

Original Research Article

# Mild Cognitive Impairment Reversion and Progression: Rates and Predictors in Community-Living Older Persons in the Singapore Longitudinal Ageing Studies Cohort

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## Keywords

Mild cognitive impairment · Dementia · Rates · Predictors

## Abstract

**Background:** Studies report varying rates and predictors of mild cognitive impairment (MCI) progression and reversion. **Methods:** We determined MCI reversion and progression among 473 community-living adults aged  $\geq 55$  years in the Singapore Longitudinal Ageing Study with an average of 6 years of follow-up and estimated association with baseline variables. **Results:** A total of 208 MCI participants reverted to normal cognition (44.0%) and 19 progressed to dementia (4.0%). In a model adjusted for age, gender, education, ethnicity, cardiovascular risk factors/diseases, APOE  $\epsilon 4$  status, depressive symptoms, leisure-time activities (LTA), and baseline Mini-Mental State Examination (MMSE), we found that LTA score (OR = 1.07, 95% CI 1.02–1.13), MMSE score (OR = 1.21, 95% CI 1.11–1.31), and subjective memory complaint (OR = 1.83, 95% CI 1.16–2.90) significantly predicted MCI reversion. Controlling for all variables, age (OR = 1.09, 95% CI 1.02–1.17), lower education (OR = 3.26, 95% CI 1.01–10.49), and the metabolic syndrome (OR = 3.13, 95% CI 1.12–8.77) significantly predicted MCI progression. Controlling for age, sex, ethnicity, and education, diabetes significantly predicted MCI progression (OR = 3.19, 95% CI 1.23–8.26), but the presence of other cardiometabolic factors reduced this

association to an OR of 2.18 (95% CI 0.72–6.60). **Conclusion:** In this relatively younger population, there were higher rates of MCI reversion and lower rates of MCI progression which were predicted by the positive effects of LTA and a higher MMSE score as well as by the deleterious effect of the metabolic syndrome and diabetes.

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## Introduction

Mild cognitive impairment (MCI) is thought to be a transition stage between normal cognitive aging and dementia [1, 2]. Although subjects with MCI may progress to dementia, a significant number may remain stable over time and some even return to a cognitively normal state after follow-up [3, 4]. Better estimates of the rates and an understanding of predictors of MCI progression to dementia or return to normal cognition are essential to slow or prevent further cognitive deterioration among individuals with MCI or to promote MCI reversion to normal cognition. Improving our ability to predict MCI outcome is of great importance for clinicians in terms of counseling patients and their families, making therapeutic decisions, and selecting candidates for clinical trial intervention.

To date, the rates of MCI reversion to normal cognition or progression to dementia reported across studies have varied widely. Findings from several population-based cohort studies suggested that MCI reversion to normal cognition occurs frequently with reversion rates ranging from 29 to 55%. On the other hand, lower rates of MCI reversion were observed in clinical settings ranging from 4 to 15% [5]. The annual MCI progression rates ranged from 4 to as high as 17%, with lower rates reported in community-based studies [6]. Demographic and clinical factors, including age, gender, educational level, apolipoprotein E (APOE)  $\epsilon$ 4 allele, hypertension, depressive symptoms, cognitive function, white matter lesions, and hippocampal atrophy, which may contribute to either MCI progression or reversion, have been explored in different studies [7–9]. Differing sets of predictors have been identified from individual studies for either MCI reversion or progression.

Rates of MCI reversion and progression could vary by the age of the study population, among other things [5]. Most studies have reported rates of MCI progression or reversion among community-dwelling older persons older than 65 or 75 years. Few studies have reported MCI conversion rates in younger ageing cohorts, in whom different sets of risk and protective factors may contribute to MCI reversion or progression. In the present study, we aimed to estimate the rates of MCI reversion to cognitively normal and progression to dementia over an average of 6 years of follow-up in a younger ageing cohort of community-living older adults aged 55 years and above in Singapore and to investigate the contributing factors associated with MCI conversion.

## Materials and Methods

### *Study Population*

The Singapore Longitudinal Ageing Study (SLAS) is a population-based epidemiological prospective cohort study of community-dwelling older adults in Singapore. The first-wave cohort (SLAS-1) recruited 2,804 participants between 2003 and 2005 and completed 2 follow-ups at approximately 3-year intervals: from March 2005 to September 2007 and from November 2007 to December 2009. Details of the SLAS-1 methodology have previously been described elsewhere [10]. Briefly, Singaporean citizens aged 55 years and above living in the South-East region of Singapore were invited to participate through a door-to-door visit by

research nurses. Those who were physically or mentally unable to give informed consent or participate, including those with a history of stroke aphasia, profound dementia, terminal illness, and severe psychiatric disorders (depression, anxiety, etc.), were excluded from the study enrollment. Participants underwent an extensive range of face-to-face interviews, assessments, and tests which were performed by trained research nurses and research assistants in the preferred language or dialect (English/Mandarin/dialects). The study was approved by the National University of Singapore Institutional Review Board, and all participants signed informed consents.

Among the SLAS-1 participants, we identified 473 participants who had MCI from baseline assessments and determined their reversion to cognitively normal and progression to dementia over an average of 6 years of follow-up.

### *Measurements*

#### *Cognitive Screening and Assessment*

Global cognitive function was measured by the locally modified and validated English, Chinese, and Malay translated versions of the Mini-Mental State Examination (MMSE; total scores ranged from 0 to 30) with appropriate education- and ethnic-stratified cutoffs [11, 12]. Subjective cognitive complaint was ascertained from self-report (“Do you feel you have more problems with memory than most?”) and informant reports (Informant Questionnaire on Cognitive Decline in the Elderly [IQCODE]) of memory and cognitive problems [13, 14]. Depressive symptoms were determined by a summed score of 5 or above on the locally validated version of the 15-item Geriatric Depression Scale (GDS) [15].

The test battery of neurocognitive assessments included (1) attention (digit span forward and backward) [16] and spatial span forward and backward [16]; (2) memory (Rey Auditory Verbal Learning Test immediate and delayed recall [17] and visual reproduction immediate and delayed recall [16]); (3) executive function (Symbol Digit Modality Test [18], Design Fluency [19], and Trail Making Test Part B [20]); (4) language (categorical verbal fluency) [19]; and (5) visuospatial abilities (block design) [16]. Details of the neurocognitive tests and their normative values have been published elsewhere [21, 22].

#### *Diagnosis of MCI, Dementia, and Cognitively Normal*

Cases of MCI and dementia were determined from 2-staged screening and assessment and diagnosis by a 3-member expert panel of geriatricians and psychiatrists who reviewed the clinical assessment findings and finalized the consensus diagnosis based on DSM-V criteria.

The diagnosis of MCI was operationally defined according to published criteria [1, 2]: (1) subjective memory and cognitive difficulties or IQCODE score >3.3; (2) objective cognitive impairment in 1 or more domains: MMSE global score ranging from 24 to 27, or a decline of MMSE  $\geq 2$  points from baseline; and at least 1 neurocognitive domain (attention, memory, executive function, language, or visuospatial abilities) score of 1–2 standard deviations (SD) less than the age- and education-adjusted mean values, or drop from baseline of 0.5 SD during follow-up assessments; (3) Clinical Dementia Rating scale (CDR) global score  $\geq 0.5$  [23]; (4) essentially independent in performing Basic Activities of Daily Living (BADL); and (5) not demented.

Diagnosis of dementia required (1) evidence of an objective cognitive deficit (MMSE total score  $\leq 23$ , or neurocognitive domain score 2 SD less than the mean values adjusted by age and education), and (2) presence of functional disability (needing help with at least 1 BADL or CDR global score  $\geq 1$ ).

Participants who did not meet the criteria for MCI or dementia were classified as cognitively normal.

### Patient Characteristics

Demographic variables included ethnicity, age, gender, and educational level (primary and below, secondary and above). Engagement in leisure-time activities was measured by asking the participants about the number and frequency of their usual participation in 18 different categories of physically, socially, or mentally engaging activities which are common among older adults in the local population [24]. The total score, with higher values representing increasing level of participation, was calculated from the number and frequency of participation for all categories of activities.

Functional ability was evaluated by the subject's dependency in performing BADL which had been validated for local use [25, 26]. Functional disability was defined as requiring help with 1 or more BADL tasks.

Weight and height were measured by a portable Seca stadiometer (Model 708, Vogel & Hake, Hamburg, Germany), with body mass index (BMI) computed as kg/m<sup>2</sup>. Respondents with a BMI  $\geq 27.5$  were considered as obese. Fasting venous blood samples were taken in the morning (9:00 to 9:30 a.m.) following standard operational procedures. Blood samples kept in ice were sent to Singapore National University Hospital Referral Laboratory within 2 h. Plasma or serum was isolated and stored at a temperature of  $-80^{\circ}\text{C}$  prior to laboratory analysis.

The APOE genotyping was carried out by polymerase chain reaction (PCR) amplification followed by restriction endonuclease digestion of the PCR product (PCR-RFLP). Participants with either 1 or both  $\epsilon 4$  alleles were classified as APOE  $\epsilon 4$  allele carriers.

The presence of cardiovascular risk factors/diseases was defined as any of the following: hypertension, dyslipidemia, diabetes, cardiac disease, coronary heart disease, and self-reported history of stroke. Hypertension was defined as a self-reported history of high blood pressure (BP), or a systolic BP of  $>140$  mm Hg or a diastolic BP of  $>90$  mm Hg, or a history of medication with antihypertensive drugs. Dyslipidemia was defined as a self-reported history of high cholesterol, or total serum cholesterol  $\geq 4.1$  mmol/L or triglycerides  $\geq 2.3$  mmol/L or high-density lipoprotein  $<1.0$  mmol/L, or the ratio of total cholesterol:high-density lipoprotein  $>4.5$ , or a history of medication for high cholesterol. Diabetes was defined as a self-reported history of diabetes, or a fasting blood glucose level of  $\geq 7.0$  mmol/L, or a history of medical treatment for diabetes. Cardiac diseases included ischemic heart disease, heart failure, or atrial fibrillation. Orthostatic hypotension was defined as a systolic BP drop of at least 20 mm Hg (irrespective of the diastolic change), or a diastolic BP fall of at least 10 mm Hg (irrespective of the systolic change), or both (consensus orthostatic hypotension) 3 min after standing up from a lying position [27–29].

Metabolic syndrome was defined using the International Diabetes Federation (IDF) criteria [10]: central obesity (waist circumference  $\geq 90$  cm for male and  $\geq 80$  cm for female) plus at least 2 cardiovascular risk factors: raised triglyceride level ( $\geq 150$  mg/dL [1.7 mmol/L] or specific treatment for this lipid abnormality); reduced high-density lipoprotein cholesterol ( $<40$  mg/dL [1.03 mmol/L] in males and  $<50$  mg/dL [1.29 mmol/L] in females or specific treatment for this lipid abnormality); raised BP (systolic BP  $\geq 130$  mm Hg or diastolic BP  $\geq 85$  mm Hg, or treatment of previously diagnosed hypertension), and raised fasting plasma glucose ( $\geq 100$  mg/dL or 5.6 mmol/L), or previously diagnosed type 2 diabetes.

### Statistical Analysis

Differences in baseline characteristics between those who progressed from MCI and those who did not, and between those who reverted from MCI and those who did not, were compared using the  $\chi^2$  test for categorical variables and the independent *t* test for continuous variables. Binary logistic regression was used to estimate the strength of associations of candidate risk or protective factors with MCI reversion or progression. In the multivariable

**Table 1.** Baseline characteristics of baseline MCI subjects ( $n = 473$ )

Age, years	68.2±7.7
Gender, female	312 (66.0)
Education, primary and below	366 (77.4)
Ethnicity, Chinese	427 (90.3)
Leisure-time activities total score	8.4±4.1
IADL disability	137 (29.0)
BADL disability	32 (6.8)
Subjective memory complaint	186 (39.3)
MMSE total score	24.6±3.0
BMI	24.0±4.1
Hypertension	257 (54.3)
Orthostatic hypotension	91 (19.2)
Dyslipidemia	269 (56.9)
Diabetes	108 (22.8)
Coronary heart disease	28 (5.9)
Cardiac disease	40 (8.5)
Stroke	25 (5.3)
Depressive symptoms	91 (19.2)
APOE ε4 carrier	93 (19.7)

Values are means ± standard deviations or  $n$  (%). MCI, mild cognitive impairment; IADL, Instrumental Activities of Daily Living; BADL, Basic Activities of Daily Living; MMSE, Mini-Mental State Examination; BMI, body mass index; APOE, apolipoprotein E.

adjusted models, the independent associations controlling for mutual confounding were estimated for age, gender, educational level, leisure-time activities summed score, APOE ε4 carrier status, depressive symptoms, baseline MMSE total score, and cardiovascular risk factors/diseases. Odds ratios (ORs) of associations were estimated with their 95% confidence intervals (CIs).

The data analysis was conducted using SPSS 24.0 (SPSS Inc., Chicago, IL, USA). All statistical tests were two-sided, and a  $p$  value of  $<0.05$  was regarded as statistically significant.

## Results

The present study focused on the 473 participants with MCI at baseline and determined their reversion to cognitively normal and progression to dementia during 6 years of follow-up (Table 1). The average age of the 473 baseline MCI participants was  $68.2 \pm 7.7$  years, ranging from 55 to 93. More than half were female ( $n = 312$ , 66.0%) and more than three-quarters (77.4%) had low education (6 years of primary schooling and below). Among them, 208 reverted to normal cognition (44.0%), 246 remained as MCI (52.0%), and 19 progressed to dementia (4.0%) at follow-up.

The baseline characteristics of those who progressed from MCI ( $n = 19$ ) and those who did not ( $n = 454$ ) are summarized in Table 2. Compared to those who did not progress from MCI, those who progressed from MCI were more likely to be older ( $p = 0.011$ ), non-Chinese ( $p = 0.029$ ), and diabetic ( $p = 0.021$ ) and to have the metabolic syndrome ( $p = 0.002$ ) at baseline. In binary logistic regression analysis (Table 3), 5 baseline candidate factors, including Chinese ethnicity (OR = 0.28, 95% CI 0.095–0.81), age (OR = 1.08, 95% CI 1.02–1.14), baseline

**Table 2.** Baseline characteristics between those who progressed from MCI and those who did not

	MCI progression group ( <i>n</i> = 19)	MCI nonprogression group ( <i>n</i> = 454)	<i>p</i> value
Age, years	72.6±8.1	68.1±7.6	0.011
Gender, female	15 (78.9)	297 (56.4)	0.351
Education, primary and below	13 (68.4)	353 (77.8)	0.399
Ethnicity, Chinese	14 (73.7)	413 (91.0)	0.029
Leisure-time activities total score	7.5±4.5	8.5±4.1	0.334
BADL disability	2 (10.5)	30 (6.6)	0.375
Subjective memory complaint	7 (38.9)	179 (39.6)	1.000
MMSE total score	22.8±4.0	24.7±2.9	0.058
BMI	25.0±4.3	24.0±4.1	0.273
Hypertension	11 (57.9)	246 (54.2)	0.817
Orthostatic hypotension	6 (31.6)	85 (18.9)	0.230
Dyslipidemia	13 (68.4)	256 (56.4)	0.351
Diabetes	9 (47.4)	99 (21.8)	0.021
Cardiovascular disease or stroke	3 (15.8)	57 (12.6)	0.721
Metabolic syndrome	11 (57.9)	109 (24.0)	0.002
Depressive symptoms	4 (22.2)	87 (19.2)	0.761
APOE ε4 carrier	2 (11.1)	91 (20.4)	0.547

Values are means ± standard deviations or *n* (%). MCI, mild cognitive impairment; BADL, Basic Activities of Daily Living; MMSE, Mini-Mental State Examination; BMI, body mass index; APOE, apolipoprotein E.

MMSE total score (OR = 0.86, 95% CI 0.76–0.96), diabetes (OR = 3.23, 95% CI 1.28–8.16), and the metabolic syndrome (OR = 4.35, 95% CI 1.71–11.1), were significantly associated with MCI conversion to dementia in the unadjusted model (model 1). After adjustment for age, gender, ethnicity, and education (model 2) and multiple other variables (model 3), age (OR = 1.09, 95% CI 1.02–1.17) and lower educational level (OR = 3.26, 95% CI 1.01–10.49) remained significantly associated with MCI progression to dementia. Controlling for age, sex, ethnicity, and education, diabetes (OR = 3.19, 95% CI 1.23–8.26) and the metabolic syndrome (OR = 3.72, 95% CI 1.42–9.69) were significantly associated with MCI progression. Further adjustments for leisure-time activities score, APOE ε4 carrier status, depressive symptoms, baseline MMSE score, and other cardiometabolic risk factors (BMI, hypertension, dyslipidemia, and diabetes), reduced the OR estimate for diabetes (OR = 2.18, 95% CI 0.72–6.60), but the metabolic syndrome (OR = 3.13, 95% CI 1.12–8.77) remained significantly associated with MCI progression to dementia.

On the other hand, compared to those who did not revert from MCI (*n* = 265), those who did revert from MCI (*n* = 208) were found to be significantly younger (mean age 66.9 years, *p* = 0.001), to be more educated (*p* = 0.011), to have more frequently participated in leisure-time activities (*p* = 0.000), and to have a higher baseline MMSE total score (*p* = 0.000) (Table 4). In binary logistic regression analysis with adjustment for covariates, including age, gender, education, ethnicity, cardiovascular risk factors/diseases, APOE ε4 allele carrier status, depressive symptoms, leisure-time activities total score, and baseline MMSE total score, statistically significant estimates of association were found for subjective memory complaint (OR = 1.83, 95% CI 1.16–2.90), leisure-time activity total score (OR = 1.07, 95% CI 1.02–1.13), and MMSE total score (OR = 1.21, 95% CI 1.11–1.31) (Table 5).

**Table 3.** Logistic regression analysis of association between baseline factors and MCI progression to dementia

	Model 1		Model 2		Model 3	
	OR (95% CI)	p value	OR (95% CI)	p value	OR (95% CI)	p value
Age	1.08 (1.02–1.14)	0.013	1.09 (1.02–1.17)	0.005	1.09 (1.02–1.17) <sup>c</sup>	0.012
Gender, female	1.98 (0.65–6.07)	0.23	2.30 (0.72–7.38)	0.16	2.84 (0.74–10.91) <sup>c</sup>	0.13
Education, primary and below	1.61 (0.60–4.35)	0.35	2.63 (0.89–7.73)	0.079	3.26 (1.01–10.49) <sup>c</sup>	0.048
Ethnicity, Chinese	0.28 (0.10–0.81)	0.019	0.27 (0.09–0.83)	0.022	0.34 (0.09–1.23) <sup>c</sup>	0.099
Leisure-time activities total score	0.94 (0.84–1.06)	0.33	0.96 (0.84–1.09)	0.49	0.97 (0.84–1.11) <sup>c</sup>	0.60
IADL disability	1.82 (0.71–4.62)	0.21	1.26 (0.47–3.43)	0.65	1.02 (0.32–3.25) <sup>c</sup>	0.98
BADL disability	1.66 (0.37–7.50)	0.51	1.26 (0.27–5.90)	0.77	1.06 (0.19–5.85) <sup>c</sup>	0.95
Subjective memory complaint	0.97 (0.37–2.55)	0.95	0.83 (0.31–2.24)	0.71	0.63 (0.19–2.10) <sup>c</sup>	0.45
MMSE	0.86 (0.76–0.96)	0.01	0.91 (0.79–1.04)	0.17	0.94 (0.79–1.12) <sup>c</sup>	0.50
BMI	1.05 (0.96–1.17)	0.27	1.02 (0.92–1.14)	0.67	1.00 (0.89–1.12) <sup>b</sup>	0.95
Hypertension	1.16 (0.46–2.94)	0.75	1.11 (0.43–2.88)	0.83	1.05 (0.30–3.74) <sup>b</sup>	0.94
Orthostatic hypotension	1.98 (0.73–5.35)	0.18	2.17 (0.77–6.13)	0.14	1.95 (0.62–6.12) <sup>b</sup>	0.25
Dyslipidemia	1.68 (0.63–4.49)	0.30	1.73 (0.63–4.78)	0.29	5.56 (0.67–46.23) <sup>b</sup>	0.11
Diabetes	3.23 (1.28–8.16)	0.013	3.19 (1.23–8.26)	0.017	2.18 (0.72–6.60) <sup>b</sup>	0.17
Metabolic syndrome	4.35 (1.71–11.1)	0.002	3.72 (1.42–9.69)	0.007	3.13 (1.12–8.77) <sup>b</sup>	0.030
Cardiovascular disease and stroke	1.94 (0.43–8.83)	0.39	1.43 (0.30–6.86)	0.66	1.56 (0.29–8.41) <sup>a</sup>	0.61
Depressive symptoms	1.20 (0.39–3.74)	0.75	1.32 (0.42–4.22)	0.64	0.86 (0.22–3.37) <sup>c</sup>	0.83
APOE ε4 carrier	0.49 (0.11–2.15)	0.34	0.45 (0.10–2.09)	0.31	0.25 (0.032–2.00) <sup>c</sup>	0.19

MCI, mild cognitive impairment; OR, odds ratio; CI, confidence interval; IADL, Instrumental Activities of Daily Living; BADL, Basic Activities of Daily Living; MMSE, Mini-Mental State Examination; BMI, body mass index; APOE, apolipoprotein E. Model 1: unadjusted. Model 2: adjusted for age, gender, ethnicity, and education. Model 3: adjusted for <sup>a</sup> age, gender, ethnicity, education, leisure-time activities total score, APOE ε4 carrier status, depressive symptoms, and baseline MMSE total score; <sup>b</sup> cardiovascular risk factors (BMI, hypertension, dyslipidemia, and diabetes); and <sup>c</sup> cardiovascular diseases (coronary heart disease and cardiac diseases) and stroke.

**Table 4.** Baseline characteristics between those who reverted from MCI and those who did not

	MCI reversion group (n = 208)	MCI nonreversion group (n = 265)	p value
Age, years	66.9±7.3	69.3±7.8	0.001
Gender, female	132 (63.5)	180 (67.9)	0.329
Education, primary and below	149 (71.6)	217 (81.9)	0.011
Ethnicity, Chinese	192 (92.3)	235 (88.7)	0.213
Leisure-time activities total score	9.2±3.9	7.8±4.2	0.000
IADL disability	51 (24.5)	86 (32.5)	0.053
BADL disability	14 (6.7)	18 (6.8)	1.000
Subjective memory complaint	92 (44.4)	94 (35.7)	0.058
BMI	24.0±4.1	24.0±4.0	0.953
MMSE total score	25.5±2.3	23.9±3.3	0.000
Hypertension	103 (49.5)	154 (58.1)	0.064
Orthostatic hypotension	35 (17.0)	56 (21.4)	0.242
Dyslipidemia	119 (57.2)	150 (56.6)	0.926
Diabetes	47 (22.6)	61 (23.0)	1.000
Cardiovascular disease and stroke	22 (10.6)	38 (14.3)	0.222
Metabolic syndrome	48 (23.1)	72 (27.2)	0.310
Depressive symptoms	39 (18.8)	52 (19.7)	0.906
APOE ε4 carrier	37 (18.0)	56 (21.7)	0.352

Values are means ± standard deviations or n (%). MCI, mild cognitive impairment; IADL, Instrumental Activities of Daily Living; BADL, Basic Activities of Daily Living; BMI, body mass index; MMSE, Mini-Mental State Examination; APOE, apolipoprotein E.

**Table 5.** Logistic regression analysis of association between baseline factors and MCI reversion to normal cognition

	Model 1		Model 2		Model 3	
	OR (95% CI)	p value	OR (95% CI)	p value	OR (95% CI)	p value
Age	0.96 (0.94–0.98)	0.001	0.96 (0.93–0.98)	0.000	0.98 (0.95–1.00) <sup>c</sup>	0.063
Gender, female	0.82 (0.56–1.20)	0.31	0.77 (0.52–1.14)	0.19	0.84 (0.54–1.31) <sup>c</sup>	0.43
Education, primary and below	1.79 (1.16–2.76)	0.009	1.55 (0.99–2.44)	0.058	1.18 (0.73–1.91) <sup>c</sup>	0.50
Ethnicity, Chinese	0.65 (0.35–1.23)	0.19	0.63 (0.33–1.21)	0.17	0.90 (0.49–1.80) <sup>c</sup>	0.77
Leisure-time activities total score	1.09 (1.04–1.14)	0.000	1.09 (1.04–1.14)	0.001	1.07 (1.02–1.13) <sup>c</sup>	0.007
IADL disability	1.67 (0.44–1.00)	0.050	0.81 (0.52–1.25)	0.34	0.91 (0.57–1.46) <sup>c</sup>	0.70
BADL disability	0.98 (0.48–2.03)	0.961	1.17 (0.56–2.45)	0.69	1.42 (0.64–3.17) <sup>c</sup>	0.39
Subjective memory complaint	1.44 (0.99–2.09)	0.056	1.50 (1.03–2.20)	0.036	1.83 (1.16–2.90) <sup>c</sup>	0.010
MMSE total score	1.25 (1.15–1.35)	0.000	1.22 (1.13–1.33)	0.000	1.21 (1.11–1.31) <sup>c</sup>	0.000
BMI	1.00 (0.96–1.05)	0.953	1.01 (0.96–1.06)	0.71	1.02 (0.97–1.08) <sup>b</sup>	0.41
Hypertension	0.71 (0.49–1.02)	0.063	0.73 (0.50–1.06)	0.097	0.83 (0.51–1.33) <sup>b</sup>	0.43
Orthostatic hypotension	0.75 (0.47–1.20)	0.235	0.76 (0.47–1.22)	0.25	0.67 (0.40–1.12) <sup>b</sup>	0.12
Dyslipidemia	1.03 (0.71–1.48)	0.895	0.99 (0.68–1.44)	0.96	1.01 (0.61–1.67) <sup>b</sup>	0.96
Diabetes	0.98 (0.63–1.51)	0.91	1.01 (0.65–1.57)	0.97	1.05 (0.64–1.70) <sup>b</sup>	0.85
Metabolic syndrome	0.80 (0.53–1.23)	0.31	0.86 (0.56–1.31)	0.47	0.85 (0.54–1.34) <sup>b</sup>	0.48
Cardiovascular disease and stroke	0.95 (0.44–2.06)	0.90	1.21 (0.55–2.70)	0.64	1.25 (0.54–2.89) <sup>a</sup>	0.61
Depressive symptoms	0.95 (0.60–1.50)	0.815	0.91 (0.57–1.45)	0.68	1.06 (0.63–1.75) <sup>c</sup>	0.84
APOE ε4 carrier	0.79 (0.50–1.26)	0.33	0.77 (0.48–1.23)	0.27	0.79 (0.48–1.29) <sup>c</sup>	0.34

MCI, mild cognitive impairment; OR, odds ratio; CI, confidence interval; IADL, Instrumental Activities of Daily Living; BADL, Basic Activities of Daily Living; MMSE, Mini-Mental State Examination; BMI, body mass index; APOE, apolipoprotein E. Model 1: unadjusted. Model 2: adjusted for age, gender, and ethnicity. Model 3: adjusted for <sup>a</sup> age, gender, ethnicity, education, leisure-time activities total score, APOE ε4 carrier status, depressive symptoms, and baseline MMSE total score; <sup>b</sup> cardiovascular risk factors (BMI, hypertension, dyslipidemia, and diabetes); and <sup>c</sup> cardiovascular diseases (coronary heart disease and cardiac diseases) and stroke.

## Discussion

This study showed that 4% of subjects with MCI at baseline had a subsequent diagnosis of dementia over 6 years of follow-up and 44% reverted back to normal cognition at follow-up. MCI individuals with a more subjective memory complaint, greater participation in leisure-time activities, and higher MMSE total scores are more likely to revert to normal cognition. Diabetes and the metabolic syndrome were identified as modifiable risk factors for MCI progression to dementia.

This study expands the literature by estimating the rates of MCI conversion (progression and reversion) and by delineating a set of risk and protective factors in a younger ageing Chinese cohort. Uniquely in the SLAS, the study cohort included middle-aged participants as young as 55 years. More than half of the study subjects were younger than 70 years. This partly explains the low rate and small number of MCI progression to dementia. On the other hand, it appears to explain a higher MCI reversion rate. The predictors for MCI conversion may also be different for younger aged and older aged populations. For example, the contribution of the metabolic syndrome to MCI progression to dementia, as shown in this study, appears to be most apparent in younger aged populations, in contrast to studies of older population cohorts (mean age >75 years), which are inconsistent in reporting increased or even decreased risks of dementia associated with the metabolic syndrome [10].

Our estimations on rates of MCI reversion and progression fall within the wide range that has been reported in other community-based/population-based studies. Reported estimates of MCI reversion rates are generally lower, and MCI progression is higher, in studies of



patients in the clinical setting than in population-based studies of community-dwelling older persons. For example, in a retrospective study in Japan in a hospital setting, it was reported that 39.2% of 74 baseline MCI subjects progressed to dementia at 1-year follow-up and 8.1% improved to cognitively normal [9]. The variability of MCI reversion and progression rates could be due to diagnostic classification criteria, age at recruitment of the study cohort, and length of follow-up [5]. The estimated rate of MCI progression to dementia in the present cohort of older adults aged  $\geq 55$  years was much lower than in other community-based cohort studies [30, 31], such as the Personnes Agées QUID (PAQUID) cohort of people aged  $\geq 65$  years over 5 years of follow-up [30], which estimated the annual MCI conversion rate at 8.3%.

In the present study, we positively identified a number of protective factors that support MCI reversion to normal cognition. In agreement with a Japanese longitudinal study which found that a higher baseline MMSE score was significantly associated with increasing probability of MCI reversion [9], our findings suggest that baseline cognitive reserve may promote MCI reversion to normal cognition. Better baseline performance on other cognitive screening tests, e.g., Modified Mini-Mental State Examination (3MS), was also reportedly associated with MCI reversion to normal cognition [32]. We also found that MCI persons with greater participation in leisure-time activities were more likely to return to normal cognition at follow-up. The result supports our previous finding on the association between increased leisure-time activities, especially productive activities, and lower risk of cognitive decline [33]. The Sydney Memory and Ageing Study also reported that MCI reversion was more frequently observed among those who engaged more frequently in mental or physical activities after 2 years from baseline [34]. Together, these findings indicate the important role of brain stimulation and lifestyle change for the promotion of cognitive reserve and an MCI interventional strategy. Interestingly, our study showed that a baseline subjective memory complaint was associated with a higher likelihood of MCI reverting back to normal cognition. Slavin et al. [35] reported a correlation between subjective cognitive complaints and psychological factors, e.g., depression, anxiety, openness, and neuroticism, in a community-living older population. A relationship between self-reported cognitive complaints and depressive symptoms has also been reported by Edmonds et al. [36]. For this reason, these authors have questioned the usefulness of subjective cognitive complaints as a core criterion for the diagnosis of MCI. It is possible that for some participants the MCI diagnosis at baseline was made during a transitory period of cognitive worsening caused by transient stressors, such as a stressful situation or psychiatric illness. Under such circumstances, the initial MCI status at baseline may be overestimated and, hence, be reversible during follow-up.

Of note, we found diabetes and the metabolic syndrome to be potential modifiable risk factors for MCI progression to dementia. To date, many studies have consistently shown that diabetes and the metabolic syndrome increase the risk of cognitive decline and dementia and increase the risk of MCI conversion to dementia [10, 37–39]. A diagnosis of diabetes leads to a 20–70% higher risk of developing cognitive decline and a 60% increased risk of future dementia [37]. According to a Sweden cohort study, diabetes or pre-diabetes accelerates the MCI progression to dementia by 3.18 years over 9 years of follow-up [39].

The present study has several strengths. First, the study design was a population-based prospective cohort research. Participants had been closely followed up for an average of 6 years from baseline. Second, repeated assessments were performed by trained research staff to capture a wide range of multi-domain predictor variables. Third, compared to clinical samples, there is less selection bias and the study population was more representative of the general population.

There are some limitations. First, the number of those who progressed from MCI to dementia was small and possibly underestimated due to more cognitively impaired participants being lost to follow-up. This limits the number of potential risk factors that could be

investigated meaningfully with adequate statistical power. Despite this, diabetes and the metabolic syndrome were clearly found to be associated with an increased risk of MCI progression to dementia. Secondly, this study lacks neuroimaging data, such as brain regional volumes, which could be usefully investigated. Previous studies have, for example, reported that the volumes of the left hippocampus and of the left amygdala were larger in those who reverted from MCI than in those who did not [34], and smaller hippocampal volumes and atrophy in the CA1 subregion and subiculum predicted MCI conversion to Alzheimer disease [8]. Thirdly, the study does not exclude the possibility that the sample included participants whose cognitive decline could be better explained by other medical conditions, psychiatric disorders, or transient stressors, although depressive symptoms and cardiovascular medical conditions (e.g., hypertension, dyslipidemia, diabetes, coronary heart disease, cardiac diseases, and stroke) were adjusted for in the estimation of the strength of associations of candidate factors with MCI reversion or progression. Given the younger age of the cohort, the study has focused on ascertaining a sufficient number of incident cases of dementia among presumably more stable cases of MCI to estimate the rate of MCI progression to dementia over 6 years. MCI conversions, especially reversions to normal cognition, may be expected to occur at shorter intervals within the 6 years. It would, hence, be interesting to study changes in cognition and MCI reversion to normal cognition over consecutive 3-year periods. However, we were not able to do this because cognitive diagnostic data were incomplete at the first follow-up at year 3.

In conclusion, this study shows that in a relatively younger population of community-living older persons, there were higher rates of MCI reversion to normal cognition and lower rates of MCI progression to dementia. MCI reversion was related to the positive effects of leisure-time activities and high cognitive reserve, and MCI progression was related to the deleterious effect of diabetes. More studies are needed to explain the association of subjective memory complaint with MCI reversion to normal cognition.

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