



Diagnostic Assessment & Prognosis

Evolution of dementia diagnosis over time (1988–2013): Evidence from French and English cohorts. Implication for secular trends analyses

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Dementia; Secular trends; Diagnosis; Incidence; Prevalence

1. Introduction

Dementia is a syndrome consisting of deterioration in cognitive functions sufficient to impair a person's daily life and activities. To describe the extent of dementia as a public health priority, many population-based studies following older people over time have been undertaken during the past 30 years [1,2]. Research on the descriptive epidemiology of dementia has identified several challenges in the field: standardization of diagnostic approaches for

dementia subtype and mild forms of cognitive decline; dealing with participant selection and attrition, differential mortality, and incidence for prevalence estimations; dementia at the end of life and terminal decline; substantial underdiagnosis by the health care system [3]. Diagnosis of the dementia syndrome is sensitive to such challenges [4,5]. Recently researchers have evaluated changes in dementia prevalence and incidence over time [6–14]. However, to provide accurate estimations, consistent dementia diagnosis across studies and time is required. The relationship of both clinical and consensus diagnosis of dementia can be examined across time, and also in relation to other types of measurement. The diagnosis of dementia, a clinical syndrome, is based on a

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diagnostic process, usually a version of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM) [15]. These diagnostic criteria do not have clear thresholds or specific measures to define the level of cognitive decline and its consequences, leaving the ultimate decision to clinical judgment or consensus diagnosis. Although diagnostic criteria have not fundamentally changed, there have been substantial societal and clinical shifts in dementia awareness, likely to have resulted in interclinician and intraclinician variability.

Recently, a few studies on the evolution of dementia over time have hypothesized that the diagnosis of dementia is likely to have evolved over 20 years and that algorithmic diagnosis could be more stable [16–18]. Changes in prevalence and incidence of any disorder, including dementia, are known to be influenced when diagnostic processes change over time, resulting in systematically different estimations (e.g., diabetes mellitus, hypertension) [19]. The studies presented in this work have determined dementia cases using two different algorithms in place of or in addition to clinical diagnosis: the Automated Geriatric Examination for Computer-Assisted Taxonomy (AGECAT) algorithm, a well-known and validated automated computer algorithm used in the British cohorts in the Cognitive Function and Aging Study (CFAS) I and CFAS II [20,21] and a “Comparative Dementia Algorithm (CDA)” developed from French cohorts [17]. Clinical diagnoses in French cohorts showed no change in dementia incidence over 2 decades, whereas the algorithmic diagnosis revealed a decrease, supporting the evolution hypothesis and highlighting the importance of using a stable diagnosis of dementia.

This study aimed (1) to examine the evolution of clinical dementia diagnosis over 3 decades, by analyzing the cognitive performance of people given a study diagnosis of incident dementia. A comparison of these with the cases diagnosed by a CDA method on French data was also conducted to establish the nature of change, if any; (2) as a validation of this algorithm, an adaptation was also applied to the British data to perform prevalence and incidence analysis, to provide a comparison with the validated AGECAT algorithm.

2. Methods

2.1. Study populations

Participants, aged 65 years and older, from four different population-based cohorts from France (Personnes Agées Quid [PAQUID] and Three-City) and UK (CFAS I and II) have been used in this study (cf. [Supplementary Fig. 1](#)).

The PAQUID cohort was formed in 1988–1989 with a representative sample of 3777 participants living at home in the departments of Gironde and Dordogne. The selection was stratified by sex, age, and size of urban unit. Respondents have been followed up for 27 years. The Three-City (3C-Bordeaux) cohort, starting in 1999, recruited 2104

participants from the Urban Community of Bordeaux, within 10 districts. Participants have been followed up for 14 years. For these two French cohorts, standardized questionnaires assessing sociodemographic, medical, cognitive, and functional data were administered by trained neuropsychologists during face-to-face interviews, at baseline and at each follow-up. Participants were followed-up every 2 to 3 years even after institutionalization. At each follow-up, vital status was systematically recorded for all the participants.

The Medical Research Council CFAS I: between 1989 and 1994, baseline interviews were conducted in six geographical areas in England and Wales, and subjects were followed up for 10 years. A two stage process, with screening followed by diagnostic assessment, was used in CFAS I, weighted across the cognitive performance as Mini-Mental State Examination (MMSE) and AGECAT original items in screen. Data from three of the English areas of Medical Research Council CFAS—Cambridgeshire, Newcastle, and Nottingham [22], where interviews were carried out between December 1990 and July 1993—were selected for analyses, providing 7635 subjects, from which a subpopulation of 1459 individuals underwent assessment. Between November, 2008, and October, 2011, new fieldwork in the same geographical areas was carried out to provide CFAS II estimates on 7762 subjects, which could be directly compared with CFAS I. CFAS I and CFAS II had identical sampling approaches, methods, and diagnostic approach apart from the simplification of design from two stage to one stage at baseline and incidence phase through combination of screening and assessment interviews. Full details of the studies have been described elsewhere [16,22–24].

2.2. Diagnostic methods

In the French cohorts, a clinical diagnosis was available, whereas in the British cohorts, the AGECAT algorithm was applied. Moreover, in the four studies, a CDA was applied.

For both PAQUID and 3C populations, the clinical diagnosis was made following a three-step procedure. The first step was a cognitive evaluation made by the neuropsychologist through a series of psychometric tests. Participants who had a high likelihood of dementia, based on their neuropsychological performances or decline relative to a previous examination, were then examined by a senior neurologist. The diagnosis of dementia was based on the DSM-III-R or the DSM-IV criteria. In case of refusal or death between the first and second steps, additional information was gathered from the informant and the medical practitioner. Then, each case was discussed by a validation committee composed of neurologists and geriatricians and directed by J.F.D. to provide a final diagnosis.

In CFAS I and II, the AGECAT algorithm used was based on the Geriatric Mental State Examination that provides relevant information to determine dementia syndrome in older population [20,25]. Missing data within an interview could prevent the algorithmic diagnosis, and for

individuals with missing data, the same approach was taken for CFAS II as for CFAS I, which was a review of all available information by diagnostician (C.B.), applying DSM-III-R criteria. Many of these individuals with missing data had severe cognitive impairment and were not able to respond to the interview questions. The Geriatric Mental State-AGECAT has been validated against internationally accepted earlier diagnostic criteria (DSM-III-R) [21].

The CDA approach was a cognition-disability algorithm. For the French data, we used a previously published algorithm [17]. This diagnosis was based on cognitive and functional assessments using MMSE and four Instrumental Activities of Daily Living (4IADL) associated with cognition (ability to use the telephone, transportation, responsibility for medications, and ability to manage its budget) to fit dementia definition. The algorithmic diagnosis was then defined by an MMSE score of <24 (or a missing MMSE score for "cognitive reason" such as major aphasia, mutism, comprehension problem) AND a 4IADL score of >1 (disability, even mild, for more than one activity out of the 4). For the English data, information on disability was not recorded in the same way as in France, so the algorithm has been adapted for comparative purposes. It was based on the MMSE score and on disability on IADLs and ADLs (ability to wash all over or bath, to prepare and cook a hot meal, and to put on shoes and socks or stockings). The algorithm was defined by an MMSE score of <24 AND if the respondent need more than partial help with at least one of the three abilities.

2.3. Statistical analyses

Sociodemographic characteristics, MMSE, and disability score at baseline have been compared between populations.

To explore evolution of the clinical diagnosis over time, cognitive status at diagnosis using the MMSE score was described. The scores of incident clinical cases at each follow-up of the whole PAQUID and 3C-Bordeaux studies were described using mean scores according to study and educational level. Prevalent cases at inclusion were removed, and only incident cases at each follow-up were kept. Linear splines regression of MMSE scores according to time, age at diagnosis, gender, study, and educational level were also performed.

The cases diagnosed during the first 10 years of follow-up from PAQUID and 3C-Bordeaux were then classified according to the concordance or divergence of clinical and algorithmic diagnosis. A comparison of the characteristics of discordant cases was analyzed with sociodemographic, cognitive, and functional factors according to two categories: dementia in clinical diagnosis but no dementia in the algorithmic approach, and no dementia in clinical diagnosis but dementia in the algorithmic approach.

Finally, to validate the CDA, prevalence and incidence in both CFAS I and II have been estimated and discussed in relation to previously published prevalence and incidence results obtained based on AGECA algorithm. For CFAS I, the

prevalence was provided from the first wave (inclusion) on all subjects. For CFAS II, prevalence was provided from the first wave on all subjects. Prevalence has been weighted and standardized on the age and sex repartition of the 2011 UK population. Two-year incidence has been estimated with a weighted Poisson regression on all subjects for both CFAS I and II. An inverse probability weighting has been used based on both the probability of being included in the study, taking participation rate difference into account, and the probability of having a diagnosis, taking attrition into account. Finally, comparisons of both prevalence and incidence between CFAS I and CFAS II are provided.

3. Results

3.1. Population characteristics

Global characteristics of the four cohort populations are presented in Table 1 (including the CFAS I subpopulation). The mean age at inclusion was around 75 years with more women than men. PAQUID and CFAS I participants reported less years of education and had a lower MMSE score at baseline than 3C and CFAS II. Flow charts of the four populations are presented in Supplementary Fig. 1.

3.2. Evolution of the clinical diagnosis

In total, 1318 incident cases were clinically diagnosed in 3C and PAQUID over the follow-up, with 1250 with values allowing for adjustment of MMSE scores at diagnosis. The crude means of the MMSE at clinical diagnosis for each follow-up in PAQUID and 3C-Bordeaux are shown in Fig. 1. The means of the MMSE at diagnosis were higher in higher-educated subjects of 3C-Bordeaux than in lower-educated subjects of 3C and in PAQUID at all follow-up times. Overall, the regression model showed a significant increase in the MMSE score at diagnosis before 2001 ($\beta = 0.30/y$, $P < .0001$) and then a significant decrease of the MMSE score after 2001 ($\beta = -0.34/y$, $P < .0001$), adjusted on age at diagnosis, sex, study, and educational level. Subjects from 3C had significantly higher levels of MMSE scores at diagnosis ($\beta = 1.16$, $P = .006$), as well as subjects with higher educational level compared with those without diploma ($\beta = 2.87$, $P < .0001$).

3.3. Characteristics of diagnostic discordance

Cases from the 10-year follow-up of 3777 subjects of PAQUID and 2104 subjects of 3C-Bordeaux have been classified according to both clinical and algorithmic diagnosis (CDA). On the 5881 subjects, 4801 (81.6%) did not have dementia at either diagnosis and 535 (9.1%) were diagnosed with dementia by the two diagnosis over the 10-year follow-up; 389 (6.6%) subjects were algorithmic cases only, and 156 (2.6%) subjects were clinical cases only. The characteristics of discordant cases are described in Table 2. In 3C-Bordeaux, people were more likely to be diagnosed by clinical diagnosis than algorithm. They were

Table 1
Descriptive data on cohorts

Characteristic	PAQUID	CFAS I	3C	CFAS II
Inclusion date	1988–1989	1990–1993	1999–2000	2008–2011
Number of participants				
Total population	3777	7635	2104	7762
Subpopulation*	-	1459	-	-
Age at baseline: mean (SD)				
Total population	75.5 (6.9)	75.8 (7.1)	74.6 (5.1)	75.7 (7.3)
Subpopulation*	-	77.4 (7.9)	-	-
Gender (women): n (%)				
Total population	2200 (58.3)	4594 (60.1)	1288 (61.2)	4228 (54.5)
Subpopulation*	-	921 (63.6)	-	-
Low educational level†: n (%)				
Total population	2980 (78.9)	5532 (74.1)	872 (41.5)	2045 (26.8)
Subpopulation*	-	1065 (79.3)	-	-
MMSE score at baseline: mean (SD)				
Total population	25.6 (3.7)	24.8 (6.1)	27.2 (2.4)	26.8 (3.5)
Subpopulation*	-	20.9 (7.4)	-	-

Abbreviations: PAQUID, Personnes Agées Quid; CFAS, Cognitive Function and Aging Study; MMSE, Mini-Mental State Examination.

*Subjects with assessment by AGECA algorithm diagnosis.

†Low educational level: less than 10 years of study.

also better educated and had less disability than the cases diagnosed by the algorithm. Age at diagnosis was the same for both categories, but the MMSE score at diagnosis was higher for subjects diagnosed by clinical diagnosis than for the one diagnosed by algorithm only.

3.4. CFAS prevalence and incidence estimates: The cognition-disability algorithm approach. Comparison with AGECA estimates

3.4.1. Prevalence

In CFAS I total population at baseline, the CDA algorithm was incomplete for 274 individuals. On the 7365 remaining individuals, 601 were classified as having the algorithmic

diagnosis of dementia (CDA) (weighted and standardized percentage = 8.8%). Previously published results on CFAS based on the AGECA algorithm estimated a prevalence of 8.3%. Of the CFAS II total population at baseline, 404 of the 7762 had incomplete data for the CDA and were not in the analysis. CDA then classified 367 as having dementia (weighted and standardized percentage = 5.7%). Previously published results on CFAS II based on the AGECA algorithm reported a prevalence of 6.5%.

Based on the CDA, dementia prevalence has declined by 35% between 1990–1993 and 2008–2011.

3.4.2. Incidence

For CFAS I, 4648 of the 6135 respondents without prevalent dementia (CDA defined) were seen at the 2-year

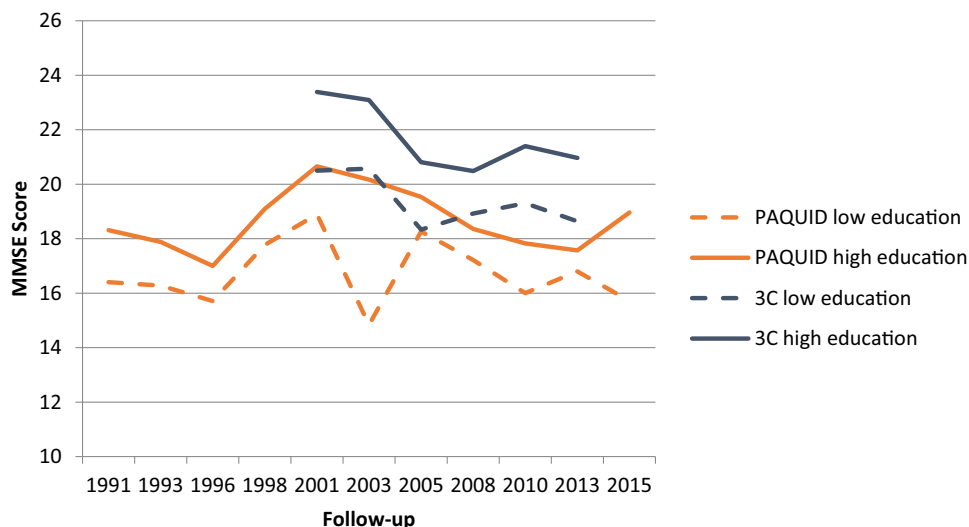


Fig. 1. MMSE (mean) at time of study clinical diagnosis (incident) across time in 3C-Bordeaux and PAQUID. Abbreviations: PAQUID, Personnes Agées Quid; MMSE, Mini-Mental State Examination.

Table 2
Characteristics of participants according to clinical or algorithmic diagnostic method in the first 10 years of follow-up in PAQUID and 3C-Bordeaux, n = 545

Diagnostic type*	Clinical = 1 Algorithm = 0 N = 156	Clinical = 0 Algorithm = 1 N = 389
	3C/PAQUID, % (n)	60.9 (95)
Women, % (n)	60.3 (94)	72.7 (283)
Low education, % (n)	21.1 (33)	57.8 (225)
Diagnosis Rosow disability, % (n)	90.2 (138)	98.2 (376)
Diagnosis Katz disability, % (n)	13.1 (20)	29.7 (114)
Diagnosis age, mean (s.d.)	83.4 (5.5)	83.5 (6.2)
Diagnosis MMSE, mean (s.d.)	23.5 (3.0)	19.9 (4.0)

Abbreviations: PAQUID, Personnes Agées Quid; CFAS, Cognitive Function and Aging Study; MMSE, Mini-Mental State Examination.

*Diagnosis type = 0: no dementia and 1: dementia.

follow-up. Of these, 247 (5.3%) individuals had developed dementia (based on the CDA definition) during the 2 years. For CFAS II, 4964 of 6574 without prevalent dementia defined by CDA were re-interviewed at 2 years, of whom 137 (2.7%) individuals fulfilled the CDA. The 2-year age and sex adjusted incidence rates were thus 31.2/1000 (95% confidence interval [CI] = 28.0–34.8) for CFAS I and 15.0/1000 (95% CI = 13.5–16.7) for CFAS II. Previously published results on CFAS based on the AGECA algorithm have found an incidence of 20.0/1000 (95% CI = 16.9–23.8) for CFAS I and 17.7/1000 (95% CI = 15.2–20.9) for CFAS II. Incidence rates and confidence intervals per age and sex based on the CDA definition have been provided for both CFAS I and II in Table 3. CFAS II incidence estimates were lower than CFAS I, for both men and women and each age category, and women always had a higher incidence rate than men, although somewhat reduced in CFAS II compared with CFAS I.

Table 3
Incidence rates in CFAS I and CFAS II by age and gender, defined using CDA and weighted for nonresponse and population selection

/1000 PY	CFAS I		CFAS II	
	Rate	95% CI	Rate	95% CI
Men				
65–69	8.5	6.6–11.0	4.1	3.2–5.3
70–74	11.4	9.0–14.4	5.5	4.3–6.9
75–79	19.5	15.8–24.0	9.4	7.6–11.5
80–84	53.0	44.4–63.4	25.5	21.5–30.2
85+	106.9	88.7–128.7	51.3	43.4–60.8
Women				
65–69	12.8	10.1–16.2	6.1	4.8–7.8
70–74	17.1	13.7–21.3	8.2	6.6–10.3
75–79	29.3	24.4–35.3	14.1	11.6–17.1
80–84	79.7	68.9–92.2	38.3	33.0–44.4
85+	160.7	139.0–185.7	77.2	67.5–88.3

Abbreviations: CFAS, Cognitive Function and Aging Study; CDA, Comparative Dementia Algorithm.

4. Discussion

This article has described the evolution over 25 years of the cognitive status of incident cases of dementia when they were diagnosed based on clinical diagnosis. Compared with cases solely diagnosed by CDA, those with a clinical diagnosis only were more highly educated and diagnosed with a higher MMSE score. Prevalence and incidence estimates were a little higher using the CDA approach compared with the AGECA algorithm in CFAS I and similar in CFAS II.

An important strength of this study was the use of four well-recognized cohort studies, with longitudinal follow-up covering a 25-year period and with a high number of subjects. Moreover, results are based on three different diagnostic approaches already published, one clinical and two algorithmic. Among the different algorithms used, gold standards will depend on purpose and motivation for diagnosis and whether research or clinical settings. However, the CDA approach has the advantage of being simple and easy to use in a large number of studies. It needs to be stated that the diagnostic approach must be appropriate for the purpose [26]. When studying secular trends of dementia, stability of the diagnosis over time is the main requirement. A limitation is that our results on possible evolution or boundary creep of dementia diagnosis are only based on the two French studies with a clinical diagnosis available. Further replication on other population studies is necessary to confirm our results. Another issue is a limit of our CDA definition that does not allow disentangling the part of functional and/or cognitive deficits attributable to comorbidities unrelated to dementia. For example, disabilities due to comorbidities such as blindness, Parkinson's disease, or stroke are similarly accounted for by the algorithm as disabilities due to repercussion of cognitive impairment. This could explain part of the difference between cases diagnosed by clinic and by algorithm only (6.6% CDA+/clin-).

The analysis of MMSE scores at clinical diagnosis from the beginning of the 90s to the beginning of 2010 demonstrates an evolution of cognitive status of participants at time of dementia diagnosis across time and study in France. Between 1992 and 2001 in PAQUID, we found that subjects were increasingly diagnosed earlier—at a less severe stage—over time. The improvement of disease knowledge and the introduction of treatments may have led to diagnosis at earlier stage. A German study based on memory clinics also found a trend to earlier diagnosis between 1985 and 2009 [27]. After 2001 however in the French studies, we found that incident cases were progressively diagnosed when more severely cognitively impaired over time. This decrease may be the result of the aging of the whole cohorts, although regression models have been adjusted on age at diagnosis. Failure to find new efficient treatments and public perception of the impact of diagnosis on patients could also be possible explanations for this change. The diagnosis of dementia was made earlier in 3C than in PAQUID. The

higher educational level of the 3C participants partly explains this difference. It may also be explained by the introduction of the Free and Cued Selective Reminding Test in the 3C questionnaires [28]. This provides a finer/more subtle indication of episodic memory impairments of the participants and may have led to the differences with the PAQUID study. Only later follow-up, with validation through knowledge of progression, can the comparison of relative performance be known and it may be that overdiagnosis is occurring.

The instability of the clinical diagnosis led to the emergence of the algorithmic approach to diagnose dementia in cohort studies. The comparison of dementia incidence 10 years apart in PAQUID and 3C has shown that the type of diagnosis used can lead to mixed results and have an influence on conclusions about secular trends [17]. Only the algorithmic diagnosis showed a decrease in the incidence of dementia with the trends stable for clinical diagnosis. Similar observations have been made in the comparison of dementia prevalence 20 years apart in the PAQUID and Agrica-MSA-IFR de Santé Publique, Aging Multidisciplinary Investigation studies [29]. In the Framingham study, the authors have reviewed a second time each case diagnosed before 2001 to apply up-to-date criteria [8]; however, the same indicators are needed to control for evolution. In the Health and Retirement Study, an algorithmic approach based on cognitive deficit assessed with a 27-point scale has also been used [14,30]. These results provide further evidence to support the use of approaches that are less prone to secular changes in diagnostic thresholds when evaluating time trends and computing projections. When comparing cases diagnosed by either the clinical or the CDA diagnosis in the two French populations, it appeared that cases diagnosed by purely clinical diagnosis were more educated and had a higher MMSE score at diagnosis than the cases diagnosed by the algorithm only, thus diagnosing people earlier in the disease course than the algorithm (or indeed overdiagnosis). The CDA items and cut points were mapped to the dementia syndrome criteria. In 2015, the major change between the DSM-IV and the latest edition, the DSM-V, heralded the “end” of the word dementia within the diagnostic criteria, with substitution of “major neurocognitive disorder,” where the loss of independent functioning remains an important criterion. Algorithms have become even more relevant as these are highly compatible with this approach.

The AGE-CAT algorithm was validated according to the DSM-III-R criteria, and prevalence and incidence estimates and time trends have already been published for CFAS I and II [16,18]. One difficulty in CFAS I was the two-phase design where a majority of individuals had not undergone the assessment process, although sampling and assessment was across the cognitive spectrum. The estimations show that the CFAS CDA prevalence is slightly higher for CFAS I, and for CFAS II lower when compared with the prevalence estimated using AGE-CAT diagnosis, from a full likelihood

model for study design, missing data, and inverse probability weighting for initial nonresponse. For CFAS I, the incidence estimates using the CDA were much higher than the incidence rates found with the AGE-CAT and Bayesian procedure but slightly lower for CFAS II. Using the CDA approach thus showed an even more marked reduction in incidence of dementia between CFAS I and II than has been published. The results also showed a significant decline in women, not found with the AGE-CAT. This could be explained by the fact that disability in women has improved between the two generations and these measures of disability were not directly part of the AGE-CAT algorithm unlike the CDA algorithm [31].

To conclude, secular trends analyses of dementia are important and have attracted considerable attention. Investigating the best ways to provide the most accurate estimations is critical when such estimations are used to predict future dementia numbers, and hence facilitate policy and care planning, worldwide. It is therefore essential to employ a stable diagnosis over time and studies. We provide here a simple and easy to use algorithmic approach that can be applied to most pre-existing cohorts. Further studies exploring secular trends of dementia in multiple cohorts could stabilize/standardize their methods over time by using this approach.

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to all the data in the study and had final responsibility for the decision to submit for publication.

Supplementary data

Supplementary data related to this article can be found at <https://doi.org/10.1016/j.dadm.2018.07.005>

RESEARCH IN CONTEXT

1. **Systematic review:** We reviewed the literature using traditional (e.g., PubMed) sources. While secular trends of dementia prevalence and incidence have been reported in several recent publications, there have been only few studies investigated evolution of clinical diagnosis of dementia. These relevant citations are appropriately cited.
2. **Interpretation:** This work shows a significant evolution of the clinical diagnosis of dementia between time and studies, with dementia being progressively diagnosed earlier before 2000 and with a trend toward more advanced cognitive impairment after 2000. It also confirms the evidence of a decrease in the prevalence and incidence of dementia over the last decades, using an algorithmic diagnostic approach.
3. **Future directions:** This finding highlights the importance to apply stable diagnosis over time and studies when studying secular trends of dementia. Further investigations regarding potential reasons for the declining trends of dementia are required.

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