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Association of change in cognitive function from early adulthood to middle-age with risk of cause-specific mortality: the Vietnam Experience Study

Running title: Cognitive function change & mortality

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Abstract

Background: Studies with single baseline measurements of cognitive function consistently reveal inverse relationships with mortality risk. The impact of change in functioning, particularly from early in the life course, which may offer additional insights into causality, has not, to the best of our knowledge, been tested.

Aims: To examine the association of change in cognition between late adolescence and middle-age with cause-specific mortality using data from a prospective cohort study.

Methods: The analytic sample consisted of 4289 US male former military personnel who were administered the Army General Technical Test in early adulthood (mean age 20.4 yr.) and again in middle-age (mean age 38.3 yr.).

Results: A 15 year period of mortality surveillance subsequent to the second phase of cognitive testing gave rise to 237 deaths. Following adjustment for age, a ten unit increase in cognitive function was related to a reduced risk of death from all-causes (hazard ratio; 95% confidence interval: 0.84; 0.75, 0.93) and cardiovascular disease (0.78; 0.64, 0.95) but not from all cancers (1.14; 0.88, 1.47) nor injury (1.02; 0.81, 1.29). Adjustment for markers of socioeconomic status in middle-age resulted in marked attenuation in the magnitude of these associations and statistical significance at conventional levels was lost in all analyses.

Conclusions: Increases in cognitive function earlier in the life course were associated with lower mortality risk, and these effects were mediated by socioeconomic status in the present study.

Key words: cognitive function, cohort, mortality

What is already known on this subject?

- Studies with single baseline measurements of cognitive function consistently reveal inverse relationships with mortality risk.

What does this study add?

- The impact of *change* in cognitive function, particularly from early in the life course, which may offer additional insights into causality, has not been examined.
- Increases in cognitive function earlier in the life course appear to be associated with lower risk of death, most notably for total and cardiovascular disease mortality.
- These effects were mediated by socioeconomic status.

Introduction

Findings from numerous prospective cohort studies indicate that scores from standard tests of cognitive function administered at a single point in the life course are related to total mortality risk, such that higher-scoring people typically have lower death rates. [1-5] Inverse relationships have also been observed for cognition and selected chronic diseases, including coronary heart disease[6,7] and stroke,[8,9] but rarely cancer[10,11] The strongest effects are apparent for unintentional and intentional injury.[12-15] As informative as these findings have been, they inevitably have methodological weaknesses that hamper data interpretation. Being based exclusively on observational data, an obvious and perennial concern is the impact of confounding, such that cognitive ability is related to an array of risk factors for chronic disease and injury, most obviously socioeconomic position and somatic illness, and it could be some or all of these covariates, rather than lower cognitive function *per se*, that generate the relation with future death. Whereas the standard statistical adjustments are often made for covariates, some may be unmeasured or, in the case of morbidity, selected diseases may be hidden at study entry.

In principle, confounding could be resolved by the use of randomised controlled trials,[16] but these are probably logistically prohibitive in the context of mortality and chronic diseases, many of which have extended induction periods. Additionally, the interventions that might be effective in raising cognitive ability, or slowing decline, are currently unclear.[17] An alternative approach is to simulate a trial within the context of an observational study.[18-21] Although also not free from confounding, if, in a cohort study with repeat assessments of cognition, the lowest risk of later mortality is apparent in people with gains in cognitive functioning, this would provide stronger evidence of causality than studies with a single baseline measurement. A further important advantage of this repeat assessment of cognition is that, in keeping with many other potential determinants of mortality, such as health behaviours and biomedical risk markers, cognitive function is time-

varying.[22,23] Serial measurements would therefore result in an enhanced characterisation of the exposure.

Few studies are sufficiently large, long running, and well-characterised enough to have the capacity to examine the link between change in cognitive function and mortality risk. Those that have these qualities have typically sampled older aged people (>=70 years) where a drop in cognitive ability has been shown to be related to an elevation in death rate.[24,25] Using data from the Vietnam Experience Study, we have previously shown a relationship between higher cognitive function in early adulthood and lower mortality risk.[26] The same test of cognitive function was re-administered in middle-age, so allowing us to also explore the association of change in cognitive ability with later mortality risk in this sample. To the best of our knowledge, this is the first study to examine whether cognitive change from as early as adolescence to middle-age is associated with subsequent mortality.

Methods

The Vietnam Experience Study has been described in detail elsewhere.[26-30] In brief, 18,313 male US military personnel who entered the service between 1965 and 1971 qualified for inclusion in this cohort study (mean age 20.4, SD 1.7). Information pertaining to military rank, ethnicity, and cognitive ability were extracted from military archives. Based on attained military rank, the monthly income of the army personnel using 1964 pay scales was derived. The ethnic origin of the study members was classified as 'white', 'black', or 'other' (Hispanics, Asians, Pacific Islanders, American Indians, and Alaskan Natives). To give guidance as to the potential rank of the soldier, the Army General Technical Test, a general cognitive aptitude test, was routinely administered. Scores from this test correlate moderately highly with well-established devices such as the Wechsler Adult Intelligence Scale.[31]

Data collection in middle-age

The 17,867 men known to be alive were invited to be resurveyed in middle-age. Data were collected via a telephone interview in 1985 and medical examination one year later. In the telephone interview, enquiries were made about the study participants' health, health behaviours, and socio-economic characteristics (years of completed education, household income, and an index of occupational prestige[32,33]). Smoking habits and marital status were ascertained using standard questions. Study members were also asked about the existence of a range of physician-diagnosed health problems which included hypertension, cancer, diabetes, and coronary heart disease.[34] The presence of one or more of these conditions was used to denote extant chronic disease.

A random sample of telephone interview respondents (N=6443) was invited to attend a three day medical examination; 4462 did so (mean age 38.3 yr, SD 2.5).[32,35,36] The same Army General Technical Test used at service entry was re-administered. Additionally, following an overnight fast, blood was drawn, and blood pressure, lung function, resting heart rate, height and weight (to derive body mass index) were assessed using standard protocols. Study participants were considered positive for depression, generalized anxiety disorder, and post-traumatic stress disorder if they reported a pattern of symptoms in the previous year that satisfied criteria from the Diagnostic and Statistical Manual of Mental Disorders (version III).[29,37] The participants also reported their frequency of alcohol bingeing (defined as five or more 'drinks' on one occasion; a bottle/can beer, glass of wine, a cocktail, or measure of spirits constituted a drink).[38]

Statistical analyses

We used two approaches to quantify change in cognitive function. In the first, employing a method common to epidemiology,[39] change was computed by subtracting scores in early adulthood from those in middle-age. In sensitivity analysis, we also show the results for another frequently used approach which involves additional adjustment of the change score for the baseline cognitive

function score in the regression models. In the second approach, one more common to the field of psychology,[40] we estimated the change in cognitive function by computing the residuals derived from regressing scores from the Army General Technical Test in middle-age on those obtained in early adulthood. This method has the advantage of ensuring that the change score is orthogonal to the baseline test score. With both methods yielding similar findings, we present the results from the first method in the paper and the other results in the supplementary tables (supplemental tables S1 and S2).

The relations between cognitive change and covariates with a continuous distribution were assessed by regressing the study covariates on the cognitive change score with adjustment for age at the time of the medical examination. For dichotomous covariates, logistic regression was used to estimate odds ratios, 95% confidence intervals and p-values associated with change in cognitive function. These relationships are presented as the change in the covariates associated with a 10 unit increase in cognitive function (approximating to an increase of one half of a standard deviation in cognitive function).

We examined the association between change in cognitive function and mortality by fitting this exposure in Cox proportional hazards regression models[41] with follow-up time as the underlying time scale. We estimated hazard ratios and accompanying 95% confidence intervals for mortality associated with a 10 unit increase in cognitive function. In these analyses, we first adjusted for age, then ethnicity and army rank, and finally variables according to theme (behavioural, chronic disease, physiological, socioeconomic). Follow-up time was taken from the date of the medical examination until censoring, death, or December 31st 2000 – whichever came first. All analyses were performed with the use of SAS software, version 9.4 (SAS Institute).

Results

The final analytic sample comprised 4289 men with complete data. In this group, the mean (SD) cognitive score in early adulthood (mean age 20.4; SD 1.7) was 106.1 (20.4). At follow-up, after an average of eighteen years (mean age 37.9; 2.5), the overall mean cognitive score was 110.7 (21.8). Thus, 69% of the sample had an increase in performance whereby the mean improvement was 4.6 (11.4) units.

In table 1 we present the association of study covariates with change in cognitive function between early adulthood and middle-age. Greater increases in cognitive function were evident in the younger men. Taking these age effects into account, higher increases in cognitive function between early and later adulthood were associated with a more favourable risk factor profile. Thus, a greater improvement in cognition was associated with lower levels of blood pressure, resting heart rate, and blood glucose. Similarly, men whose cognitive function change between the two points of measurement was higher than their peers were less likely to subsequently be in poorer socioeconomic circumstances, to smoke, to drink alcohol, or experience generalised anxiety disorder.

Table 2 depicts the association between change in cognitive function and later mortality risk. A mean follow-up period of 14.6 years (SD 1.8) gave rise to 237 deaths from all-causes (including 62 from cardiovascular disease, 47 from all cancers, and 51 from external causes). In analyses in which hazard ratios were controlled for age, men with a greater increase in the cognitive score had a lower risk of mortality from all-causes and cardiovascular disease. There was, however, essentially no apparent link between cognitive change and deaths from cancer of combined sites or deaths from injury. Only small attenuations of these effect estimates were apparent after controlling for the behavioural, chronic disease, and physiological factors. By contrast, adjustment for a range of indicators of socioeconomic status weakened these associations markedly, and statistical

significance at conventional levels was lost. When all covariates were added together additional attenuation of the hazard ratios was apparent and results were again non-significant at conventional levels.

We conducted two sets of sensitivity analyses. In the first, in all models, the associations between cognitive change and mortality were additionally adjusted for baseline cognitive test scores (correlation coefficient between both measurements 0.85; p-value <0.001). The results are shown in Supplementary table S1, and they are very similar to those in table 2. In the second set of analyses, the cognitive changes scores were calculated by saving residuals from analyses that regressed scores from the second cognitive test on the first. The results are shown in supplementary table S2, and, again, they are very similar to those in table 2.

Discussion

The main finding of this study was that men whose cognitive test scores increased more markedly from young adulthood to middle-age experienced a lower risk of total and cardiovascular disease mortality, though we found no discernible links with all cancers combined and external cause of death. That adjusting for markers of socioeconomic position in adult life – education, income, occupational prestige – led to the greatest reduction in the strength of the relation between cognitive change and mortality ascribed to all-causes and cardiovascular disease points to a plausible mediation pathway: enhanced cognitive function might lead to educational success, and on to well remunerated, higher prestige employment, and it might be the latter which confers protection against premature mortality. There are at least two alternative explanations. First, adult socio-economic position might serve as a proxy for cognitive change which itself has a direct effect on mortality risk. Second, socio-economic position may have a cognition-enhancing impact via, for instance, occupational characteristics such as job complexity. The present study is not able to distinguish between these explanations, however.

Study strengths and limitations

This study is, to our knowledge, the first study to explore the health impact of change in cognition from late adolescence/early adulthood. It is not without limitations, however. First, this cohort solely comprises men and therefore the extent to which our results are transportable to women is unclear. In general, the links between cognition function and death appear to be the same in men and women. Second, the present analyses are largely based on a sample with complete information from a cognitive test, covariates at telephone interview and medical exam, and vital status (N=4289). This group represents 67% of the random sub-sample invited to the medical examination, and 26% of persons originally enrolled in the study. Although the latter is itself based on a random sample of surviving men, concerns are nonetheless raised about selection bias; that is, if the reported results differ markedly between persons included in the analyses and those not. As previously shown,[26] men in the excluded group had a marginally lower baseline cognitive function score than those in the analytical sample; however, there was generally little evidence of any systematic differences between the groups. This was confirmed when we computed the relation between baseline cognitive test score and all-cause mortality in each of the groups for persons with the available data. The strength of this association (hazard ratio for a 1 SD increase in cognition; 95% confidence interval) was similar in men included (0.71; 0.63, 0.81) and excluded (0.79; 0.75, 0.84) from the analyses (p-value for difference = 0.22).

Third, the overall improvement in cognitive function in the present cohort could reflect development and/or familiarity with testing. However, the analyses here use the individual differences in change, and the fact that there is an overall mean increase does not affect those. Fourth, if our measure of cognition, the Army General Technical Test, misclassified study members' and this was not differential with respect to the outcome, our hazard ratios are likely to be underestimates for the true value. Relatedly, using a longer, more detailed cognition battery on both assessment occasions would have resulted in less error and, again, effect estimates that were closer

to the true value. Lastly, it would have been optimal to have data on inflammatory and hemostatic biomarkers, such as C-reactive protein, fibrinogen, and von Willebrand factor, which in their own right, or their correlates, have been linked to cognition[42,43] and/or risk of death.[44-46]

In conclusion, in the present study, we found an association of change in cognitive function between early adulthood and middle-age with mortality that was seemingly mediated via socioeconomic factors. Further examination of this observation is justified, particularly in women and minority groups.

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Table 1. Association of a 10 unit increase in cognitive function between early adulthood and middle-age with risk factors for mortality in middle-age (N=4289)

	Absolute difference in risk factor (95% confidence interval)	**P-value**
Age at medical examination (yr)	-0.28 (-0.35, -0.22)	<0.001
Forced expiratory volume in one second (l)	0.02 (0.00, 0.04)	0.034
Total cholesterol (mmol/l)	0.01 (-0.01, 0.04)	0.34
High density lipoprotein cholesterol (mmol/l)	-0.01 (-0.02, 0.00)	0.029
Systolic blood pressure (mmHg)	-0.5 (-0.9, -0.2)	<0.001
Diastolic blood pressure (mmHg)	-0.5 (-0.8, -0.3)	<0.001
Pulse rate (beats/min)	-0.5 (-0.9, -0.2)	<0.001
Blood glucose (mg/dl)	-0.5[b] (-0.8, -0.1)	0.008
Body mass index (kg/m^2)	0.1 (0.0, 0.2)	0.25
Height (m)	0.002 (0.000, 0.004)	0.046
	Odds ratios (95% confidence interval)	
Non-white ethnicity	0.86 (0.81, 0.92)	<0.001
Not married	0.85 (0.80, 0.90)	<0.001
Low occupational prestige	0.86 (0.80, 0.92)	<0.001
Low income	0.85 (0.80, 0.90)	<0.001
Low education	0.89 (0.82, 0.96)	0.003
Current smoker	0.97 (0.92, 1.02)	0.28
Current alcohol drinker	0.88 (0.83, 0.94)	<0.001
Binge drinker (among current drinkers)	0.93 (0.87, 0.99)	0.017
Generalised anxiety disorder	0.89 (0.82, 0.98)	0.012
Post-traumatic stress disorder	1.05 (0.95, 1.17)	0.33
Depression	0.94 (0.85, 1.04)	0.24
Somatic disease	0.97 (0.90, 1.05)	0.51

[a] Effect estimates from linear regression and logistic regression analyses are adjusted for age, except age.
[b] Blood glucose effect shown as a percentage change since distribution skewed. Median blood glucose is 92 mg/dl.

Table 2. Hazard ratio (95% confidence interval) for the association of a 10 unit increase in cognitive function between early adulthood and middle-age with selected causes of mortality (N=4289)

Adjustment	All causes (237 deaths)	CVD (62 deaths)	All cancers (47 deaths)	Injury (51 deaths)
Age	0.84 (0.75, 0.93)	0.78 (0.64, 0.95)	1.14 (0.88, 1.47)	0.96 (0.76, 1.22)
Age + army rank, ethnicity	0.87 (0.79, 0.97)	0.82 (0.67, 0.99)	1.14 (0.89, 1.46)	0.96 (0.76, 1.22)
Age + behavioural factors[a]	0.85 (0.77, 0.95)	0.79 (0.65, 0.96)	1.13 (0.88, 1.46)	0.97 (0.76, 1.23)
Age + chronic disease factors[b]	0.85 (0.77, 0.95)	0.79 (0.65, 0.97)	1.14 (0.89, 1.47)	0.97 (0.76, 1.23)
Age + physiological factors[c]	0.88 (0.79, 0.98)	0.81 (0.66, 0.98)	1.17 (0.91, 1.51)	0.97 (0.77, 1.23)
Age + socioeconomic factors[d]	0.91 (0.82, 1.00)	0.84 (0.69, 1.02)	1.13 (0.88, 1.46)	1.02 (0.81, 1.28)
All above covariates	0.94 (0.85, 1.04)	0.86 (0.71, 1.06)	1.14 (0.89, 1.47)	1.02 (0.81, 1.29)

CVD, cardiovascular disease

[a] Behavioural factors are: smoking habit, alcohol consumption

[b] Chronic disease factors are: somatic disease, psychiatric factors (depression, post traumatic stress disorder, anxiety)

[c] Physiological factors are: systolic blood pressure, diastolic blood pressure, pulse rate, blood glucose, FEV1, BMI, cholesterol

[d] Socioeconomic factors are: marital status, occupational prestige, education, family income