Progression of mild cognitive impairment to dementia due to AD in clinical settings

Karim Tifratene, MD
Philippe Robert, MD, PhD
Asya Metelkina, PhD
Christian Pradier, MD, PhD
Jean François Dartigues, MD, PhD

Correspondence to Dr. Tifratene: tifratene.k@chu-nice.fr

ABSTRACT

Objectives: To describe the positive predictive value of mild cognitive impairment (MCI) and the factors associated with progression in routine practice.

Methods: A retrospective cohort study was conducted from the French National Alzheimer Database. Among 446,439 patients cared for in the participating centers between January 2009 and January 2014, 45,386 (10.2%) were classified as having MCI and 23,676 had at least one follow-up visit. Annual progression rate was used to describe the progression of patients with MCI to dementia due to Alzheimer disease. Hazard ratios of dementia due to Alzheimer disease were estimated using Cox regression model.

Results: Annual progression rate (95% confidence interval) was 13.7% person-years (py) (13.5%–13.9%) with higher rate for amnestic MCI (aMCI) (18.2% py [17.9%–18.5%]) than for nonamnestic MCI (naMCI) (9.5% py [9.3%–9.6%]). Separate regression models were performed for each MCI subtype. Higher education, older age, female sex, and lower Mini-Mental State Examination score were associated with an increased risk of progression for both subtypes. Use of anxiolytics (adjusted hazard ratio [95% confidence interval]: 0.77 [0.66–0.91]) was a protective factor for aMCI whereas antidepressant drugs (1.16 [1.04–1.29]) were associated with an increased risk. For naMCI, prescriptions of antidepressants (0.85 [0.74–0.98]) and antipsychotics (0.55 [0.32–0.93]) were protective for progression.

Conclusions: Under circumstances emulating routine clinical practice, the positive predictive value of an MCI diagnosis is in line with previous clinical studies and the external validity of the concept is strengthened. Distinguishing between aMCI and naMCI is particularly relevant.
Neurology® 2015;85:1–8

GLOSSARY

AD = Alzheimer disease; **aMCI** = amnestic mild cognitive impairment; **APR** = annual progression rate; **BNA** = Banque Nationale Alzheimer; **CI** = confidence interval; **CMRR** = center of memory resources and research; **HR** = hazard ratio; ***ICD-10*** = *International Classification of Diseases, Tenth Revision*; **MC** = memory center; **MCI** = mild cognitive impairment; **MMSE** = Mini-Mental State Examination; **naMCI** = nonamnestic mild cognitive impairment; **py** = person-years.

The diagnosis of mild cognitive impairment (MCI) can be considered a means to identify persons at high risk of progression to dementia due to Alzheimer disease (AD) or other etiologies at short term (1–3 years),[1] but it is also characterized by its variability. Estimations of its prevalence, incidence, and conversion rates vary widely from one study to another.[2–4] Studies reported variable progression rates depending on the diagnostic criteria, the MCI subtype, the setting (community vs clinic), the duration of follow-up, and the sample size.[5–7] In a recent review, the annual progression rates (APRs) ranged from 5.4% to 16.5% person-years (py).[6]

In daily practice, an additional potential factor contributing to variability is that the diagnosis is ultimately based on clinical judgment rather than strict criteria.[8]

Given the variability associated with MCI, evaluating its positive predictive value on a daily practice basis (i.e., without applying uniform and standardized diagnostic criteria) is of interest both conceptually and for the practitioner. Our aim was to determine how the progression rate

Supplemental data at Neurology.org

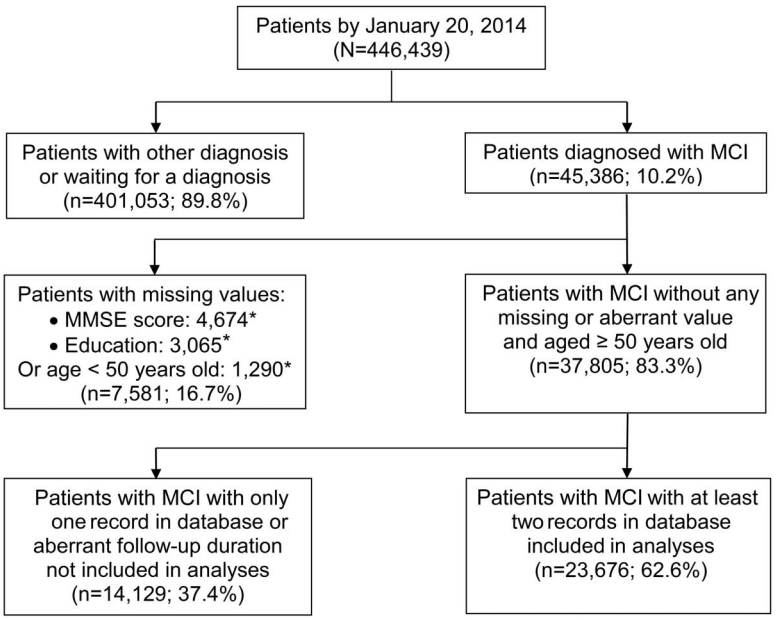
From the Department of Public Health (K.T.) and CMRR de Nice (P.R.), CHU de Nice and EA Cobtek, Université de Nice Sophia Antipolis, Nice; Laboratoire d'Informatique (A.M.), Signaux et Systèmes de Sophia-Antipolis (I3S), UMR 7271, UNS CNRS; Department of Public Health (C.P.), CHU de Nice; and ISPED (J.F.D.), Université de Bordeaux, INSERM U897, France.

Go to Neurology.org for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.

and the progression-associated factors identified through a clinical and administrative database are comparable to those highlighted by cohorts and specific studies in more controlled situations.

METHODS **Database sources and study population.** The French Alzheimer Databank (Banque Nationale Alzheimer [BNA]) contains demographic, diagnostic, and treatment information of persons consulting a memory center (MC) or a private specialist (neurologists, psychiatrists, or geriatricians) (both considered as secondary care levels) or who are managed by the 28 centers of memory resources and research (CMRR) (tertiary care level). Each time a patient consults a center, a minimum dataset summarizing the appointment is integrated anonymously in the BNA.[9] Diagnoses in the BNA are collected according to the *ICD-10* (table e-1 on the *Neurology*® Web site at Neurology.org). The definition of AD dementia was based on the corresponding *ICD-10* code F00.9 and MCI was based on code F06.7. According to a BNA steering committee decision based on clinical considerations, the database distinguishes between 2 subtypes of MCI: amnestic MCI (aMCI) if memory impairment is present, and nonamnestic MCI (naMCI) if not.[10] No mandatory criteria are requested by the system to complete a diagnosis in the BNA. As long as the patients receive their care in the network, it is possible to use the BNA to conduct longitudinal research and follow patients over serial evaluations. We conducted a retrospective cohort analysis of all patients diagnosed with MCI by medical doctors in the BNA since its inception (January 2009) to January 20, 2014. To maintain a homogeneous group of patients, we excluded patients younger than 50 years. We did not include patients with only one visit and no follow-up visits. We did not specify a minimum duration between 2 records because it varied according to particular physician–patient relationships.

Figure 1 **Flowchart of the study**



*One patient can have missing or aberrant value for several variables. MCI = mild cognitive impairment; MMSE = Mini-Mental State Examination.

Standard protocol approvals, registrations, and patient consents. The BNA is fully compliant with the conditions of the Commission Nationale de l'Informatique et des Libertés (CNIL) responsible in France for data protection and use regarding human identity and human rights. Because all patient-level data are certified anonymous, institutional review board approval and patient informed consents were not required for this study.

Statistical analysis. Patients with MCI who progressed to the diagnosis of AD dementia during the follow-up visits were considered as MCI progressors. We compared patients who were excluded to those included in the analysis. We tested for associations between the progression to AD dementia and the baseline characteristics of patients using the Pearson χ^2 test for categorical variables and variance analysis or Wilcoxon test for continuous variables.

Because it is difficult to define the exact date of onset of dementia, which is generally insidious, the date of first AD dementia diagnosis reported in the database was used as the date of occurrence of the event. APRs were estimated with the following formula: (Pmci/Tmci)/D, where Pmci denotes the number of progressors, Tmci the total number of MCI, and D the mean follow-up time. APRs are reported as per 100 py.

Survival intervals were measured from first appointment as an MCI to progression to dementia due to AD. Patients evolving to other types of dementia were censored at the date of new diagnosis. Data for patients in whom the progression or death was not reached were censored as of the last follow-up. Kaplan–Meier analysis was performed to report survival times and associations between progression, and variables were tested with log-rank and Wilcoxon tests. We also calculated estimated progression rates with 95% confidence interval (CI) at 1 and 3 years.

We used a Cox proportional hazards regression model to examine simultaneously the effects of multiple covariates on progression. According to the different models considered, we introduced available variables of interest in the BNA: sex, age, Mini-Mental State Examination (MMSE) score, education level, center type (private specialist, MC, CMMR), MCI subtypes, antidementia medications, psychotropic medications, and lifestyle.

We checked the adequacy of all models using graphical techniques. A test for interaction between pairs of variables in the final models was performed. For covariates strongly associated with time, we modeled discrete time-covariate associations, tested with likelihood and Wald tests for its significance. The effect of each variable in these models was assessed with the use of the Wald test and described by the hazard ratio (HR), with CI. Patients with missing MMSE scores or education values were excluded and there were no missing values for previously considered variables.

The final models were developed by introducing all variables of interest in a stepwise backward multivariate analysis. We used a significance level of 0.05 as the cutoff to exclude a variable from the model and described HR with a 95% CI. All reported p values are 2-sided. Statistical analyses were performed with SAS software version 4.1 (SAS Inc., Cary, NC).

RESULTS **Population.** The study flowchart is presented in figure 1. Among the 45,286 patients with MCI, 44.5% (20,195) where recorded with the diagnosis of aMCI and 55.5% (25,191) as naMCI. After the selection process, 23,676 patients with MCI (52.2% of initial patients) were followed up at least one time and included in the analyses. Among them, 11,451 patients (48.4%) were classified as aMCI and 12,225 patients (51.6%) as naMCI. Patients who

were excluded were older (mean age 75.7 vs 73.8 years, $p < 0.001$), had a lower mean MMSE score, and took more drugs (except neuroleptics) than those included in the analyses. Mean MMSE scores were clinically similar although significantly different (25.5 for included population and 25.4 for the excluded one, $p = 0.004$). Characteristics of the included population are shown in tables 1 and e-2.

Progression rates and APRs per 100 py. Mean follow-up time was 405.6 days (1.1 years) and ranged from 1 to 1,882 days (5 years). The mean follow-up duration was slightly higher in aMCI (406.5 days) than in naMCI (404.3 days). During the study, 3,603 patients (15.2%) progressed to AD dementia.

Global APR was 13.7% py (13.5%–13.9%). Patients diagnosed with aMCI had higher APR than patients with naMCI (18.2% py [17.9%–18.5%] vs 9.5% py [9.3%–9.6%]). Progression rates respectively at 1 and 3 years were as follows: 12.7% (12.2%–13.2%) and 34.3% (33.1%–35.4%) for all patients with MCI, 15.8% (15.0%–16.7%) and 44.0% (42.3%–45.8%) for aMCI, and 9.4% (8.8%–10.1%) and 23.9% (22.5%–25.4%) for naMCI. There was a tendency for increase in APR with worse MMSE score levels and lower education levels. Tables 2 and e-2 show separate APRs for patients with aMCI and naMCI. APRs to other dementias were 9.9% py (9.6%–10.2%) globally, 6.6% py (6.3%–7.0%) for aMCI, and 13.0% py (12.5%–13.6%) for naMCI. Some patients were reclassified as having a memory complaint (3%, 723). Among patients initially diagnosed as aMCI, 598 patients (5.2%) converted to naMCI. Similarly, among patients diagnosed with naMCI, 483 patients (3.9%) converted to aMCI. Death during follow-up was collected in 105 patients (0.4%).

Table 1 Baseline characteristics of the included population by MCI subtypes

Characteristic	aMCI (n = 11,451)	naMCI (n = 12,225)	All patients (n = 23,676)
Sex, female, n (%)	6,568 (57.4)	7,360 (60.2)	13,928 (58.8)
Age group,[a] y, n (%)			
50–59	413 (3.6)	912 (7.5)	1,325 (5.6)
60–69	1,549 (13.5)	2,196 (18)	3,745 (15.8)
70–79	4,982 (43.5)	4,860 (39.8)	9,842 (41.6)
80–89	4,293 (37.5)	4,020 (32.9)	8,313 (35.1)
≥90	214 (1.9)	237 (1.9)	451 (1.9)
Age, y, mean (SD)	76.5 (7.8)	74.8 (9)	75.7 (8.5)
MMSE score group, n (%)			
≤18	518 (4.5)	645 (5.3)	1,163 (4.9)
19–23	2,165 (18.9)	2,188 (17.9)	4,353 (18.4)
24–27	5,719 (49.9)	5,364 (43.9)	11,083 (46.8)
28–30	3,049 (26.6)	4,028 (33)	7,077 (29.9)
MMSE score, mean (SD)	25.3 (3.2)	25.5 (3.4)	25.4 (3.2)
Education, y, n (%)			
0–5	5,270 (46)	5,830 (47.7)	11,100 (46.9)
6–9	2,775 (24.2)	2,980 (24.4)	5,755 (24.3)
10–12	1,697 (14.8)	1,641 (13.4)	3,338 (14.1)
≥13	1,709 (14.9)	1,774 (14.5)	3,483 (14.7)
Lifestyle, n (%)			
Living alone	3,766 (33.9)	4,243 (34.7)	8,009 (33.8)
Living with family	7,169 (62.6)	7,342 (60.1)	14,511 (61.3)
Other living arrangement	516 (4.5)	640 (5.2)	1,156 (4.9)

Abbreviations: aMCI = amnestic mild cognitive impairment; MCI = mild cognitive impairment; MMSE = Mini-Mental State Examination; naMCI = nonamnestic mild cognitive impairment.
[a] Age was determined at first consultation with a diagnosis of MCI.

Regression models. We created 2 separate models for aMCI and naMCI because the proportional hazard assumption was not met for the MCI subtype covariate. The 2 models for each MCI subtype are reported in tables 3 and e-3. The regression models identified common and distinctive factors associated with progression. Common risk factors were female sex, older age, lower MMSE score, higher education, and MC location. Among medications, antidepressants were associated with increased risk for patients with aMCI and anxiolytics were protective. For patients with naMCI, antidepressants and antipsychotics lowered the risk and anti-AD drug increased it. Adjusted survival curves of aMCI and naMCI from the 2 Cox models are shown in figure 2.

DISCUSSION

In this large retrospective cohort study based on a national medical database, we showed that the APR to dementia due to AD of MCI was 13.7% py with higher progression risks for patients with aMCI than patients with naMCI. Second, a small proportion of patients with MCI converted to the other subtype or reverted to subjective memory complaint but a significant proportion progressed to other dementias. Third, our study confirmed the role of some well-known risk factors and showed that patients with higher education consulting memory clinics had an increased rate of progression.

Existing guidelines for the diagnosis of MCI allow considerable latitude for clinical judgment.[8,11,12] Extrapolation of studies conducted in research environments to current clinical practice is difficult because of the differences in how the diagnosis of MCI is made. The current study reflects the use and predictive value of MCI diagnostic in current specialized practice where contact with the system is initiated by the patient or their family. To our knowledge, this large study is unique in this context.

The reported APR % py is in line with previously reported studies in research settings but without the

Table 2 Annual progression rate among specified subgroups

Characteristic	aMCI (n = 11,451)	naMCI[a] (n = 12,225)	All patients (n = 23,676)
All patients	18.2	9.5	13.7
Sex			
Female	19.8	10.3	14.8
Male	16.1	8.2	12.2
Age group, y			
50–59	7.7	3.2	4.6
60–69	13.1	4.5	8
70–79	18.6	10.4	14.2
80–89	21.3	12.3	17
≥90	25.8	16.6	20.8
MMSE score group			
≤18	36.4	26.3	30.1
19–23	26.8	16.8	21.7
24–27	19.3	9.4	14.5
28–30	9.5	4.1	6.5
Education, y			
0–5	19.1	10.3	14.5
6–9	17.8	9.3	13.5
10–12	18.1	8.8	13.6
≥13	16.3	7.5	11.9
Lifestyle			
Living alone	19	10.8	14.6
Living with family	18	8.6	13.3
Other living arrangement	15.5	9.7	12.3

Abbreviations: aMCI = amnestic mild cognitive impairment; MMSE = Mini-Mental State Examination; naMCI = nonamnestic mild cognitive impairment.
Data represent percentage person-years.
[a] All *p* values for annual progression rate comparison between aMCI and naMCI are <0.0001.

strict MCI inclusion criteria used in those studies.[6,13,14] The prognosis for MCI varies according to the MCI subtype with aMCI having higher risk for progression to dementia due to AD than naMCI. Although most of the available studies and a theoretical rationale support aMCI as a higher risk condition for AD dementia than naMCI,[10,15–17] when adding the number of affected cognitive domains, the conversion rates to AD or to dementia become more controversial.[18,19] The classification in 4 subtypes (single or multiple-domain amnestic or nonamnestic) depends on the number and type of neuropsychological tests performed, and the slightly greater proportion of naMCI here may reflect the fact that more tests were performed in the nonmemory assessment.[20] Because a consensus concerning the appropriate tests and the operationalization of these tests has not been reached, the distinction between aMCI and naMCI seems to be the most relevant for medico-administrative databases such as the BNA. As previously described, MCI is also a risk factor for progression to non-AD dementias,[10,15] and the APR to other dementias in our study was substantial. This APR was higher for naMCI confirming the utility of subtype distinction in clinical practice.

A small proportion of patients changed from a subtype to another during the study. This instability of diagnosis is probably attributable to the proper evolution of the underlying disease and the variation of the number and type of neuropsychological investigations. Three percent of patients with MCI improved their cognitive status and were secondarily considered as having subjective memory complaints. If we consider this situation as a normal state, this proportion is in the low end of other study results in the clinical context with rates ranging from 4% to 38%[21–23] and confirms that MCI is a more stable condition in clinic settings than in population studies.[24] The low reversion rate could be explained by the relatively short follow-up, the specialty nature of the referral clinical settings, and the fact that physicians were not blinded to the previous diagnosis.

The risk difference of progression to dementia due to AD between aMCI and naMCI increased with time. We modeled each separately because we assumed that MCI subtype was an important variable with only 2 possible states and that stratification was a less informative strategy leading to difficult interpretation of HRs. Moreover, the large sample allowed us to perform separate analyses without losing power.

Some variables appeared to be common risk factors for progression in both subtypes. Older age and lower MMSE score at baseline are well-documented predictors of progression and markers of a probably more advanced disease. The issue of sex-related differences in the rate of progression has led to controversial results.[25] Our study suggests that women with MCI have higher risk of progression irrespectively of age and education. It would be of interest to further investigate this point taking into account potential explanations such as social or hormonal factors but also by selection of men with better cardiovascular risk profiles.[26] Patients with MCI with the highest levels of education were also at increased risk of progression. Education can be an indirect way to estimate the brain reserve and is usually associated with lower risk of incident AD,[27] but longitudinal studies have shown that higher educated patients with AD have a faster decline than others once the disease becomes symptomatic.[28] In this study, post hoc analysis showed that the mean MMSE score at clinical diagnosis of AD dementia was higher in highly educated patients (23.8 for higher level and 21.2 for lowest). According to the BNA data, in current practice,

Table 3 Separate Cox regression models for aMCI and naMCI populations

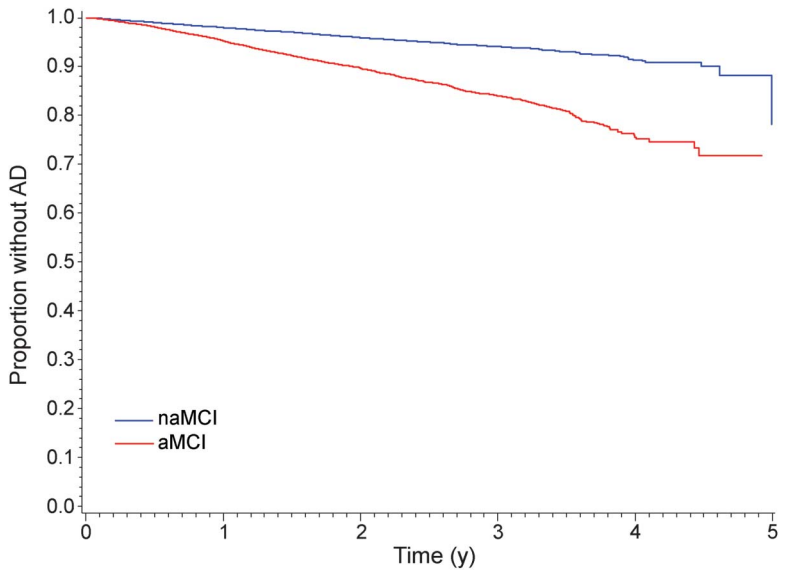
	aMCI (n = 11,451)		naMCI (n = 12,225)	
Characteristic	HR (95% CI)	*p* Value	HR (95% CI)	*p* Value
Sex				
Male	1		1	
Female	1.16 (1.06–1.28)	0.001	1.15 (1.02–1.28)	0.03
Age group, y				
50–59	1		1	
60–69	1.52 (1.06–2.16)	0.022	1.24 (0.83–1.84)	0.29
70–79	2.02 (1.44–2.83)	<0.0001	2.42 (1.68–3.49)	<0.0001
80–89	2.27 (1.62–3.19)	<0.0001	2.61 (1.81–3.77)	<0.0001
≥90	2.75 (1.76–4.32)	<0.0001	3.04 (1.85–5.01)	<0.0001
MMSE score group				
28–30	1		1	
24–27	1.99 (1.76–2.24)	<0.0001	2.15 (1.83–2.54)	<0.0001
19–23	2.82 (2.46–3.23)	<0.0001	3.86 (3.23–4.62)	<0.0001
≤18	3.9 (3.20–4.68)	<0.0001	6.31 (5.08–7.84)	<0.0001
Education, y				
0–5	1		1	
6–9	1.08 (0.98–1.20)	0.13	1.25 (1.08–1.43)	0.002
10–12	1.21 (1.07–1.38)	0.002	1.29 (1.08–1.55)	0.005
≥13	1.22 (1.07–1.39)	0.003	1.38 (1.14–1.66)	0.001
Lifestyle			Not in the final model	
Living with family	1		—	—
Living alone	0.91 (0.84–1.00)	0.047	—	—
Other living arrangement	0.75 (0.60–0.94)	0.012	—	—

Abbreviations: aMCI = amnestic mild cognitive impairment; CI = confidence interval; HR = hazard ratio; MMSE = Mini-Mental State Examination; naMCI = nonamnestic mild cognitive impairment.

patients with MCI and high education levels who consult a specialized center can be considered more at risk than those with lower education levels. We observed a substantial reduction of the risk of progression when patients consulted a CMRR rather than an MC (table e-3). The CMRRs constitute a tertiary level of care in France with specific missions: reference for care, education, research, and network entertainment. Although specialized centers are usually associated with increased rate of progression, 2 hypotheses could explain the opposite phenomenon in CMRRs. First, it is probable that CMRRs handle different MCI populations than CMs. Second, the diagnostic modalities according to center type may vary and the validity of the diagnosis across the centers is questionable.

Treatments prescribed to patients have different roles in aMCI and naMCI. Among the psychotropic drugs, antidepressants are the most frequently prescribed drug to patients with MCI in the BNA (17.9%). This result is consistent with the fact that depressive symptom is one of the most frequent neuropsychiatric disturbances among patients with MCI.[29] Antidepressants were associated with an increased risk of progression for patients with aMCI. The role of affective symptoms as a risk factor for the progression of patients with MCI to AD dementia is still debated with studies showing that depression is an at-risk situation[30] and others failing to show any relation with progression.[31] Antidepressants can be considered a surrogate marker of depression and a recent study showed that taking an antidepressant did not modify the relation between depression and transition from MCI to AD dementia.[13] Using this model, our finding suggests that depression is a risk factor or a prodromal sign for aMCI but seems protective for patients with naMCI. Anxiety as a risk factor of progression has been less extensively studied but has also shown inconsistent results.[32,33] Taking an anxiolytic is associated with a reduced risk of progression for patients with aMCI. A rational explanation could be that anxiolytics themselves impair memory

Figure 2 Adjusted survival curves of patients with aMCI and naMCI from the 2 different Cox models



AD = Alzheimer disease; aMCI = amnestic mild cognitive impairment; naMCI = nonamnestic mild cognitive impairment.

performance. Thus, use of anxiolytics could lead to amnestic presentation of MCI with no underlying neurodegenerative process. However, in another study, anxiety was associated with AD biomarkers (CSF β-amyloid 42 and total tau) in subjects with MCI.[34] In the current study, antipsychotics were prescribed more frequently to patients with naMCI compared with aMCI (2.3% vs 1.3%) and were an independent protective factor of progression for naMCI but not aMCI. Psychotic signs of AD are seen at a relatively advanced stage of the disease whereas nonamnestic forms of MCI evolve more frequently to other types of dementia with earlier psychotic symptoms (e.g., dementia with Lewy bodies or frontotemporal lobar degenerations).[35,36]

Our study has some potential limitations. First, the mean follow-up duration was short, and duration of observation is known to have a significant influence on the APR % py.[37] Second, we did not control for diagnosis modalities of patients with MCI included in this study and because of the clinical daily routine setting, we expected an increase of variability of the results. If the recognition of MCI as a clinical diagnosis is accepted,[11] little is known regarding the criteria used in daily practice to affirm the diagnosis and how and for what purpose the diagnosis is used by the doctors. This validity question is an issue that can limit the meaning of the presented results to a strict clinical point of view and would have to be investigated. Third, a patient with MCI who reverts to a "normal" state should be excluded from the at-risk population. Only a few reversions were registered by the BNA system, but it is probable that more arose without any information in the database because clinicians can be reluctant to diagnose "normal" once they have labeled someone as MCI. Moreover, the principle of freedom of choice in France allows the patient to consult any health provider including those not in the BNA system. Fourth, the BNA does not reflect practice in the primary care setting. In addition, because there is no registry in France collecting data on cases with AD or MCI in primary care settings, it is difficult to discuss the representativeness of the BNA. Fifth, the available variables were limited and information on specific predictors such as biomarkers was not available.[38]

The BNA database constitutes an opportunity to obtain complementary information beside specific studies and prospective cohorts.[39] By reproducing some of the main features associated with the MCI concept, this study strengthens the external validity of the MCI construct. Subtyping of amnestic and nonamnestic forms of MCI was feasible and yielded useful prognostic information.

AUTHOR CONTRIBUTIONS

Karim Tifratene: study concept, drafting/revising the manuscript, statistical analysis, analysis and interpretation of data. Philippe Robert: revising the manuscript. Asya Metelkina: statistical analysis of data, revising the manuscript. Christian Pradier: revising the manuscript. Jean François Dartigues: analysis and interpretation of data, revising the manuscript, study supervision.

ACKNOWLEDGMENT

The authors thank the participating centers and professionals contributing to the BNA, Roland Chevrier (CHU de Nice) for technical assistance in data collection, and Cécile Balandier (Direction Générale de l'Offre de Soin) for general advice.

STUDY FUNDING

The French Alzheimer Databank (Banque Nationale Alzheimer) is supported by the Direction Générale de la Santé, Ministère de la Santé.

DISCLOSURE

K. Tifratene is a former employee of GlaxoSmithKline and served on a scientific advisory board for Lilly. P. Robert reports no disclosures relevant to the manuscript. A. Metelkina received funding from Laboratory I3S, UNS CNRS for the study of human depression and funding from INRIA Sophia Antipolis and CHU of Nice for the study of a brain–computer interface in patients with disability. C. Pradier served on a scientific advisory board for Gilead and received honoraria from MSD, ViiV Healthcare, and Pfizer. J. Dartigues received grants from Novartis and IPSEN and honoraria from Novartis, IPSEN, and Newron. Go to Neurology.org for full disclosures.

Received December 13, 2014. Accepted in final form March 26, 2015.

REFERENCES

1. Sperling RA, Aisen PS, Beckett LA, et al. Toward defining the preclinical stages of Alzheimer's disease: recommendations from the National Institute on Aging–Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement 2011;7:280–292.

2. Ward A, Arrighi HM, Michels S, Cedarbaum JM. Mild cognitive impairment: disparity of incidence and prevalence estimates. Alzheimers Dement 2012;8:14–21.
3. Petersen RC, Roberts RO, Knopman DS, et al. Prevalence of mild cognitive impairment is higher in men. The Mayo Clinic Study of Aging. Neurology 2010;75:889–897.
4. Luck T, Luppa M, Briel S, Riedel-Heller SG. Incidence of mild cognitive impairment: a systematic review. Dement Geriatr Cogn Disord 2010;29:164–175.
5. Mitchell AJ, Shiri-Feshki M. Rate of progression of mild cognitive impairment to dementia: meta-analysis of 41 robust inception cohort studies. Acta Psychiatr Scand 2009;119:252–265.
6. Ward A, Tardiff S, Dye C, Arrighi HM. Rate of conversion from prodromal Alzheimer's disease to Alzheimer's dementia: a systematic review of the literature. Dement Geriatr Cogn Dis Extra 2013;3:320–332.
7. Ganguli M, Snitz BE, Saxton JA, et al. Outcomes of mild cognitive impairment by definition: a population study. Arch Neurol 2011;68:761–767.
8. Albert MS, DeKosky ST, Dickson D, et al. The diagnosis of mild cognitive impairment due to Alzheimer's disease: recommendations from the National Institute on Aging–Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement 2011;7:270–279.
9. Le Duff F, Develay AE, Quetel J, et al. The 2008–2012 French Alzheimer plan: description of the National Alzheimer Information System. J Alzheimers Dis 2012;29:891–902.
10. Petersen RC. Mild cognitive impairment as a diagnostic entity. J Intern Med 2004;256:183–194.
11. 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 Intern Med 2004;256:240–246.
12. Roberts JS, Karlawish JH, Uhlmann WR, Petersen RC, Green RC. Mild cognitive impairment in clinical care: a survey of American Academy of Neurology members. Neurology 2010;75:425–431.
13. Steenland K, Karnes C, Seals R, Carnevale C, Hermida A, Levey A. Late-life depression as a risk factor for mild cognitive impairment or Alzheimer's disease in 30 US Alzheimer's disease centers. J Alzheimers Dis 2012;31:265–275.
14. Gainotti G, Quaranta D, Vita MG, Marra C. Neuropsychological predictors of conversion from mild cognitive impairment to Alzheimer's disease. J Alzheimers Dis 2014;38:481–495.
15. Busse A, Hensel A, Gühne U, Angermeyer MC, Riedel-Heller SG. Mild cognitive impairment: long-term course of four clinical subtypes. Neurology 2006;67:2176–2185.
16. Ravaglia G, Forti P, Maioli F, et al. Conversion of mild cognitive impairment to dementia: predictive role of mild cognitive impairment subtypes and vascular risk factors. Dement Geriatr Cogn Disord 2006;21:51–58.
17. Rasquin SM, Lodder J, Visser PJ, Lousberg R, Verhey FR. Predictive accuracy of MCI subtypes for Alzheimer's disease and vascular dementia in subjects with mild cognitive impairment: a 2-year follow-up study. Dement Geriatr Cogn Disord 2005;19:113–119.
18. Han JW, Kim TH, Lee SB, et al. Predictive validity and diagnostic stability of mild cognitive impairment subtypes. Alzheimers Dement 2012;8:553–559.
19. Tabert MH, Manly JJ, Liu X, et al. Neuropsychological prediction of conversion to Alzheimer disease in patients with mild cognitive impairment. Arch Gen Psychiatry 2006;63:916–924.
20. Lee SB, Kim KW, Youn JC, et al. Prevalence of mild cognitive impairment and its subtypes are influenced by the application of diagnostic criteria: results from the Korean Longitudinal Study on Health and Aging (KLoSHA). Dement Geriatr Cogn Disord 2009;28:23–29.
21. Gallassi R, Oppi F, Poda R, et al. Are subjective cognitive complaints a risk factor for dementia? Neurol Sci 2010;31:327–336.
22. Koepsell TD, Monsell SE. Reversion from mild cognitive impairment to normal or near-normal cognition: risk factors and prognosis. Neurology 2012;79:1591–1598.
23. Roberts RO, Geda YE, Knopman DS, et al. The Mayo Clinic Study of Aging: design and sampling, participation, baseline measures and sample characteristics. Neuroepidemiology 2008;30:58–69.
24. Larrieu S, Letenneur L, Orgogozo JM, et al. Incidence and outcome of mild cognitive impairment in a population-based prospective cohort. Neurology 2002:59:1594–1599.
25. Mielke MM, Vemuri P, Rocca WA. Clinical epidemiology of Alzheimer's disease: assessing sex and gender differences. Clin Epidemiol 2014;6:37–48.
26. Chêne G, Beiser A, Au R, et al. Gender and incidence of dementia in the Framingham Heart Study from mid-adult life. Alzheimers Dement 2015;11:310–320.
27. Meng X, D'Arcy C. Education and dementia in the context of the cognitive reserve hypothesis: a systematic review with meta-analyses and qualitative analyses. PLoS One 2012;7:e38268.
28. Hall CB, Derby C, LeValley A, Katz MJ, Verghese J, Lipton RB. Education delays accelerated decline on a memory test in persons who develop dementia. Neurology 2007;69:1657–1664.
29. Monastero R, Mangialasche F, Camarda C, Ercolani S, Camarda R. A systematic review of neuropsychiatric symptoms in mild cognitive impairment. J Alzheimers Dis 2009;18:11–30.
30. Modrego PJ, Ferrández J. Depression in patients with mild cognitive impairment increases the risk of developing dementia of Alzheimer type: a prospective cohort study. Arch Neurol 2004;61:1290–1293.
31. Palmer K, Di Iulio F, Varsi AE, et al. Neuropsychiatric predictors of progression from amnestic-mild cognitive impairment to Alzheimer's disease: the role of depression and apathy. J Alzheimers Dis 2010;20:175–183.
32. Devier DJ, Pelton GH, Tabert MH, et al. The impact of anxiety on conversion from mild cognitive impairment to Alzheimer's disease. Int J Geriatr Psychiatry 2009;24:1335–1342.
33. Palmer K, Berger AK, Monastero R, Winblad B, Bäckman L, Fratiglioni L. Predictors of progression from mild cognitive impairment to Alzheimer disease. Neurology 2007;68:1596–1602.
34. Ramakers IH, Verhey FR, Scheltens P, et al. Anxiety is related to Alzheimer cerebrospinal fluid markers in subjects with mild cognitive impairment. Psychol Med 2013;43:911–920.
35. Ferman TJ, Smith GE, Kantarci K, et al. Nonamnestic mild cognitive impairment progresses to dementia with Lewy bodies. Neurology 2013;81:2032–2038.

36. Petersen RC. Clinical practice: mild cognitive impairment. N Engl J Med 2011;364:2227–2234.
37. Mitchell AJ, Shiri-Feshki M. Temporal trends in the long term risk of progression of mild cognitive impairment: a pooled analysis. J Neurol Neurosurg Psychiatry 2008;79: 1386–1391.
38. Vos SJ, van Rossum IA, Verhey F, et al. Prediction of Alzheimer disease in subjects with amnestic and nonamnestic MCI. Neurology 2013;80:1124–1132.
39. Roos LL Jr, Nicol JP, Cageorge SM. Using administrative data for longitudinal research: comparisons with primary data collection. J Chronic Dis 1987;40:41–49.