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# Predictive validity and diagnostic stability of mild cognitive impairment subtypes

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**Abstract**

**Background:** Mild cognitive impairment (MCI) is subclassified into four subtypes by the presence of impairment in the memory domain (amnestic vs nonamnestic) and the number of impaired cognitive domains (single vs multiple). However, predictive validity for outcomes of these criteria and the diagnostic stability of the subtypes are questionable.

**Methods:** We investigated the outcomes of 140 patients with MCI who participated in the baseline study of the Korean Longitudinal Study on Health and Aging and completed the 18-month follow-up evaluation (mean duration of follow-up = 1.57 ± 0.24 years). We evaluated the predictive validity of the criteria using multinomial logistic regression analyses, and the diagnostic stability of MCI subtypes using annual conversion rates between subtypes.

**Results:** Compared with the single-domain type (MCIs), the multiple-domain type (MCIm) had a lower chance of reversion to normal cognition (MCIm = 10.94%, MCIs = 43.42%) and higher risk of conversion to dementia (MCIm = 23.44%, MCIs = 5.26%). The difference in the reversion rate between the multiple- and single-domain type was statistically significant (odds ratio = 0.233, 95% confidence interval = 0.070–0.771, $P = .017$). However, neither the chance of reversion nor the risk of conversion was different between amnestic and nonamnestic subtypes. Among the 81 participants who neither converted to dementia nor reverted to normal cognition, 39 converted to different subtype (annual conversion rate = 17.74%).

**Conclusions:** The number of impaired cognitive domains, but not the presence of memory impairment, predicted poor outcomes in people with MCI. However, MCI subtype was diagnostically unstable.



*Keywords:* Mild cognitive impairment subtypes; Predictive validity; Diagnostic stability; Dementia; Reversion to normal; Cohort studies

## 1. Introduction

Mild cognitive impairment (MCI), a high-risk condition of dementia, is characterized by an acquired cognitive deficiency with no significant decline in the functional activities of daily living [1]. However, MCI is a heterogeneous condition and can be further classified into four subtypes according to the presence of impairment in the memory domain and the number of impaired cognitive domains: amnestic MCI, single-domain type; amnestic MCI, multiple-domain type; nonamnestic MCI, single-domain type; and nonamnestic MCI, multiple-domain type [2].

Even though this classification is drawn from the neuropsychological tests administered for evaluating objective cognitive impairments, each subtype is supposed to reflect

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different etiologies and outcomes. For example, amnestic MCI (aMCI) may be a precursor of Alzheimer's disease (AD), whereas nonamnestic MCI (naMCI) may be a precursor of one of the other types of dementia. A recent hospital-based study found that MCI was biologically meaningful, particularly at the level of distinguishing aMCI from naMCI, as persons with aMCI had significantly smaller hippocampi, were significantly more likely to carry the apolipoprotein E (*APOE*) e4 allele, and had a lower incidence of vascular risk factors and of white matter hyperintensities on magnetic resonance images of the brain [3]. It was found that aMCI was more predictive of incident dementia, particularly AD, than the naMCI [4,5].

However, further studies are required before clear conclusions can be drawn about the validity of these MCI subtypes for etiologies or outcomes, as MCI's clinical course is reportedly unstable [5]. Although a sizable proportion of people with MCI revert to normal cognition [5,6], few studies have examined reversion to normal cognition by different MCI subtypes. Most studies have focused on conversion from MCI to dementia. Furthermore, the diagnostic stability between MCI subtypes over time has rarely been studied.

This study primarily aimed to investigate the impact of two criteria for classifying MCI (i.e., the presence of impairment in the memory domain [amnestic vs nonamnestic] and the number of impaired cognitive domains [single vs multiple]) on both the chances of conversion to dementia and of reversion to normal cognition in the 1.5-year follow-up study of a community-based elderly cohort. The secondary aim was to examine the diagnostic stability between MCI subtypes during the follow-up period.

## 2. Methods

### 2.1. Subjects

This study was part of the Korean Longitudinal Study on Health and Aging (KLoSHA) [7]. The KLoSHA, launched in 2005, is a population-based prospective cohort study on the health, aging, and common geriatric diseases of the Korean elderly population aged ≥65 years. A random sample (N = 1118) was drawn from a pool of 61,730 residents aged ≥65 years living in Seongnam, one of the largest satellite cities of Seoul, Korea, having a total population of 931,019 in 2005. Of the 1118 randomly sampled individuals, 714 (63.9%) agreed to participate in the KLoSHA [7].

At the baseline study of the KLoSHA, 197 of the 714 randomly sampled individuals were diagnosed with MCI [8]. Of these, 140 (71.07%) completed the first KLoSHA follow-up study, conducted approximately 1.5 years after the baseline study.

This study's protocol was approved by the Institutional Review Board of Seoul National University Bundang Hospital. All subjects were fully informed of the study protocol. All subjects provided written informed consent, which was signed by either the subjects or their legal guardians.

### 2.2. Assessment

Geriatric neuropsychiatrists with expertise in dementia research conducted standardized clinical interviews with the subjects, as well as subjects' neurological and physical examinations. Baseline and follow-up parameters were evaluated using the Korean version of the Consortium to Establish a Registry for Alzheimer's Disease Clinical Assessment Battery (CERAD-K-C) [9] and the Korean version of the Mini International Neuropsychiatric Interview [10]. In addition, research neuropsychologists administered the Korean version of the Consortium to Establish a Registry for Alzheimer's Disease Neuropsychological Assessment Battery, Lexical Fluency Test [11], and Digit Span Test [12] to the subjects, to collect baseline and follow-up data. The Consortium to Establish a Registry for Alzheimer's Disease Neuropsychological Assessment Battery consists of nine neuropsychological tests, including the Categorical Fluency Test, the modified Boston Naming Test, the Mini-Mental State Examination (MMSE), the Word List Memory Test, the Constructional Praxis Test, the Word List Recall Test, the Word List Recognition Test, the Constructional Recall Test, and the Trail Making Test A. We evaluated subjects' activities of daily living using the CERAD-K-C Blessed Dementia Scale (BDS) [9]. To determine the global severity of dementia, we used the Clinical Dementia Rating scale [13], and we evaluated depressive symptoms using the Korean version of the Geriatric Depression Scale (GDS) [14]. The chronic medical illness burden was evaluated quantitatively using the Cumulative Illness Rating Scale (CIRS) [15,16].

All subjects underwent routine blood examinations, *APOE* genotyping, urinalysis, and electrocardiograms during the baseline and follow-up studies. When CERAD-K-C data indicated that a subject might have dementia or suffered a stroke, we performed magnetic resonance imaging of the brain to confirm the suspicion. All assessments were performed at the Seoul National University Bundang Hospital.

### 2.3. Diagnosis

The subjects' MCI was diagnosed according to the revised diagnostic criteria for MCI proposed by the International Working Group on MCI [8]. We ascertained the presence of objective cognitive impairment if a subject scored worse than −1.5 SD on the age-, gender-, and education-adjusted norms for Korean elders on any of the 11 neuropsychological tests. Impairment in memory function was determined using the Word List Memory Test, Word List Recall Test, Word List Recognition Test, and Constructional Recall Test. Impairment in the executive domain was determined using the Categorical Fluency