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Long-term associations between physical frailty and performance in specific cognitive domains

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ABSTRACT

Objectives: No longitudinal epidemiological research has reported associations between physical frailty and performance in specific cognitive domains. Our aim was to investigate whether such associations existed in the absence of accompanying neurodegenerative disorders such as mild cognitive impairment (MCI) and dementia.

Method: We addressed this issue in a population-based sample of 896 adults aged 70 years and older over 4 waves of data covering a 12-year period. Physical frailty was assessed and a cognitive battery included measures of processing speed, verbal fluency, face and word recognition, episodic memory and simple and choice reaction time (RT).

Results: Latent growth models showed frailty was associated with poorer baseline performance in processing speed, verbal fluency, simple and choice RT, and choice intraindividual RT variability. However, no significant effects of frailty on slopes of cognition were observed, suggesting that frailty was not associated with cognitive decline. Importantly, when the models took possible dementia into account, significant effects were retained suggesting that differences were not associated with dementia-related neurodegenerative disorders.

Discussion: The findings suggest that frailty-related cognitive deficits may exist independently of mechanisms underpinning neurodegenerative disorders such as MCI and dementia. If confirmed, this finding suggest a new avenue for preventative and therapeutic interventions in clinical and public health contexts for older adults.

Key words: Physical fitness, frailty, cognition, epidemiology

Together with dementia, the increasing prevalence of frailty in older populations represents a major challenge to clinicians and public healthcare systems. Frailty refers to the decreased ability to restore homeostasis after a stressful event (e.g., Fried et al., 2001; Walston et al., 2006) which may increase the likelihood of adverse outcomes such as falls, delirium, disability and, indeed, mortality. Models of frailty (e.g., Fried et al., 2001; Rockwood et al., 2005) tend to treat the construct as the presence of either frailty-related "phenotypes" (e.g., weight loss, exhaustion, low energy expenditure, slow gait speed and weak grip strength) or "deficit" markers (e.g., symptoms, signs, abnormal laboratory values, presence of disease and disability); the greater the number of such phenotypes or markers, the more likely the presence of frailty. However, such models do not take into account cognition and brain function adequately and in particular, the interplay between frailty and deficits in specific cognitive domains.

To date, only a handful of studies have investigated frailty in relation to specific cognitive domains (for reviews see Clegg, Young, Iliffe, Rikkert, & Rockwood, 2013; Panza et al., 2015; Panza et al., 2011; Robertson, Savva, & Kenny, 2013). The majority of these have been cross-sectional, non-population-based, and have relatively small samples. Current cross-sectional evidence suggests that frailty is associated with various measures of executive function (Langlois et al., 2012; Patrick, Gaskovski, & Rexroth, 2002), processing speed (Boyle, Buchman, Wilson, Leurgans, & Bennett, 2010; Langlois et al., 2012; Patrick et al., 2002), within-person reaction time (RT) variability (O'Halloran, Finucane, Savva, Robertson, & Kenny, 2014; O'Halloran et al., 2011) and immediate memory (Macuco et al., 2012). In the only longitudinal study of specific cognitive domains we identified (Boyle et al., 2010), frailty was associated with more precipitous decline across a range a variables including global

cognition, episodic and working memory, perceptual speed and visuospatial abilities. However, this study involved a select population and more broadly, there is considerable inconsistency across studies in cognitive variables for which significant associations have been found.

Inconsistencies in findings may stem from differences in study population (e.g., community-based versus care home), sample size, and the frailty measure used. It is particularly striking that no current epidemiological research has examined the longitudinal association between frailty and specific cognitive domains such as processing speed, executive function and memory. This is an important omission as there are notable gaps in our understanding of the relationship between frailty and cognitive decline. First, much of the research has been undertaken within the context of mild cognitive impairment (MCI) or dementia assessment using global measures of cognition that provide no information of the cognitive domains associated with frailty. Information on the specific cognitive deficits associated with frailty is important as such markers may help early identification of persons at risk of the condition of frailty and help facilitate early public health intervention. Additionally, little research has delineated between cognitive deficits associated with neurodegenerative disorders such as MCI and dementia, and those that are directly linked to frailty. This is an important distinction because if the mechanisms linking frailty to cognition are independent of such age-related neurodegenerative disorders and stem from direct linkage between the physical condition and cognitive function, it would suggest the need for new and novel interventions in clinical contexts. Finally, although several population-based studies have examined frailty, none have longitudinally focused on associations with specific cognitive domains using comprehensive measures of frailty (e.g., Fried et al., 2001). Frequently, only single measures (e.g., grip strength) have been used in research.

In the present study, therefore, we investigated frailty and specific cognitive domains over a 12-year period in a large epidemiological population-based sample of 896 adults aged 70 years and over. Critically, we used a comprehensive measure of frailty widely used in the literature (following Fried et al., 2001) and examined associations across an extensive battery of cognitive variables. These included processing speed, verbal fluency, face and word recognition, episodic memory and global cognition. Importantly, as there is uncertainty concerning overlap between cognitive deficits related to dementia and those related to frailty, we adjusted our analyses for effects attributable to possible dementia. We expected that frailty would be associated with poorer cognitive performance at baseline and also with more precipitous decline over the subsequent 12 years.

METHODS

Participants

Eight hundred and ninety-six persons (440 women) aged 70-97 years participating in the Canberra Longitudinal Study (Christensen et al., 2004) were recruited for the investigation. Participants stratified by age and gender were sampled from the compulsory electoral roll (69% responding). Approval for the research was obtained from the Ethics in Human Experimentation Committee of The Australian National University. Here, we report data collected over four waves at 4-year intervals for 12 years between 1990 and 2002. Of the original sample of 896 participants, 185 (20.6%) were deceased by 4 years, 363 (40.5%) were deceased by 8 years and 544 (60.7%) were deceased by 12 years. Of the participants who remained in the study, 14.1% (100/711) refused or were unable to complete the first follow-up interview primarily due to ill health, 21.1% (100/474) for the second follow-up and 21.1% (57/270) for the third follow-up. Attrition was higher in the frail group at each of the three follow-ups (48%, 76%, 90%) than in the pre-frail group (29%, 58%, 75%) and the non-frail

group (25%, 47%, 69%). Attrition due to mortality or other reasons resulted in sample sizes of 896, 611 (68.2%), 374 (41.7%) and 213 (23.8%) for the four waves.

Frailty assessment

Frailty assessment was operationalized (Fried et al., 2001) as the presence of three or more of the following: unintentional weight loss, self-reported exhaustion, weakness (grip strength), slow walking speed, and low physical activity. Presence of 1-2 of these symptoms indicates pre-frailty. *Unintentional weight loss* and *exhaustion* were based on single binary self-report items regarding weight loss in the past month and lacking energy, taken from the Goldberg Depression Scale (Goldberg, Bridges, Duncan-Jones, & Grayson, 1988). *Grip strength* was measured in kilograms using a hand dynamometer, with the lowest 20% among each gender classified as having weak grip strength. *Slow walking speed* was assessed from a scale assessing Activities of Daily Living (ADL), based on a single item asking about ease of walking 400 metres. Participants who responded "Some problem", "A lot of problems", "Severe problems" or "Cannot walk" were classified as having slow walking speed. Finally, *low physical activity* was assessed using a single categorical self-report item assessing frequency of physical activity, with participants responding "once a week", "once a month", "less than once a month" or "not at all" classified as having low physical activity. In the present sample, 83 persons reported weight loss (9.5%), 337 (38.4%) lacking energy/exhaustion, 178 (20.3%) weak grip strength, 248 (28.2%) walking problems and 282 (32.1%) low physical activity.

Cognitive variables

A cognitive battery was administered at each wave. *Processing speed* was measured by the Symbol-Letters Modalities Test (SLMT), a task similar to Smith's (1973) Symbol-Digit Modalities Test and Wechsler's (1981) Digit-Symbol Substitution. The number of correct symbol-letter pairs made in 90 s was summed. *Episodic memory* consisted of brief episodic

memory tasks testing word, face, name and address recall and figure reproduction (Jorm, 1992). *Verbal fluency* was assessed as the number of animals named in 30 s. *Global function* was tested using the Mini-Mental State Examination (MMSE: Folstein, Folstein, & McHugh, 1975), scored out of 30. *Face and word recognition* tasks were based on the Rivermead Behavioural Memory Test (Wilson, Cockburn, Baddeley, & Hiorns, 1989). *Simple and 2-choice RT* were both assessed over 20 trials (see Christensen et al. (2000) for specific details). Computation of intraindividual RT variability followed procedures commonly used elsewhere (Hultsch, Strauss, Hunter, & MacDonald, 2008) where age and time-on-task effects were partialled from the intraindividual *SD*s (ISD).

Additional measures

Presence of *possible preclinical dementia* was determined using the MMSE, based on scoring ≤24 at any of the four assessments where data were available. *Physical health* measures included smoking status (never, previous or current), *Activities of Daily Living* (ADL, a scale ranging from 0 to 22), *disease count* (self-reported history from a list of 14 diseases), and self-reported use of *anti-hypertensive medication*. *Functional ability* was assessed using the eight-item ADL scale and a four-item instrumental ADL scale, with scores ranging 0-22 for ADL and 0-8 for IADL, with higher scores indicating greater functional impairment (Christensen et al., 1994).

Statistical analyses

Separate latent growth models with covariates (McArdle & Epstein, 1987; Muthén, 1997) were used to identify associations between frailty and cognitive performance. Separate models simultaneously estimated the intercept and slope of the cognitive variable over time (measurement occasion), while controlling for the effects of frailty and control variables, age,

gender and education. For three of the models (episodic memory, mean simple RT, choice RT ISD), the residual variance for the slope parameter was estimated as a negative value due to the parameterization of the model. Therefore, slope residuals were constrained to zero for these models, with no change to the resulting effects of frailty on each outcome. SPSS v20 (IBM Corp, Chicago) was used for descriptive analyses and Mplus v6.12 (Muthén L & Muthén B, 2010) was used for the latent growth analyses.

RESULTS

Descriptive data according to frailty status are presented in Table 1. Greater frailty was associated with older age, being female and poorer scores for smoking status, disease count, ADL and IADL. Notably, group differences in possible dementia (i.e., MMSE scores ≤24) were nonsignificant. In Table 2, for the majority of cognitive variables, deficits were greater with increasing frailty. The exceptions were word and face recognition where differences were nonsignificant.

Tables 1 and 2 about here

Estimated effects of frailty status and demographic covariates on intercepts and slopes for cognitive variables are presented in Table 3 with estimates of intercepts and residuals for the intercept/slope parameters presented in a Supplementary Table. Significant effects of frailty on intercepts of cognitive performance were obtained for SLMT, verbal fluency, mean simple and choice RT, and choice RT intraindividual variability. In all cases, being frail was associated with poorer initial cognitive performance. An additional significant effect on intercept indicated that pre-frail persons were slower than non-frail on the choice RT task. By contrast, effects of frailty on cognition intercepts were nonsignificant for face and word recognition, and episodic memory. With regard to the linear change in cognition over time (slopes) as a function of frailty, it is of note that all frailty effects were nonsignificant. This clearly suggests that

although cognitive differences are apparent, particularly between the frail and non-frail groups, declines over time in cognition were not more precipitous for frail persons.

Tables 3 and 4 about here

Finally, models were re-estimated having excluded participants with possible dementia. All significant intercept effects remained significant, with the exception of the association of pre-frailty on choice RT ($p = 0.08$). This minimal variation from the findings of the initial models suggests that the mechanisms linking frailty to cognition are independent of those related to possible dementia.

For the above models, fit statistics (see Table 4) indicated good fit based on RMSEA < 0.05 for all models except for face recognition (RMSEA = 0.12), SLMT (RMSEA = 0.08) and MMSE (RMSEA = 0.08). Similarly, CFI and TLI indicated adequate fit (>0.90) for all models except SLMT, MMSE, face recognition (inestimable) and choice RT. These models were re-estimated, freeing the middle time points (Waves 2 and 3) to test whether misfit was due to minor non-linearities, rather than misspecification of the effects of frailty. The re-estimated models all had excellent fit (RMSEA < 0.02), with effects of frailty remaining unchanged. The inclusion of slope in each of the models was associated with significantly improved fit for each of the domains examined, based on change in -2 log likelihood (see Table 4).

DISCUSSION

To our knowledge, this is the first epidemiological study to longitudinally examine the association between frailty and specific cognitive domains in a large community sample of older adults. The investigation has produced some important findings. First, baseline differences indicated that relative to non-frail persons, frail individuals exhibited deficits in processing speed, verbal fluency, simple and choice RT and choice within-person RT variability. Second, contrary to our expectations, analyses of the slopes estimating subsequent

variation over time according to frailty status did not reveal significant change for any of the cognitive variables. Finally, an important finding was that when the models were repeated having excluded participants with possible dementia, the results remained largely unchanged. This suggests the link between frailty and cognition is independent of age-related neurodegenerative disorders such as MCI and dementia.

The findings provides important information about the association between physical frailty and specific cognitive domains. First, clear effects of frailty were found at baseline for cognitive measures relating to either executive function (i.e., verbal fluency, within-person RT variability) or processing speed. Within-person RT variability is held to reflect fluctuations in attentional or executive control mechanisms (Bunce, MacDonald, & Hultsch, 2004; Bunce, Warr, & Cochrane, 1993; West, Murphy, Armilio, Craik, & Stuss, 2002) supported by circuitry in the frontal cortex. Together with evidence that compromised frontal circuitry is related to one of the key elements of frailty, gait impairment (e.g., Parihar, Mahoney, & Verghese, 2013), the findings suggest that a potential contributory factor to physical frailty is compromised frontal circuitry, that also supports executive control. This finding is consistent with the view expressed elsewhere (Canevelli & Cesari, 2015) that executive function may be one of the mechanisms providing a clinical distinction between cognitive impairment related to physical factors and impairment due to neurodegenerative disorders. Although the present study does not infer causality and it is possible that a shared condition (e.g., cardiovascular disease) affects frailty and cognition concurrently, the absence of effects for cognitive domains supported by temporal structures (i.e., face and word recognition, episodic memory) that commonly exhibit deficits in relation to MCI and dementia, supports this view. Also, frailty implies longitudinal change (e.g., inability over time to recover from a stressful event), but is typically operationalized as a static condition. Although beyond the scope of the present study, it is

clearly important for future research to examine longitudinal associations between frailty and cognition while taking into account potential explanatory mechanisms linking these variables.

Second, contrary to our expectations, initial frailty-related differences established in the cognitive variables at baseline did not subsequently vary over time. This finding contrasts with another study where frailty was associated with more precipitous decline in several cognitive domains (Boyle et al., 2010). However, these contrasting findings may stem from the samples used. Here, we used a population-based sample whereas the earlier study investigated participants from retirement communities and homes, social service agencies and church groups. Also, that study had a specific focus on relations between frailty and cognitive decline accompanying MCI. Thus, it is not clear whether the effects of frailty and MCI on cognition were independent. Clearly, the contrasting findings suggest that more longitudinal research is required in population-based samples.

Finally and importantly, we obtained evidence suggesting that the association between physical frailty and cognitive deficits were independent of neurodegenerative disorders. Having repeated the analyses excluding participants with possible dementia, the results remained largely unchanged. This finding provides evidence that although individuals suffering neurodegenerative disorders can also be physically frail, the mechanism by which frailty affects cognition may be independent. As noted earlier, the overlapping circuitry of the frontal cortex governing motor coordination and supporting executive control may provide a link. It is important that further work investigates the potential mediating role of executive control and the frontal cortex in frailty-cognition relations in non-demented populations.

Although the present study has a number of strengths including a large population-based sample, comprehensive battery of cognitive measures and analysis of four waves of data spanning 12 years using powerful statistical modelling procedures, there are some limitations

we should acknowledge. First, although we adjusted for *possible* dementia, we did not use formal clinical diagnoses. However, evidence demonstrating that MMSE scores ≤24 discriminate persons with dementia-related cognitive impairment (Holsinger, Deveau, Boustani, & Williams, 2007) suggests that participants with possible dementia were eliminated. That said, it is clearly important that further epidemiological investigations employing clinical dementia diagnosis confirm our findings. Additionally, elements of the frailty measure drew on single self-report items. However, consideration of Tables 1 and 2 show that at baseline, more frail individuals exhibited poorer physical and mental health, fewer activities and poorer cognition. This suggests that the frailty measure captured the construct reliably. Finally, although the statistical approach was robust to data missing at random, it should be noted that there was differential attrition primarily in the frail group, which may have limited power to observe changes in cognition over time within this group.

The present study has shown that in a large population-based sample, cognitive deficits are associated with physical frailty but that deficits in frail relative to non-frail do not change over time. Importantly, the analyses suggest that the cognitive effects of frailty are independent of neurodegenerative disorders and are possibly mediated by the shared circuitry of the frontal cortex governing motor coordination and supporting executive control. Given that with the aging population the incidence of frailty is likely to increase, it is important that future research addresses the association with cognitive function further in older populations. In particular, additional insights are needed into how far the effects of physical frailty on cognition are mediated by frontal circuits, how they are temporally related, and to what extent they are independent of age-related neurodegenerative disorders. If the present findings are confirmed, it would suggest that models of frailty need to be revised to accord higher weighting to cognition as a frailty-related phenotype. Work to develop the constructs of brain frailty (Clegg et al., 2013) and cognitive frailty (Kelaiditi et al., 2013) represent a notable step in this

direction. Also, if future research does confirm that frailty can impact on cognition in the absence of neurodegenerative disorders, it may signal the clinical potential of neurocognitive measures as early markers of the condition. Additionally, it would suggest the need for new and novel interventions and preventative strategies in clinical and public health contexts to help attenuate and possibly reverse the adverse effects of frailty. The distinction between frontal and temporal lobe underlying circuitry may represent a starting point for such work.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest

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Table 1. Descriptive statistics according to level of frailty

	Frailty category							
	Non-frail (N = 305)		Pre-frail (N = 417)		Frail (N = 156)			
	n	Row %	n	Row %	n	Row %	χ^2	p
Age group (at baseline)							59.0	<0.001
70-74	163	44.1%	168	45.4%	39	10.5%		
75-80	93	32.9%	140	49.5%	50	17.7%		
80-85	40	25.6%	77	49.4%	39	25.0%		
85+	9	13.0%	32	46.4%	28	40.6%		
Gender							11.9	0.003
Male	173	38.6%	213	47.5%	62	13.8%		
Female	132	30.7%	204	47.4%	94	21.9%		
Marital status							11.7	0.070
Married	184	38.0%	230	47.5%	70	14.5%		
Single	8	23.5%	19	55.9%	7	20.6%		
Widowed	97	30.7%	149	47.2%	70	22.2%		
Divorced/separated	16	36.4%	19	43.2%	9	20.5%		
Smoking status							13.1	0.011
Never	125	32.1%	194	49.7%	71	18.2%		
Previous	149	38.9%	178	46.5%	56	14.6%		
Current	30	29.1%	44	42.7%	29	28.2%		
Possible dementia							3.9	0.145
MMSE ≤24	23	7.6%	42	10.2%	22	14.3%		
MMSE >24	281	92.4%	369	89.8%	132	85.7%		
	M	SD	M	SD	M	SD	F	p
Years of education	11.59	2.69	11.19	2.59	11.30	2.38	2.1	0.124
Disease count	2.37	1.51	2.79	1.65	3.80	1.82	39.7	<0.001
ADL score	0.68	0.95	1.60	1.86	4.75	3.50	212.2	<0.001
IADL score	0.12	0.41	0.55	1.04	2.29	2.26	171.6	<0.001

Notes: MMSE = Mini-Mental State Examination; ADL = Activities of Daily Living; IADL = Instrumental Activities of Daily Living

Table 2. Baseline cognitive data according to frailty status

	Frailty category										
	Non-frail			Pre-frail			Frail				
	n	Mean	SD	n	Mean	SD	n	Mean	SD	F	p
SLMT score	297	99.83	15.62	400	96.21	16.51	147	90.07	18.00	17.3	<0.001
Word recognition (%)	299	0.96	0.07	406	0.94	0.08	153	0.94	0.09	2.9	0.053
Face recognition (%)	303	0.79	0.10	410	0.79	0.11	150	0.77	0.12	1.3	0.284
Episodic memory score	305	13.49	2.09	417	13.32	2.14	156	12.85	2.76	4.2	0.015
Verbal fluency score	304	11.53	3.52	415	10.58	3.23	154	10.11	3.20	11.4	<0.001
Mean simple RT (ms)	291	281.50	82.19	384	295.05	101.22	150	338.96	115.73	17.4	<0.001
Mean choice RT (ms)	284	327.26	73.69	375	349.39	102.22	143	388.85	103.49	20.7	<0.001
Simple RT ISD	291	4.58	2.53	384	5.14	3.18	150	6.00	3.55	10.9	<0.001
Choice RT ISD	220	5.43	2.19	263	5.72	2.79	68	7.08	3.56	10.0	<0.001

Notes: SLMT = Symbol-Letters Modalities Test; RT = reaction time; ISD = Intraindividual *SD*

Table 3. Estimated effects of frailty status and demographic covariates on intercepts and slopes for cognitive variables

		Cognition intercept			Cognition slope		
		Estimate	SE	p	Estimate	SE	p
SLMT	Pre-frail vs non-frail	-0.241	0.731	0.742	-0.036	0.392	0.927
	Frail vs non-frail	-2.727	0.707	**<0.001**	0.099	0.363	0.785
	Age	-0.613	0.063	**<0.001**	-0.160	0.039	**<0.001**
	Gender	1.465	0.603	**0.015**	-0.045	0.301	0.881
	Education	1.280	0.117	**<0.001**	-0.159	0.058	**0.006**
MMSE	Pre-frail vs non-frail	-0.038	0.786	0.961	-0.226	0.580	0.697
	Frail vs non-frail	-0.236	0.761	0.756	-0.524	0.550	0.341
	Age	-0.487	0.067	**<0.001**	-0.342	0.056	**<0.001**
	Gender	1.552	0.650	**0.017**	0.310	0.454	0.495
	Education	0.786	0.126	**<0.001**	0.111	0.088	0.207
Word recognition	Pre-frail vs non-frail	0.607	0.775	0.433	0.049	0.661	0.941
	Frail vs non-frail	-0.043	0.751	0.954	-1.092	0.627	0.082
	Age	-0.445	0.066	**<0.001**	-0.221	0.062	**0.000**
	Gender	1.949	0.641	**0.002**	0.044	0.520	0.932
	Education	0.550	0.124	**<0.001**	-0.001	0.100	0.993
Face recognition	Pre-frail vs non-frail	-0.457	0.794	0.565	0.592	0.654	0.365
	Frail vs non-frail	-1.352	0.767	0.078	-0.084	0.611	0.890
	Age	-0.428	0.068	**<0.001**	-0.009	0.065	0.889
	Gender	1.327	0.657	**0.043**	-0.139	0.511	0.785
	Education	0.168	0.127	0.188	0.039	0.099	0.695
Episodic memory	Pre-frail vs non-frail	-0.561	0.752	0.456	0.186	0.501	0.710
	Frail vs non-frail	-1.273	0.726	0.079	-0.095	0.465	0.838
	Age	-0.306	0.064	**<0.001**	-0.060	0.048	0.207
	Gender	1.191	0.620	0.055	0.629	0.388	0.105
	Education	0.671	0.120	**<0.001**	-0.067	0.076	0.376
Verbal fluency	Pre-frail vs non-frail	-0.604	0.778	0.438	1.022	0.535	0.056
	Frail vs non-frail	-1.673	0.749	**0.026**	0.125	0.493	0.799
	Age	-0.450	0.066	**<0.001**	-0.026	0.051	0.611
	Gender	-0.350	0.642	0.586	0.143	0.412	0.728
	Education	0.507	0.124	**<0.001**	-0.070	0.081	0.382
Mean simple RT	Pre-frail vs non-frail	13.418	7.690	0.081	-4.727	4.408	0.284
	Frail vs non-frail	16.247	7.423	**0.029**	-4.291	3.996	0.283
	Age	3.420	0.660	**<0.001**	1.090	0.431	**0.012**
	Gender	50.369	6.321	**<0.001**	-1.055	3.326	0.751

		Cognition intercept			Cognition slope		
		Estimate	SE	p	Estimate	SE	p
	Education	-3.805	1.215	**0.002**	-0.371	0.642	0.564
Mean choice RT	Pre-frail vs non-frail	18.447	7.545	**0.014**	-5.038	5.403	0.351
	Frail vs non-frail	14.480	7.281	**0.047**	1.636	5.020	0.745
	Age	4.265	0.642	**<0.001**	1.646	0.506	**0.001**
	Gender	37.362	6.190	**<0.001**	0.126	4.153	0.976
	Education	-3.887	1.192	**0.001**	-0.763	0.798	0.339
Simple RT ISD	Pre-frail vs non-frail	0.233	0.234	0.320	-0.145	0.183	0.428
	Frail vs non-frail	0.288	0.226	0.204	0.166	0.170	0.329
	Age	0.109	0.020	**<0.001**	0.021	0.017	0.234
	Gender	1.210	0.192	**<0.001**	-0.128	0.142	0.365
	Education	-0.143	0.037	**<0.001**	0.015	0.027	0.577
Choice RT ISD	Pre-frail vs non-frail	0.227	0.190	0.231	-0.187	0.148	0.208
	Frail vs non-frail	0.374	0.184	**0.042**	0.113	0.136	0.405
	Age	0.139	0.016	**<0.001**	0.017	0.014	0.233
	Gender	-0.066	0.156	0.669	0.214	0.113	0.059
	Education	-0.052	0.030	0.080	0.033	0.022	0.127

Notes: SLMT = Symbol-Letters Modalities Test; MMSE: Mini Mental State Examination; RT = reaction time; ISD = Intraindividual *SD.* For episodic memory, mean simple RT and choice RT ISD, slope residuals were constrained to zero. Estimates of intercepts and residuals for the intercept/slope parameters presented in a Supplementary Table. Cognition variables (but not RT variables) were scaled to M=100, SD=10, to facilitate comparisons between cognitive domains. Age and years of education were not scaled.

Table 4. Model fit statistics and tests of slope

	Model fit				Test of improved model fit associated with slope	
	χ^2 (df=26)	RMSEA	CFI	TLI	χ^2	p
SLMT	173.0	0.083	0.88	0.82	720.18	<0.001
MMSE	170.7	0.083	0.76	0.65	867.47	<0.001
Word recognition	29.5	0.033	0.97	0.95	181.22	<0.001
Face recognition	204.7	0.120			197.58	<0.001
Episodic memory	26.0	0.029	0.95	0.91	17.96	0.022
Verbal fluency	42.5	0.046	0.94	0.90	62.12	<0.001
Mean simple RT	19.4	0.019	0.99	0.99	53.86	<0.001
Mean choice RT	33.0	0.038	0.97	0.95	99.15	<0.001
Simple RT ISD	30.5	0.035	0.95	0.91	49.81	<0.001
Choice RT ISD	37.0	0.042	0.92	0.87	40.29	<0.001

Note: SLMT = Symbol-Letters Modalities Test; MMSE: Mini Mental State Examination; RT = reaction time; ISD = Intraindividual *SD.*