La maladie d'Alzheimer en population : un autre monde, la bonne voie ?

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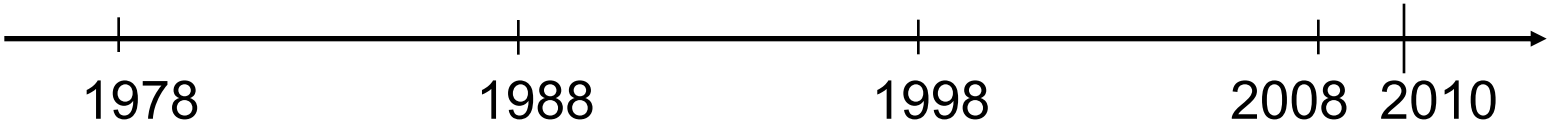
3 cohortes populationnelles françaises

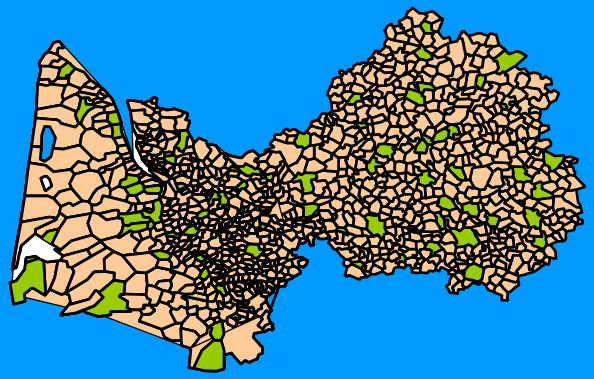


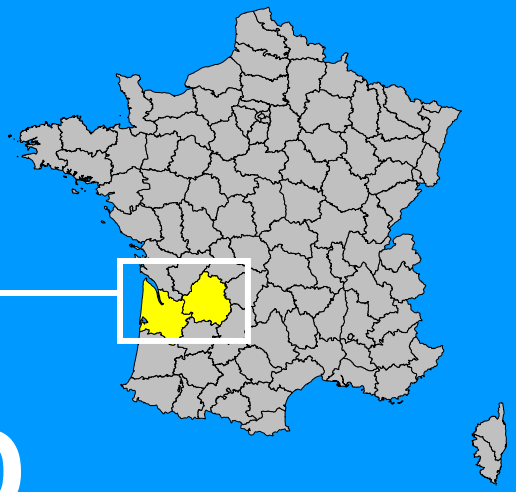
Paquid (65+, N=3777, T1 T3 T5 T8 T10 T13 T15 T17 T20…)

3C (65+, N=9285, T2 T4 T7 T10…)

AMI (65+, N=1000, T1, T2…)

→ Au total 14 062 personnes âgées de 65 ans et plus





PAQUID

T0 T1 T3 T5 T8 T10 T13 T15 T17 T20

1988 1989 1991 1993 1996 1998 2001 2003 2005 2008

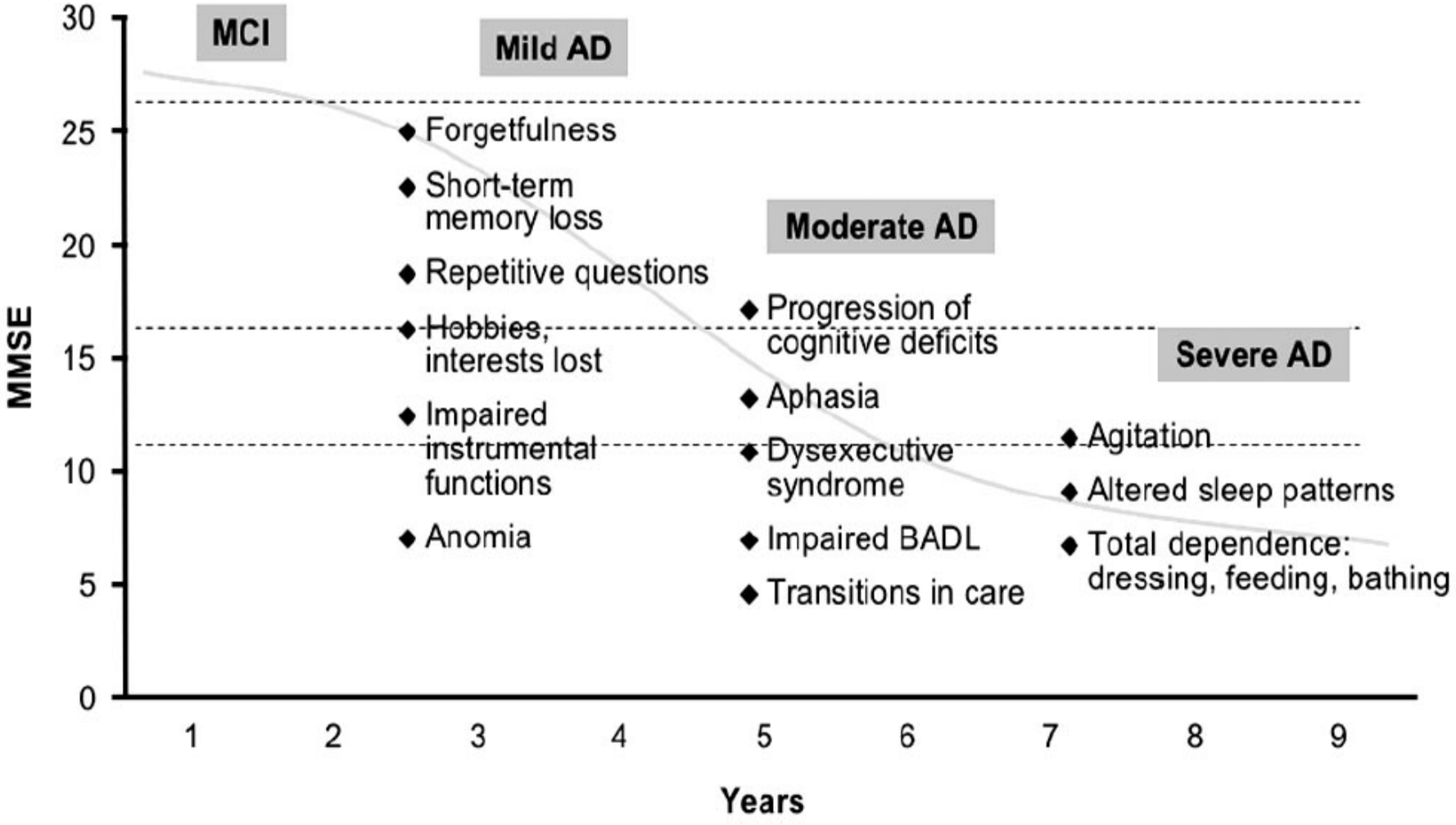
N=3777

Active research of Dementia

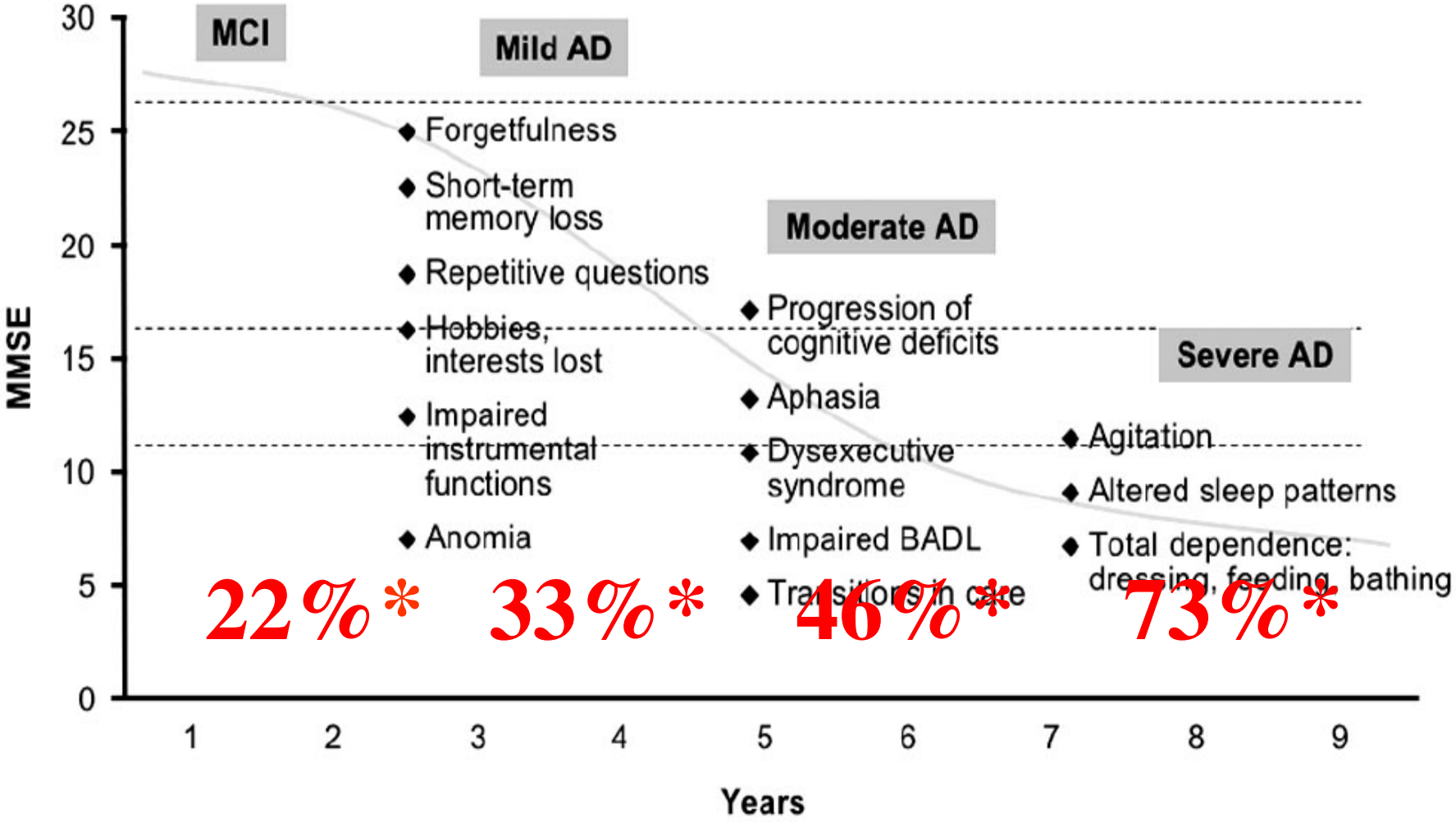
Interview
Tests
DSM III-R

Neurological Diagnosis

DIAGNOSIS OF AD IN THE GENERAL POPULATION



Evolution of AD according to Feldman et Woodward, Neurology 2005



Evolution of AD according to Feldman et Woodward, Neurology 2005

* Proportion of diagnosed cases according to Lopponen et al, (Age and Aging, 2004) and 3C

Recourse to specialist for the diagnosis of dementia in incident cases (3C)

Year of Follow-up	2002	2004	2007	2010
Proportion of recourse to specialist	**30%**	**33%**	**30%**	**31%**
French Alzheimer's Plan	**1st**	**2nd**		**3rd**

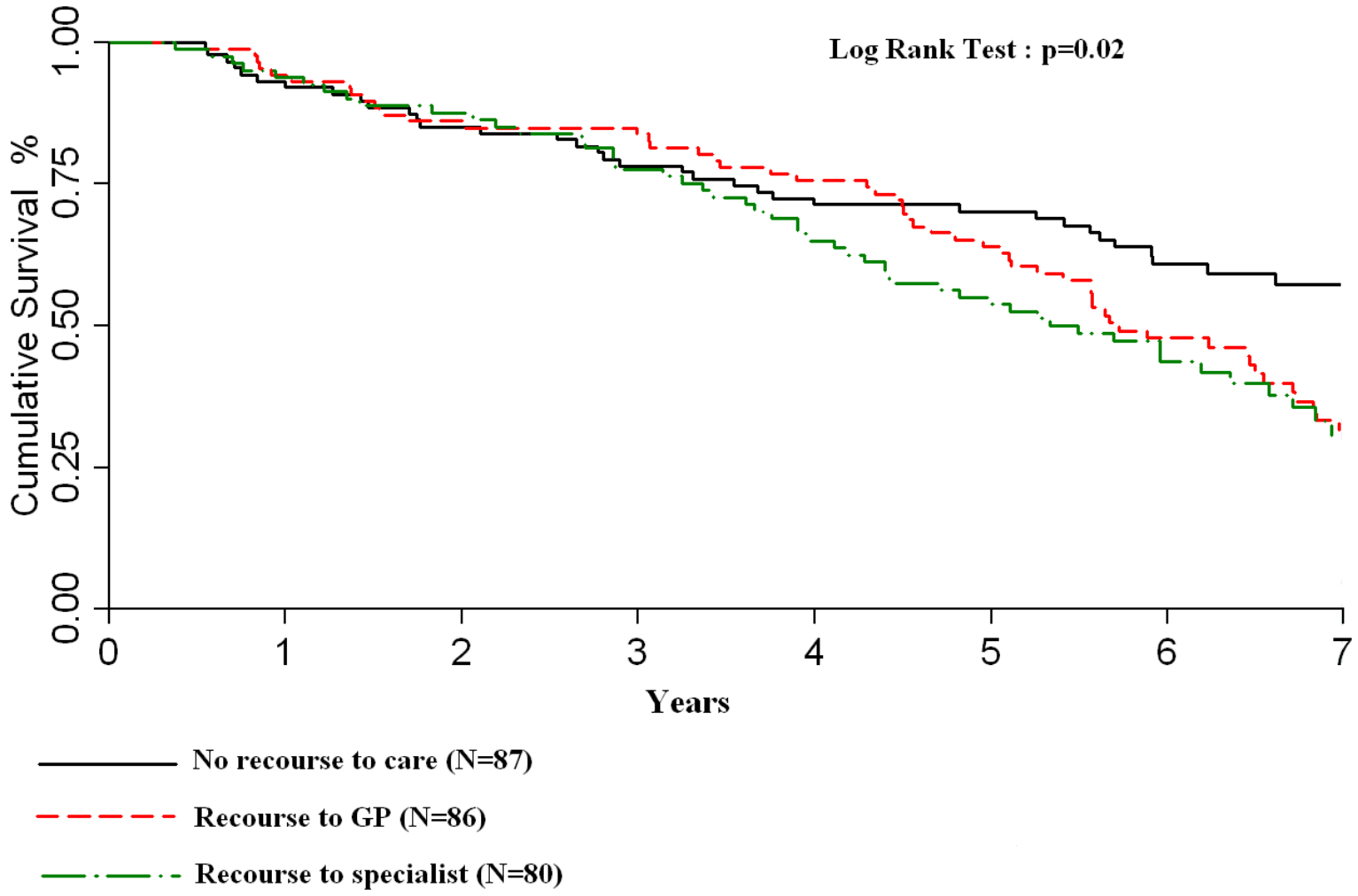
Reasons for lack of recourse to specialist

- **Lack of efficacy of antidementia drugs**
- Lack of time for diagnosis and management
- Lack of interest for dementia, not a priority
- Risk of stigma for patients and caregivers
- Alzheimer's Disease is not a disease. It is a construction of specialists and big pharma…

Etude DRSMA

- Étude qualitative par entretiens avec les malades, les aidants et les médecins sur des cas sélectionnés dans les études 3C, Paquid et AMI
- Comparaisons des cas avec recours et sans recours au spécialiste
- Premiers résultats : le recours au spécialiste est lié à un désaccord aidant-aidé et à un manque de structures médico-sociales dans le territoire !!!

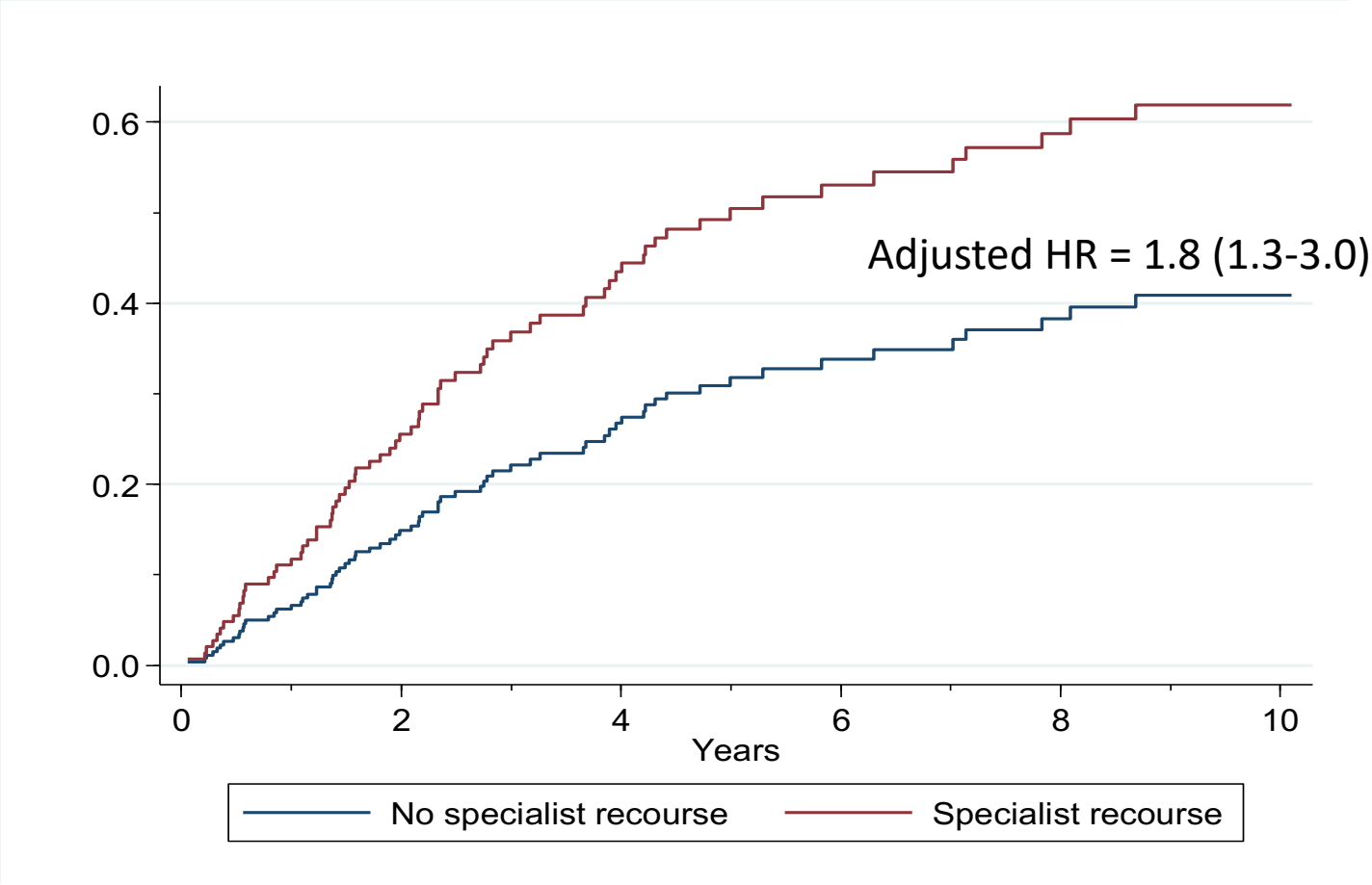
Survival of incident AD according to recourse to care. 3C study, Pimouguet et al 2015



Characteristics of subjects at the diagnosis of dementia according to recourse to care (3C study, France)

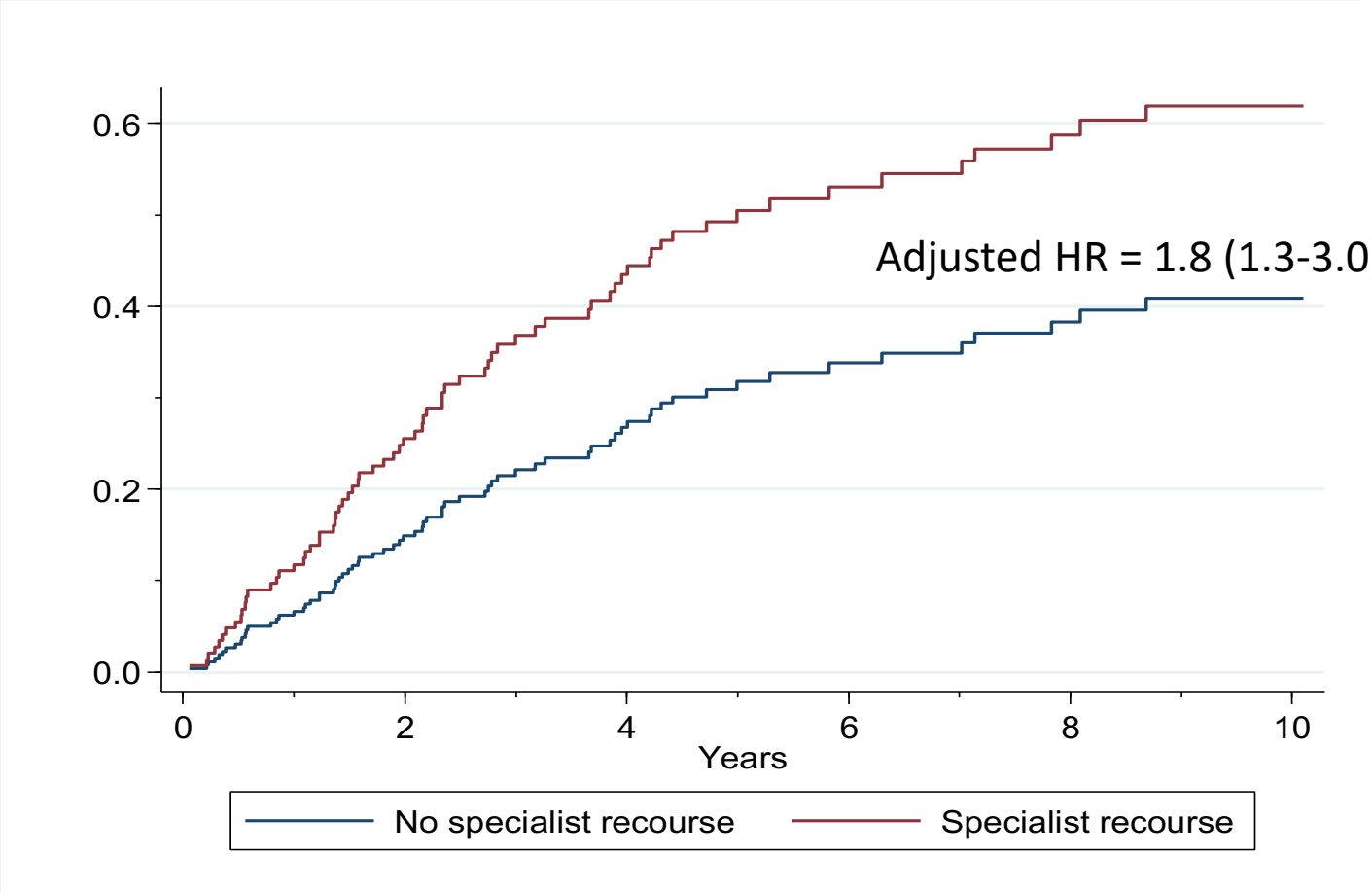
	No consultation (n=87)	Primary care consultation (n=86)	Secondary care consultation (n=80)	Global P-value
Age, mean (SD)	79.67 (5.95)	80.14 (5.21)	78.79 (5.54)	0.29
Women, n (%)	52 (59.77)	44 (51.16)	46 (57.50)	0.50
Primary level of education	40 (45.98)	42 (48.84)	23 (28.75)	0.007
Alzheimer dementia, n (%)	62 (71.26)	55 (63.95)	47 (58.75)	0.23
Diabetes, n (%)	11 (12.6)	10 (11.63)	7 (8.86)	0.73
Myocardialinfarction, n (%)	7 (8.05)	7 (8.14)	5 (6.33)	0.89
Stroke, n (%)	4 (4.60)	3 (3.49)	5 (6.33)	0.69
Depressive symptomatology, n (%)	21 (24.14)	19 (22.09)	20 (25.00)	0.88
Behavioral troubles, n (%)	13 (14.94)	13 (15.12)	24 (30.00)	0.03
Mean annual MMS decline (SD)*	1.82 (1.59)	1.73 (1.59)	1.47 (1.67)	0.36
Mean annual IADL decline (SD) *	0.43 (1.10)	0.66 (1.05)	0.98 (1.21)	0.008

*before dementia



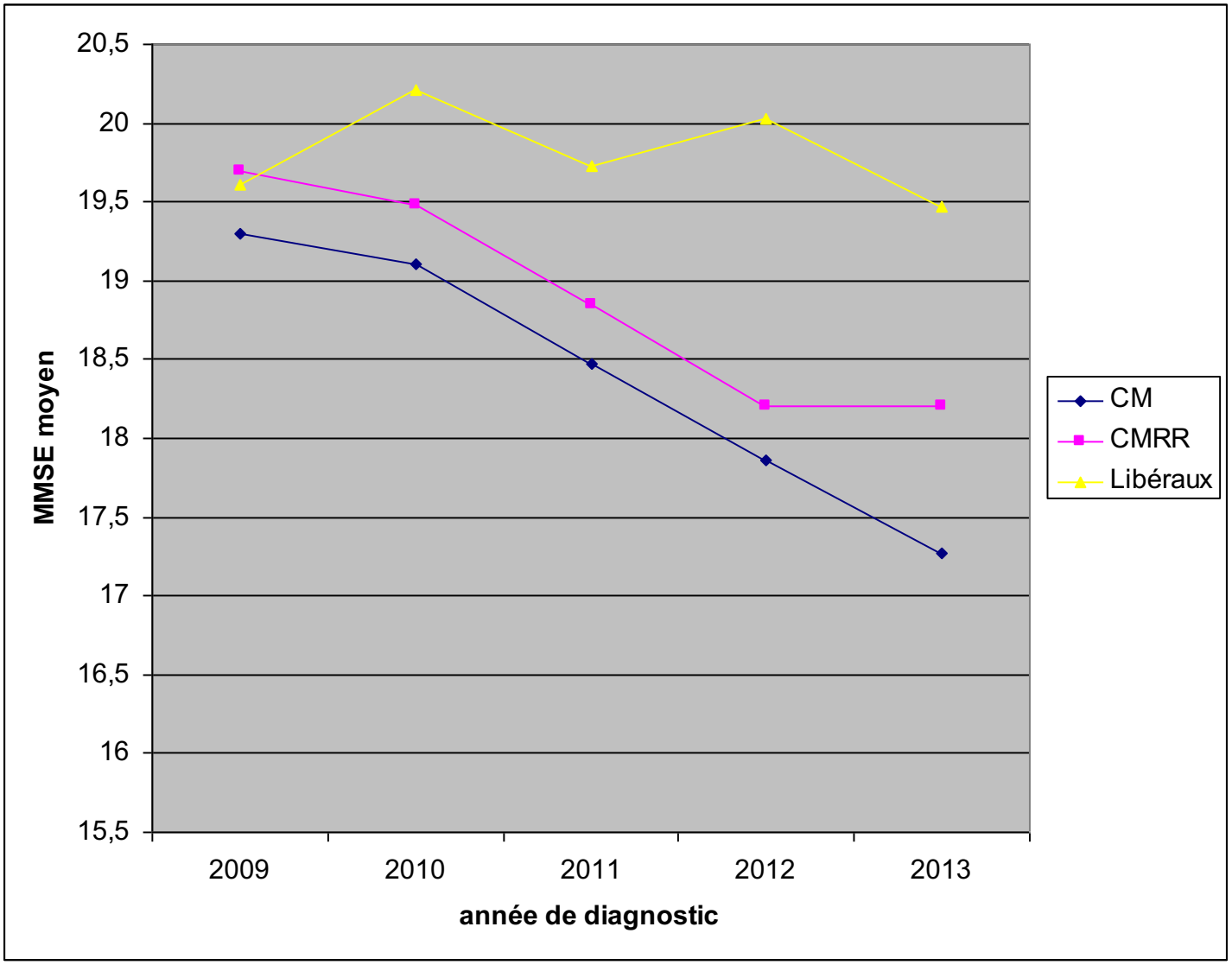
Cumulative incidence of entry in institution according to recourse to specialist for incident AD. 3C study. Pimouguet et al (J Alz Dis 2015)

Risk of incident BADL dependency in those who recoursed to specialist : 1.4 (0.9-2.2)



Cumulative incidence of entry in institution according to recourse to specialist for incident AD. 3C study. Pimouguet et al (JAD 2015)

Mean scores of MMSE for new cases of AD in France 2009-2013



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Valid biomarkers without treatment

Reasons for lack of recourse to specialist

- ~~**Lack of efficacy of antidementia drugs**~~
- ~~Lack of time for diagnosis and management~~
- ~~Lack of interest for dementia, not a priority~~
- ~~Risk of stigma for patients and caregivers~~
- ~~Alzheimer's Disease is not a disease. It is~~ a construction of specialists and big pharma…

Valid biomarkers with treatment

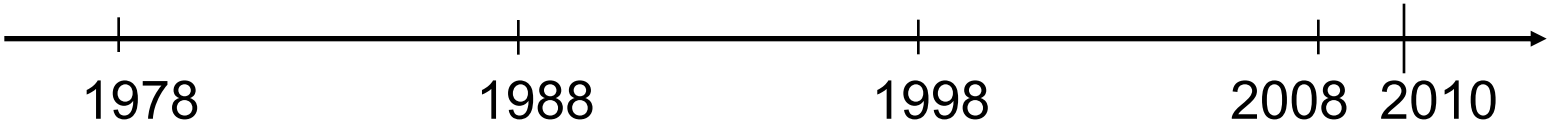
Conclusion

- In spite of the development of valid biomarkers of AD, and of the capacity to detect AD even before dementia, the interest of biomarkers in clinical practice and in general population remains low.
- Only efficacious treatments of AD could change this situation
- However biomarkers of AD could improve inclusion and judgment criteria in drug development

Et la prévention ?

- La prévalence et l'incidence de la maladie d'Alzheimer et des maladies apparentées baissent.
- Est-ce vrai en France ? Pourquoi ?
- Quelle voie de prévention ? Qu'en attendre ?

3 cohortes populationnelles françaises



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Trends in dementia incidence: evolution over a 10-year period in France. Grasset L et al, Alzheimer's Dementia 2015

Evolution du diagnostic clinique de démence
Globale : HR = 0.92 (0.73-1.15)
Hommes : HR = 1.21 (0.76-1.93)
Femmes : HR = 0.90 (0.69-1.17)

Evolution des déficits cognitifs sévères (MMS < 24 et 2 IADL atteints)
Globale : HR = **0.65 (0.53-0.81)**
Hommes : HR = 1.10 (0.69-1.78)
Femmes : HR = **0.62 (0.48-0.80)**

Ajustement sur l'évolution du niveau d'études, les facteurs de risque vasculaire et la dépression
Globale : HR = **0.77 (0.61-0.97)**
Hommes : HR = 1.10 (0.69-1.78)
Femmes : HR = **0.73 (0.57-0.95)**

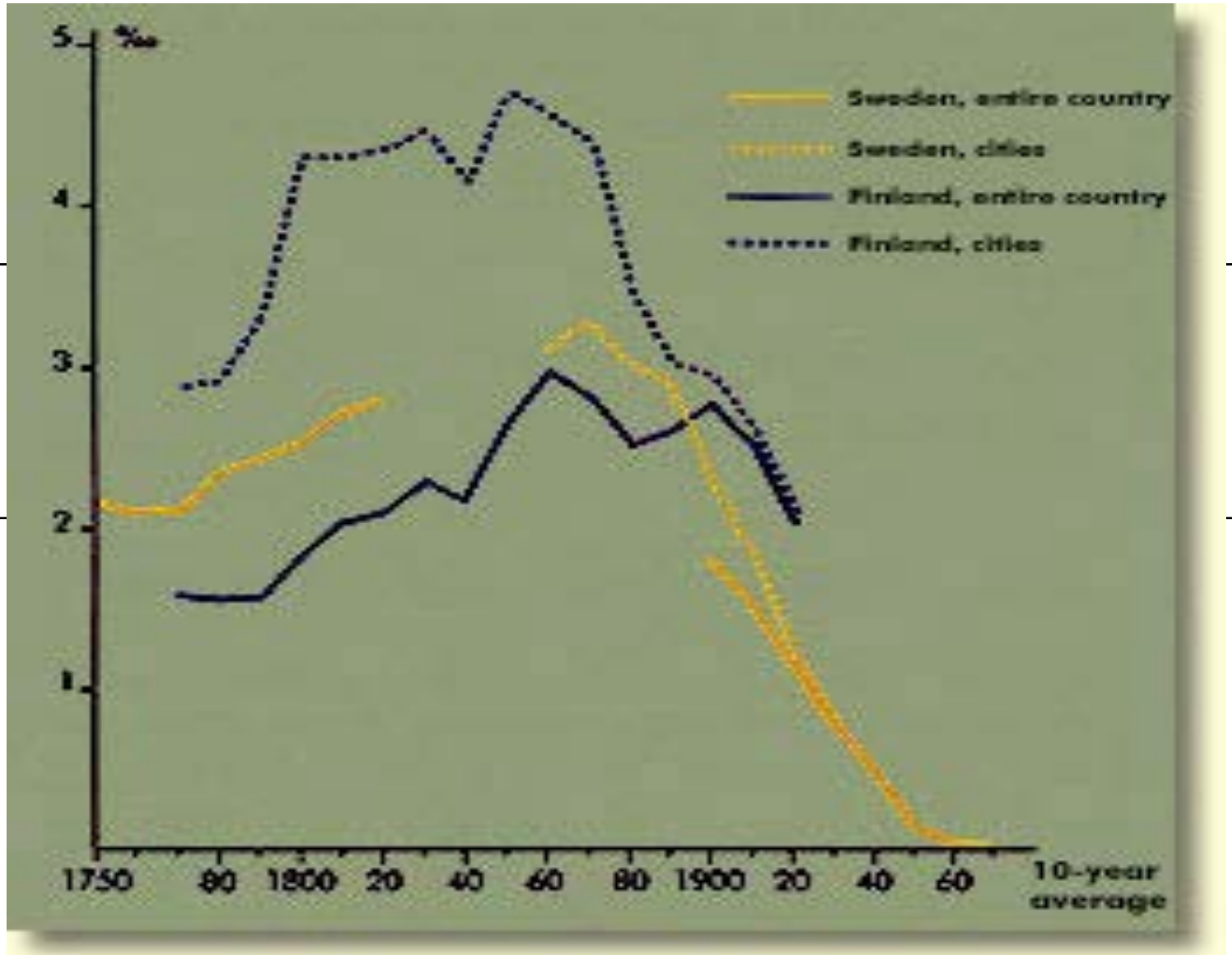


Fig. 8 (click for more information)

Protective factors

Five factors :

- Better Management of Vascular Risk Factors
- Physical Exercise
- Diet
- Stimulating activities
- Good psychological and social state


Ceci n'est pas une pipe.
Magritte

Etude SYST-EUR

Forette et al, Lancet 1998

	Placebo	Traitement
Nombre de patient-années	2737	2885
Maladie d'Alzheimer	15	8
Démence mixte	4	3
Démence vasculaire	2	0

Un problème de méthode

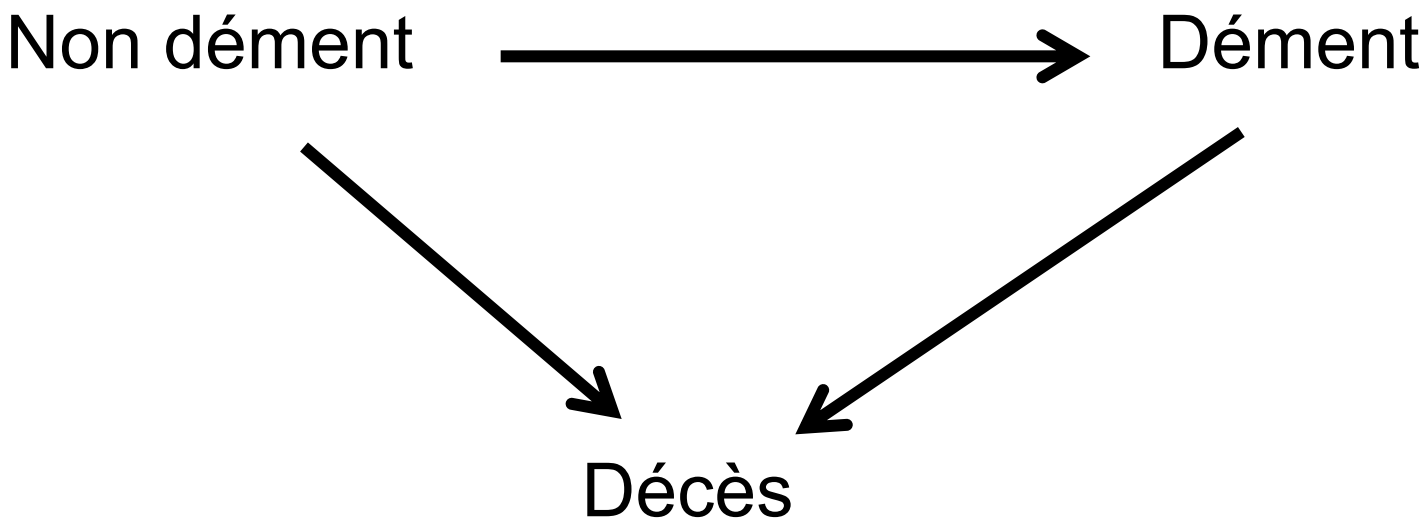
- La mort est beaucoup plus fréquente que la démence (au moins quatre fois plus)
- Quand on est mort, on ne risque plus développer une démence
- Ces deux événements sont donc compétitifs et il faut en tenir compte dans les analyses…
- Car un facteur qui protège de la mort peut majorer le risque de démence

Relationship between sport practice, death and dementia
Paquid study

	No sport practice N=2927	Sport practice N=743
Incident cases of dementia	691 (23.6)	168 (22.6)
Death	2556 (87.3)	577 (77.7)
Age at dementia diagnosis	84.7 (5.86)	84.25 (5.47)

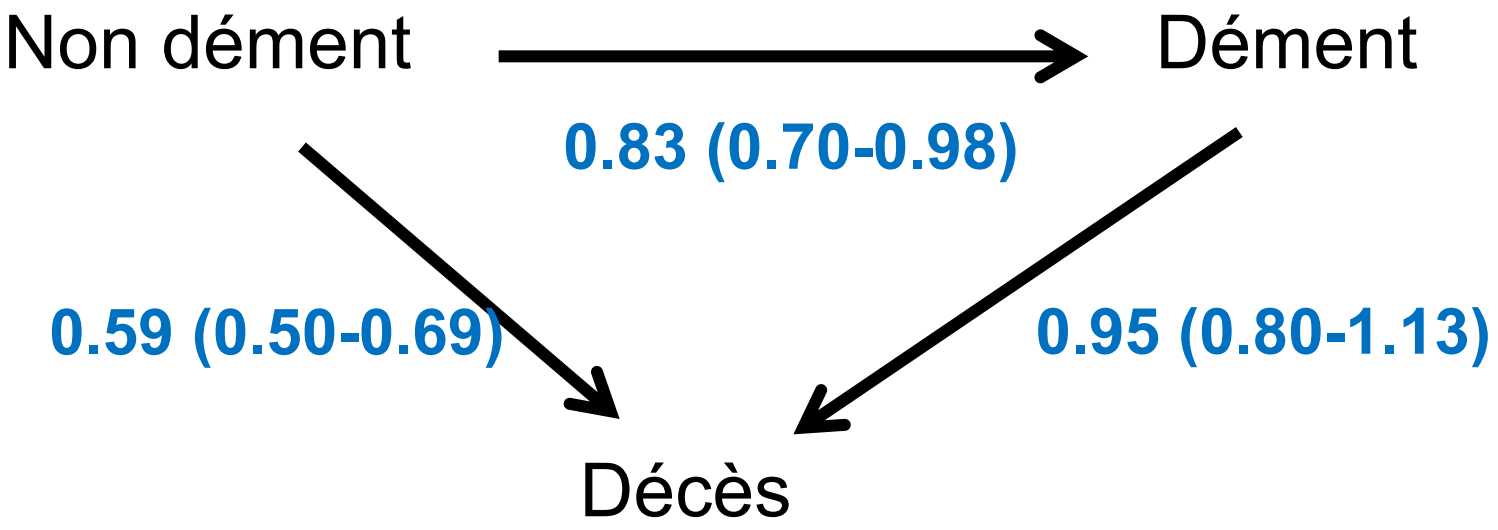
Activité sportive, démence et décès

Illness-death model

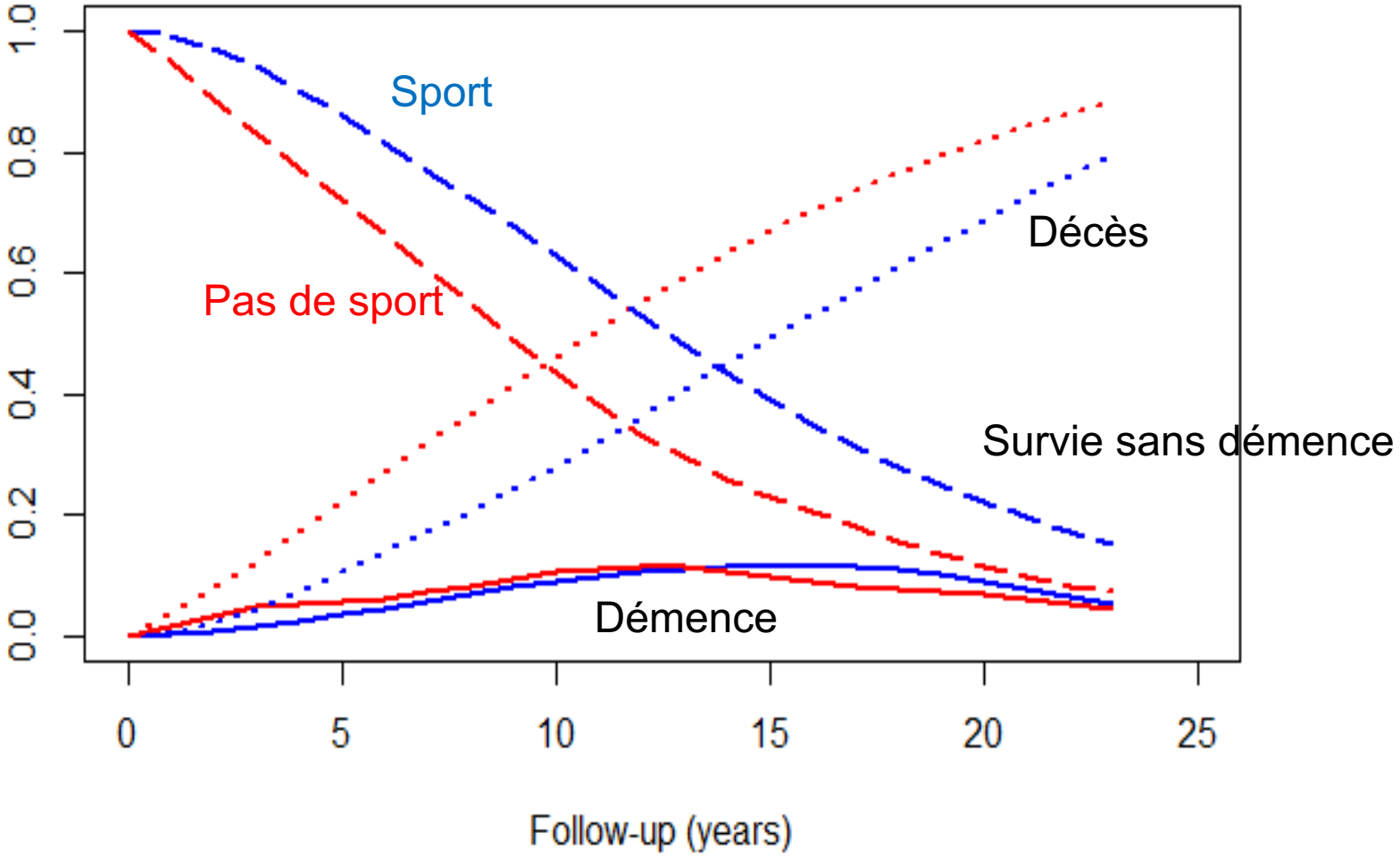


Activité sportive, démence et décès

Illness-death model

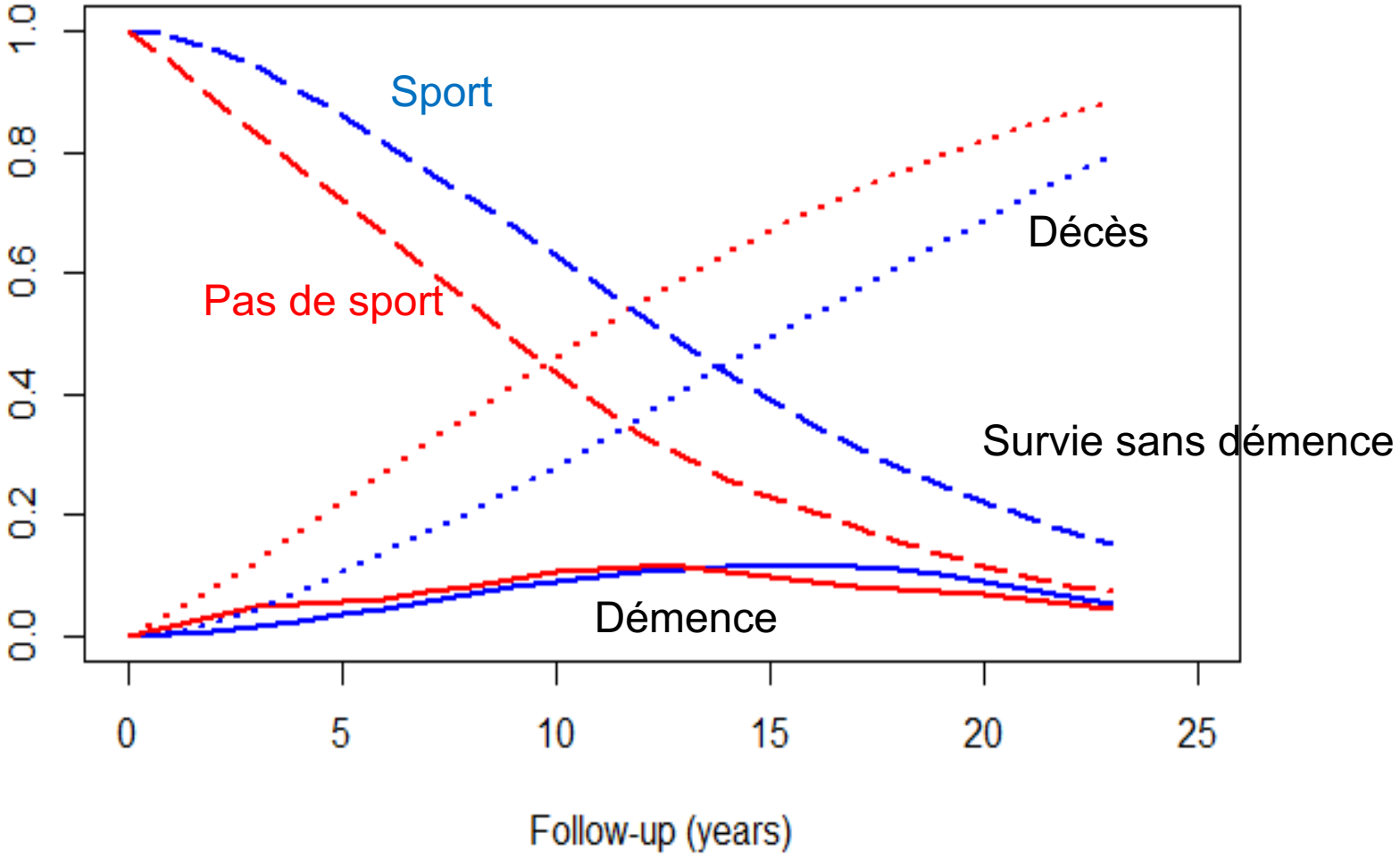


Risques associés à une activité sportive régulière


Sport
Pas de sport
Décès
Survie sans démence
Démence
0.0
0.2
0.4
0.6
0.8
1.0
0
5
10
15
20
25
Follow-up (years)

Durée de vie sans démence:
Avec activité sportive :
13.2 ans (12.6 - 13.6)
Sans activité sportive:
10.0 ans (8.9 - 10.2)

Durée de vie avec démence:
Avec activité sportive:
3.9 ans (3.4 - 4.3)
Sans activité sportive:
3.9 ans (3.6 - 4.2)



Mean lifetime without dementia according to age, sex, diploma for Elderly people practicing sport (EPPS) or not.					
		Men		**Women**	
		Without diploma	**With diploma**	**Without diploma**	**With diploma**
70 years	**EPPS**	13.3 (11.6 – 14.1)	14.4 (12.9 – 14.9)	15.0 (13.0 – 15.6)	16.2 (14.5 – 16.7)
	No EPPS	10.7 (10.0 – 11.2)	12.2 (11.7 – 12.6)	12.5 (11.8 – 12.9)	14.5 (13.9 – 14.8)
80 years	**EPPS**	8.0 (5.9 – 8.5)	8.9 (6.8 – 9.4)	9.4 (6.6 – 9.9)	10.5 (7.6 – 11.1)
	No EPPS	5.8 (5.4 – 6.1)	6.8 (6.4 – 7.1)	7.1 (6.5 – 7.4)	8.6 (8.1 – 8.9)
85 years	**EPPS**	6.1 (3.5 – 6.5)	6.8 (4.3 – 7.2)	7.3 (3.8 – 7.7)	8.2 (4.7 – 8.7)
	No EPPS	4.2 (3.8 – 4.4)	4.9 (4.6 – 5.2)	5.2 (4.6 – 5.4)	6.3 (5.8 – 6.6)

Adherence to a Mediterranean Diet, Cognitive Decline, and Risk of Dementia

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Cécilia Samieri, MPH
Virginie Rondeau, PhD
Hélène Amieva, PhD
Florence Portet, MD, PhD
Jean-François Dartigues, MD, PhD
Nikolaos Scarmeas, MD
Pascale Barberger-Gateau, MD, PhD

Context Higher adherence to a Mediterranean-type diet is linked to lower risk for mortality and chronic diseases, but its association with cognitive decline is unclear.

Objective To investigate the association of a Mediterranean diet with change in cognitive performance and risk for dementia in elderly French persons.

Design, Setting, and Participants Prospective cohort study of 1410 adults (≥65 years) from Bordeaux, France, included in the Three-City cohort in 2001-2002 and reexamined at least once over 5 years. Adherence to a Mediterranean diet (scored as 0 to 9) was computed from a food frequency questionnaire and 24-hour recall.

Main Outcome Measures Cognitive performance was assessed on 4 neuropsychological tests: the Mini-Mental State Examination (MMSE), Isaacs Set Test (IST), Benton Visual Retention Test (BVRT), and Free and Cued Selective Reminding Test (FCSRT). Incident cases of dementia (n=99) were validated by an independent expert committee of neurologists.

Results Adjusting for age, sex, education, marital status, energy intake, physical activity, depressive symptomatology, taking 5 medications/d or more, apolipoprotein E genotype, cardiovascular risk factors, and stroke, higher Mediterranean diet score was associated with fewer MMSE errors (β=–0.006; 95% confidence interval [CI], –0.01 to –0.0003; *P*=.04 for 1 point of the Mediterranean diet score). Performance on the IST, BVRT, or FCSRT over time was not significantly associated with Mediterranean diet adherence. Greater adherence as a categorical variable (score 6-9) was not significantly associated with fewer MMSE errors and better FCSRT scores in the entire cohort, but among individuals who remained free from dementia over 5 years, the association for the highest compared with the lowest group was significant (adjusted for all factors, for MMSE: β=–0.03; 95% CI, –0.05 to –0.001; *P*=.04; for FCSRT: β=0.21; 95% CI, 0.008 to 0.41; *P*=.04). Mediterranean diet adherence was not associated with the risk for incident dementia (fully adjusted model: hazard ratio, 1.12; 95% CI, 0.60 to 2.10; *P*=.72), although power to detect a difference was limited.

Conclusions Higher adherence to a Mediterranean diet was associated with slower MMSE cognitive decline but not consistently with other cognitive tests. Higher adherence was not associated with risk for incident dementia.

JAMA. 2009;302(6):638-648 www.jama.com

THE TRADITIONAL MEDITERRANEAN diet is characterized by high consumption of plant foods (vegetables, fruits, legumes, and cereals), high intake of olive oil as the principal source of monounsaturated fat but low intake of saturated fat, moderate intake of fish, low to moderate intake of dairy products, low consumption of meat and poultry, and wine consumed in low to moderate amounts, normally with meals.[1] Adherence to a Mediterranean-type diet has been associated with longer survival, reduced risk of cardiovascular or cancer mortality, and reduced risk of neurodegenerative disease.[2,3]

A Mediterranean diet might also have protective effects against cognitive decline in older individuals, because it combines several foods and nutrients potentially protective against cognitive dysfunction or dementia, such as fish, monounsaturated fatty acids, vitamins B_{12} and folate, antioxidants (vitamin E, carotenoids, flavonoids), and moderate amounts of alcohol.[4-10] A single study showed a reduced risk for Alzheimer disease and mild cognitive impairment in participants with greater Mediterranean diet adherence.[11,12] These results were obtained in a non-Mediterranean older population, mainly US Hispanics and blacks (<30% whites), which limits its generalizability.

See also pp 627 and 686 and Patient Page.

Author Affiliations: Research Center INSERM U897, Université Victor Segalen Bordeaux 2, Bordeaux, France (Drs Féart, Rondeau, Amieva, Dartigues, and Barberger-Gateau and Ms Samieri); INSERM U888, Université Montpellier 1, Montpellier, France (Dr Portet); and Department of Neurology, Columbia University Medical Center, New York, New York (Dr Scarmeas).
Corresponding Author: Catherine Féart, PhD, Equipe Epidémiologie de la nutrition et des comportements alimentaires, INSERM U897, Université Victor Ségalen Bordeaux 2, ISPED case 11, 146 rue Léo-Saignat, F-33076 Bordeaux Cedex–France (catherine.feart@isped.u-bordeaux2.fr).

MeDi et risque de démence à long terme (cas incidents après 5 ans de suivi)

	Number of dementia cases per category/total number of demented participants	Overall population (**N=1228**)					
		Model 1			Model 2		
		HR (95% CI)	P-value	Overall (trend)	HR (95% CI)	P-value	Overall (trend)
MeDi score (0-9)		0.84 (0.74-0.96)	**0.009**		0.85 (0.74-0.96)	**0.01**	
Low MeDi adherence (0-3) *	38/97	1.00		**0.01**	1.00		**0.008 (0.01)**
Middle MeDi adherence (4-5)	38/97	0.52 (0.32-0.83)	**0.006**		0.51 (0.32-0.81)	**0.005**	
High MeDi adherence (6-9)	21/97	0.52 (0.30-0.91)	**0.02**		0.51 (0.30-0.89)	**0.02**	

* The lowest category was chosen as reference

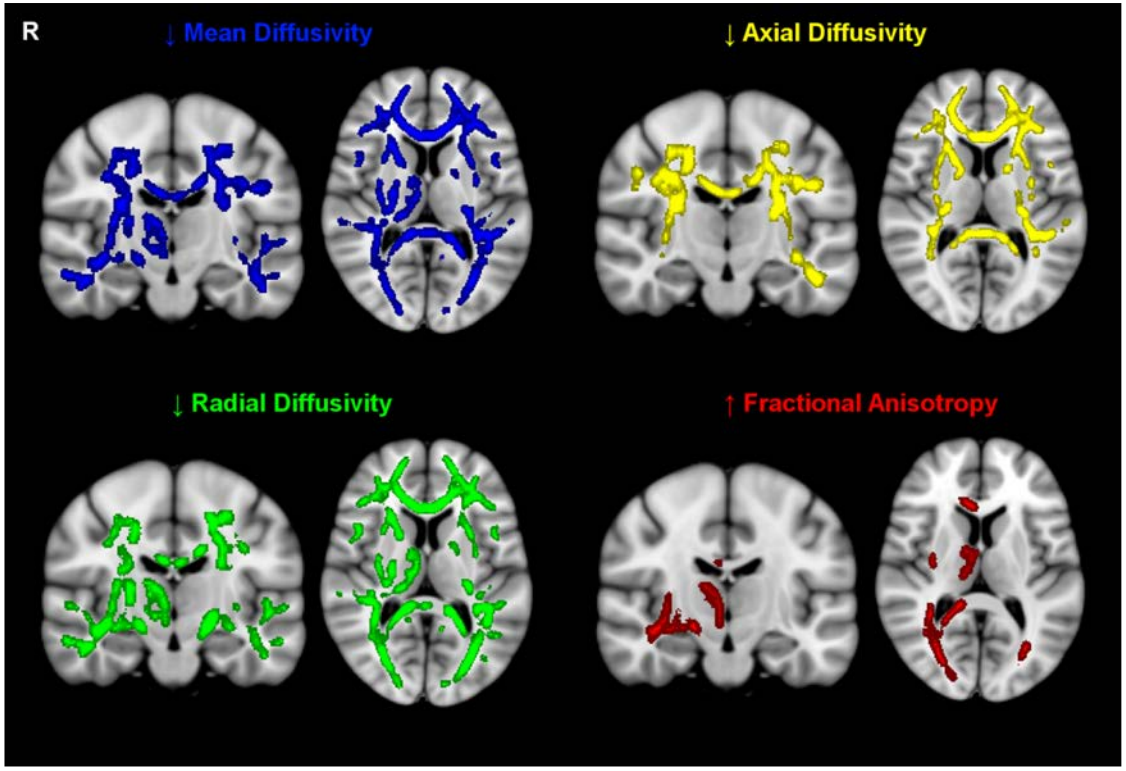
Model 1: Model adjusted for age, sexe, marital status, education,total energy intake, practice of physical exercise, taking >= 5 drugs/d, apolipoprotein E4, Center for Epidemiological Studies-Depression score + Body Mass Index, diabetes, cardiovascular history (including stroke), hypertension, tobacco use and hypercholesterolemia

Model 2: Model 1 + Mini-Mental State Examination score

MeDi et préservation de la microstructure de la substance blanche 10 ans après

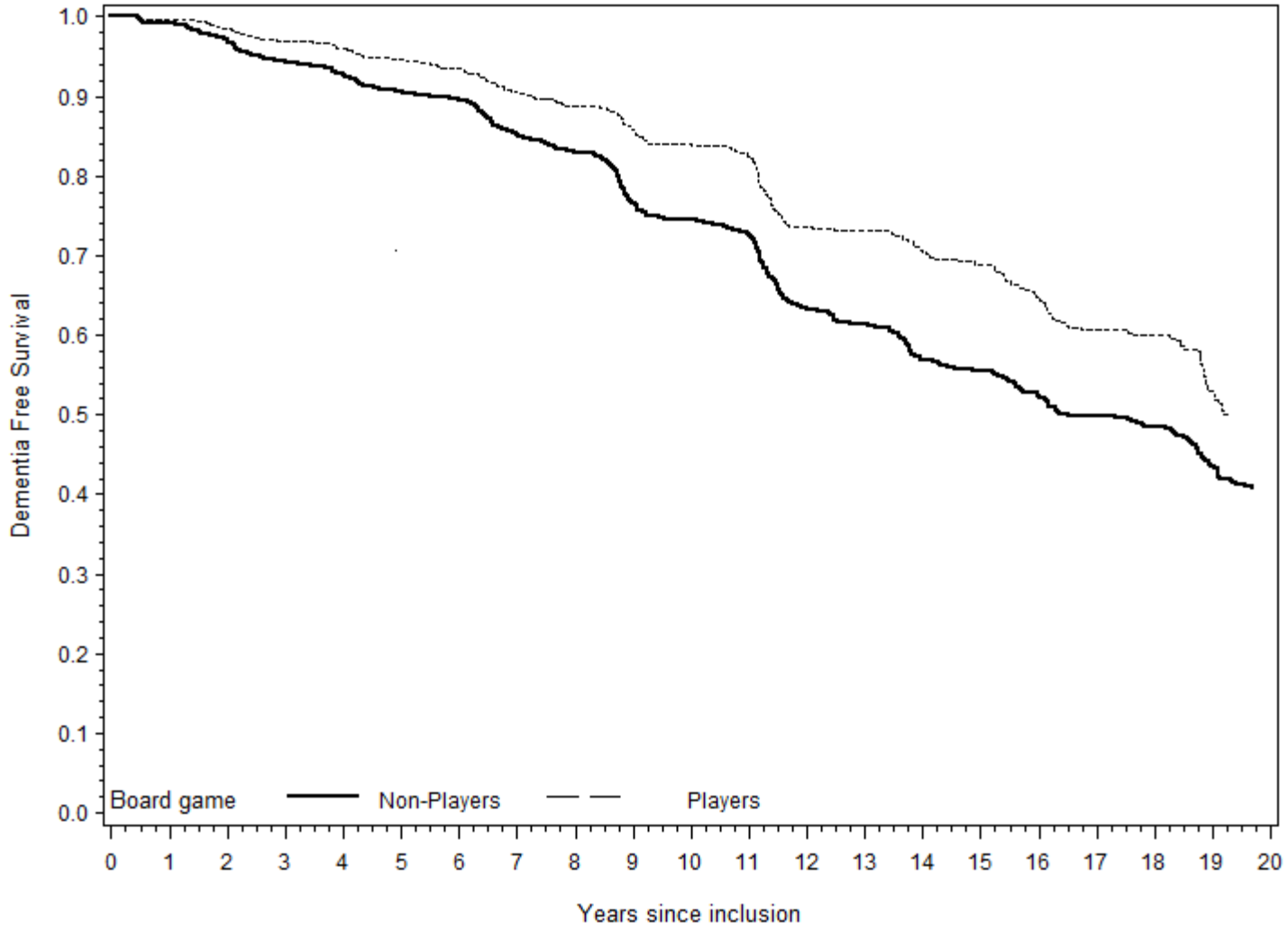
(N=146 3C Bordeaux) - Alzheimers Dement. 2015 Sep;11(9):1023-31.

The figure represents **WM regions where each 1 point-increase of the MeDi score was significantly associated with lower diffusivity** (axial and radial diffusivities, which reflect the magnitude of diffusion along the principal and perpendicular directions of fibers, respectively, and mean diffusivity, represents a global measure of diffusion) **and higher fractional anisotropy, after adjustment for age, gender, education and APOEε4, and correcting for multiple comparisons.** The results were unchanged after further adjustment for a larger set of potential confounders (energy intake, regular exercise, BMI, smoking, vascular risk factors and the Isaacs' set test score at baseline).

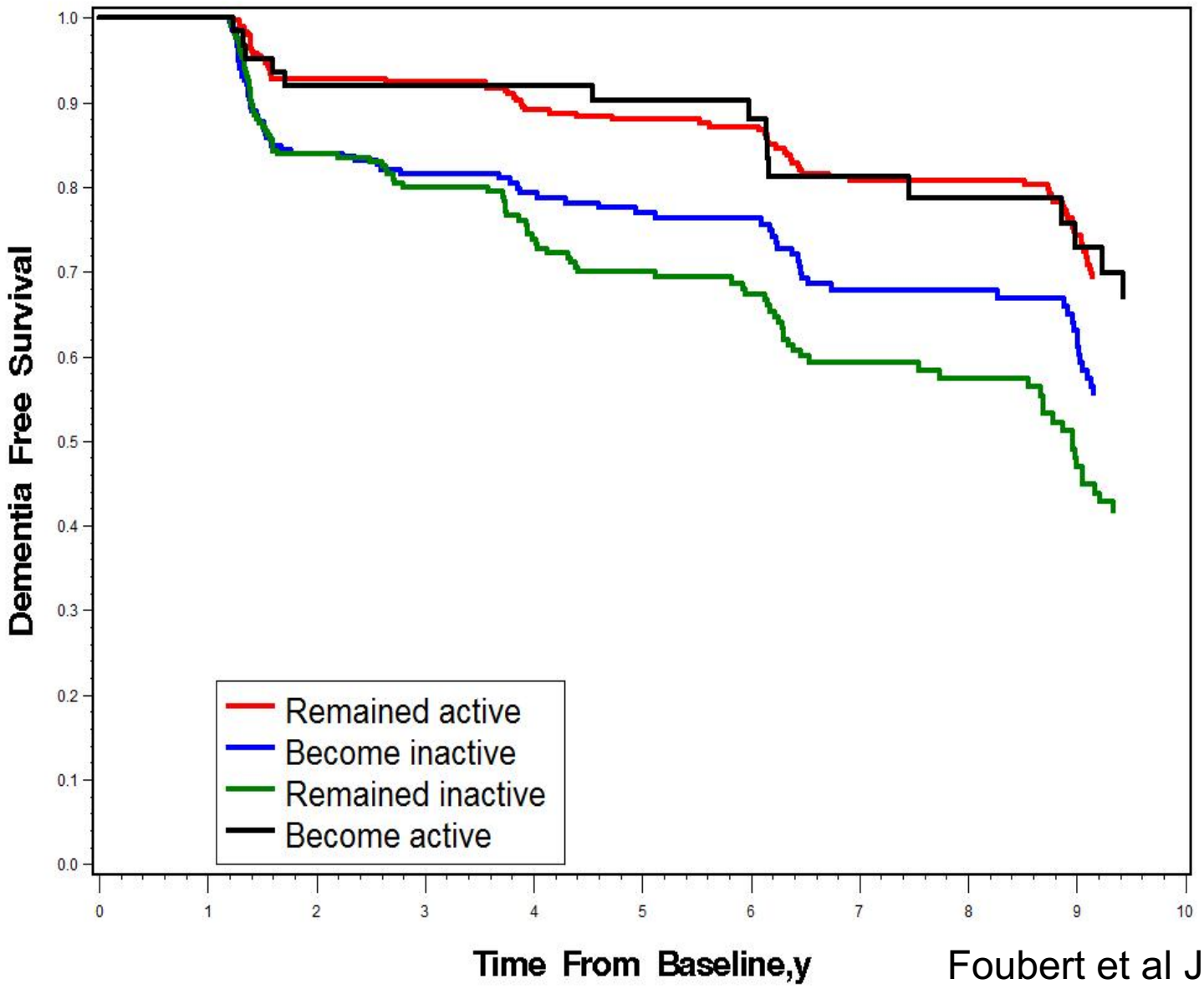


In multivariate voxel-by-voxel analyses, adherence to the MeDi was associated with preserved WM microstructure in extensive areas – **a gain in structural connectivity which was related to strong cognitive benefits**; however, there were no relation with GM or WM volumes.

Playing Board Game and Risk of Dementia (Paquid)



Dartigues et al BMJ Open 2013



Foubert et al JNHA 2014

Et la physiopathologie ?

- Quelle est la piste causale de la maladie ?
- Quelle est la séquence d'apparition des anomalies morphologiques et fonctionnelles ?

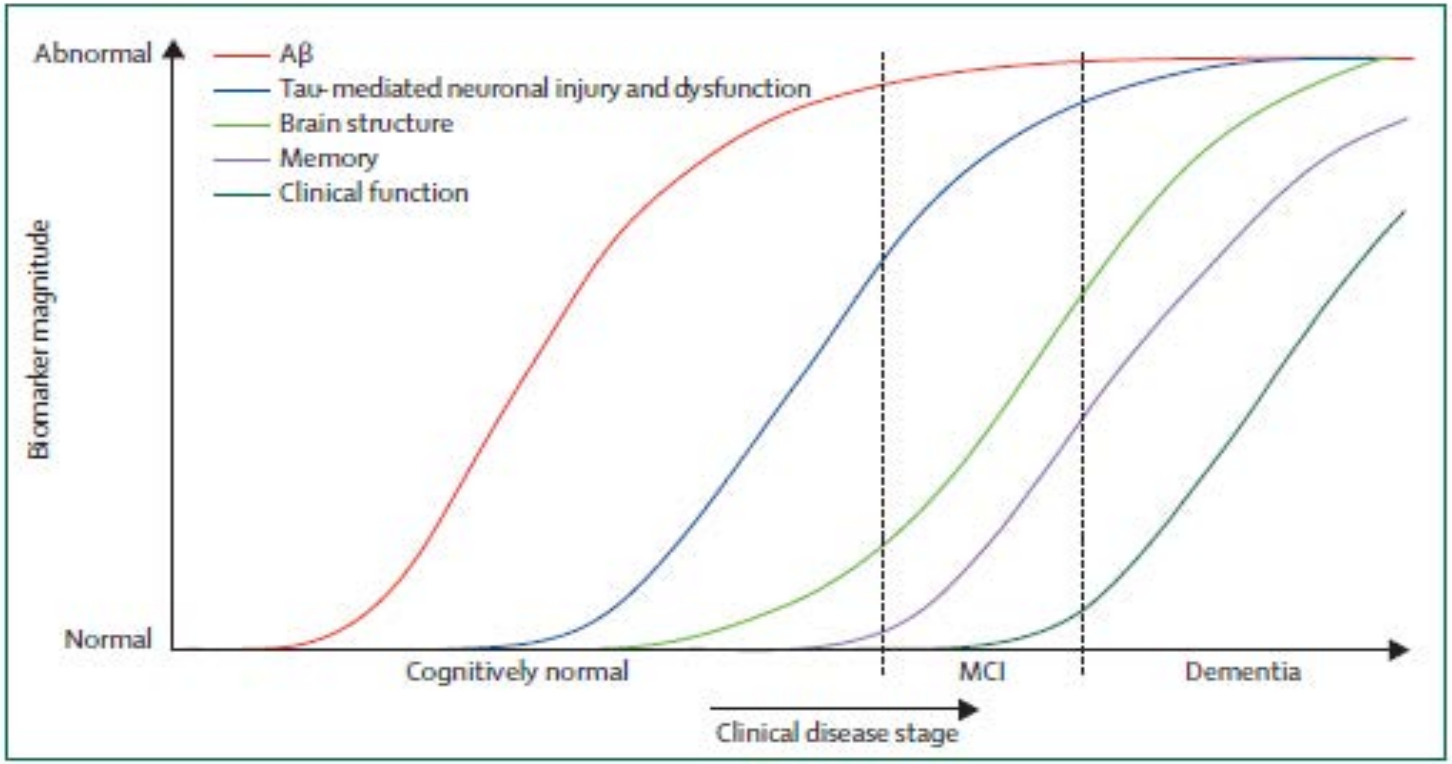


Figure 1: **2010 model of dynamic biomarkers of the Alzheimer's disease pathological cascade**
Aβ is identified by CSF $A\beta_{42}$ or PET amyloid imaging. Tau-mediated neuronal injury and dysfunction is identified by CSF tau or fluorodeoxyglucose PET. Brain structure is measured by structural MRI. Aβ=amyloid β. MCI=mild cognitive impairment. Reproduced from Jack and colleagues,[18] by permission of Elsevier.

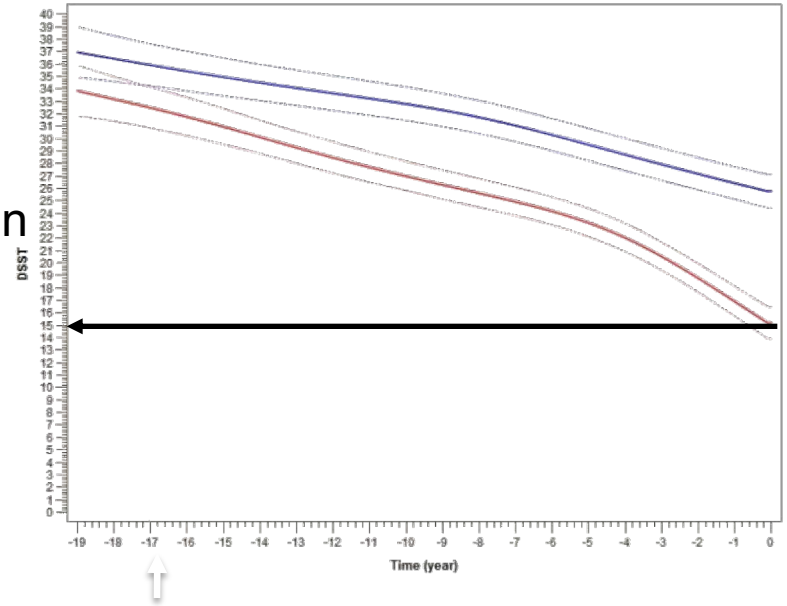
6. Jack CR, Jr., Therneau TM, Wiste HJ, Weigand SD, Knopman DS, Lowe VJ, et al. **Transition rates between amyloid and neurodegeneration biomarker states and to dementia: a population-based, longitudinal cohort study**. Lancet Neurol 2016;15(1):56-64.

	65 ans	85 ans
A-N- → A+N-	4,0	6,9
A-N- → A-N+	1,6	17,2
A+N- → A+N+	6,1	20,8
A-N+ → A+N+	2,6	13,2
A+N+ → Démence	0,8	7,0
A-N+ → Démence	0,6	1,7

Digit Symbol Substitution task

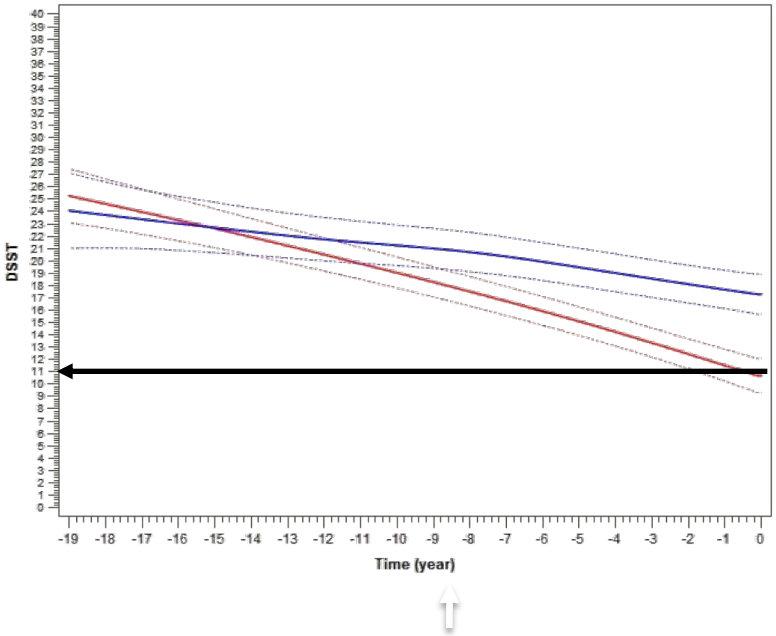
High education

35 à 15



Low education

25 à 11



Controls

Pre-demented

Amieva et al, Brain 2014

Controls

Pre-demented

Alors la maladie en population ?

- 85% des cas au moins des cas de MA et des maladies apparentées ont 75 ans et plus
- A cet âge, les MAMA ne sont-elles pas plus des « syndromes gériatriques » que des maladies parfaitement identifiées ?
- A cet âge, les aspects médicaux, psychologiques et sociaux s'entremêlent et sont en fait un tout.

	3C Bordeaux 2010	INSEE Bordeaux 2010
Age (Mean)	83.3 years	83.0 years
Men (%)	30,6%	32,1%
Living in institution (%)	8,4%	9,1%
Living alone (%)	48,6%	48,4%

La démence à Bordeaux en 2011(3C) chez les 75+

- Avec un taux de prévalence de 14,3%, on peut estimer le nombre des déments prévalents à Bordeaux à 2 750.
- Parmi les 90 sujets classés déments, 63 sont des femmes (70%). La prévalence observée chez les hommes (14%) est la même que celle des femmes (14,4%), ce qui confirme l'évolution épidémiologique de la maladie en ville. Le risque de démence incidente chez les femmes qui était plus fort que celui des hommes il y a 20 ans, a baissé
- Rapporté à la population bordelaise, selon nos estimations il y a tout de même beaucoup plus de femmes démentes que d'hommes : 1 880 femmes contre 860 hommes seulement.

La démence à Bordeaux (3C) en 2011 chez les 75+

- La prévalence de la démence augmente avec l'âge passant de 5,5% entre 75 et 79 ans, à 9,7% entre 80 et 84 ans et 25,3% après 85 ans. Ainsi une personne sur quatre serait démente après 85 ans.
- Près de la moitié des déments vivent en institution (42 personnes, 46,7%) vs. 53,3% à domicile. En institution, la prévalence de la démence est de 79,3% (environ 4 résidents sur 5), ce qui signifie que 20,7% seulement des sujets de 75 ans et plus vivant en institution ne sont pas déments (un sur 5).

La démence à Bordeaux (3C) en 2011 chez les 75+

- Parmi les 90 déments, 25 vivent seuls à leur domicile soit 27,8%. Ainsi à Bordeaux, 4% des sujets de 75 ans et plus sont déments et vivent seuls à leur domicile.
- Ces sujets sont particulièrement vulnérables pour de multiples risques : iatrogénie, accidents domestiques ou de la voie publique, chute, maltraitance financière ou physique et bien sûr hospitalisation(s), recours inadaptés aux urgences, institutionnalisation en situation de crise et décès évitable.
- Ainsi, c'est 770 bordelais âgés qui mériteraient d'être repérés et protégés, et dont la moitié ne sont pas diagnostiqués.

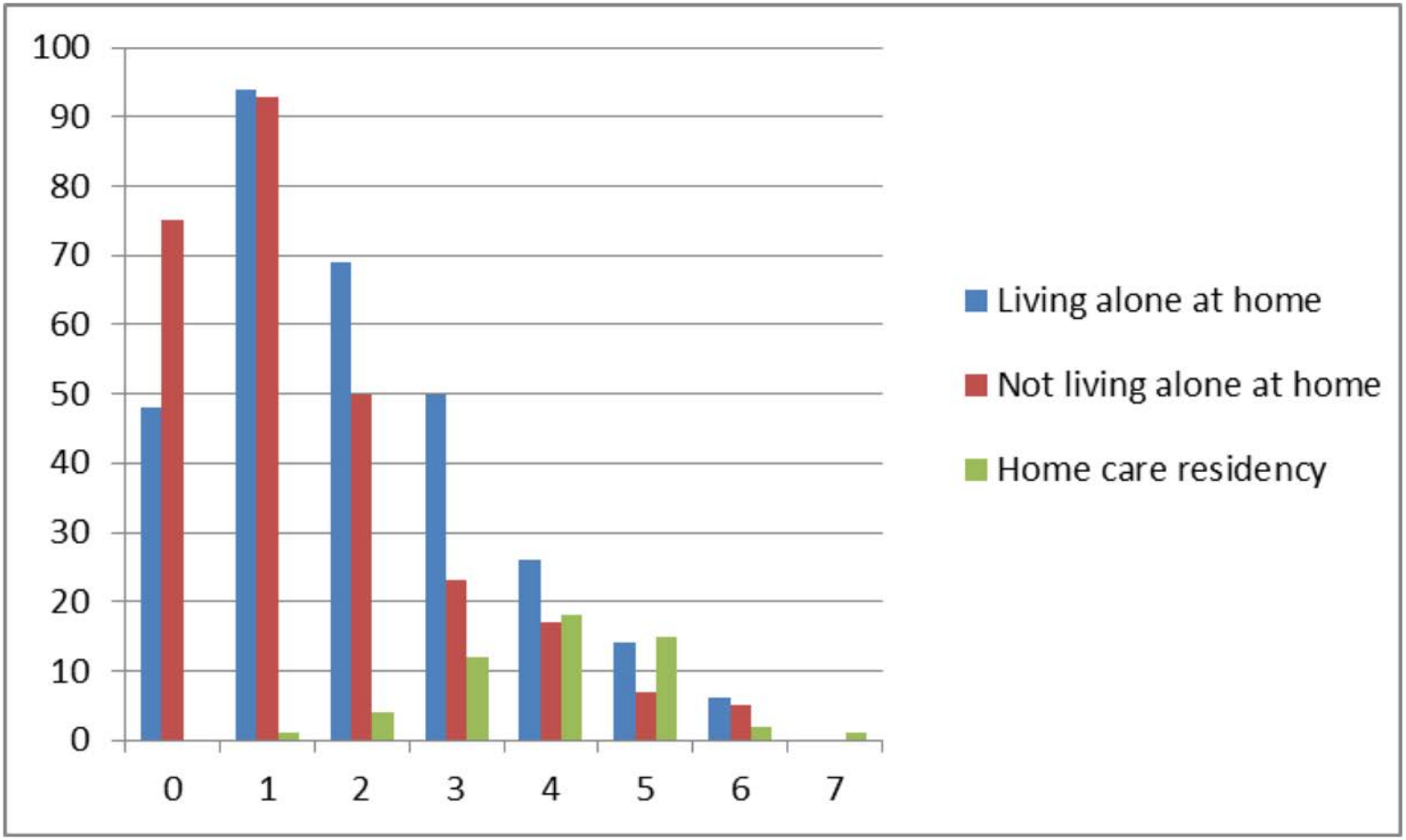
La démence à Bordeaux (3C) en 2011 chez les 75+

- Pour 81 déments parmi les 90 identifiés, nous avons recueilli des informations concernant leur suivi médical (soit pour 90% des malades). Seuls 13 sont vus au moins une fois par an par un spécialiste neurologue, gériatre ou psychiatre (16,1%).
- Ce très faible pourcentage traduit le faible recours au soin de niveau secondaire dans une pathologie qui a pourtant fait l'objet de trois plans nationaux successifs.

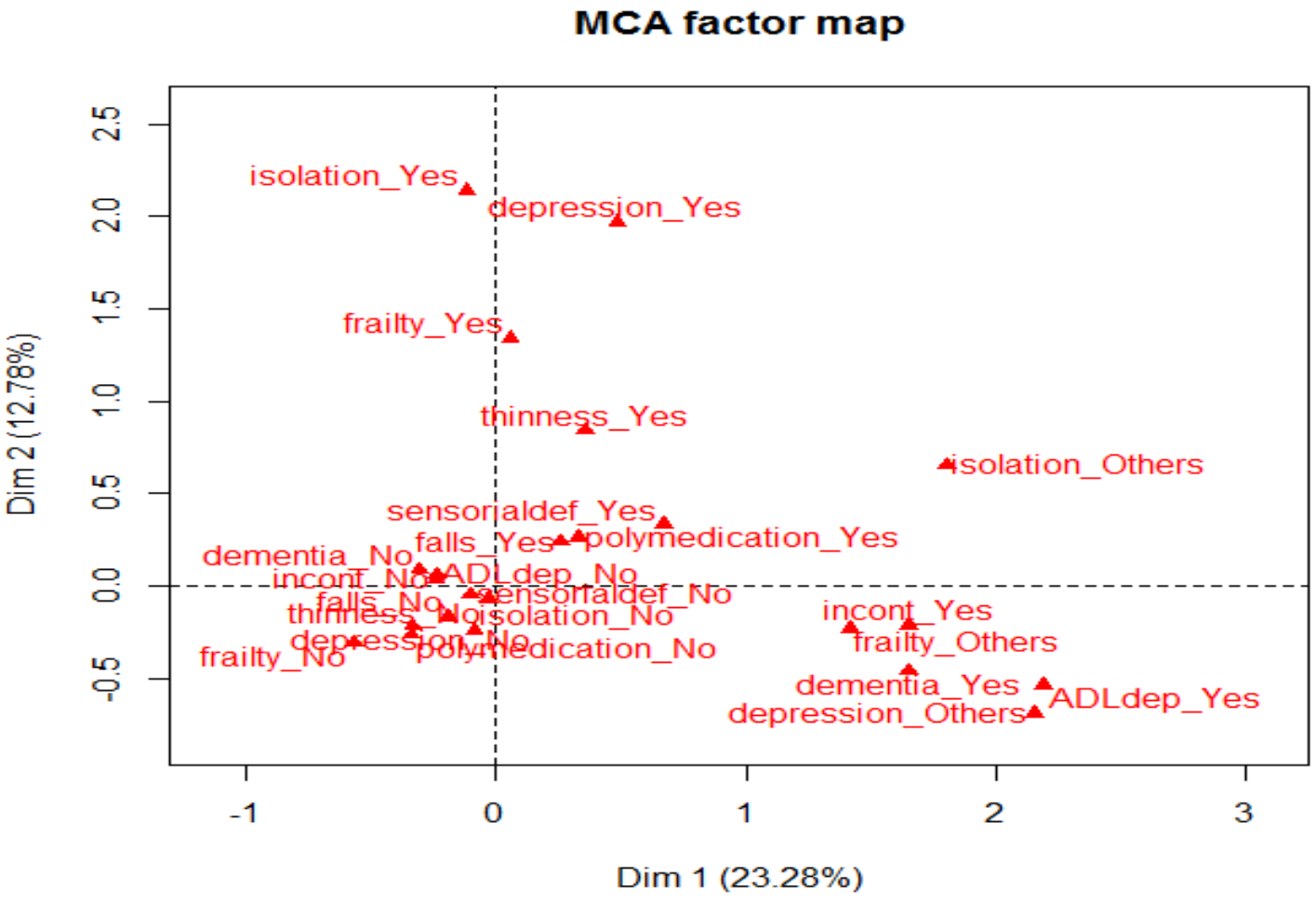
Les syndromes gériatriques en médecine générale

- Chaque MG à Bordeaux a en moyenne soixante cinq patients 75+.
- Sur la base des estimations de prévalence, un MG de Bordeaux a en moyenne dans sa clientèle 30 à 35 polymédications, 21 à 30 chutes, 10 à 13 fragiles, **8 à 12 démences**, 7 à 10 troubles sensoriels majeurs, 6 à 10 incontinences, 6 à 9 dépressions, 5 à 8 ADL dépendance T/H, 4 à isolements et 3 à 7 maigreurs.

Les syndromes gériatriques en médecine générale



Les syndromes gériatriques en médecine générale



Conclusion

- La MA en population est bien un autre monde que la MA dans nos consultations mémoire et CMRR
- Si nous voulons mieux la comprendre et surtout comprendre la réticence des MG à nous confier les malades, il est indispensable de la traquer là où elle est vraiment.