4-2017

Outcomes after Diagnosis of Mild Cognitive Impairment in a Large Autopsy Series

Erin L. Abner
University of Kentucky, erin.abner@uky.edu

Richard J. Kryscio
University of Kentucky, kryscio@uky.edu

Frederick A. Schmitt
University of Kentucky, fascom@uky.edu

David W. Fardo
University of Kentucky, david.fardo@uky.edu

Daniela C. Moga
University of Kentucky, daniela.moga@uky.edu

Outcomes after Diagnosis of Mild Cognitive Impairment in a Large Autopsy Series

Digital Object Identifier (DOI)
https://doi.org/10.1002/ana.24903

Notes/Citation Information

Published in *Annals of Neurology*, v. 81, issue 4.

Authors

Erin L. Abner, Richard J. Kryscio, Frederick A. Schmitt, David W. Fardo, Daniela C. Moga, Eseosa T. Ighodaro, Gregory A. Jicha, Lei Yu, Hiroko H. Dodge, Chengjie Xiong, Randall L. Woltjer, Julie A. Schneider, Nigel J. Cairns, David A. Bennett, and Peter T. Nelson

HHS Public Access

Author manuscript

Ann Neurol. Author manuscript; available in PMC 2018 April 01.

Published in final edited form as:

Ann Neurol. 2017 April ; 81(4): 549–559. doi:10.1002/ana.24903.

Outcomes after diagnosis of mild cognitive impairment in a large autopsy series

Erin L. Abner, PhD,
University of Kentucky, Department of Epidemiology

Richard J. Kryscio, PhD,
University of Kentucky, Department of Biostatistics

Frederick A. Schmitt, PhD,
University of Kentucky, Department of Neurology

David W. Fardo, PhD,
University of Kentucky, Department of Biostatistics

Daniela C. Moga, MD, PhD,
University of Kentucky, Department of Pharmacy Practice and Science

Eseosa T. Ighodaro, BS,
University of Kentucky, Department of Anatomy and Neurobiology

Gregory A. Jicha, MD, PhD,
University of Kentucky, Department of Neurology

Lei Yu, PhD,
Rush University Medical Center, Department of Neurological Sciences

Hiroko H. Dodge, PhD,
Oregon Health & Science University, Department of Neurology

Chengjie Xiong, PhD,
Washington University, Division of Biostatistics

Randall L. Woltjer, MD, PhD,
Oregon Health & Science University, Department of Pathology

Julie A. Schneider, MD,
Rush University Medical Center, Department of Pathology

Nigel J. Cairns, PhD, FRCPath,
Washington University, Department of Neurology

Corresponding author: Erin Abner, PhD, 230 A Sanders-Brown Center on Aging, University of Kentucky, Lexington, KY 40536-0230 USA, Work ph: 859-218-3825, erin.abner@uky.edu.

AUTHOR CONTRIBUTIONS

Conception and design of the study: ELA, RJK, FAS, DWF, DAB, PTN. Acquisition and analysis of data: ELA, RJK, FAS, DCM, ETI, GAJ, LY, HHD, CX, RRW, JAS, NJC, PTN. Drafting manuscript and figures: ELA, RRW, JAS, NJC, DAB, PTN.

POTENTIAL CONFLICTS OF INTEREST

None of the authors of this paper has any commercial interest in any aspect of the design, analysis, or interpretation of this study.

David A. Bennett, MD, and
Rush University Medical Center, Department of Neurological Sciences

Peter T. Nelson, MD, PhD
University of Kentucky, Department of Pathology

Abstract

Objective—Determine clinical and neuropathological outcomes following a clinical diagnosis of mild cognitive impairment (MCI).

Methods—Data were drawn from a large autopsy series (N=1,337) of individuals followed longitudinally from normal or MCI status to death, derived from four Alzheimer's Disease (AD) Centers in the United States.

Results—Mean follow-up was 7.9 years. Of the 874 individuals ever diagnosed with MCI, final clinical diagnoses were varied: 39.2% died with an MCI diagnosis, 46.8% with a dementia diagnosis, and 13.9% died with a diagnosis of intact cognition. The latter group had pathological features resembling those with a final clinical diagnosis of MCI. In terms of non-AD pathologies, both primary age-related tauopathy ($p<0.05$) and brain arteriolosclerosis pathology ($p<0.001$) were more severe in MCI than cognitively intact controls. Among the group that remained MCI until death, Mixed AD neuropathologic changes (ADNC) (≥1 comorbid pathology) was more frequent than Pure ADNC pathology (55% vs. 22%); "suspected non-Alzheimer's pathology" (SNAP) comprised the remaining 22% of cases. A majority (74%) of subjects who died with MCI were without "high" level ADNC, Lewy body disease, or hippocampal sclerosis pathologies; this group was enriched in cerebrovascular pathologies. Subjects who died with dementia and were without severe neurodegenerative pathologies tended to have cerebrovascular pathology and carry the MCI diagnosis for a longer interval.

Interpretation—MCI diagnosis usually was associated with comorbid neuropathologies; less than one-quarter of MCI cases showed "pure" AD at autopsy.

INTRODUCTION

Mild cognitive impairment (MCI) is a clinical term referring to a portion of the cognitive continuum between intact (or "normal") cognition and dementia. By definition, individuals with MCI are not demented; have cognitive deficits that may or may not include memory impairment; and are functionally fairly intact in terms of activities of daily living [1]. Most estimates of MCI prevalence among adults over age 60 range between 16% and 20% of the population [2].

MCI often precedes dementia due to Alzheimer's disease (AD), but persons diagnosed with MCI may later be diagnosed as cognitively normal, remain diagnosed with MCI until death, or in many cases progress to clinical dementia due to non-AD brain diseases [3]. Studies of MCI suggest an annual progression rate to dementia of about 10% when conducted in specialist settings and about 5% when conducted in community settings [3]. Such rates imply that after 10 years of follow-up, many MCI cases will not progress to dementia; however, in this meta-analysis of MCI transition [3], studies with less than three years of

follow-up were excluded. Progression rates and survival time in MCI depend on many factors, including severity at diagnosis and diagnostic criteria [4,5], but the role of specific neuropathologies in progression rates is not clear.

Prior MCI studies underscore disease heterogeneity underlying this clinical condition [6–8]. For example, up to 30% of community-based MCI subjects have biomarker profiles that are consistent with neurodegeneration but inconsistent with AD (i.e., suspected non-Alzheimer pathophysiology or SNAP) [9]. Prior clinical-pathologic studies have reported that MCI is often associated with mixed pathologies [10], and there have been recent advances in the study of non-AD pathologies. For example, there is new understanding of the frequency of hippocampal sclerosis of aging (HS-Aging) [11], primary age-related tauopathy (PART) [12], and arteriolosclerosis [13], which may contribute to a clinical MCI diagnosis. These associations have not to our knowledge, yet been evaluated in large autopsy cohorts focusing on MCI. In the current study, we examined part of the Statistical Modeling of Aging and Risk of Transition (SMART) project database [14], analyzing longitudinal clinical data and neuropathologic outcomes of individuals from four Alzheimer's Disease Centers (ADCs). The inclusion of multiple large autopsy cohorts with longitudinal follow-up provides the basis for a study of neuropathologic correlates of MCI among adults who died in old age.

METHODS

Subjects

Cases were drawn from the SMART database, a harmonized set of data elements drawn from 11 longitudinal studies of aging and cognition [14]. Based on availability of necessary variables, the following cohorts were included: Oregon Brain Aging Study [15], African American Dementia Project (see [14]), Klamath Exceptional Aging Project [16], Religious Orders Study [17], Rush Memory and Aging Project [18], Memory and Aging Project at Washington University [19], and Biologically Resilient Adults in Neurological Studies [20]. A total of 1,657 autopsies were initially available. Inclusion criteria for the current study were available autopsy data and a cognitive diagnosis (i.e., clinical assessment) within two years of death (this excluded 165 cases). Participants with dementia at study baseline, or who transitioned to dementia without an intervening MCI diagnosis, were also excluded (n=155). Individuals who died with final clinical diagnoses of intact cognition, MCI, or dementia were included. The included cohorts all originated from National Institute on Aging-funded ADCs. Research procedures were approved by Institutional Review Boards at each cohort's home institution. All participants provided written informed consent.

MCI and dementia classification

To operationalize MCI over multiple research centers, an MCI designation indicated a clinical diagnosis of MCI (if available) or Clinical Dementia Rating (CDR) global score = 0.5 [21]. Participants with a CDR global score of 0.5 often have AD pathology at autopsy regardless of subsequent CDR global scores of 0 [22]. Back transitions (e.g., a diagnosis of MCI followed by subsequent diagnosis of intact cognition) may be explained by many factors including inter-clinician differences in application of diagnostic criteria, within-patient variability due to medical illness, polypharmacy, psychosocial factors, and/or

resistance to cognitive decline due to cognitive reserve [7,23]. Study participants were classified into four groups: 1) never diagnosed with MCI or dementia ("No Impairment"); 2) diagnosed with MCI but diagnosed with normal cognition at the last assessment before death ("MCI Reverters"); and 3) diagnosed with MCI and remained MCI until death ("Stable MCI"), and 4) diagnosed with MCI followed by subsequent diagnosis of dementia ("Dementia after MCI"). Centers used standard-at-the-time criteria for diagnoses of all-cause dementia [24] and clinical AD [25].

Neuropathological classification

Autopsies were conducted within the original cohort studies [15,19,20,26]. Neuropathological assessments were performed blind to clinical data, and neuropathological data were scored according to a format of the National Alzheimer's Coordinating Center (NACC) dataset, as described previously [14], because most SMART neuropathologists contribute to NACC (see https://www.alz.washington.edu/NONMEMBER/NP/rdd_np.pdf). Briefly, study neuropathologists made determinations of Braak NFT stage [27]; CERAD neuritic plaque rating [28]; HS-Aging [10]; presence of neocortical Lewy body disease [29]; arteriolosclerosis rating [12]; cerebral amyloid angiopathy (CAA) rating [30]; presence of large artery cerebral infarcts, lacunes, cortical microinfarcts, and hemorrhages. For comparisons that would be correlated with biomarkers that assess A® amyloidosis (as opposed to SNAP), CERAD neuritic amyloid plaque rating was used. PART was operationalized as CERAD neuritic plaque rating of None plus Braak NFT stage of I-IV [12]. "Large" infarcts were defined as any infarct with maximum diameter greater than 1 cm; lacunes were defined as infarcts or hemorrhages 1 cm or less in diameter in the small parenchymal vessels, but visible to the naked eye; and, microinfarcts were defined as cortical infarcts detected microscopically only.

For comparisons of broader pathological profiles related to AD, we classified cases into three groups of amyloid determined pathologies based on the National Institute on Aging-Alzheimer's Association criteria for AD neuropathologic changes (ADNC). Applying these criteria, the presence of any diffuse plaque or any CERAD neuritic plaque of at least sparse results in a classification of at least low level ADNC [31]: Pure ADNC = ADNC of at least low plus the absence of any cerebrovascular pathology other than mild arteriolosclerosis, neocortical Lewy body pathology, HS-Aging, or PART; Mixed ADNC = ADNC of at least low plus the presence of any cerebrovascular pathology other than mild arteriolosclerosis, neocortical Lewy body pathology, HS-Aging, or PART; and pathologies that relate to the biomarker-defined entity of SNAP [32] = no diffuse plaques plus CERAD neuritic plaque rating of None, with or without any comorbid pathologies. We did not include CAA in these group classifications since CAA is not part of ADNC or PART consensus-based criteria, and it is currently unclear how CAA relates to neurodegeneration.

Statistical analysis

Participant characteristics and neuropathological outcomes were summarized using descriptive statistics within each group. Group demographic differences were assessed with analysis of variance (ANOVA) or chi-square tests. Adjusted between-group differences on neuropathological outcomes were assessed using binary or multinomial logistic regression

models. Covariates were age at death, sex, *APOE* (any ε4 vs. no ε4), years of education, survival time following MCI diagnosis, time between the last assessment and death, and research center. Since over 97% of the study sample was white, race was not considered as a covariate. Survival time was defined as the duration in years between the first diagnosis of MCI and either death or dementia, whichever came first.

To assess whether the survival time following an MCI diagnosis was associated with pathology type, participants in the Stable MCI and Dementia after MCI groups were divided into mutually exclusive major neurodegenerative disease and no major neurodegenerative disease groups. Cases with high level of ADNC (CERAD Moderate or Frequent plaques and Braak NFT stages V/VI), HS-Aging, or Lewy body disease were classified into the major neurodegeneration group, while all others were classified into the no major neurodegeneration group. To account for differences in observed survival times in prevalent vs. incident MCI, we included an indicator for baseline MCI in addition to the covariates listed above. Stable MCI and Dementia after MCI were analyzed separately.

RESULTS

Inclusion criteria yielded data from 1,337 autopsied subjects, stratified into four groups: No Impairment (N=463), MCI Reverters (N=122), Stable MCI (N=343), and Dementia after MCI (N=409). Participant characteristics are given in Table 1. Baseline age was significantly different in all groups ($p<0.0001$ for all pairwise comparisons except MCI Reverters vs. Stable MCI, where $p=0.049$). Mean age at death was greater than 85 years in all groups, but there were differences: the No Impairment group was significantly younger than any other group ($p<0.0001$ for all), and the Dementia after MCI group was significantly older than any other group ($p<0.001$ for all). There was no difference in age at death between the MCI Reverters and Stable MCI groups (Table 1). About 60% of the No Impairment and both MCI groups were female, compared to 67% in the dementia group ($p=0.10$). Mean educational attainment was similar in the groups and high overall in this sample (approximately 16 years), but the MCI Reverters had a significantly higher education level than the No Impairment ($p=0.02$) and Stable MCI groups ($p=0.004$). Frequency of *APOE*-ε4 was significantly higher in the Stable MCI and Dementia after MCI groups compared to the No Impairment and MCI Reverters groups ($p<0.0001$). Approximately one-third of participants in both the MCI Reverters and Stable MCI groups were diagnosed with MCI at the baseline visit, while over 44% of participants in the Dementia after MCI group carried a baseline MCI diagnosis ($p=0.003$). Time on study was similar between the MCI Reverters and Dementia after MCI groups, but the No Impairment and Stable MCI groups were followed about 2 and 1.5 fewer years, respectively, than the Dementia after MCI group ($p<0.0001$). Time between last clinical assessment and death was restricted to less than or equal to two years; the mean time was less than one year in all groups, and was shorter for the Dementia after MCI group relative to the No Impairment ($p<0.001$), MCI Reverters ($p=0.005$), and Stable MCI ($p<0.001$) groups. The largest absolute difference translated to about one month. Mean time between annual assessments was just over one year in all groups with no significant differences. Mean final MMSE was the same between the No Impairment and MCI Reverters groups ($p=0.83$) and significantly different for all other pairwise comparisons

(p<0.0001). There were no significant differences in time between groups for the first diagnosis of MCI and dementia or death (p=0.27).

Distributions of neuropathological features are presented in Table 2. Adjusted odds ratios (OR) and 95% confidence intervals (95% CI) for MCI Reverters vs. No Impairment, Stable MCI, and Dementia after MCI are presented in Table 3. Confidence intervals that do not include 1.00 are statistically significant. Compared to the No Impairment group, MCI Reverters were only significantly more likely to have CERAD neuritic plaque ratings of Frequent. Compared to the Stable MCI group, MCI Reverters were significantly less likely to have Braak NFT stages of V/VI and moderate arteriolosclerosis. Compared to the Dementia after MCI group, the MCI Reverters were significantly less likely to have Braak NFT stages of V/VI, CERAD ratings of Moderate or Frequent, Lewy body disease, HS-Aging, and moderate arteriolosclerosis.

Adjusted OR and 95% CI for Stable MCI vs. No Impairment and Dementia after MCI are presented in Table 4. Compared to the No Impairment group, the Stable MCI group was significantly more likely to have Braak NFT stages of V/VI, CERAD ratings or moderate or frequent, PART, Lewy body disease, and severe arteriolosclerosis. Compared to the Dementia after MCI group, the Stable MCI group was significantly less likely to have Braak NFT stages of V/VI, CERAD ratings of Moderate or Frequent, Lewy body disease, and HS-Aging.

There was substantial heterogeneity of amyloid plaque pathology in the impaired groups (Figure 1). SNAP-type pathology was twice as common in the MCI Reverters and Stable MCI groups as in the Dementia after MCI group (~22% vs. 9%, p<0.0001). Pure ADNC was relatively constant across the groups, ranging from 17% in the Dementia after MCI group to 24% in the MCI Reverters group (p=0.10), while Mixed ADNC was highest in the Dementia after MCI group (73%) and lowest in the MCI Reverters group (51%) (p<0.0001). Higher proportion of Braak NFT stage V/VI was associated with Dementia after MCI. Distributions of non-amyloid pathologies within the SNAP and Mixed ADNC categories are characterized in Table 5. For MCI Reverters, SNAP mostly comprised PART (43%) and PART plus cerebrovascular disease (CVD) (39.3%) pathologies. In the Stable MCI group PART plus CVD (73%) was the most common SNAP pathology, followed by PART alone (15%). In the Dementia after MCI group, PART plus CVD (60%) was again the most common SNAP pathology, followed by PART plus HS-Aging plus CVD (11%). For Mixed ADNC, ADNC plus CVD was the most commonly observed pathology type in all three groups: MCI Reverters (74%), Stable MCI (73%), and Dementia after MCI (62%).

Time elapsed between first diagnosis of MCI and death did not predict neurodegenerative vs. non-neurodegenerative pathology in the Stable MCI group (for a 1-year difference, OR=0.97, 95% CI 0.90–1.04). However, for the Dementia after MCI group, longer time in MCI (i.e., time between first diagnosis of MCI and first diagnosis of dementia) was associated with non-neurodegenerative pathologies (for a 1-year difference, OR=1.09, 95% CI 1.01–1.17).

DISCUSSION

Here we report on a large series of autopsied research volunteers after extensive longitudinal clinical follow-up, focusing on outcomes after the first or only diagnosis of MCI. The study design enabled assessment of the distribution of neuropathological findings, the variability of progression through the clinical state of MCI, and the interactions among these factors. In this combined sample, only 22% of individuals who died with MCI (i.e., Stable MCI) had neuropathologic evidence of "pure" AD-type pathology. Importantly, we found novel and solid evidence that both severe arteriolosclerosis and PART pathologies are associated with a clinical MCI diagnosis. A second novel finding was that persons with MCI of longer duration, prior to dementia diagnosis, tended to have a profile of pathology more skewed toward cerebrovascular than neurodegenerative-type pathologies.

The themes that emerge from the interpretation of these results relate to the heterogeneous diseases that underlie MCI diagnoses, and the correspondingly varied clinical course of those diseases. The neuropathology of MCI has been addressed in prior studies that established that MCI is not necessarily a result of AD pathology in a given patient [8,10,33–35]. However, this large autopsy series provides further direct evidence of disease heterogeneity underlying MCI: over half of the individuals who died with MCI had "mixed" pathologies with ADNC and other conditions, primarily CVD; 22% had non-AD conditions that would correspond to the concept of SNAP, similar to the 23% of participants with subtle cognitive change and who had neuropathology data in a prior study [36]; and only 22% of the cohort who died with MCI diagnoses had what could be described as "Pure ADNC".

Persons with relatively severe PART (i.e., Braak NFT stages III-IV) were more likely to be diagnosed with MCI than they were to remain cognitively intact until death. Almost every elderly individual has some hippocampal NFTs, with or without other AD pathology [12]. However, among cases lacking cerebral neuritic plaques, there is variability in the NFT burden, i.e. severity of PART. In the first PART paper, we found that advanced PART (Braak NFT stages III-IV) was associated with worse cognition [11]. In the current study we now establish that PART is a common pathologic substrate for MCI. However, neuritic plaques (CERAD rating) were used to help operationalize PART, so we note that this would mean we are often describing "Possible" PART, rather than "Definite" PART according to the pathologic diagnostic criteria [12]. Further, it is not known how PART contributes to the clinical, biomarker-defined, phenomenon of SNAP, so more work is required at the interface of cognitive assessment, neuroimaging, cerebrospinal fluid analyses, and pathology.

The current study also suggests the importance of moderate to severe brain arteriolosclerosis in contributing to the transition from cognitively normal to MCI. Moderate arteriolosclerosis was more common among participants with Stable MCI and Dementia than among participants in the MCI Reverters group. Severe arteriolosclerosis was more common in the Stable MCI group compared to the No Impairment group, but the wide confidence interval for that result suggests the need for cautious interpretation. Previously, autopsy-confirmed severe brain arteriolosclerosis was shown to be associated with impaired global cognition [12,37]. Taken together, these findings indicate that small vessel changes may have an important impact in terms of cognitive status. We did not find strong evidence in the current

study that CAA was associated with transition to or from MCI when comorbid ADNC (plaques and tangles) were included in the statistical model.

In addition to cross-sectional analyses of the autopsy data, the long-term longitudinal data on these research subjects enabled characterization of differences in clinical course through MCI among individuals with and without neurodegenerative diseases (the latter comprising high level ADNC, Lewy body disease, and HS-Aging). Although these conditions are what most people would consider to be associated with MCI, a large majority of cases in the Stable MCI group (74%) lacked severe levels of these pathologies. Among those who progressed to dementia, those without high level ADNC, Lewy body disease, or HS-Aging tended to progress more slowly, with each additional year without a dementia diagnosis being associated with 9% increase in the odds that no severe burden of neurodegenerative disease pathologies would be observed at autopsy. This translates to a 54% increase in the odds of no severe neurodegenerative pathologies when the time between MCI and dementia diagnoses is 5 years. There have long been indications in the literature of a subgroup of MCI cases that does not progress to dementia [3], and cerebrovascular factors may help explain this phenomenon which is probably of interest to patients, clinicians, and clinical trial researchers.

The nature of the research sample and study design—combining results of autopsied subjects from multiple institutions—entailed both strengths and weaknesses. A key strength is the many subjects who were followed from normal cognition, and the large number of longitudinal visits for most subjects. However, there are basic challenges in recruitment bias for any sample of autopsied subjects. These include a relative lack of minority and other at-risk populations. This autopsy series included mostly highly educated white females. We also note that the ages of the persons studied needs to be considered. A younger, more ethnically, racially, and socioeconomically diverse cohort would probably have different neuropathologic and clinical features. As we were not able to characterize MCI into amnestic vs. non-amnestic type, or single vs. multi-domain diagnoses, neuropathological underpinnings for different types of MCI diagnoses could not be assessed. Additionally, there is likely to be selection bias within each cohort in terms of who does and does not come to autopsy. There are some analytical methods for adjusting for this type of selection bias, such as inverse probability weighting [38]. Inverse probability weighting creates a pseudo-population by giving more weight to autopsied participants who were least likely to be autopsied, and less weight to participants who were most likely to be autopsied. We explored using inverse probability of autopsy weights to adjust for selection bias, but center effects and small cell sizes for some pathologies, such as severe arteriolosclerosis, led to unstable results. Thus, we present the weighted analyses in Supplemental Tables 1 and 2. We note that results were generally in the same direction in the both the unweighted and weighted analyses, and exceptions were mostly limited to the MCI Reverters analysis, which had the smallest sample size. The weighted analyses suggests a stronger association between MCI and both arteriolosclerosis and CAA than was observed in the unweighted analyses. Further study into the association between these two pathologies and MCI is warranted.

Additionally, the stage of MCI (e.g., early or late) at first diagnosis likely varied among participants, particularly given the mixture of clinical diagnosis and CDR ratings that made

up our case operationalizations. This has implications for the expected survival time in MCI [4,5]. However, prior research has demonstrated that individuals with any instances of CDR = 0.5 show increased AD-type neuropathological burden at autopsy [21], suggesting that these classifications are indicative of underlying disease. Further, classification of the clinical state was independent of autopsy findings, which suggests that bias due to misclassification would be nondifferential.

Additionally, while we had an emphasis on including state-of-the-art neuropathologic assessment data, we did not include TDP-43 or argyrophilic grain disease (AGD) pathologies in the study due to inadequate collection and harmonization across centers. Since both TDP-43 and AGD pathologies have been shown to be associated with cognitive status [39–41], this probably led to insensitivity in parsing out causes of SNAP and delineating all the cases with “neurodegenerative conditions.” Moreover, the term “SNAP” was developed in the biomarker field, and as such, while it can be generalized to neuropathology, issues such as thresholds and cutoffs would be different, for example, in neuropathological cases versus subjects in imaging studies. This study also combined autopsied cases assessed by multiple neuropathologists, who had different methods and criteria for classifying neuropathology. However, this approach may better approximate the experience of community neuropathologists in comparison to an approach that employs only a single academic neuropathologist. Interrater variability also applies to the MCI diagnosis, which was done by different clinicians at different centers. Although we controlled for center in our analyses, there is likely to be additional variation that was not captured with this approach. A further implication of diagnostic variability is that the group of subjects diagnosed previously with MCI but who were diagnosed with intact cognition at the time of death should not be taken to be representative of all other patients carrying an MCI diagnosis. The true proportion of MCI diagnoses that would permanently revert to intact cognition is unknown.

We conclude that MCI is a clinical state that has heterogeneous underlying pathologies with a clinical course that varies according to those pathologies and likely also varies according to participant characteristics. Not only are different diseases linked to MCI, but, more often than not, the clinical condition reflects the impact of multiple brain diseases. These data highlight the complexity of brain changes in old age, and the importance of better biomarkers to help characterize the combination of mechanisms that underlie a given patient’s cognitive impairment.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

We are grateful to our participants and their families. We thank Robin Guariglia, Elizabeth Washington, and John Gibbons for their assistance in preparing the SMART data. SMART is supported by NIA grant R01-AG038651 (R. Kryscio and F. Schmitt co-PIs). Cohort studies were supported by NIA grants P30-AG10161 and R01-AG15819 (ROS), R01-AG17917 (Rush MAP), P30-AG028383 (BRAiNS/UK-ADC), P50-AG005681 (Wash U MAP), P30-AG008017 (OBAS, KEAP, AADAPt). Additional support came from R01 NS014189.

References

1. Petersen RC. Mild cognitive impairment as a diagnostic entity. J Int Med. 2004; 256:183–194.
2. Roberts R, Knopman DS. Classification and epidemiology of MCI. Clin Geriatr Med. 2013; 29:753–72. [PubMed: 24094295]
3. Mitchell AJ, Shiri-Feski M. Rate of progression of mild cognitive impairment to dementia – meta-analysis of 41 robust inception cohort studies. Acta Psychiatr Scand. 2009; 119:252–265. [PubMed: 19236314]
4. Abner EL, Kryscio RJ, Cooper GE, et al. Mild cognitive impairment: Statistical models of transition. Int J Alzheimer's Dis. 2012 doi:2012:291920.
5. Kryscio RJ, Abner EL, Lin Y, et al. Adjusting for mortality when identifying risk factors for transitions to mild cognitive impairment and dementia. J Alz Dis. 2013; 35:823–32.
6. Knopman DS, Jack DR Jr, Wiste HJ, et al. Brain injury biomarkers are not dependent on β-amyloid in normal elderly. Ann Neurol. 2013; 73:472–480. [PubMed: 23424032]
7. Jicha GA, Abner E, Schmitt FA, et al. Clinical features of mild cognitive impairment differ in the research and tertiary clinic settings. Dement Geriatr Cogn Disord. 2008; 26:187–192. [PubMed: 18724049]
8. Jicha GA, Parisi JE, Dickson DW, et al. Neuropathologic outcome of mild cognitive impairment following progression to clinical dementia. Arch Neurol. 2006; 63:674–681. [PubMed: 16682537]
9. Petersen RC, Aisen P, Boeve BF, et al. Criteria for mild cognitive impairment due to Alzheimer's disease in the community. Ann Neurol. 2013; 74:199–208. [PubMed: 23686697]
10. Schneider JA, Arvanitakis Z, Leurgans SE, Bennett DA. The neuropathology of probable Alzheimer disease and mild cognitive impairment. Ann Neurol. 2009; 66:200–208. [PubMed: 19743450]
11. Nelson PT, Schmitt FA, Lin Y, et al. Hippocampal sclerosis in advanced age: clinical and pathological features. Brain. 2011; 134:1506–1518. [PubMed: 21596774]
12. Crary JF, Trojanowski JQ, Schneider JA, et al. Primary age-related tauopathy (PART): a common pathology associated with human aging. Acta Neuropathol. 2014; 128:755–766. [PubMed: 25348064]
13. Ighodaro ET, Abner EL, Fardo DW, et al. Risk factors and global cognitive status related to brain arteriolosclerosis in elderly individuals. J Cereb Blood Flow Metab. 2016; doi: 10.1177/0271678X15621574
14. Abner EL, Schmitt FA, Nelson PT, et al. The Statistical Modeling of Aging and Risk of Transition Project: Data Collection and Harmonization Across 11 Longitudinal Cohort Studies of Aging, Cognition, and Dementia. Observational Studies. 2015; 1:56–73. [PubMed: 25984574]
15. Green MS, Kaye JA, Ball MJ. The Oregon Brain Aging Study: Neuropathology accompanying healthy aging in the oldest old. Neurology. 2000; 54:105–113. [PubMed: 10636134]
16. Kaye J, Michael Y, Calvert J, et al. Exceptional brain aging in a rural population-based cohort. J Rural Health. 2009; 25:320–325. [PubMed: 19566620]
17. Bennett DA, Wilson RS, Schneider JA, et al. Natural history of mild cognitive impairment in older persons. Neurology. 2002; 59:198–205. [PubMed: 12136057]
18. Bennett DA, Schneider JA, Buchman AS, et al. The Rush Memory and Aging Project: Study design and baseline characteristics of the study cohort. Neuroepidemiology. 2005; 25:163–175. [PubMed: 16103727]
19. Berg L, McKeel DW, Miller JP, et al. Clinicopathologic studies in cognitively healthy aging and Alzheimer's disease. Relation of histologic markers to dementia severity, age, sex, and apolipoprotein E genotype. Arch Neurol. 1998; 55:326–335. [PubMed: 9520006]
20. Schmitt FA, Nelson PT, Abner E, et al. University of Kentucky Sanders-Brown Health Brain Aging Volunteers: Donor characteristics, procedures, and neuropathology. Curr Alzheimer Res. 2012; 9:724–733. [PubMed: 22471862]
21. Morris JC, Storandt M, Millller JP, et al. Mild cognitive impairment represents early-stage Alzheimer disease. Arch Neurol. 2001; 58:397–405. [PubMed: 11255443]

22. Morris JC, Fulling K. Early Alzheimer's disease. Diagnostic considerations. Arch Neurol. 1988; 45:345–349. [PubMed: 3341960]
23. Stern Y. The concept of cognitive reserve: a catalyst for research. J Clin Exp Neuropsychol. 2003; 25:589–93. [PubMed: 12815497]
24. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. Fourth. Washington, DC: American Psychiatric Association; 1994.
25. McKhann G, Drachman D, Folstin M, et al. Clinical diagnosis of Alzheimer's disease: Report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. Neurology. 1984; 34:939–944. [PubMed: 6610841]
26. Schneider JA, Wilson RS, Bienias JL, et al. Cerebral infarctions and the likelihood of dementia from Alzheimer disease pathology. Neurology. 2004; 62:1148–55. [PubMed: 15079015]
27. Braak H, Braak E. Neuropathological stageing of Alzheimer-related changes. Acta Neuropathol. 1991; 82:239–259. [PubMed: 1759558]
28. Mirra SS, Heyman A, McKeel D, et al. The Consortium to Establish a Registry for Alzheimer's Disease (CERAD). Part II. Standardization of the neuropathologic assessment of Alzheimer's disease. Neurology. 1991; 41:479–486. [PubMed: 2011243]
29. McKeith LG, Dickson DW, Lowe J, et al. Diagnosis and management of dementia with Lewy bodies. Third report of the DLB consortium. Neurology. 2005; 65:1863–1872. [PubMed: 16237129]
30. Brenowitz WD, Nelson PT, Besser LM, Heller KB, Kukull WA. Cerebral amyloid angiopathy and its co-occurrence with Alzheimer's disease and other cerebrovascular neuropathologic changes. Neurobiol Aging. 2015; 36:2702–8. [PubMed: 26239176]
31. Montine TJ, Phelps CH, Beach TG, et al. National Institute on Aging-Alzheimer's Association guidelines for the neuropathological assessment of Alzheimer's disease: a practical approach. Acta Neuropathol. 2012; 123:1–11. [PubMed: 22101365]
32. Jack CR, Knopman DS, Chételat G, et al. Suspected non-Alzheimer disease pathophysiology—concept and controversy. Nat Rev Neurol. 2016; 12:117–124. [PubMed: 26782335]
33. Markesbery WR, Schmitt FA, Kryscio RJ, et al. Neuropathologic substrate of mild cognitive impairment. Arch Neurol. 2006; 63:38–46. [PubMed: 16401735]
34. Storandt M, Grant EA, Miller JP, Morric JC. Longitudinal course and neuropathologic outcomes in original vs revised MCI and in pre-MCI. Neurology. 2006; 67:467–473. [PubMed: 16894109]
35. Dugger BN, Davis K, Malek-Ahmadi M, et al. Neuropathological comparisons of amnestic and nonamnestic mild cognitive impairment. BMC Neurology. 2015; 15:146. [PubMed: 26289075]
36. Vos SJ, Xiong C, Visser PJ, et al. Preclinical Alzheimer's disease and its outcome: a longitudinal cohort study. Lancet Neurol. 2013; 12:957–965. [PubMed: 24012374]
37. Arvanitakis Z, Capuano AW, Leurgans SE, et al. Relation of cerebral vessel disease to Alzheimer's disease dementia and cognitive function in elderly people: a cross-sectional study. Lancet Neurol. 2016; doi: 10.1016/S1474-4422(16)30029-1
38. Haneuse S, Schildcrout J, Crane P, et al. Adjustment for selection bias in observational studies with application to the analysis of autopsy data. Neuroepidemiolgy. 2009; 32:229–239.
39. Nelson PT, Abner EL, Schmitt FA, et al. Modelling the association between 43 different clinical and pathological variables and the severity of cognitive impairment in a large autopsy cohort of elderly persons. Brain Pathol. 2010; 10:66–79.
40. Nag S, Yu L, Capuano AW, et al. Hippocampal sclerosis and TDP-43 pathology in aging and Alzheimer disease. Ann Neurol. 2015; 77:942–52. [PubMed: 25707479]
41. Jicha GA, Petersen RC, Knopman DS, et al. Argyrophilic grain disease in demented subjects presenting initially with amnestic mild cognitive impairment. J Neuropathol Exp Neurol. 2006; 65:602–609. [PubMed: 16783170]

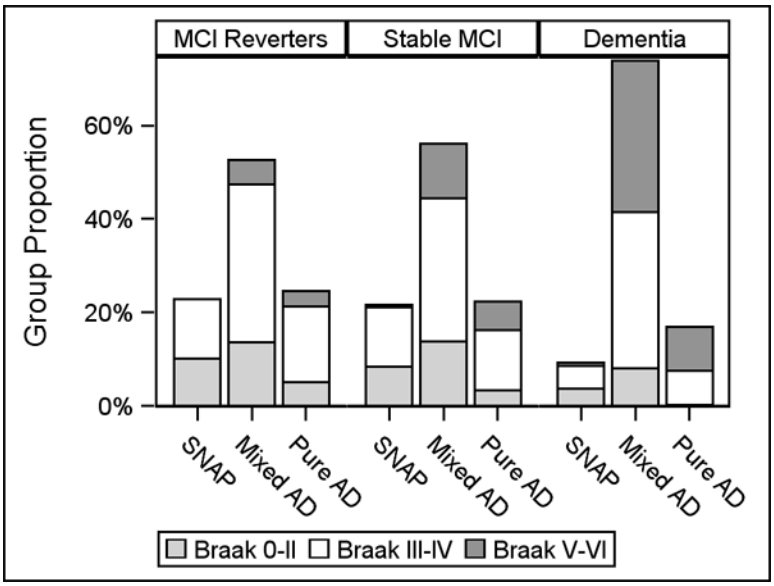

Figure 1.

Distribution of major pathology types among participants who died after MCI diagnosis. SNAP = suspected non-Alzheimer's pathology, ADNC = Alzheimer's disease neuropathologic changes.

Table 1

Participant characteristics by diagnosis group

Characteristics	No Impairment (N=463)	MCI Reverters (N=122)	Stable MCI (N=343)	Dementia after MCI (N=409)
Baseline age, y	79.1±7.8	84.2±6.6	85.7±7.1	82.5±6.7
Age at death, y	85.9±7.3	89.2±6.2	89.5±6.6	91.5±6.1
Female (n %)	281 (60.7)	72 (59.0)	205 (60.0)	275 (67.2)
Education, y	15.8±3.4	16.6±3.5	15.6±3.7	16.1±3.5
APOE, ≥ 1 ε4 (n %)	76 (16.4)	21 (17.2)	76 (22.2)	128 (31.3)
Baseline diagnosis (n %)				
Intact cognition	463 (100)	86 (70.5)	221 (64.4)	228 (55.8)
MCI	0 (0)	36 (29.5)	122 (35.6)	181 (44.3)
Time on study, y	6.9±4.7	8.9±4.5	7.5±4.5	9.0±4.2
Time from last diagnosis to death, y	0.7±0.4	0.7±.04	0.7±0.4	0.6±0.4
Time between clinical assessments, y	1.05±0.27	1.05±0.37	1.05±0.39	1.05±0.32
Final MMSE[a]	28.0±2.0	27.9±1.7	25.7±3.3	14.3±8.1
Median MCI Duration Time[b], y (IQR)	–	5.1 (1.9, 9.3)	4.4 (1.7, 9.3)	4.1 (2.1, 8.1)

Note: results are mean±sd unless otherwise noted.

[a]MMSE score is last score reported within two years of death (Normal: n=423; MCI Reverters: n=112; Stable MCI: n=300; Dementia after MCI: n=349);

[b]duration time is time from first MCI diagnosis to either first dementia diagnosis (Dementia after MCI) or death (MCI Reverters and Stable MCI).

Table 2

Neuropathological characteristics by diagnosis group

Characteristics	No Impairment (N=463)	MCI Reverters (N=122)	Stable MCI (N=343)	Dementia after MCI (N=409)
Braak NFT stage				
0/I/II	202 (43.6)	34 (27.9)	85 (24.8)	48 (11.7)
III/IV	195 (42.1)	74 (60.7)	187 (54.5)	183 (44.7)
V/VI	22 (4.8)	10 (8.2)	61 (17.8)	171 (41.8)
CERAD neuritic plaque rating				
None	196 (42.3)	40 (32.8)	93 (27.1)	48 (11.7)
Sparse	76 (16.4)	19 (15.6)	57 (16.6)	44 (10.8)
Moderate	125 (27.0)	36 (29.5)	128 (37.3)	135 (33.0)
Frequent	52 (11.2)	24 (19.7)	58 (16.9)	177 (43.3)
PART[a]				
Braak NFT I/II	116 (65.9)	19 (48.7)	39 (43.8)	19 (44.2)
Braak NFT III/IV	60 (34.1)	20 (51.3)	50 (56.2)	24 (55.8)
Lewy body disease	18 (3.9)	6 (4.9)	25 (7.3)	66 (16.1)
Hippocampal sclerosis of aging	12 (2.6)	7 (5.7)	18 (5.3)	66 (16.1)
Large artery infarct	70 (15.1)	20 (16.4)	59 (17.2)	97 (23.7)
Lacunar infarct	130 (28.1)	40 (32.8)	117 (34.1)	159 (38.9)
Microinfarct	96 (20.7)	22 (18.0)	78 (22.7)	104 (25.4)
Hemorrhage	56 (12.1)	10 (8.2)	30 (8.8)	26 (6.4)
Arteriolosclerosis				
None	137 (29.6)	13 (10.7)	31 (9.0)	27 (6.6)
Mild	197 (42.6)	60 (49.2)	134 (39.1)	173 (42.3)
Moderate	82 (17.7)	31 (25.4)	128 (37.3)	142 (34.7)
Severe	8 (1.7)	4 (3.3)	25 (7.3)	33 (8.1)
Cerebral amyloid angiopathy				
None	179 (38.7)	29 (23.8)	115 (33.5)	88 (21.5)
Mild	151 (32.6)	53 (43.4)	130 (37.9)	145 (35.5)
Moderate	71 (15.3)	27 (22.1)	49 (14.3)	100 (24.5)
Severe	32 (6.9)	7 (5.7)	31 (9.0)	62 (15.2)

[a]PART = primary age-related tauopathy. PART cases are CERAD None.

Table 3

Comparison of neuropathological features between participants who were diagnosed with MCI and but later died with a diagnosis of intact cognition ("MCI Reverters"), participants with no diagnosed cognitive impairment ("No Impairment"), participants who were diagnosed with MCI and remained MCI until death ("Stable MCI"), and participants who were diagnosed with MCI and later developed dementia ("Dementia after MCI").

Characteristics	MCI Reverters vs. No Impairment OR (95% CI)[a]	MCI Reverters vs. Stable MCI OR (95% CI)[a]	MCI Reverters vs. Dementia after MCI OR (95% CI)[a]
Braak NFT stage			
0/I/II	ref	ref	ref
III/IV	1.37 (0.57, 3.30)	0.89 (0.52, 1.52)	0.57 (0.30, 1.08)
V/VI	1.24 (0.20, 7.84)	**0.31 (0.12, 0.78)**	**0.08 (0.03, 0.20)**
CERAD neuritic plaque rating			
None	ref	ref	ref
Sparse	1.86 (0.63, 5.55)	0.99 (0.50, 1.98)	0.64 (0.28, 1.50)
Moderate	2.21 (0.83, 5.86)	0.74 (0.41, 1.33)	**0.40 (0.21, 0.76)**
Frequent	**4.33 (1.29, 14.53)**	1.08 (0.53, 2.21)	**0.18 (0.09, 0.38)**
PART[b]			
Braak NFT I/II	ref	ref	ref
Braak NFT III/IV	1.17 (0.31, 4.42)	0.84 (0.36, 1.95)	1.05 (0.32, 3.44)
Lewy body disease	0.93 (0.10, 8.98)	0.30 (0.08, 1.08)	**0.13 (0.04, 0.43)**
Hippocampal sclerosis of aging	0.40 (0.06, 2.48)	1.42 (0.54, 3.72)	**0.35 (0.15, 0.81)**
Large artery infarct	0.70 (0.25, 1.94)	0.97 (0.53, 1.76)	0.65 (0.37, 1.17)
Lacunar infarct	0.84 (0.38, 1.86)	0.89 (0.56, 1.42)	0.77 (0.48, 1.22)
Microinfarct	0.77 (0.29, 2.05)	0.85 (0.49, 1.49)	0.71 (0.41, 1.24)
Hemorrhage	0.50 (0.13, 1.91)	0.92 (0.41, 2.07)	1.22 (0.52, 2.90)
Arteriolosclerosis			
None	ref	ref	ref
Mild	0.75 (0.21, 2.67)	1.05 (0.44, 2.52)	0.68 (0.29, 1.63)
Moderate	0.25 (0.05, 1.18)	**0.29 (0.10, 0.80)**	**0.30 (0.11, 0.84)**
Severe	1.29 (0.05, 32.99)	0.24 (0.03, 2.09)	0.18 (0.03, 1.02)
Cerebral amyloid angiopathy[c]			
None	ref	ref	ref
Mild	1.02 (0.39, 2.70)	1.77 (0.96, 3.28)	1.74 (0.88, 3.44)
Moderate	2.20 (0.58, 8.31)	2.37 (0.99, 5.69)	2.35 (0.95, 5.80)
Severe	0.26 (0.02, 2.83)	0.86 (0.26, 2.82)	0.50 (0.15, 1.65)

Note:

[a] Odds ratios are adjusted for age at death, sex, years of education, *APOE*, time in the MCI state prior to dementia or death, time between last assessment and death, and research center;

[b] PART = primary age-related tauopathy. PART cases are CERAD None.

[c] Odds ratios for Cerebral amyloid angiopathy are also adjusted for Braak NFT stage and CERAD neuritic plaque rating.

Table 4

Comparison of neuropathological features between participants who were diagnosed with MCI and remained MCI until death ("Stable MCI"), participants with no diagnosed cognitive impairment ("No Impairment"), and participants who were diagnosed with MCI and later developed dementia ("Dementia after MCI").

Characteristics	Stable MCI vs. No Impairment OR (95% CI)[a]	Stable MCI vs. Dementia after MCI OR (95% CI)[a]
Braak NFT stage		
0/I/II	ref	ref
III/IV	1.53 (0.93, 2.53)	0.77 (0.49, 1.21)
V/VI	**5.20 (2.41, 11.23)**	**0.24 (0.14, 0.41)**
CERAD neuritic plaque rating		
None	ref	ref
Sparse	1.49 (0.77, 2.87)	0.85 (0.47, 1.54)
Moderate	**2.75 (1.61, 4.68)**	**0.62 (0.39, 0.98)**
Frequent	**2.08 (1.00, 4.32)**	**0.17 (0.10, 0.29)**
PART[b]		
Braak NFT I/II	ref	ref
Braak NFT III/IV	**2.33 (1.01, 5.40)**	1.52 (0.64, 3.61)
Lewy body disease	**2.40 (1.00, 5.73)**	**0.39 (0.24, 0.66)**
Hippocampal sclerosis of aging	1.76 (0.64, 4.88)	**0.31 (0.18, 0.55)**
Large artery infarct	1.05 (0.61, 1.82)	0.75 (0.51, 1.10)
Lacunar infarct	1.17 (0.76, 1.80)	0.84 (0.61, 1.17)
Microinfarct	1.01 (0.61, 1.68)	0.77 (0.53, 1.12)
Hemorrhage	1.14 (0.59, 2.19)	1.47 (0.82, 2.65)
Arteriolosclerosis		
None	ref	ref
Mild	0.74 (0.36, 1.51)	0.80 (0.41, 1.55)
Moderate	1.00 (0.44, 2.29)	0.72 (0.36, 1.40)
Severe	**7.36 (1.62, 33.49)**	0.23 (0.06, 0.92)
Cerebral amyloid angiopathy[c]		
None	ref	ref
Mild	0.78 (0.45, 1.34)	0.97 (0.61, 1.54)
Moderate	0.59 (0.27, 1.31)	0.89 (0.49, 1.64)
Severe	1.10 (0.42, 2.87)	0.59 (0.29, 1.20)

Note:

[a] Odds ratios are adjusted for age at death, sex, years of education, *APOE*, time in the MCI state prior to dementia or death, time between last assessment and death, and research center;

[b] PART = primary age-related tauopathy. PART cases are CERAD None.

[c] Odds ratios for Cerebral amyloid angiopathy are also adjusted for Braak NFT stage and CERAD neuritic plaque rating.

Table 5

Distribution of non-Alzheimer pathologies within SNAP and Mixed ADNC groups

SNAP	MCI Reverters (n=28)	Stable MCI (n=74)	Dementia after MCI (n=37)
PART	12 (42.9)	11 (14.9)	2 (5.4)
CVD	1 (3.6)	3 (4.1)	3 (8.1)
PART + Lewy body disease	0	2 (2.7)	0
PART + HS-Aging	1 (3.6)	0	1 (2.7)
PART + CVD	11 (39.3)	54 (73.0)	22 (59.5)
PART + Lewy body disease + HS-Aging	0	0	2 (5.4)
PART + Lewy body disease + CVD	1 (3.6)	2 (2.7)	3 (8.1)
PART + HS-Aging + CVD	2 (7.1)	1 (1.4)	4 (10.8)
Lewy body disease + CVD	0	1 (1.4)	0

Mixed ADNC	MCI Reverters (n=62)	Stable MCI (n=188)	Dementia after MCI (n=299)
PART	1 (1.6)	4 (2.1)	1 (0.3)
Lewy body disease	0	3 (1.6)	17 (3.1)
HS-Aging	1 (1.6)	7 (3.7)	13 (4.4)
CVD	46 (74.2)	138 (73.4)	184 (61.5)
PART + CVD	6 (9.7)	10 (5.3)	7 (2.3)
PART + Lewy body disease + CVD	1 (1.6)	0	1 (1.6)
PART + HS-Aging + CVD	0	2 (1.1)	0
Lewy body disease + HS-Aging	0	0	3 (1.0)
Lewy body disease + CVD	4 (6.5)	16 (8.5)	31 (10.4)
Lewy body disease + HS-Aging + CVD	0	0	9 (3.0)
HS-Aging + CVD	3 (4.8)	8 (4.3)	33 (11.0)

Note: SNAP = suspected non-Alzheimer pathology; ADNC = Alzheimer's disease neuropathologic changes; CVD = cerebrovascular disease; HS-Aging = hippocampal sclerosis of aging; PART = primary age-related tauopathy.