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Maladie d'Alzheimer : traiter plus tôt, de la prévention à l'intervention

Julien Delrieu

RENCONTRES MALADIE D'ALZHEIMER

Le 9 Novembre 2018

Toulouse GÉRONTOPÔLE

UMR 1027

Hôpitaux de Toulouse

Quelques questions

- Pourquoi traiter plus tôt?
- Qu’est-ce que la prévention de la MA?
- Quels types d’intervention?

Editorial

Solanezumab: too late in mild Alzheimer's disease?

On Dec 8, 2016, at the Clinical Trials on Alzheimer's Disease (CTAD) meeting in San Diego, CA, USA, Lawrence Honig presented results of EXPEDITION3, a randomised, placebo-controlled phase 3 trial of solanezumab in 2129 patients with mild Alzheimer's disease. Solanezumab was not expected to be a cure for Alzheimer's disease, but many hoped that the drug would be the first treatment to slow disease progression and the first anti-amyloid drug to be brought to the clinic. The negative results of EXPEDITION3 were disappointing for the Alzheimer's disease community and for Eli Lilly, the manufacturer of solanezumab and trial funder. Nevertheless, these findings should not discourage investment in the development and assessment of drugs for Alzheimer's disease.

The decision to do EXPEDITION3 was based on the results of a subgroup analysis of pooled data from the previous phase 3 trials EXPEDITION1 and EXPEDITION2 of solanezumab in patients with mild-to-moderate Alzheimer's disease. Although the previous two trials were negative for the cognitive and functional primary outcomes, this subgroup analysis showed a significant reduction of 34% in cognitive decline at week 80 in individuals with mild Alzheimer's disease in the solanezumab group. However, in reality, the primary endpoint in EXPEDITION3 showed a non-significant 11% reduction in worsening of cognition—assessed with the Alzheimer's Disease Assessment Scale Cognitive 14-item subscale at week 80—in favour of the solanezumab group. This small effect size was weaker than in EXPEDITION1 plus EXPEDITION2.

The best results in terms of effect size and significance presented for EXPEDITION3 were obtained for Clinical Dementia Rating Sum of Boxes, one of the clinical secondary outcomes, which showed a 15% difference between the solanezumab and placebo groups. The other clinical secondary outcomes included change in cognition on the Mini-Mental State Examination and change in activities of daily living on the Alzheimer's Disease Cooperative Study-Instrumental Activities of Daily Living; both showed significant differences in favour of the solanezumab group. The analyses presented at CTAD were not corrected for multiple comparisons. Other analyses are still in progress for EXPEDITION3, including the analysis of CSF amyloid β.

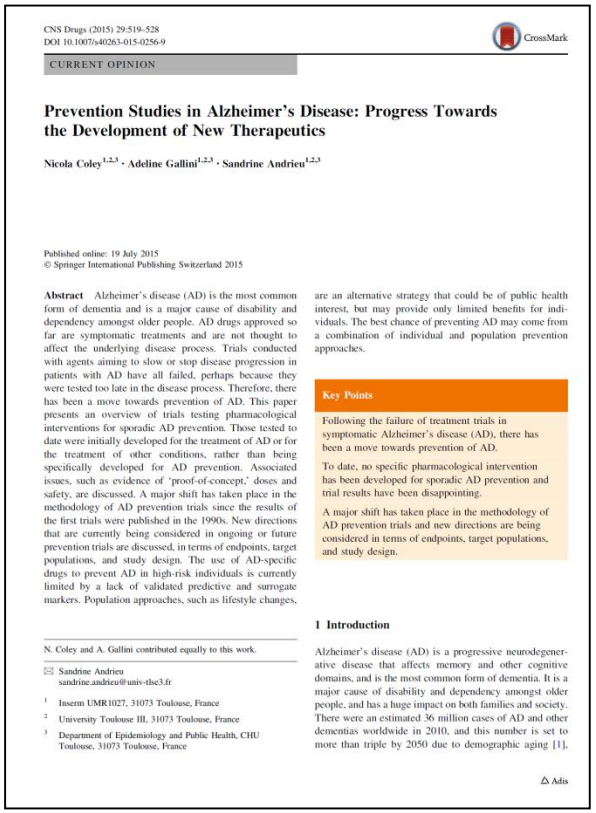
In EXPEDITION3, solanezumab was deemed to be safe because 85% of participants completed treatment and fewer had serious or treatment-emergent adverse events or died in the drug group than in the placebo group. Whether a higher dose of solanezumab than the 400 mg every 4 weeks used in EXPEDITION3 would have resulted in a bigger and significant effect size for the primary outcome is not known, but any discussion about increasing the dose would also need to take safety into consideration.

Solanezumab has been compared with other monoclonal antibodies—including aducanumab—that are also being assessed in Alzheimer's disease. However, as pointed out during the panel discussion of the EXPEDITION3 findings at the CTAD meeting, not all monoclonal antibodies are created equal. Solanezumab recognises soluble, monomeric amyloid β and presumably reduces its concentration in the brain, whereas aducanumab binds to fibrillary amyloid β. Therefore, the results of the solanezumab trials should not be used to forecast the results of trials of other monoclonal antibodies that are in progress.

All three EXPEDITION trials were negative for the primary outcome of change in cognition. A hypothesis put forward at CTAD was that treatment effects would have been larger at an earlier disease stage than at 80 weeks because at this timepoint the disease might have been too advanced; indeed, the ADAS-Cog$_{14}$ results were significantly in favour of solanezumab at weeks 28, 40, 52, and 64.

Solanezumab is also being assessed in individuals with prodromal Alzheimer's disease in the EpreditionPRO trial (NCT02760602), which will be completed in April, 2021, and in the A4 trial (NCT02008357) in people with amyloid plaques in their brains who might be at risk of memory loss and cognitive decline because of Alzheimer's disease. Perhaps the drug will prove to be effective in people who are at an earlier stage of Alzheimer's disease than the participants in EXPEDITION3.

A concerted effort has to be maintained to find a cure for Alzheimer's disease. Investigators and drug companies should be encouraged to be swift in sharing trial results. Disappointing primary outcome results aside, Eli Lilly should be commended for sharing and discussing the findings from EXPEDITION3 at CTAD. The results are hopefully only a temporary setback for the Alzheimer's disease community and drug manufacturers and must not deter the continued investment in the development of treatments for Alzheimer's disease.



CNS Drugs (2015) 29:519–528
DOI 10.1007/s40263-015-0256-9

CURRENT OPINION

Prevention Studies in Alzheimer's Disease: Progress Towards the Development of New Therapeutics

Nicola Coley[1,2,3] · Adeline Gallini[1,2,3] · Sandrine Andrieu[1,2,3]

Published online: 19 July 2015

Abstract Alzheimer's disease (AD) is the most common form of dementia and is a major cause of disability and dependency amongst older people. AD drugs approved so far are symptomatic treatments and are not thought to affect the underlying disease process. Trials conducted with agents aiming to slow or stop disease progression in patients with AD have all failed, perhaps because they were tested too late in the disease process. Therefore, there has been a move towards prevention of AD. This paper presents an overview of trials testing pharmacological interventions for sporadic AD prevention. Those tested to date were initially developed for the treatment of AD or for the treatment of other conditions, rather than being specifically developed for AD prevention. Associated issues, such as evidence of 'proof-of-concept,' doses and safety, are discussed. A major shift has taken place in the methodology of AD prevention trials since the results of the first trials were published in the 1990s. New directions that are currently being considered in ongoing or future prevention trials are discussed, in terms of endpoints, target populations, and study design. The use of AD-specific drugs to prevent AD in high-risk individuals is currently limited by a lack of validated predictive and surrogate markers. Population approaches, such as lifestyle changes, are an alternative strategy that could be of public health interest, but may provide only limited benefits for individuals. The best chance of preventing AD may come from a combination of individual and population prevention approaches.

Key Points

Following the failure of treatment trials in symptomatic Alzheimer's disease (AD), there has been a move towards prevention of AD.

To date, no specific pharmacological intervention has been developed for sporadic AD prevention and trial results have been disappointing.

A major shift has taken place in the methodology of AD prevention trials and new directions are being considered in terms of endpoints, target populations, and study design.

1 Introduction

Alzheimer's disease (AD) is a progressive neurodegenerative disease that affects memory and other cognitive domains, and is the most common form of dementia. It is a major cause of disability and dependency amongst older people, and has a huge impact on both families and society. There were an estimated 36 million cases of AD and other dementias worldwide in 2010, and this number is set to more than triple by 2050 due to demographic aging [1].

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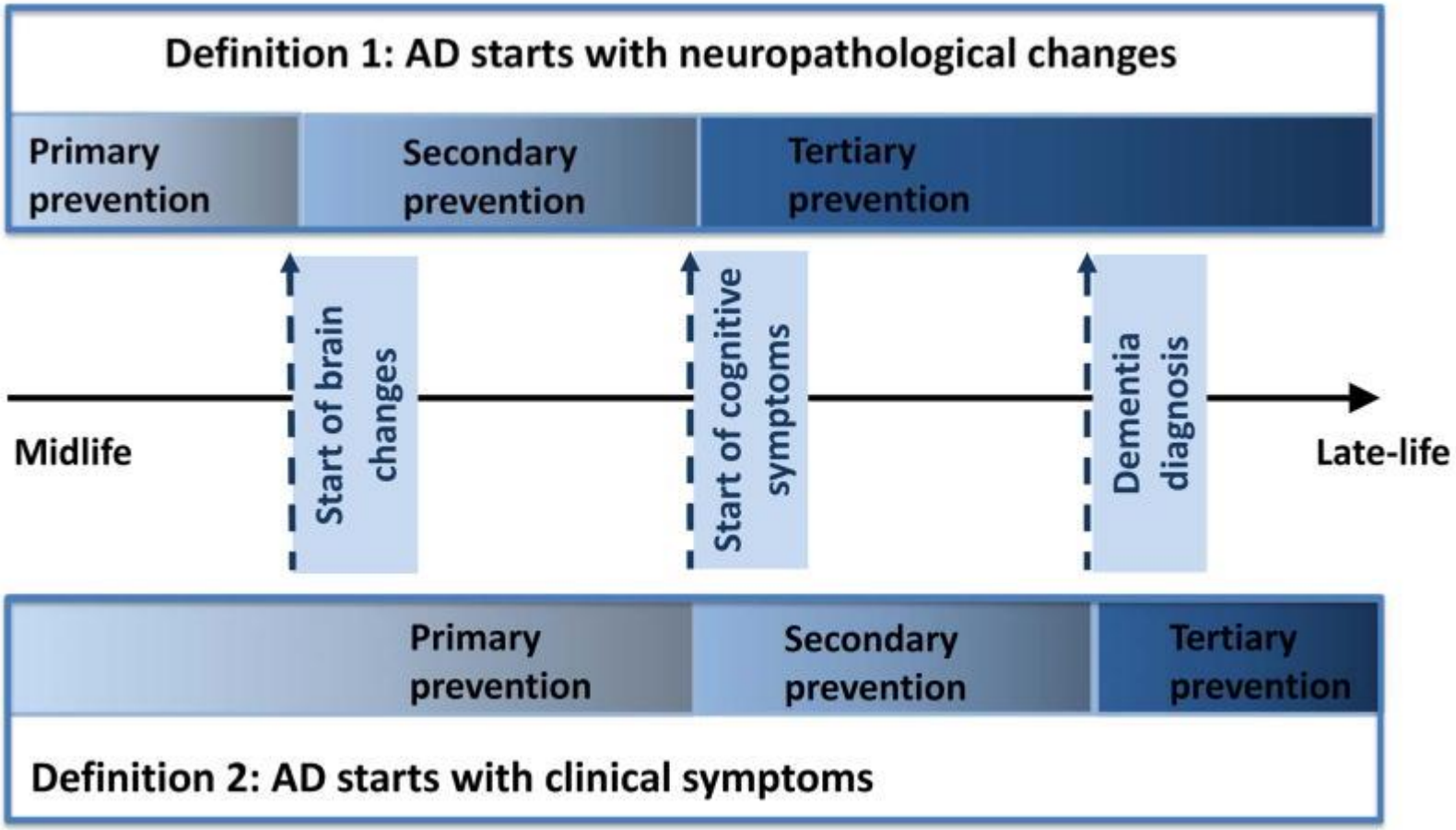
De la prévention primaire à secondaire

VERS UN NOUVEAU PARADIGME: TRAITER PLUS TÔT

Prévention et MA

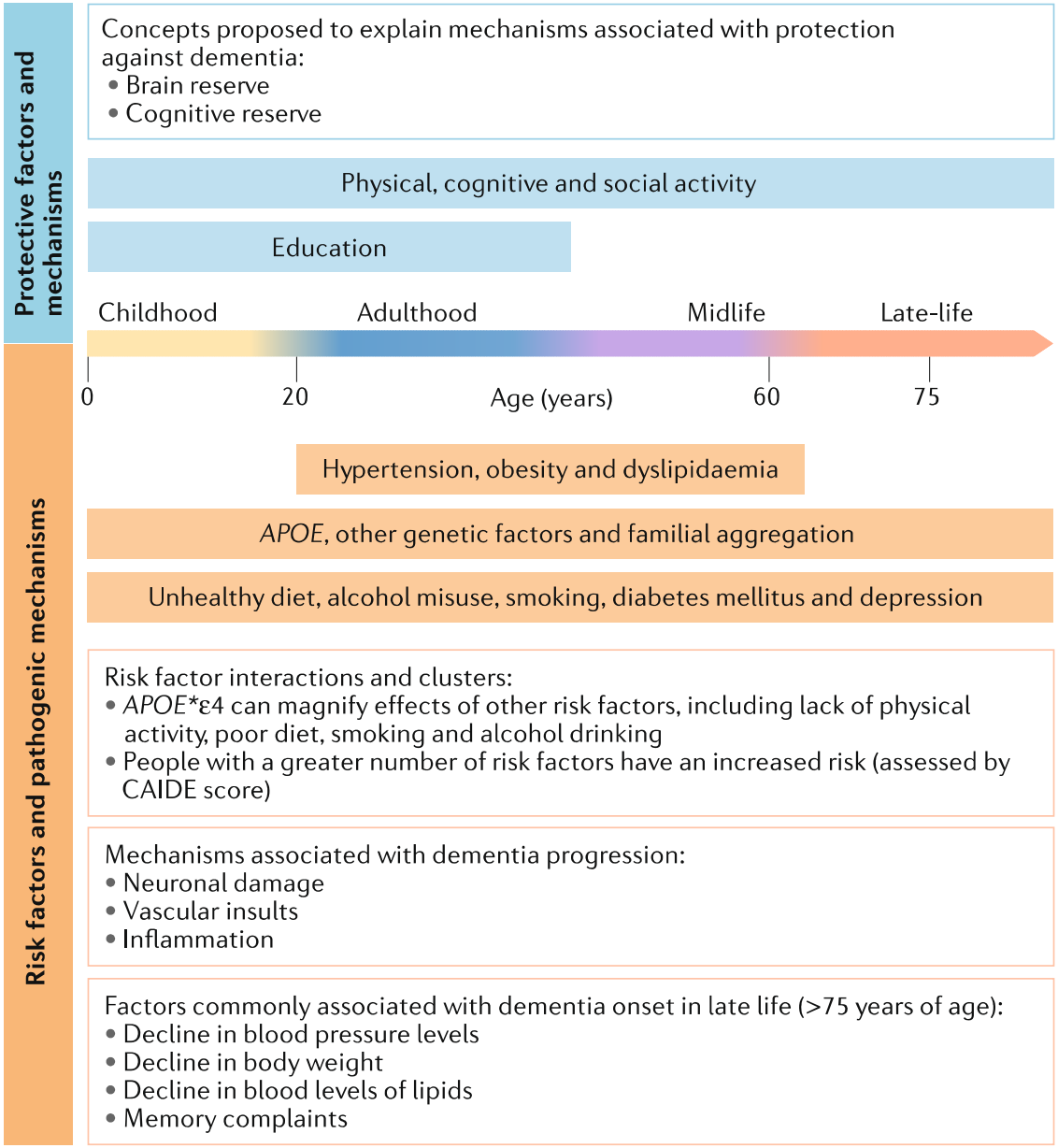


Les thérapies ciblées vs « life style »

	Life style/Population	Thérapies ciblées/volontaires sélectionnés
Avantages	- Nombre important de sujets à traiter - Facile à identifier (pas de nécessité de biomarqueurs)	- Mise en évidence par biomarqueur des mécanismes physiopathologiques: homogénéité - Bénéfice potentiel important à l'échelon individuel
Inconvénients	- Coût de l'intervention - Diagnostic incertain (population hétérogène)	- Nombre limité de sujets - Nécessité de biomarqueurs (disponibilité, acceptabilité, coût, standardisation)
Stratégies de traitement	• "Symptomatique" pour les stades légers à modérés de MA clinique • Prevention (Multidomaine intervention)	• Intervention ciblée aux stades précoces et très précoces de la MA

Ousset et al. Should interventions to treat or prevent Alzheimer's disease be tested in a population or as targeted treatment of highly selected study participants? Alzhiemer Res Ther 2013.

LES ETUDES « LIFE STYLE »



The CAIDE dementia risk score

Risk factor		Points
Age	<47 years	0
	47–53 years	3
	>53 years	4
Education	≥10 years	0
	7–9 years	2
	<7 years	3
Sex	Female	0
	Male	1
Blood pressure	≤140 mmHg	0
	>140 mmHg	2
BMI	≤30 kg/m^2	0
	>30 kg/m^2	2
Total cholesterol	≤6.5 mmol/l	0
	>6.5 mmol/l	2
Physical activity	Yes	0
	No	1

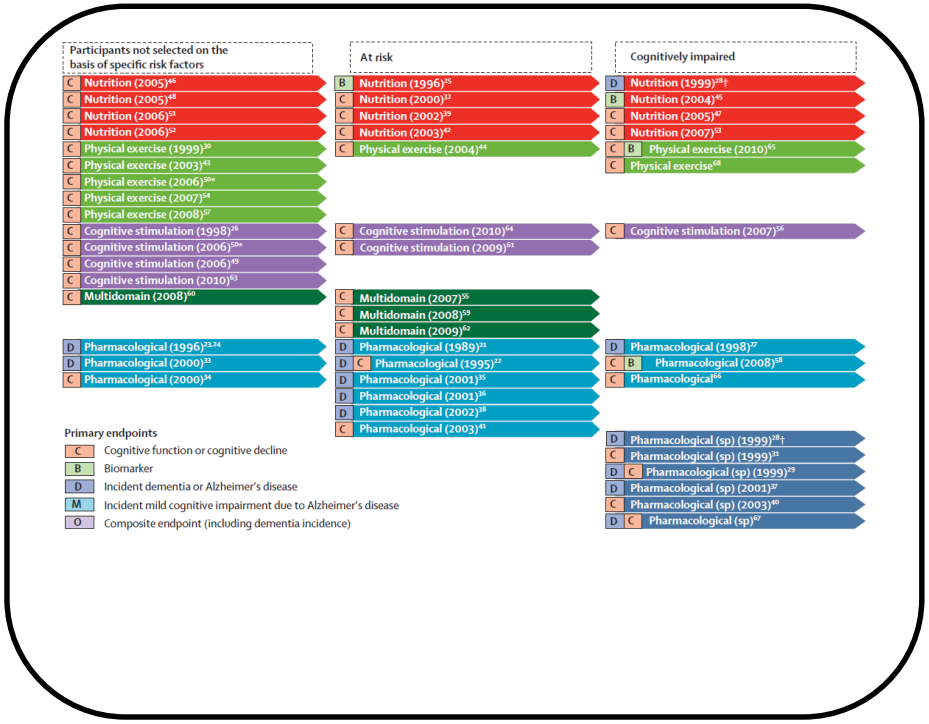
Kivipelti m et al. Lifestyle interventions to prevent cognitive impairment, dementia and Alzheimer disease. Nature Reviews Neurology 2018.

Les RCTs simple-domaine

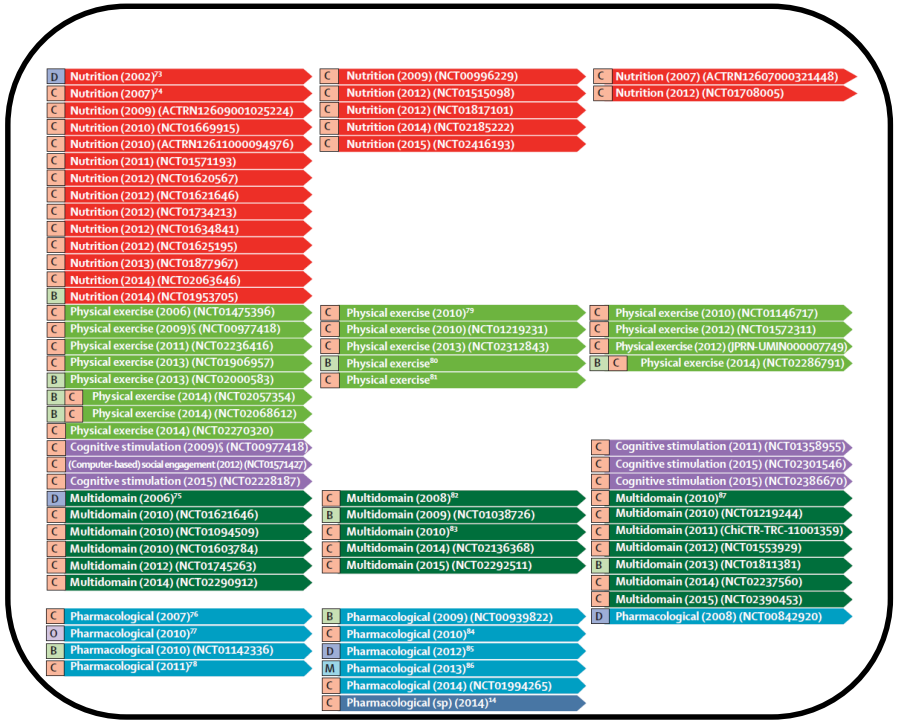
Etudes	Intervention/durée	Population	Outcome	Objectif principal	Autres résultats
Interventions nutritionnelles					
OPAL (UK)	200 mg EPA + 500 mg DHA/24 mois	867, 70-79 ans	CVLT	Pas de différence significative	Pas de différence sur les autres tests cognitifs
Interventions « activité physique »					
LIFE (US)	Intervention d'intensité modérée (marche)/24 mois	1635, 70-89 ans avec sédentarité	Incapacité motrice majeure Tests cognitifs en critères secondaires	Effet sur l'incapacité motrice majeure	Pas de différence sur les tests cognitifs
Interventions « stimulation cognitive »					
ACTIVE (US)	Entrainement mémoire vs raisonnement vs vitesse de traitement/2 ans mais suivi à 5 et 1O ans	2802, >65 ans	Activités de la vie quotidienne Mémoire épisodique, raisonnement, vitesse de traitement	**Chaque intervention est efficace sur la capacité cognitive ciblé, effet durable à 2 et 5 ans**	Pas d'impact sur l'incidence de démence à 5 ans, effet positif à 10 ans de l'intervention vitesse de traitement et raisonnement
IHAMS (US)	Entrainement vitesse de traitement informatisé/1 an	681, >50 ans, internet	Mesure d'attention TMT-A et –B, stroop, COWAT, DVT, SDMT	**Effet d'amplitude légère à moyenne**	Effets sur les outcomes secondaires sur le plan cognitif

Les interventions spécifiques s'intègrent de plus en plus dans une intervention multidomaine

Essais publiés



Essais en cours et/ou non publiés



Andrieu S, Coley N, Lovestone S, Aisen PS, Vellas B.
Prevention of sporadic Alzheimer's disease: lessons learned from clinical trials and future directions. Lancet Neurol. 2015

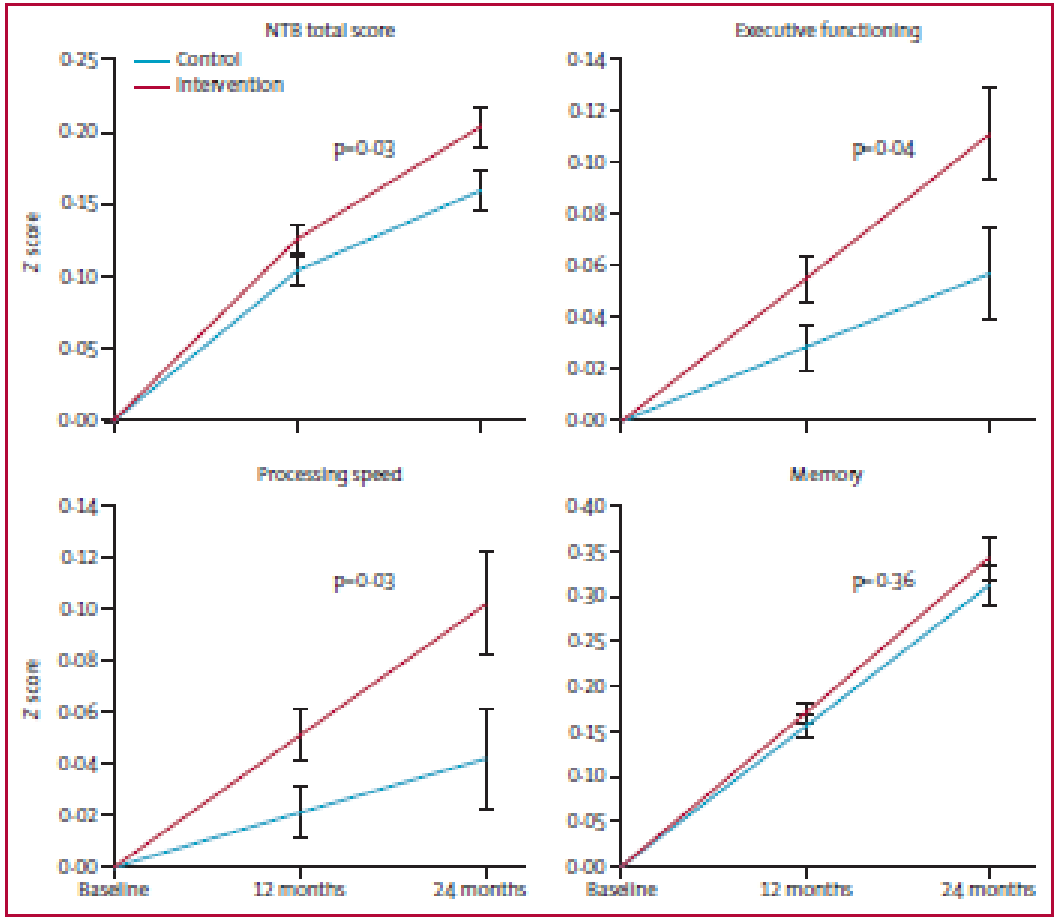
Études européennes de prévention des troubles cognitifs

Crous-Bou *et al. Alzheimer's Research & Therapy* (2017) 9:71

Études	FINGER	MAPT	PreDIVA
Population	1282 PA au domicile 70 – 78 ans	1686 PA au domicile > 70 ans	3533 PA au domicile 70 -78 ans
Critères d'inclusion	CAIDE Risque de démence FDR cardiovasculaires	Fragilité : plainte mémoire subjective, lenteur à la marche, limitation aux IADL	PA non démentes bénéficiant d'un suivi par des médecins généralistes
Intervention multidomaine	**Ateliers** avec exercice physique, stimulation cognitive, activités sociales, prise en charge des facteurs de risque vasculaire	**Ateliers** avec exercice physique, stimulation cognitive, activités sociales, prise en charge des facteurs de risque vasculaire (consultation de prévention); **Supplémentation en acides gras oméga-3** (DHA)	**Infirmière** coordonnant la prise en charge vasculaire (incluant le traitement médical des facteurs de risque, des conseils nutritionnels et des recommandations pour la pratique d'activité physique)
Durée	2 ans + 5 ans de suivi	3 ans + 2 ans de suivi	6 ans
Critère de jugement	Évolution des fonctions cognitives	Evolution des fonctions cognitives	Démence, incapacités

Résultats de l'étude FINGER

Amélioration significative des performances cognitives (score composite) dans le groupe multidomaine comparé au groupe témoin à 2 ans. Un effet significatif a également été retrouvé dans le groupe multidomaine pour chacun des domaines cognitifs suivants : les fonctions exécutives et la vitesse d'exécution des tâches



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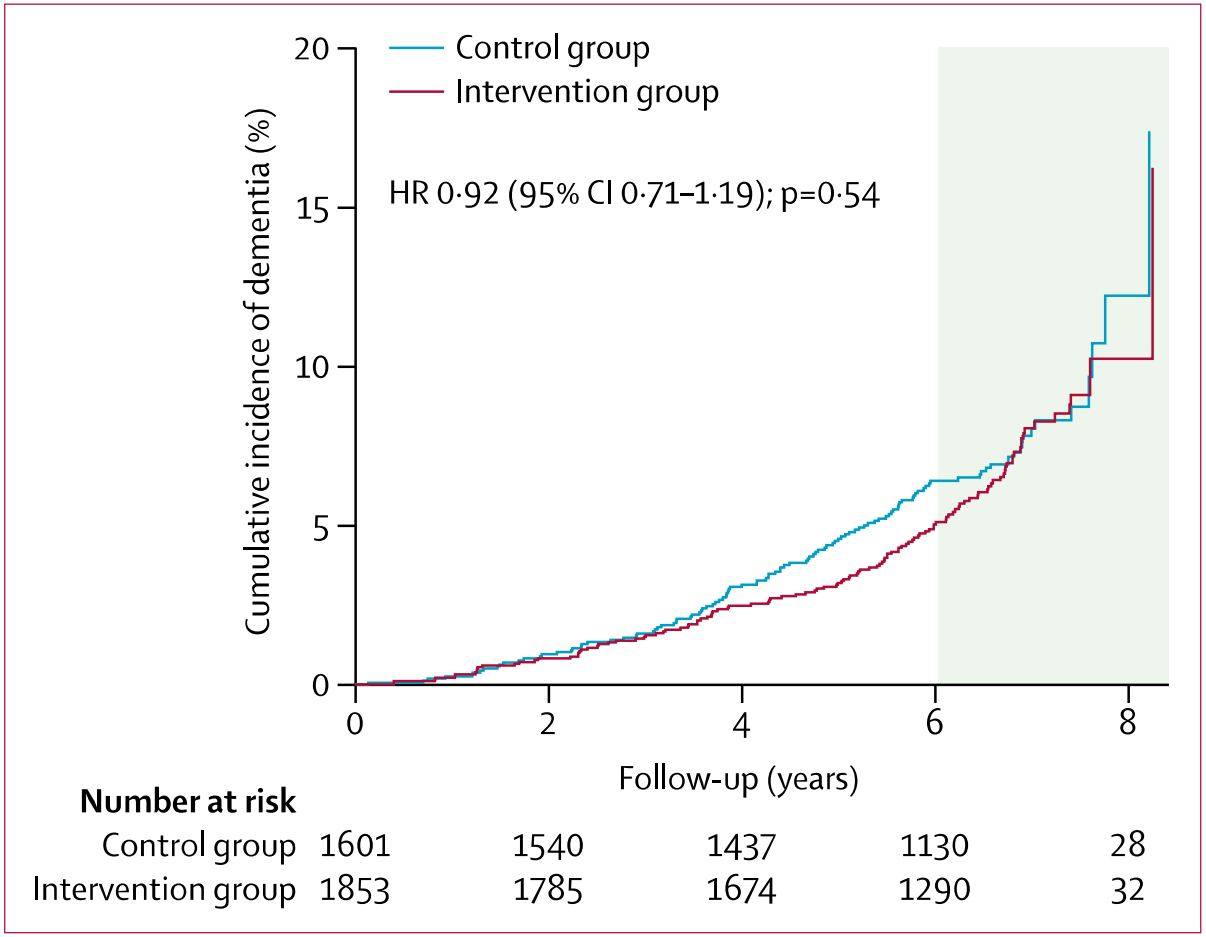
Résultats de l'étude preDIVA



Effectiveness of a 6-year multidomain vascular care intervention to prevent dementia (preDIVA): a cluster-randomised controlled trial.

Eric P Moll van Charante et al. Lancet 2016.

Études européennes de prévention des troubles cognitifs

Crous-Bou *et al. Alzheimer's Research & Therapy* (2017) 9:71

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Critères d'inclusion	CAIDE Risque de démence FDR cardiovasculaires	Fragilité : plainte mémoire subjective, lenteur à la marche, limitation aux IADL	PA non démentes bénéficiant d'un suivi par des médecins généralistes
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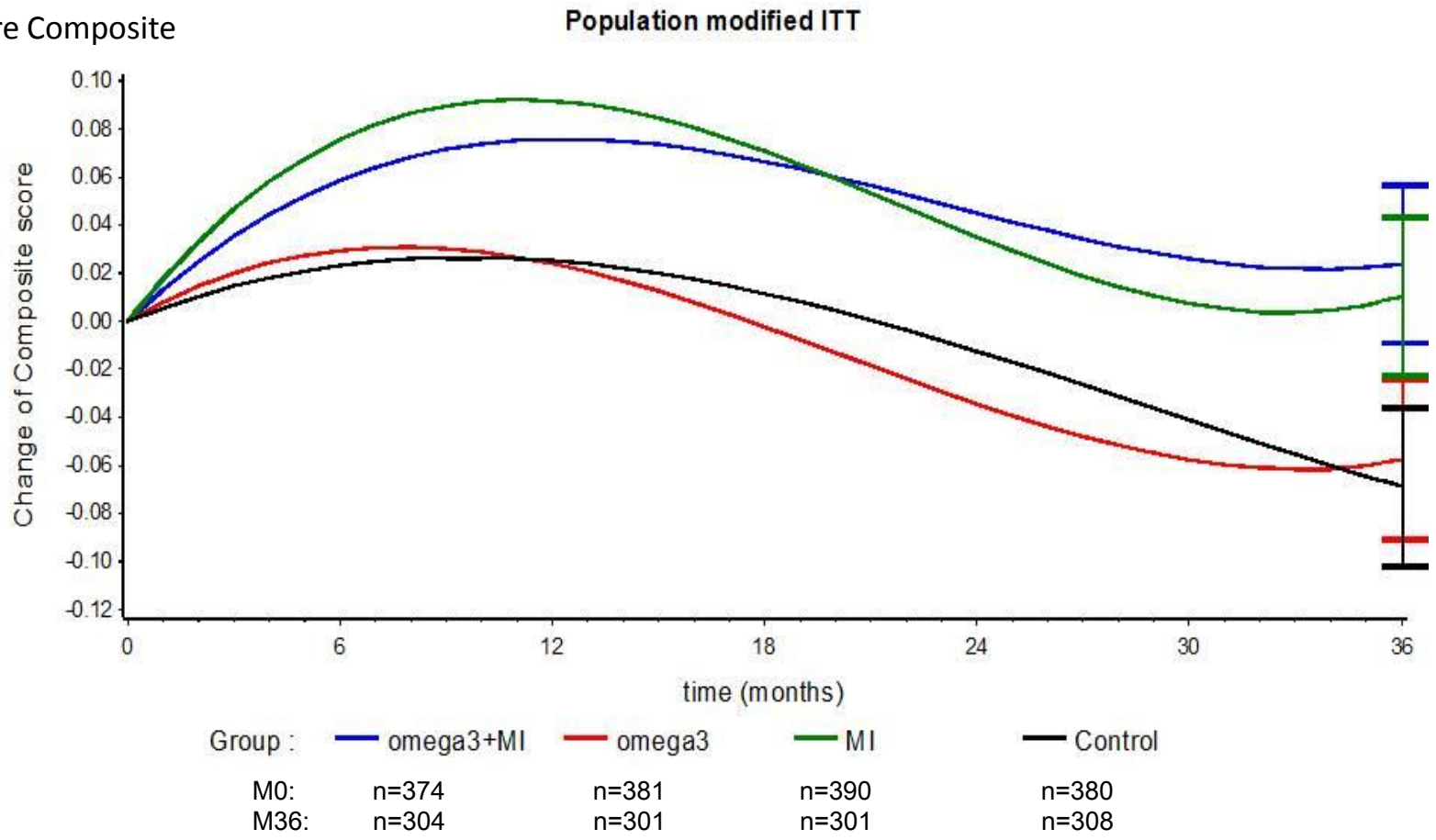
Durée	2 ans + 5 ans de suivi	3 ans + 2 ans de suivi	6 ans
Critère de jugement	Évolution des fonctions cognitives	Evolution des fonctions cognitives	Démence, incapacités

MAPT: Critère Principal ITT (N=1525)

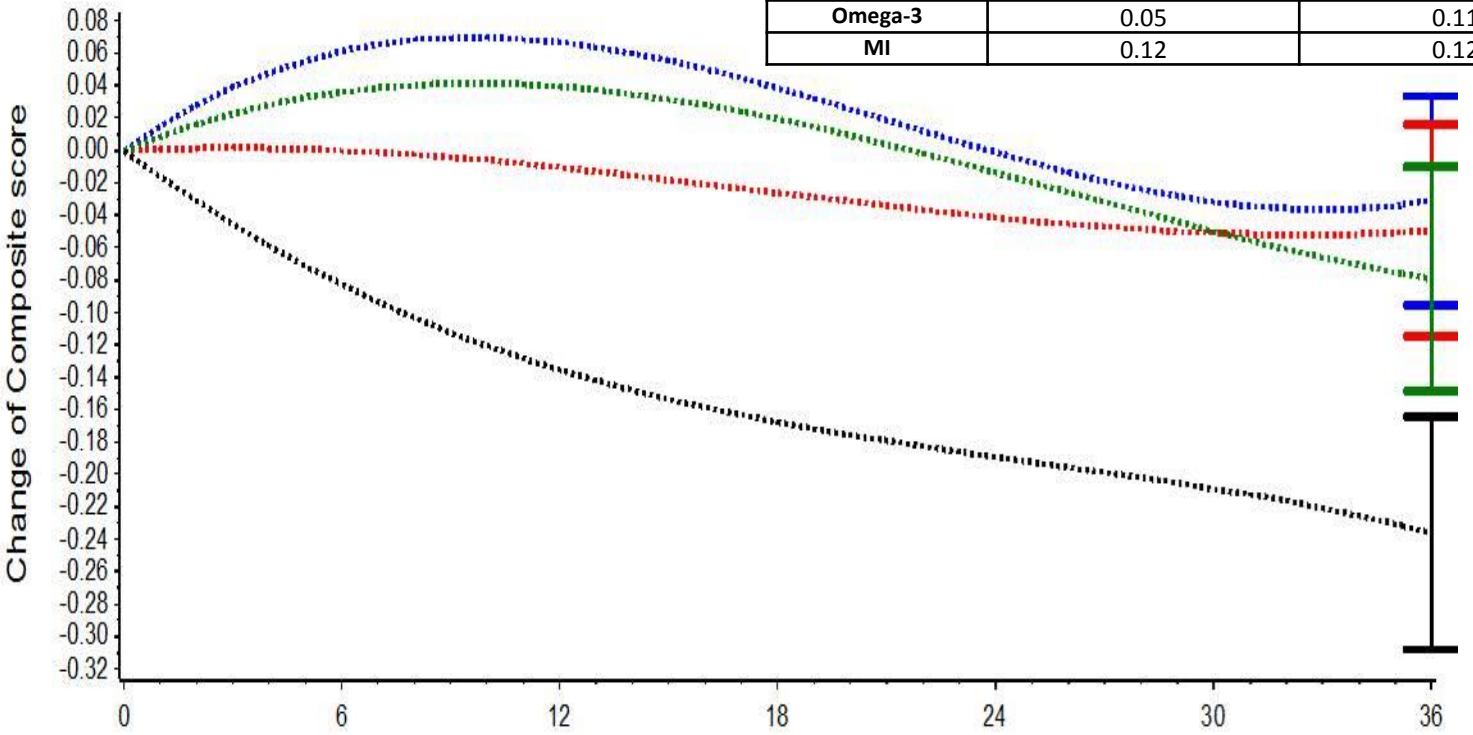
Group	Mean change from baseline to 36 months (95% CI)	Mean difference (95% CI) vs placebo	P value (raw)	P value (Hochberg)
Omega3 + MI	0.02 (-0.04 ; 0.09)	0.09 (0.00 ; 0.18)	0.0473	0.1419
Omega-3	-0.06 (-0.12 ; 0.01)	0.01 (-0.08 ; 0.10)	0.8121	0.8121
MI	0.01 (-0.05 ; 0.07)	0.08 (-0.01 ; 0.17)	0.0896	0.1792

Score Composite



MAPT: Critère principal ITT
Sous-groupe “DHA érythrocytaire bas”

Group	P value (raw)	P value (Hochberg)
Omega-3 + MI	0.03	0.1
Omega-3	0.05	0.11
MI	0.12	0.12



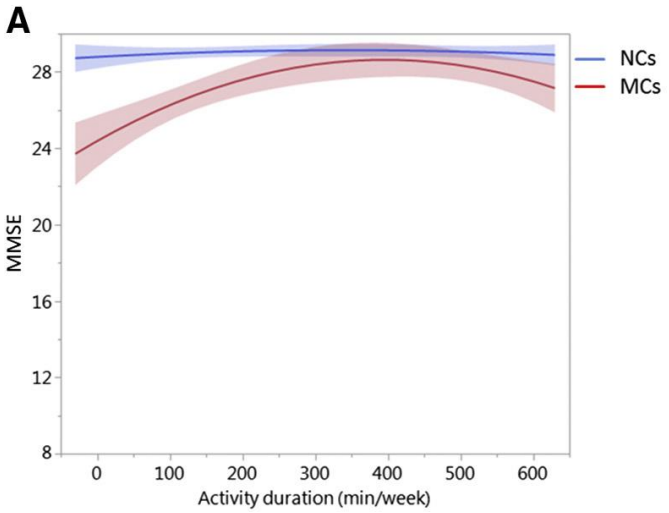
M0:	n=96	n=98	n=83	n=85
M36:	n=75	n=73	n=64	n=59

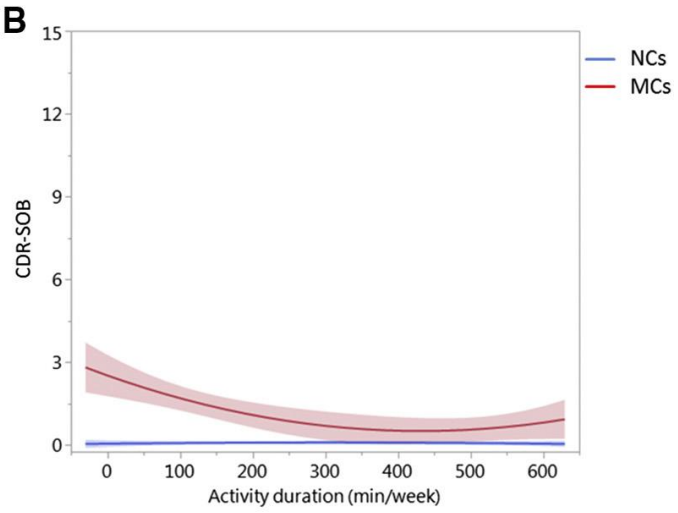
Perspectives : Étude LO-MAPT

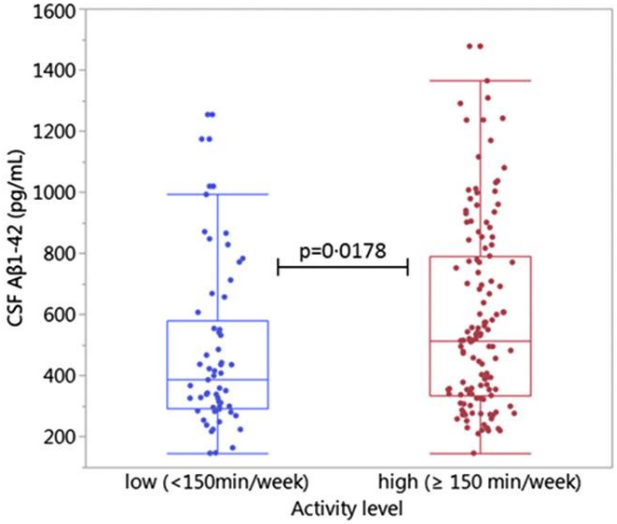
- PREVENTION OF COGNITIVE DECLINE IN OLDER ADULTS WITH LOW DHA/EPA INDEX IN RED BLOOD CELLS

Acronym : LO MAPT (Low OMega 3 Alzheimer Preventive Trial)

L'activité physique dans la MA asymptomatique? Que dit DIAN?







Muller et al. Relationship between physical activity, cognition, and Alzheimer pathology in autosomal dominant Alzheimer's disease. Alzheimer and dementia 2018.

Les interventions life style chez les sujets APO-E4 positifs? Que dit FINGER?

Cognitive End Point by *APOE* ε4 Carrier Status	Mean (SE) Change[a]		Difference Between Intervention and Control Groups per Year[b]		Difference Between Carriers and Noncarriers per Year (Intervention × Time × *APOE*)	
	Control	Intervention	Estimate (95% CI)	*P* Value	Estimate (95% CI)	*P* Value
NTB total score (primary end point)						
Carrier	0.096 (0.025)	0.170 (0.027)	0.037 (0.001 to 0.073)	.045	0.023 (−0.021 to 0.067)	.30
Noncarrier	0.194 (0.018)	0.222 (0.018)	0.014 (−0.011 to 0.039)	.28		
Executive functioning (secondary end point)						
Carrier	0.016 (0.032)	0.105 (0.034)	0.045 (−0.002 to 0.091)	.059	0.022 (−0.034 to 0.078)	.44
Noncarrier	0.079 (0.023)	0.123 (0.023)	0.022 (−0.010 to 0.054)	.17		
Processing speed (secondary end point)						
Carrier	0.010 (0.035)	0.077 (0.037)	0.034 (−0.015 to 0.083)	.18	0.013 (−0.047 to 0.073)	.68
Noncarrier	0.051 (0.025)	0.093 (0.024)	0.021 (−0.013 to 0.055)	.22		
Memory (secondary end point)						
Carrier	0.200 (0.042)	0.285 (0.044)	0.042 (−0.017 to 0.102)	.16	0.041 (−0.031 to 0.113)	.27
Noncarrier	0.370 (0.030)	0.373 (0.030)	0.001 (−0.040 to 0.043)	.95		
Abbreviated memory (post hoc end point)						
Carrier	0.099 (0.045)	0.239 (0.048)	0.070 (0.006 to 0.135)	.03	0.048 (−0.030 to 0.127)	.22
Noncarrier	0.207 (0.033)	0.250 (0.032)	0.022 (−0.023 to 0.066)	.34		

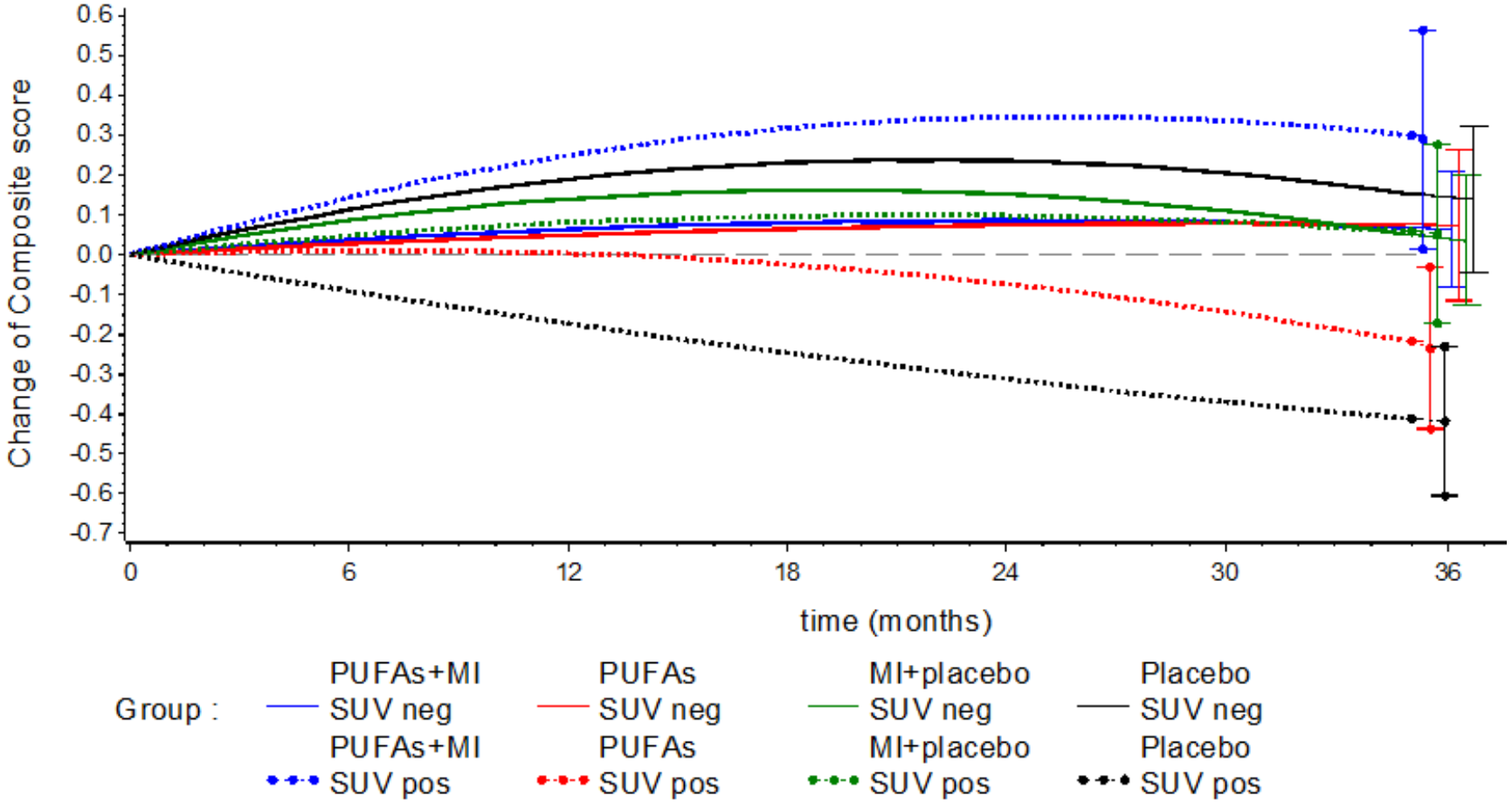
Abbreviations: *APOE*, apolipoprotein E; NTB, Neuropsychological Test Battery.

[a] A positive mean change indicates improvement.

[b] A positive value of the estimate of differences between intervention and control groups indicates the effect is in favor of the intervention group.

Salomon et al. Effect of the Apolipoprotein E Genotype on Cognitive Change During a Multidomain Lifestyle Intervention A Subgroup Analysis of a Randomized Clinical Trial. JAMA Neurol 2018.

Les interventions life style chez les sujets « amyloïde » positifs? Que dit MAPT?



Perspectives: Etude MIND-AD mini

Intervention

- **Intervention multidomaine** adaptée de l'étude FINGER
- **+/- Supplémentation**: EPA/DHA, uridine monophosphate, choline, vitamins B12, B6, C, E, acide folique, phospholipides

Populations cible

- **MA prodromale** (LCR ou TEP ou IRM)
- **Index life style > ou égal à 3**
  - Activité physique < 2,5 heures par semaine
  - Diet : < 5 portions de fruits et légumes par jour
  - Diet : < 2 portions de poissons par semaine
  - HTA
  - Diabète de type 1 ou 2
  - Symptômes en cours/ troubles de du sommeil, symptômes dépressifs, stress psychologique depuis au moins 1 mois

LES ETUDES DE THERAPIES CIBLÉES

Les stades précoces de la MA

LIVRE BLANC

- Stade démentiel léger?
- Stade prodromal
- Stade asymptomatique

LES DIFFERENTS CRITERES

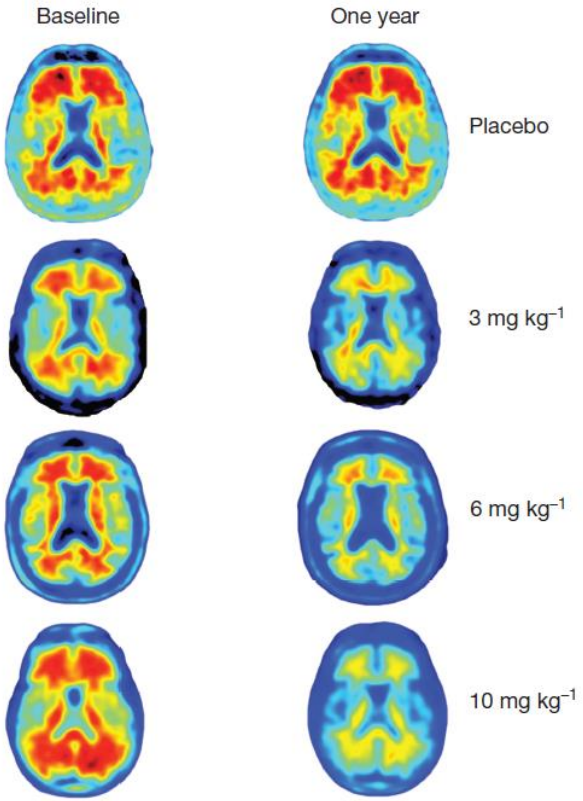
- MA prodromale
- MCI due to AD
- Asymptomatique à risque de MA
- MA pré-symptomatique
- Stades précliniques de MA (stades 1, 2 et 3)

Dubois et al. A new lexicon. Lancet Neurol 2010.
Albert et al. The diagnosis of MCI due to AD. Alzheimer and dementia 2011.
Sperling et al. Toward defining the preclinical stages of Alzheimer's disease. Alzheimer and dementia 2011.
Dubois et al. Preclinical Alzheimer's disease: Definition, natural history, and diagnostic criteria. Alzheimers Dement. 2016.

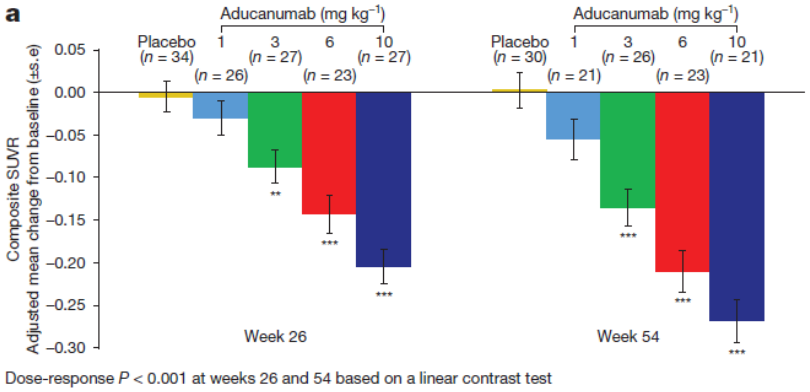
QUELQUES RÉSULTATS ENCOURAGEANTS

Effet de l'aducanumab sur la pathologie amyloïde

Effet sur la charge amyloïde à 1 an



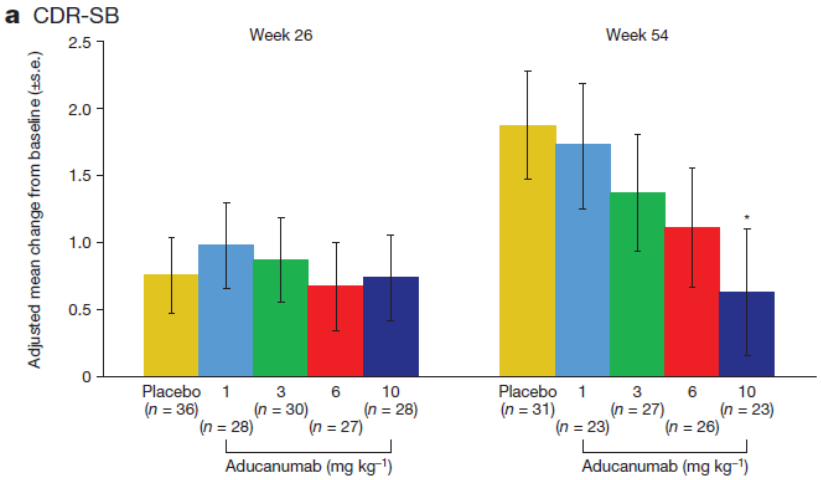
Effet en fonction de la dose



Jeff Sevigny et al. The antibody aducanumab reduces Aß plaques in Alzheimer's disease. Nature 2016.

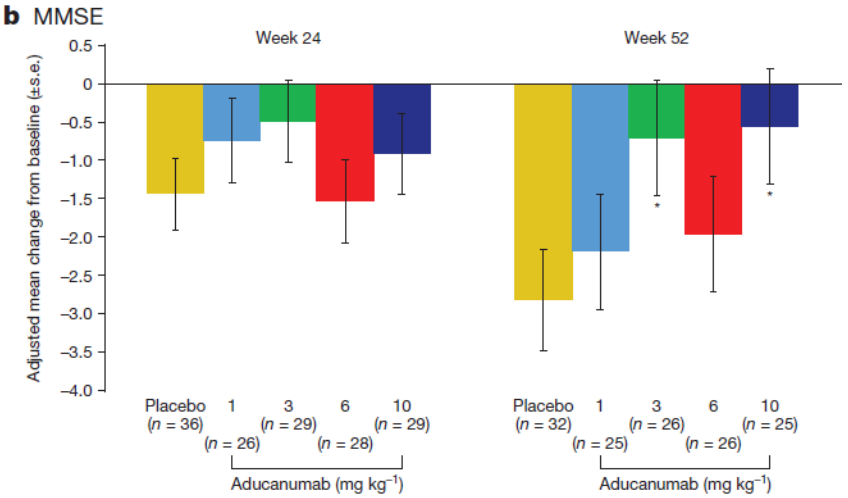
Impact clinique de l'aducanumab

Impact sur la CDR-SB



Dose-response $P < 0.05$ at week 54 based on a linear contrast test

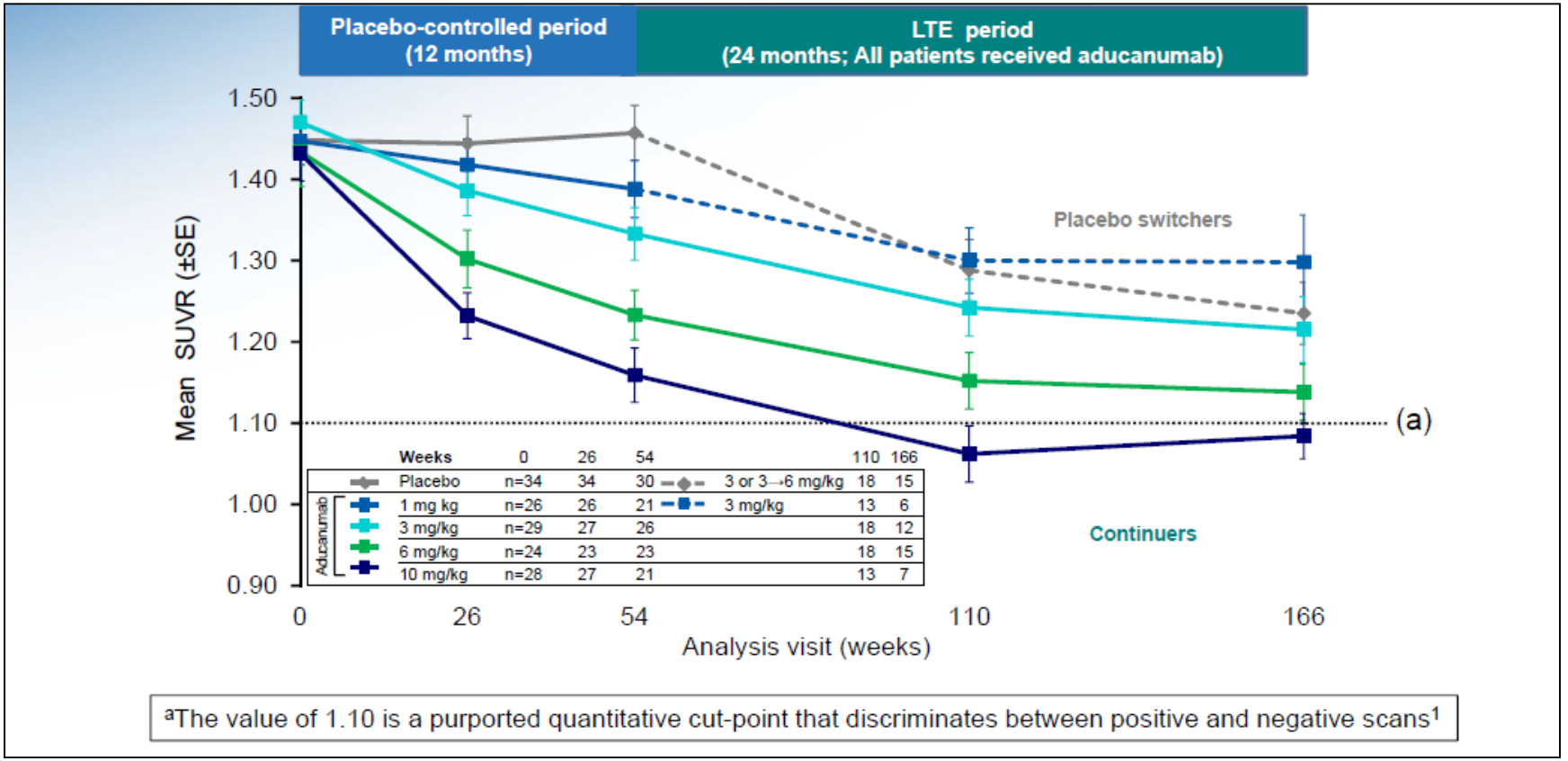
Impact sur le MMSE



Dose-response $P < 0.05$ at week 52 based on a linear contrast test

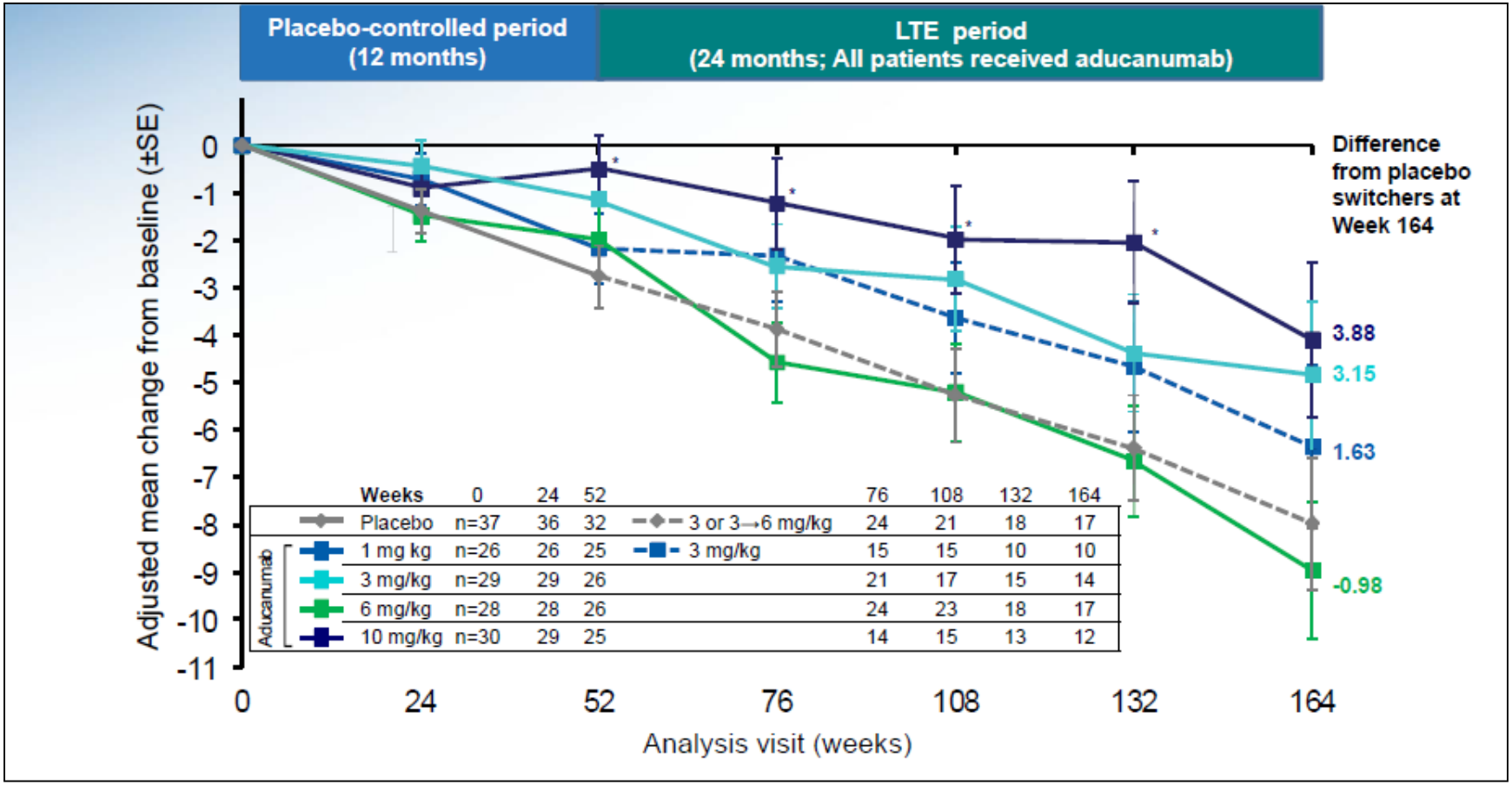
Jeff Sevigny et al. The antibody aducanumab reduces Aβ plaques in Alzheimer's disease. Nature 2016.

Effet de l'aducanumab sur la charge amyloïde, PRIME-LTE



[a]The value of 1.10 is a purported quantitative cut-point that discriminates between positive and negative scans[1]

Effet de l'aducanumab sur le MMSE, PRIME-LTE

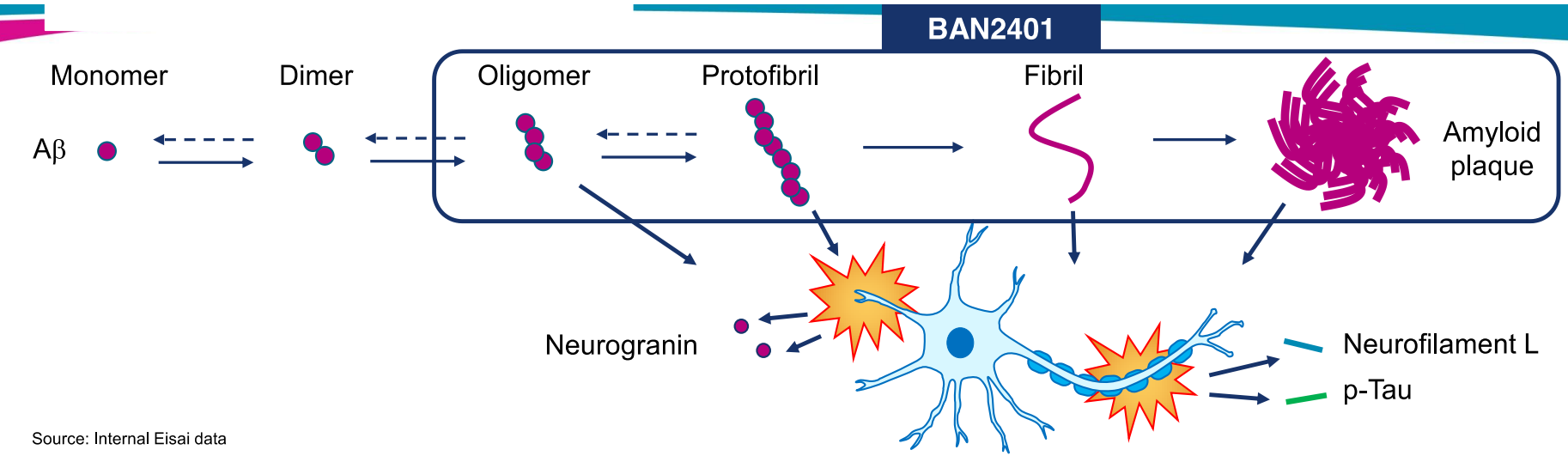


PRIME-LTE à 48 mois

At 48 months from the start of the Phase 1b study:	Adjusted Mean Change from Baseline in Amyloid PET SUVR*	Adjusted Mean Change from Baseline in CDR-SB	Adjusted Mean Change from Baseline in MMSE
Placebo switchers to aducanumab	-0.260	6.95	-10.24
Switchers from 1 to 3 mg/kg	-0.232	8.44	-9.49
3 mg/kg treatment group	-0.261	5.57	-8.22
6 mg/kg treatment group	-0.324	7.75	-12.62
10 mg/kg treatment group	-0.340	3.87	-4.82

* Parameter: Amyloid PET composite ROI SUVR measure (Reference Region = cerebellum)

Le BAN2401



Source: Internal Eisai data

Presented at the 11th Clinical Trials on Alzheimer's Disease (CTAD) Conference October 24-27, 2018

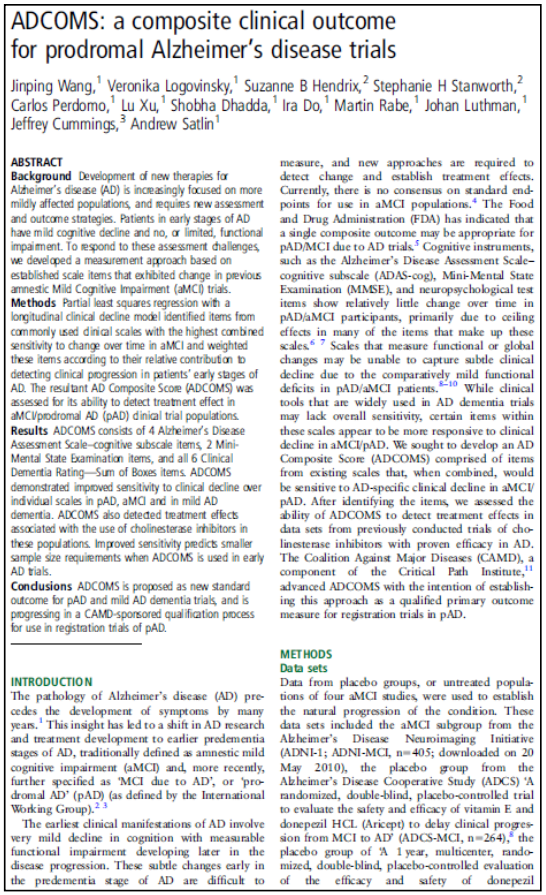
CTAD 2018. Barcelone.

L'étude 201

Critères d'inclusion

- **MA précoce**
  - MCI due to AD ou MA légère
    - Amyloïde + en TEP ou LCR
    - MMSE 22-30
    - CDR globale: 0,5-1

Critère de jugement principal



ADCOMS: a composite clinical outcome for prodromal Alzheimer's disease trials

Jinping Wang,[1] Veronika Logovinsky,[1] Suzanne B Hendrix,[2] Stephanie H Stanworth,[2] Carlos Perdomo,[1] Lu Xu,[1] Shobha Dhadda,[1] Ira Do,[1] Martin Rabe,[1] Johan Luthman,[1] Jeffrey Cummings,[3] Andrew Satlin[1]

ABSTRACT

Background Development of new therapies for Alzheimer's disease (AD) is increasingly focused on more mildly affected populations, and requires new assessment and outcome strategies. Patients in early stages of AD have mild cognitive decline and no, or limited, functional impairment. To respond to these assessment challenges, we developed a measurement approach based on established scale items that exhibited change in previous amnestic Mild Cognitive Impairment (aMCI) trials.

Methods Partial least squares regression with a longitudinal clinical decline model identified items from commonly used clinical scales with the highest combined sensitivity to change over time in aMCI and weighted these items according to their relative contribution to detecting clinical progression in patients' early stages of AD. The resultant AD Composite Score (ADCOMS) was assessed for its ability to detect treatment effect in aMCI/prodromal AD (pAD) clinical trial populations.

Results ADCOMS consists of 4 Alzheimer's Disease Assessment Scale–cognitive subscale items, 2 Mini-Mental State Examination items, and all 6 Clinical Dementia Rating—Sum of Boxes items. ADCOMS demonstrated improved sensitivity to clinical decline over individual scales in pAD, aMCI and in mild AD dementia. ADCOMS also detected treatment effects associated with the use of cholinesterase inhibitors in these populations. Improved sensitivity predicts smaller sample size requirements when ADCOMS is used in early AD trials.

Conclusions ADCOMS is proposed as new standard outcome for pAD and mild AD dementia trials, and is progressing in a CAMD-sponsored qualification process for use in registration trials of pAD.

INTRODUCTION

The pathology of Alzheimer's disease (AD) precedes the development of symptoms by many years.[1] This insight has led to a shift in AD research and treatment development to earlier predementia stages of AD, traditionally defined as amnestic mild cognitive impairment (aMCI) and, more recently, further specified as 'MCI due to AD', or 'prodromal AD' (pAD) (as defined by the International Working Group).[2 3]

The earliest clinical manifestations of AD involve very mild decline in cognition with measurable functional impairment developing later in the disease progression. These subtle changes early in the predementia stage of AD are difficult to measure, and new approaches are required to detect change and establish treatment effects. Currently, there is no consensus on standard endpoints for use in aMCI populations.[4] The Food and Drug Administration (FDA) has indicated that a single composite outcome may be appropriate for pAD/MCI due to AD trials.[5] Cognitive instruments, such as the Alzheimer's Disease Assessment Scale–cognitive subscale (ADAS-cog), Mini-Mental State Examination (MMSE), and neuropsychological test items show relatively little change over time in pAD/aMCI participants, primarily due to ceiling effects in many of the items that make up these scales.[6 7] Scales that measure functional or global changes may be unable to capture subtle clinical decline due to the comparatively mild functional deficits in pAD/aMCI patients.[8–10] While clinical tools that are widely used in AD dementia trials may lack overall sensitivity, certain items within these scales appear to be more responsive to clinical decline in aMCI/pAD. We sought to develop an AD Composite Score (ADCOMS) comprised of items from existing scales that, when combined, would be sensitive to AD-specific clinical decline in aMCI/pAD. After identifying the items, we assessed the ability of ADCOMS to detect treatment effects in data sets from previously conducted trials of cholinesterase inhibitors with proven efficacy in AD. The Coalition Against Major Diseases (CAMD), a component of the Critical Path Institute,[11] advanced ADCOMS with the intention of establishing this approach as a qualified primary outcome measure for registration trials in pAD.

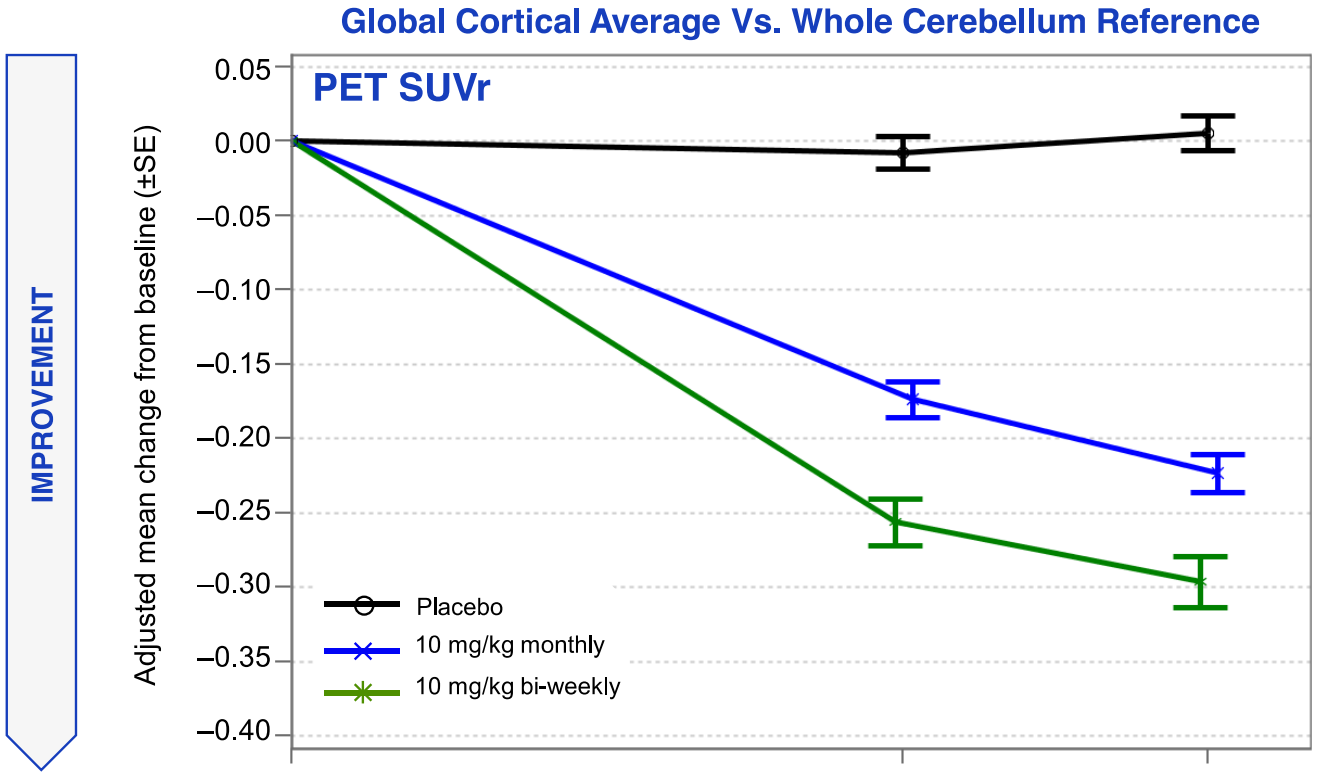
METHODS

Data sets

Data from placebo groups, or untreated populations of four aMCI studies, were used to establish the natural progression of the condition. These data sets included the aMCI subgroup from the Alzheimer's Disease Neuroimaging Initiative (ADNI-1; ADNI-MCI, n=405; downloaded on 20 May 2010), the placebo group from the Alzheimer's Disease Cooperative Study (ADCS) 'A randomized, double-blind, placebo-controlled trial to evaluate the safety and efficacy of vitamin E and donepezil HCL (Aricept) to delay clinical progression from MCI to AD' (ADCS-MCI, n=264),[8] the placebo group of 'A 1 year, multicenter, randomized, double-blind, placebo-controlled evaluation of the efficacy and safety of donepezil

J Neurol Neurosurg Psychiatry. 2016 Sep; 87(9): 993–999.

Impact du BAN2401 sur la charge amyloïde



N with PET data			
Placebo	98	96	88
10 mg/kg monthly	88	88	82
10 mg/kg bi-weekly	44	43	37

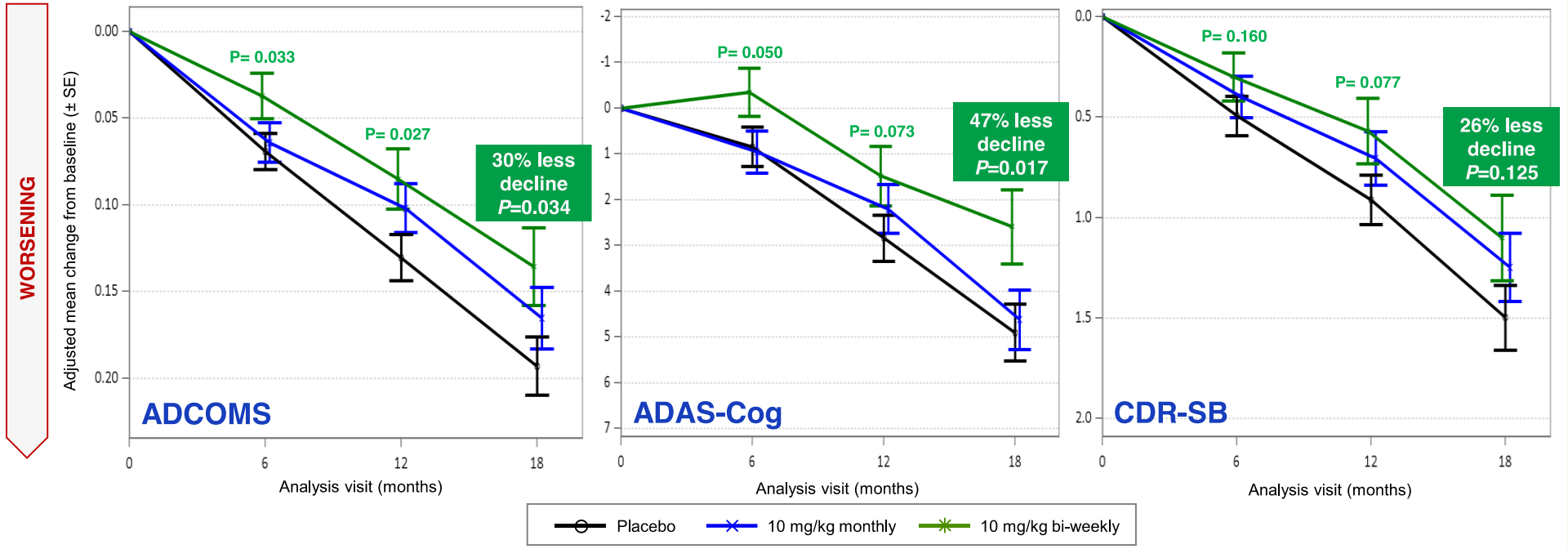
0.01 increase in PET SUVr

0.22 reduction in PET SUVr
***P*<0.0001**

0.30 reduction in PET SUVr
***P*<0.0001**

CTAD 2018. Barcelone.

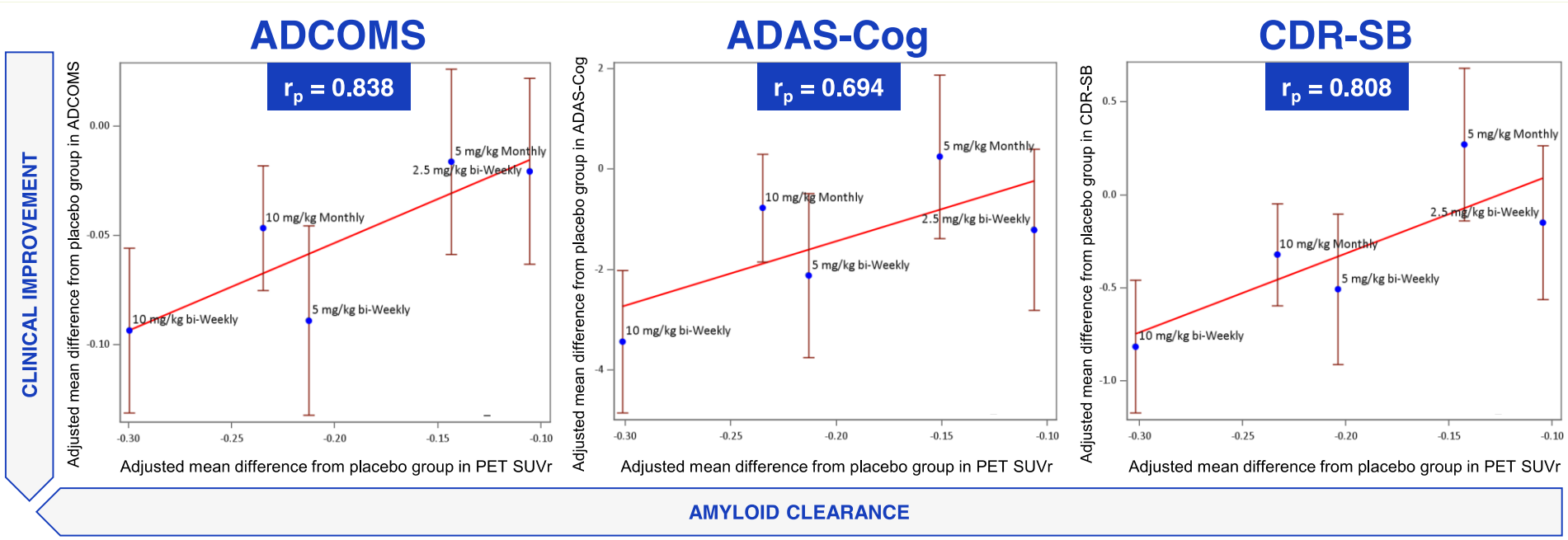
Impact du BAN2401 sur le plan cognitif



N with data	0 mo.	6 mo.	12 mo.	18 mo.
Placebo	238	216	187	160
10 mg/kg monthly	246	208	165	146
10 mg/kg bi-weekly	152	130	93	79

CTAD 2018. Barcelone.

Impact cognitif et charge amyloïde



	2.5 mg/kg bi-weekly	5 mg/kg monthly	5 mg/kg bi-weekly	10 mg/kg monthly	10 mg/kg bi-weekly
N with 18 mo. PET data	23	23	24	82	37

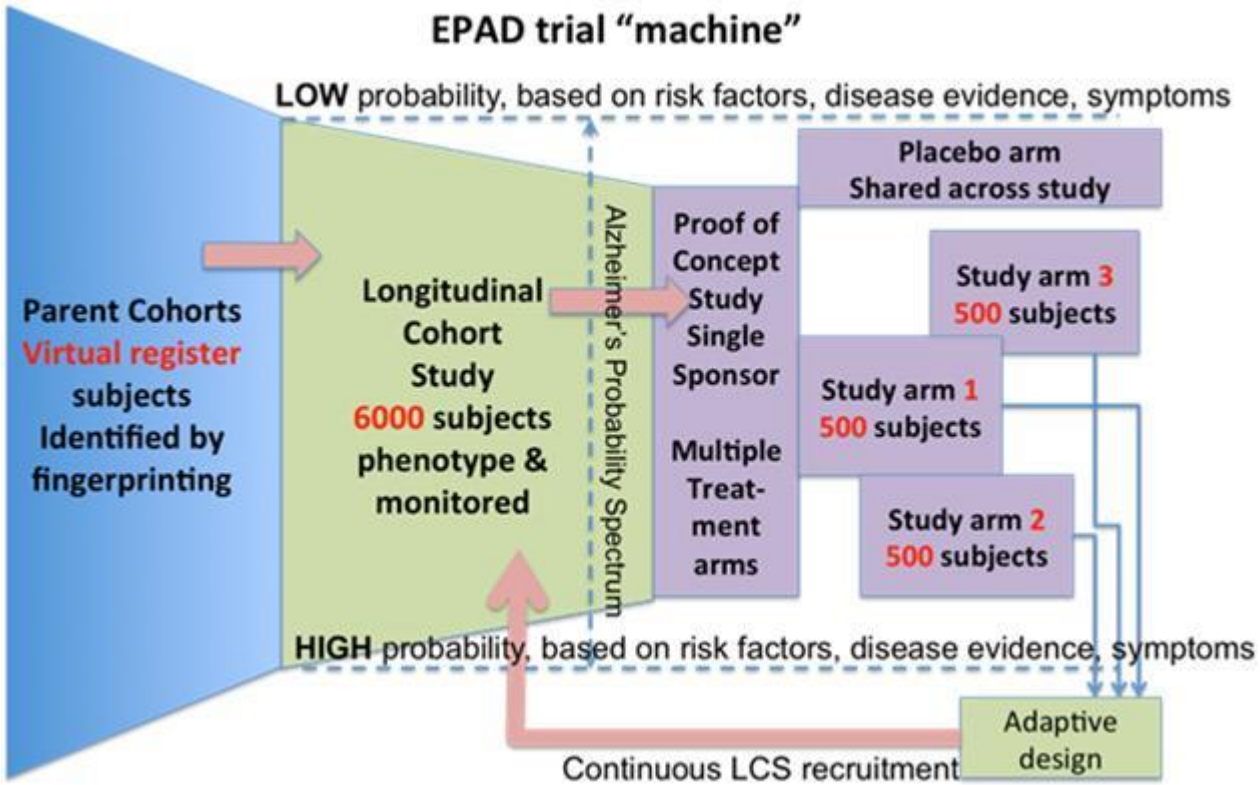
CTAD 2018. Barcelone.

LES ESSAIS AU STADE ASYMPTOMATIQUE

ÉTUDE	CRITÈRES D'INCLUSION	INTERVENTION	DURÉE	ENDPOINTS
Anti Amyloid treatment in Asymtomatic AD	Sujets normaux (CDR=0) Amyloïde +	Solanezumab	3 ans	Score cognitif composite (PACC)
API-ADAD (Famille colombienne)	Mutation autosomique dominante PS1	Crenezumab	5 ans	Score cognitif composite (APCC)
CAPIO15A2201J (GENERATION)	Asymptomatique APOE-4 homozygote APO-E4 hétérozygote/A+	Immunothérapie active (CAD106) et BACE inhibiteur (CNP-520)	5 ans	Score cognitif composite (APCC)
Dominantly Inherited Alzheimer Network	Individus à risque d'une MA autosomique dominante	Solanezumab Gantenerumab	4 ans	Score cognitif composite Biomarqueurs (LCR et TEP)

EPAD

European Prevention of
Alzheimer's Dementia Consortium



En conclusion

- Négativité des essais à un stade léger à modéré dans la MA
- Quelques résultats encourageants des thérapies ciblées au stade précoce
- Développement des interventions life style multi-domaine
  - Cibler les populations « déclinantes »: CAIDE, life style index, MA asymptomatiques ou peu symptomatiques?