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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

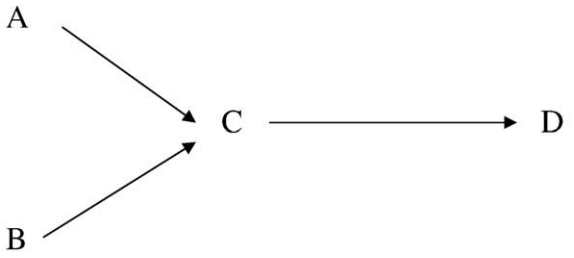

Fig. 1. Illustrative directed acyclic graph (DAG).

exists between 'A', 'C' and 'D'. 'A' is hypothesised to directly affect 'C' and to indirectly affect 'D' (via 'C'). 'A' is an ancestor to 'C' and 'D' is a descendent of 'C'. A path also exists and also between 'A', 'C' and 'B'. In this path two arrowheads point to 'C', the causes of that variable are said to collide and the variable is know as a 'collider.' A path that wholly follows the direction of causation e.g. 'A' 'C' 'D' is known as a directed path. A path also exists from 'D', through 'C' to 'B'. This is said to be a 'backdoor' path as it involves going against one or more directions of causality. Two variables in a DAG will be statistically independent conditional on a set of covariates if every path between them is 'blocked'. A path is 'blocked' by conditioning upon a proposed covariate set if a non-collider on the path is in the covariate set. For example, the path 'A' 'C' 'D' is blocked by conditioning on 'C'. A path is also 'blocked' by the presence of a collider. Under these circumstances the path will become unblocked by conditioning upon a covariate that includes the collider or any of its descendents i.e. a (spurious) statistical association between 'A' and 'B' will be induced by adjusting for 'C' or 'D'.

On the basis of the above, DAGs were constructed to test the common cause, cognitive decline and behavioural hypotheses (Fig. 2). The common cause hypothesis was modelled by adjustment for early-life cognition in order to block the backdoor path from mid-life cognition to mortality via genetic and developmental factors (Fig. 2, model a). The cognitive decline hypothesis was modelled by adjusting for mid-life disease risk in order to block the backdoor path from mid-life cognition to mortality through mid-life disease risk (Fig. 2, model b). The behavioural hypothesis was modelled by adjusting for lifestyle factors to block the path from mid-life cognition to mortality (Fig. 2, model c). For this last analysis, adjustment for socioeconomic environment was also made to block the backdoor path from mid-life cognition to mortality via early-life cognition without removing the legitimate effect of early-life cognition on mid-life cognition. It also prevents generating a spurious association being generated between mid-life cognition and socioeconomic factors. None of these models are mutually exclusive and all are overly simplistic as they assume no other pathways. For example model (b) assumes no common antecedents to mid-life disease risk which themselves predict mortality. These analyses were conducted to contrast with a standard fully adjusted model. In conventional analyses, researchers usually undertake a final "fully adjusted" model that would include all or some of the above risk factors. We believe this approach is problematic as it risks over adjustment, may induce spurious associations with unmeasured confounders and doesn't take account of time-dependent confounding (Sterne et al., 2005). This last issue is illustrated in Fig. 2, model 'd', which is a more realistic development of the behavioural hypothesis. In model 'd' mid-life cognition measured at one point in time (t_1), not only affects lifestyle factors mortality, but also affects mid-life cognition and hence lifestyle factors and mortality at a later point in time (t_2). Adjusting for lifestyle at t_1, may block the pathway from mid-life cognition to mortality at t_1, but it also blocks the indirect pathway from mid-life cognition at t_1 to mid-life cognition at t_2 that operates via lifestyle factors at t_1 thus potentially resulting in a biased estimate of the association between mid-life cognition at t_1 and mortality.

3. Statistical methods

The distribution of reaction time was positively skewed and we used a log transformation to normalise the distribution. All cognitive scores were standardised (z-scores) for multivariable analysis. Multiple linear regression was used for analyses involving cognitive performance as outcome. Cox's proportional hazard models were used for analyses involving all cause and cause specific mortality as outcome creating risk sets corresponding to age as the time axis (Kirkwood & Sterne, 2003).

Our analytical strategy was to test our various models (Fig. 2a–c). All multivariable analyses included adjustment for age as a confounder. Age was modelled as a continuous variable. We had no direct measure of developmental factors. NART score was used as a proxy for cognitive function in early-life (Crawford et al., 2001). AH4 scores and CRT scores were used as indicators of mid-life cognitive function. Sociodemographic indicators included social class, marital status, employment status and education level. Social class was considered as a three level factor (semi and unskilled, manual, and non-manual) as was education (no qualifications, non-professional qualifications, and professional qualifications). Marital status was modelled as a two level factor (married, not married). Socioeconomic factors were entered as a block. Lifestyle factors included smoking, alcohol consumption and leisure time activity. The distribution of alcohol consumption (ml/week) was highly skewed and was log transformed as ln(4 + alcohol), the addition of 4 allowing the log transformation of zero for non-drinkers; the resulting variable was modelled as a continuous variable. Smoking was modelled as a three level factor (never smoked, ex-smoker, and current smoker). Leisure activity was measured as the frequency of engaging in a range of activities and was modelled as a three level factor (low, medium and high tertiles). Lifestyle factors were entered as a block. Disease risk indicators included the main vascular risk factors (blood pressure, body mass index and total cholesterol), all of which were modelled as continuous variables, respiratory function (FEV_1/FVC ratio) and pre-existing diseases (myocardial infarction (using WHO criteria), angina, stroke, lung function and self reported diabetes). Disease risk indicators were entered as a block. We initially examined all cause mortality and then cause specific mortality. For the cognitive decline hypothesis, digestive and other causes of death were omitted as the available mid-life disease risk covariates were unlikely to confound these two outcomes.

Men who encountered difficulty with computer testing were omitted from all multivariable analyses. For most covariates men with missing data were omitted from all analyses making the change in coefficients comparable. For stroke and leisure time activity, men with missing data were considered to be a separate category within the analysis.

4. Results

Of 2205 men eligible for the third examination 1870 (85%) completed cognitive assessment and are the subject of this analysis. As of 30th April 2006, 696 (37%) men had died. Most of these were due to circulatory disease (299, 16%) and cancer (250, 13%). Other main causes were respiratory disease (73, 4%) and digestive disease (25, 1%). All other causes were considered as a single category (49, 3%). Of the 299 men who died due to circulatory disease, 212 died of coronary heart disease. The follow-up period ranged from 12.5 years to 16.4 years (median follow-up = 14.5 years). Complete data was available for 1444 men. The number of deaths available for each analysis is given in the tables.

The distributions of scores for crystallised intelligence (mean NART 23.5, SD 11.9) and fluid intelligence (mean AH4 25.0, SD 11.0) were Gaussian. Choice reaction time (CRT mean 0.90, SD 0.23) was positively skew and normalised by a log normal transformation. The Pearson correlation between NART and AH4

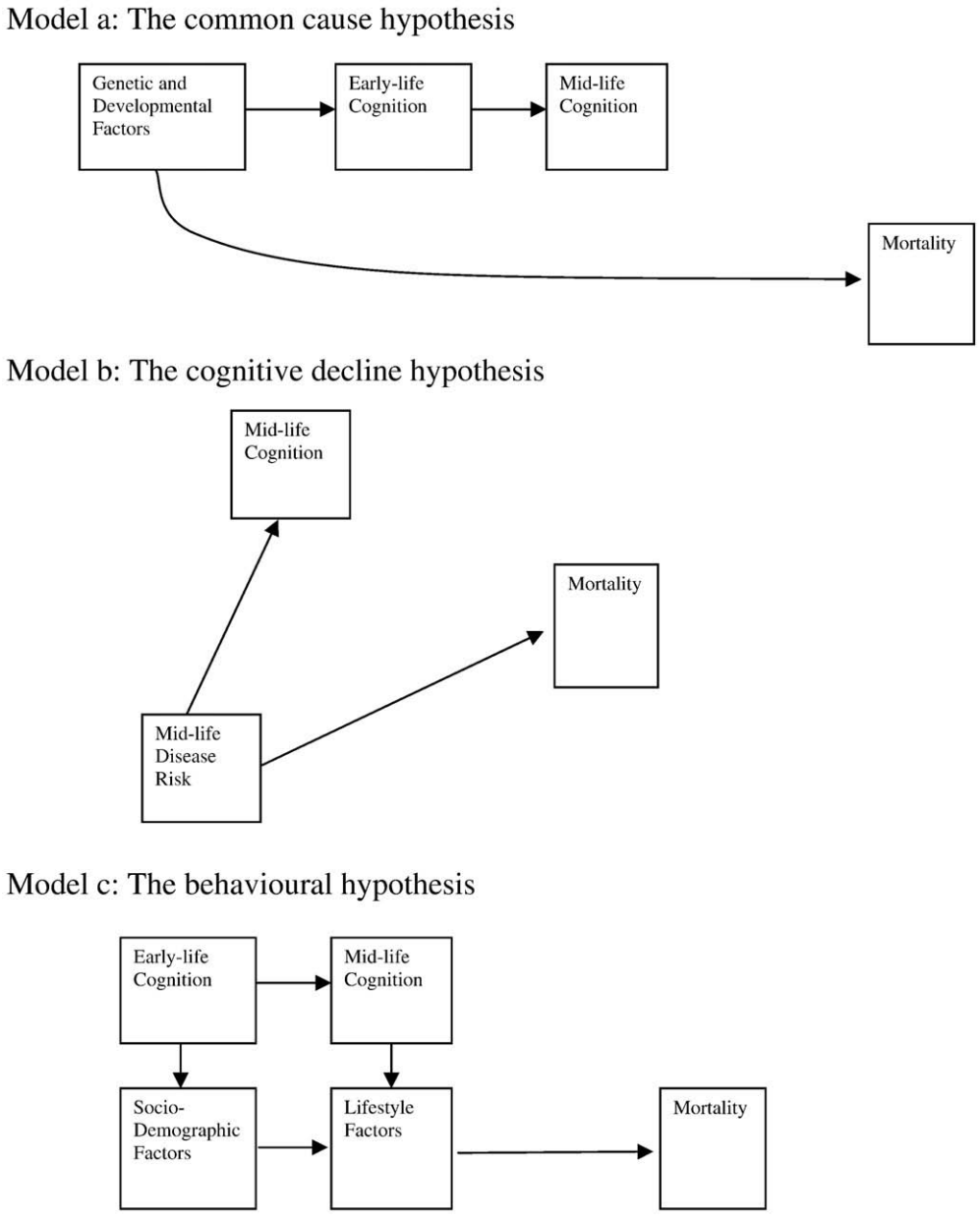

Fig. 2. Putative causal models.

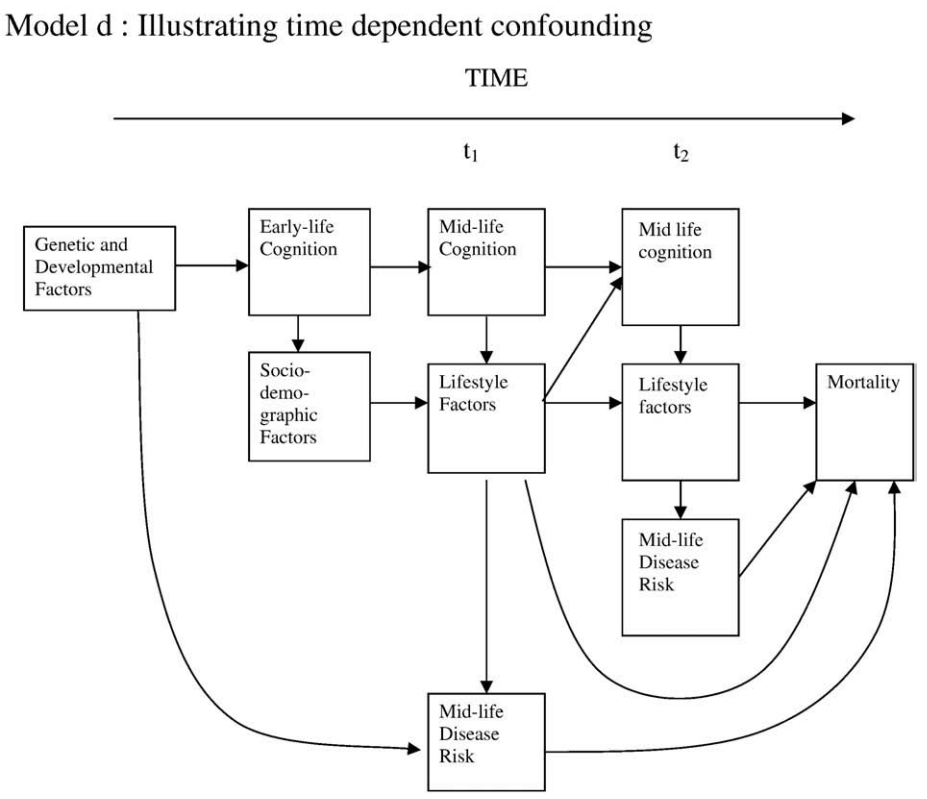

Fig. 2 (*continued*).

was 0.73, between NART and CRT was −0.27 and between AH4 and CRT was −0.44. All correlations were highly statistically significant ($p<0.001$). As anticipated, longer reaction times were associated with poorer scores on the other cognitive tests.

Preliminary analysis found strong associations of cognitive function and mortality with most of the proposed covariates (Table 1). Only for total cholesterol, alcohol consumption, BMI and Stroke was there no association with mortality.

Crude associations between cognitive scores and mortality showed crystallised intelligence (NART score) to be inversely associated with all cause mortality (HR 0.83 (95%CI 0.75, 0.90) $p=<0.001$) as was fluid intelligence (AH4 score) (HR 0.87 (95%CI 0.79, 0.95) $p=0.002$) (Table 2). Longer reaction time (CRT) was associated with greater risk of mortality (HR 1.14 (95%CI 1.05, 1.24) $p=0.001$). Similar trends were found for each specific cause of mortality. These hazard ratios refer to a change in relative hazard associated with one standard deviation change in cognitive function. No associations were found between AH4 score or CRT with cancer mortality. Associations with cancer mortality will not be considered further.

4.1. The common cause hypothesis

The common cause hypothesis (model a) was tested by adjusting for NART score, this latter used as a proxy for early-life cognition (Table 3).

4.1.1. Ah4

For all cause mortality the age adjusted association with AH4 was HR = 0.84 (95%CI = 0.76, 0.92; $p<0.001$). Further adjustment for NART attenuated this association to HR = 0.95 (95%CI = 0.83, 1.09; $p=0.46$). Similar patterns were found with mortality from circulatory disease, coronary heart disease and respiratory disease. No association was found with mortality from digestive disease. For 'other' disease further adjustment for NART increased the strength of association (HR = 0.53; 95%CI = 0.32, 0.88; $p=0.015$).

4.1.2. Crt

For choice reaction time, the age adjusted association with all cause mortality (HR = 1.19; 95%CI = 1.10, 1.29; $p<0.001$) was little affected by further adjustment for NART (HR = 1.14; 95%CI = 1.05, 1.25; $p=0.002$). A similar pattern of association was found with mortality from circulatory disease, coronary heart disease and respiratory disease. The strongest associations were found for digestive disease mortality ($HR_{age}=1.71$; 95%CI = 1.19, 2.47; $p=0.004$) and mortality from other causes ($HR_{age}=1.86$; 95%CI = 1.46, 2.38; $p<0.001$). Both associations being robust to further adjustment by NART score.

4.2. The cognitive decline hypothesis

The cognitive decline hypothesis (model b) was tested by adjusting for a range of mid-life disease risk variables (Table 3) and was not tested for mortality from digestive of other disease.

4.2.1. Ah4

For all cause mortality, further adjustment for mid-life disease risk had a slight attenuating effect on the age adjusted estimates ($HR_{age+disease}=0.89$; 95%CI = 0.81, 0.98; $p=0.018$).

Table 1
Association of covariates with cognitive function and mortality.

	Covariate		AH4 [a]	CRT [a]	NART [a]	Mortality [b]
			(coeff., 95% CI, *p*-value)	(coeff., 95% CI, *p*-value)	(coeff., 95% CI, *p*-value)	(HR, 95% CI, *p*-value)
General	Age		−0.046 (−0.056, −0.036) <0.001	0.049 (0.039, 0.059) <0.001	−0.016 (−0.027, −0.006) 0.002	0.95 (0.94, 0.97) <0.001
Lifestyle factors	Alcohol consumption		0.076 (0.026, 0.127) 0.003	−0.083 (−0.135, −0,031) 0.002	0.030 (−0.020, 0.081) 0.24	0.99 (0.91, 1.08) 0.87
	Smoking	Non-smoker	0	0	0	1
		Ex smoker	−0.139 (−0.266, −0.013) 0.031	0.003 (−0.124, 0.131) 0.96	−0.105 (−0.231, 0.020) 0.10	1.33 (1.03, 1.71) 0.03
		Current smoker	−0.373 (−0.507, −0.240) <0.001	0.154 (0.019, 0.289) 0.026	−0.367, (−0.500, −0.234) < 0.001	2.17 (1.69, 2.80) <0.001
	Leisure activity	Low	0	0	0	1
		Moderate	0.269 (0.157, 0.381) <0.001	−0.069 (−0.184, 0.047) 0.24	0.196 (0.084, 0.309) 0.001	0.64 (0.53, 0.77) <0.001
		High	0.159 (−0.048, 0.366) 0.13	−0.066 (−0.278, 0.146) 0.54	0.315 (0.108, 0.522) 0.003	0.69 (0.49, 0.99) < 0.001
Sociodemographic factors	Educational qualifications	None	0	0	0	1
		Non-professional	0.659 (0.570, 0.748) <0.001	−0.319 (−0.417, − 0.222) <0.001	0.536 (0.446, 0.626) <0.001	1.02 (0.87, 1.20) 0.78
		Professional	1.378 (1.232, 1.524) <0.001	−0.467 (−0.628, −0.306) <0.001	1.357 (1.210, 1.505) <0.001	0.62 (0.45, 0.87) 0.005
	Marital status	Not married	0	0	0	1
		Married	0.365 (231, 0.500) <0.001	0.352 (0.490, 0.214) <0.001	0.303 (0.168, 0.437) <0.001	0.76 (0.62, 0.92) 0.006
	Social class	I, I–III non-manual	0	0	0	1
		III manual	−0.893 (−0.984, −0.802) < 0.001	0.242 (0.139, 0.345) <0.001	−0.879 (−0.971, −0.787) <0.001	1.12 (0.94, 1.33) 0.21
		IV and V	−1.077 (−1.194, −0.961) < 0.001	0.561 (0.429, 0.692) <0.001	−1.025 (−1.142, −0.908) <0.001	1.29 (1.05, 1.59) 0.02
	Employment status	Not employed	0	0	0	1
		Employed	0.546 (0.450, 0.643) <0.001	0.497 (−0.597, −0.398) <0.001	0.346 (0.248, 0.445) <0.001	0.81 (0.67, 0.99) 0.04
Mid life disease risk	Lung function		1.062 (0.517, 1.608) <0.001	−1.296 (−1.845, −0.747) <0.001	0.628 (0.079, 1.178) 0.02	0.13 (0.57, 0.30) <0.001
	BMI		0.016 (−0.112, 0.143) 0.81	−0.051 (−0.181, 0.079) 0.44	−0.073 (−0.200, 0.543) 0.26	0.88 (0.71, 1.10) 0.26
	Cholesterol		−0.0002 (−0.0005, 0.0001) 0.06	0.001 (−0.001, 0.005) 0.26	−0.001 (−0.001, 0.000) 0.05	1.00 (1.00, 1.00) 0.72
	Systolic pressure		−0.002 (−0.008, 0.004) 0.53	0.001 (−0.006, 0.006) 0.99	−0.001 (−0.007, 0.004) 0.65	1.01 (1.00, 1.02) 0.005
	MI phase 2	No	0	0	0	1
		Yes	−0.128 (−0.260, 0.004) 0.06	0.129 (−0.004, 0.262) 0.06	−0.086 (−0.217, 0.046) 0.20	3.34 (2.82, 3.95) <0.001
	Angina phase 2	No	0	0	0	1
		Yes	−0.384 (−0.534, −0.233) <0.001	0.364 (0.208, 0.519) <0.001	−0.270 (−0.420, −0.119) <0.001	1.65 (1.35, 2.02) <0.001
	ECG phase 2	None	0	0	0	1
		Possible	−0.087 (−0.240, 0.066) 0.26	0.116 (−0.041, 0.272) 0.15	−0.058 (−0.211, 0.942) 0.45	1.32 (1.06, 1.65) 0.015
		Probable	0.110 (−0.142, 0.362) 0.39	−0.019 (−0.271, 0.233) 0.88	−0.009 (−0.257, 0.239) 0.94	1.49 (1.05, 2.13) 0.03
	MI phase 3	No	0	0	0	1
		Yes	−0.122 (−0.251, 0.007) 0.07	0.199 (0.678, 0.330) <0.003	−0.106 (−0.236, 0.024) 0.11	1.72 (1.43, 2.07) <0.001
	Angina phase 3	No	0	0	0	1
		Yes	−0.329 (−0.451, −0.207) <0.001	0.158 (0.321, 0.283) 0.01	−0.321 (−0.443, −0.198) <0.001	1.60 (1.35, 1.91) <0.001
	ECG phase 3	None	0	0	0	1
		Possible	−0.123 (−0.248, 0.001) 0.052	0.134 (0.008, 0.260) 0.04	−0.089 (−0.212, 0.035) 0.16	1.46 (1.22, 1.75) <0.001
		Probable	−0.144 (−0.352, 0.065) 0.18	0.076 (−0.136, 0.289) 0.48	−0.091 (−0.300, 0.119) 0.40	1.97 (1.49, 2.59) <0.001
	Stroke phase 3	No	0	0	0	1
		Yes	0.052 (−0.207, 0.310) 0.70	0.082 (−0.176, 0.340) 0.53	0.177 (−0.081, 0.434) 0.18	1.14 (0.77, 1.68) 0.52
	Diabetes phase 3	No	0	0	0	1
		Yes	−0.327 (−0.514, −0.139) 0.001	0.258 (0.060, 0.456) 0.01	−0.208 (−0.395, −0.021) 0.03	1.98 (1.55, 2.52) <0.001

[a] Linear regression coefficient.
[b] Cox's proportional hazard ratio, HR = hazard ratio.

Table 2
Crude associations (Hazard ratios) of mortality on standardised (z) scores of cognitive tests in 1444 men with complete data.

Mortality	NART	AH4	CRT
	(HR, 95% CI, *p*-value)	(HR, 95% CI, *p*-value)	(HR, 95% CI, *p*-value)
All cause (number of deaths = 495)	0.83 (0.75, 0.90) $p<0.001$	0.87 (0.79, 0.95) $p=0.002$	1.14 (1.05, 1.24) $p=0.001$
Circulatory disease (number of deaths = 210)	0.86 (0.75, 0.99) $p=0.037$	0.86 (0.75, 0.99) $p=0.040$	1.15 (1.02, 1.31) $p=0.026$
Coronary heart disease (number of deaths = 155)	0.83 (0.71, 0.98) $p=0.025$	0.83 (0.71, 0.98) $p=0.029$	1.24 (1.08, 1.43) $p=0.002$
Cancer (number of deaths = 173)	0.79 (0.68, 0.92) $p=0.002$	0.89 (0.76, 1.04) $p=0.14$	1.03 (0.88, 1.21) $p=0.67$
Respiratory disease (number of deaths = 58)	0.66 (0.51, 0.85) $p=0.002$	0.72 (0.55, 0.95) $p=0.020$	1.34 (1.06, 1.70) $p=0.015$
Digestive disease (number of deaths = 18)	0.78 (0.49, 1.24) $p=0.29$	0.81 (0.50, 1.31) $p=0.39$	1.66 (1.15, 2.39) $p=0.007$
Other (number of deaths = 36)	0.81 (0.58, 1.13) $p=0.22$	0.64 (0.45, 0.92) $p=0.015$	1.82 (1.43, 2.33) $p<0.001$

Note: coronary heart disease mortality is a sub-set of circulatory disease mortality; HR = hazard ratio.

However, the association was more fully attenuated for circulatory disease mortality ($HR_{age+disease}=0.92$; 95%CI = 0.79, 1.07; $p=0.26$), coronary heart disease mortality ($HR_{age+disease}=0.91$; 95%CI = 0.76, 1.09; $p=0.30$) and respiratory disease mortality ($HR_{age+disease}=0.88$; 95%CI = 0.66, 1.17; $p=0.39$).

4.2.2. Crt

Further adjustment for mid-life disease risk reduced slightly the strength of the association between CRT and all cause mortality ($HR_{age+disease}=1.13$; 95%CI = 1.04, 1.23; $p=0.003$). Although formal levels of significance were not achieved for associations with mortality from circulatory disease, coronary heart disease and respiratory disease, the point estimates for coronary heart disease mortality and respiratory disease mortality were similar to those found with all cause mortality.

4.3. The behavioural hypothesis

The behavioural hypothesis (model c) was tested by adjusting for lifestyle and socioeconomic variables (Table 3).

4.3.1. Ah4

For all cause mortality, further adjustment for lifestyle and socioeconomic factors had a slight attenuating effect on the age adjusted estimates ($HR_{age+lifestyle+socioeconomic}=0.90$; 95%CI = 0.80, 1.00; $p=0.053$). However, the association was more fully attenuated for circulatory disease mortality ($HR_{age+lifestyle+socioeconomic}=0.90$; 95%CI = 0.76, 1.07; $p=0.24$), coronary heart disease mortality ($HR_{age+lifestyle+socioeconomic}=0.90$; 95%CI = 0.74, 1.10; $p=0.31$) and respiratory disease mortality ($HR_{age+lifestyle+socioeconomic}=0.83$; 95%CI = 0.59, 1.16; $p=0.27$). For other disease mortality there was no effect of further adjustment for lifestyle and socioeconomic factors ($HR_{age+lifestyle+socioeconomic}=0.61$; 95%CI = 0.40, 0.94; $p=0.025$).

4.3.2. Crt

Further adjustment for mid-life disease risk reduced slightly the strength of the association between CRT and all cause mortality ($HR_{age+lifestyle+socioeconomic}=1.14$; 95%CI = 1.04, 1.24; $p=0.003$). Similar effect sizes were found with mortality from circulatory disease ($HR_{age+lifestyle+socioeconomic}=1.13$; 95%CI = 0.99, 1.29; $p=0.07$) and coronary heart disease ($HR_{age+lifestyle+socioeconomic}=1.19$; 95%CI = 1.03, 1.38; $p=0.021$). For respiratory disease mortality smaller numbers may explain the lack of formal levels of significance but the point estimate was comparable to that found with all cause mortality ($HR_{age+lifestyle+socioeconomic}=1.16$; 95% CI = 0.90, 1.51; $p=0.25$). Further adjustment for lifestyle and socioeconomic factors enhanced the association with digestive disease mortality ($HR_{age+lifestyle+socioeconomic}=1.94$; 95%CI = 1.26, 3.00; $p=0.003$) and had no impact on other disease mortality ($HR_{age+lifestyle+socioeconomic}=1.89$; 95%CI = 1.42, 2.51; $p<0.001$).

4.4. The fully adjusted model

The fully adjusted model was tested by adjusting for age, disease risk, lifestyle and socioeconomic variables (Table 3).

4.4.1. Ah4

For all cause mortality, full adjustment severely attenuated the association ($HR_{full}=1.06$; 95%CI = 0.92, 1.23; $p=0.41$). Similar impacts were found for circulatory disease ($HR_{full}=1.05$; 95%CI = 0.83, 1.33; $p=0.68$), coronary heart disease ($HR_{full}=1.12$; 95%CI = 0.85, 1.49; $p=0.42$) and respiratory disease ($HR_{full}=1.11$; 95%CI = 0.70, 1.77; $p=0.65$). For other diseases, there was no impact of the fully adjusted model on the age adjusted association ($HR_{full}=0.56$; 95%CI = 0.32, 0.98; $p=0.042$).

4.4.2. Crt

Similarly, for CRT full adjustment severely attenuated associations with all cause mortality ($HR_{full}=1.07$; 95%CI = 0.98, 1.17; $p=0.16$), circulatory disease mortality ($HR_{full}=0.98$; 95% CI = 0.84, 1.13; $p=0.75$), mortality from coronary heart disease ($HR_{full}=1.01$; 95%CI = 0.85, 1.20; $p=0.90$) and respiratory disease mortality ($HR_{full}=1.01$; 95%CI = 0.75, 1.35; $p=0.96$). For mortality from digestive disease full adjustment enhanced the association ($HR_{full}=1.82$; 95% CI = 1.14, 2.91; $p=0.013$) and for other disease mortality had no impact ($HR_{full}=1.82$; 95%CI = 1.34, 2.49; $p<0.001$).

5. Discussion

Cognitive performance has been shown to be associated with all cause and cause specific mortality in a population sample of men aged 55–69 at recruitment and who were followed for up to 16 years.

5.1. Strengths

The Caerphilly Study has achieved high levels of participation throughout and the sample used for this analysis reflected a response rate of 85% making the likely effect of selection bias small. Cognitive testing was conducted largely in a standard clinic environment (95%) and mostly by a single technician (89%). Associations between cognitive tests were similar to those reported previously (Deary & Der, 2005). Men who encountered difficulty with the computer used for cognitive testing were omitted from the analysis. The cognitive domains tested represented a range of variation with age and so to be differentially susceptible to exogenous influence. Crystallised intelligence is considered to be comparatively invariant with age whilst fluid intelligence and reaction time reaction time are considered to change with age. Mortality follow-up was through the Office for National Statistics so unless the man had emigrated from the United Kingdom there would be virtually complete ascertainment.

5.2. Limitations

This is a male cohort so one must be cautious in generalising associations to women especially in relation to lifestyle factors where there may be interactions between cognitive function and gender. Our analysis is based on cognitive function assessed at one point in time, although we do have a proxy measure of peak cognitive attainment. Covariates relevant to the full spectrum of mortality were not assessed. For example, adjustment for disease status, although reasonably comprehensive for vascular related disorders, did not include assessments of neoplastic or inflammatory conditions. The same would be true for risk factors, which were designed to capture vascular disease. The Caerphilly Study may have been considered sufficiently large at inception; however, it is small for cause specific mortality analyses.

All statistical models have limitations in terms of unmeasured confounders and measurement error. In the current analyses, for example, genetic, developmental factors and early-life cognition were not directly assessed and so our attempts to adjust for the developmental model may have been inadequate. Our use of DAGs highlights additional difficulties in interpreting these and similar data. The three DAG models (models a–c) provide clear definitions for the rationale underlying the selection of covariates. However, these models were simplifications. Full adjustment, however, also has its difficulties. Apart from being a blunt instrument, full adjustment is frequently uninformative as to which causal pathways are being tested. Selective adjustment, without the use of formal rules such as those visualised by DAGs, is also problematic. Although, specific mechanisms may be proposed careful selection of covariates is required to achieve unbiased estimates. In the present study, for example, socioeconomic status was included in the covariate set in part to prevent biasing arising from adjustment of lifestyle factors.

Table 3
All cause and cause specific mortality according to standardised (z) scores of cognitive tests adjusting for various models in 1444 men with complete data.

Mortality	Model	Adjustments	AH4	CRT
			(HR, 95% CI, *p*-value)	(HR, 95% CI, *p*-value)
All-cause	Reference	Age	0.84 (0.76, 0.92) $p<0.001$	1.19 (1.10, 1.29) $p<0.001$
(number of deaths = 495)	a: Common cause	Age and NART	0.95 (0.83, 1.09) $p=0.46$	1.14 (1.05, 1.25) $p=0.002$
	b: Cognitive decline	Age and disease risk	0.89 (0.81, 0.98) $p=0.018$	1.13 (1.04, 1.23) $p=0.003$
	c: Behavioural	Age, lifestyle and sociodemographic factors	0.90 (0.80, 1.00) $p=0.053$	1.14 (1.04, 1.24) $p=0.003$
	Full adjustment	Age, NART, sociodemographic, lifestyle and disease	1.06 (0.92, 1.23) $p=0.41$	1.07 (0.98, 1.17) $p=0.16$
Circulatory disease	Reference	Age	0.85 (0.74, 0.98) $p=0.027$	1.17 (1.03, 1.33) $p=0.016$
(number of deaths = 210)	a: Common Cause	Age and NART	0.90 (0.73, 1.11) $p=0.33$	1.14 (1.00, 1.30) $p=0.056$
	b: Cognitive decline	Age and disease risk	0.92 (0.79, 1.07) $p=0.26$	1.07 (0.93, 1.23) $p=0.34$
	c: Behavioural	Age, lifestyle and sociodemographic factors	0.90 (0.76, 1.07) $p=0.24$	1.13 (0.99, 1.29) $p=0.07$
	Full adjustment	Age, NART, sociodemographic, lifestyle and disease	1.05 (0.83, 1.33) $p=0.68$	0.98 (0.84, 1.13) $p=0.75$
Coronary heart disease	Reference	Age	0.83 (0.70, 0.98) $p=0.024$	1.26 (1.09, 1.45) $p=0.001$
(number of deaths = 155)	a: Common Cause	Age and NART	0.89 (0.70, 1.14) $p=0.37$	1.22 (1.06, 1.41) $p=0.007$
	b: Cognitive decline	Age and disease risk	0.91 (0.76, 1.09) $p=0.30$	1.14 (0.98, 1.34) $p=0.10$
	c: Behavioural	Age, lifestyle and sociodemographic factors	0.90 (0.74, 1.10) $p=0.31$	1.19 (1.03, 1.38) $p=0.021$
	Full adjustment	Age, NART, sociodemographic, lifestyle and disease	1.12 (0.85, 1.49) $p=0.42$	1.01 (0.85, 1.20) $p=0.90$
Respiratory disease	Reference	Age	0.71 (0.54, 0.94) $p=0.017$	1.36 (1.07, 1.73) $p=0.011$
(number of deaths = 58)	a: Common Cause	Age and NART	0.98 (0.65, 1.48) $p=0.92$	1.25 (0.98, 1.61) $p=0.08$
	b: Cognitive decline	Age and disease risk	0.88 (0.66, 1.17) $p=0.39$	1.14 (0.88, 1.50) $p=0.31$
	c: Behavioural	Age, lifestyle and sociodemographic factors	0.83 (0.59, 1.16) $p=0.27$	1.16 (0.90, 1.51) $p=0.25$
	Full adjustment	Age, NART, sociodemographic, lifestyle and disease	1.11 (0.70, 1.77) $p=0.65$	1.01 (0.75, 1.35) $p=0.96$
Digestive disease	Reference	Age	0.79 (0.49, 1.28) $p=0.34$	1.71 (1.19, 2.47) $p=0.004$
(number of deaths = 18)	a: Common Cause	Age and NART	0.92 (0.45, 1.87) $p=0.81$	1.67 (1.14, 2.45) $p=0.009$
	c: Behavioural	Age, lifestyle and sociodemographic factors	0.77 (0.42, 1.41) $p=0.41$	1.94 (1.26, 3.00) $p=0.003$
	Full adjustment	Age, NART, sociodemographic and lifestyle factors	0.88 (0.39, 1.99) $p=0.76$	1.82 (1.14, 2.91) $p=0.013$
Other	Reference	Age	0.63 (0.44, 0.90) $p=0.011$	1.86 (1.46, 2.38) $p<0.001$
(number of deaths = 36)	a: Common Cause	Age and NART	0.53 (0.32, 0.88) $p=0.015$	1.85 (1.43, 2.39) $p<0.001$
	c: Behavioural	Age, lifestyle and sociodemographic factors	0.61 (0.40, 0.94) $p=0.025$	1.89 (1.42, 2.51) $p<0.001$
	Full adjustment	Age, NART, sociodemographic and lifestyle factors	0.56 (0.32, 0.98) $p=0.042$	1.82 (1.34, 2.49) $p<0.001$

Note: coronary heart disease mortality is a sub-set of circulatory disease mortality; HR = hazard ratio.

The clarity in describing the causal relationships of the analytical model graphically, enable covariates to be selected more appropriately for each analysis and highlights the implicit assumptions (correct or incorrect) one makes in modelling relationships. Epidemiologists and other scientists have generally argued that one can estimate direct effects by examining the change in effect estimates before and after introducing a mediating or intermediary variable. If such a variable is the only pathway between the exposure and outcome then, assuming no measurement error, conditioning on this variable will abolish the association. However as Cole and Hernan (2002) have demonstrated both at a theoretical and empirical level, this can be misleading if the mediator is itself confounded by other factors which may be determined by exposure. In our case, for example, when testing the behavioural hypothesis (Fig. 2c), lifestyle factors may be intermediaries between cognitive function in mid-life and mortality but they are also confounded by sociodemographic factors, which are determined in part by cognitive function in earlier life, which is the strongest determinant of cognitive function in mid-life. Thus a full adjustment approach i.e. conditioning on all of these factors, may result in a biased estimate as any effect of mid-life cognition on mortality will be underestimated.

5.3. Interpretation

5.3.1. The common cause hypothesis

The idea that the association of mid-life cognition and mortality is driven by common causes underlying both mid-life cognition and mortality received strong support for the AH4 but not for reaction time. For the AH4 age adjusted associations were severely attenuated for all cause and cause specific mortalities. The exception to this being other causes of disease. Associations with reaction time were largely independent of NART score (the proxy used for early-life influences). This may be due to the NART being a better proxy for early-life AH4 performance than for early-life reaction time. This would be consistent with the observation that NART is more strongly correlated with the AH4 than CRT in these data. The effect of early-life cognition on mortality has been shown previously for both childhood cognitive function (Whalley & Deary, 2001; Hart et al., 2003) and cognitive function in young adulthood (Batty et al., 2008).

5.3.2. The cognitive decline hypothesis

Evidence was also found for the cognitive decline hypothesis in that for both AH4 and CRT adjusting for mid-life disease risk modestly attenuated associations with the cause specific mortalities for which the covariate set was relevant (circulatory, coronary heart and respiratory disease). Although adjusted for mid-life disease risk, that little attenuation was found for all cause mortality, is not surprising given the cause specificity of the mid-life disease risk covariate set.

5.3.3. The behavioural hypothesis

The behavioural hypothesis received mixed support. For circulatory disease, coronary heart disease and respiratory disease, the association of both the AH4 and CRT with mortality was attenuated by adjustment for socioeconomic and lifestyle factors. For mortality from digestive and 'other' disease associations with the AH4 and CRT were little affected.

5.3.4. The fully adjusted model

The fully adjusted model nullified all associations except those with digestive disease and 'other' disease mortality. That the association between reaction time and 'other' disease mortality appeared invulnerable to adjustment illustrates difficulties of this approach. On the one hand CRT may be considered to be robustly associated with 'other' disease mortality. On the other, the adequacy of the model can be questioned. It is particularly important to realise that the fully adjusted model does not represent a conservative approach to identifying independent risk factors. On the contrary, the independence of risk factors ultimately demonstrates a lack of understanding of the mechanisms that may be involved. Of greater epidemiologic interest is characterising the inter-relatedness of risk factors in order to identify causal pathways.

5.3.5. Conclusions

In summary, these data provide an interesting pattern and should be considered in the light of the relevance of the covariate sets for each outcome. As CaPS was designed to investigate cardiovascular disease, which is largely influenced by lifestyle and its antecedents, it is not surprising that stronger support for each model was found for outcomes that have a large vascular component (circulatory disease, coronary heart disease and respiratory disease). For these outcomes the models may be considered to be more adequately tested. For digestive disease and the 'potpourri' category of 'other' disease, there was little or no support for any of the models in relation to reaction time although behavioural factors did attenuate the association of the AH4 with digestive disease mortality. The pattern of an association of mid-life cognition with circulatory, coronary heart disease and respiratory disease mortality has been reported previously (Shipley et al., 2008). However, due to more detailed covariate measurement including the objective measurement of mid-life disease risk, the present analysis allows a more detailed examination of possible causal pathways linking cognitive function to mortality. From these data it is clear that factors affecting cognitive decline (mid-life disease risk) affects associates with both the AH4 and CRT when the covariate set is relevant to outcome.

In conclusion, the association between cognitive performance and cause specific mortality is complex. Our data show that where the covariate set is most relevant, determinants of early-life cognition attenuate, sometimes markedly, the association between mid-life cognition and mortality. The data also show that, where the covariate set is relevant, mid-life disease and lifestyle factors also have a marked effect on nullifying the association of mid-life cognitive function with mortality. Finally, limitations of the statistical methods cannot ensure that these estimates are unbiased. It may be that confounding has been induced by adjustment or that legitimate effects have been inadvertently excluded by adjustment due to a poorly explicated or incorrectly applied model. The complex confounding structures that are present, particularly in all cause mortality data, highlight the difficulties in identifying the effects of specific pathways leading

from cognitive function to outcome. We believe that a simple empirical interpretation is not possible using conventional methods. Future studies should explore natural experiments, use different populations where the confounding structures may be different and evaluate more complex statistical methods that may be able to deal with the inherent complexities of a life course approach.

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