An Exploration of Subgroups of Mild Cognitive Impairment Based On Cognitive, Neuropsychiatric and Functional Features: Analysis of Data from the National Alzheimer's Coordinating Center

John Hanfelt, *Emory University*
Joanne Wuu, *Emory University*
Ann B. Sollinger, *Department of Physical Medicine and Rehabilitation, Carilion Clinic, Roanoke, Virginia*
Melanie C Greenaway, *Emory University*
James J Lah, *Emory University*
Allan I Levey, *Emory University*
Felicia Goldstein, *Emory University*

Journal Title: American Journal of Geriatric Psychiatry
Volume: Volume 19, Number 11
Publisher: Lippincott, Williams & Wilkins | 2011-11, Pages 940-950
Type of Work: Article | Post-print: After Peer Review
Publisher DOI: 10.1097/JGP.0b013e31820ee9d2
Permanent URL: http://pid.emory.edu/ark:/25593/d6nwc

Final published version: http://dx.doi.org/10.1097%2FJGP.0b013e31820ee9d2

Published in final edited form as:
Am J Geriatr Psychiatry. 2011 November ; 19(11): 940–950. doi:10.1097/JGP.0b013e31820ee9d2.

An Exploration of Subgroups of Mild Cognitive Impairment Based On Cognitive, Neuropsychiatric and Functional Features: Analysis of Data from the National Alzheimer's Coordinating Center

John J. Hanfelt, PhD[1], **Joanne Wuu, ScM**[2], **Ann B. Sollinger, PhD**[3], **Melanie C. Greenaway, PhD**[2], **James J. Lah, MD, PhD**[2], **Allan I. Levey, MD, PhD**[2], and **Felicia C. Goldstein, PhD**[2]

[1] Department of Biostatistics and Bioinformatics, Emory University Rollins School of Public Health, Emory Alzheimer's Disease Research Center

[2] Department of Neurology, Emory University School of Medicine, Emory Alzheimer's Disease Research Center

[3] Department of Physical Medicine and Rehabilitation, Carilion Clinic, Roanoke, Virginia

Abstract

Objectives—To empirically expand the existing subtypes of mild cognitive impairment (MCI) by incorporating information on neuropsychiatric and functional features, and to assess whether cerebrovascular disease (CVD) risk factors are associated with any of these subgroups.

Design—Latent class analysis using 1,655 patients with MCI.

Setting—Participants in the Uniform Data Set (UDS) from 29 NIH Alzheimer's Disease Centers.

Participants—Patients with a consensus diagnosis of MCI from each center and with a Mini-Mental State Examination (MMSE) score of 22 or greater.

Measurements—UDS cognitive battery, Neuropsychiatric Inventory Questionnaire (NPI-Q), and Functional Assessment Questionnaire (FAQ) administered at initial visit.

Results—Seven empirically-based subgroups of MCI were identified: (1) minimally impaired (relative frequency, 12%); (2) amnestic only (16%); (3) amnestic with functional and neuropsychiatric features (16%); (4) amnestic multi-domain (12%); (5) amnestic multi-domain with functional and neuropsychiatric features (12%); (6) functional and neuropsychiatric features (15%); and (7) executive function and language impairments (18%). Two of these subgroups with functional and neuropsychiatric features were at least 3.8 times more likely than the minimally impaired subgroup to have a Rosen-Hachinski score ≥ 4, an indicator of probable CVD.

Conclusions—Findings suggest there are several distinct phenotypes of MCI characterized by either prominent cognitive features, prominent functional and neuropsychiatric features, or a combination of all three. Subgroups with functional and neuropsychiatric features are significantly more likely to have CVD, which suggests there might be distinct differences in disease etiology from the other phenotypes.

Correspondence may be sent to John J. Hanfelt, PhD, Department of Biostatistics and Bioinformatics, Emory University Rollins School of Public Health, 1518 Clifton Road, N.E., Atlanta, Georgia 30322 Phone: 404-727-2876; Fax: 404-727-1370, jhanfel@emory.edu.
Alternate correspondent: Felicia C. Goldstein, PhD, Department of Neurology, Emory University School of Medicine, 1841 Clifton Road, N.E., Atlanta, Georgia 30329 Phone 404-728-6680; Fax: 404-728-6685 fgoldst@emory.edu

No Disclosures to Report

Keywords

mild cognitive impairment; neuropsychiatric symptoms; functional impairment; vascular risk factors; latent class analysis

INTRODUCTION

In the 1990s, the term mild cognitive impairment (MCI) was introduced to denote an intermediate stage between normal aging and dementia. [1] An early conceptualization of MCI focused on an amnestic subtype that was defined as the presence of a memory complaint, objective evidence of abnormal memory for age, normal general cognitive function, and normal activities of daily living. [2] Subsequent research, however, revealed tremendous heterogeneity in the clinical presentation of MCI, leading to a need to broaden the definition. [3] As a result, the classification system for MCI now utilized across the NIH supported Alzheimer's Disease Centers (ADCs) encompasses four subtypes: 1) Amnestic MCI – memory impairment only; 2) Multi-domain MCI-Amnestic (memory plus one or more non-memory domains), 3) Multi-domain MCI-Non-Amnestic (more than one non-memory domain), or 4) Single Non-Memory MCI (one non-memory domain). [4] The expanded classification scheme for MCI has provided researchers with a platform from which to develop hypotheses about specific characteristics that are predictive of underlying etiologies of cognitive decline. In addition, the classification fosters a common language across centers for inclusion of patients in clinical trials.

The current MCI classification system is based on a consideration of the number (single or multiple) and type (memory, non-memory, or both) of affected cognitive domains. Research indicates, however, that features apart from cognition provide additional information about MCI phenotypes. With respect to neuropsychiatric characteristics, it has been reported that depression, apathy, anxiety, agitation, and irritability are more prevalent in patients with MCI compared to cognitively normal comparison groups. [5, 6] Moreover, the presence of behavioral disturbances in MCI patients is a risk factor for progression to dementia, including Alzheimer's disease (AD). [7, 8] Concerning activities of daily living, studies have found that MCI patients can be compromised in performing complex instrumental activities such as driving, taking medication and managing their finances. [9, 10] Since the transition from a diagnosis of MCI to dementia is based on functional dependence, knowledge concerning a range of capacity could provide additional predictive information. The simultaneous presence of neuropsychiatric disturbances coupled with functional impairments may contribute to a specific presentation. Lee and colleagues, for example, found a significantly higher frequency of delusions, aggression, irritability and eating disturbances in an MCI group characterized as functionally dependent. [11]

These previous investigations have examined the presence of neuropsychiatric disturbances and functional decline in MCI patients by either comparing them as a group to a cognitively normal reference group or based on particular subtypes of MCI (e.g., amnestic versus nonamnestic). To our knowledge, no study has yet empirically verified whether there are MCI patients that present with primarily cognitive symptoms alone, neuropsychiatric features and/or functional deficits alone, or a combination of these features. Such information could help to identify at-risk subgroups with particular etiologies and disease courses.

One goal of the current study was to incorporate information concerning scores on a neuropsychological battery as well as measures of neuropsychiatric symptoms and functional status in order to arrive at empirically defined subgroups of MCI. This was

accomplished using latent class analysis (LCA), a powerful statistical method to investigate empirically the structure of heterogeneous syndromes. LCA is based on the intuitive concept that the statistical associations among the observed variables are a manifestation of underlying ('latent') subgroups or classes in the study population. Within a given latent class, the observed variables are assumed to be independent, which is known as the 'conditional independence' or 'local independence' assumption. [12] An attractive feature of LCA is that it is rooted within a rigorous statistical framework, unlike many clustering procedures that are heuristic, and thus LCA provides inferences with many appealing properties, such as the most precise available estimates of the LCA model parameters through the use of the maximum likelihood estimation approach; standard errors and confidence intervals to assess the uncertainty of results; and probabilities of misclassification are available for consideration when assigning study participants to the subgroups to which they most likely belong. [12]

In the current study, we used the LCA approach to analyze variables collected as part of the Uniform Data Set (UDS), a standardized assessment and data protocol maintained by the National Alzheimer's Coordinating Center (NACC) with 29 participating NIH ADCs nationwide. [13, 14] Data are collected by trained clinicians and assistants at each site using structured interviews. As part of the assessment, research participants receive a battery of cognitive measures. In addition, study partners provide subjective observations regarding the presence and severity of neuropsychiatric symptoms and the level of functional ability in performing instrumental activities of daily living. We hypothesized that cognitive performance would distinguish subgroups of MCI, but that the additional consideration of neuropsychiatric features and range of independence in IADLs would expand the phenotype.

A second purpose of this study was to examine whether there is an association between cerebrovascular disease (CVD) and empirically derived MCI subgroups. CVD is a risk factor for MCI, and can influence the neuropsychological presentation, especially on measures of executive functioning. [15–18] CVD is also associated with behavioral and mood changes including depression and apathy in normal elderly and patients with MCI. [19–21] We hypothesized that if our empirically derived subgroups of MCI have validity, then we should see an association between CVD and a phenotype characterized by greater executive dysfunction and neuropsychiatric disturbances. In the current study, the Rosen Modification of Hachinski Ischemic Score (RMHIS), a shortened version of the original 13 item Hachinski Ischemic Scale, was used as a marker for probable CVD. [22] The RMHIS rates eight features (abrupt onset, stepwise deterioration of cognitive status, somatic complaints, emotional incontinence, hypertension, history of stroke, and focal neurological signs and symptoms) associated with CVD, and has been validated in neuropathological studies of vascular dementia. [23] In addition to the RMHIS, a related covariate of interest was a history of cigarette smoking, a well-known risk factor for both ischemic and hemorrhagic stroke. [24]

METHODS

Participants

We used information from the UDS as of the November, 2007 data freeze. Recruitment strategies vary across the ADCs, and participants may come from clinics or the community. [14] Criteria used by all of the ADCs for diagnosis of MCI follow the guidelines set forth by an Expert Panel. [4] The first step of the algorithm is to determine whether a person has normal cognition or dementia using standard criteria for AD or non-Alzheimer type dementia. If the answers to both items are "no," the next step is to characterize the subtype of MCI. Based on clinical judgment and cognitive test scores, a person may be classified as having 1) Amnestic MCI-memory impairment only; 2) Multi-domain MCI-Amnestic (memory plus one or more non-memory domains), 3) Multi-domain MCI-Non-Amnestic

(more than one non-memory domain), or 4) Single Non-Memory MCI (one non-memory domain).

Inclusion criteria for the current study required that participants had: 1) a consensus diagnosis of MCI from the clinicians at each center and 2) non-missing information on age, years of education, and race. In addition, we required that participants have a Mini-Mental State Examination (MMSE) [25] score of 22 or greater, in order to exclude a small number of MCI subjects with suspiciously low MMSE scores. We considered the additional requirement that participants have a Clinical Dementia Rating [26] score of 0.5. However, we rejected this cutoff since this would place the emphasis on a memory impaired sample and thus miss other cognitive subtypes.

Using the above criteria, data from 1,655 participants were available for analysis.

Measures

Phenotypes of MCI—To characterize the diversity of phenotypes of MCI, we selected the following variables from the UDS. Cognitive test scores were based on the core battery of measures collected by the ADCs. [14] Measures evaluate overall cognitive status (MMSE), executive functioning (Trail Making Test [27]), language (Boston Naming Test [28]; category fluency [29]), attention (Digit Span and Digit Symbol subtests [30]) and episodic memory (Logical Memory Story A[31]). Functional abilities were evaluated by having the informant complete the Functional Assessment Questionnaire (FAQ), which measures dependence performing IADLs over the previous four weeks. [32] Performance on 10 items was assessed including the ability to balance one's checkbook and write/pay bills, assemble tax records and other complicated financial papers, shop alone, play complicated games/maintain a hobby, perform simple kitchen related tasks such as heating water and turning off the stove, prepare a complicated meal, keep track of events, travel, pay attention to/follow information such as a television program, and remember events and tasks such as to take medication. A count was made of the number of activities that each participant was rated as having difficulty/needing assistance (range=0–10). Informants also received the Neuropsychiatric Inventory Questionnaire (NPI-Q) to provide a reliable assessment of problematic behavioral changes in the last month. [33] This structured interview assesses 12 behaviors including delusions, hallucinations, agitation/aggression, depression/dysphoria, apathy/indifference, elation/euphoria, anxiety, disinhibition, irritability/lability, aberrant motor behavior, nighttime behaviors, and appetite/eating. Participants provided a self-report of depressive symptoms via the Geriatric Depression Scale (GDS; 15 items). [34] The GDS-15 is highly correlated with the full version of the GDS and is a valid screen for depression. [35] The GDS score was dichotomized as 0–4 points (no depression) or 5–15 points (depression) based on published guidelines. [34]

Marker of CVD—Clinicians completed the RMHIS to document the likelihood of associated CVD. An RMHIS score of 4 points or greater is considered an indicator of probable CVD. [22]

Analysis

We entered the collection of neuropsychological, functional, and neuropsychiatric information into an LCA model in order to explore the number and clinical characteristics of MCI subgroups. We converted the raw cognitive test scores to standardized scores (z scores) using the demographic characteristics of the UDS cognitively normal participants as the reference group. Normal participants were volunteers at the ADCs with a consensus diagnosis based on UDS guidelines including a clinical judgment that the participant did not have MCI, dementia, or other conditions resulting in cognitive impairment. [14] We required

that these normal participants were not missing information on age, education, and race, and had attained an MMSE score of 25 points or higher. We fitted a linear regression model to each of the ten neuropsychological measures in the cognitively normal sample of 2,916 UDS participants, using age (in years), education (in years), race (here dichotomized as white or non-white), and the education × race interaction as explanatory variables in the regression models. Using this approach, for example, a standardized test score of −1.5 indicated that the MCI participant's score was 1.5 standard deviations lower than the mean among UDS cognitively normal subjects of the same age, educational level, and race.

Some MCI subjects were missing one or more of the above study variables. The most frequently missing item, in 8% of the participants, was the WAIS-R Digit Symbol test. We included all MCI participants with missing values in the latent class analysis, an approach that was valid under the assumption of missing at random; that is, given a participant's observed study variables and latent class, we assumed that the missingness mechanism did not depend on his or her unobserved study variables. [12]

Separate from the above response variables used to characterize the MCI subgroups, we also entered into the model two covariates, RMHIS and decades of smoking (0 for nonsmokers). The relationships between the MCI latent classes and these risk factors were modeled using polytomous logistic regression, and were estimated simultaneously with the latent class model parameters using maximum likelihood. [12]

To select the appropriate number of latent classes, we fitted a series of models of progressively finer resolution of the structure of MCI, limiting the maximum number of latent classes so as to enforce the guideline that there should be at least 10 times as many research participants as there are unknown parameters to be estimated in the LCA model. [36] To choose the LCA model that provided the best compromise between parsimony and the ability to explain the heterogeneity exhibited among the MCI participants, we used three objective model selection criteria: the Akaike Information Criterion (AIC); the Bayesian Information Criterion (BIC); and the Integrated Classification Likelihood-BIC (ICL-BIC). [12] The latent class model that minimized the value of AIC, BIC, or ICL-BIC was selected as the best-fitting model. [12] We used the Latent GOLD 4.0 software package to conduct LCA. [37]

RESULTS

MCI participants' demographic and clinical characteristics are given in Table 1.

In our first analysis, we included each of the 12 neuropsychiatric features in the NPI-Q as individual responses in the LCA model, together with the other 12 response variables (10 standardized scores from the neuropsychological battery, count of the number of IADLs impaired, and presence vs absence of depression on the GDS). We fitted a series of models with 1 – 5 latent classes and 24 response variables, and found that the 5-class model was preferred according to our three objective model selection criteria: that is, AIC, BIC, and ICL-BIC all attained their minimum values at the 5-class solution. In the 5-class solution, it was clear that the specific subgroups of MCI with the highest rates of depression also had the highest rates of other neuropsychiatric disturbances, see Figure 1.

As a result, we could safely reanalyze the data with the 12 individual NPI-Q variables replaced by a count of the number of neuropsychiatric disturbances, without sacrificing any information related to the MCI subclassifications. Under this more parsimonious model with only 13 response variables (10 standardized scores from the neuropsychological battery, count of the number of IADLs impaired, count of the number of neuropsychiatric symptoms, and presence vs absence of depression on the GDS)., we were able to investigate finer

resolutions of the structure of MCI without compromising statistical validity. We fitted a series of models with 1 – 7 latent classes, and found that the 7-class model was preferred according to both our objective model selection criteria (that is, AIC, BIC, and ICL-BIC all attained their minimum values at the 7-class solution) and clinical interpretation, thus revealing a remarkable amount of heterogeneity in the clinical presentation of MCI. The results indicated that not only the performance on a neuropsychological battery but also the information on functional status and neuropsychiatric symptoms were important for delineating phenotypic subclassifications of MCI; see Table 2. The evidence supported the following subgroups of MCI (where we have interpreted cognitive test scores that were at least 1.5 SDs worse than the cognitively normal reference group as evidence of impairment): (1) 'minimally impaired' (relative frequency, 12%), a subgroup indistinguishable from the cognitively normal group based on the UDS variables analyzed here; (2) ' amnestic only' (16 %), characterized by a subtle impairment in delayed memory; (3) 'amnestic with functional impairments and neuropsychiatric features' (16%), characterized by impairments in both immediate and delayed memory, difficulties performing IADLs, and neuropsychiatric disturbances; (4) 'amnestic multi-domain' (12%), characterized by impairments across cognitive domains including episodic and semantic memory, language, and executive function; (5)'amnestic multi-domain with functional impairments and neuropsychiatric features' (12%), a subtype that differed from the 'amnestic multi-domain' subgroup in also having difficulties performing IADLs and in having neuropsychiatric disturbances, as well as impairments across a broader spectrum of cognitive domains including attention and visuomotor skills; (6) 'functional impairments and neuropsychiatric features' (15%), a subgroup experiencing functional and behavioral impairments but with no cognitive impairment detected in the neuropsychological exam; and finally, (7) 'executive function and language impairments' (18%), a subgroup distinguished neuropsychologically by impairment in non-memory domains. All twelve study variables contributed to the MCI subclassifications (multivariate Wald tests (6 df) yielded $P < 0.001$ for each variable; not shown in Table 2). The fit of the above 7-class model was significantly better than the fit under an order restricted 7-class model that posited a single dimension of severity (likelihood ratio test: $L = 926.7$; bootstrap p-value, $p < 0.001$).

We estimated additional parameters (see Table, Supplemental Digital Content 1, which reports latent class-specific standard deviations of the cognitive measures) related to the 7-class model shown in Table 2.

The results indicated an association between the covariate RMHIS and the empirically derived subgroups of MCI; see Table 3. Two specific subgroups, 'amnestic multi-domain with functional impairments and neuropsychiatric features' and 'functional impairments and neuropsychiatric features' alone, were at least 3.8 times as likely (based on the lower limit of the 95% confidence interval) compared to participants in the 'minimally impaired' subgroup to meet the criterion RMHIS ≥ 4, an indicator of probable CVD. The second covariate included in the latent class model, decades of smoking, was not associated with the empirically defined subgroups of MCI; see Table 3. In the analysis, we did not include current smoking as a covariate, since only 4% of MCI participants were current smokers (Table 1). Refitting the latent class model with current smoking included as a covariate confirmed that current smoking was not associated with the empirically derived subgroups of MCI (Wald test: $W = 3.14$ (6 df), $p = 0.79$; not reported in Table 3).

We investigated demographic characteristics (see Table, Supplemental Digital Content 2, which summarizes the relationships between demographic factors and the seven latent classes) and found them to be significantly associated with the empirically defined subgroups of MCI.

DISCUSSION

The results of this study support current conceptualizations of MCI as a heterogeneous disorder. Previous approaches to understanding the contribution of neuropsychiatric and functional features in MCI patients have examined samples predefined by cognitive phenotype (e.g., amnestic or nonamnestic, single or multi-domain MCI) in order to determine whether the groups differ in neuropsychiatric disturbances or level of independence. [5–11] A unique feature of the present study, we believe, is a statistical approach that allowed us to simultaneously and objectively consider all features without predefining the structure of the subgroups.

Using the latent class statistical approach, we delineated seven MCI subgroups. Three of these include a relatively "pure" cognitive phenotype of MCI which is characterized primarily by either memory problems alone, memory problems with other affected cognitive domains, or a nonamnestic subtype. A separate identified subgroup, 'minimally impaired,' exhibited preserved cognitive functioning across all domains according to the UDS neuropsychological test battery and yet, the clinicians making a consensus diagnosis agreed that these individuals should not be characterized as such. This was possible since individual centers might employ their own cutoff scores on the UDS cognitive test battery that differ from the cutoff scores we used in this study. In addition, centers might incorporate additional clinical information not included in the UDS to make the consensus diagnosis. Moreover, the recruitment of patients from memory clinics could bias judgments towards a tacit assumption that memory problems are present. It would be interesting to follow the persons in the 'minimally impaired' subgroup over time to see if they do progress to dementia.

The addition of variables from the FAQ, GDS and the NPI-Q identified three additional MCI subgroups with functional impairments and neuropsychiatric disturbances. Two of these subgroups had prominent cognitive deficits, whereas the third showed relatively normal cognitive performance. The 'amnestic multi-domain with functional impairments and neuropsychiatric features' and 'functional impairments and neuropsychiatric features' subgroups were more likely than participants in the 'minimally impaired' subgroup to meet the criterion RHMIS ≥ 4, an indicator of probable CVD. These groups may be comparable to the subtype of MCI termed "vascular cognitive impairment" and may be at risk for vascular dementia in addition to other neurodegenerative conditions including AD and frontotemporal dementia. [19, 38] We did not observe an elevated RHMIS score in the subgroup characterized by executive function and language impairments alone. The lack of an association particularly with executive functioning is surprising, given the evidence in the literature for CVD risk factors including hypertension to be associated with this cognitive phenotype. [17, 39] The measures employed in the UDS battery assess set shift ability only (Trails B, Digit Span Backwards). It is possible that the inclusion of additional measures of executive functioning that tap subdomains such as reasoning may have detected a relationship. For example, Reitz and colleagues [17] found that hypertension is associated with a greater decline in performance of MCI patients on measures of verbal and nonverbal reasoning. In patients with mild-moderate AD, we have also found that hypertension is associated with poorer abstract reasoning and concept formation. [39] An additional consideration is that the confidence intervals for the odds ratios reported in Table 3 are relatively broad, indicating that our estimates of the associations between the CVD risk factors and the MCI subgroups are relatively imprecise. This imprecision is a natural result of partitioning the original sample into seven smaller subgroups and also the relatively small proportion (6%) of MCI participants with an RMHIS score that met the strict threshold of 4 points or higher. Since the odds ratios were estimated imprecisely, we have chosen to report conservative estimates, that is, the lower limits of the 95% confidence intervals.

A major clinical implication of our findings, we believe, concerns early detection since recognition of diverse MCI subtypes as a prodromal state for specific diseases is critical for evaluating disease modifying therapies for AD and other disorders. The consideration of additional features apart from cognition could help to identify persons at risk for other forms of dementia apart from AD. For example, frontotemporal dementia and Lewy body dementia may present with prominent neuropsychiatric features including personality changes and visual hallucinations with relative preservation of cognition in the prodomal phase.

In our final latent class model, the individual items of the NPI-Q were pooled into a total count variable of the number of neuropsychiatric symptoms present, ranging from 0 to 12. The NPI-Q measures disparate symptoms, but little or no information about MCI subtypes was lost in our study by pooling the symptoms. This is seen graphically in Figure 1, where the empirical derived subgroups of MCI with the highest rates of depression also had the highest rates of the other neuropsychiatric features; moreover, psychotic symptoms such as delusions and hallucinations were rare in all the MCI subgroups and so provided negligible information about the structure of MCI. It is possible that if future latent class analyses use MCI samples enriched with relatively rare neuropsychiatric symptoms such as delusions and hallucinations, then the individual items in the NPI-Q might contribute to the discovery of new subtypes of MCI.

In this study we have capitalized on the unique resource of the UDS, which represents 29 ADCs nationwide and has uniform definitions of all study variables. The UDS is not a community-based sample, however. UDS subjects often are motivated to participate in research based on their concerns of a family history of dementia and are not fully representative of the community. Another limitation of our study is the absence of sensitive neuroimaging techniques such as diffusion tensor imaging to document the extent of CVD. Although the latent class approach was statistical, it also involved clinical judgment in labeling the subgroups based on the resulting categories. Findings from the latent class analysis are exploratory; clinical validation would be needed before accepting the identified subgroups as clinical subtypes of MCI. The overall results highlight the fact that the definition of subtypes and prevalence estimates of MCI are heavily dependent on the samples (e.g., memory clinic versus population based) and definitions used to identify these impairments, including statistical cutoff scores. [40] Moreover, our findings are dependent on the measures available in the national database. For example, different cognitive tests or more extensive functional assessments may have identified different or additional subgroups not currently observed. The UDS lacked information on risk factors of AD such as ApoE status and hippocampal atrophy. As extensive information on dementia risk factors becomes more widely available to supplement the clinical features analyzed here, it will be interesting to examine the association between these risk factors and the empirically derived MCI subgroups.

An important feature of the UDS sample is that follow-up data are being collected on the participants. A future direction of our research is to study differences in disease progression among these empirically defined subgroups of MCI patients.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

This work was supported in part by NIH P50 AG025688. This project was accomplished through the auspices of the US National Alzheimer's Coordinating Center in Seattle, WA, which is a US National Institute on Aging–

funded Center that facilitates collaborative research among NIA-funded ADCs. The authors thank the NACC for kindly providing the data used in this article under cooperative agreement number U01 AG016976. We also thank the ADC participants for their willingness to devote their time to research and the staff members who work tirelessly to make the research possible.

This research was partially funded by the National Institutes of Health.

References

1. Gauthier S, Reisberg B, Zaudig M, et al. Mild cognitive impairment. Lancet. 2006; 367:1262–1270. [PubMed: 16631882]
2. Petersen RC, Smith GE, Waring SC, et al. Mild cognitive impairment: clinical characterization and outcome. Arch Neurology. 1999; 56:303–308.
3. Petersen RC, Doody R, Kurz A, et al. Current concepts in mild cognitive impairment. Arch Neurology. 2001; 58:1985–1992.
4. Winblad B, Palmer K, Kivipelto M, et al. Mild cognitive impairment - beyond controversies, towards a consensus: report of the International Working Group on Mild Cognitive Impairment. J Internal Med. 2004; 256:240–246. [PubMed: 15324367]
5. Geda YE, Roberts RO, Knopman DS, et al. Prevalence of neuropsychiatric symptoms in mild cognitive impairment and normal cognitive aging: population-based study. Arch Gen Psychiatry. 2008; 65:1193–1198. [PubMed: 18838636]
6. Muangpaisan W, Intalapaporn S, Assantachai P. Neuropsychiatric symptoms in the community-based patients with mild cognitive impairment and the influence of demographic factors. Int J Geriatr Psychiatry. 2008; 23:699–703. [PubMed: 18172914]
7. Stepaniuk J, Ritchie LJ, Tuokko H. Neuropsychiatric impairments as predictors of mild cognitive impairment, dementia, and Alzheimer's disease. Am J Alzheimers Dis Other Dement. 2008; 23:326–333.
8. Teng E, Lu PH, Cummings JL. Neuropsychiatric symptoms are associated with progression from mild cognitive impairment to Alzheimer's disease. Dement Geriatr Cogn Disord. 2007; 24:253–259. [PubMed: 17700021]
9. Farias ST, Mungas D, Reed BR, et al. MCI is associated with deficits in everyday functioning. Alzheimer Dis Assoc Disorders. 2006; 20:217–223.
10. Kim KR, Lee KS, Cheong HK, et al. Characteristic profiles of instrumental activities of daily living in different subtypes of mild cognitive impairment. Dement Geriatr Cogn Disord. 2009; 27:278–285. [PubMed: 19246913]
11. Lee KS, Cho HS, Hong CH, et al. Differences in neuropsychiatric symptoms according to mild cognitive impairment subtypes in the community. Dement Geriatr Cogn Disord. 2008; 26:212–217. [PubMed: 18781071]
12. McLachlan, GJ.; Peel, D. Finite Mixture Models. New York, NY: Wiley; 2000.
13. Beekly DL, Ramos EM, Lee WW, et al. The National Alzheimer's Coordinating Center (NACC) database: the Uniform Data Set. Alzheimer Dis Assoc Disord. 2007; 21:249–258. [PubMed: 17804958]
14. Weintraub S, Salmon D, Mercaldo N, et al. The Alzheimer's Disease Centers' Uniform Data Set (UDS): the neuropsychologic test battery. Alzheimer Dis Assoc Disord. 2009; 23:91–101. [PubMed: 19474567]
15. Di Carlo A, Lamassa M, Baldereschi M, et al. CIND and MCI in the Italian elderly: frequency, vascular risk factors, progression to dementia. Neurology. 2007; 68:1909–1916. [PubMed: 17536047]
16. Solfrizzi V, Panza F, Colacicco AM, et al. Vascular risk factors, incidence of MCI, and rates of progression to dementia. Neurology. 2004; 63:1882–1891. [PubMed: 15557506]
17. Reitz C, Tang MX, Manly J, et al. Hypertension and the risk of mild cognitive impairment. Arch Neurol. 2007; 64:1734–1740. [PubMed: 18071036]
18. Lopez OL, Jagust WJ, Dulberg C, et al. Risk factors for mild cognitive impairment in the Cardiovascular Health Study Cognition Study: part 2. Arch Neurol. 2003; 60:1394–1399. [PubMed: 14568809]

19. Bowler, JV.; Hachinski, V., editors. Vascular Cognitive Impairment. Oxford: Oxford University Press; 2003.
20. Kales HC, Maixner DF, Mellow AM. Cerebrovascular disease and late-life depression. Am J Geriatr Psychiatry. 2005; 13:88–98. [PubMed: 15703317]
21. Wendell CR, Hosey MM, Lefkowitz DM, et al. Depressive symptoms are associated with subclinical cerebrovascular disease among healthy older women, not men. Am J Geriatr Psychiatry. 2010; 18:940–947. [PubMed: 20808084]
22. Rosen WG, Terry RD, Fuld PA, et al. Pathological verification of ischemic score in differentiation of dementias. Ann Neurol. 1980; 7:486–488. [PubMed: 7396427]
23. Moroney JT, Bagiella E, Desmond DW, et al. Meta-analysis of the Hachinski Ischemic Score in pathologically verified dementias. Neurology. 1997; 49:1096–1105. [PubMed: 9339696]
24. Shinton R, Beevers G. Meta-analysis of relation between cigarette smoking and stroke. Brit Med J. 1989; 298:789–794. [PubMed: 2496858]
25. Folstein MF, Folstein SE, McHugh PR. “Mini-mental state”: A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Research. 1975; 12:189–198. [PubMed: 1202204]
26. Morris J. The Clinical Dementia Rating (CDR): Current version and scoring rules. Neurology. 1993; 43:2412–2414. [PubMed: 8232972]
27. Army US. Army Individual Test Battery. Washington, D.C: War Department, Adjutant General’s Office; 1944.
28. Kaplan, E.; Goodglass, H.; Weintraub, S. Boston Naming Test. Philadelphia, PA: Lea & Febiger; 1983.
29. Strauss, E.; Sherman, EMS.; Spreen, O. Norms, and Commentary. 3. New York, NY: Oxford University Press; 2006. A Compendium of Neuropsychological Tests: Administration.
30. Wechsler, D. The Wechsler Adult Intelligence Scale-Revised. San Antonio, TX: The Psychological Corporation; 1981.
31. Wechsler, D. Wechsler Memory Scale-Revised. San Antonio, TX: The Psychological Corporation; 1987.
32. Pfeffer RI, Kurosaki TT, Harrah CH, et al. Measurement of functional activities in older adults in the community. J Gerontol. 1982; 37:323–329. [PubMed: 7069156]
33. Kaufer DI, Cummings JL, Ketchel P, et al. Validation of the NPI-Q, a brief clinical form of the Neuropsychiatric Inventory. J Neuropsychiatry Clin Neurosci. 2000; 12:233–239. [PubMed: 11001602]
34. Sheikh, J.; Yesavage, JA. Geriatric Depression Scale (GDS): Recent evidence and development of a shorter version, in Clinical Gerontology: A Guide to Assessment and Intervention. Brink, TL., editor. New York, NY: The Hawthorne Press; 1986. p. 165-173.
35. Chattat R, Ellena L, Cucinotta D, et al. A study of the validity of different short versions of the Geriatric Depression Scale. Arch Gerontol Geriatr Supplem. 2001; 7:81–86.
36. Hagenaars, JA.; McCutcheon, AL., editors. Applied Latent Class Analysis. Cambridge: Cambridge University Press; 2002.
37. Latent GOLD [computer program]. Version 4.0. Belmont, MA: Statistical Innovations Inc; 2005.
38. O’Brien JT. Vascular cognitive impairment. Am J Geriatr Psychiatry. 2006; 14:724–733. [PubMed: 16943169]
39. Goldstein FC, Ashley AV, Endeshaw YW, et al. Effects of hypertension and hypercholesterolemia on cognitive functioning in patients with Alzheimer’s disease. Alzheimer Dis & Assoc Dis. 2008; 22:336–342.
40. Kochan NA, Slavin MJ, Brodaty H, et al. Effect of different impairment criteria on prevalence of “objective” mild cognitive impairment in a community sample. Am J Geriatr Psychiatry. 2010; 18:711–722. [PubMed: 21491632]

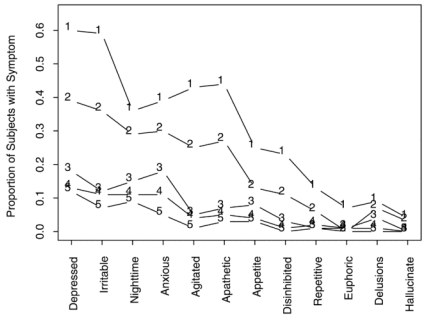

Figure 1.

Proportion of subjects within each of 5 latent subclasses of MCI who had specific neuropsychiatric symptoms according to an informant. Key: 1= latent class #1, 2 = latent class #2, etc.

Table 1

Demographic and clinical characteristics of 1,655 MCI participants from the Uniform Data Set: Mean ± SD or frequency (%).

		MCI
Demographic	Age, y	74.9 ± 9.1
	Sex: Male	800 (48%)
	Race: White	1367 (83%)
	Black/African American	262 (16%)
	Asian	25 (2%)
	American Indian	1 (0.1%)
	Hispanic	71 (4%)
	Education, y	14.9 ± 3.2
	MMSE	27.4 ± 2.1
Functional	# IADLs Rated as Difficult to Perform/Requiring Assistance (10 Maximum)	2.3 ± 2.7
Neuropsychiatric	GDS ≥5	237 (15%)
	# NPI-Q Items Rated as Present # Persons with an NPI-Q Symptom Present:	1.5 ± 1.9
	Depressed	443 (28%)
	Irritable	390 (25%)
	Nighttime behavior	303 (19%)
	Anxious	308 (19%)
	Agitated	241 (15%)
	Apathetic	267 (17%)
	Change in appetite	169 (11%)
	Disinhibited	117 (7%)
	Repetitive activities	74 (5%)
	Euphoric	30 (2%)
	Delusions	58 (4%)
	Hallucinations	23 (1%)
Cognitive (standardized scores*)	MMSE	−1.47 ± 1.89
	Logical Memory: Immediate	−1.05 ± 1.14
	Logical Memory: Delayed	−1.21 ± 1.20
	Semantic Memory: Category Fluency	−0.89 ± 0.93
	Attention: Trails A **	0.69 ± 1.58
	Attention: Digit Span Forward	−0.27 ± 1.02
	Language: Boston Naming	−0.99 ± 1.78
	Executive Function: Trails B **	1.17 ± 1.75
	Executive Function: Digit Span Backward	−0.43 ± 0.95
	Visuo-Motor: Digit Symbol	−0.78 ± 1.10
UDS	Amnestic, Single Domain	705 (43%)
MCI	Amnestic, Multi-Domain	583 (35%)

		MCI
Subclassification	Non-Amnestic, Single Domain	235 (14%)
	Non-Amnestic, Multi-Domain	132 (8%)
Risk Factors	RMHIS ≥4	102 (6%)
	Decades of smoking	1.16 ± 1.65
	# Persons who smoked in last 30 days	71 (4%)

* All cognitive scores were converted to age-, education-, and race-adjusted z-scores (see Methods section)

** Positive values of Trail Making Tests A and B indicate greater impairment, i.e., took a longer time to complete the test.

Number of subjects for whom data were unavailable: GDS n=33, NPI-Q n=73, Logical Memory – Immediate n=47, Logical Memory – Delayed n=40, Category Fluency n=41, Trails A n=26, Digit Span Forward n=28, Boston Naming n=40, Trails B n=55, Digit Span Backward n=28, Digit Symbol n=131.

Am J Geriatr Psychiatry. Author manuscript; available in PMC 2012 November 1.

Table 2

Maximum likelihood estimates of means (for functional and NPI-Q variables), percentages (for GDS variable), or standardized means (for cognitive variables) from a model with seven latent subclasses of MCI.

	1. Minimally Impaired, relative frequency = 12 %	2. Amnestic Only, relative frequency = 16 %	3. Amnestic with Functional Impairments & Neuro-psychiatric Features, relative frequency = 16 %	4. Amnestic Multi-Domain, relative frequency = 12 %	5. Amnestic Multi-Domain with Functional Impairments & Neuro-psychiatric Features, relative frequency = 12 %	6. Functional Impairments & Neuro-psychiatric Features, relative frequency = 15 %	7. Executive Function & Language Impairments, relative frequency = 18 %
FUNCTIONAL:							
# IADLs impaired	0.3	0.9	4.8	1.3	4.2	4.1	0.3
NEUROPSYCHIATRIC:							
% with GDS ≥ 5	10	9	18	13	24	25	6
# NPI-Q Symptoms Present	0.4	0.8	2.7	0.8	2.2	3.1	0.4
COGNITIVE:							
Global:							
MMSE	0.0	−0.6	−2.4	−2.6	−2.6	−0.9	−1.3
Logical Memory:							
Immediate	0.4	−1.2	−2.0	−2.5	−1.3	−0.3	−0.6
Delayed	0.5	−1.5	−2.4	−2.6	−1.6	−0.4	−0.7
Semantic Memory:							
Category Fluency	−0.3	−0.5	−1.1	−1.5	−1.3	−0.8	−0.8
Attention:							
Trails A *	−0.2	−0.2	0.3	0.7	3.2	0.6	0.8
Digit Span Forward	0.0	−0.0	−0.1	−0.6	−0.7	−0.2	−0.5
Language:							
Boston Naming	−0.5	−0.0	−0.5	−1.9	−2.0	−0.6	−1.7
Executive Function:							
Trails B *	−0.0	−0.0	0.4	1.8	3.8	1.0	1.7
Digit Span Backward	0.0	−0.2	−0.3	−0.8	−0.9	−0.4	−0.6
Visuo-Motor:							
Digit Symbol	−0.1	−0.2	−0.6	−1.1	−2.0	−0.8	−0.9

* Positive values on Trail Making Tests A and B indicate greater impairment, i.e., took a longer time to complete the test.

Table 3

Estimated odds ratios (and 95 % confidence intervals) for the associations between vascular risk factors and empirically based MCI subclassifications

Risk Factor	*1. Minimally Impaired*	*2. Amnestic Only*	*3. Amnestic with Functional Impairments & Neuro-psychiatric Features*	*4. Amnestic Multi-Domain*	*5. Amnestic Multi-Domain with Functional Impairments & Neuro-psychiatric Features*	*6. Functional Impairments & Neuro-psychiatric Features*	*7. Executive Function & Language Impairments*
RMHIS ≥ 4 *	1.00	5.4 (1.1, 26.3)	2.8 (0.4, 18.5)	5.6 (1.1, 27.9)	18.9 (4.2, 84.7)	16.9 (3.8, 75.5)	1.0 (0.1, 10.5)
Per Decade of Smoking**	1.00	0.8 (0.7, 1.0)	0.9 (0.8, 1.0)	0.8 (0.7, 1.0)	0.9 (0.8, 1.0)	0.9 (0.8, 1.0)	0.9 (0.8, 1.0)

* Multivariate Wald test: W = 41.3 (6 df), p < 0.001

** Multivariate Wald test: W = 10.5 (6 df), p = 0.10