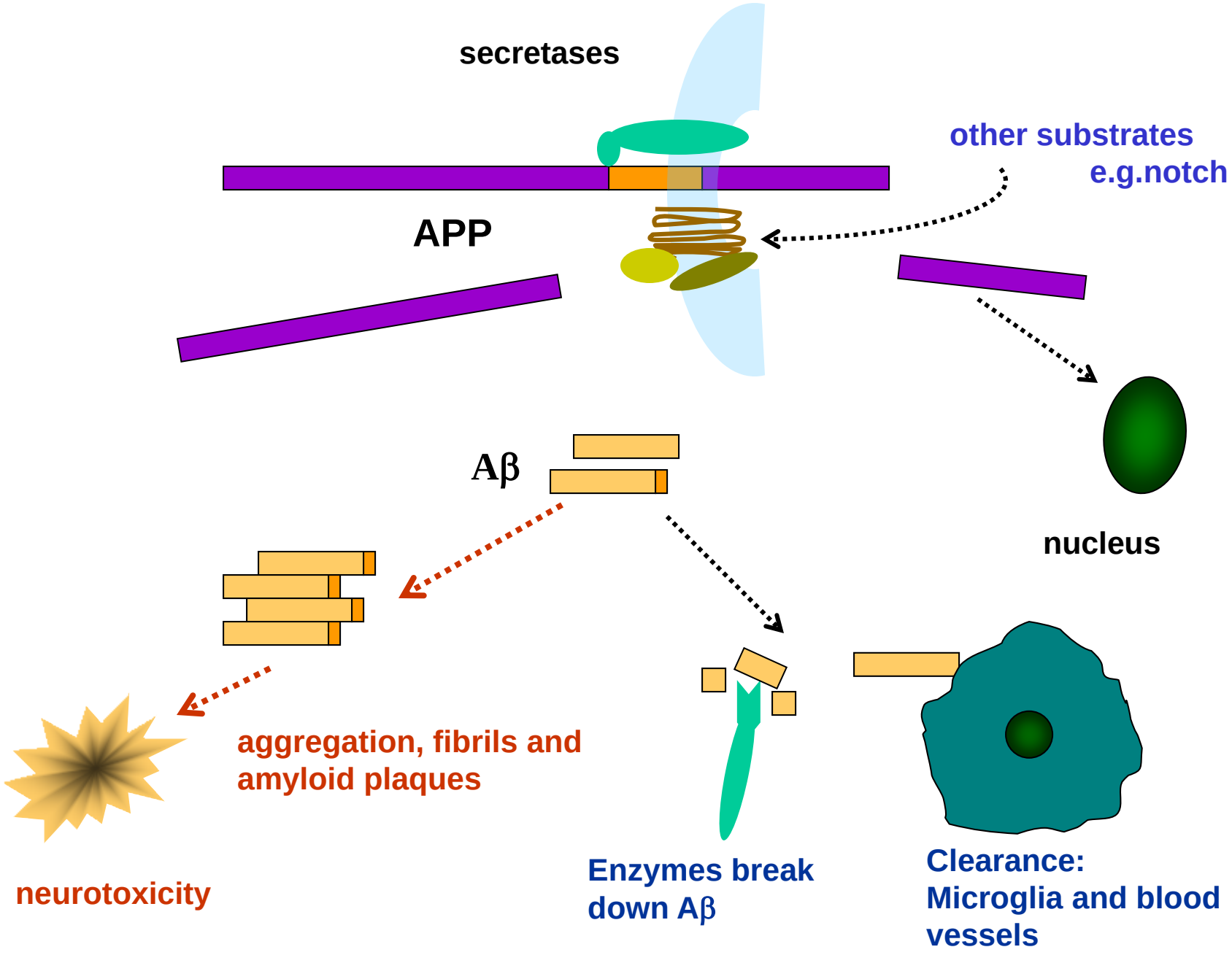
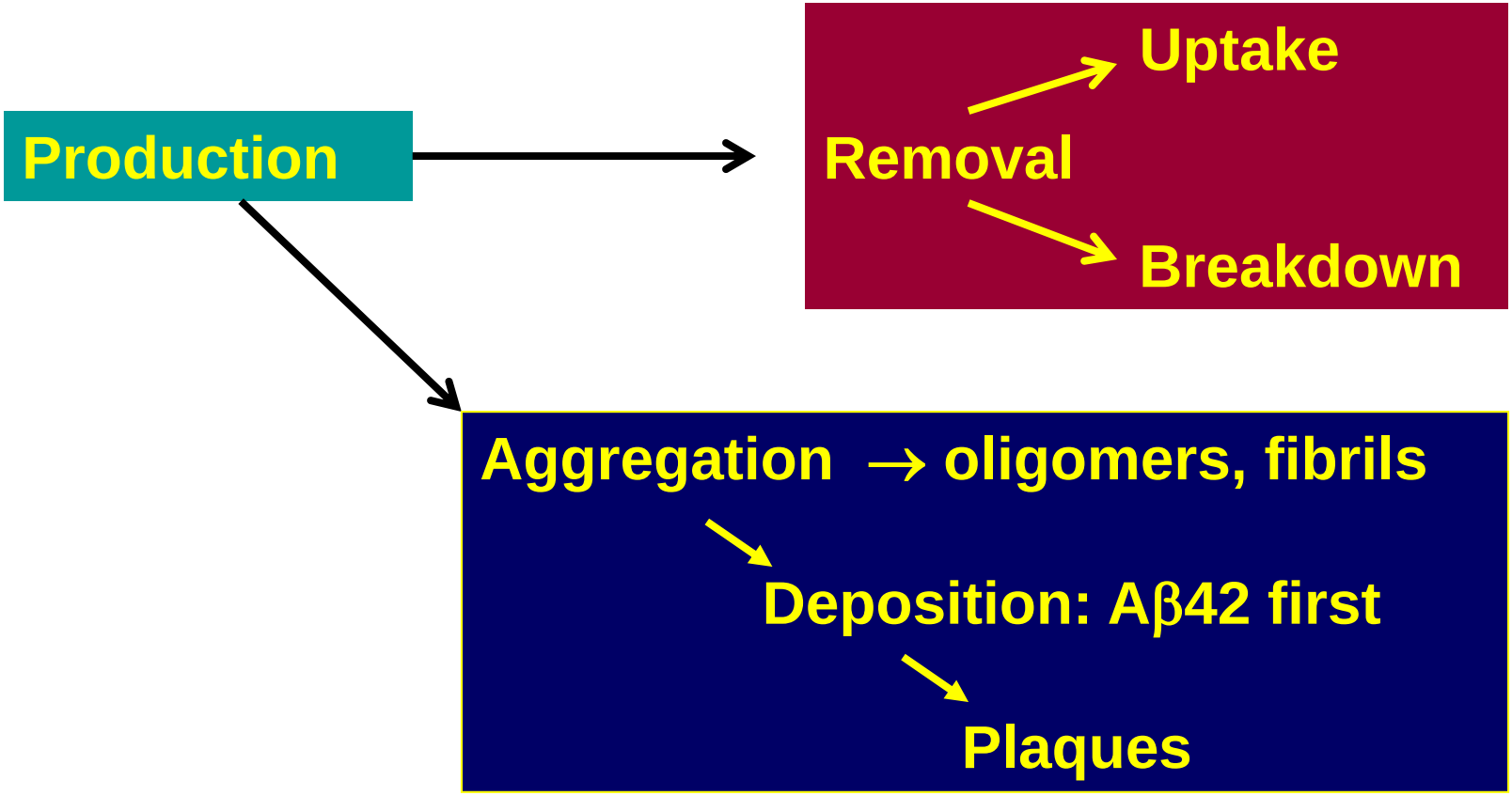
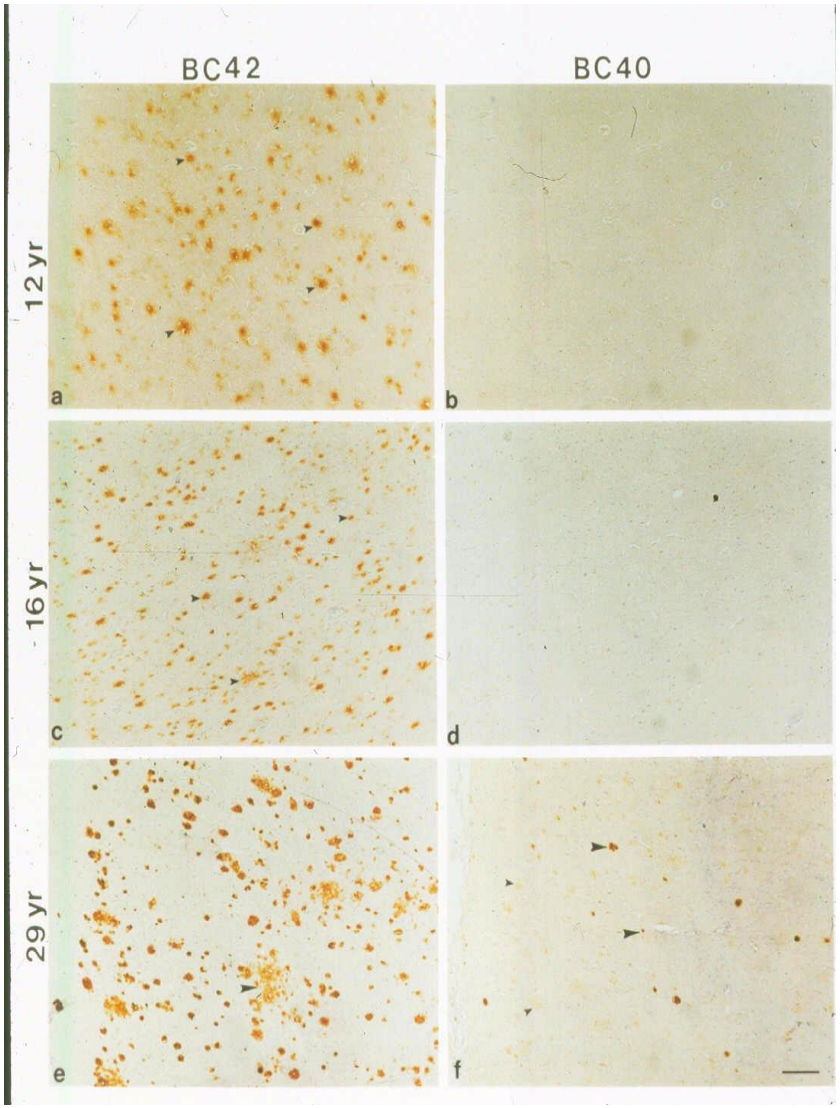
Amyloid beta protein may initiate a cascade leading to AD pathology.


secretases
other substrates
e.g.notch
APP
nucleus
Aβ
aggregation, fibrils and
amyloid plaques
neurotoxicity
Enzymes break
down Aβ
Clearance:
Microglia and blood
vessels

CSF Aβ equilibrium depends on:



Aβ42 is the initiator and main culprit in amyloid deposition



- Aβ42 is the initial amyloid species deposited in brain
- Aβ42 exceeds Aβ40 in amyloid deposits
- Toxicity and amyloid fibril formation: Aβ42 > 40
- Selectively ↑ in presenilin mutations
- ↑ in most APP mutations
- High plasma Aβ42 is linked to a LOAD locus on chr 10

Down's syndrome study by C. Lemere

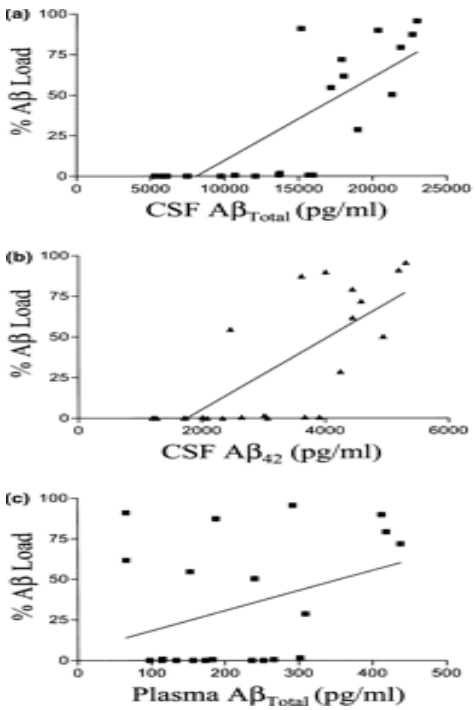
CSF Aβ in AD

- **Total Aβ or Aβ1-40 do not differ in AD and controls**
- **Aβ42 levels are decreased in CSF in AD vs controls, by about 50%.**
- **Aβ42 levels increase in the brain.**

  ? deposits act as a 'sink', which binds more Aβ42
- **Meta-analysis of CSF Aβ42, AD vs controls:**
  - 18 studies, 980 AD, 499 controls
  - Effect size = 1.56 (Sunderland 2003)
- **Aβ42 levels decrease in CJD, and in about 15-25% of non-AD dementias …**

  ? due to ↓ production, or concomitant AD pathology

CSF Aβ and brain Aβ deposition

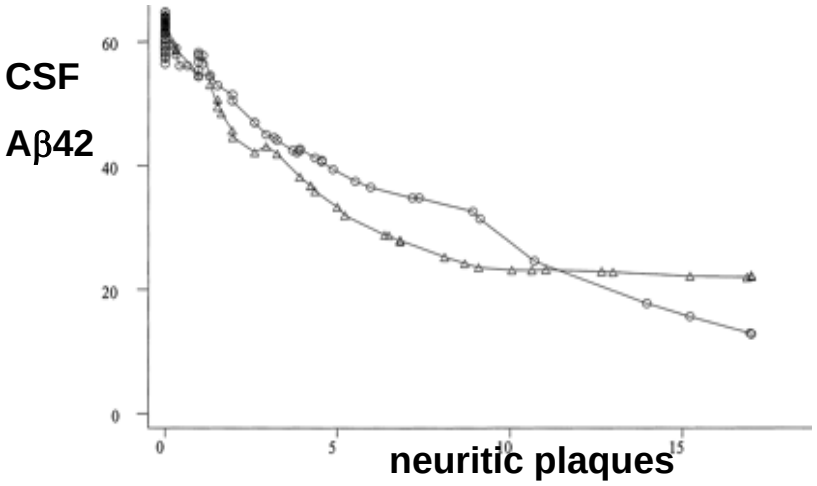


$R^2 = 0.63$

$R^2 = 0.57$

APP tg mouse: brain vs CSF Aβ

De Mattos, 2002

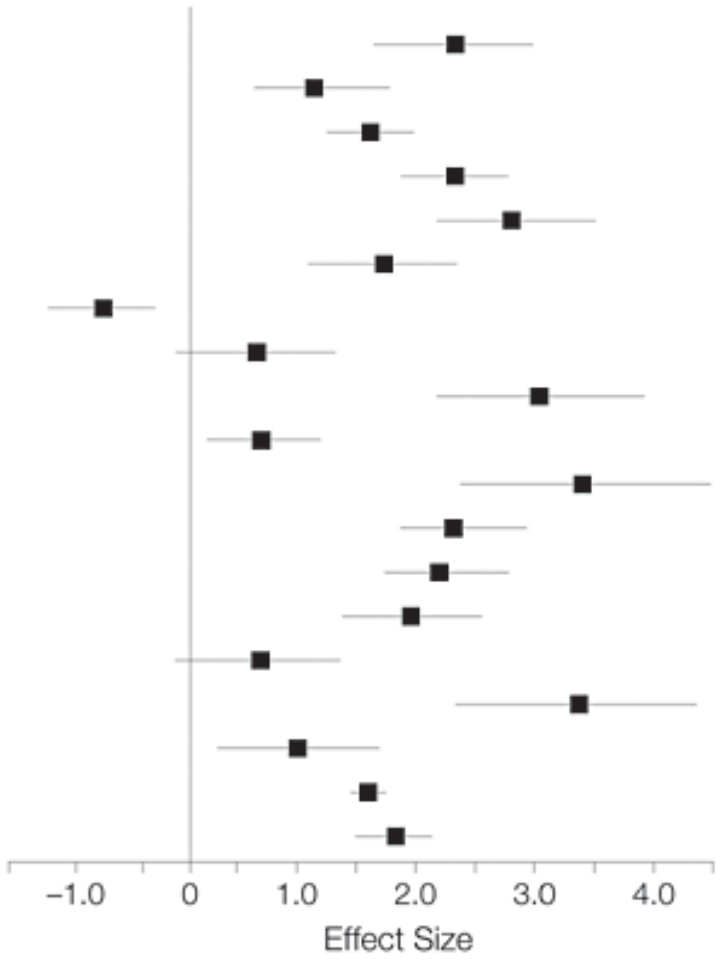


Human: postmortem CSF Aβ42 vs neuritic plaque count

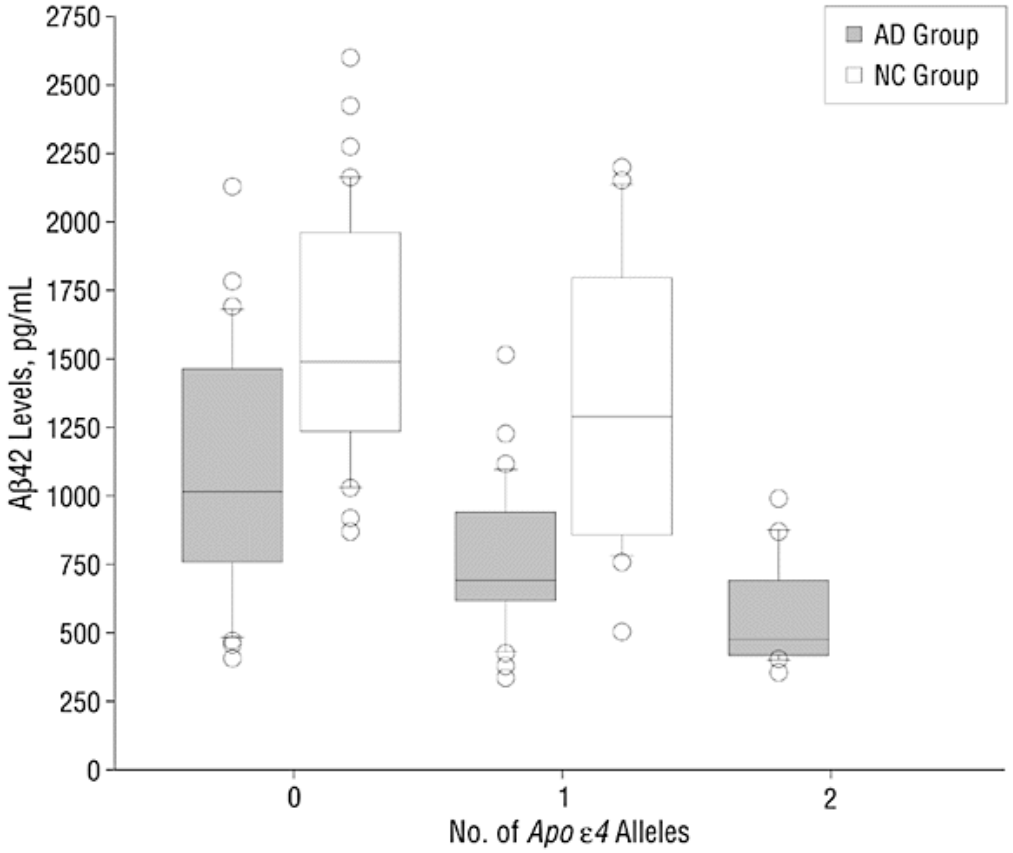
Strozyk, 2003

CSF Aβ42 meta-analysis (Sunderland, JAMA 2003)

Study	Effect Size (95% CI)
Motter et al,[4] 1995	2.26 (1.57 to 2.94)
Tamaoka et al,[34] 1997	1.12 (0.53 to 1.72)
Galasko et al,[5] 1998	1.55 (1.17 to 1.93)
Kanai et al,[14] 1998	2.27 (1.82 to 2.73)
Andreasen et al,[33] 1999	2.80 (2.12 to 3.48)
Hulstaert et al,[13] 1999	1.68 (1.01 to 2.35)
Jensen et al,[16] 1999	–0.79 (–1.26 to –0.32)
Fukuyama et al,[35] 2000	0.56 (–0.13 to 1.26)
Kanemaru et al,[36] 2000	3.02 (2.13 to 3.91)
Mehta et al,[6] 2000	0.63 (0.13 to 1.13)
Otto et al,[51] 2000	3.41 (2.33 to 4.49)
Riemenschneider et al,[38] 2000	2.35 (1.82 to 2.88)
Sjogren et al,[39] 2000	2.22 (1.68 to 2.76)
Andreasen et al,[7] 2001	1.97 (1.41 to 2.53)
Csemansky et al,[40] 2002	0.60 (–0.12 to 1.33)
Sjogren et al,[41] 2002	3.35 (2.31 to 4.37)
Skoog et al,[42] 2003	0.94 (0.23 to 1.65)
Total	**1.53 (1.39 to 1.69)**
Current Study	1.76 (1.42 to 2.10)



CSF A-beta42 and APO-E

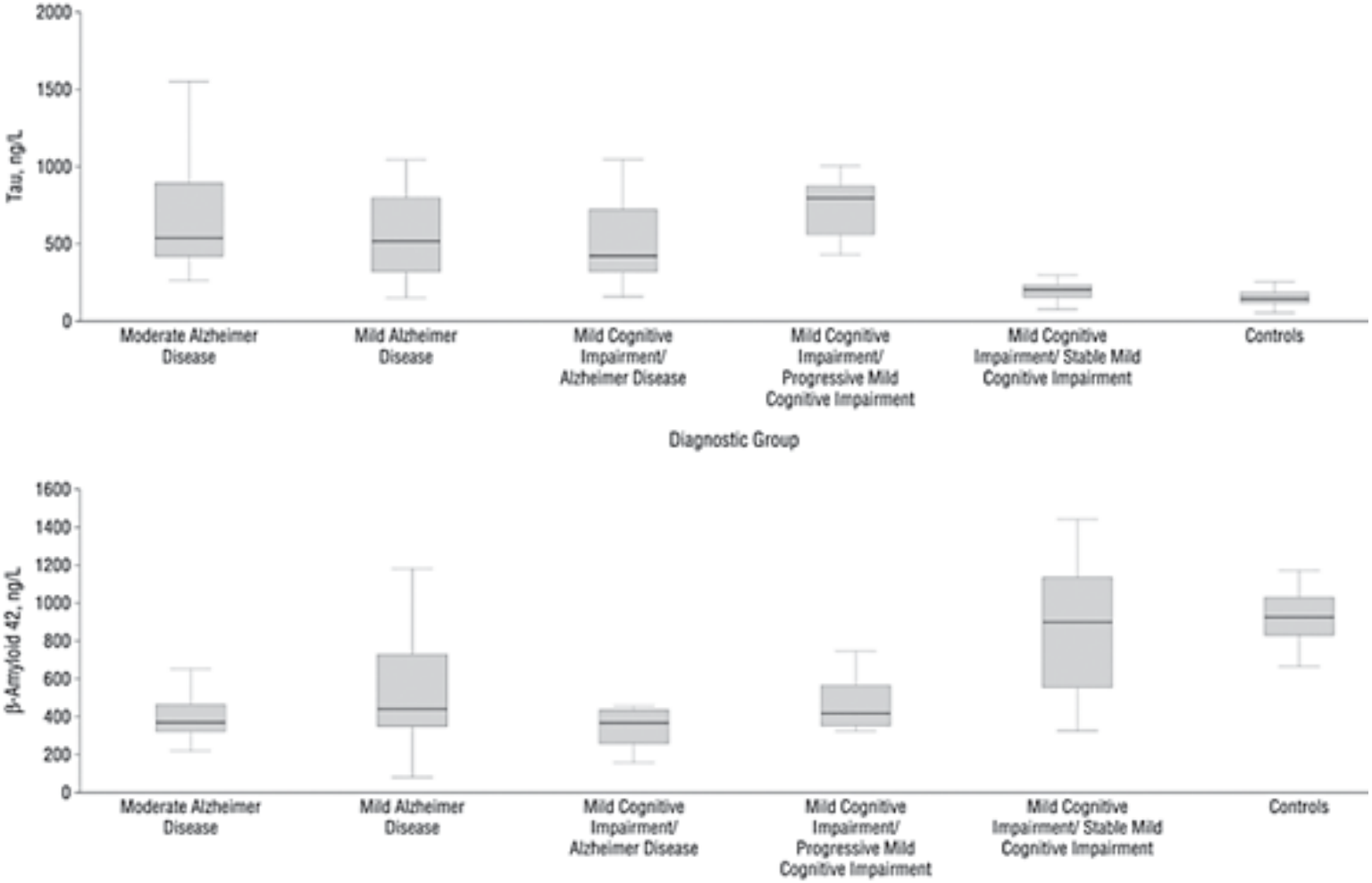


CSF Aβ42 in very mild AD/MCI

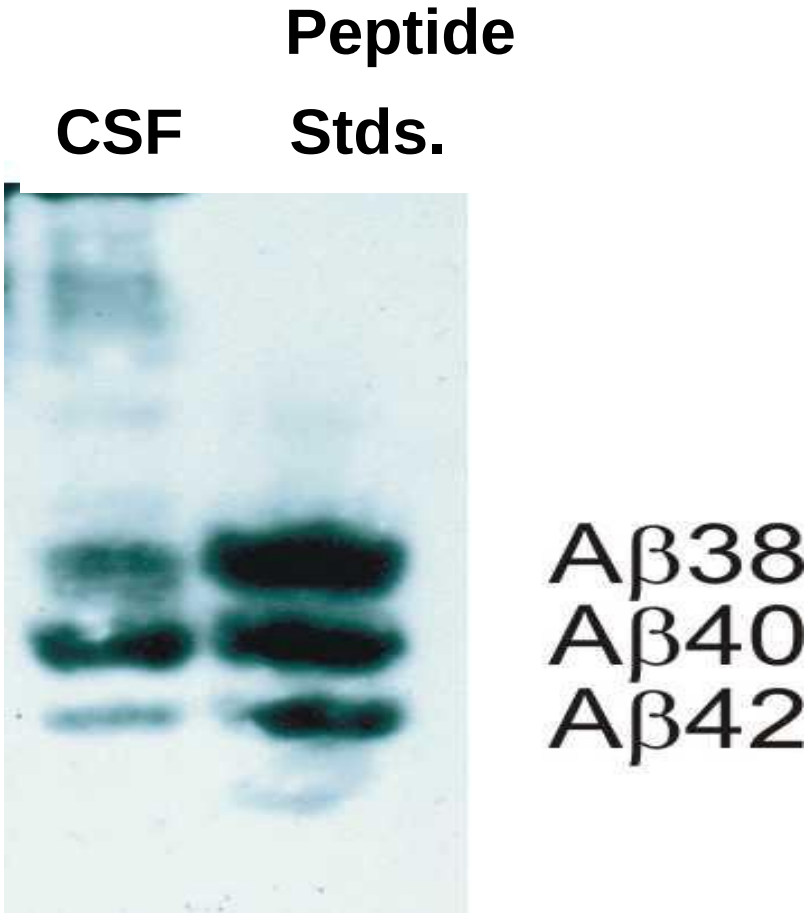
	N	% with CSF Aβ42 in AD range
MMSE > 23/30		
Galasko et al 1998	24	64 %
Hulstaert et al, 1999	23	70 %
Riemenschneider et al, 2000	25	72 %
Andreasen et al, 2000	20	75 %
MCI with progression		
Maruyama et al, 2001	19	45 %
Riemenschneider et al, 2002	18	85 %
Andreasen et al, 2003	44	77 %

CSF biomarkers in MCI and early AD

Riemenschneider et al, 2002

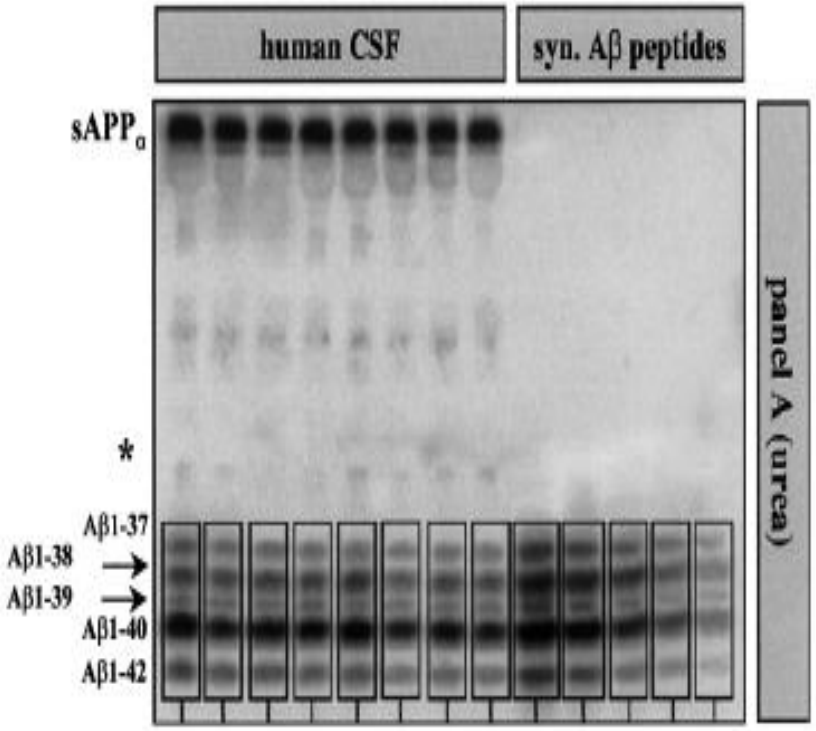


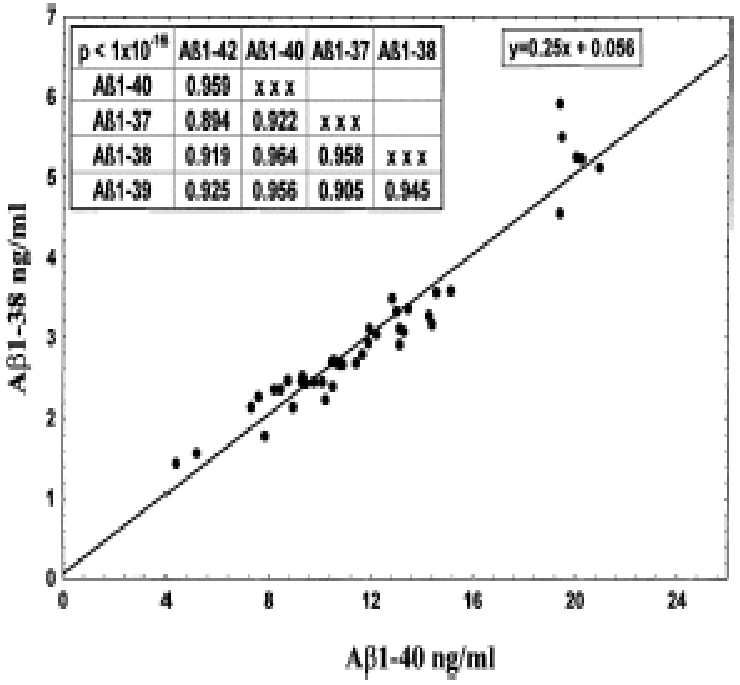
Measuring Aβ subtypes



Aβ was immunoprecipitated from 2 ml of CSF from an AD patient, and visualized on a bicine gel that resolves Aβ38, 40 and 42

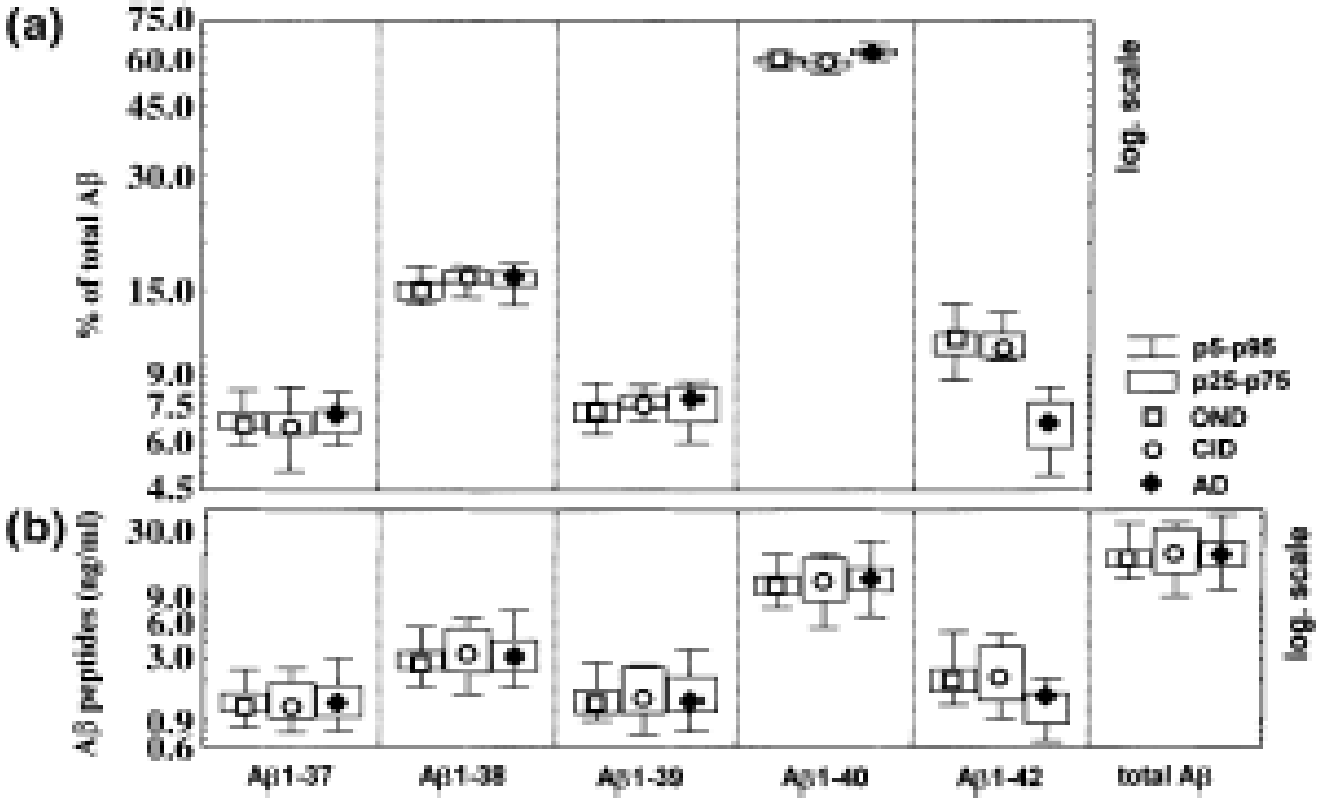
Aβ species in CSF





Wiltfang et al, J Neurochem 2002

Relative decrease in Aβ42 in CSF in AD



CSF Aβ as an index of drug treatment?

- **Half-life of Aβ in CSF is about 30 minutes**
- **CSF and plasma Aβ are not correlated in humans**
- **May be easier to show effects in controls than in AD, because levels are not already decreased.**

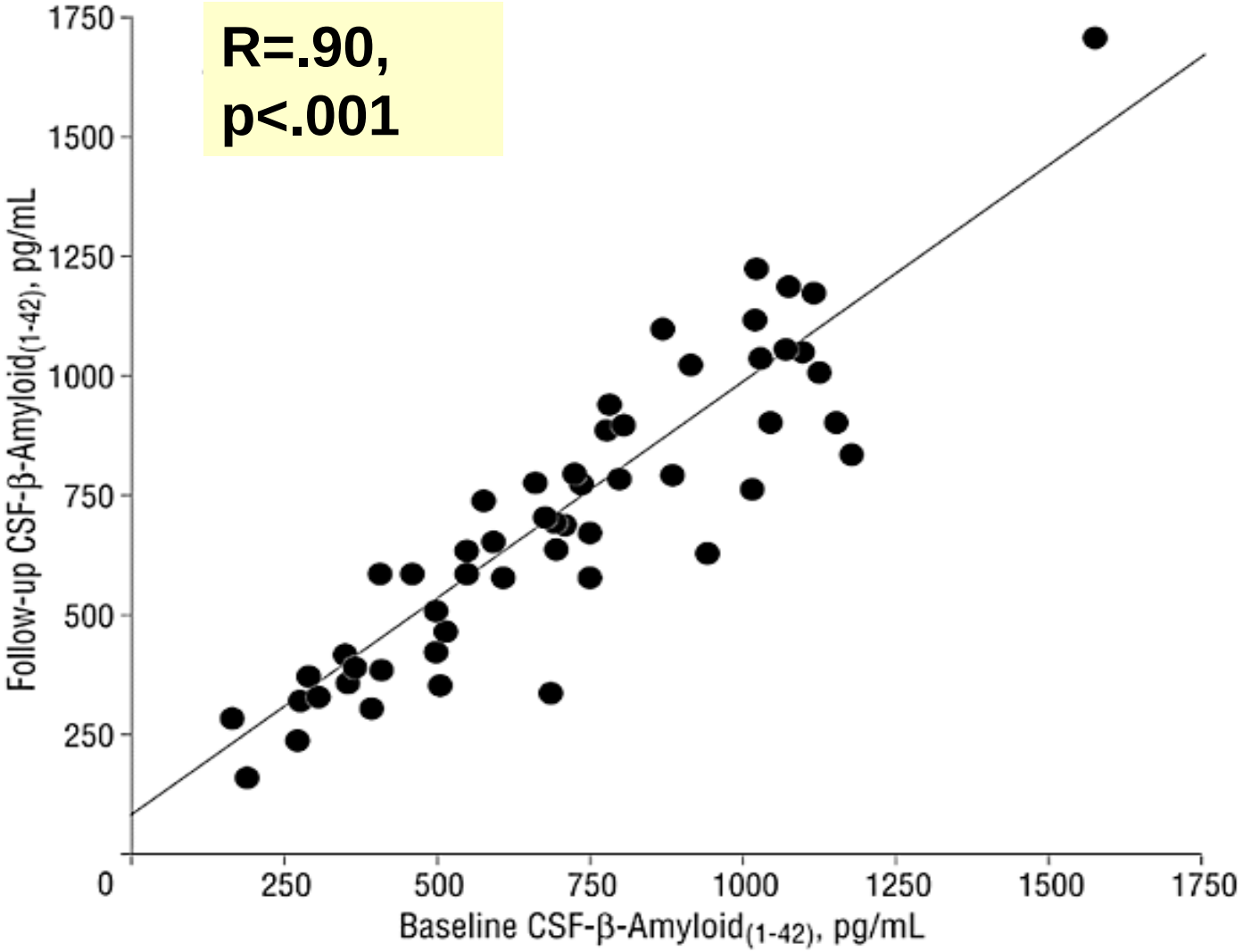
- **Limited published data ….**

  - γ-secretase inhibitors: CSF and plasma Aβ40 and 42 ↓ in APP tg mice

  - Some NSAIDs may selectively decrease Aβ42 in tg mice and increase Aβ38

  - Rivastigmine x 1 year had no effect on CSF Aβ42

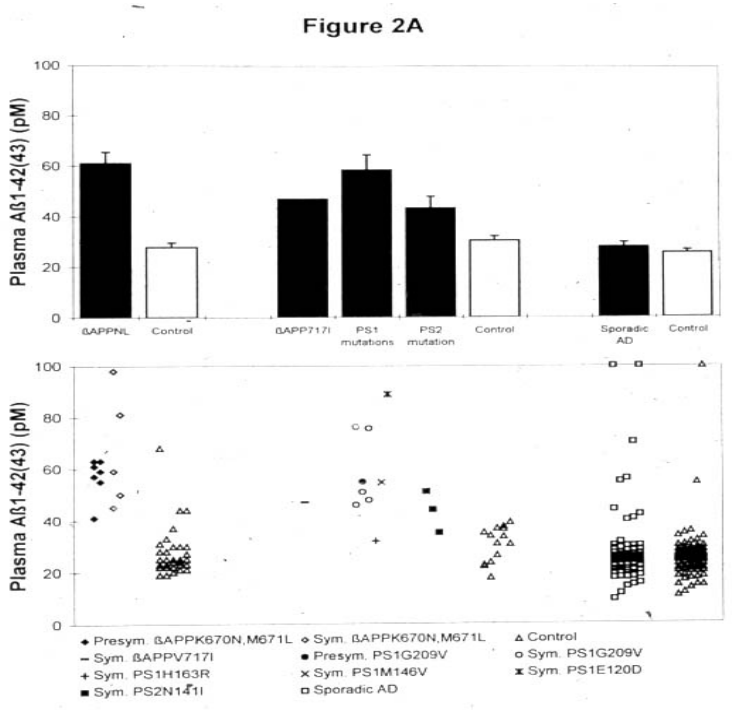
CSF Aβ42 remains stable in AD over 12 months



Summary

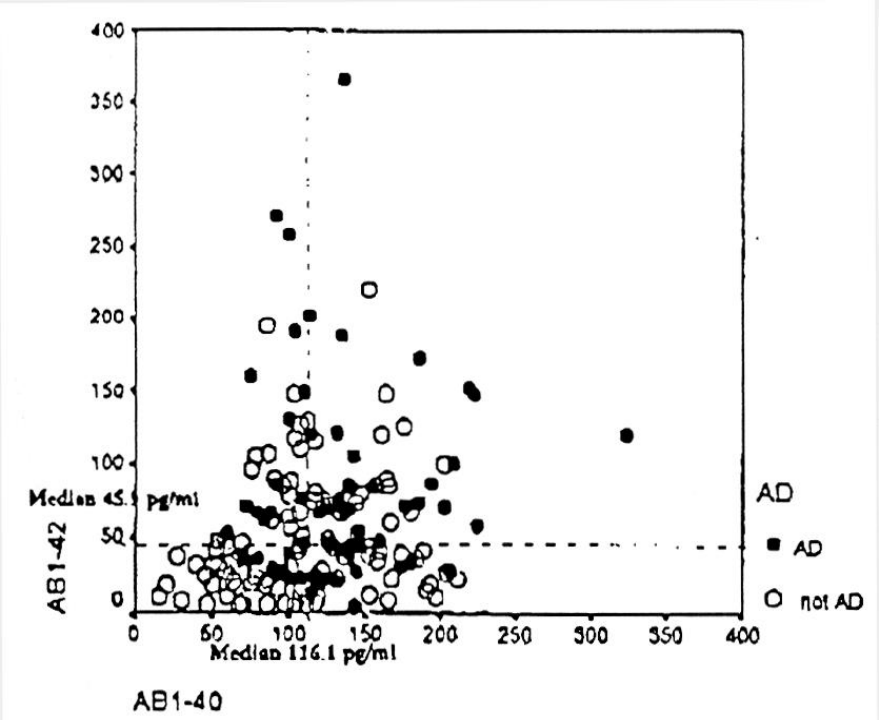
- **CSF Aβ42 is decreased in AD, in 70-85% of patients, but less consistently so in MCI.**
- **Aβ40 levels are not altered.**
- **Diagnostic potential of CSF Aβ42 is limited, but may improve if it is part of a panel of biomarkers.**
- **CSF and possibly plasma Aβ may be used to monitor certain types of anti-amyloid therapy, e.g. for proof of principle, or dose finding**
- **Several forms of Aβ can be measured in CSF; data on Aβ subtypes and on oligomers will be of interest.**

Plasma Aβ in inherited and sporadic AD



Scheuner 1996

↑ in PS and APP mutations and DS, not sporadic AD



Mayeux 1999

↑ risk of developing AD for highest quartile of plasma Aβ42