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Running Head: THINK FAST FEEL FINE LIVE LONG

**Think Fast, Feel Fine, Live Long: A 29-Year Study of Cognition, Health, and Survival in Middle-Aged and Older Adults**

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### **Abstract**

In a 29-year study of 6203 individuals with ages ranging 41–96 years at initial assessment, we evaluated the relative and combined influence of 65 mortality risk factors—which included socio-demographic variables, lifestyle attributes, medical indices, and multiple cognitive abilities. Reductions in mortality risk were most associated with higher self-rated health, being female, fewer years smoking, and smaller life span decrements in processing speed. Thus, two psychological variables—subjective health status and processing speed—were among the top survival predictors. We suggest that these psychological attributes, unlike more narrowly defined risk factors, are indicative of (and influenced by) a broad range of health-related behaviors and characteristics. Information about these attributes can be obtained with relatively little effort or cost and—given the tractability of these measures in different cultural contexts—may prove expedient for prevention, diagnosis, and treatment of conditions related to increased mortality risk in diverse human populations.

**KEYWORDS:** aging, cognitive ability, death and dying, cognitive development, health

## Introduction

Substantial empirical evidence links cognitive ability to mortality risk—a relation that persists across decades of the life span (e.g., Anstey, Mack, & von Sanden, 2006; Whalley & Deary, 2001). Age-related decrements in certain abilities, such as processing speed, may be particularly informative of increased mortality risk (Aichele, Rabbitt, & Ghisletta, 2015; Ghisletta, McArdle, & Lindenberger, 2006). However, age alone does not explain differences in cognitive decline or, by extension, associations between cognitive decline and survival (Spiro & Brady, 2011). Especially in older populations, health and well-being depend on complex interactions between physiological conditions, functional abilities, psychological attributes, and social support (Ocampo, 2010). Relations between mortality risk and cognitive abilities measured in youth similarly implicate other variables, such as socio-economic advantage, education, and nervous system constitution (Deary, 2008).

Therefore, in evaluating cognition-survival associations, it is essential to also consider demographic, lifestyle, and health variables. For example, different medical conditions (e.g., aging of the central nervous system, metabolic disease, or compromised physical mobility) may affect both cognitive function and mortality risk. Anstey et al. (2006) reviewed 47 longitudinal studies of cognition and mortality risk in patient samples of stroke, cancer, and coronary heart disease. The authors concluded that reciprocal relations between cognition, lifestyle, and health variables indicated multiple causal pathways linked to mortality risk. Evidence of intertwined relations between diverse mortality risk factors prompts questions about differences in magnitudes of influence. Specifically, are cognitive variables stronger than other indicators of

mortality risk? And how might cognitive variables combine with demographic, health, and lifestyle risk factors to maximize predictive efficacy?

Few studies have directly addressed these questions. Batty, Shipley, Gale, Mortensen, and Deary (2008) compared general intelligence (IQ) and established risk factors (e.g., chronological age, socio-economic status, smoking, pulse rate, blood glucose and cholesterol levels) as predictors of 15-year survival rates in a group of 4166 male USA Vietnam war veterans. Across analyses conducted independently by predictor and adjusted only for chronological age, IQ was more strongly linked to survival rates than were most demographic and health indices. However, when all risk factors were included in a single survival model (i.e., predictive effects were mutually adjusted), the influence of IQ was eclipsed by family income, smoking, pulse rate, and HDL cholesterol. In a second study, Roberts, Der, Deary, and Batty (2009) assessed the relative influence of choice reaction time (CRT), psychological distress, lifestyle, and physical health variables on mortality risk in a sample of 5606 Scottish men and women with age range 18–94 years. In analyses conducted independently by predictor and adjusted for age, sex, and socio-economic status, CRT was stronger than all other risk factors except for smoking and systolic blood pressure. However, there was no follow-up analysis to determine if CRT remained influential after mutual-adjustment with other risk factors.

The literature currently lacks studies in which baseline levels and life span changes in multiple cognitive abilities, lifestyle attributes, and health indices are included as joint predictors of mortality risk. Such a comprehensive examination is necessary to determine the degree to which specific cognitive variables influence mortality risk relative to a wide range of

well-known risk factors—an important starting point in coming to better understand the pathways linking cognition and survival.

This was the aim of the present work, which stems from the Manchester Longitudinal Study of Cognition (MLSC)—an investigation of changes in cognition, lifestyle, and health in 6203 individuals with ages 41–96 years at initial assessment (Rabbitt et al. , 2004). MLSC data span a period of 29 years (i.e., from study inception in 1983 to most recently updated survival information in 2012). Cognitive abilities were assessed on four occasions spaced at 4-year intervals. Previous MLSC analyses have examined cognition-survival relations (see Aichele et al., 2015), but this is the first MLSC study to combine demographic, lifestyle, medical, and cognitive variables (65 in total) to predict mortality risk.

We used random forest survival analysis (RFSA) to compare mortality risk factors. RFSA is a nonparametric statistical technique related to classification and regression trees (Breiman, 2001; Strobl, Malley, & Tutz, 2009). Regression trees recursively partition observations according to predictor/threshold criteria that best discriminate differences in an outcome (e.g., mortality risk). Thus, the “root node” of a regression tree represents the strongest predictor (and associated cut point) using all observations, whereas subsequent nodes represent the best predictors within nested, increasingly smaller sub-samples of observations. RFSA extends this single tree approach (hence “forest”) by providing built-in cross-validation: Results are pooled across multiple trees, where each tree is derived from randomly sampled subsets of observations and predictors.

RFSA has distinct advantages over traditional multivariate methods. First, because predictor selection occurs within a recursive branching structure, and because a given predictor can be re-selected at multiple nodes in that structure, RFSA estimation implicitly adjusts for all possible linear, non-linear, and higher-order interaction effects between variables. Second, built-in cross-validation protects against multicollinearity (i.e., strongly overlapping predictive information) and model over-fit (i.e., spurious variable selection). However, RFSA was not developed within a standard probabilistic framework. Therefore, we also examined a subset of the strongest risk predictors using Cox Proportional Hazards analysis (Cox PH [Cox, 1972])—which is better-suited to effect size interpretation based on a known statistical distribution. This combined methodology thus allowed us to assess the relative importance of numerous, interrelated mortality risk factors and also to estimate effect sizes for the strongest predictors.

We hypothesized that metabolic pathways underlying both cognitive function and mortality risk would most strongly influence predictor-outcome relations. Specifically, we expected risk factors related to respiratory and cardiovascular health (e.g., symptoms such as blood pressure, chest pain, difficulty breathing) to be of primary importance. Of the cognitive variables, we previously found that processing speed decrements were most indicative of increased mortality risk (Aichele, 2015). Processing speed decrements have also been linked to declining cardiovascular health (Bosworth & Siegler, 2002). Therefore, given overlapping predictive information in processing speed and cardiovascular variables, we hypothesized that Cox PH analysis would favor cardiovascular health (the stronger risk factor)—whereas RFSA results would present a more balanced picture, with both processing speed and cardiovascular variables among the top predictors that we could consider.

## Methods

### Participants

These analyses used data from MLSC participants who completed one or more cognitive assessments ( $N = 6203$ ). Demographic variables were (a) chronological age at induction into the study, (b) sex, (c) city of residence (Newcastle upon Tyne or Manchester, U.K.), (d) study cohort by year of entry (1983–1993), (e) socio-economic advantage (SEA, graded according to the Registrar General's Scale of Occupational Categories [Office-of-Population-Censuses-and-Surveys, 1980]), (f) marital status, (g) number of persons living in the home, and (h) number of children. Tobacco and alcohol use (i.e., current status, years of use, and units of alcohol consumed per day) were also recorded. These variables are summarized in Table 1.

Participants were recruited by advertisements placed in magazines or broadcast on television and radio (Rabbitt et al., 2004). None had severe visual or auditory handicaps, and those with mild, correctable sensory handicaps were assessed with their spectacles or hearing aids in place. Mortality information was obtained from Her Majesty's Registry Office U.K. for dates and proximate causes for all deaths between 1983 (when the study began) and August, 2012 (the most recent update).

**Table 1. Participant Demographic Information, Including Tobacco & Alcohol Use**

Variable	Summary	
Participants ( <i>n</i> )	6203	(100.0%)
Age in Years at Study Induction (m)	64.7	[41.0–93.0]
Deceased ( <i>n</i> , 2012 Census)	4484	(72.3%)
Age in Years at Death (m)	83.5	[52.5–108.0]
Women ( <i>n</i> )	4379	(70.6%)
Newcastle Residents ( <i>n</i> )	3384	(54.5%)
Occupational Class or SEA ( <i>n</i> )		
Professional	289	(4.7%)
Intermediate	1961	(31.6%)
Skilled (non-manual)	1660	(26.8%)
Skilled (manual)	1342	(21.6%)
Partly Skilled	456	(7.4%)
Unskilled	52	(0.8%)
Unknown	443	(7.1%)
Marital Status ( <i>n</i> )		
Married	3313	(53.4%)
Single	484	(7.8%)
Widowed (not re-married)	1484	(23.9%)
Divorced (not re-married)	327	(5.3%)
Separated	66	(1.1%)
Unknown	529	(8.5%)
Persons in the Home ( <i>n</i> )	1.9	( <i>SD</i> = 1.0)
Children ( <i>n</i> )	1.9	( <i>SD</i> = 1.4)
<i>Tobacco and Alcohol Use</i>		
Smokers ( <i>n</i> )	1006	(16.2%)
Years Smoking (m)	17.1	( <i>SD</i> = 18.3)
Alcohol Drinkers ( <i>n</i> )	4051	(65.3%)
Years Drinking Alcohol (m)	29.4	( <i>SD</i> = 18.0)
Alcohol Consumption (m units/day)	2.0	( <i>SD</i> = 1.7)

Note: Statistics are based on information obtained from participants at induction into the study unless otherwise noted. (*n*) = number of. (m) = average. Brackets denote ranges of observed values: [min–max]. For brevity, cohort information is not shown (see Rabbitt et al., 2004).

## **Cognitive Abilities**

Cognitive performance variables were baseline levels (intercepts) and life span changes (linear slopes) in five domains of ability: crystallized intelligence, fluid intelligence, verbal memory, visual memory, and processing speed. These variables were previously derived by aggregating data from 15 cognitive tasks (three per domain) administered up to four times, at four-year intervals during a twelve-year period. Detailed descriptions of these tasks, task selection rationale, and corresponding testing procedures are provided in Rabbitt et al. (2004). Analyses by which we obtained domain-specific performance scores (i.e., intercepts centered at age 70, slopes spanning participant ages of 42–97 years) are described at length in Aichele et al. (2015). We thus only provide a short description here.

Cognitive tasks were selected on the basis that they (a) are appropriate for assessment of cognitive change in adult and older samples according to life span developmental theory (Baltes, Lindenberger, & Staudinger, 2006), (b) are well-known and documented in the empirical literature, and (c) could be administered by pencil-and-paper. Crystallized intelligence was measured by the Raven (1965) Mill Hill Vocabulary A and B (synonyms and word definitions) tests and by the Wechsler Adult Intelligence Scale-Revised (WAIS-R) vocabulary scale (Wechsler, 1986). Fluid intelligence was assessed by the Heim (1970) AH4-1 and AH4-2 tasks (logic, arithmetic, number series, verbal and visuospatial object comparisons) and from the Cattell and Cattell (1960) Culture Fair Intelligence Test. Verbal memory was examined using measures of free verbal recall, cumulative verbal recall, and delayed verbal recall (three variations of a task in which participants recalled a series of six-letter nouns).

Visuospatial memory was assessed with a picture recognition task, a "memory for objects" task (recall of names and positions of line drawings of easily-nameable objects), and recall of shapes and their spatial locations. Processing speed was measured with a visual search task, the Savage (1984) alphabet coding task, and a semantic reasoning task (Baddeley, Emslie, & Nimmo-Smith, 1992).

Within each cognitive domain, we used factor analytic methods to aggregate performance across tasks (i.e., as factor scores at each measurement occasion), and we used multilevel growth modeling to estimate levels (intercepts) and changes (slopes) in these factor scores. Thus, we obtained variables corresponding to baseline performance level (at age 70) and change in performance (spanning the range of participant ages at assessment, 42–97 years) for each cognitive domain. All models obtained good to excellent statistical fit values.

The resulting variables are summarized in Table 2. Note that estimates are given in standardized units scaled per decade (e.g., there is a  $-.49$  SD change in processing speed per decade of life). On average, cognitive performance decreased across the life span (negative linear slope) in all domains. This was most evident in verbal memory and, as predicted by life span theories of cognitive development (Lindenberger, 2001), least evident in crystallized intelligence. Between-person variation (random effects) in linear slopes was highest for verbal memory and processing speed and lowest for crystallized intelligence and visual memory (See Aichele et al., 2015).

**Table 2. Life span Changes in Cognitive Performance**

Variable	Intercept (Age 70yr.)	Linear Slope ( $\Delta/10\text{yr.}$ )	$\rho(I,S)$
Crystallized Intelligence	-0.02 [-0.04, 0.01]	-0.08 [-0.09, -0.06]	.65
Fluid Intelligence	0.03 [0.01, 0.06]	-0.30 [-0.32, -0.28]	.11
Verbal Memory	0.13 [0.10, 0.15]	-0.66 [-0.68, -0.64]	.24
Visual Memory	0.21 [0.19, 0.24]	-0.55 [-0.56, -0.53]	.79
Processing Speed	0.36 [0.33, 0.38]	-0.49 [-0.50, -0.47]	.32

Note: All estimates are in standardized units. Brackets indicate 95% confidence intervals.  $\rho(I,S)$

denotes the correlation between intercept and linear slope.

### Daily Life Attributes (DLA)

When first recruited into the study, and on two subsequent occasions separated by intervals of approximately three and nine years, participants provided subjective ratings of (a) their general health status, (b) the number of prescribed medications currently taken, (c) information about sleep patterns (hours of sleep and times awoken each night), (d) number of hobbies, (e) amount of time spent (e.g., hours per month) in 14 different types of leisure activity (e.g., housework, exercise, driving), (f) difficulty in performing 12 different daily life activities (e.g., climbing stairs, preparing meals, traveling locally), and (g) number of weekly social interactions (casual contacts; short conversations with relatives, friends, or colleagues; and long conversations with relatives, friends, or colleagues).

**Preparatory analyses.** As described in sections S1 and S2 of the supplemental material available online, we used factor analysis to reduce the 26 variables subsumed by (e) and (f) to three latent variables: “Difficulty Performing Housework,” “Impaired Physical Mobility,” and “Leisure Activity.” In total then, DLA variables spanned 11 attributes across categories (a)–(g). We used multilevel growth models (see section S3 of the supplemental material available online) to derive individual scores of baseline performance (intercepts at age 70) and life span changes (linear slopes across participant ages at DLA assessments, 41–95 years) in each of these attributes.

These scores are summarized in Table 3. On average, subjective health, sleep per night, and number of hobbies decreased across the life span (negative linear slopes). Use of prescribed medications, difficulty performing housework, and leisure activity increased across the life

span. Given the relatively older participant pool (mean age ~ 70 years), increases in leisure activity may reflect decreased work commitments and re-orientation of daily activities toward increased personal errands, social visitations, and light exercise. Between-person variation (random effects) in linear slopes was significant for five attributes: subjective health, use of prescribed medications, sleep per night, Difficulty Performing Housework, and Leisure Activity.

**Table 3. Life span Changes in Daily Life Attributes**

Variable	Intercept (Age 70yr.)	Linear Slope ( $\Delta/10$ yr.)	$\rho(I,S)$
Subjective Health <sup>a,c</sup>	3.77 [3.66, 3.89]	-0.20 [-0.39, -0.02]	-.06
Prescribed Medications <sup>c</sup>	1.75 [1.40, 2.10]	0.97 [0.16, 1.78]	.34
Sleep (hours/night) <sup>c</sup>	6.69 [6.46, 6.92]	-0.40 [-0.81, 0.01]	.19
Wake-ups (amount/night)	1.80 [1.53, 2.07]	— —	—
Number of Hobbies	4.13 [3.74, 4.51]	-0.64 [-1.38, 0.01]	-.17
Difficulty Performing Housework <sup>b,c</sup>	-0.12 [-0.27, 0.03]	0.65 [0.37, 0.92]	.39
Impaired Physical Mobility <sup>b</sup>	-0.02 [-0.52, 0.47]	0.62 [-0.18, 1.42]	.14
Leisure Activity <sup>b,c</sup>	-0.22 [-0.41, -0.02]	0.79 [0.21, 1.38]	.50
<i>Social Interactions (per week)</i>			
Casual Contacts	61.27 [48.98, 73.56]	— —	—
Short Conversations	41.93 [26.15, 57.71]	— —	—
Long Conversations	19.75 [14.66, 24.83]	— —	—

Note: Brackets indicate 95% confidence intervals.  $\rho(I,S)$  denotes the correlation between intercept and linear slope. Dashes (—) indicate that linear slope did not improve model fit and hence was excluded in the model from which parameter estimates were obtained.

<sup>a</sup> Subjective Health estimates reflect ratings scaled from 1(worst) – 5(best).

<sup>b</sup> Estimates for these attributes are based on standardized units.

<sup>c</sup> Random effects for linear slopes were significant.

**Cornell Medical Index (CMI)**

Starting in 1993 (10 years following study inception), participants completed the Cornell Medical Index (CMI; Brodman, Erdmann, & Wolff, 1949), which was thereafter administered on three separate occasions at intervals ranging between three and six years. The CMI assesses key medical and psychiatric data with minimal time and financial expense. This inventory consists of detailed checklists of pathological symptoms (195 in total) categorized into 18 domains: Sections A–L relate to physical disorders, and sections M–R correspond to psychiatric or psychological problems. Note that data from CMI index "D" is here sub-divided into D1 (Teeth) and D2 (Gastrointestinal, Liver).

In a previously published analysis of two sub-groups of MLSC participants ( $n = 101, 88$ ), Pendleton et al. (2004) validated diagnostic outcomes based on CMI scores against corresponding diagnostic outcomes from structured medical assessments conducted by two experienced physicians. Structured medical evaluation was based on a modified version of the SENIUR protocol (Ligthart et al., 1984). The identified medical conditions included hypertension, diabetes, ischemic heart disease, stroke, myocardial infarction, epilepsy, and Parkinson's disease. Predictive accuracy of the CMI was found to be excellent, ranging 89–99% across conditions.

**Preparatory analyses.** We converted CMI scores at each measurement occasion from sums (i.e., total positive symptoms within each category) to percentages (i.e., positive symptoms divided by total possible symptoms within a given category, multiplied by 100). We then estimated baseline performance (intercept at age 70) and life span change (across participant

ages at CMI assessments, 47–98 years) in each CMI domain using multilevel growth models (see section S3 of the supplemental material available online).

Summary statistics for these variables are shown in Table 4. Life span increases in symptoms were observed in five specific areas: A: Eyes/Ears, C: Cardiovascular, D1: Teeth, I: Fatigue, and J: Frequency of Illness. No life span increases were observed in symptoms related to “mood and feeling patterns” (CMI indices M–R). Intercepts and linear slopes were strongly negatively correlated for all CMI variables, indicative of baseline effects (i.e., individuals with higher overall health had “more room” to decline across the life span). Between-person variation (random effects) in linear slopes was significant for five indices: J: Frequency of Illness, L: Addiction, O: Anxiety, Total: A–L (physical symptoms), and Total: M–R (mood/feeling patterns).

**Table 4. Life span Changes in Pathological Symptoms**

Domain	Intercept (Age 70yr.)		Linear Slope ( $\Delta/10\text{yr.}$ )		$\rho(I,S)$
<i>Physical Conditions</i>					
A: Eyes/Ears	23.32	[20.45, 26.19]	3.98	[1.25, 6.72]	-.65
B: Nose/Throat/Respiration	13.34	[11.78, 14.90]	0.63	[-0.86, 2.12]	-.72
C: Cardiovascular	18.44	[16.46, 20.42]	3.84	[1.46, 6.22]	-.69
D1: Teeth	19.44	[16.98, 21.89]	2.63	[-0.02, 5.28]	-.67
D2: Gastrointestinal/Liver	12.68	[11.07, 14.30]	0.67	[-1.44, 2.78]	-.70
E: Musculoskeletal	14.92	[11.88, 17.97]	2.40	[-0.99, 5.78]	-.68
F: Skin	10.90	[8.29, 13.52]	0.59	[-2.13, 3.32]	-.72
G: Nervous System	6.89	[5.90, 7.87]	0.11	[-0.99, 1.20]	-.73
H: Reproductive/Urinary	21.94	[18.58, 25.30]	-1.88	[-5.38, 1.63]	-.71
I: Fatigue	10.71	[8.76, 12.57]	4.82	[1.77, 7.86]	-.69
J: Frequency Illness <sup>a</sup>	1.90	[0.81, 2.98]	2.60	[0.96, 4.23]	-.66
K: Miscellaneous	10.61	[9.03, 12.19]	-0.12	[-1.80, 1.56]	-.69
L: Addiction <sup>a</sup>	16.86	[14.64, 19.07]	-1.75	[-4.25, 0.75]	-.74
Total: A–L <sup>a</sup>	13.16	[12.42, 13.90]	1.17	[0.41, 1.92]	-.75
<i>Mood and Feeling Patterns</i>					
M: Inadequacy	11.40	[8.99, 13.80]	1.92	[-0.21, 4.05]	-.69
N: Depression	6.49	[3.62, 9.35]	2.18	[-1.17, 5.52]	-.66
O: Anxiety <sup>a</sup>	9.45	[6.45, 12.45]	0.43	[-2.13, 2.99]	-.73
P: Sensitivity	17.73	[8.47, 16.64]	-0.35	[-5.36, 4.66]	-.75
Q: Anger	12.55	[8.46, 13.66]	-0.02	[-4.02, 3.98]	-.73
R: Tension	11.06	[12.42, 13.90]	0.81	[-1.87, 3.49]	-.71
Total: M–R <sup>a</sup>	11.29	[9.45, 13.12]	0.89	[-0.99, 2.77]	-.77

Note: Estimates are based on raw scores scaled as percentages (i.e., % positive of total symptoms, by domain). Brackets indicate 95% confidence intervals.  $\rho(I,S)$  denotes correlation of intercept and linear slope.

<sup>a</sup> Random effects for linear slopes were significant.

### Attrition and Missing Data

No data collection "stopping rule" was defined a priori; rather, data were gathered at repeated assessments as permitted by available funding. Except for possible survival status updates, data collection has now ceased. Number of participants, average age, and age range at each assessment are shown in Table 5. Participant attrition due to death or dropout from the study appears to have been the primary source of missing data, indicated by rapidly declining values of  $n$  across subsequent assessments. MLSC participants who voluntarily withdrew between 1983 and 1994 were retrospectively identified as older, from less advantaged socio-economic groups, and had lower scores on all cognitive tests than individuals who continued to participate. Additionally, participants first recruited in 1983 who died within the first 11 years of the study were found to perform relatively worse on all cognitive tests and to have elevated levels of depression in comparison to survivors (Rabbitt et al., 2004).

Non-ignorable missingness due to attrition is a common occurrence in longitudinal, epidemiological studies (Diggle, P. J., Heagerty, P., Liang, K-Y, & Zeger, S. L., 2002). Missing data methods that exclude incomplete observations (e.g., list-wise deletion) are ill-suited to such studies because outcomes based only on complete observations will likely be biased toward healthier, higher-performing individuals. Therefore, we used multiple imputation (MI) to account for missing data (Schafer & Graham, 2002). MI derives estimates for missing values based on individuals' observed data, adding random noise to preserve a statistically reasonable degree of variability. To reduce bias in the estimates of missing values, we took an "inclusive" approach as proposed by Spratt et al. (2010): All predictor and outcome variables were included

in data imputation. We used the package mice (Van Buuren, 2011) within R statistical computing software (R Development Core Team, 2014) to impute 30 “complete” data sets using all available information from all variables included in the current study. Subsequent analyses were conducted independently for each of these datasets, and results were then aggregated across these analyses to derive final summary statistics as recommended by Rubin (1987).

**Table 5. Participant Sample Size and Age by Assessment**

Measure	Statistic	Assessment <sup>a</sup>			
		1	2	3	4
CI	<i>n</i>	6181	3875	2190	1113
	age	65.7 [43–93]	69.2 [47–92]	72.5 [52–93]	75.5 [54–97]
FI	<i>n</i>	6172	3874	2188	1112
	age	65.7 [43–93]	69.2 [47–92]	72.5 [52–93]	75.5 [54–97]
Mver	<i>n</i>	5510	3565	1861	1067
	age	65.8 [43–93]	69.1 [47–92]	72.5 [52–93]	75.5 [54–97]
Mvis	<i>n</i>	5510	3564	1858	1065
	age	66.5 [43–95]	70.1 [47–92]	73.6 [52–94]	75.7 [54–97]
PS	<i>n</i>	4288	2435	1184	487
	age	67.7 [42–96]	72.5 [47–95]	75.8 [51–96]	77.1 [54–95]
DLA	<i>n</i>	5683	3000	580	
	age	65.1 [41–95]	67.6 [51–92]	75.7 [53–93]	
CMI	<i>n</i>	2514	1821	605	748
	age	71.9 [47–94]	75.4 [51–97]	76.3 [54–97]	80.8 [68–98]

Note: Cognitive variables were CI (crystallized intelligence), FI (fluid intelligence), Mver (verbal memory), Mvis (visual memory), and PS (processing speed). DLA = daily life attributes. CMI = Cornell medical index. *n* = number of observations by measure at each assessment. age = mean age in years, with range shown in brackets.

- a. The timing of assessments differed by measure (e.g., for the first study cohort, the first DLA assessment occurred in 1983-1984, whereas the first CMI assessment occurred in 1993). Thus, differences in *n* across measures (i.e., within columns, across rows) reflect timing-dependent differences in participant availability. Testing intervals for each measure are described in the corresponding Methods sub-sections.

## Survival Analyses

Our aims were to examine the relative and combined influence of multiple predictors of mortality risk. In total, the set of predictors included 65 variables: demographic attributes (8), tobacco and alcohol use (5), intercepts and slopes of cognitive abilities (10), intercepts and slopes of daily life attributes (16), and intercepts and slopes for each of the pathological domains in the Cornell Medical Index (26). Survival analyses were conducted independently for each of the 30 imputed data sets (see Methods), and results were combined by standard procedures (Rubin, 1987). Individuals with missing survival information prior to data imputation ( $n = 245$ , or 4% of participants) were removed from the survival analyses. With respect to longitudinal variables (cognitive performance, daily life attributes, CMI indices), linear slopes were included as predictors in survival models only when corresponding estimates of between-person variation (random effects) were significant. Two survival analyses were conducted: random forest survival analysis, and Cox Proportional Hazards survival analysis. The data were randomly divided into two sub-samples so that each of the survival analyses could be conducted independently.

**Random forest survival analysis (RFSa).** A “survival tree” is a nonparametric regression method that recursively partitions observations by sequences of decision criteria that maximally discriminate mortality risk within increasingly smaller, nested subsets of observations. The resulting tree is thus composed of bifurcating “nodes” (predictor variables and corresponding split values) and “branches” (pathways linking nodes). Nodes closer to the

root (start point) of the tree represent variables with stronger predictive influence (i.e., they are effective within a larger sample of observations).

The branching, recursive algorithm used in regression trees makes them more effective than traditional step-wise approaches in accounting for all possible linear and non-linear associations and higher-order interactions among covariates and in estimating predictor importance (Strobl et al., 2009). Indeed, a standard regression model tests only the predictors (and possible interactions) explicitly specified by the analyst, whereas the regression tree algorithm tests all possible interactions (linear and nonlinear) between independent variables.

However, as noted by Ghisletta, Aichele, & Rabbitt (2014), a single survival tree may also over-fit the available data: That is, observations may be classified with respect not only to their survival information (signal) but also as a function of sampled randomness (noise). Thus, Breiman (2001) proposed the use of “random forests,” in which regression trees are repeatedly generated from (a) randomly-sampled subsets of observations and (b) with predictors at a given node selected from a randomly sampled (with replacement) subset of the total variables. This procedure provides a “built-in” method for cross-validation (using bootstrapping or “bagging”) and is robust to the problem of over-fitting, both to the sample and to the variables.

The relative influence of each predictor, or variable importance, in a random forest can be derived by aggregating estimates of predictor-outcome strength across all individual trees. Permutation accuracy, a statistic frequently used for this purpose, is a measure of the difference in prediction accuracy before and after randomly permuting a variable (to break its association with the outcome), averaged over all trees (Strobl et al., 2009). In other words, this method

compares observed vs. randomized associations between predictors and the given outcome across multiple trees to ascertain change in predictive accuracy.

We used the `randomForestSRC` package (Ishwaran & Kogalur, 2013) within the R statistical software framework (R Development Core Team, 2014) to examine the relative influence on mortality risk of the 65 predictor variables. We generated 160 trees per random forest and computed predictors' importance by the method of permutation accuracy, rescaled as a percentage of the maximum importance observed across variables. Results obtained from the 30 imputed data sets were then aggregated (Rubin, 1987).

**Cox proportional hazards survival models (Cox PH).** We also conducted a more conventional survival analysis (Cox Proportional Hazards [Cox, 1972]), incorporating data from only the most important predictor variables; i.e., those with estimated RFSA relative importance  $\geq .25$ . Here we examined the predictive influence of each of these variables via likelihood ratio tests (LRT), or change in model fit ( $\Delta\chi^2$ ) per change in degrees of freedom ( $\Delta df$ ). LRT were applied sequentially, starting with the "full" model (i.e., all predictors included) and removing variables in descending order according to their relative importance determined from the RFSA. We calculated standardized effect size estimates for each predictor (i.e., percent change in mortality risk per standard unit change in the given predictor). This analysis was carried out using the `survival` package (Therneau, 2014) in R statistical software.

## Results

**Random forest survival analyses.** Predictive error rates for the random forests converged to minimum values (ranging from .35— .36 mean-squared error) after approximately

150 trees had been generated.<sup>1</sup> Predictors with estimated relative importance ( $I_{rel}$ ) greater than .25 are listed in Table 6. Thirteen of the original 65 predictors met this criterion. Of these variables, subjective health (intercept,  $I_{rel} = .77$ ) was the strongest predictor, followed by sex ( $I_{rel} = .76$ ), years smoking ( $I_{rel} = .68$ ), and Processing Speed (linear slope,  $I_{rel} = .59$ ). Note that  $I_{rel}$  of the strongest predictor would be expected to equal 1.00 in a single RFSA, but because we aggregated results from 30 analyses (i.e., conducted across the multiply imputed data sets), the estimated maximum  $I_{rel}$  after aggregation was .77 (i.e., for subjective health), which indicates that subjective health was the top predictor in most, but not all, of the imputed data sets.

Of the remaining demographic and smoking/alcohol variables, only age at induction into the study and current smoking status made the list of top predictors. Other cognitive variables with  $I_{rel} \geq .25$  were Fluid Intelligence (linear slope) and Processing Speed (intercept). Verbal Memory, Visual Memory, and Crystallized Intelligence were of low importance in predicting mortality risk in the presence of lifestyle and medical risk factors. Other influential DLA and CMI predictors included frequency of illness (linear slope), Difficulty Performing Housework (intercept and linear slope), Leisure Activity (intercept), and number of prescribed medications (intercept).

**Cox proportional hazards survival models.** Cox PH outcomes are also shown in Table 6. Results were mostly consistent with those from the RFSA; however, only five predictors produced notable changes in model fit ( $\Delta\chi^2$ ) and also significant changes in hazard ratios (i.e., 95% CIs for  $\%\Delta$  Hazard Ratio did not include 0). These variables, in descending order of

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<sup>1</sup> In RFSA, prediction error is minimized as a function of number of trees (Ishwaran & Kogalur, 2013).

importance ( $\Delta\chi^2$ ), were subjective health (intercept), sex, Processing Speed (linear slope), age at induction into the study, and years smoking. Of these variables, only years smoking was related to increased mortality risk (+1SD lifetime smoking = +11.4% risk). Better overall subjective health (+1SD health = -16.2% risk), being a woman (-33.0% risk), and smaller life span decrements (more positive slopes) in Processing Speed (+1SD = -10.9% risk) were all predictive of reduced mortality risk. Age at induction into the study was also negatively related to mortality risk (i.e., being older at the start of the study was predictive of being older at time of death); this is a well-known selection effect (Lindenberger, Singer, & Baltes, 2002). With the exception of age at induction into the study, these top predictors had RFSA relative importance estimates  $\geq .59$ .

**Table 6. Comparative Influence of Mortality Risk Predictors**

Variable	RFSA		Cox PH			
	Rel. Importance		$\Delta\chi^2$	% $\Delta$ Hazard Ratio		
Subjective Health (I)	.77	[.69, .85]	144	-16.2	[-28.7, -3.7]	*
Sex (= female)	.76	[.68, .84]	76	-33.0	[-44.4, -21.6]	*
Years Smoking	.68	[.61, .75]	36	11.4	[4.9, 17.9]	*
Processing Speed (LS)	.59	[.51, .67]	66	-10.9	[-16.8, -5.0]	*
CMI J: Frequency of Illness (LS)	.42	[.30, .54]	21	7.7	[-2.7, 18.1]	
Difficulty Performing Housework (I)	.37	[.27, .47]	61	6.8	[-10.1, 23.7]	
Smoker (= yes)	.34	[.30, .38]	15	13.9	[-3.3, 31.1]	
Leisure Activity (I)	.33	[.27, .39]	58	8.6	[-4.9, 22.1]	
Fluid Intelligence (LS)	.32	[.26, .38]	9	-5.9	[-10.6, -1.2]	
Prescribed Medications (I)	.32	[.20, .44]	28	8.6	[-10.0, 27.2]	
Difficulty Performing Housework (LS)	.29	[.17, .41]	8	1.6	[-22.7, 25.9]	
Processing Speed (I)	.29	[.23, .35]	7	-7.8	[-14.1, -1.5]	
Age at Induction into Study	.28	[.24, .32]	42	-18.1	[-30.1, -6.1]	*

Note : Random forest survival analysis (RFSA) and Cox proportional hazards analysis (Cox PH) were conducted in different subsets of participants ( $n \cong 3000$  each sample). Rel. Importance = relative importance in predicting mortality risk.  $\Delta\chi^2$  = improvement in Cox PH model fit: Higher values = more influential variables. (I) = intercept. (LS) = linear slope. Brackets indicate 95% confidence intervals. Cox PH estimates of % $\Delta$  hazard ratio are scaled in standardized units of the corresponding predictor variable (e.g., an individual with years of smoking = group mean +1SD would, on average, have an increased mortality risk of 11.4%).

\* influential  $\Delta\chi^2$  and non-null 95% CI for % $\Delta$  Hazard Ratio

## Discussion

In a 29-year study of 6203 individuals with ages ranging 41–96 years at initial assessment, we compared the influence of 65 mortality risk factors. These included demographic variables, levels of tobacco and alcohol use, cognitive abilities, lifestyle attributes, and health indices. Results showed that better subjective health, being female, and smaller life span decrements in Processing Speed were most strongly linked to reductions in mortality risk. More years smoking (tobacco) was most predictive of increased mortality risk. Thus, these analyses showed that two psychological variables—subjective health status and life span changes in Processing Speed—were among the top survival predictors (Figure 1) and that they accounted for substantial variation in mortality risk even in the presence of well-established risk factors (e.g., male sex, smoking).

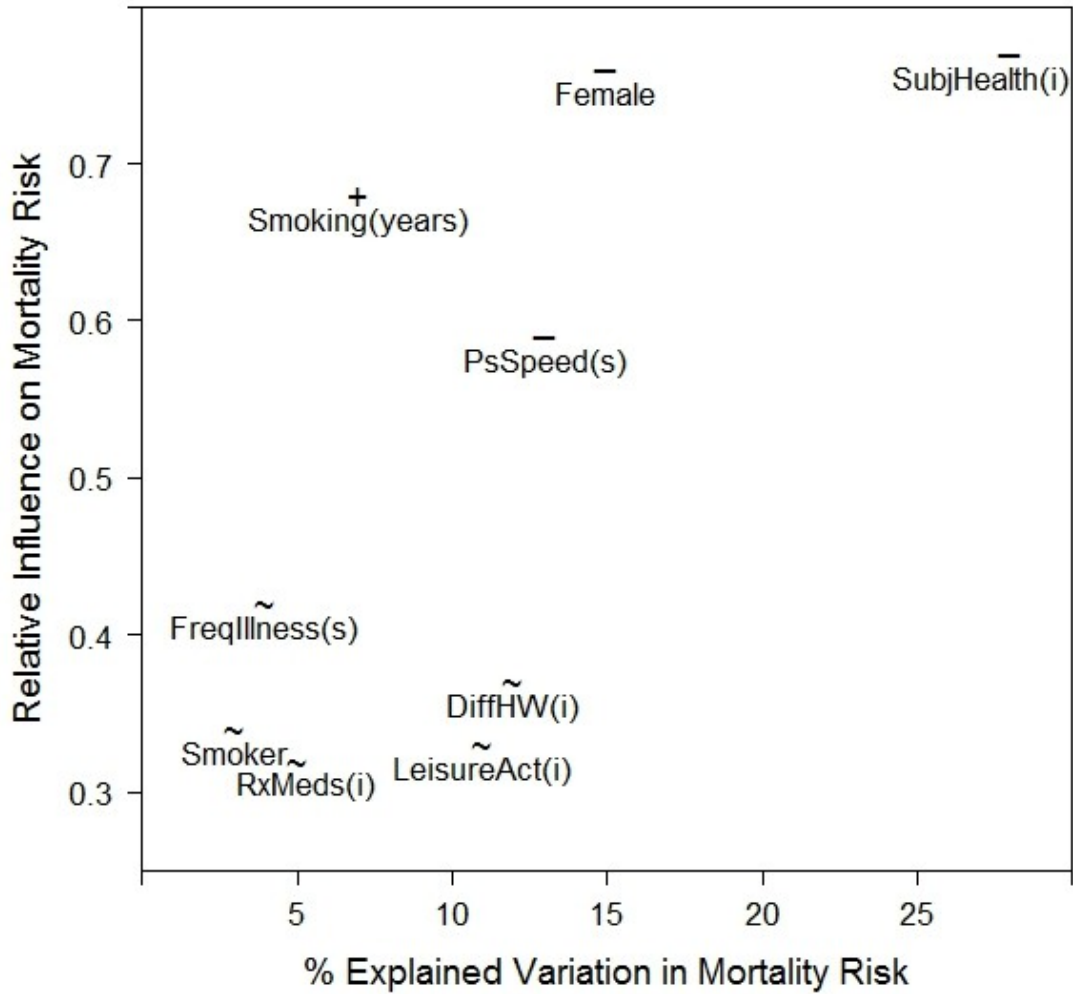


Figure 1. The nine most influential (of 65) mortality risk factors as determined jointly by random forest survival analysis (y-axis) and Cox PH analysis (x-axis). Only variables with relative importance  $> .30$  and improved model fit  $\Delta\chi^2 \geq 15$  are shown (see Table 6). SubjHealth = subjective health status. PsSpeed = Processing Speed. FreqIllness = frequency of illness. DiffHW = Difficulty Performing Housework. Leisure Act = monthly leisure activity. RxMeds = number of prescribed medications. (i) = intercept (age 70 years). (s) = slope, or life span change. + indicates increased mortality risk. - indicates decreased mortality risk. ~ indicates non-significant change in mortality risk.

Subjective health status has previously been shown to be a reliable, valid, and relatively sensitive indicator of mortality risk (e.g., Idler & Benyamini, 1997). However, some studies have demonstrated strong attenuation in the strength of association between subjective health status and mortality risk after adjusting for health and lifestyle factors (e.g., Murata, Kondo, Tamakoshi, Yatsuya, & Toyoshima, 2006), whereas others have found this not to be the case (e.g., Heistaro, Jousilahti, Lahelma, Vartiainen, & Puska, 2001). Also, severe (but not mild or moderate) cognitive impairment has been shown to reduce the predictive influence of self-rated health on mortality risk (Walker, Maxwell, Hogan, & Ebly, 2004). The current findings show that subjective health is a powerful risk indicator even in the presence of socio-demographic, lifestyle, medical, and cognitive variables. Ocampo (2010) noted that self-rated health reflects complex interrelations among biological, mental, social, and functional aspects of an individual: This higher-order integration (*vis-à-vis* more narrowly defined risk factors) may be especially important for predicting mortality risk in middle-aged and older adults.

Processing speed has been shown to be more sensitive than other cognitive abilities to the effects of aging (Salthouse, 1993), so processing speed may also signal variation in multiple underlying processes linked to mortality risk. Notably, decrements in processing speed have been linked to cardiovascular disease (Bosworth & Siegler, 2002) and, in a sub-sample of participants from the present study, to cerebral white matter lesion prevalence (Rabbitt et al., 2007). Superior psychometric properties of processing speed (e.g., reliability and accuracy of measurement) may also contribute to its predictive efficacy (Bäckman & MacDonald, 2006).

We are aware of only one other survival study comparing processing speed to established demographic, lifestyle, and medical risk factors: Roberts et al. (2009) found that, after adjustment for age and sex, processing speed (choice reaction time) predicted mortality risk more strongly than physical activity, resting heart rate, psychological distress, waist/hip ratio, weekly alcohol consumption, body-mass index, and socio-economic advantage. Only smoking status and systolic blood pressure were stronger predictors than processing speed. We used a broader range of risk factors (including multiple measures of cognitive ability) and state-of-the-art analyses (multiple imputation, RFSA, and Cox PH analysis)—and, importantly, we mutually-adjusted all risk factors. We similarly found processing speed to be a stronger predictor than all but three of the 65 risk factors examined (i.e., only subjective health, sex, and smoking were stronger).

We further note that smaller life span decrements in processing speed, rather than higher baseline levels of processing speed, were most telling of reduced mortality risk. This suggests that relations between processing speed and mortality risk mainly hinge on pathologies that develop in mid-to-late adulthood (i.e., rather than genetic precursors or early-life events)—though we cannot state this definitively as we did not assess risk factors during youth. More broadly, both subjective health status and processing speed likely mediate relations between other risk factors and mortality outcomes: These associations merit further investigation given that causal pathways linking psychological variables to mortality risk remain ambiguous.

An important caveat to the current results concerns the Cornell Medical Index, which for most participants was administered several years following initial assessment of cognitive and lifestyle variables. Individuals with CMI data therefore likely represented a slightly healthier population than those who left the study prior to CMI assessment, as confirmed by median age at death in each sub-sample (85.4 years vs. 83.6 years, respectively). Though we used all available information to impute missing CMI values (see Methods), accuracy of CMI variables may have been adversely affected by the comparatively large degree of missing data.

As a further check against this possibility, we conducted a follow-up sensitivity analysis to predict survival in individuals who provided CMI data on at least one occasion. Results (reported in section S4 of the online supplemental materials) showed that risk factors identified as most influential in the original analysis remained so, with only minor changes in order of importance. An exception to this outcome was that years smoking dropped in importance from position three in the full sample to position nine in the CMI sample—probably because smokers were more likely to drop out of the study early-on (smokers comprised 13.5% of CMI participants vs. 16.2% in the broader participant pool).

In short, processing speed and subjective health status appeared as key risk factors in both analyses. Specific medical risk factors—in particular cardiovascular symptoms (which we hypothesized to be key to risk prediction)—appeared to play less of a role than expected. It may be that these specific health markers (e.g., difficulty breathing, blood pressure, chest pain) are of greater importance for predicting mortality risk in populations with more sharply declining health (e.g., smokers). Further research is needed to explore this possibility.

## Conclusions

To address the needs of an aging global population, it will be necessary to account for numerous morbidity and mortality risk factors, such as demographic variables, health conditions, functional capacities, mental abilities, and social support (Ocampo, 2010). To our knowledge, the current work represents the most comprehensive account to date, in terms of both the life spheres investigated and the statistical procedures adopted, of the comparative and combined influence of these diverse risk factors (65 in total) on mortality outcomes in middle-aged and older adults. Our findings showed that two psychological variables, subjective health and processing speed, were better indicators of mortality risk than nearly all of the other included predictors. This information can be obtained with relatively little effort or cost and—given the tractability of these measures in different cultural contexts (e.g., Cores et al., 2015; French et al., 2012)—may prove expedient in screening for elevated mortality risk in diverse human populations.

### **Author Contributions**

P. Rabbitt developed the concept and design for the broader research project from which stems the current study. All authors contributed to the concept for the current study. P. Rabbitt oversaw data collection. S. Aichele performed data analysis and interpretation under the supervision of P. Ghisletta. S. Aichele drafted the manuscript, and P. Rabbitt and P. Ghisletta provided critical edits. All authors approved the final version of the manuscript.

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### Recommended Readings

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*A review of studies of cognitive performance and mortality within samples of patients suffering from stroke, cancer, or coronary heart disease.*

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*An broad overview of the field of cognitive epidemiology.*

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*A literature review and discussion of the theoretical determinants, related outcomes, and utility of self-rated health in elderly adults.*

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*A review of health and medical risk factors in elderly populations as rationale for inclusion of these variables in studies of cognitive aging.*