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Original Study

Spontaneous Reversion of Mild Cognitive Impairment to Normal Cognition: A Systematic Review of Literature and Meta-Analysis

Marco Canevelli MD [a,*], Giulia Grande MD [b], Eleonora Lacorte MSci [c], Elisa Quarchioni MStat [c], Matteo Cesari PhD [d,e], Claudio Mariani MD [b], Giuseppe Bruno PhD [a], Nicola Vanacore PhD [c]

[a] *Department of Neurology and Psychiatry, "Sapienza" University of Rome, Italy*
[b] *Center for Research and Treatment on Cognitive Dysfunctions, Biomedical and Clinical Sciences Department, "Luigi Sacco" Hospital, University of Milan, Italy*
[c] *National Centre for Epidemiology, Surveillance, and Health Promotion, National Institute of Health, Rome, Italy*
[d] *Gérontopôle, Centre Hospitalier Universitaire de Toulouse, Toulouse, France*
[e] *Université de Toulouse III Paul Sabatier, Toulouse, France*

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A B S T R A C T

Objectives: The issue of subjects with mild cognitive impairment (MCI) reverting to normal cognition (NC) has to date been taken in limited consideration, and no conclusive data are available on the rate of reversion. We aimed at systematically reviewing available longitudinal studies on MCI and meta-analyzing data with the purpose of estimating the proportion of subjects reverting to NC.

Design: We performed a systematic bibliographic search on PubMed, the Cochrane Library, and the ISI Web of Science databases. We included in the review all longitudinal studies on MCI published from 1999 up to November 2015. Only studies with a longitudinal design, a follow-up ≥2 years, enrolling subjects with MCI, and reporting the number or the percentage of subjects reverting to NC were included. Data extraction was performed independently by 2 authors. The methodological quality of studies was also assessed by 2 independent authors using the QUIPS tool.

Results: Twenty-five studies were included. The quality of evidence was found to be moderate. We observed an overall 18% (95% CI 14–22) reversion rate from MCI to NC. Results from the metaregression showed a significant association between effect size and study setting. In particular, estimates significantly varied according to study setting, with an 8% (95% CI 4–11) reversion rate in clinical-based studies and a 25% (95% CI 19–30) rate in population-based studies. The frequency of reversion from MCI to NC further increased to 26% when considering only studies of better quality. Only a few studies were designed to specifically investigate the reversion from MCI to NC, thus relevant information on this topic was frequently missing.

Conclusion: Our data confirm that reversion to normality is a common outcome in subjects with MCI, thus leading to recommend a more balanced view when approaching the construct of MCI both in a clinical and in a research setting.

Mild cognitive impairment (MCI) is usually described as an intermediate phase between normal cognition and dementia.[1,2] A subject with MCI is defined as having an objective deficit in cognitive abilities that does not affect his or her functional independence. The interest in investigating this condition has progressively increased over the last years. In particular, MCI is considered as being a relevant risk factor for dementia, and thus a promising target for specific pharmacologic and nonpharmacologic interventions. Subjects with MCI, in fact, show an annual rate of progression to dementia ranging from 5% to 15%, varying according to the setting and the operational definitions

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* Address correspondence to Marco Canevelli, MD, Memory Clinic, Department of Neurology and Psychiatry, "Sapienza" University of Rome, Viale dell'Università 30, 00185 Rome, Italy.

E-mail address: marco.canevelli@gmail.com (M. Canevelli).

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considered.[2] MCI is therefore frequently the object of investigation in the attempt of detecting the early pathophysiological modifications that may be responsible for the progression to dementia.[3]

The actual nature of MCI is not yet fully clarified, and several issues are still insufficiently explored. As an example, although a large amount of resources has been dedicated to studying cognitive decline and the way MCI progresses to dementia, relatively few efforts have been focused on investigating the possible reversion of subjects with MCI to normal cognition.[4] Such tendency at univocally looking at MCI as a prodromal stage of dementia produces an unbalanced use of this construct.[5,6] This negative connotation of MCI due to such a biased approach frequently leads to underestimating its fluctuations over time, and forgetting its potential to (spontaneously) revert to normal cognition. An increasing amount of longitudinal data show that the majority of subjects with MCI do not experience a worsening of cognition over time,[7] and that a relevant proportion of them eventually reverts to normal cognition.[8,9] Available estimates of reversion from MCI to normal cognition are quite heterogeneous, ranging from 2.1%[10] to as far as 53%.[11]

Investigating the reversion from MCI to normal cognition (NC) has some relevant practical implications. A more accurate identification of subjects with a positive cognitive outcome may allow to better allocate healthcare resources among the heterogeneous population of MCI subjects.[5] It may also prevent the misdiagnosis of cognitively normal subjects and its consequences (eg, discrimination, stigmatization, and overmedicalization).[12] Moreover, a better understanding of the nature of MCI may improve the design and interpretation of clinical trials, particularly those focused on the prevention of dementia. For example, the enrollment of subjects with MCI whose cognitive status is unlikely to decline over time may result in reducing the effect size of potentially effective interventions.

The aim of this study is to systematically review, analyze, and discuss results from available longitudinal studies with the aim of obtaining a more accurate estimate of the proportion of subjects with MCI reverting to NC. Analyses will also explore the role of some well-known confounding factors that affect the outcome of MCI [ie, setting, age of participants, length of follow-up, operational definition of MCI and NC, concomitant depression, functional independence, and apolipoprotein E (ApoE) genotype].[1]

Methods

The review was performed according to the methodology recommended by the Cochrane Collaboration group[13] and reported according to the PRISMA statement[14] and the MOOSE checklist.[15]

Data Sources and Searches

All studies published between 1999 (year of the first MCI operationalization[16]) and November 2015 were retrieved through a structured search on PubMed, Cochrane Library, and the ISI Web of Science databases carried out by a researcher with experience in bibliographic searches. The following search terms were used: ((“mild” AND “cognitive” AND “impairment”) OR “MCI”) AND (reversion* OR remission* OR remitter* OR reverter* OR revertion OR *conversion* OR *converter* OR *progressi*) AND (“normal” OR “normality” OR “dementia” OR “dementias” OR alzheimer*) AND (cohort* OR longitudinal OR prospective OR prognos* OR “follow up” OR “follow-up” OR “followup”). All longitudinal studies enrolling subjects with MCI and investigating any type of main outcome (ie, MCI progression to dementia and/or MCI reversion to NC) were considered for evaluation. This conservative approach allowed us to consider also studies providing either marginally or nonexplicitly information on reversion from MCI to NC (eg, reporting this information as a secondary outcome or “between the lines”).

Study Selection

Records identified through the bibliographic searches were independently reviewed by 2 authors (M.C. and G.G.). Articles relevant and pertinent to the topic of the review were thus selected, based on the analysis of titles and abstracts, and retrieved in full text. Disagreements in the selection process, when present, were solved by discussion, consensus, or involving a third reviewer. Possible sources of gray literature and the references of considered studies were also reviewed to identify further potentially relevant publications. Articles considered for inclusion were then individually applied a set of predefined inclusion and exclusion criteria. Only studies in English, with a longitudinal design and a follow-up equal to or longer than 2 years, enrolling subjects with MCI defined according to the original Mayo Clinic criteria[16] or subsequent operationalizations, and reporting the number or percentage of subjects reverting to NC during the follow-up were included.

Studies focusing on other cognitive deficits or similar conditions with the potential of being considered as prodromal stages of dementia or predementia (ie, “cognitive impairment no dementia” [CIND], “age-associated memory impairment” [AAMI], and “age-associated cognitive decline” [AACD]) were excluded in order to obtain a more homogeneous body of evidence. Conference proceedings, abstracts, and letters were also excluded.

Data Extraction and Quality Assessment

Two authors (M.C. and G.G.) independently extracted the following data for each included study: setting, number of participants, sociodemographic characteristics (ie, age, gender, and education), criteria adopted for defining MCI and NC, cognitive performance, functional independence, concomitant depression, ApoE genotype, length of follow-up, number and percentage of MCI participants reverting to NC, and response rate. Disagreements on the extracted information, where present, were resolved by consensus.

Two different authors (E.L. and N.V.) independently assessed the quality of included studies using the Quality in Prognostic Studies (QUIPS) tool.[17,18] This tool has been developed for systematic appraisal in studies on prognostic factors and considers 6 domains for analysis of potential biases: (1) inclusion, (2) attrition, (3) prognostic factor measurement, (4) confounders, (5) outcome measurement, and (6) analysis and reporting. A total of 3 to 7 prompting items is provided for each domain, to help assessing the presence of risk of bias and score it as high, moderate, or low.[18] The QUIPS has been successfully adopted in several systematic reviews with moderate to substantial interrater reliability.[18]

Data Synthesis and Analysis

Preliminary descriptive statistics [n, mean, standard deviation (SD)] were conducted to describe the samples to be included in the meta-analysis. Weighted mean values of some variables (ie, age, educational level) were calculated when only data referring to subgroups of participants were provided.

A meta-analysis of the reported frequencies of MCI reversion to NC (whenever available) was conducted. All analyses were carried out using Stata (version 11.0). Meta-analyses were performed adopting a specific Stata module, *Metaprop*, designed to perform meta-analyses of proportions in Stata. Building on the existing Stata procedure *Metan* (typically used to pool risk ratios, odds ratios, mean differences, and proportions), *Metaprop* applies procedures that are specific to binomial data.[19] Overall estimates were calculated with random effects models and a test for heterogeneity was applied using chi-square and the I^2 statistics. The random effects model was chosen because the