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ORIGINAL ARTICLE

Frailty is associated with the clinical expression of neuropsychological deficits in older adults

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Abstract

Background and purpose: The aim was to determine whether frailty is associated with the relationship between neuropsychological markers and global cognition in older adults.

Methods: Cross-sectional analyzes were conducted of baseline data from three large cohort studies: National Alzheimer's Coordinating Center (NACC), Rush Memory and Aging Project (MAP) and Alzheimer's Disease Neuroimaging Initiative (ADNI). Studies recruited North American participants along the spectrum of cognitive functioning (44% no cognitive impairment at baseline). A frailty index was computed in each dataset. Frailty indices, neuropsychological tests (including measures of processing speed, episodic, semantic and working memory) and Mini-Mental State Examination (MMSE) scores were the variables of interest, with age, sex, education and apolipoprotein E ε4 evaluated as confounders.

Results: Across all studies, 23,819 participants aged 55–104 (57% female) were included in analyzes. Frailty index scores were significantly and inversely associated with MMSE scores and significantly moderated relationships between neuropsychological test scores and MMSE scores. In participants with higher frailty index scores, lower neuropsychological test scores were more strongly associated with lower MMSE scores (standardized interaction coefficients ranged from −0.19 to −1.17 in NACC, −0.03 to −2.27 in MAP and −0.04 to −0.38 in ADNI, depending on the neuropsychological test). These associations were consistent across the different databases and were mostly independent of the composition of frailty indices (i.e., after excluding possible symptoms of dementia).

Conclusions: Amongst older Americans, frailty is associated with the cognitive expression of neuropsychological deficits. Implementation of frailty assessment in routine neurological and neuropsychological practice should be considered to optimize care outcomes for older adults.

KEYWORDS
ageing, aging, cognition, dementia, frailty, neuropsychological tests, neuropsychology

INTRODUCTION

Neuropsychological tests play a pivotal role in the clinical approach to cognitive disorders. Even with the growing availability and use of biomarkers [1], standardized neuropsychological measurements of cognitive skills and impairments remain essential in diagnosing dementia, discriminating between dementia aetiologies, monitoring trajectories of progression over time and developing individualized therapeutic strategies [2, 3]. These measurements are also used to identify dementia risk conditions (e.g., mild cognitive impairment [MCI]; subjective cognitive decline) [4, 5] and are commonly used in research protocols to determine participant eligibility and as endpoints (either alone or combined into composite scores) [6]. For neuropsychological testing to be most valuable in these contexts, factors impacting their scores and interpretation must be well understood.

Frailty is defined as the age-related decline in physiological capacity across several organ systems. It is manifest in a greater risk for adverse outcomes, which can reflect a lesser ability to resist a given stress or to recover from it in a timely fashion [7]. Frailty has recently been demonstrated to moderate the relationships between the neuropathological hallmarks of Alzheimer's disease and the clinical presentation of dementia [8]; polygenic dementia risk and dementia development [9]; and Alzheimer's disease biomarkers and cognitive status [10]. Previous work has consistently reported lower cognitive test scores for people with higher degrees of frailty [11–13], and the concept of 'cognitive frailty' has been introduced to explain the adverse outcomes commonly seen amongst people with the combined presence of both frailty and cognitive deficits [14].

Increasingly, too, it is recognized that the degree of frailty may play a role in moderating the relationship between test scores and their expression as a disease [15]. For these reasons, frailty assessment might be important when interpreting the relationship between neuropsychological tests and underlying neural substrates. In other words, frailty may influence the expression of cognitive change and alter the accuracy of neuropsychological tests, hampering their interpretability.

In the present study, the aim was to understand the clinical utility of measuring a patient's degree of frailty regarding its impact on the interpretation of neuropsychological testing. Here, recent advancements on the role of frailty assessment in clinical neurological practice [16–20] are built upon to test two hypotheses: (i) a higher degree of frailty is associated with worse global cognitive functioning as measured by the Mini-Mental State Examination (MMSE), and (ii) frailty moderates the relationship between neuropsychological measures and global cognitive functioning, independently of common confounding factors.

METHODS

Sample and datasets

Participants were drawn from the baseline assessments of three large, independent cohort studies of dementia and cognitive decline (Table 1): the National Alzheimer's Coordinating Center (NACC), the Rush Memory and Aging Project (MAP) and the Alzheimer's Disease Neuroimaging Initiative (ADNI). Participants were eligible for inclusion in the analytical sample if they were 55 years of age or older, had data available on covariates (age, sex, education level and apolipoprotein E [*APOE*] ε4 status), had sufficient demographic and health data to calculate a frailty index at their baseline assessment and had valid performance data for at least one of the included cognitive tests (Table 2).

TABLE 1 Characteristics of the analytical sample.

Characteristic	Subsample		
	NACC	MAP	ADNI
N	21,474	1,575	770
Age, years			
Mean (SD)	73.3 (8.8)	80.1 (7.4)	72.7 (7.2)
Range	55–104	55–101	55–91
Sex, *N* (%)			
Men	9,350 (44)	420 (27)	404 (53)
Women	12,124 (57)	1,155 (73)	366 (48)
Education, years, mean (SD)	15.1 (3.4)	14.6 (3.2)	16.3 (2.6)
Cognitive status, *N* (%)			
Dementia	7,544 (35)	77 (5)	145 (19)
MCI	4,831 (23)	402 (26)	335 (44)
Not cognitively impaired	9,099 (42)	1,095 (70)	290 (38)
MMSE score			
Median (IQR)	28 (5)	28 (2)	28 (4)
Mean (SD)	25.7 (5.2)	27.5 (3.2)	27.4 (2.7)
Range	0–30	1–30	19–30
Frailty index score			
Median (IQR)	0.13 (0.14)	0.19 (0.15)	0.20 (0.13)
Range	0.00–0.65	0.00–0.77	0.00–0.56
APOE ε4 carrier, *N* (%)	8,764 (41)	348 (22)	354 (46)

Note: Proportions may not sum to 100% due to rounding.

Abbreviations: ADNI, Alzheimer's Disease Neuroimaging Initiative; APOE, apolipoprotein; IQR, interquartile range; MAP, Memory and Aging Project; MCI, mild cognitive impairment; MMSE, Mini-Mental State Examination; NACC, National Alzheimer's Coordinating Center; SD, standard deviation.

National Alzheimer's Coordinating Center (NACC)

NACC data are contributed by Alzheimer's Disease Research Centers (ADRCs) in the United States (https://naccdata.org). Since 2005, these ADRCs have employed prospective, standardized and longitudinal data collection methods involving detailed clinical evaluations of study participants. The resulting Uniform Data Set (UDS) comprises information on participants' sociodemographics, neurological examination findings, functional status, neuropsychological test results and clinical diagnoses, with UDS visits conducted

TABLE 2 Means and standard deviations for neuropsychological tests included from each study.

		NACC		MAP		ADNI	
Cognitive domain	**Test**	**Mean (SD)**	***n***	**Mean (SD)**	***n***	**Mean (SD)**	***n***
Episodic memory	Logical memory (delayed)	7.7 (5.9)	20,872	8.7 (4.7)	1,570	8.2 (5.3)	770
Semantic memory	Boston naming test	23.9 (6.4)	20,960	13.7 (1.6)	1,551	26.4 (4.2)	768
	Animal naming	15.7 (6.9)	21,318	16.0 (5.4)	1,574	17.9 (6.1)	770
Working memory	Digit span forwards	6.3 (1.3)	21,176	8.2 (2.1)	1,574	–	–
	Digit span backwards	4.3 (1.4)	21,121	6.1 (2.1)	1,572	–	–
Processing speed	Digit-symbol coding	37.7 (15.9)	19,616	36.6 (11.6)	1,535	–	–
	Trail-making test A	49.9 (33.3)	20,433	–		40.2 (19.2)	761
	Trail-making test B	136.5 (85.6)	18,570	–		99.9 (52.6)	693

Note: The summary statistics presented here were calculated from raw test scores. Neuropsychological tests without values denote tests that were not included in the protocol of that study. The MAP used a short form of the Boston naming test (15 rather than 30 items).

Abbreviations: ADNI, Alzheimer's Disease Neuroimaging Initiative; MAP, Memory and Aging Project; NACC, National Alzheimer's Coordinating Center; SD, standard deviation.

approximately annually. Participants contributing data to the NACC UDS include healthy volunteers as well as people with MCI, dementia and related disorders. Informed consent was obtained at the individual ADRCs. The NACC is approved by the University of Washington Institutional Review Board. Baseline data from 21,474 NACC participants assessed at 34 ADRCs between September 2005 and February 2020 were used in this study.

Memory and Aging Project (MAP)

The Rush MAP is a clinical-pathological cohort study that, since its inception in 1997, has enrolled over 2,100 older adults with annual clinical evaluations [21]. This study recruited from residential facilities, senior and subsidized housing, church groups and social service agencies in northeastern Illinois (USA). Participants were eligible for enrolment if they were able and willing to sign (i) an informed consent and (ii) an Anatomical Gift Act, agreeing to donate their brain, spinal cord and other biospecimens at their death. Participants also signed a repository consent that allowed their data to be repurposed for other studies. MAP was approved by an Institutional Review Board of Rush University Medical Center, Chicago, IL, USA. Data access can be requested at www.radc.rush.edu. Baseline data from 1,575 MAP participants were used in the present analyzes.

Alzheimer's Disease Neuroimaging Initiative (ADNI)

Data used in the preparation of this study were also obtained from the ADNI database (http://adni.loni.usc.edu). The ADNI was launched in 2003 as a public–private partnership led by Professor Michael W. Weiner. The primary goal of ADNI has been to test whether serial magnetic resonance imaging, positron emission tomography, other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of MCI and early Alzheimer's disease. Written informed consent was obtained from all participants. Study procedures were approved by local institutional review boards. Full details of ethics approval, study design, participant recruitment and clinical testing have been published previously and are available at adni-info.org. Baseline data from 770 persons participating in phase 2 of the ADNI project (ADNI2) were included in the analytical sample.

Global cognitive functioning and cognitive status

Global cognitive functioning was assessed in all studies using the MMSE [22]. Briefly, the MMSE is a 30-point scale comprising several cognitive domains, including visuospatial, language, attention, memory recall, orientation. Higher scores indicate better cognitive performance. Despite only providing a rough measure of the individual's cognitive functioning, the MMSE is amongst the most widely used tools to screen for cognitive impairment, track changes in cognitive functions over time and define the severity of cognitive deficits [23]. On occasions and in settings where an extensive and formal neuropsychological evaluation is not available, it often plays a central role in the diagnosis of dementia [24].

Cognitive status was determined by clinical assessment in each study. In the NACC, either a consensus team or a single physician used standard diagnostic criteria to classify participants as either normal cognition, MCI [25, 26] or all-cause dementia [27, 28]. In the MAP, presumptive diagnoses of dementia and Alzheimer's disease were calculated via an algorithmic decision tree using accepted clinical criteria [28] and confirmed by a clinician. Participants were diagnosed with MCI based on cognitive impairment in the absence of a dementia diagnosis [29]. In the ADNI, the diagnosis of MCI was based on the Petersen criteria [5, 30]. In contrast, patients with Alzheimer's disease dementia met the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association criteria for probable Alzheimer's disease [28].

Neuropsychological tests

Individual neuropsychological tests covering several domains were used in the analyzes presented here (Table 2). As test batteries were not identical across studies, tests were grouped and analyzed in domains: episodic memory (delayed logical memory [31] for all studies), semantic memory (Boston naming [32] and animal naming [33] for all studies), working memory (digits forward and backward [34] for NACC and MAP) and processing speed (digit symbol pairs [34] for NACC and MAP, trail-making tests A and B [35] for NACC and ADNI).

Frailty index

A separate frailty index operationalized the degree of age-related health-deficit accumulation in each dataset (see Table S1). A frailty index is a common measure of health status and closely reflects an individual's risk for adverse health events and mortality, independently of chronological age [36–38]. Variables included in a frailty index can be symptoms, signs, functional disabilities and comorbidities [39]. To calculate a frailty index, the number of health deficits present in an individual is divided by the total number of deficits considered in the clinical evaluation, with higher scores representing higher frailty. For example, if a person has 10 deficits out of 50 variables considered, the frailty index will be 10/50 = 0.20. For our analyzes, frailty was evaluated as a continuous measure (0–1) as well as a categorical variable using cut-points to indicate low (scores <0.10), intermediate (scores ≥0.10 and <0.25) and high frailty (scores ≥0.25) [40]. For a sensitivity analysis, the frailty indices generated in the three datasets were recalculated excluding deficits that could potentially represent symptoms of dementia (i.e., functional deficits, stroke, psychiatric disorders and psychiatric symptoms; Table S1) [41].

Demographics and covariates

All models evaluated age, sex, education and *APOE* ε4 status as potential confounders and these were included as covariates. Age and education were measured in years, sex was a self-reported binary variable (male/female) and *APOE* ε4 status was categorized as any *APOE* ε4 allele or none. Covariate selection was guided by recommendations published elsewhere [42] and based on our previous work demonstrating strong links between these characteristics and later-life cognition [19].

Statistical analysis

Sample characteristics and descriptive summary statistics were calculated for variables of interest in each dataset. Characteristics of the frailty indices were examined by plotting the distribution of frailty index scores (density plots) and calculating their relationship with age using Pearson correlations.

As the scoring was different for some neuropsychological tests across datasets (NACC, MAP, ADNI), standardized scores (*Z* scores) for these variables were used in statistical models. Within the analytical sample of each dataset, means and standard deviations were first calculated for each neuropsychological test. Next, *Z* scores were calculated for each participant for each neuropsychological test by subtracting their test score from the sample mean and dividing by the sample standard deviation. These *Z* scores were transformed so that higher scores represented better performance for all neuropsychological tests. Multiple linear regression models were used to quantify the relationships between frailty index scores and neuropsychological test *Z* scores (the independent variables) with MMSE scores (the dependent variable) whilst adjusting for known confounders (age, sex, years of education and *APOE* ε4 status). Statistical models were built in two steps. First, frailty index scores and all confounders were added to the model to quantify the strength of the confounder-adjusted relationship between frailty index scores and MMSE scores (objective 1). Next, scores from a neuropsychological test *Z* score were added to the model and an interaction term was included with frailty index scores to evaluate whether the strength and/or direction of the relationship between neuropsychological test scores and MMSE scores differed as a function of frailty (objective 2). Separate models were constructed for each neuropsychological test and associations were expressed as the change in MMSE scores associated with a 0.1 increase in frailty index scores and accompanied by 95% confidence intervals (95% CI). To aid in visualization and provide further specificity to any statistically significant interactions, the continuous frailty index scores were replaced with a categorical frailty group variable to assess the relationships between neuropsychological test scores and MMSE scores at three different levels of frailty.

Three sensitivity analyzes were undertaken to explore the consistency and robustness of the results. First, to compare the cohorts more directly, the initial analyzes were repeated using samples restricted to participants with normal cognition or MCI between the ages of 65 and 75. This coordinated approach to analyzes across datasets has been made with other studies of ageing, allowing for more reliable and generalizable results [43]. Secondly, to examine whether symptoms closely related to dementia were driving the relationship between frailty index scores and MMSE scores, the analyzes were repeated with frailty indices that excluded these items (Table S1). The third sensitivity analysis was to determine whether associations differed in strength or direction between men and women; however, as associations did not differ meaningfully between these populations, sex-stratified results are not presented. Pooled results were not calculated given the considerable heterogeneity in study samples, and associations were examined in each study sample separately. Statistical analyzes were undertaken using R (NACC, MAP) and SPSS (ADNI), and visualizations were conducted using R.

RESULTS

Sample characteristics

Of 23,819 participants included in the analytical sample, 90% were participating in the NACC (Table 1). Participants ranged in age from 55 to 104 years and were somewhat older in the MAP than the other studies. Dementia was most common amongst NACC participants and least common amongst MAP participants. Compared with ADNI or MAP participants, NACC participants had frailty index scores 0.06–0.07 points lower (Figure 1); the highest frailty index scores were observed in MAP (submaximal limit, 99th percentile 0.56), followed by NACC and ADNI (submaximal limits 0.46 and 0.44, respectively). Frailty index scores were positively correlated with participant age in each study (MAP, $r=0.31$, $p<0.001$; ADNI, $r=0.20$, $p<0.001$; NACC, $r=0.14$, $p<0.001$).

Frailty and MMSE

The association between frailty indices and MMSE scores was assessed in each sample. After adjusting for possible confounders (age, sex, education and *APOE* ε4), higher levels of frailty were associated with worse MMSE performance in all study samples (Figure 2). This relationship was particularly strong in the NACC, where each 0.1 increase in frailty index was associated with 2.49 points decrease in MMSE scores ($B=-2.49$, 95% CI −2.55 to −2.43), and weaker in ADNI ($B=-0.73$, 95% CI −0.92 to −0.53) and MAP ($B=-0.68$, 95% CI −0.82 to −0.55). When the study samples were restricted to participants aged between 65 and 75 years with normal cognition or MCI, associations were weaker and more similar amongst the three samples

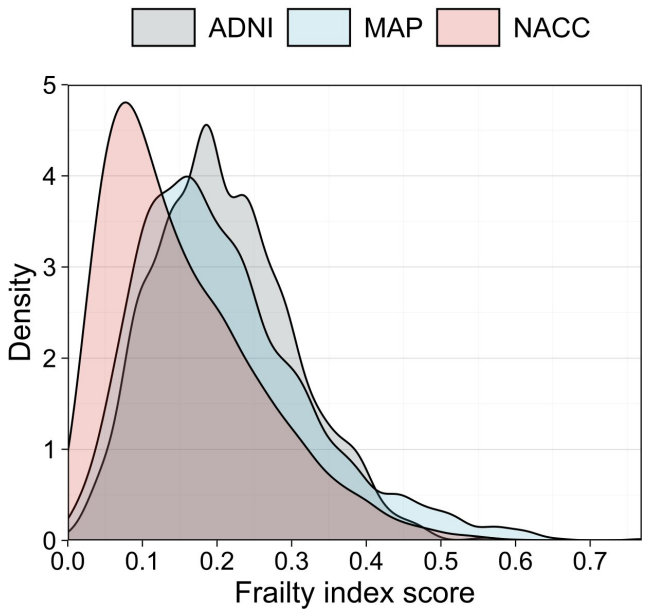

FIGURE 1 Density plot of frailty index scores in NACC ($N=21,474$), MAP ($N=1,575$) and ADNI ($N=770$).

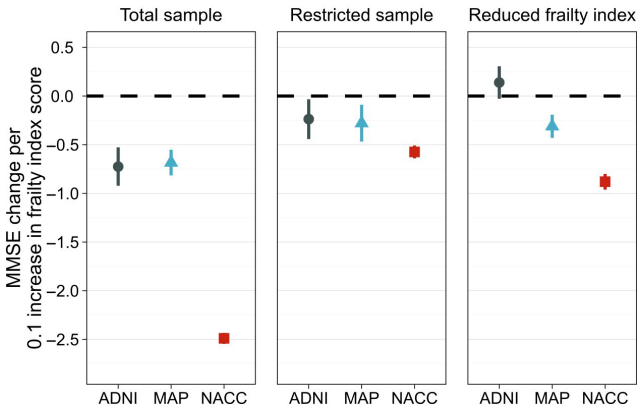

FIGURE 2 Associations of frailty index scores and MMSE scores in each study sample. Estimates (*B* values) and 95% confidence intervals were calculated using linear models adjusted for age, sex, education and *APOE* ε4 status.

(NACC, $B=-0.57$, 95% CI −0.64 to −0.51; MAP, $B=-0.28$, 95% CI −0.47 to −0.09; ADNI, $B=-0.24$, 95% CI −0.44 to −0.03). When a reduced frailty index not considering possible symptoms of dementia was used, statistically significant associations were confirmed for NACC ($B=-0.88$, 95% CI −0.96 to −0.80) and MAP ($B=-0.31$, 95% CI −0.43 to −0.19) but not ADNI ($B=0.14$, 95% CI −0.03 to 0.31).

Frailty, neuropsychological tests and MMSE

The degree to which frailty index scores moderated the relationship between neuropsychological test scores and MMSE scores was next assessed. The frailty index score by neuropsychological test score interaction term was consistently negative in value and statistically significant across neuropsychological tests and study samples (Table S2). However, although consistent in the direction of effect, this interaction was not statistically significant for the trail-making test A and trail-making test B in ADNI. Given a one standard deviation decrease in neuropsychological test scores, participants classified as having low frailty had the smallest decrease in MMSE scores, and participants classified as having high frailty had the largest decrease in MMSE scores (Figure 3). In sensitivity analyzes that used either the restricted sample or the reduced frailty index, the continuous interaction effects were most often negative in direction and statistically significant for NACC and MAP. Still, associations in ADNI varied in both directions and statistical significance.

DISCUSSION

In this analysis of 23,819 older adults, two main findings are reported: (i) a higher degree of frailty was associated with worse cognitive function; (ii) the relationship between neuropsychological and global cognitive function was dependent on frailty. Specifically, robust older people (i.e., with low frailty) tended to have relatively preserved overall cognitive functioning despite discrete

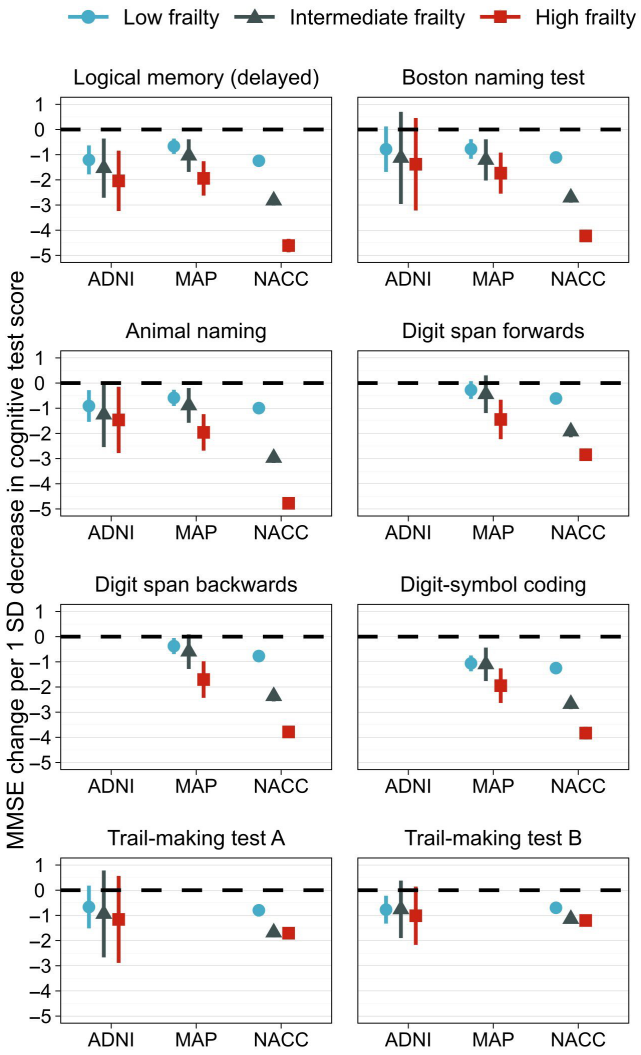

FIGURE 3 Associations of neuropsychological test *Z* scores and MMSE scores in each study sample at low frailty (frailty index scores 0.000–0.100), intermediate frailty (frailty index scores 0.101–0.250) and high frailty (frailty index scores 0.251–1.000). Estimates (*B* values) and 95% confidence intervals were calculated using linear models with a frailty group by neuropsychological test interaction term and adjusted for age, sex, education and *APOE* ε4 status.

neuropsychological deficits, whereas frail older people showed more global cognitive impairment as a result of neuropsychological deficits. These findings were robust to several investigations of bias and sensitivity.

These results bolster the notion that frailty exerts a detrimental influence on late-life cognition. Frailty has been consistently associated with impaired cognitive functioning [44, 45]. It represents a risk factor for incident MCI and dementia in cognitively normal older adults [9, 46, 47], MCI conversion to overt dementia [19, 20, 48] and steeper cognitive decline amongst patients already diagnosed with dementia [49]. Moreover, it reduces the likelihood of more favourable cognitive trajectories, such as recovering from MCI to normal cognition [19]. Interestingly, these associations were present even after adjusting for major confounders (e.g., age, education, *APOE* genotype). Consequently, there is growing consensus on promoting the inclusion of frailty assessment in the risk reduction strategies towards dementia [50].

Previous work by our groups has found that frailty moderates the relationship between the neuropathological hallmarks of Alzheimer's disease and the clinical presentation of dementia [8], the relationship between genetic profile and dementia [9] and the association between Alzheimer's disease biomarkers and cognitive status [16]. In our present study, frailty emerged as a moderator of the association of domain-specific neuropsychological abilities/impairments with overall cognition. Thus, there is increasing evidence that, by reducing the physiological reserves of the organism, frailty contributes to the biological and phenotypic heterogeneity of cognitive disorders. Furthermore, it may be hypothesized that frailty counteracts the effect of other moderators (e.g., cognitive reserve, brain reserve) that may positively influence the individual's susceptibility to exhibit clinical manifestations of neuropathology and the trajectories of cognitive decline.

This study also suggests how the interpretation of the neuropsychological assessment may be significantly biased by a person's frailty status [15]. Indeed, the same neuropsychological impairment may assume different clinical implications depending on the degree of frailty of the tested individual; our data indicate that cognitive deficits detected via neuropsychological tests may reflect larger losses in global cognitive functioning amongst people with higher degrees of frailty. In the absence of frailty assessment, this clinically relevant information is hidden. There is a need to develop scoring and standardization systems that may reflect the clinical complexity of the older person. Indeed, frailty and cognitive deficits co-occur commonly and are sometimes conceptualized as cognitive frailty, which reflects high clinical complexity [14]. A sole focus on cognitive frailty, however, may hide interactions between these phenomena that are here shown to have clinical relevance. A continuous rather than dichotomous quantification of frailty degrees and cognitive deficits may instead support a more accurate/granular appreciation of their mutual interplay. Either way, these considerations assume essential public health implications in the light of the ongoing demographic and epidemiological transformations, namely population ageing and the increasing prevalence of age-related chronic pathological conditions [51].

Limitations

The results from this study should be interpreted taking into account some limitations. First, although a large sample of participants drawn from three independent cohort studies was analyzed, each of these studies was based in North America. Therefore, the degree to which these results extend to other international populations is unclear. Similarly, the study samples were predominantly composed of highly educated older people who probably do not

represent the 'real world' clinical scenario; it is important to acknowledge that these people were probably healthier and higher functioning than those in the broader population, on average. Secondly, the MMSE, the primary outcome used in our analyzes, provides only a rough measure of the individual's overall cognitive functioning. For example, it does not include an assessment of executive functions. Furthermore, it only marginally captures the complex mechanisms underlying human cognition. However, it was the only measure of global cognition consistently present in the three datasets and is still the most widely used tool in clinical practice to describe overall cognitive performance and define the severity of cognitive impairment. Further research on the potentially differential links between frailty and decline or maintenance across the range of cognitive domains would be advantageous. Thirdly, the associations reported here are cross-sectional; directionality and temporality could not be addressed. Although a recent genetic investigation into the relationship between frailty and Alzheimer's disease did not find evidence of a causal pathway [52], our sensitivity analysis excluding possible symptoms of dementia from the calculation of frailty indices supported our original results. Moreover, a recent longitudinal study that employed in a sensitivity analysis a landmark period to reduce the impact of undetected dementia on results found support for frailty preceding dementia [9]. Similarly, the cross-sectional nature of our results also limits the understanding of the mechanisms underpinning the reported associations. Further longitudinal research is needed to better understand the interplay between frailty, neuropsychological and global cognitive functioning, and other patient characteristics. Fourthly, other potentially relevant covariates, such as race, culture and socioeconomic status, were not considered in our analyzes. Further research is necessary to detail whether the associations reported here are observed in different population groups.

CONCLUSIONS

In conclusion, frailty is strongly related to the level of cognitive functioning amongst older persons and is associated with the cognitive expression of neuropsychological deficits. Accumulating evidence supports the implementation of frailty assessment in routine neurological and neuropsychological practice to optimize care and outcomes for older adults.

AUTHOR CONTRIBUTIONS

Marco Canevelli: Conceptualization; formal analysis; writing—original draft; investigation; methodology. Lindsay M. K. Wallace: Conceptualization; formal analysis; writing—original draft; investigation; methodology. Giuseppe Bruno: Conceptualization; writing—review and editing; supervision. Matteo Cesari: Conceptualization; writing—review and editing; supervision. Kenneth Rockwood: Conceptualization; writing—review and editing; supervision. David D. Ward: Conceptualization; formal analysis; writing—original draft; investigation; methodology.

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CONFLICT OF INTEREST STATEMENT

KR is Co-founder of Ardea Outcomes, which (as DGI Clinical) in the last 3 years has contracts with pharma and device manufacturers on individualized outcome measurement. MCa, LMKW, GB, MCe and DDW have nothing to report.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the National Alzheimer's Coordinating Centre (NACC, https://www.naccdata.org/), the Rush Memory and Aging Project (MAP, https://www.radc.rush.edu/) and the Alzheimer's Disease Neuroimaging Initiative (ADNI, https://adni.loni.usc.edu). Some restrictions may apply to the availability of these data.

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REFERENCES

1. Scheltens P, De Strooper B, Kivipelto M, et al. Alzheimer's disease. *Lancet*. 2021;397(10284):1577-1590. doi:10.1016/S0140-6736(20)32205-4
2. Arvanitakis Z, Shah RC, Bennett DA. Diagnosis and management of dementia: review. *JAMA*. 2019;322(16):1589-1599. doi:10.1001/jama.2019.4782
3. Jacova C, Kertesz A, Blair M, Fisk JD, Feldman HH. Neuropsychological testing and assessment for dementia. *Alzheimers Dement*. 2007;3(4):299-317. doi:10.1016/j.jalz.2007.07.011
4. Jessen F, Amariglio RE, Buckley RF, et al. The characterisation of subjective cognitive decline. *Lancet Neurol*. 2020;19(3):271-278. doi:10.1016/S1474-4422(19)30368-0
5. Petersen RC. Clinical practice. Mild cognitive impairment. *N Engl J Med*. 2011;364(23):2227-2234. doi:10.1056/NEJMcp0910237
6. Schneider LS, Goldberg TE. Composite cognitive and functional measures for early stage Alzheimer's disease trials. *Alzheimers Dement (Amst)*. 2020;12(1):e12017. doi:10.1002/dad2.12017
7. Howlett SE, Rutenberg AD, Rockwood K. The degree of frailty as a translational measure of health in aging. *Nat Aging*. 2021;1(8):651-665. doi:10.1038/s43587-021-00099-3
8. Wallace LMK, Theou O, Godin J, Andrew MK, Bennett DA, Rockwood K. Investigation of frailty as a moderator of the relationship between neuropathology and dementia in Alzheimer's disease: a cross-sectional analysis of data from the Rush Memory and Aging Project. *Lancet Neurol*. 2019;18(2):177-184. doi:10.1016/S1474-4422(18)30371-5
9. Ward DD, Ranson JM, Wallace LMK, Llewellyn DJ, Rockwood K. Frailty, lifestyle, genetics and dementia risk. *J Neurol Neurosurg Psychiatry*. 2022;93(4):343-350. doi:10.1136/jnnp-2021-327396
10. Wallace LMK, Theou O, Darvesh S, et al. Neuropathologic burden and the degree of frailty in relation to global cognition and dementia. *Neurology*. 2020;95(24):e3269-e3279. doi:10.1212/WNL.0000000000010944
11. Armstrong JJ, Mitnitski A, Andrew MK, Launer LJ, White LR, Rockwood K. Cumulative impact of health deficits, social vulnerabilities, and protective factors on cognitive dynamics in late life: a multistate modeling approach. *Alzheimers Res Ther*. 2015;7(1):38. doi:10.1186/s13195-015-0120-7
12. Mitnitski A, Fallah N, Rockwood MRH, Rockwood K. Transitions in cognitive status in relation to frailty in older adults: a comparison of three frailty measures. *J Nutr Health Aging*. 2011;15(10):863-867. doi:10.1007/s12603-011-0066-9
13. Thibeau S, McDermott K, McFall GP, Rockwood K, Dixon RA. Frailty effects on non-demented cognitive trajectories are moderated by sex and Alzheimer's genetic risk. *Alzheimers Res Ther*. 2019;11(1):55. doi:10.1186/s13195-019-0509-9
14. Kelaiditi E, Cesari M, Canevelli M, et al. Cognitive frailty: rational and definition from an (I.A.N.A./I.A.G.G.) international consensus group. *J Nutr Health Aging*. 2013;17(9):726-734. doi:10.1007/s12603-013-0367-2
15. Canevelli M, Cesari M, Raganato R, et al. Role of frailty in the assessment of cognitive functioning. *Mech Ageing Dev*. 2019;181:42-46. doi:10.1016/j.mad.2019.111122
16. Canevelli M, Arisi I, Bacigalupo I, et al. Biomarkers and phenotypic expression in Alzheimer's disease: exploring the contribution of frailty in the Alzheimer's disease neuroimaging initiative. *Geroscience*. 2021;43(2):1039-1051. doi:10.1007/s11357-020-00293-y
17. Canevelli M, Cesari M, Remiddi F, et al. Promoting the assessment of frailty in the clinical approach to cognitive disorders. *Front Aging Neurosci*. 2017;9:36. doi:10.3389/fnagi.2017.00036
18. Pascual-Leone A. To reduce the risk of dementia, focus on the patient. *Ann Neurol*. 2021;89(6):1080-1083. doi:10.1002/ana.26086
19. Ward DD, Wallace LMK, Rockwood K. Cumulative health deficits, *APOE* genotype, and risk for later-life mild cognitive impairment and dementia. *J Neurol Neurosurg Psychiatry*. 2021;92(2):136-142. doi:10.1136/jnnp-2020-324081
20. Ward DD, Wallace LMK, Rockwood K. Frailty and risk of dementia in mild cognitive impairment subtypes. *Ann Neurol*. 2021;89(6):1221-1225. doi:10.1002/ana.26064
21. Bennett DA, Buchman AS, Boyle PA, Barnes LL, Wilson RS, Schneider JA. Religious orders study and Rush Memory and Aging

Project. *J Alzheimers Dis*. 2018;64(s1):S161-S189. doi:10.3233/JAD-179939
22. Folstein MF, Folstein SE, McHugh PR. 'Mini-mental state'. A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res*. 1975;12(3):189-198. doi:10.1016/0022-3956(75)90026-6
23. Karimi L, Mahboub-Ahari A, Jahangiry L, Sadeghi-Bazargani H, Farahbakhsh M. A systematic review and meta-analysis of studies on screening for mild cognitive impairment in primary healthcare. *BMC Psychiatry*. 2022;22(1):97. doi:10.1186/s12888-022-03730-8
24. Di Pucchio A, Vanacore N, Marzolini F, et al. Use of neuropsychological tests for the diagnosis of dementia: a survey of Italian memory clinics. *BMJ Open*. 2018;8(3):e017847. doi:10.1136/bmjopen-2017-017847
25. Petersen RC. Mild cognitive impairment as a diagnostic entity. *J Intern Med*. 2004;256(3):183-194. doi:10.1111/j.1365-2796.2004.01388.x
26. Winblad B, Palmer K, Kivipelto M, et al. Mild cognitive impairment—beyond controversies, towards a consensus: report of the International Working Group on Mild Cognitive Impairment. *J Intern Med*. 2004;256(3):240-246. doi:10.1111/j.1365-2796.2004.01380.x
27. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders: DSM-IV*. American Psychiatric Association; 1994.
28. McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA work group under the auspices of Department of Health and Human Services Task Force on Alzheimer's disease. *Neurology*. 1984;34(7):939-944. doi:10.1212/wnl.34.7.939
29. Bennett DA, Schneider JA, Buchman AS, Barnes LL, Boyle PA, Wilson RS. Overview and findings from the Rush Memory and Aging Project. *Curr Alzheimer Res*. 2012;9(6):646-663. doi:10.2174/156720512801322663
30. Petersen RC, Smith GE, Waring SC, Ivnik RJ, Tangalos EG, Kokmen E. Mild cognitive impairment: clinical characterization and outcome. *Arch Neurol*. 1999;56(3):303-308. doi:10.1001/archneur.56.3.303
31. Abikoff H, Alvir J, Hong G, et al. Logical memory subtest of the Wechsler memory scale: age and education norms and alternate-form reliability of two scoring systems. *J Clin Exp Neuropsychol*. 1987;9(4):435-448. doi:10.1080/01688638708405063
32. Kaplan E, Goodglass H, Weintraub S. *Boston Naming Test*. Lippincott Williams & Wilkins; 2001.
33. Morris JC, Heyman A, Mohs RC, et al. The consortium to establish a registry for Alzheimer's disease (CERAD). Part I. Clinical and neuropsychological assessment of Alzheimer's disease. *Neurology*. 1989;39(9):1159-1165. doi:10.1212/wnl.39.9.1159
34. Wechsler D. *WMS-R: Wechsler Memory Scale—Revised: Manual*. Psychological Corporation; 1987.
35. Reitan RM, Wolfson D. *The Halstead–Reitan Neuropsychological Test Battery: Theory and Clinical Interpretation*. Neuropsychology Press; 1985.
36. Li X, Ploner A, Wang Y, et al. Longitudinal trajectories, correlations and mortality associations of nine biological ages across 20-years follow-up. *Elife*. 2020;9:e51507. doi:10.7554/eLife.51507
37. Mitnitski AB, Mogilner AJ, Rockwood K. Accumulation of deficits as a proxy measure of aging. *ScientificWorldJournal*. 2001;1:323-336. doi:10.1100/tsw.2001.58
38. Rockwood K, Howlett SE. Age-related deficit accumulation and the diseases of ageing. *Mech Ageing Dev*. 2019;180:107-116. doi:10.1016/j.mad.2019.04.005
39. Searle SD, Mitnitski A, Gahbauer EA, Gill TM, Rockwood K. A standard procedure for creating a frailty index. *BMC Geriatr*. 2008;8(1):24. doi:10.1186/1471-2318-8-24
40. Guaraldi G, Malagoli A, Theou O, et al. Correlates of frailty phenotype and frailty index and their associations with clinical outcomes. *HIV Med*. 2017;18(10):764-771. doi:10.1111/hiv.12527
41. Song X, Mitnitski A, Rockwood K. Nontraditional risk factors combine to predict Alzheimer disease and dementia. *Neurology*. 2011;77(3):227-234. doi:10.1212/WNL.0b013e318225c6bc
42. VanderWeele TJ. Principles of confounder selection. *Eur J Epidemiol*. 2019;34(3):211-219. doi:10.1007/s10654-019-00494-6
43. Hofer SM, Piccinin AM. Integrative data analysis through coordination of measurement and analysis protocol across independent longitudinal studies. *Psychol Methods*. 2009;14(2):150-164. doi:10.1037/a0015566
44. Armstrong JJ, Godin J, Launer LJ, et al. Changes in frailty predict changes in cognition in older men: the Honolulu–Asia aging study. *J Alzheimers Dis*. 2016;53(3):1003-1013. doi:10.3233/JAD-151172
45. Robertson DA, Savva GM, Kenny RA. Frailty and cognitive impairment—a review of the evidence and causal mechanisms. *Ageing Res Rev*. 2013;12(4):840-851. doi:10.1016/j.arr.2013.06.004
46. Borges MK, Canevelli M, Cesari M, Aprahamian I. Frailty as a predictor of cognitive disorders: a systematic review and meta-analysis. *Front Med (Lausanne)*. 2019;6:26. doi:10.3389/fmed.2019.00026
47. Song X, Mitnitski A, Rockwood K. Age-related deficit accumulation and the risk of late-life dementia. *Alzheimers Res Ther*. 2014;6(5–8):54. doi:10.1186/s13195-014-0054-5
48. Trebbastoni A, Canevelli M, D'Antonio F, et al. The impact of frailty on the risk of conversion from mild cognitive impairment to Alzheimer's disease: evidence from a 5-year observational study. *Front Med (Lausanne)*. 2017;4:178. doi:10.3389/fmed.2017.00178
49. Kelaiditi E, Canevelli M, Andrieu S, et al. Frailty index and cognitive decline in Alzheimer's disease: data from the impact of cholinergic treatment USe study. *J Am Geriatr Soc*. 2016;64(6):1165-1170. doi:10.1111/jgs.13956
50. Ismail Z, Black SE, Camicioli R, et al. Recommendations of the 5th Canadian consensus conference on the diagnosis and treatment of dementia. *Alzheimers Dement*. 2020;16(8):1182-1195. doi:10.1002/alz.12105
51. Cesari M, Marzetti E, Thiem U, et al. The geriatric management of frailty as paradigm of 'The end of the disease era'. *Eur J Intern Med*. 2016;31:11-14. doi:10.1016/j.ejim.2016.03.005
52. Liu W, Zhang L, Fang H, et al. Genetically predicted frailty index and risk of stroke and Alzheimer's disease. *Eur J Neurol*. 2022;29(7):1913-1921. doi:10.1111/ene.15332

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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