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Original Study

Conversion and Reversion Rates in Japanese Older People With Mild Cognitive Impairment

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A B S T R A C T

Objectives: Approximately 25% of individuals who are diagnosed with amnestic mild cognitive impairment (aMCI) revert to normal cognition (NC) rather than progressing to Alzheimer disease (AD). However, the prevalence of progression and reversion among older people in Asia remains unclear.
Design: A prospective cohort study.
Setting: A community in Japan.
Participants: A total of 4153 individuals without dementia aged ≥65 years were classified as having NC, aMCI single domain (aMCIs), non-aMCI single domain (naMCIs), aMCI multiple domain (aMCIm), non-aMCI multiple domain (naMCIm), or global cognitive impairment (GCI).
Measurements: The National Center for Geriatrics and Gerontology-Functional Assessment Tool and the Mini-Mental State Examination were used to conduct cognitive screening. The participants completed baseline (August 2011 to June 2012) and follow-up (August 2015 to June 2016) assessments. We followed up monthly for newly incident AD, as recorded by the Japanese National Health Insurance and Later-Stage Medical Care systems. Multiple imputation was used to adjust for selection bias and loss of information.
Results: At 4-year follow-up, the reversion rates to NC in aMCIs, naMCIs, aMCIm, naMCIm, and GCI were 38.7%, 57.0%, 25.7%, 20.9%, and 43.7%, respectively. Of the participants with NC, aMCIs, naMCIs, aMCIm, naMCIm, and GCI at baseline, 4.7%, 4.5%, 13.1%, 20.6%, 21.6%, and 14.3%, respectively, were subsequently diagnosed with AD. We found significant associations between incident AD and naMCIs [hazard ratio (HR) compared to NC: 2.18, 95% confidence interval (CI): 1.45-3.26], and between AD and aMCIm (HR: 4.39, 95% CI: 2.06-9.39) and between AD and naMCIm (HR: 3.60, 95% CI: 2.13-6.08). However, the association between incident AD and aMCIs and between AD and GCI did not reach significance.
Conclusion: Reversion to NC from MCI and GCI was frequent, and individuals with aMCIs and GCI did not show higher risk of incident AD than those with NC. Older adults with multiple cognitive impairments may be potential targets for preventing dementia.

Individuals categorized with the widely used umbrella term of mild cognitive impairment (MCI) are at a higher risk of developing dementia,[1] and numerous studies have been undertaken with a view to therapeutic intervention to prevent the incidence of dementia.[2] A systematic review indicated that annual progression rates from MCI to Alzheimer disease (AD) ranged from 7.5% to 16.5% per person/year in clinical studies, and from 5.4% to 11.5% per person/year for community settings.[3] Another meta-analysis concluded that the annual progression rate from MCI to AD is approximately 5% to 10%, and that most people with MCI will not progress to dementia even after 10 years of follow-up.[4]

In fact, MCI is associated with a relatively high probability of returning to normal cognitive function: about 25% of individuals who are diagnosed as having amnestic MCI (aMCI) subsequently revert to

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normal cognition (NC) rather than progressing to AD or other types of dementia.[5] This transitional instability is a major issue for intervention studies aimed at preventing the incidence of AD, as this instability may be a strong confounding factor. A recent meta-analysis found an overall reversion rate of approximately 24%.[5] When the studies were separated into clinical and community-based settings, clinic-based studies exhibited a much lower reversion rate (14% vs 31%). North American and European studies had high heterogeneity of reversion rates, whereas Asian studies had moderate levels of heterogeneity and significantly lower rates of reversion.[5] However, only 2 of 25 studies in the meta-analysis, both with small sample sizes, were from Asian countries. Further studies with large sample sizes are needed to identify accurate reversion rates from MCI to NC. Furthermore, global cognitive impairment is also a critical risk factor for dementia. The Mini-Mental State Examination (MMSE) is the most frequently used brief global cognitive instrument,[6] and a score of 23 or lower indicates dementia.[7] In the community, the pooled accuracy to detect dementia at a cut point of 23/24 had sensitivity 0.85 [95% confidence interval (CI) 0.74-0.92] and specificity 0.90 (95% CI 0.82-0.95).[8] However, cognitive impairment is only one of the components of a dementia diagnosis. The American Psychiatric Association's *Diagnostic and Statistical Manual of Mental Disorders*, fifth edition (DSM-5), task forces are methodically revising the criteria for various disorders, including neurocognitive disorders.[9] DSM-5 has now classified acquired neurocognitive disorders of all age groups under 3 major headings: delirium, major neurocognitive disorders (NCD), and mild NCD. The key distinction between major and mild NCD is that individuals with major NCD experience a substantial decline in function (loss of independence) as a result of profound cognitive impairment, whereas patients with mild NCD experience only modest cognitive decline and, as a result, function relatively independently.[10] In this study, no participants had loss of independence and some participants had cognitive decline. They were divided into an MCI group, which showed cognitive decline in multicomponent neurocognitive tests, and a global cognitive impairment (GCI) group, which had an MMSE score of 23 or lower.[11] There is insufficient evidence if MCI or GCI is a stronger predictor of AD.

In this study, we examined the proportion of elderly participants with MCI and GCI who reverted to NC at the follow-up examination and compared these data to that from participants who still had cognitive impairment or had progressed to AD at follow-up. We used data from the National Center for Geriatrics and Gerontology—Study of Geriatric Syndromes (NCGG-SGS), a Japanese national cohort study.[12] We also determined the incidence rates of AD within the large population-based cohort of Japanese elderly with and without MCI or GCI at baseline, compared rates of progression across MCI subtypes and GCI, and determined the antecedents for progression. We hypothesized that individuals with multiple domains of MCI and GCI would show greater effects of incident dementia than would individuals with single domain of MCI or older individuals with NC, and that individuals with MCIs would show greater effects of reversion to NC than those with MCI multiple domain (MCIm) or GCI.

Methods

Participants

Of the people recruited from Obu, Japan, for the NCGG-SGS, 4153 community-dwelling older individuals aged ≥65 years participated in this study.[12]

The baseline participants were 5104 older adults who completed the examinations of the NCGG-SGS between August 2011 and February 2012. Of these, 3095 (60.6%) took part in the second-wave cognitive examination between August 2015 and August 2016. The data on AD incidence were collected from the Japanese Health Insurance System for all participants who were assessed at baseline except those who had died or relocated. The inclusion criteria were residence in Obu and age ≥65 years at the time of the first examination (August 2011 to March 2013). The exclusion criteria were as follows: health problems such as AD, Parkinson disease, depression, or stroke (n = 549); inability to perform basic daily living tasks such as eating, grooming, bathing, and climbing up and down stairs (n = 26); need for support or care as certified by the Japanese public long-term care insurance due to disability (n = 69); missing data on exclusion criteria (n = 14); inability to complete cognitive tests at baseline (n = 143); and relocation (n = 38) or death (n = 112) during the follow-up period. Of the initial 5104 participants, 951 were excluded, and data from 4153 participants (1995 men and 2158 women) were analyzed. Their mean age was 71.6 ± 5.2 years (range: 65-96 years). Multiple imputation was used to adjust for selection bias and loss of information. Cognitive status, which was divided into NC, MCI, and GCI, was imputed for participants with missing data on the variable. Fifty imputed values were generated for each participant with missing data, yielding 50 complete data sets. The main advantages of using multiple imputation over the complete sample were (1) to increase power to detect associations in a multiple regression model by using the partial information available on some participants and (2) to anticipate the likely possibility that the presence of missing scores was not completely random, but that, among participants with similar known characteristics, the distribution of missing values would resemble that of known values.[13] All participants gave their informed consent before they were included in the study. The study protocol was approved by the Ethics Committee of the National Center for Geriatrics and Gerontology.

Operationalization of MCI and GCI

The NCGG-FAT, an iPad application, was used to conduct the cognitive screening.[14] The NCGG-FAT consists of the following domains: (1) memory [word list memory—I (immediate recognition) and word list memory—II (delayed recall)]; (2) attention [a tablet version of the Trail Making Test (TMT)—part A]; (3) executive function (a tablet version of the TMT—part B); and (4) processing speed (a tablet version of the Digit Symbol Substitution Test). Participants were given approximately 20 minutes to complete the battery. The NCGG-FAT has been shown to have high test-retest reliability and moderate to high validity among community-dwelling older persons.[15] The assessments of cognitive functioning in the community were conducted by well-trained study assistants using community facilities, such as community halls. All staff received training from the authors on the protocols for administering the assessments before the study began. Established standardized thresholds were used for all tests conducted in this study to define impairment in the corresponding domain for a population-based cohort comprising community-dwelling older persons (scores > 1.5 standard deviations below the age- and education-specific means). The MMSE was used to measure global cognitive function.[7] We used <24 points on the MMSE as a cutoff score for GCI, in accordance with previous findings.[11]

Based on their cognitive test scores, participants were first placed into GCI and no-GCI groups, according to their MMSE scores. Then, participants in the no-GCI group were further categorized into the following groups: (1) NC; (2) amnestic MCI single domain (aMCIs); (3) nonamnestic MCI single domain (naMCIs); (4) amnestic MCI multiple domain (aMCIm); and (5) nonamnestic MCI multiple domain (naMCIm).[16] For the aMCIs group, a deficit on word list memory and no other test was required. For the naMCIs group, a deficit in TMT-part A, TMT-part B, or Digit Symbol Substitution Test was required and no memory deficit. For the aMCIm group, a deficit in word list memory plus at least 1 additional deficient domain was required, and for the naMCIm group deficits in 2 or more domains, other than memory,