

The 9 year cognitive decline before dementia of the Alzheimer type: a prospective population-based study

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Summary

Better knowledge of the preclinical phase of Alzheimer's disease would be an important advance to allow earlier treatment of this ominous disease. This prodromal period was investigated in the Paquid cohort by analysing change in cognitive performances at five time points over a 9 year period. Neuropsychological measures including global cognitive functioning (Mini-Mental State Examination), visuo-spatial memory (Benton Visual Retention Test), verbal fluency (Isaacs Set Test) and abstract thinking (Wechsler Similarities Test) were assessed in 215 future Alzheimer's disease subjects and 1050 individuals without dementia. The results showed that cognitive performances of the pre-morbid subjects at baseline were already lower

than those of individuals without dementia (1.4 points less on the Mini-Mental State Examination; 1.8 points less on the Benton Visual Retention Test; 4 points less on the Isaacs Set Test and 0.8 points less on the Wechsler Similarities Test). For some neuropsychological tests, an acceleration of the decline occurred ~3 years before the diagnosis and, for each test, the course of decline was modulated by education level. These findings show that abnormally low performances can be evidenced 9 years before the clinical diagnosis of Alzheimer's disease in several domains of cognition beyond memory and that cognitive change over time can be influenced by education.

Keywords: dementia; subclinical phase; cognitive decline; prospective study

Abbreviations: BVRT = Benton Visual Retention Test; IST = Isaacs Set Test; MMSE = Mini-Mental State Examination; WST = Wechsler Similarities Test

Received January 20, 2004. Revised December 8, 2004. Accepted January 27, 2005. Advance Access publication March 17, 2005

Introduction

With the recent development of effective anti-dementia drugs, pharmacological treatments of Alzheimer's disease are now available. However, the diagnosis of this disease is often made at a late stage, and identifying prodromal markers allowing patients to be identified at a subclinical stage of cognitive decline has become an increasingly important matter of investigation.

The prospect of early pharmacological interventions aimed at preventing or delaying the onset of dementia has driven researchers to establish criteria to define a clinical entity that could be the target of intervention trials. Among the attempts to define a stage preceding dementia, the syndrome called mild cognitive impairment has been proposed. It is defined as a transitional state occurring between normal

ageing and dementia in which patients present slight cognitive deficits but are not yet demented (Flicker *et al.*, 1991; Petersen *et al.*, 1999). Another way to characterize the stage preceding dementia is to refer to longitudinal population-based cohort studies. Adopting this point of view does not require use of the *a priori* definition of mild cognitive impairment. Indeed, longitudinal epidemiologic studies allow variables to be measured before the end-point of dementia is reached, providing an unbiased description of the period that preceded dementia. These studies yield important contributions to the knowledge of the subclinical phase of dementia and, in particular, they may provide information on two major questions that remain unclear: the duration of the period preceding dementia in Alzheimer's

disease and the nature of cognitive processes that are prone to decline first.

In the Framingham cohort, low cognitive performances measured >10 years before dementia onset were found to be predictors of dementia (Elias *et al.*, 2000). Furthermore, measures of linguistic skills assessed 50 years before dementia diagnosis were found to be a risk factor of future Alzheimer's disease as reported in the Nuns study (Snowdon *et al.*, 1996). Nonetheless, the main limitation of these studies is that they only involved one preclinical measurement point. Thus, it is not possible to establish whether the low performances of pre-morbid subjects were related to a real decline in cognitive function that could be in favour of a long-term ongoing pathological process, or to a baseline status of poor cognitive functioning that could be in itself a risk factor for dementia. In the study of Rubin *et al.* (1998), 82 elderly volunteers were assessed repeatedly during a 15 year follow-up. Before the onset of dementia, the cognitive changes between the future Alzheimer's disease subjects and those remaining free of dementia were not different except for the Wechsler Logical Memory subtest, although when the cognitive decline began, an abrupt and general deterioration of performances was observed. However, the comparability of these results with those previously cited is difficult since the diagnostic outcome was a clinical dementia rating score greater than 0 which includes very mild cognitive impairment instead of the more conservative DSM-IV criteria for dementia.

Concerning the nature of cognitive processes that deteriorate early in dementia, it is usually considered that loss of episodic memory is the core feature of the dementing process (Small *et al.*, 2000; Bäckman *et al.*, 2001; Albert, 2002). It is, however, worth noting that numerous studies have shown that other domains of cognition are also impaired in the preclinical phase of Alzheimer's disease (Masur *et al.*, 1994; Jacobs *et al.*, 1995; Linn *et al.*, 1995; Dartigues *et al.*, 1997; Howieson *et al.*, 1997; Fabrigoule *et al.*, 1998; Schmand *et al.*, 2000) and that some of these cognitive deficits may be the cause of slight impairments on instrumental activities of daily living (Barberger-Gateau *et al.*, 1999).

Personal and socio-demographic factors such as age or gender seem to have an influence on the occurrence of dementia and the course of decline (Letenneur *et al.*, 1999). Education is also an important factor (Katzman *et al.*, 1993; Letenneur *et al.*, 1999; Karp *et al.*, 2004). Its influence is often explained by the hypothesis that people with high educational level have a greater 'cognitive reserve capacity' than people less educated (Stern *et al.*, 1994). This so-called 'cognitive reserve' would be due to positive effects of early education on cerebral and cognitive development and would therefore delay in later life the clinical manifestations of dementia by compensating the cognitive expression of the pathology. It is therefore mandatory to take these factors into consideration when interpreting any cognitive decline occurring prior to the diagnosis of Alzheimer's disease in elderly adults.

The focus of this report is to describe the decline of cognitive functioning occurring in the preclinical period of

Alzheimer's disease. With the long follow-up of the Paquid study (Dartigues *et al.*, 1992), we have had the opportunity to investigate this decline over 9 years with serial measurements of global cognitive performances, verbal fluency, abstract thinking and visuo-spatial memory obtained at five time points of the follow-up.

Methods

Participants and follow-up

The detailed methodology of the Paquid study has been presented previously (Dartigues *et al.*, 1992). Briefly, Paquid is a population-based study made up of 3777 elderly adults aged ≥ 65 years, living at home in the South-western part of France (Gironde and Dordogne) at enrolment. Individuals were seen at home by psychologists trained in home interviews at the initial visit (V0) and at 1 (V1), 3 (V3), 5 (V5), 8 (V8) and 10 years (V10) after the initial visit in Gironde and the same, except for the 1 year visit, in Dordogne. Each visit included a neuropsychological evaluation and a standardized diagnosis of dementia. This cohort is part of an epidemiological programme on ageing, particularly focused on the incidence, natural history and non-genetic risk factors of dementia.

Neuropsychological measurements

Four neuropsychological tests were systematically proposed to the subjects at each visit: a French version of the Mini-Mental Status Examination (MMSE) (Folstein *et al.*, 1975) was used as an index of global cognitive performance. The multiple choice recognition form of the Benton Visual Retention Test (BVRT) (Benton, 1965) was used to measure visual memory (scores range from 0 to 15). The Isaacs Set Test (IST) (Isaacs and Kennie, 1973) assessed verbal fluency by measuring the ability to generate lists of words in four semantic categories (colours, animals, fruits and cities) in a 15 s interval. We stopped the counting if the subject generated >10 words in each category, thus possible scores ranged from 0 to 40. Finally, the Similarities subtest of the Wechsler Adult Intelligence Scale (WST) (Wechsler, 1981) assessed abstract thinking by measuring the ability to find in what way two things are alike (e.g. 'orange-banana'). Only the first five pairs of the subtest were considered, so possible scores ranged from 0 to 10.

In addition to the neuropsychological examination, the psychologists recorded socio-demographic factors, measures of functional abilities assessed with the Instrumental Activities of Daily Living (Lawton and Brody, 1969) and the Activities of Daily Living (Katz, 1983) scales, depressive symptomatology and a medical questionnaire including health measures, self-reported morbidity and medication.

Dementia diagnosis

According to this evaluation, the psychologists completed a standardized questionnaire designed to obtain the A (memory impairment), B (impairment of at least one other cognitive function) and C (interference with social or professional life) DSM-III-R criteria for dementia. Individuals who met criteria for dementia as well as those presenting a decline of 3 points or more on the MMSE since the previous visit were seen by a senior neurologist who was not informed about the cognitive scores obtained by the subjects during their interview with the psychologist. The neurologist confirmed dementia criteria and assessed the NINCDS-ADRDA criteria

(McKahn et al., 1984) for Alzheimer's disease, and the Hachinski score (Hachinski et al., 1975) for vascular dementia. Ancillary examinations (such as CT scan or MRI, thyroid-stimulating hormone, vitamin B12 and folate blood level determinations, informant interview) were then performed if accepted by the general practitioner and the subject. All available information was reviewed by a panel of senior neurologists who applied the following criteria for each aetiological category: NINCDS-ADRDA criteria (McKahn et al., 1984) for Alzheimer's disease, NINDS-AIREN criteria (Roman et al., 1983) for vascular dementia, Lund and Manchester criteria (Lund and Manchester Groups, 1994) for frontotemporal dementia, McKeith et al. (1996) criteria for Lewy body disease and history of Parkinson disease treated for at least 6 months before the onset of dementia for Parkinson dementia. This procedure for case finding and aetiological classification of incident cases of dementia was done for each follow-up as for the initial screening.

Sample

The aim of this work is to compare the cognitive change over time of future Alzheimer's disease subjects in the 9 years preceding the diagnosis with that of subjects remaining non-demented until the 10 year visit of the Paquid study. For this analysis, the 1 year visit (V1) was considered as the baseline and thus cognitive measures collected at V0 were not included. Indeed, in previous analyses, we have shown a test-retest improvement between V0 and V1 (Jacqmin-Gadda et al., 1997). This may be explained either by a practice effect or by a stress effect due to the testing situation which was new for the subjects at V0. Inclusion of the V0 scores would have required adding a parameter in the model (the V0 effect) without increasing the precision of the other parameters.

We have compared two samples. To be included in the Alzheimer's disease sample, subjects had to be: (i) non-demented at the baseline visit (V1); (ii) diagnosed with Alzheimer's disease during the 9 years of follow-up after baseline (i.e. at V3, V5, V8 or V10); and (iii) seen at the last visit preceding the diagnosis.

As the period of time directly preceding the occurrence of dementia is crucial in this type of analysis, condition (iii) was added to obtain an accurate estimate of the time of dementia onset and of the evolution of the cognition in the last years preceding the diagnosis. Among the 320 subjects diagnosed with Alzheimer's disease after V1, 215 were seen at the previous visit and thus were included in the sample. Subjects diagnosed with other types of dementia were not included (48 vascular dementia, 34 Parkinson dementia and 14 other dementias).

To be included in the sample of normal controls, subjects had to be: (i) seen and free of dementia at the 10 year follow-up (V10); and (ii) seen at the 8 year visit (V8). Condition (ii) was used to mimic condition (iii) of the Alzheimer's disease sample and make the selection procedure as similar as possible for the two samples. Thus, among 1201 subjects considered as free of dementia at V10, 148 subjects were not seen at V8 and three other subjects were excluded because they performed none of the tests during the 9 years of follow-up, leading to a sample of 1050 subjects without dementia. Table 1 describes demographic and health characteristics of the two samples.

Outcome variables

For each of the four neuropsychological tests described above, cognitive change over time was estimated separately on the sample of

Table 1 Demographic and health characteristics of subjects at entry in the Paquid cohort

	Non-Alzheimer's disease subjects (n = 1050) %	Alzheimer's disease subjects (n = 215) %
Age at diagnosis or 10 year follow-up		
<86	80.5 (n = 845)	50.2 (n = 108)
≥86	19.5 (n = 205)	49.8 (n = 107)
Sex		
Men	39.3 (n = 413)	28.4 (n = 61)
Women	60.3 (n = 637)	71.6 (n = 154)
Educational level		
No diploma	22.7 (n = 238)	49.3 (n = 106)
Primary school with diploma or +	77.3 (n = 812)	50.7 (n = 109)
Rural place of residence	35.8	38.6
Tobacco consumption		
Smoker	9.2	8.0
Ex-smoker	25.5	16.0
Non-smoker	65.3	76.0
Diabetes	6.8	8.9
History of stroke	0.57 (n = 6)	2.82 (n = 6)
History of head trauma	13.5	11.6
Angor	17.0	20.7
Myocardial infarction	10.1	9.8
Angina	14.9	10.8
HTA	14.7	21.4

Alzheimer's disease subjects and on the sample of individuals without dementia. The outcome variables were repeated measurements of the test scores collected between the baseline visit and the visit of diagnosis for the Alzheimer's disease cases and between the baseline visit and the 10 year follow-up for those without dementia. Measures collected after the visit of diagnosis were not used.

Explanatory variables

For Alzheimer's disease cases, we studied cognitive change as a function of the time interval between each measurement occasion and the date of diagnosis. For subjects without Alzheimer's disease, the cognitive change was studied as a function of the time interval between each measurement occasion and the 10 year follow-up. Thus, for both samples, the value of the time variable ranges from -9 years to 0. Time 0 is the date of diagnosis for Alzheimer's disease cases and the 10 year follow-up for subjects not developing dementia.

Covariates taken into account were gender, age at time 0 (diagnosis or 10 year follow-up) in two classes defined by the median age at diagnosis for incident cases (86 years) and educational level (no diploma versus primary school diploma or higher level). This categorization for education was found previously to be the best education-related predictor of dementia in the Paquid study (Letenneur et al., 1999).

Statistical model

The linear mixed model (Laird and Ware, 1982) is one of the standard models to evaluate longitudinal change of an outcome measured repeatedly over time because it takes into account the correlation between repeated measures on the same subjects. Moreover, this

method allows analysis of repeated data with unequal numbers and times of measurements per subject and is robust against data missing at random. However, a drawback of this model is that it assumes a parametric form (generally linear or polynomial) for the change over time, while we suspect that cognition in the pre-diagnosis phase of dementia has a non-linear evolution with an acceleration of the decline just before the diagnosis. As we are particularly interested in the shape of the cognitive decline before the diagnosis of dementia, we used a semi-parametric extension of the linear mixed model which requires no *a priori* assumption on the shape of this curve (except that it is smooth, i.e. without very abrupt changes). Details on the statistical method are given in Jacqmin-Gadda *et al.* (2002). The curves were estimated for each sample (Alzheimer's disease or non-Alzheimer's disease subjects) and, to avoid making assumptions about the impact of covariates on the shape of the curve, the curves presenting cognitive change over time of Alzheimer's disease and non-Alzheimer's disease subjects were re-estimated separately for each age group, each gender and each educational level. Sample sizes for each subanalysis are reported in Table 1. Computation of 95% confidence bands for each curve allows comparison of the curves for each group. In all analyses, the correlation between responses of the same subject is assumed to have an auto-regressive structure, i.e. the correlation decreases exponentially with the delay between measurements.

Results

The mean age at inclusion in the Paquid cohort was 71.9 (SD = 5.0) for the 1050 individuals without Alzheimer's disease and 78.7 (SD = 6.1) for the 215 pre-morbid subjects. The proportion of subjects with a low level of education was 22.7% among the subjects not developing dementia and 49.3% among the future Alzheimer's disease subjects. Other characteristics are shown in Table 1. Among the 215 Alzheimer's disease cases, 38 were diagnosed at the 3 year follow-up, 43 at 5 years, 44 at 8 years and 91 at the 10 year follow-up.

The age at diagnosis was not significantly different for the 215 Alzheimer's disease cases included (86.0, SD = 6.0) and the 105 cases excluded because they were not seen at the visit preceding the diagnosis (84.8, SD = 5.8, $P = 0.10$). These two groups were different neither in gender and educational level nor in the scores on the MMSE, BVRT and IST at the penultimate visit before diagnosis. However, excluded subjects had a lower mean score at diagnosis for the MMSE ($P = 0.001$) and IST ($P = 0.05$), suggesting, as expected, that these subjects had been demented for a longer time. They also had a higher rate of missing data at the time of diagnosis.

Age and gender were found to have little influence on test scores so only the influence of Alzheimer's disease status and educational level are presented in the following section.

Change in the MMSE score

Figure 1A displays the estimated mean change over time of the MMSE score for the sample of Alzheimer's disease cases and the sample of individuals without Alzheimer's disease.

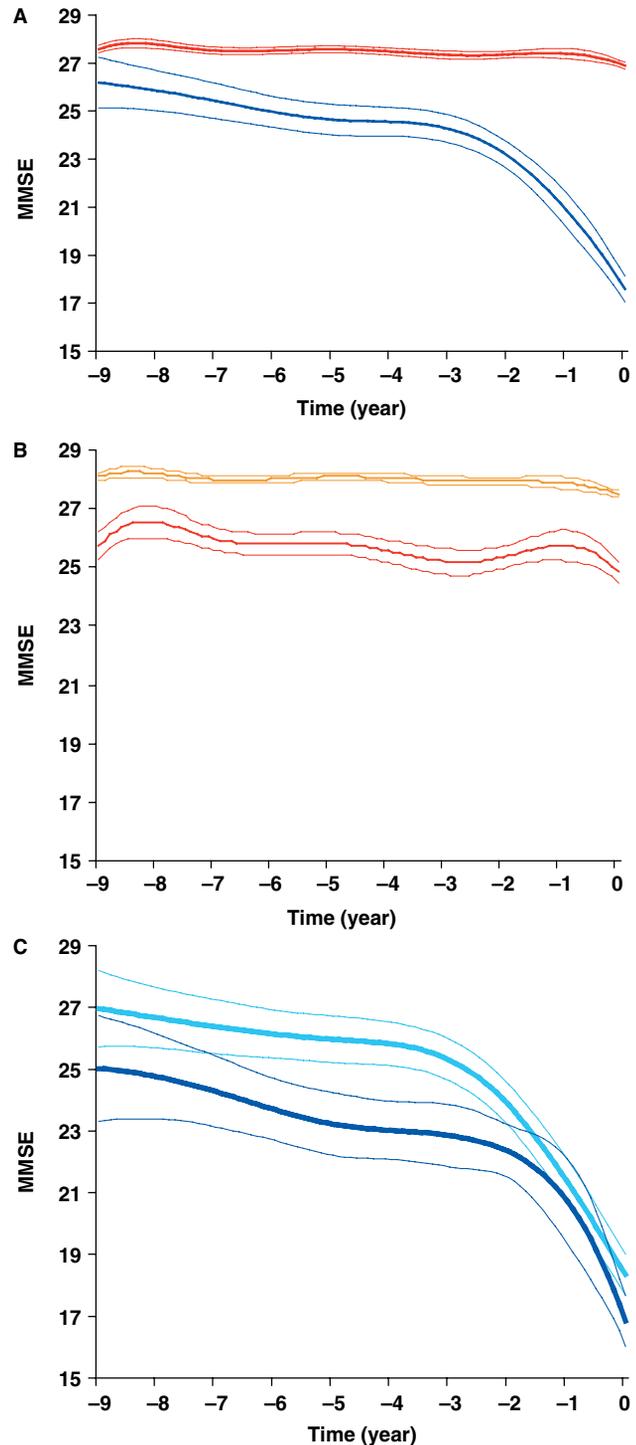


Fig. 1 Estimated evolution of the mean MMSE score (and 95% confidence bands) during the 9 years preceding the last visit (for non-Alzheimer's disease cases) or the diagnosis (for Alzheimer's disease subjects). (A) Whole sample: red curve, non-Alzheimer's disease cases; blue curve, Alzheimer's disease cases. (B) Non-Alzheimer's disease cases according to educational level: yellow curve, non-Alzheimer's disease cases with high education level; red curve, non-Alzheimer's disease cases with low education level. (C) Alzheimer's disease subjects according to educational level: pale blue curve, Alzheimer's disease cases with high education level; dark blue curve, Alzheimer's disease cases with low education level.

Among the latter, the mean MMSE score decreased very slightly over the 9 years, from 27.6 to 26.9. Nine years before the diagnosis, the score of the pre-morbid cases was already lower than that of individuals without dementia 26.2 versus 27.6. Between T-9y and T-3y, the score of Alzheimer's disease subjects decreased more than that of subjects without Alzheimer's disease, with an approximated slope of 0.32 point per year. Between T-3y and T0, their score decreased much faster, with a slope of ~ 2.2 points per year. Thus, throughout the 9 years preceding the diagnosis, subjects who would develop Alzheimer's disease had a faster decline of the MMSE score than subjects without Alzheimer's disease, with an acceleration of this decline ~ 3 years before the diagnosis. Figure 1B and C displays the change over time of the MMSE score according to educational level for the individuals without dementia and the future Alzheimer's disease cases, respectively. Figure 1B shows that subjects without Alzheimer's disease with low educational level have a lower score but a similar cognitive change over the 9 years than those with higher education. On the contrary, Fig. 1C shows that education has an important impact on the pattern of evolution of the MMSE score in the future Alzheimer's disease cases, subjects with high educational level having a sharper decline in the 4 years preceding the diagnosis of Alzheimer's disease.

Change in the BVRT score

Figure 2A displays the estimated change over time of the BVRT score for the sample of Alzheimer's disease cases and the sample of subjects without dementia. The mean BVRT score of non-Alzheimer's disease subjects decreased very slightly from 11.5 at T-9y to 11.0 at T0, and their score at T-9y was higher than that of the future Alzheimer's disease subjects (9.7) without overlap of confidence intervals. The decline of BVRT score in the future Alzheimer's disease subjects appeared to be more regular than for the MMSE, with a less abrupt acceleration of the decline after T-4y (change of slope from ~ 0.14 point per year between T-9y and T-4y to 0.56 point per year between T-4y and T0). Figure 2B and 2C displays the estimated change on the BVRT according to educational level for the subjects without Alzheimer's disease and the pre-morbid cases, respectively. Whatever the Alzheimer's disease status (Fig. 2B and C), subjects with a low educational level had a lower estimated score at T-9y than their more educated counterparts. Among the subjects without Alzheimer's disease (Fig. 2B), the evolution is parallel for the two educational level groups. Among the future Alzheimer's disease subjects (Fig. 2C), the decline before diagnosis appears nearly linear in less educated subjects, while highly educated subjects show a dramatic increase in the rate of decline ~ 3 years before the diagnosis.

Change in the IST score

Figure 3A displays the estimated change over time of the IST score for the sample of Alzheimer's disease cases and the

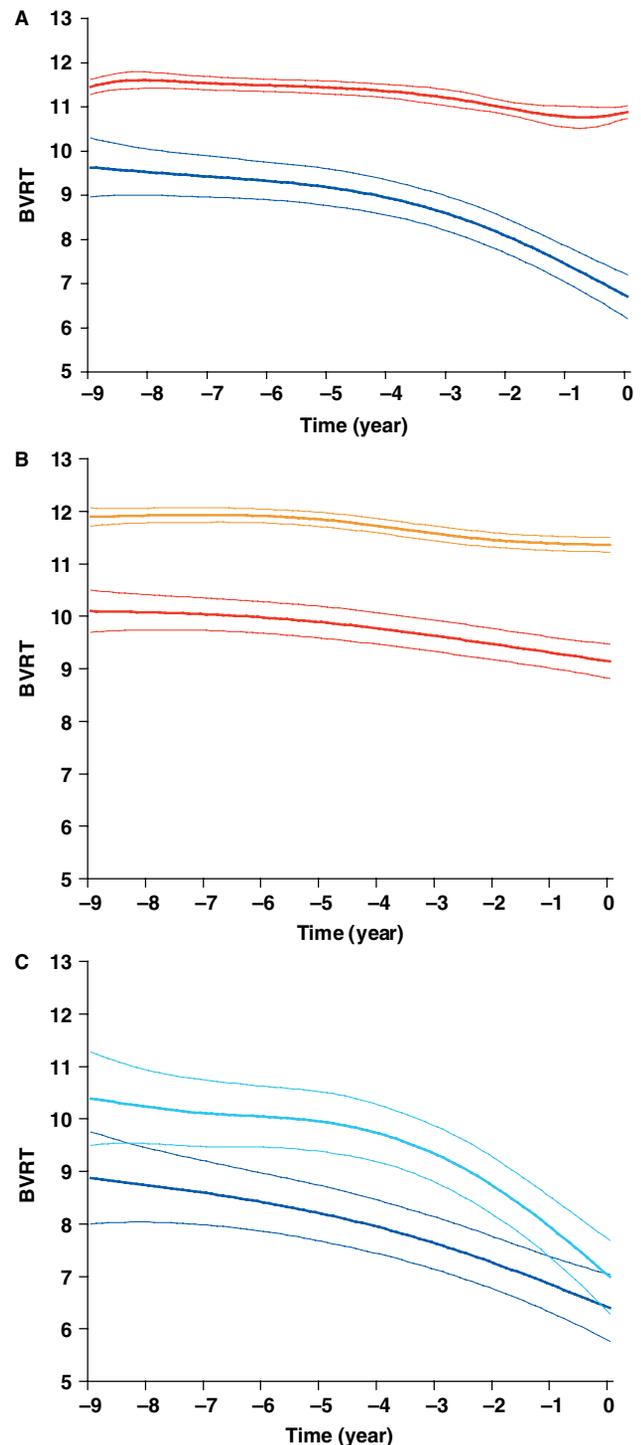


Fig. 2 Estimated evolution of the mean BVRT score (and 95% confidence bands) during the 9 years preceding the last visit (for non-Alzheimer's disease cases) or the diagnosis (for Alzheimer's disease subjects). (A) Whole sample: red curve, non-Alzheimer's disease cases; blue curve, Alzheimer's disease cases. (B) Non-Alzheimer's disease cases according to educational level: yellow curve, non-Alzheimer's disease cases with high education level; red curve, non-Alzheimer's disease cases with low education level. (C) Alzheimer's disease subjects according to educational level: pale blue curve, Alzheimer's disease cases with high education level; dark blue curve, Alzheimer's disease cases with low education level.

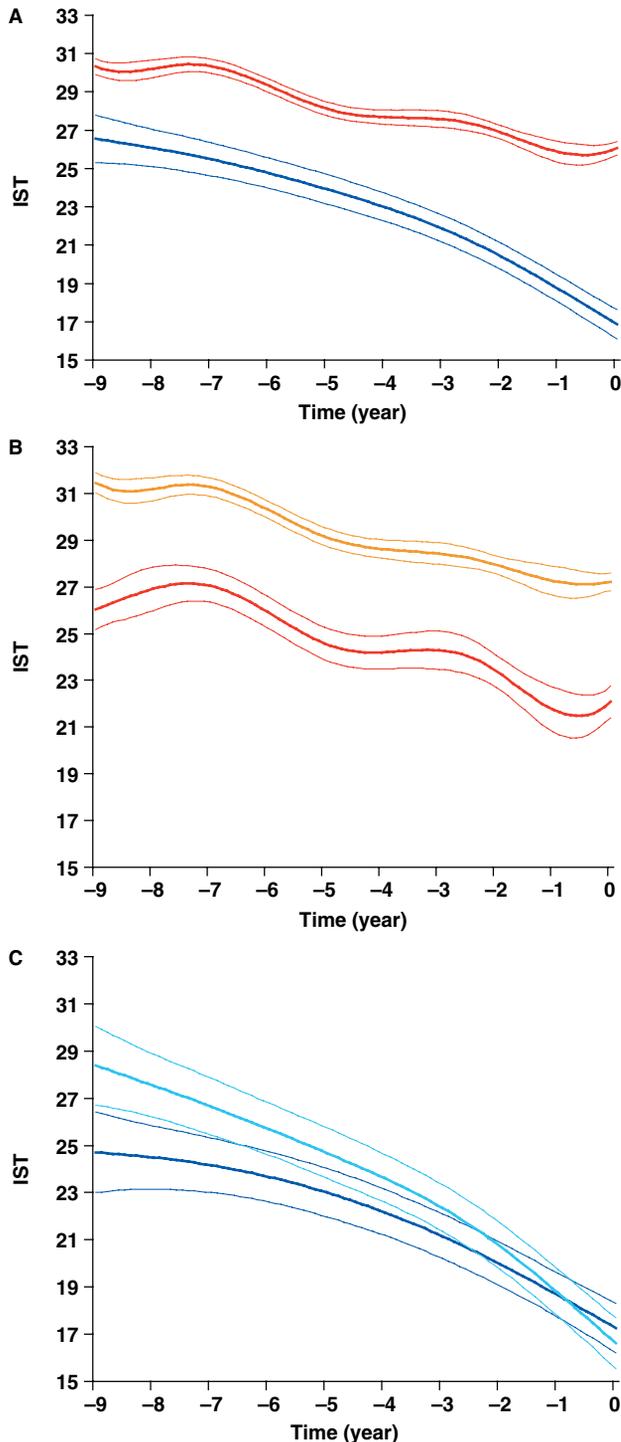


Fig. 3 Estimated evolution of the mean IST score (and 95% confidence bands) during the 9 years preceding the last visit (for non-Alzheimer's disease cases) or the diagnosis (for Alzheimer's disease subjects). (A) Whole sample: red curve, non-Alzheimer's disease cases; blue curve, Alzheimer's disease cases. (B) Non-Alzheimer's disease cases according to educational level: yellow curve, non-Alzheimer's disease cases with high education level; red curve, non-Alzheimer's disease cases with low education level. (C) Alzheimer's disease subjects according to educational level: pale blue curve, Alzheimer's disease cases with high education level; dark blue curve, Alzheimer's disease cases with low education level.

sample of individuals without Alzheimer's disease. Figure 3B and C presents the curves according to educational level for the normal controls and the future Alzheimer's disease subjects, respectively. The IST scores decreased, with some minor fluctuation over time, from 30.5 to 26.5 in subjects not developing dementia (Fig. 3A). Their baseline score was higher than that of the future Alzheimer's disease subjects (26.5) without overlap of confidence intervals. The decline of IST scores in the future Alzheimer's disease subjects was steeper and more regular than that of BVRT, with only a slightly more rapid decline at the end of the course. The score of the future Alzheimer's disease subjects declined faster in highly educated than in less educated subjects (Fig. 3C).

Change in the WST score

Figure 4A displays the estimated change over time of the WST score for the sample of Alzheimer's disease cases and the sample of subjects without Alzheimer's disease. Figure 4B and C presents the estimated curves according to educational level for the normal controls and the future Alzheimer's disease subjects, respectively. In non-Alzheimer's disease subjects, the WST score decreased very slightly from 7.2 to 6.8 and their T-9y score was higher than that of the future Alzheimer's disease subjects (6.4) without overlap of confidence intervals (Fig. 4A). In the future Alzheimer's disease subjects, the WST score declined almost linearly from 6.4 at T-9y to 3 at T0. Among the Alzheimer cases, Fig. 4C shows that more educated subjects had a higher score all along the 9 years preceding the diagnosis and declined faster than less educated subjects in the 3 years preceding the diagnosis.

Discussion

This descriptive approach of the time course of well established markers of cognitive functioning up to 9 years before Alzheimer's disease onset allows validation and quantification of the assumption that a long-lasting and progressive preclinical phase exists before the clinical onset of dementia. Three sets of results came out of the present study.

Few cohort studies have analysed more than one measurement point before dementia and could be compared with our results. In the MoVies Study, Chen *et al.* (2001) showed that several cognitive measures assessed in elderly people who would later become demented decreased between 3.5 and 1.5 years before dementia onset. The Kungsholmen project (Bäckman *et al.*, 2001) showed that tasks of episodic memory were impaired 3 and 6 years before the occurrence of dementia. The Bronx cohort (Hall *et al.*, 2001) analysed cognitive decline up to 15 years before dementia in 75 cases of probable Alzheimer's disease and mixed dementia. It showed an accelerated memory decline starting 7 years before dementia diagnosis. However, mixed dementia was included in the outcome point, so that additional deficits related to stroke

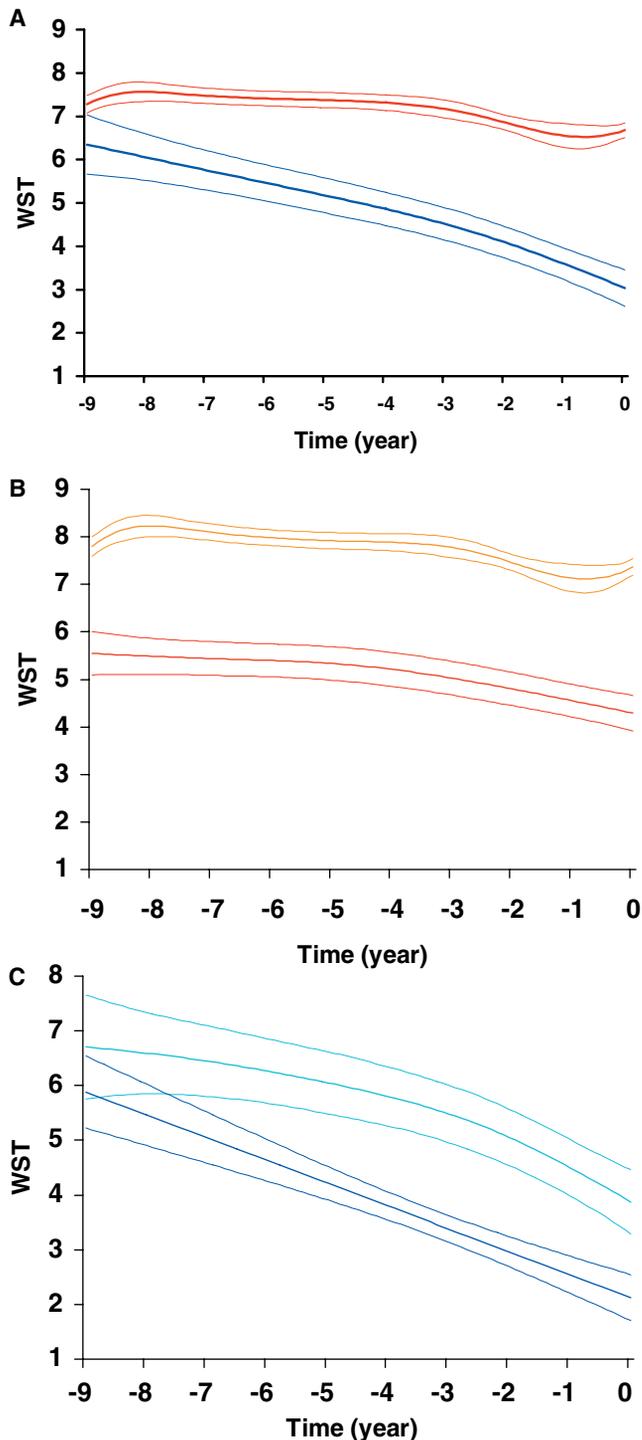


Fig. 4 Estimated evolution of the mean WST score (and 95% confidence bands) during the 9 years preceding the last visit (for non-Alzheimer's disease cases) or the diagnosis (for Alzheimer's disease subjects). (A) Whole sample: red curve, non-Alzheimer's disease cases; blue curve, Alzheimer's disease cases. (B) Non-Alzheimer's disease cases according to educational level: yellow curve, non-Alzheimer's disease cases with high education level; red curve, non-Alzheimer's disease cases with low education level. (C) Alzheimer's disease subjects according to educational level: pale blue curve, Alzheimer's disease cases with high education level; dark blue curve, Alzheimer's disease cases with low education level.

may have interfered with the course of the decline due to Alzheimer's disease, which could explain this difference from our findings (decline during only 7 versus at least 9 years).

Secondly, the course of cognitive decline before dementia is clearly related to education. Highly educated subjects had higher performances at T-9y and experienced a faster decline in the few years preceding dementia, so that their performances joined the curves of the less educated subjects. This non-linear decline suggests more a greater 'cognitive reserve capacity' in highly educated subjects than a true protective effect of education against Alzheimer's disease. The exhaustion of this 'reserve capacity' in highly educated subjects may well account for the accelerated decline which occurs in the 3 years preceding the detection of dementia.

Thirdly, our results confirmed that not only episodic memory tasks are impaired long before the onset of dementia syndrome, as previously suggested (Masur *et al.*, 1994; Jacobs *et al.*, 1995; Linn *et al.*, 1995; Dartigues *et al.*, 1997; Howieson *et al.*, 1997; Fabrigoule *et al.*, 1998; Schmand *et al.*, 2000). Over a more extended 22 year surveillance period, a study from the Framingham cohort (Elias *et al.*, 2000) showed that low scores of verbal memory and abstract thinking (assessed by the WST) were predictive of the onset of Alzheimer's disease 10 years after baseline assessment. We also found the WST and a test of memory, albeit although visuo-spatial memory, to be predictive of future dementia occurring at a comparable delay. The course of decline in future Alzheimer's disease patients seems to be different across the tests. This could be explained by the differences in the metrological properties of the tests. For the MMSE, the acceleration of the decline could be due to the fact that this test is taken as an indicator of cognitive deterioration in the NINCDS-ADRDA criteria and thus was used for the purpose of diagnosis in the Paquid study. So it is not unexpected that an important decline in MMSE score was observed between the last visit at which a subject was considered as non-demented and the visit at which the subject was classified as an incident case of Alzheimer's disease. However, a similar acceleration of decline was observed over the same period (or even before), at least in highly educated subjects, with other tests measuring cognitive functions not assessed in the MMSE, i.e. visuo-spatial memory, verbal fluency and abstract thinking. Thus the change in speed of cognitive decline 3-4 years before the clinical diagnosis of Alzheimer's disease may be a real phenomenon. In the Kungsholmen study, there was no evidence of accelerated decline of memory from 6 to 3 years before dementia diagnosis. In this study, however, only 15 future Alzheimer's disease subjects were followed-up and the memory performances were actually slightly lower at T-3y than at T-6y (Bäckman *et al.*, 2001).

One limitation of this study is due to the attrition of the cohort. Indeed, the group of individuals without Alzheimer's disease consists of subjects alive and seen at the 8 year and 10 year visits. As we have previously shown that drop-out in the Paquid cohort was associated with lower MMSE scores (Jacqmin-Gadda *et al.*, 1997), it is likely that included

non-Alzheimer's disease subjects have slightly higher neuropsychological performances than excluded ones. On the other hand, to be included, Alzheimer's disease subjects had to be diagnosed before their drop-out. Among subjects who satisfied the above conditions, all those having completed at least one cognitive test during the follow-up were included. The inclusion of subjects with incomplete data limits possible biases due to attrition. Indeed, analyses are unbiased if non-responses to cognitive tests are associated with previously observed scores but independent from the current missing scores (missing at random assumption). If subjects with incomplete measures had been excluded, the hypothesis that non-responses are completely independent from past and current cognitive performances would have been required (missing completely at random assumption) and we have shown previously that this hypothesis is false (Dartigues *et al.*, 1997; Jacqmin-Gadda *et al.*, 1997).

Two non-exclusive patho-physiological models could explain the patterns of evolution of cognitive performances in future Alzheimer's disease patients observed in this study. The first possible model would postulate that the pathological process of Alzheimer's disease does begin >8–9 years before its clinical stage. During an initial period, cognitive decline is slow, expressing the balance between the progression of the pathological process (Delacourte *et al.*, 2002) and the biological, psychological or environmental mechanisms of compensation (Armstrong and Barker, 2001). In a second phase, cognitive decline accelerates, due either to the failure of compensatory mechanisms or to a faster progression of the pathological process. In the second model, the pathological process occurs only 3–4 years before the clinical expression of Alzheimer's disease and explains the accelerated cognitive decline. The first period of cognitive decline would then be explained by the effect of exposure to risk factors for Alzheimer's disease, such as low education levels or old age, or by as yet unidentified causes of cognitive decline that may accelerate the clinical expression of Alzheimer's disease such as vascular brain damage (Wermeier *et al.*, 2003). The difference between these models could have important implications for preventive strategies for this disease. In the first model, the best time for preventive strategies would be the first period of decline, in order to arrest the disease process or enhance compensatory mechanisms. In the second model, the best time for treatment would be the second period of fast decline, to interfere directly with the pathological process. The present findings are more in favour of the first model since, after adjusting for the effect of known risk factors, especially education, the early decline of cognitive function remained faster in pre-morbid subjects than in individuals without the disease.

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