

American Journal of Epidemiology: Original Contribution

**Cognitive Function in Middle- and Older-age in Relation to Cause-Specific Mortality:
Follow-up of Participants in the English Longitudinal Study of Ageing**

Short title: Cognitive function in older adults and mortality

G. David Batty, DSc^{1,2,3}
Reader in Epidemiology

Ian J Deary, PhD²
Professor of Differential Psychology

Paola Zaninotto, PhD¹
Lecturer in Statistics

¹Department of Epidemiology and Public Health, University College, London, UK

²Centre for Cognitive Ageing & Cognitive Epidemiology, Department of Psychology, University of Edinburgh, UK

³Alzheimer Scotland Dementia Research Centre, University of Edinburgh, UK

Correspondence to: Dr. David Batty, Department of Epidemiology and Public Health, University College, 1-19 Torrington Place, London, UK. E: david.batty@ucl.ac.uk. T: 00 44 20 3108 3149

Word count: 3366 (excluding a 195 word abstract)

Acknowledgements: The English Longitudinal Study of Ageing was developed by a team of researchers based at University College London, the Institute for Fiscal Studies, and the National Centre for Social Research. Funding is provided by the National Institute on Aging (2RO1AG7644–01A1, 2RO1AG017644) and a consortium of UK government departments. GDB and IJD are members of the Alzheimer Scotland Dementia Research Centre funded by Alzheimer Scotland, and of the University of Edinburgh Centre for Cognitive Ageing and Cognitive Epidemiology, part of the cross council Lifelong Health and Wellbeing Initiative. Funding for the latter is provided by the Biotechnology and Biological Sciences Research Council, Engineering and Physical Sciences Research Council, Economic and Social Research Council, and United Kingdom Medical Research Council. The authors have no involvements that might raise the question of bias in the work reported or in the conclusions, implications, or opinions stated.

Abstract

We examined the little-tested associations between general cognitive function in mid- to older-age and later risk of the chronic diseases. In the English Longitudinal Study of Ageing (2002-12), 11,391 study members, aged 50 to 100 years at study induction, were administered a battery of cognitive tests and provided a range of collateral data. In an analytical sample of 9,204 people (4982 women), a mean duration of follow-up of 9.0 years gave rise to 1,488 deaths. Using a summation of four cognition tests representing three acknowledged key domains of cognitive functioning (memory, executive function, processing speed), cognition was inversely associated with mortality rates ascribed to cancer (hazard ratios; 95% confidence interval per one standard deviation lower general cognitive function score: 1.21; 1.10, 1.33), cardiovascular disease (1.71; 1.55, 1.89), 'other' causes (2.07; 1.79, 2.40), and respiratory illness (2.48; 2.12, 2.90). Controlling for a range of covariates which included health behaviours and socioeconomic status, and left-censoring to explore reverse causality, had very little impact on the strength of these relationships. These findings indicate that cognitive test scores can provide relatively simple indicators of mortality risk for an array of chronic diseases and these associations are independent of other commonly-assessed risk factors.

Key words: ageing, cancer, cardiovascular disease, cognitive function, mortality, respiratory illness

Abbreviations: ELSA, English Longitudinal Study of Ageing

Introduction

Since the first-reported examination of a link between cognition and mortality risk over five decades ago,¹ investigators using a series of cohort studies have shown that lower cognitive function measured in middle- and older-aged populations is associated with elevated rates of total mortality.²⁻⁸ These relationships do not appear to be ascribed to confounding by co-morbidity, socioeconomic status, or health behaviours, and are apparent not only in convenience samples but also general population-based groups.

Aside from the occurrence of cardiovascular disease which has also been shown to be related to lower cognition,⁹⁻¹² less well understood is the predictive value, if any, of cognitive function for other chronic diseases that comprise total mortality, including cancer and respiratory illness. Those studies that have been conducted not only reveal discordant findings – for the two studies with all cancers as an outcome, for example, inverse¹³ and null³ associations with cognition are apparent – but methodological shortcomings also frequently hamper data interpretation. These include the modest size of many studies which lead to endpoint rarity and the inability to explore gender-specific effects and dose-response relationships.¹³ There is also a common focus on patient populations (e.g., people with diabetes¹⁴), so potentially restricting insights into the generalizability of findings. It is also the case that the utilisation of crude clinical assessments which capture cognitive impairment (e.g., the Mini-Mental State Examination^{3;6}) rather than the broader normal range of functioning, results in ‘ceiling effects’ (the majority of subjects score highly on a test so reducing discrimination), and offer no information about different intellectual domains.

The English Longitudinal Study of Ageing (ELSA) is a large-scale prospective cohort study of the general population whose more than 11,000 members were administered a battery of cognitive tests at baseline and have provided a range of collateral data.¹⁵ Now in its 10th year of mortality surveillance, the study population has matured to the point where a high number of deaths have

accumulated to facilitate analyses of the little-tested relation of cognitive function with causes of death other than cardiovascular disease.

Methods

Data were taken from ELSA, an on-going, representative, prospective cohort study of older, non-institutionalised men and women in England.¹⁵ The cohort is based on individuals of 50 years of age or older who took part in one of three cross-sectional studies that comprise the Health Surveys for England (1998, 1999, and 2001).¹⁶ The first active phase of data collection in ELSA took place in 2002-03 when 11,391 men and women participated.¹⁵ Comparisons of the socio-demographic characteristics of participants against results from the national census indicate that the sample was broadly representative of the English population.¹⁵ Over the last decade years there have been six biennial face-to-face examinations of study members. For the purposes of the present analyses, our ‘baseline’ is the first wave of data collection in ELSA in 2002-03. Participants gave their informed consent to take part in the study, and ethical approval was granted by the London multicentre research ethics committee.

Measurement of cognitive function

Cognitive function was assessed using a battery of tests.¹⁵ For the purposes of the present analyses, we selected four measures comprising three acknowledged key domains of cognitive functioning: memory, processing speed, and executive function. *Memory* was measured using the word-list learning test in which ten words were presented orally to study participants who were then asked to recall as many as possible immediately after the reading, and then again after an approximately five minute delay during which they completed other survey questions. We computed an overall memory score (range: 0 to 20) using both the immediate and delayed recall (between-test correlation coefficient: 0.70). *Executive function* was ascertained using a word finding task (semantic verbal fluency), a test of how quickly participants can name as many different animals as

possible in one minute (score range: 0 to 60). *Processing speed* was measured using a letter cancellation test. The participant was handed a page of randomly generated letters of the alphabet set out in rows and columns with the request that they cross out as many of the target letters ('P' and 'W') as possible within one minute. The total number of letters searched provides a measure of speed of processing (range: 0 to 64). All scores are normally distributed with no evidence of floor and ceiling effect. The cognitive function module in ELSA also included the following four tests: self-rated memory, orientation in time (day, month and year), prospective memory (remembering to carry out some actions during the clinical examination), and numerical ability (three simple problems requiring numerical calculations). *A priori*, we elected not to use these tests for the following reasons. Two tests were not capable of discriminating across the cognitive function range (ceiling effects were apparent) owing to overly simple questions with few response options (orientation in time test) or, indeed, having only two response options (prospective memory test). One additional test captured educational performance rather than cognitive function (numerical ability test). The final 'test' was not actually a cognitive test and, lacking a correlation with the validated cognitive tests, showed poor concurrent validity (self-rated memory test). It is also the case that these omitted tests do not represent new cognitive domains relative to those already featured in our analyses.

Covariate data

Self-reported health behaviours included smoking status (current, ex-smokers, and never), frequency of alcohol consumption in the past year (daily/almost daily, 1–2 times/week, 1–2 times/month, never/almost never), and physical activity (medium and high physical activity were denoted by vigorous or moderate intensity exertion at least once per week; all other activity was recorded as low). Major illness at wave 1 was denoted by a self-report of physician diagnosis of diabetes, cancer, or coronary heart disease. Enquiries were also made concerning any difficulties study members may have experienced in carrying out six activities of daily living (e.g., dressing,

bathing, using the toilet) and seven instrumental activities of daily living (e.g. taking medications, preparing a hot meal). Participants reporting one or more difficulty for at least three months in each domain were classified as having an impairment.

We measured depressive symptoms using the eight-item Center for Epidemiological Studies-Depression scale, a widely used self-report device to identify people at risk of depression in population studies. Finally, body mass index (kg/m^2) was computed from height and weight data collected during a home visit as part of the Health Survey for England (1998-2001). We used three indicators of socioeconomic status, selected to capture the life course of study members. Paternal occupational social class was used as an indicator of social status and divided into three levels (high [e.g., managerial], intermediate [e.g., trade- and services-related job], and low [e.g., manual/casual job; unemployed]). Subject's own educational attainment was used as a marker of interim social position and, again, categorised into three groups (high [e.g., university degree or higher], intermediate [e.g., ordinary or advanced level secondary school examinations, or equivalent], and low [compulsory school leaving]). Wealth, which was based on age-adjusted quintiles for the purposes of analysis, was measured according to total household wealth, including financial wealth (savings and investments), the value of any home and other property (less mortgage), the value of any business assets, and physical wealth such as artwork and jewelry, net of debt.

Mortality ascertainment

Study members were linked to the National Health Service's Central Registry at Southport UK, the procedures of which provide vital status data. Owing to reasons of anonymity, cause of death data are provided for broad classifications of disease according to International Classification of Disease chapters (version 10):¹⁷ cardiovascular disease (I00-I99), cancer (C00-C97), respiratory disease (J00-J99), and 'other [remaining] causes'. Follow-up began on the date of study induction

(2002/3) with study members censored at date of death, or end of follow-up (March 2012) – whichever came first.

Statistical Analyses

From a starting sample of 11,391 individuals at study induction (figure 1), exclusions owing to a failure to consent to linkage to death data, and missing data on cognitive function, covariates or cause of death, resulted in an analytical sample of 9,204 people (4,982 women). In this group the magnitude of the correlation between each of the three domains of cognitive function were moderate (spearman correlation coefficient range: 0.33 to 0.46). Cognitive function in each domain also revealed a similar pattern of association with the five mortality outcomes (web tables 1-3).

This observation supports others in the field of cognitive epidemiology where, in general, individual cognitive domains are not found to be better predictors of disease outcomes than a more general cognitive score. On this basis, and in the interests of brevity of presentation, we utilized total cognitive function as our main exposure (hereafter referred to as *general cognitive function*) by summing results from the three intellectual domains (range: 0 to 144).

---insert figure 1---

Having ascertained that the proportional hazards assumption had not been violated, to summarise the relationship between cognitive function and mortality rates we used the Cox model¹⁸ to compute hazard ratios with accompanying 95% confidence intervals. With both cognition and mortality rates being strongly patterned by age, we explored the impact on our results of using two different time scales: calendar time (with adjustment for age) and age itself. With both approaches producing near-identical results, our Cox model was set with calendar time as the time scale. As there was no evidence of differential cognition–mortality relationship in men and women, data were pooled and gender-adjusted. We used a series of multivariable models that were designed to assess the impact,

if any, of controlling for a range of covariates organised by theme (e.g., health behaviours [physical activity, smoking, alcohol intake], socioeconomic status [parental social class, educational attainment, wealth], and so on).

Results

In table 1 we show study member baseline characteristics according to quintiles of general cognition function. As anticipated, lower cognitive function was apparent in study members who were older, had more physical and psychological co-morbidities (diabetes, cancer, heart disease, depression), and, to a moderate extent, those who smoked. An impairment in carrying out activities of daily living, including those instrumental to self-care, were around three times more common in the lower cognition group relative to the highest performers. Similarly strongly related to cognition were the markers of social circumstances, such that lower social class of origin, a more basic education, and reduced wealth index were all strongly patterned by general cognitive function.

---insert table 1---

In an analytical sample of 9,204 people (4982 women), a mean duration of follow-up of 9.0 years (standard deviation 2.3) gave rise to 1,476 deaths, comprising 517 from cardiovascular disease, 509 from cancer, 210 from respiratory causes, and 240 from other causes (largely made up of external causes of death). In table 2 we depict the relation of a standard deviation lower cognitive function score with the five mortality endpoints. When the rate of total mortality was the outcome of interest, in age- and sex-adjusted analyses, a one standard deviation lower score on general cognitive function was associated with 64% elevated risk of death. Adding groups of covariates by theme separately to the model resulted in only modest attenuation with no particular set having a greater impact than another.

---insert table 2---

In analyses featuring specific classifications of cause death, there was again evidence of an inverse association with general cognition such that a higher mortality risk was seen across all outcomes in people who had lower cognition scores. There was, however, evidence of heterogeneity whereby the weakest association was seen for deaths from cancer of all sites combined (age- and sex-adjusted hazard ratio; 95% confidence interval: 1.21; 1.10, 1.33) and the strongest for respiratory disease (2.48; 2.12, 2.90); relationships of intermediate magnitude were apparent for cardiovascular disease (1.71; 1.55; 1.89) and ‘other’ causes (2.07; 1.79; 2.40). As per the analyses of total mortality, hazard ratios for cognitive function and these disease categories were largely robust to the adjustment of an array of potential covariates.

We conducted a series of planned sub-group analyses to scrutinise these general cognition–death relationships further. Given its correlation with cognitive function ($r=0.3$, $p\text{-value}<0.001$), having education in a multivariable model raises concerns regarding co-linearity. Therefore, we computed hazard ratio in a multiply-adjusted model with *and* without the presence of education and there was essentially no difference (results available upon request). Also, undetected physical co-morbidity, particularly in an elderly population, is likely to be commonplace, raising short-term mortality risk and possibly lowering cognitive function and so potentially generating a spurious cognition–death relationship. To explore this potential for reverse causality, we excluded from our analyses deaths occurring in the first year of follow-up (‘left-censoring’), reasoning that these might be apportioned to such hidden co-morbidity. Taking this approach did not produce any discernible impact on the magnitude of our hazard ratios (results available upon request).

Hitherto, we have presented the relations of cognition with mortality rates according to a one standard deviation change in the exposure. In order to provide insight into the ‘shape’ of the

association (e.g., threshold versus dose-response effects), in figure 2 we show the risk of mortality from each cause across the full range of general cognition scores (deciles of cognition in analyses of total mortality rates; quintiles for the other endpoints owing to smaller numbers). For the risk of total mortality there was a clear stepwise associations with cognition ($p[\text{trend}] = <0.001$), such that study participants in the highest decile of cognition had around one third of the risk of those in the lowest. Stronger cognition–mortality risk gradients were apparent for categories of death where people in the highest fifth of general cognition scores experienced around one fifth (cardiovascular disease [figure 3A], other [figure 3D]) or one tenth (respiratory [figure 3C]) of the risk relative to those in the lowest quintile. Although higher cognitive function was associated with a somewhat lower risk of all malignancies combined (figure 3B), no trend was seen.

---insert figures 2 and 3---

Discussion

The main finding of the present study was that, in addition to being related to elevated rates of total mortality and cardiovascular disease, lower general cognitive function assessed between the ages of 50 and 100 years was also associated with an elevated risk of death ascribed to cancer and respiratory disease. Whereas the strength of these relationships differed according to the endpoint in question, controlling for a range of covariates had modest impact, as did left-censoring in an effort to explore reverse causality owing to occult disease. These findings indicate that cognitive test scores can provide simple indicators of risk for an array of chronic diseases and these associations are independent of other commonly-assessed risk factors. With the evidence that cognitive decline in older groups may be slowed,¹⁹ our findings have potential public health significance.

Comparison with other studies of cognition and chronic disease

Our findings closely accord with those seen in other studies of cognition in middle- and older-age in relation to all-cause mortality rates²⁻⁷ and cardiovascular disease⁹⁻¹² where inverse associations are consistently reported. For cancer deaths which, as discussed, has been little related to cognition, there are very few relevant studies and what findings exist are discrepant. Thus, whereas one study found a null effect,³ an apparently protective association of higher cognition was evident in a smaller-scale investigation.¹³ Reaction time, a measure of information processing speed, has also been related to cancer risk in general population-based cohort studies with null results apparent for both all malignancies combined²⁰ and site-specific presentations.²¹ The predictive role for cognition in relation to respiratory disease is less well examined still: in the only study of a middle/older aged group of which we are aware, there was no apparent link.³

Potential mechanisms

That the cognition-death relationships reported here were not heavily confounded nor explained by reverse causality raises questions as to the potential mechanisms involved. Although it is likely that the relations of cognition with categories of death will be ascribed to specific mechanisms – a biomedical model encompassing vascular changes would seem to have little relevance for malignancy, for instance – some general explanations may be advanced. First, health literacy, which concerns the skills required to gain access to and synthesise health information is often advanced in this regard, not least because it is directly related to cognitive function.²² Similarly, people with lower cognitive function scores are also less likely to seek preventative advice when disease-free, and, when illness does occur, recognize symptoms, seek medical care, and comply with treatment.⁶ It is therefore possible that health literacy, as it often tends to be assessed, does little more by way of explanation than providing an alternative assessment of cognition, adding little to cognitive ability in accounting for disease variance.^{23;24} A second possibility is the system

integrity explanation which posits that higher cognition may be a marker for a superior body functioning body.²⁵ That is, higher cognition might be a characteristic of a “well-wired” physiology that responds more robustly to common environmental insults. However, given that the participants were already in middle-age or older at the baseline cognitive testing session, and that system integrity refers to cognitive and bodily state in youth, it is more likely that the lower cognition and poorer health could be due to some set of ageing-related common causes that affect both health and cognition.²²

Strengths and limitations

Whereas ELSA has a number of strengths over many other ageing studies – its higher resolution cognitive function measurement for a large scale investigation, the generalizability of findings from a geographically representative sample, and the large number of deaths – it has some limitations. First, in the interests on anonymity, not being provided with specific cause of death for deceased study members, including individual presentations of cardiovascular disease phenotypes (stroke, peripheral vascular disease, heart failure) cancer (breast, colorectal) is a drawback. Second, with mortality comprising both disease incidence *and* survival, a cognition–mortality relation may, in part, be due to the choice of medical treatment in study members with diagnosed illness. To the best of our knowledge, there are no studies of cognition and treatment choice. To explore this issue for major chronic diseases such as cancer and cardiovascular disease in the present study we would need to examine the association between cognition and treatment choice for the same severity of illness (e.g., cancer stage) as treatments options differ by severity. Unfortunately, we do not have these data. An alternative approach would be to use disease incidence as the outcome of interest to ascertain if the relation with cognition differs relative to the results for mortality. Again, however, we do not have these data in ELSA. In a study which examined the predictive value of a range of established risk factors for both morbidity (hospital records) and mortality ascribed to cerebrovascular disease, similar relationships were seen irrespective of how the outcome was

ascertained.²⁶ We are unaware of any such studies in which the exposure was cognition, however. Third, diet, in keeping with other behaviours, appears to be under a degree of cognitive control,^{27;28} and is itself related to some of the mortality outcomes features herein. However, we had no such detailed data on diet to allow us to explore their potential confounding or mediating effects. Fourth, having cognition scores from an older-aged group means that the inverse associations with mortality rates could be at least partly generated by undetected disease at study induction, resulting in both lower cognitive function^{29;30} and elevated mortality risk. While our hazard ratios did not appear to be sensitive to left-censoring – a standard procedure for exploring reverse causality – an alternative approach is to utilise scores from early in adulthood or youth where chronic disease is rare and therefore of little potential influence on cognition.³¹⁻³³ With ELSA having been initiated in middle/older-age, no such data are available. Lastly, while participants in ELSA are generally well-characterised, so allowing us to adjust our effect estimates for a range of covariates, there is inevitably a problem of residual confounding that is common to all observational studies. Thus, either some potential covariates were unmeasured at study baseline (e.g., markers of systemic inflammation) or may not have been captured fully (e.g., severity of disease).

In conclusion, in the present study, in addition to mortality from all causes and cardiovascular disease, lower cognitive function was related to the risk of cancer and respiratory illness risk. These findings indicate that cognitive test scores can provide simple indicators of mortality risk for an array of chronic diseases and this is independent of other commonly-assessed risk factors.

References

- (1) Sanderson R, Inglis J. Learning and mortality in elderly psychiatric patients. *J Gerontol* 1961; 16:375-376.
- (2) Johnson JK, Lui LY, Yaffe K. Executive function, more than global cognition, predicts functional decline and mortality in elderly women. *J Gerontol A Biol Sci Med Sci* 2007; 62(10):1134-1141.
- (3) Newman AB, Sachs MC, Arnold AM, Fried LP, Kronmal R, Cushman M et al. Total and cause-specific mortality in the cardiovascular health study. *J Gerontol A Biol Sci Med Sci* 2009; 64(12):1251-1261.
- (4) Sabia S, Gueguen A, Marmot MG, Shipley MJ, Ankri J, Singh-Manoux A. Does cognition predict mortality in midlife? Results from the Whitehall II cohort study. *Neurobiol Aging* 2010; 31(4):688-695.
- (5) Sachs GA, Carter R, Holtz LR, Smith F, Stump TE, Tu W et al. Cognitive impairment: an independent predictor of excess mortality: a cohort study. *Ann Intern Med* 2011; 155(5):300-308.
- (6) Iwasa H, Kai I, Yoshida Y, Suzuki T, Kim H, Yoshida H. Global cognition and 8-year survival among Japanese community-dwelling older adults. *Int J Geriatr Psychiatry* 2013; 28(8):841-849.
- (7) Iwasa H, Kai I, Yoshida Y, Suzuki T, Kim H, Yoshida H. Information processing speed and 8-year mortality among community-dwelling elderly Japanese. *J Epidemiol* 2014; 24(1):52-59.
- (8) Deary IJ, Der G. Reaction time explains IQ's association with death. *Psychol Sci* 2005; 16(1):64-69.
- (9) de Moraes SA, Szklo M, Tilling K, Sato R, Knopman D. Cognitive functioning as a predictor of ischemic stroke incidence. *Epidemiology* 2003; 14(6):673-679.
- (10) Elkins JS, Knopman DS, Yaffe K, Johnston SC. Cognitive function predicts first-time stroke and heart disease. *Neurology* 2005; 64(10):1750-1755.
- (11) DeFries T, Avendano M, Glymour MM. Level and change in cognitive test scores predict risk of first stroke. *J Am Geriatr Soc* 2009; 57(3):499-505.
- (12) Singh-Manoux A, Sabia S, Kivimaki M, Shipley MJ, Ferrie JE, Marmot MG. Cognition and incident coronary heart disease in late midlife: The Whitehall II study. *Intelligence* 2009; 37(6):529-534.
- (13) Katsoulis M, Kyroziis A, Trichopoulou A, Bamia C, Trichopoulos D, Lagiou P. Cognitive impairment and cancer mortality: a biological or health care explanation? *Cancer Causes Control* 2014; 25(11):1565-1570.
- (14) O'Donnell M, Teo K, Gao P, Anderson C, Sleight P, Dans A et al. Cognitive impairment and risk of cardiovascular events and mortality. *Eur Heart J* 2012; 33(14):1777-1786.
- (15) Steptoe A, Breeze E, Banks J, Nazroo J. Cohort Profile: The English Longitudinal Study of Ageing. *Int J Epidemiol* 2013; 42(6):1640-1648.
- (16) Mindell J, Biddulph JP, Hirani V, Stamatakis E, Craig R, Nunn S et al. Cohort profile: the health survey for England. *Int J Epidemiol* 2012; 41(6):1585-1593.
- (17) Anon. International Statistical Classification of Diseases and Related Health Problems (10th revision). Geneva: WHO; 1992.
- (18) Cox DR. Regression models and life-tables. *J R Stat Soc [Ser B]* 1972; 34:187-220.
- (19) Edwards JD, Wadley VG, Vance DE, Wood K, Roenker DL, Ball KK. The impact of speed of processing training on cognitive and everyday performance. *Aging Ment Health* 2005; 9(3):262-271.
- (20) Hagger-Johnson G, Deary IJ, Davies CA, Weiss A, Batty GD. Reaction time and mortality from the major causes of death: the NHANES-III study. *PLoS ONE* 2014; 9(1):e82959.

- (21) Roberts BA, Deary IJ, Dykiert D, Der G, Batty GD. Reaction time and incident cancer: 25 years of follow-up of study members in the UK Health and Lifestyle Survey. *PLoS ONE* 2014; 9(4):e95054.
- (22) McDougall GJ, Jr., Mackert M, Becker H. Memory performance, health literacy, and instrumental activities of daily living of community residing older adults. *Nurs Res* 2012; 61(1):70-75.
- (23) Mottus R, Johnson W, Murray C, Wolf MS, Starr JM, Deary IJ. Towards understanding the links between health literacy and physical health. *Health Psychol* 2014; 33(2):164-173.
- (24) Wolf MS, Curtis LM, Wilson EA, Revelle W, Waite KR, Smith SG et al. Literacy, cognitive function, and health: results of the LitCog study. *J Gen Intern Med* 2012; 27(10):1300-1307.
- (25) Deary I. Looking for 'system integrity' in cognitive epidemiology. *Gerontology* 2012; 58(6):545-553.
- (26) Hart CL, Hole DJ, Davey Smith G. Comparison of risk factors for stroke incidence and stroke mortality in 20 years of follow-up in men and women in the Renfrew/Paisley Study in Scotland. *Stroke* 2000; 31(8):1893-1896.
- (27) Batty GD, Deary IJ, Schoon I, Gale CR. Childhood mental ability in relation to food intake and physical activity in adulthood: the 1970 British Cohort Study. *Pediatrics* 2007; 119(1):e38-e45.
- (28) Gale CR, Deary IJ, Schoon I, Batty GD. IQ in childhood and vegetarianism in adulthood: 1970 British cohort study. *BMJ* 2007; 334(7587):245.
- (29) Manolio TA, Olson J, Longstreth WT. Hypertension and cognitive function: pathophysiologic effects of hypertension on the brain. *Curr Hypertens Rep* 2003; 5(3):255-261.
- (30) Awad N, Gagnon M, Messier C. The relationship between impaired glucose tolerance, type 2 diabetes, and cognitive function. *J Clin Exp Neuropsychol* 2004; 26(8):1044-1080.
- (31) Batty GD, Wennerstad KM, Smith GD, Gunnell D, Deary IJ, Tynelius P et al. IQ in early adulthood and mortality by middle age: cohort study of 1 million Swedish men. *Epidemiology* 2009; 20(1):100-109.
- (32) Batty GD, Shipley MJ, Mortensen LH, Boyle SH, Barefoot J, Gronbaek M et al. IQ in late adolescence/early adulthood, risk factors in middle age and later all-cause mortality in men: the Vietnam Experience Study. *J Epidemiol Community Health* 2008; 62(6):522-531.
- (33) Jokela M, Batty GD, Deary IJ, Gale CR, Kivimaki M. Low Childhood IQ and Early Adult Mortality: The Role of Explanatory Factors in the 1958 British Birth Cohort. *Pediatrics* 2009; 124:e380-e388.

Table 1. Baseline characteristics of study members according to general cognitive function quintile – The English Longitudinal Study of Ageing, 2002–2012 (N=9,204)

	Cognitive function quintile ^a										
	1 (n = 1,902)		2 (1,889)		3 (1,940)		4 (1,697)		5 (1,776)		
	Mean (SD)	%	Mean (SD)	%	Mean (SD)	%	Mean (SD)	%	Mean (SD)	%	
Cognition score	31.4 (5.9)		42.2 (2.0)		48.5 (1.7)		54.3 (1.7)		64.4 (6.2)		
Age	69.8 (10.5)		65.2 (9.4)		62.8 (8.8)		60.7 (7.8)		59.1 (7.5)		<0.001
Male		49.1		48.5		46.0		43.5		41.7	<0.001
Low physical activity		49.4		31.6		25.1		20.8		18.9	<0.001
Current smoker		18.6		18.3		19.0		17.0		17.6	<0.001
Alcohol intake daily/almost daily		21.8		28.7		26.4		30.9		35.1	<0.001
Body mass index (kg/m ²)	27.6 (4.4)		27.8 (4.7)		27.6 (4.5)		27.7 (4.6)		27.3 (4.6)		<0.05
Diabetes		11.3		7.5		6.6		4.8		4.1	<0.001
Cancer		7.1		7.0		5.3		6.2		5.1	<0.05
Coronary heart disease		21.0		14.1		10.7		8.5		6.3	<0.001
Depressive symptoms	2.1 (2.2)		1.6 (2.0)		1.4 (1.8)		1.2 (1.7)		1.2 (1.7)		<0.001
Impaired activities of daily living		30.1		20.6		15.0		14.7		11.0	<0.001
Impaired instrumental activities of daily living		32.0		20.4		15.8		13.6		10.6	<0.001
Lowest quintile of wealth		32.2		19.6		14.1		11.8		9.2	<0.001
Low parental social class		48.1		42.8		36.7		35.5		29.3	<0.001
Low education		70.7		62.9		53.8		44.6		31.8	<0.001

^a1 (lowest, ≤ 38); 2 (39-45); 3 (46-51); 4 (52-57); 5 (58-103).

^bP-value for trend for dichotomous and continuous measures; otherwise, p-value for heterogeneity.

SD, standard deviation

Table 2. Hazard ratios (95% CI) for the relation of a one standard deviation disadvantage (lower) in general cognitive function with total and cause-specific mortality rates – English Longitudinal Study of Ageing, 2002–2012 (N=9204)

Adjustments	All-cause (n = 1,476)		CVD (517)		Cancer (509)		Respiratory illness (210)		Other causes (240)	
	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI
Age + sex	1.64	1.54, 1.74	1.71	1.55, 1.89	1.21	1.10, 1.33	2.48	2.12, 2.90	2.07	1.79, 2.40
Age, sex + health behaviours ^a	1.53	1.44, 1.63	1.60	1.45, 1.77	1.15	1.04, 1.27	2.20	1.88, 2.58	1.94	1.67, 2.26
Age, sex + existing illness ^b	1.57	1.48, 1.67	1.64	1.48, 1.82	1.18	1.07, 1.31	2.31	1.97, 2.71	1.97	1.70, 2.29
Age, sex + physical function ^c	1.53	1.44, 1.62	1.58	1.43, 1.75	1.17	1.06, 1.29	2.24	1.91, 2.63	1.90	1.64, 2.21
Age, sex + socioeconomic status ^d	1.56	1.47, 1.66	1.62	1.46, 1.79	1.19	1.07, 1.31	2.26	1.92, 2.65	2.00	1.71, 2.33
Fully adjusted ^e	1.45	1.36, 1.54	1.49	1.35, 1.66	1.13	1.02, 1.26	1.97	1.67, 2.33	1.81	1.55, 2.12

^aHealth behaviours is denoted by: physical activity, cigarette smoking, alcohol intake, body mass index.

^bExisting illness is denoted by: self-reported physician diagnosed diabetes, cancer, and coronary heart disease, and depression score.

^cSocioeconomic status is denoted by: adult wealth and parental occupational social class.

^dPhysical function is denoted by: number of limitations with activities of daily living and instrumental activities of daily living.

^eFull adjustment is adjustment for all above covariates.

CVD, cardiovascular disease.

HR, hazard ratio

CI, confidence interval

Figure 1. Numbers of study members from induction through to analytic sample: the English Longitudinal Study of Ageing, 2002–2012

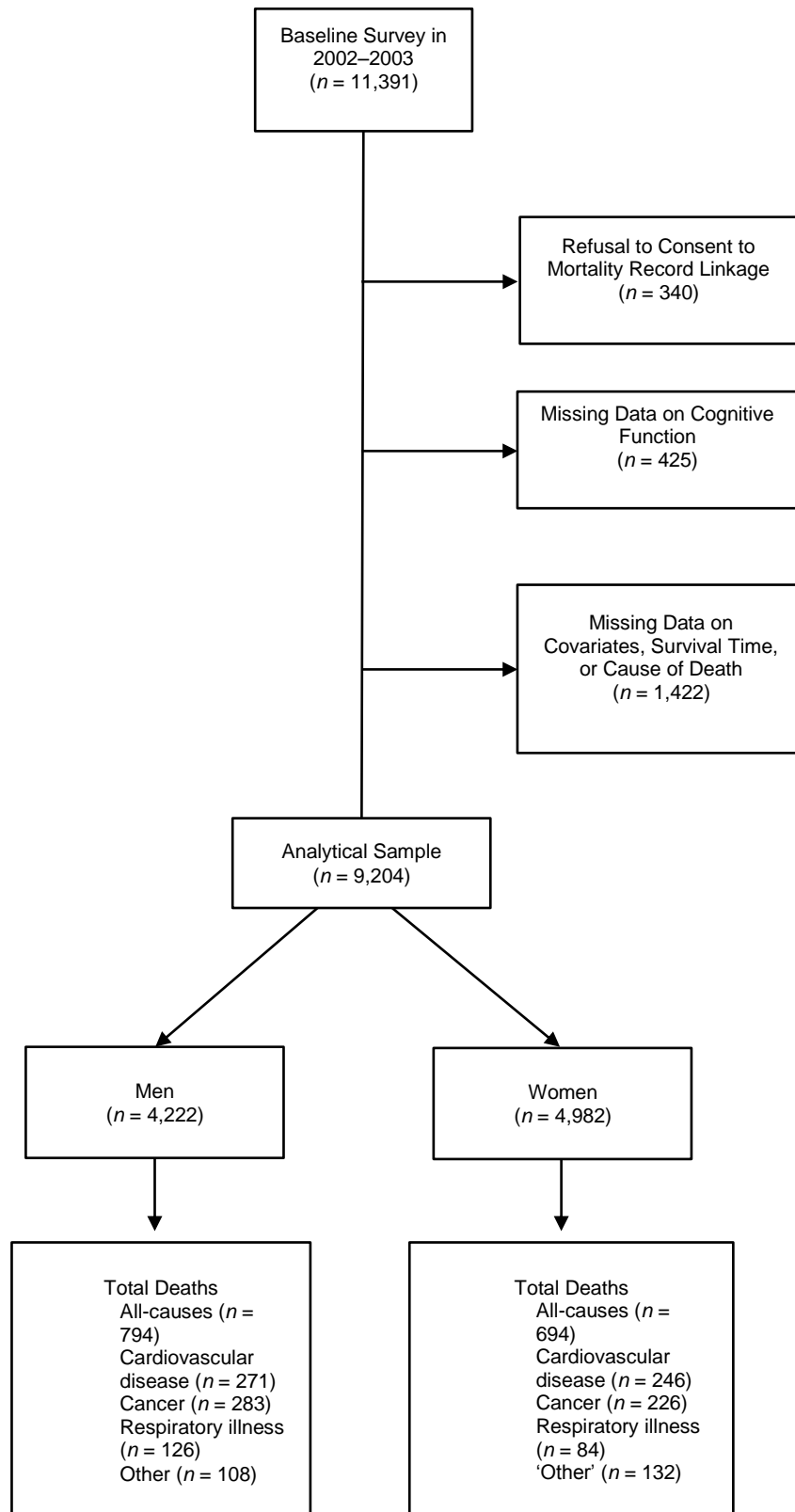
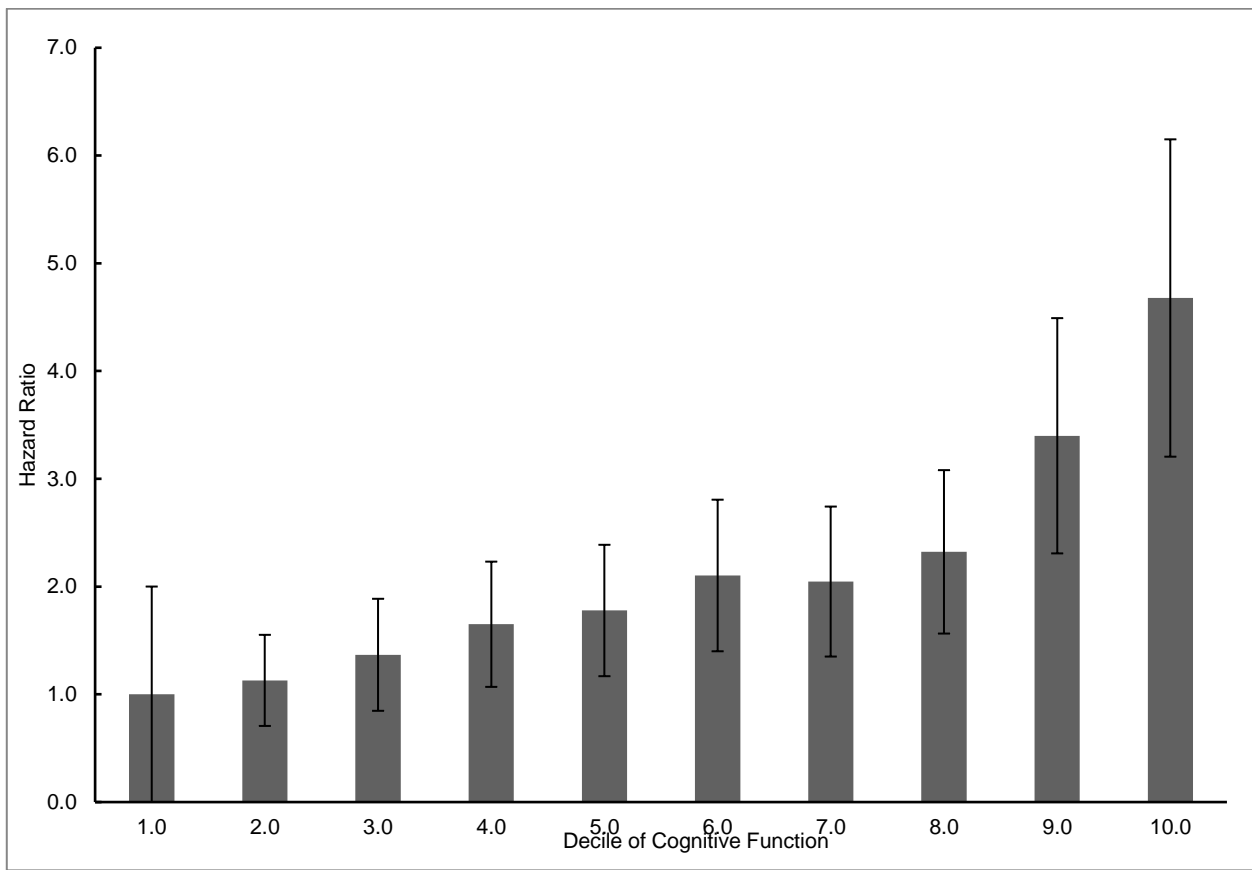


Figure 2. Hazard ratios for the association of general cognitive function scores with total mortality rates – English Longitudinal Study of Ageing (N=9,204), 2002–2012

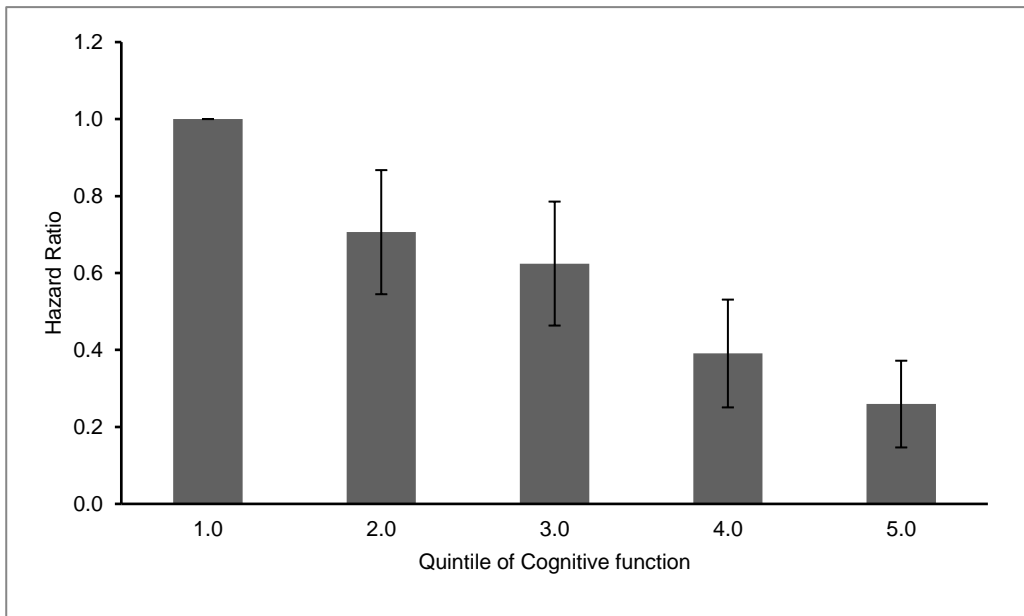


Higher deciles represent higher cognitive function scores

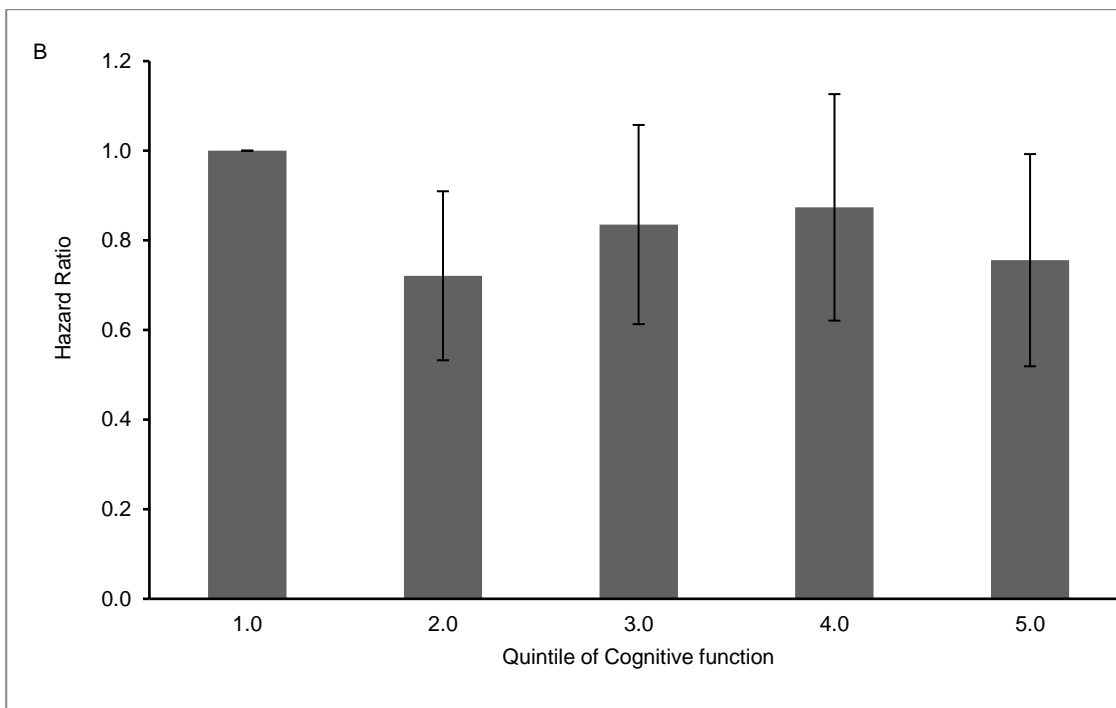
Hazard ratios are fully adjusted as per covariates in table 3. Errors bars are 95% confidence intervals.

Figure 3. Hazard ratios for the association of general cognitive function scores with category-specific mortality rates – English Longitudinal Study of Ageing (N=9,204), 2002–2012

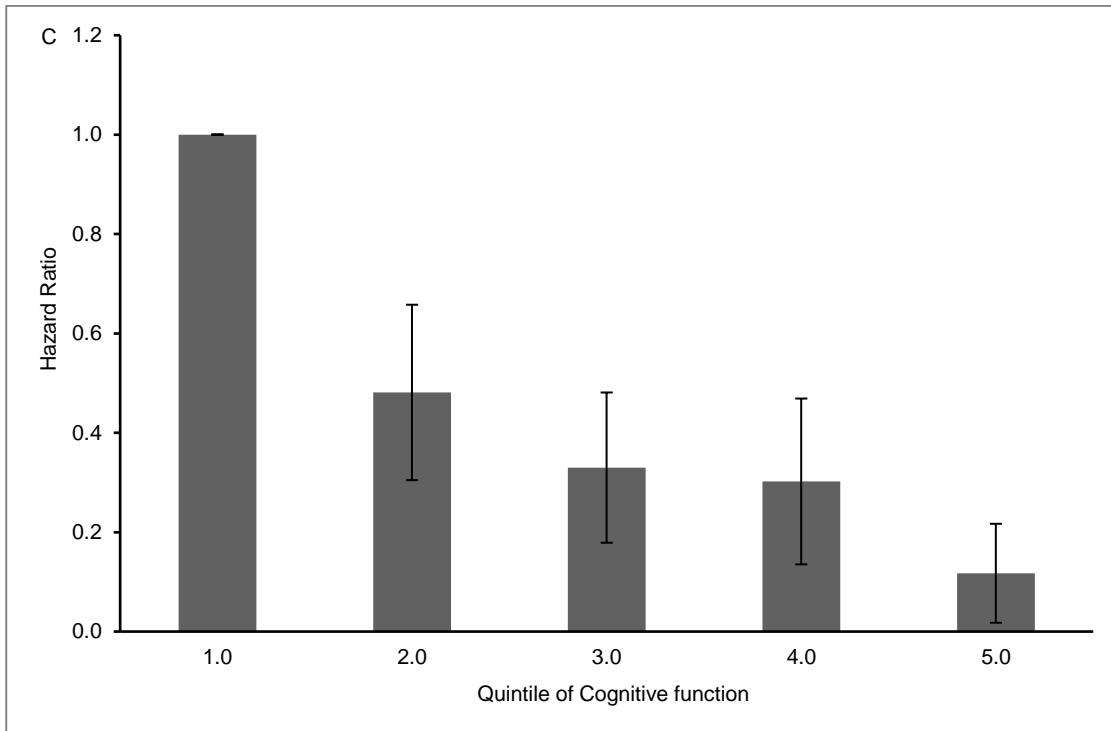
A.



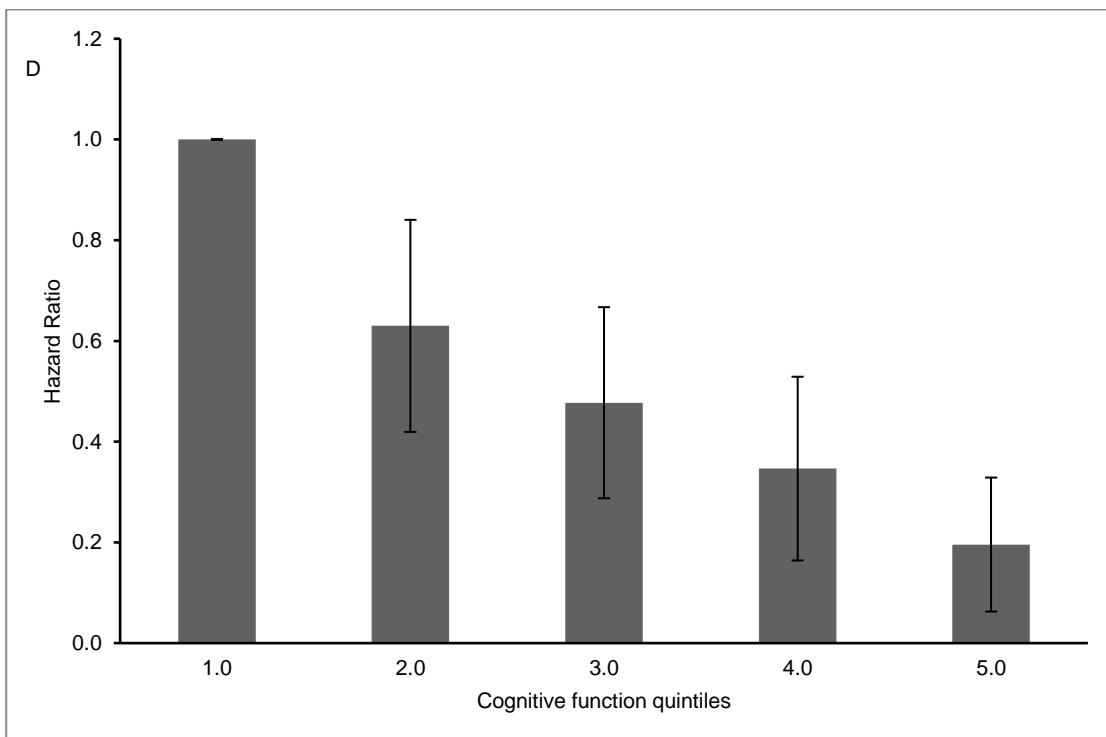
B.



C.



D.



A, Cardiovascular disease deaths (p-value for trend <0.001); B, All cancer deaths (p-value for trend 0.141); C, Respiratory deaths (p-value for trend <0.001); D, Other causes of death (p-value for trend <0.001)

Higher quartiles represent higher cognitive function scores. Hazard ratios are fully adjusted as per covariates in table 3. Errors bars are 95% confidence intervals.

Web Table 1. Hazard ratios (95% CI) for the relation of a one SD disadvantage (lower) in *memory*^f score with category-specific mortality – English Longitudinal Study of Ageing, 2002–2012 (N=9204)

Adjustments	All-cause (n = 1,476)		CVD (517)		Cancer (509)		Respiratory illness (210)		Other causes (240)	
	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI
Age + sex	1.47	1.39, 1.56	1.61	1.46, 1.77	1.08	0.98, 1.19	1.97	1.70, 2.30	1.94	1.68, 2.24
Age, sex + health behaviours ^a	1.40	1.33, 1.49	1.53	1.39, 1.69	1.04	0.95, 1.15	1.82	1.56, 2.12	1.85	1.60, 2.13
Age, sex + existing illness ^b	1.41	1.34, 1.50	1.53	1.39, 1.69	1.05	0.96, 1.16	1.86	1.59, 2.16	1.86	1.61, 2.15
Age, sex + physical function ^c	1.40	1.32, 1.48	1.51	1.37, 1.66	1.05	0.96, 1.16	1.81	1.55, 2.11	1.81	1.57, 2.10
Age, sex + socioeconomic status ^d	1.41	1.33, 1.49	1.53	1.39, 1.69	1.05	0.96, 1.16	1.83	1.56, 2.14	1.87	1.61, 2.16
Fully adjusted ^e	1.33	1.25, 1.41	1.43	1.30, 1.58	1.01	0.92, 1.12	1.67	1.42, 1.95	1.74	1.51, 2.02

^aHealth behaviours is denoted by: physical activity, cigarette smoking, alcohol intake, body mass index.

^bExisting illness is denoted by: self-reported physician diagnosed diabetes, cancer, and coronary heart disease, and depression score.

^cSocioeconomic status is denoted by: adult wealth and parental occupational social class.

^dPhysical function is denoted by: number of limitations with activities of daily living and instrumental activities of daily living.

^eFull adjustment is adjustment for all above covariates.

^fMemory was measured using a word-list learning task.

CVD, cardiovascular disease.

HR, hazard ratio

CI, confidence interval

Web Table 2. Hazard ratios (95% CI) for the relation of a one SD disadvantage (lower) in *executive function*^f score with category-specific mortality – English Longitudinal Study of Ageing, 2002–2012 (N=9204)

Adjustments	All-cause (n = 1,476)		CVD (517)		Cancer (509)		Respiratory illness (210)		Other causes (240)	
	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI
Age + sex	1.37	1.29, 1.45	1.37	1.24, 1.51	1.14	1.03, 1.25	1.82	1.55, 2.13	1.64	1.41, 1.90
Age, sex + health behaviours ^a	1.29	1.22, 1.37	1.29	1.17, 1.43	1.09	0.99, 1.21	1.64	1.40, 1.92	1.54	1.32, 1.79
Age, sex + existing illness ^b	1.32	1.25, 1.40	1.31	1.19, 1.45	1.13	1.02, 1.25	1.70	1.45, 1.99	1.56	1.34, 1.82
Age, sex + physical function ^c	1.29	1.21, 1.37	1.27	1.15, 1.41	1.11	1.01, 1.22	1.66	1.42, 1.95	1.52	1.30, 1.77
Age, sex + socioeconomic status ^d	1.30	1.22, 1.38	1.28	1.16, 1.42	1.11	1.01, 1.23	1.65	1.40, 1.94	1.56	1.34, 1.82
Fully adjusted ^e	1.23	1.15, 1.30	1.21	1.09, 1.34	1.09	0.99, 1.20	1.47	1.25, 1.73	1.44	1.23, 1.69

^aHealth behaviours is denoted by: physical activity, cigarette smoking, alcohol intake, body mass index.

^bExisting illness is denoted by: self-reported physician diagnosed diabetes, cancer, and coronary heart disease, and depression score.

^cSocioeconomic status is denoted by: adult wealth and parental occupational social class.

^dPhysical function is denoted by: number of limitations with activities of daily living and instrumental activities of daily living.

^eFull adjustment is adjustment for all above covariates.

^fExecutive function was measured using a word finding task.

CVD, cardiovascular disease.

HR, hazard ratio

CI, confidence interval

Web Table 3. Hazard ratios (95% CI) for the relation of a one SD disadvantage (lower) in *processing speed*^f score with category-specific mortality – English Longitudinal Study of Ageing, 2002–2012 (N=9204)

Adjustments	All-cause (n = 1,476)		CVD (517)		Cancer (509)		Respiratory illness (210)		Other causes (240)	
	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI
Age + sex	1.50	1.41, 1.59	1.56	1.41, 1.73	1.20	1.09, 1.32	2.18	1.85, 2.56	1.69	1.46, 1.97
Age, sex + health behaviours ^a	1.43	1.34, 1.51	1.48	1.33, 1.63	1.16	1.05, 1.28	2.01	1.70, 2.37	1.60	1.38, 1.86
Age, sex + existing illness ^b	1.45	1.37, 1.54	1.52	1.37, 1.69	1.17	1.06, 1.29	2.07	1.75, 2.45	1.63	1.40, 1.89
Age, sex + physical function ^c	1.41	1.33, 1.50	1.46	1.32, 1.62	1.17	1.06, 1.29	1.99	1.69, 2.34	1.57	1.35, 1.82
Age, sex + socioeconomic status ^d	1.44	1.36, 1.53	1.49	1.34, 1.65	1.18	1.07, 1.31	2.00	1.69, 2.36	1.61	1.39, 1.88
Fully adjusted ^e	1.35	1.27, 1.44	1.40	1.26, 1.55	1.13	1.03, 1.25	1.82	1.54, 2.16	1.49	1.28, 1.74

^aHealth behaviours is denoted by: physical activity, cigarette smoking, alcohol intake, body mass index.

^bExisting illness is denoted by: self-reported physician diagnosed diabetes, cancer, and coronary heart disease, and depression score.

^cSocioeconomic status is denoted by: adult wealth and parental occupational social class.

^dPhysical function is denoted by: number of limitations with activities of daily living and instrumental activities of daily living.

^eFull adjustment is adjustment for all above covariates.

^fExecutive function was measured using a word finding task.

CVD, cardiovascular disease.

HR, hazard ratio

CI, confidence interval

^fProcessing speed was measured using a letter cancellation test.