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Research Article

Disentangling Cognitive-Frailty: Results From the Gait and Brain Study

Manuel M. Montero-Odasso[1,2,3], Brittany Barnes[1], Mark Speechley[1,2,3], Susan W. Muir Hunter[1,2], Timothy J. Doherty[4], Gustavo Duque[5], Karen Gopaul[1], Luciano A. Sposato[6], Alvaro Casas-Herrero[7], Michael J. Borrie[2], Richard Camicioli[8], and Jennie L. Wells[2]

[1]Gait and Brain Lab, Parkwood Institute and Lawson Health Research Institute, London, Canada. [2]Department of Medicine and Division of Geriatric Medicine, Schulich School of Medicine & Dentistry, University of Western Ontario, London, Canada. [3]Department of Epidemiology and Biostatistics, University of Western Ontario, London, Canada. [4]Department of Physical Medicine and Rehabilitation, Schulich School of Medicine & Dentistry, University of Western Ontario, London, Canada. [5]Australian Institute for Musculoskeletal Sciences, University of Melbourne, Melbourne, Australia. [6]Department of Clinical Neurological Sciences, University of Western Ontario, London, Canada. [7]Division of Geriatric Medicine, Complejo Hospitalario de Navarra, Pamplona, Spain. [8]Department of Medicine, Division of Neurology, Faculty of Medicine and Dentistry, University of Alberta, Edmonton, Canada.

Address correspondence to Manuel M. Montero-Odasso, MD, PhD, Gait and Brain Lab, Department of Medicine and Division of Geriatric Medicine, University of Western Ontario, 801 Parkwood Hospital, Commissioners Road East, London, ON N6C2N8, Canada. E-mail: mmontero@uwo.ca

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Abstract

Background: Cognitive-frailty, defined as the presence of both frailty and cognitive impairment, is proposed as a distinctive entity that predicts dementia. However, it remains controversial whether frailty alone, cognitive-frailty, or the combination of cognitive impairment and slow gait pose different risks of incident dementia.

Methods: Two hundred and fifty-two older adults free of dementia at baseline (mean age 76.6 ± 8.6 years) were followed up to 5 years with bi-annual visits including medical, cognitive, and gait assessments. Incident all-cause of dementia and cognitive decline were the main outcomes. Frailty was defined using validated phenotypic criteria. Cognition was assessed using the Montreal Cognitive Assessment while gait was assessed using an electronic walkway. Cox Proportional Hazards models were used to estimate the risk of cognitive decline and dementia for frailty, cognitive-frailty, and gait and cognition models.

Results: Fifty-three participants experienced cognitive decline and 27 progressed to dementia (incident rate: 73/1,000 person-years). Frailty participants had a higher prevalence of cognitive impairment compared with those without frailty (77% vs. 54%, p = .02) but not significant risk to incident dementia. Cognitive-frailty increased incident rate (80/1,000 person-years) but not risk for progression to dementia. The combination of slow gait and cognitive impairment posed the highest risk for progression to dementia (hazard ratio: 35.9, 95% confidence interval: 4.0–319.2; p = 0.001, incident rate: 130/1,000 person-years). None of the models explored significantly predicted cognitive decline.

Conclusions: Combining a simple motor test, such as gait velocity, with a reliable cognitive test like the Montreal Cognitive Assessment is superior than the cognitive-frailty construct to detect individuals at risk for dementia. Cognitive-frailty may embody two different manifestations, slow gait and low cognition, of a common underlying mechanism.

Keywords: Frailty—Cognitive frailty—Gait velocity—Dementia.

Cognitive-frailty, defined as the presence of both physical frailty and cognitive impairment, in the absence of dementia, has been recently proposed as a distinctive entity (1). The rationale behind this construct suggests that the cognitive impairment component in these patients is primarily due to physical deterioration rather than neurodegenerative processes. Cognitive-frailty, as a concept, faces

some challenges mainly because the causal relationship between physical frailty and cognitive impairment over time is not yet fully understood.

Although physical and cognitive impairment frequently overlap in older adults (2), cognition is not included in the physical frailty phenotype (2). It has been consistently shown that physical frailty is cross-sectionally associated with cognitive impairment and dementia (3). Longitudinally, whether physical frailty per se increases the risk of incident dementia has shown inconsistent results. The Rush Memory and Aging Project, a community-based cohort study, has shown that physical frailty, in the absence of cognitive impairment at baseline, accelerates the rate of cognitive decline and predicts incidence of mild cognitive impairment and Alzheimer's disease (AD) dementia (4,5). However, the French Three-City Study, a large population-based study, failed to demonstrate an association between physical frailty alone and subsequent risk of dementia, although the subgroup of individuals with physical frailty and cognitive impairment did show a higher risk of progression to dementia (6). Another large population-based study found that physical frailty was associated with only non-AD dementia (7).

Based on these conflicting data, it remains unknown whether physical frailty with cognitive impairment really constitutes a unique phenotype as suggested by the cognitive-frailty construct or, on the contrary, they embody two different consequences of a common underlying mechanism (e.g. neurodegenerative or vascular processes). This question is of considerable importance and has potential therapeutic implications since, according to the cognitive-frailty hypothesis, progression to dementia could possibly be delayed by reversing physical frailty.

Therefore, our first objective was to compare the risk of cognitive decline and incident dementia between physical frailty alone (frailty phenotype) versus the combination of physical frailty with cognitive impairment (cognitive-frailty construct). In order to address our second objective, to determine whether the cognitive-frailty construct may embody two different consequences (physical impairment and cognitive impairment) of a common underlying mechanism, we compared the risk of further cognitive decline and incident dementia for each of the five criterion of physical frailty combined with baseline cognitive status.

Methods

Design and Participants

The "Gait and Brain Study" is a prospective cohort study designed to determine whether quantitative gait impairments can predict incident cognitive and mobility decline, and progression to dementia among community older adults. Design and logistics have been described in detail elsewhere (3,8,9). To increase probability of enrolling participants with frailty and cognitive impairment, recruitment was done from geriatric clinics and from a retirement community in London, Ontario. After consent was obtained, participants underwent a comprehensive baseline evaluation and biannual assessments during a maximum of 5 years of follow-up. For this analysis, participants were required to have at least two assessments, including baseline visit. All participants were community-living adults with the following inclusion criteria: aged 65 years and older, English speaking, and being able to ambulate one city block. Participants who used walking aids were included only if they were able to walk at least 10 meters independently without use of the mobility aid. Exclusion criteria included diagnosis of a terminal illness, life expectancy less than 12 months, nursing home placement pending, hip or knee joint arthroplasty within the preceding 6 months, Parkinsonism, neurological diseases with residual motor deficits (e.g. stroke), major depression, and diagnosis of dementia as ascertained by using criteria from *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (DSM-IV). Ethics approval was obtained from the University of Western Ontario Research Ethics Board for Health Sciences Research Involving Human Subjects, and participant's signed informed consent was obtained at enrollment. Data collection occurred between July 2007 and July 2015.

Medical, Cognitive, and Mobility Assessments

Sociodemographic characteristics, comorbidities, chronic medications, physical activity level, history of falls, and basic and instrumental activities of daily living were collected using standardized questionnaires and corroborated by using information from participants's electronic medical records (Table 1). Presence of diabetes, heart failure, hypertension, angina, myocardial infarction, stroke, Parkinson's disease, chronic lung disease, depression, atrial fibrillation, hearing and visual problems, and arthritis were recorded in face-to-face interview. Study clinicians performed a physical examination including a neurological examination in all the participants.

Cognition was assessed using the Mini-Mental State Examination and the Montreal Cognitive Assessment (MoCA) based on an established protocol. Alternative versions of the MoCA test were used in consecutive assessments to avoid potential learning effects. Clinical Dementia Rating scale was also performed at all visits.

Gait velocity (centimeter per second) during normal pace was evaluated using an electronic walkway with embedded pressure sensors (GAITRite® System, 6 meters long) using a validated gait protocol, described in detail elsewhere (8). Start and end points were marked on the floor 1 meter from either mat end to avoid recording acceleration/deceleration phases. The GAITRite system is widely used in clinical and research settings and has excellent validity and reliability (8). Participants were asked to walk on the walkway at their usual pace in a quiet well-lit room wearing comfortable footwear and without any attached monitors.

Physical Frailty Definition

Physical frailty was defined using the Fried/Cardiovascular Health Study criteria that include slow gait velocity, low physical activity, weakness, shrinking/weight loss, and exhaustion (10). As previously validated (11), we have operationalized these criteria as follows: slow gait velocity was met if participant walked below 1 m/s at a usual and comfortable pace (11,12).

Low physical activity criterion was met when Physical Activity Scale for the Elderly scores were less than 64 for men and less than 52 for women and/or if participants indicated that prefered more sedentary activities on a general activity level question. The weakness criterion was met when grip strength in the dominant hand, measured as the average of three readings using a handheld dynamometer (Jamar, Sammons Preston, Bolingbrook, IL), was less than or equal to the cutoff points used in the Cardiovascular Health Study (10). The shrinking criterion was met if participant reported having unintentionally lost more than 10 pounds in the previous 12 months or when body mass index was less than 18.5 (13). The exhaustion criterion was evaluated using two questions from the Center for Epidemiologic Studies Depression Scale (affirmative answer that everything they did was an effort or they felt they could not get going in the previous two months) and with a negative answer to the

Table 1. Baseline Characteristics for Full Sample and Stratified by Frailty Status

Variable	Full Sample, *n* = 252	Baseline Physical Frailty Status			*p* Value
		Nonfrail, *n* = 86 (34.1%)	Prefrail, *n* = 131 (52.0%)	Frail, *n* = 35(13.9%)	
Age, mean (*SD*)	76.7 (8.6)	75.1 (7.0)	76.7 (7.8)	80.6 (13.2)	.006*
Female, *n* (%)	158 (62.7%)	44 (51.2%)	87 (66.4%)	27 (77.1%)	.012*
Education, y, mean (*SD*)	13.6 (3.2)	14.1 (3.15)	13.2 (3.2)	13.09 (3.6)	.150
MMSE, mean (*SD*)	27.8 (2.5)	28.2 (2.1)	27.8 (2.6)	27 (2.9)	.063
MOCA, mean (*SD*)	24.2 (4.0)	24.6 (3.62)	24.3 (4.30)	22.7 (3.6)	.065
MOCA < 26, *n* (%)	140 (55.6%)	46 (53.5%)	67 (51.1%)	27 (77.1%)	.020*
Number of meds, mean (*SD*)	7.3 (4.7)	6.24 (4.0)	7.12 (4.6)	10.29 (5.3)	<.001*
Comorbidities, mean (*SD*)	4.8 (2.73)	4.55 (3.03)	4.74 (2.5)	5.57 (2.8)	.168
ADLs, mean (*SD*)	7.6 (0.9)	6.0 (0.0)	6.0 (0.3)	6.0 (0.0)	.643
IADLs, mean (*SD*)	6.0 (0.2)	7.7 (0.6)	7.7 (0.7)	6.8 (2.0)	.009*
Gait Speed, cm/s, mean (*SD*)	107.9 (25.8)	121.5 (16.7)	104.9 (26.5)	78.7 (15.9)	<.001*
Gait variability, %CoV, mean (*SD*)	3.2 (2.9)	2.7 (2.1)	3.1 (2.8)	5.4 (4.2)	<.001*
History of falls, 12 mo, *n* (%)	59 (23.4%)	17 (22.7%)	37 (28.2%)	5 (14.3%)	.238
Frailty criteria, *n* (%)					
Slow gait velocity	91 (36.1%)	1 (1.2%)	58 (44.3%)	32 (91.4%)	<.001*
Shrinking	7 (2.8%)	0 (0%)	2 (1.5%)	5 (14.3%)	<.001*
Weakness	28 (11.1%)	0 (0%)	13 (9.9%)	15 (42.9%)	<.001*
Exhaustion	68 (27.0%)	0 (0%)	41 (31.3%)	27 (77.1%)	<.001*
Low activity level	70 (27.8%)	0 (0%)	53 (40.5%)	17 (48.6%)	<.001*
Main Comorbidities, *n* (%)					
Hypertension	133 (52.8%)	40 (46.5%)	70 (53.4%)	23 (65.7%)	.278
Diabetes	39 (15.5%)	15 (17.4%)	19 (14.5%)	5 (14.3%)	.806
Parkinson's	2 (0.8%)	0 (0%)	1 (0.8%)	1 (2.9%)	.281
Osteoporosis	36 (14.3%)	10 (11.6%)	18 (13.7%)	8 (22.9%)	.286
Chronic lung disease	19 (7.5%)	8 (9.3%)	8 (6.1%)	3 (8.6%)	.659
Osteoarthritis	98 (38.9%)	24 (27.9%)	52 (39.7%)	22 (62.9%)	.002*
Cancer	83 (32.9%)	33 (38.4%)	39 (29.8%)	11 (31.4%)	.379
Hearing problems	97 (38.5%)	30 (34.9%)	52 (39.7%)	15 (42.9%)	.672
Depression	48 (19.0%)	14 (16.3%)	26 (19.8%)	8 (22.9%)	.691
Stroke	14 (5.6%)	2 (2.3%)	7 (5.3%)	5 (14.3%)	.034*
Visual impairment	153 (60.7%)	59 (68.6%)	82 (62.6%)	12 (34.3%)	.130
CHF/MI/Angina	25 (9.9%)	7 (8.1%)	15 (11.5%)	3 (8.6%)	.724
Atrial fibrillation	10 (4.0%)	4 (4.6%)	4 (3.1%)	2 (5.7%)	.326

Note: Definition of baseline frailty strata: frail, score ≥ 3, prefrail, score of 1–2, and nonfrail, score of 0. ADL = activities of daily living; CHF = congestive heart failure; CoV: coefficient of variation; IADL = instrumental activities of daily living; MI = myocardial infarction; MMSE = Mini-Mental State Examination; MoCA = Montreal cognitive assessment. *Significant at the $p < .05$ level.

question "do you feel full of energy?" from the Geriatric Depression Scale. "Frailty status" was assigned using the number of criteria met: those with none were considered "non frail"; those with one to two, "pre-frail"; and those with three to five, "frail" (10).

Cognitive-Frailty Definition

Cognitive-frailty was defined as the simultaneous presence of physical frailty, as described above, with objective cognitive impairment, defined as a MoCA score below 26 and a Clinical Dementia Rating of 0.5, and absence of concurrent dementia (1). Therefore, for the cognitive-frailty exposure analysis, six categories were generated: nonfrail/cognitively normal, nonfrail/cognitively impaired, prefrail/cognitively normal, prefrail/cognitively impaired, frail/cognitively normal, and frail/cognitively impaired (cognitive-frailty group).

Outcome Measures

Cognitive decline and incident dementia were the main endpoints. Cognitive decline was operationalized as a decrease of at least two points in MoCA scores between baseline and the last assessment, as previously validated (14). Incident dementia was determined by a clinician investigator during follow-up visits according to DSM-IV criteria and when Clinical Dementia Rating progressed to one or higher. At the time of diagnosis, the clinician was blind to baseline frailty or previous cognitive status. Type of dementia was established using standardized criteria for AD dementia (15), frontotemporal dementia (16), Lewy body dementia (17), as well as mixed vascular dementia (18). After the ascertainment of cognitive decline or incident dementia, participants were re-assessed after 6 months to confirm cognitive deterioration, dementia status, and subtype.

Analysis

Demographics and clinical characteristics were summarized using either means and standard deviations, or frequencies and percentages, as appropriate. Comparisons across baseline physical frailty strata were made using analysis of variance or Student *t*-tests, and multiple comparisons were adjusted using Tukey-Kramer. Logistic regression was used to measure the association between each of the five individual criteria of the frailty phenotype (slow gait velocity, low physical activity, weakness, unintentional weight loss, and exhaustion) as independent variables and incidence of cognitive decline and dementia as the dependent variables, in separate models.

To address objective one, multiple Cox proportional hazards regression analyses were completed to assess the risk, measured as hazard ratios (HRs), associated between physical-frailty status alone (Model A) and cognitive-frailty status (Model B) for the two outcomes of interest: cognitive decline and incident dementia, unadjusted and adjusted for covariates. To address objective two, each frailty criterion, with and without cognitive impairment, was assessed for its predictive ability for the two outcomes of interest. All regression models were adjusted for age, sex, number of years of education, and number of comorbidities. Time to event was calculated from enrollment to the assessment at which cognitive decline or dementia was diagnosed, depending on the outcome of interest. Proportional hazards assumption was tested using methods based on scaled Schoenfeld residuals. To account for different follow-up times, incident dementia is also presented as incident rate expressed as "total person-years at risk" for the three models. All types of dementia were grouped together, as a general outcome of conversion to dementia. Statistical significance was set at $p < .05$ (two sided). Statistical analyses were conducted using SPSS (v21.0, IBM Corporation, Chicago, IL).

Results

Participant's Characteristics

Two hundred and fifty-two participants aged 65 and older (mean age 76 ± 8.63; 63% women) were assessed with a mean follow-up of 18 months (range, 6–60 months). Characteristics of the study sample, stratified by frailty status are presented in Table 1. Fourteen percent of the sample was identified as frail and 52% of the participants as prefrail. Age, number of medications, osteoarthritis, history of stroke, slowness on gait, and gait variability significantly increased through frailty status (all $p < 0.05$). Cognitive impairment, defined as a MoCA score below 26, was more prevalent in the frailty group ($p = .02$). Cognitive impairment prevalence in the frailty group is higher compared with previous population studies due to the clinic-based nature of the recruitment for this cohort.

During follow-up, 53 participants experienced cognitive decline and 27 participants progressed to dementia, with an overall incidence rate of 73 per 1,000 person-years. Twenty-three progressed to AD dementia, one to vascular dementia, two to Lewy body dementia, and one to frontotemporal dementia, behavioral variant.

Stratification by physical-frailty status (Table 2, Model A) did not show a significant risk for cognitive decline or progression to dementia when no frailty was used as a reference category. Six percent of participants with frailty progressed to dementia (incidence rate of 61 per 1,000 person-years), and they progressed significantly faster than those with no frailty (195 days vs. 921 days, $p = .037$, Figure 1A).

Similarly, stratification by cognitive-frailty status did not show a significant risk for cognitive decline or progression to dementia. Seven percent of participants with cognitive-frailty progressed to dementia (incidence rate of 80 per 1,000 person-years). The category prefrail/cognitively impaired showed a significant risk for progression to dementia (adjusted hazard ratio [aHR] = 14.48, 95% confidence interval [CI]: 1.68–125.10, $p = .015$ Table 2, Model B and Figure 1B).

Of all five criteria of the frailty phenotype, only slow gait was cross-sectionally associated with being cognitively impaired (odds ratio = 2.14, 95% CI: 1.13–4.05, $p = .019$) and, similarly, was the only criterion associated with progression to dementia (aHR = 4.93, 95% CI: 1.71–14.21, $p = .003$). When each frailty criterion was combined separately with cognitive status, low physical activity and slow gait with cognitive impairment significantly predicted incident dementia (aHR = 7.76, 95% CI: 1.48–40.81, $p = .016$, and aHR = 35.89, 95% CI: 4.03–319.24, $p = .001$, respectively). The best model, therefore, was the combination of slow gait and cognitive impairment (Table 2, Model C and Figure 1C), which posed a significantly higher risk for progression to dementia, compared with pure cognitive impairment (aHR = 14.77, 95% CI: 1.24–175.81,

Table 2. Crude and Adjusted Hazard Ratios (HR) and 95% Confidence Intervals for Developing Cognitive Decline and Dementia by Baseline Frailty, Cognitive-Frailty, and by Gait and Cognitive Status

	Cognitive Decline				Dementia			
	Unadjusted		Adjusted[a]		Unadjusted		Adjusted[a]	
	HR (95% CI)	*p* Value	HR (95% CI)	*p* Value	HR (95% CI)	*p* Value	HR (95% CI)	*p* Value
Model A: Frailty Status								
Nonfrail ($n = 86$)	1		1		1		1	
Prefrail ($n = 131$)	1.4 (0.8–2.4)	.322	1.3 (0.7–2.4)	.418	1.4 (0.6–3.1)	.491	2.4 (0.9–6.5)	.074
Frail ($n = 35$)	0.6 (0.1–2.4)	.423	0.4 (0.1–1.9)	.243	1.3 (0.3–6.1)	.763	4.1 (0.7–23.5)	.111
Model B: Cognitive-Frailty Status								
Nonfrail/cognitively normal ($n = 40$)	1		1		1		1	
Nonfrail/cognitively impaired ($n = 46$)	0.7 (0.3–1.9)	.504	0.6 (0.2–1.6)	.282	5.7 (0.7–46.4)	.104	2.0 (0.2–18.4)	.531
Prefrail/cognitively normal ($n = 64$)	1.1 (0.5–2.4)	.852	1.0 (0.4–2.1)	.907	0.8 (0.1–8.8)	.846	0.8 (0.1–8.8)	.847
Prefrail/cognitively impaired ($n = 67$)	1.3 (0.5–3.0)	.597	1.0 (0.4–2.6)	.964	14.7 (1.9–112.3)	.010*	14.5 (1.7–125.1)	.015*
Frail/cognitively normal ($n = 8$)	1.1 (0.1–8.4)	.956	0.8 (0.1–6.8)	.841	n/a	n/a	n/a	n/a
Frail/cognitively impaired ($n = 27$)	0.3 (0.1–2.4)	.251	0.2 (0.0–1.5)	.118	5.9 (0.5–65.4)	0.151	6.3 (0.5–75.8)	.145
Model C: Gait/Cognition Status								
Normal Gait/Cognitively Normal ($n = 84$)	1		1		1		1	
Normal gait/cognitively impaired ($n = 71$)	3.0 (1.4–6.4)	.006*	2.6 (1.1–6.0)	.029*	28.8 (3.8–217.8)	.001*	11.7 (1.4–95.9)	.022*
Slow gait/cognitively normal ($n = 26$)	1.0 (0.5–2.0)	.985	0.8 (0.4–1.8)	.611	12.1 (1.1–134.9)	.042*	14.8 (1.2–175.8)	.033*
Slow gait/cognitively impaired ($n = 65$)	1.4 (0.6–3.2)	.453	1.2 (0.5–3.1)	.711	28.6 (3.5–231.1)	.002*	35.9 (4.0–319.2)	.001*

Note: Model A reference category: Nonfrail; Model B reference category: Nonfrail/Cognitively Normal; Model C reference category: Normal Gait/Cognitively Normal. No participants in these reference categories progressed to dementia. N/A = not available. [a]Adjusted for age, sex, years of education, number of comorbidities. *Significant at the $p < .05$ level.

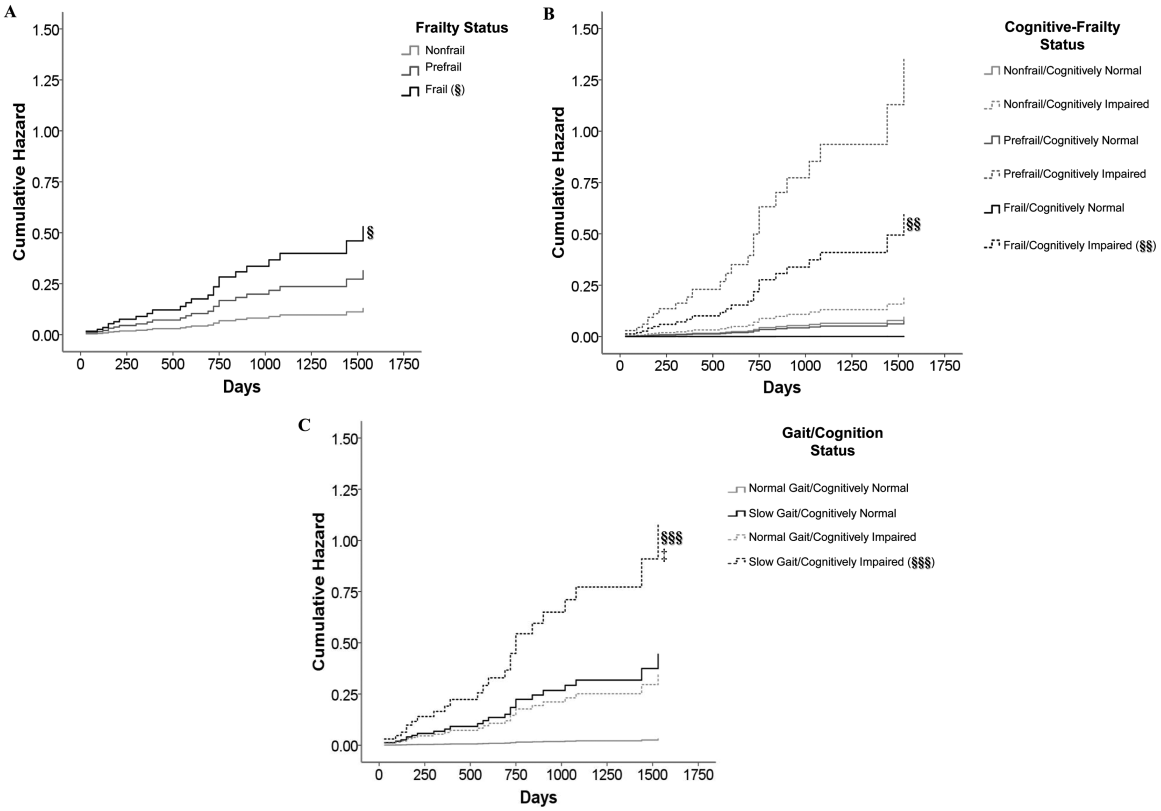

Figure 1. Cumulative hazard ratio for progression to dementia stratified by Frailty status (Model A), Cognitive-Frailty status (Model B) and Gait and Cognition status (Model C). §: Frailty group; §§: Cognitive-frailty group; §§§: Slow gait and low cognition group.

p = .033) and pure slow gait (aHR = 11.68, 95% CI: 1.42–95.91, p = .022). Participants having slow gait and cognitive impairment had significantly higher incidence of dementia, 12% (p < .001) with an incidence rate of 130 per 1,000 person-years.

As a sensitivity analysis, four additional models were explored to determine the relative contribution of cardiovascular risk factors to the association of slow gait and cognitive impairment and incident of dementia (Supplementary Table 1, Statistical models 1,3,4,5). An overall attenuation of the association was seen after adjusting for diabetes and hypertension (statistical model 3) and also after adjusting for CHF, stroke, and atrial fibrillation (statistical model 4) but associations remained significant. Finally, the cutoff of 1 m/s for slow gait has been previously validated but is also higher than what others recommend, providing a conservative estimate of the associations. Using a cut off of 0.8 m/s resulted in a similar association as presented in Supplementary Table 2.

Discussion

In this cohort study, the combination of slow gait and objective cognitive impairment posed the highest risk for progression to dementia when compared with physical frailty and cognitive-frailty models.

Participants with physical frailty had a higher prevalence of objective cognitive impairment, and the combination of physical frailty categories with cognitive impairment increased the risk of progression to dementia only for the cognitive-prefrailty category. However, the combination of slow gait and objective cognitive impairment showed the higher risk for incident dementia and time to progression to dementia in our cohort with an incident rate of 130 per 1,000 person-years.

Because physical frailty construct is composed of five criteria, we postulated that some of the criteria may have stronger associations with the development of future dementia than others. Previously, slow gait as an individual component of the physical frailty phenotype has been associated with low cognition and prospectively with incident non-AD dementia in older adults with frailty (3,19–21). In the present study, slow gait velocity was the only frailty criterion associated with incident dementia. Even though the combinations of low activity with cognitive impairment also posed a significant risk for dementia, pure low activity did not, suggesting that cognitive impairment was probably driving the dementia risk. Furthermore, slow gait and cognitive impairment individually presented a risk, with their combination increasing the risk.

Our results are in agreement with the proposed "motor signature" of cognitive decline that shows that slow gait is associated with pre-dementia syndromes (9,22,23) and with the recently described "Motoric Cognitive Risk" syndrome (24), defined as the presence of slow gait and cognitive complaints, which has been associated with a higher risk of progression to dementia.

Mechanistically, our findings raise the idea that the individuals grouped under the cognitive-frailty category are presenting two different manifestations, slow gait and cognitive impairment, of a common underlying mechanism. Therefore, disentangling cognitive and gait components of the cognitive-frailty construct may point to common or shared mechanisms, which may not be evident when comprised in a single construct (9,25).

Growing and consistent epidemiological evidence shows that the coexistence of cognitive and motor impairment, particularly slowing gait, is an early phenomenon in the pathway to age-associated cognitive decline and future dementia (2,26–28). This association is not

merely due to a high prevalence of these impairments in vulnerable populations, including older adults with frailty, but also due to a complex interplay between them particularly because gait regulation shares common brain networks with cognitive processes (2,9,29). These neural systems are essential for planning and monitoring goal-directed behavior, such as gait, which relies on executive functions (30,31). Thus, the relationship between cognitive and gait impairments in this subset of individuals with frailty and cognitive-frailty could be related to underlying processes affecting function in these shared brain networks.

Understanding gait and cognitive dysfunctions as a result of an insult to common brain networks may point to modifiable factors including vascular damage, chronic inflammation, neurodegeneration, or yet to be defined factors. Vascular burden is more prevalent in seniors with slow gait and cognitive, and mood impairments, and it is postulated that microvascular damage in frontal regions of the brain are preludes of cognitive and mobility disability (30,32,33). It has also been recently shown that microvascular and neurodegenerative changes in brain pathology are independently associated with frailty and cognitive status (25). In our study, adjustment for hypertension, diabetes, history of CHF, stroke, and atrial fibrillation attenuated the association between the gait/cognitive model and incident dementia, supporting a role of specific cardiovascular risk factor contributors. Previous studies have shown that gait slowing is associated most likely with incident of vascular dementia; however, in our cohort, 85% of those progressed to dementia were to AD dementia, supporting the emerging concept that motor/cognitive decline is also an early phenomenon seen in pre-AD stages. Additional modifiable factors previously linked with the pathogenesis frailty, slow gait, and cognitive impairment and dementia syndromes are vitamin D deficiency (34–36) and elevated inflammatory cytokines (37,38), which have been also postulated to affect frontal brain networks (34). Regardless of the underlying causal factors, gait and cognitive impairments coexist in an important proportion of older individuals placing them at higher risk of further cognitive decline and dementia. Modeling both cognitive and motor function together might, therefore, be more strongly predictive of the development of dementia, as it is in our study (39). This has substantial public health relevance, not only because of the high combined prevalence of them but also because of potential crossover effects on one impairment by treating the other. The detection of common modifiable mechanisms and common risk factors will open the opportunity to treat them together, thus, in essence, doubling the repertoire of interventions for cognitive and physical decline.

Clinically, combining a simple physical measure, such as gait velocity, with a reliable cognitive test like the MoCA seems superior than the cognitive-frailty construct to improve recognition of high-risk individuals for dementia. Both gait velocity and MoCA are easy to perform, time efficient, reliable, and easier to apply in clinical settings (12,40).

Strengths of our study include a well-characterized cohort with longitudinal bi-annual assessments, standardized study measures of frailty using the validated frailty phenotype, assignment of cognitive decline and dementia diagnoses blinded to frailty or gait categories, and robust analyses adjusting for a number of important confounders. Unlike previous studies asserting the incidence of dementia in frailty populations, cognition was evaluated using the MoCA test that is more sensitive than Mini-Mental State Examination to detect subtle changes in global cognition and progression to dementia syndromes (14). Additionally, our frailty and cognitive-frailty definitions followed established consensus criteria validating our approach.

Some limitations need to be outlined. Only 11% of our population progressed to dementia, which may have led to imprecise point estimate leading to wide confidence intervals. Some of the cognitive-frailty groups had a small number of participants, which may affect our power to find significant associations. Despite our relative low rate of events, the events per independent variable ratio in our main statistical model (27/5 = 5.4) is in the range of ratios which do not present severe problems (5–9 events per independent variable ratio) and are usually comparable to those studies with ratios higher than 10 events per variable (41).

In conclusion, slow gait and cognitive impairment combined showed a higher risk for incident dementia compared with frailty and cognitive-frailty constructs. Our results suggest that common mechanisms, probably affecting brain function, are underlying gait and cognitive impairments before dementia. Future studies assessing the functionality and integrity of common brain networks that regulate gait and cognitive processes will clarify the potential mechanisms within frailty and cognition associations.

Finally, identification of common modifiable risk factors for gait, motor, and cognitive interaction will help develop targeted interventions to prevent cognitive decline and delay progression to dementia.

Supplementary Material

Supplementary material can be found at: http://biomedgerontology.oxfordjournals.org/

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Conflict of Interest

Dr. Montero-Odasso is the first recipient of the Schulich Clinician-Scientist Award and holds the CIHR New Investigator Award.

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