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# BMJ Open How many patients are eligible for disease-modifying treatment in Alzheimer's disease? A French national observational study over 5 years

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## ABSTRACT

**Objective** We aimed to study the epidemiology of the prodromal and mild stages of Alzheimer's disease (AD) patients who are eligible for clinical trials with disease-modifying therapies.

**Settings** We analysed two large complementary databases to study the incidence and characteristics of this population on a nationwide scope in France from 2014 to 2018. The National Alzheimer Database contains data from 357 memory centres and 90 private neurologists. Data from 2014 to 2018 have been analysed.

**Participants** Patients, 50–85 years old, diagnosed with AD who had an Mini-Mental State Exam (MMSE) score of  $\geq 20$  were included. We excluded patients with mixed and non-AD neurocognitive disorders.

**Primary outcome measure** Descriptive statistics of the population of interest was the primary measure.

**Results** In the National Alzheimer Database, 550 198 patients were assessed. Among them, 72 174 (13.1%) were diagnosed with AD and had an MMSE  $\geq 20$ . Using corrections for specificity of clinical diagnosis of AD, we estimated that about 50 000 (9.1%) had a prodromal or mild AD. In the combined electronic clinical records database of 11 French expert memory centres, a diagnosis of prodromal or mild AD, certified by the use of cerebrospinal fluid AD biomarkers, could be established in 195 (1.3%) out of 14 596 patients.

**Conclusions** AD was not frequently diagnosed at a prodromal or mild dementia stage in France in 2014 to 2018. Diagnosis rarely relied on a pathophysiological marker even in expert memory centres. National databases will be valuable to monitor early stage AD diagnosis efficacy in memory centres when a disease-modifying treatment becomes available.

## BACKGROUND

Alzheimer's disease (AD) affects over 1 million people in France, 35 million

## Strengths and limitations of this study

- Use of two large, multicentric, national databases representative of the French healthcare network on Alzheimer's disease.
- Absence of data to explain the low rate of early Alzheimer's disease diagnosis in the French national Alzheimer database (BNA).
- A retrospective design for the electronic record file database that does not allow for definitive epidemiological conclusions.

individuals worldwide, and is one of the major challenges of this century for the scientific community.<sup>1</sup> Most trials aiming to hinder its progression<sup>2</sup> are now conducted in its mild or even prodromal stage.<sup>3–5</sup> Today, an early and reliable diagnosis can be made in expert centres, which have the necessary resources for core AD biomarker analyses, for example, cerebrospinal fluid (CSF) analysis.<sup>6</sup>

Although some of these trials have already shown a lack of treatment efficacy even at the mild AD stage,<sup>7,8</sup> some undergoing trials are testing treatments which showed encouraging phase Ib and II results.<sup>9,10</sup>

In France, the evaluation of patients in expert memory clinics is standardised with the use of the same neuropsychological tests and AD CSF biomarkers (A $\beta$ 42, tau and phosphorylated tau) sampling in clinical practice.

Also, since 2009, a national medical database has been running, the 'Banque Nationale Alzheimer (BNA)' (The National Alzheimer's Bank), which was set up as part

of the national Alzheimer's Plan (2008–2012) and has already been thoroughly described.<sup>11</sup>

Our aim was to evaluate the incidence of early AD patients who would be eligible for a disease-modifying drug trial in a French multicentric retrospective study in France between 2014 and 2018.

## METHODS

### Participants

Two distinct databases were analysed: the first was constituted for the purpose of this study as a collaborative effort from 11 expert memory centres in 2014 when the results from the Expedition III trial testing Solanezumab had not yet been disclosed. The second database is the ongoing BNA in which data are available from 2014 to 2018.

#### First database: electronic clinical records database

A retrospective multicentric study based on a database from 11 'Centres de mémoire, de recherche et de ressources' (Memory, Research and Resource Centres), CMRR. In alphabetical order: Dijon, Lille, Nantes, Nancy, Nice, Paris-Lariboisière, Paris-Pitié-Salpêtrière, Poitiers, Rouen, Strasbourg, Tours) volunteered to participate in this study. Each of these centres kept their patient files in local electronic clinical records (ECR). The criteria of selected patients who would be eligible for a disease-modifying drug trial were derived from that of the Expedition III clinical trial (Clinicaltrials.org: NCT02760602) and are in line with the International Working Group (IWG) guidelines.<sup>4 5</sup> The selected criteria, demographic (age, gender, education level, distance to CMRR, caregiver, referral) and medical data (conventional anti-AD treatment, participation in a clinical trial) were recorded in this population. Importantly, patients diagnosed with mixed dementia were not included in our study, once again to mirror the inclusion criteria of the disease-modifying drugs trials. More specifically, the inclusion criteria used in this study were as follows:

- ▶ Age between 50 and 85 years old.
- ▶ AD diagnosis based on the IWG-2 criteria operationalised as a Free and Cued Selective Reminding test (FCSRT) total score <42 AND a CSF phosphorylated tau/AB42 ratio above 0.11.
- ▶ A mild or prodromal (mild cognitive impairment (MCI)) stage of the disease defined by a mini-mental state exam (MMSE) score >20 also referred to as 'early AD'.

Exclusion criteria were as follows:

- ▶ The presence of significant vascular lesions on MRI defined as Fazekas and Schmidt leukopathy stage 3 or the presence of at least one lacunar or territorial infarct or supracentimetric brain haemorrhagic sequelae.
- ▶ The presence of another disease that could better explain the symptoms (eg, dementia with Lewy bodies and fronto-temporal dementia).

- ▶ Patient opposition to the use of his/her anonymised clinical data for research purposes according to the French legislation.

#### Second database: National Alzheimer database (BNA)

In order to broaden the analysis to a national level and extend it over time, the BNA was used to assess the total number of clinically diagnosed AD and MCI (divided into amnesic (aMCI) and non-amnesic MCI (naMCI) based on clinical assessment) individuals in 2014 and 2015 who had an MMSE score  $\geq 20$ . From 2016 onwards, the BNA structure changed to integrate the *Diagnostic and Statistical Manual* fifth edition nomenclature<sup>12</sup> and to require stating whether CSF biomarkers or genetic features were used to ascertain AD diagnosis or not. These results were stratified by the type of clinic (primary memory clinic, CMRR or private neuro specialist) in which the patients had been evaluated. Among the data systematically collected, we assessed the Mini Mental State Evaluation (MMSE) score<sup>13</sup> and the diagnosis according to the *International Classification of Diseases*, 10th Revision.<sup>14</sup> AD<sup>15</sup> and MCI, subcategorised as aMCI or naMCI,<sup>3 16</sup> are included among the diagnostic categories in the BNA. Both items (MMSE and diagnosis) are recorded each time a patient consults in one of the 357 participating memory clinics (representing 83.6% of all memory clinics in France) and 90 private neurology specialists. These clinics are divided into two categories: primary memory clinics (328/357) and expert memory centres (CMRR 29/357). Clinical diagnosis of AD and MCI was used to estimate the number of 'true' AD cases, taking into account the relative specificity for pathophysiologically confirmed AD of the different clinically determined diagnostic categories, that is, 70% for the specificity of the clinical AD<sup>17 18</sup> and 50% for the MCI syndrome.<sup>19</sup> BNA was also used to assess by comparing patient characteristics between the 11 CMRR cohort and the 18 that did not participate in the study.

#### Ethics

Both the ECR and BNA databases and their utilisation for the purpose of this study were approved by Paris VI Institutional Review Board and the Commission Nationale de l'Informatique et des Libertés ('National commission for informatics and liberty') responsible in France for data protection and use concerning human identity and human rights. French Legislation allows the use of anonymised clinical data if patients did not specifically object to it during consultation. Hence, every patient included in this study did not oppose to the use of his/her clinical data. However, no written consent was obtained either for the ECR or for the BNA database.

#### Patient and public involvement

Patients were not specifically involved in this study. The BNA is publicly disseminated (<http://www.innovation-alzheimer.fr/bna-fr/>).

### Neuropsychological tests

The MMSE<sup>13</sup> and the FCSRT<sup>20</sup> were collected in the ECR database. The FCSRT is a well-validated tool to diagnose AD, even at its prodromal stage.<sup>21–25</sup> It is recommended in the diagnosis of AD by the IWG guidelines.<sup>4,5</sup> This test is now implemented to screen patients in disease-modifying drug trials (eg, Clinicaltrials.org: NCT02760602). In our study, we included patients with a free recall score <20 or a total recall score <42.<sup>21</sup> The mild or prodromal stages were ascertained by an MMSE score >20. In the BNA, only the MMSE was available.

### Cerebrospinal fluid biomarkers of AD

CSF was acquired following standard procedures. The CSF was obtained by LP between the L3/L4 or L4/L5 intervertebral space, using a 22-gauge atraumatic needle. Five hundred microlitres of CSF were used to perform standardised commercially available INNOTEST sandwich ELISA according to the manufacturer's instructions (Fujirebio Europe NV, formerly Innogenetics NV). A CSF profile of the Alzheimer's type was defined by a phosphorylated tau/Aβ42 ratio >0.11.<sup>6,26</sup> CSF biomarkers results were available in the ECR database but not in the BNA.

### Statistical analysis

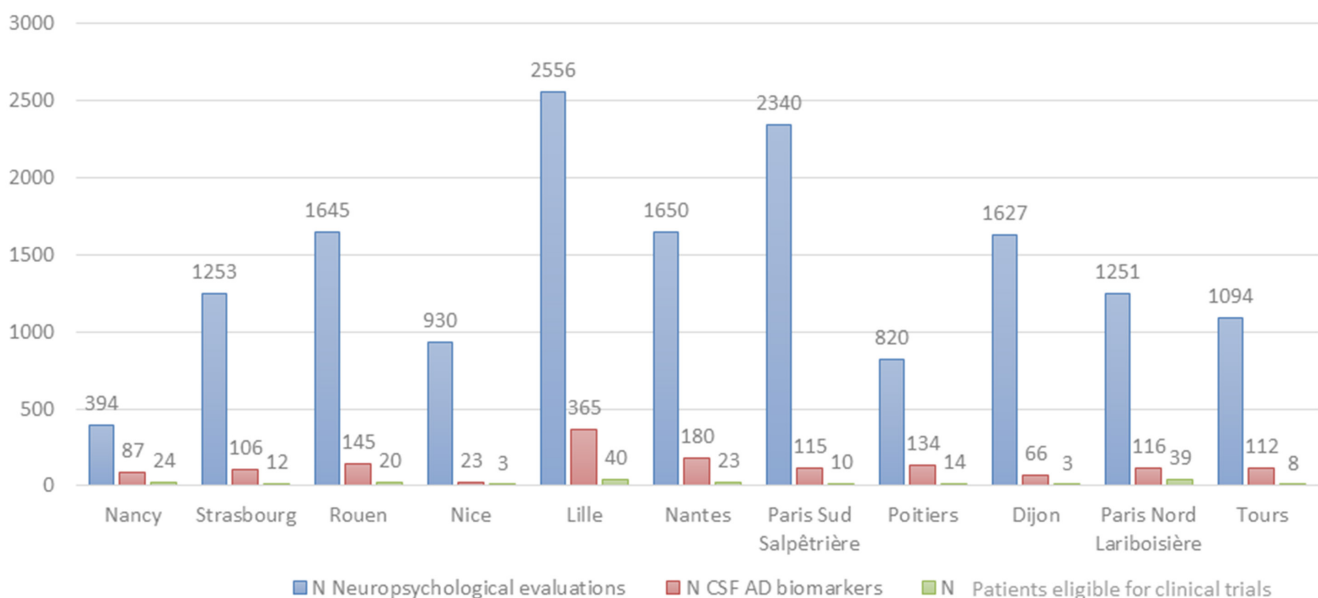
First, we studied the descriptive statistics of the population of interest derived from the analysis performed in the 11 CMRR. To assess the external validity of our results, we compared the BNA data from these 11 CMRR to those of the remaining 18 CMRR.

To compare sociodemographic and medical characteristics between the 11 CMRR that volunteered to participate in this study and the other 18 CMRR (using data that were available for these CMRR in the BNA),

we performed Student's t-tests for quantitative variables describing means and SD and X<sup>2</sup> tests for qualitative variables after an assessment of the Gaussian distribution of the continuous variables using the Kolmogorov-Smirnov test. All reported p values are two-sided. Statistical analyses and description of the cohort characteristics were performed with SAS software V.4.1 (SAS, Cary, North Carolina, USA).

### RESULTS

In 2014, 14596 patients had a cognitive evaluation in one of the 11 participating CMRRs. Among these, 1209 (8.3%) underwent a lumbar puncture with an analysis of AD CSF biomarkers. Among them, 195 (16.1%) had an 'early AD' diagnosis per our chosen criteria, 287 (23.7%) had a diagnosis of AD with an MMSE <20; 64 (5.3%) had a diagnosis of AD with an MMSE >20 but an FCSRT with subscores over our chosen thresholds; 365 (30.2%) had a mixed dementia profile (AD and vascular lesions 237 (65%); AD and suspected Lewy body dementia 84 (23%); AD and other 44 (12%)) and finally 298 (24.7%) had another diagnosis (not AD). Among the 195 patients (16.1% of patients who underwent a CSF examination, 1.3% of all patients) who had a diagnosis of early AD according to the IWG-2 criteria, 133 (68.2%) had a mild AD dementia and 62 (31.8%) had prodromal AD. The proportions of CSF examinations and of mild or prodromal AD patients among patients who performed a neuropsychological evaluation in the CMRR the same year were not statistically different from one CMRR to the next as presented in [figure 1](#). The characteristics of these early AD patients are presented in [table 1](#).



**Figure 1** Incidence of prodromal and mild IWG-2 Alzheimer's disease patients in 2014 in the electronic clinical files of 11 CMRRs. CMRRs, Centres de mémoire, de recherche et de ressources (Centres for Research and Resources on Memory); IWG, International Working Group.

**Table 1** Description of the 195 patients from the electronic clinical files database

	Mean (SD) or N (%)
Age	70.8 (0.6)
Gender—female	108 (55.1)
Educational level (years of education)	10.7 (0.4)
Distance from CMRR (km)	40.1 (6.7)
MMSE	24.7 (0.2)
FCSRT-FR	10.8 (0.4)
FCSRT-TR	29.1 (1.8)
A $\beta$ 1–42 (pg/mL)	527.7 (11.6)
tau (pg/mL)	672.5 (23.6)
Phosphorylated tau (pg/mL)	110.9 (7.4)
Phosphorylated tau/A $\beta$ 1–42 ratio	0.21 (0.01)
Caregiver (n=74)	
Spouse	59 (79.7)
Children	10 (13.5)
Other	5 (6.8)
Addressed by (n=74)	
Family	8 (13.3)
General practitioner	29 (48.3)
Neurologist	17 (28.3)
Psychiatrist	4 (6.7)
Other	2 (3.4)
Anti-AD drug (n=60)	
0	12 (20)
DONEPEZIL 5 mg	2 (3.3)
DONEPEZIL 10 mg	16 (26.7)
GALANTAMINE 16 mg LP	3 (5)
GALANTAMINE 24 mg LP	6 (10)
RIVASTIGMINE 12 mg	2 (3.3)
RIVASTIGMINE 4.6 mg patch	2 (3.3)
RIVASTIGMINE 9.5 mg patch	17 (28.3)
Included in a clinical trial	100 (51)

AD, Alzheimer's disease; CMRR, Centres de mémoire, de recherche et de ressources (Centres for Research and Resources on Memory); FCSRT, free and cued selective reminding test; MMSE, mini mental state examination.

Interestingly, and although the mean (SD) MMSE score was 24.7 (0.2), well above 20, the FCSRT free (10.8 (0.4)) and total (29.1 (1.8)) recall scores indicated a severe amnesic syndrome of the hippocampal type well below the chosen cut-off scores of 20 and 42, respectively. The mean (SD) phosphorylated tau/A $\beta$ 1–42 ratio of 0.21 (0.01) was also largely above the threshold of 0.11 suggesting an unambiguous AD pathophysiological process in the participants.

The number of new patients included in the BNA between 2014 and 2018 was 550 198. Among them, 72 174 (13%) were diagnosed with an early AD including MMSE

$\geq$ 20. These results are presented in [tables 2 and 3](#). Using specificity correction to account for the clinic-pathological accuracy of AD diagnosis, we estimate that, among the 72 174 patients diagnosed with AD between 2014 and 2018, about 50 000 had a clinical AD with probable AD brain pathology.

In the BNA, the rate of CSF biomarker use for AD diagnosis varied from 2.1% to 6.7%.

The differences between patients seen in the 11 CMRR who volunteered to participate in the detailed study and the 18 other CMRR are presented in [table 4](#).

## DISCUSSION

This observational study in a clinical setting on a national scale was specifically designed to estimate the incidence, and describe the characteristics, of patients at early stages of AD according to recent biomarker-based diagnostic criteria. As evidence suggests that disease-modifying drugs may be efficient at these stages, such an analysis is useful and timely, allowing for the discovery of how many patients can be expected to enrol in trials and in the future to be prescribed such a drug, should one become available.<sup>9 10 27</sup> This study is different from those conducted in other countries such as in the Netherlands<sup>28</sup> or in the USA<sup>19</sup> in which AD pathophysiological markers are performed in a research setting. Our main finding is that the incidence of diagnosed AD at the mild dementia and prodromal stages is lower than previously thought. We also showed that the use of the latest research criteria to diagnose early stage AD in clinical practice is rare. In France, the latest reports indicate an incidence of up to 225 000 new AD cases per year.<sup>29</sup> This number accounts for all stages of AD and is an estimation from the general population. This discrepancy between this previous finding of 225 000 new AD cases per year and our result of about 10 000 new early AD cases per year can also be explained by several points:

1. Our analysis does not include a significant portion of the clinical setting in which patients with cognitive complaints are evaluated, especially with regards to the non-hospital based or neurologists from private practice. The BNA includes data from only about 90 private specialists, providing data on 2.2% of the AD and 2.5% of the MCI patients in the BNA. As there are about 800 French private neuro specialists, although not all so active in the field of neurodegenerative disorders, one could assume that private specialists consult a large additional number of patients for cognitive problems. However, thanks to a systematically organised medical system with hierarchised and personalised care plan and management ([figure 2](#)), our results can be generalised to the French AD medical community.<sup>30</sup>
2. Patients do not consult a specialist when they have MCI or mild dementia. One should note that the databases analysed in our study only represent the patients diagnosed by memory specialists. Our analyses do not account for patients who did not consult any physi-

**Table 2** New patients with Alzheimer's disease in the National Alzheimer Database (BNA) in 2014 and 2015 stratified by MMSE values

N (%)		2014 (n=119493)				2015 (n=113585)			
Clinical syndrome	Type of clinic	MMSE <20		MMSE ≥20		MMSE <20		MMSE ≥20	
AD	Primary memory clinic	10534	(60.00)	7018	(40.00)	8363	(62.00)	5137	(38.10)
	CMRR	2365	(54.80)	1953	(45.20)	2073	(53.90)	1776	(46.10)
	Private neurologist	259	(45.30)	313	(54.70)	176	(44.00)	224	(56.00)
	Total AD	13158	(53.37)	9284	(46.63)	10612	(53.30)	7137	(46.73)
aMCI	Primary memory clinic	183	(6.40)	2668	(93.60)	197	(6.90)	2669	(93.10)
	CMRR	47	(4.50)	994	(95.50)	30	(3.30)	889	(96.70)
	Private practice neurologist	5	(2.40)	200	(97.60)	3	(2.40)	121	(97.60)
	Total aMCI	235	(4.43)	3862	(95.57)	230	(4.20)	3679	(95.80)
naMCI	Primary memory clinic	256	(6.30)	3807	(93.70)	256	(6.90)	3467	(93.10)
	CMRR	72	(4.10)	1669	(95.90)	73	(4.30)	1612	(95.70)
	Private neurologist	2	(0.90)	225	(99.10)	5	(3.90)	125	(96.20)
	Total naMCI	330	(3.77)	5701	(96.23)	334	(5.03)	5204	(95.00)
Grand total		13723	(20.52)	18847	(79.48)	11176	(20.84)	16020	(79.18)

AD, Alzheimer's disease; aMCI, amnesic mild cognitive impairment; CMRR, Centres de mémoire, de recherche et de ressources (Centres for Research and Resources on Memory); MMSE, Mini Mental State Evaluation; naMCI, non-amnesic mild cognitive impairment.

cian nor for those who consulted their general practitioner and were not referred to a specialist. It has been shown in the 3C study<sup>31</sup> that among the 201 subjects with 'prevalent dementia', 61.4% consulted a general practitioner for a 'cognitive problem' and 32.9% consulted a specialist.<sup>32</sup> After 80 years of age, only 19.7% of this elderly population did consult a memory specialist. This is also the case in other countries. In Finland, 48.2% of demented patients in the study by Lopponen *et al* had previously been diagnosed by a physician.<sup>33</sup> This percentage decreased to 33% when the MMSE was >20. This underdiagnosis of AD and dementia has also been found in population studies in Sweden,<sup>34</sup> Great Britain,<sup>35</sup> Canada<sup>36</sup> and the USA.<sup>37</sup> There are many reasons for the underdiagnosis of dementia, from the slowness of the cognitive changes<sup>38</sup> to the fearful/fatalistic attitude regarding this irreversible disease. Moreover, general practitioners do not often refer their patients to a neuro specialist as only 41% of them consider that the specific treatments of AD are efficient.<sup>39</sup> These two first points are important to consider as a selection bias. Of course, our data are not representative of the overall French incidence of early stages AD in 2014 and 2015 but only of diagnosed cases, that is, individuals who either by themselves or due to a caregiver or physician came to have a neurological evaluation. No data exist yet in France to address the discrepancy between the total number of early stages AD and the diagnosed cases. The French cohort CONSTANCES, aiming to recruit 200 000 individuals randomly selected from a population and to follow them for 5 years with a yearly cognitive assessment for elderly

participants and AD diagnosis recording will allow researchers to address this critical point.<sup>40</sup> This contrast between clinical and population-based data will be the subject of further studies.

3. Many patients are already in an advanced dementia stage when they consult for the first time. In the BNA, the mean ( $\pm$ SD) MMSE score at the time of AD diagnosis was found to be 18.9 ( $\pm$ 5.5).<sup>41</sup>
4. The thresholds chosen to ascertain episodic memory impairment of the hippocampal type or AD CSF profile may be too strict, thus resulting in some false-negative subjects.
5. The decision to exclude 'mixed dementia' patients from our analyses can certainly account for a lower number of AD patients who may be eligible for a drug trial. This choice was made to be as close as possible to the current trial inclusion criteria although, should one disease-modifying drug become available, the decision to treat these patients or not will have to be made on a case by case basis and foster new trials. As already reported in other studies, focusing on the generalisability of clinical trial criteria in community samples,<sup>42</sup> the stricter the eligibility criteria, the less generalisable the trial is. As it is, this criteria will severely limit the broad application of a disease-modifying treatment, should one become available in the coming years. There is a balance to be found between eligibility criteria that should on one hand yield an optimal internal validity to a trial and on the other hand, would accurately reflect treatment effect in clinical settings.<sup>43</sup>
6. Biomarker data as required by IWG-2 criteria are available in clinical setting to only a minority of patients. In

**Table 3** Number of AD diagnoses in the BNA from 2016 to 2018

	2016 (N=115 300)		2017 (N=115 391)		2018* (N=86 429)	
	First MMSE $\geq 20$		First MMSE $\geq 20$		First MMSE $\geq 20$	
	No (n=13 952) n (%)	Yes (n=13 545) n (%)	No (n=17 014) n (%)	Yes (n=15 020) n (%)	No (n=11 028) n (%)	Yes (n=87 42) n (%)
<b>Depending on the type of centre</b>						
Primary memory clinic	11 043 (79.2)	10 138 (47.8)	13 634 (80.1)	11 268 (75.0)	8803 (79.8)	6484 (74.2)
CMRR	2713 (19.5)	3118 (23.0)	3193 (18.8)	3425 (22.8)	2120 (19.2)	2029 (23.2)
Private neurologist	196 (1.4)	289 (2.1)	187 (1.1)	327 (2.2)	105 (1.0)	229 (2.6)
<b>Depending on the diagnostic criteria</b>						
AD—former BNA diagnostic criteria	10 039 (72.0)	6909 (51.0)	902 (5.3)	469 (3.1)	0 (0.0)	0 (0.0)
AD—clinical syndrome only	3589 (25.7)	6053 (44.7)	15 103 (88.8)	13 477 (89.7)	10 452 (94.8)	8226 (94.1)
AD—clinical syndrome and CSF	288 (2.1)	550 (4.1)	903 (5.3)	1012 (6.7)	525 (4.8)	489 (5.6)
AD—genetic mutation	31 (0.2)	30 (0.2)	83 (0.5)	49 (0.3)	37 (0.3)	25 (0.3)
AD—Down syndrome	5 (0.0)	3 (0.0)	23 (0.1)	13 (0.1)	14 (0.1)	2 (0.0)
<b>Depending on the clinical severity</b>						
<b>New BNA diagnostic criteria (&gt;2016)</b>						
Other (fortuitous discovery)	38 (0.3)	63 (0.5)	159 (0.9)	127 (0.9)	103 (0.9)	91 (1.0)
Subjective cognitive complaint	74 (0.5)	353 (2.6)	343 (2.0)	1077 (7.2)	248 (2.3)	781 (8.9)
Minor neurocognitive disorder (DSM V)	464 (3.3)	2638 (19.5)	1919 (11.3)	6205 (41.3)	1283 (11.6)	3778 (43.2)
Major neurocognitive disorder (DSM V)	3288 (23.6)	3536 (26.1)	13 524 (79.5)	7039 (46.9)	9354 (84.8)	4052 (46.3)
Not applicable	49 (0.4)	46 (0.3)	167 (1.0)	103 (0.7)	40 (0.4)	40 (0.5)
<b>Former BNA diagnostic criteria (&lt;2016)</b>						
Dementia	9115 (65.3)	5178 (38.2)	825 (4.9)	364 (2.4)	0 (0.0)	0 (0.0)
Mild cognitive impairment	750 (5.4)	1500 (11.1)	62 (0.4)	88 (0.6)	0 (0.0)	0 (0.0)
Other	172 (1.2)	223 (1.7)	15 (0.1)	16 (0.1)	0 (0.0)	0 (0.0)
Absence of cognitive complaint	2 (0.0)	8 (0.1)	0 (0.0)	1 (0.0)	0 (0.0)	0 (0.0)

\*Data available up until 18 December 2018.

AD, Alzheimer's disease; BNA, Banque Nationale Alzheimer; CMRR, Centres de mémoire, de recherche et de ressources (Centres for Research and Resources on Memory); CSF, cerebrospinal fluid; MMSE, mini mental state examination; N, total number of acts registered in the BNA for one given year; n, number of the sample of interest.

**Table 4** Comparison between two groups of patients diagnosed with AD or MCI in the BNA in 2014 either in the 11 CMRRs participating in the detailed analysis (Group 1) or in the 18 other French CMRRs

	CMRRs				P value
	Group 0 (n=5 124)		Group 1 (n=3 471)		
	Mean	(SD)	Mean	(SD)	
Age	78.12	(10.27)	74.52	(12.07)	<0.001
MMSE	20.85	(6.65)	21.71	(6.52)	<0.001
	n	(%)	n	(%)	P value
Gender					<0.001
Female	3314	(64.7)	2080	(59.9)	
Male	1810	(35.3)	1391	(40.1)	
Diagnostic					<0.001
AD	3195	(62.4)	1804	(52.0)	
aMCI	595	(11.6)	592	(17.1)	
naMCI	1045	(20.4)	906	(26.1)	
AD and aMCI	118	(2.3)	105	(3.0)	
AD and aMCI and naMCI	19	(0.4)	9	(0.3)	
aMCI and naMCI	152	(3.0)	55	(1.6)	
First MMSE					<0.001
<20	1680	(35.9)	825	(28.8)	
≥20	3000	(64.1)	2039	(71.2)	
Education level					<0.001
<12 years	2827	(55.1)	1889	(54.5)	
>12 years	1806	(35.3)	1238	(35.5)	
Missing data	461	(9.6)	350	(10)	
Referred to the CMRR by					<0.001
General practitioner	2978	(58.1)	1838	(53.0)	
Neurologist	413	(8.1)	665	(19.2)	
Psychiatrist	102	(2.0)	49	(1.4)	
Geriatrician	243	(4.7)	175	(5.0)	
Other specialist	573	(11.2)	214	(6.2)	
Direct	387	(7.6)	226	(6.5)	
Retirement home	49	(1.0)	26	(0.8)	
Primary memory clinic	17	(0.3)	31	(0.9)	
Other CMRR	24	(0.5)	34	(1.0)	
Hospitalisation unit	310	(6.1)	198	(5.7)	
Emergency unit	12	(0.2)	8	(0.2)	
Social care services	16	(0.3)	7	(0.1)	

Group 0 (18 CMRR): Bordeaux, Clermont-Ferrand, Caen, Brest, Rennes, Reims, Corse, Besançon, Paris-Broca, Montpellier, Limoges, Toulouse, Marseille, Angers, Amiens, Grenoble, Villeurbanne, Saint-Etienne.

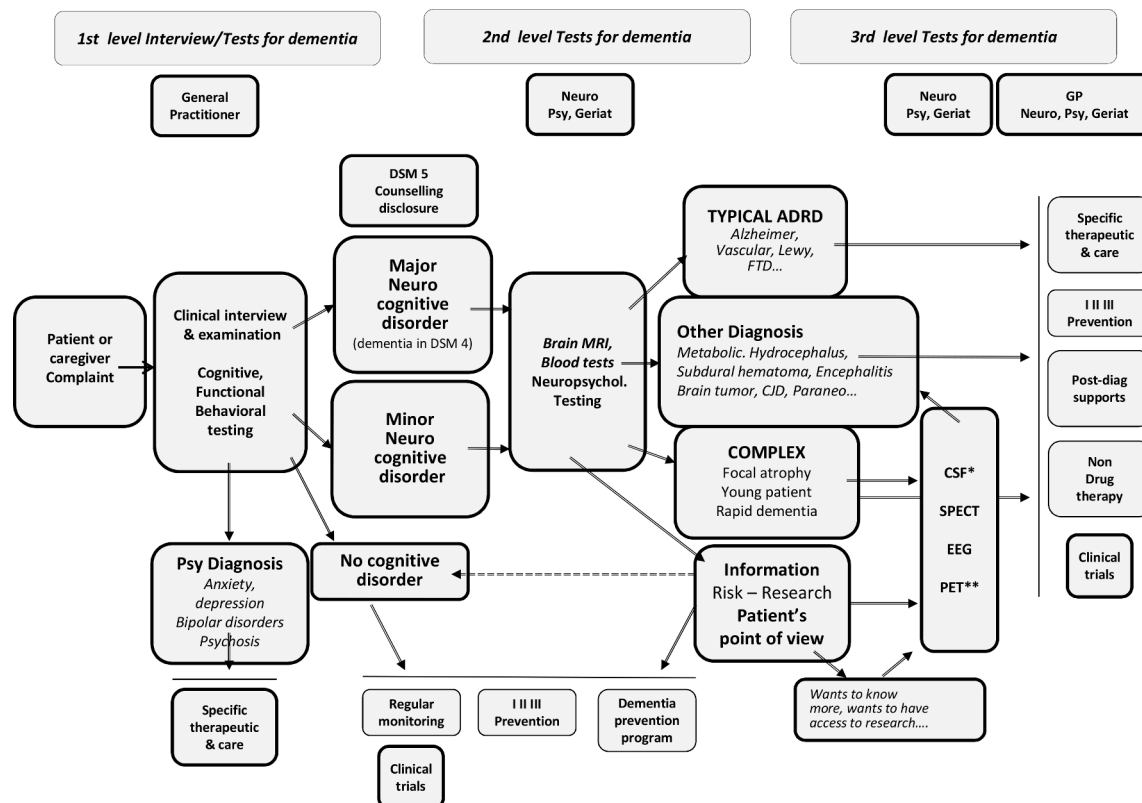
Group 1 (11 CMRR): Dijon, Lille, Nantes, Vandœuvre-Lès-Nancy, Nice, Paris -Lariboisière, Paris-Pitié Salpêtrière, Poitiers, Rouen, Strasbourg, Tours.

AD, Alzheimer's disease; aMCI, amnesic mild cognitive impairment; CMRR, Centre for memory research and resource; MCI, mild cognitive impairment; MMSE, Mini Mental State Evaluation; naMCI, non-amnesic mild cognitive impairment.

the 11 expert centres of our study, we estimate that they were performed in 10% of the prodromal to mild AD group. CSF AD biomarker sampling through lumbar puncture, although authorised in the national health

guidelines on AD diagnosis, is not systematically performed on all patients with a possible diagnosis of AD. The actual recommendations from the French health authorities stipulate that these biomarkers are espe-





**Figure 2** Clinical path of a patient consulting for a cognitive complaint in France. This scheme details the hierarchised and personalised strategy proposed for any given new patient. CJD, Creutzfeldt Jakob disease; CSF, cerebrospinal fluid; DSM, Diagnostic statistical manual; EEG, electroencephalography; FTD, fronto-temporal dementia; Geriat, Geriatrician; GP, General Practitioner; I II III prevention, primary, secondary and tertiary prevention; Neuro, Neurologist; PET, positron emission tomography; Psy, Psychiatrist; SPECT, single photon emission CT.

cially useful in young onset dementia and dementia with an atypical presentation, not in MCI or in patients with a typical clinical AD dementia profile. Indeed, a previous study, also conducted in France, showed that these markers are mainly used in cases of atypical dementia or diagnostic uncertainty.<sup>44</sup> This explains the relatively young age of the 195 patients (mean: 70.8 year) when compared with a previously published mean age of 80.9 years of all AD patients in the BNA.<sup>41</sup> Considering our findings, we can argue that CSF biomarkers be used more frequently in expert memory centres as they have been described to provide good accuracy for AD diagnosis in clinical practice<sup>45</sup> and influence clinicians in their decision-making processes.<sup>46</sup> Since March 2016, a new BNA version has been implemented. Clinicians are now asked to answer questions concerning the main syndromic alteration observed (in memory, language, praxis, executive functions, or visuospatial ability), the stage of the patient (whether they have a subjective complaint, MCI or a major cognitive disorder) and the probable aetiology of the cognitive impairment. They are also asked if AD aetiology is supported by a biomarker measurement or not. This new paradigm will allow for a finer delineation of the epidemiology of early stage AD and will be the

focus of future studies. We focused on cognitive and CSF markers of AD in this study and not on amyloid or fluorodeoxyglucose (FDG) positron emission tomography (PET) or MRI because of two main reasons. First, amyloid PET is not routinely available in French clinics, whereas CSF biomarkers are. Second, MRI and FDG PET are topographic markers with lower specificity than CSF biomarkers. The choice of the association of cognition and CSF markers to ascertain the diagnosis of AD is consistent with the IWG-2 criteria. This is also in line with the recently revised NIA AA criteria based on Jack *et al.* A/T/N classification which states that MRI and FDG PET can be used to diagnose 'neurodegeneration' considered not specific to AD.<sup>47 48</sup>

7. Finally, a worldwide decrease in the incidence of AD has been described in a number of independent studies,<sup>49-51</sup> possibly linked to an improvement of the general health risk factors and a higher education level in the countries from which these cohorts derive. Nevertheless, this element most probably could only explain a small part of the discrepancy.

In a post-hoc survey conducted in the 11 participating CMRRs, the main reasons mentioned to explain the small number of identified patients eligible for a disease-modifying drug trial were the absence of referral of AD

patients at an early stage of the disease, the fact that the lumbar puncture is not recommended in typical amnesic AD unless it occurs before 65 years of age, and the fact that some patients could have AD and not be within the chosen cognitive thresholds for this study.

Interestingly, the 195 patients identified with prodromal or mild AD in the 11 CMRRs, which are part of the third-line healthcare organisation, had been most often referred by their general practitioners, whereas one would expect they would be referred mainly by neuro specialists in the second line. This lack of 'specialised referral' is also supported by the small geographical distance (40.1±6.7 km) separating these patients from the CMRR.

This study has limitations including its retrospective design for the electronic record file database that does not allow us to draw definitive epidemiological conclusions, but still raises the level of awareness concerning the relatively low diagnostic rate of AD at its early clinical stage.

Another limitation is that our study, so far and to our knowledge, cannot be generalised to other countries because we lack recent epidemiological data on AD on the same scale as our study. Results from these studies<sup>52</sup> are usually derived from cohorts recruited in the 1990s or 2000s and not these last years. This fact alone is troublesome both because of the suggested trend in AD incidence decrease in these last decades<sup>50 51</sup> and because the recruitment in these cohorts predates the newest diagnostic criteria for AD.<sup>3 5 15</sup> Finally, early AD is never individualised in these studies focusing on AD whatever the severity at diagnosis. Also, the use of biomarkers is never disclosed in these epidemiological studies.

## CONCLUSIONS

Our study is the first and largest to address the critical question of the frequency of a specific AD diagnosis at its early stages in clinical routine. Our estimations of the incidence of clinically diagnosed prodromal or mild AD are only a fraction of previous incidence estimations of AD in the general population.<sup>29</sup> This finding, which is based on two different database analyses, is generalisable on a national scale due to the large number of included participants and the 5-year period of evaluation. Similar findings will have to be evidenced in other countries to be able to generalise these results on a global scale. This topic is important to consider since new disease-modifying drugs, specifically designed to target this population of patients, may become available in the coming years. If the ongoing trials yield positive results, we will be confronted with an unprecedented 'rush towards treatment' from a huge number of patients. These treatments should, however, only be proposed to patients if there is potential expected efficacy. Thus, the selection of patients, fitting the successful trial's inclusion criteria, should be identified by expert centres. Also, new diagnostic tests such as amyloid PET, which has recently been proved to change

the care and management plan in >60% of patients with MCI or dementia<sup>53</sup> or amyloid sampling in blood,<sup>54</sup> may transform the diagnostic procedures of patients with cognitive complaints or impairments in the near future. Large efforts will have to be made in order to improve the diagnostic procedures, and access to these procedures, for patients at an early stage of AD. National databases are valuable tools to monitor these diagnostic procedures and improve them.

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**Data sharing statement** The BNA data are available through the BNA website (<http://www.innovation-alzheimer.fr/bna-fr/>). It is required to contact the scientific committee of the BNA to gain access to the data.

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