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Batterham, PJ, Bunce, D, MacKinnon, A et al. (1 more author) (2013) Intra-individual reaction time variability and all-cause mortality over 17 years: A community-based cohort study. Age and Ageing, 43 (1). 84 - 90. ISSN 0002-0729

https://doi.org/10.1093/ageing/aft116

Appears in Age and Ageing (Accepted version)

Intraindividual reaction time variability and all-cause mortality over 17 years: A community-based cohort study

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Running head: RT variability and all-cause mortality

Word count: 2824

Abstract

Background: Very few studies have examined the association between intraindividual reaction time variability and subsequent mortality. Furthermore, the ability of simple measures of variability to predict mortality has not been compared to more complex measures.

Method: A prospective cohort study of 896 community-based Australian adults aged 70+ were interviewed up to four times from 1990-2002, with vital status assessed until June 2007. From this cohort, 770-790 participants were included in Cox proportional hazards regression models of survival. Vital status and time in study were used to conduct survival analyses. Mean reaction time and three measures of intraindividual reaction time variability were calculated separately across 20 trials of simple and choice reaction time tasks. Models were adjusted for a range of demographic, physical health and mental health measures.

Results: Greater intraindividual simple reaction time variability, as assessed by the raw standard deviation (raw SD), coefficient of variation (CV) or the intraindividual standard deviation (ISD), was strongly associated with an increased hazard of all-cause mortality in adjusted Cox regression models. Mean reaction time had no significant association with mortality.

Conclusion: Intraindividual variability in simple reaction time appears to have a robust association with mortality over 17 years. Health professionals such as neuropsychologists may benefit in their detection of neuropathology by supplementing neuropsychiatric testing with the straightforward process of testing simple reaction time and calculating raw SD or CV.

Keywords: all-cause mortality, reaction time, intraindividual variability, coefficient of variation, intraindividual standard deviation

The possibility that within-person reaction time (RT) variability for a given cognitive task is sensitive to neurobiological disturbance has created considerable empirical and clinical research interest, with behavioural investigations confirming that increased intraindividual RT variability (IIV) is associated with traumatic brain injury [1], epilepsy [2] and mild cognitive impairment or mild dementia [3, 4]. Greater IIV is also associated with older age [5, 6], mild psychopathology [7, 8], and, importantly from the present perspective, impending mortality [9]. Additionally, neuroimaging shows associations of IIV with brain structures [10-13] and function [14, 15]. Moreover, work also implicates involvement of striatal dopamine D2 receptor binding [16], a finding that is consistent with the possibility that IIV reflects neural noise in the brain [17]. Previous research on the relationship between cognition and mortality has indicated that poorer cognitive performance, particularly in the memory and processing speed domains, is associated with increased mortality [18-20]. However, other than work by Macdonald et al [9], there has been little examination of the impact of within-person performance variability on mortality. The present study aimed to address this shortfall and assess whether all-cause mortality over 17 years was predicted by mean RT and two measures of IIV in a community-based cohort of older adults. A standard measure of IIV, the intraindividual SD (ISD), was compared to two simpler measures, the raw standard deviation (raw SD) and the coefficient of variation (CV), which may be easily derived in the clinical setting. It was hypothesized that greater IIV would be associated with increased hazard for mortality, due to its sensitivity to neurobiological disturbance, while mean RT would exhibit a weaker relationship with mortality.

Method

Participants

The Canberra Longitudinal Study is an epidemiological survey of mental health and cognitive functioning in older people. Participants were sampled from the compulsory electoral roll for the cities of Canberra and Queanbeyan, Australia. Individuals sampled from the electoral roll were sent a letter inviting participation in the survey and then approached at home by a trained interviewer. The purposes and procedures of the study were explained before informed consent was obtained. Thirty-one per cent of those approached refused to participate. This refusal rate is similar to those obtained in other community samples [e.g., 21, 22, 23]. Participants were 896 community-dwelling adults (456 men and 440 women) aged 70-97 at the baseline assessment, with the sample stratified by age and gender. Participants were followed up every four years, with up to four assessments administered between 1990 and 2002. Approval for the research was obtained from the Ethics in Human Experimentation Committee of The Australian National University. Further details of the study design are provided by Christensen et al. [24].

Of the original sample of 896 participants, 185 (20.6%) were deceased by four years, 363 (40.5%) were deceased by eight years, and 544 (60.7%) were deceased by 12 years. Vital status was collected until June 2007. At this time, 687 (76.7%) participants were deceased. Of the surviving participants at each measurement occasion, response rates of 85.9%, 78.9% and 78.9% were obtained for the three follow-up interviews.

Procedure

Interviews were conducted by trained professional interviewers, who administered a comprehensive survey and conducted physical assessments. Baseline assessments lasted

87 approximately two hours, and covered background characteristics, physical health and
88 disease status, mental health status and cognitive performance.
89
90 *Measures*
91 Vital status and date of death were established using the National Death Index, a
92 register of all deaths in Australia based on data collected by the Registrars of Births, Deaths
93 and Marriages in each State and Territory in Australia. Additional sources of death reporting
94 were used to confirm the validity of the mortality status data, including contacting relatives
95 and searching death notices in the local newspaper. Vital status was followed for up to 17
96 years, from the start of baseline interviews in September, 1990 until June 30, 2007.
97 In addition to measures of mean RT and RT variability described below, models were
98 adjusted for a number of baseline risk factors for mortality. These included age, gender,
99 marital status and number of years of education. Presence of possible preclinical dementia
100 was determined using the Mini-Mental State Examination (MMSE) [25], based on scoring
101 ≤24 out of 30 at any of the four assessments. Given that very few participants met dementia
102 criteria early in the study, this liberal criterion evaluated over an extended period was used to
103 ensure that presence of preclinical cognitive decline could be adequately identified. Physical
104 health measures included smoking status (never, previous or current), Activities of Daily
105 Living (ADL, a scale ranging from 0 to 22), disease count (self-reported history from a list of
106 14 diseases), self-reported use of anti-hypertensive medication and grip strength (measured in
107 kilograms using a hand dynamometer). The ADL scale assessed the presence or extent of
108 physical disability [26]. Grip strength is a reliable and objective indicator of physical
109 functioning in late life [27] that has been shown to have strong associations with mortality
110 [18]. Mental health was adjusted for using the Goldberg Depression and Anxiety Scales [28]
111 to assess the number of depression and anxiety symptoms experienced in the two weeks prior

to the interview. These scales consist of nine binary items assessing symptoms of depression and anxiety, with scores on each scale reflecting a symptom count ranging from 0 to 9.

Reaction time assessment and computation of IIV measures

Simple and choice RT were each assessed over 20 trials. The simple RT trials consisted of ten left hand stimuli followed by ten right hand stimuli. Binary choice reaction time trials consisted of a random combination of left- and right-hand stimuli. The stimuli were two lights controlled by the interviewer away from the participant's view. Participants pressed one of two buttons in response to the corresponding light (left or right). The interviewer said "ready" before turning on the first light, with interstimulus intervals ranging from 0.5 to 2.0s. Participants were given 5 practice trials before the left hand simple RT stimuli, 4 practice trials before the 10 right hand simple RT stimuli trials and 4 practice trials before the 20 choice RT stimuli trials. Further detail of the RT protocol is provided by Christensen et al [29]. Data preparation for the computation of IIV measures followed procedures commonly used elsewhere (e.g., [30]). Initially, RTs for incorrect trials were removed together with unusually fast responses (<150 ms) and those greater than the age group mean + 3 age groups SDs. Age group means and SDs were computed for age ranges 70 to 75, 76 to 80, 81 to 85 years, and 86 years and older. These exclusions resulted in the loss < 2.1% of trials across the sample. *M*RT and three commonly-used measures of IIV were then computed. Specifically, the raw SD was simply the intraindividual *SD* across the 20 trials. The CV was computed as the raw intraindividual *SD* divided by the raw intraindividual *M* RT. A regression procedure was used to compute the ISD, where residuals were saved having partialled out categorical effects for trial (i.e., time-on-task effects), age group, and their interaction. The residuals obtained for this ISD were then standardized. The process of calculating CV and ISD was conducted separately for simple and choice reaction time data.

Analysis

Sample characteristics were tabulated based on vital status at the end of the study period. Cox proportional hazards regression models were used to assess the relationship of *M*RT, CV and ISD with all-cause mortality. Each RT measure was entered into a separate model, resulting in six models (three measures each for simple and choice RT). The models were estimated both with and without adjustment for mortality risk factors. Models that included both the effects of *M*RT and either CV or ISD were also estimated. The sample size was 790 for the simple RT models and 770 for the choice RT models, due to participants with missing RT trials [simple missing: 71 (7.9%); choice missing: 94, (10.5%)] and missingness on other independent variables (61, 6.8%). In all models, the three IIV measures were standardised (to mean = 0, sd = 1) to enable comparison between models. All analyses were conducted in SPSS version 20 (IBM Corporation, 2011).

Results

Sample characteristics based on vital status at June 2007 are displayed in Table 1. All variables in the table were assessed during the first wave, with the exception of possible dementia which was assessed as MMSE ≤24 at any wave. Participants who died in the follow-up period had significantly slower mean RT and greater RT variability than those who survived. This relationship was consistent across all measures of RT and for both simple and choice RT. Decedents were also older, had greater physical impairment, reported more diseases, had weaker grip strength, were more depressed, and were more likely to be male, meet criteria for possible dementia, or smoke. There were no significant effects of education, anxiety, marital status or medication use on mortality. Simple *M*RT ranged from 1.8s to 9.7s, choice *M*RT ranged from 2.2 to 9.3s, simple raw SD ranged from 9.9ms to 244.0ms, choice

raw SD ranged from 21.2ms to 188.2ms, simple CV ranged from 0.04 to 0.58, choice CV ranged from 0.05 to 0.48. Simple ISD was a standardised score ranging from -1.34 to 5.19, with choice ISD ranging from -1.68 to 4.78.

Table 2 shows the unadjusted and adjusted relationships between *M*RT, CV and ISD with all-cause mortality, for both simple and choice RT tasks. The third models for CV and ISD also added adjustment for *M*RT, along with other independent variables. All estimates come from Cox proportional hazard regression models, which take into account time to death and censoring for those participants who survived until the end of follow-up. The unadjusted models included only the effect of a single RT variable (*M*RT, CV or ISD) alone. Adjusted analyses were separately estimated for each of the RT variables, with adjustment for all of the variables shown in Table 3. The models that added adjustment for *M*RT were included to account for the correlations between *M*RT and raw SD (r_{simple} = 0.69, r_{choice} = 0.50), *M*RT and CV (r_{simple} = 0.24, r_{choice} = -0.11), and *M*RT and ISD (r_{simple} = 0.71, r_{choice} = 0.52).

The significant univariate hazard ratios in Table 2 indicate that a one sd increase in *M*RT was associated with 15% increased hazard of death for simple RT and 18% for choice RT. Increased RT variability, measured both by CV and ISD, was also associated with significantly increased hazard of death. Table 2 also indicates that mean RT was not significantly associated with mortality after accounting for the effects of gender, age, education, marital status, possible dementia, physical health and mental health. Table 3 provides details of the fully adjusted Cox proportional hazard regression models. There was very little attenuation of the simple RT variability measures, with all three IIV measures remaining significantly associated with all-cause mortality after adjustment. There was greater attenuation of the choice RT effects, with all three IIV effects becoming non-significant after adjustment for *M*RT and the assessed risk factors. The greater attenuation of choice RT measures was tested in three models (not displayed) that included (i) both simple

raw SD (*OR* = 1.13, *p* = 0.055) and choice raw SD (*OR* = 1.05, *p* = 0.316), (ii) both simple CV (*OR* = 1.12, *p* = 0.011) and choice CV (*OR* = 1.05, *p* = 0.328), and, (iii) both simple ISD (*OR* = 1.14, *p* = 0.037) and choice ISD (*OR* = 1.05, *p* = 0.307), along with adjustment for the variables listed in Table 3. Other consistent significant effects in the final Cox proportional hazards regression models replicated previous findings [18, 19]: male gender, older age, greater physical impairment, more diseases and weaker grip strength were associated with greater hazard of all-cause mortality.

Discussion

The present study broadly supports and extends the findings of Macdonald et al [9], with RT variability having a strong association with all-cause mortality in a community-based cohort of older adults. The findings also support those of Shipley et al [31] and Deary and Der [32], who reported comparable results in two population-based cohorts using the raw intraindividual standard deviation. Although mean RT measures exhibited univariate relationships with mortality, these effects were explained by age, gender and poor physical health. Variability on the simple RT task had the most robust association with all-cause mortality, with the three types of RT variability measures showing comparable relationships with outcome up to 17 years in the future.

These findings have important clinical implications. Although computation of ISDs may be subject to practical difficulties in clinical contexts, it is relatively straightforward for the clinician to administer a series of simple RT trials and calculate the intraindividual mean and standard deviation to obtain either the raw SD or the CV. There is no requirement to use normative regression processes to obtain standardised ISD scores. The raw SD and CV for simple RT are clearly metrics that have robust relationships with subsequent mortality. Importantly, our findings suggest similar predictive utility for all three IIV measures. This

relationship is likely to be reflected in a range of other outcomes, including presence of mild psychopathology [7, 8] and mild cognitive impairment or mild dementia [3, 4]. Further research comparing the predictive power of raw RT, CV and ISD on a range of psycho- and neuro-pathological outcomes may advance and inform the clinical utility of the simpler metrics. The raw SD and CV measures may supplement other neuropsychiatric tests in assessing risk of pathological outcomes. By illustration, an individual with simple RT CV of 0.35 would have 29% increased hazard of mortality compared to an individual with simple RT CV at the sample mean of 0.19 in the present cohort.

There are a number of possible explanations for the relationship between within-person RT variability and mortality. Increased IIV in late life is likely to be indicative of neurological dysfunction [33], which may arise from life-long accumulation of neurological insult and vascular events. This dysfunction may manifest in the form of increased neural "noise" arising from the reduced efficiency of the central nervous system generally, and neurotransmitter signalling in particular [17]. From a clinical perspective, therefore, our findings suggest that increased variability may mark neurobiological disturbance that accompanies impending mortality, and thereby may aid practitioner intervention.

As seen in the present analyses, markers for physiological integrity, including functional ability, disease count and grip strength, have strong associations with mortality and somewhat attenuate the effects of RT variability on mortality. However, our findings suggest that an independent relationship between RT variability and mortality remains. Additional research linking RT variability to direct markers of neurological dysfunction, and then linking specific neurological dysfunction to disease and terminal decline is needed. Furthermore, focused research is required to more explicitly test how the cascade of risk factors, from behavioural and biological influences, to subclinical and clinical disease, leads to mortality [34]. The finding that simple RT variability was more strongly predictive of

mortality than choice RT variability is also worth noting. Previous research has found that choice RT slows throughout adulthood, whereas simple RT begins to slow in the 50s [35]. Likewise, the effect of age on IIV has previously been shown to be stronger for simple RT than choice RT [6]. It is possible then that simple RT is more strongly influenced by age-related pathological states.

There were some limitations of the study. RT data from a single time point were used to predict mortality. It is not clear how changes in mean RT or RT variability over time might influence the findings. For example, participants may have had an aberrant result on the day of their interview due to illness or distraction. While this issue was partially addressed by careful cleaning of RT data, large sample size and adjustment for confounders, further study of changes in RT variability may shed light on the bases of the observed relationships. In addition, the examination of variability on a broader range of tasks, including verbal, numerical and memory tasks may better identify the pathways by which performance variability is associated with mortality. Likewise, additional assessment of health behaviours, cognitive performance, physical health and mental health may help to disentangle the pathways by which performance variability may lead to mortality.

In conclusion, the relationship between RT variability and all-cause mortality appears to be robust, even over extended time periods. The findings suggest that further understanding may be gained into the processes that lead to mortality through investigation of the neurobiological disturbances associated with increases in intraindividual variability. The relationship was most apparent for the simple RT task, and measures of RT variability that may be easily assessed. Simple RT variability, like other measures of health status, can be readily assessed using mobile and other portable devices by health professionals such as neuropsychologists. These tests seem to be as effective as more complex measures in

predicting subsequent mortality. By contrast, the link between mean RT and mortality may be explained by age, gender and physical health.

Acknowledgements / declaration of sources of funding

The Canberra Longitudinal Study was supported by the Australian National Health and Medical Research Council (NHMRC) Unit Grants 973301 and 933301 and NHMRC Program Grant 179805. PB is supported by NHMRC Early Career Fellowship 1035262, DB by a Leverhulme Research Fellowship (UK), and HC by NHMRC Senior Principal Research Fellowship 525411. The funding body had no input into the study or the paper.

References

1. Stuss, D.T., et al., *Characterization of stability of performance in patients with traumatic brain injury: Variability and consistency on reaction time tests.* Neuropsychology, 1994. **8**(3): p. 316.
2. Bruhn, P. and O.A. Parsons, *Reaction time variability in epileptic and brain-damaged patients.* Cortex, 1977. **13**(4): p. 373-84.
3. Bielak, A.A., et al., *Intraindividual variability in reaction time predicts cognitive outcomes 5 years later.* Neuropsychology, 2010. **24**(6): p. 731-41.
4. Hultsch, D.F., et al., *Intraindividual variability in cognitive performance in older adults: comparison of adults with mild dementia, adults with arthritis, and healthy adults.* Neuropsychology, 2000. **14**(4): p. 588-98.
5. Bunce, D., S.W. MacDonald, and D.F. Hultsch, *Inconsistency in serial choice decision and motor reaction times dissociate in younger and older adults.* Brain Cogn, 2004. **56**(3): p. 320-7.
6. Hultsch, D.F., S.W. MacDonald, and R.A. Dixon, *Variability in reaction time performance of younger and older adults.* J Gerontol B Psychol Sci Soc Sci, 2002. **57**(2): p. P101-15.
7. Bunce, D., R. Handley, and S.O. Gaines, Jr., *Depression, anxiety, and within-person variability in adults aged 18 to 85 years.* Psychol Aging, 2008. **23**(4): p. 848-58.
8. Bunce, D., et al., *Mental health and cognitive function in adults aged 18 to 92 years.* J Gerontol B Psychol Sci Soc Sci, 2008. **63**(2): p. P67-74.
9. Macdonald, S.W., D.F. Hultsch, and R.A. Dixon, *Predicting impending death: inconsistency in speed is a selective and early marker.* Psychol Aging, 2008. **23**(3): p. 595-607.

10. Bunce, D., et al., *Cognitive deficits are associated with frontal and temporal lobe white matter lesions in middle-aged adults living in the community.* PLoS One, 2010. **5**(10): p. e13567.
11. Bunce, D., et al., *White matter hyperintensities and within-person variability in community-dwelling adults aged 60-64 years.* Neuropsychologia, 2007. **45**(9): p. 2009-15.
12. Deary, I.J., et al., *White matter integrity and cognition in childhood and old age.* Neurology, 2006. **66**(4): p. 505-12.
13. Anstey, K.J., et al., *Corpus callosum size, reaction time speed and variability in mild cognitive disorders and in a normative sample.* Neuropsychologia, 2007. **45**(8): p. 1911-20.
14. Bellgrove, M.A., R. Hester, and H. Garavan, *The functional neuroanatomical correlates of response variability: evidence from a response inhibition task.* Neuropsychologia, 2004. **42**(14): p. 1910-6.
15. MacDonald, S.W., et al., *Increased response-time variability is associated with reduced inferior parietal activation during episodic recognition in aging.* J Cogn Neurosci, 2008. **20**(5): p. 779-86.
16. MacDonald, S.W., et al., *Extrastriatal dopamine D2 receptor binding modulates intraindividual variability in episodic recognition and executive functioning.* Neuropsychologia, 2009. **47**(11): p. 2299-304.
17. Li, S.C., U. Lindenberger, and S. Sikstrom, *Aging cognition: from neuromodulation to representation.* Trends Cogn Sci, 2001. **5**(11): p. 479-486.
18. Batterham, P.J., H. Christensen, and A.J. Mackinnon, *Fluid intelligence is independently associated with all-cause mortality over 17 years in an elderly*

community sample: An investigation of potential mechanisms. Intelligence, 2009. **37**(6): p. 551–560.

19. Batterham, P.J., A.J. Mackinnon, and H. Christensen, *The association between change in cognitive ability and cause-specific mortality in a community sample of older adults.* Psychol Aging, 2012. **27**(1): p. 229-36.

20. Sliwinski, M.J., et al., *Distinguishing preterminal and terminal cognitive decline.* European Psychologist, 2006. **11**(3): p. 172-181.

21. Deeg, D.J., et al., *Attrition in the Longitudinal Aging Study Amsterdam. The effect of differential inclusion in side studies.* J Clin Epidemiol, 2002. **55**(4): p. 319-28.

22. der Wiel, A.B., et al., *A high response is not essential to prevent selection bias: results from the Leiden 85-plus study.* J Clin Epidemiol, 2002. **55**(11): p. 1119-25.

23. Feldman, H.A., et al., *Age trends in the level of serum testosterone and other hormones in middle-aged men: longitudinal results from the Massachusetts male aging study.* J Clin Endocrinol Metab, 2002. **87**(2): p. 589-98.

24. Christensen, H., et al., *The Canberra Longitudinal Study: Design, aims, methodology, outcomes and recent empirical investigations.* Aging, Neuropsychology, and Cognition, 2004. **11**(2-3): p. 169-195.

25. Folstein, M.F., S.E. Folstein, and P.R. McHugh, *"Mini-mental state". A practical method for grading the cognitive state of patients for the clinician.* J Psychiatr Res, 1975. **12**(3): p. 189-98.

26. Christensen, H., et al., *The relationship between health and cognitive functioning in a sample of elderly people in the community.* Age and ageing, 1994. **23**(3): p. 204-12.

27. Frederiksen, H., et al., *Hand grip strength: a phenotype suitable for identifying genetic variants affecting mid- and late-life physical functioning.* Genet Epidemiol, 2002. **23**(2): p. 110-22.

28. Goldberg, D., et al., *Detecting anxiety and depression in general medical settings.* Bmj, 1988. **297**(6653): p. 897-9.

29. Christensen, H., et al., *Are changes in sensory disability, reaction time, and grip strength associated with changes in memory and crystallized Intelligence? A longitudinal analysis in an elderly community sample.* Gerontology, 2000. **46**(5): p. 276-92.

30. Hultsch, D.F., et al., *Intraindividual variability, cognition and aging*, in *The handbook of aging and cognition (3rd ed.)*, F.I.M. Craik and T.A. Salthouse, Editors. 2008, Psychology Press: New York. p. 491-556.

31. Shipley, B.A., et al., *Cognition and All-Cause Mortality Across the Entire Adult Age Range: Health and Lifestyle Survey.* Psychosomatic Medicine, 2006. **68**(1): p. 17-24.

32. Deary, I.J. and G. Der, *Reaction Time Explains IQ's Association With Death.* Psychol Sci, 2005. **16**(1): p. 64-69.

33. Strauss, E., et al., *Intraindividual variability in cognitive performance in three groups of older adults: cross-domain links to physical status and self-perceived affect and beliefs.* J Int Neuropsychol Soc, 2002. **8**(7): p. 893-906.

34. Schulz, R., R.A. Drayer, and B.L. Rollman, *Depression as a risk factor for non-suicide mortality in the elderly.* Biol Psychiatry, 2002. **52**(3): p. 205-25.

35. Der, G. and I.J. Deary, *Age and sex differences in reaction time in adulthood: results from the United Kingdom Health and Lifestyle Survey.* Psychol Aging, 2006. **21**(1): p. 62-73.

374 Table 1: Sample characteristics based on vital status after 17 years

		Living (n = 209)		Deceased (n = 687)			
	n	M	SD	M	SD	F	p
Simple RT – mean (ms)	825	282.38	86.65	303.27	103.21	6.63	**0.010**
Simple RT – raw SD	825	52.14	29.29	63.35	37.87	14.62	**<0.001**
Simple RT – CV	825	0.18	0.07	0.20	0.08	11.08	**0.001**
Simple RT – ISD	825	-0.24	0.80	0.08	1.04	15.49	**<0.001**
Choice RT – mean (ms)	802	331.96	80.82	353.82	99.33	7.69	**0.006**
Choice RT – raw SD	802	58.52	21.27	69.84	27.18	27.93	**<0.001**
Choice RT – CV	802	0.18	0.05	0.20	0.07	18.68	**<0.001**
Choice RT – ISD	802	-0.33	0.80	0.10	1.03	27.60	**<0.001**
Age	896	74.09	3.38	77.30	5.09	73.58	**<0.001**
Education	894	11.17	2.29	11.41	2.66	1.39	0.239
ADL score	877	0.98	1.31	2.14	2.78	34.09	**<0.001**
Disease count	896	2.35	1.66	2.96	1.72	20.15	**<0.001**
Grip strength	868	25.90	9.90	24.26	9.46	4.57	**0.033**
Goldberg depression score	865	1.71	1.79	2.13	2.00	7.06	**0.008**
Goldberg anxiety score	870	2.49	2.35	2.46	2.25	0.02	0.876
		Count	%	Count	%	χ^2	p
Gender	896					13.63	**<0.001**
Male		83	39.7%	373	54.3%		
Female		126	60.3%	314	45.7%		
Marital status	896					5.35	0.148
Married		127	60.8%	366	53.3%		
Single		10	4.8%	24	3.5%		
Widowed		63	30.1%	261	38.0%		
Divorced/separated		9	4.3%	36	5.2%		
Possible MMSE dementia	896					7.17	**0.007**
Yes		181	86.6%	537	78.2%		
No		28	13.4%	150	21.8%		
Smoking status	877					7.65	**0.022**
Never		110	52.9%	281	42.0%		
Past		78	37.5%	305	45.6%		
Current		20	9.6%	83	12.4%		
Using AH medication	879					1.00	0.317
Yes		62	29.8%	225	33.5%		
No		146	70.2%	446	66.5%		

375

376 *Notes*: **bold** values indicate $p < 0.05$; RT: reaction time; CV: coefficient of variation; ISD:

377 intraindividual standard deviation; ADL: activities of daily living; MMSE: Mini-Mental State

378 Examination; AH: antihypertensive

Table 2: Summary of Cox proportional hazards regression models of all-cause mortality

		Unadjusted				Adjusted				Adjusted + adjusted for *M*RT			
		Estimate	SE	HR	p	Estimate	SE	HR	p	Estimate	SE	HR	p
Simple RT	Mean	0.136	0.038	1.146	**<0.001**	0.054	0.045	1.055	0.231	--			
(n = 825)	Raw SD	0.170	0.039	1.185	**<0.001**	0.106	0.041	1.111	**0.010**	0.133	0.056	1.143	**0.018**
	CV	0.143	0.040	1.154	**<0.001**	0.132	0.040	1.142	**0.001**	0.128	0.041	1.137	**0.002**
	ISD	0.175	0.038	1.192	**<0.001**	0.108	0.041	1.114	**0.008**	0.140	0.057	1.150	**0.014**
Choice RT	Mean	0.168	0.039	1.183	**<0.001**	0.064	0.045	1.066	0.161	--			
(n = 802)	Raw SD	0.268	0.040	1.307	**<0.001**	0.087	0.043	1.091	**0.042**	0.076	0.049	1.079	0.123
	CV	0.196	0.040	1.217	**<0.001**	0.069	0.043	1.071	0.107	0.075	0.043	1.078	0.079
	ISD	0.269	0.040	1.309	**<0.001**	0.090	0.043	1.094	**0.037**	0.079	0.050	1.082	0.110

Notes: **bold** values indicate $p < 0.05$; RT: reaction time; CV: coefficient of variation; ISD: intra-individual standard deviation; RT measures are standardized to mean = 0, sd = 1 for comparability; adjustment was for age, gender, marital status, years of education, presence of possible preclinical dementia, smoking status, Activities of Daily Living, disease count, self-reported use of anti-hypertensive medication, grip strength, and the Goldberg Depression and Anxiety Scales.

Table 3: Fully-adjusted Cox proportional hazards regression models of all-cause mortality, based on RT variability measures

	Simple RT						Choice RT					
	Raw SD model		CV model		ISD model		Raw SD model		CV model		ISD model	
	HR	p	HR	p	HR	p			HR	p	HR	p
Mean RT	0.956	0.477	1.022	0.653	0.950	0.427	1.026	0.639	1.078	0.117	1.024	0.667
Raw SD	1.143	**0.018**					1.079	0.123				
Coefficient of variation			1.137	**0.002**					1.078	0.079		
Intraindividual SD					1.150	**0.014**					1.082	0.110
Gender (female vs. male)	1.643	**<0.001**	1.656	**<0.001**	1.643	**<0.001**	1.616	**<0.001**	1.614	**<0.001**	1.616	**<0.001**
Age	1.078	**<0.001**	1.079	**<0.001**	1.078	**<0.001**	1.076	**<0.001**	1.075	**<0.001**	1.076	**<0.001**
Years of education	1.015	0.372	1.016	0.344	1.015	0.382	1.015	0.397	1.015	0.386	1.015	0.400
Marital status		0.318		0.351		0.321		0.234		0.233		0.244
Single vs. married	0.894	0.518	0.899	0.540	0.893	0.514	0.885	0.483	0.885	0.481	0.885	0.482
Widowed vs. married	1.017	0.861	1.018	0.849	1.015	0.875	1.006	0.948	1.011	0.909	1.006	0.951
Div/sep vs. married	1.234	0.183	1.220	0.207	1.236	0.178	1.275	0.121	1.270	0.128	1.273	0.123
Possible dementia (MMSE<24)	0.904	0.065	0.906	0.069	0.904	0.066	0.913	0.099	0.912	0.091	0.913	0.097
ADL score	1.101	**<0.001**	1.102	**<0.001**	1.101	**<0.001**	1.098	**<0.001**	1.099	**<0.001**	1.098	**<0.001**
Disease count	1.087	**0.001**	1.085	**0.002**	1.088	**0.001**	1.083	**0.003**	1.081	**0.004**	1.083	**0.003**
Smoking status		0.911		0.880		0.904		0.918		0.923		0.919
Previous vs. never	0.986	0.830	0.983	0.797	0.986	0.833	0.995	0.940	0.996	0.945	0.996	0.946
Current vs. never	1.037	0.672	1.044	0.619	1.039	0.660	1.032	0.718	1.031	0.729	1.032	0.724
Taking AH medication	0.942	0.210	0.944	0.223	0.942	0.211	0.929	0.124	0.929	0.125	0.929	0.124
Grip strength	0.978	**0.002**	0.978	**0.002**	0.978	**0.002**	0.980	**0.005**	0.980	**0.005**	0.980	**0.005**
Goldberg depression	1.049	0.082	1.048	0.089	1.048	0.087	1.040	0.165	1.041	0.158	1.039	0.176
Goldberg anxiety	0.958	0.060	0.959	0.067	0.958	0.058	0.967	0.146	0.967	0.148	0.967	0.150

Notes: **bold** values indicate $p < 0.05$; RT measures are standardised to mean = 0, SD = 1; RT: reaction time; MMSE: Mini-Mental State Examination; ADL: activities of daily living; AH: anti-hypertensive