STATE OF ALZHEIMER DISEASE RESEARCH

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Conflict of interest

- Clinical trial support from Lilly and Roche in DIAN-TU, TauRx, Lundbeck
- DSMB member of ADCS, ATRI, API, Eisai
- Scientific advisor to Affiris, Boehringer-Ingelheim, Lilly, Servier, Sanofi, Schwabe, Takeda, TauRx, Roche

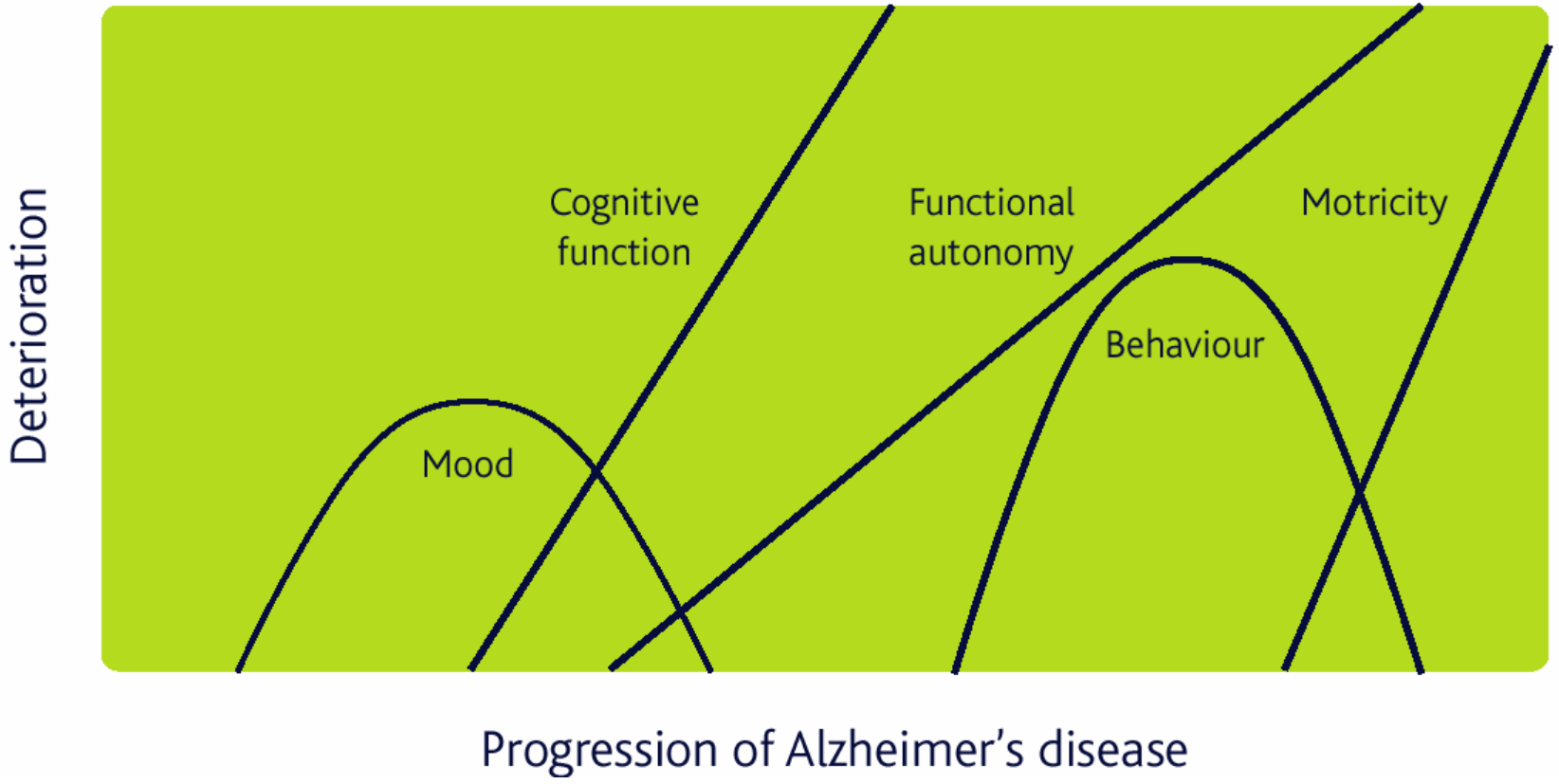
OUTLINE

- What is Alzheimer’s disease?
- What is new in the diagnosis?
- What is new in the treatment?
- What is coming next?

WHAT IS ALZHEIMER'S DISEASE?

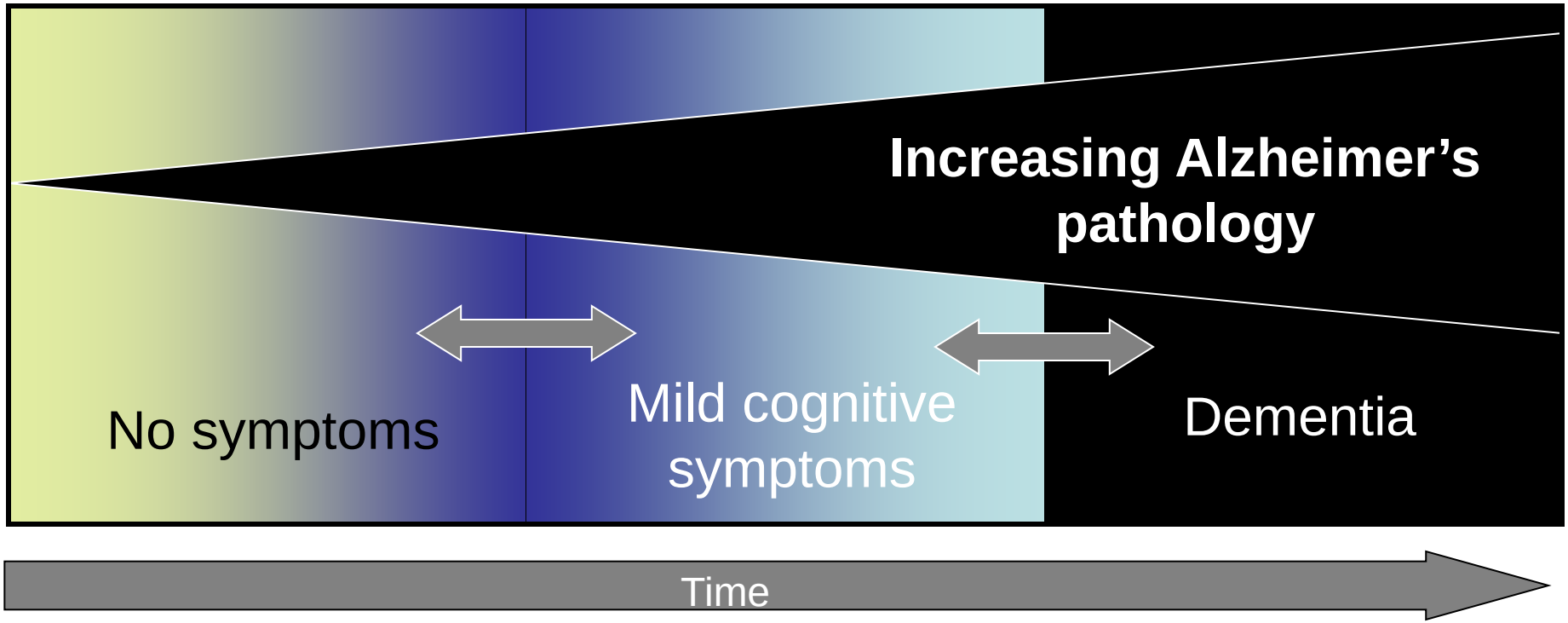
A progressive neurodegenerative disease affecting initially the temporal areas of the brain [memory], then posterior associative areas [language, spatial orientation], then frontal lobes [personality & behavior]

PROGRESSION OF SYMPTOMS IN ALZHEIMER'S DISEASE



Lovestone & Gauthier 2000

STAGES OF ALZHEIMER'S DISEASE

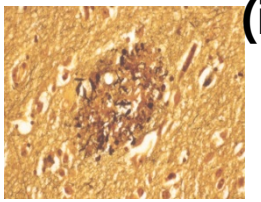


PATHOLOGIES ASSOCIATED WITH AD

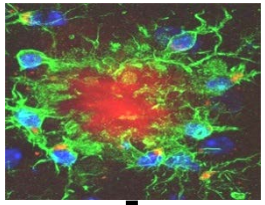
AGE

30
40
50
60
70
80
90
100

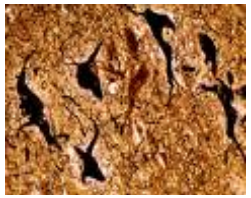
β-amyloid Deposition (plaques)



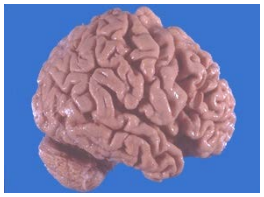
Microglial Activation (inflammation)



NFTs (tangles)



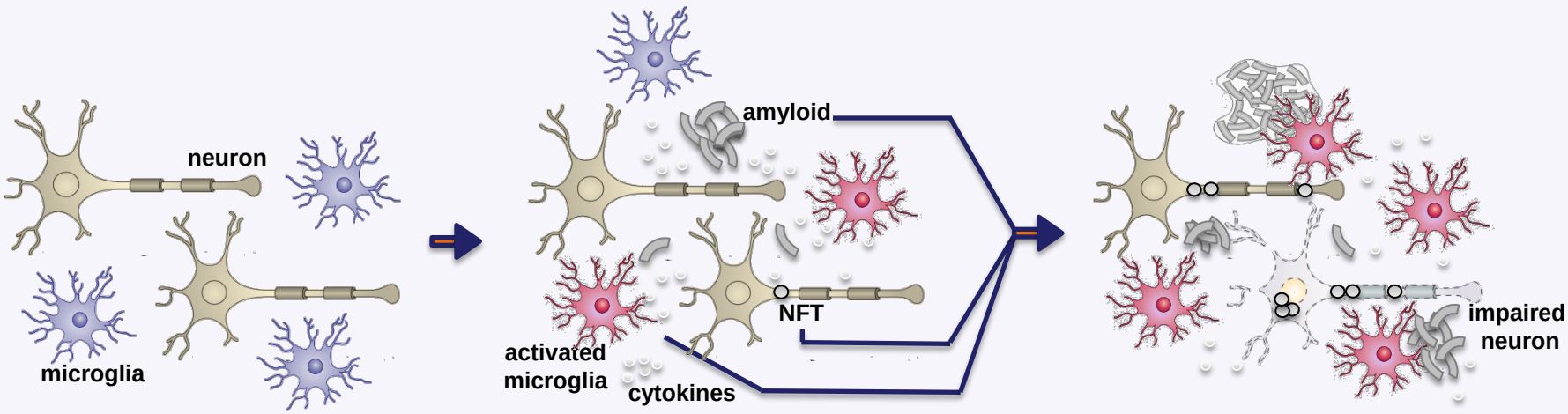
Neuronal Loss (atrophy)



Symptoms

Figure 5 - Working hypothesis

Interactions between pathological processes drive disease progression in preclinical AD



Increased tissue concentrations of amyloid in preclinical Alzheimer's disease will activate microglia.

We hypothesize that the interaction between regional amyloid, local NFT and levels of microglial activation will drive propagation of NFT and cognitive decline (see statistical methods).

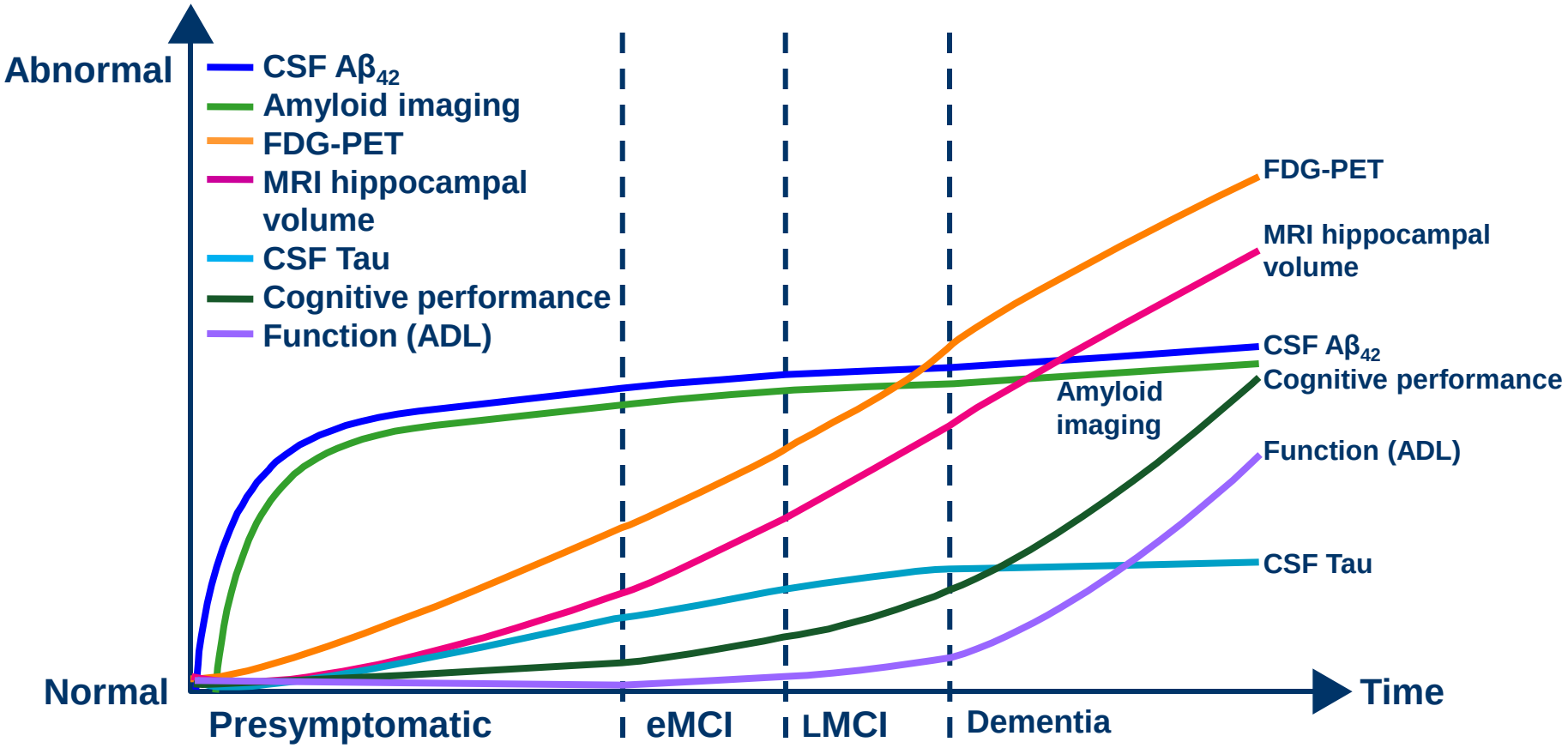
WHAT IS ALZHEIMER'S DISEASE? PATHOLOGY

- Classic pathology includes amyloid plaques and neurofibrillary tangles
- Neuroinflammation is a key factor at some stage of the disease
- Most older patients also have small strokes
- Many older patients also have Lewy Bodies

WHAT IS ALZHEIMER'S DISEASE? BIOMARKERS

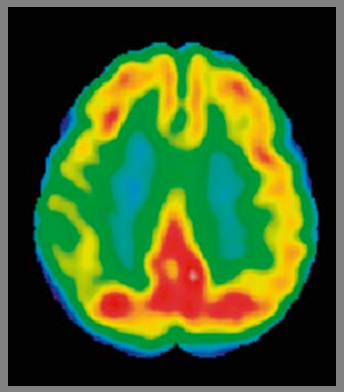
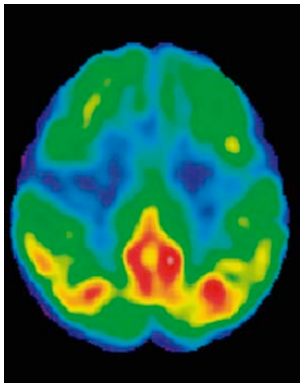
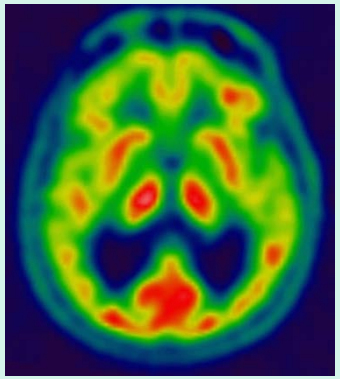
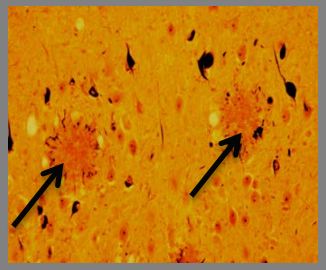
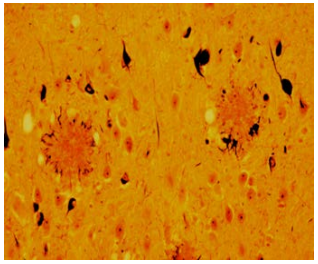
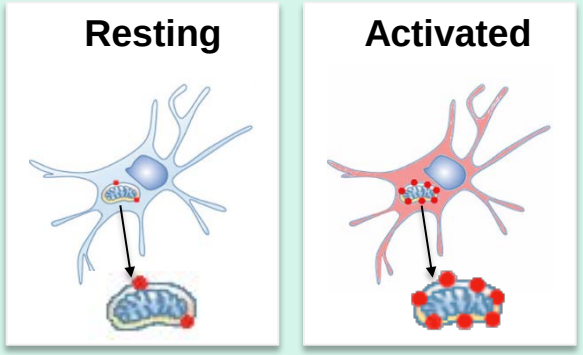
- *Pathophysiology markers* include amyloid deposition seen on PET scans and lower CSF levels of ß42
- *Neurodegeneration markers* include brain atrophy on MRI, hypometabolism on PET-FDG, higher CSF levels of phospho-tau, spread of tau pathology on PET

AD PROGRESSION USING BIOMARKERS

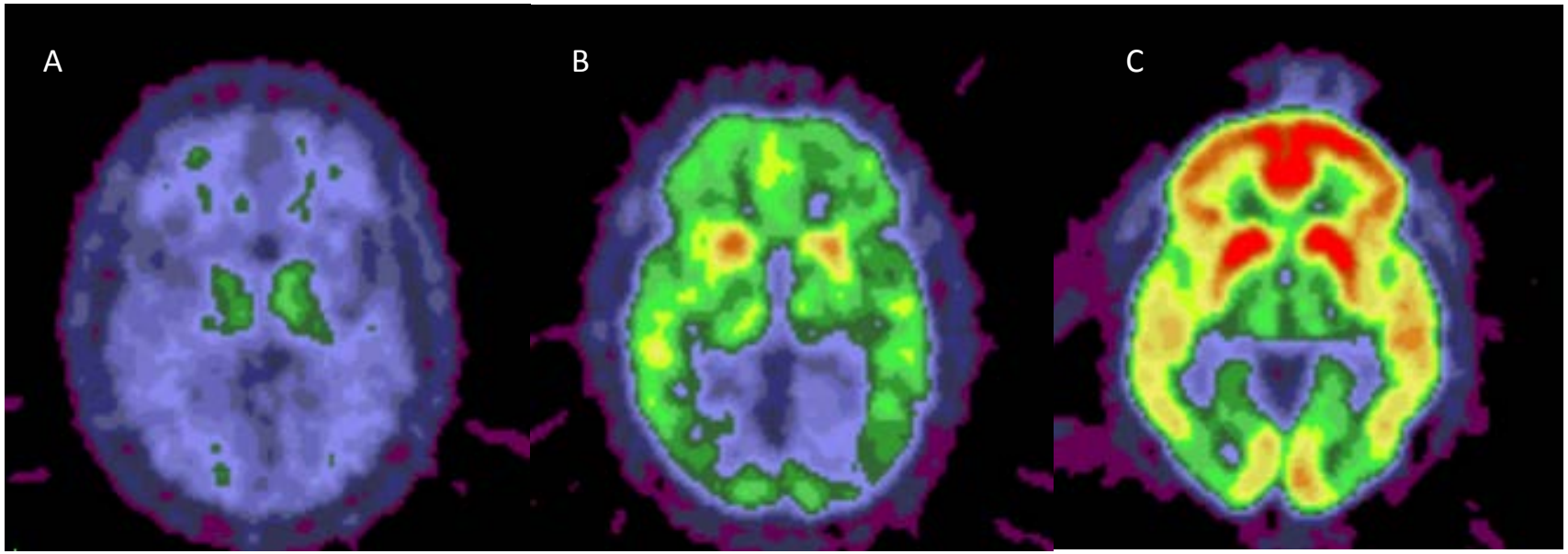


Aisen PS, Petersen RC, Donohue MC, et al. *Alzheimers Dement.* 2010;6:239-246.

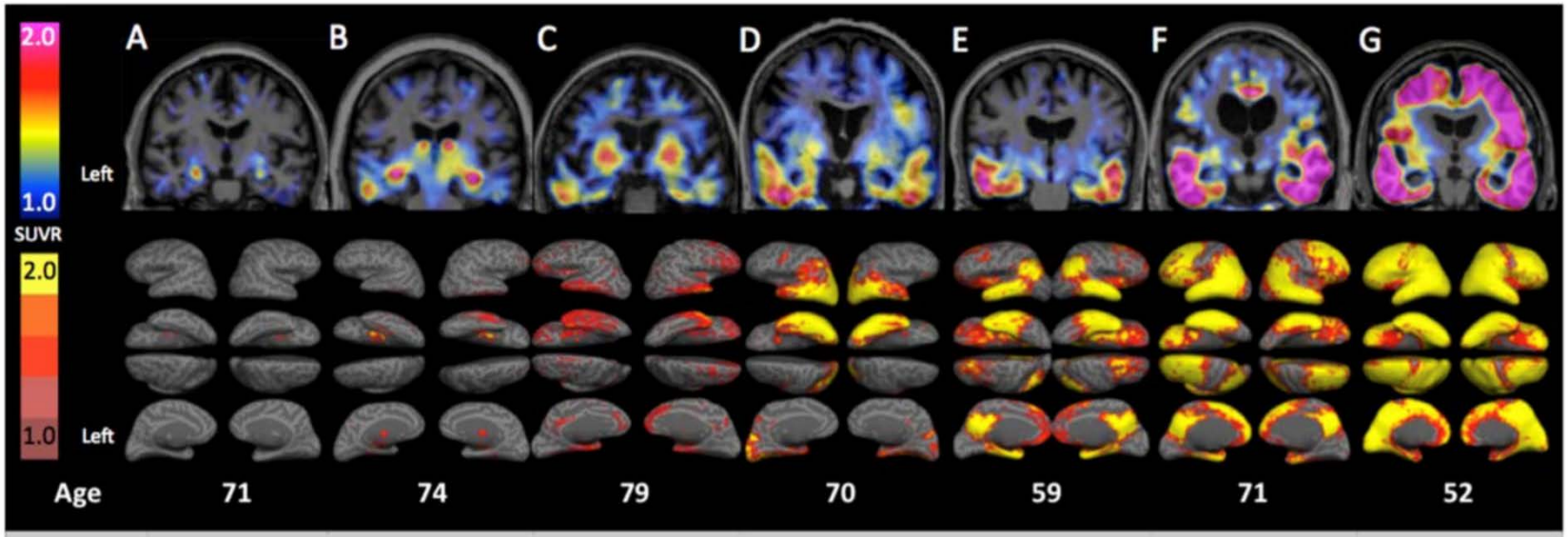
Figure 1 - Summary of the imaging agents and PET outcomes proposed

tracer	**Amyloid imaging** [^{11}C]PIB SUVR	**Tau imaging** [^{18}F]THK5351 SUVR	**TSPO imaging** [^{11}C]PBR28 SUVR
Image			
Interpretation	**Amyloid plaques**  Tissue availability of Fibrillary amyloid	**Neurofibrillary tangles**  Tissue availability of Paired Helical Filaments	**Microglia**  Tissue availability of TSPO expression • TSPO =Translocator protein (18kDa) - mitochondrial cholesterol transporter

AMYLOID PET IN MUTATION CARRIERS



Courtesy of Mark Mintun and Randy Bateman



MMSE	30	30	29	27	26	23	11
PiB (DVR)	Low (1.0)	High (1.2)	High (1.8)	High (1.5)	High (1.7)	High (1.5)	High (1.5)
Dx	CN	CN	CN	MCI	MCI	AD	AD
PET Braak	0, I-II	III-IV	III-IV	III-IV	III-IV	V-VI	V-VI

FIGURE 1: Cortical patterns of 18F T807 binding. Coronal 18F T807 positron emission tomographic (PET) images (top row) and whole-brain surface renderings of standardized uptake value ratio (SUVR; cerebellar reference; second row) from 3 clinically normal (CN) and 4 impaired (2 mild cognitive impairment [MCI] and 2 mild Alzheimer dementia [AD] dementia) participants. Top: (A) A 71-year-old CN subject with low amyloid b (Ab) by Pittsburgh compound B (PiB) PET (mean cortical distribution vol- ume ratio [DVR]51.0) had low, nonspecific 18F T807 binding in cortex, consistent with a Braak stage less than III/IV. (B) A 74- year-old CN subject with high Ab (DVR51.2) with 18F T807 binding in inferior temporal cortex, left>right, consistent with Braak stage III/IV. (C) A 79-year-old CN subject with high Ab (DVR 5 1.8) had binding in inferior temporal neocortex, consistent with Braak stage of III/IV. B and C show focally intense subcortical uptake that is likely due to off-target binding (see Discus- sion). (D–G) Cognitively impaired participants all with high Ab and with successively greater levels of cortical 18F T807 binding successively involving temporal, parietal, frontal, and occipital cortices. Bottom: 18F T807 SUVR calculated at vertices (see Sub- jects and Methods) indicating the extent of cortical binding, with left hemisphere views (lateral, inferior, superior, medial) at left. The 52-year-old AD dementia patient (G) showed confluent 18F T807 binding that is nearly pancortical, sparing only por- tions of primary cortex and consistent with Braak stage V/VI. Dx5classification; MMSE5Mini-Mental State Examination; PET Braak 5 estimate of Braak stages based on the anatomic pattern of T807 binding assessed visually and quantitatively in regions and full volume data.

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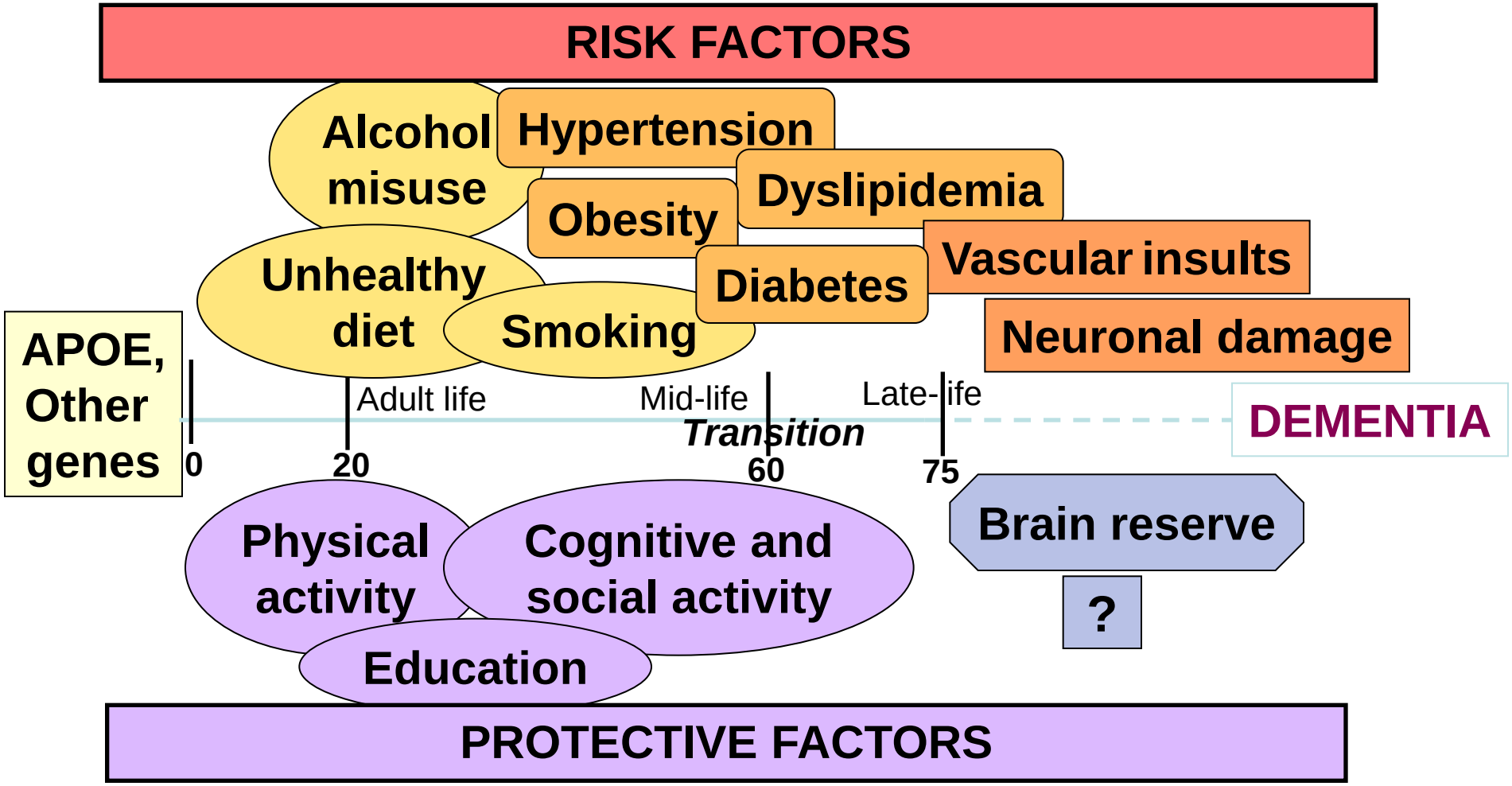
WHAT IS ALZHEIMER'S DISEASE? GENETIC FACTORS

- Autosomal dominant early onset (<65) infrequent but important as involving only amyloid mutations (PS1, PS2, APP)
- ApoE4 genotype frequent (15%) and is the major genetic risk factor in late-onset AD
- Genes effects can be additive or protective

WHAT IS ALZHEIMER'S DISEASE? RISK AND PROTECTIVE FACTORS



Mangialasche, Kivipelto et al., 2012

OUTLINE

- What is Alzheimer’s disease?
- **What is new in the diagnosis?**
- What is new in the treatment?
- What is coming next?

WHAT IS NEW IN THE DIAGNOSIS?

- Validation of new diagnostic criteria proposed by the IWG and the NIA-AA workgroups.
- There has to be a balance between sensitivity, specificity and affordability
- Sharing of data from large observational studies (ADNI, AIBL, CCNA, **DIAN**)

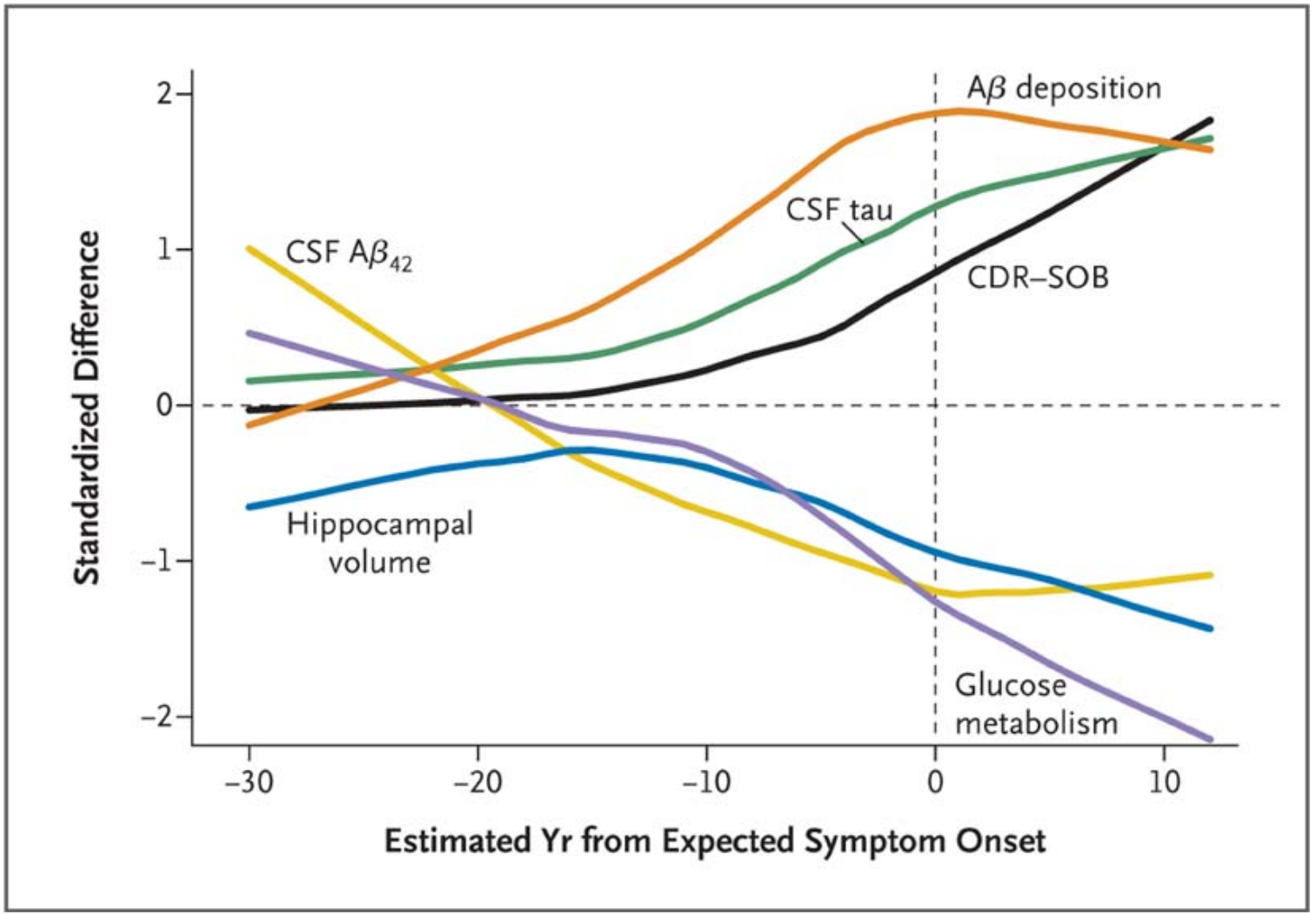
DIAGNOSTIC CRITERIA FOR DEMENTIA PROBABLY DUE TO AD USING BIOMARKERS

(Modified from McKhann et al, 2011)

	Aß	Neuronal injury
• Probable AD with high likelihood	+	+
• Probable AD with intermediate likelihood	+ or untested	untested or +
• Probable AD dementia	untested or conflicting results	
• Possible AD dementia (atypical clinical presentation)	+	+
* Unlikely AD dementia	-	-

WHAT IS NEW IN THE DIAGNOSIS?

- Interest in ‘asymptomatic AD’ for preventive studies, e.g. biomarker or ApoE4 positivity and no symptoms
- Ethical issues in disclosing results of biomarkers and genetic testing for is a “risk state”, not a clinical disease
- Special case of mutations causing familial early onset AD



OUTLINE

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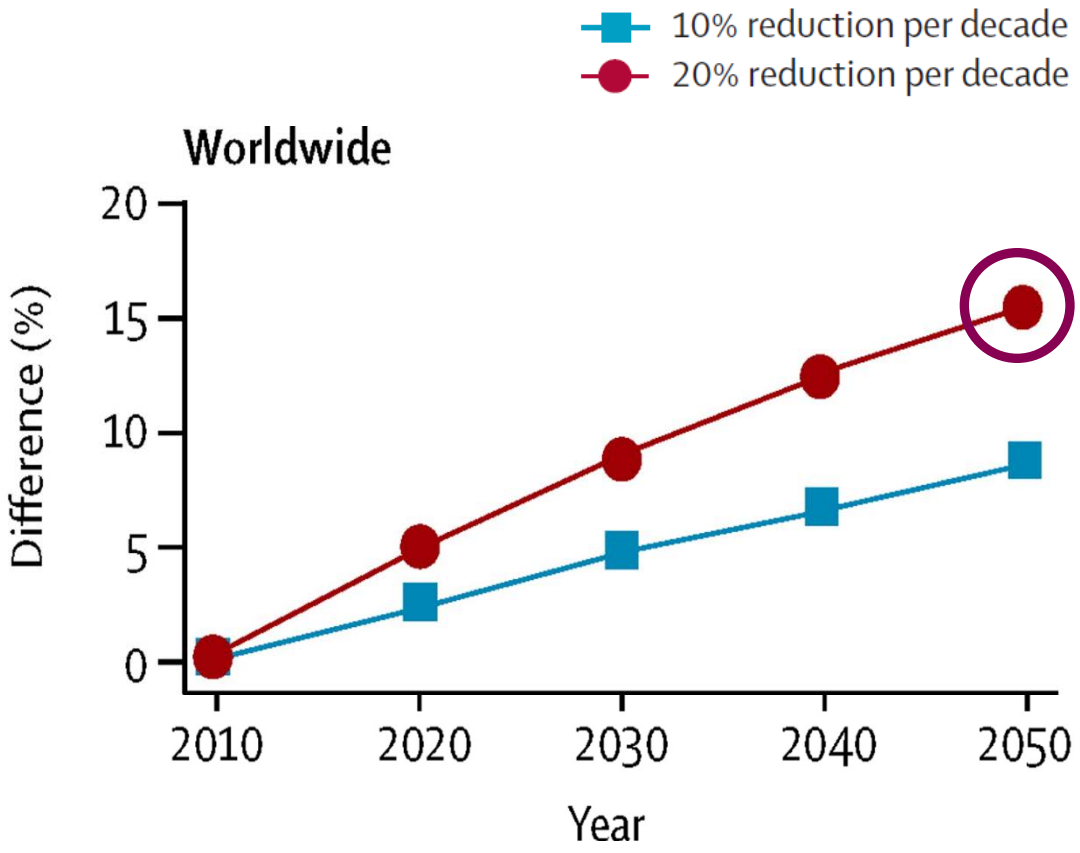
To what extent can Alzheimer dementia be prevented?

Risk factor	PAR
Diabetes mellitus	2.9%
Midlife hypertension	5.1%
Midlife obesity	2.0%
Physical inactivity	12.7%
Depression	7.9%
Smoking	13.9%
Low education	19.1%
Combined PAR*	28.2%

PAR=population-attributable risk.
*Adjusting for non-independence of the risk factors.



Norton et al., Lancet Neurol, 2014; Kivipelto and Mangialasche, Nature Neurol Rev, 2014

A 2 year multidomain intervention of diet, exercise, cognitive training, and vascular risk monitoring versus control to prevent cognitive decline in at-risk elderly people (FINGER): a randomised controlled trial

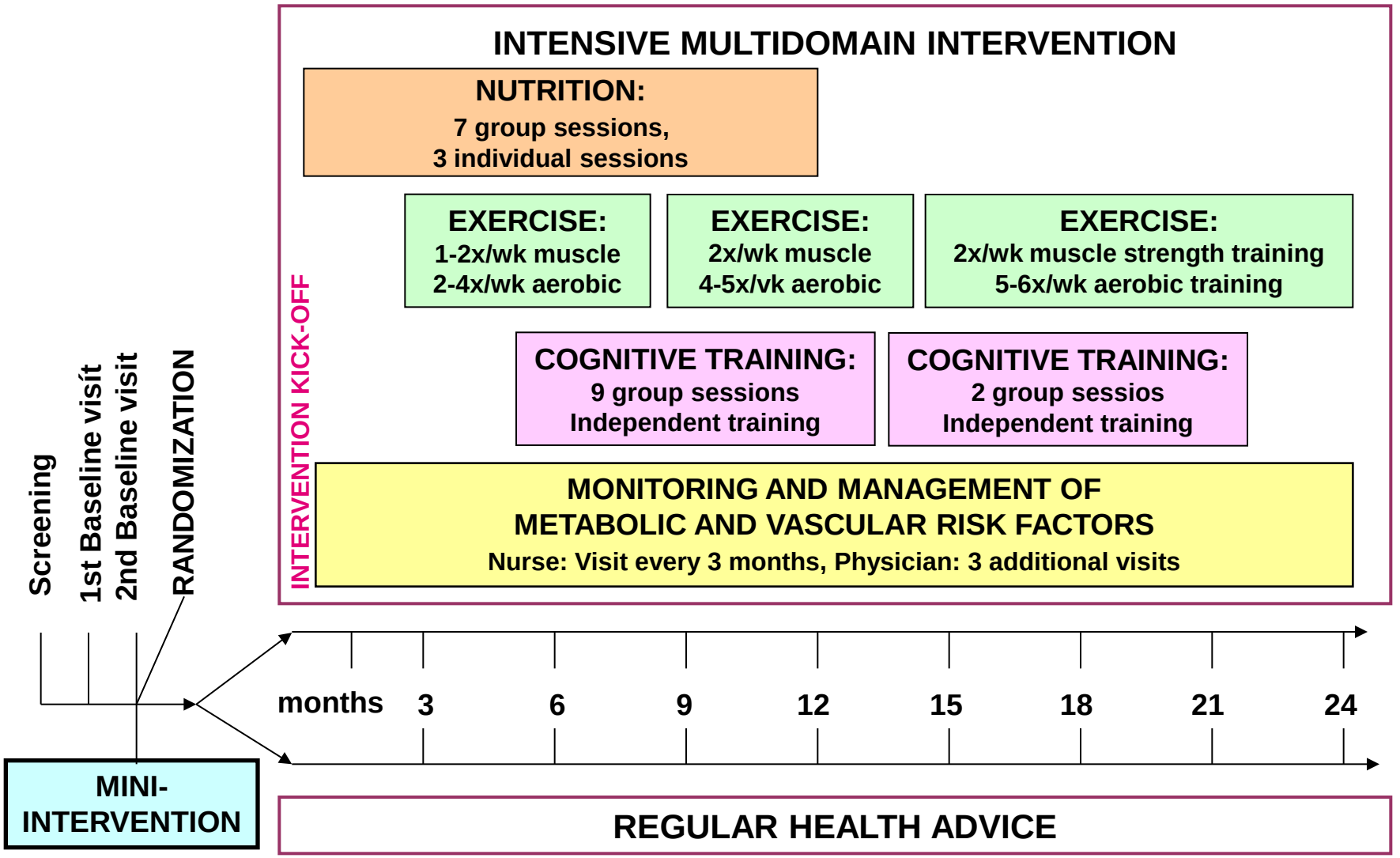
Tiia Ngandu, Jenni Lehtisalo, Alina Solomon, Esko Levälahti, Satu Ahtiluoto, Riitta Antikainen, Lars Bäckman, Tuomo Hänninen, Antti Jula, Tiina Laatikainen, Jaana Lindström, Francesca Mangialasche, Teemu Paajanen, Satu Pajala, Markku Peltonen, Rainer Rauramaa, Anna Stigsdotter-Neely, Timo Strandberg, Jaakko Tuomilehto, Hilkka Soininen, Miia Kivipelto

The Lancet, 2015

(Published online March 12 2015)

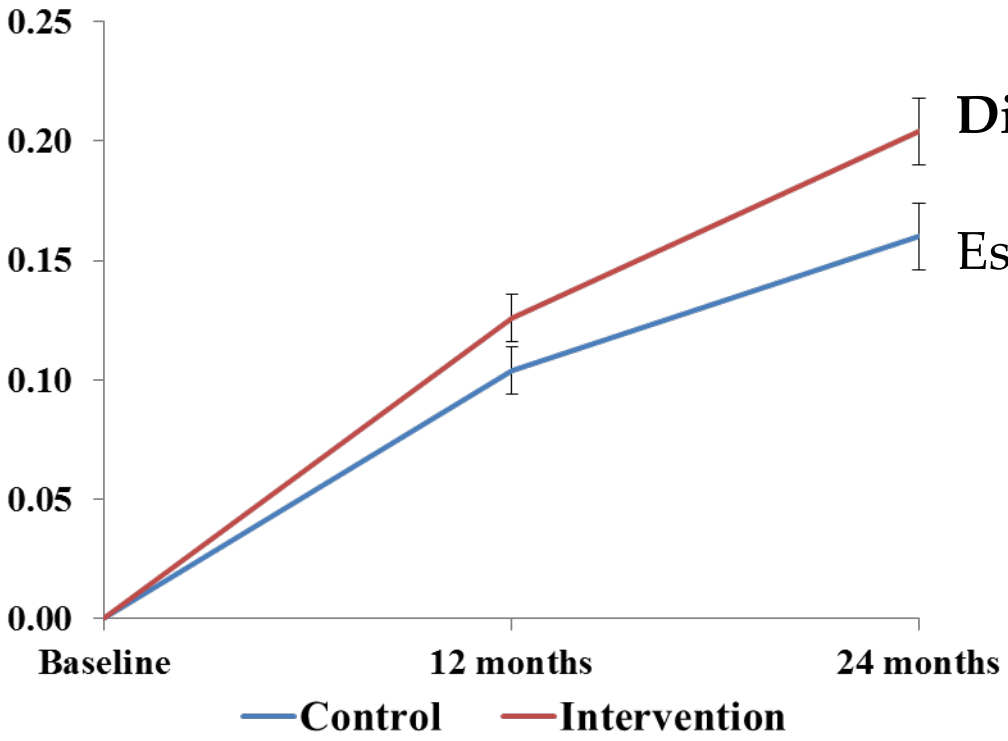
FINGER

INTERVENTION SCHEDULE



Kivipelto et al., Alzheimer & Dementia 2013

Primary efficacy outcome: overall cognition (NTB composite Z score)



Difference between intervention and control groups per year:

Estimate (95% CI) = 0.022 (0.002-0.042)

p=0.03

Kivipelto et al, Lancet 2015

Lines = estimates for cognitive change from baseline to 12 and 24 months

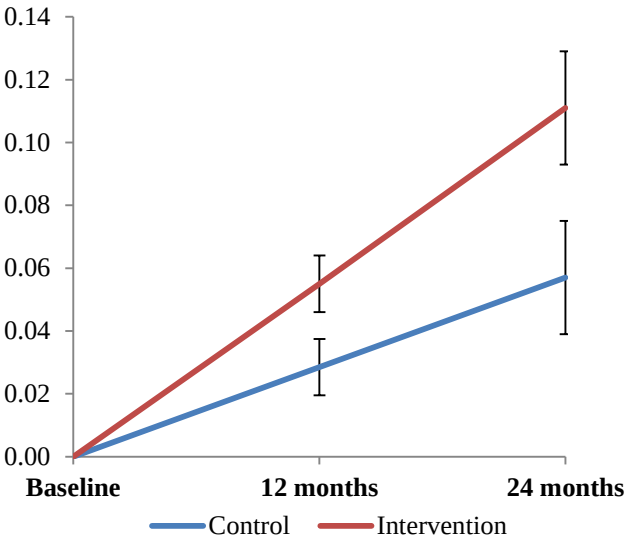
Higher scores = better performance

Error bars = standard errors.

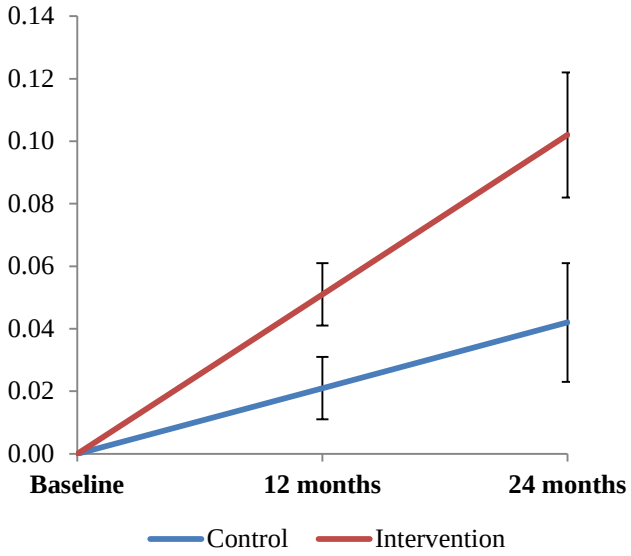
P-values = difference in trajectories over time between groups

Intervention effects on main cognitive secondary outcomes

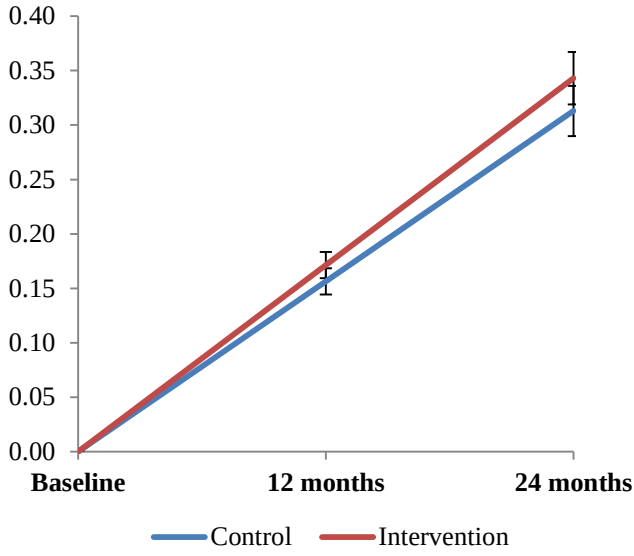
Executive functioning



Processing speed



Memory



Difference between intervention and control groups per year:

Estimate (95% CI), p-value

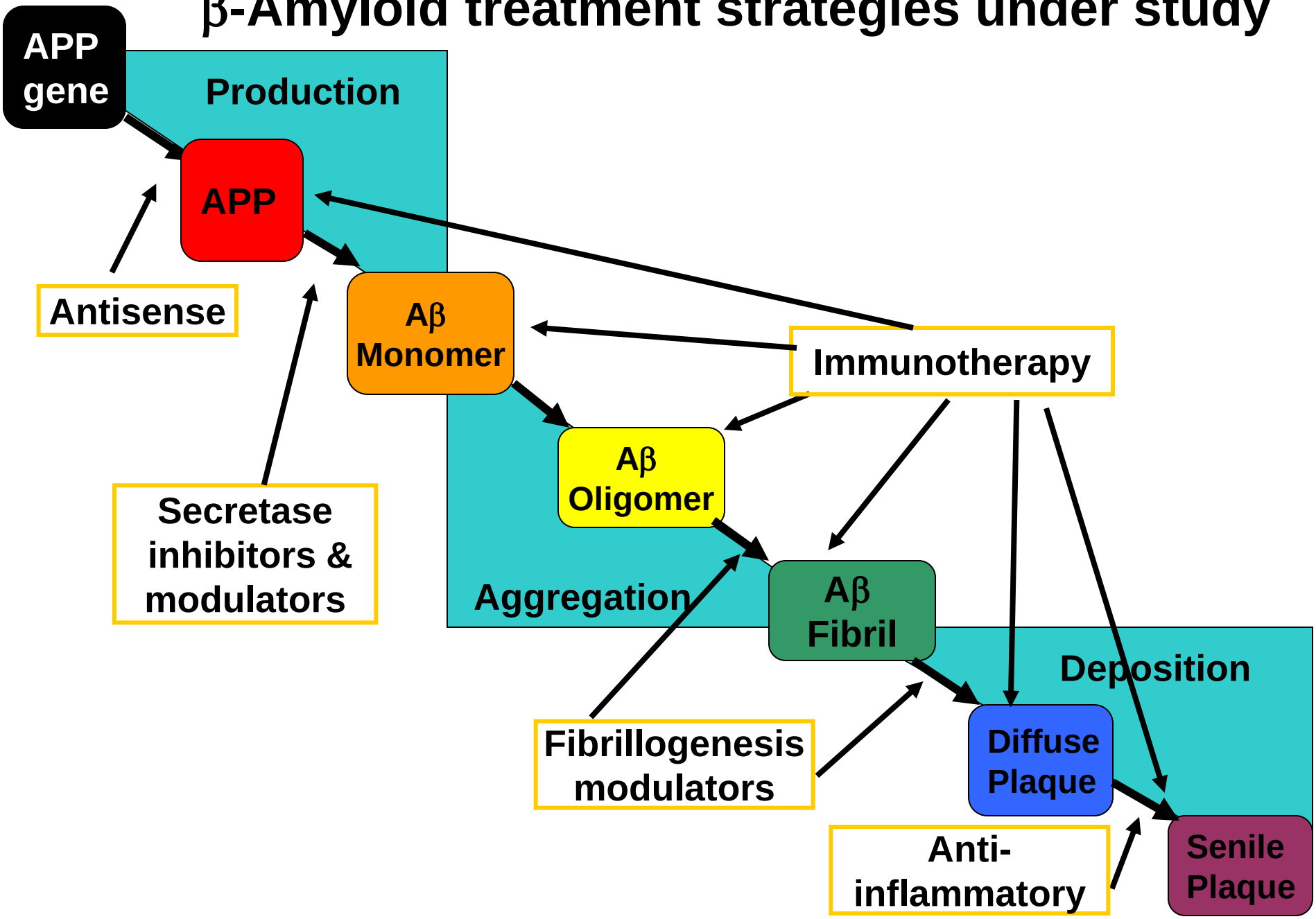
Executive functioning	Processing speed	Memory
0.027 (0.001-0.052)	0.030 (0.003-0.057)	0.015 (-0.017-0.048)
p=0.04	**p=0.03**	p=0.36

Kivipelto et al, Lancet 2015

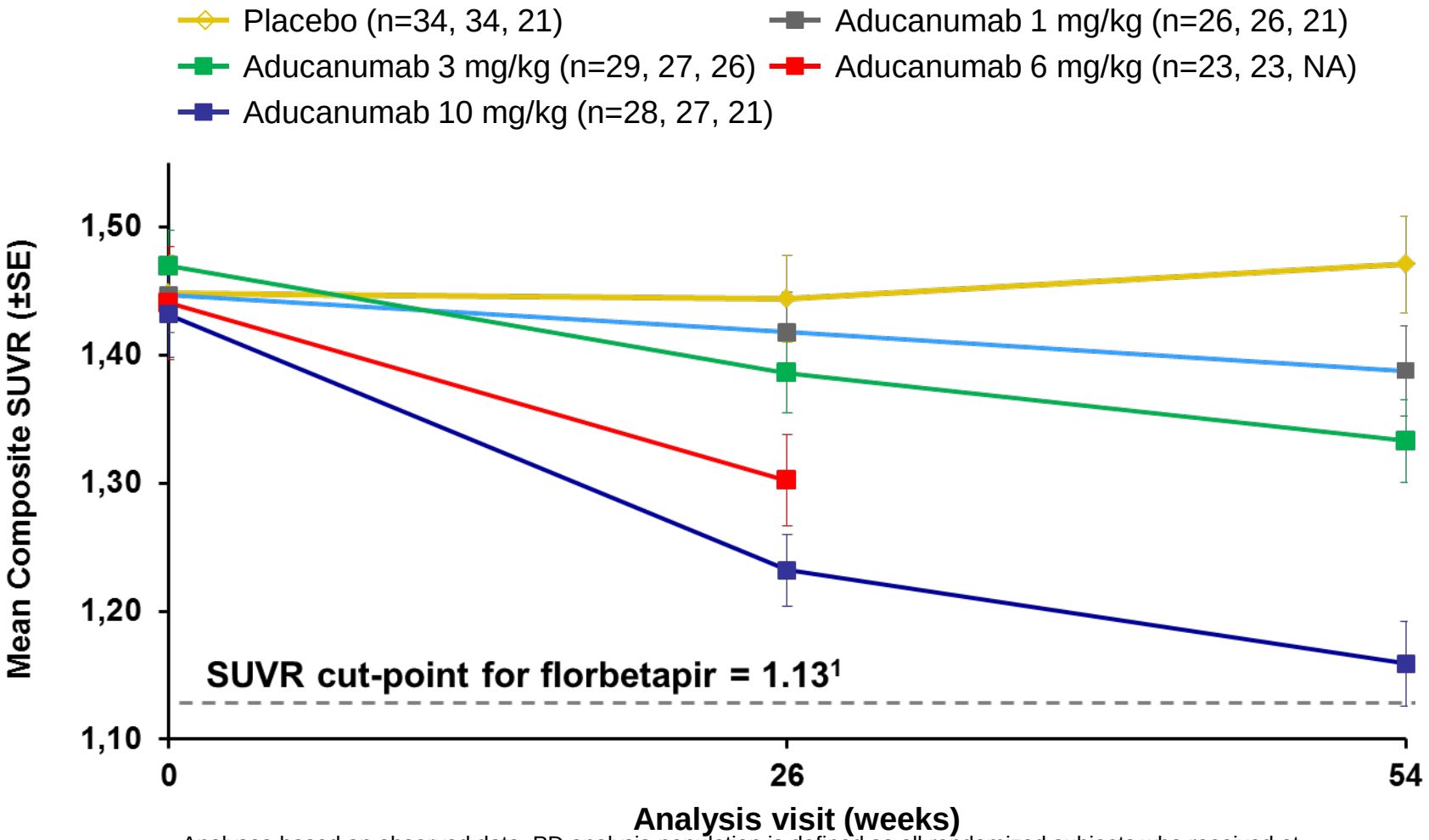
WHAT IS NEW IN TREATMENT? PHARMACOLOGIC STUDIES

- Decrease beta-amyloid deposition or break up amyloid plaques
- Decrease Tau hyperphosphorylation with LMTM or antibodies

β-Amyloid treatment strategies under study



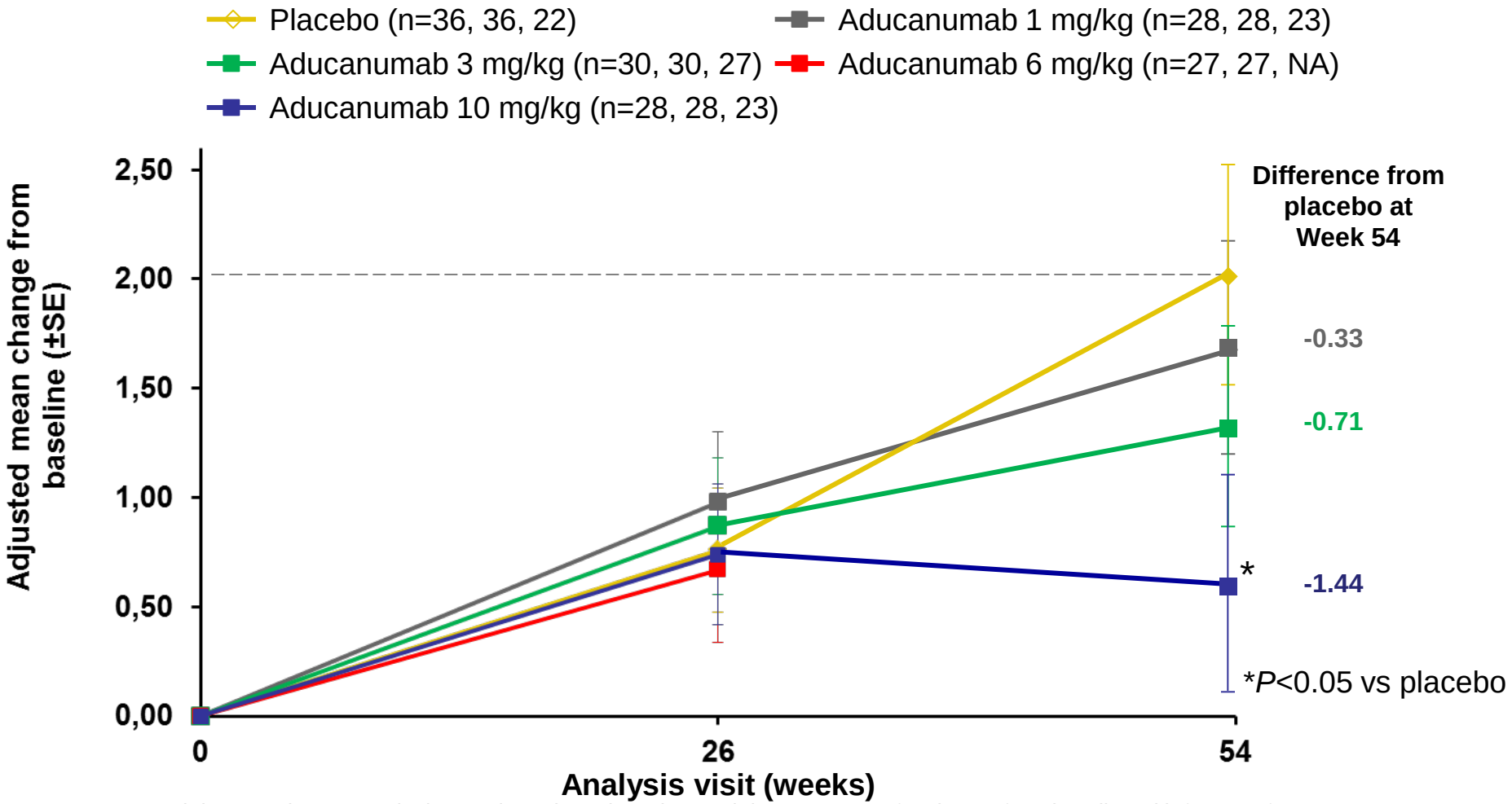
Amyloid Plaque Reduction with Aducanumab



Analyses based on observed data. PD analysis population is defined as all randomized subjects who received at least 1 dose of study medication and had at least 1 post-baseline assessment of the parameter.

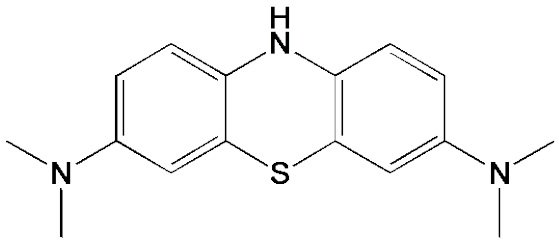
1. Landau et al. J Nucl Med 2013

Aducanumab Effect on CDR-sb



CDR-sb is an exploratory endpoint. Analyses based on observed data. ANCOVA for change from baseline with factors of treatment, laboratory ApoE ε4 status (carrier and non-carrier), and baseline CDR-sb. Efficacy analysis population is defined as all randomized subjects who received at least 1 dose of study medication and had at least 1 post-baseline questionnaire assessment.

LMTM (leuco methylthioninium dihydro-mesylate) inhibits aggregation of Tau protein



Molecule is distinct from methylene blue (where nitrogen groups are planar)

Wischik et al, (1996) PNAS 92, 11213-11218
Harrington et al., J Biol Chem, 2015, 290 10862-10875

Yamashita et al. (2009) FEBS Letters 583:2419-2424

Summary of TauRx Clinical Development Program

TRx-237-005 (in competent imaging centres)

- 18-month study in 700 (800) patients with mild Alzheimer's disease
- LMTM 200 mg/day *versus* placebo (8 mg/day)
- Primary endpoints: ADAS-cog and ADCS-CGIC (US) / ADCS-ADL (EU)
- Secondary endpoints: Volumetric MRI, FDG-PET

TRx-237-015 (diagnostic imaging only, broader recruitment base)

- 15-month study in 833 (890) subjects with mild-moderate Alzheimer's disease
- LMTM 150 mg/day *versus* LMTM 250 mg/day *versus* placebo (8 mg/day)
- Primary endpoints: ADAS-cog and ADCS-CGIC (US) / ADCS-ADL (EU)
- Secondary endpoints: Volumetric MRI, FDG-PET (150 subset)

TRx-237-007

- 12-month study in 180 (220) patients with bvFTD
- LMTM 200 mg/day *versus* placebo (8 mg/day)
- Primary endpoints: ACE-R and ADCS-CGIC
- Secondary endpoints: Volumetric MRI, ACE-III, FTD-FRS, FAQ, UPDRS

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- What is Alzheimer’s disease?
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WHAT IS COMING NEXT? - 1

- Learn from observations in people with recurrent head injuries, Down’s syndrome
- Share “big” data, e.g. pool information from around the world
- PET-tau brain scanning may be closer to the pathology causing symptoms

WHAT IS COMING NEXT? - 2

- National policies to support education and maintain healthy life-styles
- Patients and asymptomatic « trial ready» volunteer registries
- Anti-inflammatory drugs may get a second chance!

WHAT IS COMING NEXT? - 3

- Clinical trials combining anti-tau and anti-amyloid drugs, or drugs acting on different components of the amyloid pathway
- Learn from other fields such as cancer and infectious disease where such combinations are standard treatment and affordable