Anti-inflammatory treatments for Alzheimer's Disease: Helpful? Harmful?

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Faculty/Presenter Disclosure

- **Faculty:** **John C. S. Breitner, MD**

- **Relationships with commercial interests:**
  - **None**

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"Inflammation" at the heart of AD: Consider the >40 immune-related genetic risk loci for LOAD

Almost every risk locus deals with immune, vascular or lipid activity or metabolism.
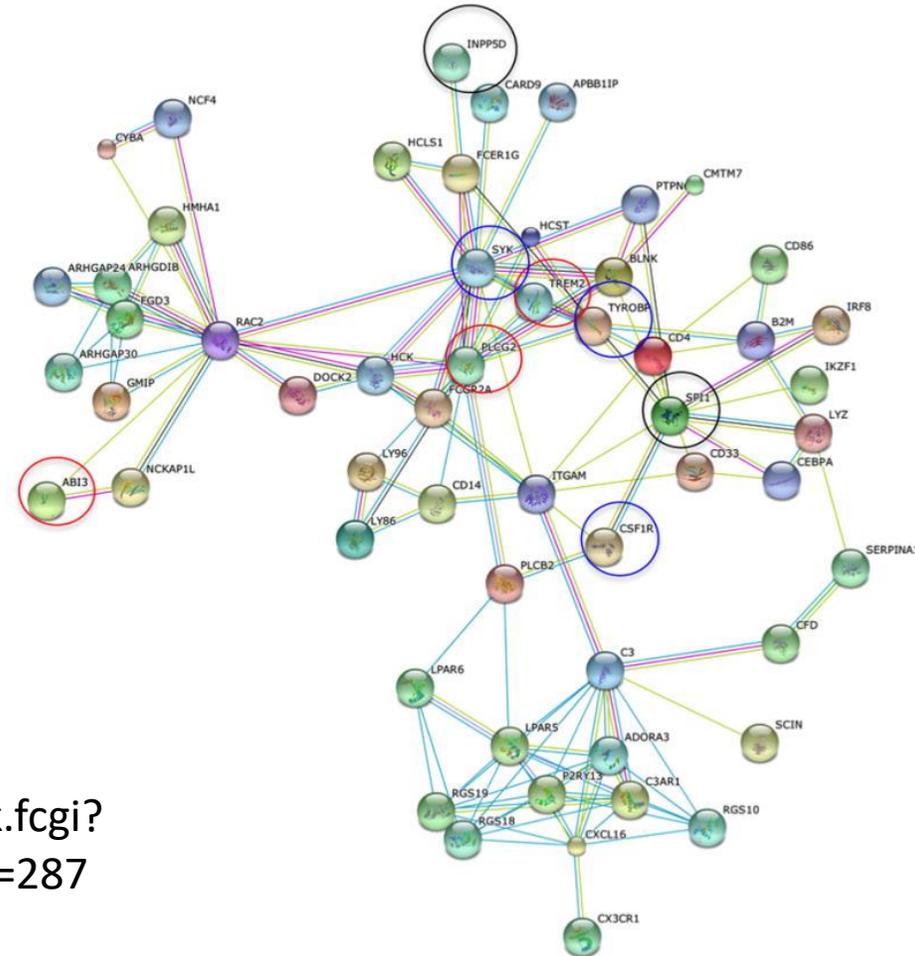
Sims et al., Nat Genet 2017 Sep 49(9): 1373-1384
https://www.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?
dbfrom=pubmed&retmode=ref&cmd=prlinks&id=287
14976

Surprisingly . . .

Most genetic variants that predispose to AD cause <u>loss of function</u> for the gene preduct.

e.g., *TREM2*, *SORL1*, *APOE*

Inflammation means <u>slower</u> brain shrinkage

CAM-CAN lifespan study

$R^2 = 0.55$***
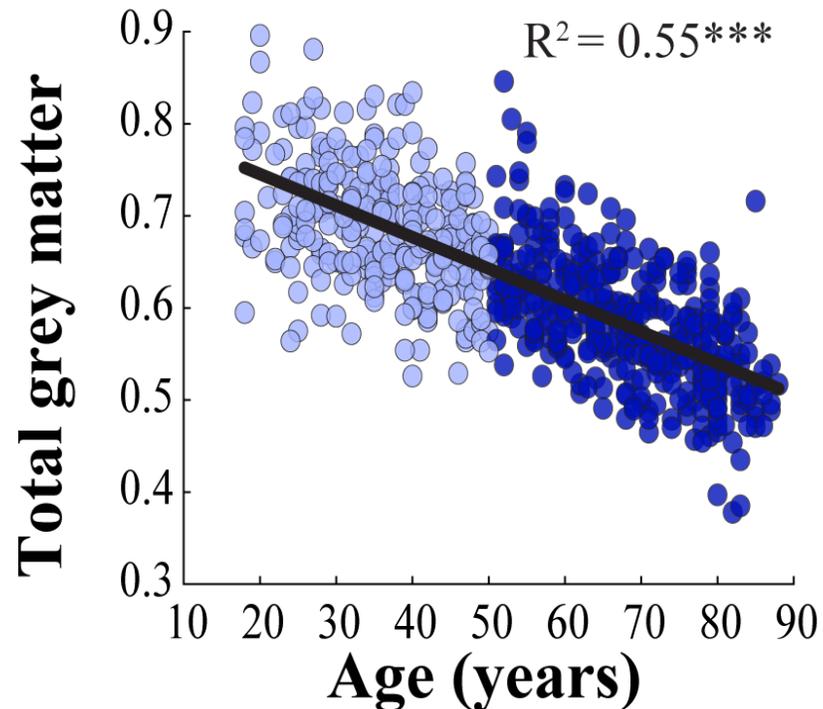
The brain shrinks with age.

PREVENT-AD cohort

$R^2 = 0.22$***
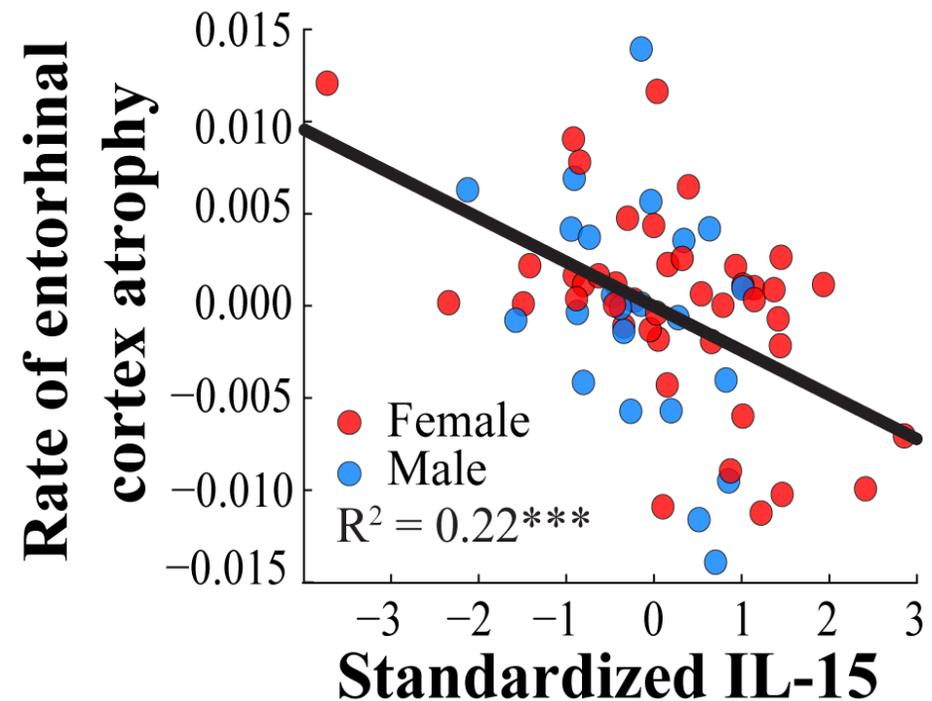
Inflammation predicts <u>slower</u> decline

We used to think the opposite . . .

- **1988 – Joe Rogers and Pat McGeer publish independently showing evidence of inflammatory processes surrounding AD plaques**

- **1990 – McGeer et al., Lancet: Surprisingly low occurrence of AD in pts with RA and *vice versa*.**

- **1993 – Joe Rogers tiny clinical trial of indomethacin (IMC): AD participants given IMC (vs. Placebo) show slower cognitive decline**

- **1992 – 2008: 25 observational studies suggesting inverse association of anti-inflammatory treatments with AD**

- **2001 – Rotterdam Study (NEJM): strong inverse relation AD - NSAIDs**

McGeer's letter to the Lancet (1990)

. . . considered as a possible explanation for rarity of AD in autopsy-confirmed RA: persons with an inflammatory diathesis (tendency) were somehow protected from getting AD.

(confounding by indication)

Randomized trials show <u>null to adverse</u> effects of NSAIDs for AD treatment

Null results in trials of:

- **prednisone (corticosteroid, potent anti-inflammatory)**
- **hydroxychloroquine (anti-malarial with immunosuppressant activity)**
- **NSAIDs: naproxen (Aleve,® conventional agent) and rofecoxib (Vioxx, COX-2 specific)**

If anything, these trials showed adverse results (harm)

Prevention trials also suggest harm

- **Merck trial of rofecoxib (Vioxx) in pts with MCI (2005)**
  - **Endpoint: "conversion" to dementia**
  - **Incidence rate ratio (IRR) with treatment = 1.5 (statistically significant 50% increase in new cases)**

- **ADAPT 1^0 prevention trial (*stopped for safety*) (2007)**
  - **Ages 75+**
  - **Endpoint: incident dementia**
  - **IRR for naproxen and for celecoxib > 3 (200% increase)**

Perhaps if NSAIDs were begun earlier??

INTREPAD

A randomized trial of naproxen to slow progress of presymptomatic Alzheimer disease
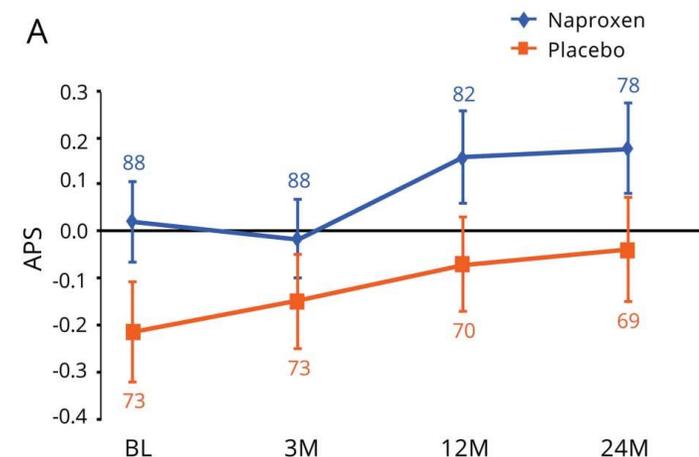
- **PREVENT-AD Cohort; Ages 60+; parental history of AD**

- **Null effect on Alzheimer Progression Score (APS) of clinical, imaging and CSF markers of AD progression.**

Meyer P-F et al., *Neurology 2019;92*

Conundrum:

So why did the observational studies suggest benefit??

# Cross-sectional levels of immune markers at stages of AD development (A/T/N classification)

PREVENT-AD and **ADNI** charts of CSF marker difference from Stage 0 across Pathological Stages
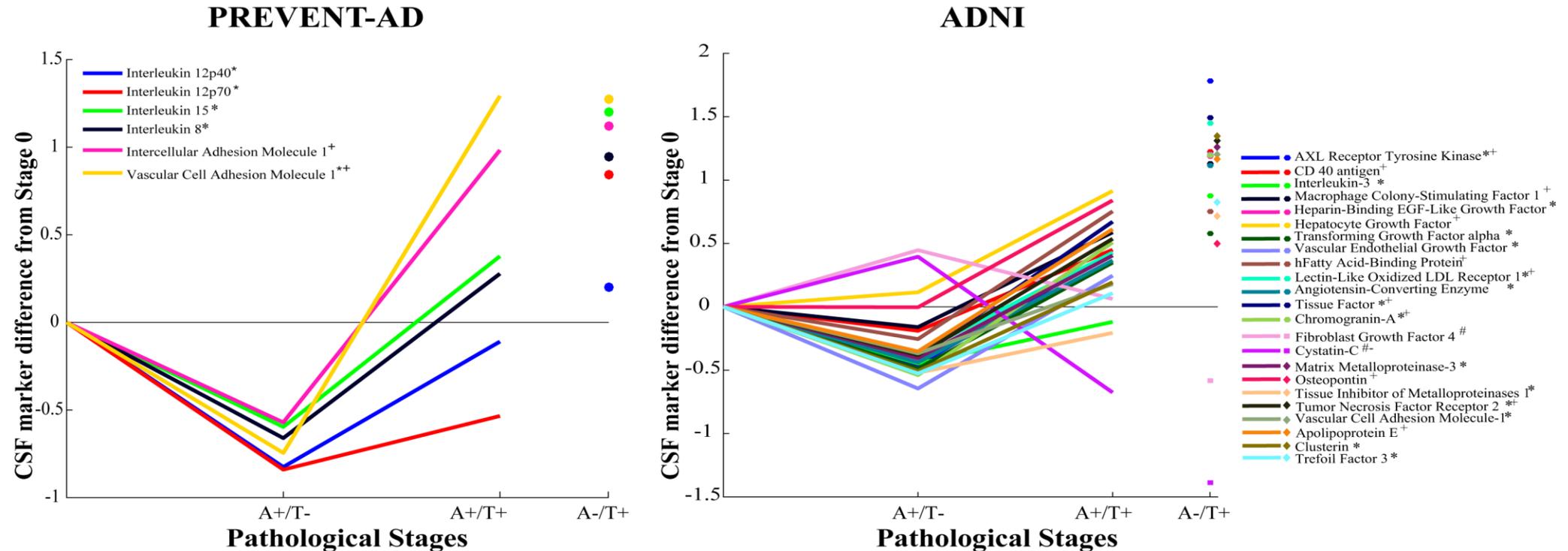
Immune marker levels are <u>reduced</u> in persons with amyloid in their brain

Meyer P-F et al. *J Alzheimer's dis* (2018)

Similar "chevron" pattern seen with sTREM2 in early stage AD

Suarez-Calvet et al., *Molecular Neurodegeneration* (2019)
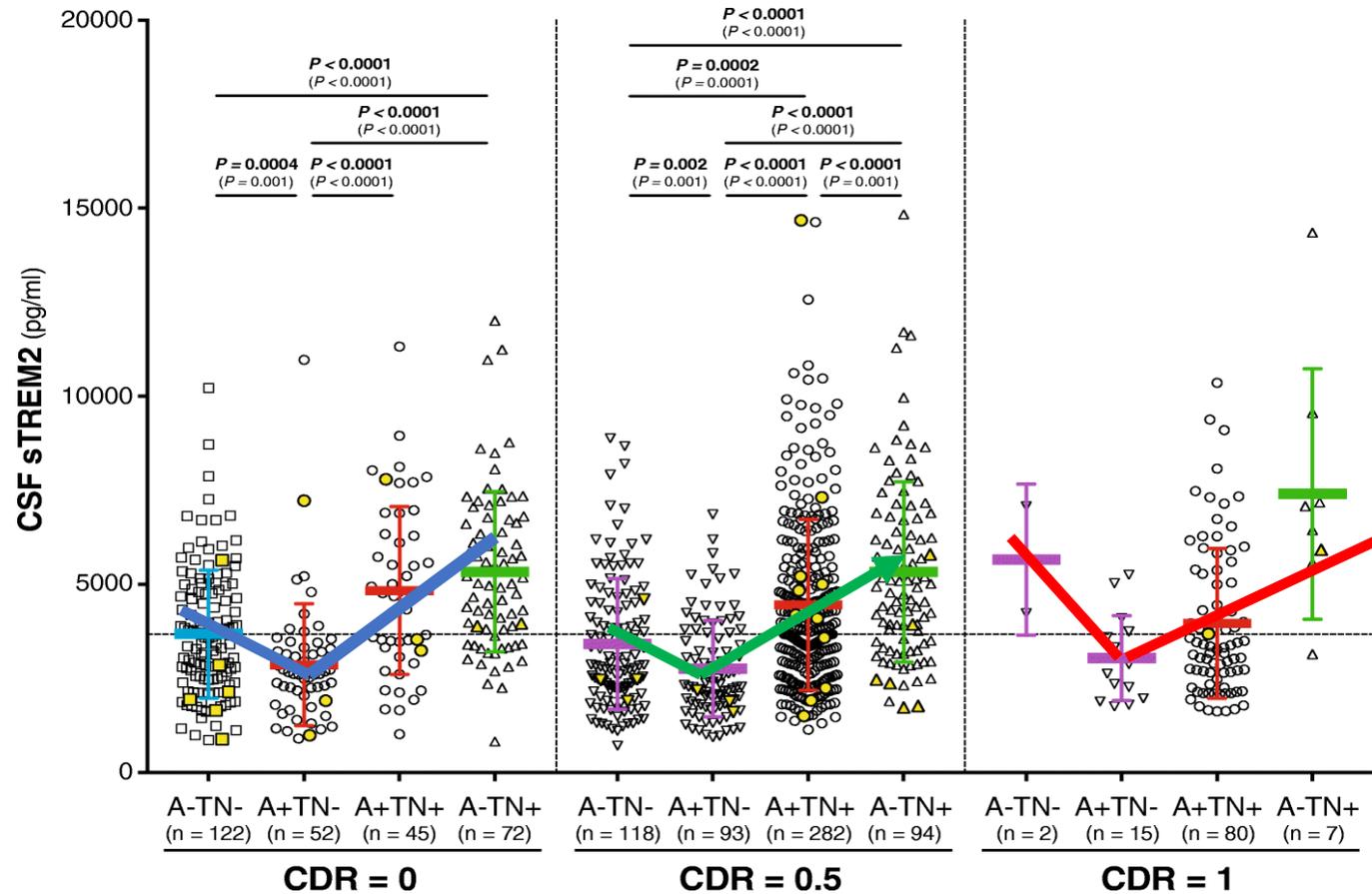
WTF?

Does amyloidosis suppress innate immune activation? (seems unlikely)

Does immune activity retard amyloid pathology? (surprising, but it makes sense)

Another surprise?

Immune / vascular – related markers in CSF predict cognitive ability (mostly) unrelated to $A\beta_{42}$ and *tau*.

Create models using CSF markers to predict cognitive performance (ADNI)

- **Machine learning approach relying on LASSO Regression *to predict cognitive performance* on the ADAS$_{cog}$-11 scale**

Training Set (n = 200)   **Validation Set (n = 106)**

Enter markers as LASSO features

10-fold cross validation to optimize model weights

Evaluation of model accuracy

Evaluation of model generalizability in unseen data
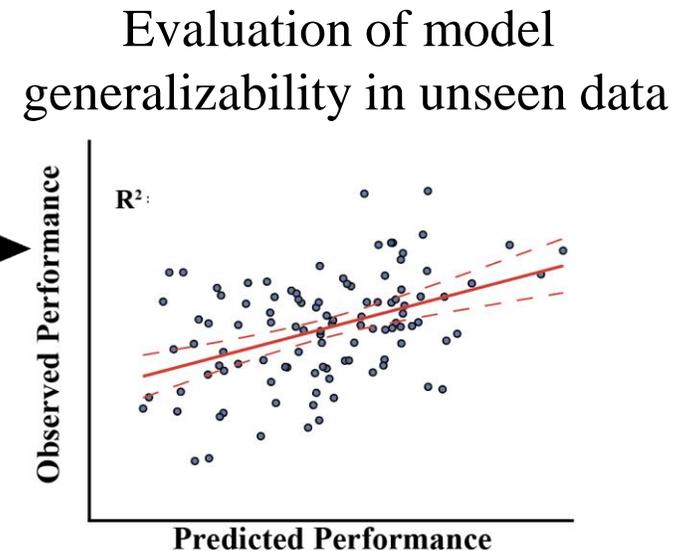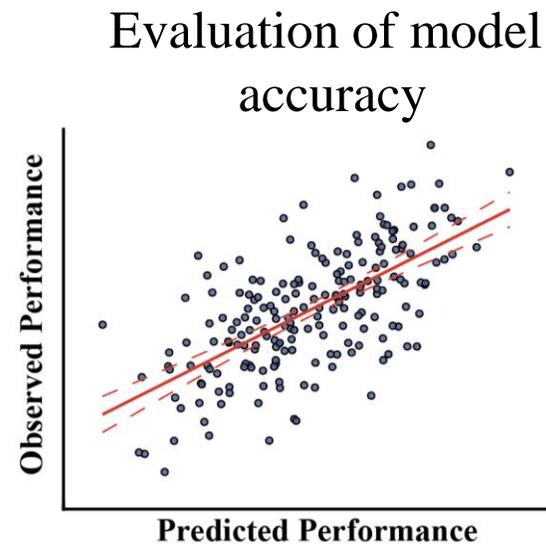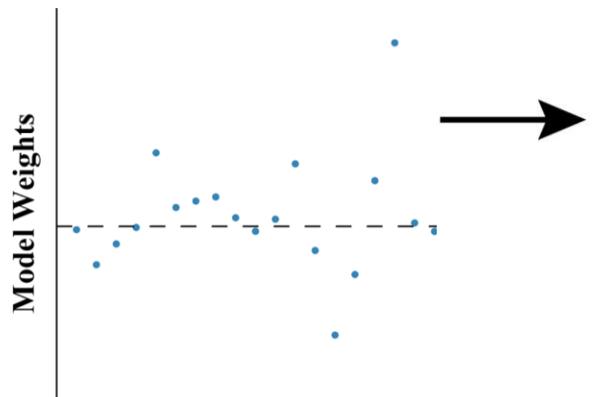
Compare different models for prediction of cognition:

1. CSF AD biomarkers $A\beta_{42}$ and *tau*

2. CSF immune- and vascular-related protein markers

3. Combination using both biomarkers and immune-vascular markers

Meyer P-F et al., *Alzheimers Dement 2019 Sep;15(9):1160-1171.*

# Model 1. AD biomarkers – 26% of variance in ADAS-11 (cognitive deficit)
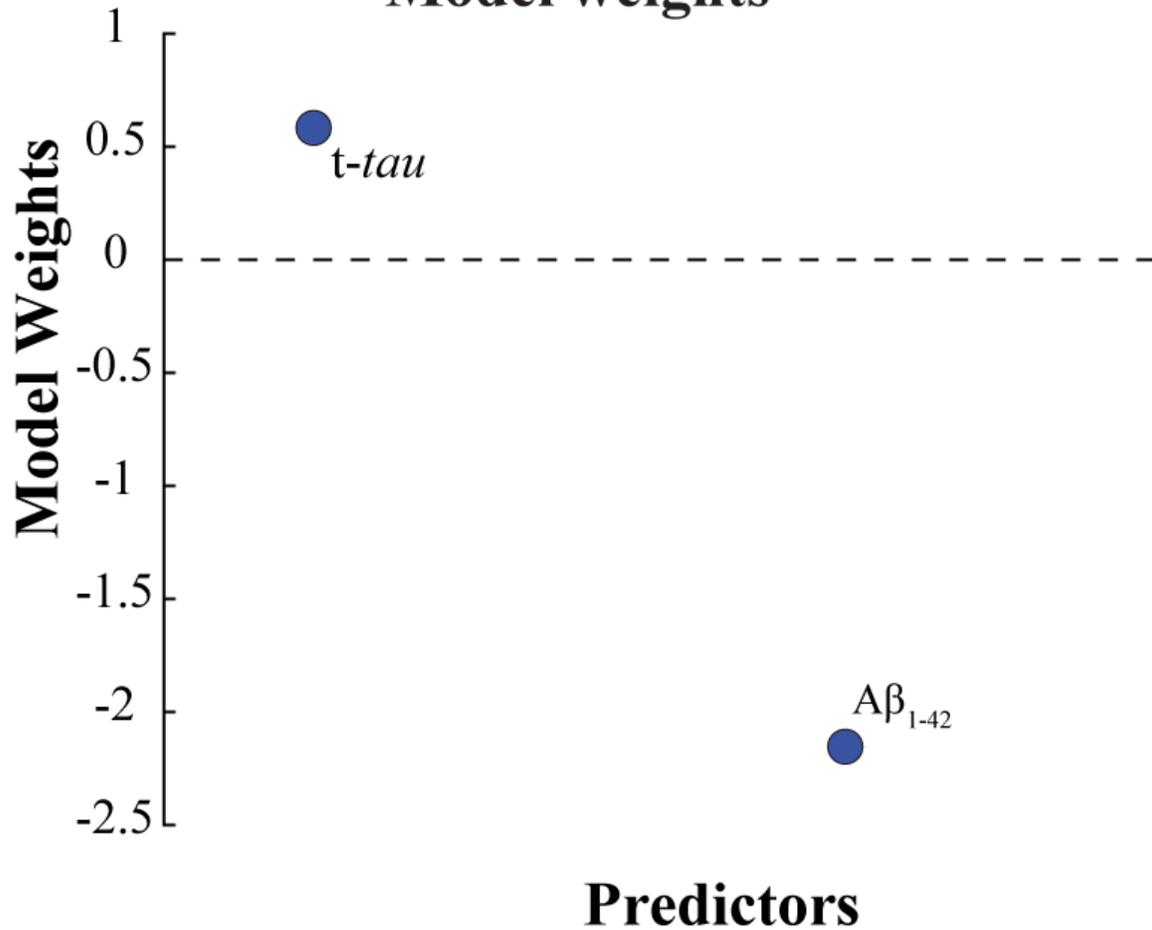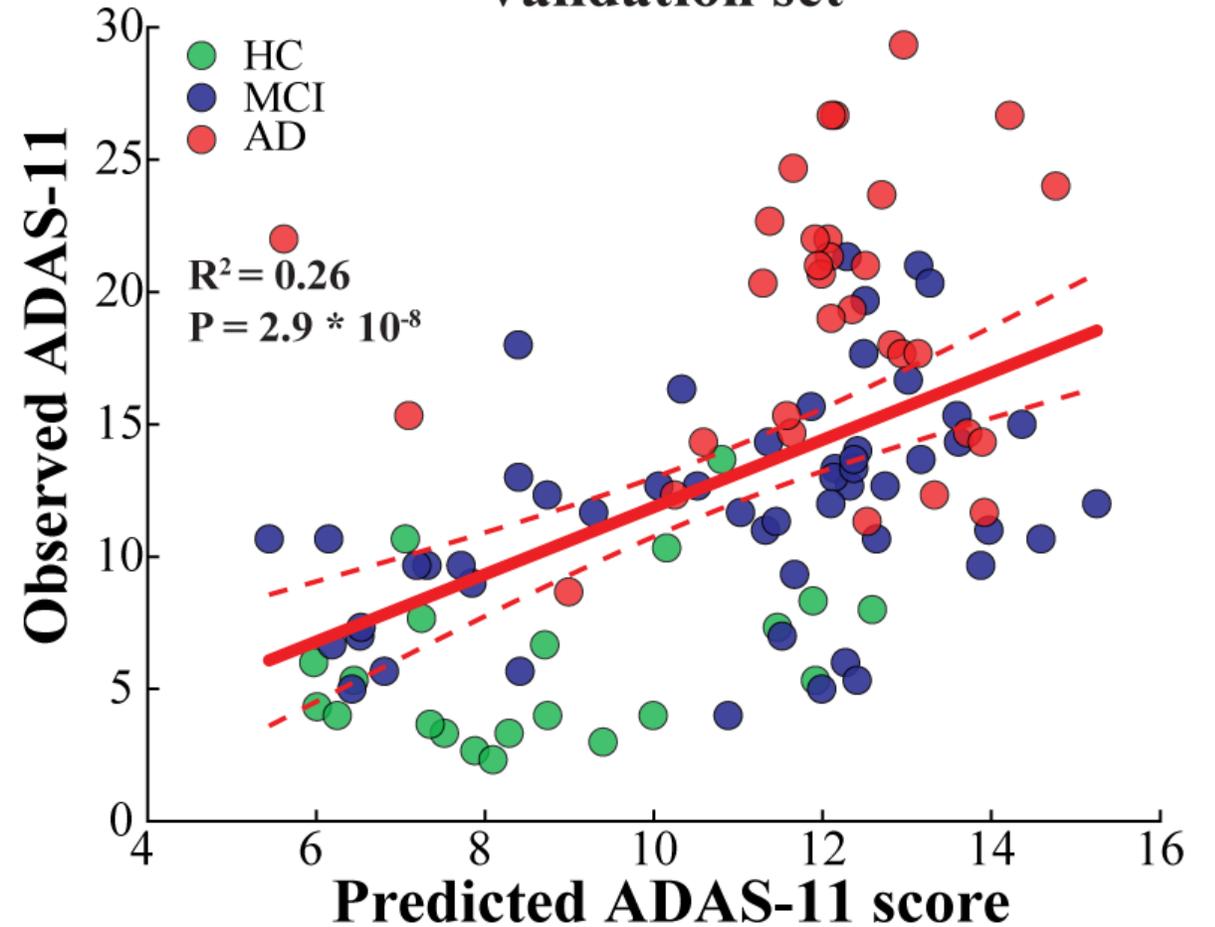
Model 2: 23 immune-vascular CSF proteins – 31% of variance in ADAS-11
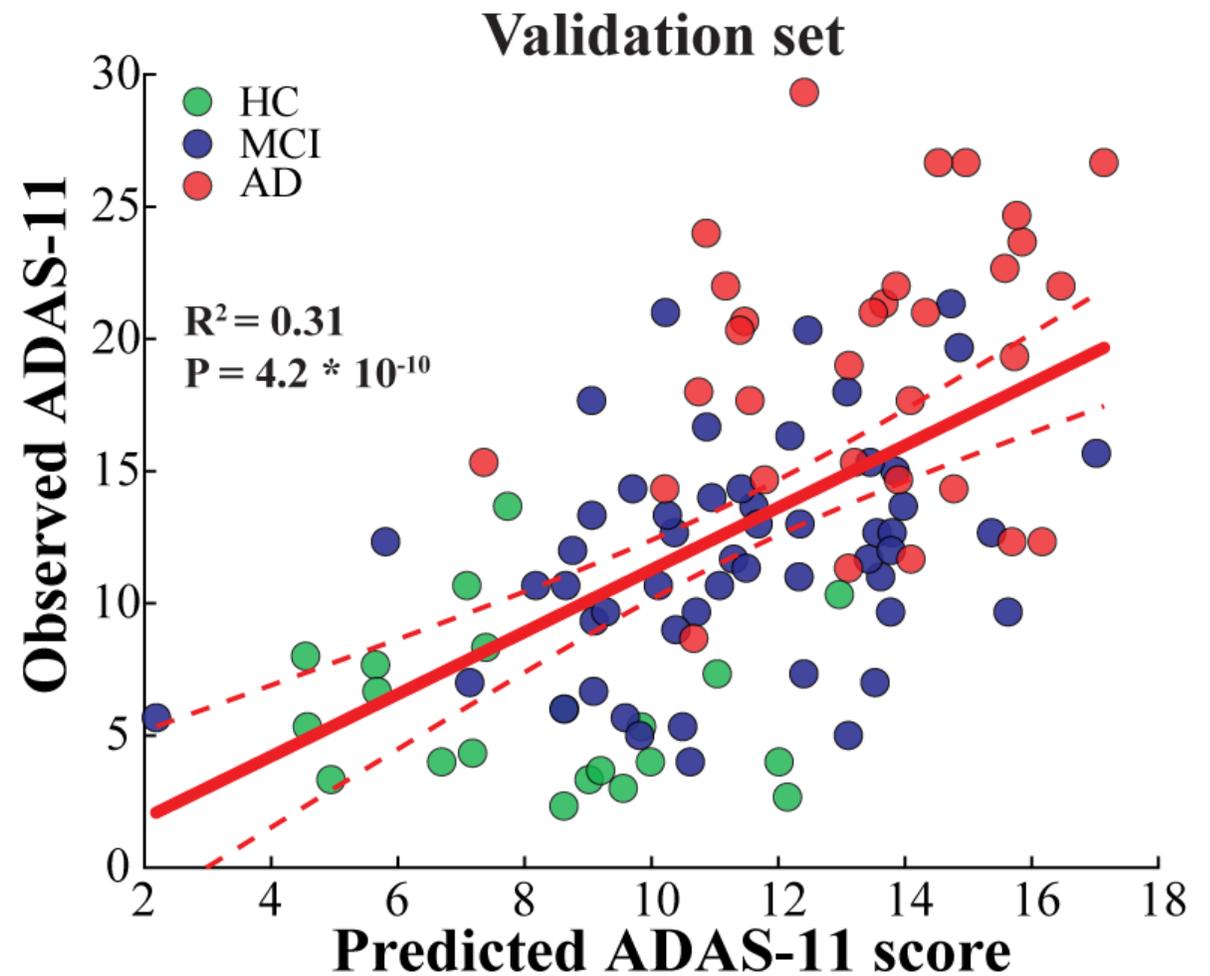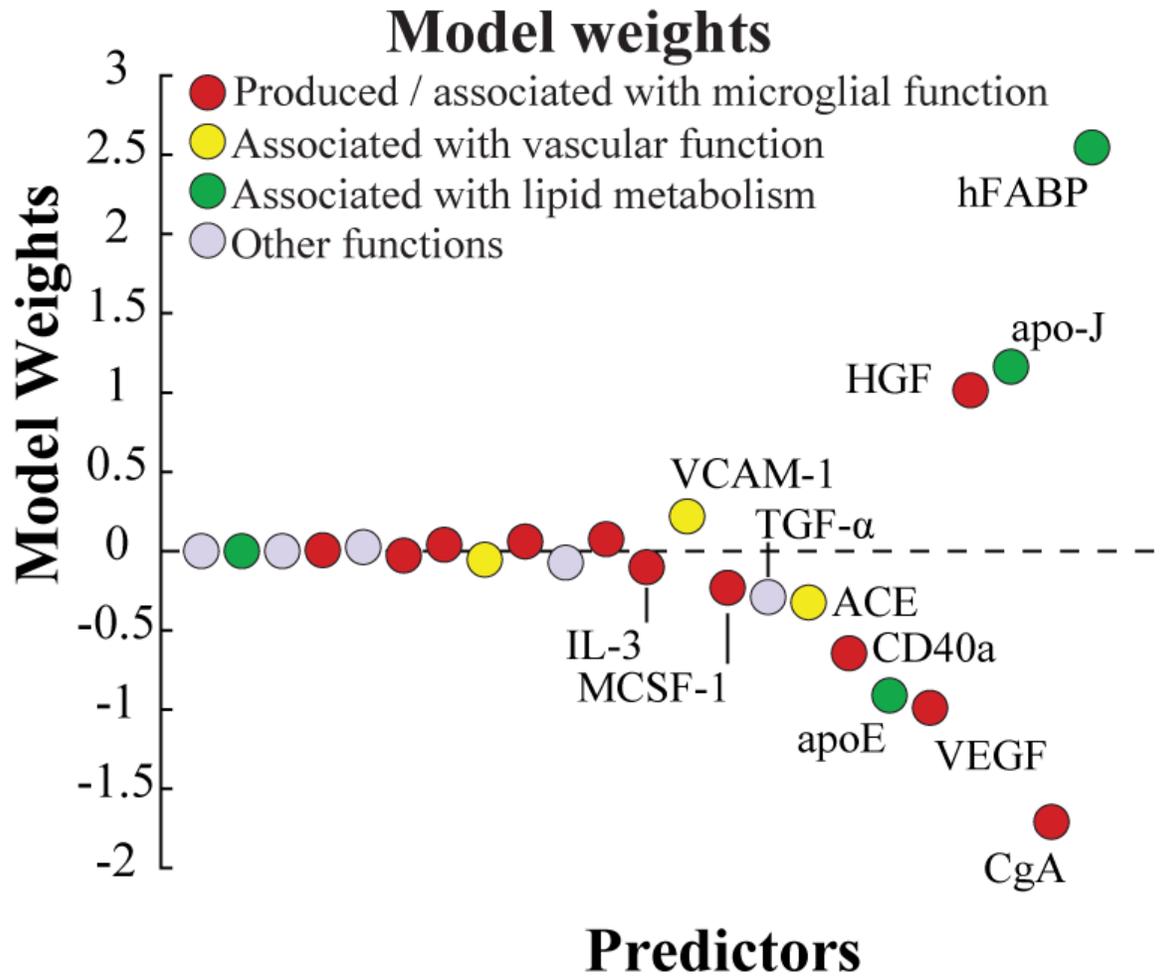
Model 3:   Combination of all markers – 42% of variance in ADAS-11
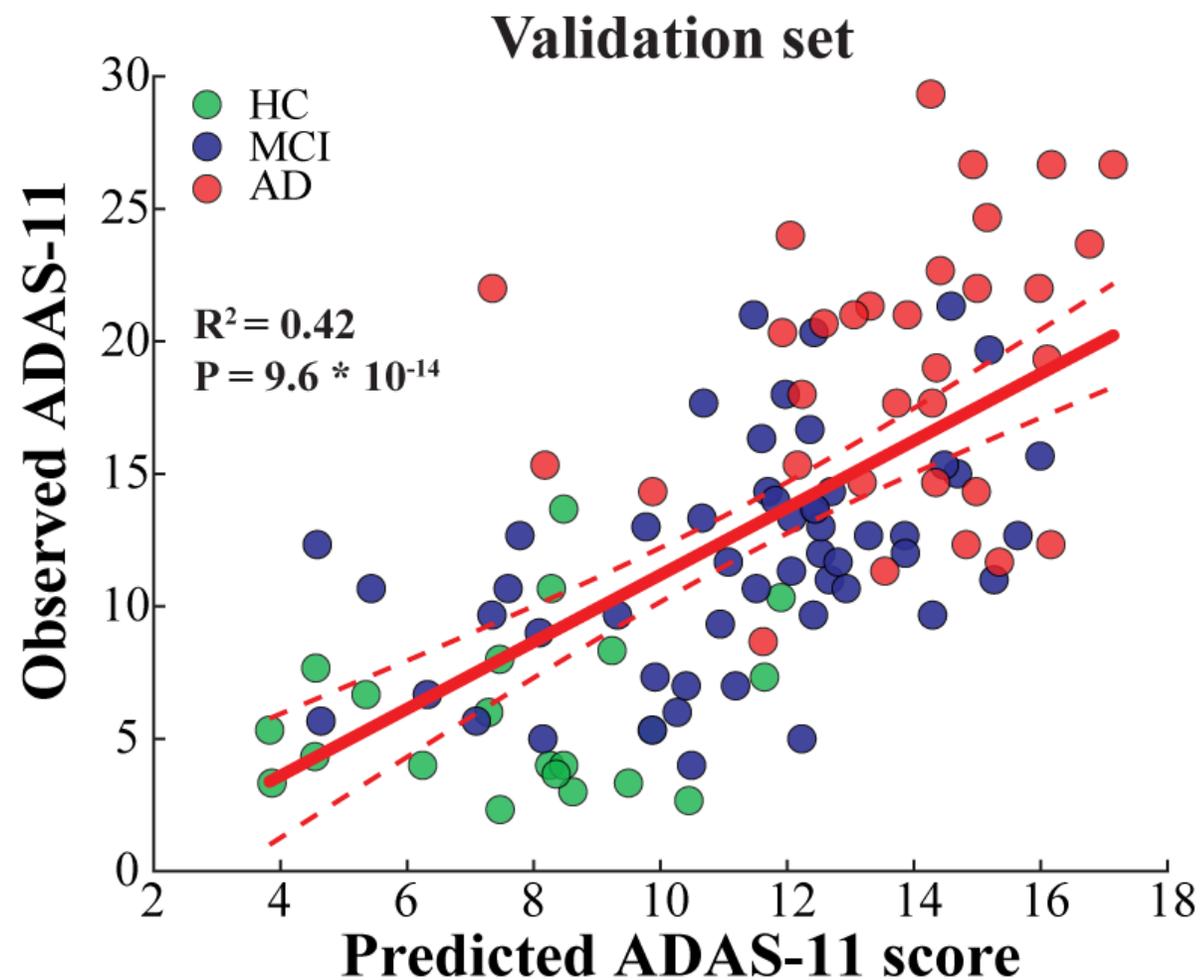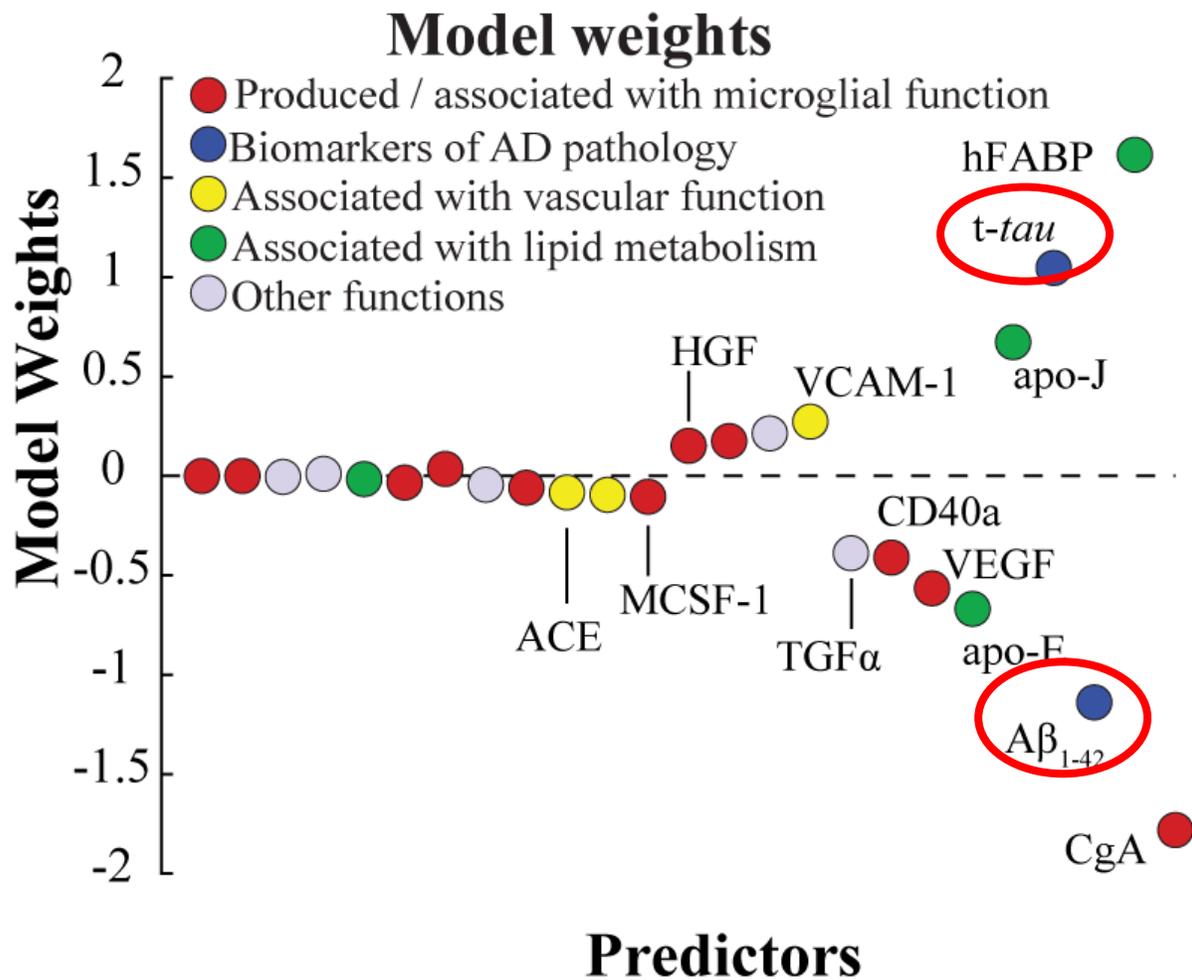
Model weights for immune proteins with or without added AD biomarkers

Model 2 : AD- related proteins

Model 3: Combination
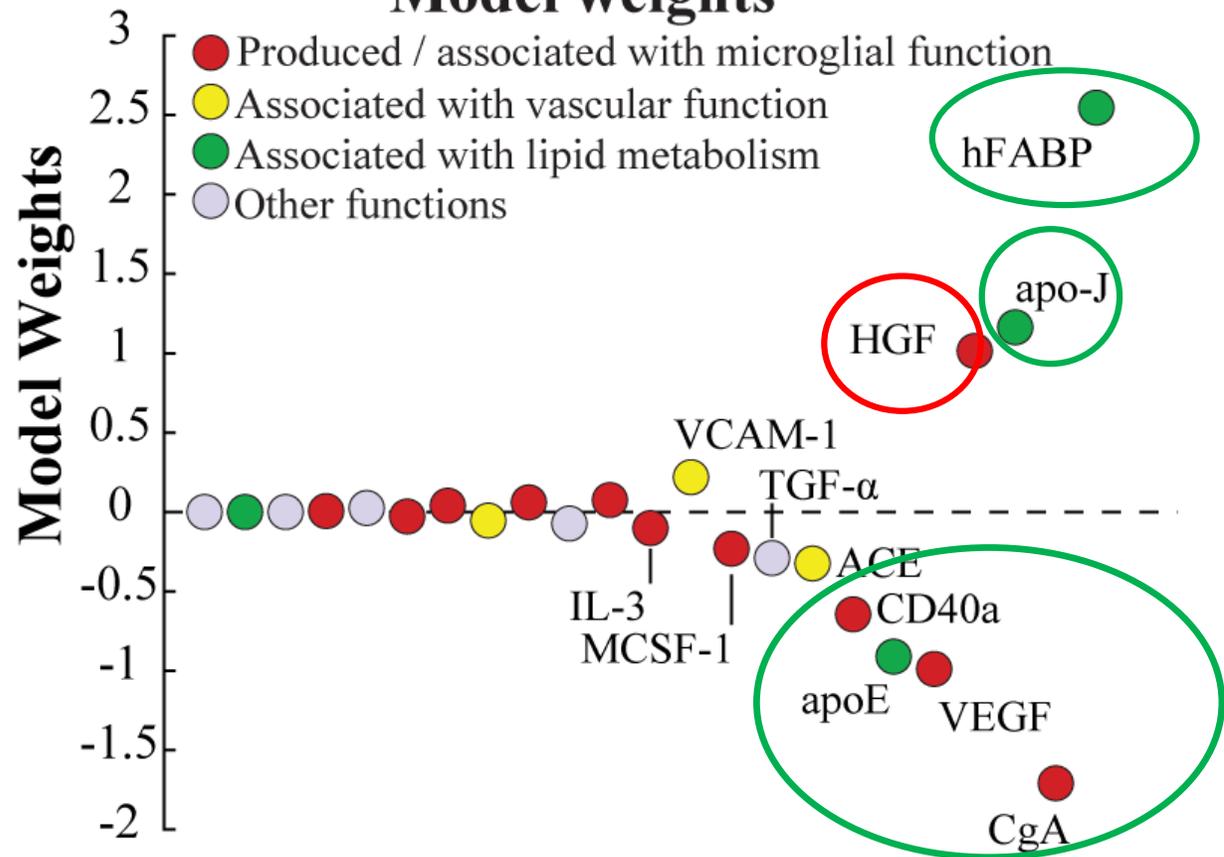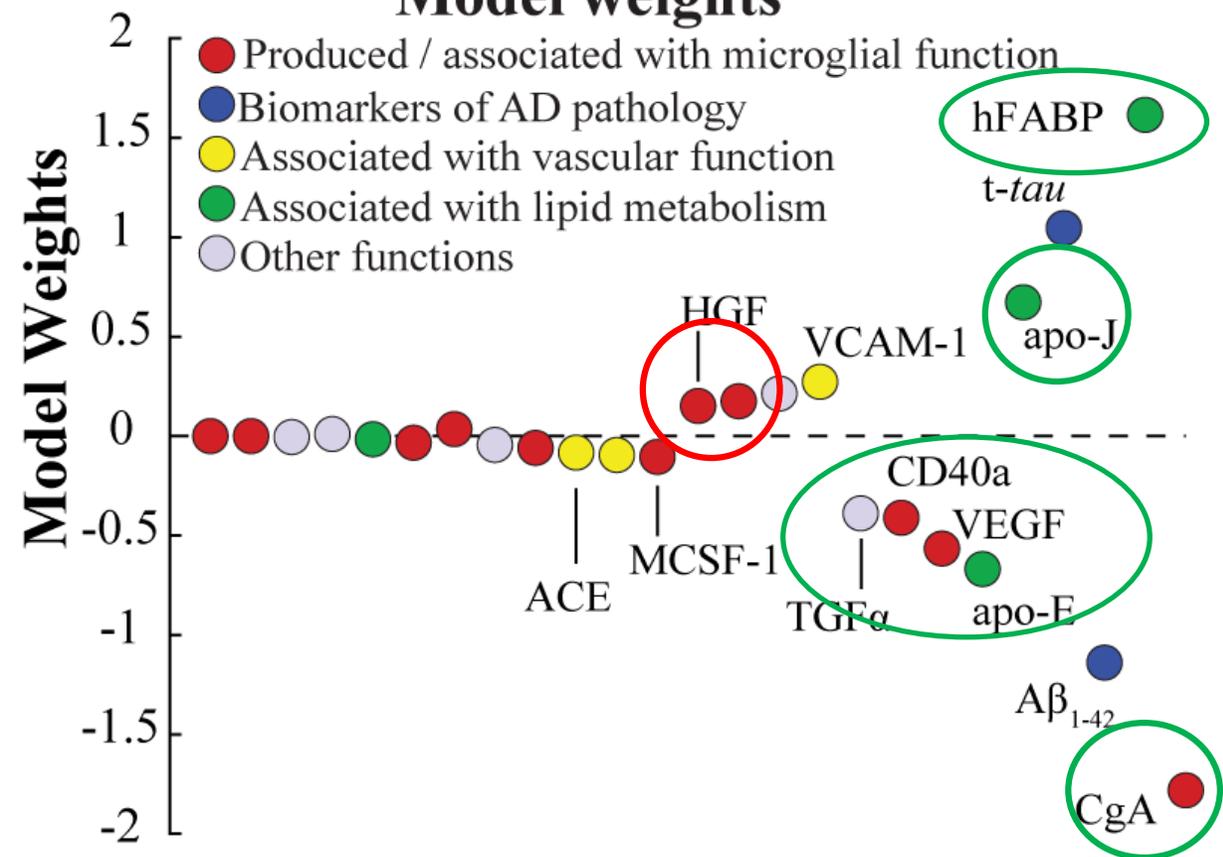
Take home messages:

1. "Inflammation" may be <u>protective against early AD</u>.

2. There is <u>no evidence</u> to suggest that anti-inflammatory treatments help or prevent AD dementia.

3. A <u>robust immune response</u> may retard or prevent amyloid accumulation early in AD pathology

4. Persons with robust immunity may therefore be less prone to develop AD (but may have inflammatory conditions that call for NSAID treatments!)

5. Markers of innate immunity predict (improved) cognitive performance for any given level of AD biomarker pathology.

Acknowledgements

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@prevent_ad

Thank you

Questions?