Death Index, which was identified using an ICD-9 or ICD-10 code, depending on the date of death. The codes for underlying cause of death were only available for deaths prior to 1996, so only the underlying cause was used for the present analyses. The ICD codes were categorized into five binary categories: cardiovascular, cancer (all malignant neoplasms), respiratory, ischemic heart disease and stroke (cerebrovascular). No cause of death was provided for 30 deceased participants (7.3%), with these participants counted as having other causes of death.

In addition to the cognitive measures, a number of baseline risk factors for cognitive decline or mortality were also included in the models. Age, gender and number of years of education were included to account for background characteristics. Physical health measures included smoking status (never, previous or current),

Activities of Daily Living (ADL, a scale ranging from 0 to 22), disease count (self-reported history from a list of 14 diseases), and grip strength (measured in kilograms using a hand dynamometer). The ADL scale assessed the presence or extent of physical disability (Christensen et al., 1994). Grip strength is a reliable and objective indicator of physical functioning in late life (Frederiksen et al., 2002) that is associated with both cognitive performance (Christensen et al., 2000) and mortality (Batterham et al., 2009a; Sasaki, Kasagi, Yamada, & Fujita, 2007). Mental health was controlled for using the Goldberg Depression and Anxiety Scales (Goldberg, Bridges, Duncan-Jones, & Grayson, 1988a) to assess the number of depression and anxiety symptoms experienced in the two weeks prior to the interview.

Analyses

The analyses were performed using the two different methods, mixed models (BLUP) and latent growth models. The mixed model approach had two stages. In the first stage, linear mixed effects regression models estimated the intercept and slope of each cognitive test over time. The mixed models included a fixed effect of time and random effects intercepts, and (linear) time which were allowed to freely correlate, with the latent growth models specified in the same way. Implemented in SEM, latent growth models typically permit the residual variance to differ between occasions of measurement. This was accommodated in the mixed model by introducing a repeated effect of time using a diagonal covariance matrix. The predicted intercepts and slopes were extracted for the second stage of the analysis. The second stage involved modeling survival time using Cox Proportional Hazards models. Surviving participants were censored at the end of the follow-up period (June 2007). Models were run separately for six mortality outcomes with each of the five cognitive tests, resulting in 30 survival models. The mortality outcomes were all-cause mortality and five

categories of cause-specific mortality: cardiovascular, heart disease (a subset of cardiovascular deaths), stroke (a subset of cardiovascular deaths), cancer and respiratory deaths. All participants were included in each analysis, with participants who did not die from the respective cause treated as censored observations at the time of death and survivors treated as censored observations the end of the study period. Both the intercept and slope estimates for the cognitive tests (estimated at the first stage) were included as predictors in each model, along with the potential confounders. SAS v9 for Windows was used for this analysis.

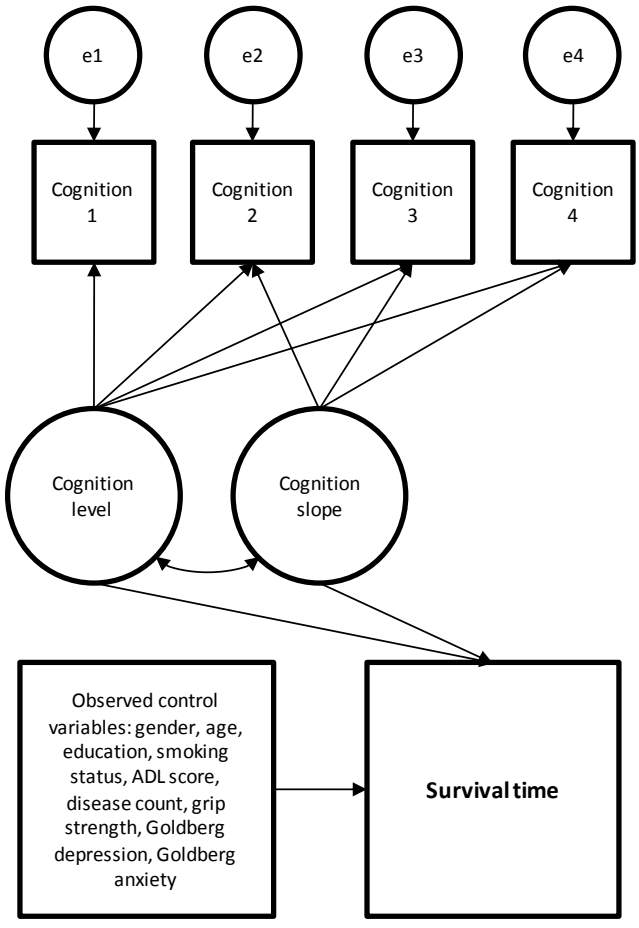

Figure 1: Latent growth model estimating the effect of level and slope of each longitudinal cognitive measure on survival time

The latent growth models assessed the same outcomes as in the BLUP approach and the Cox proportional hazards regression model was incorporated into a structural equation model which simultaneously estimated the intercept and slope for each cognitive measure (see T Asparouhov et al., 2006 for further details of the model specification). A representation of the model is shown in Figure 1. The model was estimated for each of the five cognitive tests and for each of the six mortality outcomes. Mplus version 6 was used for this analysis.

Results

Sample characteristics for the 592 participants included in the analyses are shown in Table 1. Participants included in the analysis tended to be younger, more educated, less disabled, have fewer diseases, have stronger grip strength and have fewer depression symptoms than those who were not included in the analysis. Many of these differences may be attributable to the necessary exclusion of participants who died before the second interview. Participants included in the analysis also had higher initial cognitive performance on all tasks, reflecting strong associations between cognitive performance and impending death. There were no significant differences in anxiety symptoms, gender or smoking status. Cognitive performance declined significantly across the trial period for all of the tests. Accounting for both fixed and random effects of time, the largest decline was in SLMT (-0.27 sd per year, $p < .0001$), followed by MMSE (-0.26 sd/year, $p < .0001$), verbal fluency (-0.16 sd/year, $p < .0001$), episodic memory (-0.10 sd/year, $p < .0001$) and NART (-0.06 sd/year, $p < .0001$).

At the end of the follow-up period, 410 (69.3%) of the 592 participants had died from all causes. Of these 410 decedents, 192 (46.8%) died from cardiovascular causes, including 105 (25.6%) from coronary heart disease and 41 (10.0%) from stroke. A further 64 (15.6%) died from cancer and 43 (10.5%) died from respiratory disease. The

remaining 111 (27.1%) decedents were categorized for the present analyses as having died from other causes, including 12 (2.9%) with dementia listed as the underlying cause of death and 30 (7.3%) without a listed code. The identified causes of death were comparable to Australian prevalence estimates for causes of death in the 85+ age group in 2006: 49.4% of women and 42.4% of men (vs. 46.8% of total in the present study) died from cardiovascular causes, 12.3% of women and 20.6% of men (vs. 15.6%) died from cancer, and 8.5% of women and 11.6% (vs. 10.5%) of men died from respiratory disease (Australian Institute of Health and Welfare, 2010). Among deceased participants included in the analyses, the mean time to death from baseline was 9.6 years (sd = 3.5).

To examine concordance between the two estimation methods (best linear unbiased predictors, BLUP, *vs.* latent growth models, LGM), the two estimates of level (intercept) and slope were compared. The correlations between level estimates from the two methods ranged from 0.998 to 1.000 across the five cognitive tests. The correlations between intercept estimates were 0.999 to 1.000, except for the estimate of NART slope. The mixed model used to estimate NART scores did not converge with freely correlated random effects, so an uncorrelated (variance components) matrix was used instead. Accordingly, the NART slopes estimated by BLUPs had a correlation of 0.25 with the slopes estimated by LGM, which does not allow for an uncorrelated covariance structure using present software. Examining correlations between slope and intercept revealed that participants with higher initial performance on SLMT (r = .48), NART (r = .32), MMSE (r = .27) and episodic memory (r = .52) had less decline over the follow-up period than those with lower performance, while participants with better verbal fluency had greater decline (r = -.41). Mean estimated intercepts were approximately 102 for all tests (range: 101.3-102.0), with standard deviations for the intercepts ranging from 3.9 to 8.4. As noted above, mean estimated slopes ranged

Table 1: Baseline descriptive statistics for participants included in and excluded from the analyses

	Included in analyses (n = 592)		Excluded from analyses (n = 304)			
	Mean (SD) or freq (%)		Mean (SD) or freq (%)		t or χ^2	p
Age	76.2	(4.6)	77.3	(5.4)	3.13	0.002
Years of education	11.5	(2.6)	11.0	(2.4)	-2.88	0.004
Functional disability score	1.5	(1.9)	2.6	(3.4)	4.98	<0.001
Disease count	2.7	(1.6)	3.0	(1.8)	2.09	0.038
Grip strength, kg	25.2	(9.8)	23.5	(9.0)	-2.65	0.008
Goldberg Depression score	1.9	(1.8)	2.4	(2.1)	3.66	<0.001
Goldberg Anxiety score	2.4	(2.2)	2.6	(2.4)	1.29	0.198
Gender = male (%)	292	(49.3%)	164	(53.9%)	1.72	0.190
Ever smoked (%)	261	(44.1%)	122	(40.1%)	1.28	0.257
Current smoker (%)	65	(11.0%)	38	(12.5%)	0.46	0.499
Died in follow-up period (%)	410	(69.3%)	277	(91.1%)	53.67	<0.001
Cognitive outcomes						
SLMT score	99.3	(14.9)	89.7	(18.8)	-7.47	<.0001
NART score	113.3	(9.0)	108.4	(10.3)	-6.70	<.0001
MMSE score	27.8	(2.0)	26.2	(3.7)	-7.17	<.0001
Verbal fluency score	11.3	(3.3)	9.7	(3.4)	-6.73	<.0001
Episodic memory score	13.6	(1.9)	12.7	(3.0)	-4.96	<.0001

SLMT: Symbol-Letters Modalities Test; NART: National Adult Reading Test; MMSE: Mini-Mental State Examination

between -0.6 to -2.7, with standard deviations for the slopes from 0.5 to 2.5. Estimates of intercept therefore had relatively less variance proportional to the mean than estimates of slope.

To examine concordance between the two estimation methods (best linear unbiased predictors, BLUP, *vs.* latent growth models, LGM), the two estimates of level (intercept) and slope were compared. The correlations between level estimates from the two methods ranged from 0.998 to 1.000 across the five cognitive tests. The correlations between intercept estimates were 0.999 to 1.000, except for the estimate of NART slope. The mixed model used to estimate NART scores did not converge with freely correlated random effects, so an uncorrelated (variance components) matrix was used instead. Accordingly, the NART slopes estimated by BLUPs had a correlation of 0.25 with the slopes estimated by LGM, which does not allow for an uncorrelated covariance structure using present software. Examining correlations between slope and intercept revealed that participants with higher initial performance on SLMT (r = .48), NART (r = .32), MMSE (r = .27) and episodic memory (r = .52) had less decline over the follow-up period than those with lower performance, while participants with better verbal fluency had greater decline (r = -.41). Mean estimated intercepts were approximately 102 for all tests (range: 101.3-102.0), with standard deviations for the intercepts ranging from 3.9 to 8.4. As noted above, mean estimated slopes ranged between -0.6 to -2.7, with standard deviations for the slopes from 0.5 to 2.5. Estimates of intercept therefore had relatively less variance proportional to the mean than estimates of slope.

The models predicting survival time are shown in Table 2. The models were estimated for each of the five cognitive tests (SLMT, NART, MMSE, verbal fluency and episodic memory) across six types of mortality (all-cause, cardiovascular, cancer,

respiratory, heart disease and stroke) using the two methods (latent growth models and BLUP models). Each model included the level and slope estimates for the particular cognitive test, along with the effects of age, gender, years of education, smoking status, functional disability, disease count, depression and anxiety symptoms and grip strength. An alpha value of $p < .01$ was used to account for the six comparisons made for each cognitive test. There was strong concordance between the two methods, with hazard ratios and p-values of similar magnitudes. The only discrepancies between the two methods were in the effects of MMSE level on all-cause, cardiovascular and stroke mortality, where borderline p-values meant that the BLUP models showed significant relationships where the LGM models did not.

Overall, most of the significant relationships were found in the level of initial performance. Poorer SLMT performance was associated with higher all-cause, cardiovascular and heart disease mortality rates. Poorer performance on the MMSE was associated with higher rates of all-cause, cardiovascular and stroke mortality. In addition, greater declines in MMSE performance over the follow-up period were associated with significantly higher all-cause, cardiovascular and heart mortality. Poorer performance on the verbal fluency task was not associated with overall mortality, however it was associated with higher rates of cardiovascular and stroke mortality. Neither NART nor episodic memory performance was associated with mortality. None of the cognitive tasks significantly predicted cancer or respiratory mortality, either in terms of initial performance or changes in performance.

Table 2: The effect of level and slope of cognitive performance on all-cause and cause-specific mortality, as estimated by latent growth models and best linear unbiased estimator models

Test	Method	Measure	All-cause HR (p)	Cardiovascular HR (p)	Cancer HR (p)	Respiratory HR (p)	Heart disease HR (p)	Stroke HR (p)
SLMT	BLUP	Level	**0.952 (<0.001)**	**0.949 (<0.001)**	0.947 (0.019)	0.939 (0.021)	**0.947 (0.002)**	0.944 (0.050)
		Slope	1.034 (0.547)	1.023 (0.787)	1.169 (0.293)	1.030 (0.861)	1.128 (0.302)	0.828 (0.236)
	LGM	Level	**0.949 (<0.001)**	**0.949 (<0.001)**	0.946 (0.030)	0.940 (0.048)	**0.946 (0.008)**	0.946 (0.091)
		Slope	1.028 (0.752)	0.992 (0.929)	1.231 (0.386)	0.998 (0.995)	1.140 (0.323)	0.744 (0.086)
NART	BLUP	Level	0.986 (0.043)	0.981 (0.070)	0.976 (0.158)	1.035 (0.151)	0.998 (0.862)	0.974 (0.240)
		Slope	1.093 (0.595)	1.468 (0.128)	0.980 (0.960)	0.776 (0.635)	1.151 (0.682)	1.813 (0.278)
	LGM	Level	0.985 (0.052)	0.985 (0.149)	0.974 (0.138)	1.024 (0.239)	0.999 (0.944)	0.983 (0.494)
		Slope	1.091 (0.493)	1.201 (0.248)	1.025 (0.925)	1.284 (0.478)	1.119 (0.605)	1.146 (0.770)
MMSE	BLUP	Level	**0.971 (0.002)**	**0.964 (0.010)**	0.966 (0.153)	1.017 (0.568)	0.966 (0.059)	**0.924 (0.009)**
		Slope	**0.946 (0.002)**	**0.924 (0.002)**	1.037 (0.478)	0.976 (0.681)	**0.910 (0.004)**	0.967 (0.584)
	LGM	Level	0.970 (0.011)	0.966 (0.014)	0.964 (0.140)	1.016 (0.645)	0.968 (0.062)	0.924 (0.014)
		Slope	**0.931 (0.007)**	**0.908 (0.001)**	1.055 (0.430)	0.969 (0.547)	**0.895 (0.002)**	0.953 (0.463)
Fluency	BLUP	Level	0.978 (0.011)	**0.950 (<0.001)**	1.000 (0.992)	1.027 (0.323)	0.966 (0.048)	**0.915 (0.003)**
		Slope	0.943 (0.162)	0.915 (0.176)	0.958 (0.677)	0.932 (0.588)	0.919 (0.333)	0.891 (0.429)
	LGM	Level	0.973 (0.014)	**0.945 (<0.001)**	0.997 (0.899)	1.023 (0.478)	0.960 (0.040)	**0.900 (0.004)**
		Slope	0.907 (0.170)	0.868 (0.061)	0.926 (0.633)	0.915 (0.567)	0.871 (0.178)	0.766 (0.298)
Episodic	BLUP	Level	0.976 (0.095)	0.971 (0.181)	0.955 (0.204)	1.012 (0.789)	0.957 (0.129)	0.990 (0.849)
		Slope	0.921 (0.312)	0.843 (0.155)	1.103 (0.632)	0.948 (0.825)	0.776 (0.111)	0.835 (0.507)
	LGM	Level	0.975 (0.365)	0.965 (0.181)	0.957 (0.320)	1.008 (0.811)	0.951 (0.177)	0.993 (0.919)
		Slope	0.870 (0.429)	0.832 (0.121)	1.090 (0.760)	0.960 (0.828)	0.760 (0.092)	0.751 (0.527)

Notes: Level and slope estimates were included simultaneously in each model. Separate models were estimated for each cognitive test and each cause of death. All models are adjusted for the effects of age, gender, education, smoking status, functional disability, disease count, grip strength, Goldberg depression score and Goldberg anxiety score. ***Bold*** *cells indicate $p < 0.01$.*

SLMT: Symbol-Letters Modalities Test; NART: National Adult Reading Test; MMSE: Mini-Mental State Examination; Fluency: verbal fluency task; Episodic: episodic memory task; BLUP: best linear unbiased estimator; LGM: linear growth model; HR: hazard ratio

Discussion

The present study aimed to assess the relationship between level and slope of cognitive performance on cause-specific mortality in the Canberra Longitudinal Study. Using two unbiased methods for estimating change in cognitive performance, the initial level of cognitive performance was found to be a better predictor of subsequent mortality than the rate of change in performance. Processing speed (SLMT) and global cognition (MMSE) were the strongest indicators for mortality, with poorer performance having a significant relationship with increased mortality from all-causes and cardiovascular disease, including heart disease and/or stroke. In addition, declining performance on MMSE was associated with greater rates of all-cause, cardiovascular and heart disease mortality. Poorer performance on the verbal fluency task was associated with a greater hazard of cardiovascular and stroke death. None of the cognitive tests predicted cancer or respiratory deaths. Consequently, it appears that the relationship between cognition and all-cause mortality may be largely due to late-life changes in the cardiovascular system that are associated with both cognitive performance and death.

These results concur with the findings of Shipley et al. (2008), who found that the relationship between cognitive performance and mortality was primarily evident for cardiovascular causes of death. As in the Shipley et al. (2008) study, the present study excluded participants who died early in the study and adjusted for potential confounding from background characteristics, health behaviors, and physical and mental health status. Many cognition-mortality effects remained strong after these adjustments. The findings were somewhat different to the conclusions of the review by Anstey et al. (2006), who reported stronger associations between cognition and mortality among cancer and stroke patients than heart disease patients. However, most of the papers in

Anstey's review examined all-cause mortality in these patient groups rather than cause-specific mortality. Disparate causes of death in cancer and heart disease patients may be responsible for the different findings, along with the largely clinical nature of the samples reviewed by Anstey et al. (2006). The present community-dwelling sample may have included a broader array of trajectories of decline in physical and cognitive functioning.

The finding that a range of cognitive abilities were associated with mortality was consistent with the conclusions of Ghisletta et al (2006), who reported that the effect of cognition on mortality was not specific to any domain of functioning, although tasks robust to aging effects such as vocabulary had no association with mortality. Speeded tasks such as SLMT tend to decline as a response to both normative and pathological aging processes, so the SLMT was expected to show stronger relationships with mortality outcomes. Nevertheless, measures of verbal fluency and global cognition also showed strong associations with cardiovascular deaths in particular, despite being somewhat more robust to the effects of aging. These findings are at odds with the White and Cunningham (1988) hypothesis that terminal decline is limited to abilities that are robust to aging. Our results suggest that both normative and pathological aging processes may contribute to the relationship between cognition and mortality.

Bäckman and MacDonald (2006) have suggested that because verbal fluency tasks have aspects that reflect both fluid and crystallized intelligence, it may be an important predictor of terminal decline. They observe, "verbal fluency may be particularly good for demonstrating terminal decline, because the task is simple enough for survivors but sufficiently taxing for decedents" (Bäckman & MacDonald, 2006, p225). It is plausible that this combination of fluid and crystallized abilities may also explain the SLMT effects, as the SLMT uses a novel task (transcription of symbols) to assess processing speed. The MMSE effects are likely associated with dementia and the

psychometric properties of the instrument. MMSE scores generally remain fairly stable and at a ceiling in the absence of pathology (Small & Bäckman, 2007). As the present sample was largely cognitively intact at the beginning of the study, most change in the MMSE would have occurred in the follow-up stages as the prevalence of dementia increased. This may explain why there was less effect of the level of MMSE than on the slope of MMSE, likely reflecting pathological events that were associated with death in a subset of the sample. Heart disease deaths were predicted only by changes in MMSE, whereas stroke deaths were predicted only by level, possibly because of the more acute effects of stroke on cognitive performance. Correspondingly, combined cardiovascular deaths (which includes both stroke and heart disease deaths) and all-cause mortality were predicted by both level and slope of MMSE. In contrast to the MMSE, vocabulary as measured by the NART is robust to the effects of both normative aging and preclinical dementia (McGurn et al., 2004). The lack of association between episodic memory and mortality may be related to the validity of the very brief measure used in the present study, as indicated by the relatively modest declines seen in the episodic memory task across the study period.

As the effects across all tasks were primarily associated with cardiovascular deaths, the findings suggest that a range of cognitive deficits in late-life may be indicative of cardiovascular problems including vascular events in the brain. Such vascular events may also occur in late-life or be precipitated by early- or mid-life disease or injury (Fischer et al., 2006; Herrup, 2010). Furthermore, given the high comorbidity between dementia and cardiovascular diseases (Rastas et al., 2010; Skoog, 1998), it is not surprising that cognitive performance is predictive of cardiovascular mortality, particularly changes in MMSE that may indicate dementia. As a range of vascular events are associated with dementia, including hypertension, coronary heart

disease, atrial fibrillation and stroke (Skoog, 1998), it is likely that cardiovascular morbidity leads to reduced cognitive ability and eventual mortality.

The present study expanded the investigation of the cognition-mortality relationship by including two unbiased estimates of cognitive change. However, using measures of change resulted in limited evidence for terminal decline – there were few significant relationships between the slope of change and the mortality outcomes. Such findings are similar to those of Johansson et al. (2004) and Ghisletta et al. (2006), who also reported stronger effects for level rather than slope of cognitive performance. This finding may reflect the level of cognitive ability being indicative of a lifetime of development through education, health literacy and healthy behaviors (medication compliance, help seeking), along with insult through unhealthy behaviors (particularly substance use), injury, vascular problems and other physical health problems (Bäckman & MacDonald, 2006; Deary, 2005). Other genetic and environmental influences through the lifespan may also influence the level of performance (Bäckman & MacDonald, 2006). These lifelong influences on the level of performance may be greater contributors to mortality than developmental cognitive processes that occur in proximity to death, which are reflected in the change estimates. It appears to be only when pathological events occur, as reflected by declines in the MMSE, that changes in cognition may be directly predictive of mortality. The lack of effects for slope estimates may also be related to the reliability of these estimates, which were assessed across up to four time points. Although these few time points may result in less reliable estimates of slope, reducing the power to find effects, the large sample size would have somewhat mitigated this issue. Furthermore, the variances of the slope estimates were proportionally greater than those of the level estimates, which indicate that restriction of range was likely not a problem for finding effects. Ghisletta et al (2006) reported similar findings using up to eleven measurements, and none of the slope effects (other

those reported for MMSE) came close to being significant, so it is unlikely that the null effects of slope were purely the result of the estimation process.

While latent growth models and best linear unbiased predictors (BLUPs) are unbiased, defensible methods for estimating cognitive change, linear estimates of cognitive change may not adequately capture the terminal decline phenomenon. Cognitive decline in proximity to death may be described instead as a threshold function using a change point model, as it does not accelerate continuously (Sliwinski et al., 2006). A previous analysis of the present cohort using a change point model did find evidence for terminal decline, starting around 6-8 years prior to death for different cognitive measures, with a two- to four-fold acceleration of decline in the terminal phase (Batterham, Mackinnon et al., in press). Estimating the onset and rate of cognitive decline with respect to time-to-death assesses whether those in proximity to death show greater cognitive decline, which is a different research question to the present analysis, which assessed whether those who exhibit cognitive decline were at greater risk of dying (Bäckman & MacDonald, 2006). Nevertheless, it is instructive to identify the differences in findings between these approaches. Specifically, it appears that while there may be a significant acceleration of cognitive decline in proximity to death, the overall rate of decline is generally not a critical predictor of mortality.

The second goal of the current study was to compare latent growth models and BLUPs for examining the relationship between cognitive change and mortality, as previous research on cognition and mortality has not explicitly assessed the comparability of these methods. The comparison of the two methods demonstrated that they provide very similar results. The latent growth model may be seen as a more elegant method, as the estimation of change scores and the survival analysis is done in an integrated model that is not reliant on predicted scores, in contrast to the present BLUP analysis. However, the BLUP method can be achieved in any standard statistical

software (SAS, SPSS, S-Plus, Stata, etc.), while the latent growth method requires an iterative process that is slower (hundred-fold increase in processing time) and more resource-intensive (each model must be run using a separate input file) than BLUPs. The non-convergence of the NART models using an unstructured covariance matrix was the only drawback of the BLUP models because of the reliance of these models on determining predicted scores, however, the outcome of these models was no different.

The present results also suggest that the two methods may have equivalent power for finding effects, although the BLUP models appeared to give marginally smaller p-values for some of the effects. The slight differences in the models may result from minute variations in the level and slope estimates, small differences due to the baseline hazard assumptions across the two software packages, or the difference between using a two-stage versus integrated modeling process. The present findings support the use of multiple approaches of measuring change, although either of the methods used to generate unbiased estimates of change should provide comparable results. Each of the models provide different possibilities for extending this research, for example, piecewise modeling may be possible using BLUPs but difficult to implement using latent growth models, while latent growth modeling may be extended to growth curve mixture modeling which is not feasible using BLUPs. The present analysis used a two-stage approach in which BLUPs were estimated, while Ghisletta et al (2006) used a single-stage Bayesian joint longitudinal-survival model. Although this single-stage model can be implemented in SAS as was done by Ghisletta et al (2006), its developers (Guo & Carlin, 2004) recommend the use of specialized Bayesian statistical packages, as confidence intervals produced by other approaches may be biased.

There were some limitations of the research that could not be fully addressed in the present study. Only linear changes in cognition over time were investigated.

Further research could investigate modeling cognitive change using nonlinear functions. A maximum of four measurements taken over 12 years were available for estimating change, as more measurements were not feasible given the large community-based elderly cohort. A substantial proportion of participants were assessed on fewer occasions. Such a pattern was sufficient only for estimating individual linear change using the present methods. The analyses also excluded participants who died or withdrew from the study after the first interview. This exclusion may have created a degree of bias, however, it also resulted in a more homogeneous sample, as the participants closest to death at the first interview were sicker, on average. Inclusion of these participants would have skewed initial cognitive test scores. Consequently the effects presented reflect conservative estimates that may be more reflective of the effects of normative aging than pathology. Indeed, Shipley et al. (2008) recommended examining models that omit individuals who die early in the study period, as any outcomes may otherwise be confounded by the disproportionate contribution of sick participants who were close to death at the first assessment. This relationship is reflected by the significantly lower cognitive scores among participants who were excluded from the analysis due to death or dropout before the second interview (Table 1). The cognitive measures used in the present analysis were selected prior to the beginning of the study in 1990 with the aim of briefly assessing a range of abilities. Studies using more comprehensive measures of episodic memory in particular, along with other domains of functioning may find different outcomes. The relatively small declines observed in episodic memory (-0.10 sd/year) may be due to the performance of the scale. Finally, mortality and attrition across the study period inevitably reduced the sample by the fourth wave, however, its size was large for this type of community study and most participants (62%) contributed three or more measures to the estimates of cognitive change.

In conclusion, poorer cognitive performance in several domains predicted higher rates of all-cause mortality and cardiovascular mortality, including heart disease and/or stroke mortality. These findings suggest the cognition-mortality relationship may be primarily driven by lifelong cardiovascular events which effectively overshadow subtler effects reflected by change in memory and cognition. Global ability was the only domain to show a relationship between declines in performance and increased all-cause and cardiovascular mortality. Other methods that do not rely on estimating linear trends may be more effective for capturing the terminal decline phenomenon. Nevertheless, latent growth models and BLUP models are principled and useful methods for obtaining consistent unbiased estimates of linear change, and this is the first paper to demonstrate the comparability of the two methods for predicting mortality. While results such as those presented may not be sufficiently consistent to facilitate the prediction of cause-of-death, the methods used provide greater insight into the relationship between late-life cognitive performance and mortality.

Acknowledgements: The Canberra Longitudinal Study was supported by NHMRC Unit Grants 973301 and 933301 and NHMRC Program Grant 179805. HC is supported by NHMRC Senior Principal Research Fellowship 525411.

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The effect of education on the onset and rate of terminal decline

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Published in *Psychology and Aging*, 2011, 26 (2), 339-350.

Abstract

Differences in the time of onset and magnitude of terminal decline were examined in three cognitive domains: processing speed, episodic memory and global function. In addition, cognitive reserve was investigated by testing whether education effected the onset or rate of decline across these domains. 896 community-dwelling Australian adults aged ≥70 years were assessed up to four times over 12 years, with vital status followed for 17 years. For each of the cognitive measures, a series of change point models were fitted across the 20 years prior to death to find the optimal point at which terminal decline was distinguished from preterminal decline. Change points were then assessed separately for high- and low-education groups. The change points were 8.5 years for processing speed (95% CI: 6.0-11.2 years), 7.1 years for global function (6.2-9.3), and 6.6 years for episodic memory (5.3-7.1). The rate of decline was 2-4 times greater in the terminal phase relative to the preterminal phase, depending on the domain. Increased education changed the terminal decline effect differently for each of the three tests, either by significantly hastening the onset of terminal decline and decreasing the rate of decline, or by increasing the rate of either preterminal or terminal decline. Analyses were repeated excluding participants diagnosed with dementia, with no substantive change to the outcomes. In conclusion, the rate and onset of terminal decline varied somewhat across cognitive domains. Education affected terminal decline differently across the domains, but this modification was not consistent with the predictions of cognitive reserve theory.

The terminal decline phenomenon was first described by Kleemeier (1962), and was characterized by Riegel & Riegel (1972) as a process in which cognitive functioning deteriorates in proximity to death. It is generally agreed that terminal decline is related to pathological processes occurring prior to death, which may be distinguished from normal, age-related decline (Laukka, MacDonald, & Backman, 2008; Sliwinski et al., 2006; Small & Backman, 1999; Wilson et al., 2007). This distinction also reflects the concepts of primary aging (maturational processes) and secondary aging (disease processes) (Birren & Cunningham, 1985; Busse, 1969). However, a review of studies examining the relationship between changes in cognitive function and death reported limited evidence for terminal decline (Bosworth & Siegler, 2002a). These studies generally estimated cognitive change scores to predict survival. An alternative approach has been used more recently to examine the nature of terminal decline. The aim of this method is to partition the effects of normative aging and terminal decline using change point models, resulting in estimate of both the onset and magnitude of terminal decline. This method was proposed by Hall (2000) for the purpose of identifying the onset of cognitive decline prior to the diagnosis of Alzheimer's Disease. Wilson et al. (2003), Sliwinski et al. (2006), Wilson et al. (2007) and Thorvaldsson et al. (2008) have used the method to distinguish terminal (pathological) cognitive decline from preterminal (normative, age-related) cognitive decline.

The estimates from the four studies that have used the change point method are summarized in Table 1. Change points were identified at 3.5 years for the two studies by Wilson and colleagues, while the other studies generally identified a change point between 5-9 years prior to death. The magnitude of the ratio between terminal and preterminal decline was generally in the range of 2-5, although there were exceptions to this finding which may be attributable to near-zero rates of preterminal decline.

Overall, although there is some agreement in these studies about the timing and magnitude of terminal decline, there is also variation which warrants explanation. Sliwinski et al. (2006) suggested that the slightly different method used by Wilson et al. (2003), which included participants who survived the study period in the estimates, led to a possible underestimate of the terminal decline effect. Furthermore, study design, particularly the length of follow-up, and sample composition may have an impact on the estimation of the change point (Thorvaldsson et al., 2008).

Table 1: Previous estimates of terminal decline from four studies using the change point method

Study	n	Follow-up period (years)	Cognitive domain(s)	Change point (95% CI)†	Magnitude of decline‡
Wilson et al (2003)	763	8	Global cognition	3.5	5.0
Sliwinski et al (2006)	445	25	Episodic memory	8.4 (7.1, 9.8)	1.8
Wilson et al (2007)	853	8	Global cognition	3.5	3.0
Thorvaldsson et al. (2008)	288	15	Verbal ability	6.6 (4.3, 11.7)	13.0
			Spatial ability	7.8 (6.3,10.6)	1.9
			Perceptual speed	14.8 (10.8, 16.6)	2.0

† Years prior to death
‡ Ratio of terminal to preterminal decline

Perhaps of greater importance, terminal decline appears to commence at different times for different abilities. In healthy older adults who age normatively, certain cognitive domains such as perceptual speed and explicit memory have been found consistently to decline earlier and more precipitously than other domains, such as verbal ability (Carlson, Xue, Zhou, & Fried, 2009; Royall, Palmer, Chiodo, & Polk, 2005). Bäckman, Jones, Berger, Laukka & Small (2005) have reported greater preclinical decline among participants who progressed to Alzheimer's Disease than those who did not on global cognitive ability, perceptual speed, executive functioning

and episodic memory ($d < 1.0$), while verbal ability, visuospatial skill and attention showed more modest levels of decline. In studies of age-related cognitive decline, Lindenberger and Ghisletta (2009) reported greater decline in perceptual speed than in episodic memory, while Scuteri, Palmieri, Lo Noce and Giampaoli (2005) reported that decline in perceptual speed occurs earlier and more precipitously than decline in global functioning. In examining terminal decline, Sliwinski et al. (2006) studied only an episodic memory task, while the studies of Wilson et al. (2003 and 2007) used a battery of 19 cognitive tests that were combined into a single measure. In contrast, Thorvaldsson et al. (2008) examined verbal ability, spatial ability and perceptual speed separately, finding differences in both the onset and magnitude of terminal decline for different cognitive domains. While Wilson et al. (2003 and 2007) only presented models for a composite cognitive score, many of the constituent tests they examined were reported to have change points around 3-4 years, although visuospatial ability had an earlier change point at six years. Like Thorvaldsson et al. (2008), Wilson et al. (2003) found that the magnitude of terminal decline also varied across cognitive domains, with the slope increased anywhere from three-fold to eleven-fold in the terminal period compared to the preterminal period.

It may be concluded that the processes involved in terminal decline – much like those in normative aging – affect different cognitive domains to varying extents, both in terms of the magnitude and time of onset of the decline. Bäckman et al. (2005) attributed differential decline across cognitive domains to functional impairment and structural changes in multiple brain structures, including volume reductions in the medial-temporal lobe, anterior cingulate and temporal sulcus, posterior cingulate and neocortical temporoparietal regions, and frontal regions, along with decreased blood flow, reduced glucose metabolism and amyloid deposits in other regions. Other factors including cardiovascular disease, inflammation, lifestyle and age-related

neurobiological changes may also have specific impacts on late-life cognitive performance (Deary et al., 2009). Changes to structure and function in specific brain regions prior to death, whether due to dementia or other disease processes, may have differential impacts on both the onset and magnitude of decline across various cognitive domains. Consequently, examining a range of cognitive domains is necessary to fully capture the nature of the terminal decline phenomenon (Small & Backman, 1999).

More recently, the change point method has been used to determine whether particular risk factors such as poor education or the presence of the apolipoprotein E (APOE) ε4 allele modify the onset and magnitude of terminal decline (Wilson et al., 2007). Education, childhood cognition and adult occupation are believed to protect against faster rates of cognitive decline in normal populations (Richards & Sacker, 2003), and it may have specific effects on rate or onset of terminal decline. Research suggests that the clinical onset of Alzheimer's disease appears to be delayed in those with higher education, but the rate of cognitive decline after onset is more rapid among more highly educated individuals (Stern et al., 1999). Such findings are cited as evidence for cognitive reserve, suggesting that education increases the brain's ability to compensate for pathology (Stern, 2002). The cognitive reserve hypothesis suggests that higher levels of education create a buffer against functional decline in the face of brain insult (Christensen, Anstey, Leach, & Mackinnon, 2008). Education may be associated with a greater number of healthy synapses or neurons, more efficient circuits of synaptic connectivity or more efficient use of alternative brain networks (Scarmeas, Albert, Manly, & Stern, 2006). Evidence for education being an indicator of reserve comes from functional magnetic resonance imaging studies of high-functioning older adults, which demonstrate functional compensation for declines in neural activity (Cabeza & Nyberg, 2000).

Change point models can test whether education protects against terminal decline by delaying the onset of terminal decline even if the subsequent rate of decline is accelerated. Wilson et al. (2007) examined whether education, age, sex, vascular disease, APOE genotype or mild cognitive impairment modified terminal decline. They found that the rate of decline did not accelerate during the terminal phase for individuals without an APOE ε4 allele or with a history of vascular disease, but found no effect of education on the rate of decline. However, these effects were examined using only a global cognition aggregate score (Wilson et al., 2007), without examining whether cognitive reserve may influence specific domains of cognitive decline. Hall et al. (2007) also examined the role of education in memory decline prior to dementia diagnosis. They found that increased education delayed the onset of dementia-related cognitive decline but the decline was more precipitous after onset (Hall et al., 2007), in support of the cognitive reserve theory. However, the study did not examine decline with respect to death and also examined only a single measure of cognition.

The present study examined terminal and preterminal decline in three domains as a function of education using the method proposed by Hall et al. (2000). We explored decline by examining a series of models that incremented a change point over 20 years. The definition of the preterminal and terminal phases is dependent on whether the measurement occurs before or after the change point, as illustrated in Figure 1. When a measurement occasion is before the change point (e.g., "Measurement 1" in Figure 1), the length of the preterminal phase at that measurement is defined as the individual's current age, while the length of the terminal phase is zero. When a measurement occasion is after the change point (e.g., "Measurement 2" in Figure 1), the length of the preterminal phase at that measurement is defined as the individual's age at death minus the change point, while the length of the terminal phase is the individual's current age minus their age at death plus the change point.

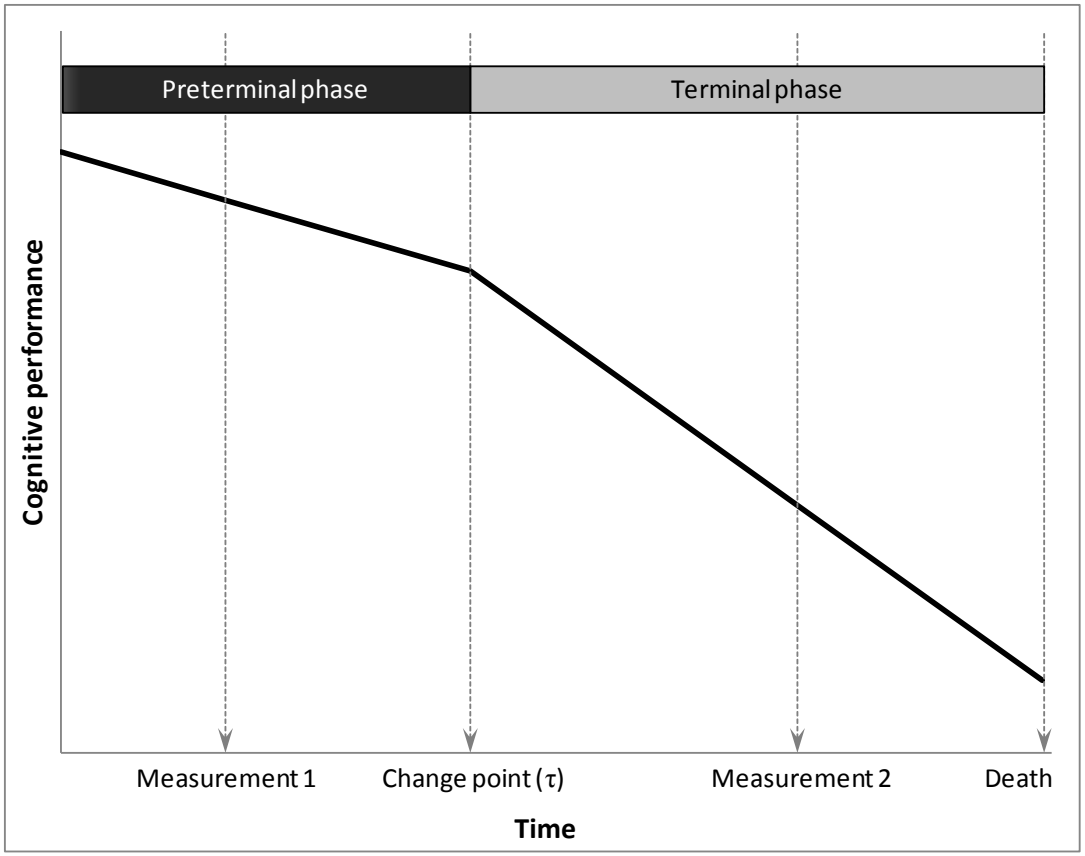

Figure 1: Preterminal and terminal phases of cognitive decline, illustrating their dependence on the time of measurement

The models included both fixed and random effects (slopes) of preterminal and terminal decline, in addition to a random intercept. The change point that optimally differentiated between preterminal and terminal slopes was determined by varying the change point to identify the model with the largest likelihood function. A 95% confidence interval for the identified change point was based on the difference in -2 log likelihood from the optimal change point, which has a chi-square distribution (Sliwinski et al., 2006). The rates of preterminal and terminal decline were then assessed using the model at the optimal change point. Taking this approach further, the present study examined the effect of education on terminal decline for each of the cognitive tasks by dividing the cohort based on educational attainment and repeating the analysis.

The Canberra Longitudinal Study (Christensen et al., 2004) included seven cognitive domains that were assessed for terminal decline in the present study: episodic

memory, processing speed, global function, verbal and facial recognition, verbal fluency and verbal ability. The three domains found to clearly exhibit terminal decline in the present study were episodic memory, processing speed and global function. Based on the findings of (Thorvaldsson et al., 2008), it was hypothesized that there would be differences in both the onset and rate of terminal decline across domains. We predicted that the onset of terminal decline would be earlier for processing speed than for other tasks, as reported by Thorvaldsson et al. (2008), while research on age-related and pathological cognitive decline suggests that the rate of decline for all three domains may be similar (Backman et al., 2005). Based on the predictions of cognitive reserve theory (Stern, 2002), where higher reserve may initially slow the rate of decline, and previous findings with respect to the onset of dementia (Hall et al., 2007; Stern et al., 1999), where education initially protects, but then precipitates decline following diagnosis, we hypothesized that higher education may shorten the length of terminal decline but accelerate the rate of decline in the terminal period. Furthermore, these differences might be more likely to be observed on tests sensitive to terminal decline such as processing speed. These observations were undertaken with and without those with dementia diagnosis to determine the effect of a dementia diagnosis and to exclude the effect of dementia for the rest of the population sample.

Method

Participants

The Canberra Longitudinal Study is an epidemiological survey of mental health and cognitive functioning in older people that commenced in 1990. The study design has previously been detailed by Christensen et al. (2004). Eight hundred and ninety-six participants (456 men and 440 women) aged 70 or older at the time of the baseline

assessment were recruited for the baseline assessment. All participants were initially living in the community in the cities of Canberra or Queanbeyan, Australia. The sample was stratified by age and gender. Participants were sampled from the compulsory electoral roll, with 69% responding. Approval for the research was obtained from the Ethics in Human Experimentation Committee of The Australian National University.

Survey Procedure

Participants were interviewed up to four times over 12 years. Baseline interviews lasted approximately two hours, incorporating a survey measuring a wide range of risk factors including socio-demographics, physical health and disease status, mental health status, cognitive performance and social support. Interviews also included physical assessments of blood pressure, lung function, grip strength, vision and reaction time. Trained professional interviewers conducted the interviews.

Of the original sample of 896 participants, 185 (20.6%) were deceased by four years, 363 (40.5%) were deceased by eight years, and 544 (60.7%) were deceased by 12 years. At the end of vital status collection in June 2007, 687 (76.7%) of the participants were deceased. Of the participants who remained in the study, 14.1% (100/711) refused or were unable to complete the first follow-up interview, 21.1% (100/474) for the second follow-up and 21.1% (57/270) for the third follow-up. Participants surviving at the end of the follow-up period (n = 209) were excluded from the analyses.

Measures

Several tests were administered to assess the cognitive performance of study participants. *Speed of processing* was measured by the Symbol-Letters Modalities Test (SLMT), a task similar to Smith's (1973) Symbol-Digit Modalities Test and Wechsler's (1981) Digit-Symbol Substitution. *Verbal ability* was measured using the National Adult Reading Test (Nelson, 1982), a test of vocabulary. An *episodic memory* task consisted of brief episodic memory tasks testing word, face, name and address recall

and figure reproduction (Jorm, 1992). *Verbal fluency* was assessed as the number of animals named in 30 seconds. *Face and word recognition* tasks were based on the Rivermead Behavioural Memory Test (Wilson, Cockburn, Baddeley, & Hiorns, 1989). *Global function* was tested using the Mini-Mental State Examination (Folstein, Folstein, & McHugh, 1975a), scored out of 30. To facilitate comparisons between tests, all of the tests were standardized to a common metric, with a mean of 100 and standard deviation of 10 at the baseline measurement.

Mortality status and date of death were established by contacting relatives, searching the National Death Index, and from death notices in the local newspaper. Missing death identifications from the National Death Index would most likely have been a rare occurrence, as the index is a register of all deaths in Australia. The additional methods used for death reporting (contacting relatives, newspaper searches) provide further confidence in the mortality status data. Mortality status was followed for up to 17 years, from the start of baseline interviews in September, 1990 until June 30, 2007. For six participants with unknown day of death, the day was set to the 15th of the month. For two participants with an unknown month of death, the month was set to June. *Date of birth (age)* was reported during the initial interview. *Educational status* was based on responses to two questions regarding the number of years in school and the highest qualification obtained. These two questions were combined into a single measure representing the number of years it took participants to attain their highest educational qualification. For the analyses based on educational status, a median split was used to differentiate those with fewer than 11 years of education (low education) from those with 11 or more years (high education), which also corresponds to the number of years taken to complete standard secondary education for this cohort. Additional analyses controlled for a number of baseline risk factors for cognitive decline or mortality: gender, heart attack history (self-report binary measure),

hypertension history (self-report binary measure), grip strength (measured in kilograms using a hand dynamometer), smoking status (never, previous or current), Activities of Daily Living (a scale of functional disability ranging from 0 to 24), disease count (self-reported history from a list of 14 diseases), and depression [Goldberg Depression Scale (Goldberg et al., 1988a), range 0-9].

To examine the effect of dementia and to determine any potential confounding arising from it, analyses were repeated with and without participants with this disorder. Participants who met criteria for an ICD-10 (World Health Organization, 1993) diagnosis of dementia or severe dementia during the study (at waves 1-4, up to 12 years after baseline) were identified. Diagnoses were made using the Canberra Interview for the Elderly (Social Psychiatry Research Unit, 1992), which provides information from which a diagnosis of dementia can be made according to ICD-10 (World Health Organization, 1993) and DSM-III-R (American Psychiatric Association, 1987) by means of a computer algorithm (Mackinnon et al., 2003). The algorithm classifies participants into categories of non-case, possible dementia, probable dementia or actual dementia. The "actual dementia" category was chosen for the selection of participants to exclude, as it is the most robust.

Analyses

Mixed model repeated measures analyses of variance (MMRM) were used to estimate the change point and magnitude of terminal decline, following the method described by Hall, et al. (2000). This process segments the participant's age (in months) at each measurement point using a change point, τ. The segmentation of age is shown in the equation (adapted from Sliwinski et al., 2006):

$$cognition_{it} = \beta_0 + \beta_1 (\min[Age_{it}, DeathAge_i - \tau]) + \beta_2 (\max[0, Age_{it} - DeathAge_i + \tau]) + \varepsilon_{it}$$

where $cognition_{it}$ represents a cognitive score for participant *i* at time *t* (each cognitive test was modeled separately), β_0 is the intercept, β_1 is the coefficient being estimated for the rate of cognitive decline during the preterminal interval, Age_{it} is the age of participant *i* age at time *t* (in months), $DeathAge_i$ is the age at death of participant *i* (in months), τ is the change point being evaluated within a range of 1-20 years (in months), β_2 is the coefficient being estimated for the rate of cognitive decline during the terminal interval, and ε_{it} is the error term. Age at study commencement was centered at 75 (i.e., 75 years were subtracted) to facilitate the interpretation of intercepts.

The model was repeatedly evaluated using values for the change point, τ, incremented from 12 to 120 months prior to death in steps of one month. The model with the largest log-likelihood value was selected, with the τ for this model representing the change point at which terminal decline begins, with the estimates of β_1 and β_2 at this value of τ representing the rates of preterminal and terminal decline respectively. Both fixed and random effects for β_1 and β_2 were included in the model and maximum likelihood estimation was used in accordance with the method used by Hall et al. (2000). An unstructured variance-covariance matrix was used and degrees of freedom were calculated using Satterthwaite's approximation (Steel & Torrie, 1980). Mixed models use all available measurement points for each participant under the assumption that missing data are missing at random. Analyses were repeated excluding participants who had received a dementia diagnosis and also repeated with the inclusion of multiple risk factors for mortality as independent fixed effects. SAS v9.1 was used for all statistical analyses.

Results

Participants who were deceased at June 2007 were included in the change point analyses (n = 687). Of these 687 decedents, 423 completed the second interview (176 deaths and 88 dropouts), 215 completed the third (183 new deaths, 57 new dropouts, including 31 former dropouts who died and one who returned to the study) and 81 completed the fourth (176 new deaths and 28 new dropouts, including 69 former dropouts who died and one who returned to the study). In all, 81 (11.8%) participants contributed data from all four time points, 135 (19.7%) from three, 208 (30.3%) from two and 263 (38.3%) from only the baseline measurement. There was no significant difference between the rates of contribution between those with lower education (<11 years, n = 376) and those with higher education [≥11 years, n = 520; χ^2 (3) = 6.1, p = 0.11]. Of the 1406 total observations from the 687 participants, 297 (21.1%) occurred 10 or more years prior to death, while 791 (56.3%) occurred five or more years prior to death.

The contribution of observations to the change point models across the span of the study is shown in Table 2, categorized by the number of years prior to death the observations were made, separately for the two education groups. Approximately 35% of the observations fell in the 5-10 years prior to death where terminal decline is most commonly found to begin, while 44% were 0-5 years before death and the remaining 21% were more than 10 years before death. There was no significant difference in the distributions of observations across the two education groups [χ^2 (16) = 7.3, p = 0.96). The mean age of participants used in the change point analyses (n = 687) was 77.3 years (sd = 5.1), with a mean educational attainment of 11.4 years (sd = 2.6). Those who had died by June 2007 were older at the start of the study than those who survived. However, there was no significant difference between decedents and survivors in the

amount of education completed. Performance on all seven cognitive tests was significantly better for survivors compared to decedents.

Table 2: Contribution of observations to the mixed effects models as a function of time to death and education

	Low education group (n=376, 553 obs)		High education group (n=520, 853 obs)	
Time to death	Frequency	Percent	Frequency	Percent
0 to <1 year	40	7.2%	68	8.0%
1 to <2 years	50	9.0%	82	9.6%
2 to <3 years	53	9.6%	82	9.6%
3 to <4 years	49	8.9%	80	9.4%
4 to <5 years	42	7.6%	69	8.1%
5 to <6 years	50	9.0%	74	8.7%
6 to <7 years	39	7.1%	65	7.6%
7 to <8 years	36	6.5%	51	6.0%
8 to <9 years	45	8.1%	53	6.2%
9 to <10 years	35	6.3%	46	5.4%
10 to <11 years	24	4.3%	44	5.2%
11 to <11 years	24	4.3%	42	4.9%
12 to <13 years	27	4.9%	36	4.2%
13 to <14 years	15	2.7%	18	2.1%
14 to <15 years	7	1.3%	20	2.3%
15 to <16 years	12	2.2%	18	2.1%
16 to 17 years	5	0.9%	5	0.6%

To determine whether change point models were justified, decline in each of the tasks was examined using base models testing linear and quadratic terms for age and, separately, time-to-death. These models found little decline on several of the tests, possibly because the participants tended to be relatively well educated, were community dwelling (non-institutionalized) and had relatively low rates of dementia. Furthermore, some of the tests were included in the study for their robustness to the effects of cognitive aging. Consequently, change points could not be reliably estimated for NART, verbal fluency, face recognition or word recognition. Three domains of

cognitive function were therefore used as outcomes in the analyses: speed of processing (SLMT), episodic memory and global function (MMSE).

To identify the optimal change point and compare change points across domains, -2 log likelihood values from the 229 models (12-240 months) were standardized to create "profile likelihood" values, fitting a range between 0-1. This was calculated by subtracting the -2LL value at each time point from the minimum -2LL value (i.e., the -2LL value at the change point), then dividing by 2 and taking the exponent (Hall et al., 2000). This was done separately for each of the three domains investigated. Profile likelihood values are plotted for the three domains in Figure 2, with time ranging from 1-15 years prior to death on the x-axis (death is time zero). The 95% confidence interval for change point estimate is also indicated, with the cutoff values for this interval being at approximately 0.15 for the transformed profile likelihood values on each of the tests. The optimal change point for processing speed was 8.5 years (95% CI: 6.0-11.2 years), the MMSE change point was 7.1 years (6.2-9.3), while the episodic memory change point was 6.6 years, (5.3-7.1). Overlap is evident between the confidence intervals for all three cognitive tests, suggesting that change points for these tests are not significantly different.

The models showing the effects of preterminal and terminal decline at the change points are displayed in Table 3. Absolute rates of decline can be compared across tests, as they were standardized to mean of 100 and sd of 10 at baseline. The parameter estimates given in the table represent monthly changes in these standardized units. Likelihood ratio chi-square tests for the null model are provided in the table, showing the models fit well. The covariance estimates for the random effects are also provided in the table. In some cases, the random effect of preterminal decline was close to zero, as indicated in the table. In these cases, models were reestimated without this random effect (not displayed). The coefficients for intercept, preterminal and terminal

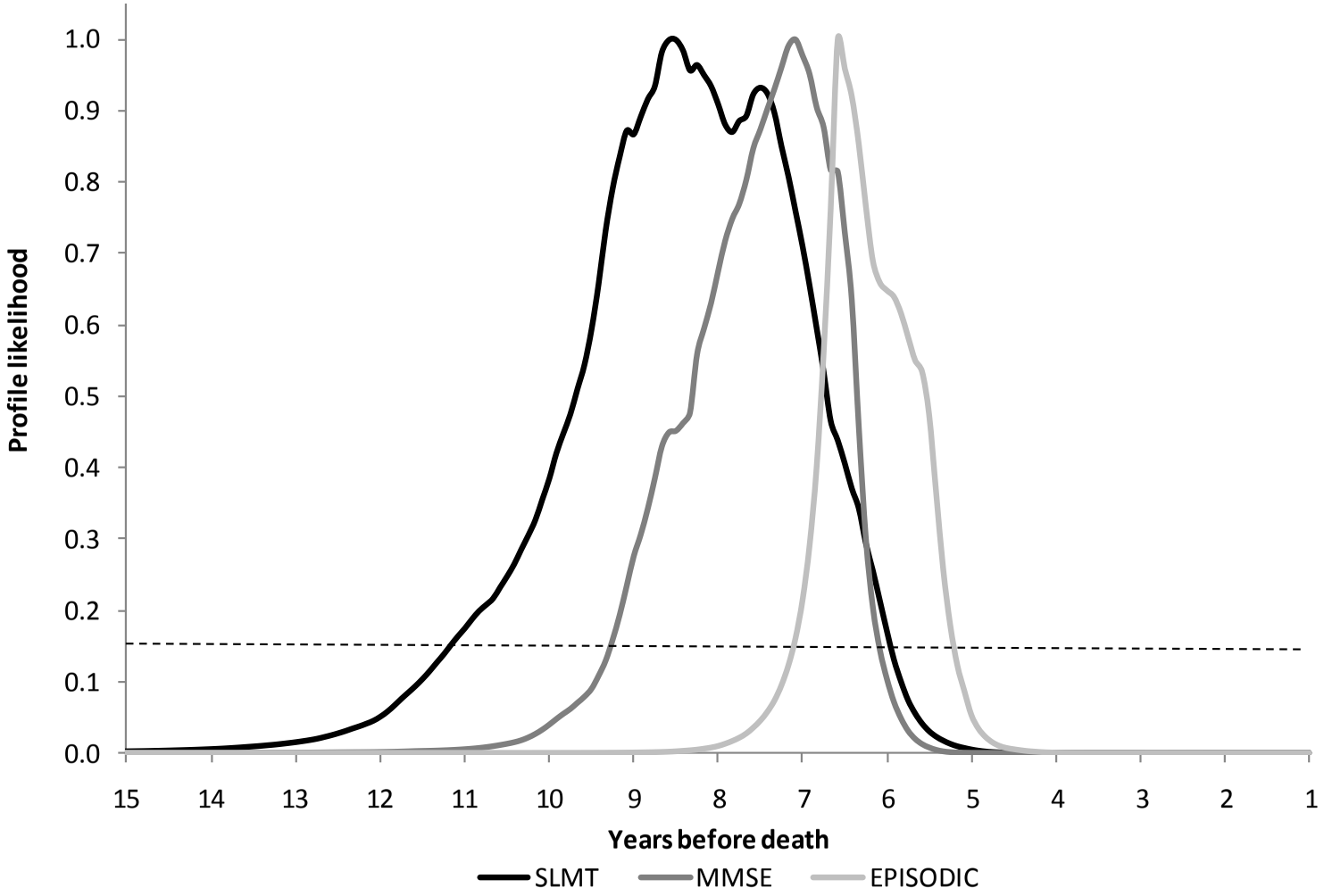

Figure 2: Profile likelihood plots for processing speed (SLMT), global function (MMSE) and episodic memory, with confidence limit indicated by dashed line

decline remained virtually unchanged when these random effects were excluded.

Rates of decline were comparable for processing speed and global function, decreasing by 0.05 standard deviations per year in the preterminal phase and around 0.1 sd per year in the terminal phase. There was slightly less decline in episodic memory: 0.02 sd per year preterminal and 0.07 sd per year terminal. However, the magnitude of terminal decline relative to preterminal decline was greater for episodic memory, with a 3.7-fold acceleration in decline over the terminal period, compared to 2.3-fold and 2.8-fold accelerations for processing speed and global function respectively. The change point models were also compared to single slope models of decline by comparing -2 log likelihood between nested models. The change point models fit significantly better than single-phase models [processing speed: χ^2 (1) = 176.4, $p < 0.0001$; global function: χ^2 (1) = 219.6, $p < 0.0001$; episodic memory: χ^2 (1) = 85.3, $p < 0.0001$].

The analyses were repeated separately for two subgroups categorized by years of education (<11 years or ≥11 years) to examine the effect of cognitive reserve. Based on profile likelihood plots, the change points and 95% confidence intervals were assessed for each of the cognitive domains, with these estimates shown in Table 4. The upper limit of the confidence interval for processing speed could not be assessed, as the profile likelihood did not asymptote to zero within the follow-up period after reaching the maximum. Regardless, the difference in the change points for the high- and low-education groups was not significant for processing speed. The change point for global function was significantly later in the low education group than the high education group, while education did not significantly alter the change point for episodic memory.

Table 3: Parameter estimates from mixed effects models of cognitive function based on preterminal and terminal decline segmented at optimal change points

Cognitive domain	Effect	Estimate	Std error	df	t/Z[1]	p
Processing speed (SLMT) (change point 8.5 yr) χ^2 (5) = 389.5, p <.0001	Intercept	102.78	0.422	442	243.4	<.0001
	Preterminal decline	-0.038	0.005	896	-7.9	<.0001
	Terminal decline	-0.086	0.006	304	-13.7	<.0001
	Random effect covariance estimates					
	β_0, β_0	*59.246*	*6.272*		*9.45*	*<.0001*
	β_1, β_0	*0.001*	*0.045*		*0.02*	*0.9826*
	β_1, β_1	*0.000*[2]	—		—	—
	β_2, β_0	*0.037*	*0.071*		*0.53*	*0.5991*
	β_2, β_1	*0.000*	*0.001*		*0.33*	*0.7421*
	β_2, β_2	*0.002*	*0.001*		*1.49*	*0.0682*
	Residual	*27.727*	*2.142*		*12.94*	*<.0001*
Global function (MMSE) (change point 7.1 yr) χ^2 (6) = 260.4, p <.0001	Intercept	102.33	0.376	322	272.0	<.0001
	Preterminal decline	-0.038	0.005	360	-7.2	<.0001
	Terminal decline	-0.106	0.010	437	-10.3	<.0001
	Random effect covariance estimates					
	β_0, β_0	*29.082*	*5.604*		*5.19*	*<.0001*
	β_1, β_0	*0.151*	*0.050*		*3.00*	*0.0027*
	β_1, β_1	*0.001*	*0.001*		*0.85*	*0.1975*
	β_2, β_0	*-0.023*	*0.122*		*-0.19*	*0.8513*
	β_2, β_1	*0.004*	*0.001*		*2.81*	*0.0049*
	β_2, β_2	*0.026*	*0.004*		*6.25*	*<.0001*
	Residual	*39.366*	*3.430*		*11.48*	*<.0001*
Episodic memory (change point 6.6 yr) χ^2 (5) = 79.4, p <.0001	Intercept	101.49	0.394	341	257.4	<.0001
	Preterminal decline	-0.016	0.005	774	-3.5	0.0005
	Terminal decline	-0.060	0.011	402	-5.3	<.0001
	Random effect covariance estimates					
	β_0, β_0	*21.205*	*5.989*		*3.54*	*0.0002*
	β_1, β_0	*0.051*	*0.042*		*1.20*	*0.2301*
	β_1, β_1	*0.000*[2]	—		—	—
	β_2, β_0	*-0.306*	*0.153*		*-2.00*	*0.0451*
	β_2, β_1	*0.001*	*0.002*		*0.47*	*0.6405*
	β_2, β_2	*0.028*	*0.006*		*4.47*	*<.0001*
	Residual	*58.153*	*4.781*		*12.16*	*<.0001*

Notes
[1] Tests of fixed effect parameters are t tests, tests of random parameter variation are Z tests.
[2] Parameter on boundary of zero, unable to be tested.

Table 4: Estimated change points (in years, with 95% confidence intervals) for segmenting preterminal and terminal decline based on cognitive function, estimated separately for each education group

	Low education (<11yr) (n=376)	High education (≥11yr) (n=520)
Processing speed (SLMT)	11.3 (4.8, >17)	7.8 (6.8, 9.3)
Global function (MMSE)	2.6 (2.1, 3.8)	8.6 (7.7, 10.1)
Episodic memory	5.5 (2.8, 8.3)	6.6 (5.5, 6.9)

Table 5: Mixed-effects models of cognitive function based on preterminal and terminal decline at the change point, estimated separately for each education group

		Low education					High education				
Cognitive domain	Effect	Estimate	SE	df	Statistic[1]	p	Estimate	SE	df	Statistic[1]	p
Processing speed (SLMT)	*Model fit (LR test)*			*6*	*120.52*	*<.0001*			*5*	*238.51*	*<.0001*
	Intercept	99.75	0.739	140	134.99	<.0001	105.32	0.486	218	216.83	<.0001
	Preterminal decline	-0.034	0.008	90	-4.12	<.0001	-0.034	0.005	254	-6.34	<.0001
	Terminal decline	-0.068	0.009	112	-7.63	<.0001	-0.103	0.008	180	-12.75	<.0001
	Random effect covariance estimates										
	β_0, β_0	*53.492*	*11.700*		*4.57*	*<.0001*	*47.765*	*7.643*		*6.25*	*<.0001*
	β_1, β_0	*-0.050*	*0.096*		*-0.52*	*0.6003*	*-0.081*	*0.058*		*-1.38*	*0.1661*
	β_1, β_1	*0.001*	*0.002*		*0.35*	*0.3621*	*0.000*[2]	—		—	—
	β_2, β_0	*0.054*	*0.109*		*0.49*	*0.6222*	*0.136*	*0.086*		*1.58*	*0.1144*
	β_2, β_1	*0.002*	*0.002*		*1.19*	*0.2338*	*0.001*	*0.001*		*0.74*	*0.4598*
	β_2, β_2	*0.001*	*0.002*		*0.7*	*0.2420*	*0.002*	*0.002*		*1.21*	*0.1139*
	Residual	*31.651*	*4.039*		*7.84*	*<.0001*	*25.012*	*2.520*		*9.93*	*<.0001*
Global function (MMSE)	*Model fit (LR test)*			*6*	*101.62*	*<.0001*			*5*	*180.86*	*<.0001*
	Intercept	99.56	0.745	162	133.71	<.0001	104.07	0.366	155	284.51	<.0001
	Preterminal decline	-0.055	0.009	129	-6.01	<.0001	-0.025	0.006	561	-4.41	<.0001
	Terminal decline	-0.224	0.078	44.9	-2.85	0.0065	-0.086	0.010	279	-8.89	<.0001
	Random effect covariance estimates										
	β_0, β_0	*63.871*	*13.025*		*4.9*	*<.0001*	*7.761*	*3.976*		*1.95*	*0.0255*
	β_1, β_0	*-0.065*	*0.141*		*-0.46*	*0.6450*	*0.133*	*0.035*		*3.74*	*0.0002*
	β_1, β_1	*0.005*	*0.002*		*2.13*	*0.0167*	*0.000*[2]	—		—	—
	β_2, β_0	*-4.265*	*1.301*		*-3.28*	*0.0010*	*0.049*	*0.081*		*0.61*	*0.5430*
	β_2, β_1	*0.031*	*0.012*		*2.55*	*0.0107*	*0.003*	*0.001*		*2.54*	*0.0111*
	β_2, β_2	*0.394*	*0.147*		*2.69*	*0.0036*	*0.018*	*0.003*		*6.23*	*<.0001*
	Residual	*47.938*	*6.684*		*7.17*	*<.0001*	*31.341*	*3.112*		*10.07*	*<.0001*
Episodic memory	*Model fit (LR test)*			*5*	*29.02*	*<.0001*			*5*	*56.9*	*<.0001*
	Intercept	99.26	0.688	198	144.37	<.0001	102.76	0.443	156	231.93	<.0001
	Preterminal decline	-0.009	0.007	246	-1.22	0.2220	-0.020	0.006	546	-3.59	0.0004
	Terminal decline	-0.069	0.025	171	-2.81	0.0056	-0.063	0.014	181	-4.58	<.0001
	Random effect covariance estimates										
	β_0, β_0	*24.235*	*9.606*		*2.52*	*0.0058*	*17.458*	*7.483*		*2.33*	*0.0098*
	β_1, β_0	*-0.048*	*0.049*		*-0.99*	*0.3237*	*0.139*	*0.054*		*2.55*	*0.0106*
	β_1, β_1	*0.000*[2]	—		—	—	*0.000*[2]	—		—	—
	β_2, β_0	*-0.468*	*0.313*		*-1.5*	*0.1341*	*-0.247*	*0.192*		*-1.29*	*0.1986*
	β_2, β_1	*0.005*	*0.003*		*1.8*	*0.0719*	*-0.001*	*0.002*		*-0.58*	*0.5607*
	β_2, β_2	*0.040*	*0.015*		*2.73*	*0.0032*	*0.031*	*0.009*		*3.52*	*0.0002*
	Residual	*78.693*	*8.560*		*9.19*	*<.0001*	*42.187*	*5.983*		*7.05*	*<.0001*

Notes

[1] Tests for model fit are χ^2 tests, fixed effect parameters are t tests, tests of random parameter variation are Z tests.

[2] Parameter on boundary of zero, unable to be tested.

Table 5 shows the parameter estimates and p-values for MMRM models at the change points identified in Table 4. The models include the likelihood ratio chi-square tests, indicating good fit, along with the fixed effects and random effects. Once again, models where random effects were close to zero were reestimated without this effect, with little change to the estimates of the fixed effects. To illustrate the models fitted, predicted cognitive scores for members of the high education group and the low education group were plotted, for age at baseline of 77.3 years and age at death of 85.3 years (corresponding to the mean values for the sample). These plots are shown in Figure 3. Steeper terminal decline in processing speed was evident in the high education group (0.12 sd per year) than the low education group (0.08 sd per year), while preterminal processing speed decline (0.04 sd per year) was similar in both groups (Figure 3a). A contrary pattern was seen in global function, where the rates of both preterminal (0.07 vs. 0.03 sd per year) and terminal decline (0.27 vs. 0.10 sd per year) were greater in the low education group than the high education group (Figure 3b). A third pattern emerged in the episodic memory measure, where those with higher education had a greater rate of preterminal decline (0.02 vs. 0.01 sd per year) but similar rate of terminal decline (0.08 sd per year for both) compared to those in the low education group (Figure 3c).

All analyses were repeated excluding 41 participants with a dementia diagnosis (n = 646). Based on the confidence intervals, the exclusion did not significantly alter the change point estimates for processing speed (7.3 years when excluding participants with dementia *versus* 8.5 years when including participants with dementia), global function (6.4 years *versus* 7.1 years) or episodic memory (6.6 years in both analyses). There was little change in the rates of preterminal decline (less than 0.004 sd per year difference on all tasks) and terminal decline (less than 0.024 sd per year) after excluding

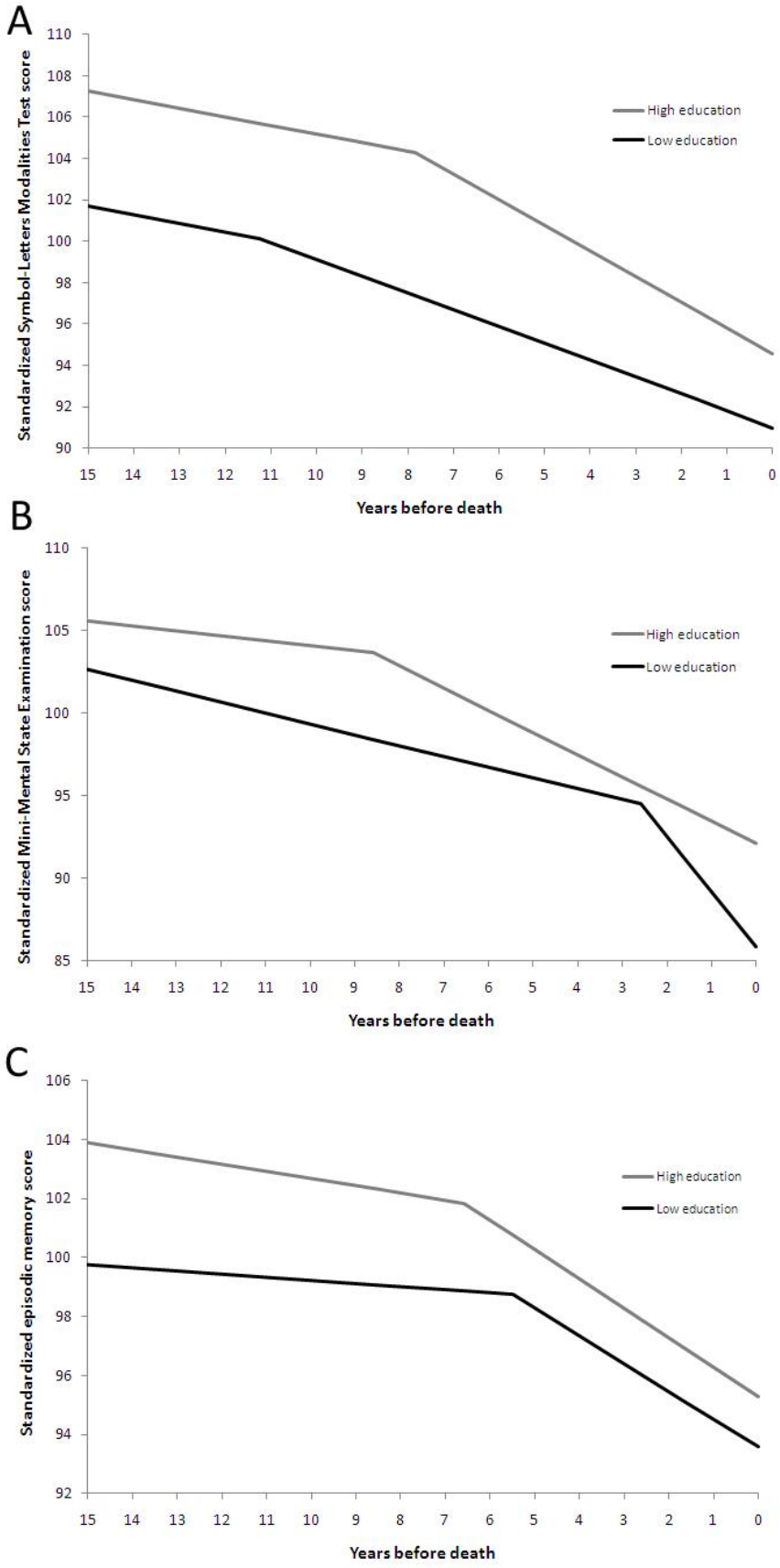

Figure 3: Predicted cognitive performance in the 15 years prior to death for prototypical participants with high or low education: (A) processing speed, (B) global function, and, (C) episodic memory

participants with dementia. For example, the largest change was in the estimate of terminal decline for MMSE, which changed from -0.106 to -0.089. The exclusion of participants with dementia also had little impact on the findings regarding the effect of education. The estimated change points varied by fewer than six months in each case. Likewise, the estimates of preterminal and terminal decline were changed little, in each case by less than 0.002 sd per year. For example, the largest change was in the terminal decline estimate for global function among the low education group, which changed from -0.086 to -0.068 after controlling for covariates.

The models for high and low education groups were also re-estimated with the inclusion of other independent risk factors for cognitive decline or mortality: gender, heart attack and hypertension history, grip strength, smoking status, functional ability, disease count and depression as covariates. Although many of these variables were significantly associated with cognitive performance, their inclusion in the models had very little impact on the estimated change points, which varied by fewer than 13 months in most cases. However, for episodic memory among the high education group, the change point was shifted from 79 to 27 months due to problems estimating the variance matrix for these models. Due to this estimation problem, models of episodic memory for the high education group were assessed at the original change point. For all of the cognitive tests, the estimates of preterminal and terminal decline were changed little by the inclusion of covariates, in each case by less than 0.002 sd per year. For example, the largest change was in the terminal decline estimate for episodic memory among the low education group, which changed from -0.069 to -0.054 after controlling for covariates.

Discussion

In a community sample of 896 adults over the age of 70, terminal decline effects were found in tasks tapping processing speed, global function and episodic memory. The onset of terminal decline was found to be around 8½ years for processing speed, 7 years for global function and 6½ years for episodic memory. Although there was less overall decline in episodic memory than in the other domains, the rate of decline in the terminal phase was increased almost fourfold compared to the preterminal phase on the episodic memory task. The ratio was 2.3 for processing speed and 2.8 for global function, suggesting that episodic memory drops later but more precipitously than these domains. While the onset of terminal decline for processing speed was not significantly later than for other domains as hypothesized, the change points for processing speed and episodic memory were similar to previous studies, particularly those of Thorvaldsson et al. (2008) and Sliwinski et al. (2006). The identified change points were earlier than those reported by Wilson et al. (2003) and Wilson et al. (2007), possibly due to the inclusion of survivors and shorter follow-up period in those studies. The rates of terminal decline were in a similar range to previous studies, while the finding of variability in both the onset and rate of terminal decline across cognitive domains (Thorvaldsson et al., 2008; Wilson et al., 2003) was also replicated.

Education changed the terminal decline effect for all three of the cognitive domains, but in different ways. The onset of decline in global function was delayed significantly for those with lower levels of education, however the rate of decline was greater in the terminal phase for the low education group. For the processing speed and episodic memory tasks, education did not significantly modify the onset of terminal decline. Rather, for processing speed, the rate of decline in the terminal phase was greater for those with higher education. For episodic memory, the rate of decline in the preterminal phase was not significantly different from zero for those with a lower level

of education, but higher in those with more education. The finding that education modifies terminal decline and that the nature of the modification varies across cognitive domains has not previously been reported. Wilson et al. (2007) found no modification by education on terminal decline. Their null finding may have resulted from using only a cognitive composite score, which could have obscured any domain-specific effects such as those identified here. The findings are also contrary to those of Hall (2007), who reported that memory decline prior to dementia diagnosis occurred later but more precipitously in participants with higher education levels.

Together, these findings suggest that terminal decline does not occur uniformly across different cognitive domains. Since the physiological basis of these forms of cognitive functioning are different, this may reflect the differential impact of particular brain or systemic disease, although the situation is likely to vary as a function of disease and individual vulnerability. For example, there is a dissociation between explicit and implicit memory performance in those with Alzheimer's Disease due to the differential affects of the disease on specific structures such as the mesial temporal lobe (Golby et al., 2005). The findings also suggest that terminal decline may reflect a diversity of physiological processes occurring in the years prior to death, including preclinical dementia (Laukka, MacDonald, & Backman, 2008), or other forms of cerebral deterioration, including stroke and cardiovascular disease (Hassing et al., 2002; Wilson et al., 2007). Such processes may affect cognitive function in different ways, such that the onset of decline may be accelerated for some tasks while the rate of decline may be increased for others.

Analyses excluding participants with a dementia diagnosis did not substantively change the outcomes. Laukka et al. (2008) proposed that terminal decline effects are largely a result of preclinical dementia, although they found selective terminal decline effects after controlling for this condition. The present study controlled only for actual

dementia cases, and found very little evidence that dementia may modify the onset and rate of terminal decline. In conjunction with similar findings by Thorvaldsson et al. (2008), it appears that the terminal decline effects cannot be fully explained by dementia. Consequently, the findings support a multifaceted model of terminal decline like the one proposed by Bäckman and MacDonald (2006), who suggest that the phenomenon is influenced by both normative age-related decline and pathological events (including dementia, cardiovascular disease and cancer), along with more distal factors such as health literacy, childhood intelligence, genes and environment.

The effect of education was contrary to what would be predicted by cognitive reserve or compensation theories of cognitive aging (Park & Reuter-Lorenz, 2009; Stern, 2002). While increased education was associated with higher initial levels of performance, it was also associated with more rapid declines in performance or earlier onset of decline. This pattern of change is not consistent with a straightforward interpretation of cognitive reserve theories which would suggest that education protects against cognitive decline either by recruiting compensatory networks or through more efficient use of existing networks (Park & Reuter-Lorenz, 2009). Other than improving initial performance, the only suggestion of a protective effect of education was seen in the global function task, where the rate of decline was lower in the group with more education. However, there was also a hastening of terminal decline on this task for those with high education, at odds with findings suggesting that cognitive reserve may delay the onset but accelerate declines that are related to pathological processes (Stern et al., 1999).

These divergent findings may be related to either the diversity of skills tested by the MMSE or its psychometric properties. The MMSE includes psychomotor, attention and recall tasks in addition to measures of orientation and registration. The earlier onset of terminal decline in global function for those with higher education may also reflect

the imperfect psychometric properties of the MMSE, specifically scaling artifacts, ceiling effects and unreliability of change scores (Hensel, Angermeyer, & Riedel-Heller, 2007). Nevertheless, the results with respect to all three cognitive domains may suggest that individuals who begin with better cognitive performance simply have more potential for decline, whereas those who initially perform poorly may not decline considerably unless significant pathology develops. There was no significant change in the onset of terminal decline in processing speed or episodic memory, and education did not slow the rate of decline in either of these domains. It could be the case that some of the biological processes associated with terminal decline are different to those associated with dementia-related cognitive decline, in that terminal decline is the response to a more diverse range of pathological events. Cognitive reserve may only buffer against specific types of brain pathology.

There are some issues in examining terminal decline that the present analysis was not able to address directly. Firstly, the present study only obtained four (or fewer) measurements, across a period of 12 years. This may have been insufficient to detect terminal decline for some of the cognitive tasks, particularly those in which there was little decline over the follow-up period. The four-year retest intervals may also have been insufficient to detect accelerated terminal decline in some domains, particularly given previous findings suggesting terminal decline may occur less than four years prior to death (Wilson et al., 2007; Wilson et al., 2003). However, the change point method estimated preterminal and terminal slopes aggregated across all participants, rather than relying on individual slope estimates. While this method of estimation may thus be robust to a paucity of data, a degree of confounding by between-person effects in the estimating the rates of decline might be expected as a consequence. However, the potential for between-person confounding was mitigated in the present study by excluding survivors (Sliwinski et al., 2006) and by the inclusion of random effect terms

for the preterminal and terminal periods in the mixed models. Further research comparing alternative methods for modeling terminal decline may determine the extent to which between-person effects might influence change point estimates. Terminal decline effects could not be reliably estimated in this cohort for tasks of verbal ability, verbal fluency, face recognition and word recognition using the change point method. Our inability to detect terminal decline on these measures may not reflect an absence of terminal decline, but a lack of power for this type of model to detect small rates of decline in this type of sample, particularly for measures which are more robust to age-related decline. Future studies studying the terminal decline phenomenon would benefit from a shorter interval between follow-up interviews and more follow-ups, although briefer retest periods or more interviews may lead to other undesirable outcomes such as increased attrition (Deeg, van Tilburg, Smit, & de Leeuw, 2002) or larger retest effects (Salthouse, Schroeder, & Ferrer, 2004).

Secondly, the analyses did not include survivors. This was because the model used was chosen to replicate that used in previous research (Sliwinski et al., 2006; Thorvaldsson et al., 2008). However, Sliwinski et al. (2006) noted that the inclusion of survivors may lead to an underestimate of the terminal decline effect. Thirdly, education was the only reliable baseline measure of cognitive reserve able to be included in the present study. Other factors that may impact reserve, such as brain atrophy and white matter hyperintensities, may provide clearer insight into the observed effects. Apolipoprotein E ε4 genotype, previously examined by Wilson et al. (2007), was only measured at the second wave of the current study, resulting in an inadequate sample size for the type of analysis used here. There were also too few cases of head injury (McMillan & Teasdale, 2007) or cognitive disorders (Wilson et al., 2007) in the present sample to examine these as separate indicators. Furthermore, the number of years of education may not a good indicator of the quality of education, which may

affect how adequately the measure reflects cognitive reserve. Fourthly, the model estimated a single change point for the whole cohort (or for each education subgroup), rather than estimating individual change points. However, Hall, Ying, Kuo, & Lipton (2003) compared the profile likelihood method used here to a Bayesian method that estimated individual change points and concluded that individual change points are not necessary to adequately model heterogeneity across subjects. Finally, change point models are not the only method that may be used to characterize terminal decline. Other methods that could be considered for future research include retrospective models that account for individual differences (Gerstorf et al., 2008) and prospective models that link individual rates of change to the hazard of mortality (Ghisletta et al., 2006).

The present study found that the onset and rate of terminal decline may be different across cognitive domains and that education can modify the onset and rate of decline. The modification of terminal decline by education is a new finding that has not previously been investigated in specific cognitive domains. These findings were not changed by excluding participants with dementia or by controlling for other risk factors for cognitive decline and mortality. As education was the only reliable baseline measure of cognitive reserve included in the present study, further research is warranted to investigate modification of terminal decline effects by other measures of reserve, such as head injury, apolipoprotein E genotype and brain characteristics including atrophy and white matter hyperintensities. Additional research into the nature of terminal decline and how this decline varies according the characteristics of individuals and their exposures will continue to illuminate the processes that lead to late-life cognitive decline.

Acknowledgements: The Canberra Longitudinal Study was supported by NHMRC Unit Grants 973301 and 933301 and NHMRC Program Grant 179805. HC is supported by NHMRC Senior Principal Research Fellowship 525411.

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Comparison of age and time-to-death in the dedifferentiation of late-life cognitive abilities

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Psychology and Aging, in press, accepted 2/2/2011.

Abstract

The dedifferentiation hypothesis proposes that specific cognitive abilities become more highly associated with general ability in old age, as a result of increasing biological constraints on fluid intelligence. There is limited evidence for the hypothesis and research has not tended to clearly distinguish age dedifferentiation from ability differentiation and other age-related phenomena. The present study examined age dedifferentiation using a structural equation model that controlled for ability differentiation, along with linear and quadratic effects of age. Time-to-death was examined as an alternative time metric to chronological age, as it may better represent biological constraints. The Canberra Longitudinal Study community-based cohort, consisting of 896 Australian adults aged 70 and over, provided data from 687 decedents who were followed for up to 17 years. Results indicated little support for the age dedifferentiation hypothesis, with only two of seven cognitive tests showing significant age dedifferentiation. The time-to-death metric showed more evidence of dedifferentiation, with four of the seven tests exhibiting dedifferentiation. However, after excluding participants with possible cognitive impairment, all of the dedifferentiation effects were attenuated to non-significance. Age dedifferentiation effects may therefore reflect dementia and other mortality-related pathology, rather than being an inevitable outcome of advanced age. Alternative developmental theories for cognitive function must better account for the diversity of late-life abilities and pathology.

The concept of a general factor of intelligence had its origins more than one hundred years ago (Spearman, 1904). Subsequent research suggested a range of specific factors of intelligence and led to the development of the theory of fluid and crystallized intelligence by Horn and Cattell (Cattell, 1941; Horn, 1968; Horn & Cattell, 1966). The fluid-crystallized theory suggests that there are two higher order factors of intelligence that form distinct dimensions: fluid intelligence, general ability derived from basic neural and sensory structures, and crystallized intelligence, knowledge-based ability derived from experience, education and acculturation (Horn & Cattell, 1966). Cattell's investment theory (Cattell, 1971, 1987) extended the fluid-crystallized theory into a developmental framework. According to the investment theory, the fluid component of intelligence develops rapidly through childhood and adolescence, peaking in the early twenties, then decreasing through adulthood, more rapidly in old age. The crystallized component grows incrementally, driven by fluid ability, peaks in mid-life and declines very little and only in late old age (Cattell, 1987). However, there has been little evidence to support the theory that fluid intelligence drives the development of crystallized intelligence, with more recent longitudinal research reporting that higher levels of fluid intelligence are not associated with subsequent increased growth in crystallized intelligence (Ferrer & McArdle, 2004). Nevertheless, research examining performance on fluid and crystallized tasks across the lifespan (Li et al., 2004; McArdle, Ferrer-Caja, Hamagami, & Woodcock, 2002; Tucker-Drob, 2009) has replicated the patterns of development and decline for fluid and crystallized ability reported by Cattell (1987). So while the investment theory may not accurately explain the processes behind the development of intelligence, the patterns of development and decline reported by Cattell (1987) have been supported.

Alternative explanations have been provided for individual differences in developmental patterns of cognitive performance. The observation that a general factor

of intelligence accounts for a greater amount of variability in children and the elderly compared to adults (Balinsky, 1941; Garrett, 1946) led to the development of the differentiation-dedifferentiation hypothesis (Baltes et al., 1980; Reinert, 1970), which suggests that intellectual abilities are unspecialized in childhood, differentiate during maturation and become undifferentiated in late life (Li et al., 2004). Contributions from the environment and non-cognitive influences, such as motivation and interest, are postulated to engender differentiation (Tucker-Drob, 2009). Late-life dedifferentiation is hypothesized to occur when, as a result of increasing biological constraints on information processing mechanisms, declines in fluid abilities limit subsequent development in crystallized abilities (Li et al., 2004). The cognitive processes involved with fluid and crystallized abilities consequently become more strongly coupled together (Li et al., 2004), such that general ability accounts for a greater proportion of performance across domains.

These constraints on information processing have been linked to decreased neurobiological efficiency (Li, Lindenberger, & Sikstrom, 2001; Li & Sikstrom, 2002; Park et al., 2002). Changes in neuromodulation and neuroanatomy result in decreasing differentiation between the patterns of neuronal representations elicited by different stimuli as people age (Li & Sikstrom, 2002). This neurocomputational model of cognitive aging posits that deficits in neuromodulation lead to increased neural noise, resulting in less distinctive cortical representations in the aging brain, and finally to cognitive aging deficits, which manifest as decreases in performance, increases in variability and increased relationships among cognitive abilities (Li et al., 2001). The relationship between neuronal dedifferentiation and cognitive dedifferentiation is purported to be based on the need for some form of compensatory neural recruitment in older adults (Park et al., 2002) as the cortical representations become less distinctive. On a neuroanatomical level, this compensation could come from contralateral

recruitment of a homologous brain area, from unique recruitment of nonhomologous sites or from substitution of brain areas (Park et al., 2002). In cognitive terms, abilities may be seen as hierarchical (Vernon, 1971), with an overall general factor of ability which comprises several broad ability factors, which can themselves be further deconstructed into specific abilities. When neuronal compensation is required in response to neuronal deficits, greater reliance may be given to broader abilities such as processing speed, retrieval and fluid and crystallized intelligence, rather than specific abilities. Recruitment of these higher order abilities to perform lower order tasks leads to declines in performance, increases in variability and, in particular, dedifferentiation of cognitive abilities.

There has, however, been mixed evidence for the late-life dedifferentiation of cognitive abilities. Several studies have reported late-life increases in the correlation between cognitive abilities (Baltes & Lindenberger, 1997; Ghisletta & Lindenberger, 2003; Li et al., 2004) while other studies have found no systematic relationship (Anstey et al., 2003; Juan-Espinosa et al., 2002; Sims et al., 2009; Tucker-Drob & Salthouse, 2008; Zelinski & Lewis, 2003). De Frias, Lovden, Lindenberger, & Nilsson (2007) found evidence for dynamic dedifferentiation beginning in old age, suggesting that common sources increasingly account for the development of abilities. Likewise, Ghisletta and colleagues (Ghisletta & de Ribaupierre, 2005; Ghisletta & Lindenberger, 2003) found longitudinal age-associated dedifferentiation, reporting that the dedifferentiation was a consequence of the constraints of mechanic ability, a notion similar to fluid intelligence.

Recently, Tucker-Drob (2009) used a statistical model able to distinguish the effects of ability differentiation from age dedifferentiation, and found no support for age dedifferentiation in a lifespan cohort. In examining the age dedifferentiation hypothesis, it is important to rule out confounding by ability differentiation, which is

defined as differences in the correlations between cognitive abilities at different ability levels, with stronger correlations often observed among groups with lower ability levels (Deary et al., 1996; Tucker-Drob, 2009). Specifically, unless ability differentiation is accounted for, any age-based dedifferentiation effect may simply reflect the poorer performance among older individuals. Other sources of individual differences should also be accounted for in examining the dedifferentiation hypothesis, to exclude more parsimonious explanations for the phenomenon and determining whether dedifferentiation is an independent phenomenon of aging. Non-normative sources of heterogeneity, particularly the influences of preclinical dementia (Sliwinski, Hofer, & Hall, 2003), should be examined to determine whether dedifferentiation is an inevitable consequence of normative aging or simply a reflection of pathological decline.

To date, research on dedifferentiation has used chronological age as the metric of time. However, ability differentiation may vary widely across individuals of the same age, depending on their lifetime accumulation of biological damage and resulting cognitive health (Lovden et al., 2005; Sliwinski, Hofer, & Hall, 2003). To observe the effects of dedifferentiation in a heterogeneous cohort, time-to-death may be a better metric for age, as it is a strong indicator of declines in both physical health and cognitive performance (Batterham et al., 2009; Hassing et al., 2002; Small & Backman, 1999). For example, while two 80-year-olds may differ markedly in their health and cognitive performance, less average variation may be expected in two individuals that are one year from death. Dedifferentiation occurring as a function of proximity to death would provide evidence that dedifferentiation occurs in response to late-life pathology, particularly if the amount of dedifferentiation is greater than when modeling as a function of age. If there was more evidence for dedifferentiation as a function of age than time to death, it may be concluded that dedifferentiation was not directly indicative of pathology.

The present study aimed to compare the two time metrics, chronological age and time to death, in modeling the degree to which dedifferentiation may be observed in late life. It was hypothesized that time to death would be a be a more sensitive metric for observing dedifferentiation than age. This hypothesis was tested with the statistical model used by Tucker-Drob (2009) that can account for non-linear relationships between cognitive measures and factors while controlling for any effects of ability differentiation. It is important that non-linear relationships can be accounted for, as the predictions of the hypothesis are inherently non-linear across the life span. Tucker-Drob's (2009) model simultaneously estimates the effects of age dedifferentiation and ability differentiation, in addition to age, age^2, the general ability factor (*G*), and the interaction between age dedifferentiation and ability differentiation. Age dedifferentiation is operationalized as the interaction between age and the general ability factor, that is, how the amount of variability accounted for by the general factor changes as a function of age. Ability dedifferentiation is defined in the model as G^2, which reflects how the amount of variability accounted for by the general factor changes as a function of the level of performance on that factor. As previous research has shown some evidence that age may modify ability differentiation (Facon, 2006; Tucker-Drob, 2009), the interaction between age dedifferentiation and ability differentiation was also included in the model. This is defined as the interaction between age and G^2, that is, how the amount of variability explained by the general factor as a function of overall performance changes in response to age.

Re-estimation of the model using time-to-death in place of age enabled a comparison of the two time metrics. It was hypothesized that a greater degree of dedifferentiation would be observed when using time to death as the time metric rather than age. Such an outcome would suggest that dedifferentiation is due to increasing pathology in proximity to death rather than being due to age-related developmental

changes. Likewise, exclusion of participants with possible cognitive impairment was hypothesized to attenuate any observed dedifferentiation due to age or proximity to death.

Method

Sample

The Canberra Longitudinal Study is an epidemiological survey of mental health and cognitive functioning in older people that commenced in 1990. The study design has previously been detailed by Christensen et al. (2004). Eight hundred and ninety-six community-dwelling adults aged 70-97, living in the cities of Canberra and Queanbeyan, Australia, participated in the baseline assessment. The sample was stratified by age and gender. Participants were sampled from the compulsory electoral roll, with 69% responding. For the present study, only participants who had died at the end of the vital status collection period (June 2007) were included in the analysis (n = 687, 76.7%), as time-to-death cannot be assessed for survivors.

Procedure

Participants were interviewed up to four times over 12 years, although only the baseline assesssment was used in the present analysis. Baseline interviews lasted approximately two hours, incorporating a survey with a wide range of measures including socio-demographics, physical health and disease status, mental health status and cognitive performance. Interviews also included physical assessments of blood pressure, lung function, grip strength, vision and reaction time. Trained professional interviewers conducted the assessments. Approval for the research was obtained from the Ethics in Human Experimentation Committee of The Australian National University.

Measures

Tests assessing a variety of cognitive domains were administered to assess the cognitive functioning of study participants. *Speed of processing* was measured by the Symbol-Letters Modalities Test (SLMT), a task similar to Smith's (1973) Symbol-Digit Modalities Test and Wechsler's (1981) Digit-Symbol Substitution. *Verbal ability* was measured using the National Adult Reading Test, a test of vocabulary (Nelson, 1982). An *episodic memory* task consisted of brief episodic memory tasks testing word, face, name and address recall and figure reproduction (Jorm, 1992). *Verbal fluency* was assessed as the number of animals named in 30 seconds. *Face and word recognition* tasks were based on the Rivermead Behavioural Memory Test (Wilson et al., 1989). *Global function* was tested using the Mini-Mental State Examination (MMSE) (Folstein, Folstein, & McHugh, 1975), scored out of 30. For the factor analysis and to facilitate comparisons across tests, all of the tests were standardized to a common metric, with a mean of 100 and standard deviation of 10 at the baseline measurement.

Mortality status and date of death were established by searching the National Death Index, contacting relatives and from death notices in the local newspaper. The National Death Index is a register of all deaths in Australia. The additional methods used for death reporting were included to provide added confidence in the mortality status data. Mortality status was followed for up to 17 years, from the start of baseline interviews in September, 1990 until June 30, 2007. For six participants with unknown day of death, the day was set to the 15th of the month. For two participants with an unknown month of death, the month was set to June. *Date of birth (age)* was reported during the initial interview.

Analysis

The model detailed by Tucker-Drob (2009) was adopted for the analyses. The model is a structural equation model that combines a nonlinear factor analysis to

estimate the general ability factor with a regression that tests the effects of age dedifferentiation and ability differentiation. The regression component uses each of the cognitive tests as dependent variables, estimating the effects of general ability (*G*, a latent variable based on the seven cognitive test scores), age [or time-to-death (TTD)], age^2 (or TTD^2), ability differentiation, age/TTD dedifferentiation, and the interaction between ability differentiation and age/TTD dedifferentiation. The age-based model may be written as:

$$g\,[x]_n = \nu\,[x] + \alpha_1[x] \times age_n + \alpha_2[x] \times age^2_n + \lambda_1[x] \times G_n + \lambda_2[x] \times G^2_n + \lambda_3[x] \times age_n \times G_n + \lambda_4[x] \times age_n \times G^2_n + u[x]_n$$

where g [*x*] represents the matrix of *n* specific cognitive abilities that were assessed, the *n* subscript indicates terms that vary, ν [*x*] represents the intercepts for each ability, $\alpha_1[x]$ and $\alpha_2[x]$ are the coefficients for age and age^2, G is general ability, $\lambda_1[x]$ are the loadings of each specfic ability on G, $\lambda_2[x]$ is the coefficient representing ability differentiation (G^2), $\lambda_3[x]$ is the coefficient for age differentiation (G × age), $\lambda_4[x]$ represents the degree to which age modifies ability differentiation (G^2 × age) and u[x] is the error term that represents the component of each broad ability not accounted for by the other terms in the model (Tucker-Drob, 2009). The time-to-death model simply replaced age with TTD. Age was centered by subtracting 70 years from chronological age (range: 0 – 27.5 years), while time to death was measured in years (range: 0 – 16.75 years), and both measures were converted to decades to enable interpretation of small estimates of the squared components. The model was estimated using seven cognitive tests to examine a range of cognitive domains. A criterion for significance of $p < .01$ was used for all analyses to adjust for the multiple comparisons across the seven cognitive tests. Finally, to examine whether dedifferentiation effects were attributable

to dementia, models were re-estimated excluding participants with MMSE scores < 24, as this criterion is a conservative indicator for cognitive impairment reflecting dementia (Folstein et al., 1975). All analyses were conducted in Mplus version 6.

Results

Sample characteristics for the analysis sample (n = 687) are shown in Table 1. Compared to participants who were excluded on the bases of survival or missing baseline data, the participants included in the analysis were significantly older (t_{894} = -8.58, p < .0001), were more likely to be male [χ^2 (1) = 13.6, p = .0002], and performed more poorly on all of the cognitive tasks, including processing speed (t_{851} = 7.52, p < .0001), vocabulary (t_{833} = 2.32, p = .0204), global cognition (t_{877} = 4.54, p < .0001), verbal fluency (t_{881} = 3.75, p = .0002), word recognition (t_{865} = 3.79, p = .0002), face recognition (t_{871} = 3.15, p = .0017), and episodic memory (t_{894} = 3.15, p = .0017) at baseline. There were, however, no significant differences in years of education (t_{892} = -1.18, p = .24) or marital status [χ^2 (3) = 5.3, p = .15]. The participants in the analysis sample were, on average, fairly well-educated and cognitively intact.

The two models testing age and time-to-death dedifferentiation are shown in Table 2. The first column of values is the estimate of the intercept for each of the cognitive tests at age 70 (or at death for the TTD model) for a participant with general ability score of zero (i.e., mean level of general ability), with each cognitive test score standardized to mean=100 and sd=10. The second column is the effect per decade of age (or per decade closer to death), while the third column is the quadratic effect per decade of age (or per decade closer to death). The fourth column is the effect of general ability, which would be expected to reflect ability on each of the tests. The fifth column is the effect of ability differentiation, where negative values indicate that *G* accounts for less of the variability in performance at higher levels of performance. The sixth column

Table 1: Descriptive statistics for the analysis sample at baseline (n = 687)

	Mean or *frequency*	SD or *percent*
Gender = male	*373*	*54.3%*
Marital status = Married	*366*	*53.3%*
Widowed	*261*	*38.0%*
Age	77.30	5.09
Years of education	11.41	2.66
Processing speed (SLMT)	93.91	16.97
Vocabulary (NART)	111.32	10.08
Global cognition (MMSE)	27.07	2.98
Verbal fluency	10.52	3.43
Word recognition	0.94	0.09
Face recognition	0.78	0.11
Episodic memory task	13.16	2.48

SLMT: Symbol-Letters Modalities Test; NART: National Adult Reading Test; MMSE: Mini-Mental State Examination

Table 2: Parameter estimates (99% confidence intervals) from the models of performance on the seven cognitive tasks based on age and time-to-death (n= 687)

	Intercept	Age/TTD	Age^2/TTD^2	*G*	Ability differentiation	Age/TTD differentiation	Ability×Age/TTD differentiation
Age model							
Processing speed	**104.80 (102.29, 107.30)**	**-1.017 (-1.558, -0.476)**	0.022 (-0.004, 0.048)	**6.903 (5.151, 8.655)**	-0.762 (-1.836, 0.312)	0.009 (-0.197, 0.215)	0.067 (-0.044, 0.178)
Vocabulary	**101.11 (98.12, 104.10)**	-0.432 (-1.035, 0.171)	0.020 (-0.008, 0.048)	**7.505 (5.885, 9.125)**	-0.224 (-1.844, 1.396)	-0.012 (-0.192, 0.168)	-0.001 (-0.163, 0.161)
Global cognition	**103.80 (101.79, 105.81)**	-0.093 (-0.539, 0.353)	-0.004 (-0.030, 0.022)	**4.063 (2.505, 5.621)**	**-1.647 (-3.041, -0.253)**	**0.348 (0.137, 0.559)**	**-0.240 (-0.425, -0.055)**
Verbal fluency	**104.58 (102.54, 106.61)**	-0.555 (-1.142, 0.032)	0.013 (-0.015, 0.041)	**6.202 (3.814, 8.590)**	0.760 (-0.919, 2.439)	-0.058 (-0.300, 0.184)	-0.074 (-0.239, 0.091)
Word recognition	**103.04 (100.30, 105.77)**	-0.189 (-0.738, 0.360)	-0.011 (-0.042, 0.020)	**3.979 (2.045, 5.913)**	**-3.320 (-5.115, -1.525)**	0.204 (-0.015, 0.423)	0.029 (-0.190, 0.248)
Face recognition	**102.35 (99.50, 105.20)**	-0.198 (-0.801, 0.405)	-0.008 (-0.039, 0.023)	1.567 (-0.532, 3.666)	-1.386 (-3.645, 0.873)	0.136 (-0.137, 0.409)	-0.006 (-0.258, 0.246)
Episodic memory	**103.99 (101.73, 106.26)**	-0.485 (-1.003, 0.033)	0.011 (-0.017, 0.039)	**4.094 (2.559, 5.629)**	**-1.710 (-3.204, -0.216)**	**0.287 (0.084, 0.490)**	0.003 (-0.262, 0.268)
TTD model							
Processing speed	**94.79 (91.48, 98.10)**	0.339 (-0.449, 1.127)	0.016 (-0.028, 0.060)	**8.202 (6.487, 9.917)**	0.572 (-0.567, 1.711)	-0.149 (-0.347, 0.049)	-0.091 (-0.248, 0.066)
Vocabulary	**97.32 (94.01, 100.63)**	0.141 (-0.683, 0.965)	0.015 (-0.031, 0.061)	**6.985 (5.166, 8.804)**	0.655 (-0.764, 2.074)	0.030 (-0.179, 0.239)	-0.135 (-0.313, 0.043)
Global cognition	**99.49 (96.62, 102.35)**	0.412 (-0.224, 1.048)	0.001 (-0.030, 0.032)	**10.316 (7.843, 12.789)**	**-3.840 (-5.244, -2.436)**	**-0.470 (-0.728, -0.212)**	0.040 (-0.171, 0.251)
Verbal fluency	**100.56 (97.81, 103.31)**	-0.087 (-0.999, 0.825)	0.032 (-0.020, 0.084)	**6.025 (3.689, 8.361)**	-0.203 (-1.700, 1.294)	-0.046 (-0.381, 0.289)	0.069 (-0.199, 0.337)
Word recognition	**99.50 (95.60, 103.41)**	-0.157 (-0.829, 0.515)	0.031 (-0.008, 0.070)	**8.040 (5.657, 10.423)**	**-3.143 (-4.943, -1.343)**	**-0.324 (-0.569, -0.079)**	0.059 (-0.183, 0.301)
Face recognition	**97.25 (94.01, 100.48)**	-0.096 (-1.016, 0.824)	0.024 (-0.028, 0.076)	**4.955 (2.521, 7.389)**	-1.409 (-3.194, 0.376)	**-0.293 (-0.553, -0.033)**	0.023 (-0.180, 0.226)
Episodic memory	**98.57 (95.05, 102.09)**	0.222 (-0.512, 0.956)	0.007 (-0.032, 0.046)	**9.335 (7.176, 11.494)**	**-1.697 (-3.338, -0.056)**	**-0.397 (-0.616, -0.178)**	0.035 (-0.145, 0.215)

Bold *values indicate $p < 0.01$; TTD: time-to-death; G: general ability factor*

is the effect of age/TTD differentiation, where positive values in the age model indicate that *G* accounts for more of the variability across cognitive domains as age increases (i.e., age dedifferentiation), whereas negative values in the TTD model indicate that *G* accounts for more of the variability across cognitive domains as time to death decreases (i.e., TTD dedifferentiation). The final column is the interaction between age/TTD differentiation and ability differentiation, where negative values in the age model or positive values in the TTD model indicate that age/TTD dedifferentiation decreases at higher ability levels.

The effect of primary interest was that of age/TTD dedifferentiation. In the age-based model, significant age dedifferentiation was observed only for global cognition and episodic memory, suggesting *G* accounted for larger amounts of variance on these two tasks at older age, independent of ability. In the time-to-death model, significant TTD dedifferentiation was observed in four of the seven domains, with *G* accounting for more of the variance in global cognition, word recognition, face recognition and episodic memory performance as death approached. In addition, significant ability differentiation was observed for global cognition, word recognition and episodic memory in both models, suggesting that *G* accounted for more of the variance on these tasks in those with poorer general ability. There was also a significant interaction between age dedifferentiation and ability differentiation on global cognition, suggesting that the effect of age dedifferentiation is decreased at higher levels of performance. There was no significant effect of TTD or TTD^2 on any of the tests, while processing speed performance decreased significantly by 0.1 sd per decade of age. Not surprisingly, general ability (*G*) had strong positive associations with all of the cognitive tests, although the effect did not reach significance ($p = .055$) for face recognition in the age-based model.

Table 3: Parameter estimates (99% confidence intervals) from the models of performance on the seven cognitive tasks based on age and time-to-death, excluding participants with MMSE < 24 (n=606)

	Intercept	Age/TTD	Age^2/TTD^2	*G*	Ability differentiation	Age/TTD differentiation	Ability×Age/TTD differentiation
Age model							
Processing speed	**105.72 (102.23, 109.21)**	**-0.951 (-1.577, -0.325)**	0.011 (-0.025, 0.047)	**6.320 (4.020, 8.620)**	-1.451 (-5.495, 2.593)	-0.063 (-0.277, 0.151)	0.240 (-0.054, 0.534)
Vocabulary	**101.72 (96.16, 107.28)**	-0.266 (-0.918, 0.386)	0.010 (-0.023, 0.043)	**6.946 (3.433, 10.459)**	-0.664 (-6.990, 5.662)	-0.128 (-0.331, 0.075)	0.095 (-0.281, 0.471)
Global cognition	**103.26 (101.07, 105.44)**	-0.004 (-0.375, 0.367)	-0.012 (-0.033, 0.009)	**2.971 (1.505, 4.437)**	-0.817 (-2.996, 1.362)	0.037 (-0.066, 0.140)	0.059 (-0.083, 0.201)
Verbal fluency	**104.66 (98.59, 110.74)**	-0.509 (-1.130, 0.112)	0.015 (-0.013, 0.043)	**6.018 (3.651, 8.385)**	1.528 (-0.319, 3.375)	-0.135 (-0.372, 0.102)	-0.102 (-0.249, 0.045)
Word recognition	**102.83 (99.56, 106.10)**	-0.112 (-0.877, 0.653)	-0.006 (-0.042, 0.030)	**3.040 (1.443, 4.637)**	-2.175 (-6.966, 2.616)	0.132 (-0.136, 0.400)	-0.032 (-0.279, 0.215)
Face recognition	**102.14 (98.99, 105.28)**	-0.293 (-1.022, 0.436)	-0.003 (-0.039, 0.033)	0.702 (-1.194, 2.598)	-0.385 (-2.654, 1.884)	0.113 (-0.165, 0.391)	0.043 (-0.284, 0.370)
Episodic memory	**103.87 (100.80, 106.94)**	-0.157 (-0.628, 0.314)	-0.007 (-0.035, 0.021)	**4.002 (0.643, 7.361)**	-2.184 (-5.847, 1.479)	0.046 (-0.178, 0.270)	0.125 (-0.117, 0.367)
TTD model							
Processing speed	**96.68 (92.74, 100.62)**	0.065 (-0.757, 0.887)	0.032 (-0.017, 0.081)	**6.201 (4.279, 8.123)**	1.743 (-1.629, 5.115)	-0.043 (-0.280, 0.194)	-0.198 (-0.414, 0.018)
Vocabulary	**99.27 (95.16, 103.38)**	-0.065 (-0.892, 0.762)	0.026 (-0.026, 0.078)	**5.197 (3.160, 7.234)**	1.222 (-2.572, 5.016)	0.092 (-0.184, 0.368)	-0.191 (-0.361, -0.021)
Global cognition	**100.94 (98.41, 103.47)**	-0.025 (-0.486, 0.436)	0.020 (-0.008, 0.048)	**4.434 (3.362, 5.506)**	0.112 (-1.598, 1.822)	-0.147 (-0.294, 0.000)	-0.074 (-0.182, 0.034)
Verbal fluency	**102.53 (99.68, 105.38)**	-0.265 (-1.092, 0.562)	0.036 (-0.016, 0.088)	**4.198 (1.906, 6.490)**	0.225 (-2.619, 3.069)	0.104 (-0.156, 0.364)	0.069 (-0.209, 0.347)
Word recognition	**99.57 (94.81, 104.33)**	-0.005 (-0.639, 0.629)	0.008 (-0.028, 0.044)	**6.588 (1.854, 11.322)**	-3.760 (-9.434, 1.914)	-0.320 (-0.642, 0.002)	0.189 (-0.099, 0.477)
Face recognition	**98.71 (95.36, 102.06)**	-0.204 (-1.165, 0.757)	0.031 (-0.023, 0.085)	**2.836 (0.332, 5.340)**	0.576 (-3.095, 4.247)	-0.154 (-0.430, 0.122)	-0.090 (-0.505, 0.325)
Episodic memory	**101.44 (96.94, 105.94)**	-0.041 (-0.662, 0.580)	0.014 (-0.022, 0.050)	**5.863 (3.638, 8.088)**	-1.582 (-5.147, 1.983)	-0.188 (-0.389, 0.013)	0.032 (-0.133, 0.197)

Bold *values indicate p < 0.01; TTD: time-to-death; G: general ability factor*

The fit of the models presented in Table 1 was tested by repeatedly excluding single cognitive tests from the models. For example, the -2 log likelihood of the age-based model increased from 44920.2 to 45029.0 [χ^2 *(6)* = 108.8, $p < .0001$] after excluding face recognition, indicating that the model fit was significantly better when face recognition was included. Exclusion of each of the cognitive tests significantly decreased the fit of both the age model [χ^2 *(6)* range 108.8 to 759.1, $p < .0001$] and the time-to-death model [χ^2 *(6)* range 105.4 to 767.3, $p < .0001$]. Consequently, all of the cognitive tests were retained in the models.

In a further analysis to examine whether the observed dedifferentiation effects were attributable to dementia, the models in Table 2 were estimated with the exclusion of participants who scored <24 on the MMSE [n = 606, 81 (11.8%) excluded]. These models are shown in Table 3. All of the age dedifferentiation, TTD dedifferentiation and ability differentiation effects became non-significant after this exclusion.

Discussion

Significant age dedifferentiation was observed on two of the seven cognitive tests, global cognition and episodic memory, while significant time-to-death (TTD) dedifferentiation was observed on four of the tests: global cognition, word recognition, face recognition and episodic memory. This is the first study to examine dedifferentiation as a function of time-to-death. As the effects of TTD dedifferentiation were more consistent than the effects of age dedifferentiation, any strengthening in the relationship between general and specific abilities as a function of advancing age appears to be attributable to increasing pathology in proximity to death. This finding was as predicted and likely reflects the closer relationship of pathology with time-to-death than chronological age (B. Johansson et al., 2004; Kerber, Whitman, Brown, & Baloh, 2006; Sliwinski, Hofer, & Hall, 2003). However, after excluding participants

with possible cognitive impairment, nearly all of the age/TTD dedifferentiation effects were markedly attenuated and all became non-significant. Consequently, the effects were not sufficiently robust to support the theory of age dedifferentiation. The findings suggest that brain pathology, both as a result of dementia and mortality-related biological events, are likely to play a significant role in any late-life dedifferentiation of cognitive abilities. Dedifferentiation was not found to be an inevitable consequence of aging.

Memory was found to be the primary domain of functioning where some evidence of dedifferentiation was observed, with episodic memory, face recognition and word recognition all showing dedifferentiation in proximity to death. As dementia results in a broad range of memory declines (Spaan, Raaijmakers, & Jonker, 2003), it is perhaps not surprising that the observed effects disappeared after accounting for cognitive impairment. Likewise, the global cognition measure, the MMSE, is sensitive to dementia (Mitchell, 2009) and showed dedifferentiation as a function of both age and time-to-death. The MMSE includes a memory component, with the recall items being the most difficult for people with dementia (Teng, Chui, Schneider, & Metzger, 1987). Processing speed also declines as a result of aging, however, decrements in processing speed are observed in the absence of pathological aging processes. The lack of dedifferentiation in processing speed is therefore further evidence that dedifferentiation is a product of pathological rather than normative aging. Verbal performance (verbal fluency, vocabulary) is generally robust to the normative and pathological effects of aging, so it is not surprising that no dedifferentiation was observed on the verbal tasks.

The absence of robust age dedifferentiation effects was in line with a growing body of research in this area (for example, Anstey et al., 2003; Tucker-Drob, 2009; Tucker-Drob & Salthouse, 2008; Zelinski & Lewis, 2003). Age related dedifferentiation is proposed to be the result of common or normative constraints on

functioning in late adulthood (Li & Lindenberger, 1999). It may be that in community-based cohorts which vary widely in both ability and pathology, age-related effects are so diverse that they cannot be classified as "common". While age dedifferentiation may be observed in certain cohorts and on specific measures, alternative developmental models for late-life cognition should be explored. Such models need to better account for multiple trajectories that occur in response to both normative aging and the range of pathologies that occur in late life. Furthermore, the lack of evidence for age dedifferentiation suggests that the decline of abilities in old age is not as analogous to the development of abilities in childhood as suggested by the differentiation-dedifferentiation hypothesis.

The results also provide little evidence for a relationship between neurobiological dedifferentiation and cognitive dedifferentiation. Park et al. (2002) suggest that while there are few changes in the structure of working memory across the lifespan, changes in processing speed may be broadly implicated in a range of cognitive abilities. This explanation for how neuronal compensation may lead to changes in the relationship between cognitive abilities is based on the common cause theory of aging (Salthouse, 1996). However, processing speed would appear to have less association with the tasks that showed any evidence of age dedifferentiation in the present study, particularly face recognition, word recognition and global function, than on tasks that showed no evidence of dedifferentiation, particularly speeded tasks such as verbal fluency. Thus it would seem that the patterns of relationships observed show little evidence of the recruitment of higher order abilities, such as processing speed, to perform lower order tasks. It could be argued that higher order retrieval processes may be implicated in the observed dedifferentiation effects, which tended to be related to memory. However, these effects do not appear to be the result of normative aging processes in the present cohort. Rather, such higher order recruitment may only be

occurring in response to pathological processes, most likely the effects of preclinical dementia. The critical link between less distinctive cortical representations in the aging brain and increased relationships among cognitive abilities proposed by Li et al. (2001) could not be supported by the present study.

There were some limitations to the present study. The cognitive measures used were selected at the beginning of the study, 20 years ago. Alternative measures covering a wider range of cognitive domains might provide further insight into the phenomena of interest. The use of single cognitive tests to measure each domain of ability also precludes assessing the common variance across multiple tests of the same ability, which may make it harder to detect dedifferentiation effects. However, it is generally not feasible to repeatedly administer a large battery of cognitive tests to a large community-based sample that is retested every four years. There are few community-based studies that have the breadth of data of the Canberra Longitudinal Study. Nevertheless, other study designs may be better able to account for a wider range of abilities and assess each ability using multiple tests. Secondly, only cross-sectional cognitive information was used in the present analysis. The complexity of the structural equation model used for this analysis precluded adaption to a longitudinal analysis. Other methods for longitudinal examination of dedifferentiation may reveal more about the phenomenon by examining within-individual patterns of change in the relationship between abilities (Anstey et al., 2003; Sliwinski, Hofer, Hall, Buschke & Lipton, 2003; Zelinski & Lewis, 2003). Other types of analyses that account for intraindividual change may also provide greater insight into relationships between terminal decline and dedifferentiation. However, the current cross-sectional analysis was sufficient to show that the dedifferentiation effects were not robust when dementia was excluded. Finally, while the role of background factors such as gender, education, social support and mental health may be investigated in relation to dedifferentiation, the

lack of evidence for age dedifferentiation in the present study rendered any such investigation largely unnecessary.

In conclusion, little support was found for the age dedifferentiation hypothesis in the present study, and dedifferentiation was found to result from dementia and terminal pathology rather than being an inevitable outcome of advanced age. The lack of robust age dedifferentiation effects is in line with the findings of Tucker-Drob (2009) who accounted for ability differentiation using a similar method. The necessity to use models that account for confounding by ability dedifferentiation remains clear. Further research should examine the conditions that are associated with the emergence of age-associated dedifferentiation effects, particularly examining whether such effects are associated with subsequent conversion to dementia. Examining the range of individual late-life cognitive trajectories (Lovden et al., 2005) or explicitly decomposing cognitive performance as a function of preclinical dementia, study attrition, terminal decline and chronological age (Sliwinski, Hofer et al., 2003) may enable further exploration of the role of pathology in dedifferentiation. The present findings with respect to dedifferentiation as a function time-to-death are novel, and suggest that dedifferentiation is not a phenomenon that results from normative aging.

Acknowledgements: The Canberra Longitudinal Study was supported by NHMRC Unit Grants 973301 and 933301 and NHMRC Program Grant 179805. HC is supported by NHMRC Senior Principal Research Fellowship 525411.

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Mental health symptoms associated with morbidity, not mortality, in an elderly community sample

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Social Psychiatry and Psychiatric Epidemiology, in press, accepted 15/10/2010.

Abstract

Purpose: Six previous reviews have found a relationship between depression and mortality. However, many past studies have failed to adequately control for the role of physical health. A proposed mechanism of the depression-mortality relationship suggests that physical health may mediate the relationship. The present study used new methods to examine relationships between mental health symptoms and mortality in an elderly community cohort while accounting for potential mediation of these relationships by physical health.

Method: 896 community-dwelling participants aged 70-97 were assessed four times over 12 years and vital status was tracked for up to 17 years. Relationships of depression and anxiety with survival time, controlling for physical health, age and gender, were tested using Cox proportional hazards regressions embedded in structural equation models.

Results: A significant unadjusted relationship between depression symptoms and mortality (HR = 1.09, $p < .001$) was attenuated to non-significance after controlling for measures of physical health (HR = 1.03, $p = .18$). No significant relationship was found between anxiety symptoms and mortality.

Conclusions: The relationship between depression and mortality was accounted for by physical health status in this cohort. This finding casts doubt on studies that report a relationship between depression and mortality without adequately considering the effect of physical health.

There is a large body of literature examining whether depression is a risk factor for death. Evidence for the relationship has been summarized in six reviews, each of which has concluded that depression is associated with an increased all-cause mortality rate (Cole & Bellavance, 1997; Cuijpers & Schoevers, 2004; Harris & Barraclough, 1998; Saz & Dewey, 2001; Schulz et al., 2002; Wulsin et al., 1999). The earliest of these, a review of 57 studies published between 1966 and 1996 (Wulsin et al., 1999) found 29 (51%) reported a positive relationship between depression and mortality. A follow-up review of 61 articles published between 1996 and 2001 (Schulz et al., 2002) reported that 72% had positive findings. A meta-analysis (Saz & Dewey, 2001) reported a combined odds ratio for mortality with depression of 1.73 (95% CI 1.53-1.95). The most recent review (Cuijpers & Schoevers, 2004) reported a relative risk for mortality in depressed subjects of 1.81 (95% CI 1.58-2.07) compared to non-depressed subjects. However, Wulsin *et al.* (1999) cautioned against drawing strong conclusions about the nature of the relationship due to (i) a lack of adequate controlling for confounders, (ii) the potential of publication bias in favor of positive studies, and (iii) the heterogeneity of samples and methods used in the studies.

With respect to the first of these limitations, 44% of the 57 studies reported by Wulsin *et al.* (1999), 33% of the 61 studies reported by Schulz *et al.* (2002), and 79% of the 21 studies reported by Saz and Dewey (2001) did not control for physical health status. Moreover, very few of the studies used objective measures of health status, with most using less reliable measures such as presence/absence of chronic disease or disease counts. Only one of the 57 studies reviewed by Wulsin *et al.* (1999) controlled for both the effect of physical health and other potential confounders of the relationship such as smoking, alcohol use and suicide. The strength of evidence for an association between depression and mortality is further diminished by the inconsistency of the effect over extended follow-up periods, in heterogeneous populations or using a variety of methods.

Saz and Dewey (2001) found that the odds ratio of depression on mortality appears to be significantly attenuated over time, in that studies with longer follow-up periods predicted smaller effect sizes. Studies examining community samples rather than clinical populations have tended to report mixed or null effects, with only four of the twelve (33%) high-quality community studies reviewed by Wulsin *et al.* (1999) reporting positive findings. Furthermore, the majority of the studies reviewed used a clinical diagnosis or a cut-off on a scale as the depression measure, rather than investigating the continuum of depressive symptomatology. Using diagnostic instruments to create binary categorizations of participants precludes drawing conclusions on the incremental impact of depression severity on mortality.

Many mechanisms for the association between depression and mortality have been proposed (Cuijpers & Schoevers, 2004). Schulz *et al.* (2002) presented a general theoretical model proposing that depressive symptoms either lead directly to mortality or are mediated by a cascade of risk factors ranging from behavioral and biological factors to subclinical and clinical disease. Cuijpers and Schoevers (2004) describe a model of the relationship that suggests physical health status might play a mediating role. Specifically, depression may directly increase vulnerability to physical illness by compromising physiological systems, particularly through changes in immune response. There is evidence that depression promotes increased production of inflammatory cytokines and reduced cellular immune response (Kiecolt-Glaser & Glaser, 2002). Such changes in immunological processes have been implicated in a range of conditions including cardiovascular disease, arthritis, type 2 diabetes, certain cancers, frailty and functional decline (Kiecolt-Glaser & Glaser, 2002). Other physiological responses associated with depression include increased platelet aggregation and heart rate variability brought about by dysregulation of the autonomic nervous system (Carney, Freedland, Miller, & Jaffe, 2002), both of which increase the risk of cardiovascular

disease. In addition, there is evidence that depression is associated with hazardous health behaviors, including smoking, alcohol use and poor diet, that lead to further declines in physical health (Cuijpers & Schoevers, 2004). As people with poorer physical health are more likely to die, the interactions between physical health and depression may account for much of the association between depression and mortality. Given the methodological inadequacies of some previous studies, the relationship between depression on mortality may have been overstated and requires more thorough testing.

There have been fewer studies on the relationship between anxiety and mortality. One review has examined the effects of a array of mental disorders on mortality among patient cohorts (Harris & Barraclough, 1998). Harris and Barraclough (1998) found increased risks of premature death for all disorders. Their review examined four studies of "neurosis", one of "anxiety neurosis" and one of panic disorder. Harris and Barraclough (1998) reported that the risk of death from all causes was significantly greater for those with neurosis or panic disorder but not for anxiety neurosis. A more recent meta-analytic review of seven studies of the impact of anxiety on mortality in elderly cohorts (Dewey & Chen, 2004) concluded that although anxiety diagnoses tended to be associated with mortality, the effect was not significant. The review also reported that there was no association found between levels of anxiety symptoms and mortality.

The present study sought to determine whether depression and anxiety symptoms were associated with long-term all-cause mortality in an elderly community sample and to explore the impact of controlling for physical health status. To better account for the complex pattern of relationships between mental health, physical health and mortality, a recently-developed statistical method was used for the analysis. The majority of studies investigating the effect of depression on mortality have used Cox

proportional hazards regression, with time to death as the outcome. However, Cox proportional hazards regression cannot directly test whether one independent variable mediates the effect of another on the survival outcome. Structural equation modeling (SEM) allows theories of mediation to be assessed, and has been applied widely to conventional regression analyses (Preacher & Hayes, 2004). However until recently SEM software has not accommodated survival data. By employing a Cox proportional hazards regression model within a SEM context using the Mplus application (Asparouhov et al., 2006), it is possible to test for mediation when modeling survival data. We hypothesized a significant direct relationship between depression and mortality. After accounting for physical health, the indirect effect of depression on mortality was hypothesized to be non-significant, particularly given the advanced age of the cohort and the extended follow-up period. Any relationship between anxiety and mortality was hypothesized to be non-significant.

Method

Participants

The Canberra Longitudinal Study was an epidemiological survey of mental health and cognitive functioning in older people that commenced in 1990. The study design has been detailed by Christensen *et al.* (2004). Eight hundred and ninety-six participants (456 men and 440 women) aged 70 or older at the time of the baseline assessment were recruited for the baseline assessment. All participants were initially living in the community in the cities of Canberra or Queanbeyan, Australia. The sample selection was stratified by age and gender. Participants were sampled from the compulsory electoral roll, with 69% responding. Approval for the research was

obtained from the Ethics in Human Experimentation Committee of The Australian National University.

Survey Procedure

Participants were interviewed up to four times over 12 years. Baseline interviews lasted approximately two hours, incorporating a survey measuring a wide range of risk factors including socio-demographics, physical health and disease status, mental health status, cognitive performance and social support. Interviews also included physical assessments of blood pressure, lung function, grip strength, vision and reaction time. Trained professional interviewers conducted the interviews.

Of the original sample of 896 participants, 185 (20.6%) were deceased by four years, 363 (40.5%) were deceased by eight years, and 544 (60.7%) were deceased by 12 years. At the end of vital status collection in June 2007, 687 (76.7%) of the participants were deceased. Of the participants who remained in the study, 14.1% (100/711) refused or were unable to complete the first follow-up interview, 21.1% (100/474) for the second follow-up and 21.1% (57/270) for the third follow-up.

Measures

Mortality status and date of death were established by contacting relatives, searching the National Death Index, and from death notices in the local newspaper. Mortality status was followed for up to 17 years, from the start of baseline interviews in September, 1990 until June 30, 2007. Survival was calculated as the time from the baseline interview to death for deceased participants, or from baseline until June 30, 2007 for surviving (right-censored) participants. For six participants with unknown day of death, the day was set to the 15th of the month. For two participants with an unknown month of death, the month was set to June.

Depression and anxiety symptoms were measured using the Goldberg Depression and Anxiety Scales (Goldberg, Bridges, Duncan-Jones, & Grayson, 1988),

which each comprise nine items that measure symptoms of affective disorders in the four weeks prior to reporting. The number of "yes" responses were summed for these scales to derive two scores (range 0-9), with higher scores reflecting a greater level of depression/anxiety. *Age and gender* were reported during the initial interview. Several indices of physical health were measured in the study. Four of these measures were chosen as being objective health measures that cover different aspects of physical wellbeing. *Heart attack history* and *hypertension history* were included as dichotomous variables, based on self-report at the initial interview. *Grip strength* was taken using a Smedley hand dynamometer which measures the force exerted in kilograms (Christensen et al., 2000). A scale of *functional ability* was based on difficulty ratings for eight Activities of Daily Living (ADLs), including transportation, walking, getting out of bed, getting out of a chair, dressing and bathing. Using a four-point response scale (no difficulty, some difficulty but no help needed, need help, bedridden) for the eight items, functional ability scores ranged from 0 to 24, with higher scores indicating greater functional disability.

Analyses

Survival time was graphed using Kaplan Meier curves and modeled using Cox proportional hazards regression analyses within a SEM framework. A series of three Cox regression analyses were completed using structural modeling (Asparouhov et al., 2006), for both depression and anxiety: (i) a univariate model (depression or anxiety only), (ii) a model with age and gender included, and (iii) a model with age, gender and physical health measures included and accounting for the relationship between depression and physical health in the structural model. Mediation by physical health of the relationship between depression/anxiety and mortality was tested by comparing model (iii) with an identical model (iv) that omitted the relationship between depression/anxiety and mortality, using the difference in -2 log likelihood values that

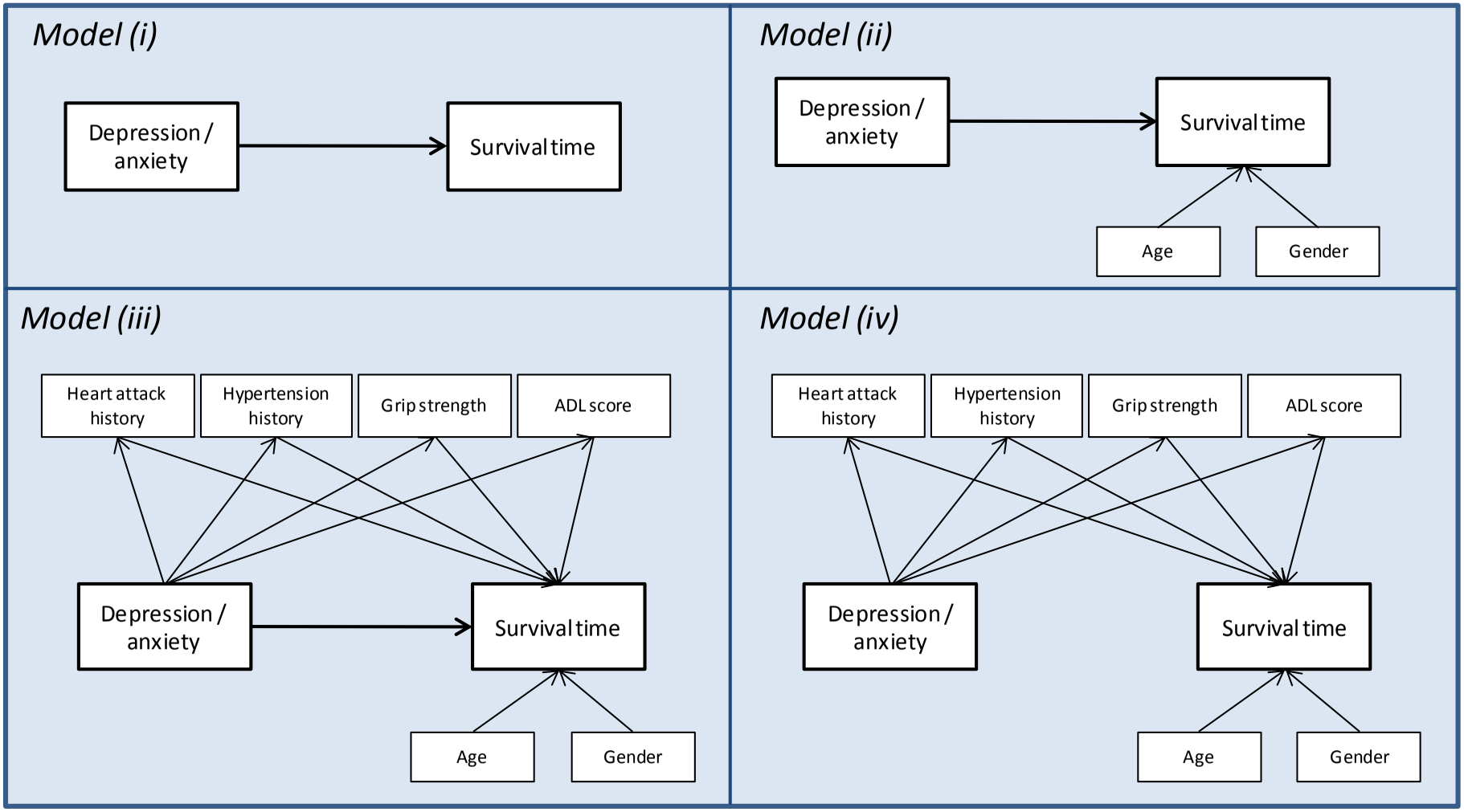

Figure 1: Structural equation / Cox regression models used to examine relationships between depression/anxiety and mortality: (i) univariate model, (ii) adjusted for age and gender, (iii) adjusted for age, gender and physical health latent variable, and, (iv) testing mediation by physical health

are distributed as χ^2 for nested models. No significant change between the fit of model (iv) and model (iii) would indicate full mediation of the depression/mortality relationship by physical health. To comprehensively measure multiple aspects of physical health, four measures were included in the model: heart attack history, hypertension history, grip strength and functional disability. These measures were chosen to be somewhat independent measures of past and present physical health, with absolute correlation coefficients less than 0.1 for every pairing except functional disability and grip strength (r = -.41). Consequently, a robust latent variable could not be constructed, so the physical health measures remained separate in the structural equation models. The four models are shown in Figure 1. Among the variables used in the analysis, 3% of the sample had one missing value and a further 3% of the sample had two or more missing values, resulting in a sample size of 865 for the depression analyses and 870 for the anxiety analyses. Stata version 10 was used to construct Kaplan-Meier survival curves, while Mplus version 5.1 was used for the modeling.

Results

Among the cohort of 896 participants, the mean initial age was 77 (range 70-97), with males representing 51% of the stratified sample. Participants had a mean of 2.0 depression symptoms and 2.5 anxiety symptoms. Thirteen percent of the sample had four or more depression symptoms, while 19% had four or more anxiety symptoms. Participants had a mean of 11 years of education. Considering the age of the cohort, participants were reasonably healthy at baseline, with 18% reporting heart attack history and 42% with hypertension history. Most of the participants had high functional ability, with 36% requiring no assistance for any of the eight listed activities and a further 46% requiring assistance for just one or two of the activities.

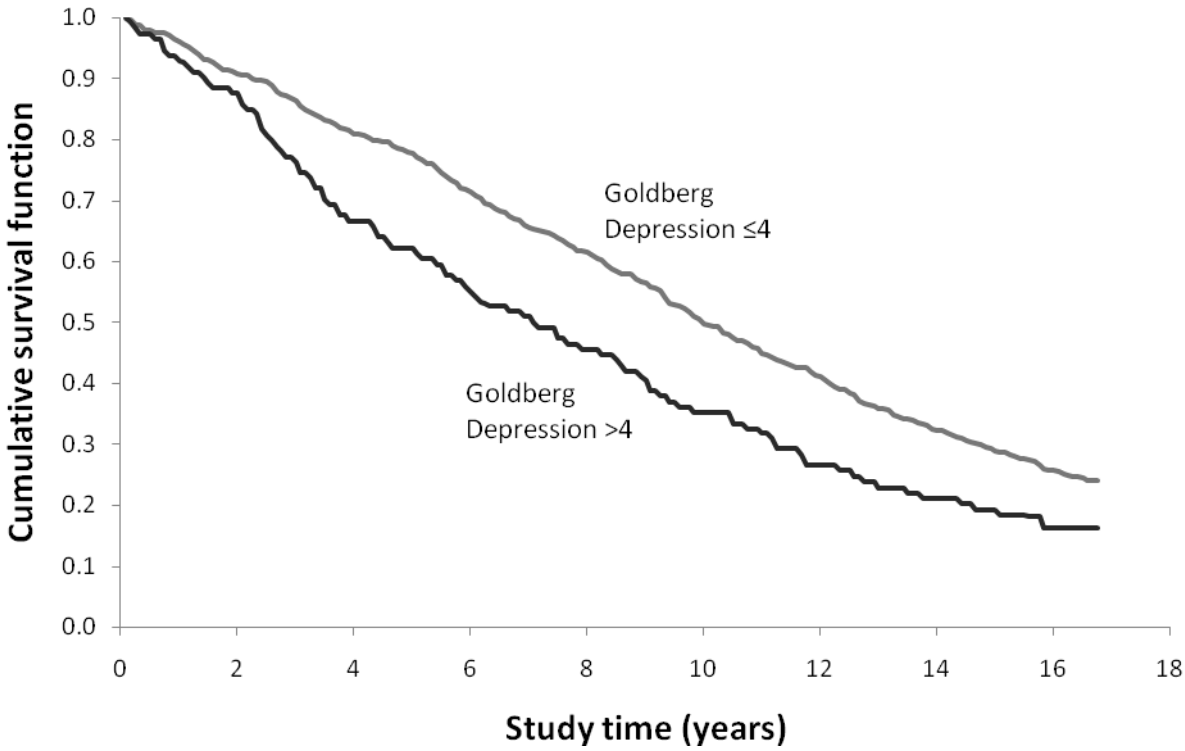

Figure 2: Kaplan-Meier curve of mortality over 17 years based on presence/absence of elevated depression symptoms

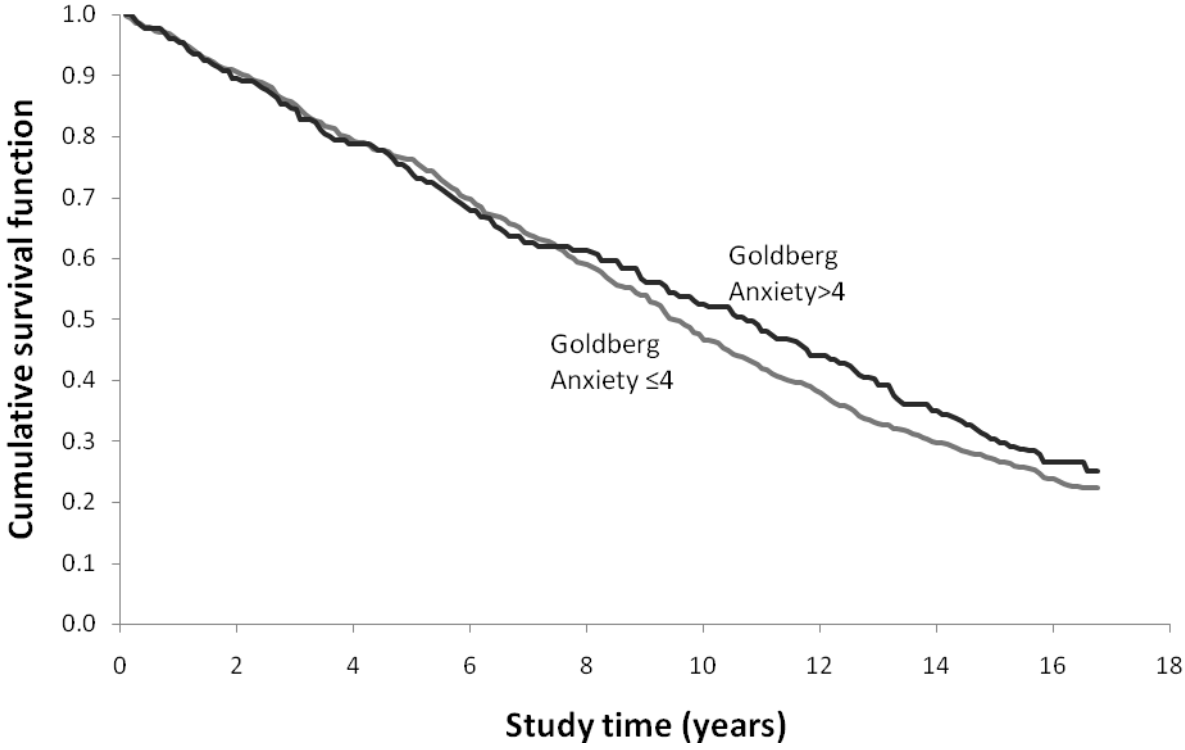

Figure 3: Kaplan-Meier curve of mortality over 17 years based on presence/absence of elevated anxiety symptoms

Kaplan-Meier curves show the univariate relationships between depression (Figure 2) and anxiety (Figure 3) with mortality. For these figures, the Goldberg scales were split at a value of four, which represented the approximate 80^{th} percentile of depression or anxiety levels in this sample. Figure 2 shows that participants with elevated depression tend to have a higher mortality rate than those lower or no depression, as there is evident separation between these groups. The overlap of the two curves in Figure 3 suggests that there is no effect of elevated anxiety, although more anxious participants appear to have a lower mortality rate after the eighth year.

Table 1 shows the Cox regression models for mortality using (i) only depression symptoms, (ii) adjusting for age and gender, and (iii) adding the effect of physical health and adjusting for the effect of depression on physical health. Table 2 shows parameters for the same models using anxiety symptoms. The coefficients in the tables are hazard ratios for the effects of depression/anxiety, age and gender on mortality, and standardized path coefficients for the effects of physical health on mortality and depression/anxiety on physical health. The univariate hazard ratio (HR) for depression on mortality was 1.09 ($p < .001$), suggesting mortality risk increased by 9% for each depression symptom. This changed little after adjusting for age and gender (HR = 1.10, $p < .001$). However, after adjusting for age, gender, the physical health measures and the relationship between depression and physical health, the HR was 1.03 ($p = .18$). To examine whether the depression-mortality relationship provided a significant contribution to the adjusted model, the likelihood functions for models (iii) and (iv) were compared (see Figure 1). The difference in -2 log likelihood, which is distributed as χ^2 (1), was 1.18 ($p = .28$), suggesting that the direct path from depression to mortality could be omitted from the model.

Anxiety symptoms had a univariate HR for mortality of 1.004 ($p = 0.82$) and 1.03 ($p = .08$) after adjusting for age and gender (Table 2). After adjusting for age,

Table 1: Cox Proportional Hazards regression models predicting time to death over 17 years of follow-up using depression symptoms

	Model (i) Univariate Hazard Ratio (95% CI)	Model (ii) + Age & gender	Model (iii) + Health status
Goldberg depression score	**1.09 (1.04, 1.13)*** **	**1.10 (1.05, 1.14)*** **	**1.03 (0.99, 1.08)**
Age		1.10 (1.08, 1.12)***	1.08 (1.06, 1.09) ***
Male gender		1.71 (1.46, 2.00)***	2.69 (2.07, 3.51) ***
Grip strength			0.97 (0.96, 0.99) ***
Physical disability (ADL)			1.11 (1.07, 1.15) ***
Heart attack history			1.40 (1.16, 1.70) ***
Hypertension history			1.28 (1.09, 1.50) **
Depression → Grip strength†			-1.19 (-1.50, -0.88)***
Depression → ADL†			0.40 (0.31, 0.49) ***
Depression → Heart attack†			0.03 (-0.06, 0.11)
Depression → Hypertension†			0.06 (-0.01, 0.13)

* $p < .05$; ** $p < .01$; *** $p < .001$; † Path coefficients presented instead of hazard ratios

Table 2: Cox Proportional Hazards regression models predicting time to death over 17 years of follow-up using anxiety symptoms

	Model (i) Univariate Hazard Ratio (95% CI)	Model (ii) + Age & gender	Model (iii) + Health status
Goldberg anxiety score	**1.00 (0.97, 1.04)**	**1.03 (1.00, 1.07)**	**0.99 (0.95, 1.02)**
Age		1.10 (1.08, 1.12)***	1.07 (1.05, 1.09) ***
Gender		1.65 (1.41, 1.93)***	0.37 (0.29, 0.48) ***
Grip strength			0.97 (0.96, 0.98) ***
Physical disability (ADL)			1.12 (1.08, 1.16) ***
Heart attack history			1.42 (1.17, 1.72) ***
Hypertension history			1.29 (1.10, 1.51) **
Anxiety → Grip strength†			-0.88 (-1.15, -0.61)***
Anxiety → ADL†			0.22 (0.15, 0.29) ***
Anxiety → Heart attack†			0.09 (0.02, 0.16) *
Anxiety → Hypertension†			0.09 (0.03, 0.15) **

* $p < .05$; ** $p < .01$; *** $p < .001$; † Path coefficients presented instead of hazard ratios

gender and physical health status, the HR was 0.99 (p = .49). The difference in -2 log likelihood between models (iii) and (iv) was 0.24 (p = .62), suggesting that the direct path from anxiety to mortality did not contribute significantly to the model. In both the depression and anxiety models, older age and male gender were, predictably, significantly associated with higher rates of death. Weaker grip strength, increased physical disability, and history of heart attack or hypertension were also associated with increased mortality. Depression and anxiety were both associated with weaker grip strength and increased physical disability, however, only anxiety was associated with an increased likelihood of reporting a history of heart attack or hypertension.

Discussion

In this cohort of community-dwelling elderly participants, the relationship between more depression symptoms and greater mortality was accounted for by physical health status. Structural models demonstrated a strong association between depression symptoms and poorer physical health. These findings provide further evidence that the observed univariate relationship between depression and mortality may be due to the strong associations of physical health with both depression and mortality. There was no relationship found between anxiety symptoms and mortality, a protective effect of anxiety on mortality was found after controlling for physical health. The present study tested the proposed mechanism that the association between depression and mortality was mediated by physical health. There was strong evidence found for a relationship between depression and physical health, supporting the hypothesis that the depression-mortality relationship is a result of physical health. This finding may be reflective of the physiological effects of depression, specifically, immunological and cardiac processes which are strongly associated with mortality risk (Carney et al., 2002; Kiecolt-Glaser & Glaser, 2002). While there is a strong

association between depression and morbidity, there appears to be no direct link between depression and mortality.

The results for depression are somewhat inconsistent with previous research. However, reviews of the depression research have noted that many of the studies examined insufficiently controlled for physical health (Saz & Dewey, 2001; Wulsin et al., 1999), with control variables often limited to binary measures of disease presence. Despite this methodological inadequacy, only 62% of the combined articles reviewed by Wulsin *et al.* (1999) and Schulz *et al.* (2002) reported positive findings, suggesting that the relationship may only be observed in specific populations, particularly clinical populations. Other differences from previous studies may also contribute to the divergence in findings. The majority of reviewed studies have examined depression or anxiety as a binary diagnostic measure. The continuous measures used in the present study allowed for the continuum of symptomatology, rather than examining the upper tail of the distribution. The reviews also included studies of clinical and medical cohorts, and studies primarily consisted of middle-aged and early-old aged cohorts. The present study used a community sample that was comparatively older. It is possible that using a more highly symptomatic clinical population may result in different relationships and that the impact of depressive illness on mortality may occur earlier in the lifespan. Furthermore, as Wulsin *et al.* (1999) reported, the relationship between depression and mortality becomes weaker over extended follow-up periods. The 17-year follow-up of the present study is longer than that of any of the reviewed community-based studies of elderly cohorts (Saz & Dewey, 2001; Schulz et al., 2002; Wulsin et al., 1999).

There are limitations to this study that should be noted. The depression and anxiety measures involved a symptom count rather than a diagnostic instrument. As previously observed, there are advantages to using a measure that assesses a range of

severities, including non-clinical states. However, this conceptualization of depression or anxiety may not always be in accordance with diagnosis based on DSM or ICD criteria. Symptom scales do not reveal the prevalence in the sample of chronic disorders (e.g., dysthymia), acute disorders (e.g., major depressive episode) or subclinical states. The administration of a more comprehensive clinical measure that could reliably assess mood and anxiety disorders was not feasible in this large epidemiological study. Secondly, depression tends to be an episodic illness, whereas the depression measure captured only those individuals who experienced symptoms in the four weeks prior to the baseline survey. Examining lifetime history of depressive episodes may result in a different outcome. Thirdly, while the model provided a formal test of mediation, it was not possible to fully account for temporal effects using the present dataset. Specifically, the onset of depression may have preceded physical health problems in some cases. Nevertheless, the strong attenuation of the direct effect of depression on mortality is clear evidence of confounding by physical health status, and indicates possible mediation of the effect. Finally, the analyses did not account for other measures related to mortality, including cognitive performance, education, socioeconomic status, subjective health, health behaviors, additional physical diseases and additional markers of physical health, including objective markers for cancer and other diseases. Measures that are closely related to depression, such as subjective health ratings, were omitted to ensure that the attenuation of the effect was not entirely due to multicollinearity. However, the small number of health indices used in the Cox regression model fully accounted for the direct effect of depression, despite no direct adjustment for the presence of cancer, respiratory disease or many other diseases. Further adjustments were consequently deemed unnecessary. While mediation of the depression-mortality effect is primarily through physical health, indirect mediation

through health behaviors such as inactivity, sleep problems or substance use (Schulz et al., 2002) and the direct effect of suicide were not tested.

Future research should aim to clarify how the type of sample and methods of measurement affect relationships between mental health and mortality. In addition, a range of specificities in the association between depression and mortality should be examined. In particular, younger cohorts may exhibit stronger relationships between depression and mortality than older cohorts, there may be decay of the relationship over long follow-up periods, and the presence of certain depressive symptoms may be more strongly predictive of death than others. Regardless of the nature of the relationship, future studies must be rigorous in accounting for the confounding effects of physical health. While the present study found no evidence of a relationship between anxiety and mortality, there is a possibility for future research to investigate whether specific types of anxiety disorders have differential impacts on physical health and mortality. Given the attenuation to non-significance of the relationship between depression and mortality after adequately controlling for physical health in the present study, a degree of uncertainty may be placed upon studies that report a strong relationship between depression and mortality without adequately controlling for physical health.

Acknowledgements: The Canberra Longitudinal Study was supported by NHMRC Unit Grants 973301 and 933301 and NHMRC Program Grant 179805. HC is supported by NHMRC Senior Principal Research Fellowship 525411. The authors thank Scott Hofer for commenting on a draft of the manuscript.

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INTEGRATED DISCUSSION

Summary of results

The aim of the thesis was to examine the relationship between cognition and mortality in late life. This aim was achieved by examining cognition-mortality relationships from multiple perspectives in a series of studies using the Canberra Longitudinal Study cohort. The first study aimed to determine whether initial performance on tasks with a fluid or crystallised intelligence component was associated with mortality, and whether this association could be explained by three previously proposed mechanisms (Batterham, Christensen & Mackinnon, 2009). The second study aimed to assess whether initial cognitive performance and changes in performance were related to mortality from a range of specific causes (Batterham, Mackinnon & Christensen, submitted). The second study also aimed to compare two unbiased methods for estimating change. The aim of the third study was to investigate evidence for terminal decline in the cohort and determine whether education modified terminal decline as predicted by the cognitive reserve theory (Batterham, Mackinnon & Christensen, in press). The fourth study aimed to test the dedifferentiation hypothesis, which suggests that a general ability factor accounts for a greater proportion of the variance in performance across different cognitive domains (Batterham, Christensen & Mackinnon, in press-a). Finally, the aim of the fifth study was to determine whether depression and anxiety symptoms were associated with mortality after accounting for physical health status (Batterham, Christensen & Mackinnon, in press-b).

In a community sample of 896 elderly Australians, cognitive performance was found to be associated with mortality. Poorer performance in several domains of cognitive ability, specifically processing speed, global cognition, and verbal fluency, was found to be significantly associated with higher mortality rates (Batterham et al., 2009; Batterham et al., submitted). These relationships existed even after accounting

for a range risk factors, including physical health, mental health, health behaviours and sociodemographics (Batterham et al., 2009). Although initial levels of performance tended to be strongly associated with mortality, changes in cognition over time tended to be poor predictors of mortality (Batterham et al., submitted). Nevertheless, using change point models to identify changes in the rate of cognitive decline with respect to time-to-death demonstrated that rates of decline increased 2-4 fold starting around 6-9 years before death (Batterham, Mackinnon et al., in press). Terminal decline was modified by education with the pattern of modification differing between the three abilities investigated. Together, these findings suggest that while terminal decline existed within the cohort, overall rates of decline were not predictive of time to death.

Performance across various cognitive domains was found to become more strongly associated with a general factor of intelligence in proximity to death, which was suggestive of the dedifferentiation of cognitive abilities (Batterham, Christensen et al., in press-a). However, this dedifferentiation did not occur with respect to age and was completely accounted for by the prevalence of possible dementia in the sample. Consequently, these findings did not support the hypothesis of late-life dedifferentiation (Baltes et al., 1980; Li & Lindenberger, 1999), as the hypothesis did not adequately portray the developmental processes of aging independent of the effects of dementia in the present sample. Finally, depression and anxiety were found to have no relationship with mortality after accounting for physical health (Batterham, Christensen et al., in press-b), providing further evidence that the cognition-mortality relationship is not an artefact of late life depression or anxiety.

Relationship to previous research and theory

Many of these findings were consistent with previous research on late-life mortality, although several of the studies presented here reported novel findings or used

novel methods. Deary (2005) summarised three mechanisms that might explain the observed relationships between levels of intelligence or cognitive ability and mortality. The mechanisms suggest that the relationship between cognition and mortality is indicative of: (i) mediation by socio-economic position reflecting disadvantage, (ii) mediation by health behaviours and knowledge reflecting inability to enact positive health behaviours and propensity to engage in unhealthy behaviours, or (iii) mediation by physical health status, which reflects both developmental events and physical integrity or the lack of pathology (Deary, 2005). In the first study (Batterham et al., 2009), these mechanisms were explicitly tested in the Canberra Longitudinal Study cohort. Although evidence was found for a univariate association between both processing speed and verbal ability with all-cause mortality, limited support was also found for each of the three proposed mechanisms. Specifically, the effects of cognition were attenuated after adjustment for measures assessing socio-economic position (education, manual work), health behaviours (smoking status, activity) and physical health status (in particular, self-rated health, cardiovascular disease history, grip strength, and anxiety symptoms). Nevertheless, poorer cognitive ability, particularly on the processing speed measure, had a strong significant association with greater mortality even after adjusting for measures of all three mechanisms. This finding suggests that some domains of cognitive ability may have an independent effect on mortality.

These relationships were explored in further detail by examining the relationship between both the level and slope of cognitive performance and cause-specific mortality (Batterham et al., submitted). This study was the first to establish the comparability of two unbiased estimates of change (Best Linear Unbiased Predictor and latent growth models) in predicting mortality from multiple causes. Initial levels of performance on tasks measuring processing speed, verbal fluency and global ability were associated with all-cause and/or cardiovascular (including stroke or heart disease) mortality in

adjusted Cox proportional hazards models. The slope of decline in performance was also associated with all-cause and cardiovascular mortality, however, this effect only occurred for the global ability measure, suggesting that late-life changes in performance are less strongly associated with mortality than initial levels of ability. Cognition was not associated with deaths from either cancer or respiratory disease, supporting previous research on cause-specific mortality (Shipley et al., 2007; Shipley et al., 2008). The relationship between cognition and mortality may therefore be largely influenced by cardiovascular events rather than overall physical health. The primacy of level of performance over slope was also consistent with previous research (Ghisletta et al., 2006; Johansson et al., 2004). The associations between level of cognitive performance and mortality may reflect the lifelong influences of education, health literacy, healthy and unhealthy behaviours, injury, vascular problems and other physical health problems on both cognitive ability and mortality (Bäckman & MacDonald, 2006; Deary, 2005). Further individual influences such as genetics, developmental events and the environment may also contribute to these associations. While the models adjusted for many of these factors, it is not possible to fully account for the multitude of influences across the lifespan that contribute to an individual's cognitive ability. Nevertheless, as the level of cognitive ability had a direct effect on mortality, cognitive performance appears to be a significant marker for predicting survival.

While there was limited evidence for terminal decline using measures of change in cognition over the study period, such estimates may not directly capture the terminal decline phenomenon. As cognitive decline does not accelerate continuously in proximity to death, it may more appropriately be described using a threshold function (Sliwinski et al., 2006). Batterham, Mackinnon and Christensen (in press) used a change point model to assess evidence for terminal decline in the cohort, providing estimates of both the onset and magnitude of decline. Similarly to other studies using

the change point methodology (Sliwinski et al., 2006; Thorvaldsson et al., 2008; Wilson et al., 2007; Wilson et al., 2003), a reliable change point was found for three cognitive domains: 8.5 years before death for processing speed, 7.1 years for global function and 6.6 years for episodic memory. The rate of decline in the terminal phase, which is the period after the change point, was 2-4 times greater than in the preterminal phase before the change point. This finding suggests that events related to impending mortality influence the rate at which cognitive performance declines.

In an extension of the change point methodology, the analysis also investigated whether education modified the onset or rate of decline (Batterham, Mackinnon et al., in press). According to the cognitive reserve theory, education and other markers of cognitive or brain reserve increases the brain's ability to compensate for pathology, such that the onset of terminal or pathological decline may be delayed but such decline accelerates more rapidly in those with more education (Stern, 2002). While education modified the terminal decline effect for all three of the cognitive domains, the changes were not consistent across domains. More education was associated with earlier onset but decreased rate of terminal decline for the global function task. On the contrary, less education was associated with a decreased rate of terminal decline for the processing speed task, although the onset of the terminal period was not significantly modified. More education was associated with an increased rate of preterminal decline on the episodic memory task but had no effect on the change point or the rate of terminal decline. Consequently, the findings did not show any systematic evidence for cognitive reserve theory and suggests that terminal decline does not occur uniformly across different cognitive domains. The differing patterns of decline may reflect the different physiological bases of various cognitive abilities, which may vary as a function of disease and individual vulnerability. The lack of evidence for cognitive reserve

suggests that the range of biological processes associated with terminal decline may be more diverse than those associated with dementia-related cognitive decline.

The developmental processes responsible for late-life decline were further investigated by assessing evidence for the dedifferentiation theory (Batterham, Christensen et al., in press-a), which suggests that cognitive abilities become more strongly associated with a general factor of intelligence in late life (Baltes et al., 1980; Li & Lindenberger, 1999). Late-life dedifferentiation is hypothesised to occur when, as a result of increasing biological constraints on information processing mechanisms, declines in fluid abilities limit subsequent development in crystallised abilities (Li et al., 2004). The dedifferentiation hypothesis was tested with the statistical model reported by Tucker-Drob (2009) to account for non-linear relationships between cognitive measures and factors and control for effects of ability differentiation. The model was extended by using two time metrics, age and time to death, the latter of which has not previously been used to examine dedifferentiation. There was evidence for dedifferentiation as a function of time to death, but not as a function of age, which is not consistent with the dedifferentiation hypothesis. Furthermore, the dedifferentiation effects were attenuated after excluding participants with possible dementia, such that none of the effects were significant. These findings indicate that the dedifferentiation of cognitive abilities was not a result of aging per se, but may be related to pathological events related to death and particularly dementia. Other recent research has also failed to find evidence for dedifferentiation in late life (Anstey et al., 2003; Tucker-Drob, 2009; Zelinski & Lewis, 2003). Any evidence of age-associated dedifferentiation effects may instead be indicative of the prevalence of subclinical or clinical dementia.

The final study assessed the effects of depression and anxiety on survival time (Batterham, Christensen et al., in press-b). Using a series of Cox regression models embedded in structural equation models, it was determined that the relationship between

depression and mortality in the Canberra Longitudinal Study cohort was fully mediated by physical health, while anxiety was not related to mortality. The findings related to depression were in contrast to four previous reviews which have reported that depression is associated with mortality (Cuijpers & Schoevers, 2004; Saz & Dewey, 2001; Schulz et al., 2002; Wulsin et al., 1999). One theoretical model suggests that physical health status might mediate the relationship between depression and mortality by increasing vulnerability to physical illness through changes in immune response (Cuijpers & Schoevers, 2004). The study (Batterham, Christensen et al., in press-b) provided evidence for this model by controlling for a range of physical health measures and suggests that there is no direct effect of depression on mortality, over and above its effects on morbidity. Up to half of the studies reported in the four previous reviews of the relationship controlled for no measures of physical health status (Cuijpers & Schoevers, 2004; Saz & Dewey, 2001; Schulz et al., 2002; Wulsin et al., 1999), which may explain the difference in findings and suggests that the direct effect of depression may have been overstated in previous research. As cognitive performance is diminished in the presence of depression (Christensen et al., 1997; Jorm, 2000; Willner, 1984), it is important to assess whether the cognition-mortality relationship may be explained by late-life depression. Given the present findings that there is no direct effect of depression and no effect of anxiety on mortality (Batterham, Christensen et al., in press-b), along with the adjustments for mental health symptoms in examining the association between cognition and mortality (Batterham et al., 2009; Batterham et al., submitted), it appears that depression and anxiety do not account for the cognition-mortality relationship.

Limitations of the research

The studies presented data from the Canberra Longitudinal Study, an epidemiological cohort of community-dwelling elderly participants. The study sample was large (n = 896) and was followed over a long period, with up to four assessments over 12 years and vital status collected for up to 17 years. The interviews assessed a wide range of domains including multiple cognitive abilities, subjective and objective measures of physical health, symptoms of anxiety and depression, health behaviours including substance and medication use, background characteristics and social support. Consequently, the study was well suited to assessing a wide range of risk factors for cognitive decline and mortality. However, as in any study, there were some aspects of the design that limited some areas of the research.

The four assessment points included in the study allowed for longitudinal analyses but limited the types of trends that could be estimated. Intraindividual estimates of linear change were assessed in both the cognitive change and terminal decline studies (Batterham, Mackinnon et al., in press; Batterham et al., submitted). While the large sample size ensured that reliable, unbiased change estimates could be made by the inclusion of random effect terms, a greater number of measurement points would allow for greater reliability of estimates and the investigation of other patterns of change, such as quadratic effects. The four-year interval between assessment points may also have reduced the power of some types of longitudinal models to detect small rates of decline. Since changes in cognition related to terminal decline may occur in a relatively small window, other studies may benefit from a shorter interval between follow-up interviews and more follow-ups. However, the need for briefer retest periods and more interviews must be balanced with undesirable outcomes that may occur in epidemiological studies, such as increased attrition (Deeg et al., 2002) or larger retest effects (Salthouse et al., 2004).

In addition, the measurement of cognition and some risk factors could be improved in future studies. The cognitive measures used in the present analysis were selected prior to the beginning of the study in 1990 with the aim of briefly assessing a range of abilities. Some of these tests, such as the episodic memory task, were very brief and may be inferior to longer or more established tests. The inclusion of more cognitive tests covering multiple domains of performance, along with tests of general intelligence, might provide further insight into relationships between cognitive ability and mortality. Once again, given the resource limits involved in large epidemiological studies, it is difficult to administer large batteries of demanding cognitive assessments. In addition, the measurement of cognitive performance at the start of the study may potentially have been influenced by the poor health of the participants, who were all aged 70 or over. Participants who were close to death at the first assessment may have influenced some the effects of poor cognitive performance on mortality. Nevertheless, the longitudinal analyses presented here excluded participants who died before the first follow-up and cross-sectional analyses were adjusted for multiple physical health measures, mitigating the effects of initial physical health status.

Clinical assessments of mental health status may also have provided more information about the mental health status of the sample. Depression and anxiety symptoms were used in place of a diagnostic assessment. Nevertheless, symptom scales are easier to administer and assess a range of severities, including non-clinical states, which are often overlooked by clinical instruments. Health behaviours were another area which could have been measured more comprehensively. The initial interview did not include measures of alcohol and other substance use, diet, healthcare utilization or medication adherence. Likewise, the collection of genetic markers, objective sensory measures such as visual acuity, brain imaging markers and additional physical

performance measures may have provided further information about risk factors for cognitive decline and mortality.

Finally, as the primary outcome of the study was mortality and the cohort was elderly, attrition due to mortality and other factors inevitably reduced the sample over time. Despite this attrition, the sample was still large for this type of cohort, with 374 participants completing three or four assessments. Further research to examine predictors of attrition from sources other than mortality may provide additional understanding of patterns of cognitive performance in late life.

Future research directions

While the studies presented examined the relationship between cognition and mortality from a range of perspectives, there are other methods, or extensions to the current methods, which may further explain the observed relationships. As previously mentioned, the current study only examined linear trends in late-life cognitive change. Modelling other types of trends, such as quadratic change, may more adequately capture the terminal decline phenomenon and provide greater insight into how cognitive performance changes in proximity to death. However, these types of analyses would require a larger number of observations for each participant, and the change point approach provides adequate estimates of terminal decline. Due to the complex nature of the models involved, the two analyses examining dedifferentiation and mental health used a cross-sectional approach. Longitudinal versions of these models would be further complicated by age effects and the potential inconstancy of factors over time. Other methods may be used to examine how within-person change might affect dedifferentiation or the relationship between mental health and mortality. Nevertheless, these two analyses had null results which are unlikely to be changed by the inclusion of longitudinal analyses. There are also different types of models for assessing terminal

decline or relationships between cognition and survival. Terminal decline may be further investigated using Bayesian models or retrospective models that estimate individual change points and account for individual differences (Gerstorf et al., 2008; Hall et al., 2003). In addition, the association between level and slope of cognitive ability may be modelled using a variety of unbiased methods similar to those presented (Ghisletta et al., 2006; Johansson et al., 2004).

Another extension of the present research would be to examine the conditions in which certain outcomes occur. For example, at an individual level, terminal decline may be precipitated by a number of health-related events, such as heart problems, strokes or falls. Likewise, the relationship between cognitive performance and mortality may be stronger among certain subgroups such as those who are older or have poorer physical health. As discussed previously, examining additional tasks assessing a wider range of cognitive abilities may also lead to a greater understanding of the cognition-mortality relationship. Indeed, it is conceivable that certain patterns of cognitive performance, or changes in these patterns, may be predictive of death from particular causes. Likewise, such patterns may be reflective of physiological events that are either manifest or subclinical. Testing these additional hypotheses may require different study designs, particularly studies with smaller samples but more observations, more frequent observations and additional cognitive measures. Additional research focussed on specific risk groups such as those with late-life conditions including cardiovascular disease would provide additional tests of these hypotheses. Such studies would ideally be integrated with data from larger population studies, like the Canberra Longitudinal Study.

While the current studies focussed on mortality as an outcome, these types of analyses could also be applied to range of different outcomes such as conversion to dementia, study attrition, hospital admissions or a range of physical or mental health

outcomes. Such analyses would further contribute to our understanding of the pathways of aging, from healthy states to disease states and death. Investigating the roles of cognitive ability and various risk factors in these outcomes may facilitate early identification and intervention to prevent disease and extend healthy aging.

Conclusions

The presented studies demonstrate that there was a strong link between cognitive ability and mortality in the Canberra Longitudinal Study cohort. The relationship was stronger for certain types of abilities, such as processing speed, and for particular causes of mortality, such as cardiovascular disease. Furthermore, level of ability was more strongly predictive of survival than changes in ability. While late-life decline in cognitive abilities did not appear to be a critical predictor of subsequent mortality, there was evidence for terminal decline in the cohort. Specifically, the rate of cognitive decline was related to time-to-death, with a two- to four-fold increase in the rate of decline at around 6-9 years prior to death. Education was shown to modify terminal decline, but the cognitive reserve theory was not supported, as the effects of education were not consistent across domains. The developmental bases for late-life decline were not related to dedifferentiation of abilities, as cognitive abilities did not become more strongly associated with a general ability factor as a function of increasing age. In addition, the effects of depression and anxiety on mortality were explained by physical health status, so mental health was unlikely to have influence on the cognition-mortality relationship.

The relationship between cognition and mortality may substantially be explained by physical health status, health behaviours and background characteristics such as socioeconomic status, education, developmental events and genetics, which influence cognitive ability across the life span. Nevertheless, cognitive ability appears to have an

independent effect on mortality, despite controlling for multiple measures of the factors that predict both cognitive performance and mortality. Consequently, cognitive ability provides a useful indicator for the risk of mortality. Continued examination of the relationship between cognition and mortality will provide a greater understanding of the changes in cognition that occur in late life.

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APPENDIX:

PRINTED COPIES OF ACCEPTED/PUBLISHED MANUSCRIPTS

Intelligence 37 (2009) 551–560

Contents lists available at ScienceDirect

Intelligence

Fluid intelligence is independently associated with all-cause mortality over 17 years in an elderly community sample: An investigation of potential mechanisms

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ARTICLE INFO

Article history:
Received 16 June 2008
Received in revised form 27 August 2008
Accepted 4 October 2008
Available online 22 November 2008

Keywords:
Mortality
Intelligence
Cognitive aging
Symbol–Letter Modalities Test
National Adult Reading Test
Socioeconomic status
Health status
Health behaviors

ABSTRACT

The long-term relationship between lower intelligence and mortality risk in later life is well established, even when controlling for a range of health and sociodemographic measures. However, there is some evidence for differential effects in various domains of cognitive performance. Specifically, tests of fluid intelligence may have a stronger association with mortality than do tests of crystallized intelligence. The present study examines the relationship between intelligence and mortality in a sample of 896 Australian community-dwelling males and females, aged 70–97 at recruitment and followed for up to 17 years. There were 687 deaths during the follow-up period. Cox proportional hazard regression models examined whether the relationship between intelligence and mortality might be mediated by socioeconomic status, by health behaviors, by health status, or a combination of these. Higher fluid intelligence — as measured by the Symbol–Letter Modalities Test — was strongly associated with lower mortality rates (Hazard ratio = 0.80; 95% confidence interval = 0.72–0.88), even after accounting for any combination of potential mediators and confounders. A significant association between crystallized intelligence, as measured by the National Adult Reading Test, and mortality (HR = 0.89; 95% CI = 0.80–0.99) was attenuated by the inclusion of socioeconomic, health status measures, and health behavior measures and when deaths from the first four years of the study were excluded. The findings show little support for the hypothesized mechanisms of the intelligence–mortality relationship.

Long-term studies of intelligence and mortality demonstrate that higher intelligence is associated with lower all-cause mortality. A recent review (Batty, Deary, & Gottfredson, 2007) examined nine studies investigating the relationship between early-life intelligence and later mortality risk. The studies followed cohorts for between 17 and 69 years. All found that higher IQ was associated with lower mortality. For example, one of the reviewed studies retrospectively traced the vital status of 2230 participants in the 1932 Scottish Mental Survey after 65 years (Whalley & Deary, 2001). The hazard of mortality over the 65 year follow-up period was decreased by 21% for each 15-point increase in intelligence as measured by the Moray House test. Studies reporting follow-up into old age have also reported consistent findings (Deeg, Hofman, & van Zonneveld, 1990; Rabbitt, Lunn, & Wong, 2006; Shipley, Der, Taylor, & Deary, 2006). However, the intelligence–mortality relationship may be dependent of the type of test administered, the age of the cohort and the length of the follow-up period.

Poor performance on *executive tests* such as the Mini-Mental State Exam (Bassuk, Wypij, & Berkman, 2000; Dartigues et al., 2007) or the Short Portable Mental Status Questionnaire (Blazer, Sachs-Ericsson, & Hybels, 2005; Liang, Bennett, Sugisawa, Kobayashi, & Fukaya, 2003) tends to be associated with higher

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0160-2896/$ – see front matter © 2008 Elsevier Inc. All rights reserved.
doi:10.1016/j.intell.2008.10.004

mortality risk, however the relationship has not always been found to be significant (Ganguli, Dodge, & Mulsant, 2002; Ostbye et al., 2006) and may be dependent on the length of the follow-up period (Ganguli et al., 2002; van Gelder, Tijhuis, Kalmijn, Giampaoli, & Kromhout, 2007). Performance on tests of *crystallized intelligence*, such as the National Adult Reading Test (Abas, Hotopf, & Prince, 2002; Anstey, Luszcz, Giles, & Andrews, 2001) or Raven's Mill Hill Vocabulary Scale (Rabbitt et al., 2002) tends to be robust to the effects of aging and is less likely to exhibit an association with mortality after health and social status are taken into account.

Tests of *fluid intelligence*, such as Digit–Symbol Substitution (Anstey et al., 2001; Ghisletta, McArdle, & Lindenberger, 2006; Pavlik et al., 2003; Portin et al., 2001) or various learning tasks (Abas et al., 2002; Ghisletta et al., 2006; Rabbitt et al., 2002; Royall, Chiodo, Mouton, & Polk, 2007) tend to decline more with age and are more strongly associated with mortality than performance on tests of general intelligence or tests of executive functioning. However, the effect size may be greater for long-term (e.g., Ghisletta et al., 2006) rather than short-term (e.g., Bosworth, Schaie, & Willis, 1999) studies and for older rather than younger cohorts (Lyyra, Heikkinen, Lyyra, & Jylha, 2006; Shipley et al., 2006). The association between *short-term memory performance* and mortality among non-demented adults is also well documented (Ghisletta et al., 2006; Portin et al., 2001; Shipley et al., 2006). In addition, two reviews have reported an association between dementia or mild cognitive disorders and mortality (Dewey & Saz, 2001; Guehne et al., 2006; Guehne, Riedel-Heller, & Angermeyer, 2005). Indeed, it has been contended that the relationship between intelligence and mortality is largely mediated by dementia (Backman & MacDonald, 2006).

Given the evidence for the relationship between intelligence and mortality, potential mechanisms driving this association warrant further examination. In early research on the relationship between cognitive decline and mortality, Riegel and Riegel (1972) described the effect in terms of "terminal drop". While the relationship between childhood intelligence and mortality cannot be explained by terminal decline alone, two theories posited by Riegel and Riegel (1972) form the basis of contemporary understanding of the intelligence–mortality relationship. Firstly, a biological theory suggested that physiological mechanisms related to cell aging were responsible for the decline and also for death. Secondly, a sociological theory suggested that performance and chance of survival drops earlier in life for those who cope less well with their environment due to disadvantages in, for example, education, income, nutrition and medical assistance.

More recently, three potential mechanisms for the relationship have been detailed by Whalley and Deary (2001) and Deary (2005) and tested by Kuh, Richards, Hardy, Butterworth, and Wadsworth (2004) and Shipley et al. (2006). First, socioeconomic status (SES) may mediate the relationship between intelligence and mortality. This theory, advocated by Siegrist and Marmot (2004), is similar to the sociological theory of Riegel and Riegel (1972), suggesting that disadvantages in intelligence lead to burdens in occupation, which are linked to poorer health outcomes. Siegrist and Marmot (2004) elaborate on the relationship by taking into account the mediating effect of control on health outcomes. The demand–control model (Karasek, 1979) proposes that high work demands interact with low levels of perceived control to cause such outcomes as depression and exhaustion, which adversely effect health outcomes and consequent mortality. A second explanation is that the relationship between intelligence and mortality is mediated by health behaviors and knowledge, which include substance use, diet, physical activity, healthcare utilization, and accident and illness prevention (Deary, 2005). Gottfredson and Deary (2004) argued that a high level of cognitive resources is required to prevent disease and to ameliorate illness through behaviors such as health monitoring, screening, medication adherence, understanding health information and becoming health literate. Failure to adequately undertake these health behaviors can lead to illness or more severe illness, resulting in hospitalization and health costs, and consequently, greater risk of mortality (Gottfredson & Deary, 2004).

A third explanation is that the relationship between intelligence and mortality may be due to a common association with health status. There are two possible explanations for an association between intelligence and health (Deary, 2005): (i) intelligence may be viewed as a marker of biological "fitness" or of system integrity, or (ii) intelligence may be an indicator of developmental problems that impact on later health. The former explanation aligns with the biological theory proposed by Riegel and Riegel (1972), with evidence from studies of the common cause hypothesis linking sensory function, lung function, grip strength and other biological markers with performance on cognitive tests (Christensen et al., 2000; Christensen, Mackinnon, Korten, & Jorm, 2001; Salthouse, Hancock, Meinz, & Hambrick, 1996). The latter explanation suggests that development in early life, such as fetal events, birth weight and early nutrition, shape future patterns of health and disease, which confound the relationship between intelligence and mortality (Deary, 2005). A refinement of (i) is that intelligence is associated with mortality because it reflects basic or core information processing mechanisms reflected in measures such as RT and grip strength (Deary & Der, 2005; Shipley et al., 2006). These two studies demonstrated that SES and health factors affect the relationship but that core processes such as reaction time are critical in predicting mortality.

The three proposed explanations of the link between mortality and intelligence are testable. The first predicts that education, employment history and other measures of lifetime opportunity will be associated with both intelligence and mortality and will consequently reduce the effect of intelligence on mortality. The second predicts that health behaviors, such as substance use history and healthcare utilization measured both currently and retrospectively over the lifespan, will likewise mediate the association between intelligence and mortality. The third set of explanations is more complex but suggests that disease status and a range of health or biological markers may account for a large proportion of the variance in the relationship between intelligence and mortality. The refinement of the explanation proposed by Deary and Der (2005) is that after accounting for core biological processes (reflected in biological measures such as grip strength, sensory processing and reaction time), the relationship between intelligence and mortality should be reduced or eliminated.

Two tests that capture the construct of intelligence are used in the present study. The Symbol–Letter Modalities Test (SLMT), a task similar to Smith's (1973) Symbol–Digit

Modalities Test and Wechsler's (Wechsler, 1981) Digit–Symbol Substitution, is a perceptual speed test that provides a measure of fluid intelligence. SLMT measures the efficiency of visual search and memory for the symbols presented in the task (Gilmore, Spinks, & Thomas, 2006) and performance on the task is correlated with measures of general intelligence such as the Wechsler Adult Intelligence Scale (Waldmann, Dickson, Monahan, & Kazelskis, 1992). The National Adult Reading Test (NART; Nelson, 1982) is a test of vocabulary that provides a measure of crystallized intelligence. NART performance is also correlated with measures of general intelligence and, unlike SLMT, is resistant to the effects of dementia (Bright, Jaldow, & Kopelman, 2002). Having the two tests allowed us to formulate differential predictions of the effect of these cognitive variables on mortality. Based on past research, SLMT performance was hypothesized to be a better predictor of mortality than NART. We also predicted that the relationship between SLMT and mortality would be more strongly mediated by health status than the relationship between NART and mortality, since NART performance is more resistant to the effects of declining health.

1. Method

1.1. Participants

The Canberra Longitudinal Study (CLS) was a large epidemiological survey of mental health and cognitive functioning that began in 1990. The study design is more fully detailed by Christensen et al. (2004). Eight hundred and ninety-six participants (456 men and 440 women) aged 70 or older at the time of the baseline assessment were recruited for the baseline assessment. All participants were initially living in the community in the cities of Canberra or Queanbeyan, Australia. Participants were sampled from the compulsory electoral roll, with 69% responding. Approval for the research was obtained from the Ethics in Human Experimentation Committee of The Australian National University.

1.2. Survey procedure

Participants were interviewed on up to four occasions over 12 years. Interviews were sought from both the participant and an informant, although the present study only examines participant data. Baseline interviews lasted approximately 2 hours, incorporating a survey measuring a wide range of risk factors including socio-demographics, physical health and disease status, mental health status, cognitive performance and social support. Interviews also included physical assessments of blood pressure, lung function, grip strength, vision and reaction time. Trained professional interviewers conducted the interviews.

Of the original sample of 896 participants, 185 (20.6%) were deceased by four years, 363 (40.5%) were deceased by eight years, and 544 (60.7%) were deceased by 12 years. At the end of vital status collection in June 2007, 687 (76.7%) of the participants were deceased. Of the participants who remained in the study, 14.1% (100/711) refused or were unable to complete the first follow-up interview, 21.1% (100/474) for the second follow-up and 21.1% (57/270) for the third follow-up.

1.3. Assessment of mortality

Mortality status and date of death were established by contacting relatives, searching the National Death Index, and from death notices in the local newspaper. The National Death Index, a register of all deaths in Australia, was searched by name and date of birth. Missing death identifications from the National Death Index would most likely have been a rare occurrence, as the index provides nationwide coverage. The additional methods used for death reporting (contacting relatives, newspaper searches) provide further confidence in the mortality status data. Mortality status was followed for up to 17 years, from the start of baseline interviews in September, 1990 until June 30, 2007. Survival was calculated as the time from the baseline interview to death for deceased participants, or from baseline until June 30, 2007 for surviving (right-censored) participants. For six participants with unknown day of death, the day was set to the 15th of the month. For two participants with an unknown month of death, the month was set to June. Taking deaths into account, the mean follow-up time was 9.7 years – 16.4 years for surviving participants and 7.6 years for deceased participants.

1.4. Assessment of intelligence

Two tasks were used to assess different domains of intelligence. The Symbol Letter Modalities Test is a test of perceptual speed that has been used as a measure of fluid intelligence. This test is based on earlier tests of fluid intelligence such as Digit–Symbol Substitution (Wechsler, 1981) and the Symbol–Digit Modalities Test (Smith, 1973). Participants were provided with a key which linked 10 symbols with letters of the alphabet (A to I). They were given 90 s to call out to the examiner the letters of the alphabet that corresponded to symbols printed in rows on the page. The key to the symbol–letter pairings was printed above the array. The test measures both fluid intelligence and cognitive speed. However, it allows an oral response to be made by the participants, thereby limiting possible contamination from impaired psychomotor functioning. The number of correct symbol–letter pairs made in 90 s was summed and the scores were standardized to produce an IQ-type score (SLMT IQ).

The National Adult Reading Test (NART; Nelson, 1982) assessed crystallized intelligence by testing the vocabulary of participants. The NART is a list of 50 words that are not pronounceable phonetically. Participants read the words aloud and testing is discontinued whenever there were 14 failures out of 15 items. The number of correct pronunciations made was summed and the scores were standardized to produce an IQ-type score (NART IQ).

1.5. Control variables

All of the control variables were measured in the baseline interview, with the exception of subsequent dementia diagnosis which was made on each wave of measurement.

1.5.1. Socio-economic status

Educational status was based on responses to two questions regarding the number of years in school and the highest qualification obtained. These two questions were combined

into a single measure representing the number of years it took participants to attain their highest educational qualification. Work history was asked as an open-ended question that was then given a standard job classification coding. From these codings, participants were classified into one of six categories: unskilled, semi-skilled, skilled, white collar, lower professional, managerial/professional. However, given the advanced age of the sample (the categorizations are based on a contemporary coding system) and a lack of predictive power provided by these categories, they were collapsed into a binary measure reflecting manual or non-manual employment. Participants who were involved in home duties were classified based on their spouse's occupational status.

1.5.2. Locus of control

A 14-item locus of control scale was administered, with participants rating items such as "I am confident of being able to deal successfully with future problems" on a six-point Likert scale from "Strongly disagree" to "Strongly agree". The scale was based on the 17-item Locus of Control of Behavior scale (Craig, Franklin, & Andrews, 1984) with three symptom-related items removed. Eight items were negatively-worded and were reverse scored. The score was a mean of the ratings (range 1–6), with higher scores indicating that the participant saw themselves as the locus of control.

1.5.3. Health behaviors

Participants reported whether they were current smokers, past smokers who had quit, or had never smoked. Level of activity was based on a six-item scale asking participants how often they engaged in activities "these days", with possible scores ranging from 0–18. The activities were reading, some sort of physical activity, active involvement in interests or hobbies, sitting at home (inactivity, negatively scored), and planned activities such as household tasks and visiting people. (Christensen et al., 1996) While there is a relationship between the activity scale and the level of physical disability ($r = -.44$), participation in social and intellectual pursuits are not captured by measures of physical disability.

1.5.4. Physical health

A brief self-reported medical history for each participant was taken during the survey. Heart attack history, stroke history (combining strokes, mini-strokes and transient ischemic attacks) and hypertension history were measured as dichotomous variables. A disease count covering 14 other diseases (including diabetes and cancer) and a symptom count for 21 symptoms (including falls, dizziness and chest pain) were generated. To measure functional ability, eight Activities of Daily Living (ADLs) were rated for difficulty on a four-point scale (no difficulty, some difficulty but no help needed, need help, bedridden) and five Instrumental Activities of Daily Living (IADLs) were rated on a three-point scale (no help needed, need help, cannot do). Two scales of functional ability were generated from these items, with ADL scores ranging from 0 to 24 and IADL scores ranging from 0 to 8. Higher scores on these scales indicate greater functional disability. Self-rated health was measured by asking participants to rate their general health on a four-point scale from "Excellent" (1) to "Poor" (4).

Sensory indicators of physical health included reaction time, grip strength, visual and auditory function. To measure choice reaction time, participants were asked to press a button with their left or right hand depending on which of two stimulus lights were illuminated (interstimulus intervals ranged from 0.5 to 2.0 s) (Christensen et al., 2000). The trials were performed mid-way through the survey, and choice reaction time was measured as the mean response time over 20 trials. Grip strength was taken using a Smedley hand dynamometer which measures the force exerted in kilograms (Christensen et al., 2000). Visual impairment was self-rated, with participants reporting "poor" eyesight or blindness classified as visually impaired. Hearing impairment was also self-rated, with participants who used a hearing aid or reported poor hearing classified as hearing impaired.

Table 1
Descriptive statistics for predictor variables by vital status after 17 years ($n = 896$).

	N	Survivors ($n = 191$–209)	Decedents ($n = 566$–687)	*p* value
		Mean (SD) or freq (%)	Mean (SD) or freq (%)	
SLMT IQ score	853	103.80 (14.10)	93.91 (16.97)	<0.001
NART IQ score	835	113.16 (8.35)	111.32 (10.08)	0.001
Age	896	74.09 (3.38)	77.30 (5.09)	<0.001
Gender: male	896	83 (39.7%)	373 (54.3%)	<0.001
Socio-economic status				
Years of education	894	11.17 (2.29)	11.41 (2.66)	0.275
Work history: manual work	896	141 (67.5%)	551 (59.7%)	0.039
Self as locus of control	759	4.36 (0.61)	4.21 (0.60)	<0.001
Health behaviors				
Smoking status	877			0.004
Never smoked		110 (52.9%)	391 (42.0%)	
Previously smoked		78 (37.5%)	383 (45.6%)	
Currently smoke		20 (9.6%)	103 (12.4%)	
Activity score	875	12.72 (2.43)	11.51 (3.17)	<0.001
Physical health				
Self-rated health	874			<0.001
Excellent		59 (28.5%)	160 (15.1%)	
Good		120 (58.0%)	478 (53.7%)	
Fair		27 (13.0%)	192 (24.7%)	
Poor		1 (0.5%)	44 (6.4%)	
Heart attack history	885	23 (11.1%)	157 (19.8%)	<0.001
Hypertension history	887	80 (38.5%)	371 (42.9%)	0.553
Stroke history	887	45 (78.4%)	269 (67.0%)	0.002
Disease count	896	1.69 (1.35)	2.12 (1.47)	<0.001
Symptom count	896	2.93 (2.74)	3.58 (2.87)	<0.001
ADL score	877	0.98 (1.31)	2.14 (2.78)	<0.001
IADL score	877	0.28 (0.67)	0.86 (1.61)	<0.001
Choice RT (s)	798	0.46 (0.12)	0.48 (0.15)	<0.001
Grip strength (kg)	877	25.95 (9.91)	24.29 (9.44)	0.012
Visual impairment	887	163 (78.4%)	455 (67.0%)	<0.001
Hearing impairment	887	156 (75.0%)	475 (70.0%)	0.069
Subsequent dementia diagnosis	896	3 (1.4%)	41 (6.0%)	0.013
Mental health				
Goldberg depression score	865	1.71 (1.79)	2.13 (2.00)	<0.001
Goldberg anxiety score	870	2.49 (2.35)	2.46 (2.25)	0.761

Notes: *p* values are from *Z* tests (binary and continuous variables) and χ^2 tests (categorical variables) from univariate Cox regressions using imputed data; SLMT IQ: Symbol–Letter Modalities Test IQ score; NART IQ: National Adult Reading Test IQ score; ADL: Activities of Daily Living; IADL: Instrumental Activities of Daily Living; RT: reaction time.

1.5.5. Mental health

Mental health ratings were included in the analysis as supplementary measures of health status. The Goldberg Depression Scale and Goldberg Anxiety Scale each consist of nine yes/no items measuring symptoms of depression and anxiety (Goldberg, Bridges, Duncan-Jones, & Grayson, 1988). Scores on these tests reflect a symptom count ranging from 0 to 9.

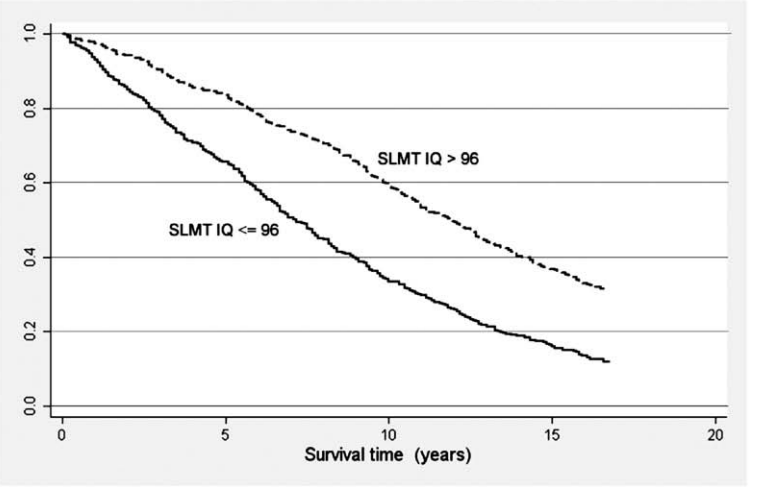
1.5.6. Dementia

To control for potential confounding by dementia, participants who were given an ICD-10 (World Health Organization, 1993) diagnosis of dementia or severe dementia later in the study (at waves 2, 3 and 4 4, 8 and 12 years after baseline) were identified. Diagnoses were made using the Canberra Interview for the Elderly (CIE) (Social Psychiatry Research Unit, 1992), which provides information from which a diagnosis of dementia can be made according to ICD-10 (World Health Organization, 1993) and DSM-III-R (American Psychiatric Association, 1987) by means of a computer algorithm.

1.6. Analyses

Descriptive analyses compared living participants to deceased participants to investigate which predictors were associated with death during the follow-up time. Survival time was graphed using Kaplan–Meier curves and modeled using Cox proportional hazards regression analyses. A series of six regression analyses included the intelligence measures with a combination of potential mediators or confounders, corresponding to the hypothesized mechanisms of the intelligence–mortality relationship. To facilitate interpretation of the Cox regression analyses, continuous variables (excluding age, years of education and disease and symptom counts) were standardized by subtracting the mean for the entire sample and dividing by the standard deviation. To account for potential confounding by end-of-life illness, specifically, sub-clinical disease states not captured by the health status measures, the analyses were repeated with the exclusion of participants who died

a) *Fluid intelligence: Symbol-Letter Modalities Test*



b) *Crystallized intelligence: National Adult Reading Test*

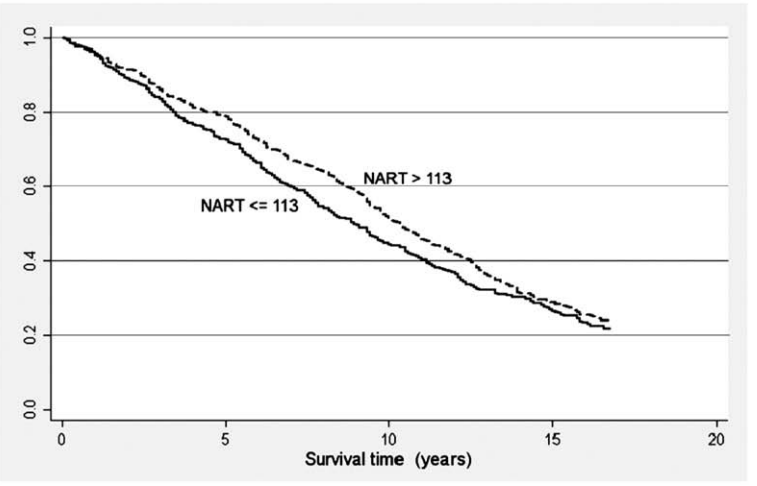


Fig. 1. Kaplan–Meier curves of cumulative survival over 17 years plotted separately for participants with IQ above and below the sample median ($n = 896$).

in the first four years of the study. The analyses were also repeated separately by gender to investigate whether the intelligence–mortality relationship differed for males and females.

Incomplete data for the survival analyses were imputed using the *ICE* procedure in Stata. Ten imputed data sets were generated by simultaneously modeling all of the independent variables from the baseline survey that were used in the analyses. The imputation procedure used linear regression to impute continuous variables, logistic regression to impute dichotomous variables and multinomial logistic regression to impute the two categorical variables (smoking status and self-rated health). Survival was not imputed, as complete data were available. Among the variables used in the analysis, 13% of the sample had one missing value and a further 10% of the sample had two or more missing values. The imputed data sets were combined using the *micombine* procedure in Stata, in conjunction with the *stcox* procedure that was used for the Cox proportional hazards regression models. SPSS version 15 was used for the descriptive analysis. Stata version 9 was used for the imputation and survival analyses.

2. Results

Descriptive statistics are shown in Table 1. These are based on the raw data, with *p*-values taken from Wald tests from univariate Cox regressions combined from analyses of the ten imputed data sets. Overall, the mean age was 76.6 years, with 11.4 years of education. With the exceptions of education, hypertension history, hearing impairment and Goldberg Anxiety score, all variables were significantly associated with mortality ($p<0.05$).

The effects of SLMT (Fig. 1a) and NART (Fig. 1b) on survival time were plotted using Kaplan–Meier curves. A median split was chosen to separate high and low performance on the two tasks. The figures show that the effect of SLMT on survival is much more pronounced than that of NART. There is a 20% difference in cumulative survival between high and low SLMT groups after approximately five years, and this difference is maintained until the end of the period of observation. The difference between high and low NART groups, however, is only apparent between approximately four and thirteen years after baseline.

Six models of mortality risk were tested using Cox proportional hazards regression models (Table 2). The univariate effect of SLMT was tested in Model 1, then age and gender were added to create Model 2. Model 3 built on Model 2, simultaneously testing the effect of SES (education and employment background) in conjunction with locus of control, a potential mediator of the effect of SES on mortality (Siegrist & Marmot, 2004). Health behaviors (smoking status and activity level) were entered into a separate model with SLMT, age and gender (Model 4). Health status, including physical health and mental health measures and dementia, was included simultaneously with SLMT, age and gender in Model 5. Finally, the significant predictors (at $p<.05$) from Models 2–5 were combined into a single model (Model 6). The six models were also fitted with the NART (Table 3).

Table 2
Cox proportional hazards regression models of mortality over 17 years using baseline fluid intelligence measure ($n=896$; 687 decedents).

Model	(1) Univariate	(2) With age & gender	(3) SES & locus of control	(4) Health behaviors	(5) System integrity	(6) Combined model
SLMT IQ score	0.69 (0.64, 0.75)***	0.76 (0.70, 0.82)***	0.74 (0.67, 0.81)***	0.81 (0.74, 0.89)***	0.81 (0.74, 0.89)***	0.80 (0.72, 0.88)***
Age		1.08 (1.07, 1.10)***	1.08 (1.06, 1.10)***	1.08 (1.06, 1.10)***	1.07 (1.05, 1.09)***	1.07 (1.05, 1.09)***
Gender = male		1.62 (1.39, 1.89)***	1.60 (1.37, 1.87)***	1.56 (1.31, 1.84)***	2.43 (1.87, 3.14)***	2.41 (1.89, 3.06)***
Yrs of education			1.06 (1.03, 1.10)***			1.06 (1.03, 1.09)***
Manual worker			1.02 (0.85, 1.22)			
Self as locus of control			0.91 (0.83, 1.00)*			0.93 (0.85, 1.02)
Smoking status						
Never				1.13 (0.95, 1.35)		
Previous				1.05 (0.81, 1.35)		
Current†				1.00		
Activity scale				0.83 (0.76, 0.90)***		0.91 (0.83, 1.00)*
Self-rated health						
Excellent					0.44 (0.27, 0.73)**	0.38 (0.24, 0.61)***
Good					0.53 (0.34, 0.83)**	0.46 (0.30, 0.69)***
Fair					0.71 (0.45, 1.13)	0.63 (0.41, 0.98)*
Poor†					1.00	1.00
Heart attack history					1.42 (1.16, 1.74)**	1.50 (1.24, 1.83)***
Hypertension history					1.24 (1.05, 1.45)*	1.28 (1.09, 1.51)**
Stroke history					1.13 (0.89, 1.43)	
Disease count					1.05 (0.99, 1.11)	
Symptom count					1.00 (0.97, 1.04)	
ADL score					1.11 (0.98, 1.25)	
IADL score					1.06 (0.94, 1.19)	
Choice RT					1.02 (0.90, 1.16)	
Grip strength					0.80 (0.70, 0.92)**	0.76 (0.67, 0.86)***
Visual impairment					1.12 (0.93, 1.34)	
Hearing impairment					0.99 (0.84, 1.18)	
Goldberg depression					1.03 (0.93, 1.14)	
Goldberg anxiety					0.89 (0.80, 0.99)*	0.91 (0.83, 0.99)*
Dementia diagnosis					1.14 (0.82, 1.58)	

†Reference category; *$p<.05$; **$p<.01$; ***$p<.001$.

SLMT IQ was significantly and substantially associated with mortality irrespective of which other variables were in the model. The effect of fluid intelligence on mortality was reduced but not fully accounted for when adjusting for age and gender, and including the 'competing' predictors measuring SES, health behavior, health status and sensory processing. A 15-point (one SD) disadvantage in SLMT IQ score was associated with between 23–45% increase in the risk of mortality (25% for the combined model), depending on which variables were included in the model. When age and gender were excluded from the models, attenuation of the SLMT hazard ratios from the inclusion of predictors representing the three proposed mechanisms ranged from 0–7%. In contrast, the effect of NART IQ on mortality was reduced when accounting for SES or health status and no longer significant after adjusting for health behaviors. A 15-point (one SD) disadvantage in NART IQ score was associated with between 8 and 14% increase in the risk of mortality, depending on the model. Attenuation for the NART hazard ratios ranged from 0–4%, after excluding the effects of age and gender. Subsequent dementia onset was not responsible for the association between intelligence and mortality.

Additional analyses were conducted to further account for potential confounding by baseline health status. Participants who died in the first four years of the study, prior to the first follow-up interview ($n = 190$ decedents), were excluded from the analysis. The effect of SLMT on mortality remained stable, as estimated by the six models presented in Tables 2 and 3. Hazard ratios remained between 0.72 and 0.84 with $p < .001$ for all models. However, the effect of NART was further attenuated, with only the univariate effect of NART significantly associated with mortality status (HR = 0.89, $p = .015$). When age and gender (HR = 0.91, $p = .055$), socioeconomic status (HR = 0.90, $p = .087$), health behaviors (HR = 0.94, $p = .223$) and health status (HR = 0.93, $p = .146$) were entered, the effect of NART became non-significant. A second supplemental analysis investigated whether the intelligence–mortality relationship was different for men and women. The effect of SLMT on mortality was consistent across males and females, with $p < .01$ for all six models across both genders and hazard ratios ranging from 0.64 to 0.84. However, the effect of NART tended to be weaker among men than women when adjusting for age ($HR_{female} = 0.86$, $p = .014$; $HR_{male} = 0.91$, $p = .078$) and when adjusting for health behaviors ($HR_{female} = 0.88$, $p = .039$; $HR_{male} = 0.95$, $p = .349$). The univariate effect of NART was significant for both genders, but after adjusting for socioeconomic variables or health status, the effect of NART did not reach significance for either males or females (HRs ranging from 0.88 to 0.90).

3. Discussion

The present study examined the intelligence–mortality relationship using data collected from the Canberra Longitudinal Study (CLS) over 17 years in an older cohort of community dwellers. Better SLMT performance was found to be significantly associated with lower mortality risk. This effect persisted after 17 years of follow-up, extending the findings

Table 3
Cox proportional hazards regression models of mortality over 17 years using baseline crystallized intelligence measure ($n = 896$; 687 decedents).

Model	(1) Univariate	(2) With age and gender	(3) SES and locus of control	(4) Health behaviors	(5) System integrity	(6) Combined model
NART IQ score	0.88 (0.81, 0.95)**	0.89 (0.82, 0.97)**	0.90 (0.81, 0.99)*	0.93 (0.85, 1.01)	0.90 (0.83, 0.98)*	0.89 (0.80, 0.99)*
Age		1.10 (1.08, 1.12)***	1.10 (1.08, 1.11)***	1.09 (1.07, 1.11)***	1.07 (1.05, 1.09)***	1.08 (1.06, 1.10)***
Gender = male		1.61 (1.38, 1.87)***	1.64 (1.40, 1.92)***	1.56 (1.32, 1.85)***	2.65 (2.05, 3.41)***	2.51 (1.97, 3.18)***
Yrs of education			1.05 (1.01, 1.08)*			1.05 (1.02, 1.09)**
Manual worker			1.09 (0.90, 1.31)			
Self as locus of control			0.87 (0.79, 0.95)**			0.92 (0.83, 1.01)
Smoking status						
Never				1.13 (0.94, 1.35)		
Previous				1.09 (0.85, 1.40)		
Current†				1.00		
Activity scale				0.78 (0.72, 0.85)***		0.86 (0.79, 0.94)**
Self-rated health						
Excellent					0.42 (0.26, 0.68)***	0.35 (0.23, 0.56)***
Good					0.51 (0.33, 0.80)**	0.43 (0.29, 0.64)***
Fair					0.69 (0.44, 1.10)	0.59 (0.38, 0.90)*
Poor†					1.00	1.00
Heart attack history					1.41 (1.15, 1.73)**	1.51 (1.24, 1.84)***
Hypertension history					1.22 (1.04, 1.44)*	1.27 (1.08, 1.50)**
Stroke history					1.14 (0.90, 1.44)	
Disease count					1.05 (0.99, 1.11)	
Symptom count					0.99 (0.96, 1.03)	
ADL score					1.12 (1.00, 1.27)	
IADL score					1.08 (0.96, 1.21)	
Choice RT					1.10 (0.97, 1.24)	
Grip strength					0.80 (0.70, 0.92)**	0.75 (0.66, 0.85)***
Visual impairment					1.09 (0.91, 1.31)	
Hearing impairment					1.02 (0.86, 1.21)	
Goldberg depression					1.04 (0.94, 1.16)	
Goldberg anxiety					0.89 (0.81, 0.99)*	0.91 (0.83, 0.99)*
Dementia diagnosis					1.16 (0.83, 1.61)	

†Reference category; *$p < .05$; **$p < .01$; ***$p < .001$.

of Korten et al. (1999) who examined the same cohort after four years. The relationship between SLMT and mortality remained when participants who died early in the study were omitted and was similar for men and women. NART performance was also significantly associated with mortality, although the effect was mitigated by controlling for health behaviors such as smoking status and activity level. Excluding participants who died in the first four years of the study diminished the effect of NART to non-significance. In addition, the effect of NART was stronger for women than men.

A set of six models tested three major proposed mechanisms for the relationship between intelligence and mortality. We tested for the effect of SES, as measured by education and type of employment. The effect of health behavior was tested using measures of smoking history and physical, mental and social activity. We tested for the effect of health status using measures of self-rated health, disease history, functional disability, grip strength and mental health status. In response to the findings of Deary and Der (2005), we controlled for sensory processing ability using measures of choice reaction time, visual impairment and hearing impairment. We also controlled for dementia diagnosis in response to the theory of Backman and MacDonald (2006) that the intelligence–mortality relationship is due largely to dementia-related deficits. The present study did not find strong support for any of the three explanations. Moreover, evidence for a particular explanation was contingent on the type of intelligence test used. For SLMT, although there was slight attenuation of the effect when controlling for SES, health behaviors or health status, the effect of SLMT remained significant, providing limited support for the three major mechanisms. The effect of intelligence on mortality when measured by the NART was also slightly attenuated by the effects of SES and health status. However, after adjusting for smoking status and activity level, the attenuation was sufficient that NART was no longer significantly associated with mortality.

The divergence in findings suggests the mediation of the relationship between intelligence and mortality by SES, health behaviors and health status is marginally stronger for fluid intelligence performance than for tests of crystallized intelligence. Fluid intelligence tasks such as the SLMT may reflect any initial and early adulthood effects of intelligence on mortality, combined with the effects of physical health decline and ageing processes not due to physical health. NART performance, on the other hand, is likely to reflect initial intelligence, education across the lifespan and consistent implementation of health behaviors, but is less susceptible to effects of independent or systemic disease and biological ageing processes.

Choice reaction time was associated with mortality, however, there was no effect of reaction time when models also included SLMT or NART score. Grip strength was associated with mortality but accounted for little of the variance in the intelligence–mortality relationship. Sensory impairments were not associated with mortality. Manual occupation was also not associated with mortality after controlling for intelligence. This finding is not due to the collapsing of occupational categories into a binary measure, as a six-category version of the measure also had no association with mortality. Smoking status was not associated with mortality, a finding divergent from past research (Tessier et al., 2000) which may be explained by the advanced age and low smoking prevalence of this sample. In the final model, which included measures of SES, health behavior and health status, a one standard deviation decrement in SLMT performance was associated with a 25% increase in mortality, while a one standard deviation decrement in NART performance was associated with an 12% increase in mortality

In this cohort, the intelligence–mortality relationship appears to be based on more than lower-level processing efficiency. There was a strong independent effect of SLMT even after adjusting for the hypothesized mechanisms of the relationship together with reaction time and sensory impairment. In addition to mental speed, SLMT measures the efficiency of visual search and memory for the symbols presented in the task (Gilmore et al., 2006). Since reaction time was controlled for, the aspects of SLMT that are associated with mortality would appear to be a combination of processing speed with memory and attention performance. Further research into which constituents of the SLMT task best predict mortality could adapt the frameworks used by Gilmore et al. (2006) and Salthouse and Kersten (1993) to modify the SLMT task into components that separately measure the processing speed, memory and attentional aspects of the task.

While the present findings were often in accordance with previous research, there were some important differences. Previous research of the relationship between poor SLMT performance and mortality risk was supported (Anstey et al., 2001; Ghisletta et al., 2006; Pavlik et al., 2003; Portin et al., 2001). Previous investigations have found little evidence for a relationship between NART performance and mortality (Abas et al., 2002; Anstey et al., 2001). While NART performance was significantly associated with mortality risk in the present study, the effect was tenuous after controlling for measures of SES, health behavior and health status. However, contrary to previous findings (Deary & Der, 2005), reaction time did not explain the effect of either of the intelligence tasks. The differences in findings may be attributable to the age of the cohort in the present study. All of the participants were 70 or older at baseline, averaging over 75 years of age, and were followed until they were in their late-80s or beyond. Previous research has shown that the effect of intelligence on mortality is most pronounced in older age groups (Lyyra et al., 2006; Shipley et al., 2006).

3.1. Limitations of the findings and directions for future research

The present study examined vital status over 17 years using baseline measurements as predictors. However, intelligence was assessed at the start of the study, when participants were already advanced in age and potentially in poor health. Participants who were close to death at the time of the baseline may have been in a state of terminal decline, leading to an overestimation of the effect of poor cognitive performance on mortality. While the follow-up analysis omitted participants who died in the early stages of the study, the baseline intelligence measurement may still have been influenced by sub-clinical health problems. Additional research into temporal variations in the intelligence–mortality relationship would further delineate the influence of time-to-death on cognitive performance, as would modeling cognitive

performance as an outcome, using time-to-death as a predictor. Another problem for the survival models is that there may have been cases where death occurred but was not recorded. Despite a thorough search protocol, the extent of missing death records could not be assessed in the present study, so all cases were treated as living if there was no evidence to the contrary. Having noted this, however, treating potential decedents as survivors would result in a more conservative estimate of the association between intelligence and mortality.

The models that were tested were operationalized using available measures from the baseline survey. Although it is difficult to articulate the models sufficiently well to test then more than in a general way, testing them is important, as it forces a theoretical articulation and reveals the difficulties of testing complex relationships among processes over long periods. Nevertheless, some of the measures that were used in this study could be further refined for the purposes of future research. Only a self-reported measure of vision impairment was included in the baseline interview, which may not accurately reflect visual functioning. Sensory function, particularly visual acuity, can influence performance on tasks like SLMT (Gilmore et al., 2006). Self-report measures of health status (disease history, functional ability) may also have been inaccurate, although objective health measures (grip strength, reaction time) were also included as predictors in the models. Additional measures of health behaviors would also have strengthened the analysis — the baseline interview did not include measures of alcohol and other substance use, diet, healthcare utilization or medication adherence. Reflecting the constraints of a large in-home epidemiological survey, the tests available to measure intelligence assessed only specific domains of cognitive performance. General intelligence tests, such as the WAIS and AH4, cover a broader array of abilities. However, simply examining the construct of general intelligence is not sufficient in investigating what aspects of intelligence are most strongly associated with mortality. Further research on the intelligence–mortality relationship should continue to examine a broad range of cognitive abilities, including memory, attention, reasoning, knowledge and executive function, in a variety of domains, including episodic, verbal and visuospatial.

Finally, examining all-cause mortality is a starting point for investigating the relationship between intelligence and mortality. There is strong evidence for a relationship between intelligence and cardiovascular mortality but less for the relationship between intelligence and cancer mortality (Hart et al., 2003; Shipley, Der, Taylor, & Deary, 2007). Examining modifiable mediators of both mortality and cognitive performance has the potential to guide future health interventions. Continuing to research the associations between various domains of cognitive performance and mortality will advance our understanding into the nature of the intelligence–mortality relationship.

Acknowledgements

The Canberra Longitudinal Study was supported by NHMRC Unit Grants 973301 and 933301 and NHMRC Program Grant 179805. HC is supported by NHMRC Principal Research Fellowship 366781.

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Psychology and Aging

0882-7974/11/$12.00 DOI: 10.1037/a0024517

The Association Between Change in Cognitive Ability and Cause-Specific Mortality in a Community Sample of Older Adults

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While there is consistent evidence that initial levels of cognitive ability predict mortality, there is mixed evidence for a relationship between changes in cognition and mortality. There have been few studies that have examined whether the level and slope of cognitive performance is predictive of subsequent mortality from all causes or from cardiovascular disease, stroke, heart disease, respiratory disease, or cancer. This study aimed to assess whether the level and slope of cognitive ability were associated with all-cause or cause-specific mortality. A cohort of 896 community-based elderly people in Australia was interviewed four times over 12 years, with vital status followed for up to 17 years. Of these, 592 participants completed two or more interviews and were included in survival models of six mortality outcomes. Cognitive change in five domains of ability was estimated using latent growth models. Poorer initial processing speed or verbal fluency was significantly associated with greater all-cause and/or cardiovascular mortality. In addition, declines in global ability were associated with greater all-cause, cardiovascular, and heart disease mortality. Vocabulary and episodic memory were not associated with mortality, and none of the cognitive tests significantly predicted respiratory or cancer mortality. Initial levels of cognitive ability tend to be better predictors of subsequent mortality than changes in ability are. The results suggest that vascular events may be largely responsible for the overall relationship between cognition and mortality.

AQ: 1 *Keywords:* cause-specific mortality, all-cause mortality, cognition, cognitive change, latent growth models, cardiovascular mortality

While prospective research has consistently shown that cognitive ability predicts mortality, there is mixed evidence for a relationship between changes in cognition and mortality. Few studies have definitively examined whether the level and slope of cognitive performance is associated with all-cause mortality and whether specific causes of mortality might explain the overall relationship. Furthermore, the use of appropriate methodologies for assessing change in cognition is critical for providing definitive evidence about relationships between cognitive change and mortality. The present study used latent growth models to obtain estimates of level and slope of cognitive ability, with the aim of assessing whether initial cognitive ability or changes in cognitive performance were associated with mortality from all causes, cardiovascular disease, cancer, respiratory disease, heart disease, or stroke.

A review by Bosworth and Siegler (2002) reported that while there was consistent evidence that initial levels of cognitive performance were predictive of mortality, there was mixed evidence for a relationship between cognitive change and mortality. Declines in crystallized abilities were more consistently associated with increased mortality than declines in memory and fluid abilities. Bosworth and Siegler (2002) attributed this differential effect to the robustness of crystallized abilities to normal aging, suggesting that changes in these abilities may reflect the types of biological deterioration associated with mortality. Relationships between cognitive change and mortality may be partly explained by common associations of both cognition and mortality with psychomotor or sensory abilities, health behaviors, physical health, or genetic factors (Bosworth and Siegler, 2002; Shipley, Der, Taylor, and Deary, 2008). However, studies of the cognition-mortality relationship often report little attenuation of the effect even after adjusting for such factors (Batterham, Christensen, and Mackinnon, 2009; Shipley et al., 2008). Bosworth and Siegler (2002) concluded that further population-based longitudinal research on the association between cognitive change and cause-specific mortality was necessary to better characterize this relationship.

Latent growth models are a class of structural equation models that represent individual level data in terms of an initial level of

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The Canberra Longitudinal Study was supported by NHMRC Unit Grants 973301 and 933301 and NHMRC Program Grant 179805. HC is supported by NHMRC Senior Principal Research Fellowship 525411.

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performance latent variable or factor (*level*), a rate of change factor (*slope*), and error (*residual*) parameters (Hofer et al., 2002; McArdle and Epstein, 1987). These structures are analogous to random intercept and slope terms in mixed models. Importantly, these models accommodate missing data, appropriately accommodate unequal numbers of individual observations, account for dependencies among observations within individuals, and account for individual differences in the rates of cognitive decline (Bäckman and MacDonald, 2006). Recent developments in structural equation modeling allow the incorporation of latent growth models into a survival model (Asparouhov, Masyn, and Muthén, 2006). One of the key problems in examining the effect of cognitive change on mortality has been inconsistency in the way that cognitive change is assessed. Previous research has measured cognitive change by (a) comparing mean differences (Bosworth and Schaie, 1999; Mortensen and Kleven, 1993), (b) categorizing participants as decliners or nondecliners based on the size of score changes (Anstey, Luszcz, Giles, and Andrews, 2001), (c) grouping the sample by time to death and comparing change in cognitive scores (Johansson and Berg, 1989), or (d) using linear regression to obtain individual intercept and slope least squares estimates to predict mortality (Deeg, Hofman, and van Zonneveld, 1990).

While latent growth models have been in use for some time, very few studies have used these models to examine the relationship between cognitive change and mortality. Johansson et al. (2004) found that declines in crystallized knowledge and verbal abilities were associated with increased risk of mortality. However, the latent growth model used by Johansson et al. (2004) did not incorporate survival analysis; this warrants the extension of the latent growth methodology in the present analysis. Ghisletta, McArdle, and Lindenberger (2006) used a mixed model approach that is analogous to a latent growth model and reported significant associations of changes in both speed and fluency on survival. While there were commonalities among the findings of these two studies, the types of abilities that were predictive of mortality were divergent. Fluid and speed-based cognitive tasks decline more rapidly than crystallized intelligence as a consequence of normative aging (Horn, 1968), so declines in crystallized abilities may be more strongly associated with biological deterioration that leads to mortality, consistent with the findings of Johansson et al. (2004). However, among cohorts that are cognitively intact (with dementia excluded at baseline or controlled for) rates of normative aging, as represented by declines in fluid abilities, may be a more dominant characteristic in predicting mortality, consistent with the findings of Ghisletta et al. (2006). Indeed, Ghisletta et al. (2006) concluded that the relationship between cognitive decline and mortality was not specific to any domain of functioning.

Nevertheless, these studies reported the common finding that the initial level of cognitive performance was more strongly and consistently associated with mortality than change in performance was. Sliwinski et al. (2006) suggested that cognitive change may only weakly predict mortality because the change does not accelerate continuously. Instead, normative cognitive change begins at a gradual pace in the preterminal phase; then, when biological constraints increase in proximity to death, cognitive decline increases more rapidly in the terminal phase (Sliwinski et al., 2006). Researchers have modeled the time course of terminal decline by using change point models to distinguish two phases of decline (Batterham, Mackinnon, and Christensen, in press; Sliwinski et al., 2006; Thorvaldsson et al., 2008). However, this methodology does not directly assess whether declines in cognition are associated with increased risk of death. Since there have been so few studies of cognition and mortality that have used a latent growth approach, it is important to further explore this relationship directly.

An additional gap in the research on cognitive change and mortality is the examination of cause-specific mortality. Small, Fratiglioni, von Strauss, and Bäckman (2003) separated cardiovascular and noncardiovascular causes of death and found no differences in the strength of the cognition–mortality associations for the two groups. However, Shipley, Der, Taylor, and Deary (2007) and Shipley et al. (2008) reported that associations between cognition and mortality were strongest for cardiovascular mortality, slightly less consistent for respiratory mortality, and nonsignificant for cancer mortality. These associations remained after adjusting for a range of sociodemographic, health behavior, and health status measures and after excluding participants who died in the first five years of follow-up (Shipley et al., 2008). The difference in findings may be due to the more specific types of mortality defined in the Shipley et al. (2007, 2008) studies, in contrast to the Small et al. (2003) study that combined cancer, respiratory causes, and other causes of death due to small cell sizes. A review of studies examining the relationship between cognition and mortality in diseased populations found strong evidence for the association in patients with stroke and cancer, although the relationship was less clear for heart disease patients (Anstey, Mack, and von Sanden, 2006). Few of these studies, however, identified the cause of death. Identification of the circumstances in which mortality is best predicted by poor cognitive performance may lead to a better understanding of this association. Likewise, identifying the causes of death predicted by *changes* in cognitive abilities may further pinpoint the mechanisms behind such associations. To date, there has been no direct examination of the relationship between cognitive change and multiple causes of death.

The present study aimed to assess the relationship between level and slope of cognitive performance on cause-specific mortality in a cohort of 896 community-based Australian participants aged 70 and older. They were assessed over a 12-year period with up to four comprehensive interviews, and vital status information, including cause of death, was collected for up to 17 years. Consequently, it was possible to assess change in cognitive performance using latent growth models to examine associations with cause-specific mortality. Models were adjusted for measures of physical and mental health to account for the roles of physical function (Prince et al., 2010; Rosano et al., 2005; Wang, Larson, Bowen, and van Belle, 2006), depression (Christensen, Griffiths, Mackinnon, and Jacomb, 1997) and anxiety (Beaudreau and O'Hara, 2008) on late-life cognitive ability. Such adjustment provided a stronger test of the hypothesized relationships between cognition and mortality. Based on previous findings (Ghisletta et al., 2006; Johansson et al., 2004), it was predicted that changes in cognitive performance would be less strongly associated with mortality than initial levels of performance would.

Furthermore, it was hypothesized that performance in all cognitive domains other than vocabulary would be associated with all-cause mortality. Similarly, changes in the five cognitive abilities were hypothesized to have comparable associations with all-cause mortality, such that declines in fluid ability were expected to be equally as predictive of survival as declines in crystallized

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ability. These hypotheses were driven by evidence from the Ghisletta et al. (2006) study and others (Batterham et al., in press; Thorvaldsson et al., 2008). This recent work appears to refute the White and Cunningham (1988) hypothesis that declines in tasks that are resistant to the effects of pathology are more strongly predictive of impending death. In examining cause-specific mortality, stronger relationships were hypothesized between cognitive performance and cardiovascular mortality than cancer or respiratory mortality, as reported by Shipley et al. (2007, 2008). These hypotheses were driven by the strong links reported between cardiovascular disease and cognitive function (Laukka, Fratiglioni, and Bäckman, 2010; Spiro and Brady, 2008) and suggest that vascular pathology may be a critical predictor of terminal decline.

Method

Participants

The Canberra Longitudinal Study is an epidemiological survey of mental health and cognitive functioning in older people. The study design has previously been detailed by Christensen et al. (2004). Eight hundred and 96 participants (456 men and 440 women) aged 70–97 were recruited for the baseline assessment in 1990. All participants were initially living in the community in the cities of Canberra or Queanbeyan, Australia. Participants were sampled from the compulsory electoral roll, with 69% responding, and the sample was stratified by age and gender. Approval for the research was obtained from the Ethics in Human Experimentation Committee of the Australian National University.

Of the original sample of 896 participants, 185 (20.6%) were deceased by four years, 363 (40.5%) were deceased by eight years, and 544 (60.7%) were deceased by 12 years. At the end of vital status collection in June 2007, 687 (76.7%) of the participants were deceased. Of the surviving participants at each measurement occasion, 14.1% (100/711) refused or were unable to complete the first follow-up interview, 21.1% (100/474) for the second follow-up, and 21.1% (57/270) for the third follow-up. Only participants who had one or more follow-up interviews were included in the analyses so that measures of cognitive change could be obtained. Nineteen participants were excluded on the basis of missing baseline data, resulting in a sample size of 592 for the analyses.

Survey Procedure

Participants were interviewed up to four times over 12 years by trained professional interviewers. Baseline interviews lasted approximately two hours and included a survey that covered background characteristics, physical health and disease status, mental health status, cognitive performance, and social support. Interviews also included physical assessments of blood pressure, lung function, grip strength, vision, and reaction time.

Measures

A range of cognitive tests were administered at each interview. *Speed of processing* was measured by the Symbol-Letters Modalities Test (SLMT), a task similar to Smith's (1973) *Symbol-Digit Modalities Test* and Wechsler's (1981) Digit-Symbol Substitution. The number of correct symbol-letter pairs made in 90 seconds was summed. *Verbal ability* was measured using the *National Adult Reading Test* (*NART*; Nelson, 1982), a test of vocabulary. The *NART* is a list of 50 words that are not phonetically pronounceable. The number of correct pronunciations made was summed. An *episodic memory* task consisted of four brief episodic memory tasks testing word, face, name, and address recall, as well as figure reproduction (Jorm, 1992). *Verbal fluency* was assessed as the number of animals named in 30 seconds. *Global function* was tested using the Mini-Mental State Examination (MMSE; Folstein, Folstein, and McHugh, 1975), scored out of 30. To facilitate comparisons between tests, all of the tests were standardized to a common metric across the full sample, with a mean of 100 and standard deviation of 10 for the full sample at baseline.

Mortality status and date of death were established by contacting relatives, searching the National Death Index (NDI), and reading death notices in the local newspaper. The NDI is a register of all deaths in Australia maintained by a government instrumentality, the Australian Institute of Health and Welfare, and based on data collected by the registrars of births, deaths, and marriages in each state and territory in Australia. Consequently, failure to identify deaths occurring in Australia would be an unusual occurrence. The additional methods used for death reporting (i.e., contacting relatives, newspaper searches) provide further confidence in the mortality status data. Mortality status was followed for up to 17 years, from the start of baseline interviews in September, 1990 until June 30, 2007. For six participants with unknown day of death, the day was set to the 15th of the month. For two participants with an unknown month of death, the month was set to June. *Cause of death* was based on the primary cause of death provided by the NDI, which was identified using an ICD-9 or ICD-10 code, depending on the date of death. The codes for underlying cause of death were only available for deaths prior to 1996, so only the underlying cause was used for the present analyses. The ICD codes were categorized into five binary categories: cardiovascular, cancer (all malignant neoplasms), respiratory, ischemic heart disease, and stroke (cerebrovascular). No cause of death was provided for 30 deceased participants (7.3%), with these participants counted as having other causes of death. AQ: 6

In addition to the cognitive measures, a number of baseline risk factors for cognitive decline or mortality were also included in the models. Age, gender and number of years of education were included to account for background characteristics. Physical health measures included smoking status (*never*, *previous*, or *current*), Activities of Daily Living (ADL, a scale ranging from 0 to 22), disease count (self-reported history from a list of 14 diseases), and grip strength (measured in kilograms using a hand dynamometer). The ADL scale assessed the presence or extent of physical disability (Christensen et al., 1994). Grip strength is a reliable and objective indicator of physical functioning in late life (Frederiksen et al., 2002) that is associated with both cognitive performance (Christensen et al., 2000) and mortality (Batterham et al., 2009; Sasaki, Kasagi, Yamada, and Fujita, 2007). Mental health was controlled for, using the Goldberg Depression and Anxiety Scales (Goldberg, Bridges, Duncan-Jones, and Grayson, 1988) to assess the number of depression and anxiety symptoms experienced in the two weeks prior to the interview.

Analyses

AQ: 7 The analyses were performed using latent growth models, which incorporated Cox proportional hazards regression models into a structural equation model to estimate the intercept and slope for each cognitive measure (see Asparouhov et al., 2006, for further details of the model specification). Separate models assessed six mortality outcomes with each of the five cognitive tests, resulting in 30 models. The mortality outcomes were all-cause mortality and five categories of cause-specific mortality: cardiovascular, heart disease (a subset of cardiovascular deaths), stroke (a subset of AQ: 8 cardiovascular deaths), cancer, and respiratory deaths. All participants were included in each analysis, with participants who did not die from the respective cause being treated as censored observations at the time of death, and surviving participants being treated as censored observations at the end of the study period (June 2007). Both the intercept and slope estimates for the cognitive tests (estimated at the first stage) were included as predictors in each model, along with the potential confounders. Mplus, ver- AQ: 9 sion 6, was used for the analyses.

Results

Sample characteristics for the 592 participants included in the T1 analyses are shown in Table 1. Participants included in the analysis tended to be younger, more educated, less disabled, have fewer diseases, have stronger grip strength, and have fewer depression symptoms than those who were not included in the analysis. Many of these differences may be attributable to the necessary exclusion of participants who died before the second interview. Participants included in the analysis also had higher initial cognitive performance on all tasks, reflecting strong associations between cognitive performance and impending death. There were no significant differences in anxiety symptoms, gender, or smoking status. Cognitive performance declined significantly across the trial period for all of the tests. Accounting for both fixed and random effects of AQ: 10 time, the largest decline was in SLMT (−0.27 *SD* per year, $p <$ .0001), followed by MMSE (−0.26 *SD*/year, $p <$ .0001), verbal fluency (−0.16 *SD*/year, $p <$ .0001), episodic memory (−0.10 *SD*/year, $p <$ .0001) and *NART* (−0.06 *SD*/year, $p <$ .0001).

At the end of the follow-up period, 410 (69.3%) of the 592 participants had died from all causes. Of these 410 decedents, 192 (46.8%) died from cardiovascular causes, including 105 (25.6%) from coronary heart disease and 41 (10.0%) from stroke. A further 64 (15.6%) died from cancer and 43 (10.5%) died from respiratory disease. The remaining 111 (27.1%) decedents were categorized for the present analyses as having died from other causes, including 12 (2.9%) with dementia listed as the underlying cause of death and 30 (7.3%) without a listed code. The identified causes of death were comparable to Australian prevalence estimates for causes of death in the 85+ age group in 2006: 49.4% of women and 42.4% of men (vs. 46.8% of total in the present study) died from cardiovascular causes, 12.3% of women and 20.6% of men (vs. 15.6%) died from cancer, and 8.5% of women and 11.6% (vs. 10.5%) of men died from respiratory disease (Australian Institute of Health and Welfare, 2010). Among deceased participants included in the analyses, the mean time to death from baseline was 9.6 years (SD = 3.5).

The latent growth models predicting survival time are shown in Table 2. The models were estimated for each of the five cognitive T2 tests (SLMT, *NART*, MMSE, verbal fluency and episodic memory) across six types of mortality (all-cause, cardiovascular, cancer, respiratory, heart disease, and stroke). Each model included the level and slope estimates for the particular cognitive test, along with the effects of age, gender, years of education, smoking status, functional disability, disease count, depression and anxiety symptoms, and grip strength. An alpha value of $p <$ .01 was used to account for the six comparisons made for each cognitive test.

Overall, stronger relationships were found for the level of initial performance than for change in performance. Poorer SLMT performance was associated with higher all-cause, cardiovascular and heart disease mortality rates, with each unit of decrement in initial performance being associated with a 5.4–5.7% increase in the

Table 1
Baseline Descriptive Statistics for Participants Included in and Excluded From the Analyses

	Included in analyses (n = 592); mean (*SD*) or freq (%)	Excluded from analyses (n = 304); mean (*SD*) or freq (%)	t or χ^2	p
Age	76.2 (4.6)	77.3 (5.4)	3.13	0.002
Years of education	11.5 (2.6)	11.0 (2.4)	−2.88	0.004
Functional disability score	1.5 (1.9)	2.6 (3.4)	4.98	<0.001
Disease count	2.7 (1.6)	3.0 (1.8)	2.09	0.038
Grip strength, kg	25.2 (9.8)	23.5 (9.0)	−2.65	0.008
Goldberg Depression score	1.9 (1.8)	2.4 (2.1)	3.66	<0.001
Goldberg Anxiety score	2.4 (2.2)	2.6 (2.4)	1.29	0.198
Gender = male (%)	292 (49.3%)	164 (53.9%)	1.72	0.190
Ever smoked (%)	261 (44.1%)	122 (40.1%)	1.28	0.257
Current smoker (%)	65 (11.0%)	38 (12.5%)	0.46	0.499
Died during follow-up period (%)	410 (69.3%)	277 (91.1%)	53.67	<0.001
Cognitive outcomes				
SLMT score	99.3 (14.9)	89.7 (18.8)	−7.47	<.0001
NART score	113.3 (9.0)	108.4 (10.3)	−6.70	<.0001
MMSE score	27.8 (2.0)	26.2 (3.7)	−7.17	<.0001
Verbal fluency score	11.3 (3.3)	9.7 (3.4)	−6.73	<.0001
Episodic memory score	13.6 (1.9)	12.7 (3.0)	−4.96	<.0001

Note. freq = frequency; SLMT = Symbol-Letters Modalities Test; *NART* = *National Adult Reading Test*; MMSE = Mini-Mental State Examination.

Table 2
Latent Growth Model Estimates of the Effects of Level and Slope of Cognitive Performance on All-cause and Cause-specific Mortality

Test	Measure	All-cause, HR (p)	Cardiovascular, HR (p)	Cancer, HR (p)	Respiratory, HR (p)	Heart disease, HR (p)	Stroke, HR (p)
SLMT	Level	**0.949 (<0.001)**	**0.949 (<0.001)**	0.946 (0.030)	0.940 (0.048)	**0.946 (0.008)**	0.946 (0.091)
	Slope	1.028 (0.752)	0.992 (0.929)	1.231 (0.386)	0.998 (0.995)	1.140 (0.323)	0.744 (0.086)
NART	Level	0.985 (0.052)	0.985 (0.149)	0.974 (0.138)	1.024 (0.239)	0.999 (0.944)	0.983 (0.494)
	Slope	1.091 (0.493)	1.201 (0.248)	1.025 (0.925)	1.284 (0.478)	1.119 (0.605)	1.146 (0.770)
MMSE	Level	0.970 (0.011)	0.966 (0.014)	0.964 (0.140)	1.016 (0.645)	0.968 (0.062)	0.924 (0.014)
	Slope	**0.931 (0.007)**	**0.908 (0.001)**	1.055 (0.430)	0.969 (0.547)	**0.895 (0.002)**	0.953 (0.463)
Fluency	Level	0.973 (0.014)	**0.945 (<0.001)**	0.997 (0.899)	1.023 (0.478)	0.960 (0.040)	**0.900 (0.004)**
	Slope	0.907 (0.170)	0.868 (0.061)	0.926 (0.633)	0.915 (0.567)	0.871 (0.178)	0.766 (0.298)
Episodic	Level	0.975 (0.365)	0.965 (0.181)	0.957 (0.320)	1.008 (0.811)	0.951 (0.177)	0.993 (0.919)
	Slope	0.870 (0.429)	0.832 (0.121)	1.090 (0.760)	0.960 (0.828)	0.760 (0.092)	0.751 (0.527)

Note. SLMT = Symbol-Letters Modalities Test; *NART* = *National Adult Reading Test*; MMSE = Mini-Mental State Examination; Fluency = verbal fluency task; Episodic = episodic memory task; HR = hazard ratio. Level and slope estimates were included simultaneously in each model. Separate models were estimated for each cognitive test and each cause of death. All models are adjusted for the effects of age, gender, education, smoking status, functional disability, disease count, grip strength, Goldberg depression score and Goldberg anxiety score. **Bold** cells indicate $p < .01$.

hazard of death from each cause. Poorer performance on the verbal fluency task was not associated with overall mortality; however, it was associated with higher rates of cardiovascular mortality (5.8% increased hazard per unit decrement in verbal fluency) and stroke mortality (11.1% times the hazard per unit decrement). Greater declines in MMSE performance over the follow-up period were associated with significantly higher all-cause, cardiovascular, and heart mortality (7.4%, 10.1%, and 11.7% increase in hazard ratio, respectively, per unit decrease in MMSE slope). There were also indications that a poorer level of performance on the MMSE was associated with higher rates of all-cause, cardiovascular, and stroke mortality, although these trends were not significant at $p < .01$. Likewise, level of SLMT performance had similar hazard ratios across causes of death although the effects were not significant for cancer, respiratory, or stroke mortality. None of the other cognitive tasks were associated with cancer or respiratory mortality, either in terms of initial performance or changes in performance. Neither *NART* nor episodic memory performance was associated with mortality.

Discussion

The present study aimed to assess the relationship between level and slope of cognitive performance on cause-specific mortality in the Canberra Longitudinal Study. Using latent growth models, initial levels of cognitive performance were found to be better predictors of subsequent mortality than the rate of change in performance. Processing speed (SLMT) and global cognition (MMSE) were the strongest indicators for mortality, with poorer performance having associations with increased mortality from all causes and from cardiovascular disease. Declining performance on MMSE was associated with greater rates of all-cause, cardiovascular, and heart disease mortality. Furthermore, poorer performance on the verbal fluency task was associated with a greater hazard of cardiovascular and stroke death. As none of the cognitive tests significantly predicted cancer or respiratory deaths, it appears that the relationship between cognition and all-cause mortality may be largely due to late-life changes in the cardiovascular system that are associated with both cognitive performance and death.

These results concur with the findings of Shipley et al. (2008), who found that the relationship between cognitive performance and mortality was primarily evident for cardiovascular causes of death. As in the Shipley et al. (2008) study, the present study excluded participants who died early in the study and adjusted for potential confounding from background characteristics, health behaviors, and physical and mental health status. Many cognition-mortality effects remained strong after these adjustments. The findings were somewhat different from the conclusions of the review by Anstey et al. (2006), who reported stronger associations between cognition and mortality among cancer and stroke patients than heart disease patients. However, most of the papers in Anstey's review examined all-cause mortality in these patient groups rather than cause-specific mortality. Disparate causes of death in cancer and heart disease patients, along with the largely clinical nature of the samples reviewed by Anstey et al. (2006), may be responsible for the different findings. The present community-dwelling sample may have included a broader array of trajectories of decline in physical and cognitive functioning.

The finding that a range of cognitive abilities were associated with mortality was consistent with the conclusions of Ghisletta et al. (2006), who reported that the effect of cognition on mortality was not specific to any domain of functioning although tasks robust to aging effects such as vocabulary had no association with mortality. Speeded tasks such as SLMT tend to decline as a response to both normative and pathological aging processes, so the SLMT was expected to show stronger relationships with mortality outcomes. Nevertheless, measures of verbal fluency and global cognition also showed strong associations with cardiovascular deaths in particular, despite being somewhat more robust to the effects of aging. These findings are at odds with the White and Cunningham (1988) hypothesis that terminal decline is limited to abilities that are robust to aging. Our results suggest that both normative and pathological aging processes may contribute to the relationship between cognition and mortality.

Bäckman and MacDonald (2006) have suggested that because verbal fluency tasks have aspects that reflect both fluid and crystallized intelligence, it may be an important predictor of terminal decline. They observe, "verbal fluency may be particularly good

for demonstrating terminal decline, because the task is simple enough for survivors but sufficiently taxing for decedents" (Bäckman and MacDonald, 2006, p. 225). It is plausible that this combination of fluid and crystallized abilities may also explain the SLMT effects, as the SLMT uses a novel task (transcription of symbols) to assess processing speed. The MMSE effects are likely associated with dementia and the psychometric properties of the instrument. MMSE scores generally remain fairly stable and at a ceiling in the absence of pathology (Small and Bäckman, 2007). As the present sample was largely cognitively intact at the beginning of the study, most changes in the MMSE would have occurred in the follow-up stages as the prevalence of dementia increased. AQ: 11 This may explain why there was less effect for the level of MMSE than there was for the slope of MMSE, likely reflecting pathological events that were associated with death in a subset of the sample. Heart disease deaths were predicted only by changes in MMSE, whereas stroke deaths were predicted only by level, possibly because of the more acute effects of stroke on cognitive performance. Correspondingly, combined cardiovascular deaths (which include both stroke and heart disease deaths) and all-cause mortality were predicted by both level and slope of MMSE. In contrast to the MMSE, vocabulary as measured by the *NART* is robust to the effects of both normative aging and preclinical dementia (McGurn et al., 2004). The lack of association between episodic memory and mortality may be related to the validity of the very brief measure used in the present study, as indicated by the relatively modest declines seen in the episodic memory task across the study period.

As the effects across all tasks were primarily associated with cardiovascular deaths, the findings suggest that a range of cognitive deficits in late life may be indicative of cardiovascular problems, including vascular events in the brain. Such vascular events may also occur in late life or be precipitated by early- or midlife disease or injury (Fischer et al., 2006; Herrup, 2010). Furthermore, given the high comorbidity between dementia and cardiovascular diseases (Rastas et al., 2010; Skoog, 1998), it is not surprising that cognitive performance is predictive of cardiovascular mortality, particularly changes in MMSE that may indicate dementia. As a range of vascular events are associated with dementia, including hypertension, coronary heart disease, atrial fibrillation, and stroke (Skoog, 1998), it is likely that cardiovascular morbidity leads to reduced cognitive ability and eventual mortality.

The present study expanded the investigation of the cognition–mortality relationship using estimates of cognitive change that incorporate all available data under the missing-at-random assumption, rather than analyzing only complete cases. However, using a measure of change resulted in limited evidence for terminal decline: There were few significant relationships between the slope of change and the mortality outcomes, with the exception of global cognition. The present findings are similar to those of Johansson et al. (2004) and Ghisletta et al. (2006), who also reported stronger effects for level rather than slope of cognitive AQ: 12 performance. This finding may reflect the level of cognitive ability indicative of a lifetime of development through education, health literacy and healthy behaviors (e.g., medication compliance, help seeking), along with insult through unhealthy behaviors (particularly substance use), injury, vascular problems, and other physical health problems (Bäckman and MacDonald, 2006; Deary, 2005). Other genetic and environmental influences through the life span may also influence the level of performance (Bäckman and MacDonald, 2006). These lifelong influences on the level of performance may be greater contributors to mortality than developmental cognitive processes that occur in proximity to death, which are reflected in the change estimates. It appears to be only when pathological events occur, as reflected by declines in the MMSE, that changes in cognition may be directly predictive of mortality. The paucity of effects for slope estimates may also be related to the reliability of these estimates, which were assessed across up to four time points. Although these few time points may result in less AQ: 13 reliable estimates of slope, thus reducing the power to find effects, the large sample size may have somewhat mitigated this issue. Ghisletta et al. (2006) reported similar findings using up to 11 measurements, and none of the slope effects (other those reported for MMSE) came close to being significant, so it is unlikely that the null effects of slope were purely the result of the estimation process.

Although latent growth models produce defensible estimates of cognitive change, linear estimates of cognitive change may not adequately capture the terminal decline phenomenon. Cognitive decline in proximity to death may be described instead as a threshold function using a change point model, as it does not accelerate continuously (Sliwinski et al., 2006). A previous analysis of the present cohort using a change point model did find evidence for terminal decline, starting around 6 to 8 years prior to death for different cognitive measures, with a two- to fourfold acceleration of decline in the terminal phase (Batterham et al., in press). Estimating the onset and rate of cognitive decline with respect to time-to-death assesses whether those in proximity to death show greater cognitive decline, which is a different research question from that of the present analysis, which assessed whether those who exhibit cognitive decline are at greater risk of dying (Bäckman and MacDonald, 2006). Nevertheless, it is instructive to identify the differences in findings between these approaches. Specifically, it appears that while there may be a significant acceleration of cognitive decline in proximity to death, the overall rate of decline is generally not a critical predictor of mortality.

There were some limitations of the research that could not be fully addressed in the present study. Only linear changes in cognition over time were investigated. Thus, further research could investigate modeling cognitive change using nonlinear functions. A maximum of four measurements taken over 12 years were available for estimating change, as more measurements were not feasible given the large community-based elderly cohort. A substantial proportion of participants were assessed on fewer occasions. Such a pattern was sufficient only for estimating individual linear change using the present methods. The analyses also excluded participants who died or withdrew from the study after the first interview. This exclusion may have created a degree of bias; however, it also resulted in a more homogeneous sample, as the participants closest to death at the first interview were sicker, on average. Inclusion of these participants would have skewed initial cognitive test scores. Consequently the effects presented reflect conservative estimates that may be more reflective of the effects of normative aging than of pathology. Indeed, Shipley et al. (2008) recommended examining models that omit individuals who die early in the study period, as any outcomes may otherwise be confounded by the disproportionate contribution of sick participants who were close to death at the first assessment. This rela-

tionship is reflected by the significantly lower cognitive scores among participants who were excluded from the analysis due to death or dropout before the second interview (see Table 1).

The cognitive measures used in the present analysis were selected prior to the beginning of the study in 1990 with the aim of briefly assessing a range of abilities. Studies using more comprehensive measures of episodic memory in particular, along with other domains of functioning, may find different outcomes. The relatively small declines observed in episodic memory (−0.10 *SD*/year) may be due to the performance of the scale. The assessment of a range of causes of death also may have limited the power to find effects. Only 11% of the sample died from respiratory disease and 10% from stroke. Despite these limited subsamples, verbal fluency was found to be significantly associated with stroke mortality, and there were strong trends suggesting a relationship between global cognition and stroke death. Further analysis of other cohorts may provide additional insight into these causes of death. In particular, the nonsignificant hazard ratios for processing speed in relation cancer, respiratory and stroke mortality were of a similar magnitude to those that were significant. Further research should examine whether processing speed has a small, independently predictive effect on death from each of the causes examined. Finally, mortality and attrition across the study period inevitably reduced the sample by the fourth wave; however, its size was large for this type of community study, and most participants (62%) contributed three or more measures to the estimates of cognitive change.

In conclusion, poorer cognitive performance in several domains predicted higher rates of all-cause mortality and cardiovascular mortality, including heart disease and/or stroke mortality. These findings suggest the cognition-mortality relationship may be primarily driven by lifelong cardiovascular events which effectively overshadow subtler effects reflected by change in memory and cognition. Global ability was the only domain to show a relationship between declines in performance and increased all-cause and cardiovascular mortality. Other methods that do not rely on estimating linear trends may be more effective for capturing the terminal decline phenomenon. Nevertheless, the joint latent growth-survival model presented here is a principled and useful method for obtaining consistent estimates of linear change, and this is the first study using this method to predict cause-specific mortality. While results such as those presented may not be sufficiently consistent to facilitate the prediction of cause-of-death, the methods used provide greater insight into the relationship between late-life cognitive performance and mortality.

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Received October 15, 2010
Revision received April 7, 2011
Accepted April 18, 2011 ■

Psychology and Aging
2011, Vol. 26, No. 2, 339–350

0882-7974/11/$12.00 DOI: 10.1037/a0021845

The Effect of Education on the Onset and Rate of Terminal Decline

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Differences in the time of onset and magnitude of terminal decline were examined in three cognitive domains: processing speed, episodic memory, and global function. In addition, cognitive reserve was investigated by testing whether education affected the onset or rate of decline across these domains. Eight hundred ninety-six community-dwelling Australian adults aged ≥ 70 years were assessed up to four times over 12 years, with vital status followed for 17 years. For each of the cognitive measures, a series of change point models were fitted across the 20 years before death to find the optimal point at which terminal decline was distinguished from preterminal decline. Change points were then assessed separately for high- and low-education groups. The change points were 8.5 years for processing speed (95% CI: 6.0–11.2 years), 7.1 years for global function (6.2–9.3), and 6.6 years for episodic memory (5.3–7.1). The rate of decline was two to four times greater in the terminal phase relative to the preterminal phase, depending on the domain. Increased education changed the terminal decline effect differently for each of the three tests, either by significantly hastening the onset of terminal decline and decreasing the rate of decline, or by increasing the rate of either preterminal or terminal decline. Analyses were repeated excluding participants diagnosed with dementia, with no substantive change to the outcomes. In conclusion, the rate and onset of terminal decline varied somewhat across cognitive domains. Education affected terminal decline differently across the domains, but this modification was not consistent with the predictions of cognitive reserve theory.

Keywords: terminal decline, change point models, cognitive reserve, education

The terminal decline phenomenon was first described by Kleemeier (1962), and it was later characterized by Riegel and Riegel (1972) as a process in which cognitive functioning deteriorates in proximity to death. It is generally agreed that terminal decline is related to pathological processes occurring before death, which may be distinguished from normal, age-related decline (Laukka, MacDonald, & Backman, 2008; Sliwinski et al., 2006; Small and Backman, 1999; Wilson, Beck, Bienias, & Bennett, 2007). This distinction also reflects the concepts of primary aging (maturational processes) and secondary aging (disease processes) (Birren and Cunningham, 1985; Busse, 1969). However, a review of studies examining the relationship between changes in cognitive function and death reported limited evidence for terminal decline (Bosworth and Siegler, 2002). These studies generally estimated cognitive change scores to predict survival. An alternative approach has been used more recently to examine the nature of terminal decline. The aim of this method is to partition the effects of normative aging and terminal decline using change point models, resulting in estimate of both the onset and magnitude of terminal decline. This method was proposed by Hall, Lipton, Sliwinski, & Stewart (2000) for the purpose of identifying the onset of cognitive decline prior to the diagnosis of Alzheimer's Disease. Wilson, Beckett, Bienias, Evans, & Bennett (2003), Sliwinski et al. (2006), Wilson et al. (2007), and Thorvaldsson et al. (2008) have used the method to distinguish terminal (pathological) cognitive decline from preterminal (normative, age-related) cognitive decline.

The estimates from the four studies that have used the change point method are summarized in Table 1. Change points were identified at 3.5 years for the two studies by Wilson and colleagues, while the other studies generally identified a change point between five and nine years before death. The magnitude of the ratio between terminal and preterminal decline was generally in the range of two to five, although there were exceptions to this finding which may be attributable to near-zero rates of preterminal decline. Overall, although there is some agreement in these studies about the timing and magnitude of terminal decline, there is also variation which warrants explanation. Sliwinski et al. (2006) suggested that the slightly different method used by Wilson et al. (2003), which included participants who survived the study period

This article was published Online First April 11, 2011.

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The Canberra Longitudinal Study was supported by National Health and Medical Research Council (NHMRC) Unit Grants 973301 and 933301 and NHMRC Program Grant 179805. H.C. is supported by NHMRC Senior Principal Research Fellowship 525411.

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Table 1
Previous Estimates of Terminal Decline From Four Studies Using the Change Point Method

Study	*n*	Follow-up period (years)	Cognitive domain(s)	Change point (95% CI)[†]	Magnitude of decline[‡]
Wilson et al. (2003)	763	8	Global cognitive functioning	3.5	5.0
Sliwinski et al. (2006)	445	25	Episodic memory	8.4 (7.1, 9.8)	1.8
Wilson et al. (2007)	853	8	Global cognitive functioning	3.5	3.0
Thorvaldsson et al. (2008)	288	15	Verbal ability	6.6 (4.3, 11.7)	13.0
			Spatial ability	7.8 (6.3, 10.6)	1.9
			Perceptual speed	14.8 (10.8, 16.6)	2.0

[†] Years before death. [‡] Ratio of terminal to preterminal decline.

in the estimates, led to a possible underestimate of the terminal decline effect. Furthermore, study design, particularly the length of follow-up, and sample composition may have an impact on the estimation of the change point (Thorvaldsson et al., 2008).

Perhaps of greater importance, terminal decline appears to commence at different times for different abilities. In healthy older adults who age normatively, certain cognitive domains such as perceptual speed and explicit memory have been found consistently to decline earlier and more precipitously than other domains, such as verbal ability (Carlson, Xue, Zhou, & Fried, 2009; Royall, Palmer, Chiodo, & Polk, 2005). Bäckman, Jones, Berger, Laukka, & Small (2005) have reported greater preclinical decline among participants who progressed to Alzheimer's Disease than those who did not on global cognitive ability, perceptual speed, executive functioning, and episodic memory ($d < 1.0$), while verbal ability, visuospatial skill, and attention showed more modest levels of decline. In studies of age-related cognitive decline, Lindenberger and Ghisletta (2009) reported greater decline in perceptual speed than in episodic memory, while Scuteri, Palmieri, Lo Noce, & Giampaoli (2005) reported that decline in perceptual speed occurs earlier and more precipitously than decline in global functioning. In examining terminal decline, Sliwinski et al. (2006) studied only an episodic memory task, while the studies of Wilson et al. (2003 and 2007) used a battery of 19 cognitive tests that were combined into a single measure. In contrast, Thorvaldsson et al. (2008) examined verbal ability, spatial ability, and perceptual speed separately, finding differences in both the onset and magnitude of terminal decline for different cognitive domains. While Wilson et al. (2003 and 2007) only presented models for a composite cognitive score, many of the constituent tests they examined were reported to have change points around three to four years, although visuospatial ability had an earlier change point at six years. Like Thorvaldsson et al. (2008), Wilson et al. (2003) found that the magnitude of terminal decline also varied across cognitive domains, with the slope increased anywhere from threefold to 11-fold in the terminal period compared to the preterminal period.

It may be concluded that the processes involved in terminal decline – much like those in normative aging – affect different cognitive domains to varying extents, both in terms of the magnitude and time of onset of the decline. Bäckman et al. (2005) attributed differential decline across cognitive domains to functional impairment and structural changes in multiple brain structures, including volume reductions in the medial-temporal lobe, anterior cingulate and temporal sulcus, posterior cingulate and neocortical temporoparietal regions, and frontal regions, along with decreased blood flow, reduced glucose metabolism, and amyloid deposits in other regions. Other factors including cardiovascular disease, inflammation, lifestyle, and age-related neurobiological changes may also have specific impacts on late-life cognitive performance (Deary et al., 2009). Changes to structure and function in specific brain regions before death, whether attributable to dementia or other disease processes, may have differential impacts on both the onset and magnitude of decline across various cognitive domains. Consequently, examining a range of cognitive domains is necessary to fully capture the nature of the terminal decline phenomenon (Small and Backman, 1999).

More recently, the change point method has been used to determine whether particular risk factors such as poor education or the presence of the apolipoprotein E (APOE) ε4 allele modify the onset and magnitude of terminal decline (Wilson et al., 2007). Education, childhood cognition, and adult occupation are believed to protect against faster rates of cognitive decline in normal populations (Richards and Sacker, 2003), and it may have specific effects on rate or onset of terminal decline. Research suggests that the clinical onset of Alzheimer's disease appears to be delayed in those with higher education, but the rate of cognitive decline after onset is more rapid among more highly educated individuals (Stern, Albert, Tang, & Tsai, 1999). Such findings are cited as evidence for cognitive reserve, suggesting that education increases the brain's ability to compensate for pathology (Stern, 2002). The cognitive reserve hypothesis suggests that higher levels of education create a buffer against functional decline in the face of brain insult (Christensen, Anstey, Leach, & Mackinnon, 2008). Education may be associated with a greater number of healthy synapses or neurons, more efficient circuits of synaptic connectivity, or more efficient use of alternative brain networks (Scarmeas, Albert, Manly, & Stern, 2006). Evidence for education being an indicator of reserve comes from functional magnetic resonance imaging studies of high-functioning older adults, which demonstrate functional compensation for declines in neural activity (Cabeza and Nyberg, 2000).

Change point models can test whether education protects against terminal decline by delaying the onset of terminal decline even if the subsequent rate of decline is accelerated. Wilson et al. (2007) examined whether education, age, sex, vascular disease, APOE genotype, or mild cognitive impairment modified terminal decline. They found that the rate of decline did not accelerate during the terminal phase for individuals without an APOE ε4 allele or with a history of vascular disease but found no effect of education on the rate of decline. However, these effects were examined using

only a global cognition aggregate score (Wilson et al., 2007), without examining whether cognitive reserve may influence specific domains of cognitive decline. Hall et al. (2007) also examined the role of education in memory decline before dementia diagnosis. They found that increased education delayed the onset of dementia-related cognitive decline but the decline was more precipitous after onset (Hall et al., 2007), in support of the cognitive reserve theory. However, the study did not examine decline with respect to death and also examined only a single measure of cognition.

The present study examined terminal and preterminal decline in three domains as a function of education using the method proposed by Hall et al. (2000). We explored decline by examining a series of models that incremented a change point over 20 years. The definition of the preterminal and terminal phases is dependent on whether the measurement occurs before or after the change point, as illustrated in Figure 1. When a measurement occasion is before the change point (e.g., "Measurement 1" in Figure 1), the length of the preterminal phase at that measurement is defined as the individual's current age, while the length of the terminal phase is zero. When a measurement occasion is after the change point (e.g., "Measurement 2" in Figure 1), the length of the preterminal phase at that measurement is defined as the individual's age at death minus the change point, while the length of the terminal phase is the individual's current age minus their age at death plus the change point.

The models included both fixed and random effects (slopes) of preterminal and terminal decline, in addition to a random intercept. The change point that optimally differentiated between preterminal and terminal slopes was determined by varying the change point to identify the model with the largest likelihood function. A 95% confidence interval for the identified change point was based on the difference in -2 log likelihood from the optimal change point, which has a χ^2 distribution (Sliwinski et al., 2006). The rates of preterminal and terminal decline were then assessed using the model at the optimal change point. Taking this approach further, the present study examined the effect of education on terminal decline for each of the cognitive tasks by dividing the cohort based on educational attainment and repeating the analysis.

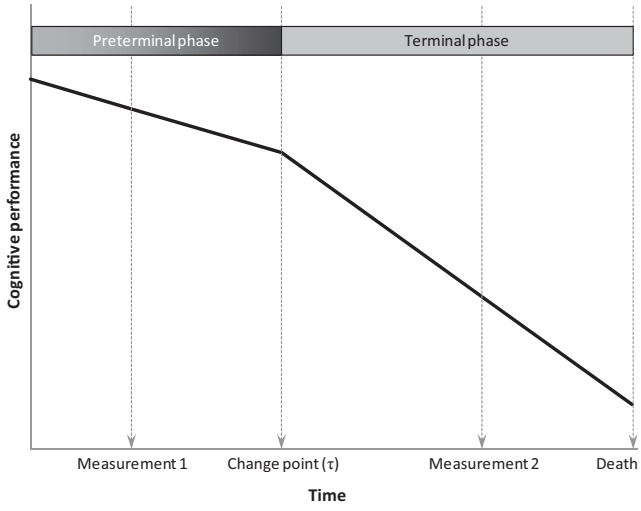

Figure 1. Preterminal and terminal phases of cognitive decline, illustrating their dependence on the time of measurement.

The Canberra Longitudinal Study (Christensen et al., 2004) included seven cognitive domains that were assessed for terminal decline in the present study: episodic memory, processing speed, global function, verbal and facial recognition, verbal fluency, and verbal ability. The three domains found to clearly exhibit terminal decline in the present study were episodic memory, processing speed, and global function. Based on the findings of (Thorvaldsson et al., 2008), it was hypothesized that there would be differences in both the onset and rate of terminal decline across domains. We predicted that the onset of terminal decline would be earlier for processing speed than for other tasks, as reported by Thorvaldsson et al. (2008), while research on age-related and pathological cognitive decline suggests that the rate of decline for all three domains may be similar (Bäckman et al., 2005). Based on the predictions of cognitive reserve theory (Stern, 2002), where higher reserve may initially slow the rate of decline, and previous findings with respect to the onset of dementia (Hall et al., 2007; Stern et al., 1999), where education initially protects but then precipitates decline after diagnosis, we hypothesized that higher education may shorten the length of terminal decline but accelerate the rate of decline in the terminal period. Furthermore, these differences might be more likely to be observed on tests sensitive to terminal decline such as processing speed. These observations were undertaken with and without those with dementia diagnosis to determine the effect of a dementia diagnosis and to exclude the effect of dementia for the rest of the population sample.

Method

Participants

The Canberra Longitudinal Study is an epidemiological survey of mental health and cognitive functioning in older people that commenced in 1990. The study design has previously been detailed by Christensen et al. (2004). Eight hundred ninety-six participants (456 men and 440 women) aged 70 or older at the time of the baseline assessment were recruited for the baseline assessment. All participants were initially living in the community in the cities of Canberra or Queanbeyan, Australia. The sample was stratified by age and gender. Participants were sampled from the compulsory electoral roll, with 69% responding. Approval for the research was obtained from the Ethics in Human Experimentation Committee of the Australian National University.

Survey Procedure

Participants were interviewed up to four times over 12 years. Baseline interviews lasted approximately two hours, incorporating a survey measuring a wide range of risk factors including sociodemographics, physical health and disease status, mental health status, cognitive performance, and social support. Interviews also included physical assessments of blood pressure, lung function, grip strength, vision, and reaction time. Trained professional interviewers conducted the interviews.

Of the original sample of 896 participants, 185 (20.6%) were deceased by four years, 363 (40.5%) were deceased by eight years, and 544 (60.7%) were deceased by 12 years. At the end of vital

status collection in June 2007, 687 (76.7%) of the participants were deceased. Of the participants who remained in the study, 14.1% (100/711) refused or were unable to complete the first follow-up interview, 21.1% (100/474) for the second follow-up, and 21.1% (57/270) for the third follow-up. Participants surviving at the end of the follow-up period ($n = 209$) were excluded from the analyses.

Measures

Several tests were administered to assess the cognitive performance of study participants. *Speed of processing* was measured by the Symbol-Letters Modalities Test (SLMT), a task similar to Smith's (1973) Symbol-Digit Modalities Test and Wechsler's (1981) Digit-Symbol Substitution. *Verbal ability* was measured using the National Adult Reading Test (Nelson, 1982), a test of vocabulary. An *episodic memory* task consisted of brief episodic memory tasks testing word, face, name and address recall, and figure reproduction (Jorm, 1992). *Verbal fluency* was assessed as the number of animals named in 30 seconds. *Face and word recognition* tasks were based on the Rivermead Behavioural Memory Test (Wilson, Cockburn, Baddeley, & Hiorns, 1989). *Global function* was tested using the Mini-Mental State Examination (Folstein, Folstein, & McHugh, 1975), scored out of 30. To facilitate comparisons between tests, all of the tests were standardized to a common metric, with a mean of 100 and standard deviation of 10 at the baseline measurement.

Mortality status and date of death were established by contacting relatives, searching the National Death Index, and from death notices in the local newspaper. Missing death identifications from the National Death Index would most likely have been a rare occurrence, as the index is a register of all deaths in Australia. The additional methods used for death reporting (contacting relatives, newspaper searches) provide further confidence in the mortality status data. Mortality status was followed for up to 17 years, from the start of baseline interviews in September 1990 until June 30, 2007. For six participants with unknown day of death, the day was set to the 15th of the month. For two participants with an unknown month of death, the month was set to June. *Date of birth (age)* was reported during the initial interview. *Educational status* was based on responses to two questions regarding the number of years in school and the highest qualification obtained. These two questions were combined into a single measure representing the number of years it took participants to attain their highest educational qualification. For the analyses based on educational status, a median split was used to differentiate those with fewer than 11 years of education (low education) from those with 11 or more years (high education), which also corresponds to the number of years taken to complete standard secondary education for this cohort. Additional analyses controlled for a number of baseline risk factors for cognitive decline or mortality: gender, heart attack history (self-report binary measure), hypertension history (self-report binary measure), grip strength (measured in kilograms using a hand dynamometer), smoking status (never, previous, or current), Activities of Daily Living (a scale of functional disability ranging from 0 to 24), disease count (self-reported history from a list of 14 diseases), and depression [Goldberg Depression Scale (Goldberg, Bridges, Duncan-Jones, & Grayson, 1988), range 0–9].

To examine the effect of dementia and to determine any potential confounding arising from it, analyses were repeated with and without participants with this disorder. Participants who met criteria for an ICD-10 (World Health Organization, 1993) diagnosis of dementia or severe dementia during the study (at waves 1–4, up to 12 years after baseline) were identified. Diagnoses were made using the Canberra Interview for the Elderly (Social Psychiatry Research Unit, 1992), which provides information from which a diagnosis of dementia can be made according to ICD-10 (World Health Organization, 1993) and DSM-III-R (American Psychiatric Association, 1987) by means of a computer algorithm (Mackinnon et al., 2003). The algorithm classifies participants into categories of non-case, possible dementia, probable dementia, or actual dementia. The "actual dementia" category was chosen for the selection of participants to exclude, as it is the most robust.

Analyses

Mixed model repeated measures analyses of variance (MMRM) were used to estimate the change point and magnitude of terminal decline, following the method described by Hall et al. (2000). This process segments the participant's age (in months) at each measurement point using a change point, τ. The segmentation of age is shown in the equation (adapted from Sliwinski et al., 2006) below:

$$cognition_{it} = \beta_0 + \beta_1 [\min (Age_{it}, DeathAge_i - \tau)] + \beta_2 [\max (0, Age_{it} - DeathAge_i + \tau)] + \varepsilon_{it}$$

where $cognition_{it}$ represents a cognitive score for participant i at time t (each cognitive test was modeled separately), β_0 is the intercept, β_1 is the coefficient being estimated for the rate of cognitive decline during the preterminal interval, Age_{it} is the age of participant i age at time t (in months), $DeathAge_i$ is the age at death of participant i (in months), τ is the change point being evaluated within a range of 1–20 years (in months), β_2 is the coefficient being estimated for the rate of cognitive decline during the terminal interval, and ε_{it} is the error term. Age at study commencement was centered at 75 (i.e., 75 years were subtracted) to facilitate the interpretation of intercepts.

The model was repeatedly evaluated using values for the change point, τ, incremented from 12 to 120 months before death in steps of one month. The model with the largest log-likelihood value was selected, with the τ for this model representing the change point at which terminal decline begins, with the estimates of β_1 and β_2 at this value of τ representing the rates of preterminal and terminal decline respectively. Both fixed and random effects for β_1 and β_2 were included in the model, and maximum likelihood estimation was used in accordance with the method used by Hall et al. (2000). An unstructured variance-covariance matrix was used, and degrees of freedom were calculated using Satterthwaite's approximation (Steel and Torrie, 1980). Mixed models use all available measurement points for each participant under the assumption that missing data are missing at random. Analyses were repeated excluding participants who had received a dementia diagnosis and also repeated with the inclusion of multiple risk factors for mortality as independent fixed effects. SAS v9.1 was used for all statistical analyses.

Results

Participants who were deceased at June 2007 were included in the change point analyses ($n = 687$). Of these 687 decedents, 423

completed the second interview (176 deaths and 88 dropouts), 215 completed the third (183 new deaths, 57 new dropouts, including 31 former dropouts who died and one who returned to the study), and 81 completed the fourth (176 new deaths and 28 new dropouts, including 69 former dropouts who died and one who returned to the study). In all, 81 (11.8%) participants contributed data from all four time points, 135 (19.7%) from three, 208 (30.3%) from two, and 263 (38.3%) from only the baseline measurement. There was no significant difference between the rates of contribution between those with lower education ($<$ 11 years, $n = 376$) and those with higher education [$\geq$ 11 years, $n = 520$; χ^2 (3) = 6.1, $p = 0.11$]. Of the 1406 total observations from the 687 participants, 297 (21.1%) occurred 10 or more years before death, while 791 (56.3%) occurred five or more years before death.

The contribution of observations to the change point models across the span of the study is shown in Table 2, categorized by the number of years before death the observations were made, separately for the two education groups. Approximately 35% of the observations fell in the 5–10 years before death where terminal decline is most commonly found to begin, while 44% were 0–5 years before death and the remaining 21% were more than 10 years before death. There was no significant difference in the distributions of observations across the two education groups [χ^2 (16) = 7.3, $p = 0.96$]. The mean age of participants used in the change point analyses ($n = 687$) was 77.3 years ($SD = 5.1$), with a mean educational attainment of 11.4 years ($SD = 2.6$). Those who had died by June 2007 were older at the start of the study than those who survived. However, there was no significant difference between decedents and survivors in the amount of education completed. Performance on all seven cognitive tests was significantly better for survivors compared to decedents.

To determine whether change point models were justified, decline in each of the tasks was examined using base models testing linear and quadratic terms for age and, separately, time-to-death. These models found little decline on several of the tests, possibly because the participants tended to be relatively well educated, were community dwelling (non-institutionalized), and had relatively low rates of dementia. Furthermore, some of the tests were included in the study for their robustness to the effects of cognitive aging. Consequently, change points could not be reliably estimated for NART, verbal fluency, face recognition, or word recognition. Three domains of cognitive function were therefore used as outcomes in the analyses: speed of processing (SLMT), episodic memory, and global function (MMSE).

Table 2
Contribution of Observations to the Mixed Effects Models as a Function of Time to Death and Education

	Low education group (n = 376,553 obs)		High education group (n = 520,853 obs)	
Time to death	Frequency	Percent	Frequency	Percent
0 to $<$ 1 year	40	7.2%	68	8.0%
1 to $<$ 2 years	50	9.0%	82	9.6%
2 to $<$ 3 years	53	9.6%	82	9.6%
3 to $<$ 4 years	49	8.9%	80	9.4%
4 to $<$ 5 years	42	7.6%	69	8.1%
5 to $<$ 6 years	50	9.0%	74	8.7%
6 to $<$ 7 years	39	7.1%	65	7.6%
7 to $<$ 8 years	36	6.5%	51	6.0%
8 to $<$ 9 years	45	8.1%	53	6.2%
9 to $<$ 10 years	35	6.3%	46	5.4%
10 to $<$ 11 years	24	4.3%	44	5.2%
11 to $<$ 11 years	24	4.3%	42	4.9%
12 to $<$ 13 years	27	4.9%	36	4.2%
13 to $<$ 14 years	15	2.7%	18	2.1%
14 to $<$ 15 years	7	1.3%	20	2.3%
15 to $<$ 16 years	12	2.2%	18	2.1%
16 to 17 years	5	0.9%	5	0.6%

To identify the optimal change point and compare change points across domains, -2 log likelihood values from the 229 models (12–240 months) were standardized to create "profile likelihood" values, fitting a range between 0–1. This was calculated by subtracting the -2LL value at each time point from the minimum -2LL value (i.e., the -2LL value at the change point), then dividing by 2 and taking the exponent (Hall et al., 2000). This was done separately for each of the three domains investigated. Profile likelihood values are plotted for the three domains in Figure 2, with time ranging from 1–15 years before death on the x axis (death is time zero). The 95% confidence interval for change point estimate is also indicated, with the cut-off values for this interval being at approximately 0.15 for the transformed profile likelihood values on each of the tests. The optimal change point for processing speed was 8.5 years (95% CI: 6.0–11.2 years), the MMSE change point was 7.1 years (6.2–9.3), while the episodic memory change point was 6.6 years, (5.3–7.1). Overlap is evident between the confidence intervals for all three cognitive tests, suggesting that change points for these tests are not significantly different.

The models showing the effects of preterminal and terminal decline at the change points are displayed in Table 3. Absolute rates of decline can be compared across tests, as they were standardized to mean of 100 and SD of 10 at baseline. The parameter estimates given in the table represent monthly changes in these standardized units. Likelihood ratio χ^2 tests for the null model are provided in the table, showing the models fit well. The covariance estimates for the random effects are also provided in the table. In some cases, the random effect of preterminal decline was close to zero, as indicated in the table. In these cases, models were reestimated without this random effect (not displayed). The coefficients for intercept, preterminal, and terminal decline remained virtually unchanged when these random effects were excluded.

Rates of decline were comparable for processing speed and global function, decreasing by 0.05 SD per year in the preterminal phase and around 0.1 SD per year in the terminal phase. There was slightly less decline in episodic memory: 0.02 SD per year preterminal and 0.07 SD per year terminal. However, the magnitude of terminal decline relative to preterminal decline was greater for episodic memory, with a 3.7-fold acceleration in decline over the terminal period, compared to 2.3-fold and 2.8-fold accelerations for processing speed and global function, respectively. The change point models were also compared to single slope models of decline by comparing -2 log likelihood between nested models. The change point models fit significantly better than single-phase models [processing speed: χ^2 (1) = 176.4, $p < 0.0001$; global function: χ^2 (1) = 219.6, $p < 0.0001$; episodic memory: χ^2 (1) = 85.3, $p < 0.0001$].

The analyses were repeated separately for two subgroups categorized by years of education ($<$11 years or $\geq$11 years) to examine the effect of cognitive reserve. Based on profile likelihood

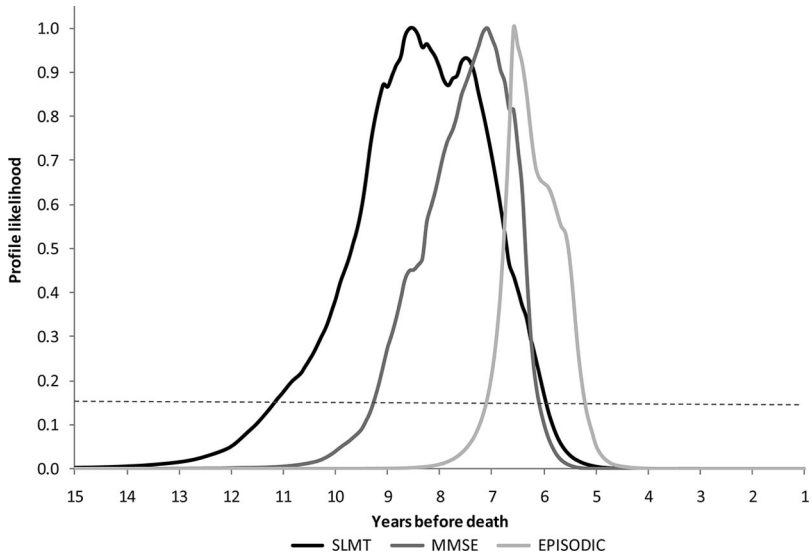

Figure 2. Profile likelihood plots for processing speed (SLMT), global function (MMSE), and episodic memory, with confidence limit indicated by dashed line.

plots, the change points and 95% confidence intervals were assessed for each of the cognitive domains, with these estimates shown in Table 4. The upper limit of the confidence interval for processing speed could not be assessed, as the profile likelihood did not asymptote to zero within the follow-up period after reaching the maximum. Regardless, the difference in the change points for the high- and low-education groups was not significant for processing speed. The change point for global function was significantly later in the low education group than the high education group, while education did not significantly alter the change point for episodic memory.

Table 5 shows the parameter estimates and p values for MMRM models at the change points identified in Table 4. The models include the likelihood ratio χ^2 tests, indicating good fit, along with the fixed effects and random effects. Once again, models where random effects were close to zero were reestimated without this effect, with little change to the estimates of the fixed effects. To illustrate the models fitted, predicted cognitive scores for members of the high-education group and the low-education group were plotted for age at baseline of 77.3 years and age at death of 85.3 years (corresponding to the mean values for the sample). These plots are shown in Figure 3. Steeper terminal decline in processing speed was evident in the high-education group (0.12 SD per year) than the low-education group (0.08 SD per year), while preterminal processing speed decline (0.04 SD per year) was similar in both groups (Figure 3A). A contrary pattern was seen in global function, where the rates of both preterminal (0.07 vs. 0.03 SD per year) and terminal decline (0.27 vs. 0.10 SD per year) were greater in the low-education group than the high-education group (Figure 3B). A third pattern emerged in the episodic memory measure, where those with higher education had a greater rate of preterminal decline (0.02 vs. 0.01 SD per year) but similar rate of terminal decline (0.08 SD per year for both) compared to those in the low-education group (Figure 3C).

All analyses were repeated excluding 41 participants with a dementia diagnosis ($n = 646$). Based on the confidence intervals, the exclusion did not significantly alter the change point estimates for processing speed (7.3 years when excluding participants with dementia versus 8.5 years when including participants with dementia), global function (6.4 years versus 7.1 years), or episodic memory (6.6 years in both analyses). There was little change in the rates of preterminal decline (less than 0.004 SD per year difference on all tasks) and terminal decline (less than 0.024 SD per year) after excluding participants with dementia. For example, the largest change was in the estimate of terminal decline for MMSE, which changed from -0.106 to -0.089. The exclusion of participants with dementia also had little impact on the findings regarding the effect of education. The estimated change points varied by fewer than six months in each case. Likewise, the estimates of preterminal and terminal decline were changed little, in each case by less than 0.002 SD per year. For example, the largest change was in the terminal decline estimate for global function among the low-education group, which changed from -0.086 to -0.068 after controlling for covariates.

The models for high- and low-education groups were also reestimated with the inclusion of other independent risk factors for cognitive decline or mortality: gender, heart attack and hypertension history, grip strength, smoking status, functional ability, disease count, and depression as covariates. Although many of these variables were significantly associated with cognitive performance, their inclusion in the models had very little impact on the estimated change points, which varied by fewer than 13 months in most cases. However, for episodic memory among the high-education group, the change point was shifted from 79 to 27 months because of problems estimating the variance matrix for these models. Because of this estimation problem, models of episodic memory for the high-education group were assessed at the original change point. For all of the cognitive tests, the estimates of preterminal and terminal decline were changed little by the inclusion of covariates, in each case by less than 0.002 SD per year. For example, the largest change was in the terminal decline estimate for episodic memory among the low-education group,

Table 3
Parameter Estimates From Mixed Effects Models of Cognitive Function Based on Preterminal and Terminal Decline Segmented at Optimal Change Points

Cognitive domain	Effect	Estimate	*SE*	*df*	*t*/*Z*†	*p*
		Random effect covariance estimates				
Processing speed (SLMT) (change point 8.5 yr)	Intercept	102.78	0.422	442	243.4	<0.0001
$\chi^2(5) = 389.5$, $p < 0.0001$	Preterminal decline	−0.038	0.005	896	−7.9	<0.0001
	Terminal decline	−0.086	0.006	304	−13.7	<0.0001
	β_0, β_0	59.246	6.272		9.45	<0.0001
	β_1, β_0	0.001	0.045		0.02	0.9826
	β_1, β_1	0.000‡	—		—	—
	β_2, β_0	0.037	0.071		0.53	0.5991
	β_2, β_1	0.000	0.001		0.33	0.7421
	β_2, β_2	0.002	0.001		1.49	0.0682
	Residual	27.727	2.142		12.94	<0.0001
Global function (MMSE) (change point 7.1 yr)	Intercept	102.33	0.376	322	272.0	<0.0001
$\chi^2(6) = 260.4$, $p < 0.0001$	Preterminal decline	−0.038	0.005	360	−7.2	<0.0001
	Terminal decline	−0.106	0.010	437	−10.3	<0.0001
	β_0, β_0	29.082	5.604		5.19	<0.0001
	β_1, β_0	0.151	0.050		3.00	0.0027
	β_1, β_1	0.001	0.001		0.85	0.1975
	β_2, β_0	−0.023	0.122		−0.19	0.8513
	β_2, β_1	0.004	0.001		2.81	0.0049
	β_2, β_2	0.026	0.004		6.25	<0.0001
	Residual	39.366	3.430		11.48	<0.0001
Episodic memory (change point 6.6 yr)	Intercept	101.49	0.394	341	257.4	<0.0001
$\chi^2(5) = 79.4$, $p < 0.0001$	Preterminal decline	−0.016	0.005	774	−3.5	0.0005
	Terminal decline	−0.060	0.011	402	−5.3	<0.0001
	β_0, β_0	21.205	5.989		3.54	0.0002
	β_1, β_0	0.051	0.042		1.20	0.2301
	β_1, β_1	0.000‡	—		—	—
	β_2, β_0	−0.306	0.153		−2.00	0.0451
	β_2, β_1	0.001	0.002		0.47	0.6405
	β_2, β_2	0.028	0.006		4.47	<0.0001
	Residual	58.153	4.781		12.16	<0.0001

† Tests of fixed effect parameters are *t* tests, tests of random parameter variation are *Z* tests. ‡ Parameter on boundary of zero, unable to be tested.

which changed from −0.069 to −0.054 after controlling for covariates.

Discussion

In a community sample of 896 adults over the age of 70, terminal decline effects were found in tasks tapping processing speed, global function, and episodic memory. The onset of terminal decline was found to be around 8½ years for processing speed, 7 years for global function, and 6½ years for episodic memory. Although there was less overall decline in episodic memory than in the other domains, the rate of decline in the terminal phase was increased almost fourfold compared to the preterminal phase on the episodic memory task. The ratio was 2.3 for processing speed and 2.8 for global function, suggesting that episodic memory drops later but more precipitously than these domains. While the onset of terminal decline for processing speed was not significantly later than for other domains as hypothesized, the change points for processing speed and episodic memory were similar to previous studies, particularly those of Thorvaldsson et al. (2008) and Sliwinski et al. (2006). The identified change points were earlier than those reported by Wilson et al. (2003 and 2007), possibly because of the inclusion of survivors and shorter follow-up period in those studies. The rates of terminal decline were in a similar range to previous studies, while the finding of variability in both the onset and rate of terminal decline across cognitive domains (Thorvaldsson et al., 2008; Wilson et al., 2003) was also replicated.

Table 4
Estimated Change Points (in Years, With 95% Confidence Intervals) for Segmenting Preterminal and Terminal Decline Based on Cognitive Function, Estimated Separately for Each Education Group

	Low education (<11 yr) (*n* = 376)	High education (≥11 yr) (*n* = 520)
Processing speed (SLMT)	11.3 (4.8, <17)	7.8 (6.8, 9.3)
Global function (MMSE)	2.6 (2.1, 3.8)	8.6 (7.7, 10.1)
Episodic memory	5.5 (2.8, 8.3)	6.6 (5.5, 6.9)

Education changed the terminal decline effect for all three of the cognitive domains, but in different ways. The onset of decline in global function was delayed significantly for those with lower levels of education, however the rate of decline was greater in the terminal phase for the low-education group. For the processing speed and episodic memory tasks, education did not significantly modify the onset of terminal decline. Rather, for processing speed,

Table 5
Mixed-Effects Models of Cognitive Function Based on Preterminal and Terminal Decline at the Change Point, Estimated Separately for Each Education Group

		Low education					High education				
Cognitive domain	Effect	Estimate	*SE*	*df*	Statistic†	*p*	Estimate	*SE*	*df*	Statistic†	*p*
					Random effect covariance estimates						
Processing speed (SLMT)	Model fit (LR test)			6	120.52	<0.0001			5	238.51	<0.0001
	Intercept	99.75	0.739	140	134.99	<0.0001	105.32	0.486	218	216.83	<0.0001
	Preterminal decline	−0.034	0.008	90	−4.12	<0.0001	−0.034	0.005	254	−6.34	<0.0001
	Terminal decline	−0.068	0.009	112	−7.63	<0.0001	−0.103	0.008	180	−12.75	<0.0001
	β_0, β_0	53.492	11.700		4.57	<0.0001	47.765	7.643		6.25	<0.0001
	β_1, β_0	−0.050	0.096		−0.52	0.6003	−0.081	0.058		−1.38	0.1661
	β_1, β_1	0.001	0.002		0.35	0.3621	0.000‡	—		—	—
	β_2, β_0	0.054	0.109		0.49	0.6222	0.136	0.086		1.58	0.1144
	β_2, β_1	0.002	0.002		1.19	0.2338	0.001	0.001		0.74	0.4598
	β_2, β_2	0.001	0.002		0.7	0.2420	0.002	0.002		1.21	0.1139
	Residual	31.651	4.039		7.84	<0.0001	25.012	2.520		9.93	<0.0001
Global function (MMSE)	Model fit (LR test)			6	101.62	<0.0001			5	180.86	<0.0001
	Intercept	99.56	0.745	162	133.71	<0.0001	104.07	0.366	155	284.51	<0.0001
	Preterminal decline	−0.055	0.009	129	−6.01	<0.0001	−0.025	0.006	561	−4.41	<0.0001
	Terminal decline	−0.224	0.078	44.9	−2.85	0.0065	−0.086	0.010	279	−8.89	<0.0001
	β_0, β_0	63.871	13.025		4.9	<0.0001	7.761	3.976		1.95	0.0255
	β_1, β_0	−0.065	0.141		−0.46	0.6450	0.133	0.035		3.74	0.0002
	β_1, β_1	0.005	0.002		2.13	0.0167	0.000‡	—		—	—
	β_2, β_0	−4.265	1.301		−3.28	0.0010	0.049	0.081		0.61	0.5430
	β_2, β_1	0.031	0.012		2.55	0.0107	0.003	0.001		2.54	0.0111
	β_2, β_2	0.394	0.147		2.69	0.0036	0.018	0.003		6.23	<0.0001
	Residual	47.938	6.684		7.17	<0.0001	31.341	3.112		10.07	<0.0001
Episodic memory	Model fit (LR test)			5	29.02	<0.0001			5	56.9	<0.0001
	Intercept	99.26	0.688	198	144.37	<0.0001	102.76	0.443	156	231.93	<0.0001
	Preterminal decline	−0.009	0.007	246	−1.22	0.2220	−0.020	0.006	546	−3.59	0.0004
	Terminal decline	−0.069	0.025	171	−2.81	0.0056	−0.063	0.014	181	−4.58	<0.0001
	β_0, β_0	24.235	9.606		2.52	0.0058	17.458	7.483		2.33	0.0098
	β_1, β_0	−0.048	0.049		−0.99	0.3237	0.139	0.054		2.55	0.0106
	β_1, β_1	0.000‡	—		—	—	0.000‡	—		—	—
	β_2, β_0	−0.468	0.313		−1.5	0.1341	−0.247	0.192		−1.29	0.1986
	β_2, β_1	0.005	0.003		1.8	0.0719	−0.001	0.002		−0.58	0.5607
	β_2, β_2	0.040	0.015		2.73	0.0032	0.031	0.009		3.52	0.0002
	Residual	78.693	8.560		9.19	<0.0001	42.187	5.983		7.05	<0.0001

† Tests for model fit are χ^2 tests, fixed effect parameters are *t* tests, tests of random parameter variation are *Z* tests. ‡ Parameter on boundary of zero, unable to be tested.

the rate of decline in the terminal phase was greater for those with higher education. For episodic memory, the rate of decline in the preterminal phase was not significantly different from zero for those with a lower level of education but higher in those with more education. The finding that education modifies terminal decline and that the nature of the modification varies across cognitive domains has not previously been reported. Wilson et al. (2007) found no modification by education on terminal decline. Their null finding may have resulted from using only a cognitive composite score, which could have obscured any domain-specific effects such as those identified here. The findings are also contrary to those of Hall et al. (2007), who reported that memory decline before dementia diagnosis occurred later but more precipitously in participants with higher education levels.

Together, these findings suggest that terminal decline does not occur uniformly across different cognitive domains. Because the physiological basis of these forms of cognitive functioning are different, this may reflect the differential impact of particular brain or systemic disease, although the situation is likely to vary as a function of disease and individual vulnerability. For example, there is a dissociation between explicit and implicit memory performance in those with Alzheimer's Disease because of the differential affects of the disease on specific structures such as the mesial temporal lobe (Golby et al., 2005). The findings also suggest that terminal decline may reflect a diversity of physiological processes occurring in the years before death, including preclinical dementia (Laukka, MacDonald, & Backman, 2008), or other forms of cerebral deterioration, including stroke and cardiovascular disease (Hassing et al., 2002; Wilson et al., 2007). Such processes may affect cognitive function in different ways, such that the onset of decline may be accelerated for some tasks while the rate of decline may be increased for others.

Analyses excluding participants with a dementia diagnosis did not substantively change the outcomes. Laukka, MacDonald, & Backman. (2008) proposed that terminal decline effects are largely a result of preclinical dementia, although they found selective terminal decline effects after controlling for this condition. The present study controlled only for actual dementia cases and found

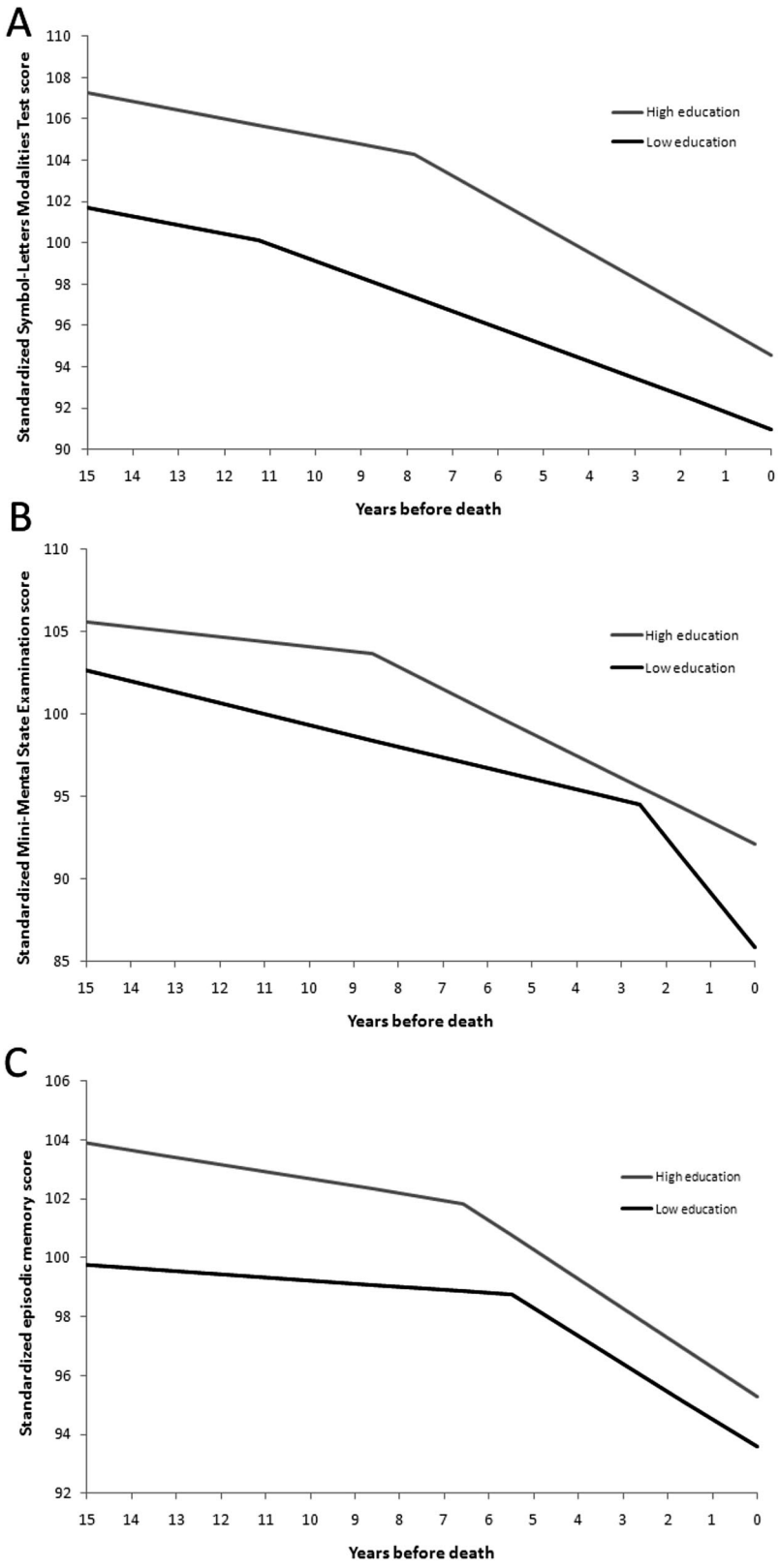

Figure 3. Predicted cognitive performance in the 15 years before death for prototypical participants with high or low education: (A) processing speed, (B) global function, and (C) episodic memory.

very little evidence that dementia may modify the onset and rate of terminal decline. In conjunction with similar findings by Thorvaldsson et al. (2008), it appears that the terminal decline effects cannot be fully explained by dementia. Consequently, the findings support a multifaceted model of terminal decline like the one proposed by Bäckman and MacDonald (2006), who suggest that the phenomenon is influenced by both normative age-related decline and pathological events (including dementia, cardiovascular disease, and cancer), along with more distal factors such as health literacy, childhood intelligence, genes, and environment.

The effect of education was contrary to what would be predicted by cognitive reserve or compensation theories of cognitive aging (Park & Reuter-Lorenz, 2009; Stern, 2002). While increased education was associated with higher initial levels of performance, it was also associated with more rapid declines in performance or earlier onset of decline. This pattern of change is not consistent with a straightforward interpretation of cognitive reserve theories, which would suggest that education protects against cognitive decline either by recruiting compensatory networks or through more efficient use of existing networks (Park and Reuter-Lorenz, 2009). Other than improving initial performance, the only suggestion of a protective effect of education was seen in the global function task, where the rate of decline was lower in the group with more education. However, there was also a hastening of terminal decline on this task for those with high education, at odds with findings suggesting that cognitive reserve may delay the onset but accelerate declines that are related to pathological processes (Stern et al., 1999).

These divergent findings may be related to either the diversity of skills tested by the MMSE or its psychometric properties. The MMSE includes psychomotor, attention, and recall tasks in addition to measures of orientation and registration. The earlier onset of terminal decline in global function for those with higher education may also reflect the imperfect psychometric properties of the MMSE, specifically scaling artifacts, ceiling effects, and unreliability of change scores (Hensel, Angermeyer, & Riedel-Heller, 2007). Nevertheless, the results with respect to all three cognitive domains may suggest that individuals who begin with better cognitive performance simply have more potential for decline, whereas those who initially perform poorly may not decline considerably unless significant pathology develops. There was no significant change in the onset of terminal decline in processing speed or episodic memory, and education did not slow the rate of decline in either of these domains. It could be the case that some of the biological processes associated with terminal decline are different from those associated with dementia-related cognitive decline, in that terminal decline is the response to a more diverse range of pathological events. Cognitive reserve may only buffer against specific types of brain pathology.

There are some issues in examining terminal decline that the present analysis was not able to address directly. Firstly, the present study only obtained four (or fewer) measurements, across a period of 12 years. This may have been insufficient to detect terminal decline for some of the cognitive tasks, particularly those in which there was little decline over the follow-up period. The four-year retest intervals may also have been insufficient to detect accelerated terminal decline in some domains, particularly given previous findings suggesting terminal decline may occur less than four years before death (Wilson et al., 2003 and 2007). However, the change point method estimated preterminal and terminal slopes aggregated across all participants, rather than relying on individual slope estimates. While this method of estimation may thus be robust to a paucity of data, a degree of confounding by between-person effects in the estimating the rates of decline might be expected as a consequence. However, the potential for between-person confounding was mitigated in the present study by excluding survivors (Sliwinski et al., 2006) and by the inclusion of random effect terms for the preterminal and terminal periods in the mixed models. Further research comparing alternative methods for modeling terminal decline may determine the extent to which between-person effects might influence change point estimates. Terminal decline effects could not be reliably estimated in this cohort for tasks of verbal ability, verbal fluency, face recognition, and word recognition using the change point method. Our inability to detect terminal decline on these measures may not reflect an absence of terminal decline but rather a lack of power for this type of model to detect small rates of decline in this type of sample, particularly for measures which are more robust to age-related decline. Future studies studying the terminal decline phenomenon would benefit from a shorter interval between follow-up interviews and more follow-ups, although briefer retest periods or more interviews may lead to other undesirable outcomes such as increased attrition (Deeg, van Tilburg, Smit, & de Leeuw, 2002) or larger retest effects (Salthouse, Schroeder, & Ferrer, 2004).

Secondly, the analyses did not include survivors. This was because the model used was chosen to replicate that used in previous research (Sliwinski et al., 2006; Thorvaldsson et al., 2008). However, Sliwinski et al. (2006) noted that the inclusion of survivors may lead to an underestimate of the terminal decline effect. Thirdly, education was the only reliable baseline measure of cognitive reserve able to be included in the present study. Other factors that may impact reserve, such as brain atrophy and white matter hyperintensities, may provide clearer insight into the observed effects. APOE ε4 genotype, previously examined by Wilson et al. (2007), was only measured at the second wave of the current study, resulting in an inadequate sample size for the type of analysis used here. There were also too few cases of head injury (McMillan and Teasdale, 2007) or cognitive disorders (Wilson et al., 2007) in the present sample to examine these as separate indicators. Furthermore, the number of years of education may not be a good indicator of the quality of education, which may affect how adequately the measure reflects cognitive reserve. Fourth, the model estimated a single change point for the whole cohort (or for each education subgroup), rather than estimating individual change points. However, Hall, Ying, Kuo, & Lipton (2003) compared the profile likelihood method used here to a Bayesian method that estimated individual change points and concluded that individual change points are not necessary to adequately model heterogeneity across subjects. Finally, change point models are not the only method that may be used to characterize terminal decline. Other methods that could be considered for future research include retrospective models that account for individual differences (Gerstorf et al., 2008) and prospective models that link individual rates of change to the hazard of mortality (Ghisletta, McArdle, & Lindenberger, 2006).

The present study found that the onset and rate of terminal decline may be different across cognitive domains and that edu-

cation can modify the onset and rate of decline. The modification of terminal decline by education is a new finding that has not previously been investigated in specific cognitive domains. These findings were not changed by excluding participants with dementia or by controlling for other risk factors for cognitive decline and mortality. As education was the only reliable baseline measure of cognitive reserve included in the present study, further research is warranted to investigate modification of terminal decline effects by other measures of reserve, such as head injury, APOE genotype, and brain characteristics, including atrophy and white matter hyperintensities. Additional research into the nature of terminal decline and how this decline varies according the characteristics of individuals and their exposures will continue to illuminate the processes that lead to late-life cognitive decline.

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Received October 28, 2009
Revision received October 1, 2010
Accepted October 14, 2010 ■

Correction to Windsor and Anstey (2010)

The article "Age differences in psychosocial predictors of positive and negative affect: A longitudinal investigation of young, midlife, and older adults" by Tim D. Windsor and Kaarin J. Anstey (*Psychology and Aging*, Vol. 25, No. 3, 641–652) contains an error in Figure 3, on page 649. The top two panels in the figure are redundant. The bottom two panels (showing estimated intercepts for positive and negative affect) display the correct data.

DOI: 10.1037/a0023715

Psychology and Aging

0882-7974/11/$12.00 DOI: 10.1037/a0023300

Comparison of Age and Time-to-Death in the Dedifferentiation of Late-Life Cognitive Abilities

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The dedifferentiation hypothesis proposes that specific cognitive abilities become more highly associated with general ability in old age as a result of increasing biological constraints on fluid intelligence. There is limited evidence for the hypothesis, and research has not tended to clearly distinguish age dedifferentiation from ability differentiation and other age-related phenomena. The present study examined age dedifferentiation using a structural equation model that controlled for ability differentiation, along with linear and quadratic effects of age. Time-to-death was examined as an alternative time metric to chronological age, as it may better represent biological constraints. The Canberra Longitudinal Study community-based cohort, consisting of 896 Australian adults aged 70 and over, provided data from 687 decedents who were followed for up to 17 years. Results indicated little support for the age dedifferentiation hypothesis, with only two of seven cognitive tests showing significant age dedifferentiation. The time-to-death metric showed more evidence of dedifferentiation, with four of the seven tests exhibiting dedifferentiation. However, after excluding participants with possible cognitive impairment, all of the dedifferentiation effects were attenuated to nonsignificance. Age dedifferentiation effects may therefore reflect dementia and other mortality-related pathology rather than being an inevitable outcome of advanced age. Alternative developmental theories for cognitive function must better account for the diversity of late-life abilities and pathology.

Keywords: dedifferentiation hypothesis, time-to-death, mortality, dementia, intelligence, aging

The concept of a general factor of intelligence had its origins more than one hundred years ago (Spearman, 1904). Subsequent research suggested a range of specific factors of intelligence and led to the development of the theory of fluid and crystallized intelligence by Horn and Cattell (Cattell, 1941; Horn, 1968; Horn & Cattell, 1966). The fluid-crystallized theory suggests that there are two higher order factors of intelligence that form distinct dimensions: fluid intelligence, general ability derived from basic neural and sensory structures, and crystallized intelligence, knowledge-based ability derived from experience, education, and acculturation (Horn & Cattell, 1966). Cattell's investment theory (Cattell, 1971, 1987) extended the fluid-crystallized theory into a developmental framework. According to the investment theory, the fluid component of intelligence develops rapidly through childhood and adolescence, peaking in the early twenties, then decreasing through adulthood, more rapidly in old age. The crystallized component grows incrementally, driven by fluid ability, peaks in mid-life, and declines very little and only in late old age (Cattell, 1987). However, there has been little evidence to support the theory that fluid intelligence drives the development of crystallized intelligence, with more recent longitudinal research reporting that higher levels of fluid intelligence are not associated with subsequent increased growth in crystallized intelligence (Ferrer & McArdle, 2004). Nevertheless, research examining performance on fluid and crystallized tasks across the lifespan (Li et al., 2004; McArdle, Ferrer-Caja, Hamagami, & Woodcock, 2002; Tucker-Drob, 2009) has replicated the patterns of development and decline for fluid and crystallized ability reported by Cattell (1987). So while the investment theory may not accurately explain the processes behind the development of intelligence, the patterns of development and decline reported by Cattell (1987) have been supported.

Alternative explanations have been provided for individual differences in developmental patterns of cognitive performance. The observation that a general factor of intelligence accounts for a greater amount of variability in children and the elderly compared to adults (Balinsky, 1941; Garrett, 1946) led to the development of the differentiation-dedifferentiation hypothesis (Baltes, Cornelius, Spiro, Nesselroade, & Willis, 1980; Reinert, 1970), which suggests that intellectual abilities are unspecialized in childhood, differentiate during maturation, and become undifferentiated in late life (Li et al., 2004). Contributions from the environment and noncognitive influences, such as motivation and interest, are postulated to engender differentiation (Tucker-Drob, 2009). Late-life dedifferentiation is hypothesized to occur when, as a result of increasing biological constraints on information processing mechanisms, declines in fluid abilities limit subsequent development in crystal-

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The Canberra Longitudinal Study was supported by NHMRC Unit Grants 973301 and 933301 and NHMRC Program Grant 179805. HC is supported by NHMRC Senior Principal Research Fellowship 525411.

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lized abilities (Li et al., 2004). The cognitive processes involved with fluid and crystallized abilities consequently become more strongly coupled together (Li et al., 2004), such that general ability accounts for a greater proportion of performance across domains.

These constraints on information processing have been linked to decreased neurobiological efficiency (Li, Lindenberger, & Sikstrom, 2001; Li & Sikstrom, 2002; Park et al., 2002). Changes in neuromodulation and neuroanatomy result in decreasing differentiation between the patterns of neuronal representations elicited by different stimuli as people age (Li & Sikstrom, 2002). This neurocomputational model of cognitive aging posits that deficits in neuromodulation lead to increased neural noise, resulting in less distinctive cortical representations in the aging brain and, finally, to cognitive aging deficits, which manifest as decreases in performance, increases in variability, and increased relationships among cognitive abilities (Li et al., 2001). The relationship between neuronal dedifferentiation and cognitive dedifferentiation is purported to be based on the need for some form of compensatory neural recruitment in older adults (Park et al., 2002) as the cortical representations become less distinctive. On a neuroanatomical level, this compensation could come from contralateral recruitment of a homologous brain area, from unique recruitment of nonhomologous sites, or from substitution of brain areas (Park et al., 2002). In cognitive terms, abilities may be seen as hierarchical (Vernon, 1971), with an overall general factor of ability that comprises several broad ability factors, which can themselves be further deconstructed into specific abilities. When neuronal compensation is required in response to neuronal deficits, greater reliance may be given to broader abilities, such as processing speed, retrieval, and fluid and crystallized intelligence, rather than to specific abilities. Recruitment of these higher order abilities to perform lower order tasks leads to declines in performance, increases in variability, and, in particular, dedifferentiation of cognitive abilities.

There has, however, been mixed evidence for the late-life dedifferentiation of cognitive abilities. Several studies have reported late-life increases in the correlation between cognitive abilities (Baltes & Lindenberger, 1997; Ghisletta & Lindenberger, 2003; Li et al., 2004), while other studies have found no systematic relationship (Anstey, Hofer, & Luszcz, 2003; Juan-Espinosa et al., 2002; Sims, Allaire, Gamaldo, Edwards, & Whitfield, 2009; Tucker-Drob & Salthouse, 2008; Zelinski & Lewis, 2003). De Frias, Lovden, Lindenberger, and Nilsson (2007) found evidence for dynamic dedifferentiation beginning in old age, suggesting that common sources increasingly account for the development of abilities. Likewise, Ghisletta and colleagues (Ghisletta & de Ribaupierre, 2005; Ghisletta & Lindenberger, 2003) found longitudinal age-associated dedifferentiation, reporting that the dedifferentiation was a consequence of the constraints of mechanic ability, a notion similar to fluid intelligence.

Recently, Tucker-Drob (2009) used a statistical model able to distinguish the effects of ability differentiation from age dedifferentiation, and found no support for age dedifferentiation in a lifespan cohort. In examining the age dedifferentiation hypothesis, it is important to rule out confounding by ability differentiation, which is defined as differences in the correlations between cognitive abilities at different ability levels, with stronger correlations often observed among groups with lower ability levels (Deary et al., 1996; Tucker-Drob, 2009). Specifically, unless ability differentiation is accounted for, any age-based dedifferentiation effect may simply reflect the poorer performance among older individuals. Other sources of individual differences should also be accounted for in examining the dedifferentiation hypothesis, to exclude more parsimonious explanations for the phenomenon and determining whether dedifferentiation is an independent phenomenon of aging. Nonnormative sources of heterogeneity, particularly the influences of preclinical dementia (Sliwinski, Hofer, & Hall, 2003), should be examined to determine whether dedifferentiation is an inevitable consequence of normative aging or simply a reflection of pathological decline.

To date, research on dedifferentiation has used chronological age as the metric of time. However, ability differentiation may vary widely across individuals of the same age, depending on their lifetime accumulation of biological damage and resulting cognitive health (Lovden, Bergman, Adolfsson, Lindenberger, & Nilsson, 2005; Sliwinski, Hofer, & Hall, 2003). To observe the effects of dedifferentiation in a heterogeneous cohort, time-to-death may be a better metric for age, as it is a strong indicator of declines in both physical health and cognitive performance (Batterham, Christensen, & Mackinnon, 2009; Hassing et al., 2002; Small & Backman, 1999). For example, while two 80-year-olds may differ markedly in their health and cognitive performance, less average variation may be expected in two individuals that are one year from death. Dedifferentiation occurring as a function of proximity to death would provide evidence that dedifferentiation occurs in response to late-life pathology, particularly if the amount of dedifferentiation is greater than when modeling as a function of age. If there was more evidence for dedifferentiation as a function of age than time-to-death, it may be concluded that dedifferentiation was not directly indicative of pathology.

The present study aimed to compare the two time metrics—chronological age and time-to-death—in modeling the degree to which dedifferentiation may be observed in late life. It was hypothesized that time-to-death would be a more sensitive metric for observing dedifferentiation than age. This hypothesis was tested with the statistical model used by Tucker-Drob (2009) that can account for nonlinear relationships between cognitive measures and factors while controlling for any effects of ability differentiation. It is important that nonlinear relationships can be accounted for, as the predictions of the hypothesis are inherently nonlinear across the life span. Tucker-Drob's (2009) model simultaneously estimates the effects of age dedifferentiation and ability differentiation, in addition to age, age^2, the general ability factor (G), and the interaction between age dedifferentiation and ability differentiation. Age dedifferentiation is operationalized as the interaction between age and the general ability factor, that is, how the amount of variability accounted for by the general factor changes as a function of age. Ability dedifferentiation is defined in the model as G^2, which reflects how the amount of variability accounted for by the general factor changes as a function of the level of performance on that factor. As previous research has shown some evidence that age may modify ability differentiation (Facon, 2006; Tucker-Drob, 2009), the interaction between age dedifferentiation and ability differentiation was also included in the model. This is defined as the interaction between age and G^2, that is, how the amount of variability explained by the general factor as a function of overall performance changes in response to age.

Reestimation of the model using time-to-death in place of age enabled a comparison of the two time metrics. It was hypothesized that a greater degree of dedifferentiation would be observed when using time-to-death as the time metric rather than age. Such an outcome would suggest that dedifferentiation is due to increasing pathology in proximity to death rather than being due to age-related developmental changes. Likewise, exclusion of participants with possible cognitive impairment was hypothesized to attenuate any observed dedifferentiation due to age or proximity to death.

Method

Sample

The Canberra Longitudinal Study is an epidemiological survey of mental health and cognitive functioning in older people that commenced in 1990. The study design has previously been detailed by Christensen et al. (2004). Eight hundred and ninety-six community-dwelling adults, aged 70–97, living in the cities of Canberra and Queanbeyan, Australia, participated in the baseline assessment. The sample was stratified by age and gender. Participants were sampled from the compulsory electoral roll, with 69% responding. For the present study, only participants who had died at the end of the vital status collection period (June, 2007) were included in the analysis (n = 687, 76.7%), as time-to-death cannot be assessed for survivors.

Procedure

Participants were interviewed up to four times over 12 years, although only the baseline assessment was used in the present analysis. Baseline interviews lasted approximately two hours, incorporating a survey with a wide range of measures, including sociodemographics, physical health and disease status, mental health status, and cognitive performance. Interviews also included physical assessments of blood pressure, lung function, grip strength, vision, and reaction time. Trained professional interviewers conducted the assessments. Approval for the research was obtained from the Ethics in Human Experimentation Committee of The Australian National University.

Measures

Tests assessing a variety of cognitive domains were administered to assess the cognitive functioning of study participants. *Speed of processing* was measured by the Symbol-Letters Modalities Test (SLMT), a task similar to Smith's (1973) Symbol-Digit Modalities Test and Wechsler's (1981) Digit-Symbol Substitution. *Verbal ability* was measured using the National Adult Reading Test, a test of vocabulary (Nelson, 1982). An *episodic memory* task consisted of brief episodic memory tasks testing word, face, name, and address recall and figure reproduction (Jorm, 1992). *Verbal fluency* was assessed as the number of animals named in 30 seconds. *Face and word recognition* tasks were based on the Rivermead Behavioural Memory Test (Wilson, Cockburn, Baddeley, & Hiorns, 1989). *Global function* was tested using the Mini-Mental State Examination (MMSE; Folstein, Folstein, & McHugh, 1975), scored out of 30. For the factor analysis and to facilitate comparisons across tests, all of the tests were standardized to a common metric, with a mean of 100 and standard deviation of 10 at the baseline measurement.

Mortality status and date of death were established by searching the National Death Index, contacting relatives, and from death notices in the local newspaper. The National Death Index is a register of all deaths in Australia. The additional methods used for death reporting were included to provide added confidence in the mortality status data. Mortality status was followed for up to 17 years, from the start of baseline interviews in September 1990 until June 30, 2007. For six participants with unknown day of death, the day was set to the 15th of the month. For two participants with an unknown month of death, the month was set to June. *Date of birth (age)* was reported during the initial interview.

Analysis

The model detailed by Tucker-Drob (2009) was adopted for the analyses. The model is a structural equation model that combines a nonlinear factor analysis to estimate the general ability factor with a regression that tests the effects of age dedifferentiation and ability differentiation. The regression component uses each of the cognitive tests as dependent variables, estimating the effects of general ability (*G*, a latent variable based on the seven cognitive test scores), age (or time-to-death; TTD), age^2 (or TTD^2), ability differentiation, age/TTD dedifferentiation, and the interaction between ability differentiation and age/TTD dedifferentiation. The age-based model may be written as

$$g\,[x]_n = \nu\,[x] + \alpha_1[x] \times age_n + \alpha_2[x] \times age_n^2 + \lambda_1[x] \times G_n + \lambda_2[x] \times G_n^2 + \lambda_3[x] \times age_n \times G_n + \lambda_4[x] \times age_n \times G_n^2 + u[x]_n$$

where g [x] represents the matrix of n specific cognitive abilities that were assessed; the n subscript indicates terms that vary; ν [x] represents the intercepts for each ability; $\alpha_1[x]$ and $\alpha_2[x]$ are the coefficients for age and age^2; G is general ability; $\lambda_1[x]$ are the loadings of each specific ability on G; $\lambda_2[x]$ is the coefficient representing ability differentiation (G^2); $\lambda_3[x]$ is the coefficient for

Table 1
Descriptive Statistics for the Analysis Sample at Baseline (n = 687)

	M or *frequency*	*SD* or *percent*
Gender, Male	*373*	*54.3%*
Marital status		
Married	*366*	*53.3%*
Widowed	*261*	*38.0%*
Age	77.30	5.09
Years of education	11.41	2.66
Processing speed (SLMT)	93.91	16.97
Vocabulary (NART)	111.32	10.08
Global cognition (MMSE)	27.07	2.98
Verbal fluency	10.52	3.43
Word recognition	0.94	0.09
Face recognition	0.78	0.11
Episodic memory task	13.16	2.48

Note. SLMT = Symbol-Letters Modalities Test; NART = National Adult Reading Test; MMSE = Mini-Mental State Examination.

Table 2
*Parameter Estimates (99% Confidence Intervals) From the Models of Performance on the Seven Cognitive Tasks Based on Age and Time-To-Death (*n = *687)*

	Intercept	Age/TTD	Age^2/TTD^2
Age model			
Processing speed	**104.80 (102.29, 107.30)**	**−1.017 (−1.558, −0.476)**	0.022 (−0.004, 0.048)
Vocabulary	**101.11 (98.12, 104.10)**	−0.432 (−1.035, 0.171)	0.020 (−0.008, 0.048)
Global cognition	**103.80 (101.79, 105.81)**	−0.093 (−0.539, 0.353)	−0.004 (−0.030, 0.022)
Verbal fluency	**104.58 (102.54, 106.61)**	−0.555 (−1.142, 0.032)	0.013 (−0.015, 0.041)
Word recognition	**103.04 (100.30, 105.77)**	−0.189 (−0.738, 0.360)	−0.011 (−0.042, 0.020)
Face recognition	**102.35 (99.50, 105.20)**	−0.198 (−0.801, 0.405)	−0.008 (−0.039, 0.023)
Episodic memory	**103.99 (101.73, 106.26)**	−0.485 (−1.003, 0.033)	0.011 (−0.017, 0.039)
TTD model			
Processing speed	**94.79 (91.48, 98.10)**	0.339 (−0.449, 1.127)	0.016 (−0.028, 0.060)
Vocabulary	**97.32 (94.01, 100.63)**	0.141 (−0.683, 0.965)	0.015 (−0.031, 0.061)
Global cognition	**99.49 (96.62, 102.35)**	0.412 (−0.224, 1.048)	0.001 (−0.030, 0.032)
Verbal fluency	**100.56 (97.81, 103.31)**	−0.087 (−0.999, 0.825)	0.032 (−0.020, 0.084)
Word recognition	**99.50 (95.60, 103.41)**	−0.157 (−0.829, 0.515)	0.031 (−0.008, 0.070)
Face recognition	**97.25 (94.01, 100.48)**	−0.096 (−1.016, 0.824)	0.024 (−0.028, 0.076)
Episodic memory	**98.57 (95.05, 102.09)**	0.222 (−0.512, 0.956)	0.007 (−0.032, 0.046)

Note. Bold values indicate $p < .01$; TTD = time-to-death; G = general ability factor.

age differentiation (G × age); $\lambda_4[x]$ represents the degree to which age modifies ability differentiation (G^2 × age); and u[x] is the error term that represents the component of each broad ability not accounted for by the other terms in the model (Tucker-Drob, 2009). The time-to-death model simply replaced age with TTD. Age was centered by subtracting 70 years from chronological age (range: 0–27.5 years), while time-to-death was measured in years (range: 0–16.75 years), and both measures were converted to decades to enable interpretation of small estimates of the squared components. The model was estimated using seven cognitive tests to examine a range of cognitive domains. A criterion for significance of $p < .01$ was used for all analyses to adjust for the multiple comparisons across the seven cognitive tests. Finally, to examine whether dedifferentiation effects were attributable to dementia, models were reestimated excluding participants with MMSE scores < 24, as this criterion is a conservative indicator for cognitive impairment reflecting dementia (Folstein et al., 1975). All analyses were conducted in Mplus version 6.

Results

Sample characteristics for the analysis sample ($n = 687$) are shown in Table 1. Compared to participants who were excluded on the bases of survival or missing baseline data, the participants included in the analysis were significantly older ($t_{894} = -8.58$, $p < .0001$), were more likely to be male [$\chi^2(1) = 13.6$, $p = .0002$], and performed more poorly on all of the cognitive tasks, including processing speed ($t_{851} = 7.52$, $p < .0001$), vocabulary ($t_{833} = 2.32$, $p = .0204$), global cognition ($t_{877} = 4.54$, $p < .0001$), verbal fluency ($t_{881} = 3.75$, $p = .0002$), word recognition ($t_{865} = 3.79$,

Table 3
*Parameter Estimates (99% Confidence Intervals) From the Models of Performance on the Seven Cognitive Tasks Based on Age and Time-To-Death, Excluding Participants With MMSE < 24 (*n = *606)*

	Intercept	Age/TTD	Age^2/TTD^2
Age model			
Processing speed	**105.72 (102.23, 109.21)**	**−0.951 (−1.577, −0.325)**	0.011 (−0.025, 0.047)
Vocabulary	**101.72 (96.16, 107.28)**	−0.266 (−0.918, 0.386)	0.010 (−0.023, 0.043)
Global cognition	**103.26 (101.07, 105.44)**	−0.004 (−0.375, 0.367)	−0.012 (−0.033, 0.009)
Verbal fluency	**104.66 (98.59, 110.74)**	−0.509 (−1.130, 0.112)	0.015 (−0.013, 0.043)
Word recognition	**102.83 (99.56, 106.10)**	−0.112 (−0.877, 0.653)	−0.006 (−0.042, 0.030)
Face recognition	**102.14 (98.99, 105.28)**	−0.293 (−1.022, 0.436)	−0.003 (−0.039, 0.033)
Episodic memory	**103.87 (100.80, 106.94)**	−0.157 (−0.628, 0.314)	−0.007 (−0.035, 0.021)
TTD model			
Processing speed	**96.68 (92.74, 100.62)**	0.065 (−0.757, 0.887)	0.032 (−0.017, 0.081)
Vocabulary	**99.27 (95.16, 103.38)**	−0.065 (−0.892, 0.762)	0.026 (−0.026, 0.078)
Global cognition	**100.94 (98.41, 103.47)**	−0.025 (−0.486, 0.436)	0.020 (−0.008, 0.048)
Verbal fluency	**102.53 (99.68, 105.38)**	−0.265 (−1.092, 0.562)	0.036 (−0.016, 0.088)
Word recognition	**99.57 (94.81, 104.33)**	−0.005 (−0.639, 0.629)	0.008 (−0.028, 0.044)
Face recognition	**98.71 (95.36, 102.06)**	−0.204 (−1.165, 0.757)	0.031 (−0.023, 0.085)
Episodic memory	**101.44 (96.94, 105.94)**	−0.041 (−0.662, 0.580)	0.014 (−0.022, 0.050)

Note. Bold values indicate $p < .01$; TTD = time-to-death; G = general ability factor.

G	Ability differentiation	Age/TTD differentiation	Ability × Age/TTD differentiation
6.903 (5.151, 8.655)	−0.762 (−1.836, 0.312)	0.009 (−0.197, 0.215)	0.067 (−0.044, 0.178)
7.505 (5.885, 9.125)	−0.224 (−1.844, 1.396)	−0.012 (−0.192, 0.168)	−0.001 (−0.163, 0.161)
4.063 (2.505, 5.621)	**−1.647 (−3.041, −0.253)**	**0.348 (0.137, 0.559)**	**−0.240 (−0.425, −0.055)**
6.202 (3.814, 8.590)	0.760 (−0.919, 2.439)	−0.058 (−0.300, 0.184)	−0.074 (−0.239, 0.091)
3.979 (2.045, 5.913)	**−3.320 (−5.115, −1.525)**	0.204 (−0.015, 0.423)	0.029 (−0.190, 0.248)
1.567 (−0.532, 3.666)	−1.386 (−3.645, 0.873)	0.136 (−0.137, 0.409)	−0.006 (−0.258, 0.246)
4.094 (2.559, 5.629)	**−1.710 (−3.204, −0.216)**	**0.287 (0.084, 0.490)**	0.003 (−0.262, 0.268)
8.202 (6.487, 9.917)	0.572 (−0.567, 1.711)	−0.149 (−0.347, 0.049)	−0.091 (−0.248, 0.066)
6.985 (5.166, 8.804)	0.655 (−0.764, 2.074)	0.030 (−0.179, 0.239)	−0.135 (−0.313, 0.043)
10.316 (7.843, 12.789)	**−3.840 (−5.244, −2.436)**	**−0.470 (−0.728, −0.212)**	0.040 (−0.171, 0.251)
6.025 (3.689, 8.361)	−0.203 (−1.700, 1.294)	−0.046 (−0.381, 0.289)	0.069 (−0.199, 0.337)
8.040 (5.657, 10.423)	**−3.143 (−4.943, −1.343)**	**−0.324 (−0.569, −0.079)**	0.059 (−0.183, 0.301)
4.955 (2.521, 7.389)	−1.409 (−3.194, 0.376)	**−0.293 (−0.553, −0.033)**	0.023 (−0.180, 0.226)
9.335 (7.176, 11.494)	**−1.697 (−3.338, −0.056)**	**−0.397 (−0.616, −0.178)**	0.035 (−0.145, 0.215)

$p = .0002$), face recognition ($t_{871} = 3.15$, $p = .0017$), and episodic memory ($t_{894} = 3.15$, $p = .0017$) at baseline. There were, however, no significant differences in years of education ($t_{892} = -1.18$, $p = .24$) or marital status [$\chi^2(3) = 5.3$, $p = .15$]. The participants in the analysis sample were, on average, fairly well educated and cognitively intact.

The two models testing age and time-to-death dedifferentiation are shown in Table 2. The first column of values is the estimate of the intercept for each of the cognitive tests at age 70 (or at death for the TTD model) for a participant with general ability score of zero (i.e., mean level of general ability), with each cognitive test score standardized to $M = 100$ and $SD = 10$. The second column is the effect per decade of age (or per decade closer to death), while the third column is the quadratic effect per decade of age (or per decade closer to death). The fourth column is the effect of general ability, which would be expected to reflect ability on each of the tests. The fifth column is the effect of ability differentiation, where negative values indicate that *G* accounts for less of the variability in performance at higher levels of performance. The sixth column is the effect of age/TTD differentiation, where positive values in the age model indicate that *G* accounts for more of the variability across cognitive domains as age increases (i.e., age dedifferentiation), whereas negative values in the TTD model indicate that *G* accounts for more of the variability across cognitive domains as time-to-death decreases (i.e., TTD dedifferentiation). The final column is the interaction between age/TTD differentiation and ability differentiation, where negative values in the age model or positive values in the TTD model indicate that age/TTD dedifferentiation decreases at higher ability levels.

G	Ability differentiation	Age/TTD differentiation	Ability × Age/TTD differentiation
6.320 (4.020, 8.620)	−1.451 (−5.495, 2.593)	−0.063 (−0.277, 0.151)	0.240 (−0.054, 0.534)
6.946 (3.433, 10.459)	−0.664 (−6.990, 5.662)	−0.128 (−0.331, 0.075)	0.095 (−0.281, 0.471)
2.971 (1.505, 4.437)	−0.817 (−2.996, 1.362)	0.037 (−0.066, 0.140)	0.059 (−0.083, 0.201)
6.018 (3.651, 8.385)	1.528 (−0.319, 3.375)	−0.135 (−0.372, 0.102)	−0.102 (−0.249, 0.045)
3.040 (1.443, 4.637)	−2.175 (−6.966, 2.616)	0.132 (−0.136, 0.400)	−0.032 (−0.279, 0.215)
0.702 (−1.194, 2.598)	−0.385 (−2.654, 1.884)	0.113 (−0.165, 0.391)	0.043 (−0.284, 0.370)
4.002 (0.643, 7.361)	−2.184 (−5.847, 1.479)	0.046 (−0.178, 0.270)	0.125 (−0.117, 0.367)
6.201 (4.279, 8.123)	1.743 (−1.629, 5.115)	−0.043 (−0.280, 0.194)	−0.198 (−0.414, 0.018)
5.197 (3.160, 7.234)	1.222 (−2.572, 5.016)	0.092 (−0.184, 0.368)	−0.191 (−0.361, −0.021)
4.434 (3.362, 5.506)	0.112 (−1.598, 1.822)	−0.147 (−0.294, 0.000)	−0.074 (−0.182, 0.034)
4.198 (1.906, 6.490)	0.225 (−2.619, 3.069)	0.104 (−0.156, 0.364)	0.069 (−0.209, 0.347)
6.588 (1.854, 11.322)	−3.760 (−9.434, 1.914)	−0.320 (−0.642, 0.002)	0.189 (−0.099, 0.477)
2.836 (0.332, 5.340)	0.576 (−3.095, 4.247)	−0.154 (−0.430, 0.122)	−0.090 (−0.505, 0.325)
5.863 (3.638, 8.088)	−1.582 (−5.147, 1.983)	−0.188 (−0.389, 0.013)	0.032 (−0.133, 0.197)

The effect of primary interest was that of age/TTD dedifferentiation. In the age-based model, significant age dedifferentiation was observed only for global cognition and episodic memory, suggesting *G* accounted for larger amounts of variance on these two tasks at older age, independent of ability. In the time-to-death model, significant TTD dedifferentiation was observed in four of the seven domains, with *G* accounting for more of the variance in global cognition, word recognition, face recognition, and episodic memory performance as death approached. In addition, significant ability differentiation was observed for global cognition, word recognition, and episodic memory in both models, suggesting that *G* accounted for more of the variance on these tasks in those with poorer general ability. There was also a significant interaction between age dedifferentiation and ability differentiation on global cognition, suggesting that the effect of age dedifferentiation is decreased at higher levels of performance. There was no significant effect of TTD or TTD^2 on any of the tests, while processing speed performance decreased significantly by 0.1 standard deviation per decade of age. Not surprisingly, general ability (*G*) had strong positive associations with all of the cognitive tests, although the effect did not reach significance ($p = .055$) for face recognition in the age-based model.

The fit of the models presented in Table 1 was tested by repeatedly excluding single cognitive tests from the models. For example, the −2 log likelihood of the age-based model increased from 44920.2 to 45029.0 [$\chi^2(6) = 108.8$, $p < .0001$] after excluding face recognition, indicating that the model fit was significantly better when face recognition was included. Exclusion of each of the cognitive tests significantly decreased the fit of both the age model [$\chi^2(6)$ range 108.8 to 759.1, $p < .0001$] and the time-to-death model [$\chi^2(6)$ range 105.4 to 767.3, $p < .0001$]. Consequently, all of the cognitive tests were retained in the models.

In a further analysis to examine whether the observed dedifferentiation effects were attributable to dementia, the models in Table 2 were estimated with the exclusion of participants who scored < 24 on the MMSE [n = 606, 81 (11.8%) excluded]. These models are shown in Table 3. All of the age dedifferentiation, TTD dedifferentiation, and ability differentiation effects became nonsignificant after this exclusion.

Discussion

Significant age dedifferentiation was observed on two of the seven cognitive tests, global cognition, and episodic memory, while significant time-to-death (TTD) dedifferentiation was observed on four of the tests: global cognition, word recognition, face recognition, and episodic memory. This is the first study to examine dedifferentiation as a function of time-to-death. As the effects of TTD dedifferentiation were more consistent than the effects of age dedifferentiation, any strengthening in the relationship between general and specific abilities as a function of advancing age appears to be attributable to increasing pathology in proximity to death. This finding was as predicted and likely reflects the closer relationship of pathology with time-to-death than chronological age (Johansson et al., 2004; Kerber, Whitman, Brown, & Baloh, 2006; Sliwinski, Hofer, & Hall, 2003). However, after excluding participants with possible cognitive impairment, nearly all of the age/TTD dedifferentiation effects were markedly attenuated and all became nonsignificant. Consequently, the effects were not sufficiently robust to support the theory of age dedifferentiation. The findings suggest that brain pathology, both as a result of dementia and mortality-related biological events, is likely to play a significant role in any late-life dedifferentiation of cognitive abilities. Dedifferentiation was not found to be an inevitable consequence of aging.

Memory was found to be the primary domain of functioning, where some evidence of dedifferentiation was observed, with episodic memory, face recognition, and word recognition all showing dedifferentiation in proximity to death. As dementia results in a broad range of memory declines (Spaan, Raaijmakers, & Jonker, 2003), it is perhaps not surprising that the observed effects disappeared after accounting for cognitive impairment. Likewise, the global cognition measure, the MMSE, is sensitive to dementia (Mitchell, 2009) and showed dedifferentiation as a function of both age and time-to-death. The MMSE includes a memory component, with the recall items being the most difficult for people with dementia (Teng, Chui, Schneider, & Metzger, 1987). Processing speed also declines as a result of aging; however, decrements in processing speed are observed in the absence of pathological aging processes. The lack of dedifferentiation in processing speed is therefore further evidence that dedifferentiation is a product of pathological rather than normative aging. Verbal performance (verbal fluency, vocabulary) is generally robust to the normative and pathological effects of aging, so it is not surprising that no dedifferentiation was observed on the verbal tasks.

The absence of robust age dedifferentiation effects was in line with a growing body of research in this area (for example, Anstey et al., 2003; Tucker-Drob, 2009; Tucker-Drob & Salthouse, 2008; Zelinski & Lewis, 2003). Age-related dedifferentiation is proposed to be the result of common or normative constraints on functioning in late adulthood (Li & Lindenberger, 1999). It may be that in community-based cohorts that vary widely in both ability and pathology, age-related effects are so diverse that they cannot be classified as "common." While age dedifferentiation may be observed in certain cohorts and on specific measures, alternative developmental models for late-life cognition should be explored. Such models need to better account for multiple trajectories that occur in response to both normative aging and the range of pathologies that occur in late life. Furthermore, the lack of evidence for age dedifferentiation suggests that the decline of abilities in old age is not as analogous to the development of abilities in childhood as suggested by the differentiation-dedifferentiation hypothesis.

The results also provide little evidence for a relationship between neurobiological dedifferentiation and cognitive dedifferentiation. Park et al. (2002) suggest that while there are few changes in the structure of working memory across the lifespan, changes in processing speed may be broadly implicated in a range of cognitive abilities. This explanation for how neuronal compensation may lead to changes in the relationship between cognitive abilities is based on the common cause theory of aging (Salthouse, 1996). However, processing speed would appear to have less association with the tasks that showed any evidence of age dedifferentiation in the present study—particularly face recognition, word recognition, and global function—than on tasks that showed no evidence of dedifferentiation, particularly speeded tasks such as verbal fluency. Thus, it would seem that the patterns of relationships observed show little evidence of the recruitment of higher order

abilities, such as processing speed, to perform lower order tasks. It could be argued that higher order retrieval processes may be implicated in the observed dedifferentiation effects, which tended to be related to memory. However, these effects do not appear to be the result of normative aging processes in the present cohort. Rather, such higher order recruitment may only be occurring in response to pathological processes, most likely the effects of preclinical dementia. The critical link between less distinctive cortical representations in the aging brain and increased relationships among cognitive abilities proposed by Li et al. (2001) could not be supported by the present study.

There were some limitations to the present study. The cognitive measures used were selected at the beginning of the study 20 years ago. Alternative measures covering a wider range of cognitive domains might provide further insight into the phenomena of interest. The use of single cognitive tests to measure each domain of ability also precludes assessing the common variance across multiple tests of the same ability, which may make it harder to detect dedifferentiation effects. However, it is generally not feasible to repeatedly administer a large battery of cognitive tests to a large community-based sample that is retested every 4 years. There are few community-based studies that have the breadth of data of the Canberra Longitudinal Study. Nevertheless, other study designs may be better able to account for a wider range of abilities and assess each ability using multiple tests. Secondly, only cross-sectional cognitive information was used in the present analysis. The complexity of the structural equation model used for this analysis precluded adaptation to a longitudinal analysis. Other methods for longitudinal examination of dedifferentiation may reveal more about the phenomenon by examining within-individual patterns of change in the relationship between abilities (Anstey et al., 2003; Sliwinski, Hofer, Hall, Buschke, & Lipton, 2003; Zelinski & Lewis, 2003). Other types of analyses that account for intraindividual change may also provide greater insight into relationships between terminal decline and dedifferentiation. However, the current cross-sectional analysis was sufficient to show that the dedifferentiation effects were not robust when dementia was excluded. Finally, while the role of background factors such as gender, education, social support, and mental health may be investigated in relation to dedifferentiation, the lack of evidence for age dedifferentiation in the present study rendered any such investigation largely unnecessary.

In conclusion, little support was found for the age dedifferentiation hypothesis in the present study, and dedifferentiation was found to result from dementia and terminal pathology rather than being an inevitable outcome of advanced age. The lack of robust age dedifferentiation effects is in line with the findings of Tucker-Drob (2009), who accounted for ability differentiation using a similar method. The necessity to use models that account for confounding by ability dedifferentiation remains clear. Further research should examine the conditions that are associated with the emergence of age-associated dedifferentiation effects, particularly examining whether such effects are associated with subsequent conversion to dementia. Examining the range of individual late-life cognitive trajectories (Lovden et al., 2005) or explicitly decomposing cognitive performance as a function of preclinical dementia, study attrition, terminal decline, and chronological age (Sliwinski, Hofer, Hall, et al., 2003) may enable further exploration of the role of pathology in dedifferentiation. The present findings with respect to dedifferentiation as a function of time-to-death are novel and suggest that dedifferentiation is not a phenomenon that results from normative aging.

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Received July 14, 2010
Revision received January 31, 2011
Accepted February 1, 2011 ■

Soc Psychiat Epidemiol
DOI 10.1007/s00127-010-0313-0

ORIGINAL PAPER

Mental health symptoms associated with morbidity, not mortality, in an elderly community sample

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Received: 1 June 2010 / Accepted: 18 October 2010

Abstract
Purpose Six previous reviews have found a relationship between depression and mortality. However, many past studies have failed to adequately control for the role of physical health. A proposed mechanism of the depression–mortality relationship suggests that physical health may mediate the relationship. The present study used new methods to examine relationships between mental health symptoms and mortality in an elderly community cohort while accounting for potential mediation of these relationships by physical health.
Method 896 community-dwelling participants aged 70–97 were assessed four times over 12 years and vital status was tracked for up to 17 years. Relationships of depression and anxiety with survival time, controlling for physical health, age and gender, were tested using Cox proportional hazards regressions embedded in structural equation models.
Results A significant unadjusted relationship between depression symptoms and mortality (HR = 1.09, $p < .001$) was attenuated to non-significance after controlling for measures of physical health (HR = 1.03, $p = .18$). No significant relationship was found between anxiety symptoms and mortality.
Conclusions The relationship between depression and mortality was accounted for by physical health status in this cohort. This finding casts doubt on studies that report a relationship between depression and mortality without adequately considering the effect of physical health.

Keywords Mortality · Depression · Anxiety · Physical health

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Introduction

There is a large body of literature examining whether depression is a risk factor for death. Evidence for the relationship has been summarized in six reviews, each of which has concluded that depression is associated with an increased all-cause mortality rate [1–6]. The earliest of these, a review of 57 studies published between 1966 and 1996 [6] found 29 (51%) reported a positive relationship between depression and mortality. A follow-up review of 61 articles published between 1996 and 2001 [5] reported that 72% had positive findings. A meta-analysis [4] reported a combined odds ratio for mortality with depression of 1.73 (95% CI 1.53-1.95). The most recent review [2] reported a relative risk for mortality in depressed subjects of 1.81 (95% CI 1.58–2.07) compared to non-depressed subjects. However, Wulsin et al. [6] cautioned against drawing strong conclusions about the nature of the relationship due to (a) a lack of adequate controlling for confounders, (b) the potential of publication bias in favor of positive studies and (c) the heterogeneity of samples and methods used in the studies.

With respect to the first of these limitations, 44% of the 57 studies reported by Wulsin et al. [6], 33% of the 61 studies reported by Schulz et al. [5], and 79% of the 21 studies reported by Saz and Dewey [4] did not control for

Published online: 05 November 2010

physical health status. Moreover, very few of the studies used objective measures of health status, with most using less reliable measures such as presence/absence of chronic disease or disease counts. Only one of the 57 studies reviewed by Wulsin et al. [6] controlled for both the effect of physical health and other potential confounders of the relationship such as smoking, alcohol use and suicide. The strength of evidence for an association between depression and mortality is further diminished by the inconsistency of the effect over extended follow-up periods, in heterogeneous populations or using a variety of methods. Saz and Dewey [4] found that the odds ratio of depression on mortality appears to be significantly attenuated over time, in that studies with longer follow-up periods predicted smaller effect sizes. Studies examining community samples rather than clinical populations have tended to report mixed or null effects, with only 4 of the 12 (33%) high-quality community studies reviewed by Wulsin et al. [6] reporting positive findings. Furthermore, the majority of the studies reviewed used a clinical diagnosis or a cut-off on a scale as the depression measure, rather than investigating the continuum of depressive symptomatology. Using diagnostic instruments to create binary categorizations of participants precludes drawing conclusions on the incremental impact of depression severity on mortality.

Many mechanisms for the association between depression and mortality have been proposed [2]. Schulz et al. [5] presented a general theoretical model proposing that depressive symptoms either lead directly to mortality or are mediated by a cascade of risk factors ranging from behavioral and biological factors to subclinical and clinical disease. Cuijpers and Schoevers [2] describe a model of the relationship that suggests physical health status might play a mediating role. Specifically, depression may directly increase vulnerability to physical illness by compromising physiological systems, particularly through changes in immune response. There is evidence that depression promotes increased production of inflammatory cytokines and reduced cellular immune response [7]. Such changes in immunological processes have been implicated in a range of conditions including cardiovascular disease, arthritis, type 2 diabetes, certain cancers, frailty and functional decline [7]. Other physiological responses associated with depression include increased platelet aggregation and heart rate variability brought about by dysregulation of the autonomic nervous system [8], both of which increase the risk of cardiovascular disease. In addition, there is evidence that depression is associated with hazardous health behaviors, including smoking, alcohol use and poor diet, that lead to further declines in physical health [2]. As people with poorer physical health are more likely to die, the interactions between physical health and depression may account for much of the association between depression and mortality. Given the methodological inadequacies of some previous studies, the relationship between depression on mortality may have been overstated and requires more thorough testing.

There have been fewer studies on the relationship between anxiety and mortality. One review has examined the effects of an array of mental disorders on mortality among patient cohorts [3]. Harris and Barraclough [3] found increased risks of premature death for all disorders. Their review examined four studies of "neurosis", one of "anxiety neurosis" and one of panic disorder. Harris and Barraclough [3] reported that the risk of death from all causes was significantly greater for those with neurosis or panic disorder but not for anxiety neurosis. A more recent meta-analytic review of seven studies of the impact of anxiety on mortality in elderly cohorts [9] concluded that although anxiety diagnoses tended to be associated with mortality, the effect was not significant. The review also reported that there was no association found between levels of anxiety symptoms and mortality.

The present study sought to determine whether depression and anxiety symptoms were associated with long-term all-cause mortality in an elderly community sample and to explore the impact of controlling for physical health status. To better account for the complex pattern of relationships between mental health, physical health and mortality, a recently developed statistical method was used for the analysis. The majority of studies investigating the effect of depression on mortality have used Cox proportional hazards regression, with time to death as the outcome. However, Cox proportional hazards regression cannot directly test whether one independent variable mediates the effect of another on the survival outcome. Structural equation modeling (SEM) allows theories of mediation to be assessed, and has been applied widely to conventional regression analyses [10]. However, until recently SEM software has not accommodated survival data. By employing a Cox proportional hazards regression model within a SEM context using the Mplus application [11], it is possible to test for mediation when modeling survival data. We hypothesized a significant direct relationship between depression and mortality. After accounting for physical health, the indirect effect of depression on mortality was hypothesized to be non-significant, particularly given the advanced age of the cohort and the extended follow-up period. Any relationship between anxiety and mortality was hypothesized to be non-significant.

Method

Participants

The Canberra Longitudinal Study was an epidemiological survey of mental health and cognitive functioning in older

people that commenced in 1990. The study design has been detailed by Christensen et al. [12]. Eight hundred and ninety-six participants (456 men and 440 women) aged 70 or older at the time of the baseline assessment were recruited for the baseline assessment. All participants were initially living in the community in the cities of Canberra or Queanbeyan, Australia. The sample selection was stratified by age and gender. Participants were sampled from the compulsory electoral roll, with 69% responding. Approval for the research was obtained from the Ethics in Human Experimentation Committee of The Australian National University.

Survey procedure

Participants were interviewed up to four times over 12 years. Baseline interviews lasted approximately 2 h, incorporating a survey measuring a wide range of risk factors including socio-demographics, physical health and disease status, mental health status, cognitive performance and social support. Interviews also included physical assessments of blood pressure, lung function, grip strength, vision and reaction time. Trained professional interviewers conducted the interviews.

Of the original sample of 896 participants, 185 (20.6%) were deceased by 4 years, 363 (40.5%) were deceased by 8 years and 544 (60.7%) were deceased by 12 years. At the end of vital status collection in June 2007, 687 (76.7%) of the participants were deceased. Of the participants who remained in the study, 14.1% (100/711) refused or were unable to complete the first follow-up interview, 21.1% (100/474) for the second follow-up and 21.1% (57/270) for the third follow-up.

Measures

Mortality status and date of death were established by contacting relatives, searching the National Death Index and from death notices in the local newspaper. Mortality status was followed for up to 17 years, from the start of baseline interviews in September 1990 until 30 June 2007. Survival was calculated as the time from the baseline interview to death for deceased participants, or from baseline until 30 June 2007 for surviving (right-censored) participants. For six participants with unknown day of death, the day was set to the 15th of the month. For two participants with an unknown month of death, the month was set to June.

Depression and anxiety symptoms were measured using the Goldberg Depression and Anxiety Scales [13], which each comprise nine items that measure symptoms of affective disorders in the 4 weeks prior to reporting. The number of "yes" responses were summed for these scales to derive two scores (range 0–9), with higher scores reflecting a greater level of depression/anxiety. *Age and gender* were reported during the initial interview. Several indices of physical health were measured in the study. Four of these measures were chosen as being objective health measures that cover different aspects of physical wellbeing. *Heart attack history* and *hypertension history* were included as dichotomous variables, based on self-report at the initial interview. *Grip strength* was taken using a Smedley hand dynamometer which measures the force exerted in kilograms [14]. A scale of *functional ability* was based on difficulty ratings for eight Activities of Daily Living (ADLs), including transportation, walking, getting out of bed, getting out of a chair, dressing and bathing. Using a four-point response scale (no difficulty, some difficulty but no help needed, need help, bedridden) for the eight items, functional ability scores ranged from 0 to 24, with higher scores indicating greater functional disability.

Analyses

Survival time was graphed using Kaplan–Meier curves and modeled using Cox proportional hazards regression analyses within a SEM framework. A series of three Cox regression analyses were completed using structural modeling [11], for both depression and anxiety: (i) a univariate model (depression or anxiety only), (ii) a model with age and gender included and (iii) a model with age, gender and physical health measures included and accounting for the relationship between depression and physical health in the structural model. Mediation by physical health of the relationship between depression/anxiety and mortality was tested by comparing model (iii) with an identical model (iv) that omitted the relationship between depression/anxiety and mortality, using the difference in -2 log likelihood values that are distributed as χ^2 for nested models. No significant change between the fit of model (iv) and model (iii) would indicate full mediation of the depression/mortality relationship by physical health. To comprehensively measure multiple aspects of physical health, four measures were included in the model: heart attack history, hypertension history, grip strength and functional disability. These measures were chosen to be somewhat independent measures of past and present physical health, with absolute correlation coefficients less than 0.1 for every pairing except functional disability and grip strength ($r = -.41$). Consequently, a robust latent variable could not be constructed, so the physical health measures remained separate in the structural equation models. The four models are shown in Fig. 1. Among the variables used in the analysis, 3% of the sample had one missing value and a further 3% of the sample had two or more missing values, resulting in a sample size of 865 for the depression analyses and 870

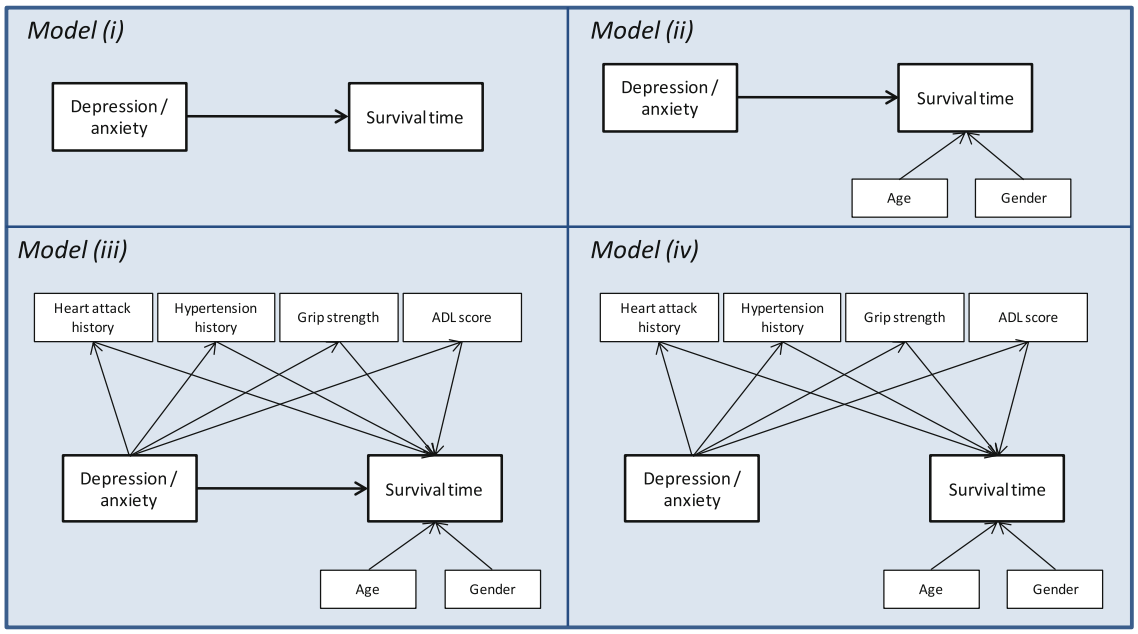

Fig. 1 Structural equation/Cox regression models used to examine relationships between depression/anxiety and mortality: (i) univariate model, (ii) adjusted for age and gender, (iii) adjusted for age, gender and physical health latent variable, and (iv) testing mediation by physical health

for the anxiety analyses. Stata version 10 was used to construct Kaplan–Meier survival curves, while Mplus version 5.1 was used for the modeling.

Results

Among the cohort of 896 participants, the mean initial age was 77 (range 70–97), with males representing 51% of the stratified sample. Participants had a mean of 2.0 depression symptoms and 2.5 anxiety symptoms. Thirteen percent of the sample had four or more depression symptoms, while 19% had four or more anxiety symptoms. Participants had a mean of 11 years of education. Considering the age of the cohort, participants were reasonably healthy at baseline, with 18% reporting heart attack history and 42% with hypertension history. Most of the participants had high functional ability, with 36% requiring no assistance for any of the eight listed activities and a further 46% requiring assistance for just one or two of the activities.

Kaplan–Meier curves show the univariate relationships between depression (Fig. 2) and anxiety (Fig. 3) with mortality. For these figures, the Goldberg scales were split at a value of four, which represented the approximate 80th percentile of depression or anxiety levels in this sample. Figure 2 shows that participants with elevated depression tended to have a higher mortality rate than those lower or no depression, as there was evident separation between these groups. The overlap of the two curves in Fig. 3 suggests that there was no effect of elevated anxiety,

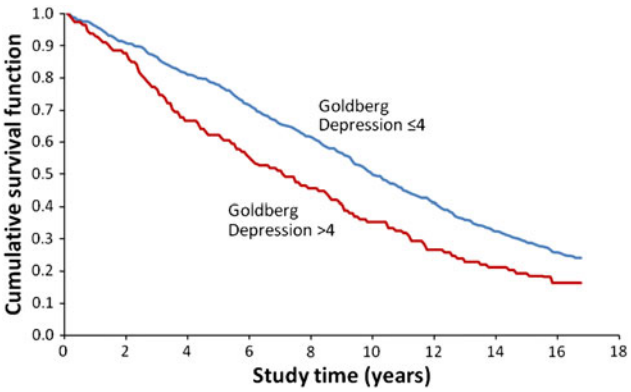

Fig. 2 Kaplan–Meier curve of mortality over 17 years based on presence/absence of elevated depression symptoms

although more anxious participants appeared to have a lower mortality rate after the eighth year.

Table 1 shows the Cox regression models for mortality using (a) only depression symptoms, (b) adjusting for age and gender and (c) adding the effect of physical health and adjusting for the effect of depression on physical health. Table 2 shows parameters for the same models using anxiety symptoms. The coefficients in the tables are hazard ratios for the effects of depression/anxiety, age and gender on mortality and standardized path coefficients for the effects of physical health on mortality and depression/anxiety on physical health. The univariate hazard ratio (HR) for depression on mortality was 1.09 ($p < .001$), suggesting mortality risk increased by 9% for each depression

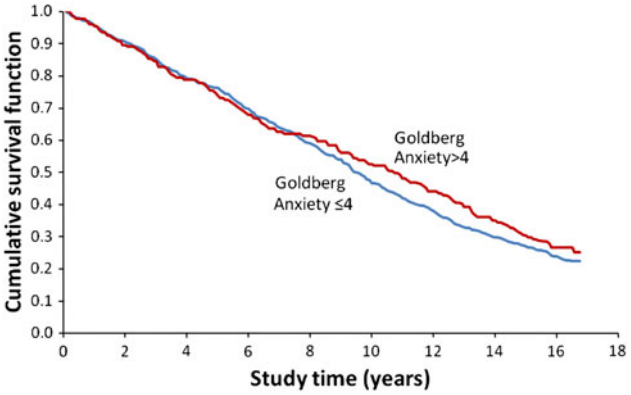

Fig. 3 Kaplan–Meier curve of mortality over 17 years based on presence/absence of elevated anxiety symptoms

symptom. This changed little after adjusting for age and gender (HR = 1.10, $p < .001$). However, after adjusting for age, gender, the physical health measures and the relationship between depression and physical health, the HR was 1.03 ($p = .18$). To examine whether the depression–mortality relationship provided a significant contribution to the adjusted model, the likelihood functions for models (iii) and (iv) were compared (see Fig. 1). The difference in −2 log likelihood, which is distributed as χ^2 (1), was 1.18 ($p = .28$), suggesting that the direct path from depression to mortality could be omitted from the model.

Anxiety symptoms had a univariate HR for mortality of 1.004 ($p = 0.82$) and 1.03 ($p = .08$) after adjusting for age and gender (Table 2). After adjusting for age, gender and physical health status, the HR was 0.99 ($p = .49$). The difference in −2 log likelihood between models (iii) and (iv) was 0.24 ($p = .62$), suggesting that the direct path from anxiety to mortality did not contribute significantly to the model. In both the depression and anxiety models, older age and male gender were, predictably, significantly associated with higher rates of death. Weaker grip strength, increased physical disability and history of heart attack or hypertension were also associated with increased mortality. Depression and anxiety were both associated with weaker grip strength and increased physical disability, however, only anxiety was associated with an increased likelihood of reporting a history of heart attack or hypertension.

Discussion

In this cohort of community-dwelling elderly participants, the relationship between more depression symptoms and greater mortality was accounted for by physical health status. Structural models demonstrated a strong association between depression symptoms and poorer physical health. These findings provide further evidence that the observed univariate relationship between depression and mortality may be due to the strong associations of physical health with both depression and mortality. There was no relationship between anxiety symptoms and mortality, a protective effect of anxiety on mortality was found after controlling for physical health. The present study tested the proposed mechanism that the association between depression and mortality was mediated by physical health. There was strong evidence for a relationship between depression and physical health, supporting the hypothesis that the depression–mortality relationship is a result of physical health. This finding may be reflective of the physiological effects of depression, specifically, immunological and cardiac processes which are strongly associated with mortality risk [7, 8]. While there is a strong association between depression and morbidity, there appears to be no direct link between depression and mortality.

The results for depression are somewhat inconsistent with previous research. However, reviews of the depression

Table 1 Cox proportional hazards regression models predicting time to death over 17 years of follow-up using depression symptoms

	Model (i) Univariate hazard ratio (95% CI)	Model (ii) +Age and gender	Model (iii) +Health status
Goldberg depression score	1.09 (1.04, 1.13)***	1.10 (1.05, 1.14)***	1.03 (0.99, 1.08)
Age		1.10 (1.08, 1.12)***	1.08 (1.06, 1.09)***
Male gender		1.71 (1.46, 2.00)***	2.69 (2.07, 3.51)***
Grip strength			0.97 (0.96, 0.99)***
Physical disability (ADL)			1.11 (1.07, 1.15)***
Heart attack history			1.40 (1.16, 1.70)***
Hypertension history			1.28 (1.09, 1.50)**
Depression → grip strength[a]			−1.19 (−1.50, −0.88)***
Depression → ADL[a]			0.40 (0.31, 0.49)***
Depression → heart attack[a]			0.03 (−0.06, 0.11)
Depression → hypertension[a]			0.06 (−0.01, 0.13)

* $p < .05$; ** $p < .01$; *** $p < .001$

[a] Path coefficients presented instead of hazard ratios

Table 2 Cox proportional hazards regression models predicting time to death over 17 years of follow-up using anxiety symptoms

	Model (i) Univariate hazard ratio (95% CI)	Model (ii) +Age and gender	Model (iii) +Health status
Goldberg anxiety score	1.00 (0.97, 1.04)	1.03 (1.00, 1.07)	0.99 (0.95, 1.02)
Age		1.10 (1.08, 1.12)***	1.07 (1.05, 1.09)***
Gender		1.65 (1.41, 1.93)***	0.37 (0.29, 0.48)**
Grip strength			0.97 (0.96, 0.98)***
Physical disability (ADL)			1.12 (1.08, 1.16)***
Heart attack history			1.42 (1.17, 1.72)***
Hypertension history			1.29 (1.10, 1.51)**
Anxiety → grip strength[a]			−0.88 (−1.15, −0.61)***
Anxiety → ADL[a]			0.22 (0.15, 0.29)***
Anxiety → heart attack[a]			0.09 (0.02, 0.16)*
Anxiety → hypertension[a]			0.09 (0.03, 0.15)**

* $p < .05$; ** $p < .01$; *** $p < .001$

[a] Path coefficients presented instead of hazard ratios

research have noted that many of the studies examined insufficiently controlled for physical health [4, 6], with control variables often limited to binary measures of disease presence. Despite this methodological inadequacy, only 62% of the combined articles reviewed by Wulsin et al. [6] and Schulz et al. [5] reported positive findings, suggesting that the relationship may only be observed in specific populations, particularly clinical populations. Other differences from previous studies may also contribute to the divergence in findings. The majority of reviewed studies have examined depression or anxiety as a binary diagnostic measure. The continuous measures used in the present study allowed for the continuum of symptomatology, rather than examining the upper tail of the distribution. The reviews also included studies of clinical and medical cohorts and studies primarily consisted of middle-aged and early-old aged cohorts. The present study used a community sample that was comparatively older. It is possible that using a more highly symptomatic clinical population may result in different relationships and that the impact of depressive illness on mortality may occur earlier in the lifespan. Furthermore, as Wulsin et al. [6] reported, the relationship between depression and mortality becomes weaker over extended follow-up periods. The 17-year follow-up of the present study is longer than that of any of the reviewed community-based studies of elderly cohorts [4–6].

There are limitations to this study that should be noted. The depression and anxiety measures involved a symptom count rather than a diagnostic instrument. As previously observed, there are advantages to using a measure that assesses a range of severities, including non-clinical states. However, this conceptualization of depression or anxiety may not always be in accordance with diagnosis based on DSM or ICD criteria. Symptom scales do not reveal the prevalence in the sample of chronic disorders (e.g., dysthymia), acute disorders (e.g., major depressive episode) or subclinical states. The administration of a more comprehensive clinical measure that could reliably assess mood and anxiety disorders was not feasible in this large epidemiological study. Secondly, depression tends to be an episodic illness, whereas the depression measure captured only those individuals who experienced symptoms in the 4 weeks prior to the baseline survey. Examining lifetime history of depressive episodes may result in a different outcome. Thirdly, while the model provided a formal test of mediation, it was not possible to fully account for temporal effects using the present dataset. Specifically, the onset of depression may have preceded physical health problems in some cases. Nevertheless, the strong attenuation of the direct effect of depression on mortality is a clear evidence of confounding by physical health status and indicates possible mediation of the effect. Finally, the analyses did not account for other measures related to mortality, including cognitive performance, education, socioeconomic status, subjective health, health behaviors, additional physical diseases and additional markers of physical health, including objective markers for cancer and other diseases. Measures that are closely related to depression, such as subjective health ratings, were omitted to ensure that the attenuation of the effect was not entirely due to multicollinearity. However, the small number of health indices used in the Cox regression model fully accounted for the direct effect of depression, despite no direct adjustment for the presence of cancer, respiratory disease or many other diseases. Further adjustments were consequently deemed unnecessary. While mediation of the depression–mortality effect is primarily through physical health, indirect mediation through health behaviors such as inactivity, sleep problems or substance use [5] and the direct effect of suicide were not tested.

Future research should aim to clarify how the type of sample and methods of measurement affect relationships

between mental health and mortality. In addition, a range of specificities in the association between depression and mortality should be examined. In particular, younger cohorts may exhibit stronger relationships between depression and mortality than older cohorts, there may be decay of the relationship over long follow-up periods and the presence of certain depressive symptoms may be more strongly predictive of death than others. Regardless of the nature of the relationship, future studies must be rigorous in accounting for the confounding effects of physical health. While the present study found no evidence of a relationship between anxiety and mortality, there is a possibility for future research to investigate whether specific types of anxiety disorders have differential impacts on physical health and mortality. Given the attenuation to non-significance of the relationship between depression and mortality after adequately controlling for physical health in the present study, a degree of uncertainty may be placed upon studies that report a strong relationship between depression and mortality without adequately controlling for physical health.

Acknowledgments The Canberra Longitudinal Study was supported by NHMRC Unit Grants 973301 and 933301 and NHMRC Program Grant 179805. HC is supported by NHMRC Senior Principal Research Fellowship 525411. The authors thank Scott Hofer for commenting on a draft of the manuscript.

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