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Dynamics of Frailty and Cognition After Age 50: Why It Matters that Cognitive Decline is Mostly Seen in Old Age

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Abstract.
Background: Frailty has been considered an antecedent and, to a lesser extent, an outcome of cognitive impairment. Both frailty and cognitive impairment are multiply determined and each is strongly related to age, making it likely that the two interact, especially as people age. In consequence, understanding their interaction and co-occurrence can offer insight into pathophysiology, prevention, and management.
Objective: To examine the nature of the relationship between frailty and cognitive impairment using longitudinal data from the Survey of Health Aging and Retirement in Europe (SHARE), assessing for bidirectionality.
Methods: We conducted secondary analyses using data from the first two waves of SHARE. The sample (N = 11,941) was randomly split into two halves: one half for model development and one half for model confirmation. We used a 65 deficit Frailty Index and combined 5 cognitive deficits into a global cognitive impairment index. Cross-lagged path analysis within a structural equation modelling framework was used to examine the bi-directional relationship between the two measures.
Results: After controlling for age, sex, social vulnerability, education, and initial cognitive impairment, each 0.10 increase in baseline frailty was associated with a 0.01 increase in cognitive impairment at follow-up ($p < 0.001$). Likewise, each 0.1 increase in baseline cognitive impairment was associated with a 0.003 increase frailty at follow-up ($p < 0.01$).
Conclusion: Our findings underscore the importance of considering cognitive impairment in the context of overall health. Many people with dementia are likely to have other health problems, which need to be considered in concert to achieve optimal health outcomes.

Keywords: Cognitive impairment, frail elderly, longitudinal study, social determinants of health

INTRODUCTION

As people age, their risk of frailty [1] and cognitive impairment [2, 3] increases. Thus, that frailty and cognitive impairment are associated with each other is not surprising. Most studies report frailty as an antecedent [4–7] of cognitive impairment and others as an outcome of cognitive impairment [8, 9]. The mutual influences between frailty and impaired cognition have been discussed [10], including a proposed construct of "cognitive frailty" [11]. This last is held to be a combination of "physical frailty", which is defined by five features, three of which (i.e., reduced activities, motor slowing, weight loss) are known to be risks for dementia and mild cognitive impairment (MCI) [12].

Despite the caveat that in considering age-related disorders it is important to consider age as more than something to be "controlled for"

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[5, 13], comparatively little research has focused on examining the potential bidirectional relationship between frailty and cognitive impairment. Possibly, the accumulation of health deficits, whether physical or cognitive, depletes available health reserves increasing the likelihood of further accumulation of physical and cognitive deficits. This would be so if each of these deficits reflected common age-related processes.

Furthermore, the social context is likely to exert important influence. A number of social factors have been linked to cognitive impairment [14–22] and are also important risk factors for and correlates of frailty [23–28]. Given the connection from social vulnerability to both frailty and cognition, the inclusion of social vulnerability may explain some of the overlap between cognition and frailty.

Our objective, using longitudinal data from the Survey of Health Aging and Retirement in Europe (SHARE), was to simultaneously examine frailty and cognitive impairment as both antecedents and outcomes.

METHODS

Participants and design

We were primarily interested in identifying the reciprocal relationship between frailty and cognitive impairment rather than the trajectories of either variable. For this reason, we conducted secondary data analyses using only the first two waves of SHARE (2004-2005 and 2006-2007)—baseline and follow-up. SHARE was designed to study population aging in Europe by examining the interplay between a wide variety of economic, health, and social factors. The SHARE study and its sampling methodology are described elsewhere [29]. Briefly, probability sampling was used to recruit community dwelling participants aged 50 years and older from most of the European Union and Israel. Partners living in the same household were also surveyed regardless of age; however, partners under 50 years of age were excluded from the current analysis. Most of the data were collected through computer-assisted personal interviews. Additional data were collected through a self-administered drop-off questionnaire. Findings from SHARE remain relevant to current knowledge and practice: The sample is a representative population-based survey that includes participants with multiple medical conditions, who are often excluded from dementia research. The Research Ethics Board of the Nova Scotia Health Authority in Halifax, Canada approved secondary analyses of SHARE data.

Of 18,120 participants who participated in the first two waves of SHARE, 12,598 completed the drop-off survey at baseline, which contained the majority of the social items. We calculated indices (i.e., Frailty Index, Social Vulnerability Index, cognitive impairment) for participants who had data for 80% of the index's items, otherwise index values were considered missing. We excluded the 657 cases which did not have calibrated sample weights or were missing data on variables included in our model, leaving a final sample size of 11,941.

Measures

A deficit accumulation approach was used to measure frailty, cognitive impairment, and social vulnerability. Variables were coded either 1 (deficit present) or 0 (deficit absent). For deficits with ordered response categories, scores were mapped to the 0-1 interval (e.g., for volunteer work: 0 – at least once a week, 0.5 – less than once a week, 1 – does not volunteer). Scores were summed for each individual and the sum was divided by the number of deficits considered.

Frailty index (FI)

With SHARE data, Theou et al. previously constructed a frailty index with 70 items covering a broad spectrum of domains including self-rated health, hospitalizations, comorbidities, signs and symptoms, function, cognition, and mental well-being [27]. We used the same FI except we excluded four cognitive impairment deficits to avoid double counting in the association between frailty and cognitive impairment. One instrumental activity of daily living (IADL) was excluded because it was included in our social vulnerability index, resulting in a 65 deficit FI (see Supplementary Table 1). Mathematically, the FI can range from 0 (fit) – 1 (frail), however, values over 0.7 are extremely rare as survival is unlikely for individuals at such a high level of frailty.

Included in the function items of the FI were activities of daily living (ADLs), instrumental activities of daily living (IADLs), stroke, Parkinson's disease, and 10 items related to depressive symptomology. Because these deficits could be strongly related to cognitive impairment, we conducted sensitivity

analyses with these items removed from the FI. This alternate FI had 41 items.

Cognitive impairment

We constructed a cognitive impairment index comprised of five deficits based on tests of orientation, numeracy, instant recall, delayed recall, and verbal fluency. Recall tests, such as instant and delayed recall, and semantic verbal fluency tasks can distinguish between healthy controls and people with MCI or Alzheimer's disease (AD) [30–33]. Immediate recall scores <5, delayed recall scores <4, and verbal fluency scores <15 were coded as "1" indicating a deficit, based on previous research [30–33]. Responses of "don't know" were also coded as "1". These variables were dichotomized into deficit present or absent because we aimed to identify whether participants were functioning within a normal range as opposed to aiming to differentiate between normal functioning and high functioning. For orientation (date, month, year, and day of the week) and numeracy deficits, participants were given a score from 0 to 1 (i.e., 0, 0.25, 0.50, 0.75, 1) based on the number of incorrect responses. The cognitive impairment index can range from 0 (no cognitive impairment) to 1 (cognitively impaired).

Social vulnerability index (SVI)

The 32 item SVI has previously been shown to predict mortality and disability in SHARE [34]. We constructed the same SVI except, because of its particular relevance for cognitive function, education was removed from the SVI and treated as a separate variable, leaving 31 deficits covering social activities, living arrangements, marital status, loneliness, conflict, access to transportation, and opportunities to provide help (see Supplementary Table 2). Similar to frailty and cognitive impairment, dichotomous deficits were coded as 0 for deficit absent and 1 for deficit present. The SVI can range from 0 (no vulnerability) to 1 (high vulnerability), however, scores of 0 are rare as most people experience at least some minor level of vulnerability.

As part of SHARE, respondents were asked to indicate the highest educational degree that they have obtained. Based on this response, years of education was then derived from the International Standard Classification of Education (ISCED) [35]. ISCED was designed to enable the comparison of education statistics across multiple countries.

Analyses

We conducted all analyses using calibrated sample weights provided by SHARE. These weights were designed to match the national populations in SHARE based on age and sex. We described the sample using descriptive statistics in SPSS version 22.

The data were randomly split into halves ($n = 6{,}002$; $n = 5{,}939$) so that we could refine the hypothesized model (training data) and then confirm the final model in the second half of the data (testing data). To ensure the randomized spilt of the data produced two approximately equal groups, independent sample *t*-tests were used to compare the training and testing data on all continuous variables. χ^2 tests of independence were used to examine the distribution of sex in the training and testing data sets.

A cross-lagged path analysis using a structural equation modelling framework was used to test the directional influences between frailty and cognitive impairment [36–38]. Using this design, we can test the direction of the relationship between frailty and cognitive impairment while controlling for baseline values and covariates (i.e., age, sex, education, social vulnerability). Path analyses were conducted using Lavaan [39] in R [40] and sample weights were applied using the lavaan.survey package [41] (see the Supplementary Material for the code used). All variables in our model were manifest variables (i.e., directly measured). The three indices (i.e., frailty, cognitive impairment, and social vulnerability) represent a proportion of deficits and were multiplied by 10 to aid interpretation. A one unit change in the analysis represents a 0.1 change in the index.

Robust fit statistics (i.e., Satorra-Bentler χ^2 (S-Bχ^2), Comparative Fit Index (*CFI), and the Root Mean Squared Error of Approximation (*RMSEA) and standardized root mean square residual (*SRMR) were examined and robust standard errors were used in the calculation of significance tests because a high normalized Mardia coefficient (32.18) indicated a violation of multivariate normality [42]. A *CFI above 0.95 indicated a good fitting model [43]. An *RMSEA below 0.08 indicated acceptable fitting model and an *RMSEA below 0.06 indicated an excellent fitting model. An *SRMR below 0.08 indicated a good fitting model [43]. Generally, a small non-significant S-Bχ^2 indicates a good fit, but of relevance here, χ^2 is heavily influenced by large sample sizes [44, 45].

During the model development stage, modification indices were examined to see if there were theoretically plausible paths that could be added to improve model fit. Scaled difference χ^2 tests were used to test whether improvements in model fit were statistically significant [46].

The final model was confirmed in the testing data. We ran a sensitivity analyses by rerunning the final model in the testing data with an alternate FI with IADLs, ADLs, depression items, stroke, and Parkinson's disease removed.

RESULTS

Sample (weighted)

Ages ranged from 50 to 99 years with an average age of 64 ($SD = 9.59$) and 54.3% were women. On average, participants had 10 ($SD = 4.74$) years of education. The FI ranged from 0 to 0.74 (99% limit = 0.51) with a mean of 0.15 ($SD = 0.11$) at baseline and ranged from 0 to 0.79 (99% limit = 0.58) with a mean of 0.16 ($SD = 0.12$) at follow-up. The SVI ranged from 0.03 to 0.74, with a mean of 0.32 ($SD = 0.09$). Cognitive impairment ranged from 0 to 1 at both times, with a mean of 0.34 ($SD = 0.26$) at baseline and 0.33 ($SD = 0.27$) at follow-up.

Testing and training data (weighted)

We found no significant differences between the two halves on education, sex, SVI, FI (baseline and follow-up), or cognitive impairment (baseline and follow-up). There was a statistically significant difference in age, $t = -4.51$, $p < 0.001$; however, because the difference was less than one year, it was felt to be unlikely to influence the results (Table 1).

Table 1
Descriptive statistics on the two random halves of the data with sampling weights

Variable	$Mean_1$	$Mean_2$	SD_1	SD_2
Age	63.81*	64.60*	9.51	9.66
Education	10.06	10.10	4.68	4.80
Social Vulnerability	0.32	0.32	0.09	0.09
Cognitive Impairment (baseline)	0.34	0.33	0.26	0.26
Frailty (baseline)	0.15	0.15	0.11	0.12
Cognitive Impairment (follow-up)	0.34	0.33	0.27	0.27
Frailty (follow-up)	0.16	0.16	0.12	0.13
	$Male_1$	$Male_2$	$Female_1$	$Female_2$
Sex	45.8%	45.6%	54.2%	54.4%

*Significantly different at $p < 0.001$.

Path analyses

The hypothesized model (Model 1) is depicted in Fig. 1. See Table 2 for fit statistics. The *SRMR indicated a good fit. The *RMSEA was slightly below the more stringent cut-off of 0.06. The *CFI indicated an acceptable fit, but was below the more stringent cut-off of 0.95. Each 0.10 increase in baseline frailty was associated with a 0.03 increase in cognitive impairment at follow-up. Likewise, each additional 0.10 increase in baseline cognitive impairment was associated with a 0.005 increase in frailty at follow-up ($p < 0.001$). Model 1 accounted for 44% of the variance in cognitive impairment at follow-up and 56% of the variance in frailty at follow-up. The modification indices indicated that a path from education to cognitive impairment at follow-up would improve fit, suggesting education is related to both baseline cognition and the change in cognition from baseline to follow-up.

In Model 2, adding a path from education to cognitive impairment at follow-up, $b = -0.11$ ($p < 0.001$), improved model fit, $\Delta S\text{-}B\chi^2 = 78.53$, ($p < 0.001$), and the *CFI was above the 0.95 cut-off. The *RMSEA indicated a good fit. Each 0.10 increase in baseline frailty was associated with a 0.03 increase in cognitive impairment at follow-up ($p < 0.001$). Likewise, each 0.10 increase cognitive impairment was associated with a 0.005 increase in frailty at follow-up ($p < 0.001$). Model 2 accounted for 47% of the variance in cognitive impairment at follow-up and 56% of the variance in frailty at follow-up. The modification indices indicated that a path from age to frailty at follow-up would improve fit; suggesting age is related to both frailty and change in frailty from baseline to follow-up.

In Model 3, adding a path from age to frailty at follow-up, $b = 0.02$, ($p < 0.001$), resulted in a significant improvement in model fit, $\Delta S\text{-}B\chi^2 = 67.82$ ($p < 0.001$). The *CFI, *SRMR, and the *RMSEA all indicated a very good fit. Each 0.10 increase in baseline frailty was associated with a 0.03 increase in cognitive impairment at follow-up ($p < 0.001$). Likewise, each 0.10 increase in baseline cognitive impairment was associated with a 0.003 increase in frailty at follow-up ($p < 0.001$). Model 3 accounted for 47% of the variance in cognitive impairment and 58% of the variance in frailty at follow-up. Modification indices indicated that a path from age to cognitive

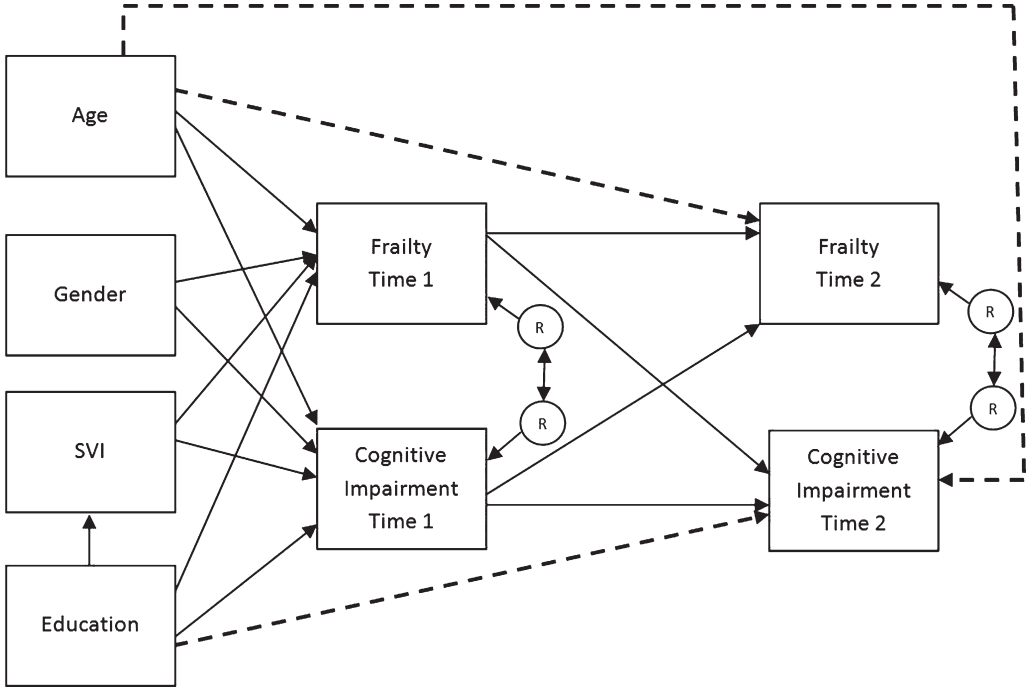

Fig. 1. Path diagram of hypothesized and confirmed models. Solid lines represent hypothesized path and dashed lines represent paths added to the model. All coefficients for displayed paths were significant at $p < 0.001$ in the final confirmed model, with the exception of the paths from baseline cognitive impairment to frailty at follow-up, sex to baseline cognitive impairment, and the correlation between the baseline residuals (R), which were significant at $p < 0.01$.

impairment at follow-up would improve fit; suggesting age is also associated with change in cognitive impairment from baseline to follow-up.

In Model 4, adding a path from age to cognitive impairment at follow-up, $b = 0.05$ ($p < 0.001$) improved model fit, $\Delta S\text{-}B\chi^2 = 83.23$ ($p < 0.001$) and all fit statistics indicated very good fit. Each 0.10 increase in baseline frailty was associated with a 0.01 increase in cognitive impairment at follow-up ($p < 0.001$). Likewise, 0.10 increase in baseline cognitive impairment was associated with a 0.003 increase frailty at follow-up ($p < 0.001$). Given that all fit statistics indicated a very good fit and there were no meaningful changes suggested by modification indices, Model 4 was our final model, accounting for 49% of the variance in cognitive impairment and 59% of the variance in frailty at follow-up.

The final model (Model 4) was confirmed in the testing data. Results were very similar to the results of Model 4 tested in the training data. All fit statistics indicated very good model fit. See Table 3 for path coefficients. The final model accounted for 50% of the variance in Wave 2 cognitive impairment and 57% of the variance in Wave 2 frailty.

The final model was confirmed in a sensitivity analysis with a 41 deficit FI that had IADLs, ADLs, depression items, stroke, and Parkinson's disease removed. These results were almost identical to the final model with the full FI with no substantive differences.

Table 2
Goodness of fit statistics for weighted analyses

Model	Observations	S-Bχ^2 (df)	*CFI	*SRMSR	*RMSEA [90% CI]	ΔS-Bχ^2 (df)
Model 1 (Hypothesized)	6002	208 (10)	0.94	0.05	0.06 [0.05, 0.06]	–
Model 2	6002	149 (9)	0.96	0.05	0.05 [0.05, 0.05]	78.53 (1)
Model 3	6002	99 (8)	0.97	0.04	0.04 [0.04, 0.05]	67.82 (1)
Model 4	6002	42 (7)	0.99	0.03	0.03 [0.03, 0.03]	83.23 (1)
Confirmed Model 4	5939	51 (7)	0.99	0.04	0.03 [0.03, 0.04]	–
Sensitivity Model 4	5939	56 (7)	0.99	0.04	0.03 [0.03, 0.04]	–

Note: All ΔS-Bχ^2 statistics were statistically significant at $p < 0.001$.

Table 3
Unstandardized coefficients for final model in the training and testing halves of the data

	Exploratory (Testing)		Confirmatory (Training)		Sensitivity (Shortened FI)	
Path	b	SE	b	SE	b	SE
Cognitive Impairment (follow-up)						
Cognitive Impairment (baseline)	0.490	0.020	0.453	0.021	0.460	0.021
Frailty (baseline)	0.130*	0.042	0.259	0.048	0.177	0.040
Education	–0.102	0.011	–0.127	0.011	–0.130	0.011
Age	0.053	0.005	0.045	0.005	0.046	0.005
Frailty (follow-up)						
Cognitive Impairment (baseline)	0.025	0.007	0.024*	0.009	0.029*	0.009
Frailty (baseline)	0.736	0.020	0.740	0.029	0.705	0.024
Age	0.023	0.002	0.019	0.002	0.021	0.003
Cognitive Impairment (baseline)						
Age	0.067	0.005	0.058	0.005	0.058	0.005
Social Vulnerability	0.541	0.059	0.505	0.059	0.505	0.059
Sex	–0.251*	0.086	–0.234*	0.083	–0.234*	0.083
Education	–0.222	0.010	–0.227	0.010	–0.277	0.010
Frailty (baseline)						
Age	0.033	0.002	0.034	0.003	0.045	0.003
Social Vulnerability	0.437	0.028	0.463	0.034	0.415	0.037
Sex	0.284	0.037	0.272	0.042	0.319	0.050
Education	–0.017	0.005	–0.019	0.005	–0.020*	0.006
Social Vulnerability						
Education	–0.066	0.004	–0.068	0.004	–0.068	0.004
	r	z	r	z	r	z
Cognitive Impairment and Frailty at baseline (residuals)	0.10	4.81	0.07*	3.01	0.04	1.76
Cognitive Impairment and Frailty at follow-up (residuals)	0.18	7.22	0.16	6.03	0.10	4.40

Note: All estimates were significant at $p < 0.001$, except those marked with an asterisk, which were significant at $p < 0.01$ and the covariance between cognitive impairment and frailty residuals at baseline in the sensitivity analysis (non-significant).

DISCUSSION

We identified a bi-directional relationship between frailty and cognitive impairment across two waves of SHARE. Frailty was a risk factor for cognitive impairment and cognitive impairment was associated with frailty at follow-up. In addition to considering basic demographic variables (i.e., age, sex, and education), we also considered the role of social vulnerability. The path from baseline frailty to cognitive impairment at follow-up remained statistically significant and clinically meaningful after controlling for age, sex, social vulnerability, education, and initial cognitive impairment as did the path from baseline cognitive impairment to frailty at follow-up. These results suggest even mild health decrements at midlife have an important impact on subsequent cognitive decline [47, 48].

A number of studies have linked frailty to cognitive decline. For example, baseline frailty measured in three ways (i.e., FI from a comprehensive geriatric assessment, clinical frailty score, and the frailty phenotype) was associated with changes in cognitive function over time regardless of which frailty measure was used [4]. Armstrong and colleagues found frailty was associated with declines in cognitive function over a 3- and 6-year period [22] and that within person changes in frailty were associated with changes in cognition even after taking into consideration baseline frailty [6]. Buchman and colleagues found frailty predicted rate of cognitive decline and incident AD and suggested that frailty occurs before dementia [49]. The results from our study support these results but also suggest that cognitive impairment may occur first and result in subsequent frailty.

Other researchers have found support for this notion that cognitive impairment may occur first and lead to subsequent frailty. Raji and colleagues found that non-frail Mexican Americans with poor cognition were more likely to become frail compared to those with normal cognition [9]. Binder et al. found

that cognitive processing speed predicted physical performance and surmised that declining processing speed may be a risk factor for physical frailty [50]. Further, frailty is associated with health-related quality of life (QOL) in the early stages of cognitive impairment [51]; this impact on QOL provides additional rationale for the concurrent examination of frailty and cognition.

Almost no studies have examined the bidirectional relationship between frailty and cognitive impairment; however, some researchers have examined a bidirectional association between physical function and cognition. Elovainio et al. found that, in middle-aged adults, cognition predicted a decline in physical function 5 years later, but physical function did not predict future cognition; [52] however, other researchers have found evidence of a bi-directional relationship. In a cross-sectional study, Bullain and colleagues found a dose-response relationship between physical function and dementia risk in participants over 90 years of age [53]. Black and Rush found that, over two years, functional status predicted cognitive decline and cognitive impairment predicted functional decline in community dwelling adults aged 75 years and older [54]. Krall et al. found that physical and cognitive functioning interact, such that these impairments build on each other [55]. None of these studies assessed frailty and they were all targeted on a more narrow age range of participants (e.g., middle-aged, over 90 years of age). Although function does contribute to frailty, frailty is a broader and more comprehensive measure which includes deficits across multiple domains (illnesses, symptoms, function, sensory impairments). Consideration of frailty thus affords an opportunity to consider a more holistic measure of health and vulnerability than a focus on function alone. Our work expands on the above research as we simultaneously examined the reciprocal relationships between frailty and cognition using a path analysis approach that takes many other factors into account as well. Further, we used a community-based sample with a wide age range (i.e., 50–99 years of age) making our results more generalizable. We demonstrated that frailty and cognitive impairment may mutually influence each other. Accumulating physical health or cognitive deficits may limit or slow down the body's ability to repair itself, leading to more deficits that could be physical and cognitive in nature [5].

Why might this be so? One potential mechanism is shared risk factors; this is clearly the case for frailty and cognitive impairment. Anstey and colleagues found that smoking and sedentary lifestyle were negatively associated with overall life expectancy and life expectancy free of cognitive impairment [56]. In cognitively unimpaired older adults, those participants who score higher on a physical performance test were less likely to be diagnosed with AD in the future [57]. Buchman and colleagues found that AD neuropathology at death (neuritic plaques, diffuse plaques, and neurofibrillary tangles) was associated with physical frailty before death; further, this association did not differ based on the presence or extent of dementia [58].

At its core, the connection between frailty and cognitive impairment may be due to pathophysiological problems that tend to accumulate with age, albeit at different rates. It should not be seen as an accident that dementia is chiefly a problem of old age [59]. Oxidative stress [60] and chronic inflammation [61] are associated with both frailty and with cognitive decline. Also, physical co-morbidities are associated with clinical manifestations of AD [62]. The heterogeneity in disease expression in people with AD may be due in part to their varying number of comorbid conditions, underscoring the importance of assessing and treating comorbidity and frailty in patients with AD. In one study, 61% of AD patients had three or more comorbidities and more severe comorbidity was associated with worse cognitive function [63]. For example, although there is a relationship between cognitive function and subsequent decline in gait speed, it appears to be attenuated after comorbidities are taken into account [64]. Furthermore, increased muscle strength in community dwelling adults is associated with a lower risk of AD and MCI [65]. Song and colleagues found that mortality and dementia diagnosis were best predicted by the number of health problems rather than by the nature of these problems, suggesting that dementia risk in older adults is determined to an important extent by overall health, presumably reflecting a range of cellular and molecular age-related changes [66].

Although basic demographic variables such as age and sex are commonly taken into account, a comprehensive assessment of social vulnerability is not often considered in studies of frailty and cognitive impairment. Older peoples' social circumstances are complex, so it is important to consider the cumulative impact of social problems. Individually, many aspects of social vulnerability have been found to predict frailty and cognitive impairment. For instance, social disengagement was associated with subsequent cognitive decline even after adjusting for demographic

factors and health, [15] and social engagement was associated with better cognitive function in adults over age 50 [67]. Peek and colleagues found that social support was associated with slower progression of frailty in older Mexican Americans [25]. Given the complexity of older adults' social circumstances, which is insufficiently captured by single social variables considered in isolation, considering different domains of social vulnerability together in a single index may shed light on the cumulative impact of different social "deficits". For this reason, we used the Social Vulnerability Index (SVI) that uses a deficit accumulation approach to measure overall social vulnerability [68].

The SVI has been previously validated in SHARE and includes a range of social factors, from income adequacy to social support and engagement [28]. The SVI was previously found to be associated with cognitive decline in community dwelling older adults over a five year period [17]. We used the SVI as a holistic measure of social circumstances and found an association with lower levels of baseline cognitive impairment and frailty; however, the modification indices did not indicate that a meaningful improvement in model fit could be achieved by allowing social vulnerability to predict follow-up cognitive impairment or frailty. This finding suggests that although people who are more socially vulnerable are frailer and more cognitively impaired, the rate at which people decline with age may be similar across grades of socially vulnerability.

Education was associated with baseline cognitive impairment and cognitive impairment at follow-up, indicating an association with the change in cognition from baseline to follow-up. This is consistent with prior findings that cognitive improvement or stable cognitive function over a five year period were more common in people who were highly educated [4]. Education has been used as an indicator for cognitive reserve and, as such, has found to offer some protection against cognitive impairment [69]. Age was associated with frailty and cognitive impairment at follow-up, indicating an association with the change in both outcomes from baseline to follow-up. Social circumstances are also relevant to the idea of reserve. Viewed in the inverse, the absence of social "deficits" can be seen as contributing to reserve. For example, cognitive reserve as indicated by leisure, social relations, reading, education, and professional achievement was associated with lower levels of cognitive impairment in patients with sporadic late onset AD [70].

Some might argue that using general indices, such as the FI, to predict dementia does not further our understanding of the underlying mechanisms and etiology of cognitive impairment because individual risk factors cannot be teased out [71]. However, the deficit accumulation approach does allow us to take into account the "real world" complexity of older people's health, and formally operationalizes the notion that "the problems of old age come as a package" [72]. For instance, Mekli and colleagues showed that there are potential association between some genetic variations and the FI [73]. There is also evidence that frailty may play a role in the association between neuropathology and the expression of dementia. Although correlated, some people appear to be able to withstand substantial neuropathology and remain cognitively intact [74]. Some attribute this discrepancy to neural reserve, which is potentially maintained through cognitive activity [75]. Another possibility supported by the current research is that frailty may deplete neural reserve, thus cognitive impairment tends to increase as individuals become frailer [6]. The fact that brain pathology commonly associated with dementia and AD has also been found to be associated with frailty provides further support for the role of frailty in neural reserve [76].

Limitations and future research

Health and social deficits in SHARE are based on self-reported responses. The use of objective deficits (e.g., clinical measurements of biometrics and lab data) could have influenced our results. Even so, the FI has been validated using self-report data [77]. The frailty index we used has 65 items, which at first might seem limiting for clinical use. However, in the era of the electronic medical records, it is often possible to make use of existing data. Further, the approach is sufficiently robust if deficit selection criteria are met: almost any version of the FI with at least 30-items can be used [78]. In this way, routine clinical use can be feasible.

Our model explained almost half of the variance in cognitive impairment and over half of the variance in frailty at follow-up, leaving approximately half of the variance in each of these constructs remains unexplained. This unexplained variance suggests that there are factors not included in our model that are associated with change over time in frailty and cognitive impairment; candidates might include neuropathology [79] and physical activity [80, 81]. Conceivably, more detailed measures (such

as biomarkers) might provide additional insight and are of interest to our group. Recent work suggests that although single biomarkers can have limited value, in the aggregate (combined using the principles of deficit accumulation modelling) they can powerfully add to understanding risk, at least in relation to mortality [82, 83].

We used data from two waves of SHARE, separated by two years. A longer follow-up interval may have influenced the results. Longer follow-up periods would allow for more intervening variables that could strengthen or attenuate the association between cognitive impairment and frailty. Assessing multiple time points would allow for the examination of more complex relationships between frailty and cognitive impairment, such as curvilinear relationships. These longitudinal approaches provide fodder for further inquiry.

We used five cognitive deficits as a global measure of cognitive impairment. Although these specific deficits have not been used together in a cognitive impairment index, they have been used as frailty deficits [27]. Combining a variety of cognitive tests into a single index is often carried out when the focus is on global cognition rather than individual domains (e.g., [74, 84, 85]). We chose to focus on overall cognitive impairment; however, results could vary for different cognitive domains. This could be of interest; Gross and colleagues found that impairment in executive function preceded the onset of physical frailty more so than memory or general cognitive performance in a sample of initially healthy women [86]. Further, although we discuss connections between frailty and dementia in the context of considering cognitive impairment more generally, SHARE lacks data on clinical diagnosis of dementia so we focused our investigation on the link between frailty and cognitive impairment.

Conclusions

Just as worsening frailty can lead to declines in cognitive function, the reverse might also be true. In this way, both frailty and cognitive impairment could herald further downward spirals in health. While this may seem pessimistic, it may serve to animate our search for interventions targeting one or the other that might in fact lead to improvements in both. To advance the field, this possibility must be investigated in interventional studies. Although controlled trials in dementia treatment typically focus on individuals who are otherwise healthy, our data suggest that persons with dementia are likely to have concurrent health deficits and may be on the verge of acquiring more deficits. As such, in order to understand, assess, and treat the vast majority of people with dementia (who also have the other problems that come as a package with aging), we must consider a broader range of factors. Dementia research has been criticized for occurring in isolation from the many other features that occur with aging [72]. By measuring overall health status, we offer a feasible means of addressing how to quantify the many problems that can come with old age, and how to demonstrate their impact on cognition (and vice versa).

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SUPPLEMENTARY MATERIAL

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REFERENCES

[1] Mitnitski A, Rockwood K (2016) The rate of aging: The rate of deficit accumulation does not change over the adult life span. *Biogerontology* **17**, 199-204.

[2] Tang EYH, Harrison SL, Errington L, Gordon MF, Visser PJ, Novak G, Dufouil C, Brayne C, Robinson L, Launer LJ, Stephan BCM (2015) Current developments in dementia risk prediction modelling: An updated systematic review. *PLoS One* **10**, 1-31.

[3] Li J-Q, Tan L, Wang H-F, Tan M-S, Tan L, Xu W, Zhao Q-F, Wang J, Jiang T, Yu J-T (2016) Risk factors for predicting progression from mild cognitive impairment to Alzheimer's disease: A systematic review and meta-analysis of cohort studies. *J Neurol Neurosurg Psychiatry* **87**, 476-484.

[4] Mitnitski AB, Fallah N, Rockwood MRH, Rockwood K (2011) Transition in cognitive status in relation to frailty in older adults: A comparison of three frailty measures. *J Nutr Health Aging* **15**, 863-867.

[5] Searle SD, Rockwood K (2015) Frailty and the risk of cognitive impairment. *Alzheimers Res Ther* **7**, 54-59.

[6] Armstrong JJ, Godin J, Launer LJ, White LR, Mitnitski AB, Rockwood K, Andrew MK (2016) Changes in frailty predict changes in cognition in older men: The Honolulu-Asia Aging Study. *J Alzheimers Dis* **53**, 1003-1013.

[7] Samper-Ternent R, Snih S Al, Raji MA, Markides KS, Ottenbacher KJ (2008) Relationship between frailty and cognitive decline in older Mexican Americans. *J Am Geriatr Soc* **56**, 1845-1852.

[8] Han ES, Lee Y, Kim J (2014) Association of cognitive impairment with frailty in community-dwelling older adults. *Int Psychogeriatr* **26**, 155-163.

[9] Raji MA, Al Snih S, Ostir GV, Markides KS, Ottenbacher KJ (2010) Cognitive status and future risk of frailty in older Mexican Americans. *J Gerontol A Biol Sci Med Sci* **65**, 1228-1234.

[10] Robertson DA, Savva GM, Kenny RA (2013) Frailty and cognitive impairment—A review of the evidence and causal mechanisms. *Ageing Res Rev* **12**, 840-851.

[11] Kelaiditi E, Cesari M, Canevelli M, van Kan GA, Ousset P-J, Gillette-Guyonnet S, Ritz P, Duveau F, Soto ME, Provencher V, Nourhashemi F, Salvà A, Robert P, Andrieu S, Rolland Y, Touchon J, Fitten JL, Vellas B (2013) Cognitive frailty: Rational and definition from an (I.A.N.A./I.A.G.G.) international consensus group. *J Nutr Health Aging* **17**, 726-734.

[12] Fried LP, Tangen CM, Walston J, Newman AB, Hirsch C, Gottdiener J, Seeman T, Tracy R, Kop WJ, Burke G, McBurnie MA (2001) Frailty in older adults: Evidence for a phenotype. *J Gerontol A Biol Sci Med Sci* **56**, M146-M156.

[13] Brayne C (2007) The elephant in the room - healthy brains in later life. *Nat Rev Neurosci* **8**, 233-240.

[14] Lang IA, Llewellyn DJ, Langa KM, Wallace RB, Huppert FA, Melzer D (2008) Neighborhood deprivation, individual socioeconomic status, and cognitive function in older people: Analyses from the english longitudinal study of ageing. *J Am Geriatr Soc* **56**, 191-198.

[15] Bassuk SS, Glass TA, Berkman LF (1999) Social disengagement and incident cognitive decline in community-dwelling elderly persons. *Ann Intern Med* **131**, 165-173.

[16] Seeman TE, Lusignolo TM, Albert M, Berkman L (2001) Social relationships, social support, and patterns of cognitive aging in healthy, high-functioning older adults: MacArthur studies of successful aging. *Health Psychol* **20**, 243-255.

[17] Andrew MK, Rockwood K (2010) Social vulnerability predicts cognitive decline in a prospective cohort of older Canadians. *Alzheimers Dement* **6**, 319-325.

[18] Fratiglioni L, Paillard-Borg S, Winblad B (2004) An active and socially integrated lifestyle in late life might protect against dementia. *Lancet Neurol* **3**, 343-353.

[19] Holwerda TJ, Deeg DJH, Beekman ATF, van Tilburg TG, Stek ML, Jonker C, Schoevers RA (2014) Feelings of loneliness, but not social isolation, predict dementia onset: Results from the Amsterdam Study of the Elderly (AMSTEL). *J Neurol Neurosurg Psychiatry* **85**, 135-142.

[20] Koster A, Penninx BWJH, Bosma H, Kempen GIJM, Newman AB, Rubin SM, Satterfield S, Atkinson HH, Ayonayon HN, Rosano C, Yaffe K, Harris TB, Rooks RN, Van Eijk JT, Kritchevsky SB (2005) Socioeconomic differences in cognitive decline and the role of biomedical factors. *Ann Epidemiol* **15**, 564-571.

[21] Wight RG, Aneshensel CS, Miller-Martinez D, Botticello AL, Cummings JR, Karlamangla AS, Seeman TE (2006) Urban neighborhood context, educational attainment, and cognitive function among older adults. *Am J Epidemiol* **163**, 1071-1078.

[22] Armstrong JJ, Mitnitski AB, Andrew MK, Launer LJ, White LR, Rockwood K (2015) Cumulative impact of health deficits, social vulnerabilities, and protective factors on cognitive dynamics in late life: A multistate modeling approach. *Alzheimers Res Ther* **7**, 1-9.

[23] St John PD, Montgomery PR, Tyas SL (2013) Social position and frailty. *Can J Aging* **32**, 250-259.

[24] Woo J, Goggins W, Sham A, Ho SC (2005) Social determinants of frailty. *Gerontology* **51**, 402-408.

[25] Peek MK, Howrey BT, Ternent RS, Ray LA, Ottenbacher KJ (2012) Social support, stressors, and frailty among older mexican american adults. *J Gerontol B Psychol Sci Soc Sci* **67**, 755-764.

[26] Salem BE, Nyamathi AM, Brecht M-L, Phillips LR, Mentes JC, Sarkisian C, Leake B (2013) Correlates of frailty among homeless adults. *West J Nurs Res* **35**, 1128-1152.

[27] Theou O, Brothers TD, Rockwood MR, Haardt D, Mitnitski AB, Rockwood K (2013) Exploring the relationship between national economic indicators and relative fitness and frailty in middle-aged and older Europeans. *Age Ageing* **42**, 614-619.

[28] Andrew MK, Mitnitski AB, Rockwood K (2008) Social vulnerability, frailty and mortality in elderly people. *PLoS One* **3**, e2232.

[29] Börsch-Supan A, Brandt M, Hunkler C, Kneip T, Korbmacher J, Malter F, Schaan B, Stuck S, Zuber S (2013) Data resource profile: The Survey of Health, Ageing and Retirement in Europe (SHARE). *Int J Epidemiol* **42**, 992-1001.

[30] Balthazar MLF, Cendes F, Damasceno BP (2007) Category verbal fluency performance may be impaired in amnestic mild cognitive impairment. *Dement Neuropsychol* **2**, 161-165.

[31] Takayama Y (2010) A delayed recall battery as a sensitive screening for mild cognitive impairment: Follow-up study

of memory clinic patients after 10 years. *J Med Dent Sci* **57**, 177-184.

[32] Sterniczuk R, Theou O, Rusak B, Rockwood K (2015) Cognition test performance in relation to health and function in 12 European countries: The SHARE study. *Can Geriatr J* **18**, 144-151.

[33] Xie H, Mayo N, Koski L (2011) Predictors of future cognitive decline in persons with mild cognitive impairment. *Dement Geriatr Cogn Disord* **32**, 308-317.

[34] Wallace LMK, Theou O, Pena F, Rockwood K, Andrew MK (2015) Social vulnerability as a predictor of mortality and disability: Cross-country differences in the survey of health, aging, and retirement in Europe (SHARE). *Aging Clin Exp Res* **27**, 365–372.

[35] (1997) United Nations Educational, Scientific and Cultural Organization: International Standard Classification of Education.

[36] Hancock GR, Mueller RO (2003) Path analysis. In *Sage Encyclopedia of Social Science Research Methods,* Lewis-Beck M, Bryman A, Liao TF, eds. Sage Publications, Thousand Oaks, CA.

[37] Streiner DL (2005) Finding our way: An introduction to path analysis. *Can J Psychiatry* **50**, 115-122.

[38] Selig JP, Little TD (2012) Autoregressive and cross–lagged panel analysis for longitudinal data. In *The Handbook of Developmental Research Methods,* Laursen B, Little TD, Card NA, eds. The Guilford Press, New York, pp. 265-278.

[39] Rosseel Y (2012) Lavaan: An R package for structural equation modeling. *J Stat Softw* **48**, 1-35.

[40] R Core Team. (2016) R: A language and environment for statistical computing.

[41] Oberski D (2014) lavaan.survey: An R package for complex survey analysis of structural equation models. *J Stat Softw* **57**, 1–27.

[42] Byrne BM (2006) *Structural Equation Modeling with EQS: Basic Concenpts, Applications, and Programming,* Routeledge, Taylor and Francis Group, New York.

[43] Hu L, Bentler PM (1999) Cutoff criteria for fit indexes in covariance structure analysis: Conventional criteria versus new alternatives. *Struct Equ Model A Multidiscip J* **6**, 1-55.

[44] Kenny DA, Kaniskan B, McCoach DB (2014) The performance of RMSEA in models with small degrees of freedom. *Sociol Methods Res* **44**, 486-507.

[45] MacCallum RC, Browne MW, Sugawara HM (1996) Power analysis and determination of sample size for covariance structure modeling. *Psychol Methods* **1**, 130-149.

[46] Satorra A, Bentler PM (2001) A scaled difference chi-square test statistic for moment structure analysis. *Psychometrika* **66**, 507-514.

[47] Chen KHM, Henderson VW, Stolwyk RJ, Dennerstein L, Szoeke C (2015) Prehypertension in midlife is associated with worse cognition a decade later in middle-aged and older women. *Age Ageing* **44**, 439-445.

[48] Norton S, Matthews FE, Barnes DE, Yaffe K, Brayne C (2014) Potential for primary prevention of Alzheimer's disease: An analysis of population-based data. *Lancet Neurol* **13**, 788-794.

[49] Buchman AS, Boyle PA, Wilson RS, Tang Y, Bennett DA (2007) Frailty is associated with incident Alzheimer's disease and cognitive decline in the elderly. *Psychosom Med* **69**, 483-489.

[50] Binder EF, Storandt M, Birge SJ (1999) The relation between psychometric test performance and physical performance in older adults. *J Gerontol A Biol Sci Med Sci* **54**, M428-M432.

[51] Mhaoláin AMN, Gallagher D, Crosby L, Ryan D, Lacey L, Coen RF, Coakley D, Walsh JB, Cunningham C, Lawlor B (2012) Frailty and quality of life for people with Alzheimer's dementia and mild cognitive impairment. *Am J Alzheimers Dis Other Demen* **27**, 48-54.

[52] Elovainio M, Kivimäki M, Ferrie JE, Gimeno D, De Vogli R, Virtanen M, Vahtera J, Brunner EJ, Marmot MG, Singh-Manoux A (2009) Physical and cognitive function in midlife: Reciprocal effects? A 5-year follow-up of the Whitehall II study. *J Epidemiol Community Health* **63**, 468-473.

[53] Bullain SS, Corrada MM, Shah BA, Mozaffar FH, Panzenboeck M, Kawas CH (2013) Poor physical performance and dementia in the oldest old: The 90+ study. *JAMA Neurol* **70**, 107-113.

[54] Black SA, Rush RD (2002) Cognitive and functional decline in adults aged 75 and older. *J Am Geriatr Soc* **50**, 1978-1986.

[55] Krall JR, Carlson MC, Fried LP, Xue Q-L (2014) Examining the dynamic, bidirectional associations between cognitive and physical functioning in older adults. *Am J Epidemiol* **180**, 838-846.

[56] Anstey KJ, Kingston A, Kiely KM, Luszcz MA, Mitchell P, Jagger C (2014) The influence of smoking, sedentary lifestyle and obesity on cognitive impairment-free life expectancy. *Int J Epidemiol* **43**, 1874-1883.

[57] Wilkins CH, Roe CM, Morris JC, Galvin JE (2013) Mild physical impairment predicts future diagnosis of dementia of the Alzheimer's type. *J Am Geriatr Soc* **61**, 1055-1059.

[58] Buchman AS, Schneider JA, Leurgans S, Bennett DA (2008) Physical frailty in older persons is associated with Alzheimer disease pathology. *Neurology* **71**, 499-504.

[59] McDowell I (2001) Alzheimer's disease: Insights from epidemiology. *Aging Clin Exp Res* **13**, 143-162.

[60] Mulero J, Zafrilla P, Martinez-Cacha A (2011) Oxidative stress, frailty and cognitive decline. *J Nutr Heal Aging* **15**, 756-760.

[61] Panza F, Seripa D, Solfrizzi V, Tortelli R, Greco A, Pilotto A, Logroscino G (2015) Targeting cognitive frailty: Clinical and neurobiological roadmap for a single complex phenotype. *J Alzheimers Dis* **47**, 793-813.

[62] Oosterveld SM, Kessels RPC, Hamel R, Ramakers IHGB, Aalten P, Verhey FRJ, Sistermans N, Smits LL, Pijnenburg YA, van der Flier WM, Olde Rikkert MGM, Melis RJF (2014) The influence of co-morbidity and frailty on the clinical manifestation of patients with Alzheimer's disease. *J Alzheimers Dis* **42**, 501-509.

[63] Doraiswamy PM, Leon J, Cummings JL, Marin D, Neumann PJ (2002) Prevalence and impact of medical comorbidity in Alzheimer's disease. *J Gerontol A Biol Sci Med Sci* **57**, M173-M177.

[64] Atkinson HH, Rosano C, Simonsick EM, Williamson JD, Davis C, Ambrosius WT, Rapp SR, Cesari M, Newman AB, Harris TB, Rubin SM, Yaffe K, Satterfield S, Kritchevsky SB (2007) Cognitive function, gait speed decline, and comorbidities: The health, aging and body composition study. *J Gerontol Med Sci* **62A**, 844-850.

[65] Boyle PA, Buchman AS, Wilson RS, Leurgans SE, Bennett DA (2009) Association of muscle strength with the risk of Alzheimer disease and the rate of cognitive decline in community-dwelling older persons. *Arch Neurol* **66**, 1339-1344.

[66] Song X, Mitnitski AB, Rockwood K (2014) Age-related deficit accumulation and the risk of late-life dementia. *Alzheimers Res Ther* **6**, 54-66.

[67] Engelhardt H, Buber I, Skirbekk V, Prskawetz A (2010) Social involvement, behavioural risks and cognitive functioning among older people. *Ageing Soc* **30**, 779-809.
[68] Andrew MK, Keefe JM (2014) Social vulnerability from a social ecology perspective: A cohort study of older adults from the National Population Health Survey of Canada. *BMC Geriatr* **14**, 90.
[69] Fairjones SE, Vuletich EJ, Pestell C, Panegyres PK (2011) Exploring the role of cognitive reserve in early-onset dementia. *Am J Alzheimers Dis Other Demen* **26**, 139-144.
[70] Sánchez Rodríguez JL, Torrellas C, Martín J, José Fernandez M (2011) Cognitive reserve and lifestyle in Spanish individuals with sporadic Alzheimer's disease. *Am J Alzheimers Dis Other Demen* **26**, 542-554.
[71] Anstey KJ, Dixon RA (2014) Applying a cumulative deficit model of frailty to dementia: Progress and future challenges. *Alzheimers Res Ther* **6**, 84.
[72] Fontana L, Kennedy BK, Longo VD, Seals D, Melov S (2014) Treat ageing. *Nature* **511**, 405-407.
[73] Mekli K, Marshall A, Nazroo J, Vanhoutte B, Pendleton N (2015) Genetic variant of Interleukin-18 gene is associated with the Frailty Index in the English Longitudinal Study of Ageing. *Age Ageing* **44**, 938-942.
[74] Negash S, Wilson RS, Leurgans SE, Wolk DA, Schneider JA, Buchman AS, Bennett DA, Arnold SE (2013) Resilient brain aging: Characterization of discordance between Alzheimer's disease pathology and cognition. *Curr Alzheimer Res* **10**, 844-851.
[75] Wilson RS, Barnes LL, Krueger KR, Hoganson G, Bienias JL, Bennett DA (2005) Early and late life cognitive activity and cognitive systems in old age. *J Int Neuropsychol Soc* **11**, 400-407.
[76] Buchman AS, Yu L, Wilson RS, Schneider JA, Bennett DA (2013) Association of brain pathology with the progression of frailty in older adults. *Neurology* **80**, 2055-2061.
[77] Mitnitski AB, Song X, Rockwood K (2004) The estimation of relative fitness and frailty in community-dwelling older adults using self-report data. *J Gerontol* **59**, M627-632.
[78] Searle SD, Mitnitski AB, Gahbauer EA, Gill TM, Rockwood K (2008) A standard procedure for creating a frailty index. *BMC Geriatr* **8**, 24.
[79] Negash S, Bennett DA, Wilson RS, Schneider JA, Arnold SE (2011) Cognition and neuropathology in aging: Multidimensional perspectives from the rush religious orders study and rush memory and aging project. *Curr Alzheimer Res* **8**, 336-340.
[80] Blodgett J, Theou O, Kirkland S, Andreou P, Rockwood K (2014) The association between sedentary behaviour, moderate–vigorous physical activity and frailty in NHANES cohorts. *Maturitas* **80**, 187-191.
[81] Aichberger MC, Busch MA, Reischies FM, Ströhle A, Heinz A, Rapp MA (2010) Effect of physical inactivity on cognitive performance after 2.5 years of follow-up: Longitudinal results from the Survey of Health, Ageing, and Retirement (SHARE). *GeroPsych (Bern)* **23**, 7-15.
[82] Mitnitski AB, Collerton J, Martin-Ruiz C, Jagger C, von Zglinicki T, Rockwood K, Kirkwood TB (2015) Age-related frailty and its association with biological markers of ageing. *BMC Med* **13**, 161.
[83] Howlett SE, Rockwood M, Mitnitski AB, Rockwood K (2014) Standard laboratory tests to identify older adults at increased risk of death. *BMC Med* **12**, 171.
[84] Boyle PA, Buchman AS, Wilson RS, Leurgans SE, Bennett DA (2010) Physical frailty is associated with incident mild cognitive impairment in community-based older persons. *J Am Geriatr Soc* **58**, 248-255.
[85] Wilson RS, Mendes De Leon CF, Barnes LL, Schneider JA, Bienias JL, Evans DA, Bennett DA (2002) Participation in cognitively stimulating activities and risk of incident Alzheimer disease. *JAMA* **287**, 742-748.
[86] Gross AL, Xue Q, Bandeen-Roche K, Linda P, Varadhan R, McAdams-DeMarco MA, Walston J, Carlson MC (2016) Declines and impairment in executive function predict onset of physical frailty. *J Gerontol A Biol Sci Med Sci* **71**, 1624-1630.