



## Dossier de Presse

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# De nouvelles pistes pour la prévention de la maladie d'Alzheimer « Eude MAPT3 »

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## Dossier de Presse

### De nouvelles pistes pour la prévention de la maladie d'Alzheimer « Etude MAPT »

La maladie d'Alzheimer (MA) représente la forme la plus fréquente des démences affectant d'après les dernières estimations près de 850 000 personnes en France. En l'absence de traitements curatifs, le développement de stratégies préventives permettant de retarder la survenue de la maladie est indispensable. Une étude a montré que de retarder le déclin cognitif d'un an permettrait de diminuer de plus de 9 millions la prévalence de la maladie.

#### Quelles sont les pistes à envisager pour la prévention de la maladie d'Alzheimer ?

La survenue d'une démence aux âges avancés pourrait être la conséquence de l'exposition cumulée à différents facteurs de risque tout au long de la vie. La recherche des facteurs de risque modifiables est un des enjeux majeurs de la recherche épidémiologique étiologique de la MA. Elle est actuellement dominée par des travaux de recherche sur les facteurs liés au mode de vie et sur les facteurs de risque vasculaires. Plusieurs études épidémiologiques ont montré que l'alimentation, l'exercice physique, l'exercice cognitif et le maintien des activités sociales, jouaient un rôle significatif dans le maintien des facultés intellectuelles supérieures. A ce stade des connaissances, la mise en place d'études d'intervention pour la prévention de la démence s'avère nécessaire. Deux études d'intervention publiées dans le JAMA rapportent des résultats encourageants. Elles montrent qu'un entraînement de la mémoire et d'autres fonctions cognitives chez des personnes âgées de 65 ans et plus permet de réduire la perte d'autonomie (**étude ACTIVE**) et que la pratique régulière de l'exercice physique (comme la marche active) améliore la cognition chez des sujets présentant une plainte mnésique subjective (**étude FABS**). Du fait de la nature multifactorielle de la MA, il semble actuellement pertinent de proposer **une intervention « multidomaine »**, combinant des interventions ciblant plusieurs facteurs associés à la survenue de la maladie, afin de potentialiser les effets protecteurs de chacun des facteurs. Le Gérontopôle de Toulouse coordonne actuellement l'étude MAPT (Multidomain Alzheimer Preventive Trial) qui vise à démontrer l'efficacité d'un programme d'intervention « multidomaine » associant des recommandations nutritionnelles, des exercices cognitifs, des exercices physiques, le dépistage des troubles sensoriels et la prise en charge des maladies cardiovasculaires, dans la prévention de la perte de certaines fonctions cognitives parmi lesquelles la mémoire.

#### L'étude « MAPT (Multidomain Alzheimer Preventive Trial) » : le premier essai d'intervention « multidomaine » dans la prévention des troubles de la mémoire chez les personnes âgées

L'objectif principal de l'étude MAPT est de déterminer si la mise en place de mesures préventives peut protéger contre la perte de la mémoire.  
Les mesures préventives testées dans cette étude sont :

- la prise quotidienne d'un traitement à base d'oméga-3 (un certain nombre de travaux de recherche semble en effet établir qu'une prise régulière de produits riches en oméga-3 exercerait un effet protecteur sur différentes maladies) ;
- la pratique d'exercices physiques et cognitifs associés à des recommandations nutritionnelles (« intervention multidomaine »),
- ou l'association des deux mesures précédentes.

Cette étude se déroule à Bordeaux, Limoges, Montpellier et Toulouse. Au total, 1200 personnes âgées seront recrutées et suivies durant 3 ans. Les sujets recrutés dans cette étude sont des sujets âgés de 70 ans et plus, vivant au domicile, et fragiles présentant au moins l'un des critères suivants : une incapacité à réaliser une des activités instrumentales de la vie quotidienne évaluées (échelle IADL), une plainte mnésique subjective spontanée exprimée au médecin traitant, ou une vitesse de marche ralentie. Après 3 ans de suivi, cette étude devrait nous apporter des arguments scientifiques supplémentaires dans la prévention des troubles de la mémoire avec l'âge.

### **La pratique régulière de l'exercice physique améliore la cognition chez des sujets présentant une plainte mnésique subjective (étude FABS).**

Un groupe de sujets âgés de 50 ans et plus, a bénéficié d'une intervention recommandant la pratique de l'exercice physique à domicile pendant au moins 150 minutes par semaine (essentiellement représentée par la pratique de la marche active). Ils ont été comparés à un groupe de sujets bénéficiant seulement de conseils en matière de nutrition et de mode de vie à l'exception de l'exercice physique. Après 18 mois de suivi, les sujets ayant bénéficié de l'intervention à domicile avaient de meilleures performances cognitives.

Référence:

*Lautenschlager NT et al. JAMA 2008, Vol 320, n°9: 1027-1037*

# Effect of Physical Activity on Cognitive Function in Older Adults at Risk for Alzheimer Disease

## A Randomized Trial

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AS THE WORLD POPULATION ages, the number of older adults living with Alzheimer disease (AD) is estimated to increase from the current 26.6 million to 106.2 million by 2050.<sup>1</sup> If illness onset could be delayed by 12 months, 9.2 million fewer cases of AD would occur worldwide.<sup>1</sup> For this reason, attempts have been made to identify individuals who are at increased risk of AD and to test interventions that might delay the progression of prodromal symptoms to full-blown dementia. The results from observational studies suggest that older people who are free of dementia but report memory decline or show objective evidence of cognitive impairment are more likely to develop AD over time.<sup>2,3</sup>

Seven clinical trials have investigated whether cholinesterase inhibitors (donepezil, rivastigmine, and galantamine), vitamin E, piracetam, and rofecoxib (a cyclooxygenase 2 inhibitor) can prevent cognitive decline and progression to dementia in older adults with mild cognitive impairment. In a trial by Petersen et al,<sup>4</sup> 769 participants with mild

**Context** Many observational studies have shown that physical activity reduces the risk of cognitive decline; however, evidence from randomized trials is lacking.

**Objective** To determine whether physical activity reduces the rate of cognitive decline among older adults at risk.

**Design and Setting** Randomized controlled trial of a 24-week physical activity intervention conducted between 2004 and 2007 in metropolitan Perth, Western Australia. Assessors of cognitive function were blinded to group membership.

**Participants** We recruited volunteers who reported memory problems but did not meet criteria for dementia. Three hundred eleven individuals aged 50 years or older were screened for eligibility, 89 were not eligible, and 52 refused to participate. A total of 170 participants were randomized and 138 participants completed the 18-month assessment.

**Intervention** Participants were randomly allocated to an education and usual care group or to a 24-week home-based program of physical activity.

**Main Outcome Measure** Change in Alzheimer Disease Assessment Scale-Cognitive Subscale (ADAS-Cog) scores (possible range, 0-70) over 18 months.

**Results** In an intent-to-treat analysis, participants in the intervention group improved 0.26 points (95% confidence interval, -0.89 to 0.54) and those in the usual care group deteriorated 1.04 points (95% confidence interval, 0.32 to 1.82) on the ADAS-Cog at the end of the intervention. The absolute difference of the outcome measure between the intervention and control groups was -1.3 points (95% confidence interval, -2.38 to -0.22) at the end of the intervention. At 18 months, participants in the intervention group improved 0.73 points (95% confidence interval, -1.27 to 0.03) on the ADAS-Cog, and those in the usual care group improved 0.04 points (95% confidence interval, -0.46 to 0.88). Word list delayed recall and Clinical Dementia Rating sum of boxes improved modestly as well, whereas word list total immediate recall, digit symbol coding, verbal fluency, Beck depression score, and Medical Outcomes 36-Item Short-Form physical and mental component summaries did not change significantly.

**Conclusions** In this study of adults with subjective memory impairment, a 6-month program of physical activity provided a modest improvement in cognition over an 18-month follow-up period.

**Trial Registration** anzctr.org.au Identifier: ACTR12605000136606

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www.jama.com

cognitive impairment were randomly assigned to receive 10 mg of donepezil, 2000 IU of vitamin E, or placebo daily for 36 months. By study end, progres-

sion to dementia and change in cognitive score did not differ by treatment group. A study of rivastigmine to prevent conversion from mild cognitive

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See also p 1077 and Patient Page.

## Un programme d'entraînement des fonctions cognitives retarde le déclin fonctionnel lié à l'âge (étude ACTIVE).

Un groupe de sujets âgés de 65 ans et plus a bénéficié de différents programmes d'entraînement des fonctions cognitives. Les interventions étaient composées de 10 sessions d'entraînement cognitif de 60 minutes centré soit sur la mémoire (stratégies de mémorisation), soit sur le raisonnement faisant intervenir la logique, soit sur la vitesse de traitement de l'information. Les résultats ont montré que les sujets ayant bénéficié d'une des interventions avaient moins de difficultés pour effectuer les activités de la vie quotidienne que les autres sujets n'ayant bénéficié d'aucune prise en charge particulière ; l'effet était significatif pour le groupe ayant suivi un entraînement cognitif centré sur le "raisonnement logique".

### Référence:

Willis S et al. JAMA 2006 ; Vol 296, n°23: 2805-2814

#### ORIGINAL CONTRIBUTION

## Long-term Effects of Cognitive Training on Everyday Functional Outcomes in Older Adults

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**D**ECLINE IN COGNITIVE ABILITIES has been shown to lead to an increased risk of difficulty in performing instrumental activities of daily living (IADL).<sup>1-3</sup> However, whether interventions to maintain or enhance cognitive abilities in older adults will prevent or delay these functional difficulties is unclear. Prior interventions with older adults have targeted those with cognitive deficits or functional disabilities and have focused on remediation rather than prevention.<sup>4,5</sup> Prior studies have shown that cognitive interventions can improve cognitive abilities in normal elders but have not included functional outcome measures and have been limited by small, homogeneous samples and lack of randomization.<sup>6-11</sup>

For editorial comment see p 2852.

**Context:** Cognitive training has been shown to improve cognitive abilities in older adults but the effects of cognitive training on everyday function have not been demonstrated.

**Objective:** To determine the effects of cognitive training on daily function and durability of training on cognitive abilities.

**Design, Setting, and Participants:** Five-year follow-up of a randomized controlled single-blind trial with 4 treatment groups. A volunteer sample of 2832 persons (mean age, 73.6 years; 26% black), living independently in 6 US cities, was recruited from senior housing, community centers, and hospitals and clinics. The study was conducted between April 1998 and December 2004. Five-year follow-up was completed in 67% of the sample.

**Interventions:** Ten-session training for memory (verbal episodic memory), reasoning (inductive reasoning), or speed of processing (visual search and identification); 4-session booster training at 11 and 35 months after training in a random sample of those who completed training.

**Main Outcome Measures:** Self-reported and performance-based measures of daily function and cognitive abilities.

**Results:** The reasoning group reported significantly less difficulty in the instrumental activities of daily living (IADL) than the control group (effect size, 0.29; 99% confidence interval [CI], 0.08-0.55). Neither speed of processing training (effect size, 0.26; 99% CI, -0.002 to 0.51) nor memory training (effect size, 0.20; 99% CI, -0.06 to 0.46) had a significant effect on IADL. The booster training for the speed of processing group, but not for the other 2 groups, showed a significant effect on the performance-based functional measure of everyday speed of processing (effect size, 0.30; 99% CI, 0.08-0.52). No booster effects were seen for any of the groups for everyday problem-solving or self-reported difficulty in IADL. Each intervention maintained effects on its specific targeted cognitive ability through 5 years (memory: effect size, 0.23 [99% CI, 0.11-0.35]; reasoning: effect size, 0.26 [99% CI, 0.17-0.35]; speed of processing: effect size, 0.76 [99% CI, 0.62-0.90]). Booster training produced additional improvement with the reasoning intervention for reasoning performance (effect size, 0.28; 99% CI, 0.12-0.43) and the speed of processing intervention for speed of processing performance (effect size, 0.85; 99% CI, 0.61-1.09).

**Conclusions:** Reasoning training resulted in less functional decline in self-reported IADL. Compared with the control group, cognitive training resulted in improved cognitive abilities specific to the abilities trained that continued 5 years after the initiation of the intervention.

**Trial Registration:** [clinicaltrials.gov](http://clinicaltrials.gov) Identifier: NCT00298558

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[www.jama.com](http://www.jama.com)

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## La fragilité : un facteur de risque de déclin cognitif et de démence chez le sujet âgé.

La fragilité est un concept nouveau prenant de plus en plus d'importance et découlant à la fois des soins cliniques apportés aux personnes âgées et de la recherche sur le vieillissement. Le terme de « fragilité » est souvent utilisé pour faire référence aux personnes âgées vulnérables, incapables de résister à des agressions telles que des perturbations du milieu environnant, des blessures ou des maladies aiguës. Ces agressions risquent de provoquer un cercle vicieux où la personne âgée fragile ne réussit pas à se rétablir et à revenir à son état de santé antérieur. Les handicaps physiques et/ou psychosociaux semblent être les principaux facteurs de fragilité des sujets âgés. Actuellement, des études montrent que la fragilité est un facteur de risque de déclin cognitif et de maladie d'Alzheimer chez les sujets âgés (*Références : Buchman AS et al, Psychomatic Medicine 2007 ; 69 : 483-489 ; Samper-Ternent et al, J Am Geriatr Soc 2008 : 1-8*). Une association a également été retrouvée entre la fragilité et les lésions cérébrales caractéristiques de la maladie d'Alzheimer chez des sujets âgés (*Référence : Buchman AS et al, Neurology 2008 ; 71 : 499-504*).

### Frailty is Associated With Incident Alzheimer's Disease and Cognitive Decline in the Elderly

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**Objective:** To assess the association between frailty and incident Alzheimer's disease (AD) and cognitive decline. Frailty is common in older persons and associated with adverse health outcomes. **Methods:** Study subjects included 823 older persons without dementia who participated in the Rush Memory and Aging Project, a longitudinal study of aging, and underwent annual assessments of frailty, cognition, and diagnostic evaluation for AD. **Results:** During a 3-year follow-up, 89 of 823 participants developed AD. In a proportional hazards model, both baseline level of frailty and annual rate of change in frailty were associated with an increased risk of incident AD. Each additional one tenth of a unit increase on the frailty scale at baseline was associated with >9% increased risk of AD (hazard ratio: 2.44; 95% confidence interval (CI): 1.49, 3.37); each one tenth of a unit increase in annual rate of change in frailty was associated with a 12% increased risk of AD (hazard ratio: 3.30; 95% CI: 1.52, 7.13). These results were unchanged in analyses controlling for vascular risk factors and vascular diseases. Results were similar with a categorical measure of frailty instead of a continuous measure. Further, linear mixed-effects models showed that the level of and rate of change in frailty were also associated with the rate of cognitive decline. **Conclusion:** Increasing frailty is associated with incident AD and the rate of cognitive decline in older persons. These findings suggest that frailty and AD may share similar etiologies. **Key words:** aging, frailty, cognitive decline, Alzheimer's disease, dementia.

## Physical frailty in older persons is associated with Alzheimer disease pathology

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### ABSTRACT

**Objective:** We examined the extent to which physical frailty in older persons is associated with common age-related brain pathology, including cerebral infarcts, Lewy body pathology, and Alzheimer disease (AD) pathology.

**Methods:** We studied brain autopsies from 165 deceased participants from the Rush Memory and Aging Project, a longitudinal clinical-pathologic study of aging. Physical frailty, based on four components, including grip strength, time to walk 8 feet, body composition, and fatigue, was assessed at annual clinical evaluations. Multiple regression analyses were used to examine the relation of postmortem neuropathologic findings to frailty proximate to death, controlling for age, sex, and education.

**Results:** The mean age at death was 88.1 years (SD = 5.7 years). The level of AD pathology was associated with frailty proximate to death ( $\beta = 0.252$ , SE = 0.077,  $p = 0.001$ ), accounting for 4% of the variance of physical frailty. Neither cerebral infarcts ( $\beta = -0.121$ , SE = 0.115,  $p = 0.294$ ) nor Lewy body disease pathology ( $\beta = 0.07$ , SE = 0.156,  $p = 0.678$ ) was associated with frailty. These associations were unchanged after controlling for the time interval from last clinical evaluation to autopsy. The association of AD pathology with frailty did not differ by the presence of dementia, and this association was unchanged even after considering potential confounders, including physical activity; parkinsonian signs; pulmonary function; or history of chronic diseases, including vascular risk factors, vascular disease burden, falls, joint pain, or use of antipsychotic or antihypertensive medications.

**Conclusion:** Physical frailty in old age is associated with Alzheimer disease pathology in older persons with and without dementia. *Neurology*® 2008;71:499-504



## Relationship Between Frailty and Cognitive Decline in Older Mexican Americans

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**OBJECTIVES:** To examine the association between frailty status and change in cognitive function over time in older Mexican Americans.

**DESIGN:** Data used were from the Hispanic Established Population for the Epidemiological Study of the Elderly.

**SETTING:** Five southwestern states: Texas, New Mexico, Colorado, Arizona, and California.

**PARTICIPANTS:** One thousand three hundred seventy noninstitutionalized Mexican-American men and women aged 65 and older with a Mini-Mental State Examination (MMSE) score of 21 or higher at baseline (1995/96).

**MEASUREMENTS:** Frailty, defined as three or more of the following components: unintentional weight loss of more than 10 pounds, weakness (lowest 20% in grip strength), self-reported exhaustion, slow walking speed (lowest 20% in 16-foot walk time in seconds), and low physical activity level (lowest 20% on Physical Activity Scale for the Elderly score). Information about sociodemographic factors, MMSE score, medical conditions (stroke, heart attack, diabetes mellitus, arthritis, cancer, and hypertension), depressive symptoms, and visual impairment was obtained.

**RESULTS:** Of the 1,370 subjects, 684 (49.9%) were not frail, 626 (45.7%) were prefrail (1–2 components), and 60 (4.4%) were frail ( $\geq 3$  components) in 1995/96. Using general linear mixed models, it was found that frail subjects had greater cognitive decline over 10 years than not frail subjects (estimate =  $-0.67$ , standard error =  $0.13$ ;  $P < .001$ ). This association remained statistically significant after controlling for potential confounding factors.

**CONCLUSION:** Frail status in older Mexican Americans with MMSE scores of 21 or higher at baseline is an independent predictor of MMSE score decline over a 10-year period. Future research is needed to establish pathophysi-

ological components that can clarify the relationship between frailty and cognitive decline. *J Am Geriatr Soc* 2008.

**Key words:** frailty; cognitive decline; Mexican Americans

Frailty is an important clinical and public health problem in older adults that is characterized by vulnerability to stressors, weakness, risk of morbidity, disability, and mortality.<sup>1</sup> The prevalence of frailty increases with age and varies according to ethnicity and sex.<sup>1–3</sup> Research shows that predictors of frailty in older Mexican Americans include sociodemographic variables (e.g., marital status and education), body mass index (BMI), cognitive function, and disability.<sup>4</sup>

The relationship between frailty and cognition across different ethnic groups is unclear and has received little research attention.<sup>5</sup> Some authors have reported significantly lower Mini-Mental State Examination (MMSE) scores in Hispanics than in non-Hispanic whites.<sup>6,7</sup> Several factors have been associated with cognitive decline in older Hispanic adults. Altered executive function was reported in 31.1% of older Mexican Americans based on results from a clock-drawing task.<sup>8</sup> Slow gait speed and weak grip strength were also associated with decline in cognitive function in this population.<sup>9,10</sup> Older age, lower education, and living alone, along with diabetes mellitus, stroke, depression, and visual alterations have been linked to impaired cognition in older Mexican-American adults,<sup>11</sup> but there is no information on the relationship between frailty status and subsequent change in cognitive function.

Given the expected growth in the population of older Mexican-American adults in the United States, it is important to understand the relationship between frailty and health outcomes such as cognition that increase health costs and decrease quality of life. The purpose of this study was to examine the relationship between frailty and cognition over 10 years in a large sample of older Mexican-American adults living in the community. It was hypothesized that

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## Comment participer à l'étude MAPT ?

Le GÉrontopôle recherche des volontaires âgées de 70 ans et plus pour participer à une étude de prévention des troubles de la mémoire.

### **Etude de prévention des troubles de la mémoire chez la personne âgée de 70 ans et plus**

Cette étude a pour objectif d'évaluer le rôle protecteur d'un complément nutritionnel à base d'acides gras oméga-3 et d'une « intervention multidomaine » comprenant des séances d'informations sur :

- « comment entretenir sa mémoire »
- « comment se maintenir en forme physique »
- « comment garder une alimentation équilibrée »
- « comment rester actif »

**Pour plus de renseignements concernant l'étude MAPT, vous pouvez nous contacter**

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MAPT

