The Prevalence of Amyloid Positivity by Age, APOE Genotype and Cognitive Status - Implications for the Diagnosis of Alzheimer's Disease

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Outline

- Background
- Prevalence of amyloid in normals and MCI
  - Influence of APOE
- Prevalence of amyloid in demented
  - Influence of APOE
- Diagnosis and prognosis
- Ongoing work
- Conclusions

Most dementias are proteinopathies

Table 1: pathologic proteins underlying some of the main dementia types

Dementia	Aβ	tau	p-tau	α-synuclein	TDP-43
AD	X	X	X	X	
DLB	X	X		X	
FTD	X	X			X
PSP		X			
CBD	X	X			
CTE	X		X	X	X

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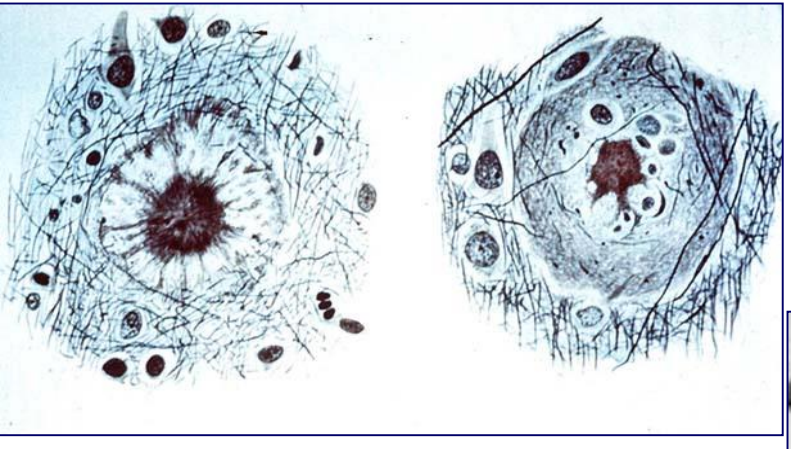
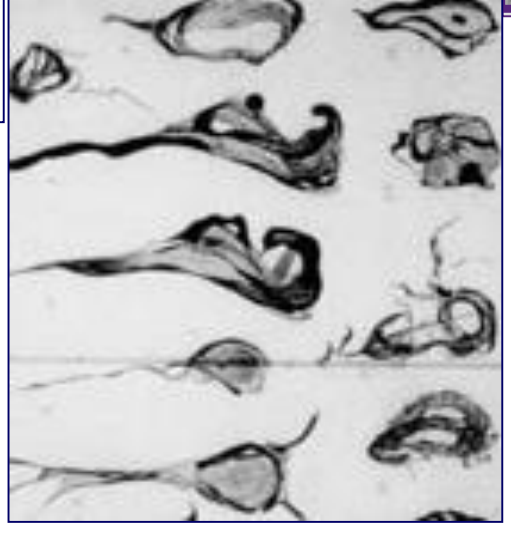
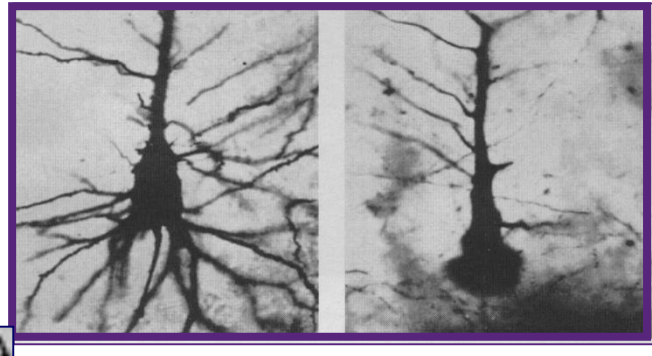
Alzheimer: 3 fundamental processes



plaques

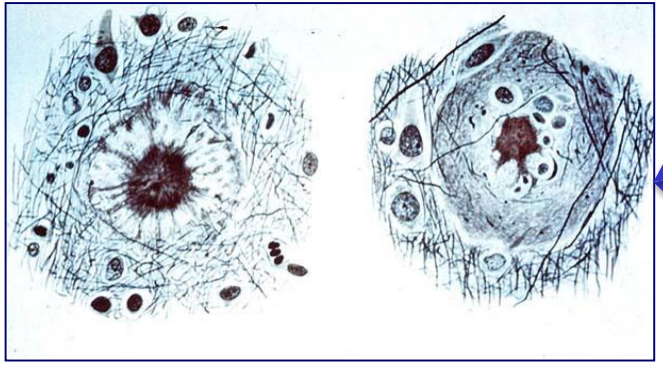
Tangles

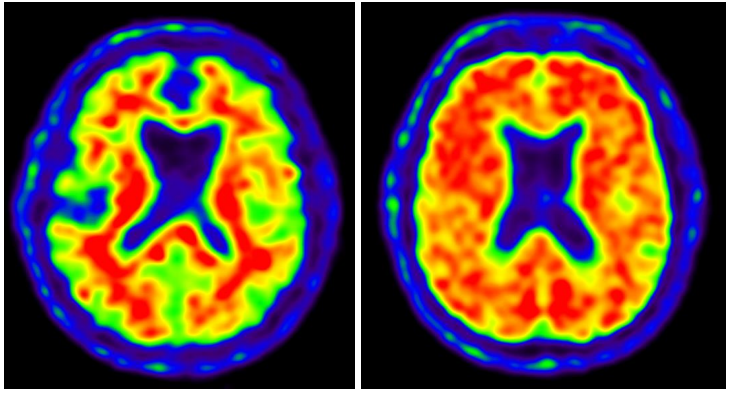


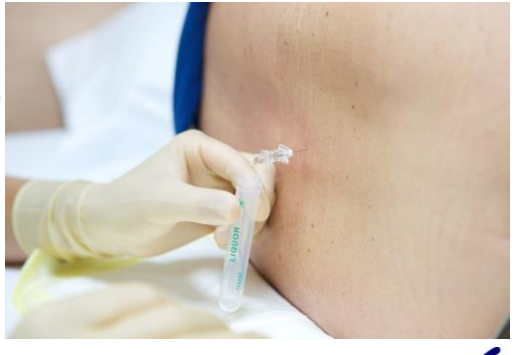


Synapse loss

Amyloid in vivo





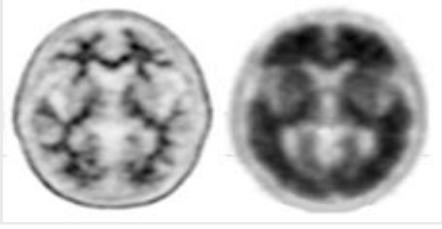
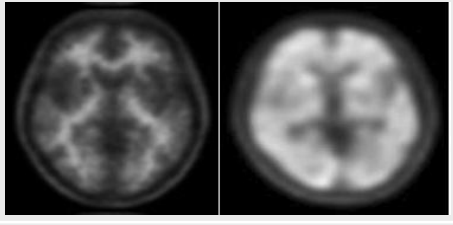
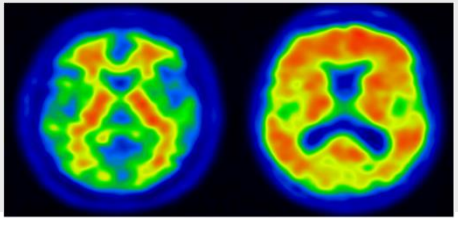


Abeta
1-42

Entering a new era: the case of AD

- Prodromal AD: diagnosing AD before dementia
- Preclinical AD: AD without symptoms
- Clinical trials include earlier populations; target protein needs to be identified
- Patients want to be informed
- Dementia field follows the oncology pathway: Personalized / precision medicine
- Emphasizes the need for biomarkers for diagnosis, tracking disease and measure effect
- Healthcare providers and payors need to be informed and prepared.

[^{18}F] labeled Amyloid PET tracers

Florbetapir (Amyvid)	
Florbetaben (Neuraceq)	
Flutemetamol (Vizamyl)	

Amyloid binding is associated with decline

Molecular Psychiatry (2014) 19, 1044–1051

www.nature.com/mp

OPEN

ORIGINAL ARTICLE

Florbetapir F 18 amyloid PET and 36-month cognitive decline: a prospective multicenter study

PM Doraiswamy[1], RA Sperling[2], K Johnson[2], EM Reiman[3], TZ Wong[1], MN Sabbagh[4], CH Sadowsky[5], AS Fleisher[3,6], A Carpenter[7], AD Joshi[7], M Lu[7], M Grundman[6,8], MA Mintun[7], DM Skovronsky[7], MJ Pontecorvo[7] For the AV45-A11 Study Group[9]

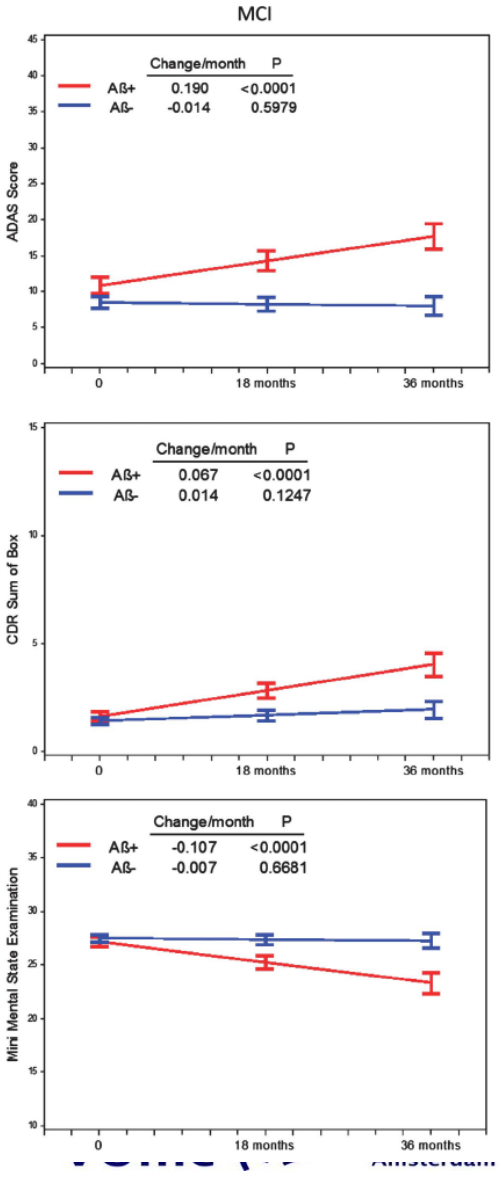
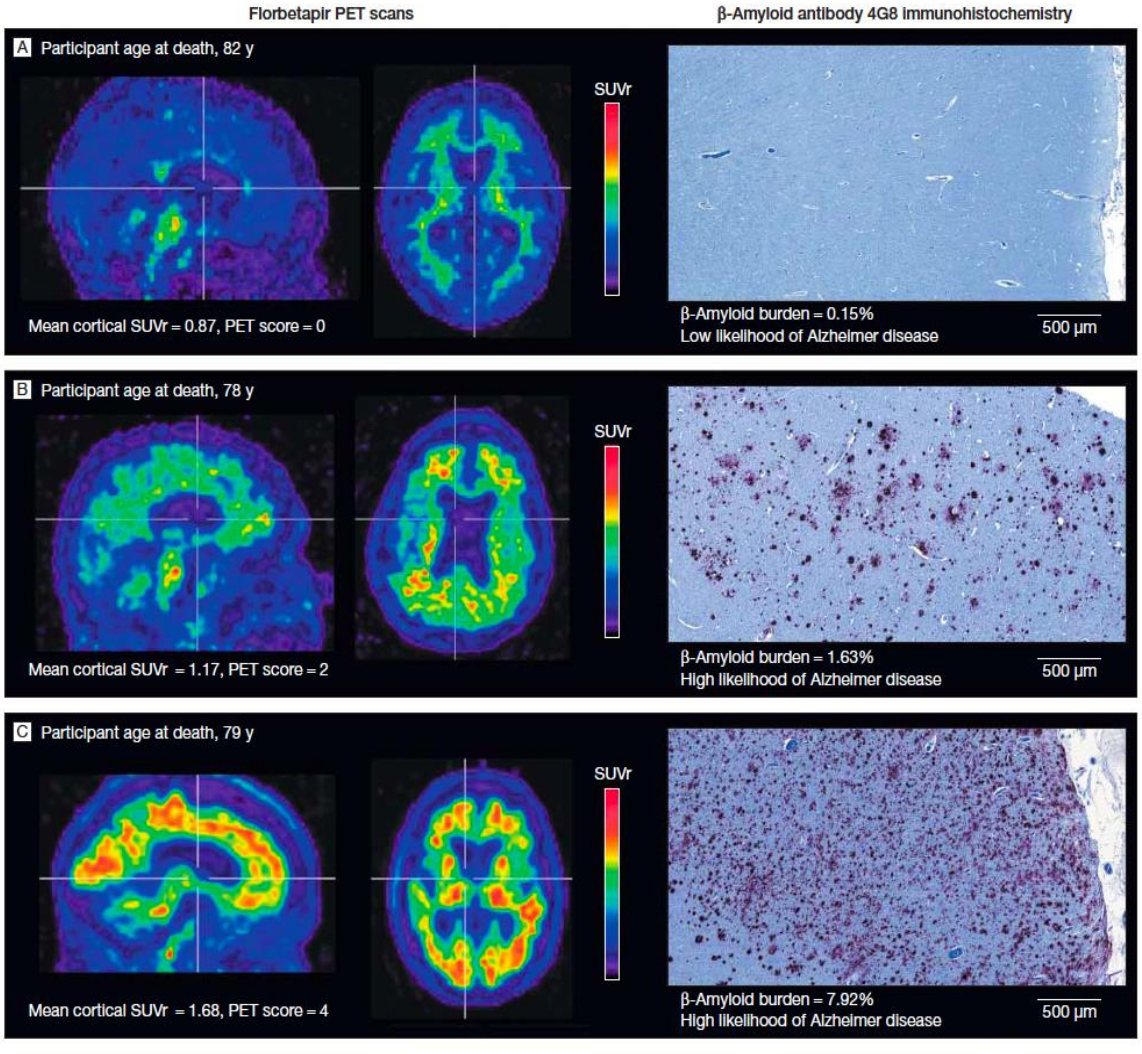
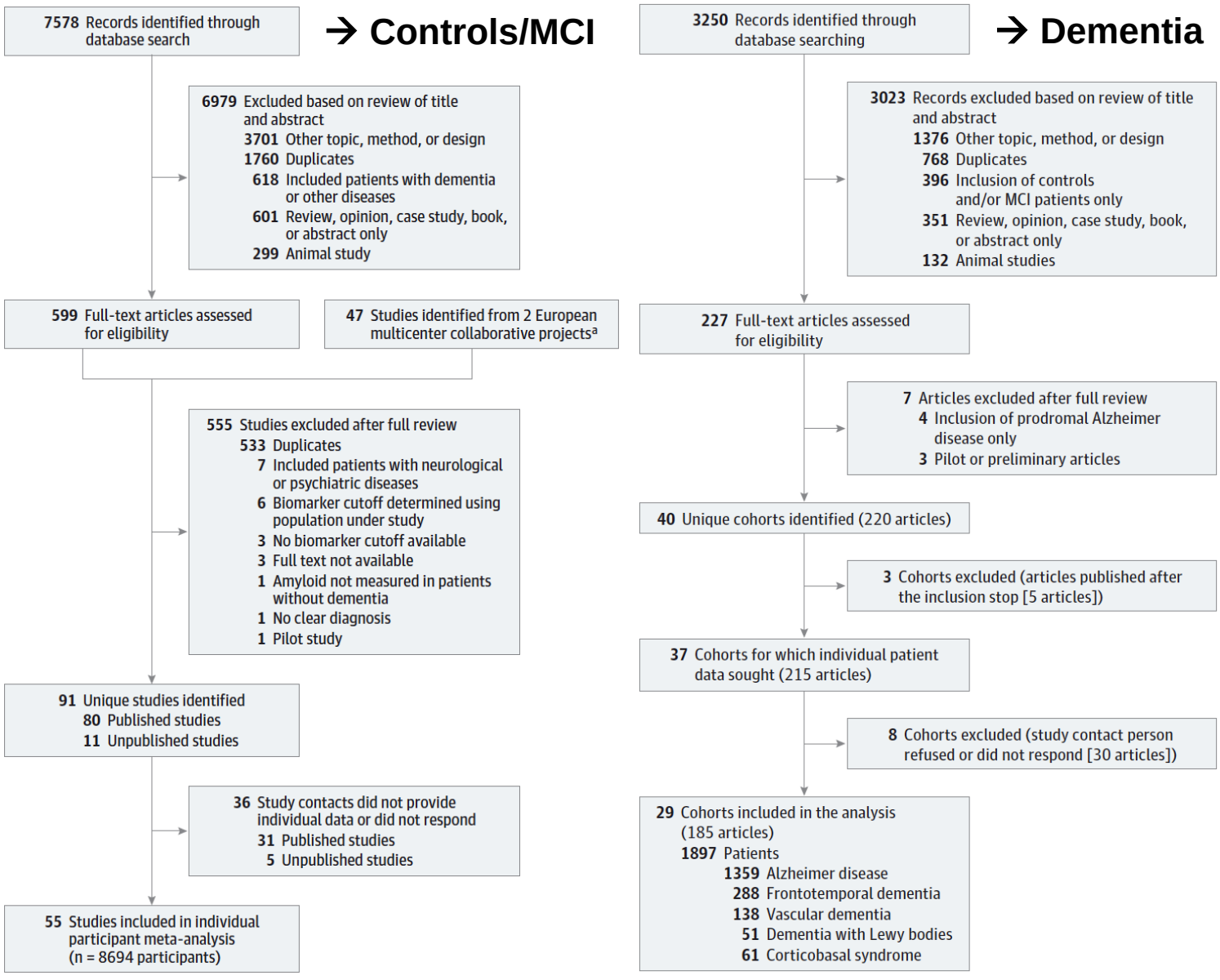


Figure. Paired Representative Florabetapir-PET Scans and β-Amyloid Antibody 4G8 Immunohistochemistry Photo Micrographs



Prevalence of amyloid positivity

- Subject-level meta-analysis
  - Non-demented subjects (Jansen et al JAMA 2015)
    - Normal cognition, subjective cognitive impairment, mild cognitive impairment
    - Amyloid assessed in CSF or by PET imaging
    - Data from 55 studies
  - Demented subjects (Ossenkoppele et al JAMA 2015)
    - AD and other dementias
    - Amyloid assessed by PET imaging
    - Data from 29 studies



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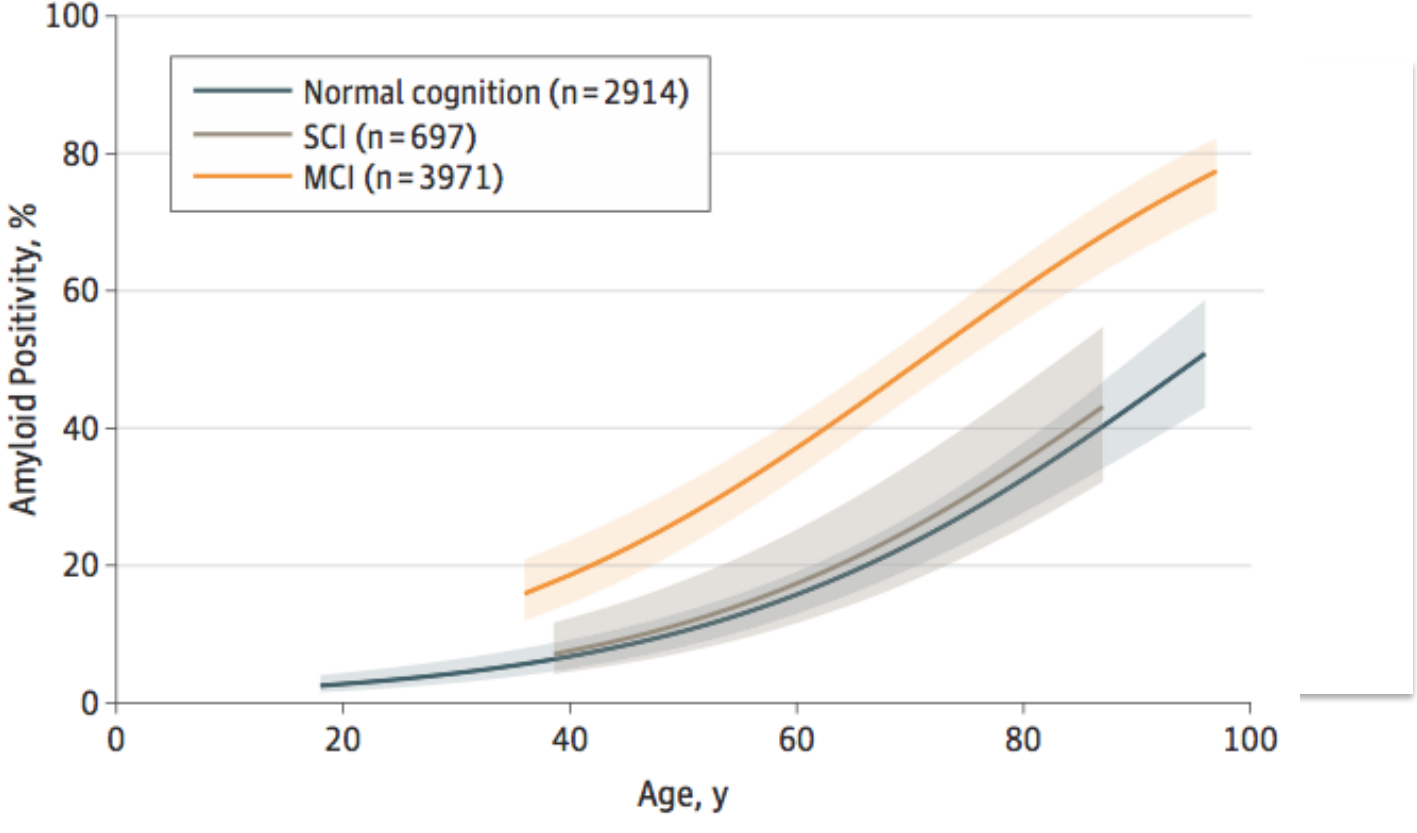
Prevalence amyloid positivity in non-demented subjects



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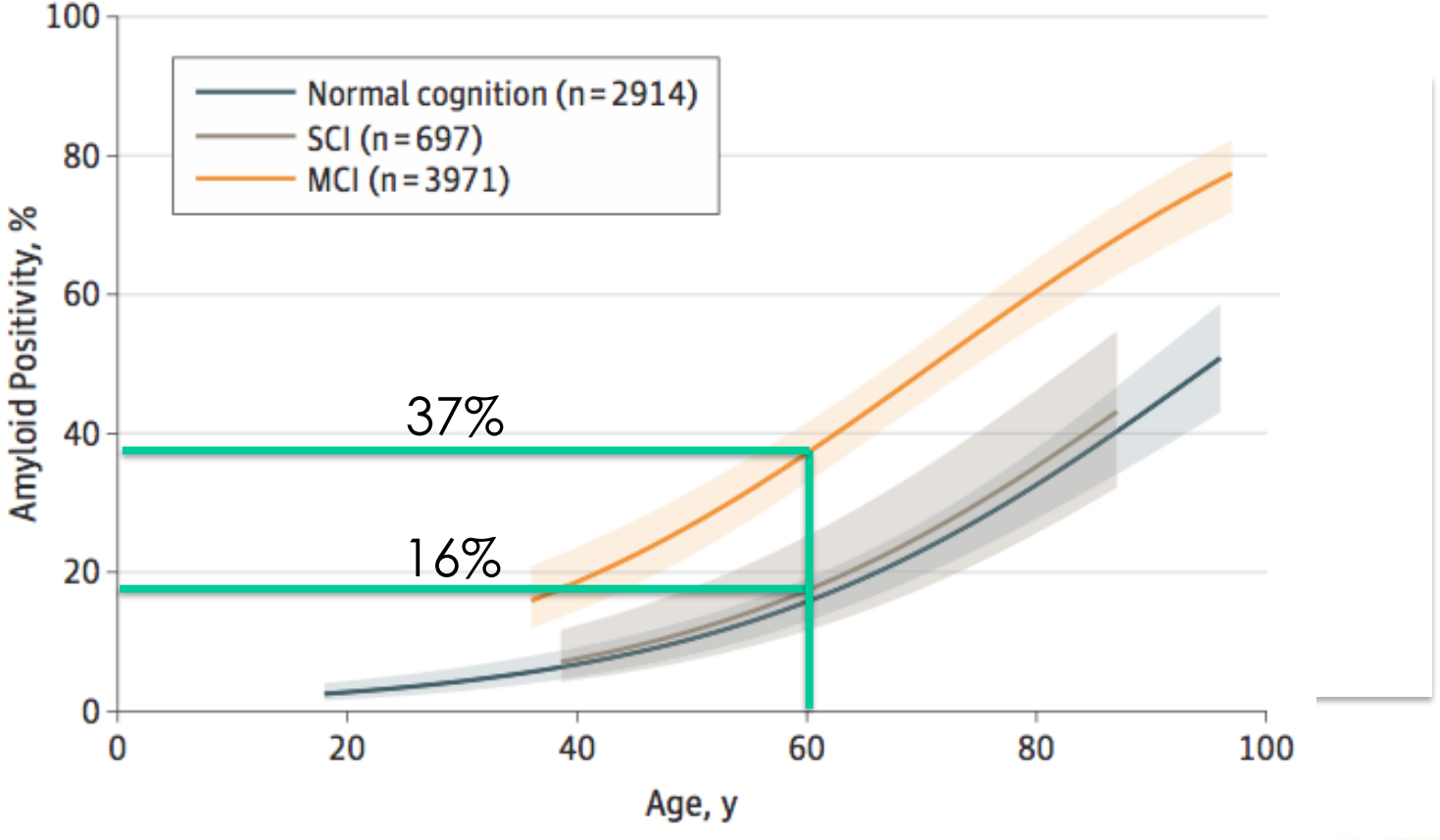
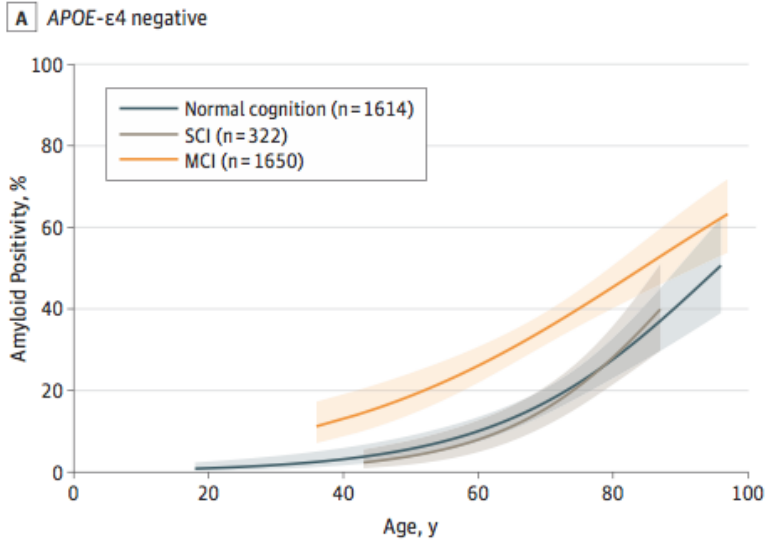
Prevalence amyloid positivity in non-demented subjects



Prevalence amyloid positivity in non-demented subjects: effect of APOE



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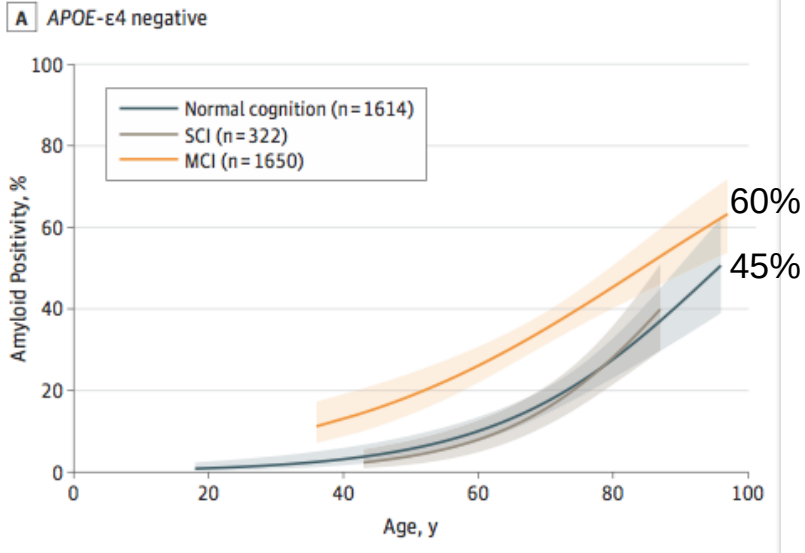
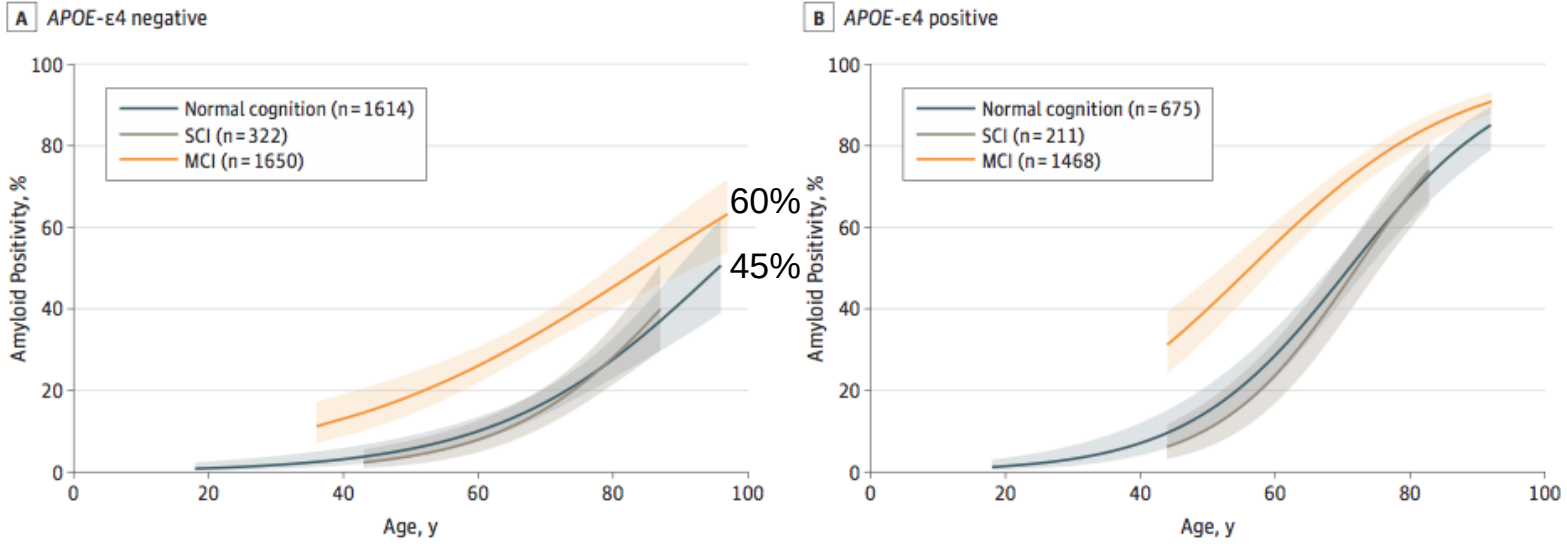
Prevalence amyloid positivity in non-demented subjects: effect of APOE



Prevalence amyloid positivity in non-demented subjects: effect of APOE



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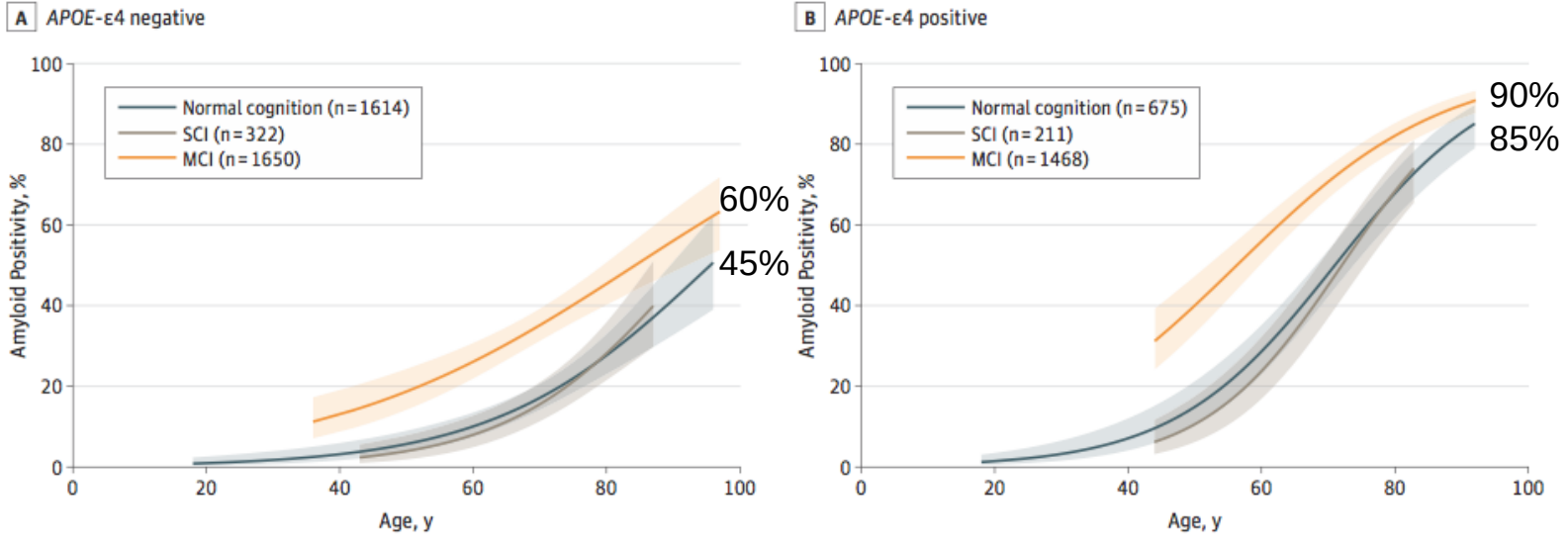
Prevalence amyloid positivity in non-demented subjects: effect of APOE



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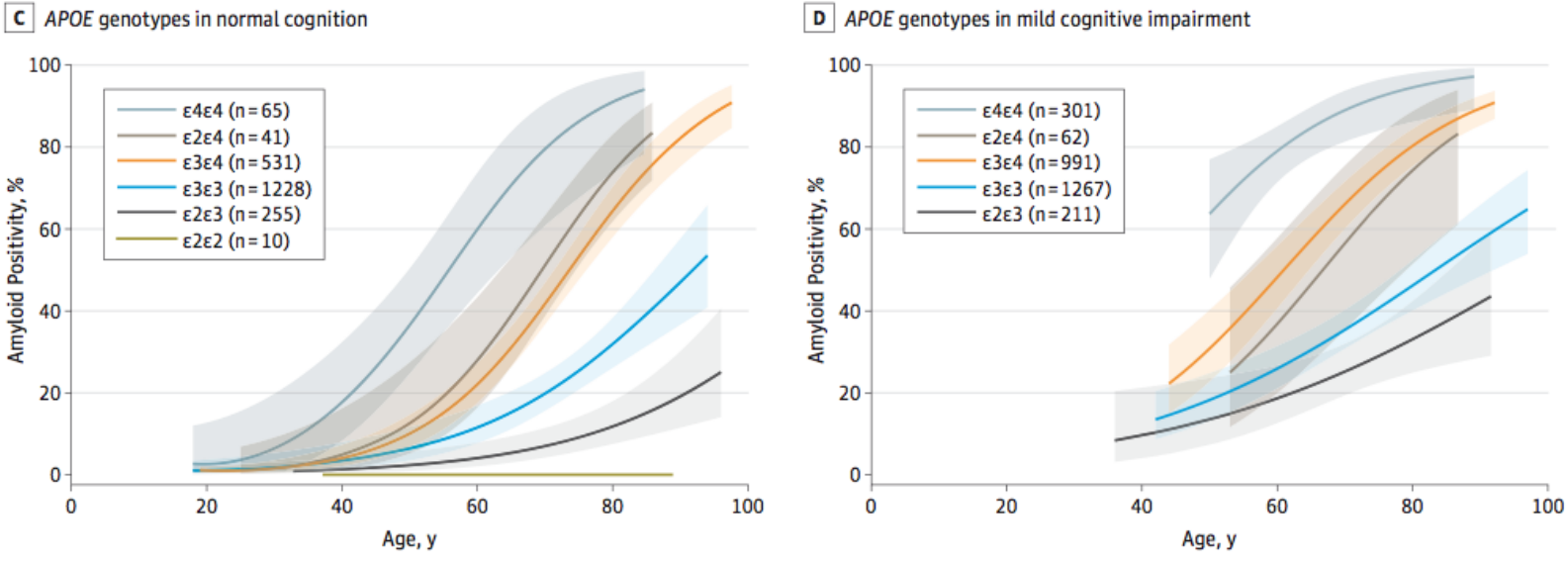

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Implications for screening for amyloid positivity-1

eTable 6. Number needed to screen according to age, cognitive status and *APOE* genotype

Group	50 yr	60 yr	70 yr	80 yr	90 yr
Number needed to screen if *APOE* genotype is known					
Participants with normal cognition					
Total group	10.0 (7.7-12.5)	6.3 (5.3-7.7)	4.3 (3.7-5.3)	3.0 (2.6-3.6)	2.3 (2.0-2.7)
APOE-ε4-	16.7 (11.1-25.0)	10.0 (7.7-14.3)	5.9 (4.8-7.1)	3.6 (3.0-4.3)	2.4 (2.0-3.0)
APOE-ε4+	6.7 (4.8-10.0)	3.4 (2.7-4.5)	2.1 (1.9-2.4)	1.5 (1.4-1.6)	1.2 (1.1-1.3)
APOE-ε4ε4	2.8 (2.0-4.0)	1.7 (1.4-2.4)	1.3 (1.1-1.7)	1.1 (1.0-1.4)	1.0 (1.0-1.3)
Patients with MCI					
Total group	3.7 (3.3-4.3)	2.7 (2.4-3.0)	2.0 (1.9-2.2)	1.7 (1.5-1.8)	1.4 (1.3-1.5)
APOE-ε4-	5.3 (4.2-7.1)	3.8 (3.2-4.5)	2.9 (2.6-3.2)	2.2 (2.0-2.5)	1.8 (1.6-2.1)
APOE-ε4+	2.5 (2.1-3.0)	1.8 (1.6-2.0)	1.4 (1.4-1.5)	1.2 (1.2-1.3)	1.1 (1.1-1.2)
APOE-ε4ε4	1.6 (1.3-2.1)	1.3 (1.2-1.4)	1.1 (1.1-1.2)	1.1 (1.0-1.2)	1.0 (1.0-1.1)

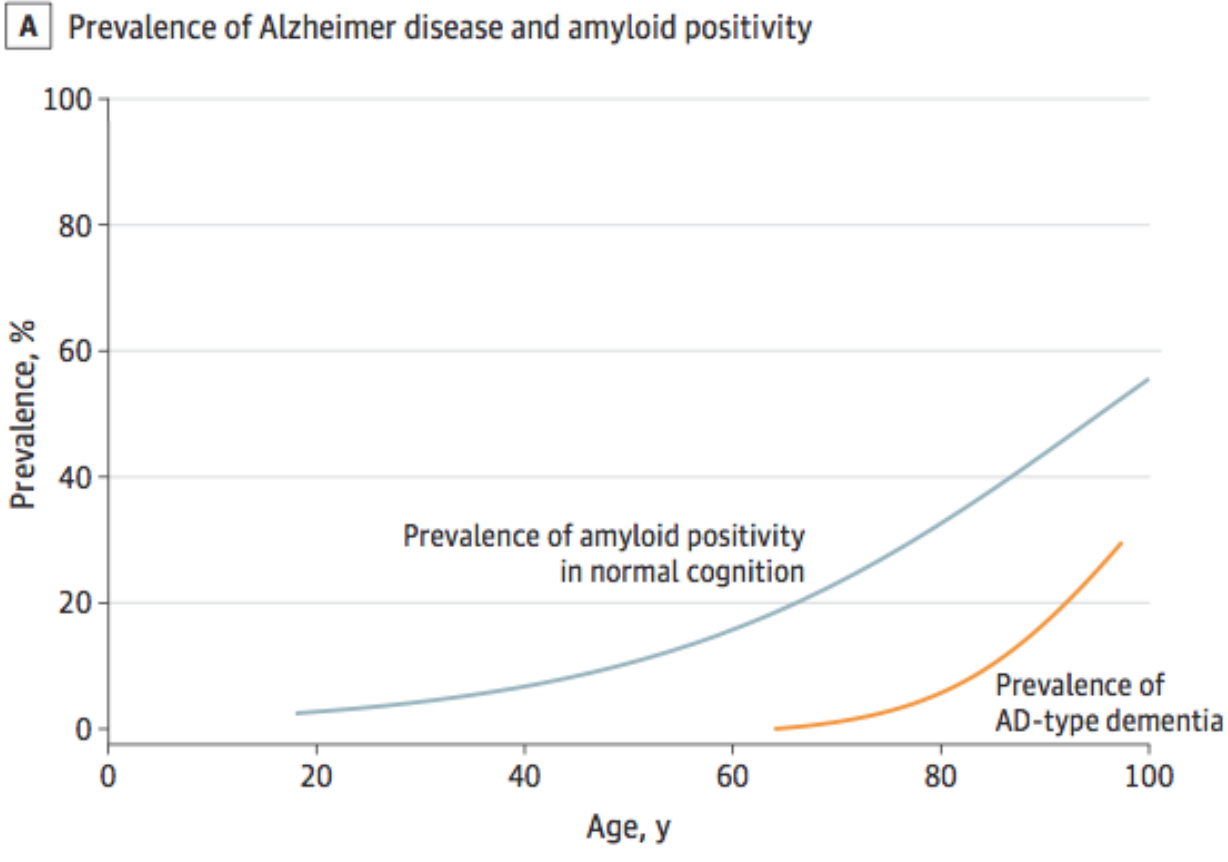
Implications for screening for amyloid positivity-2

eTable 6. Number needed to screen according to age, cognitive status and *APOE* genotype

Group	50 yr	60 yr	70 yr	80 yr	90 yr
Number of participants needed for *APOE* genotyping in order to find 1 amyloid positive participant *					
Participants with normal cognition					
APOE-ε4-	23.6 (15.8-35.5)	14.2 (10.9-20.3)	8.3 (6.8-10.1)	5.1 (4.3-6.2)	3.5 (2.8-4.3)
APOE-ε4+	22.6 (16.9-33.9)	11.7 (9.2-15.4)	7.1 (6.3-8.1)	5.0 (4.6-5.5)	4.1 (3.9-4.4)
APOE-ε4ε4	89.6 (64.5-129.0)	55.6 (45.4-76.8)	40.3 (35.8-54.7)	35.4 (32.9-43.6)	34.3 (32.6-41.4)
Patients with MCI					
APOE-ε4-	9.9 (7.9-13.5)	7.3 (6.1-8.6)	5.4 (4.8-6.1)	4.2 (3.7-4.7)	3.4 (3.0-3.9)
APOE-ε4+	5.3 (4.5-6.4)	3.8 (3.5-4.2)	3.0 (2.9-3.2)	2.6 (2.5-2.7)	2.4 (2.3-2.5)
APOE-ε4ε4	14.7 (12.3-19.7)	11.9 (11.1-13.1)	10.6 (10.0-11.6)	9.9 (9.6-11.0)	9.7 (9.5-10.6)

* If *APOE* genotype is unknown, participants need to be screened for this first. The number needed to screen now indicate the number of participants for whom *APOE* genotyping needs to be performed in order to find one participant with that *APOE*-ε4 carrier status who is amyloid positive. It is calculated as the inverse of the point estimates for the prevalence of amyloid pathology multiplied by the *APOE*-ε4 background prevalence in our sample.

Comparison prevalence amyloid positivity and AD-type dementia



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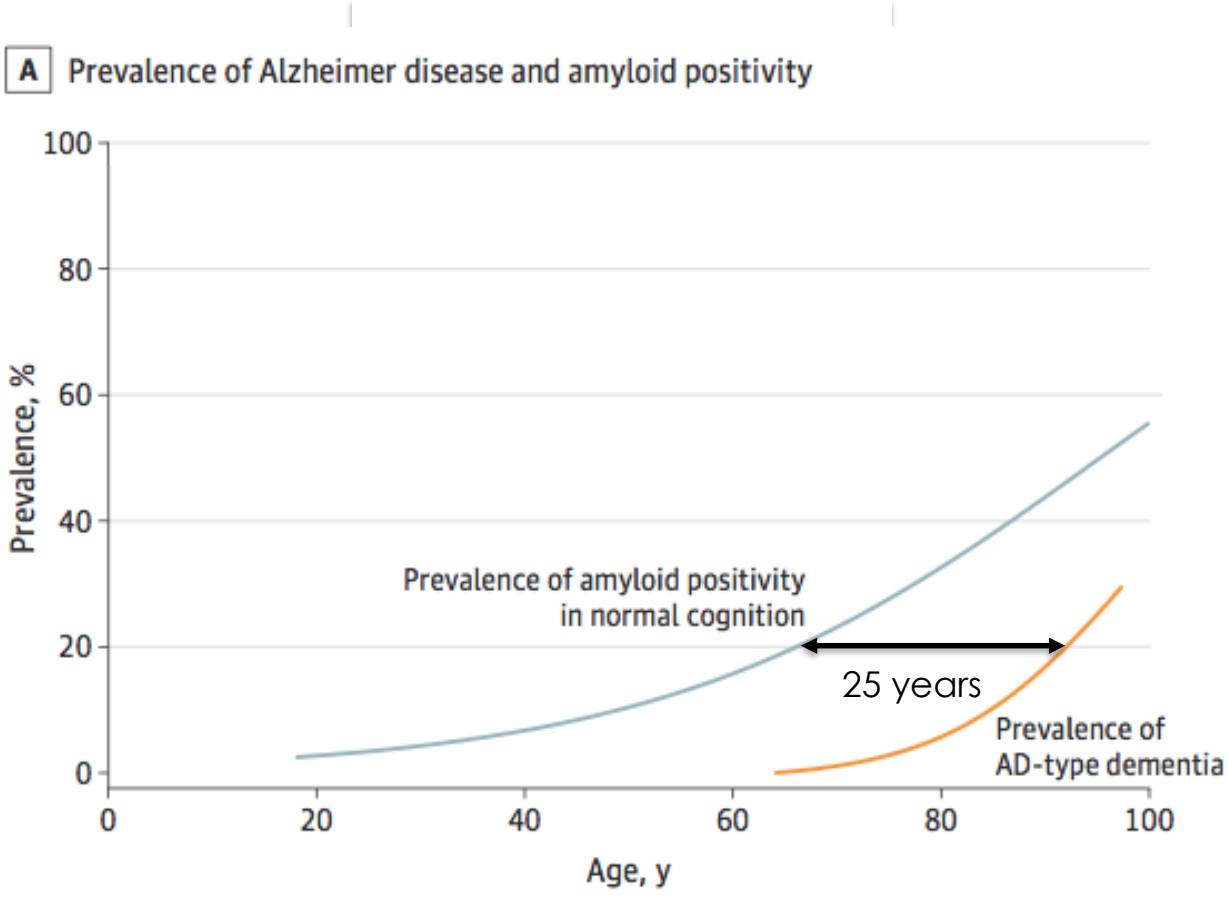
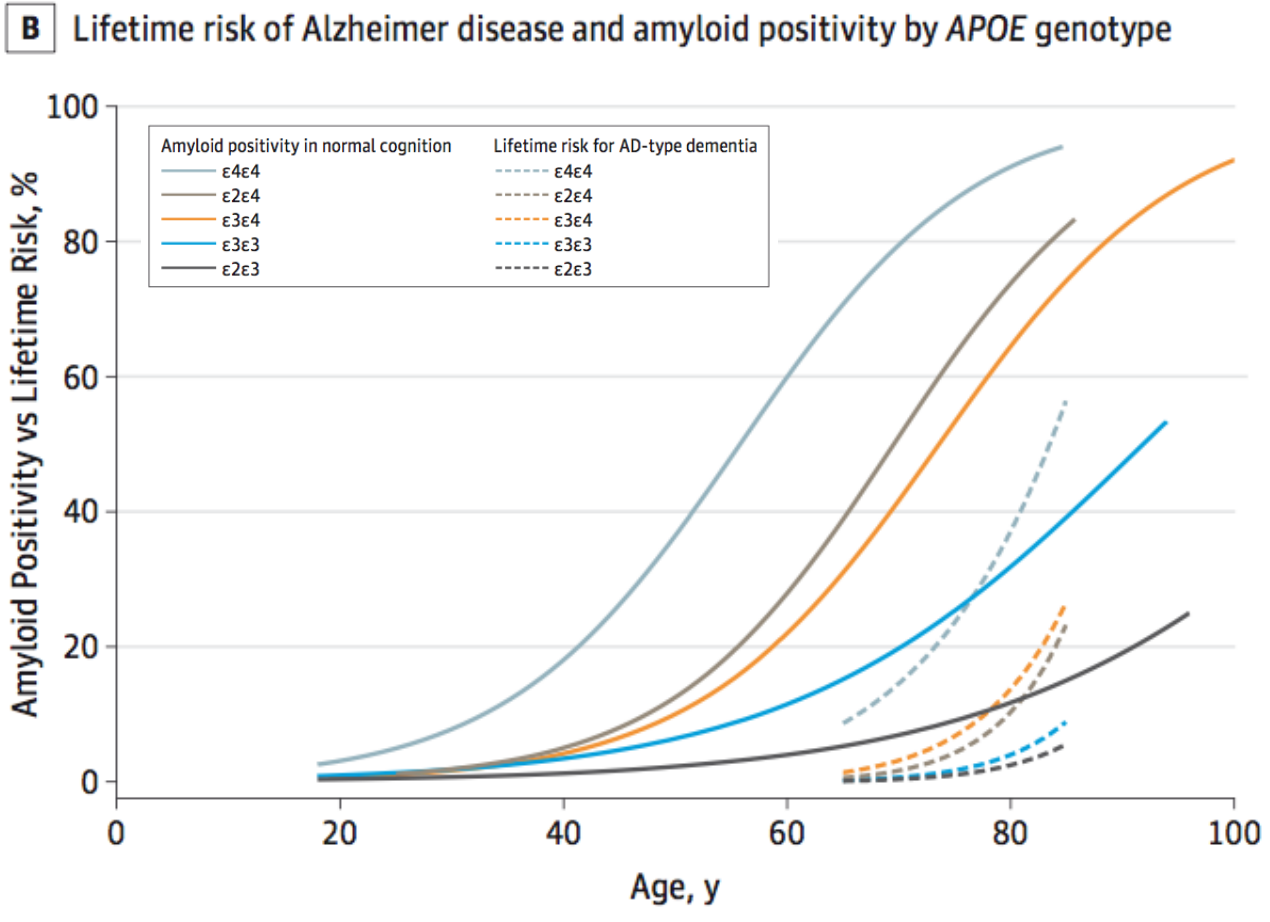
Comparison prevalence amyloid positivity and AD-type dementia



Comparison prevalence amyloid positivity and AD-type dementia



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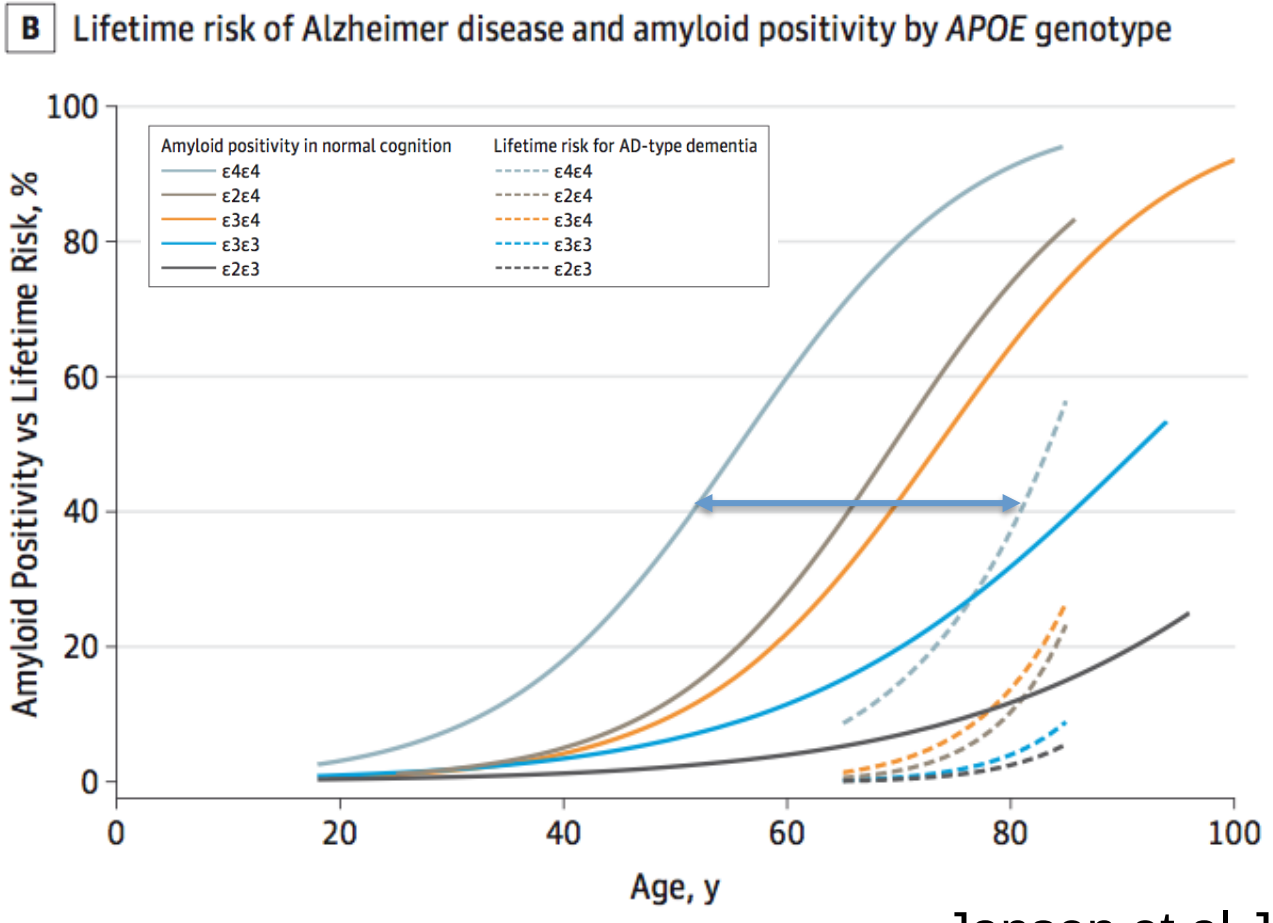
Comparison prevalence amyloid positivity and AD-type dementia



Jansen et al JAMA 2015

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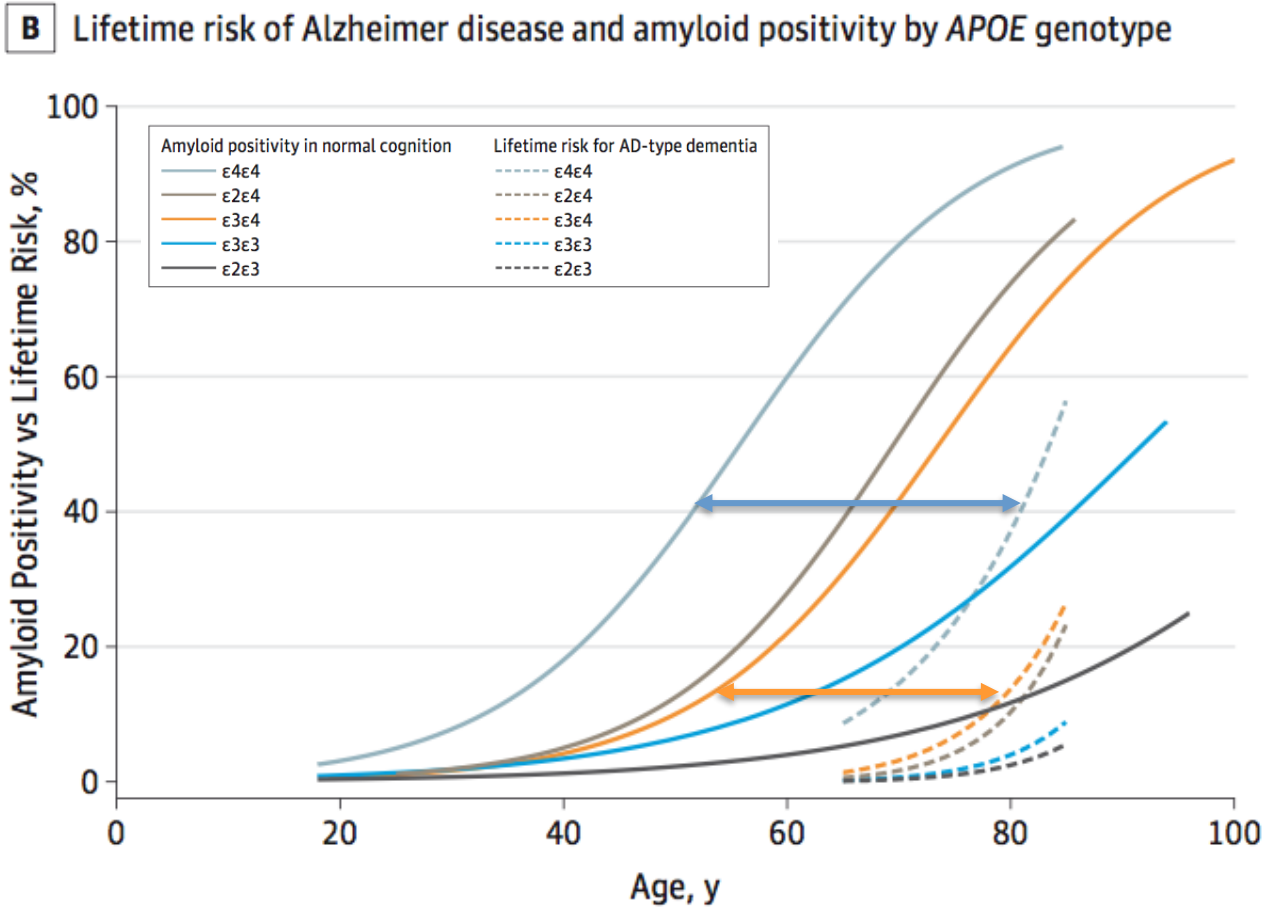
Comparison prevalence amyloid positivity and AD-type dementia



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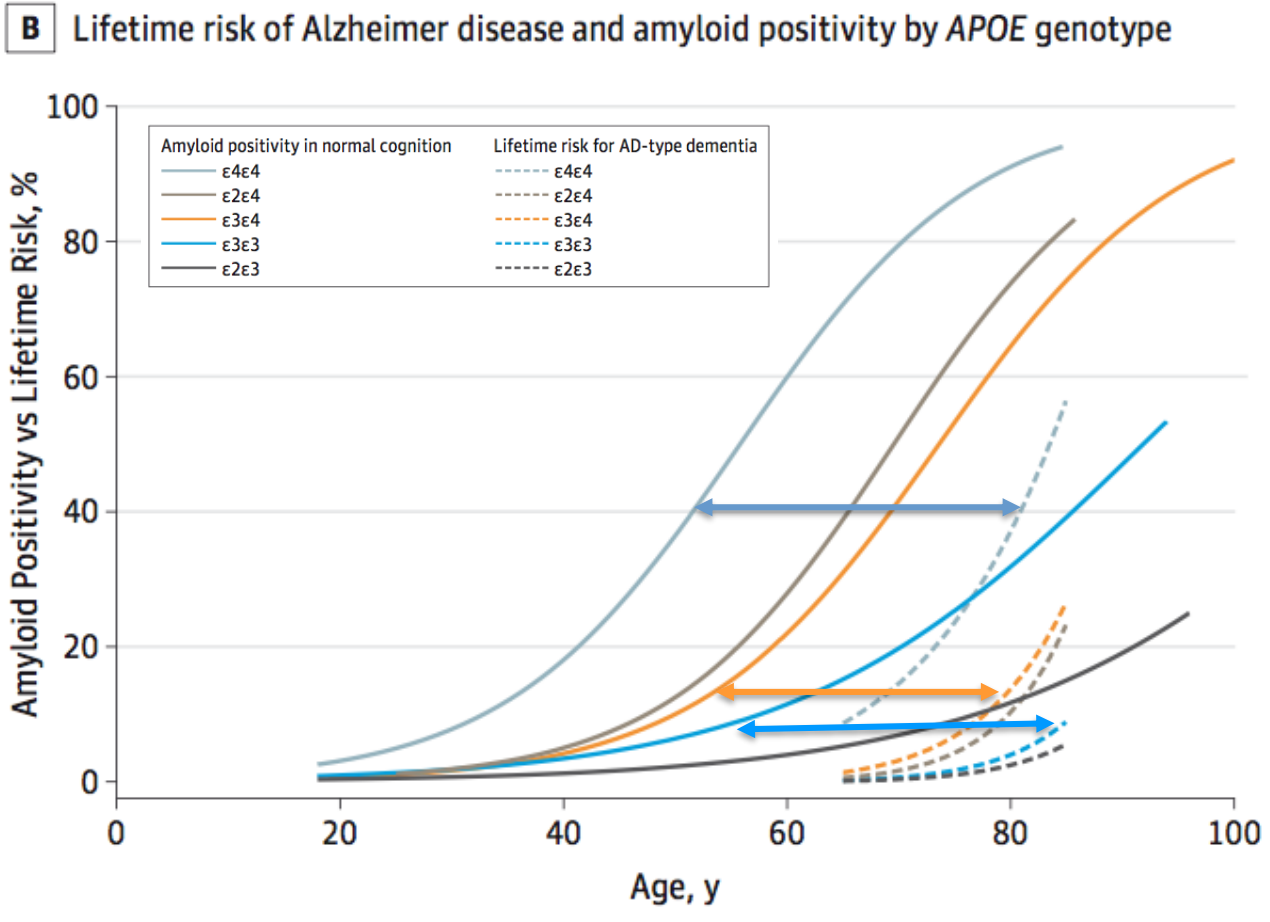
Comparison prevalence amyloid positivity and AD-type dementia



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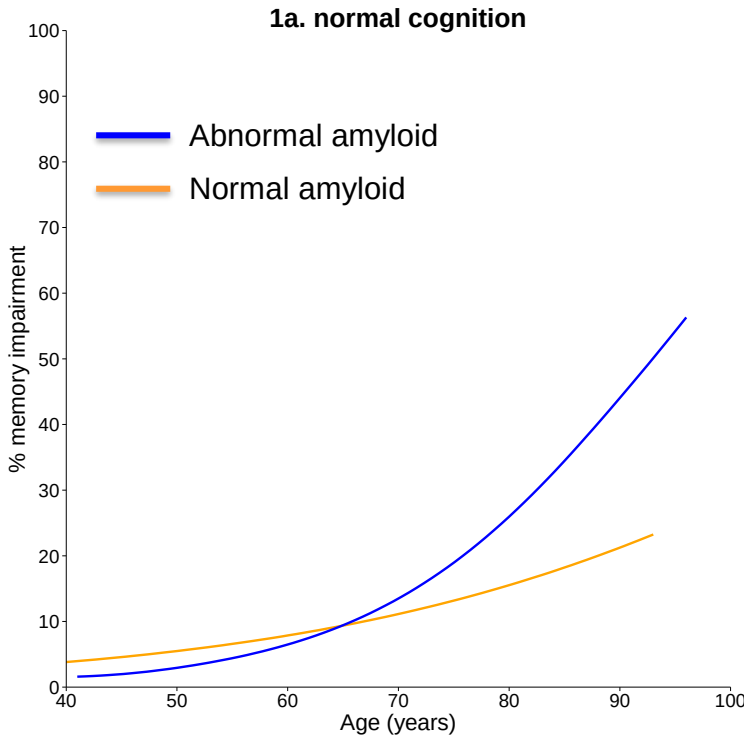
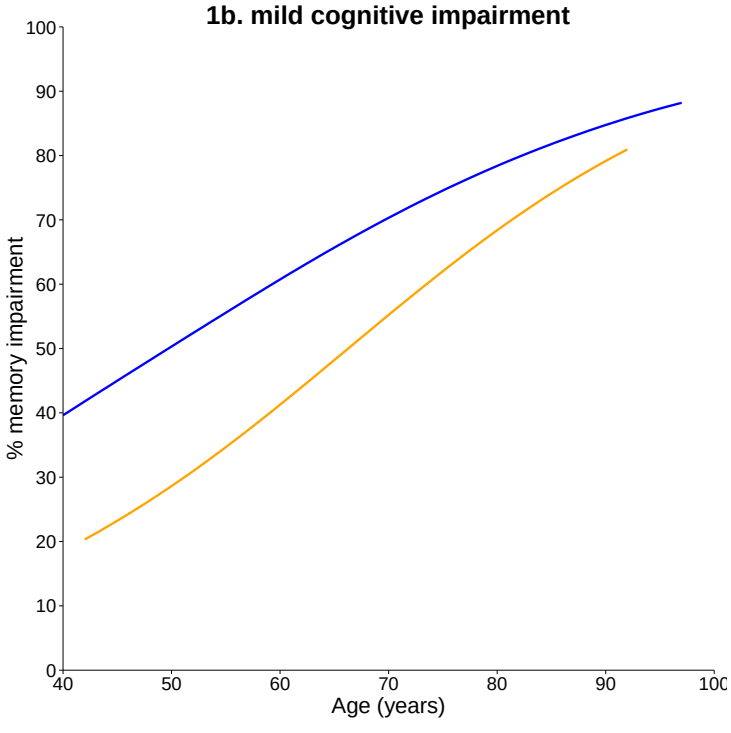
Relation with memory score





1a Frequency of memory impairment (z-score <= -1.28) in participants with normal cognition, n=2544
1b Frequency of memory impairment in participants with MCI, n=2960

Jansen et al in preparation

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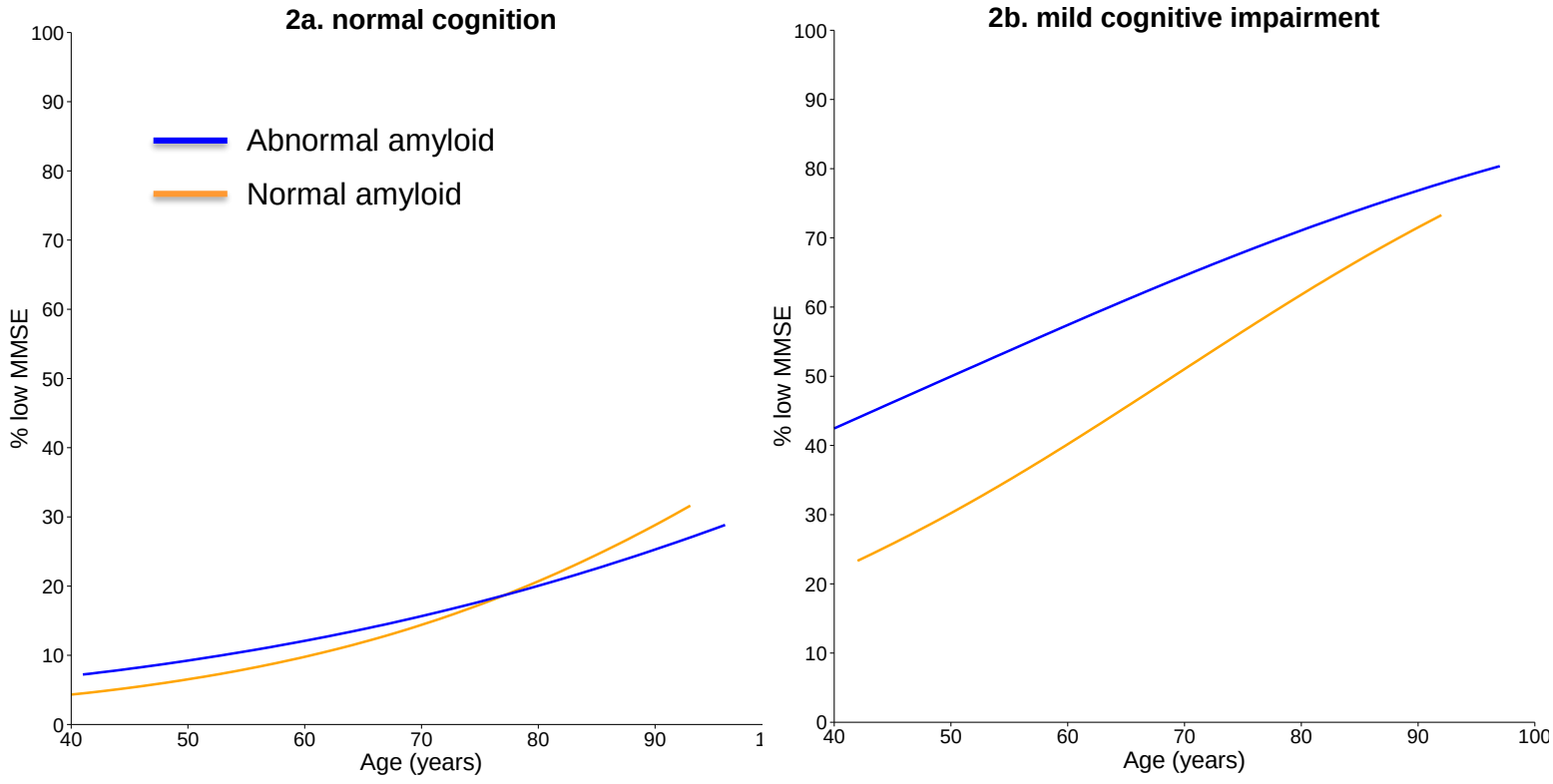
Relation with MMSE score



2a Frequency of low MMSE (MMSE <= 27) in participants with normal cognition, n=2885
2b Frequency of low MMSE in participants with MCI, n=4126

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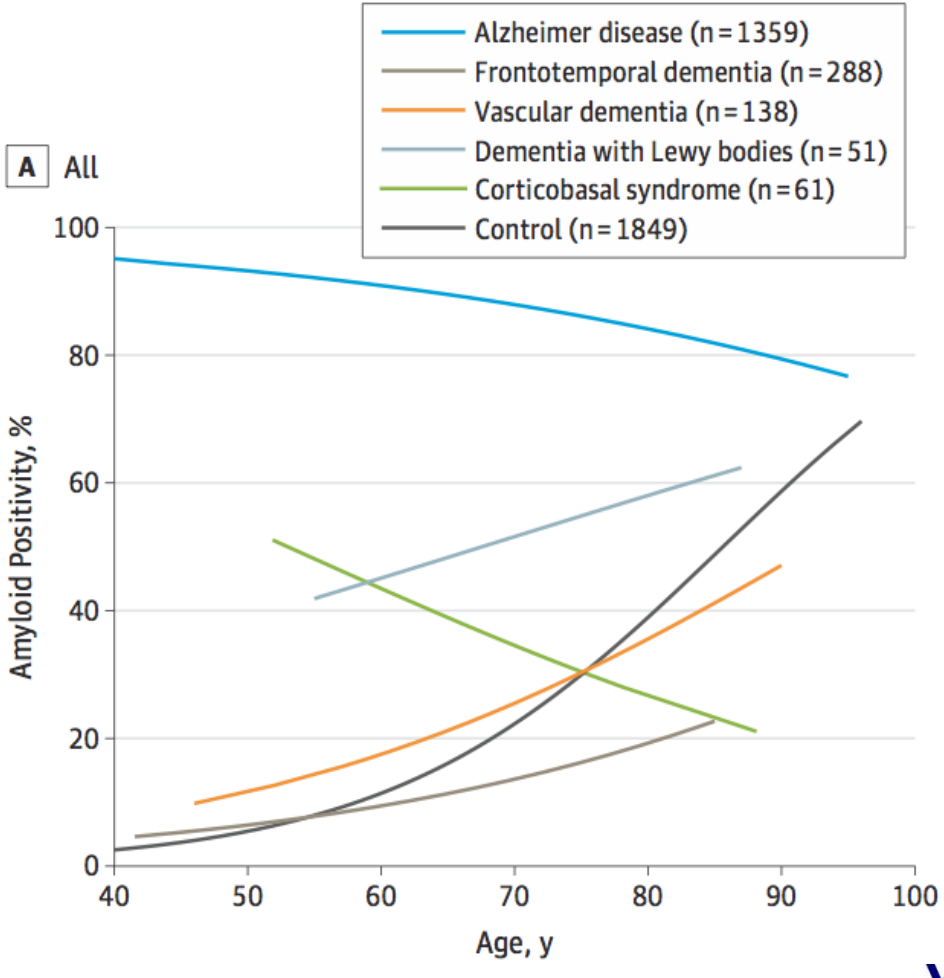
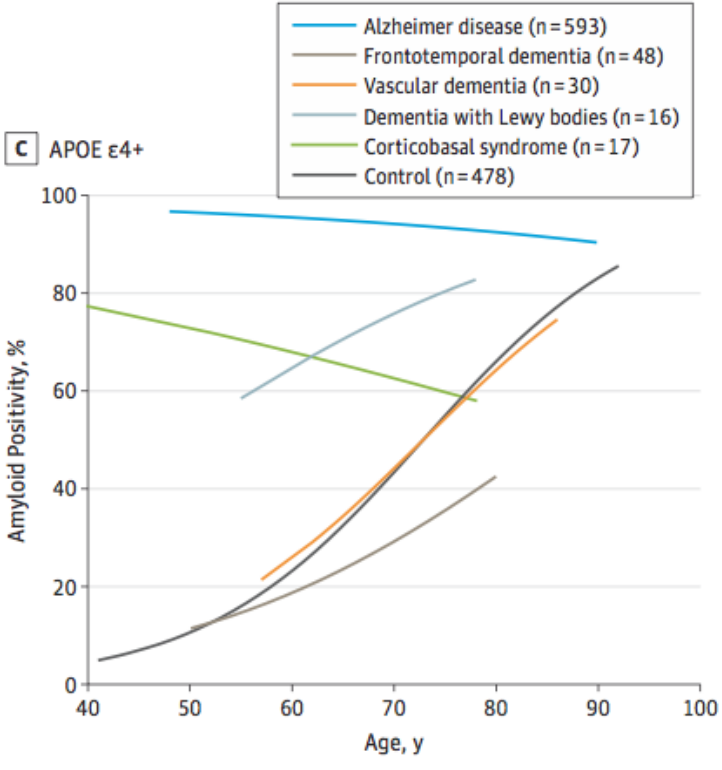
Summary prevalence amyloid positivity in non-demented subjects

- Higher in MCI than in cognitively normal and SCI
- Strongly dependent on age and APOE genotype
- Amyloid positivity in cognitively normal subjects precedes AD-type dementia by >25 years

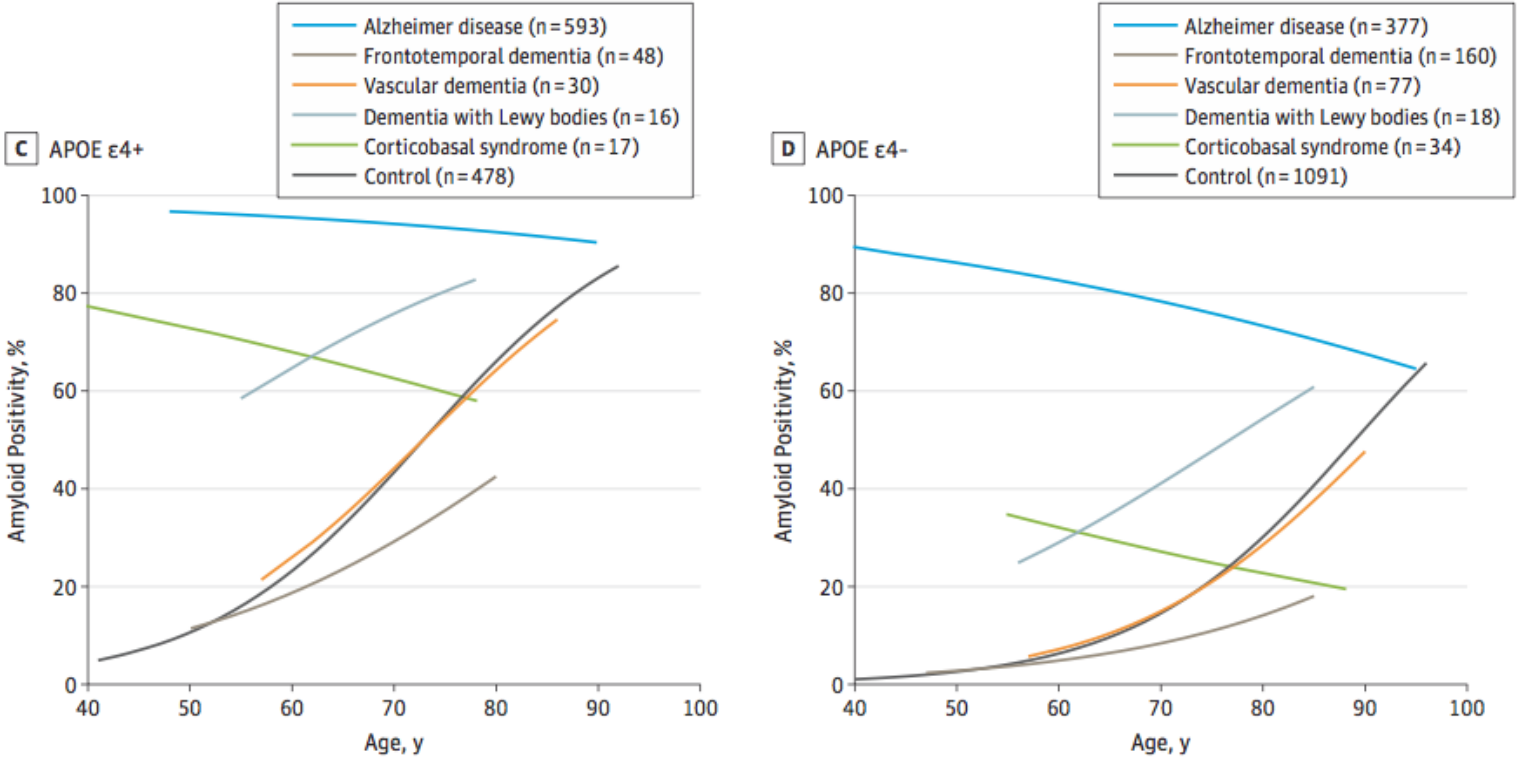
Prevalence amyloid positivity in demented subjects



Prevalence amyloid positivity in demented subjects: effect of APOE



Prevalence amyloid positivity in demented subjects:effect of APOE



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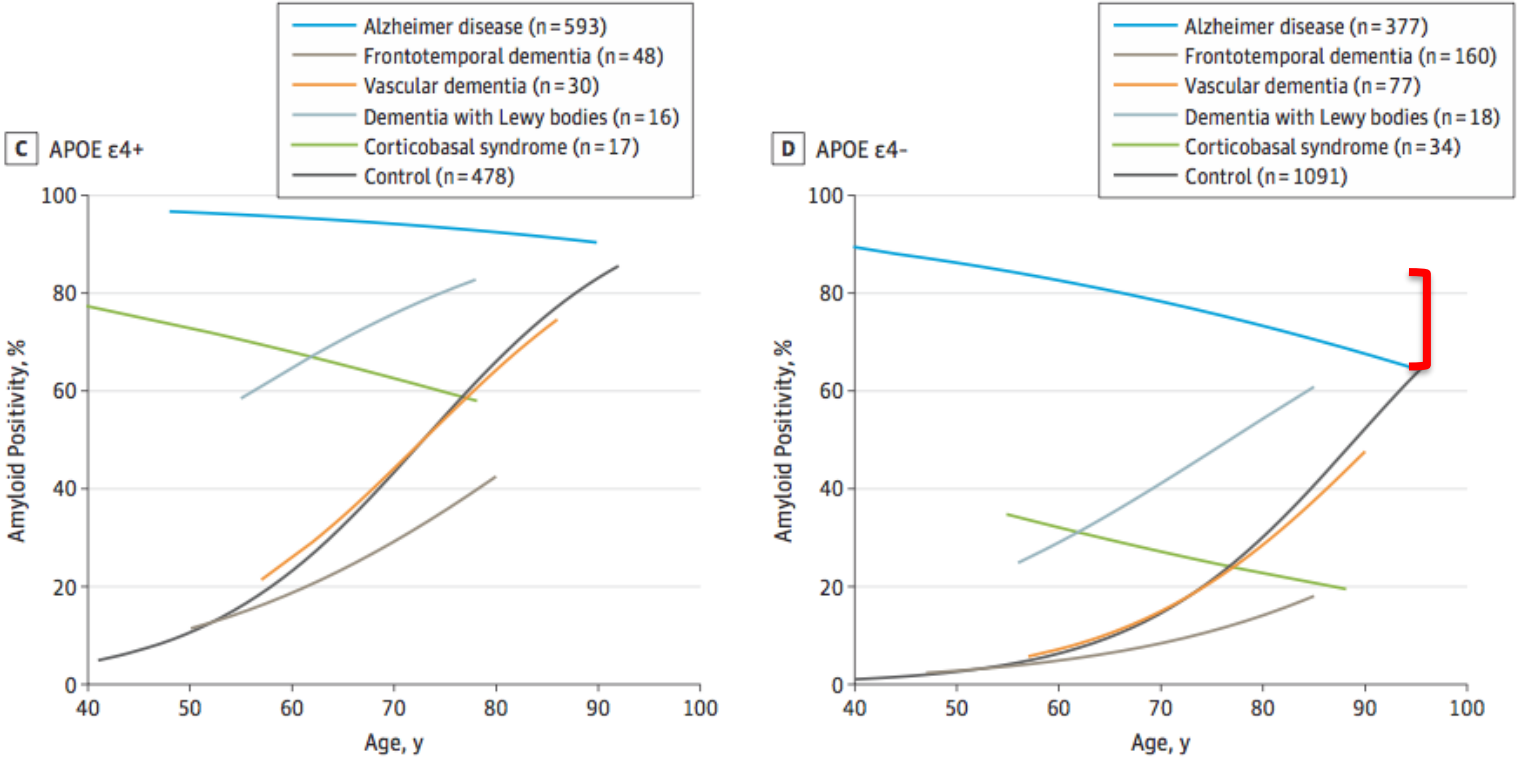
Prevalence amyloid positivity in demented subjects



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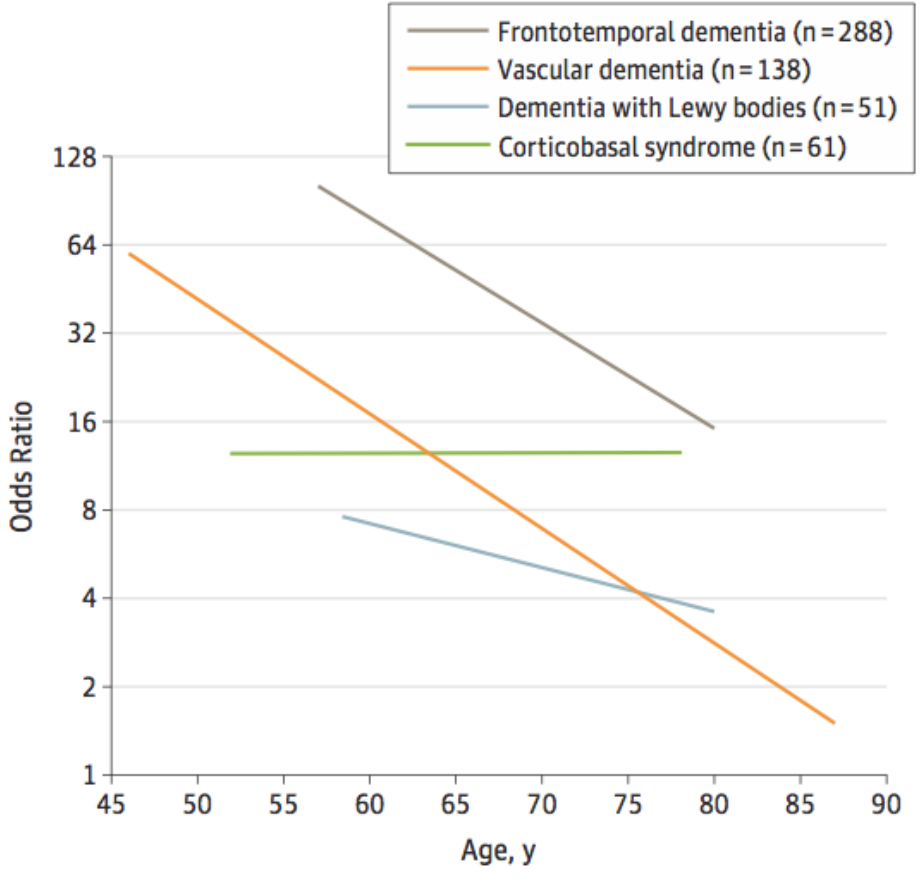
Effect amyloid positivity on MMSE score in non-AD dementia

	Amyloid positive	Amyloid negative	P-value
Any dementia	20.6	23.2	<0.001
DLB	19.6	25.3	<0.001
VaD	19.5	22.3	<0.05
FTLD	22.4	23.9	0.17
CBS	21.6	23	0.48

Ossenkoppele et al JAMA 2015

Diagnostic accuracy amyloid positivity for distinction from AD



Summary prevalence amyloid positivity in demented subjects

- Amyloid positivity converges at high age across dementias
- Not all subjects with a clinical AD diagnosis are amyloid positive
- Clinical diagnosis AD and e4+:
  - >90% amyloid positive
- Clinical diagnosis AD and e4-:
  - At age 70: 90% amyloid positive
  - At age 90: 65% amyloid positive
- Amyloid positivity common in non-AD dementia
- Odds ratio decreases for clinical dementia subtype diagnosis
- Clinical relevance?
- Misdiagnosis?
- Co-morbidity?

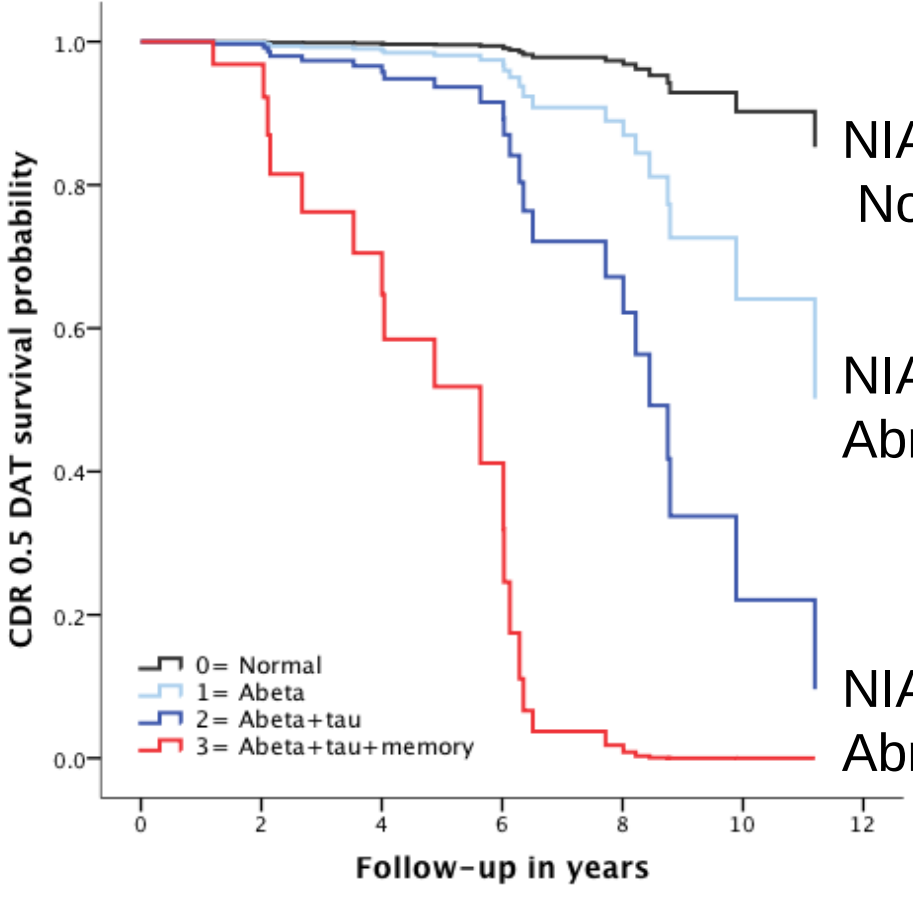
Diagnosis and prognosis

- Amyloid markers for diagnosis
- Injury markers for prognosis

- AD stages:

AD stage	Cognition	AD biomarker
Preclinical stage	Normal	Abnormal
MCI stage	MCI	Abnormal
Dementia stage	Dementia	Abnormal

Prognosis preclinical AD (n=311): progression to MCI



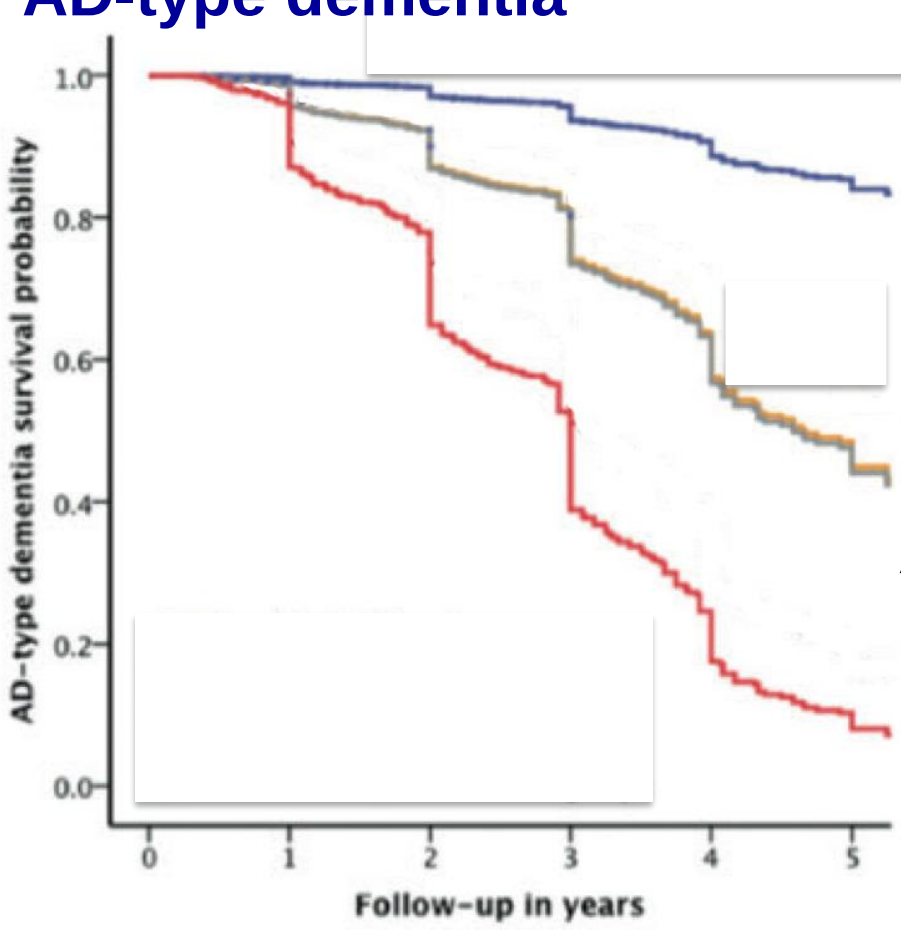
NIA-AA stage 0
Normal amyloid and tau

NIA-AA stage 1
Abnormal amyloid and normal tau

NIA-AA stage 2/3
Abnormal amyloid and abnormal tau

Vos et al Lancet Neurology 2013

Prognosis prodromal AD (n=1607): progression to AD-type dementia



NIA-AA low likelihood
Normal amyloid and tau

NIA-AA conflicting
Normal amyloid and abnormal tau
Abnormal amyloid and normal tau

NIA-AA high likelihood
Abnormal amyloid and abnormal tau

Vos et al Brain 2015

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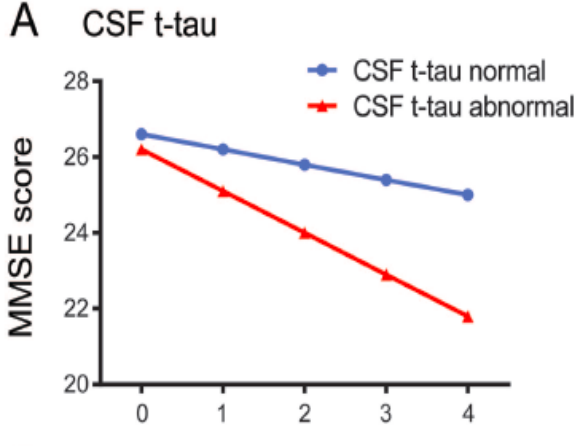
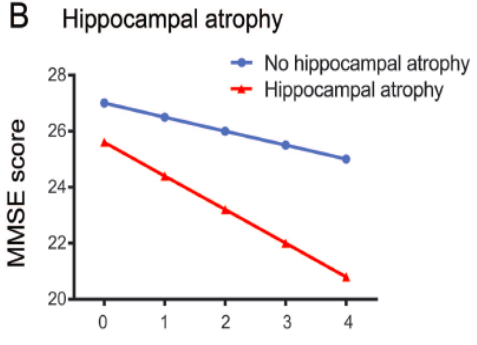
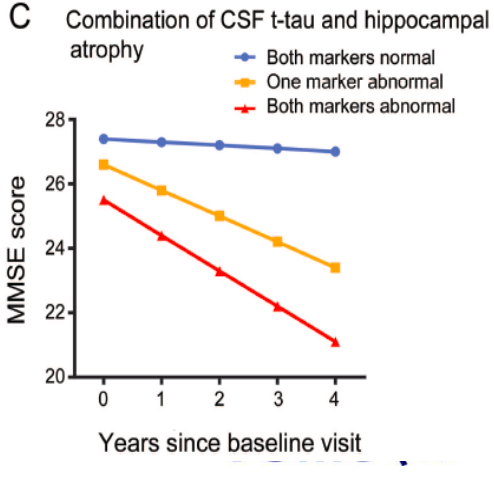
Pieter Jelle Visser, MD, PhD

Injury markers predict time to dementia in subjects with MCI and amyloid pathology

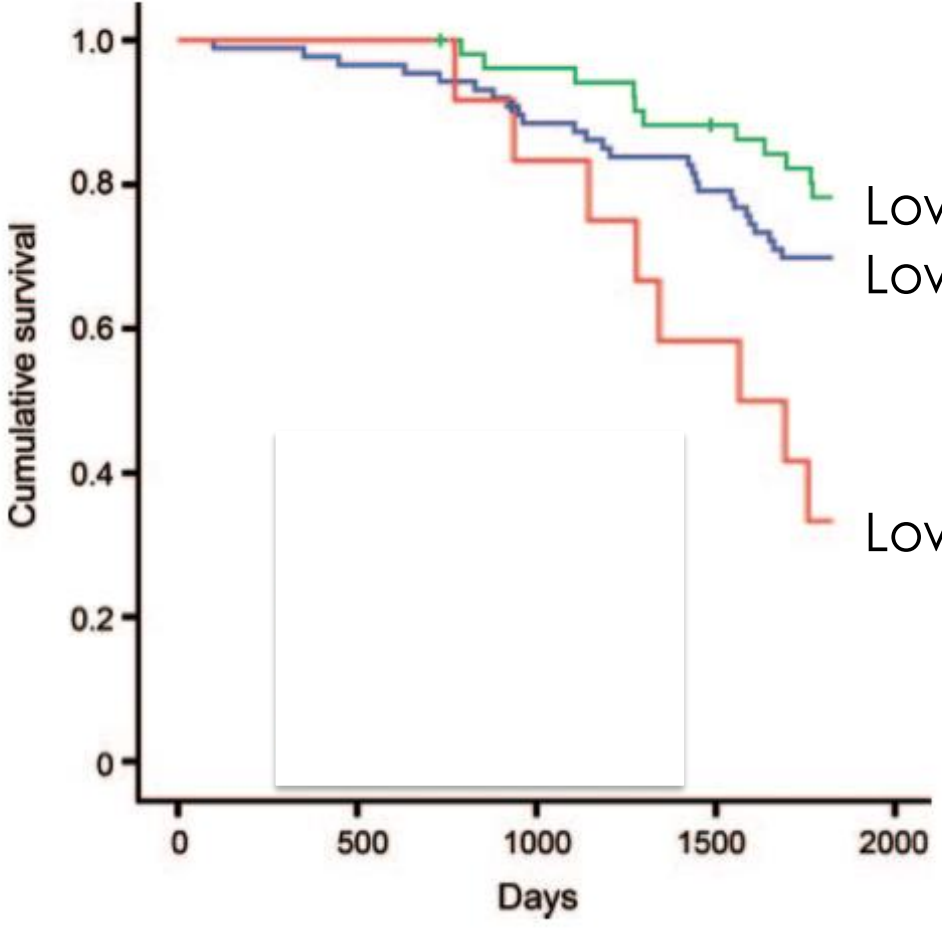
Figure 2 Decline in Mini-Mental State Examination (MMSE) score in subjects with mild cognitive impairment (MCI) and abnormal CSF $A\beta_{1-42}$ according to CSF total tau (t-tau) and hippocampal volume







Prognosis AD dementia stage



Low abeta low tau

Low abeta high tau

Low abeta very high tau

Wallin et al Neurology 2010

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Mrs H, 1911

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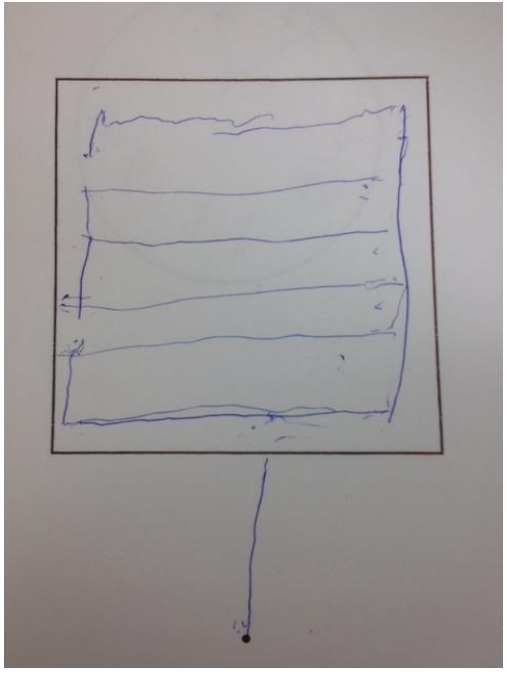
100 plus study

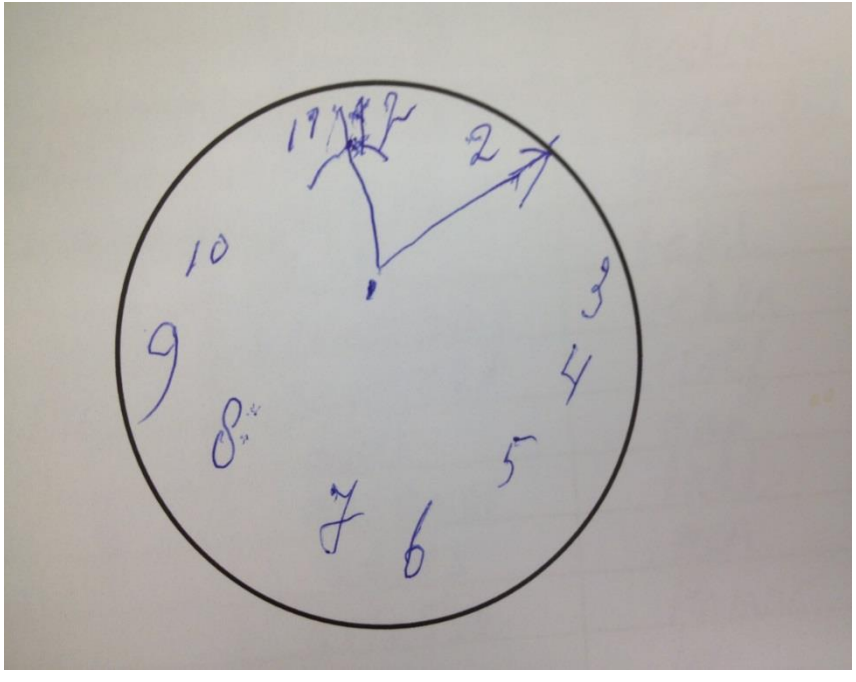
- Grew up in Rotterdam
- At age 28 she moved to Groningen
- Grew up in a familiy of musicians and became a musician herself (piano teacher)
- Oldest of 6 children
- 3 children

- Lab: ApoE 3/3
- MMSE 27/30

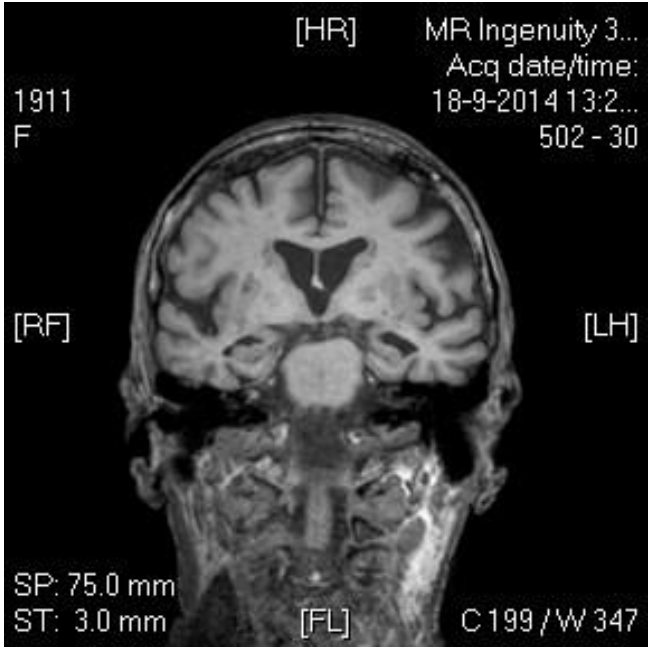
- One sigaret per week for 14 years (till age of 50)
- 69-90 years:
  - 3 glasses of (white/red) wine a week
- wide social network, lots of friends

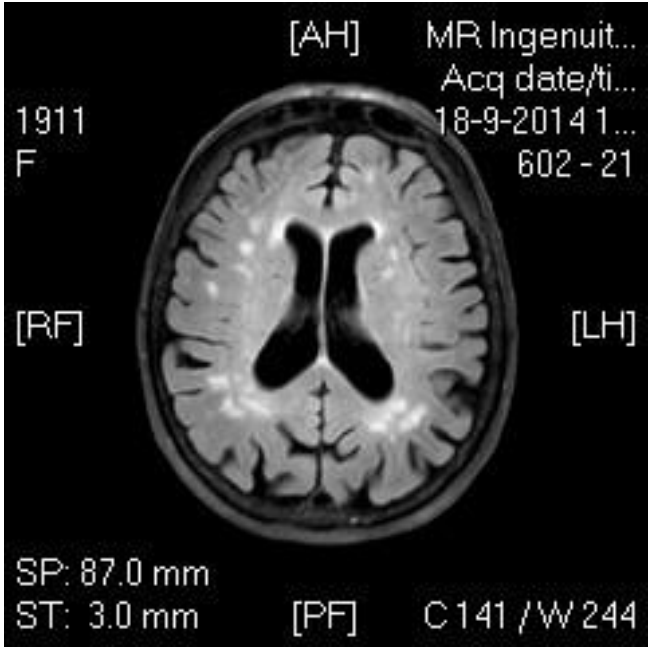
Neuropsychological examination





Mrs H. 1911; MTA 2/2; Faz 2; ApoE 3/3





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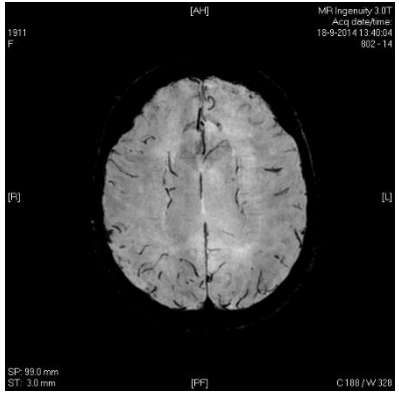
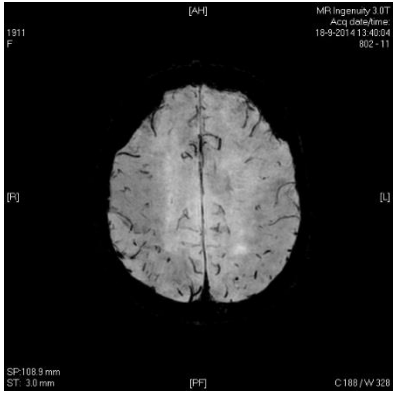
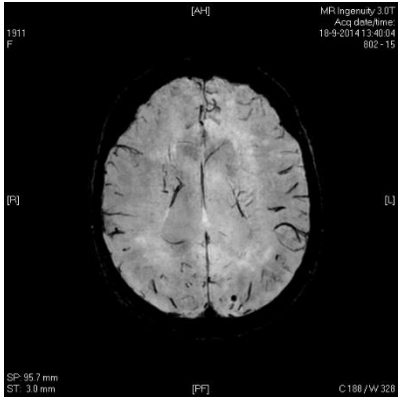
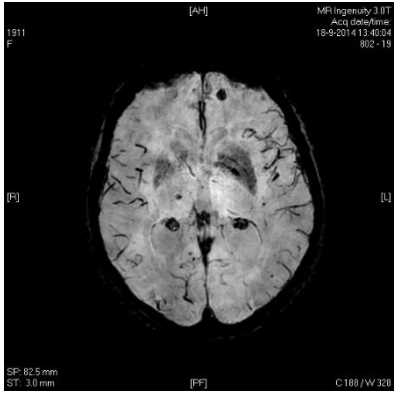
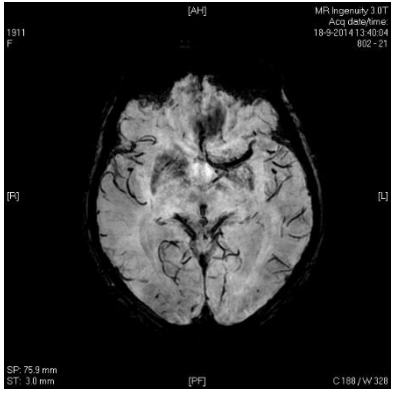
Mrs H. 1911; MMSE 27; amyloid angiopathy

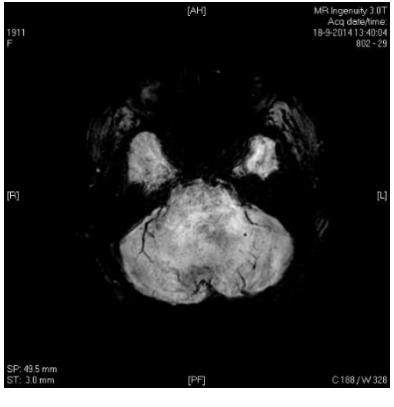


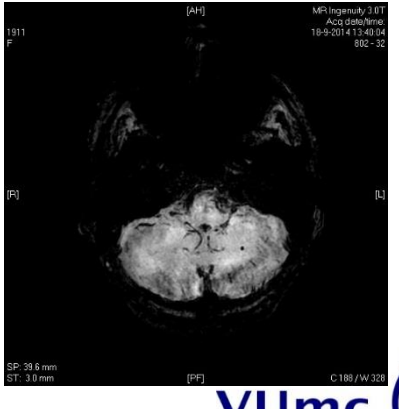












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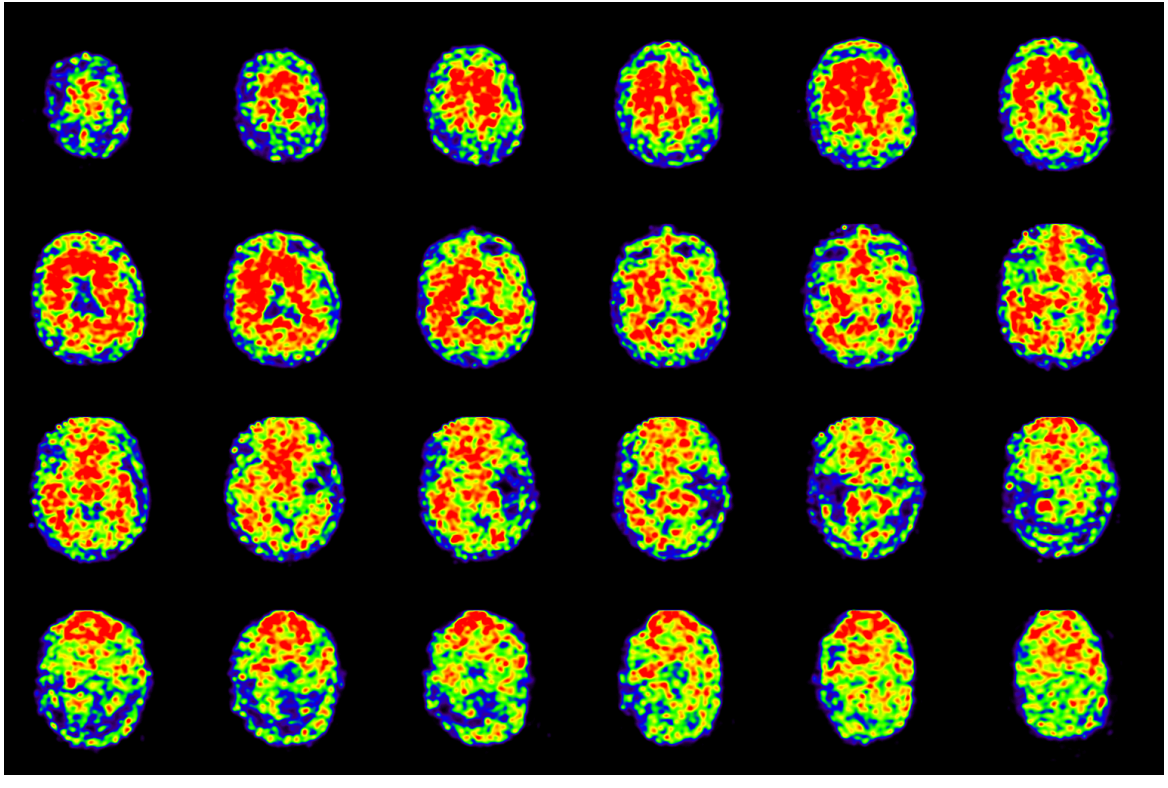
Mrs H, 1911. C^{11}PIB at 103



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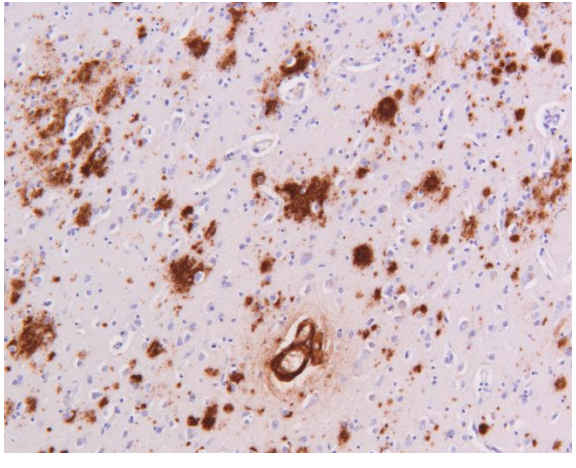
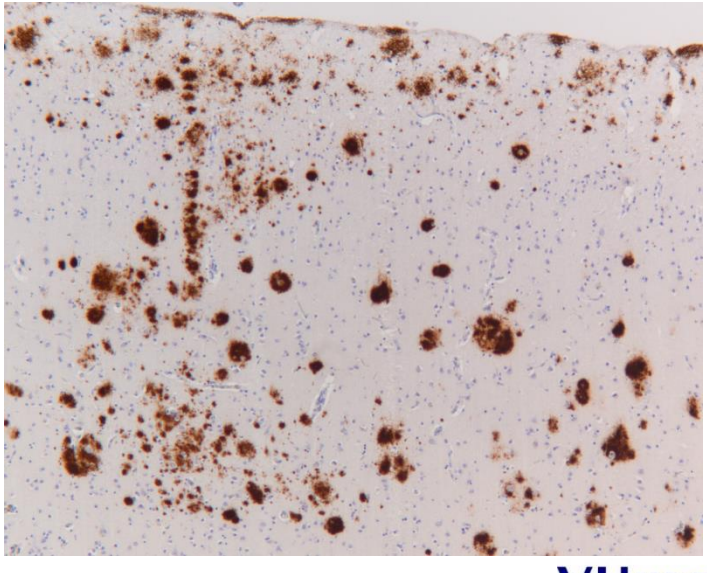
Pathology

Braak 3 tau/tangles
Thal 3/5 plaques.
CAA 1/ 3 (Thal).

Frontal abeta (10x)



Temporal Abeta



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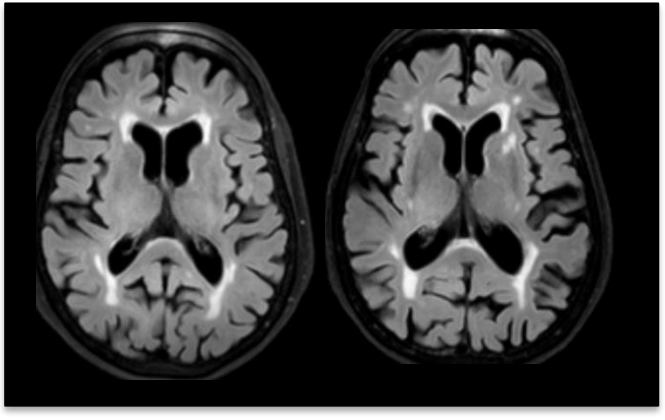
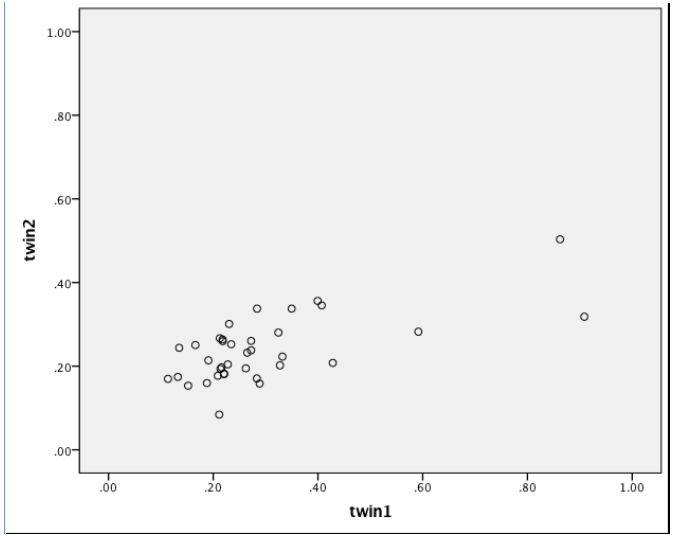
Heritability



White matter lesions in monozygotic twin pair



Correlation in PET amyloid binding between monozygotic twins

Konijnenberg/Ten Kate in preparation

Conclusions

- Field has changed dramatically due to biomarkers
- Amyloid positivity strongly related to age and APOE
- In normal aging and dementia(s)
- Diagnostic information decreases with age
- By itself not diagnostic for AD and not be used outside of clinical context
- May be used to select patients for interventions

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