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Article

Frailty and Cognition Transitions and the Development of Cognitive Frailty among Community-Living Older Adults in the Singapore Longitudinal Ageing Studies

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ABSTRACT

Background: Studies of the natural progression and temporal co-occurrence of physical frailty and cognitive impairment are needed to validate the construct of cognitive frailty, a state of mild cognitive impairment caused by physical frailty.

Method: We analysed data from Singapore Longitudinal Ageing Studies (SLAS-1 and SLAS-2) participants (*N* = 2554), free of functional disability, dementia, neurodegenerative diseases, and stroke, who were categorized at baseline as robust and cognitive normal (*N* = 1252), physically frail alone (*N* = 913), cognitively impaired alone (*N* = 197), and concurrently frail and cognitively impaired (*N* = 232) with average 5-years of follow up. Physical frailty was defined as pre-frailty/frailty (Fried criteria scores 1–5) and cognitive impairment MMSE scores <27 (age and education adjusted).

Results: Among cognitively normal and robust participants, the occurrence of pre-frailty/frailty alone was 80.4%, cognitive impairment alone was 0.6%, and co-occurring pre-frailty/frailty and cognitive impairment (*cognitive frailty*) was 3.8%. Among cognitively normal and pre-frail/frail participants, the occurrence of cognitive frailty (5.9%) was significantly higher (OR = 1.53, 95% CI: 1.02–2.28, adjusted for sex and age). Among cognitively normal and robust individuals, baseline number of comorbid medical comorbidities (OR = 1.37 (95% CI: 1.08–1.74) significantly predicted cognitive frailty. From following up a hypothetical cohort of 1000 robust and cognitively normal individuals, 88 of 91 outcome cases of co-occurring frailty and cognitive impairment were preceded by frailty alone (*N* = 48), or concurrent frailty and cognitive impairment (*N* = 40); only 3 cases were preceded by cognitive impairment alone (not cognitive frailty).

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Conclusions: The validity of cognitive frailty as a construct of mild cognitive impairment due to physical frailty is supported.

KEYWORDS: frailty; cognitive impairment; cognitive frailty; co-temporal transition

INTRODUCTION

Cognitive frailty is proposed as a new clinical entity representing a premorbid state of mild cognitive impairment caused by physical frailty rather than neurodegenerative pathology [1]. It thus holds potential as a preventive or therapeutic target for dementia and age-related functional decline. As proposed by a consensus workgroup of the International Academy on Nutrition and Aging and the International Association of Gerontology and Geriatrics in April 2013, cognitive frailty is diagnosed by the concurrent presence of physical frailty and cognitive impairment in the absence of a clinical diagnosis of dementia.

However, research so far has not adequately established the clinical construct validity of cognitive frailty as a state of mild cognitive impairment caused by physical frailty. In support of this temporal association, longitudinal studies have indeed shown that physical frailty at baseline is associated with significantly increased future risk of cognitive decline, incident MCI, and dementia [2–5]. However, studies have also shown that older adults who were cognitively-impaired or showed cognitive decline were significantly at higher risk for pre-frailty/frailty onset [6,7]. By definition and the temporal ordering of events, non-frail cognitively impaired individuals who become physically frail while remaining cognitively impaired over time cannot be considered to have cognitive frailty.

Reports have indicated that as many as one third of MCI patients have impaired instrumental activities of daily living functioning and two thirds have physical pre-frailty or frailty at the same time [8,9]. In diagnosing cognitive frailty at a point in time or in a cross-sectional study, cases of co-occurring physical frailty and cognitive impairment without dementia include indeterminate proportions of MCI cases secondary to physical frailty and physical frailty cases secondary to cognitive impairment [10]. Estimating the extent to which the co-occurrence of frailty and cognitive impairment is attributable to primary physical frailty is important if cognitive frailty is to be a useful target for preventing dementia and age-related functional decline.

Studies of the natural progression of physical frailty and cognitive impairment are needed to understand temporal patterns of co-occurrence that reflect this causal relationship and the mechanistic pathway(s) underlying the development of cognitive frailty [10–12]. We found only one recent US study with 5-year follow up of community-living older persons who were free of frailty and cognitive impairment/dementia at

baseline which found that those with incident dementia were more likely to develop cognitive impairment first, or frailty and cognitive frailty concurrently, and less likely to show physical frailty before cognitive impairment [11], suggesting that dementia-related pathology is less likely to be the cause of cognitive impairment if preceded by physical frailty. On the other hand, the number of comorbidities was found to be strongly associated with first onset of physical frailty.

In this study, we used data from the Singapore Longitudinal Ageing Studies (SLAS) to examine the transitions of discrete states of incident physical frailty, cognitive impairment and concurrent frailty with cognitive impairment from an average 4.5 years of follow up of community-living older persons who were classified in four groups at baseline as those who were:

(1) Free of pre-frailty/frailty and cognitive impairment (physically robust and cognitively normal)
(2) Physically pre-frail/frail only
(3) Cognitively impaired only
(4) Both physically pre-frail/frail and cognitive impaired.

To determine the validity of the cognitive frailty construct, we ascertained the development of cognitive impairment from physical pre-frailty or frailty (henceforth aka “frailty”) from follow up of two groups of individuals:

(1) Those who were free of frailty and cognitive impairment at baseline, among whom some subsequently became frail alone, some remained cognitively impaired alone, and others became frail and cognitively impaired (*cognitive frailty*),
(2) Those who are only frail at baseline, among whom some may remain frail and become cognitively impaired (*cognitive frailty*).

We tested the hypothesis that the new occurrence of cognitive frailty in (1) was significantly greater than in (2). To assess whether the observed association was unique in reflecting underlying mechanistic pathways known to be associated with physical frailty, we explored significant baseline risk factors that predict newly occurring cognitive frailty in this sub-cohort of robust and cognitively normal participants.

A second aim was to estimate the attributable proportion of physical frailty in cognitive frailty by constructing a developmental model of cognitive frailty in the incipient sub-cohort of robust and cognitively normal individuals. We used estimates derived from each of the four sub-cohorts to construct this hypothetical model, from which we estimated the prior and final conditional probabilities of physical frailty, cognitive impairment and co-occurring frailty and cognitive impairment in this incipient cohort.

METHOD

Study Population

The data in this study were derived from two population cohorts in the Singapore Longitudinal Ageing Study (SLAS-1 and SLAS2), a long-term population-based ageing cohort study with 3 to 5 years of follow up. The cohort study recruited a total of 6074 community-dwelling older adults aged 55 years and above from different geographical areas in two separate waves in 2004–2005 (SLAS-1) and 2008–2013 (SLAS-2). Details of the methodology of the SLAS-1 and SLAS-2 cohorts have been described in previous papers [13,14]. The study was approved by the National University of Singapore Institutional Review Board (NUS IRB 04-140, 17 June 2004) and all participants provided informed consent.

In this study, we excluded at baseline 236 participants with stroke or CNS degenerative disorders, and 221 participants with baseline disability in activities of daily living (ADL), and 15 participants with no ADL data. Among the remaining 5647 participants, 64 participants with no baseline data on measures of frailty or cognitive impairment were also excluded. Among N = 5583 participants who were followed up, there were N = 505 deaths. In this study, we used available follow-up data for frailty and cognitive impairment outcomes of 2554 participants. The study population included 1252 participants who were robust and cognitively normal at baseline who were followed up for cognitive frailty.

Measurements

Frailty status at baseline and follow-up

The physical frailty phenotype was assessed using five criteria in the Cardiovascular Health Study (CHS)[15]:

(1) Shrinking or weight loss: body mass index (BMI) of less than 18.5 kg/m^2 and/or unintentional weight loss of ≥4.5 kg (10 pounds) in the past 6 months.
(2) Weakness: In SLAS-2 participants, this was defined as the lowest quintile of knee extension strength within sex and BMI strata. In SLAS-1 participants, this was defined as lowest quintile of score of rising from chair test in the sitting position with arms folded, derived from the Performance Oriented Mobility Assessment (POMA) battery [16].
(3) Slowness: In SLAS-2, this was defined as gait speed less than 0.8 m/s from the fast gait speed test over 6 metres. In SLAS-1, this was assessed by POMA gait test (subject walks 6 meters and returned to the starting point quickly), and defined by POMA gait score of less than 9 out of a possible maximum of 12.
(4) Exhaustion was determined by response of “not at all” to the question from SF-12 quality of life scale: “Do you have a lot of energy?”
(5) Low activity was determined by self-report of “none” for participation in any physical activity (walking or recreational or sports activity).

One-point was assigned for the presence of each component, and the total score categorizes participant as frail (3–5 points), pre-frail (1–2 points), or robust (0 point).

Cognitive status at baseline and follow-up

Global cognitive function was assessed by the locally translated and validated version of the Mini-Mental State Examination (MMSE)[17]. A cut-off value of age- and education-corrected MMSE cut-off below 27 was used to define cognitive impairment, as it was previously shown to have good discriminant accuracy in screening for mild cognitive impairment [18].

Baseline variables

Data collected at baseline on risk factor variables that were known to predict physical frailty and/or cognitive impairment or dementia included sex, age, ethnicity, education level (primary or no education, secondary or post-secondary), housing types (1–2 room public, 3-room public, 4–5 rooms public, private condo and landed housing), marital status (single/divorced/widowed versus married), living alone, smoking (non-smoker, ex-smoker, current smoker), daily alcohol (≥1 drinks) consumption, leisure-time activities score (computed as a total and sub-total scores of physical, social and productive activities)[13], depressive symptoms (score of 5 or more on the Geriatric Depression Scale, 15-items (GDS-15)[19], central obesity (local population definition: waist circumference in men, >90 cm, and in women, >80 cm), diabetes or raised fasting blood glucose (use of any antidiabetic medications or fasting glucose ≥6.1 mmol/L), hypertension (use of any antihypertensive drugs or elevated blood pressure, systolic ≥ 130 or diastolic ≥ 85 mm Hg), elevated triglycerides ≥ 1.7 mmol/L, or using any lipid-lowering drugs; low HDL-cholesterol ≤ 0.9 mmol/L in men and ≤1.1 mmol/L in women, or using lipid-lowering agent, number of metabolic syndrome components, metabolic syndrome (US National Cholesterol Education Program Adult Treatment Panel III (2001), cardiac disease (coronary heart disease, heart failure, atrial fibrillation), number of comorbid medical conditions, polypharmacy (use of ≥5 drugs), National Nutrition Initiative (NSI) total score, low total cholesterol (<4.14 mmol/L), low lymphocyte count (<1200/mL), anemia (haemoglobin: female: <11 g/L; male: <12 g/L), low albumin (<40 g/L), renal dysfunction (estimated glomerular filtration rate (MDRD) < 60 mL/min).

Statistical analysis

Continuous variables were presented as means ± standard deviation (SD) and categorical variables as number (percentage). Group differences in proportions were examined with chi-squared test for categorical outcome variables. Significant baseline risk factor predictors of cognitive frailty were explored using stepwise selection logistic regression, and estimates of association were expressed as odds ratio (OR) and 95%

confidence intervals (95% CI). Results were deemed as statistically significant if *P*-values were lower than 0.05. IBM SPSS Statistical Package (v25.0; SPSS, Inc., Chicago, IL, USA), was used for statistical analysis.

RESULTS

At baseline assessment, half of the participants were robust and cognitively normal. The baseline prevalence of pre-frailty/frailty alone without cognitive impairment was 35.7%, while the prevalence of cognitive impairment alone without pre-frailty/frailty was only 6.1%. Co-occurring pre-frailty/frailty and cognitively impairment was present in 9.1% (Table 1.)

Across all categories, the underlying pattern overall was for all participants regardless of baseline physical or cognitive status to become or remain pre-frail/frail (87%), while few participants (11%) became or remained only cognitively impaired at follow up. Extremely few participants were found at follow up to be cognitively impaired alone without pre-frailty/frailty (1%).

Among robust and cognitively normal participants who were followed up, 84% became physically pre-frail/frail overall, whereas only 4% became cognitively impaired overall. The frequency of occurrence of incident pre-frailty/frailty alone was 80.4%, and incident cognitive impairment alone was 0.6%. The frequency of co-occurring pre-frailty/frailty and cognitive impairment (*cognitive frailty*) was 3.8%.

Among pre-frail/frail and cognitively normal participants, 84% remained as such, and the occurrence of cognitive frailty was 5.9%, significantly higher than the occurrence of 3.8% estimated in the comparator group of robust and cognitively normal participants (OR = 1.53, 95% CI: 1.02–2.28, adjusted for sex and age).

Among physically robust but cognitively impaired participants, 60% reverted to normal cognition, 92% became physically pre-frail/frail, but the resultant 32% incident cases of co-occurring frailty and cognitive impairment are not considered to be cognitive frailty cases.

Among participants who were concurrently pre-frail/frail and cognitively impaired at baseline, 47% remained as such, while 43% became pre-frail/frail alone without being cognitively impaired.

Table 1. Baseline characteristics of SLAS study population.

Characteristics	% Mean	(*N*) ±SD
Robust and Cognitively normal	49.0	(1252)
Pre-frail/frail and Cognitively normal	35.7	(913)
Robust and Cognitively impaired	6.1	(157)
Pre-frail/frail and Cognitively impaired	9.1	(232)
Female sex	65.4	(1671)
Age, years	65.3	±6.9
Chinese ethnicity	93.3	(2384)
Primary or no education	31.4	(802)
Secondary education	37.2	(951)
Post-secondary education	31.4	(801)
Housing: 1–2 room public	10.9	(278)
3 room public	27.0	(689)
4–5 rooms public	44.5	(1136)
Private condo and landed	17.7	(451)
Single Divorced Widowed	29.3	(748)
Live alone	11.1	(284)
Smoking: Ex-smoker	8.9	(225)
Current smoker	7.2	(179)
Alcohol (≥1 drinks) daily	3.8	(96)
Leisure-time activities total score	9.7	±4.3
Social activities score	3.3	±2.5
Productive activities score	4.1	±1.8
Fitness activities score	2.4	±1.8
Depression: GDS ≥ 5	5.1	(130)
Waist circumference (Male: >90 cm, Female: >80 cm)	48.6	(1240)
Diabetes or raised FBG	21.1	(539)
Elevated BP (≥130/85 mm Hg) or anti HPT drugs	65.5	(1673)
Elevated TG (≥150 mg/dL or lipid-lowering drugs	46.6	(1191)
Reduced HDL cholesterol (men: <40 mg/dL, women: <50 mg/dL)	30.4	(777)
No of Metabolic syndrome components	2.2	±1.4
Abnormal lipid levels	61.2	(1562)
Metabolic syndrome (NCEP)	40.7	(1039)
Cardiac disease	7.2	(187)
No of comorbid medical conditions	2.4	±1.6
Comorbid medical conditions ≥ 5	9.7	(249)
Polypharmacy ≥ 5 drugs	11.9	(203)
NSI total score	1.6	±1.9
Low total cholesterol < 4.14 mmol/L	9.6	(246)
Low lymphocyte count (<1200/mL)	5.7	(146)
Anemia (haemoglobin: female: <11 g/L; male: <12 g/L)	3.6	(93)
Low albumin (<40 g/L)	22.4	(571)
Renal dysfunction (eGFR < 60 mL/min)	20.8	(530)

Table 2. Baseline and follow-up categories of frailty, cognition and functional status in SLAS-1 and SLAS-2 participants (*N* = 2554) free of IADL-BADL disability at baseline.

	Baseline categories				Follow-up categories						Follow-up categories		
	Pre-frailty/ Frailty	Cognition		All participants	Robust Normal cognition	Pre-frail/Frail Normal cognition	Robust Cognitively impaired	Pre-frail/Frail Cognitively impaired	All Pre-frail/Frailty		All Cognitive impairment		IADL-ADL Disability
				N (%)	*N* (%)	*N* (%)	*N* (%)	*N* (%)	*N* (%)	Δ ± SE	*N* (%)	Δ ± SE	*N* (%)
A	Robust	Normal	*N*	1252	192	1006	7	47 †	1053	0.85	54	0.24	82
			%	[49.0]	(15.3)	(80.4)	(0.6)	(3.8)	(84.1)	±0.04	4.3	±0.10	(6.6)
B	Pre-frail/	Normal	*N*	913	89	767	3	54 †	821	0.10	57	0.29	97
	Frail		%	[35.7]	(9.7)	(84.0)	(0.3)	(5.9) §	(89.9)	±0.03	6.2	±0.10	(10.6) §§
C	Robust	Impaired	*N*	157	6	95	6	50 ‡	145	0.94	56	0.14	16
			%	[6.1]	(3.8)	(60.5)	(3.8)	(31.8)	(92.4)	±0.06	35.7	±0.18	(10.2)
D	Pre-frail/	Impaired	*N*	232	9	101	13	109	210	0.09	122	-0.56	60
	Frail		%	[9.1]	(3.9)	(43.5)	(5.6)	(47.0) *	(90.5)	±0.04 *	52.6 *	±0.17 *	(25.9) *
	All		*N*	2554	296	1969	29	260	2229	0.50	289	0.03	255
			%	[100]	(11.6)	(77.1)	(1.1)	(10.2)	87.3	±0.03	11.3	±0.10	10.0%

Figures shown in square brackets [ ] are column percentages. Figures shown in round brackets ( ) are row percentages. † considered as incident cognitive frailty; ‡ not considered as cognitive frailty; § OR = 1.53 (1.02–2.28), $p = 0.041$; B *versus* A (reference); §§ OR = 1.52 (1.11–2.09) $p < 0.010$; B *versus* A (reference), age and sex adjusted. Δ(SE): estimated change of CHS frailty score or MMSE score (follow up minus baseline), adjusted for sex, age, education, baseline CHS frailty score (or MMSE score). * $p < 0.001$, D *versus* A, B, C (Bonferron-adjusted). Significance tests were performed for specific hypotheses of relevance.

Table 2 also shows a corresponding increased incidence of IADL-ADL disability associated with the increased incidence of cognitive frailty among cognitively normal individuals who were physically frail compared to robust. Unsurprisingly, individuals who were both physically frail and cognitively impaired at baseline showed the highest incidence of disability. At the same time, this group with co-occurring prevalence of frailty and cognitively impairment showed distinctly much divergent rates of MMSE and physical frailty scores compared to all other groups.

Stepwise forward conditional selection procedures were used in logistic regression analyses to explore baseline risk factor variables (Table 1) that significantly predict the new occurrence of cognitive frailty in the sub-cohort of robust and cognitively normal individuals. Significant baseline risk factor variables that were significantly associated with incident cognitive frailty (Table 3) included male sex, age, Chinese ethnicity, education, eGFR < 60 mL/min, and number of comorbid medical conditions.

Table 3. Significant baseline risk factor predictors of cognitive frailty among SLAS participants who were robust and cognitively normal at baseline (*N* = 1140) from stepwise selection logistic regression.

Baseline predictor variables	OR	95% CI	*p*
Female sex	1.30	(1.12–1.84)	0.002
Age, per year	1.10	(1.04–1.17)	0.001
Non-Chinese *vs* Chinese	1.27	(1.07–2.32)	0.026
Nil or Primary education †	3.78	(1.14–12.5)	0.030
Secondary education †	1.56	(0.46–5.29)	0.474
eGFR < 60 mL/min	2.57	(1.14–5.79)	0.023
No of medical comorbidities	1.37	(1.08–1.74)	0.008

† *Versus* post-secondary education.

Using estimates derived from each of the four sub-cohorts, we constructed a developmental model of cognitive frailty in a hypothetical cohort of 1000 robust and cognitively normal persons followed up over time. In this model, the estimated prior and final conditional probabilities of physical frailty, cognitive impairment and co-occurring frailty and cognitive impairment in this incipient cohort are shown in Figure 1. In the sub-cohort of those who were only cognitively impaired at baseline, the individuals who became physically frail while remaining cognitively impaired constitutes the non-attributable proportion of co-occurring frailty and cognitive impairment that do not represent cognitive frailty. The estimated number of incident cases of cognitive frailty over time was 91. Among them, 48 first became physically frail before becoming cognitively frail, 40 became frail and cognitively impaired concurrently. There were only 3 cases who were cognitively impaired alone before becoming frail, and they were not considered to have cognitive frailty. Thus, among followed up individuals who developed co-occurring frailty and cognitive impairment, the overwhelming majority (96%) were

previously robust or frail and/or cognitively normal, only 4% (N = 3) were prior cases with cognitive impairment alone.

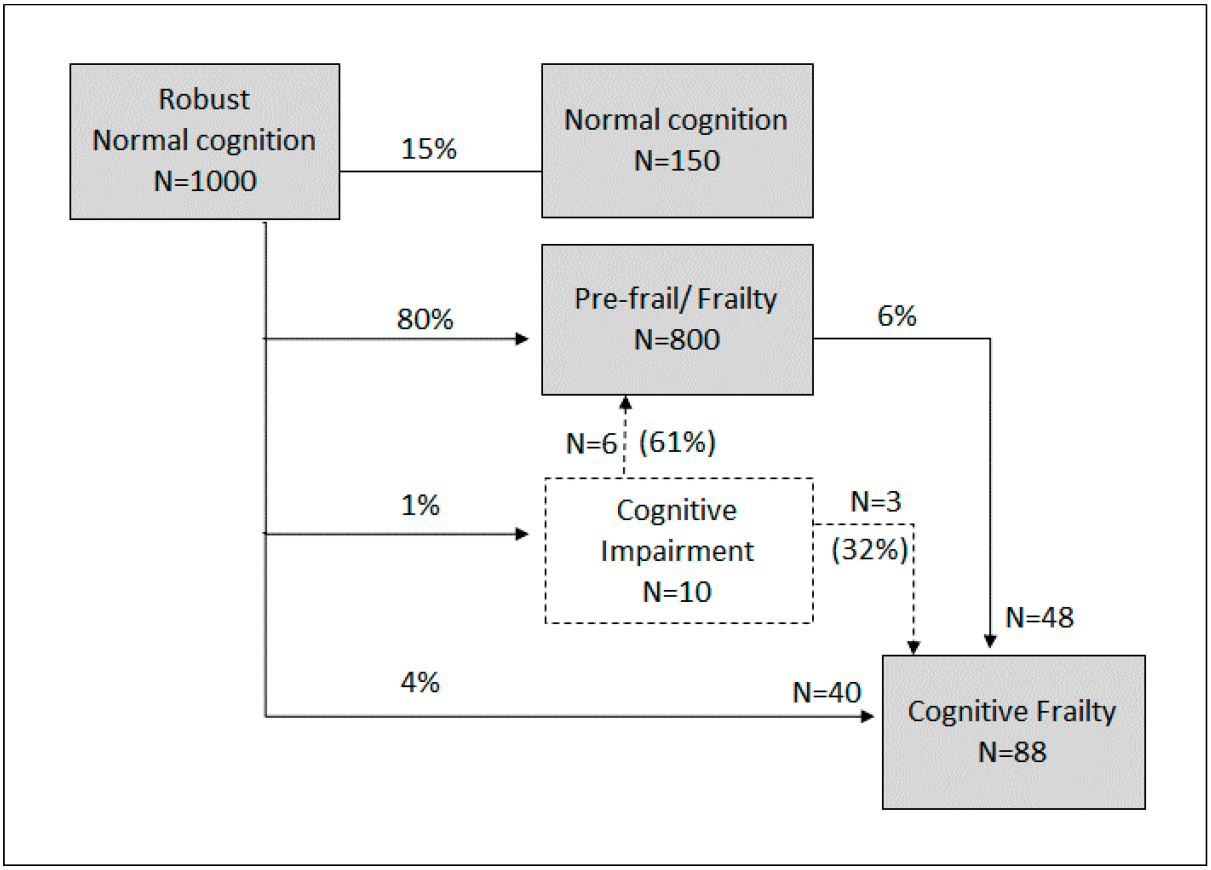

Figure 1. Developmental model estimates of new occurrence of cognitive frailty preceded by physical frailty and cognitive state transitions among a hypothetical cohort of 1000 robust and cognitively normal individuals.

DISCUSSION

We observed that among cognitively normal older participants, those who were pre-frail/frail were significantly more likely to become cognitively impaired, and therefore showed a significantly higher incidence of cognitive frailty, compared to those who were physically robust. Together with the associated greater incidence of cognitive frailty, there was also a corresponding greater incidence of functional disability. This is in agreement with studies which showed that cogntive frailty was associated with significantly increased risks of adverse outcomes including dementia and functional disability [20–24]. Uniquely, the number of comorbid medical conditions, a known strong risk factor for physical frailty, was observed to predict cognitive frailty, suggesting that mechanistic pathways associated with physical frailty may be underlying this association. The construct of cognitive frailty as a state of cognitive impairment caused by prior physical frailty is thus supported by the observations in this study.

In operationalizing the clinical diagnosis of cognitive frailty as the simultaneous presence of both physical frailty and cognitive impairment in the absence of dementia in a cross-sectional study, the individuals labelled in this way at a single point in time may include those with physical frailty resulting from cognitive decline. As was previously reported, older persons who were robust but cognitively impaired, compared to their cognitively intact counterparts at baseline were more likely to develop pre-frailty/frailty 4 years later [6]. Indeed, our study also shows that in the sub-cohort who were cognitively impaired alone, 32% became physically pre-frail/frail while remaining cognitively impaired, significantly much higher than that among cognitively normal and robust or frail individuals (3.8% and 5.9% respectively). However, these resultant cases of co-occurring frailty and cognitive impairment are not considered to be cognitive frailty.

Our results provide interesting perspectives in appraising the relative contributions of physical and cognitive (neurodegenerative) factors to eventual risks of dementia and functional dependency. With few exceptions, studies have customarily reported occurrences of cognitive impairment ignoring its co-morbidity with physical frailty. As shown in this Asian study population, the predominant occurrence of physical frailty over cognitive impairment should be carefully noted. Although cognitive impairment overall was prevalent in at least 15% of the aged population (in line with most population estimates in the age range)[25], the prevalence of cognitive impairment alone was actually rather low (6%), and the prevalence of physical frailty alone was much higher (36%). This was not due to the threshold values used, as equally the lowest cut-offs were used to define physical pre-frailty/frailty and cognitive impairment alike. The age- and education-adjusted MMSE cut-off below 27 used in this study has also been validated in a previous study to have good discriminant accuracy in screening for MCI [18].

The sub-cohort of those who were cognitively impaired alone at baseline apparently accounts for one third of the total cases of co-occurring frailty and cognitive impairment derived from combining unconditional probabilities estimated from concurrent follow ups of the three sub-cohorts. This sub-cohort estimate may however be influenced by prevalence bias. In this group, there is a high proportion (60%) of reversion to normal cognition, consistent with the known state variability of the MCI syndrome, hence the remnant who remain stably impaired to be studied at baseline were more likely to develop dementia. Furthermore, there is a greater attrition due to higher mortality and follow up non-participation among cognitively impaired participants. Our previous observations in this cohort show that cognitive impairment compared to pre-frailty or frailty was indeed associated with significantly higher mortality [24]. Participants who were not assessed at follow up were older, and had poorer socioeconomic, lifestyle and health characteristics, and more of them were cognitively impaired at baseline. The sequential

developmental model and conditional probabilities derived from singly following up an incipient cohort of robust and cognitively normal individuals gives a much smaller estimate of eventual occurrence of incident cognitive frailty. Among these cases, the overwhelming majority (96%) were previously cognitively normal and robust or frail, only 4% were prior cases with cognitive impairment alone.

Our study thus shows that the large majority of cases of co-occurring frailty and cognitive impairment observed at a single point in time or over time were preceded by physical frailty rather than cognitive decline, at least in this Asian population. This is important for assessing the potential impact of targeting cognitive frailty for dementia and disability prevention.

Our finding is in line with parallel observations that prior motor decline (measured by gait velocity) contributed more to risk for incident dementia than did cognitive decline [20].

The contribution of physical frailty in accelerating cognitive impairment and enhancing future risk of MCI and dementia in cognitively normal populations is supported by a growing body of research [2–5]. Frail older persons are typically bearers of many chronic medical disorders together in the same person, and interestingly multiple co-morbidity as an established risk factor of frailty emerges as a significant predictor of cognitive frailty in this study. Impaired renal function also emerged as a significant risk factor of cognitive frailty, in line with recent research suggesting its link with both cognitive decline and physical frailty. Malnutrition is also strongly associated with frailty, and highly prevalent in as much as one-third of older persons in population studies [14]. These factors are generally prevalent in most other elderly populations. Our finding should be widely generalizable to many other populations, but may be limited by the younger age of this study population and the notably greater contribution of poor nutrition to frailty than in Western populations [14]. Thus, it is likely that a higher prevalence of health and nutritional risk factors may explain a particularly high attribution of physical frailty to cognitive impairment in this study population. More studies should be conducted to ascertain if there are variations in estimates of this attribution in other populations.

There are strengths and limitations in this study. By following up a large and relatively younger ageing cohort, we were able to better discretize early temporal transitions of pre-disability physical and cognitive states of frailty than in an older cohort with its higher rates of functional disability. However, the follow up intervals (especially in the SLAS-2 cohort) may not be sufficiently optimal to disentangle an unknown number of cases of physical frailty preceding cognitive impairment and vice versa among the incident cases of co-occurring physical frailty and cognitive impairment. On the other hand, it is also not unlikely that physical frailty and cognitive impairment did occur simultaneously. Another limitation in the study is that cognitive impairment was not

defined by clinical diagnoses of MCI or dementia.

CONCLUSIONS

The findings support the validity of cognitive frailty as a construct of mild cognitive impairment caused by physical frailty. In this Asian study population, the great majority of incident cases of co-occurring frailty and cognitive impairment were previously cognitively normal and robust or frail.

AUTHOR CONTRIBUTIONS

TPN had full access to all of the data in the study and has primary responsibility for final content. TPN reviewed the literature, designed the study, analysed the data, drafted and revised the manuscript. MSZN, QG, XYG, KBY contributed to the study design, data collection, reviewed the results and drafts of the manuscript. All authors read and approved the final manuscript.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest. The sponsors had no role in the conduct of the study or preparation of this manuscript.

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REFERENCES

1. Kelaiditi E, Cesari M, Canevelli M, van Kan GA, Ousset PJ, Gillette-Guyonnet S, 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):726-34. doi: 10.1007/s12603-013-0367-2
2. Buchman AS, Boyle PA, Wilson RS, Tang Y, Bennett DA. Frailty is associated with incident Alzheimer's disease and cognitive decline in the elderly. Psychosom Med. 2007;69:483-9.
3. Boyle PA, Buchman AS, Wilson RS, Leurgans SE, Bennett DA. Physical frailty

is associated with incident mild cognitive impairment in community-based older persons. J Am Geriatr Soc. 2010;58:248-55. doi: 10.1111/j.1532-5415.2009.02671.x

4. Auyeung TW, Lee JS, Kwok T, Woo J. Physical frailty predicts future cognitive decline—a four-year prospective study in 2737 cognitively normal olderadults. J Nutr Health Aging. 2011;15(8):690-4.
5. Feng L, Nyunt MS, Gao Q, Feng L, Lee TS, Tsoi T, et al. Physical frailty, cognitive impairment, and the risk of neurocognitive disorder in the Singapore Longitudinal Ageing Studies. J Gerontol A. 2017;72(3):369-75. doi: 10.1093/gerona/glw050
6. Yu R, Morley JE, Kwok T, Leung J, Cheung O, Woo J. The Effects of Combinations of Cognitive Impairment and Pre-frailty on Adverse Outcomes from a Prospective Community-Based Cohort Study of Older Chinese People. Front Med. 2018;5:50. doi: 10.3389/fmed.2018.00050
7. Gross AL, Xue QL, Bandeen-Roche K, Fried LP, Varadhan R, McAdams-DeMarco MA, et al. Declines and Impairment in Executive Function Predict Onset of Physical Frailty. J Gerontol A Biol Sci Med Sci. 2016;71(12):1624-30.
8. Morris JC. Revised criteria for mild cognitive impairment may compromise the diagnosis of Alzheimer disease dementia. Arch Neurol. 2012;69(6):700–8.
9. Nyunt MSZ, Soh CY, Gao Q, Gwee X, Ling ASL, Lim WS, et al. Characterisation of Physical Frailty and Associated Physical and Functional Impairments in Mild Cognitive Impairment. Front Med. 2017;4:230. doi: 10.3389/fmed.2017.00230
10. Ruan Q, Yu Z, Chen M, Bao Z, Li J, He W. Cognitive frailty, a novel target for the prevention of elderly dependency. Ageing Res Rev. 2015;20:1-10. doi: 10.1016/j.arr.2014.12.004
11. Chu N, Tian J, Gross AL, Bandeen-Roche K, Carlson MC, Xue Q. Hierarchical development of physical frailty and cognitive impairment: clues into etiological pathways. Innov Aging. 2018;2(S1):23. doi: 10.1093/geroni/igy023.083
12. Xue QL, Buta B, Ma L, Ge M, Carlson M. Integrating Frailty and Cognitive Phenotypes: Why, How, Now What? Curr Geri Rep. 2019;8(2):97-106. doi: 10.1007/s13670-019-0279-z
13. Niti M, Yap KB, Kua EH, Tan CH, Ng TP. Physical, social and productive leisure activities, cognitive decline and interaction with APOE-epsilon4 genotype in Chinese older adults. Int Psychogeriatr. 2008;20(2):237-51. doi: 10.1017/S1041610207006655
14. Wei K, Nyunt MSZ, Gao Q, Wee SL, Ng TP. Frailty and Malnutrition: Related and Distinct Syndrome Prevalence and Association among Community-Dwelling Older Adults: Singapore Longitudinal Ageing Studies. J Am Med Dir Assoc. 2017;18(12):1019-28. doi: 10.1016/j.jamda.2017.06.017
15. Fried LP, Tangen CM, Walston J, Newman AB, Hirsch C, Gottdiener J, et al. Frailty in older adults: evidence for a phenotype. J Gerontol A. 2001;56:M146-56.
16. Tinetti ME. Performance-oriented assessment of mobility problems in elderly patients. J Am Geriatr Soc. 1986;34:119-26.
17. Ng TP, Niti M, Chiam PC, Kua EH. Ethnic and educational differences in

cognitive test performance on mini-mental state examination in Asians. Am J Geriatr Psychiatry. 2007;15:130-9.

18. Feng L, Chong MS, Lim WS, Ng TP. The Modified Mini-Mental State Examination test: normative data for Singapore Chinese older adults and its performance in detecting early cognitive impairment. Singapore Med J. 2012;53(7):458-62.
19. Nyunt MS, Fones C, Niti M, Ng TP. Criterion-based validity and reliability of the Geriatric Depression Screening Scale (GDS-15) in a large validation sample of community-living Asian older adults. Aging Ment Health. 2009;13:376-82. doi: 10.1080/13607860902861027
20. Montero-Odasso M, Speechley M, Muir-Hunter SW, Sarquis-Adamson Y, Sposato LA, Hachinski V, et al. Motor and cognitive trajectories before dementia: Results from Gait and Brain Study. J Am Geriatr Soc. 2018;66(9):1676-83. doi: 10.1111/jgs.15341
21. Solfrizzi V, Scafato E, Seripa D, Lozupone M, Imbimbo BP, D'Amato A, et al. Reversible Cognitive Frailty, Dementia, and All-Cause Mortality. The Italian Longitudinal Study on Aging. J Am Med Dir Assoc. 2017;18(1):89.e1-89.e8. doi: 10.1016/j.jamda.2016.10.012
22. Shimada H, Doi T, Lee S, Makizako H, Chen LK, Arai H. Cognitive Frailty Predicts Incident Dementia among Community-Dwelling Older People. J Clin Med. 2018;7(9). doi: 10.3390/jcm7090250
23. Roppolo M, Mulasso A, Rabaglietti E. Cognitive frailty in Italian community-dwelling older adults: Prevalence rate and its association with disability. J Nutr Health Aging. 2017;21(6):631-6.
24. Feng L, Nyunt MSZ, Gao Q, Feng L, Yap KB, Ng TP. Cognitive Frailty and Adverse Health Outcomes: Findings From the Singapore Longitudinal Ageing Studies (SLAS). J Am Med Dir Assoc. 2017;18(3):252-8.
25. Sachdev PS, Lipnicki DM, Kochan NA, Crawford JD, Thalamuthu A, Andrews G, et al. Cohort Studies of Memory in an International Consortium (COSMIC). The Prevalence of Mild Cognitive Impairment in Diverse Geographical and Ethnocultural Regions: The COSMIC Collaboration. PLoS One. 2015;10(11):e0142388. doi: 10.1371/journal.pone.0142388

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