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Predicting conversion to dementia in a memory clinic: A standard clinical approach compared with an empirically defined clustering method (latent profile analysis) for mild cognitive impairment subtyping

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Abstract

Introduction: Mild cognitive impairment (MCI) has clinical value in its ability to predict later dementia. A better understanding of cognitive profiles can further help delineate who is most at risk of conversion to dementia. We aimed to (1) examine to what extent the usual MCI subtyping using core criteria corresponds to empirically defined clusters of patients (latent profile analysis [LPA] of continuous neuropsychological data) and (2) compare the two methods of subtyping memory clinic participants in their prediction of conversion to dementia.

Methods: Memory clinic participants (MCI, n = 139) and age-matched controls (n = 98) were recruited. Participants had a full cognitive assessment, and results were grouped (1) according to traditional MCI subtypes and (2) using LPA. MCI participants were followed over approximately 2 years after their initial assessment to monitor for conversion to dementia.

Results: Groups were well matched for age and education. Controls performed significantly better than MCI participants on all cognitive measures. With the traditional analysis, most MCI participants were in the amnestic multidomain subgroup (46.8%) and this group was most at risk of conversion to dementia (63%). From the LPA, a three-profile solution fit the data best. Profile 3 was the largest group (40.3%), the most cognitively impaired, and most at risk of conversion to dementia (68% of the group).

Discussion: LPA provides a useful adjunct in delineating MCI participants most at risk of conversion to dementia and adds confidence to standard categories of clinical inference.

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Keywords: Mild cognitive impairment; Cognitive profiles; Latent profile analysis; Alzheimer's disease; Longitudinal study

1. Introduction

Mild cognitive impairment (MCI) is a syndrome defined as cognitive decline greater than expected for an individual's age and education level that does not interfere notably with activities of daily living [1]. It is clinically valuable in the prediction of later dementia. An annual conversion rate of 10%–15% has been widely cited, but a meta-analysis from memory clinic settings gave a more precise annual conversion rate of 9.6% to dementia [2]. Along with deficits in memory, patients may present with deficits in language, visuospatial processing, and executive function or with symptoms in a combination of domains [3].

There have been attempts to create subtypes of MCI based on levels of impairment deemed to be of statistical and clinical significance. These describe combinations of

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neuropsychological impairments. The combinations themselves are derived from imposed cutoff scores that divide continuous neuropsychological data into binary variables of impaired/not impaired and are as follows: amnestic single domain (ASD; deficit in memory only), amnesic multidomain (AMD; deficit in memory plus another domain e.g., language), nonamnestic single domain (NASD; deficit in a single nonmemory domain e.g., executive function), and nonamnestic multidomain (NAMD; deficits in >1 in nonmemory domains e.g., language and visuospatial function) [4]. Several studies have assessed these MCI subgroups and their predictive value for conversion to dementia. Initial research suggested ASD MCI had the least favorable outcome [5], but more recently, the AMD type has been shown to have a less favorable prognosis [6–8].

Advances in statistical analysis offer the opportunity to empirically validate the Petersen and Morris (2005) [4] classifications including latent profile analysis (LPA). Although this type of analysis has been widely used in related disciplines such as mental health [9], it has only been applied twice in MCI. Both these studies demonstrated added benefit in this type of analysis in terms of classification and maximizing predictive power for dementia conversion [10,11].

This study examined people who were assessed and diagnosed with MCI shortly after their entry to a memory clinic service. The objectives of this study were as follows:

1. To examine whether the usual MCI subtypes [4] correspond to empirically defined (LPA of neuropsychological data) clusters of patients and
2. To explore which of the two methods of categorization of MCI participant data best predicted conversion to dementia in the clinic.

2. Methods

2.1. Participants and diagnostic procedure

MCI participants were recruited from the Belfast City Hospital memory clinic. This is a dual consultant-led memory service providing a regional diagnostic and treatment service. They presented with memory problems usually but were functionally independent and scored ≥24 of 30 on the mini-mental state examination (MMSE) [12] and 82–88 of 100 on the Addenbrooke's Cognitive Examination-Revised (ACE-R) [13]. Participants were diagnosed with MCI according to criteria developed by an international working group on MCI [14]. The Office for Research Ethics Committees Northern Ireland approved this study (reference 06/NIR02/55). Written informed consent was obtained from all participants; they were recruited sequentially as they presented to the clinic with no age or sex restriction. Participants with major depressive or other severe psychiatric disorders were excluded, whereas those with minor depressive and anxiety symptoms were not (score of <5 of 15 on the Geriatric Depression Scale Short Version [15]). Additional exclusion criteria were any

psychoactive medication with possible impact on cognition and chronic alcohol or drug abuse. Participants had neuroimaging carried out (computerised tomography or magnetic resonance imaging brain) for differential diagnosis and were followed up yearly through the memory clinic. The major objective of the follow-up examination was to determine the diagnostic status of the study participants (no cognitive impairment of clinical significance, stable MCI, or dementia). Conversion to a diagnosis of Alzheimer's disease (AD) was based on National Institute of Neurological Disorders and Stroke -Alzheimer Disease and Related Disorders (NINCDS-ADRDA) criteria [15]; vascular dementia based on National Institute of Neurological Disorders and Stroke and the Association Internationale pour la Recherche et l'Enseignement en Neurosciences (NINDS-AIREN) criteria [16]; and mixed dementia based on International Classification of Diseases, Tenth Revision criteria (World Health Organization, Geneva, 1993).

Controls were recruited from groups of volunteers that have previously assisted with studies of this type or were spouses of patients. They had no cognitive complaints, subjectively or on objective assessment and were judged physically and mentally healthy by their clinician (B.M./P.P.).

2.2. Neuropsychological assessment

The neuropsychological evaluation comprised learning and episodic memory, visuospatial function, language, executive function, and attention. Within each cognitive domain, several aspects of function were assessed to obtain as complete a picture as possible. The specific tests were chosen on the basis of their demonstrated validity for use within a population with MCI.

1. Everyday function: It was assessed using the disability assessment for dementia [17]. Scores range from 0 to 80 with higher scores indicating higher function.
2. Premorbid intelligence quotient (IQ): It was estimated using the National Adult Reading Test (NART) [18].
3. Immediate and delayed memory: It was tested using the New York University immediate and delayed paragraph recall test (NYU 1 and 2, respectively) [19] and the paired associate learning (PAL) test from the Cambridge Neuropsychological Test Automated Battery (http://www.camcog.com/cantab-tests.asp).
4. Executive function and attention: These were primarily assessed using the clock drawing task (CLOX) 1 [20], the Stroop color word test [21], Hayling sentence completion test [22], and color trails (CTs) 1 and 2 [23].
5. Language ability: It was assessed using the controlled oral word association test (COWAT) [24] which has two parts: Letter fluency (FAS) and category fluency [25].
6. Visuospatial function: It was assessed using CLOX 2 [20] and the Brixton spatial anticipation test [22]. Additional to its measurement of visuospatial abilities, the latter is reliant on executive functioning.

3. MCI subclassification

Neuropsychological data were adjusted for age and education, plotted, and examined for normality and homogeneity of variance (Levene's test). Z scores were then calculated for each neuropsychological measure relative to the control groups' performance. To differentiate participants with MCI on the different cognitive domains affected, a cutoff for each test was set at 1.5 standard deviations (SD) below the control mean, thus designating this level of impairment to be of clinical significance, as per previous studies of this type [26]. An impaired result on at least one test in each cognitive domain was required to be considered impaired in the domain. MCI participants were then assigned to one of five groups on the basis of the number of domains affected: no impairment of clinical significance (NICS), ASD, AMD, NASD, and NAMD.

3.1. Statistical analysis

Mean neuropsychological differences between MCI and healthy controls at time 1 (i.e., intake to the memory clinic) were explored using t tests (with effect sizes) in SPSS version 17. An LPA was run on z-scores for category fluency, CT1, CT2, Stroop, CLOX 1, CLOX 2, Hayling, Brixton, FAS, NYU1, and NYU2 at time 1 to empirically explore the structure of heterogeneous neuropsychological impairment in MCI. LPA is based on the concept that the statistical associations among selected continuous observed variables are a manifestation of underlying "latent" subgroups or classes in the study population [27]. It is a technique which can model the skewed distributions typical of neuropsychological research, with the distributional characteristics of the data determining the profiles generated [28]. Parameters from the model include profile membership probabilities for individuals with MCI and profile-specific symptom means and variances. To avoid local maxima solutions, two through five profiles were run using a range of random starts and final stage optimizations ensuring the best log-likelihood value were replicated. The final model was to be determined using a consensus of several fit criteria including lowest values of Akaike information criterion (AIC) [29], Bayesian information criterion (BIC) [30], and sample size–adjusted Bayesian information criterion (SSA-BIC) [31]. In addition, the Lo-Mendell-Rubin likelihood ratio test (LMR–LRT) compares a k-profile solution to k−1 profile solution, where k is a given number of latent profiles. If the probability value (P) is <.05, the k model is superior and additional profiles are added until the P value for the statistic is >.05. At this point, the k and k−1 models are considered to fit equivalently, typically the previous (k−1) model is accepted for reasons of parsimony; however, the k model may be preferred if supported by other criteria including the theoretical relevance and distinctiveness of the additional profile [32]. A range of random starts and final stage optimizations was ran on each of the two to avoid local maxima solutions. Entropy is a measure which indicates how distinct the latent profiles are from one another; a number close to one suggests a clear classification [33].

Once a suitable latent profile structure of MCI was determined, the latent profile model parameters were fixed, thus the correlates did not affect the formation of the latent variable. The conditional probabilities of individuals were regressed on sex (1 = male; 2 = female), age (in years), numbers of years education, NART-IQ, and two dummy-coded variables indicating status at follow-up as either normal (=1, all other valid values = 0) or progressed to dementia (=1, all other valid values = 0). The reference category for this logistic regression model was the profile with the highest impairment. This provides an opportunity to explore the validity of the latent variable (e.g., [9]). Both LPA and regressions were performed using Mplus version 6.01 (34) [34]. Finally, the latent profiles were cross tabulated with the Petersen and Morris (2005) [4] categories using SPSS version 17 to understand the overlap between categorizations.

4. Results

4.1. Characteristics of MCI participants versus healthy controls

Over a two and a half year period, 237 participants were recruited: 139 participants with MCI and 98 controls. Demographic and clinical characteristics are listed in Table 1. Groups were well balanced on most variables but differed on the MMSE and the ACE-R; the MCI group had poorer performance than the control group, as might be expected, on these measures.

4.2. Neuropsychological performance of MCI patients at entry to the service (time 1)

Table 2 lists the mean neuropsychological test results in the two study groups at time 1. The MCI group performed

Table 1
Characteristics of MCI and control participants

	MCI, n = 139	Control, n = 98	t(df); P or χ²(df); P
Age, y, mean (SD)	72.84 (9.47)	74.73 (9.01)	−1.55 (237); .12
Range, min–max	43–93	52–94	
NART IQ, mean (SD)	113.71 (8.47)	113.48 (8.41)	0.20 (237); .84
Years of education, mean (SD)	12.17 (3.0)	11.61 (3.1)	1.48 (237); .14
MMSE, mean (SD)	27.88 (1.69)	29.38 (0.82)	−8.11 (237); **.01**
ACE-R, mean (SD)	84.78 (5.70)	91.60 (4.39)	−2.22 (237); **.03**
DAD, mean (SD)	79.51 (1.01)	79.61 (2.16)	−0.50 (237); .62
Sex F:M (%)	81:58 (58:42)	54:44 (55:45)	0.24 (2); .63

Abbreviations: MCI, mild cognitive impairment; df, degree of freedom; SD, standard deviation; NART, National Adult Reading Test; IQ, intelligence quotient; MMSE, mini-mental state examination; ACE-R, Addenbrooke's Cognitive Examination-Revised; DAD, disability assessment in dementia.

NOTE. P values are indicated for the comparison between the MCI and control groups by unpaired t-test (significant P values are shown in bold)

Table 2
Baseline neuropsychological performance of MCI and control participants

Domains	MCI n = 139, mean score (SD)	Controls n = 98, mean score (SD)	t(df) P	Cohen's d
Immediate and delayed memory				
NYU immediate paragraph recall (words recalled)	3.6 (2.2)	5.6 (2.3)	−6.7 (236); <.01	0.89
NYU delayed paragraph recall (words recalled)	3.8 (3.1)	7.0 (2.8)	−8.2 (236); <.01	1.00
PAL stage reached	6.0 (1.5)	6.7 (0.9)	−3.0 (236); <.01	0.56
Executive function and attention				
CLOX1	11.0 (2.7)	12.0 (2.1)	−3.1 (236); <.01	0.41
Color trails 1 (s)	83.9 (39.7)	64.6 (22.8)	4.7 (236); <.01	0.59
Color trails 2 (s)	165.3 (65.2)	133.2 (46.5)	4.4 (236); <.01	0.57
Stroop color word (number in 45 s)	24.5 (10.7)	29.8 (9.5)	−3.9 (236); <.01	0.52
Hayling sentence completion (total performance)	13.4 (3.4)	15.5 (3.4)	−4.4 (236); <.01	0.62
Language				
COWAT letter fluency	10.8 (4.3)	12.3 (4.2)	−2.6 (236); .01	0.35
COWAT category fluency	13.6 (4.5)	16.8 (3.7)	−5.8 (236); <.01	0.78
Visuospatial function				
CLOX 2	13.1 (1.5)	13.8 (1.3)	−3.8 (236); <.01	0.50
Brixton spatial anticipation test (numberof errors)	18.3 (8.0)	15.4 (6.2)	2.8 (236); <.01	0.40

Abbreviations: MCI, mild cognitive impairment; SD, standard deviation; NYU, New York University; PAL, paired associate learning; COWAT, controlled oral word association test.

significantly worse than healthy controls on all cognitive tests.

4.3. Neurocognitive decline and conversion to dementia

MCI patients were followed for a mean of 18.4 months (SD, 10.2 months). Seventy-one patients remained stable at follow-up, 11 showed improvement to normal, 41 patients developed AD, one developed vascular dementia (VaD), and two developed mixed dementia; 13 patients were lost to follow-up due to illness (n = 9), moving from the area (n = 2), and death (n = 2). As there were such small numbers in the VaD and mixed dementia groups, these participants were added to the AD group to provide a final dementia diagnosis. There was adequate full neuropsychological follow-up in 116 patients from the neurocognitive study (23 patients had incomplete data collection) to allow for subdivision into cognitive domains. Category/subtype of MCI at time 1 and risk of progression to dementia were analyzed using Cox proportional hazard ratio (HR) in addition to a Kaplan-Meier analysis (Fig. 1). Two of 22 (9.1%) MCI participants from the NICS group, 1 of 12 (8.3%) from the ASD group, 35 of 55 (63.6%) from the AMD group, 3 of 19 (15.7%) from the NASD, and 2 of 8 (25.0%) from the NAMD group converted to dementia. When compared with the NICS group, the HR for conversion to dementia was 0.6 (95% confidence interval [CI], 0.1–6.2) in the ASD group, 3.9 (95% CI, 0.9–16.5) in the AMD group, 1.2 (95% CI, 0.2–7.2) in the NASD group, and 1.6 (95% CI, 0.2–11.7) in the NAMD group. The HR for conversion to dementia was 3.7 (95% CI, 1.7–8.0) in the AMD group compared with all other groups (P = .001). Rate of conversion from MCI to dementia was 15.7% per year. Of note, those who converted to dementia were significantly older at time 1 than those who remained stable or improved (F = 9.2,

$P < .01$); MMSE and ACE-R score at time 1 were also significantly lower in those who converted to dementia compared with those who remained stable or improved (F = 6.2, $P < .0$; F = 6.4, $P < .01$, respectively).

4.4. Latent profile analysis

The fit criteria for the latent profile analysis on 139 patients are given in Table 3. The AIC and SSABIC information criterion continued to decline with the addition of further latent profiles and were, thus, inconclusive; the lowest value of BIC suggested a four-profile solution was preferred. The LRT suggested a three-profile solution and a two-profile solution fitted equivalently well. Fit criteria were not equivocal in highlighting the best fitting model. Consequently, and with parsimony in mind, the two-, three-, and four-profile solutions were inspected. The two- and three-profile solution fit the data equivalently well
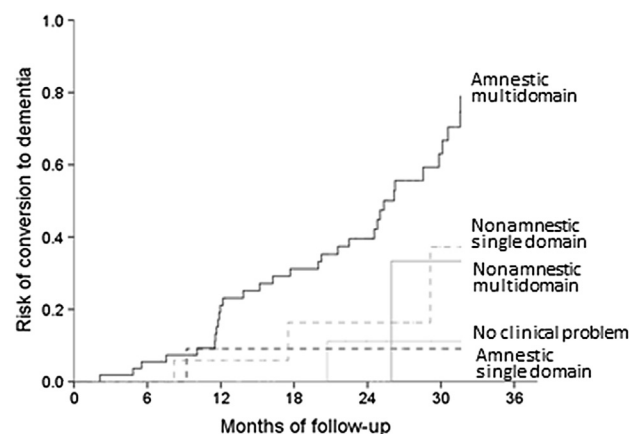

Fig. 1. Kaplan-Meier analysis of risk of conversion to dementia using Petersen and Morris criteria.

Table 3
Standard deviations below the mean in each neurocognitive test

Neurocognitive test	Profile 1: Memory deficit, n = 51	Profile 2: Least cognitively impaired, n = 32	Profile 3: Multiple deficit, n = 56
Category fluency	−0.84	−0.14	−1.72
CT1	0.14	−0.25	−1.62
CT2	0.12	−0.08	−1.48
Stroop	−0.26	−0.07	−1.48
CLOX 1	−0.17	−0.08	−1.21
CLOX 2	−0.55	−0.03	−1.12
Hayling	−0.80	−0.30	−1.21
Brixton	−0.36	0.07	−1.32
Letter fluency	−0.11	−0.08	−1.01
NYU 1	−1.07	0.27	−1.36
NYU 2	−1.43	0.34	−1.76

Abbreviations: CT, color trails; NYU, New York University.

Table 4
Odds ratios and 95% confidence intervals between predictors and latent profile membership

	Profile 1: Memory deficit	Profile 2: Least cognitively impaired
Age, continuous years	0.99 (0.94–1.05)	**0.92 (0.86–0.99)***
Sex, female	0.76 (0.35–1.66)	0.80 (0.27–2.38)
Education level, years in education	0.98 (0.83–1.14)	0.92 (0.75–1.13)
NART IQ score	0.99 (0.94–1.05)	**1.09 (1.01–1.18)***
Improved to normal at follow-up	**14.99 (2.84–79.10)***	**41.33 (4.62–260.03)***
Progressed to dementia at follow-up	**0.18 (0.08–0.40)***	**0.11 (0.02–0.60)***

Abbreviations: NART, National Adult Reading Test; IQ, intelligence quotient; MCI, mild cognitive impairment.

NOTE. Using profile 3: Multiple deficit MCI as reference category figures in bold and * denotes significance at .05 level.

according to the LRT. The addition of a third profile provided a qualitatively different neurocognitive profile to the existing two profiles; however, the four-profile solution did not provide four qualitatively distinct profiles. As such, the three-profile solution was preferred.

The largest profile group (profile 3) displayed the greatest degree of neuropsychological impairment at around 40% (n = 56) of the sample (Table 3). This grouping scored below 1 SD from mean performance on the cognitive tests examined, with category fluency, CT 1, and NYU 2 all 1.5 SD below mean performance. We would consider this profile to be best described as multiple deficit MCI.

The next largest group was profile 1 (36.7%; n = 51). This group was characterized by deficits primarily in NYU 1 and NYU 2 (>1 SD below the mean) along with less significant deficits in a number of other domains (at least 0.5 SD below the mean on category fluency and Hayling) but with CT 1 and CT 2 scores above the mean. This group most likely corresponds to a memory deficit MCI. Finally, there was a third group with scores generally around the mean for this sample (profile 2; n = 32), and with scores slightly above the mean on Brixton, NYU 1, and NYU 2; this group may best be described as least cognitively impaired.

However, to validate these three classes, a regression was run using the proportional membership for individuals in each profile. The odds ratios and 95% CIs are given in Table 4. From this, it can be seen that higher IQ and younger age were associated with membership of profile 2 compared with profile 3, and both membership of profiles 1 and 2 significantly differed from profile 3 in relation to change in MMSE with profiles 1 and 2 showing considerably higher odds of improving to normal, and considerably lower odds of progression to dementia on follow-up. The least cognitively impaired group unsurprisingly appeared less likely to progress to dementia and more likely to improve to normal than the memory deficit group.

On investigation of LPA naming, we found some agreement with the subtypes that were broadly derived from the Petersen and Morris (2005) criteria [4] (Table 5). Those classified as having NICS according to original criteria had most common overlap with profile 2, (56%) with the remainder in profile 1 (Table 4). The classification of ASD was almost entirely found in profile 1. The NASD had some overlap with profile 1 (31%) but most overlap with profile 2 (58%). The two "multidomain" categories were most commonly found in profile 3 as might be expected.

Nine of 47 participants (19.1%) in profile 1, 2 of 22 (9.1%) in profile 2, and 32 of 47 (68%) in profile 3 converted to dementia during follow-up (Fig. 2). Compared with profile 2, the HR for conversion to dementia was 1.5 (95% CI, 0.3–6.9) in profile 1 and 5.0 (95% CI, 1.2–21.1) in profile 3. The HR for conversion to dementia was 3.7 (95% CI, 1.8–7.4) in profile 3 compared with the other profiles ($P < .001$).

5. Discussion

Initial analyses showed the MCI participants were impaired on all cognitive tests compared with the control group. As in previous studies, most MCI participants were in the AMD subgroup (46.8%) [26,35,36]. The Goteborg MCI study [26] found a small percentage of MCI subjects could be categorized as ASD (1.8%) and 17% showed no impairment compared with controls, similar to the results reported here.

The AMD group of MCI participants was most at risk of conversion to dementia. Again, this has been found in several other studies [7,8]. The misconception that ASD MCI has the worst prognosis was also disproved: the category of ASD MCI was the most benign in terms of conversion and this replicates previously mentioned studies [7,8].

When an LPA was carried out, a three-profile solution was obtained. There was some agreement with the most likely latent profiles and the subtypes derived from the Petersen and Morris criteria (2005) [4]. Profile 3 was the largest group and most neuropsychologically impaired. This was felt to most closely represent the previously described AMD group, although there was some overlap also with the NAMD

Table 5
Classification of MCI participants According to the methods of Petersen and Morris (2005)

Group categorization by Petersen criteria	Number of MCI patients (%)	Of the total MCI patients in each category, breakdown in each profile (from LPA)		
		Profile 1: Memory deficit, n = 51 (36.7%)	Profile 2: Least cognitively impaired, n = 32 (23.0%)	Profile 3: Multiple deficit, n = 56 (40.3%)
No impairment of clinical significance	25 (18.0)	11 (44.0)	14 (56.0)	0 (0.0)
Amnestic single domain	13 (9.4)	12 (92.3)	1 (7.7)	0 (0.0)
Amnestic multidomain	65 (46.8)	17 (26.2)	1 (1.5)	47 (72.3)
Nonamnestic single domain	26 (18.7)	8 (30.8)	15 (57.7)	3 (11.5)
Nonamnestic multidomain	10 (7.2)	3 (30.0)	1 (10.0)	6 (60.0)

Abbreviations: MCI, mild cognitive impairment; LPA, latent profile analysis.

group. In this profile group, category fluency, CT 1, and NYU 2 were most impaired in keeping with deficits across several domains. A previous study using LPA in cognitively normal individuals demonstrated poor performance in CT 2 and delayed recall significantly predicted later cognitive impairment [37]. This study illustrated a similar pattern in MCI participants.

Profile 1 contained 92% of the previously defined ASD group. This group had considerable deficits in memory and smaller deficits in verbal fluency and executive function. Some individuals in profile 1, however, had no impairment of clinical significance with individual mean scores around the mean for some of the neuropsychological indicators. Profile 2 contained most of the previously ascribed no NICS or NASD group with preserved memory and recall and very small deficits in executive function.

Interestingly, those in the least impaired profile 2 were younger and had a higher IQ compared with those in profile 3. These participants had health seeking behavior regarding their memory but on in-depth neurocognitive testing were mostly found to have NICS. There may be protective elements from younger age and higher IQ at play. The cognitive reserve hypothesis postulates that cognitive reserve in the form of higher IQ, education, or occupational attainment reduces the prevalence of cognitive decline [38]. Profiles 1 and

Fig. 2. Kaplan-Meier analysis of risk of conversion to dementia using latent profile analysis.

3 did not differ in terms of years of education but in terms of premorbid IQ. Assessment of IQ has been shown to be a more accurate estimation of optimal cognitive functioning than years of education especially in an older cohort who do not accurately remember their years of education [39].

Older age was a significant predictor of decline in the traditional analysis and its impact is borne out again in the LPA analysis; participants in profile 3 similar to the AMD group were older and were significantly more likely to convert to dementia and significantly less likely to improve to normal at time 2. This has been demonstrated previously in similar studies [40,41] where age was either a very significant variable or the only variable influencing likelihood of conversion to dementia. Lower MMSE at entry has also been demonstrated previously as a significant risk factor for conversion to dementia; similar to this study [40,41].

MCI is a highly heterogeneous construct that defines the gray area between intact cognitive functioning and clinical dementia. The construct has evolved over the past 10 years, but controversial issues in classification remain due to differences in operationalization of the original criteria, differences in the setting, selection of subjects, and length of follow-up in longitudinal studies [42]. The five Petersen and Morris criteria were found in our sample, and the neurocognitive battery revealed three distinct profiles when LPA was used to empirically explore the scores. A previous study [11] discovered five latent classes within a group of MCI and subjective memory impairment participants but they did not include visuospatial function or language within their neuropsychological battery. Our study included assessment of all neurocognitive domains so can be considered more extensive in this regard. Not finding similar profiles in this data may have been a function of (1) the sample size and variability, (2) the additional neurocognitive tests, or (3) as a function of the relationships between the domains in the data. Confirmatory latent variable modeling in subsequent data sets may help to understand differences, and we recommend using the wide range of neurocognitive tests as used here to better represent the clinically defined condition.

Our study demonstrated both methods were useful in predicting conversion to dementia with identical HR for conversion to dementia in the AMD group and profile 3. This reinforces the fact that impairment in more than one
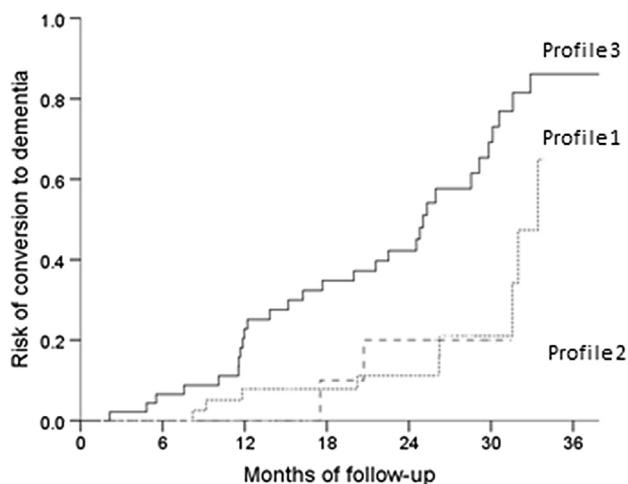
cognitive domain places one at greater risk of conversion to dementia. Membership of other Petersen and Morris (2005) classifications or latent profiles appears relatively benign and so patients in these groups could be reassured regarding their risk of conversion to dementia.

Shortfalls of our study include short follow-up time and attrition rate. Follow-up was limited by funding constraints, and high attrition is a risk factor in longitudinal studies in the elderly; mean age in our MCI group was 72.8 years and participants had multiple comorbidities. One–2 year follow-up, however, provides data during the most clinically relevant period for management of those with MCI.

The use of LPA to explore the patterns of neurocognitive deficit is a useful addition to better understanding the differences between patients. To the best of our knowledge, this is the first study to explore MCI in this way. In order for this method to be useful in a clinical setting, future research should attempt replication and validation in similar samples, and a comparison of latent class and latent profile methods. The exploration of these profiles in terms of patient-reported outcomes and other clinical outcomes would also be greatly welcomed.

Acknowledgments

RESEARCH IN CONTEXT

1. Systematic review: Previous research was identified by an online search (using PubMed) of neurocognitive studies in mild cognitive impairment (MCI) and of latent profile analysis in dementia/MCI. Results from the searches were collated and assessed by two authors (B.M. and G.W.S.). Relevant studies were referenced in the text.

2. Interpretation: Findings from this study contribute to the knowledge base regarding cognitive profiles of MCI and their risk of conversion to dementia. Amnestic multidomain MCI participants were most at risk of conversion and this finding adds to the literature base in this area. We used latent profile analysis, a novel statistical analysis in this cohort of participants to empirically define extent of impairment.

3. Future directions: Future research should attempt replication of the patterns and follow participants over a longer period of time.

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