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Can we understand why cognitive function predicts mortality? Results from the Caerphilly Prospective Study (CaPS)

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ABSTRACT

The association between cognitive function and mortality is of increasing interest. We followed 1870 men aged 55–69 years at cognitive assessment for 16 years to establish associations with all case and cause specific mortality. Cognitive assessment included AH4, 4 choice reaction time (used as estimates of mid-life cognition) and the National Adult Reading Test (used as an estimate of early-life cognition). Causal models were tested for the effects of a) early-life cognition, b) confounding through mid-life disease, and c) the effects of sociodemographic and lifestyle factors. A fully adjusted model was also tested. Age adjusted associations with mid-life cognitive function were found with mortality from circulatory, coronary, respiratory and digestive disease but not from cancer mortality. Age adjusted associations were attenuated and in some cases nullified by further adjustment for each of early-life cognition, mid-life disease risk and sociodemographic and lifestyle factors. These associations cannot be assumed to be unbiased estimates of effect due to the complex confounding structures that exist in these data. Future studies should explore natural experiments, use different populations where the confounding structures may be different and evaluate more complex methods that may be able to deal with the inherent complexities of a life course perspective.

1. Introduction

Many studies have reported an association between cognitive performance, at different stages in the life course, and mortality(Bosworth, Schaie, & Willis, 1999; Ghisletta, McArdle, & Lindenberger, 2006; Shipley, Der, Taylor, & Deary, 2006). The two main lines of enquiry have been focussed on either characterising the trajectory of decline leading to death (Rabbitt, Lunn, & Wong, 2006; Sliwinski et al., 2006; Thorvaldsson, Hofer, & Johansson, 2006) and, to a lesser degree, identifying the potential determinants of the association (Shipley, Der, Taylor, & Deary, 2008).

There are several possible reasons for the observed consistent association (Whalley & Deary, 2001). One possible reason is that cognitive performance in mid-life is itself unrelated to mortality directly, but the association is confounded by common causes acting across the life course that determine both cognitive performance in mid-life (Ben-Shlomo & Kuh, 2002), mainly through peak cognitive attainment in early-life, and future mortality. A developmental perspective on this hypothesis would argue that genetic as well as pre and/or post natal factors determine cerebral development as well as, for example, arterial wall elasticity (Martyn & Greenwald, 1997) so that children with better development are more likely to perform at a higher cognitive level as well as less likely to develop hypertension, ischaemic heart disease and stroke (the "common cause hypothesis").

Another possibility is that risk factors for major causes of diseases e.g. inflammation, oxidative stress and disease status, including clinical or sub-clinical disease, influence

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cognitive decline (and hence performance in mid to later life) as well as other causes of death. Again the association of cognitive function with mortality is confounded, but in this case it relates to the determinants of physiologic decline rather than of cognitive growth and maintenance (the "cognitive decline hypothesis").

A third possibility is that cognitive function has an indirect effect on mortality, which is mediated through social and behavioural lifestyle differences. Hence cognition influences the likelihood of initiating or stopping smoking, for example, which in turn affects risk of mortality (the "behavioural hypothesis").

Obviously, the picture may be more complex as one or all of the above may operate and early and/or mid-life cognition may influence factors such as mid-life disease risk which in turn influence later cognition. Such a model is extremely difficult to analyse and the conventional approach of adjusting for all available covariates may not be the most informative strategy.

The Caerphilly Prospective study (CaPS) provides an opportunity to test the above hypotheses. It is a well characterised cohort with detailed measures of cognitive function as well as sociodemographic, lifestyle and measures of morbidity at the time of assessment. Aspects of cognition assessed include crystallised intelligence, fluid intelligence and reaction time. Crystallised intelligence is considered to be comparatively constant until old age (Salthouse, 1991) and may be used as a proxy for peak level attainment i.e. cognitive function in early-life (Crawford, Deary, Starr, & Whalley, 2001; Starr & Lonie, 2008; Richards, Shipley, Fuhrer, & Wadsworth, 2004), whilst fluid intelligence and reaction time peak in early adulthood and slowly decline (Salthouse, 1991) and, in this cohort, are indicators of mid-life cognitive function. These hypotheses were explicated using directed acyclic diagrams (DAGs) where the proposed direction of causality between covariates and the impact of adjustment is made visually explicit.

2. Methods

2.1. Study population and survey methods

The Caerphilly Prospective Study (CaPS) is a population based male cohort, in South Wales, UK, which has been described elsewhere (The Caerphilly and Speedwel Collaborative Group, 1984). The population for recruitment was all men who reside in Caerphilly aged 45–59 years. Cognitive assessment was introduced to the CaPS at the third examination. The men who are the subject of this report are those seen at the third examination between 1989 and 1993 when the men were aged 55–69 years ($n = 1870$). Ethics committee approval was obtained at each phase and at recruitment participants gave consent for their past and future medical records to be consulted for purposes of study follow-up.

2.2. Baseline measures

Baseline measures included a detailed medical examination and lifestyle history. Measurements included blood pressure, cholesterol, smoking habit and alcohol consumption (ml/week), social class, marital status, employment status, and the London School of Hygiene and Tropical Medicine chest pain questionnaire (Yarnell et al., 2001). A full 12 lead electrocardiogram (ECG) was recorded. WHO criteria were used to identify clinically diagnosed MI and silent MI enabling rigorous identification of the presence of heart disease at the time of cognitive measurement. Lung function was assessed by spirometry.

2.3. Cognitive tests

CaPS cognitive testing has been described elsewhere (Gallacher et al., 1999). For this analysis the tests were selected to represent a range of susceptibility to change over time. Crystallised intelligence was assessed using the National Adult Reading Test (NART) (Nelson & Willison, 1991). Fluid intelligence was assessed using the AH4 (part 1) which is a 10 minute test of numeric and verbal reasoning (Heim, 1970). Reaction time was assessed using a four choice reaction time task (CRT) (Stollery, 1996). The AH4 and CRT were computer administered.

2.4. Follow-up

All members of the cohort were flagged with the Office for National Statistics and, where appropriate, underlying cause of death was recorded using the International Statistical Classification of Diseases and Related Health Problems version 9 (ICD-9) and version 10 (ICD-10). The ICD system provides a widely used standardised classification of disease. Circulatory disease mortality was defined as ICD9 codes 390–459 and ICD10 codes I00–I99. Both versions were used as the ICD system changed during the course of follow-up. Cancer mortality was defined as ICD9: 140–239 and ICD10: C00–D48. Respiratory mortality was defined as ICD9: 460–519 and ICD10: J00–J99. Digestive disease mortality was defined as ICD9: 520–579 and ICD10: K00–K99. All other causes of mortality including musculoskeletal, metabolic, mental disorders, injuries, infections and genitourinary disease each occurred in very small numbers and were collapsed into a single category of 'other disease' mortality. Coronary heart disease mortality (a sub-set of circulatory disease mortality) was identified for further analysis and defined as ICD9: 410–414 and ICD10: I20–I25.

2.5. Causal modelling

Causal models were constructed using directed acyclic diagrams (DAGs) (Greenland, Pearl, & Robins, 1999; Glymour, Weuve, Berkman, Kawachi, & Robins, 2005).

DAGs were used as a visually explicit method of describing the causal pathways being modelled. Of particular interest in this analysis is the use of DAGs to identify appropriate adjustment for confounding. For those unfamiliar with DAGS, we have included a brief summary but recommend more detailed references (Greenland et al., 1999; Glymour et al., 2005). Fig. 1 provides an illustrative DAG. In DAG terminology, a pathway is defined as any sequence of lines linking variables (regardless of direction of arrowheads). Variables upstream of an arrowed path (direct and indirect causes) are called ancestors and variables downstream of arrowed paths (direct and indirect effects) are called descendents. In Fig. 1, a path