J Frailty Aging 2022;in press
Published online April 1, 2022, http://dx.doi.org/10.14283/jfa.2022.28

Original Research

Association of Intrinsic Capacity with Frailty, Physical Fitness and Adverse Health Outcomes in Community-Dwelling Older Adults

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Abstract

BACKGROUND: Intrinsic capacity (IC) and frailty are complementary in advancing disability prevention through maintaining functionality.
OBJECTIVES: We examined the relationship between IC and frailty status at baseline and 1-year, and evaluated if IC decline predicts frailty onset among robust older adults. The secondary objectives investigated associations between IC, physical fitness and health-related outcomes.
DESIGN: Prospective cohort study.
SETTING: Community-based assessments.
PARTICIPANTS: Older adults aged>55 years, who were independent in ambulation (walking aids permitted).
MEASUREMENTS: 5 domains of IC were assessed at baseline: locomotion (Short Physical Performance Battery, 6-minute walk test), vitality (nutritional status, muscle mass), sensory (self-reported hearing and vision), cognition (self-reported memory, age- and education adjusted cognitive performance), psychological (Geriatric Depression Scale-15, self-reported anxiety/ depression). Composite IC (0-10) was calculated, with higher scores representing greater IC. Frailty status was based on modified Fried criteria, with frailty progression defined as incremental Fried score at 1-year.
RESULTS: 809 participants (67.6+6.8 years) had complete data for all 5 IC domains. 489 (60.4%) participants were robust but only 213 (26.3%) had no decline in any IC domain. Pre-frail and frail participants were more likely to exhibit decline in all 5 IC domains ($p<0.05$), with decremental composite IC [9 (8-9), 8 (6-9), 5.5 (4-7.5), $p<0.001$] across robust, prefrail and frail. IC was significantly associated with fitness performance, independent of age and gender. Higher composite IC reduced risk for frailty progression (OR=0.62, 95% CI 0.48-0.80), and reduced frailty onset among robust older adults (OR=0.53, 95% CI 0.37-0.77), independent of age, comorbidities and social vulnerability. Participants with higher IC were less likely to experience health deterioration (OR=0.70, 95% CI 0.58-0.83), falls (OR=0.76, 95% CI 0.65-0.90) and functional decline (OR=0.64, 95% CI 0.50-0.83) at 1-year.
CONCLUSION: Declining IC may present before frailty becomes clinically manifest, increasing risk for poor outcomes. Monitoring of IC domains potentially facilitates personalized interventions to avoid progressive frailty.

Key words: Intrinsic capacity, frailty, fitness, elderly.

Received January 13, 2022
Accepted for publication February 21, 2022

Introduction

Against the background of an ageing population globally, healthy ageing – the process of developing and maintaining functional ability to enable well-being in older life – is a key priority of the World Health Organization (WHO) (1). This has shifted the focus from a traditional disease-centric approach to ensuring that older people retain capabilities to be and to do what they value. Intrinsic capacity (IC) is central to functional ability, representing the composite of all physical and mental capacities an individual can draw upon, while interacting with the environment and social factors to define a person's functional ability (2). The delineation of 5 core domains of IC – locomotion, vitality, sensory, psychological and cognition – facilitates initial attempts to operationalize the IC concept in clinical settings even as the expert community continues to work towards standardizing an IC score that can be used for monitoring trajectories (3). Specifically, these domains have been incorporated in WHO Integrated Care for Older People (ICOPE) screening tool to identify older adults at risk of IC decline for person-centred assessment, intervention and follow-up with personalized goals (4).

IC and frailty can be seen as complementary in their common goal of advancing disability prevention through the maintenance of functionality. Frailty has been conceptualized as a geriatric syndrome characterized by vulnerability to adverse outcomes following stressor events (5). Decline in IC may underlie the diminished homeostatic reserves that culminate in the extreme vulnerability of frail older persons. Current studies of IC have largely focused on validating the construct of IC, including its predictive validity for care dependence and mortality (6-8). With the exception of a cross-sectional analysis of the relationship between frailty and IC, and the increased risk for incident frailty with each additional IC domain impairment (9, 10), no longitudinal study has evaluated pre-frailty or frailty as an outcome of IC decline. Yet, the intermediate pre-frailty and frailty states are likely to represent early declines in functional capacity, with potential for reversibility through timely intervention to avoid progression to functional debility (11). While individual components of the 5 IC domains have been associated with frailty and adverse health events in older adults (12, 13), the construct of IC is integrative by nature, such that a global score may be more informative in identifying at-risk older adults for preventive care (10, 14, 15).

The monitoring of IC offers an avenue to measure an individual's biological - as opposed to choronological - age. This is supported by the demonstrated association between allostatic load and IC, alluding to the possible biological substrate of IC and the potential for intervention through modification of biological parameters (16). However, the clinical utility of biochemical biomarkers as adopted in the measure of allostatic load may be limited by the availability of reference values, interpretation of widely varying concentrations that fall outside of normal reference ranges dedicated to disease states, and laboratory accessibility that may not be feasible for community-based monitoring. Similar to IC and frailty, physical fitness is a multi-dimensional construct which can be operationalized as a set of measurable health- and skill-related attributes including cardiorespiratory endurance, muscle strength, flexibility, balance, agility and gait speed (17). Additionally, several components of physical fitness, such as strength and gait speed, are conventionally included in frailty criteria. A recent systematic review highlighted the association between physical fitness components and frailty, although its utility as a clinical biomarker for IC decline has yet been examined (18).

The objective of this study was to examine the relationship between IC and frailty status, investigating the association at baseline as well as the risk for frailty progression at 1-year, among community-dwelling older adults. We performed sub-group analysis to determine if IC decline predicts frailty onset among robust older adults. The secondary objectives were to interrogate the associations between physical fitness components and IC, and examine the relationship between IC and health-related outcomes.

Methods

Study Setting and Participants

IPPT-S (Individual Physical Proficiency Test for Seniors) is an ongoing community-based initiative to promote fitness and prevent or delay frailty progression in older adults. The mobile screening platform is based at the void decks of public housing blocks, senior activity centres, and community clubs in the northeastern region of Singapore served by a regional healthcare facility, Sengkang General Hospital. Participants in the programme return for yearly follow-ups. Any individual who is aged >55 years, community-dwelling and able to ambulate independently (with or without walking aid) is eligible for participation. Residents of sheltered or nursing homes, and persons who are unable to ambulate for at least four meters independently are excluded.

All participants complete a multi-domain geriatric screen and physical fitness assessment administered by trained study team members. 1,078 participants have been recruited, of whom 809 had complete baseline data for assessment of IC and were included in this study. Owing to restrictions imposed by the COVID-19 pandemic, only 238 of 404 participants at 1-year follow-up attended the on-site physical fitness assessment, although questionnaire administration was performed for all follow-up participants via telephone interview (Supplementary Figure).

All participants provided written informed consent. The study protocol was reviewed and ethics approval provided by SingHealth Institutional Review Board.

Measures

Intrinsic Capacity

Measures representative of the 5 domains of IC – locomotion, vitality, sensory, cognitive and psychological – were derived from the multi-domain geriatric screen and physical fitness assessment.

Locomotion was based on the Short Physical Performance Battery (SPPB, range 0-12) consisting of chair-stand, gait speed and standing balance, and the 6-minute walk test (6MWT) (19, 20). A score of <9 on SPPB, and total distance walked of <400m in 6MWT were considered impaired performance for the respective tests. Locomotion domain was scored as 0 (impaired performance in both SPPB and 6MWT), 1 (impaired performance in either SPPB or 6MWT) or 2 (both SPPB and 6MWT unimpaired).

Vitality was represented by nutritional status and appendicular skeletal muscle mass (ASM). In the Mini Nutritional Assessment-Short Form questionnaire (MNA-SF, range 0-14), a score of 8-11 indicates being at-risk of malnutrition, while <8 indicates being malnourished (21). Body composition was measured using multi-frequency segmental Bioelectrical Impedance Analysis (BIA, MC-780 M, TANITA, Tokyo, Japan), with appendicular skeletal mass index (SMI) calculated as the sum of fat-free lean mass of all 4 limbs divided by height-squared (ASM/ht2). Low muscle mass was defined using Asian Working Group for Sarcopenia 2019 (AWGS2019) cut-off values of <7.0kg/m2 for men and <5.7kg/m2 for women (22). The vitality domain was scored as 0 to 2, with a score of 0 assigned for participants who were both at-risk of malnutrition/ malnourished and had low muscle mass, 1 when either at-risk of malnutrition/ malnourished or demonstrating low muscle mass, and 2 with normal nutritional status and normal muscle mass.

Sensory domain was assessed using self-reported responses to the questions "problems due to poor hearing" and "problems due to poor vision". Participants with a positive response to both hearing and visual problems scored 0, those reporting either hearing or visual problems scored 1, while those with neither hearing nor visual problems scored 2 in the sensory domain.

Cognitive domain was evaluated using both subjective report and performance on the modified Chinese version of the Mini Mental State Examination (CMMSE, range 0-28). Participants responded with yes or no to the question "Do you feel you have more problems with memory than most?". We used locally validated age- and education-thresholds to define impaired cognitive performance on the CMMSE (21 and 24 for participants <75 years with 0-6 and >6 years of education; 19 and 23 for participants >75 years with 0-6 and >6 years of education) (22). The cognition domain was scored as 0 for participants with CMMSE performance below threshold values for their age and education, 1 for participants with subjective memory problems but unimpaired CMMSE performance, and 0 for participants reporting no memory problem and unimpaired CMMSE.

Psychological domain was assessed using the 15-item Geriatric Depression Scale (GDS-15, range 0-15), and a single question from the EuroQol-5 Dimensions (EQ-5D) question on anxiety/ depression. GDS-15 score >5 suggests depression (24), while the EQ-5D question was assigned scores from 0 (not anxious/ depressed) to 4 (extremely anxious/ depressed) (25). The psychological domain was scored as 0 for participants with GDS-15 >5, 1 when EQ-5D anxiety/ depression >1 but GDS-15 <5, and 2 for participants with GDS-15 <5 and EQ-5D anxiety/ depression=0.

With each domain assigned a score of 0, 1 or 2, we summed all 5 domains to derive a composite score for IC ranging from 0 to 10, with higher scores representing greater IC. For each component domain, decline in capacity was defined as a score of 0 or 1.

Frailty

Physical frailty was objectively assessed using modified Fried phenotypic criteria, with frailty defined by the presence of at least 3 and pre-frailty as 1-2 of 5 components – exhaustion (Centre for Epidemiological Studies-Depression Scale), slow gait speed, weak grip strength, low body mass index (BMI<18.5kg/m^2) and low physical activity (26). Grip strength was measured using a JAMAR hand dynamometer, with 2 trials for each hand, and alternating sides during the test. The maximum value was used for analysis. Gait speed was based on time taken to walk 10m at usual pace, allowing for a 2m acceleration and deceleration zone before and after the timed 10m walk. Each participant performed 2 trials, and the better performance was adopted for scoring. AWGS2019 reference values were applied to identify weak grip strength (<18kg for women and <28 kg for men) and slow gait speed (<1.0m/s) (22). We used the Physical Activity Vital Sign (PAVS) to quantify engagement in moderate to vigorous-intensity physical activity (walking, cycling, jogging, swimming, Tai Chi, golf and housework), documenting the time spent on each activity in the preceding 7 days (27). The lowest quartile was employed as cut-off for physical inactivity.

Frailty progression was defined as incremental Fried score at 1-year follow-up relative to baseline, or remaining frail on the Fried phenotype.

Physical Fitness

The physical fitness test battery was modified from the Senior Fitness Test (28), and participants who reported feeling unwell on pre-assessment screening were exempted.

The chair stand test is a measure of lower body strength and power. Participants were instructed to rise as fast as possible from seated to a full standing position, while keeping the arms folded across the chest. The time taken to complete 5 chair stands as well as the number of full chair stands performed in 30 seconds was recorded (29).

In addition to grip strength, participants performed the box-and-block test as a measure of dexterity (30). This test involved participants picking blocks and placing them in the box on the other side across a barrier as quickly as possible in 1 minute, and the number of blocks transferred was recorded. Each participant completed 2 trials, one for each arm, and the better performance was used for analysis.

The back-scratch and chair sit-and-reach tests are measures of upper and lower body flexibility respectively (31). Participants performed 2 trials for each test, and the better performance was adopted for analysis. The back-scratch test required the participant to place one hand behind the shoulder and the other hand up the middle of the back, fingers extended. The distance (cm) the middle fingers were short of touching (-) or overlapping (+) was recorded. In the chair sit-and-reach test, participants sat on the edge of a chair with one leg extended in front while reaching forward with the hands toward the toes. The distance (cm) from the extended third finger to tip of toe (+ for beyond, and - for behind the toe) was recorded.

The Timed Up-and-Go Test is used for assessment of dynamic balance (agility). This test involved the participant standing from a seated position, walking as quickly as possible around a cone 3m ahead of the chair, and returning to a fully seated position (32).

The 6MWT performance reflects an individual's cardiorespiratory endurance and functional exercise capacity (20). We used a walkway of at least 20m, recording the total distance walked in 6 minutes. As per protocol, rest was permitted anytime during the test.

Health Outcomes

Self-reported health outcomes included hospitalization and falls, capturing events occurring in the year preceding the baseline assessment, and subsequently at yearly follow-ups using a standardized questionnaire. Self-rated health was measured using a visual analogue scale, in which participants marked their health on a scale from 0 (best health) to 100 (worst imaginable health). Participants also responded to a question on how they perceived their health to have changed over the past 1 year, with responses of "better/ same or worse". Functional performance in activities of daily living (ADLs) and instrumental ADLs (iADLs) was assessed using Barthel Index (BI) and Lawton and Brody's scale respectively (33, 34). We defined functional decline as a loss of >2 points on BI or Lawton's iADLs at follow-up relative to baseline (35).

Other Covariates

Sociodemographic data included age, gender and education level. We assessed social vulnerability based on socio-economic status (self-reported adequacy of expenses) and social support (availability of a confidant and maintaining social contact with friends or relatives). Participants were considered socially vulnerable if they reported having insufficient expenses, lacking a confidant, or social isolation. Medical comorbidities were recorded based on self-reported physician diagnoses of hypertension, diabetes mellitus, malignancy, chronic lung disease, heart disease (myocardial infarction, angina), congestive heart failure, chronic kidney disease, stroke, asthma and arthritis.

Statistical Analysis

Descriptive data are presented as means (+SD) or median (interquartile range, IQR) for quantitative variables and as absolute and relative frequencies for categorical variables. We examined univariate associations of individual components representative of the 5 IC domains with frailty status at baseline. Pearson correlation was performed to investigate the association between composite IC score and performance on the individual physical fitness tests. To address for possible type 1 error from multiple correlations, we conducted Bonferroni correction such that any correlation between composite IC and physical fitness will be considered statistically significant only if p value < 0.006 (œaltered=0.05/8). This was followed by multiple linear regression of physical fitness tests with significant univariate correlation, with composite IC, adjusting for age and gender.

Multiple regression, adjusted for age, gender, comorbidities and social vulnerability, was performed to examine the relationship of IC domains and composite score with baseline frailty status and risk for frailty progression at 1 year.

Statistical analysis was performed using STATA SE 15.0 (Stata Corp., College Station, TX). All statistical tests were two-tailed, with p value < 0.05 considered statistically significant.

Results

Of 1,078 participants who attended baseline assessment, complete data for all 5 IC domains was available for 809 participants who constituted the study cohort for this analysis. The mean age of the study cohort was 67.6 (6.8) years, with female predominance (75.6%) and majority of Chinese ethnicity (87.3%). Composite IC decreased significantly with increasing age (r=-0.298, p<0.001). 213 (26.3%) participants had no impairment in any IC domain at baseline. Progressive decline in IC from a single domain being affected to loss of capacity across all 5 IC domains was observed in 262 (32.4%), 190 (23.5%), 94 (11.6%), 42 (5.2%) and 8 (1.0%) of the participants respectively.

Intrinsic Capacity and Frailty Status at Baseline

At baseline, 489 (60.4%) participants were robust, 296 (36.6%) were prefrail and 24 (3.0%) were frail. Age increased progressively across robust, pre-frail and frail, and women were significantly less likely to be frail. Loss of capacity in all 5 IC domains was significantly more prevalent among prefrail and frail participants compared with their robust counterparts (Table 1). Specifically, within the locomotion and vitality domains, decremental capacity in all representative measures (SPPB, 6MWT, MNA-SF and SMI) was observed across robust, prefrail and frail participants (p<0.001). In the sensory domain, decline in hearing but not vision was significantly more common across robust, prefrail and frail, with decline in overall sensory domain being more commonly observed in prefrail and frail compared with robust participants (28.6%, 37.8%, 37.5%, p=0.024). In the psychological domain, prevalence of depression increased progressively across robust, prefrail and frail (GDS-15 >5: 9.0%, 22.3%, 33.3%; p<0.001). Decline in the cognition domain with increasing frailty status was largely driven by self-reported memory problems. The number of domains exhibiting declining capacity increased across robust, prefrail and frail, in parallel with decremental composite IC score with increasing frailty [9 (8-9), 8 (6-9), 5.5 (4-7.5), p<0.001].

In multinomial logistic regression adjusted for age, gender, comorbidity burden and social vulnerability, preserved capacity in locomotion, vitality, psychological and cognition domains were associated with reduced risk of being prefrail, while preserved capacity in locomotion, vitality and psychological domains independently reduced the risk for being frail. Each point increase in composite IC score conferred 30% and 52% reduced risk for prefrailty and frailty respectively (RR 0.70, 95% CI 0.63-0.77 and RR 0.48, 95% CI 0.38-0.61) (Table2).

Intrinsic Capacity and Measures of Physical Fitness

Composite IC score correlated significantly with all measures of physical fitness at baseline (p<0.001), with the strongest correlation observed for cardiorespiratory endurance (r=0.400). Flexibility (r=0.149 and r=0.167 for sit-and-reach and back-scratch tests) and grip strength (r=0.195) correlated weakly with composite IC score. Lower body performance on 30-second chair stand exhibited weak to moderate correlation (r=0.265) with composite IC. Dexterity (r=0.312), gait speed (r=0.351) and dynamic balance (r=-0.364) exhibited moderate correlations with composite IC. Focusing on participants who were robust at baseline, only tests of dexterity, dynamic balance, cardiorespiratory endurance and gait speed correlated significantly with composite IC (p<0.006).

After adjusting for age and gender, all individual physical fitness tests remained significantly associated with composite IC. Among robust older adults, Box-and-Block, Timed-Up-Go, 6MWT and gait speed were associated with composite IC, independent of age and gender (Table 3).

Table 1. Baseline Characteristics

	Overall Cohort (N=809)	Frailty Status			p value
		Robust (N=489)	Prefrail (N=296)	Frail (N=24)	
Socio-demographics					
Age	67.6 (6.8)	66.5 (6.3)	69.0 (7.2)	72.4 (8.7)	0.004
Gender (Female)	612 (75.6%)	389 (79.6%)	210 (71.0%)	13 (54.2%)	0.001
Ethnicity (Chinese)	706 (87.3%)	424 (86.7%)	262 (88.5%)	20 (83.3%)	0.909
Education (<Primary)	371 (45.9%)	221 (45.7%)	137 (47.4%)	20 (83.3%)	0.561
Insufficient expenses	164 (20.3%)	85 (17.7%)	73 (25.4%)	6 (27.2%)	0.028
Lack confidant	117 (14.5%)	56 (11.5%)	57 (19.5%)	4 (17.4%)	0.008
Living alone	142 (17.6%)	78 (16.0%)	62 (21.0%)	2 (8.3%)	0.101
No social contact	23 (2.8%)	7 (1.4%)	15 (5.1%)	1 (4.5%)	0.026
Number of comorbidities	1 (0-2)	1 (0-1)	1 (0-2)	2 (1-2)	0.003
Locomotion					
SPPB<9	83 (10.3%)	23 (4.7%)	44 (14.9%)	16 (66.7%)	<0.001
Distance 6MWT<400m	160 (19.8%)	51 (10.4%)	89 (30.1%)	19 (79.2%)	<0.001
Decline in locomotion	168 (20.8%)	59 (12.1%)	90 (30.4%)	19 (79.2%)	<0.001
Vitality					
MNA-SF malnutrition	146 (18.1%)	52 (10.6%)	81 (27.4%)	13 (54.2%)	<0.001
Low muscle mass	174 (21.5%)	70 (14.3%)	91 (30.7%)	13 (54.2%)	<0.001
Decline in vitality	246 (30.4%)	105 (21.5%)	126 (42.6%)	15 (62.5%)	<0.001
Sensory					
Hearing problems	135 (16.7%)	66 (13.5%)	62 (21.0%)	7 (29.2%)	0.006
Visual problems	168 (20.8%)	94 (19.2%)	70 (23.7%)	4 (16.7%)	0.294
Decline in sensory	261 (32.3%)	140 (28.6%)	112 (37.8%)	9 (37.5%)	0.024
Psychological					
GDS>5	118 (14.6%)	44 (9.0%)	66 (22.3%)	8 (33.3%)	<0.001
Feel anxious/depressed	91 (11.3%)	47 (9.6%)	39 (13.2%)	5 (20.8%)	0.101
Decline in psychological	169 (20.9%)	75 (15.3%)	85 (28.7%)	9 (37.5%)	<0.001
Cognition					
Report memory problem	229 (28.3%)	117 (23.9%)	102 (34.5%)	10 (41.7%)	0.002
CMMSE impaired	89 (11.0%)	51 (10.4%)	35 (11.8%)	3 (12.5%)	0.809
Decline in cognition	288 (35.6%)	149 (30.5%)	128 (43.2%)	11 (45.8%)	0.001
Global IC					
Number of domains with decline	1 (0-1)	1 (0-2)	2 (1-3)	3 (2-3.5)	<0.001
Composite IC score	8 (7-10)	9 (8-9)	8 (6-9)	5.5 (4-7.5)	<0.001

CMMSE: modified Chinese version of Mini Mental State Examination (range 0-28); GDS: Geriatric Depression Scale-15 (range 0-15); IC: Intrinsic Capacity (Composite IC range 0-10); MNA-SF: Mini-Nutrition Assessment Short Form (range 0-14); SPPB: Short Physical Performance Battery (range 0-12); 6MWT: 6-minute Walk Test

Intrinsic Capacity and Frailty Progression

Progressive frailty was observed in 26 (10.9%) of 238 participants with complete physical assessments at 1-year follow-up. 162 (68.1%), 70 (29.4%), and 6 (2.5%) were robust, prefrail and frail respectively at 1-year. Frailty progressors were significantly more likely to have exhibited decline in locomotion and cognition domains at baseline. Nutritional status but not muscle mass in the vitality domain was associated with frailty progression. In the sensory domain, hearing but not visual problem was more commonly observed among frailty progressors. Frailty progressors were more likely to screen positive for depression on GDS-15 in the psychological domain, but self-reported anxiety/ depression did not differentiate between frailty progressors vs non-progressors. There was a significantly higher number of IC domains exhibiting impairment at baseline [1 (0-2), 2 (1-3), p<0.001], accompanied by lower composite IC score [9 (8-1), 7 (5-8), p<0.001] among frailty progressors compared with non-progressors (Table 4A). Higher capacity in locomotion, vitality and cognition

Table 2. Multi-nomial Logistic Regression of IC with Baseline Frailty Status

	Locomotion	Vitality	Sensory	Psychology	Cognition	Composite
Prefrail	RRR=0.51	RRR=0.42	RRR=0.83	RRR=0.65	RRR=0.83	RRR=0.70
	(0.38-0.68)	(0.33-0.54)	(0.64-1.08)	(0.53-0.81)	(0.67-1.03)	(0.63-0.77)
	P<0.001	P<0.001	P=0.161	P<0.001	P=0.095	P<0.001
Frail	RRR=0.13	RRR=0.19	RRR=0.82	RRR=0.56	RRR=0.79	RRR=0.48
	(0.07-0.24)	(0.11-0.34)	(0.42-1.60)	(0.33-0.95)	(0.43-1.46)	(0.38-0.61)
	P<0.001	P<0.001	P=0.558	P=0.031	P=0.454	P<0.001

Reference group: Robust; RRR=Relative risk ratio; Adjusted for age, gender, comorbidities and social vulnerability

Table 3. Multiple Linear Regression of Composite IC with Physical Fitness Tests

	Overall Cohort (N=809) B coefficient (95% CI)	Robust (N=489) B coefficient (95% CI)
Flexibility		
Sit-and-reach test	0.019 (0.009, 0.029)**	
Back-scratch test	0.010 (0.000, 0.020)*	
Dexterity		
Box-and Block test	0.044 (0.031, 0.057)**	0.020 (0.005, 0.036)*
Agility		
Timed-Up-Go test	-0.162 (-0.200, -0.124)**	-0.143 (-0.212, -0.070)**
Cardiorespiratory endurance		
6-minute walk test	0.006 (0.005, 0.007)**	0.003 (0.001, 0.005)**
Lower limb strength & power		
Number chair stands in 30sec	0.067 (0.043, 0.091)**	
Grip strength	0.079 (0.056, 0.102)**	
Gait speed	1.931 (1.457, 2.421)**	0.823 (0.227, 1.422)*

Adjusted for age and gender; **p<0.001; *p<0.05

domains independently reduced risk for frailty progression, after adjusting for age, gender, comorbidity burden and social vulnerability. Each point increment in composite IC score at baseline significantly reduced risk of frailty progression by 38% (OR 0.62, 95% CI 0.48-0.80) (Table 4B).

In subgroups analysis focused on participants who were robust at baseline (N=145), 17 (11.7%) progressed to prefrailty or frailty at 1-year follow-up. Declines in locomotion (29.4% vs 7.0%, p=0.003), psychological (29.4% vs 11.7%, p=0.047) and cognition (52.9% vs 25.0%, p=0.016) domains were associated with progression to being prefrail or frail. Composite IC score at baseline was significantly lower among robust participants who progressed to prefrailty or frailty [9 (8-10), 8 (6-9), p<0.001] (Table 4A). In multiple logistic regression, higher composite IC significantly reduced odds for frailty onset among robust older adults (OR=0.53, 95% CI 0.37-0.77) (Table 4B).

Intrinsic Capacity and Health Outcomes

In multiple linear regression adjusted for age, gender and comorbidities, composite IC was independently associated with better self-rated health (β=2.81, 95% CI 2.20-3.43, p<0.001) at baseline and 1-year (β=2.68, 95% CI 1.62-3.73, p<0.001). Among 404 participants who completed follow-up telephone interviews, higher composite IC reduced odds for falls over 1 year (OR=0.76, 95% CI 0.65-0.90, p=0.001), independent of age, gender and comorbidity burden. There was no significant association between IC and hospitalization risk in the intervening year. Participants with higher composite IC were significantly less likely to report deterioration in health status (OR=0.70, 95% CI 0.58-0.83, p<0.001), and had lower risk for iADL decline (OR=0.64, 95% CI 0.50-0.83, p=0.001).

Discussion

This study has established the association of IC with frailty, physical fitness and health-related outcomes in community-dwelling older adults. Higher IC was associated with reduced likelihood of being prefrail or frail at baseline, and conferred protection against frailty progression at 1-year follow-up. Among robust older adults, higher IC reduced the risk for frailty onset. The positive impact of preserved IC on frailty and health outcomes appears to be independent of comorbidity burden and social vulnerability.

Only one-quarter of the cohort could be considered as having preserved IC, with unimpaired performance across all 5 IC domains. This was despite 60% of the cohort being robust at baseline. Our observation corroborates the findings in a Chinese population, in which the prevalence of IC decline was approximately 5-fold higher than frailty prevalence (9).

Table 4A. Intrinsic Capacity and Frailty Progression at 1-year Follow-Up

	Overall (N=238)			Robust at baseline (N=145)		
	Non-progressor (N=212)	**Progressor (N=26)**	**p value**	**Remained Robust (N=128)**	**Progressed Prefrail/frail (N=17)**	**p value**
Locomotion						
SPPB<9	18 (8.5%)	8 (30.8%)	<0.001	1 (0.8%)	4 (23.5%)	<0.001
6MWT<400m	32 (15.1%)	10 (38.5%)	0.003	9 (7.0%)	4 (23.5%)	0.025
Decline locomotion	34 (16.0%)	10 (38.5%)	0.005	9 (7.0%)	5 (29.4%)	0.003
Vitality						
MNA-SF malnutrition	38 (17.9%)	9 (34.6%)	0.044	13(10.2%)	4 (23.5%)	0.107
Low muscle mass	49 (23.1%)	10 (38.5%)	0.087	17(13.3%)	4 (23.5%)	0.259
Decline vitality	64 (30.2%)	12 (46.2%)	0.099	26(20.3%)	6 (35.3%)	0.162
Sensory						
Hearing problems	32 (15.1%)	8 (30.8%)	0.044	18(14.1%)	5 (29.4%)	0.104
Visual problems	45 (21.2%)	5 (19.2%)	0.814	28(21.9%)	4 (23.5%)	0.877
Decline in sensory	68 (32.1%)	10 (38.5%)	0.513	39(30.5%)	7(41.2%)	0.373
Psychological						
GDS>5	25 (11.8%)	7 (26.9%)	0.033	8 (6.3%)	4 (23.5%)	0.015
Anxious/depressed	20 (9.4%)	5 (19.2%)	0.124	12 (9.4%)	2 (11.8%)	0.754
Decline psychological	36 (17.0%)	8 (30.8%)	0.087	15(11.7%)	5 (29.4%)	0.047
Cognition						
Memory problem	61 (28.8%)	12 (46.2%)	0.070	27(21.1%)	7 (41.2%)	0.066
CMMSE impaired	12 (5.7%)	7 (26.9%)	<0.001	8 (6.3%)	3 (17.7%)	0.095
Decline cognition	68 (32.1%)	16 (61.5%)	0.003	32(25.0%)	9 (52.9%)	0.016
Global IC						
Number of domains with decline	1 (0-2)	2 (1-3)	<0.001	1 (0-2)	2 (1-2)	0.002
Composite IC score	9 (8-10)	7 (5-8)	<0.001	9 (8-10)	8 (6-9)	<0.001

CMMSE: modified Chinese version of Mini Mental State Examination (range 0-28); GDS: Geriatric Depression Scale-15 (range 0-15); IC: Intrinsic Capacity (Composite IC range 0-10); MNA-SF: Mini-Nutrition Assessment Short Form (range 0-14); SPPB: Short Physical Performance Battery (range 0-12); 6MWT: 6-minute Walk Test

Table 4B. Multiple Logistic Regression of IC with Frailty Progression at 1-year

	Locomotion	**Vitality**	**Sensory**	**Psychology**	**Cognition**	**Composite**
Frailty progression in overall follow-up cohort	OR=0.47	OR=0.60	OR=0.77	OR=0.65	OR=0.36	OR=0.62
	(0.25-0.89)	(0.36-1.00)	(0.40-1.49)	(0.38-1.11)	(0.20-0.66)	(0.48-0.80)
	P=0.020	P=0.050	P=0.437	P=0.112	P=0.001	P<0.001
Frailty onset among robust	OR=0.14	OR=0.46	OR=0.63	OR=0.48	OR=0.45	OR=0.53
	(0.04-0.46)	(0.20-1.03)	(0.17-2.41)	(0.24-0.99)	(0.22-0.92)	(0.37-0.77)
	P=0.002	P=0.060	P=0.501	P=0.046	P=0.029	P=0.001

OR=Odds Ratio; Adjusted for age, gender, comorbidities, social vulnerability

In parallel, it was observed that decline in at least one domain affected over 85% of a population of adults aged 50 years or older (36). Thus, while frailty is dynamic and potentially reversible, the present reliance on frailty manifestations to identify older adults for adapted care may result in missed opportunities for earlier intervention to address declining functional reserves. Indeed, just one-third of robust participants in this study had no decline in any of the 5 IC domains, and 85% of pre-frail participants had varying IC declines ranging from losses in a single to all 5 IC domains. These data suggest that even with the intermediate pre-frail state, significant losses of capacity would already have occurred. Current multi-domain interventions for prefrailty and frailty emphasize the combination of physical activity and nutritional intervention, which address only the locomotion and vitality domains. While such combined interventions generally yielded greater improvements in frailty characteristics and physical function compared with mono-domain interventions, effects on functional abilities, falls, psychosocial well-being and depression were less consistent (37). With transition to robustness observed in only 30% of pre-frail older adults in a multi-component physical exercise and nutritional intervention programme (38), the current observation suggests that addressing decline across all components to improve IC may be necessary to promote the reversibility of prefrailty and frailty.

We observed a differential association of the individual IC domains with frailty. Locomotion and vitality domains were consistently associated with baseline frailty status and risk for frailty progression at follow-up. Preserved capacity in the psychological domain was associated with reduced likelihood of being prefrail or frail, but was protective against frailty progression only among participants who were robust at baseline. The cognition domain was not associated with baseline frailty status but predicted risk for frailty progression. These observations parallel our earlier study detailing the association of depression, malnutrition and sarcopenia with all frailty measures (12). However, notwithstanding the differential associations of the individual IC domains, it is likely that the IC domains are inter-dependent and complementary. In this regard, IC representing the composite of physical and mental capacities of the older person offers a more holistic multi-dimensional indicator of functional reserves. This is supported by the consistent association of composite IC score with both baseline frailty status, as well as risk for frailty progression even when limited to the subgroup of participants who were robust at baseline. It had also been suggested that the five domains of IC may be operating on different levels, such that cognition, psychological, locomotion and sensory domains can be considered overt expressions of capacity driven by underlying biological changes representative of the vitality domain (6, 39). This guided our inclusion of muscle mass in the vitality domain, given its nutritional and hormonal underpinnings, and skeletal muscle being often considered the biological substrate for physical frailty. Our study builds on the recent work by Ma and colleagues (9), who demonstrated the cross-sectional relationship between IC and frailty risk, and further support the notion that the extreme vulnerability representative of frailty stems from clinically relevant decline in IC. Beyond providing a means to support early identification of an individual's fragilization, the monitoring of IC and the component domains can facilitate tailored care interventions even among older adults who may well be on the frailty trajectory (40).

The correlation of physical fitness measures with IC serves to reiterate how the maintenance of functional fitness is integral to successful ageing. Declines in physical fitness - represented by muscle strength, endurance, balance, agility, and flexibility – may begin as early as middle life, evident by progressive loss of muscle strength of 1.5-3% per year, and reduction in aerobic capacity from the age of 40 years (41, 42). Despite early losses in aerobic ability, the manifestation of exhaustion is typically observed much later in the frailty cycle (43, 44). Composite IC has been associated with functional ability and falls, both in our cohort as well as earlier studies (9). The reduced falls risk with higher IC may be accounted for by higher levels of physical fitness, as evident by the reported dose-response relationship between measures of functional fitness and fall risk in older adults (45). Although in need of further validation, the multiple components of physical fitness testing may offer potential clinical biomarkers of IC decline through simple and objective measures that serve as surrogates of the older person's biological age and health status. This is supported by the observed relationships between various measures of physical fitness and composite IC among robust older adults. In this regard, measures of physical fitness may also offer an intervenable target to ameliorate IC decline, preventing frailty and disability. Specifically, a multi-modal exercise programme incorporating resistance, aerobic, balance and flexibility training should be encouraged for older adults with declining physical fitness to prevent loss of IC. This is especially salient considering the impact of IC on self-rated health, and older adults with higher IC being less likely to report deterioration in their health status and functional decline during follow-up.

Several limitations are acknowledged. There was an over-representation of women who comprised almost two-thirds of the cohort. Owing to missing data, the association of IC with fitness and frailty could be examined in only 75% of the recruited cohort. Although age was similar between participants included and those excluded from analysis, men were more likely to be excluded due to incomplete IC data, reducing confidence in generalizability of the study findings. At the time of analysis, only 50% had completed 1-year follow-up with at least a telephone interview. There was no difference in age and baseline frailty status between those with and without follow-up, However, there were significantly more men in the group without follow-up data (28.0% vs 21.1%, p=0.021), which also had higher baseline composite IC compared with the follow-up group [9 (7-10) vs 8 (7-9), p=0.038]. While the potential influence of the differential baseline characteristics on examined outcomes cannot be dismissed, gender was not associated with frailty progression or any of the outcomes evaluated. Further, due to disruptions to on-site follow-up imposed by the ongoing COVID-19 pandemic, 40% of 404 participants at 1-year follow-up did not have physical measures of gait speed and grip strength for assessment of frailty status, potentially reducing power when examining IC with frailty progression. There was however no difference in baseline frailty status and composite IC between follow-up participants with and without physical re-assessment. Both hearing and visual problems in the sensory domain were based on self-reported problems, potentially underestimating the effect of sensory capacity on outcomes analyses. The study's strengths include a well characterized cohort of older adults with assessments including an extensive battery of physical fitness tests, which allowed us to disaggregate measures of IC, especially the locomotion and vitality domains, from criteria used for assessment of physical frailty (gait speed and grip strength). Additionally, with the exception of the sensory domain, we endeavoured to employ validated and objective measures for assessment of capacity in the component domains of IC. Even as we explored domain by domain associations, the adoption of a composite IC score aligns with the integrative nature of the IC construct, although future work should consider using a weighted approach according to each domain's risk for negative outcomes.

In conclusion, decline in IC is prevalent in community-dwelling older adults, and is likely to present before overt clinical manifestation of frailty. Maintenance of high IC is protective against frailty onset and progression. The association between IC and all aspects of physical fitness suggests the utility of physical fitness as biomarkers for monitoring intervention response and physical training as a potential target for enhancing IC in older adults.

Ethical standards: The study protocol had been reviewed with ethics approval by SingHealth Institutional Review Board (CIRB Ref No 2018/2115). Written informed consent for study participation was provided by all participants before recruitment, or their legally acceptable representative for patients who were unable to provide informed decision.

Acknowledgement: We thank the study participants, staff of the Senior Activity Centres and Resident Committees in the NorthEast region of Singapore for their gracious support extended to this study.

Funding support: This study was funded by National Medical Research Council Centre Grants (CGAug16C027 and CGAug16M0), and National Innovation Challenge on Active and Confident Ageing (MOH/NIC/HAIG04/2017). The grants funded the research staff, assessment equipment and on-site conduct of the trial, and the researchers were independent from funders.

Conflict of interest: All the authors have no conflict of interest or financial disclosure of note.

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How to cite this article: L. Tay, E.-L. Tay, S.M. Mah, et al. Association of Intrinsic Capacity with Frailty, Physical Fitness and Adverse Health Outcomes in Community-Dwelling Older Adults. J Frailty Aging 2022; http://dx.doi.org/10.14283/jfa.2022.28