Characterisation of Physical Frailty and Associated Physical and Functional Impairments in Mild Cognitive Impairment

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Objective: To characterize the physical frailty phenotype and its associated physical and functional impairments in mild cognitive impairment (MCI).

Method: Participants with MCI ($N = 119$), normal low cognition (NLC, $N = 138$), and normal high cognition (NHC, $N = 1,681$) in the Singapore Longitudinal Ageing Studies (SLAS-2) were compared on the prevalence of physical frailty, low lean body mass, weakness, slow gait, exhaustion and low physical activity, and POMA balance and gait impairment and fall risk.

Results: There were significantly higher prevalence of frailty in MCI (18.5%), than in NLC (8.0%) and NHC (3.9%), and pre-frailty in MCI (54.6%), NLC (52.9%) than in NHC (48.0%). Age, sex, and ethnicity-adjusted OR (95% CI) of association with MCI (versus NHC) for frailty were 4.65 (2.40–9.04) and for pre-frailty, 1.67 (1.07–2.61). Similar significantly elevated prevalence and adjusted ORs of association with MCI were observed for frailty-associated physical and functional impairments. Further adjustment for education, marital status, living status, comorbidities, and GDS significantly reduced the OR estimates. However, the OR estimates remained elevated for frailty: 3.86 (1.83–8.17), low body mass: 1.70 (1.08–2.67), slow gait: 1.84 (1.17–2.89), impaired gait: 4.17 (1.98–8.81), and elevated fall risk 3.42 (1.22–9.53).

Conclusion: Two-thirds of MCI were physically frail or pre-frail, most uniquely due to low lean muscle mass, slow gait speed, or balance and gait impairment. The close associations of frailty and physical and functional impairment with MCI have important implications for improving diagnostic acuity of MCI and targetting interventions among cognitively frail individuals to prevent dementia and disability.

Keywords: mild cognitive impairment, frailty, physical function, gait, strength

INTRODUCTION

Late life cognitive impairment and physical impairment are principal causes of disability, falls, hospitalisation, institutionalisation, and death among the elderly. In elderly persons, chronic disability rather than multi-morbidity is the strongest negative prognostic factor for functionality and survival (1), and in the oldest old, known predictors such as smoking and obesity lose their importance,

whereas high disability level, poor physical, and cognitive performance, predict mortality (2). Based on accumulating evidence, it is increasingly appreciated that cognitive and physical impairment in late life are inter-related through shared pathophysiological mechanisms and could probably be manifestations of a single complex phenotype (3).

Mild cognitive impairment (MCI) and the physical frailty phenotype are early cognitive and physical syndromes preceding the development of dementia and disability among older people. MCI is a transitional state of cognition between normal ageing and dementia that may progress to dementia, remain stable, or reverse to normal cognition over a defined period of time. MCI is defined by subjective or objective evidence of cognitive decline greater than expected for the individual's age and education level but that does not interfere notably with activities of daily life (4). Studies show that older individuals with MCI compared to their counterparts without cognitive impairment performed more poorly not just on tests of neurocognitive performance tasks, but also on tests of complex motor and psychomotor domains tasks (5–7), and exhibited greater gait impairment especially on tests that include motor-cognitive dual tasks (8–12). These motor functional deficiencies in MCI are also present in physical frailty, a syndrome that may also reverse to the robust state or progress to functional disability (13). The physical phenotype of frailty is represented by low levels of lean body mass, muscle strength, gait performance, physical activity (PA), and energy.

Studies suggest that gait and other physical manifestations of the frailty syndrome are associated with cognitive decline and dementia. For example, the presence of weight loss or being underweight is well known to precede the onset of Alzheimer's disease (14), lower grip strength, and extremity motor performance are associated with cognitive decline and decreased risk of MCI, and MCI conversion to AD (7, 15), frailty was associated with incident AD and cognitive decline (14, 15), and low levels of PA was associated with cognitive decline (16).

Some authors have argued that motor functional changes should be considered clinical features of MCI, and complex psychomotor tests such as gait speed may be as useful as cognitive tests in the identification of MCI particularly among elderly patients with less education (17). Converging lines of research and consensus also advocate defining MCI more precisely in terms of cognitive-physical constructs of "cognitive frailty" (the simultaneous presence of both physical frailty and MCI) (18), or the analogous motoric cognitive risk (MCR) syndrome (presence of cognitive complaints and slow gait) (19). Few studies have described the prevalence of frailty and its physical and functional impairments in MCI. The associations of specific physical and functional impairments of frailty with MCI are also unclear.

In this population-based study of community dwelling, older persons in the second Singapore Longitudinal Ageing Study (SLAS-2), we compared the prevalence of the physical frailty syndrome, low lean muscle mass, low muscle strength, slow gait speed, exhaustion, low PA, impaired balance, impaired gait, and elevated fall risk between individuals with MCI and non-MCI individuals with normal (high and low) cognitive functioning. We also examined the effects of psycho-social and health-related factors on these associations. We hypothesise that the prevalence of the physical frailty syndrome and its physical and functional impairments are higher in MCI compared to their cognitively normal counterparts, and this association is independent of psycho-social and health-related factors.

MATERIALS AND METHODS

Participants

This study was conducted as part of the Singapore Longitudinal Ageing Studies (SLAS), an ongoing prospective cohort observational study of community-dwelling older adults, aged 55 and above. A first wave (SLAS-1) cohort was recruited between 2003 and 2004 from the South-East region of Singapore. A second wave (SLAS-2) cohort was recruited between 2009 and 2011 in the South West and South-Central regions of Singapore. Participants were identified by door-to-door census, which had demographic characteristics similar to the rest of the population. Residents who were severely physically or mentally ill and incapacitated to give informed consent or participate were excluded. The study was approved by the National University of Singapore Institutional Review Board, and all participants signed written informed consent. Detailed descriptions of the methodology in the SLAS cohorts have been previously described (20).

In this study, we used baseline data from the participants of SLAS-2. A total of 3,270 older adults were enrolled at baseline with an estimated response rate of 78%. Trained research nurses and psychologists conducted questionnaire interviews, testing, and assessment to collect an extensive range of sociodemographic and health-related data. These included questionnaire and physical testing of frailty status, and multi-phasic cognitive screening, assessment and diagnosis of neurocognitive disorders. The participants included 2,844 Chinese, 259 Malay, 148 Indian, and 15 other ethnicities. After excluding participants who did not participate in neurocognitive tests, and those with dementia, there were 2,052 participants who were identified as MCI or normal cognition. Among them, 114 did not have complete frailty data. The final study sample thus comprised 1,938 subjects for analysis.

Identification of MCI and Normal Cognition

The participants' cognitive status was determined using a two-stage screening and diagnostic assessment process. In the first stage, global cognitive assessments were performed using the MMSE (21), and the Montreal Cognitive Assessment (MoCA) (22), which has been previously validated for use in the multiethnic population of Singapore in English, Malay, and Chinese languages (23, 24). Participants who were screened positive by scoring 26 or below on either the MMSE or MoCA underwent the Clinical Dementia Rating (CDR) assessment conducted by trained research nurses, and a comprehensive battery of neurocognitive testing conducted by psychology-trained research assistants, prior to consensus diagnosis of MCI (and dementia) or normal cognition by a panel of geriatricians and psychiatrists, who reviewed all relevant interview, testing, and assessment data.

The neurocognitive assessment included tests of memory [Rey Auditory Verbal Learning Test (25) and Story Memory (26)]; attention [longest span of the digit span subtest, forwards and backwards, from WAIS-III (27)]; visuospatial ability [Brief Visuospatial Memory Test-Revised (28) and Clock Reading Test (29)]; language [Boston Naming Test (30)]; executive functioning [Colour Trails Test 1 and 2 (31)]; and the Block Design subtest from the WAIS-III (27).

At a screening interview, a total of 1,681 participants who scored 27 and above on the MMSE and MOCA were denoted as normal (high) cognition (NHC) (32). There were a total of 138 participants who were screened positive on the MMSE or MOCA but were not assessed ($N = 60$) or provided incomplete or unreliable responses ($N = 23$) on the neurocognitive testing or the CDR, or did not meet the criteria for diagnosis of MCI or dementia ($N = 55$). These participants who were not successfully adjudicated as cases of MCI (or dementia) were assigned the status of normal low cognition (NLC). In 119 participants, MCI was defined according to criteria recommended by the MCI Working Group of the European Consortium on Alzheimer's disease (33):

1. Personal or informant report of cognitive decline relative to previous abilities during the past year.
2. Objective deficit in one or more cognitive domains; defined as a score that was 1.5 SD below age and education adjusted norms (34).
3. CDR of 0.5 or Sum of Boxes score less than 3 (35).
4. Functional independence on basic activities of daily living (Barthel Index).
5. No dementia.

Frailty and Physical Function Measures

Physical frailty was assessed by scores (1 = present, 0 = absent) for five components (shrinking, weakness, slowness, exhaustion, and low PA) proposed by Fried et al. (36) and used in the Cardiovascular Health Study (CHS), with the following operational modifications:

(i) Shrinking was defined by unintentional weight loss of 4 kg or more in the past 6 months, or a body mass index of less than 18.5 kg/m², or calf circumference of 31 cm or less.
(ii) Weakness was assessed using knee extension strength measured using dominant knee extension, using the average value from three trials in kilograms, standardised on gender and BMI strata.
(iii) Slowness was assessed by the 6-m fast gait speed test using the average of two measurements, and the lowest quintile values stratified for gender and height to classify participants as slow, based on data in a previous large population-based study (17).
(iv) Exhaustion was measured as a combined score of three questions from the SF-12 quality of life scale, "Did you have lots of energy?" "Did you feel tired?" (reverse-scored) and, "Did you feel worn out?" (reverse-scored) (37). A score of <10 was used to denote exhaustion.
(v) Low PA was determined by the total amount of time spent on performing moderate and vigorous activities per week

based on questions in the LASA PA questionnaire (38) that fell below the gender-specific lowest quintile determined in the forerunner SLAS-1 study.

As per the CHS criteria, participants were categorised by their total scores as robust (score = 0), pre-frail (score = 1–2), and frail (score = 3–5).

Falls risk was assessed using the Tinetti performance-oriented mobility assessment (POMA) (39). Balance was assessed using standard scoring criteria (0, 1, or 2) to grade sitting balance, standing balance immediately after arising, turning around, and other manoeuvres (total score 0–16). Gait performance (gait initiation, step length and height, symmetry, continuity, path deviation, trunk sway, and walking stance) by having the subject stand with examiner, walks down hallway or across the room, first at "usual" pace, then back at "rapid, but safe" pace (using usual walking aids), total score (0–12). Falls risk was assessed by total balance and gait scores of <19 = high fall risk, 19–24 = medium fall risk, and 25–28 = low fall risk.

Covariates measured included (i) sociodemographic data including age, gender, and education, living status (live alone), (ii) medical comorbidity (determined from self-reports of a known diagnosis and/or treatment of 14 specific conditions (hypertension, diabetes, high cholesterol, stroke, heart attack, atrial fibrillation, heart failure, cataracts, kidney failure, asthma, chronic obstructive pulmonary disease, arthritis, hip fracture), and/or other chronic conditions in the past year, and the total number of medical illnesses), (iii) lifestyle including current smoking and daily alcohol drinking, (iv) depressive symptoms [assessed by the Geriatric Depression Scale (GDS) (40)], (v) disability status assessed by dependency on basic activity of daily living (BADL) (41) and instrumental activities of daily living (42).

Statistical Analyses

The prevalence of frailty and pre-frailty, low lean body mass, weakness, slow gait, exhaustion, low PA, impaired balance, impaired gait, and elevated fall risk were compared between MCI, NLC, and NHC using chi-squared tests of significance, and odds ratio and 95% confidence intervals (95% CI) of association estimated from logistic regression, adjusted for age, sex, and ethnicity. Further adjustment for education, marital status, living status, comorbidities, GDS, and IADL ability were performed to assess the effects of common psycho-social and health-related factors in mediating these associations.

RESULTS

The study participants comprised 119 (6.3%) MCI, 138 (7.2%) NLC (MMSE and MOCA scores <27), and 1,681 (85.5%) NHC (MMSE and MOCA scores ≥27) (**Table 1**). Among MCI participants, 18.5% were frail, compared to 8.0% among NLC and 3.9% among NHC. The prevalence of pre-frailty was similarly higher in MCI (54.6%) and in NLC (52.9%) than in NHC (48.0%) (**Table 2**). Age, sex, and ethnicity-adjusted OR (95% CI) of association with MCI (versus NHC) for frailty was 4.65 (2.40–9.04) and for pre-frailty was 1.67 (1.07–2.61). In addition, significantly

TABLE 1 | Demographic and personal characteristics among mild cognitive impairment (MCI), normal high cognition (NHC), normal low cognition (NLC) groups.

Variables (N = 1,938)	NHC[a]		NLC[b]		MCI		P-value*
Sample N		1,681		138		119	
Age; 55–64	38.8	(653)	23.2	(32)	31.9	(38)	<0.001
65–74	53.4	(897)	55.8	(77)	46.2	(55)	
≥75	7.8	(131)	21.0	(29)	21.9	(26)	
Male gender	37.8	(636)	33.3	(46)	36.1	(43)	0.55
Chinese ethnicity	91.1	(1,530)	90.6	(125)	80.7	(96)	0.001
Single, divorced, widow	27.4	(460)	57.2	(59)	49.6	(60)	<0.001
Education: none	8.1	(136)	38.4	(53)	43.7	(52)	<0.001
Primary	41.4	(694)	44.9	(62)	44.5	(53)	
Living status: alone	13.7	(229)	27.5	(38)	19.7	(23)	<0.001
Alcohol: yes	3.4	(57)	2.9	(4)	2.5	(3)	0.85
Smoking: non smoker	80.9	(1,360)	71.7	(99)	75.6	(90)	0.07
Ex-smoker	10.4	(175)	16.7	(23)	14.3	(17)	
Current smoker	8.7	(146)	11.6	(16)	10.1	(12)	
APOE-e4 allele	17.5	(264)	24.8	(29)	15.0	(18)	
MMSE	28.97	±1.14	25.85	±2.98	24.59	±3.50	<0.001
MoCA	27.7	±1.26	21.37	±3.74	19.57	±4.64	<0.001
GDS	0.51	±1.04	1.20	±2.15	1.10	±1.89	<0.001
Noof comorbidities	2.16	±1.41	2.61	±1.47	3.1	±1.71	<0.001
IADL disability	5.9	(98)	11.0	(15)	25.2	(30)	<0.001

[a]NHC have MMSE and MOCA scores ≥27.
[b]NLC have MMSE and/or MOCA <27, but have no MCI diagnosis.
Figures are % (N) and mean ± SD.
P-values of significance are derived from Chi square test for categorical variables and ANOVA for continuous variables.

higher prevalence of low lean body mass, weakness, slow gait, exhaustion, low PA, impaired balance, impaired gait, and elevated falls risk were observed in the MCI group than in the NLC and NHC groups (**Table 2**). The age, sex, and ethnicity-adjusted ORs of association with MCI ranged between 1.71 and 6.99 for these factors (**Table 3**).

To determine the effects of psycho-social and health-related factors influencing the observed association, further adjustment for education, marital status, living status, comorbidities, GDS, and IADL ability were performed and found to significantly reduce the OR of association (**Table 3**). However, the OR (95% CI) of association with MCI (versus NHC) remained significantly elevated for frailty: 3.86 (1.83–8.17); low body mass: 1.70 (1.08–2.67); slow gait: 1.84 (1.17–2.89); impaired gait: 4.17 (1.98–8.81); and elevated falls risk: 3.42 (1.22–9.53).

DISCUSSION

This study supports the strong and intimate relationship between cognitive and physical impairment, which are present in both MCI and physical frailty. The relationship may be explained by common underlying pathophysiological factors, which include pathways involved in the development of cardiovascular and cerebrovascular diseases, insulin-mediated metabolic disturbances, protein-calorie undernutrition, sex steroids, growth hormones, vitamin D, chronic inflammation, and oxidative stress (3).

In this study, almost two-thirds of community dwelling older adults with MCI manifested the physical syndrome of frailty or pre-frailty, including low lean muscle mass, low muscle strength,

TABLE 2 | Physical frailty characteristics among mild cognitive impairment (MCI), normal high cognition (NHC), normal low cognition (NLC) groups.

Variables (N = 1,938)	NHC		NLC		MCI		P*
Sample N		1,681		138		119	
Frailty status (global)							
Robust	48.1	(809)	39.1	(54)	26.9	(32)	<0.001
Pre-frail	48.0	(807)	52.9	(73)	54.6	(65)	
Frail	3.9	(65)	8.0	(11)	18.5	(22)	
Frailty status (domains)							
Shrinking	18.5	(310)	28.3	(39)	33.6	(40)	<0.001
Slowness	15.0	(252)	21.7	(30)	37.8	(45)	<0.001
Weakness	11.3	(190)	16.7	(23)	24.4	(29)	<0.001
Exhaustion	14.3	(241)	12.3	(17)	23.5	(28)	0.017
Low physical activity (PA)	13.1	(220)	16.7	(23)	23.5	(28)	0.004
Impaired balance (POMA ≤14)	2.9	(48)	6.5	(9)	10.4	(12)	<0.001
Impaired gait (POMA ≤10)	2.3	(38)	6.5	(9)	14.3	(17)	<0.001
Medium-high fall risk (POMA ≤24)	1.1	(19)	3.6	(5)	8.7	(10)	<0.001
Physical function measures							
Frailty scores	0.74	±0.86	0.98	±0.99	1.43	±1.19	<0.001
Calf circumference	34.41	±3.72	33.67	±4.03	34.02	±5.83	0.07
BMI, kg/m²	59.89	±10.81	57.16	±10.47	59.45	±12.44	0.018
Gait speed, s	4.66	±1.49	5.25	±1.81	6.14	±2.77	<0.001
Knee extension, kg	16.40	±6.22	14.14	±6.23	12.93	±4.51	<0.001
Energy score	12.06	±2.19	11.94	±2.10	11.54	±2.34	0.041
PA level	11.53	±1.91	10.97	±1.48	10.85	±1.41	<0.001
POMA Balance score	15.86	±0.61	15.77	±0.19	15.68	±0.86	0.004
POMA Gait score	11.87	±0.74	11.70	±0.98	11.41	±1.42	<0.001
POMA total score	27.73	±1.13	27.47	±1.50	27.10	±1.88	<0.001

Figures are % (N) and mean ± SD.
P-values of significance are derived from Chi square test for categorical variables and ANOVA for continuous variables.

TABLE 3 | Odds ratio of association of physical frailty status and components with cognitive status [mild cognitive impairment (MCI), normal low cognition (NLC), normal high cognition (NHC)].

		Unadjusted			Adjusted: age, sex, ethnicities			Adjusted: age, gender, ethnicity, education, APOE-e4, marital status, living status, comorbidities, GDS, IADL		
		OR	95% CI	P	OR	95% CI	P	OR	95% CI	P
Frailty versus robust	NHC	1			1			1		
	NLC	2.54	1.26–5.08	0.009	1.47	0.70–3.08	0.31	1.28	0.50–3.26	0.602
	MCI	8.56	4.70–15.57	<0.001	4.65	2.40–9.04	<0.001	3.49	1.47–8.31	0.005
Pre-frail versus robust	NHC	1			1			1		
	NLC	1.36	0.94–1.95	0.103	1.67	0.80–1.70	0.42	1.02	0.67–1.56	0.929
	MCI	2.04	1.32–3.14	0.001	1.67	1.07–2.61	0.02	1.37	0.85–2.23	0.197
Low body mass (Calf circumference ≤31)	NHC	1			1			1		
	NLC	1.74	1.18–2.57	0.005	1.37	0.91–2.06	0.13	1.28	0.81–2.04	0.294
	MCI	2.24	1.50–3.34	<0.001	1.74	1.14–2.64	0.01	1.58	0.96–2.59	0.071
Low muscle strength	NHC	1			1			1		
	NLC	1.57	1.0–2.52	0.06	1.21	0.74–1.96	0.45	1.10	0.63–1.92	0.747
	MCI	2.53	1.62–3.95	<0.001	1.79	1.12–2.86	0.02	1.65	0.95–2.87	0.075
Slow gait speed	NHC	1			1			1		
	NLC	1.58	1.03–2.41	0.04	1.19	0.76–1.85	0.45	0.89	0.53–1.49	0.667
	MCI	3.45	2.33–5.11	<0.001	2.36	1.56–3.58	<0.001	1.68	1.02–2.79	0.042
Impaired gait (POMA) (POMA ≤10)	NHC	1			1			1		
	NLC	2.35	1.13–4.90	0.02	2.78	1.28–6.02	0.01	1.97	0.78–4.95	0.148
	MCI	3.93	2.03–7.63	<0.001	5.53	2.87–10.65	<0.001	3.71	1.62–8.46	0.002
Impaired balance POMA (POA ≤16)	NHC	1			1			1		
	NLC	3.00	1.42–6.34	0.004	1.84	0.86–3.96	0.12	1.36	0.55–3.35	0.507
	MCI	7.17	3.91–13.14	<0.001	2.75	1.35–5.59	0.01	1.90	0.79–4.53	0.149
Medium-high fall risk (POMA ≤ 24)	NHC	1			1			1		
	NLC	3.25	1.20–8.84	0.02	3.17	1.13–8.91	0.03	1.55	0.40–6.03	0.528
	MCI	8.24	3.74–18.16	<0.001	6.99	2.96–16.51	<0.001	3.02	0.95–9.53	0.060
Exhaustion	NHC	1			1			1		
	NLC	0.84	0.50–1.42	0.52	0.81	0.47–1.38	0.43	0.51	0.26–0.98	0.042
	MCI	1.84	1.18–2.87	0.007	1.73	1.09–2.75	0.02	1.21	0.69–2.12	0.499
Low PA	NHC	1			1			1		
	NLC	1.33	0.83–2.12	0.24	1.14	0.70–1.84	0.60	1.03	0.60–1.77	0.921
	MCI	2.04	1.31–3.19	0.002	1.71	1.07–2.73	0.02	1.29	0.74–2.23	0.371

Adjusted for age, sex, ethnicity, education, APOE-e4, marital status, living status, comorbidities, GDS, and IADL ability.

slow gait speed, exhaustion and low PA, as well as balance and gait impairment, which pose elevated risk of falls, in greater proportions compared to their cognitively normal counterparts. Psycho-social and health-related factors did not wholly account for the association, such that frailty, low lean body mass, slow gait speed, gait impairment, and impaired gait and balance measure of elevated falls risk remained independently associated with MCI. The OR estimates suggest a very strong association and appears to be specific for phenotypic measures of low lean body mass, slow gait speed, and gait and balance impairment, but not exhaustion or low PA.

Prior studies have shown that older persons with MCI exhibited greater gait variability especially during dual-tasking walking than cognitively normal controls (8, 9). Walking is a complex activity that involves executive functioning, spatial orientation, navigation, and memory, among other cognitive functions (43). The use of simple measures of gait speed or POMA balance and gait scores may thus complement cognitive tests in the identification of MCI among elderly patients especially those with less education (44). At least one other study have shown that the combination of cognitive complaints and slow gait (MCR syndrome) successfully predict increased risk of cognitive decline and dementia (19). However, it remains unclear which components or combinations of physical frailty and cognitive impairment are most optimal in identifying cognitively frail older persons.

In the years, since the conceptual definition of MCI was first proposed, numerous studies have shown that non-cognitive manifestations such as depressive and neuropsychiatric symptoms (45–47), sensory impairment such as in hearing (48), or smell (49), and subtle IADL impairments involving complex functions (50, 51) are over-represented in MCI significantly more than non-MCI controls, and were able to enhance the ability of MCI to predict future risks of dementia. This is also true of physical functional impairment that co-occurs in MCI. Cases

of MCI with concomitant physical frailty may be considered to fulfil the criteria for cognitive frailty (18). Taken together, these findings suggest that the understanding of MCI beyond the conceptual confines of cognitive impairment may help to improve diagnostic acuity and present meaningful targets for interventions among cognitively frail individuals to prevent dementia and disability.

In this regard, the cognitive frailty concept has potential clinical and research advantages in better stratifying the risk profiles of older people for developing dementia and functional disability. Recent studies have shown that the cognitive frailty construct more accurately predict greater risks of cognitive decline and dementia than MCI alone (15, 44, 52, 53). However, it has not been determined whether it is also in fact a more stable construct than MCI, in being less liable to revert to cognitive normal. Another point to note is the prevalence of the cognitive frailty construct. In this study, the prevalence is very low (1.1%) if cases were defined by 22 frail MCI subjects (out of 1,938 participants), but is higher (4.5%) if cases were defined by 65 pre-frail plus 22 frail MCI subjects. It is possible that in this study, the overly restrictive criteria used to define both the cognitive and physical components of this construct may contribute to under-estimating its prevalence, as further discussed below.

The diagnosis of MCI in this study was based on clinical panel consensus review of relevant data according to internationally recommended criteria and is a strength of this study. However, the restrictive criteria for diagnosis of MCI may exclude subjects akin to cases labelled in some studies as "cognitive impairment-no dementia" (CIND). Doubtful cases of MCI were consigned into the category of NLC, a heterogeneous group of subjects, which also included those with below normal global performance on the MMSE or MOCA but who failed to provide supportive cognitive domain or CDR data to merit a MCI diagnosis or otherwise. On close scrutiny, this NLC group appeared to include significantly more participants who were living alone and with higher GDS depression scores, a possible explanation for their failed clinical assessment. The results for NLC showed a pattern of relationship with frailty and its associated physical and functional impairments that was intermediate between cognitive (high) normal and MCI, but with no significantly strong associations with physical functional impairments.

The results for frailty components of exhaustion (fatigue) and low PA were negative. However, this may reflect the limitations of our operationalised measurement of these phenotypic features, and further studies using more sensitive and discriminating instruments are required to ascertain the replicability of these findings. Because of the small numbers, we did not further distinguish MCI participants into amnestic or non-amnestic subtypes. Further studies should investigate the ability of combined cognitive, physical, and functional markers of MCI in predicting future risks of developing dementia.

ETHICS STATEMENT

This study was carried out in accordance with the recommendations of Human Biomedical Research Act, Singapore Ministry of Health; with written informed consent from all subjects. All subjects gave written informed consent in accordance with the Declaration of Helsinki. The protocol was approved by the National University of Singapore IRB.

ROLE OF THE SPONSORS

The sponsors had no role in the conduct of the study or preparation of this manuscript.

AUTHOR CONTRIBUTIONS

TN formulated the hypothesis, designed the study, reviewed the data, and revised the manuscript. WL, TL, PY, and KY reviewed clinical data and adjudicated on MCI diagnosis. GQ performed the data preparation. MN analysed the data. CYS reviewed the literature, drafted and revised the manuscript; all authors participated in the study design and data collection, reviewed the results and manuscript, and approved the manuscript submission.

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