CHAPTER 4

STUDY 3

Mild Cognitive Impairment is a Predictor of Physical Decline in Community-Dwelling Older People

4.1 Introduction

Ageing is associated with progressive physical decline and changes in sensorimotor, muscular and cognitive function (162, 163). Balance and mobility require a complex integration of each of these systems. Recent evidence has suggested that higher level cognitive function plays an essential role in the integration and interpretation of sensory information by compromising motor planning and responses in complex everyday environments (105). Therefore, impaired cognitive function can increase a person's risk of falling through diminished cognitive resources to compensate for age-related gait and postural disturbances (105).

Studies in older adults with dementia show that this group is more prone to impaired balance and gait slowing than those without cognitive impairment (164-167). Further, older adults with cognitive impairment fall at an annual incidence of 60%, which is about twice that of cognitively intact older adults (168, 169). Recently, researchers have been looking into individuals who are at risk for further progression to dementia as people MCI (35, 170). Besides the decline in cognitive function, individuals with MCI also show impairments in physical functions (15, 171-173). Specifically, individuals with MCI have been associated with greater postural sway, slower reaction time, worse performance on mobility tasks compared to cognitively intact controls that drive them predispose to fall (15, 171-173).

Physiological Profile Assessment (PPA) is a valid and reliable measure for quantifying physiological fall risk in older people (22). The PPA comprises a combination of well-recognized fall risk factors (i.e. vision, peripheral sensation, muscle strength, reaction time and postural sway). Previous studies have revealed that

the PPA can predict older people at risk for falls with 75% accuracy (162). PPA test scores have also strongly associated with gait speed and functional mobility in community-dwelling older people (174, 175). Therefore, PPA would be a suitable quantitative method to monitor physical decline over time among older people. Two previous studies have found that older people with MCI had higher composite PPA scores and greater postural sway, suggesting the presence of a higher fall risk compared to cognitively intact older people (136, 151). However, to the best of our knowledge, no previous studies have investigated whether MCI is associated with a progressive decline of physical function over time and associated increased fall risk. It has been suggested that the impaired instrumental daily activities and increased fall risk in people with MCI may be attributable to deficits in the executive functioning domain (161, 176-178). Therefore, the present study aimed to investigate whether objectively defined MCI is a risk factor for further physical decline using a valid and reliable method as PPA. In addition, we were interested to further investigate whether impaired executive function in individuals with MCI is associated with physical decline over 1 year.

4.1.1 Research questions, purposes and hypotheses of the study

Research questions

1) Is objectively defined MCI associated with physical decline over 1 year?
2) Which cognitive domains (i.e. memory, language, attention, and executive functions) are associated with physical decline over 1 year?

Purposes

1) To investigate whether MCI is a risk factor for accelerated physical decline over 1 year
2) To investigate whether executive function is a risk factor for accelerated physical decline over 1 year

Hypotheses

1) Physical performance (i.e. greater increase in PPA scores) will decline significantly more in individuals with MCI compare to cognitively intact controls over 1 year.
2) Among cognitive domains, executive function is the most strongly associated with physical decline over 1 year.

4.2 Review Literatures

4.2.1 Evidence of impaired physical function in individuals with MCI

Traditionally, impairment in cognitive function, especially reporting of memory loss was solely reflected a subsequent cognitive decline (179). To date, the increasing evidence has revealed that individuals with MCI is not only showing cognitive deficits, but also showing some physical dysfunctions. In line with this notion is the finding that individuals with MCI had poorer gait and balance function, poorer lower limb coordination as well as slower reaction time and greater inter-individual reaction time variability compared to those without cognitive declines (15, 171-173, 180).

Franssen et al (180) have initially investigated physical function in individuals with MCI via examining of balance (i.e. tandem stand and single-leg-stance tests) and lower-limb coordination performance (i.e. foot tapping, alternating pronation-supination, and sequential finger to thumb tapping). Results revealed that individuals with MCI demonstrated poorer equilibrium and lower limb coordination that cause them more potentially predispose to fall than those cognitively intact persons. Moreover, Aggarwal et al (171) have investigated motor function among 3 groups of participants including cognitively intact elders, individuals with MCI and demented patients. The physical functions were assessed using 5 performance-based measures of upper-limb function (i.e. manual dexterity) and lower-limb function (i.e. 10-ft timed walk, sit-to-stand time test, full-tandem stand; eyes open, semi-tandem stand; eyes open, side-by-side stand; eyes open and eyes closed) and a modified Unified Parkinson's Disease Rating Scale. In a large group of elderly persons,

researchers found that upper and lower limb functions as well as parkinsonian sign, especially bradykinesia in individuals with MCI were more impaired than those without cognitive impairment. Interestingly, among individuals with MCI the degree of impairment in lower-limb function was related to the risk of AD. In addition, Leandri et al (173) found that impaired static balance performance assessed by stabilometry technique could be found among individuals with MCI. Results showed that antero-posterior sway under eye closed condition in individuals with MCI were greater than those cognitively intact controls. Therefore, postural sway can be reflected the cortical control of postural stability. The evidence of impairment in reaction time among individuals with MCI was reported by Gorus et al (181). Individuals with MCI were assessed hand reaction time in different conditions graded from simple- to complex task. The results found that individuals with MCI demonstrated greater reaction time variability (compared performance within persons across repeated trials) and slower reaction time than non-cognitive impaired persons. There were only few studies that assessed gait changes in term of temporospatial domain. Findings from limiting studies suggested that participants with MCI have significant shorter stride length, slower gait speed and greater variability in stride length and swing time compared to non-cognitive impaired controls (15, 113).

In summary, physical decline especially impaired gait and balance was more pronounced in individuals with MCI compared with those who are cognitively intact. It implies that cognitive and physical functions are closely related. Therefore, the changes on physical and cognitive function in individuals with MCI underscore the greater risk of falls among this population.

4.2.2 Evidence of impaired executive function is a risk factor of falls

It is well-established that cognitive impairment is significant risk factor of falls (168, 169, 182). Traditionally, the relationship between falls and cognitive function was examined using global measures of cognitive function such as Mini-Mental State Examination (MMSE); however, the association between global cognitive impairment and falls among older adults is controversial (183, 184). There is some evidences show that increased risk of falls is specific to the domain of cognitive functions. Specifically, researchers have suggested that specific cognitive domains in particular executive function play an important role in gait control even in routine walking condition and also associated with increased risk of single and recurrent falls (98, 125). From this perspective, it seems only natural that executive function deficits would exacerbate the risk of falls. Herman et al (185) demonstrated that among cognitively intact older adults with worse executive function at baseline assessment were more likely to falls during 2-year follow-up compared to those with better executive function. Consistently, Mirelman et al (186) found that executive function performance was associated with future fall over the course of 5-year follow-up period among older adults without cognitive impairment at initial visit. Interestingly, other cognitive domains (i.e. attention, memory, visuospatial function and global cognitive function) were not associated with falls. In addition, Delbaere et al (161) suggested that among individuals with MCI, impaired executive function showed the strongest association with future falls during 1-year follow-up period. This finding is congruent with the notion that walking is not an automatic task but

requires the higher cognitive control, thus the risk of future falls can be predicted by executive function performance.

Recent evidence suggests that falls and gait performance during dual-task condition is related specifically to executive function (185, 187, 188). Indeed, dual tasking relies upon executive function and the ability to allocate or divide attention between two tasks when performed simultaneously (126, 127). Consistent findings reveal that while walking and performing attentional-demanding task, demented patients and individuals with MCI exhibit significant gait changes (i.e. greater stride time variability, slower walking speed and shorter stride length) compared to when walking without a secondary task (14, 96, 98, 109, 134). One explanation is that gait control requires more attentional resources in cognitive impairment persons. Combining a cognitive task with walking may create a competitive demand for executive functions that influence gait control efficiency (131). These findings suggest that as cognitive function declines, the ability to maintain a stable gait pattern while performing dual-task decreases in parallel.

4.2.3 Evidence of brain change related to physical decline among older adults

Recently, the pathophysiological mechanism underlying physical declines among older adults is investigated via neuroimaging technique including Magnetic Resonance Imaging (MRI). Evidence from MRI studies from both cross-sectional and longitudinal studies has indicated that high white matter lesions (WMLs) volume was associated with physical declines including impaired balance, slower gait speed and reduced mobility ability (189-192). Specifically, several studies

have reported that white matter hyperintensities (WMHs) in the frontal lobe and periventricular regions had the strongest relationships with balance, gait, and mobility impairment (193). The high volume of WMLs at baseline is proposed to be a predictor of gait and mobility declines over time (192, 194-196). There is only one study (197) have examined the impact of specific WMHs on sensorimotor physical decline over time among community-dwelling older adults. The results showed that WMHs in the deep fronto-parietal and periventricular parieto-occipital regions had the strongest associations with physical decline. There is an evidence that people with high total WML volume (highest quintile) at initial visit have a greater risk of fall compared to those low total WMLs volume (lowest quintiles) (198). Based on our knowledge, there is only one study that examined the relation of specific WMLs location and falls and found that the presence of periventricular WMLs in frontal regions was the best regional of fall risk (199). One explanation is that frontal lobe covers a variety of cognitive processes, in particular executive function, which has previously established to be a critical area in controlling posture (200-202). These findings reflect an important role of higher-level of cognitive function on physical function.

4.3 Methods

4.3.1 Participants

Four hundred and nineteen people aged 70-90 years participated in a prospective cohort study with a 1-year follow-up for physical function. Participants were randomly recruited from 1,037 community-dwelling elders living in eastern Sydney. All of them participated in the wave 1 of cohort Sydney Memory and Ageing Study (MAS) that begun in January 2006 and completed by October, 2007.

Inclusion criteria

1) Community-dwelling men and women elders living in eastern Sydney
2) Native English speaker
3) Able to comprehend instructions and willing to participate

Exclusion criteria

1) Diagnosis of dementia or presence of global cognitive impairment, as determined by DSM-IV or MMSE score lesser than 24 after adjustment for age and years of education (203)
2) Presence of IADL decline, as determined by Bayer Activities of Daily Living Scale (B-ADL) scale equal or greater than 3 (204).
3) Presence of neurological conditions (e.g. Parkinson's disease, Stroke) or uncontrolled medical conditions (e.g. uncontrolled hypertension, Coronary artery disease)

4) Previous diagnosis of medical or/and psychological conditions that precluded participants in completing the testing protocol (e.g. progressive malignancy, mental disorders)

4.3.2 Materials

1) Personal data collection form

2) Manual and record forms of eleven standard neuropsychological tests:

2.1 Logical Memory-Delayed Recall

2.2 Rey Auditory Verbal Learning Test; Total learning-Delayed Recall

2.3 Rey Auditory Verbal Learning Test; Short term-Delayed Recall

2.4 Rey Auditory Verbal Learning Test; Long term-Delayed Recall

2.5 Boston Visual Retention Test-Recognition

2.6 Boston Naming Test

2.7 Semantic Fluency

2.8 Digit Symbol Substitution Test

2.9 Trail Making Test part A

2.10 Trail Making Test part B

2.11 Controlled Oral Word Association Test

3) Physiological Profile Assessment kits and record form (Appendix L)

3.1 Melbourne Edge Test transparency (visual contrast sensitivity test)

3.2 Protractor and tall chair (proprioception/lower-limb matching test)

3.3 Spring gauge and tall chair (quadriceps muscle strength test)

3.4 Hand-held electronic timer (hand reaction time test)

3.5 Swaymeter, foam rubber mat, adjustable-height table, stopwatch and graph paper sheet (postural sway test)

4.3.3 Independent and dependent variables

Independent variables were:

1) Diagnosis of MCI at initial visit
2) Cognitive score in each cognitive domain at initial visit (i.e. memory, language ability, attention and executive functions)

Dependent variable was: Change of PPA score over 1 year

4.3.4 Procedures

4.3.4.1 Participant characteristics examination

The study protocol was submitted for approval by the Human Ethical Review Board of New South Wales University. The eligible participants were informed about the study purposes before signing an informed consent. After that, they completed a comprehensive assessment by trained research assistant on sociodemographic information, health status, medication history and history of falls. Fear of falling across a wide range of activities of daily living was assessed using Fall Efficacy Scale-International (FES-I; total score range, 16-64); higher scores indicate poorer confidence (205). Disability across six domains (i.e. understanding and communicating, mobility, self-care, interpersonal interactions, house hold and work activities, and participation in society) was assessed using the 12-item World Health Organization Disability Assessment Schedule (WHODAS II; total score range, 12-60); higher scores indicate poorer status (206). Quality of life on six dimensions (i.e. independent living,

social relationship, mental health, coping, pain and sensory perception) were obtained using the 20-item Assessment of Quality of Life Instrument (AQoL II; total score range, 0-100); lower scores indicate impaired function (207). The average weekly physical activity that covers the frequency and duration of planned exercise as well as incidental physical activity over the past 3 months was assessed using the Incidental and Planned Exercise Questionnaire (IPEQ); lower scores indicate poorer status (208).

4.3.4.2 Determination of cognitive profiles (Normal versus MCI)

Participants were evaluated on their cognitive function across four cognitive domains including memory, language ability, attention, and executive function using 11 standard neuropsychological tests. The Logical Memory-Delayed Recall (209), Rey Auditory Verbal Learning test (i.e. Total learning, Short term-and Long term Delayed Recall) (210) and the Benton Visual Retention Test-Recognition (211) test were used to examine the participant's memory. The Boston Naming Test (30 items) (212) and the semantic fluency (animals) (210) were used to assess the participant's language. The Digit Symbol Substitution test (209) and Trail Making Test part A (210) were used to assess the participant's attention. The Trail Making Test part B (210) and the Controlled Oral Word Association Test (210) were used to assess the participant's executive function. Raw test score of each cognitive test was transformed to z scores based on means and standard deviation of total MAS sample. Standardized composite score for each cognitive domain was obtained by averaging z scores across cognitive tests. Based on the score obtained from the neuropsychological tests, participants were

identified as normal or impaired cognitive function according to the most recent international criteria (213).

The diagnosis of MCI required: (1) a self-reported memory complaint compared to 5 years ago (214), (2) the absence of dementia (determined by DSM-IV) (215), (3) no ADL deficits or present of minimal impairment in instrumental activities of daily living (determined by B-ADL scale < 3) (204), and (4) present of cognitive impairment at least one domain on composite measures, using an impairment threshold below 1.5 SD (35). The determination of cognitive profiles was performed at baseline. Administration of these standard neuropsychological tests was executed by trained research assistants.

4.3.4.3 Physical function assessment

Physical function was measured at baseline and at 1-year follow up using short-form Physiological Profile Assessment (PPA) (22). PPA can be used to quantify and attribute a degree of fall risk with 75% accuracy in both community and institutional settings (162, 163). Therefore, it would be suitable for monitoring change in physical function over time. The short-form PPA consists of five physiologic performance parameters including 1) visual contrast sensitivity, 2) proprioception, 3) quadriceps muscle strength, 4) simple hand reaction time and 5) postural sway.

1) Visual contrast sensitivity

Visual contrast sensitivity was assessed using Melbourne Edge Test (MET). The chart has 20 circular 25-mm-diameter patches containing edges with reducing contrast with variable orientation as the identifying feature (i.e. horizontal, vertical, 45 degrees left and 45 degrees right) (Figure 3). In this test, participants were seated at a table and were able to wear their own glasses. MET transparency was leaned back at an angle of approximately 45 degrees with the bottom edge resting on a table at usual reading distance (50-60 cm). Participants were instructed to identify the orientation of the edge on the patches (by pointing to one of the four edge options on the respond card), starting at the top row and then proceed to the down row. This test was ceased if participants wrongly identified the orientation of the edge on the patches. The lowest contrast patch (highest number) correctly identified was recorded. Correct identification of the orientation of the edge on the patches provides a measure of contrast sensitivity in decibel units, where 1 dB = 10 $\log_{10}$ contrast.

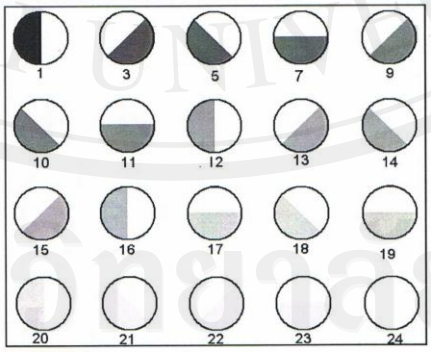

Figure 3 MET transparency

2) Proprioception

Proprioception was measured using a lower-limb matching test. In this test, participants were seated with their eyes closed. After that they were instructed to align their lower limbs simultaneously on either side of a vertical clear acrylic sheet (60 x 60 x 1 cm) inscribed with a protractor placed between the legs (Figure 4). The performance was determined by assessing how closely participants can align their two great toes. The difference (or error) in matching the great toes was measured in degrees. Two practice trials were given prior to testing. Each participant performed 5 experimental trials, with rests between trials. An average value over 5 trials was recorded.

Figure 4 Lower-limb matching test

3) Quadriceps muscle strength

Quadriceps muscle strength was assessed in the dominant leg using spring gauge. In this test, participants were seated on the tall chair with the hip and the knee joint at 90◦ of flexion (Figure 5). The hook connected to the spring gauge was attached over the crossbar position at the back of the tall chair. The strap connected to the spring gauge was placed around participant's leg approximately 10 cm above the lateral malleolus. Participants were encouraged to pull their leg against the strap as strongly as they can. Each participant performed 3 trials, with rests between trials. The greatest force in kilogram was recorded.

Figure 5 Quadriceps muscle strength test

4) Simple hand reaction time

Hand reaction time was assessed using a hand-held electronic timer wherewith a light was used as the stimulus (located on the left mouse button) and a finger-depression of switch was used (located on the right mouse button) as the responses (Figure 6). Participants were seated on standard chair and were instructed to place their finger lightly on the surface of the right mouse button (the mouse was positioned comfortably for the participants on the standard table). After that, they were asked to press the button as quickly as possible as soon as the red light comes on (it presents in a random time). Five practice trials were given prior to testing. Each participant performed 10 experimental trials. An average value over 10 trials in milliseconds was recorded.

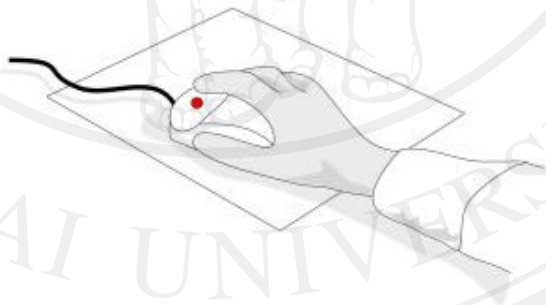

Figure 6 Hand reaction time test

5) Postural sway

Postural sway was assessed using a swaymeter (consisted of a 40-cm-long rod with a vertically mounted pen at the end of the rod) that measures the displacement of the body. The swaymeter was attached to participants by a firm belt at waist level with the rod extending posteriorly. The tip of the pen was positioned over the sheet of millimeter graph paper that located on an adjustable-height table. After that, participants were instructed to stand on a foam rubber mat (40 x 40 x 7.5 cm and 15 cm think) with eyes open as still as possible for 30 seconds. The pen recorded participant's sway both antero-posterior; AP and medio-lateral; ML directions). Total sway path in square millimeter (mm^2) was calculated by multiplying the maximal AP sway excursion by the maximal ML sway excursion.

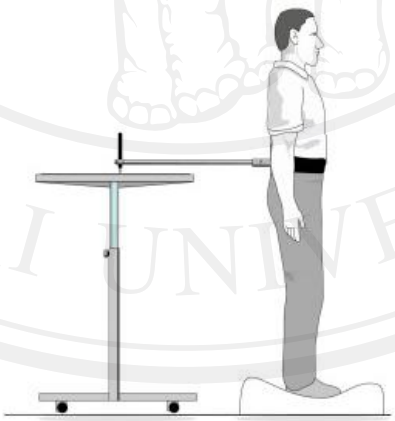

Figure 7 Postural sway test

With respect to participant's performance, the 5 key components on PPA were weighted and computed to composite PPA fall risk score (z score), with scores of less than 0 indicating a low risk of falling, scores between 0 and 1 indicating a mild risk of falling, score between 1 and 2 indicating a moderate risk and score above 2 indicating a high risk of falling (22).

4.3.5 Data Analyses

Changes of physiologic fall risk over 1 year were calculated by subtracting the PPA scores at follow-up from the initial baseline, with a greater increase in PPA scores indicating decrement in physical function. Participants in both groups (i.e. normal and MCI) were divided into a group greater and less PPA decline at 1-year follow-up on a basis of median split. To permit parametric analyses of variables with skewed distributions, data with non-normal distributions were square root or log transformed. The Chi-square tests for contingency tables were used for comparing the proportion of gender and prevalence of faller. Analyses of Covariance were used for detecting differences in the continuous variables.

In order to investigate the associations between MCI and PPA decline over 1 year, relative risk (RR) with 95% confidence intervals (CI) were computed using Modified Poisson Regression Analysis. In a first model, the analyses were controlled for age, education level and baseline PPA scores; in a second model, the analyses were additionally controlled for disability (WHODAS II score); in the last model, the analyses were additionally adjusted for physical activity (IPEQ score). In addition, RR was computed to quantify the associations between composite score in each cognitive domain

and PPA scores while controlling for age, educational level, baseline PPA score, disability and physical activity. SPSS for Window version 19 (SPSS, Chicago, IL) was used for data analysis.

4.3.6 Data collection location

The study was conducted at the Neuroscience Research Australia, New South Wale, Sydney, Australia.

4.4 Results

4.4.1 Participants characteristics

Table 12 shows the characteristics of the total study population and compares participant characteristics based on physical function (PPA; cut-off: median) and MCI (normal versus MCI). With respect to the PPA score at baseline assessment, participants with low physical function were older and more likely to be female, perform worse on cognitive tests (i.e. MMSE ($F_{[1, 414]} = 5.00$, p=0.03), attention ($F_{[1, 414]} = 16.51$, $p < 0.001$) and executive function domains ($F_{[1, 414]} = 8.78$, p=0.003) than those high physical function. In addition, compared to participants with a high physical function, participants with a low physical function had greater composite PPA score both at baseline ($F_{[1, 414]} = 588.10$, $p < 0.001$) and at 1-year follow-up ($F_{[1, 355]} = 67.18$, $p < 0.001$).

When comparing participants with less and greater PPA decline, there was no statistically significant difference in term of age, gender, educational level, disability, medical conditions, fall history and cognitive performance at initial visit. However, when comparing characteristics between groups, using analyses of covariance after controlling for age and gender, significant differences were observed in physiologic fall risk at baseline ($F_{[1, 355]} = 69.60$, $p < 0.0001$) and 1-year follow-up assessments ($F_{[1, 355]} = 82.61$, $p < 0.0001$). Specifically, participants with greater PPA decline function had lower PPA score at baseline and higher PPA score at 1-year follow-up compared to those with less PPA decline.

At baseline assessment, 342 (81.6%) were identified as normal cognitive function whereas 77 (18.4%) participants were classified as MCI. Among participants with MCI, 19 (4.5%) participants were classified as having amnestic MCI and 58 (13.8%) participants were classified as having nonamnestic MCI. Participants with MCI did not show any significant differences on age, gender, educational level, medical conditions and fall history compared with those without MCI. The differences between the two groups were observed in disability ($F_{[1, 403]} = 6.76$, $p = 0.01$) and physiologic fall risk at baseline ($F_{[1, 414]} = 4.28$, $p = 0.04$) and 1-year follow-up ($F_{[1, 355]} = 18.74$, $p < 0.0001$). Participants in the MCI group had higher WHODAS II score and greater composite PPA score both at baseline and follow-up than those in the normal group. With respect to neuropsychological performance, participants with MCI performed worse on MMSE ($F_{[1, 414]} = 21.70$, $p < 0.001$) and all specific cognitive domains including memory ($F_{[1, 414]} = 62.03$, $p < 0.001$), language ($F_{[1, 414]} = 108.03$, $p < 0.001$), attention ($F_{[1, 414]} = 71.42$, $p < 0.001$) and executive functioning ($F_{[1, 414]} = 126.91$, $p < 0.001$) than those without MCI.

Table 12 Characteristics of the study population, compared between people with greater and less PPA decline over 1 year (PPA; cut-off: median) and MCI and normal at baseline

Variables♦	Group			PPA decline over 1 year		
	Normal (n=342)	MCI (n=77)	*p*-value	≤median (n=186)	>median (n=175)	*p*-value
Age (yrs)	77.92 ± 4.62	77.49 ± 4.49	0.63	77.70 ± 4.54	77.54 (4.46)	0.74
Gender (female), n (%)	188 (55.0%)	39 (50.0%)	0.43	105 (56.5%)	91 (52.0%)	0.40
Educational level (yrs)	11.34 ± 3.39	11.25 ± 3.33	0.69	11.23 ± 3.36	11.60 (3.52)	0.61
At least 1 fall in the past 1 yr, n (%)	100 (29.2%)	28 (36.0%)	0.50	52 (28.0%)	55 (31.4%)	0.75
Medication use (total number)	5.29 ± 3.43	5.34 ± 3.74	0.84	5.18 ± 3.59	5.30 (3.45)	0.72
Medical conditions (total number)	3.09 ± 1.51	2.95 ± 1.52	0.57	3.17 ± 1.58	2.91 (1.36)	0.11
MMSE (score)	28.23 ± 1.35	27.47 ± 1.65	0.001[b]	28.12 ± 1.48	28.15 (1.44)	0.88
FES-I (score)	22.29 ± 5.87	23.61 ± 7.96	0.07	22.13 ± 5.91	22.35 (6.48)	0.69
GDS (score)	2.12 ± 1.80	2.31 ± 2.19	0.37	2.22 ± 1.95	1.99 (1.76)	0.26
WHODAS II (score)	17.65 ± 5.60	19.37 ± 7.05	0.01[a]	17.61 ± 5.69	17.36 (5.37)	0.74

AQoL II (score)	89.95 ± 7.59	89.05 ± 9.15	0.37	89.81 ± 7.60	90.86 ± 6.82	0.21
IPEQ (h/week)	1.56 ± 2.26	1.38 ± 2.67	0.49	1.46 ± 2.24	1.59 ± 2.39	0.60
PPA (z score) [#]						
-Baseline assessment	0.86 ± 0.91	1.05 ± 0.99	0.04[a]	1.22 ± 0.88	0.51 ± 0.83	0.001[b]
-1-year follow-up assessment	0.60 ± 0.92	1.15 ± 1.02	0.001[b]	0.32 ± 0.85	1.09 ± 0.91	0.001[b]
Cognitive assessment (z score)						
-Memory domain	0.19 ± 0.91	-0.67 ± 1.06	0.001[b]	0.02 ± 0.95	0.12 ± 1.01	0.52
-Language domain	0.28 ± 0.81	-0.75 ± 1.05	0.001[b]	0.12 ± 0.84	0.16 ± 0.97	0.86
-Attention domain	0.20 ± 0.89	-0.71 ± 1.12	0.001[b]	0.06 ± 1.08	0.07 ± 0.88	0.79
-Executive functioning domain	0.24 ± 0.88	-0.93 ± 1.00	0.001[b]	0.03 ± 0.96	0.08 ±1.04	0.80

♦Data are shown as mean ± SD. MMSE, total score = 30 points; FES-I, total score = 64 points; GDS, total score = 30 points; WHODAS II, total score = 60 points; AQoL II, total score = 100 points

Univariate analyses of covariance were used to compare the differences of continuous variables between groups (i.e. greater versus less PPA decline and MCI versus Normal).

[#]PPA scores at baseline and 1-year follow-up was calculated from 361 participants.

[a] p-value ≤ 0.05

[b] p-value < 0.001

4.4.2 Use of MCI diagnosis to predict physical decline

Of the 419 participants assessed at baseline, 58 (14.0%) were lost to follow-up and not reassessed at 1 year. Compared to those with follow-up data, participants without PPA follow-up were older, more concerned about falling, had poorer general health and lower quality of life. Participants without follow-up data were also more likely to have MCI (29.3% versus 16.6%) and scored worse on the language and executive function domain scores when compared to participants with follow-up data. Among three hundreds and sixty-one participants with follow-up data, the mean change in PPA score was +0.58 (SD 0.61) for the greater PPA decline group (n= 175) and -0.91(SD 0.56) for the remainder (n=186).

The relative risk of having greater PPA decline was significantly higher for MCI when adjusting for age, education level and baseline PPA scores in a Modified Poisson Regression (RR = 1.60, 95% CI = 1.16 - 2.22, p = 0.004) (Table 13). This association remained after adjusting for disability and physical activity (RR = 1.57, 95% CI = 1.12 - 2.20, p = 0.011). Further models that included the cognitive domain variables (cut-off: median) entered separately revealed that reduced executive functioning was the only significant cognitive domain associated with physical decline after controlling for potential confounders (RR = 1.42, 95% CI = 1.15 - 1.76, p = 0.001) (Table 13).

Table 13 Modified poisson regression outputs of factors associated with physical decline during 1-year follow-up period

Clinical status	RR (95% CI)[a]	RR (95% CI)[b]	RR (95% CI)[c]
MCI (yes)	1.60 (1.16-2.22)[d]	1.54 (1.11-2.14)[d]	1.57 (1.12-2.20)[d]
Memory domain composite (z score)	0.91 (0.75-1.11)	0.90 (0.73-1.10)	0.90 (0.73-1.10)
Language domain composite (z score)	1.11 (0.91-1.36)	1.07 (0.87-1.32)	1.07 (0.87-1.32)
Attention domain composite (z score)	1.19 (0.97-1.45)	1.17 (0.95-1.45)	1.19 (0.96-1.47)
Executive functioning domain composite (z score)	1.44 (1.17-1.77)[e]	1.41 (1.15-1.75)[e]	1.42 (1.15-1.76)[e]

[a] Model adjusted for age, educational level and baseline PPA score

[b] Additional adjustment for disability (WHODAS II score)

[c] Additional adjustment for physical activity (IPEQ score)

[d] p-value ≤ 0.01

[e] p-value ≤ 0.001

4.5 Discussion

The present study was designed to determine whether the presence of MCI is associated with a progressive decline of physical function over time. In this large community-dwelling older cohort, we found that older people with MCI were more likely to show a decline in physical function over 1 year, independent of age, baseline physical function, disability and physical activity. When looking at individual domains, impaired executive functioning was the only significant cognitive domain associated with physical decline.

The current study used the PPA as composite measure of physiological fall risk factors to provide an estimate of physical functioning decline over 1 year (22). Our results demonstrated that individuals with MCI were at nearly twice the risk of developing physical decline than people with normal cognitive functioning, independent of potential confounders. Previous study has supported that individuals with MCI had a significantly higher composite PPA score and had a greater rate of falls during a 1-year follow-up than those without MCI (161). This suggested that physiological functioning could be affected earlier in the course of dementia disease before cognitive impairment is markedly observed (15, 171, 173, 216). Our study was able to build further on that knowledge and was able to show that people with MCI do not only have poorer physiological functioning at baseline, but also suffer a faster physical decline over time.

Impaired physical function in individuals with MCI has clinical significance beyond fall risk. Longitudinal studies have now accepted that physical decline (e.g. slowing of gait, poor balance and lower limb function) can be considered

as potential marker for developing dementia (113, 171, 216). Furthermore, it has been suggested that individuals with MCI in combination with physical decline may develop dementia faster than those impaired in only one area (113). It can thus be suggested that changes in physical function may be a reflection of cognitive changes among people with MCI. Therefore, the evidence of physical decline in participants with MCI in this study may indicate the higher risk for developing dementia and fall risk. This combination of findings provides some support for the conceptual promise that adding the physical assessment onto the traditional cognitive assessment may help to identify and monitor people who are at greater risk of developing dementia over time.

Another important finding was that the association between impaired executive function and physical decline was stronger than with other cognitive domains. This is consistent with other studies and suggests that impaired executive function may contribute to physical decline and fall risk (161, 177). One explanation is that impaired executive function may reduce the attentional capacity, central processing and integration ability as well as diminish self-regulation that limit the individual's physical ability to respond to complex everyday environments such as when walking while performing cognitive tasks (dual-tasking) or walking in busy environments (217-219). Therefore, impaired executive function and physical function may restrict the ability to compensate for age-associated change in balance and gait that increase a person's risk of falling. It is possible that people with MCI have a greater impairment of executive and physical functions than those without MCI because of development of structural brain abnormalities. Recent neuroimaging

studies reveal that structural and functional brain lesion including development of WMHs in the frontal lobe, especially prefrontal cortex and periventricular regions that control executive function had the strongest relationships with balance, gait, and mobility impairment (189-192).

One of the issue that emerges from these findings is the progressive physical decline in older adults with MCI may be used as a clinical marker in predicting subsequent onset of falls. It has been suggested that falls and fall-related injuries can lead to a negative spiral of physical inactivity and frailty in older people, which can accelerate a person's transition from MCI to dementia. Therefore, fall risk screening among this population should cover both physical and cognitive tests, especially executive functioning domain.

4.5.1 Clinical implications and limitations

The evidence of physical decline and impaired executive function in individuals with MCI in the present study may potentially reflect the risk of fall among individuals with MCI. Therefore, fall risk screenings that include both physical and cognitive components should be key components in the clinical management of individuals with MCI. Recent studies report that exercise programs have specific benefits on functional plasticity in brain regions that are related to executive functioning (220, 221). Cognitive and motor-cognitive interventions also have a positive effect on physical functioning such as postural control, walking ability and general functions of upper and lower extremities (222, 223). Therefore, an effective program that targets on training both physical and cognitive aspects should be implemented at an early stage.

To the best of our knowledge, this is the first prospective study that has investigated the association between physical decline and clearly defined MCI. However, limitations more related to the measures, not tested for stability-over-time. Therefore, long term follow-up for physical function and actual incidence of falls is still needed to confirm whether individuals with MCI who had an accelerated physical decline are indeed greater risk of falls than those without MCI.

4.5.2 Conclusion

Individuals with MCI did not only have poorer physical function but suffer a faster decline over 1 year. Among cognitive domains, executive function was found to be significantly associated with physical decline. This finding indicates that fall risk screening may be prudent in individuals with MCI.