The Flexibility of Physio-Cognitive Decline Syndrome: A Longitudinal Cohort Study

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The mutual presence of impairments in physical and cognitive functions in older adults has been reported to predict incident disability, dementia, and mortality. The longitudinal transitions of phenotypes between these functional impairments, either individually or in combination, remain unclear. To investigate the natural course and prevalence of physical and/or cognitive impairments (CIs), we enrolled participants from a community-based population. Data were retrieved from the first (August 2011 and December 2012) and second wave (August 2013 and June 2015) of the I-Lan Longitudinal Aging Study (ILAS). All participants were classified into four groups: robust, mobility impairment (MI), CI, and physio-cognitive decline syndrome (PCDS). MI was diagnosed with weakness and/or slowness. CI was diagnosed if a subject met a cutoff below 1.5 standard deviations (SDs) of age-, sex-, and education-matched norms of any neuropsychological assessments. PCDS was combined with MI and CI. Our results showed that 38, 14, 30, and 18% of the participants were on the robust, MI, CI, and PCDS at the first wave, respectively. After 2.5 years, 17% robust, 29% MI, and 37% CI progressed to PCDS. In contrast, 33% of PCDS was reversed to non-PCDS. Predictors of conversion to PCDS included worse memory and language functions, older age, lower muscle mass, and the presence of diabetes. In PCDS, a stronger hand-grip strength, younger age, and better memory functions predicted reversion to non-PCDS status. In summary, we probed the transition of PCDS. The skeletal muscle mass/function and memory function are crucial factors associated with PCDS reversion or progression.

Keywords: flexibility, reverse, cognitive decline, physical frailty, cognitive frailty

INTRODUCTION

Physical frailty is a state of vulnerability characterized by reduced muscle strength, endurance, slowness, and reduced physiologic reserve (1), which affects 11–14% of people aged 65 years and older and predicts falls, disability, institutionalization, mortality (2, 3), and cognitive impairment [CI; (4–7)]. A meta-analysis study has shown that the risk for dementia was higher among those with the co-occurrence of physical frailty and CI than among those with CI alone (7).

The co-occurrence of impairments in physical and cognitive functions is clinically common, and several terms have been proposed for this specific phenotype, such as cognitive frailty and motoric cognitive risk (MCR) syndrome. The major difference between these terms is the operational definition of impairments in physical and cognitive functions. Our research group defined this unique phenotype as physio-cognitive decline syndrome (PCDS) (8).

The operational definition of PCDS was based on the findings of our previous cohort studies. We found that the mobility components of frailty (slowness and weakness cluster) were associated with poorer cognitive performance and higher mortality risk than the non-mobility components of frailty (fatigue and weight loss cluster) (9, 10). Therefore, we defined PCDS as a certain condition with slowness and/or weakness as mobility impairment (MI) as well as cognitive performance a minimum of 1.5 standard deviation (SD) below the mean for age-, sex-, and education-matched norms in any cognitive domain. We also identified the specific neuroanatomical signatures of PCDS with low skeletal muscle mass, and those with frailty had gray matter deficits in the hippocampus, cerebellum, and middle frontal gyri in the magnetic resonance imaging (MRI) study (10, 11).

Physio-cognitive decline syndrome affects 10–15% of community-dwelling older adults and deserves further research (10). The pathophysiology between CIs only and the concomitant presence of impairments in physical and cognitive functions may be different, which is still unclear. A recent post-mortem pathological study further demonstrated that the neuropathologic burden was related to frailty and mild CI, or dementia. This study showed that neuropathologic features, including β-amyloid deposition, hippocampal sclerosis, Lewy bodies, tangle density, TDP-43, cerebral amyloid angiopathy, arteriolosclerosis, atherosclerosis, and gross and chronic cerebral infarcts (12), are different from β-amyloid and tangle density in Alzheimer's dementia (13). These findings suggest that there is an extraordinary pathophysiological relationship between physical frailty and related cognitive decline, which may differ from the well-recognized neurodegenerative Alzheimer's disease (AD). The clinical outcomes of PCDS may also differ from those of mild CI or prodromal AD without physical frailty.

Hence, this study aimed to evaluate longitudinal transitions in the phenotypes of older adults with MI, CI, and PCDS to explore the potential reversibility of PCDS (1, 14–16), and to identify factors associated with phenotypic transitions using the data from the I-Lan Longitudinal Aging Study (ILAS).

MATERIALS AND METHODS

Study Design and Participants

The ILAS was a community-based aging cohort study in I-Lan County, Taiwan, which was designed to evaluate the complex interrelationship between aging, frailty, and cognitive function (9). ILAS enrolled community-dwelling adults aged 50 years and above from I-Lan County with the following inclusion criteria: (1) inhabitants of I-Lan County, (2) aged 50 years or above, and (3) no recent plans to move to other counties. ILAS excluded people with the following conditions for participation: (1) inability to communicate and complete an interview, (2) unable to complete assessments due to poor functional status, (3) having a life expectancy <6 months due to a major illness, and (4) being institutionalized. Data retrieved for this study further excluded participants with major neuropsychiatric diseases such as dementia, stroke, brain tumor, or major depression based on self-report or assessment results. Data of the first (baseline) and second wave (follow-up) were included for analysis in the present study. All participants provided written informed consent. This study was approved by the institutional review board of the National Yang-Ming Chiao-Tung University.

Demographic Data and Functional Assessments

Demographic information, including age, sex, years of education, body weight, and height, were collected in both first and second waves of evaluation. The medical history of each participant was assessed by trained research nurses, including diabetes mellitus (DM), hypertension, hyperlipidemia, and cardiovascular disease. According to Fried's criteria, physical frailty is defined by five components: weight loss, exhaustion, low physical activity, weakness, and slowness (17). In this study, weight loss was identified as an unintentional weight loss >5% in the past year or >3 kg in the last 3 months, and exhaustion was defined using the Center for Epidemiologic Studies Depression Scale (18). Physical activity was assessed using the International Physical Activity Questionnaire-Taiwan edition (19), and low physical activity was defined as the lowest quintile within sex. Handgrip strength was measured using a digital dynamometer (Smedlay's Dynamo Meter; TTM, Tokyo, Japan) of the dominant hand, and the best result of the three trials was recorded as the muscle strength. The 6-m usual walking speed with static start and without deceleration was used to define slowness. The lowest quintile of walking speed was defined as the cutoff for slowness, and the sex-specific lowest quintile of handgrip strength was defined as weakness. We used the appendicular skeletal muscle mass (ASM) index to represent the amount of muscles in individuals (20).

Cognitive Function Assessment

In addition to the Chinese version of the Mini-Mental Status Examination (MMSE), all participants underwent comprehensive neuropsychological assessments across multiple cognitive domains in both first and second waves of evaluation, which included (1) verbal memory: a delayed recall in the Chinese Version Verbal Learning Test (CVVLT) (21), (2) language: Boston Naming Test (BNT) (22), and category

(animal) Verbal Fluency Test (VFT) (3, 23) Visuospatial function: Taylor Complex Figure Test (CFT) (24); and (4) executive function: Clock Drawing Test (CDT) (25). All these neuropsychological assessments were culturally adapted and validated (21, 26–29).

Definition of MI, CI, and PCDS

In this study, MI was defined as the presence of weakness and/or slowness of participants, where the cutoffs recommended by the Asian Working Group for Sarcopenia were used (30). CI was defined as 1.5 SD below the mean for age-, sex-, and education-matched norms in any cognitive domain; however, without global CI. PCDS was defined as the concomitant presence of MI and CI (10). According to the epidemiological studies on the Taiwanese population, global CI was indicated as MMSE < 24 in the well-educated participants (education years ≥6) or <14 in less-educated participants (education years <6) (31). In this case, we excluded participants who had the above conditions for possible global CI or dementia.

Statistical Analysis

All participants in the first and second wave were classified into four clinical phenotype categories: robust, MI only, CI only, and PCDS. Continuous variables are expressed as mean ± SD and categorical variables as numbers (proportions). To compare the characteristics of study participants across the different groups (robust, MI, CI, and PCDS groups), we used the chi-squared test for dichotomous variables and one-way analysis of variance (ANOVA) for continuous variables. To explore the possible predictors for the transition of phenotypes, Tukey' test was used for post hoc analysis due to its sensitivity for multiple comparisons. The cumulative probability (95% confidence interval) of transitions among the four groups in a 2.5 year follow-up was calculated using the cumulative distribution function of the standard normal distribution.

To investigate the factors that influence the categorical transition of four different groups, we first used the chi-squared test for dichotomous variables and one-way ANOVA for comparisons of continuous variables of four transitioned groups in a 2.5-year follow-up in each category classified at baseline (the first wave of assessment). Variables showing statistical significance after post hoc analyses between those who remained in the same group and who progressed to a more severe group or reversed to a milder group were included in the following multivariate binomial logistic regression models. For example, in the robust group classified at baseline, the variables that showed statistically significant differences between those who remained in the robust group and those who progressed to the PCDS group in a 2.5 year follow-up in post hoc analyses were put into the multivariate binomial logistic regression model (transition vs. maintenance) to determine whether the factors were the significant predictors of PCDS transition in the robust subjects. SPSS software (version 15.0; SPSS, Inc., Chicago, IL, USA) was used for statistical analysis. All tests were two-sided, and the value of $p < 0.05$, was considered significant.

RESULTS

Demographic Characteristics

In the first wave of the ILAS, data from 1,223 participants were eligible for analysis. Due to funding and administrative limitations, the second wave of the ILAS was applied to a smaller random sample using the simple random sampling method. Overall, 531 participants, aged 51–87 years, completed both the first and second wave assessments with a mean follow-up of 2.5 years. Comparisons between participants from both the waves ($n = 531$) and wave 1 only ($n = 692$) are shown in **Supplementary Table 1**. Participants who received assessments in both the waves were older (64.46 ± 8.58, vs. 61.61 ± 8.82, $p < 0.001$), had fewer educational years (5.88 ± 4.72 vs. 7.67 ± 5.08, $p < 0.001$), slower walking speeds (1.49 ± 0.44 vs. 1.68 ± 0.46, $p < 0.001$), a lower BNT score in language function (9.51 ± 2.93, vs. 14.69 ± 2.79, $p < 0.001$), and a lower CDT score in executive function (7.28 ± 2.59, 8.08 ± 2.53, $p < 0.001$) than those who were not selected in the second wave study.

In this study, we only included data from participants who attended both wave assessments for further analyses. **Table 1** summarizes the baseline characteristics and comparisons between the groups. There are no significant differences in gender and past medical history. There are significant changes in age, education, weight, height, physical functions (walking speed and grip-strength), cognitive tests (CVVLT, BNT, VFT, CFT, and CDT), MMSE, and muscle mass index (ASM). *Post hoc* analysis showed that the MI group had significantly lower height and lower ASM compared with the robust group. In contrast, the CI group had significantly older age and weaker handgrip strength than the robust group. Notably, the PCDS group was older than the MI group and had less education and poorer performance in several cognitive domains and MMSE than the CI group.

The Phenotypic Transition During Follow-Up

At baseline, the prevalence of robust, MI, CI, and PCDS groups was 38, 14, 30, and 18%, respectively (**Figure 1B**). After 2.5 years, the PCDS group had a higher risk of developing dementia (4.0%), which was similar to the CI group (3.75%, $p = 0.889$); however, it was higher than the robust group (0.48%, $p = 0.04$). However, no participant in the MI group had a high risk of dementia during follow-up (**Figure 1A**). As dementia is an irreversible state, this study focused on the flexibility of PCDS. Next, we examined the transition among these four groups after excluding participants who were already demented at the second wave.

In the second wave, the distribution of the four groups was 20, 29, 16, and 33%, respectively (**Figure 1B**). About 2% of the participants progressed to dementia after 2.5 years. More than half (63%) of the PCDS participants remained in PCDS at a follow-up. Moreover, 4.0% of PCDS participants returned to be robust, 19.0% became MI only, and 10.0% became CI only. In contrast, 17.4% of robust, 29.3% of MI, and

TABLE 1 | Demographic characteristics of four categories at baseline.

	Total	Robust	MI	CI	PCDS	*p*-Value
n	531	206	75	154	96	
Sex, Female, *n* (%)	246 (46%)	91 (44%)	35 (47%)	68 (44%)	52 (54%)	0.385
Age, year	64.38 ± 8.57	62.51 ± 8.06	63.18 ± 8.52	65.94 ± 8.55[b]	66.81 ± 8.78[ce]	0.001
Education, year	5.88 ± 4.72	6.84 ± 4.88	5.89 ± 4.82	5.69 ± 4.40	4.09 ± 4.29[cf]	0.001
Weight, kg	62.79 ± 11.03	63.88 ± 11.31	61.56 ± 10.39	63.46 ± 10.02	60.36 ± 12.08[c]	0.042
Height, cm	159.03 ± 8.00	160.50 ± 8.29	157.56 ± 7.72[a]	159.72 ± 7.10	155.91 ± 7.97[cf]	0.001
Physical function assessments						
Walking- speed, m/s	1.49 ± 0.44	1.65 ± 0.41	1.25 ± 0.39[a]	1.56 ± 0.43[d]	1.21 ± 0.35[cf]	0.001
Grip- strength, KGs	29.44 ± 9.41	32.90 ± 8.96	26.07 ± 9.38[a]	30.31 ± 7.84[bd]	23.25 ± 8.88[cf]	0.001
Cognitive function assessments						
CVVLT						
Score	6.79 ± 2.14	7.70 ± 1.18	7.64 ± 1.19	6.04 ± 2.39[bd]	5.38 ± 2.64[cef]	0.001
Impairment, *n* (%)	91 (17.1%)	0 (0%)	0 (0%)	54 (35.1%)	37 (38.5%)	0.001
BNT						
Score	9.51 ± 2.93	10.92 ± 2.38	10.21 ± 2.05	8.50 ± 2.95[bd]	7.56 ± 2.88[cef]	0.001
Impairment, *n* (%)	93 (17.5%)	0 (0%)	0 (0%)	53 (34.4%)	40 (41.7%)	0.001
VFT						
Score	14.81 ± 4.66	16.65 ± 4.50	15.68 ± 4.08	13.24 ± 4.39[bd]	12.70 ± 4.16[ce]	0.001
Impairment, *n* (%)	54 (10.2%)	0 (0%)	0 (0%)	38 (24.7%)	16 (16.7%)	0.001
CFT						
Score	30.86 ± 5.95	33.01 ± 3.43	31.88 ± 4.41	29.69 ± 6.25[bd]	27.33 ± 8.28[cef]	0.001
Impairment, *n* (%)	43 (8.1%)	0 (0%)	0 (0%)	28 (18.2%)	15 (15.6%)	0.001
CDT						
Score	7.28 ± 2.59	8.54 ± 1.58	8.07 ± 1.76	6.49 ± 2.72[bd]	5.25 ± 2.96[cef]	0.001
Impairment, *n* (%)	112 (21.1%)	0 (0%)	0 (0%)	63 (40.9%)	49 (51.0%)	0.001
MMSE Score	26.15 ± 3.44	27.29 ± 2.65	27.12 ± 2.40	25.71 ± 3.42[bd]	23.63 ± 4.16[cef]	0.001
Muscle mass index						
ASM	18.22 ± 4.07	18.84 ± 4.32	17.40 ± 3.96[a]	18.47 ± 3.76	17.14 ± 3.83[c]	0.002
Medical history						
HTN	41%	39%	44%	40%	45%	0.732
DM	17%	18%	21%	16%	16%	0.710
HLD	11%	12%	12%	9%	14%	0.131
CAD	4%	2%	1%	7%	3%	0.133

ASM, appendicular skeletal muscle mass index; BNT, Boston Naming Test; CAD, cardiovascular disease; CDT, Clock Drawing Test; CFT, Taylor Complex Figure Test; CI, cognitive impairment; CVVLT, Chinese Version Verbal Learning Test; DM, diabetes mellitus; HLD, hyperlipidemia; HTN, hypertension; MI, mobility impairment; MMSE, Mini-Mental State Examination; PCDS, physio-cognitive decline syndrome; VFT, Verbal Fluency Test.
Data showed mean ± standard deviation (SD).
Significant after post hoc analyses between groups. a: significance between MI and robust group; b: significance between CI and robust group; c: significance between PCDS and robust group; d: significance between MI and CI; e: significance between MI and PCDS; f: significance between CI and PCDS.
Chi-squared test for dichotomous variables and ANOVA for continuous variables, significantly (p < 0.05).

36.9% of CI participants progressed to PCDS in a follow-up (**Figure 1C**).

Factors Associated With Phenotypic Transitions

One-way ANOVA with *post hoc* Tukey' test was used to identify variables with significant differences at baseline between each group of phenotypic transitions (**Table 2**, **Supplementary Tables 2–4**), and those variables that reached statistical significance were then entered into the multivariate binomial logistic regression model as independently associated factors (**Table 3**).

Transition of Baseline Robust Group and the Predictive Factors for Transition

Compared to participants who remained robust, participants progressed to CI were older and had a lower CVVLT score in memory function at baseline, and those progressed to PCDS group had lower education years, a lower CVVLT score in memory function, and a lower VFT score in language function (**Supplementary Table 2**). Multivariate binomial logistic regression showed that a lower CVVLT score in memory function was a significant predictor of CI conversion (odds ratio [OR] = 0.55, *p* = 0.004), and a lower CVVLT score in memory function (OR = 0.63, *p* = 0.03) or a VFT score in language
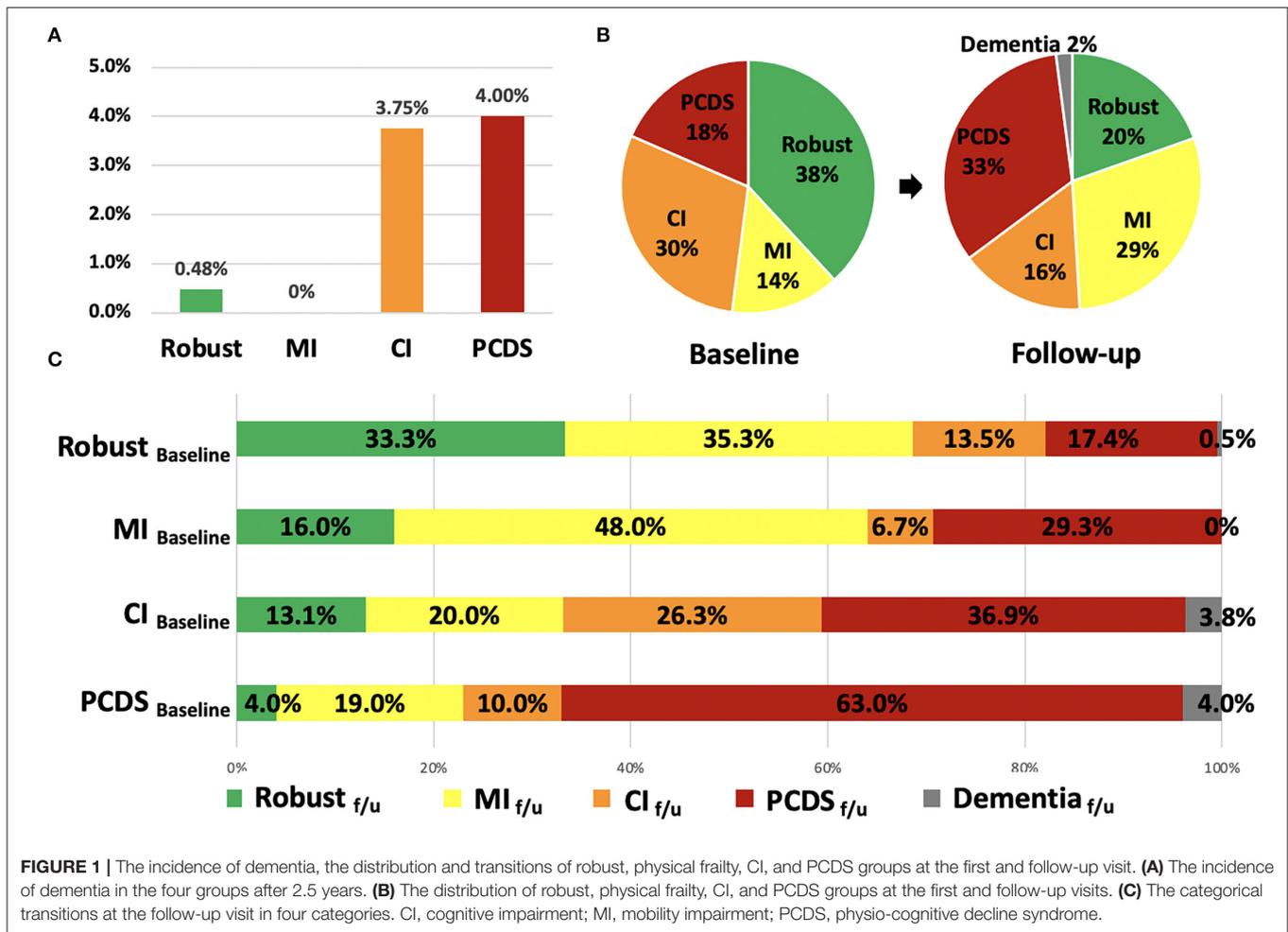
FIGURE 1 | The incidence of dementia, the distribution and transitions of robust, physical frailty, CI, and PCDS groups at the first and follow-up visit. **(A)** The incidence of dementia in the four groups after 2.5 years. **(B)** The distribution of robust, physical frailty, CI, and PCDS groups at the first and follow-up visits. **(C)** The categorical transitions at the follow-up visit in four categories. CI, cognitive impairment; MI, mobility impairment; PCDS, physio-cognitive decline syndrome.

function (OR = 0.83, p = 0.01) were significant factors for PCDS conversion in the robust group (**Table 3**).

Transition of Baseline MI Group and the Predictive Factors for Transition

Compared to participants who remained in MI, those who progressed to PCDS were older, had fewer years of education, slower walking speed, weaker hand-grip strength, lower ASM, lower BNT and VFT scores in language function, the CDT score in executive function, and the MMSE score compared to those in the MI group (**Supplementary Table 3**). Only older age and lower ASM were significantly associated with PCDS conversion in MI participants (age: OR = 1.13, p = 0.004; ASM: OR = 0.76, p = 0.01) (**Table 3**). In the MI group, no associated factors were identified among MI to become CI.

Transition of Baseline CI Group and the Predictive Factors for Transition

Compared to participants who remained in CI, those who reversed CI to robust were younger and had a higher BNT score in language function (**Supplementary Table 4**), which remained statistically significant in the binomial regression model (age:

OR = 0.83, p = 0.002; BNT: OR = 1.47, p = 0.01) (**Table 3**). And those who converted to MI were younger and had a higher CVVLT score in memory function at baseline than those who remained in CI (**Supplementary Table 4**). Further logistic regression showed that only older age was an independent factor associated with CI to MI conversion (OR = 1.25, p = 0.0001) (**Table 3**). In CI participants, those who progressed to PCDS had DM (**Supplementary Table 4**). Moreover, DM was an independent factor associated with progression to PCDS (OR = 6.82, p = 0.01) (**Table 3**).

Transition of Baseline PCDS Group and the Predictive Factors for Transition

Compared to participants who remained in PCDS, those who reversed to robust had stronger hand-grip strength (**Table 2**), and better hand-grip strength remained to be an independent associated factor in the binomial regression model (OR = 1.36, p = 0.01) (**Table 3**). And those who reversed PCDS to the CI group had a higher CVVLT score in memory function, and those who reversed to MI had a younger age (**Table 2**). Younger age was an independent associated factor for PCDS to MI, a higher CVVLT score in memory function was an independent associated factor

TABLE 2 | Comparisons of the baseline physical and cognitive performance of four groups transited from participants with PCDS ($n = 96$).

2.5 years of follow-up	Baseline: PCDS				p-value
	Robust	**MI**	**CI**	**PCDS**	
n	4	19	10	63	
Sex (F)	50%	58%	50%	54%	0.981
Age	60.13 ± 5.05	62.27 ± 5.76[e]	66.97 ± 6.25	68.58 ± 9.44	0.022
Education	6.75 ± 1.50	5.68 ± 4.85[e]	3.90 ± 2.85	3.48 ± 4.30	0.143
Weight	57.23 ± 9.84	60.1 ± 9.80	67.52 ± 18.89	59.50 ± 11.38	0.248
Height	157.60 ± 8.18	157.22 ± 8.10	154.48 ± 8.29	155.63 ± 7.99	0.789
Walking speed	1.02 ± 0.13	1.30 ± 0.42	1.33 ± 0.38	1.18 ± 0.32	0.251
Hang grip strength	35.75 ± 11.53[c]	24.90 ± 10.80[e]	23.60 ± 7.49	21.91 ± 7.72	0.024
CVVLT	5.00 ± 3.56	6.53 ± 1.87[e]	7.00 ± 1.49[f]	4.79 ± 2.75	0.010
BNT	10.25 ± 1.71[c]	8.79 ± 2.32[e]	6.80 ± 2.74	7.14 ± 2.95	0.031
VFT	11.50 ± 4.80	14.21 ± 3.61	12.50 ± 4.50	12.35 ± 4.21	0.347
CFT	34.75 ± 1.50[c]	29.97 ± 5.21	28.35 ± 8.85	25.91 ± 8.82	0.056
CDT	7.25 ± 1.50	6.21 ± 2.74	5.90 ± 2.77	4.73 ± 3.02	0.101
MMSE	27.00 ± 2.45[c]	25.32 ± 3.46[e]	24.00 ± 3.74	22.84 ± 4.30	0.043
ASM	17.76 ± 3.91	17.76 ± 4.31	17.52 ± 4.39	16.85 ± 3.65	0.800
HTN	0%	26%	60%	51%	0.051
DM	0%	0%	20%	21%[e]	0.143
HLD	0%	5%	10%	18%	0.458
CAD	0%	0%	0%	5%	0.666

ASM, appendicular skeletal muscle mass index; BNT, Boston Naming Test; CAD, cardiovascular disease; CDT, Clock Drawing Test; CFT, Taylor Complex Figure Test; CI, cognitive impairment; CVVLT, Chinese Version Verbal Learning Test; DM, diabetes mellitus; HLD, hyperlipidemia; HTN, hypertension; MI, mobility impairment; MMSE, Mini-Mental State Examination; PCDS, physio-cognitive decline syndrome; VFT, Verbal Fluency Test.

*Significant after post hoc analyses between groups. a: significance between the MI and robust group; b: significance between the CI and robust group; c: significance between the PCDS and robust group; d: significance between MI and CI; e: significance between MI and PCDS; f: significance between CI and PCDS.

**Chi-squared analysis using Tukey' test with corrected p-value, significantly ($p < 0.05$).

for PCDS to CI (age: OR = 0.92, $p = 0.01$; CVVLT: OR = 1.57, $p = 0.03$) (**Table 3**).

DISCUSSION

Overall, our study demonstrated that the phenotypes of physio-cognitive decline are potentially reversible. It included 18% robust, 29% MI, and 39% CI groups that progressed to PCDS. Notably, 34.4% of the PCDS participants reversed their phenotypes into robust (4.2%), MI (19.8%), and CI (10.4%). In our studies, we probe the trajectories of PCDS. Skeletal muscle mass and mobility function are the most important factors for the phenotypic transitions of physical and CI. A lower appendicular skeletal muscle mass index (ASM) in MI participants was more likely to progress to PCDS, and PCDS participants with stronger handgrip strength, younger age, and better verbal fluency were more likely to revert to the non-PCDS status.

Mobility impairment and skeletal muscle mass loss are important in PCDS progression. These findings persisted not only in our epidemiological study but also in our basic research results. In our aging cell and animal model study, exosomal miR-29b-3p secreted by atrophic skeletal muscle impairs the development of neurons and induces neuronal senescence (32). Our previous

neuroimaging study also demonstrated that individuals with physical prefrailty or frailty were present with gray matter deficits in the hippocampus, cerebellum, and middle frontal gyri (8, 11, 33). All of these evidences reinforce that phenotypic transitions in the physio-cognitive decline phenomenon are associated with a skeletal muscle–brain crosstalk.

Studies have reported that people with cognitive frailty have a poor cognitive function in some specific cognitive domains, such as working memory, verbal fluency, and processing speed (34, 35). Few studies have reported sequential changes in the specific cognitive function of PCDS (or cognitive frailty) (36, 37). Our previous study revealed that both non-memory and memory domains are associated with physical frailty (9). In this study, we also found that both memory and non-memory cognitive functions (CVVLT and VFT scores) could predict the progression from robustness to PCDS. Non-memory cognitive functions are involved earlier in physical frailty-related CI in our previous study (9). People with physical frailty tend to progress and develop PCDS during the decline of the memory function. The memory function (CVVLT score) appears to be a significant predictor of PCDS conversion in our study. In contrast, patients with PCDS with a good memory function are more likely to revert.

TABLE 3 | Statistically significant factors affecting categorical transitions in a 2.5-year follow-up revealed by multivariate binomial logistic regression.

	Factors	OR	95% CI	p-value
Baseline Robust				
Transition to:				
MI	None detectable			
CI	CVVLT	0.55	0.37–0.82	0.004
PCDS	CVVLT	0.63	0.41–0.96	0.030
	VFT	0.83	0.73–0.95	0.011
Baseline MI				
Transition to:				
Robust	None detectable			
CI	None detectable			
PCDS	Age	1.13	1.04–1.22	0.004
	ASM	0.76	0.61–0.94	0.012
Baseline CI				
Transition to:				
Robust	Age	0.83	0.74–0.94	0.002
	BNT	1.47	1.11–1.93	0.014
MI	Age	1.25	1.12–1.38	0.0001
PCDS	DM	6.82	1.47–31.69	0.012
Baseline PCDS				
Transition to:				
Robust	Hand-grip strength	1.36	1.07–1.73	0.011
MI	Age	0.92	0.86–0.98	0.013
CI	CVVLT	1.57	1.05–2.35	0.032

ASM, appendicular skeletal muscle mass index; BNT, Boston Naming Test; CI, cognitive impairment; CVVLT, Chinese Version Verbal Learning Test; DM, diabetes mellitus; MI, mobility impairment; PCDS, physio-cognitive decline syndrome; VFT, Verbal Fluency Test.

In our study, the PCDS group had a higher incidence of dementia (4.0%) than the robust group (0.48%). Based on our study, PCDS may be one of the main contributors to frailty-related incidental dementia instead of physical frailty alone. Our findings are in line with previous reports that CI and frailty were found to be significant risk factors for dementia instead of physical frailty [38]. Alternatively, those with a combination of physical frailty and CI had a higher risk of dementia than those with physical frailty or CI alone. Therefore, CI in the MI group should be assessed for detecting PCDS. These findings also support the hypothesis that PCDS may differ from dementia in its patho-etiology [39, 40].

The criteria of original cognitive frailty are defined as physical frailty and the Clinical Dementia Rating scale 0.5 scores [41]. Moreover, the following criteria further define "potentially reversible cognitive frailty" and "reversible cognitive frailty" based on the presence of objective or only subjective cognitive decline [42]. Additionally, MCR was recognized as a state of concurrent physical frailty and CI. It is defined as a predementia syndrome characterized by slow gait and cognitive complaints [43, 44]. Both cognitive frailty and MCR have been associated with a higher risk of incident dementia and all-cause mortality.

Compared to cognitive frailty and MCR, PCDS defines physical decline as weakness and/or slowness, but not the other components of physical frailty, and CI as objective CI in any domain. This definition is based on our previous findings that CI is more likely to be associated with MI (weakness and slowness) [9–11]. MI was a good predictor of low survival rate (hazard ratio: 6.82) and poorer overall health outcomes (hazard ratio: 1.67) in our previous study [45]. A recent longitudinal cohort study showed that MI was associated with a functional decline and the progression of multimorbidity, compared with the subtypes of no mobility and low physical activity [46]. MI was also associated with a fast clinical decline using a data-driven approach [47]. MI is an important predictor of cognitive frailty. Additionally, only subjective cognitive decline in the MCR criteria is not sufficient for CI [8]. Therefore, the criteria of PCDS, including MI (weakness and/or slowness) and CI, are suitable for further studies.

Regarding comorbidities, we found that DM [48] was an independent factor for CI participants to progress to PCDS. DM has been reported to be associated with the development of frailty and dementia [49, 50]. DM was at a greater risk of developing cognition impairment [49, 51]; therefore, older patients with diabetes may experience CI earlier than PCDS. However, more studies are needed to confirm the pathophysiological roles of DM in the development of PCDS. Additionally, other comorbidities, including hypertension, hyperlipidemia, and cardiovascular disease, were not significantly associated

with PCDS progression in our study. This might be related to the fact that most of our participants were on medications for these comorbidities. In such cases, the risk of PCDS may be low.

We have demonstrated that PCDS is a variable status with flexibility. In addition to its ability to predict poor physical and cognitive functions after 2.5 years, its flexibility was also shown in the present study. Recently, people with cognitive frailty underwent multidomain interventions, including physical, nutritional, cognitive, and psychosocial aspects, showed improvements in physical and psychosocial functions, which indicated the flexibility of cognitive frailty (52, 53). Several studies have showed factors that are associated with the reversal of frailty progression, including exercise (muscle strength training), protein supplementation, and high self-rated health (54–57). Accumulating evidences also showed the reversion from mild CI to normal cognition (58–60). Although the relationship between frailty and cognitive function impairment and how they interacted with each other are still lacking, the present study showing the factors associated with the reversion of PCDS provided clues to understand the pathophysiology of physical frailty-related CI. In addition, this study provided the nature of the flexibility of PCDS, which highlighted that early intervention is important to prevent falls, disability, institutionalization, and mortality (2, 3).

Our result suggests that, although PCDS is supposed to be a prodromal accelerated aging phenotype, it is also an important potential intervention target to prevent poor prognosis in older adults. Although in our study, there was no further intervention such as care program, policy implementations, or treatment process. Only those with chronic diseases such as hypertension, DM, or hyperlipidemia used medication. We showed that factors associated with the reversion and progression of PCDS also provided directions for interventions. We anticipate our criteria to define a high-risk PCDS group, which has the possibility of reversion for further intervention studies. Our PCDS definition supports the efficacy of a multidomain intervention to improve the function of individuals with PCDS, who are vulnerable but reversible and flexible (61–63). In addition, our study demonstrated that skeletal muscle mass and function are key factors associated with the reversion or progression of PCDS, which indicated that exercise training may be a good intervention to prevent physical and CIs (15, 52, 53, 64).

This study has some limitations. First, the participants in this study were living in rural communities and had lower educational status and good physical function, which may have overestimated the extent of CI and underestimated the extent of MI in our study population. We would need another cohort of different backgrounds to validate the present results. Second, the present longitudinal study only analyzed the follow-up data at 2.5 years. Because age-related physical or/and cognitive decline is a long-term process, we would need a longer follow-up duration to elucidate the entire disease course of PCDS. Third, this study did not record the medication used in our participants. We did not know the effect of medication on PCDS. Fourth, we did not

have the data of intermediate status changes, which are important for a convertible or reversible process. Finally, we did not check for biomarkers related to degenerative dementia. According to a recent study, the potential for reversibility of cognitive frailty should be supported by the evidence of biomarkers of amyloid, tau, and neuronal damage (65). Further studies involving these biomarkers and a revised definition of cognitive frailty according to multidimensional subtyping may be needed.

In conclusion, our study showed that the phenotypes of physio-cognitive decline are potentially convertible and reversible. In the first wave, 38, 14, 30, and 18% of the participants were in the robust, MI, CI, and PCDS, respectively. After 2.5 years, 17% robust, 29% MI, and 37% CI progressed to PCDS. Skeletal muscle mass and mobility function are the most important factors for the phenotypic transitions of physical and CI. Lower ASM in MI participants was more likely to progress to PCDS, and PCDS participants with stronger handgrip strength, younger age, and better verbal fluency were more likely to revert to the non-PCDS status. We probed the transition of PCDS. Skeletal muscle mass/function and memory function are crucial factors associated with the reversion or progression of PCDS.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Institutional Review Board of the National Yang-Ming Chiao-Tung University. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

P-NW designed the experiments. P-NW, K-HC, L-HC, and Y-JL enrolled the participants. P-LL, Y-CL, S-YL, and C-PL analyzed the data. Y-CL, C-PC, and P-NW wrote this manuscript. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

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