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Visual memory tests enhance the identification of amnestic MCI cases at greater risk of Alzheimer's disease

Javier Oltra-Cucarella, MSc[a,b], **Miriam Sánchez-SanSegundo, PhD**[a], **Darren M Lipnicki, PhD**[c], **John D Crawford, PhD**[c], **Richard B Lipton, PhD**[d], **Mindy J Katz, PhD**[d], **Andrea R Zammit, PhD**[d], **Nikolaos Scarmeas, PhD**[e,f], **Efthimios Dardiotis, PhD**[g], **Mary H Kosmidis, PhD**[h], **Antonio Guaita, PhD**[i], **Roberta Vaccaro, PhD**[i], **Ki Woong Kim, PhD**[j,k], **Ji Won Han, PhD**[j], **Nicole A Kochan, PhD**[c], **Henry Brodaty, DSc**[c,l], **José A Pérez-Vicente, MD**[b], **Luis Cabello-Rodríguez, MD**[b], **Perminder S Sachdev, MD**[c,l], **Rosario Ferrer-Cascales, PhD**[a,*], **Cohort Studies of Memory in an International Consortium (COSMIC)**

[a]Department of Health Psychology, University of Alicante (Spain). Campus de San Vicente del Raspeig s/n, 03690 San Vicente del Raspeig, Alicante, Spain.

[b]Unit of Cognitive Impairments and Movement Disorders, Hospital General Universitario Santa María del Rosell. Paseo Alfonso XIII, 61, 30203 Cartagena, Murcia

[c]Centre for Healthy Brain Ageing, UNSW Medicine, School of Psychiatry, NPI, Euroa Centre, Barker Street, Randwick, NSW 2031 Australia.

[d]Albert Einstein College Of Medicine. 1225 Morris Park Avenue, Room 3C12B. Bronx, NY 10461

[e]Columbia University. Medical Center, Department of Neurology, 622 West 168th street, 10032, New York, NY

[f]National and Kapodistrian University of Athens, Department of Medicine, 1st Neurology Clinic, Aeginition Hospital, 72 Vasilissis Sofias Avenue, 11528, Athens, Greece

[g]Neurology Department, University Hospital of Larissa, University of Thessaly

[h]Laboratory of Cognitive Neuroscience, School of Psychology, Aristotle University of Thessaloniki, 54124 Thessaloniki, Greece

[i]Golgi Cenci Foundation, Corso San Martino 10, 20081 Abbiategrasso (Milan) Italy

[*]Corresponding author: Rosario Ferrer-Cascales. Department of Health Psychology, University of Alicante (Spain). Campus de San Vicente del Raspeig s/n, 03690 San Vicente del Raspeig, Alicante, Spain. Phone number: +34 965 90 34 00 Ext. 9420. rosario.ferrer@ua.es.

Description of authors' roles

Javier Oltra-Cucarella, Miriam Sánchez-SanSegundo, Rosario Ferrer-Cascales, José A. Pérez-Vicente and Luis Cabello-Rodríguez designed the study.

Javier Oltra-Cucarella, Darren Lipnicki, Perminder Sachdev and John Crawford analyzed the data.

Perminder Sachdev, Darren Lipnicki, John Crawford, Richard Lipton, Mindy Katz, Andrea Zammit, Nikolaos Scarmeas, Efthimios Dardiotis, Mary Kosmidis, Antonio Guaita, Roberta Vaccaro, Ki Woong Kim, Ji Won Han, Nicole Kochan and Henry Brodaty collected data.

Javier Oltra-Cucarella and Darren Lipnicki drafted the original manuscript.

Javier Oltra-Cucarella, Miriam Sánchez-SanSegundo, Rosario Ferrer-Cascales, José A. Pérez-Vicente, Luis Cabello-Rodríguez, Perminder Sachdev, Darren Lipnicki, John Crawford, Richard Lipton, Mindy Katz, Andrea Zammit, Nikolaos Scarmeas, Efthimios Dardiotis, Mary Kosmidis, Antonio Guaita, Roberta Vaccaro, Ki Woong Kim, Ji Won Han, Nicole Kochan and Henry Brodaty reviewed the paper for intellectual content

Conflict of interest

The authors report no disclosures. Dr. Henry Brodaty is on the advisory board for Nutricia.

[j]Department of Psychiatry, Seoul National University Bundang Hospital, 82 Gumi-ro 173beongil Bundang-gu, Seongnam-si,Gyeonggi-do, 13620, Korea.

[k]Department of Brain and Cognitive Science, Seoul National University College of Natural Sciences, Kwanakro 1, Kwanakgu, Seoul, 08826, Korea. Department of Psychiatry, Seoul National University, College of Medicine, 103 Daehak-ro, Jongnogu, Seoul, 03080, Korea

[l]Dementia Centre for Research Collaboration, University of New South Wales, Sydney, Australia.

Abstract

OBJECTIVES: To investigate whether aMCI identified with visual memory tests conveys an increased risk of Alzheimer's disease (risk-AD), and if the risk-AD differs from that associated with aMCI based on verbal memory tests.

PARTICIPANTS: 4,771 participants aged 70.76 (SD=6.74, 45.4% females) from five community-based studies, each a member of the international COSMIC consortium and from a different country, were classified as having normal cognition (NC) or one of visual, verbal or combined (visual and verbal) aMCI using international criteria and followed for an average of 2.48 years. Hazard ratios (HR) and individual patient data (IPD) meta-analysis analyzed the risk-AD with age, sex, education, single/multiple domain aMCI, and MMSE scores as covariates.

RESULTS: All aMCI groups (n=760) had a greater risk-AD than NC (n=4,011, HR range: 3.66–9.25). The risk-AD was not different between visual (n=208, 17 converters) and verbal aMCI (n=449, 29 converters, HR=1.70, 95%CI: 0.88, 3.27, p=.111). Combined aMCI (n=103, 12 converters, HR=2.34, 95%CI: 1.13, 4.84, p=.023) had a higher risk-AD than verbal aMCI. Age and MMSE scores were related to the risk-AD. The IPD meta-analyses replicated these results, though with slightly lower HR estimates (HR range: 3.68, 7.43) for aMCI vs. NC.

CONCLUSIONS: While verbal aMCI was most common, significant proportions had visual only or combined visual and verbal aMCI. Compared to verbal aMCI, the risk-AD was the same for visual aMCI and higher for combined aMCI. Our results highlight the importance of including both verbal and visual memory tests in neuropsychological assessments to more reliably identify aMCI.

Keywords

Alzheimer's disease; memory; mild cognitive impairment; progression

Introduction

Episodic memory impairment is the prominent feature of both amnestic mild cognitive impairment (aMCI) and Alzheimer's Disease (AD) (Albert et al., 2011; McKhann et al., 2011). Accordingly, individuals with aMCI (Marcus et al., 2014) and AD (Hoffman et al., 2000) both show evidence of hypometabolism in bilateral temporal regions associated with verbal (left medial temporal lobe) and visual (right medial temporal lobe) memory processes (Bonner-Jackson et al., 2015). However, not all individuals with aMCI present with impairments of both verbal and visual memory. Indeed, even if both impairments develop, one may arise years before the other (Mistridis et al., 2015). This means that

aMCI can present as verbal aMCI (only verbal memory impaired), visual aMCI (only visual memory impaired), or combined aMCI (both verbal and visual memory impaired).

Poor performance on verbal and visual memory tasks predicts progression to dementia (Schmid et al., 2013; Didic et al., 2013; Kawas et al., 2003). A recent study found that middle-aged individuals who had a parent diagnosed with dementia exhibited poorer-than-normal test scores for visual memory, while verbal memory test scores were unaffected (Ritchie et al., 2017). Despite this, literature seems to suggest that verbal memory impairments may be a better predictor of AD (Dierckx et al., 2009). Grey matter reductions in the left hippocampus and parahippocampal gyrus are reportedly the strongest imaging predictor of AD in MCI (Ferreira et al., 2011), and significant thinning in left temporal regions was identified in individuals with verbal aMCI, but not in individuals with visual aMCI (Kim et al., 2011). However, recent evidence suggests that aMCI is associated with bilateral hippocampal atrophy (Szamosi et al., 2013), and that hippocampus volume is associated with both verbal and visual memory test scores (Zammit, Ezzati, Katz, et al., 2017; Zammit, Ezzati, Zimmerman, et al., 2017).

While the evidence suggests that both verbal and visual memory test scores can predict AD, research on the risk of progression to AD (risk-AD) for visual or verbal aMCI has been scarce. Previous studies found that individuals with visual aMCI were at greater risk-AD than normal controls, but did not compare the rates against individuals with verbal aMCI (Larrieu et al., 2002; Kawas et al., 2003). Another study found that verbal aMCI and combined aMCI were both more likely to progress to AD than visual aMCI (Ye et al., 2015). However, their cut-off of <1 standard deviation (SD) for defining objective cognitive impairment was more liberal than the <1.5 SD of standard international guidelines for diagnosing MCI (Albert et al., 2011; Winblad et al., 2004), and the generalizability of the study is further limited by having been conducted in Korean individuals and a relatively short follow-up (1.8 years).

The current study aimed to investigate the risk-AD among mutually exclusive groups of visual, verbal and combined aMCI in a sample of community-dwelling individuals. We expand upon previous work by analyzing verbal, visual and combined aMCI data from five cohorts. These studies were from five different countries, and share the relatively rare characteristic of having administered both verbal and visual tests of memory. Knowing the relative risk-AD for visual, verbal and combined aMCI will have implications for the choice of memory tests when diagnosing aMCI, and also might help to interpret and compare the results of earlier studies, particularly those that used only one type of memory test, visual or verbal. We hypothesized that both visual and verbal aMCI would convey an increased risk-AD relative to normal cognition, but considered the existing evidence too insubstantial to predict a difference in risk between these.

Methods

Data for this study were obtained from members of the Cohort Studies of Memory in an International Consortium (COSMIC) (https://cheba.unsw.edu.au/group/cosmic) (Sachdev et al., 2013). Five longitudinal studies of community-dwelling older adults participated: the

Sydney Memory and Ageing Study (Sydney MAS) (Sachdev et al., 2010), the Korean Longitudinal Study on Cognitive Aging and Dementia (KLOSCAD) (Kim et al., 2013), the Einstein Aging Study (EAS) (Katz et al., 2012), the Invecchiamento Cerebrale in Abbiategrasso (Invece.Ab) study (Guaita et al., 2013), and the Hellenic Longitudinal Investigation of Aging and Diet (HELIAD) (Dardiotis et al., 2014). The references for these studies contain details of their recruitment process and selection criteria.

We included individuals with 1) either a classification of normal cognition (NC) or diagnosis of aMCI at baseline (as provided by the participating studies), 2) data for verbal and visual memory tests, and 3) follow-up assessment for AD. Exclusion criteria were Clinical Dementia Rating scale score ≥1 at baseline and missing data. Each study made aMCI classifications based on international criteria that included subjective cognitive complaints, objective cognitive impairment based on neuropsychological test results across different cognitive domains, minimal impairment in activities of daily living, and the absence of dementia (Petersen, 2004; Winblad et al., 2004; Artero et al., 2006; Petersen et al., 2001). Objective cognitive impairment was defined as performance ≥1.5 SD below the mean of a normative group in all studies except for Invece.Ab (z-scores ≤−1.64). All studies ensured adequate vision and hearing of participants prior to assessments. Further details of the criteria, cognitive tests and other diagnostic instruments used are shown in table S1 published as supplementary material online attached to the electronic version of this paper at https://www.cambridge.org/core/journals/international-psychogeriatrics. NCs were participants from within the same samples as those with aMCI, but not meeting the criteria for MCI and without dementia.

Visual and verbal memory test scores were used to further classify participants with aMCI as verbal, visual or combined aMCI. While all five studies had used a list learning test, three also used a story recall test. To maximize the comparability of verbal aMCI diagnoses across studies, and to match the use of only one visual memory test per study, we did not include story recall data when assigning aMCI subtypes. Performance on neuropsychological tests measuring cognitive abilities other than memory (table S1) was used to classify aMCI cases as single-domain aMCI (only memory) vs. multiple-domain MCI (memory and at least one other cognitive domain). All studies provided z-scores based on the performance of a normative reference group, corrected for age and education where available. Consensus diagnoses of AD were made by EAS, HELIAD, Invece.Ab, and KLOSCAD using the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association criteria (McKhann et al., 1984), and by Sydney MAS using the revised version of these by the National Institute on Aging and the Alzheimer's Association (NIA-AA) (McKhann et al., 2011).

This COSMIC project was approved by the University of New South Wales Human Research Ethics Committee (Ref: # HC17292). Each of the five contributing studies had previously obtained ethics approval from their respective institutional review boards, and all participants provided informed consent.

Data analysis

A series of one-way Analysis of Variance (ANOVA) was conducted to compare age, education and time to progression to AD between groups. Each ANOVA was run with Bonferroni correction for multiple comparisons. Partial eta-squared (h^2_p) was used to quantify effect size, with values of 0.01, 0.059 and 0.138 being the cut-off values for defining small, medium and large effects (Richardson, 2011).

The effects of diagnostic group (aMCI subtype or NC) on progression to AD were determined as hazard ratios using Cox proportional regressions, with time to progression calculated as the midpoint between the assessment when AD was first classified and the preceding assessment. We ran two regression models. The first model tested our hypothesis of a greater risk-AD for each of the three aMCI subtypes than for NCs (the reference group), with sex, age, education and MMSE included as covariates. The second model investigated whether the risk-AD for visual aMCI and combined aMCI differed from the risk-AD for verbal aMCI. The NC group was omitted, and sex, age, education, MMSE, single-domain vs. multiple-domain and aMCI group were included as covariates; verbal aMCI was the reference as it had the largest sample size and its association with risk-AD is better known (Mitchell and Shiri-Feshki, 2009). For each of the models, the proportional hazards assumption was assessed with log-minus-log survival plots (Vittinghoff et al., 2005).

To investigate the reliability of our results, we conducted a one-stage individual patient data meta-analysis (IPD-MA) for survival data. The one-stage IPD-MA analyzes patient-level data nested within studies, avoids the assumption of within-study normality and known within-study variance (Burke et al., 2017), and handles the differences in numbers of individuals with particular aMCI subtypes across the five studies investigated. We modeled each group with sex, age, education, MMSE and single-domain vs. multiple-domain aMCI as fixed effects allowing for random intercepts for each study and a Weibull distribution. ANOVAs and Cox regressions were conducted with SPSS v.22. IPD-MA were conducted using the *stmixed* command for a flexible parametric framework (Crowther et al., 2014) for Stata 15.1. All comparisons were considered statistically significant for an $\alpha < .05$.

Results

The five contributing studies provided data for 6,175 individuals (4,061 NC and 2,114 MCI). Of these, we excluded 1332 (60.31%) classified as naMCI, 33 who converted to dementia other than AD, 37 missing MMSE scores and 2 missing time to follow-up. Of the 4,771 remaining participants, 4,011 were classified as NC and 760 as aMCI, of whom 449 (59.1%) had verbal aMCI, 208 (27.4%) had visual aMCI, and 103 (13.5%) had combined aMCI. Verbal aMCI was more prevalent than visual aMCI in Sydney MAS (51.2% vs. 40.7%), KLOSCAD (63.1% vs. 24.2%), and Invece.Ab (54.8% vs. 28.6%). Visual aMCI was more prevalent than verbal aMCI in HELIAD (40% vs. 13.3%) and EAS (58.3% vs. 16.7%).

ANOVAs showed differences between the NC and three aMCI groups in age, education, MMSE scores and length of follow-up (Table 1). The NC group was younger than individuals with verbal aMCI and visual aMCI, with no differences among the MCI groups. The NC group was more educated than the verbal and visual aMCI groups, while

participants with verbal aMCI were less educated than participants with visual aMCI and combined aMCI. The length of follow-up was higher for visual aMCI than for verbal aMCI and combined aMCI. The NC group had higher MMSE scores than all aMCI groups, while the verbal aMCI group had lower scores than the visual aMCI group. Effect sizes suggest these differences were negligible for length of follow-up, small for age and education, and medium for MMSE scores. There were no statistically significant differences with regards to sex. The percentage of participants with multiple-domain MCI was higher in the visual (72.1%) and combined aMCI (70.9%) than in verbal aMCI (59.2%) (χ^2 (2, N = 760) = 12.48, p = .002).

Risk of progression to AD

Of the 4,771 participants analyzed, 41 (1%) NC, 29 (6.5%) verbal aMCI, 17 (8.2%) visual aMCI, and 12 (11.7%) combined aMCI participants progressed to AD. Compared to non-progressors, progressors were older (Progressors: M = 77.68, SD = 5.39, Non-progressors: M = 70.62, SD = 6.69, F(1, 4,770) = 108.79, p < .001, η^2 = .022), had a shorter follow-up (Progressors: M = 2.05, SD = 1.37, Non-progressors: M = 2.52, SD = 1.23, F(1, 4,770) = 14.10, p < .001, η^2 = .003) and had lower MMSE scores (Progressors: M = 24.01, SD = 4.66, Non-progressors: M = 26.72, SD = 2.69, F(1, 4,770) = 94.50, p < .001, η^2 = .019). Effect sizes suggest these differences were negligible for length of follow-up and small for age and MMSE scores. There were no differences in sex ratio (χ^2 (1, N = 4,771) = 0.00, P value > .99) or level of education (Progressors: M = 8.63, SD = 5.47, Non-progressors: M = 9.35, SD = 5.14, F(1, 4,770) = 1.96, p = .16, η^2 = .00).

Risk-AD for aMCI versus NC

All aMCI groups had a greater risk-AD compared to the NC group (Table 2). Older age and lower MMSE scores were both associated with an increased risk-AD. Neither sex (p = .136) nor education (p = .086) were associated with the risk-AD. Log-minus-log survival plot curves did not suggest non-proportionality (Figure 1a).

Risk-AD for visual and combined aMCI versus verbal aMCI

The risk-AD for visual aMCI was not significantly different than the risk-AD for verbal aMCI (Table 2). However, combined aMCI had a two-fold increased risk-AD compared to verbal aMCI. Across all the aMCI groups, older age and lower MMSE scores were both associated with an increased risk-AD. The risk-AD was not affected by sex (p = .883), education (p = .113), or single/multiple domain MCI (p = .516). Log-minus-log survival plot curves did not suggest non-proportionality (Figure 1b).

Individual Patient Data meta-analysis

The IPD-MA produced very similar results to those found using Cox regressions. Each aMCI group showed a greater risk-AD than the NC group (Figure 2a), though with slightly lower hazard ratios estimates, and with older age and MMSE scores again associated with an increased risk-AD (Table 3). This model showed heterogeneity in baseline hazard functions, indicating significant different baseline hazards among the studies included. With regards to the aMCI groups, combined aMCI again showed an increased risk-AD compared to verbal

aMCI (Figure 2b), and both older age and lower MMSE scores were again associated with an increased risk-AD (Table 3). This model showed no heterogeneity in baseline hazard functions, indicating that baseline hazards were similar for aMCI groups among the studies included.

Discussion

As hypothesized on the basis of previous research (Mitchell and Shiri-Feshki, 2009), we found that the risk-AD for both verbal and visual aMCI was greater than the risk-AD for NCs. We also found that compared to verbal aMCI, the risk-AD was similar for visual aMCI but greater for combined aMCI, and believe our study is the first to make these comparisons having classified aMCI in community-dwelling older adults using internationally recognized criteria. A previous report of greater risk-AD for verbal than visual aMCI in a clinical sample (Ye et al., 2015) did not use such criteria, featured a more liberal cut-point for cognitive impairment (−1SD vs. −1.5SD), and had a shorter follow-up duration (1.8 vs 2.5 years).

Our results have important implications in light of diagnostic criteria for MCI that have focused on verbal memory tests (Petersen et al., 1999; Winblad et al., 2004), or that have included a visual memory test in a recommended list of tests but not stipulated that both verbal and visual tests be used (Albert et al., 2011). We found that some participants can perform normally on a verbal memory test but be classified as aMCI because of poor visual test scores, and that these individuals exhibit the same risk-AD as those with verbal aMCI. Though the prevalence of visual aMCI was less than verbal aMCI, it was still considerable at 27.4%, and certainly sufficient to suggest that assessments of MCI should include both verbal and visual memory tests to more reliably identify individuals at increased risk-AD. It could be argued that having two memory tests instead of one increases the chances of detecting aMCI, and could simply be achieved with two verbal memory tests. However, it must be remembered that some individuals with a familial risk of AD perform poorly on visual memory tests but normally on verbal memory tests (Ritchie et al., 2017), and that visual aMCI can arise independently of verbal aMCI (Mistridis et al., 2015). There is also evidence that future AD is better predicted by visual memory test scores than verbal memory test scores in some individuals (Didic et al., 2013). Even so, individuals with visual aMCI (or poor visual test scores) show similar regions of brain pathology as individuals with verbal aMCI (or poor verbal test scores) (Bonner-Jackson et al., 2015; Zammit, Ezzati, Katz, et al., 2017; Zammit, Ezzati, Zimmerman, et al., 2017). With a similar risk-AD, it thus seems that visual and verbal aMCI may be different behavioral expressions of the same underlying disease process.

The greater risk-AD for combined aMCI does not seem to be an effect of having two impairments rather than one, as multiple domain aMCI did not show a greater risk-AD than single domain aMCI, and suggests that memory impairment severity is the primary cognitive predictor of the risk-AD. This idea is consistent with findings from a previous study where verbal aMCI was defined as having three or more test scores at least 1.5 standard deviations below the mean (Oltra-Cucarella et al., 2018), which reported on a higher progression rate to AD for single-domain aMCI (three low memory scores) than for multiple-domain aMCI

with combined memory and non-memory impairments. Our findings are also consistent with a previous report that among individuals with single-domain aMCI, converters to AD had lower scores than non-converters on both verbal and visual memory tests, but similar scores on tests assessing other cognitive domains (Didic et al., 2013).

Strengths of our study include the large sample size and the inclusion of individuals from different countries, all of them assessed with a cognitive battery covering several cognitive domains and classified as MCI or NC using similar standard criteria, which makes our results generalizable to many populations. Further, we avoided the limitations of a group-based meta-analytic approach by analyzing individual level data with a one-stage IPD-MA, which allowed us analyzing survival data with a hierarchical structure, thus controlling data from individual participants nested within studies. The finding of similar hazard estimates between Cox regression and the one-stage IPD-MA validates our results and increases their generalizability.

Limitations of our study include not using biomarker data, such as white matter lesion load, amyloid-beta, tau, brain atrophy levels, or *APOE ε4* allele prevalence, to better characterize our aMCI subtypes. This also prevented us exploring whether the risk-AD for verbal and visual aMCI diagnoses made using NIA-AA diagnostic criteria (Albert et al., 2011) are different from those with similar cognitive criteria but that do not utilise biomarker data (Petersen, 2004; Winblad et al., 2004). While the studies administered similar sorts of verbal memory tests, the type of visual memory tests differed. This may have contributed to differences in, as well as the overall prevalence of, visual aMCI. It must also be considered that verbal memory processes may have a role in visual memory test performance, and thus the distinction between types of memory assessed by visual and verbal memory tests may not be clear cut (Moye, 1997). This would create a tendency for similar results for verbal and visual aMCI, as would the use by one of the contributing studies of a list learning test that presented items visually (Katz et al., 2012).

Finally, the relatively small number of progressors to AD in our groups may have restricted our ability to detect any true difference in the risk-AD between visual and verbal aMCI. While the 1.7 times higher risk of progressing to AD for visual aMCI compared to verbal aMCI suggests there may be a difference, this was not significant ($p = .111$). However, even if significant, a HR of 1.70 would only indicate a small effect size (Azuero, 2016). Thus, future works should not only expand upon our findings by including biomarkers to help distinguish between aMCI subtypes, but also by investigating whether the same pattern is found in studies with larger samples and with samples taken from specialized memory clinics, where rates of progression from MCI to AD are typically higher than for community-based samples (Mitchell and Shiri-Feshki, 2009).

Visual impairments have been shown to predict AD several years before diagnosis (Kawas et al., 2003; Zonderman et al., 1995), and analyzing longer follow-up periods may help clarify whether verbal and visual memory impairments differ in sensitivity to identify individuals at an increased risk-AD. A recent meta-analysis of tests for differentiating MCI from NC reported that delayed visual memory tests showed lower sensitivity than delayed verbal memory tests (Weissberger et al., 2017). It will be important to determine if there is an

optimal type of visual memory test for inclusion in MCI assessments, with consideration being given to the degree of contamination by verbal memory processes, the psychometric properties for identifying aMCI and predicting AD, and the practicalities of administration and scoring in both clinic and community contexts.

This is, to our knowledge, the first work analyzing the risk-AD for visual aMCI in a large sample of community-dwelling individuals from different countries. Our results show that over one quarter of individuals in our sample with aMCI would have been missed if only the list-learning, verbal memory test had been used. This suggests that neuropsychological assessments should include both verbal and visual memory tests to avoid misdiagnosing or missing a considerable proportion of individuals at enhanced risk-AD. As individuals with visual-only aMCI had a greater risk-AD compared to individuals with normal cognition, using only verbal memory tests to define aMCI would render these individuals ineligible for further assessment in prevention trials and for preventive treatments once they are approved, as they would be labeled either as having normal cognition or as having non-amnestic MCI. Relatedly, as combined aMCI had a greater risk than verbal-only aMCI, using only verbal memory tests to define aMCI would bias true progression rates downwards, and individuals at the greater risk-AD would be erroneously misclassified. These implications are not simply clinical, but apply also to research. Findings from the widely-used Alzheimer's Disease Neuroimaging Initiative (Petersen et al., 2010) might be affected, because low scores only on verbal memory tests are used to classify MCI. The Uniform Data Set (UDS) from the National Alzheimer's Coordinating Center (Beekly et al., 2007) has recently included a visual memory test (Weintraub et al., 2018), which may help identify the full range of individuals at greater risk-AD.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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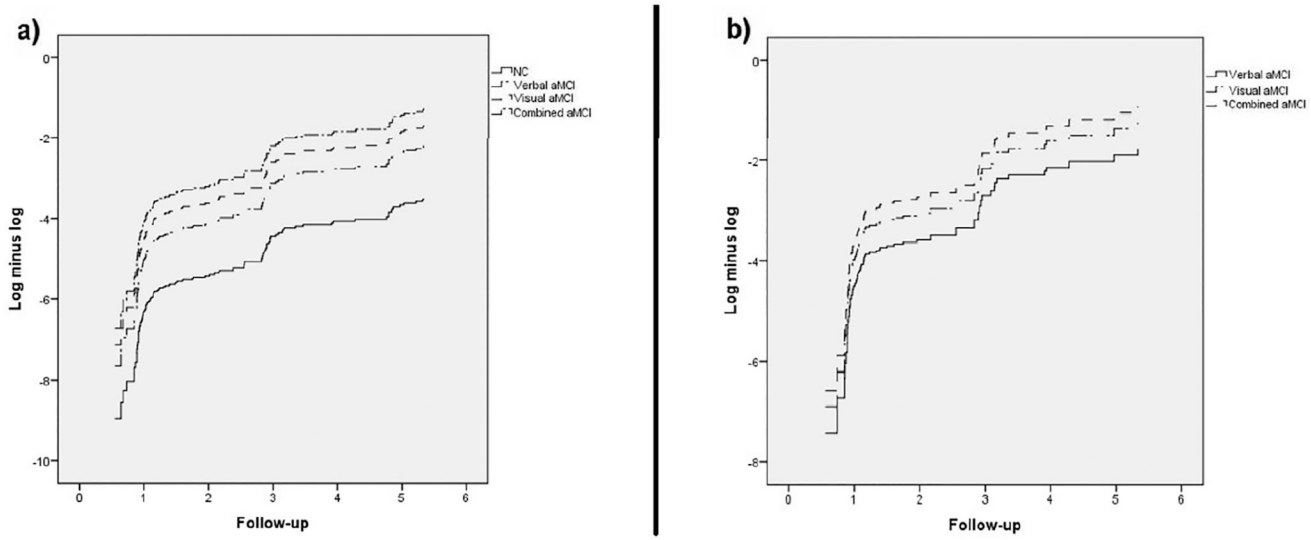

Figure 1.

Log minus log plots for proportionality assumption

NC: normal cognition. aMCI: amnestic Mild Cognitive Impairment

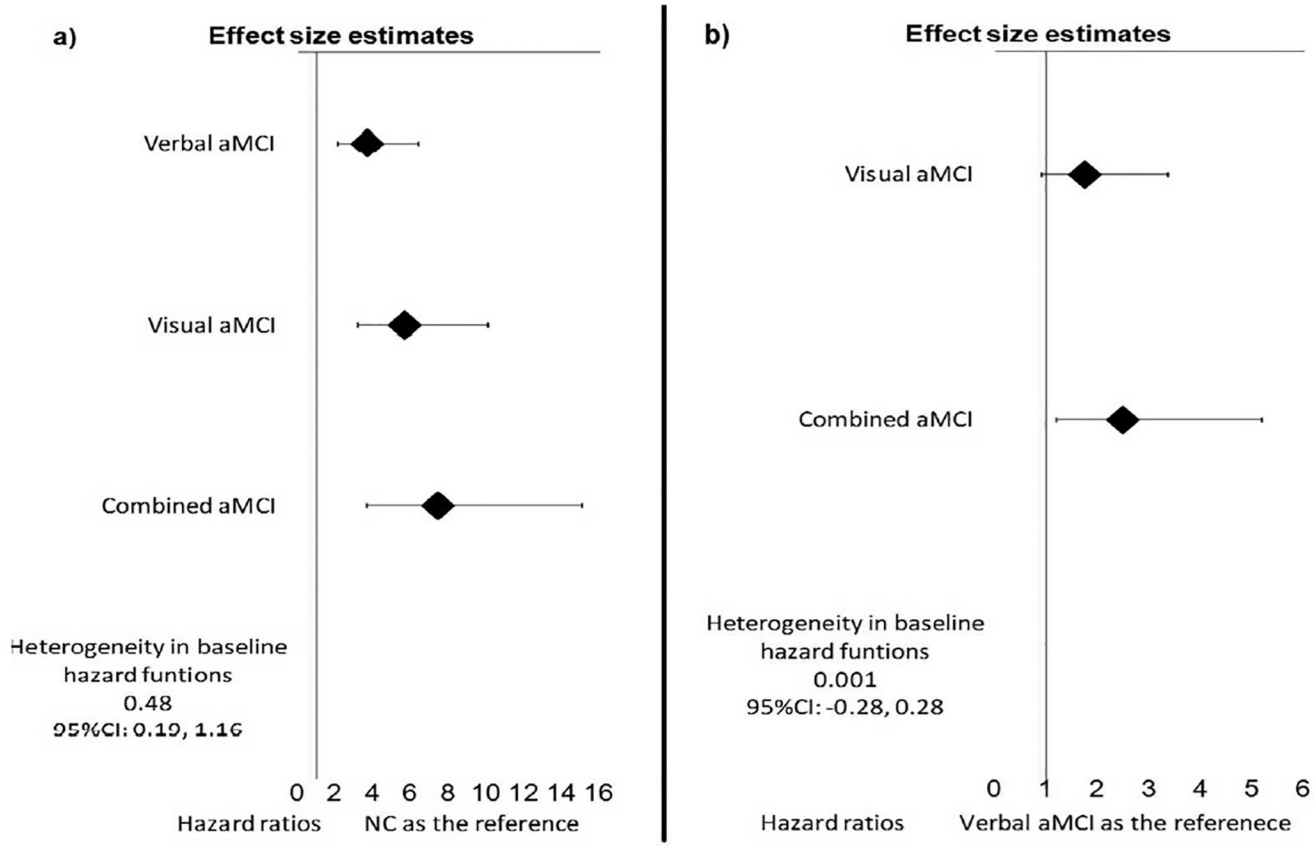

Figure 2.

Forest plots of hazard ratios stratified by groups

NC: normal cognition. aMCI: amnestic Mild Cognitive Impairment. CI: confidence interval.

Table 1.

Characteristics of the NC and aMCI groups. Values are presented as means (and standard deviations)

	NC (n = 4,011)	Verbal aMCI (n = 449)	Visual aMCI (n = 208)	Combined aMCI (n = 103)	F	*p*	η^2_p
Age	70.38	72.95	72.90	71.95			
	(6.70)	(6.71)	(6.81)	(5.60)	28.67	<.001	0.018
Education	9.65	7.14	8.34	8.87			
	(5.15)	(4.85)	(4.53)	(4.79)	35.95	<.001	0.022
Follow-up	2.52	2.42	2.66	2.32			
	(1.25)	(1.09)	(1.33)	(1.05)	2.75	.041	0.002
MMSE	26.99	24.64	25.63	25.02			
	(2.42)	(3.97)	(3.46)	(3.15)	128.96	<.001	0.075
Sex (M/F)	2169/1842	265/184	121/87	50/53	6.58[a]	.087	0.037[b]

n = sample size. aMCI: amnestic Mild Cognitive Impairment. M: male. F: female.

[a] χ^2-test.

[b] Carmer's V

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Table 2.

Cox survival regression. Hazard ratios for the risk of conversion to Alzheimer's disease among verbal, visual and combined aMCI groups

	NC* (ref)				Verbal aMCI† (ref)			
	HR	**99%CI**	**Wald**	***p***	**HR**	**99%CI**	**Wald**	***p***
Verbal	3.66	(2.12,6.31)	21.69	<.001		-		
Visual	6.15	(3.48,10.85)	39.24	<.001	1.70	(0.88, 3.27)	2.54	.111
Combined	9.25	(4.79,17.87)	43.93	<.001	2.34	(1.13,4.84)	5.20	.023

NOTE. Analyses were controlled for age, sex, education and MMSE scores. Cox regressions for aMCI subtypes also included a single/multiple domain variable.

HR: hazard ratio. NC: normal control group. aMCI: amnestic mild cognitive impairment.

*Significant covariates: age (HR = 1.08, 95%CI: 1.04, 1.11, p < .001) and MMSE (HR = 0.81, 95%CI: 0.77, 0.86, p < .001)

†Significant covariates: age (HR = 1.05, 95%CI: 1.01, 1.09, p < .001), and MMSE (HR = 0.80, 95%CI: 0.74, 0.86, p < .001).

Table 3.

Independent Patient Data meta-analysis. Hazard ratios for the risk of conversion to Alzheimer's disease among verbal, visual and combined aMCI groups

	NC* (ref)				Verbal aMCI† (ref)			
	HR	**99%CI**	**z**	***p***	**HR**	**99%CI**	**z**	***p***
Verbal	3.68	(2.11,6.39)	4.61	<.001				
Visual	5.66	(3.17,10.09)	5.86	<.001	1.74	(0.90, 3.36)	1.66	.097
Combined	7.43	(3.66,15.08)	5.56	<.001	2.48	(1.19,5.18)	2.42	.016

NOTE. Analyses were controlled for age, sex, education and MMSE scores. IPD meta-analysis for aMCI subtypes also included a single/multiple domain variable.

HR: hazard ratio. NC: normal control group. aMCI: amnestic mild cognitive impairment.

*Significant covariates: age (HR = 1.08, 95%CI: 1.04, 1.12, p < .001) and MMSE (HR = 0.75, 95%CI: 0.70, 0.80, p < .001).

†Significant covariates: age (HR = 1.07, 95%CI: 1.03, 1.12, p = .001), and MMSE (HR = 0.76, 95%CI: 0.71, 0.82, p < .001).