Research Article



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 6,203 individuals ranging in age from 41 to 96 years at initial assessment, we evaluated the relative and combined influence of 65 mortality risk factors, which included sociodemographic variables, lifestyle attributes, medical indices, and multiple cognitive abilities. Reductions in mortality risk were most associated with higher self-rated health, female gender, fewer years as a smoker, and smaller decrements in processing speed with age. Thus, two psychological variables—subjective health status and processing speed—were among the top predictors of survival. We suggest that these psychological attributes, unlike risk factors that are more narrowly defined, reflect (and are 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

Received 6/2/15; Revision accepted 12/21/15

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 wellbeing 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 socioeconomic 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 among 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

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Stephen Aichele, Faculty of Psychology and Educational Sciences, University of Geneva (Uni-Mail), Boulevard du Pont d'Arve 40, 1205 Geneva, Switzerland E-mail: stephen.aichele@unige.ch 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, socioeconomic status, smoking, pulse rate, blood glucose and cholesterol levels) as predictors of 15-year survival rates in a group of 4,166 male U.S. veterans of the Vietnam War. 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 high-density lipoprotein cholesterol. In a second study, Roberts, Der, Deary, and Batty (2009) assessed the relative influence of choice reaction time, psychological distress, lifestyle, and physical health variables on mortality risk in a sample of 5,606 Scottish men and women (age range = 18-94 years). In analyses conducted independently by predictor and adjusted for age, gender, and socioeconomic status, choice reaction time was stronger than all other risk factors except for smoking and systolic blood pressure. However, there was no follow-up analysis to determine whether choice reaction time remained influential after mutual adjustment with other risk factors.

The literature currently lacks studies in which baseline levels and changes with age 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 6,203 individuals (age range at initial assessment = 41–96 years; Rabbitt et al., 2004). MLSC data span a period of 29 years (i.e., from study inception in 1983 to the most recent update of survival information in 2012). Cognitive abilities were assessed on four occasions spaced at 4-year intervals. Previous MLSC analyses have examined relations between cognition and survival (see Aichele et al., 2015), but this is the first analysis of MLSC data 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 or 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 subsamples of observations. RFSA extends this singletree 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 reselected at multiple nodes in that structure, RFSA estimation implicitly adjusts for all possible linear, nonlinear, and higher-order interaction effects between variables. Second, built-in crossvalidation protects against multicollinearity (i.e., strongly overlapping predictive information) and model overfit (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 interpretation of effect sizes 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 et al., 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.

Method

Participants

These analyses used data from MLSC participants who completed one or more cognitive assessments (N = 6,203). Demographic variables were as follows: (a)

chronological age at induction into the study, (b) gender, (c) city of residence (Newcastle upon Tyne or Manchester, United Kingdom), (d) study cohort by year of entry (1983–1993), (e) socioeconomic advantage (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; those with mild, correctable sensory handicaps were assessed with their spectacles or hearing aids in place. Mortality information (dates and proximate causes for all deaths between 1983, when the study began, and August 2012, the most recent update) was obtained from a search of death certificates performed by Her Majesty's General Registry Office.

Cognitive abilities

Our cognitive-performance variables were baseline levels (intercepts) and changes with age (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 4-year intervals during a 12-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 predictors (i.e., intercepts centered at age 70, slopes spanning participant ages of 42–97 years) are described at length in Aichele et al. (2015). Thus, we provide only a short description here.

Cognitive tasks were selected on the basis that they were appropriate for assessment of cognitive change in adult and older samples according to life-span developmental theory (Baltes, Lindenberger, & Staudinger, 2006), were well-known and documented in the empirical literature, and 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 vocabulary scale (Wechsler, 1986). Fluid intelligence was assessed by the Heim (1970) AH4-1 and AH4-2 tasks (logic, arithmetic, number series, and 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 **Table 1.** Characteristics of the Sample (N = 6,203)

Variable	Value
Age at induction into the study (years)	<i>M</i> = 64.7, range = 41.0–93.0
Deceased (<i>n</i>)	4,484 (72.3%)
Age at death (years)	M = 83.5, range = 52.5–108.0
Women (<i>n</i>)	4,379 (70.6%)
Newcastle residents (n)	3,384 (54.5%)
Occupational class	
Professional	289 (4.7%)
Intermediate	1,961 (31.6%)
Skilled (nonmanual)	1,660 (26.8%)
Skilled (manual)	1,342 (21.6%)
Partly skilled	456 (7.4%)
Unskilled	52 (0.8%)
Unknown	443 (7.1%)
Marital status (n)	
Married	3,313 (53.4%)
Single	484 (7.8%)
Widowed (not remarried)	1,484 (23.9%)
Divorced (not remarried)	327 (5.3%)
Separated	66 (1.1%)
Unknown	529 (8.5%)
Number of persons in the home	M = 1.9, SD = 1.0
Number of children	M = 1.9, SD = 1.4
Smokers (<i>n</i>)	1,006 (16.2%)
Time smoking (years)	M = 17.1, SD = 18.3
Alcohol drinkers (<i>n</i>)	4,051 (65.3%)
Time drinking alcohol (years)	M = 29.4, SD = 18.0
Alcohol consumption (units/ day)	M = 2.0, SD = 1.7

Note: All information was obtained from participants at their induction into the study, except for death information, which was last updated in 2012 (see Method section). One unit of alcohol is equivalent to 10 ml of pure alcohol.

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) alphabetcoding 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 (linear slopes) in these factor scores. Thus, we obtained variables corresponding to baseline performance level (centered at age 70 years, approximately the median participant age) and change in performance (spanning the range of participants' ages at assessment, 42–97 years) for each cognitive domain. The statistical fit values for all models were good to excellent.

The resulting variables are summarized in Table 2. Note that estimates are given in standardized units scaled per decade (e.g., there is a -0.49-SD change in processing speed per decade of life). On average, cognitive performance decreased with age (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).

Daily-life measures

At recruitment and approximately 3 and 6 years after recruitment, 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).

As described in Sections S1 and S2 of the Supplemental Material available online, we used factor analysis to reduce the 26 variables subsumed by leisure activities and daily-life activities (see last paragraph) to three latent variables: Difficulty Performing Housework, Impaired Physical Mobility, and Leisure Activity. In total, then, we used 11 daily-life variables in our analyses. We used multilevel growth models (see Section S3 of the Supplemental Material) to derive individual scores of baseline performance (intercepts at age 70) and changes with age (linear slopes across participant ages at daily-life variable 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 with age (negative linear slopes). Use of prescribed medications, Difficulty Performing Housework, and Leisure Activity increased with age. Given the relatively older participant pool (mean age \approx 70 years), increases in Leisure Activity may reflect decreased work commitments and reorientation 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.

Cornell Medical Index

Starting in 1993 (10 years after study inception), participants completed the Cornell Medical Index (CMI; Brodman, Erdmann, & Wolff, 1949), which was thereafter administered on three separate occasions at 3- to 6-year intervals. 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 through L relate to physical disorders, and sections M through R correspond to psychiatric or psychological problems. Note that data from CMI index D is here subdivided into D1: teeth and D2: gastrointestinal, liver.

In a previously published analysis of two subgroups of MLSC participants (n = 101, n = 88), Pendleton et al. (2004) validated diagnostic outcomes that had been derived from CMI scores against corresponding diagnostic outcomes from structured medical assessments conducted

	Intercept (at age 70)		Liı (cha		
Variable	Mean	95% CI	Mean	95% CI	r(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

Table 2. Summary of Cognitive Performance

Note: All estimates are in standardized units. r(I,S) = correlation between intercept and linear slope; 95% CI = 95% confidence interval.

	Interce	ept (at age 70)	Linear slope (change/decade)			
Variable	Mean	95% CI Mean		95% CI	r(I,S)	
Subjective health ^{a,b}	3.77	[3.66, 3.89]	-0.20	[-0.39, -0.02]	06	
Prescribed medications ^b	1.75	[1.40, 2.10]	0.97	[0.16, 1.78]	.34	
Sleep (hours/night) ^b	6.69	[6.46, 6.92]	-0.40	[-0.81, 0.01]	.19	
Awakenings (number/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 ^{b,c}	-0.12	[-0.27, 0.03]	0.65	[0.37, 0.92]	.39	
Impaired Physical Mobility ^c	-0.02	[-0.52, 0.47]	0.62	[-0.18, 1.42]	.14	
Leisure Activity ^{b,c}	-0.22	[-0.41, -0.02]	0.79	[0.21, 1.38]	.50	
Social interactions (number/week)						
Casual contacts	61.27	[48.98, 73.56]		_	_	
Short conversations	41.93	[26.15, 57.71]		_	_	
Long conversations	19.75	[14.66, 24.83]	—			

Table 3. Summary of Daily-Life Measures

Note: A dash (—) indicates that linear slope did not improve model fit and hence was excluded in the model from which parameter estimates were obtained. r(I,S) = correlation between intercept and linear slope; 95% CI = 95% confidence interval.

^aEstimates are on a scale from 1 (*worst*) to 5 (*best*). ^bFor these variables, the random effects for linear slopes were significant. ^cFor these variables, standardized estimates are reported.

by two experienced physicians. The structured medical assessments were based on a modified version of the SENIEUR 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 from 89% to 99% across conditions.

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 change with age (across participant ages at CMI assessments, 47–98 years) in each CMI domain using multilevel growth models (see Section S3 of the Supplemental Material).

Summary statistics for these variables are shown in Table 4. Increases in symptoms with age were observed in five specific areas: A: eyes and ears, C: cardiovascular, D1: teeth, I: fatigue, and J: frequency of illness. No age-related 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 with age). Between-person variation (random effects) in linear slopes was significant for five indices: J: frequency of illness, L: addiction, O: anxiety, total physical symptoms (A–L), and total mood or feeling patterns (M–R).

Attrition and missing data

No stopping rule for data collection 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. The number of participants, their average age, and the age range of participants at each assessment are shown in Table 5. Participant attrition because of death or dropout from the study appears to have been the primary source of missing data, indicated by rapidly declining numbers of participants across subsequent assessments. MLSC participants who voluntarily withdrew between 1983 and 1994 were retrospectively identified as older, being from less advantaged socioeconomic groups, and having lower scores on all cognitive tests than individuals who continued to participate. In addition, 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 relative to survivors (Rabbitt et al., 2004).

Nonignorable missingness as a result of attrition is a common occurrence in longitudinal, epidemiological studies (Diggle, Heagerty, Liang, & Zeger, 2002). Methods for handling missing data that exclude incomplete observations (e.g., list-wise deletion) are ill suited to such studies because outcomes based only on complete observations are likely to be biased toward healthier, higher-performing individuals. Therefore, to account for missing data (Schafer & Graham, 2002), we used multiple imputation, which derives estimates for missing

	Interce	pt (at age 70)	Lir (char		
Domain	Mean	95% CI	Mean	95% CI	r(I,S)
Physical conditions					
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 of illness ^a	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 ^a	16.86	[14.64, 19.07]	-1.75	[-4.25, 0.75]	74
Total ^a	13.16	[12.42, 13.90]	1.17	[0.41, 1.92]	75
Mood and feeling patterns					
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 ^a	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 ^a	11.29	[9.45, 13.12]	0.89	[-0.99, 2.77]	77

Table 4.	Summary	of Patho	ological	Symptoms
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Note: Participants' scores for Cornell Medical Index (CMI) symptoms were derived as percentages within each CMI domain (e.g., number of observed fatigue symptoms divided by total number of fatigue

symptoms). Thus, the estimates in this table are scaled as percentage of manifest symptoms at age

70 (intercept) and as change in percentage of manifest symptoms per decade (linear slope). r(I,S) =

correlation between intercept and linear slope; 95% CI = 95% confidence interval.

^aFor these variables, the random effects for linear slopes were significant.

values on the basis of individuals' observed data and adds 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 mice package (Van Buuren & Groothuis-Oudshoorn, 2011) for the R software environment (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 data sets, and results were then aggregated across these analyses to derive final summary statistics, as recommended by Rubin (1987).

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 measures (16), and intercepts and slopes for each of the pathological domains in the CMI (26). Survival analyses were conducted independently for each of the 30 imputed data sets (see Method), and results were combined by standard procedures (Rubin, 1987). Individuals for whom survival information was missing before data imputation (n =245, or 4% of participants) were removed from the survival analyses. For longitudinal variables (cognitive performance, daily-life measures, 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: RFSA and Cox PH. The data were randomly divided into two subsamples so that each of the survival analyses could be conducted independently.

Table 5. Sample for Each Measure and Assessme	nt
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	Assessment					
Measure and statistic	1	2	3	4		
Crystallized Intelligence						
n	6,181	3,875	2,190	1,113		
Mean age (years)	65.7	69.2	72.5	75.5		
Age range (years)	43-93	47-92	52-93	54–97		
Fluid Intelligence						
n	6,172	3,874	2,188	1,112		
Mean age (years)	65.7	69.2	72.5	75.5		
Age range (years)	43-93	47-92	52-93	54–97		
Verbal Memory						
n	5,510	3,565	1,861	1,067		
Mean age (years)	65.8	69.1	72.5	75.5		
Age range (years)	43-93	47-92	52-93	54–97		
Visual Memory						
n	5,510	3,564	1,858	1,065		
Mean age (years)	66.5	70.1	73.6	75.7		
Age range (years)	43-95	47-92	52-94	54–97		
Processing Speed						
n	4,288	2,435	1,184	487		
Mean age (years)	67.7	72.5	75.8	77.1		
Age range (years)	42-96	47-95	51-96	54-95		
Daily-life measures						
n	5,683	3,000	580	_		
Mean age (years)	65.1	67.6	75.7	_		
Age range (years)	41-95	51-92	53-93	_		
Cornell Medical Index						
п	2,514	1,821	605	748		
Mean age (years)	71.9	75.4	76.3	80.8		
Age range (years)	47-94	51–97	54-97	68–98		

Note: The timing of assessments differed by measure (e.g., for the first study cohort, the first assessment of daily-life measures occurred in 1983 and 1984, whereas the first administration of the Cornell Medical Index occurred in 1993). Thus, differences in n across measures (i.e., within columns, across rows) reflect timing-dependent differences in the availability of participants. Testing intervals for the measures are described in the corresponding Method subsections.

RFSA. A *survival tree* is the result of 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 stepwise approaches in accounting for all possible linear and nonlinear 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, and Rabbitt (2014), a single survival tree may also overfit 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 (a) from randomly sampled subsets of observations and (b) with predictors at a given node selected from a randomly sampled subset of the total variables. This procedure provides a built-in method for cross-validation (using bootstrapping or *bagging*) and is robust to the problems of overfitting to the sample and overfitting to the variables.

The relative influence of each predictor (i.e., *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 a variable is randomly permuted (to break its association with the outcome) averaged over all trees (Strobl et al., 2009). In other words, this method compares observed and 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 software environment (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. We estimated predictors' relative importance as a percentage of the maximum observed permutation accuracy across predictors. Results obtained from the 30 imputed data sets were then aggregated (Rubin, 1987).

Cox PH survival models. We also conducted Cox PH, a more conventional survival analysis (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, or change in model fit ($\Delta \chi^2$) per change in degrees of freedom. Likelihood-ratio tests were applied sequentially, starting with the full model (i.e., all predictors included) and removing variables in descending order according to their relative importance, as determined from the RFSA. We calculated standardized effect-size estimates for each

predictor (i.e., percentage change in mortality risk per standard unit change in the given predictor). This analysis was carried out using the survival package (Therneau, 2014) in the R software environment.

Results

RFSA

Predictive error rates for the random forests converged to minimum values (mean squared error ranging from 0.35 to 0.36) after approximately 150 trees had been generated.¹ Predictors with estimated relative importance ($I_{\rm rel}$) greater than .25 are listed in Table 6. Thirteen of the original 65 predictors met this criterion. Of these variables, intercept of subjective health ($I_{\rm rel} = .77$) was the strongest predictor, followed by gender ($I_{\rm rel} = .76$), years smoking ($I_{\rm rel} = .68$), and linear slope of Processing Speed ($I_{\rm rel} =$.59). Note that relative importance 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 relative importance 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 relative importance of at least .25 were the linear slope of Fluid Intelligence and the intercept of Processing Speed. 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 daily-life measures and CMI predictors included the linear slope of Frequency of illness, the intercept and the linear slope of Difficulty Performing Housework, the intercept of Leisure Activity, and the intercept of number of prescribed medications.

Cox PH 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 both notable changes in model fit ($\Delta \chi^2$) and significant change in hazard ratios (i.e., 95% confidence intervals for percentage change in hazard ratio that did not include 0). These variables, in

Table 6. Comparative Influence of the Predictors of Mortality Risk

	RFSA: relative		Cox PH			
		importance		Change in	hazard ratio	
Variable	Mean	95% CI	$\Delta\chi^2$	Mean percentage	95% CI	
Intercept of subjective health ^a	.77	[.69, .85]	144	-16.2	[-28.7, -3.7]	
Gender (female) ^a	.76	[.68, .84]	76	-33.0	[-44.4, -21.6]	
Years smoking ^a	.68	[.61, .75]	36	11.4	[4.9, 17.9]	
Linear slope of Processing Speed ^a	.59	[.51, .67]	66	-10.9	[-16.8, -5.0]	
Linear slope of J: frequency of illness (CMI)	.42	[.30, .54]	21	7.7	[-2.7, 18.1]	
Intercept of Difficulty Performing Housework	.37	[.27, .47]	61	6.8	[-10.1, 23.7]	
Smoker (yes)	.34	[.30, .38]	15	13.9	[-3.3, 31.1]	
Intercept of Leisure Activity	.33	[.27, .39]	58	8.6	[-4.9, 22.1]	
Linear slope of Fluid Intelligence	.32	[.26, .38]	9	-5.9	[-10.6, -1.2]	
Intercept of prescribed medications	.32	[.20, .44]	28	8.6	[-10.0, 27.2]	
Linear slope of Difficulty Performing Housework	.29	[.17, .41]	8	1.6	[-22.7, 25.9]	
Intercept of Processing Speed	.29	[.23, .35]	7	-7.8	[-14.1, -1.5]	
Age at induction into study ^a	.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; the data were randomly divided into two subsamples ($n \cong 3,000$) so that each of the survival analyses could be conducted independently. *Relative importance* refers to relative importance in predicting mortality risk. $\Delta \chi^2$ indicates the improvement in the fit of the Cox PH model with the inclusion of each predictor; more influential variables have higher values. Cox PH estimates of percentage change in the hazard ratio are scaled in standardized units of the corresponding predictor variable (e.g., an individual whose number of years smoking was 1 *SD* higher than the group mean would, on average, have an increased mortality risk of 11.4%). CMI = Cornell Medical Index.

^aFor these variables, $\Delta \chi^2$ was influential and 95% CI for percentage change in hazard ratio was nonnull.

descending order of importance, according to change in model fit, were the intercept of subjective health, gender, the linear slope of Processing Speed, age at induction into the study, and years smoking. Of these variables, only years smoking was related to increased mortality risk (increase of 1 SD in lifetime smoking increases risk by +11.4%). Better overall subjective health (increase of 1 SD in health = decreases risk by 16.2%), being a woman (increase of 1 SD decreases risk by -33.0%), and smaller decrements with age (more positive slopes) in Processing Speed (increase of 1 SD decreases risk by 10.9%) 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 of .59 or higher.

Discussion

In a 29-year study of 6,203 individuals, ages 41 to 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 decrements in processing speed with age 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 changes in processing speed with age—were among the top survival predictors (Fig. 1) and that they accounted for substantial variation in mortality risk even in the presence of well-established risk factors (e.g., male gender, smoking).

Subjective health status has been shown previously 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 other studies have found this not to be the case (e.g., Heistaro, Jousilahti, Lahelma, Vartiainen, & Puska, 2001). In addition, severe (but not

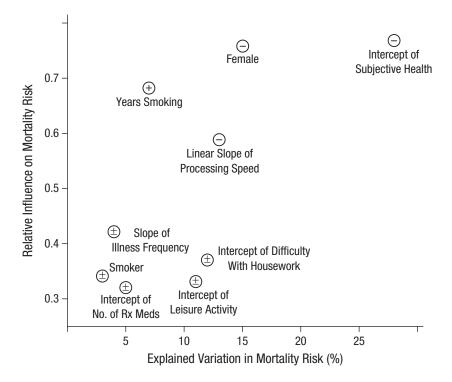


Fig. 1. The nine most influential mortality risk factors. Relative influence on mortality risk (as determined by random forest survival analysis) is graphed as a function of the percentage of explained variation in mortality risk (as determined by Cox proportional hazard analysis). Only variables with relative importance greater than .30 and associated with improved model fit of at least 15 are shown (see Table 6). The symbols indicate the factors that significantly increase mortality risk (+), significantly decrease mortality risk (–), or do not change mortality risk significantly (±). Rx Meds = prescription medications.

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 sociodemographic, 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 (compared with 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. Decrements in processing speed have been linked to cardiovascular disease (Bosworth & Siegler, 2002) and, in a subsample of participants from the present study, to the prevalence of cerebral white-matter lesions (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 with established demographic, lifestyle, and medical risk factors: Roberts et al. (2009) found that, after adjusting for age and gender, processing speed (choice reaction time) predicted mortality risk more strongly than did physical activity, resting heart rate, psychological distress, waist-to-hip ratio, weekly alcohol consumption, body mass index, and socioeconomic 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-theart 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, gender, and smoking were stronger).

We further note that smaller decrements in processing speed with age, 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)—although we cannot state this definitively because 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 CMI, which for most participants was administered several years after initial assessment of cognitive and lifestyle variables. Individuals with CMI data were therefore likely to represent a slightly healthier population than people who left the study before CMI assessment, as confirmed by median age at death in each subsample (85.4 years vs. 83.6 years, respectively). Although we used all available information to impute missing CMI values (see Method), the accuracy of the 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 Supplemental Material) showed that risk factors identified as most influential in the original analysis remained so, and there were 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 accounted for 13.5% of CMI participants and 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

Addressing the needs of an aging global population will require accounting 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 the current study stems. 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.

Acknowledgments

We thank Phillip R. Shaver for help in editing this manuscript.

Declaration of Conflicting Interests

The authors declared that they had no conflicts of interest with respect to their authorship or the publication of this article.

Funding

This work was supported by Swiss National Science Foundation Grant 100014_146535.

Supplemental Material

Additional supporting information can be found at http://pss .sagepub.com/content/by/supplemental-data

Note

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

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