1 **Title: Fast cognitive decline at the time of dementia diagnosis: a major prognostic factor**

2 **for survival in the community.**

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1 **Abstract**

2 *Background/Aims:* Current findings suggest the existence of a category of fast cognitive

3 decliners with poorer prognosis but better treatment response. Our study aimed at confirming the

4 concept of fast decliner at the time of Alzheimer's disease (AD) diagnosis which best predicts

5 mortality, in an unselected sample.

6 *Methods:* 245 incident cases of AD were selected from the French longitudinal cohort PAQUID.

7 We investigated different threshold of cognitive decline (measured by the annual loss of points

8 in MMSE score) to define when a subject could be considered as a fast decliner. We used Cox

9 proportional hazard models to study the relation between cognitive decline and mortality.

10 *Results:* The significant threshold of decline associated with higher mortality rate was a loss of 3

11 points per year in MMSE score. Among the 245 AD cases, 83 (33.9%) subjects were considered

12 as fast decliners. Of them, 78.3% died during the follow-up compared with 63.0% of the slow

13 decliners (RR=1.7, 95% CI [1.2 – 2.5]).

14 *Conclusion:* These results constituted an empirical validation of the concept of fast decliners in

15 community based AD patients and justified the cut-off of 3 points for the definition of this

16 condition.

17

18 Key words: Rapid progression, mortality, Alzheimer's disease

19

1 Introduction

2 A progressive cognitive decline is the main characteristic of Alzheimer's disease (AD).

3 However, this decline widely varies among subjects at the onset of the disease and the distinction

4 between slow and fast decliners has been recently emphasized [1]. In addition, the association

5 between severe cognitive decline during the course of AD and a higher mortality has already

6 been described [2-5].

7 On the whole, current findings suggest that fast decliners need a particular clinical attention as

8 they have poorer prognosis with higher mortality rates [6]. Yet, the notion of fast decliners

9 remains arbitrary and needs more validation. Indeed, such a category of patients was identified

10 during post-hoc analyses, in selected clinical samples participating to clinical trials [7]. These

11 samples were constituted with patients previously chosen because they presented specific

12 characteristics and thus were not representative of the population. In addition, the previous

13 studies on the relationship between cognitive decline and mortality have analyzed the decline

14 over the whole course of the disease but not specifically at the phase following the diagnosis [2,

15 8, 9] while this period of time seems the more relevant phase to provide adequate early

16 information and to better manage the patient and his family.

17 Thus, the practical interest of the concept of fast decliner needs to be confirmed for its prognostic

18 value at the time of AD diagnosis, in an unselected sample. Longitudinal population-based

19 studies with long term follow-ups are necessary to conduct such a validation. The French

20 longitudinal PAQUID study [10] allowed us to analyze unselected new cases of AD occurring in

21 the general population. Moreover, this cohort provides data on the evolution of cognitive

22 performances over the 13 years of follow-up and thus the cognitive decline at the time of

23 dementia diagnosis, as well as a long term follow-up of the patients until death.

24 The aim of this study was to define a category of fast cognitive decliners at the time of AD

25 diagnosis which best predicts mortality, in a sample of AD cases in the general population. We

26 investigated different thresholds of decline to define when a subject could be considered as a fast

1   decliner. To do so, we selected 245 subjects prospectively screened for AD from the PAQUID

2   cohort and we focused on the relation between the annual rate of cognitive decline at the time of

3   AD diagnosis and the risk of mortality.

4

1 **Methods**

2 *Study design*

3 Our data came from the PAQUID (Personnes Agées QUID) cohort, study on cerebral and

4 functional aging. The detailed methodology of the PAQUID study has been described in full

5 elsewhere [10]. The baseline visit began in 1988-1989.

6 Overall, 3777 subjects accepted to participate and signed a written consent. At baseline the

7 participants were visited at home by a neuropsychologist and re-interviewed similarly 1 (in

8 Gironde only), 3, 5, 8, 10 and 13 years after the baseline assessment.

9 An active research of dementia with confirmation by a senior neurologist was conducted at each

10 follow-up as detailed below.

11 *Sample selection*

12 In the present study, after exclusion of the 102 subjects demented at baseline, our sample

13 included all the cases of possible or probable AD diagnosed between the 1-year-visit and the 10-

14 year-visit (n=328). We did not include the demented subjects diagnosed after the 10-year-visit.

15 Let us refer to the visit of diagnosis of AD as "ADV". In order to study the cognitive decline,

16 subjects had to be seen at the visit preceding ADV ("ADV-1") and had to have performed the

17 global cognitive evaluation test: Mini Mental Status Examination (MMSE) at both these visits.

18 Finally, our sample included 245 subjects, after exclusion of 83 subjects with missing value for

19 MMSE either at ADV or at ADV-1. There was no statistical difference on age, sex or education

20 between these 83 subjects and the rest of the sample.

21 *Data collection and dementia diagnosis*

22 Interviews were performed at home by a trained psychologist with a standardized questionnaire,

23 which contained socio demographic characteristics, objective and subjective physical health, and

24 a set of neuropsychological tests. This battery of tests included an evaluation of the global

25 mental status (with the MMSE) [11], visual memory (Benton's Visual Retention Test) [12],

26 visuo-spatial attention (Zazzo's cancellation test) [13], verbal fluency (Isaac Set Test) [14], and

1   simple logical reasoning and attention (Wechsler's Digit Symbol Test) [15]. At the end of the

2   neuropsychological interview, the psychologist filled in the Diagnostic and Statistical Manual of

3   Mental Disorders 3rd ed., revised (DSM-IIIR) to select subjects suspected of being demented

4   [16]. Those suspected cases were seen by a senior neurologist, blinded to the psychometric

5   battery and functional assessment, to confirm or rule out the diagnosis of dementia. The

6   specialist also precise the etiology of dementia with the NINCDS-ADRDA criteria for

7   Alzheimer's disease [17] and the Hachinski score for vascular dementia [18]. Cases were

8   classified as probable or possible Alzheimer disease, vascular dementia, and other types of

9   dementia.

10   For all the incident cases of dementia, the same procedure of diagnosis was used at each follow-

11   up, but in order to increase the screening sensitivity, the criterion of a cognitive loss of three

12   points in MMSE score from the previous visit was added to qualify for neurological

13   examination.

14   Finally, the survival status was collected throughout the follow-up for each participant up to the

15   13-year-visit.

16   *Rate of cognitive decline: calculation*

17   The annual rate of cognitive decline at the time of AD diagnosis was based on the MMSE

18   evolution between ADV-1 and ADV. This score ranges from 0 to 30, and higher scores indicate

19   better cognitive functioning. The annual rate of decline was calculated by subtracting the MMSE

20   score obtained at ADV-1 from the score reached at ADV (in order to have a positive indicator, as

21   the last measure is mostly lower than the previous one). Finally, the annual rate of cognitive

22   decline was obtained by dividing this difference by the delay (in years) between the two visits.

23   *Data analysis*

24   After describing the sample, we studied the association between rate of cognitive decline and

25   mortality. Survival time was considered from ADV to death for deceased subjects or to the 13-

1 year-visit for not deceased subjects. We tested five different thresholds of decline: a loss of at

2 least one, two, three, four and five points per year in the MMSE between ADV and the ADV-1.

3 Risk of mortality was assessed using Cox proportional hazards models [19]. For each of the five

4 thresholds of cognitive decline investigated, we represented, on the same figure, estimated

5 univariate survival curves and the curve corresponding to the loss of less than 1 point a year.

6 Then, we controlled our models for potential confounding factors: age at ADV, sex, level of

7 education (subjects were considered as highly educated if they had obtained the French primary

8 school certificate, corresponding to about seven years of schooling, which was previously

9 validated as the best cut-off for the prediction of dementia in the PAQUID study) [20], and

10 MMSE score at ADV in two categories (less or more than 19). We previously examined whether

11 age and MMSE scores should be modeled as continuous or categorical variables and we

12 concluded that age should be used as a continuous variable and MMSE scores as a categorical

13 variable with a cut off of 19. Validity of the proportional hazard assumption was evaluated by

14 testing interaction time dependant variables and by a graphical evaluation.

15 Afterwards, we investigated if the category of fast decliners associated with a higher risk of

16 mortality had other characteristics that could explain their faster decline. To do so, we compared

17 slow and fast decliners on sex, age at inclusion and at ADV, education, level of MMSE at ADV

18 and ADV-1, social situation at ADV (family situation, type of residence, and number of close

19 family or friends), bed restriction at ADV, blindness and deafness at ADV, etiology of the

20 disease (probable or possible AD), symptomatic depression at ADV and ADV-1, medications at

21 ADV and ADV-1 (antidepressant and anticholinergic).

22

1   **Results**

2   *Sample description*

3   Our sample was constituted with 245 subjects with AD. Table 1 presents the main socio

4   demographic and health characteristics of our sample. The mean age was 78.8 years old at

5   inclusion and it was 85.5 years old at ADV. Seventy percents of the sample were women, 26.9%

6   of the subjects were living alone, and 81.9% had more than 3 close family or friends. Possible

7   AD cases represented more than 52.0% of total AD diagnosed. In all, 18.7% suffered from

8   symptomatic depression at ADV and 13.9% at the ADV-1.

9   *Variable of interest*

10   The mean MMSE score was 17.5 at ADV and 23.2 at ADV-1 (table 1). The mean delay between

11   these two visits was 2.2 years (SD=0.6) and ranged from 0.9 to 4.0 years. The annual loss of

12   points in MMSE between ADV and ADV-1 was 2.2 (SD=2.3) in average and ranged from -3.3

13   (a gain of 3.3 points per year) to 16.1 points (Fig. 1).

14   Regarding the different thresholds of decline, 205 subjects (83.7%) lost one point or more per

15   year in MMSE, 133 subjects (54.3%) lost two points or more, 83 (33.9%) lost three points or

16   more, 44 (18.0%) lost four points or more, and 21 (8.6%) lost five points or more.

17   *Thresholds of cognitive decline and risk of mortality*

18   Between ADV and the 13-year-visit, 167 (68.2 %) subjects died. According to the thresholds of

19   1, 2, 3, 4 and 5 points loss, respectively 139 (67.8%), 95 (71.4%), 65 (78.3%), 37 (84.1%), and

20   17 (81.0%) subjects died in the category of fast decliners.

21   Table 2 presents both univariate and multivariate results of the Cox proportional hazard models

22   for each of the three thresholds. The univariate Relative Risks (RR) of death among subjects who

23   lost at least more than 2, 3, 4 and 5 points were significantly increased. The risk of death was not

24   significantly different between slow and fast decliners with the threshold of 1 point. Fig. 2 shows

25   the estimated survival curves following ADV for the five thresholds of loss and for the loss of

1   less than 1 point per year in MMSE. The survival time is different (shorter) for the decline of 3, 4

2   and 5 points or more.

3   Controlled for age, sex, level of education, and MMSE score at ADV, the risk of death remained

4   non significant for the threshold of 1 point (p = 0.593) and no longer reached the significance for

5   the threshold of 2 points (p = 0.193). For the thresholds of 3, 4 and 5 points, the risk of death

6   remained significantly increased after adjustments (respectively, RR=1.7, 95% CI: 1.2-2.5,

7   RR=2.1, 95% CI: 1.4-3.2, RR=2.1, 95% CI: 1.2-3.6). As expected, the risk of death increased

8   with age and was higher among men, whereas there was no association with MMSE score at

9   ADV, irrespective of the threshold.

10   *Characteristics of fast decliners*

11   We choose to define the category of fast decliners according to the 3 points threshold as it was

12   the first threshold to significantly increase the risk of mortality. Table 3 presents socio

13   demographic and health characteristics of slow and fast decliners defined on the threshold of 3

14   points. Neither sex nor education was associated with the category of decline. However, fast

15   decliners were older at ADV and at inclusion. Fast decliners had significantly lower MMSE

16   scores at ADV (13.2 versus 19.7) although they had similar scores at ADV-1 (23.5 versus 23.0).

17   In addition, fast decliners were more likely to be in a nursing home (44.6% versus 14.8%). No

18   significant difference was observed between slow and fast decliners in terms of family situation

19   and number of close family or friends. Six subjects were bed restricted at ADV and they were all

20   fast decliners. Yet, neither blindness nor deafness was related to the category of decline. More

21   fast decliners were diagnosed as possible AD than slow decliners (61.5% versus 47.5%).

22   Symptomatic depression at ADV and at ADV-1 was not associated with the category of decline.

23   However, it is to be noted that 26.9% of the fast decliners suffered from symptomatic depression

24   at ADV, compared with 15.4% of the slow decliners. Fast decliners had been more often

25   hospitalized during the year before the diagnosis than slow decliners (54.4% versus 31.7%).

26   Concerning medications, whereas slow and fast decliners were as much under antidepressant at

1 ADV, fast decliners were significantly less treated by antidepressant at ADV-1 (3.9% versus

2 14.2%). On the contrary, compared with slow decliners, fast decliners were significantly more

3 treated with anticholinergic at ADV (28.9% versus 17.4%) although there was no difference at

4 ADV-1.

5

Discussion

In this population-based prospective study, we found that in AD patients, fast cognitive decline at the time of the disease was a strong prognostic factor for survival. The significant threshold of decline was 3 points loss or more per year in the MMSE score, while the thresholds of 2 or 1 points per year were not significantly associated with survival after appropriate adjustments. According to the threshold of 3 points, we searched if specific characteristics could explain this faster decline. None of the socio demographic characteristics appeared to be different according to this threshold. Fast decliners were more likely to have been hospitalized during the year before ADV than slow decliners and were more often living into nursing home. In addition, fast decliners were more often under anticholinergic drugs than slow decliners. This last result is consistent with the association, previously found in the PAQUID study, between anticholinergic drugs and low cognitive performances [21]. Moreover, as cholinergic drugs are assumed to avoid fast decline, this association between fast decline and anticholinergic drugs deserves further investigations. These findings constituted an empirical validation of the concept of fast decliner in community-based AD patients and justified the cut-off of 3 points for the definition of this condition.

The strength of this study is that it was conducted on an unselected sample of AD patients and that the decline of MMSE was effectively measured before the diagnosis of dementia and not only estimated as proposed by Doody et al [22]. Some authors have already pointed out this 3-points per year threshold [7], but their data were not validated by a follow-up study.

The loss of 3 points or more in MMSE at the time of AD diagnosis may traduce an aggravation of the disease. One assumption is the faster progression of the underlying pathological process of AD. Indeed, the rate at which senile plaques and neurofibrillary tangles accumulate in the brain may increase and thus lead to a diminution of cognitive functions. Another assumption is the failure of compensatory mechanisms. It is well known that cognitive reserves decrease the

deleterious effect of senile plaques on cognitive abilities [23, 24]. Thus, the collapse of these reserves could explain the decrease of cognitive functions.

Our study presents some limitations. It is known that before 1995, in many countries, subjects with Lewy Body disease were often classify as possible AD. In the PAQUID study, demented subjects with Parkinsonism were excluded from the possible AD group. Therefore, only a minority of subjects with Lewy Body disease may be included in the class of possible AD group. Hence, our results should not be affected by the presence of these subjects.

Moreover, we tested five different thresholds of decline; therefore we are under the possibility of accepting a false positive association because of multiple testing. However, using the correction advised by Bonferroni, the p-value associated with the 3-points threshold remains significant as it has to be compared with 0.01.

In the PAQUID study, subjects were visited every 2 or 3 years and thus, there is an imprecision on the actual date of diagnosis. When a subject is diagnosed, it can actually be demented for more than 2 years as well as for only a few months. Thus, one could be considered as a fast decliner and another could be considered as a slow decliner. This bias may lead to overestimate the relation between cognitive decline and mortality. However, our analyses were adjusted for cognitive level at ADV which prevent our results from such overestimation.

To conclude, the loss of 3 points per year in MMSE identifies a group of fast decliners with a higher risk of mortality. This category of patients seems to have consistently a more aggressive disease and thus needs a particular attention at follow-up. In addition, their treatments must be adapted. As the great majority of our subjects were not treated by cholinesterase inhibitors, this finding enhances the interest of knowing that fast decliners better respond to this type of medication [6]. Indeed, reducing the speed of cognitive decline may prevent the subjects from a precipitated death. Clinical trials should be conducted in order to determine whether or not the risk of death can be reduced among this category of fast decliners.

Table 1: Socio demographic and health characteristics of the subjects

	n	%
Female (versus male)	171	69.8
Primary education level (versus no diploma)	122	49.8
Family situation at ADV[1] (alone versus not alone)	66	26.9
Number of close family or friends at ADV (3 or more versus less than 3)	95	81.9
Etiology (possible AD versus probable AD)	128	52.2
Symptomatic depression at ADV	34	18.7
Symptomatic depression at ADV-1[2]	32	13.9

	m	SD
Age at baseline	78.84	6.0
Age at ADV	85.48	6.0
MMSE at ADV	17.48	5.5
MMSE at ADV-1	23.21	3.7

Values are number (n), % or mean (m), standard deviation (SD)
[1] ADV = Visit of Alzheimer's disease diagnosis
[2] ADV-1 = Visit before ADV

Table 2: Univariate and multivariate risks of death for the three thresholds of cognitive decline

	Univariate			Multivariate		
	RR	**95% CI**	**p-value**	**RR**	**95% CI**	**p-value**
Model 1						
Annual loss of points in MMSE >=1	1.19	(0.79-1.79)	0.399	0.89	(0.58-1.37)	0.593
Sex (male versus female)				1.58	(1.11-2.26)	0.012
Age at ADV[1]				1.08	(1.05-1.12)	<.001
At least primary education				1.23	(0.90-1.69)	0.186
MMSE at ADV >=19				0.73	(0.53-1.02)	0.063
Model 2						
Annual loss of points in MMSE >=2	1.36	(1.00-1.85)	0.048	1.24	(0.90-1.71)	0.193
Sex (male versus female)				1.59	(1.11-2.27)	0.011
Age at ADV				1.09	(1.05-1.12)	<0.001
At least primary education				1.17	(0.86-1.60)	0.326
MMSE at ADV >=19				0.79	(0.57-1.10)	0.161
Model 3						
Annual loss of points in MMSE >=3	1.78	(1.30-2.43)	<0.001	1.71	(1.18-2.47)	0.005
Sex (male versus female)				1.62	(1.13-2.32)	0.009
Age at ADV				1.09	(1.06-1.12)	<0.001
At least primary education				1.06	(0.77-1.47)	0.714
MMSE at ADV >=19				0.95	(0.66-1.37)	0.779
Model 4						
Annual loss of points in MMSE >=4	2.33	(1.61-3.37)	<0.001	2.11	(1.39-3.20)	<0.001
Sex (male versus female)				1.57	(1.10-2.24)	0.014
Age at ADV				1.08	(1.05-1.12)	<0.001
At least primary education				1.16	(0.85-1.58)	0.363
MMSE at ADV >=19				0.93	(0.65-1.33)	0.692
Model 5						
Annual loss of points in MMSE >=5	3.11	(1.95-5.21)	<0.001	2.19	(1.20-3.61)	0.009
Sex (male versus female)				1.53	(1.07-2.19)	0.019
Age at ADV				1.08	(1.05-1.11)	<0.001
At least primary education				1.21	(0.89-1.65)	0.226
MMSE at ADV >=19				0.82	(0.59-1.15)	0.258

Values are relative risks (RR), 95% confidence interval (CI)
[1] ADV = Visit of Alzheimer's disease diagnosis

Table 3: Characteristics of subjects according to the threshold of 3 points

	Threshold 3		
	<3 n = 162	>=3 n = 83	**p-value**
	n (%)	**n (%)**	
Female (versus male)	111 (68.5)	60 (72.3)	0.543
Primary education level (versus no diploma)	75 (46.3)	47 (56.6)	0.126
Family situation at ADV[1] (alone versus not alone)	48 (29.6)	18 (21.7)	0.185
Type of residence at ADV:			<0.001
Home or old people housing	135 (83.3)	41 (49.4)	
Nursing home	24 (14.8)	37 (44.6)	
Other	3 (1.9)	5 (6.0)	
Number of close family or friends at ADV (3 or more versus less than 3)	66 (84.6)	29 (76.3)	0.276
Bed restricted at ADV	0	6 (7.4)	0.001
Total blindness at ADV	3 (1.9)	2 (2.5)	0.733
Deafness at ADV	17 (10.6)	10 (12.8)	0.605
Etiology (possible AD versus probable AD)	77 (47.5)	51 (61.5)	0.039
Symptomatic depression at ADV	20 (15.4)	14 (26.9)	0.071
Symptomatic depression at ADV-1	20 (13.2)	12 (15.4)	0.644
Hospitalized during the year before ADV	51 (31.7)	43 (54.4)	0.001
Antidepressant at ADV	31 (20.0)	15 (19.7)	0.963
Antidepressant at ADV-1	22 (14.2)	3 (3.9)	0.019
Anticholinergic at ADV	27 (17.4)	22 (28.9)	0.044
Anticholinergic at ADV-1	28 (18.1)	17 (22.4)	0.438
	m (SD)	**m (SD)**	
Age at inclusion	78.0 (5.9)	80.5 (6.0)	0.002
Age at ADV	84.8 (5.8)	86.8 (6.1)	0.013
MMSE at ADV	19.7 (3.5)	13.2 (6.2)	<0.001
MMSE at ADV-1	23.0 (3.8)	23.5 (3.5)	0.323

Values are number (%) or mean (SD)
[1] ADV = Visit of Alzheimer's disease diagnosis
[2] ADV-1 = Visit before ADV

Acknowledgements

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Legends to figures

Figure 1. Annual loss of points in the MMSE prior to AD diagnosis

Figure 2. Kaplan-Meier survival curves after the diagnosis of AD stratified by the rate of cognitive decline