

Inflammatory Biomarkers Associated with Cognitive Function and Dementia: Framingham Heart Study Offspring Cohort

Jiachen Chen (chenjc@bu.edu)

Outline



STUDY SAMPLE



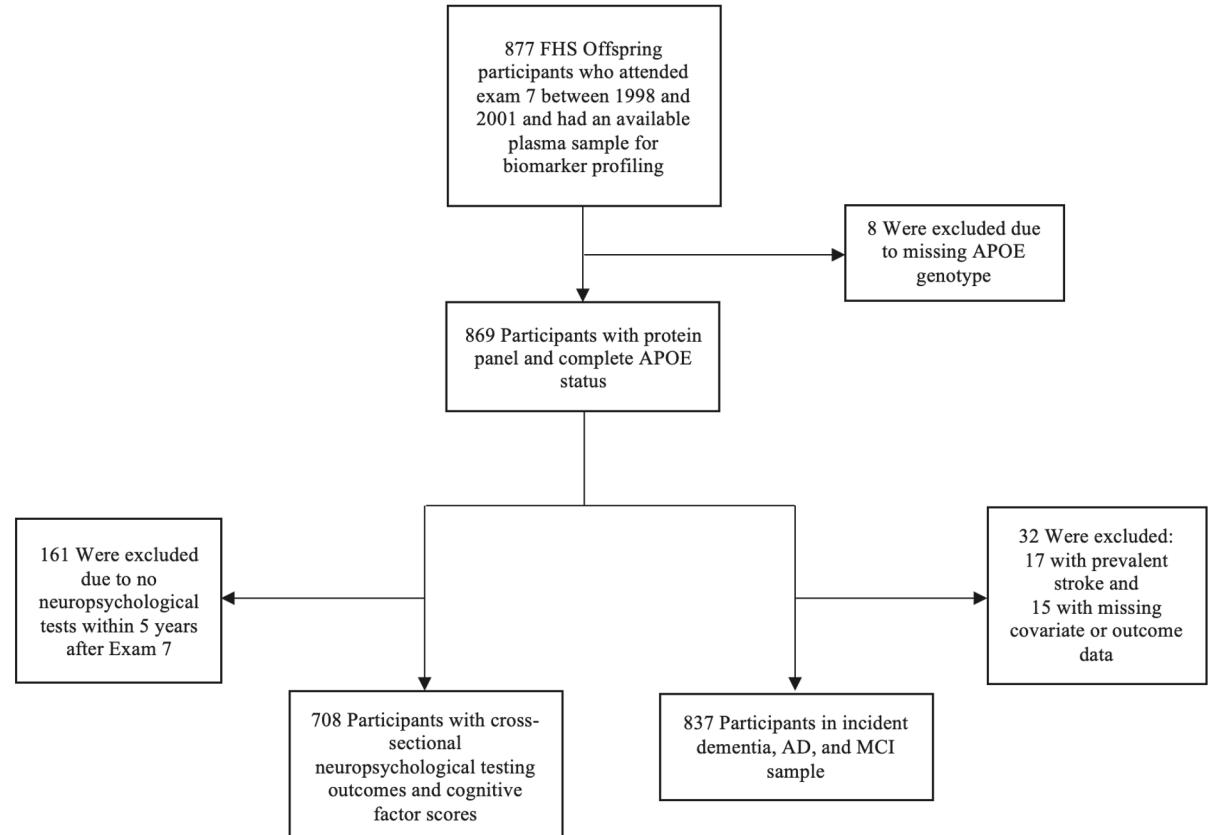
STATISTICAL ANALYSES



RESULTS

Study Sample

A sample of 879 Offspring participants who were dementia-free at FHS Offspring examination 7 (1998-2001) and had an existing stored plasma sample underwent inflammatory biomarker profiling and 877 of these participants passed the quality control processes.



Study Sample

- OLINK Inflammation Panel
 - The OLINK Inflammation panel measured 92 protein biomarkers using existing plasma samples from exam 7 of the FHS Offspring cohort.
 - Proteins with >50% of values below LOD were excluded from analyses, leaving 68 proteins for downstream analyses.
 - According to the OLINK guidelines, we used the actual data below LOD for the subset of proteins with values below LOD.
 - The rank-based inverse normal transformation was utilized to standardize the protein levels and reduce the skewness.
- Neuropsychological Tests and Factor Scores
 - Four domains were considered: memory, executive function, language, and visual perceptual.
 - Factor scores for three of the domains – memory, executive function, and language, were developed based on the NP tests using data across all FHS NP testing visits.
 - The rank-normalized HVOT test scores were used to represent the visuospatial domain.
 - Our analyses used the cognitive scores obtained from the NP testing visit closest to the participant's examination 7 core visit.
- FHS Dementia Ascertainment
 - The diagnoses of incident dementia, AD, and MCI were adjudicated by FHS consensus panel.
 - Full follow-up from the date of examination 7 through the year 2021 was recorded for participants, with the maximum follow-up time around 20.6 years.

Statistical Analysis

- For each outcome, we conducted a **combined** analysis for the full sample adjusting for APOE genotype and **stratified** analyses within three subgroups defined by APOE genotype status.
- The combined analysis used additive coding for numbers of $\epsilon 2$ and $\epsilon 4$ alleles to adjust the APOE genotype.
- For the stratified analyses, we excluded those genotyped $\epsilon 2\epsilon 4$ and defined participants according to APOE status into three subgroups: $\epsilon 2$ carrier ($\epsilon 2\epsilon 2$ and $\epsilon 3\epsilon 2$ genotypes), $\epsilon 4$ carrier ($\epsilon 4\epsilon 4$ and $\epsilon 3\epsilon 4$ genotypes), and $\epsilon 3\epsilon 3$ genotype (the reference group).
- All models accounted for familial relationships. The false discovery rate (FDR) was utilized to control the false rejections of true null hypotheses, and FDR ≤ 0.1 was set as the threshold to declare significant associations.

Association of NP cognitive scores with inflammatory proteins

- We individually tested each of the 68 proteins for association with each of the four domain scores using linear mixed-effects regression.
- Stratified analyses within the three APOE status strata were also included with the same set of covariates.
- Model 1:
 - Covariates: sex, age, education level, time in years between exam 7 (blood sample) and cognitive testing date, a retest indicator suggesting whether the cognitive function test was the first one taken by this participant, and APOE genotype.
- Model 2:
 - Incorporated all covariates in Model 1 and additional covariates including CVD risk factors and indicators for prevalent cardiovascular diseases such as prevalent stroke, prevalent CVD, and prevalent atrial fibrillation (AF) at examination 7.
 - The CVD risk factors included systolic and diastolic blood pressures (mmHg), diabetes status, treatment for hypertension, body-mass index (kg/m²), current smoking status, high-density lipoprotein cholesterol levels (HDL, measured in mg/dL), and use of lipid-lowering agents at examination 7.

Association of dementia-related outcomes with the inflammatory proteins

- We used Cox proportional hazard models to test for association between each of the 68 proteins and time to diagnosis of incident dementia, AD, or MCI individually, using the same covariates as used for the cognitive score outcome models.
- Similarly, stratified analyses within each stratum by APOE status were considered as well.

Sensitivity analyses

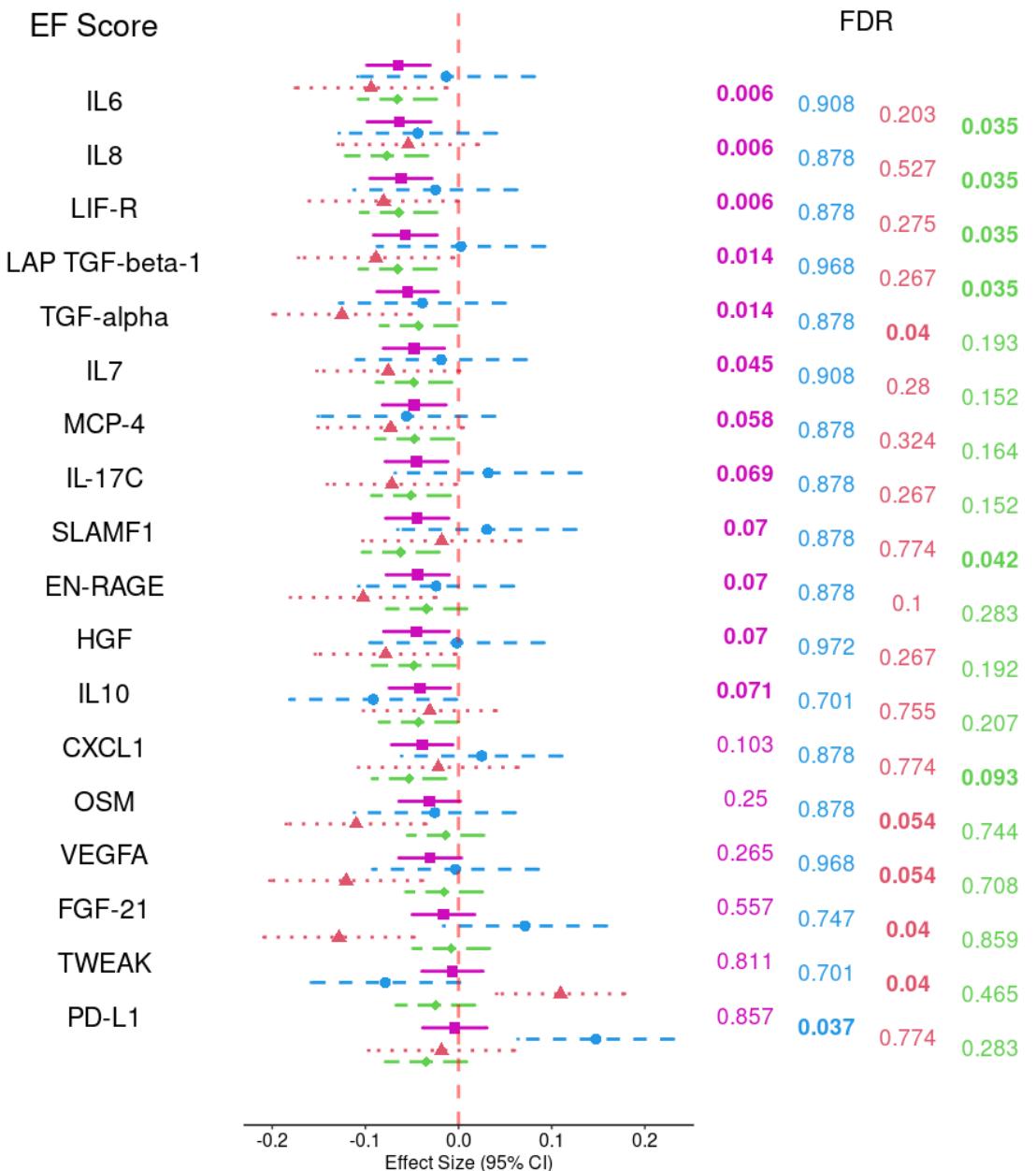
- The robustness of the association analyses was further assessed on our samples with additional restrictions.

Forest Plots

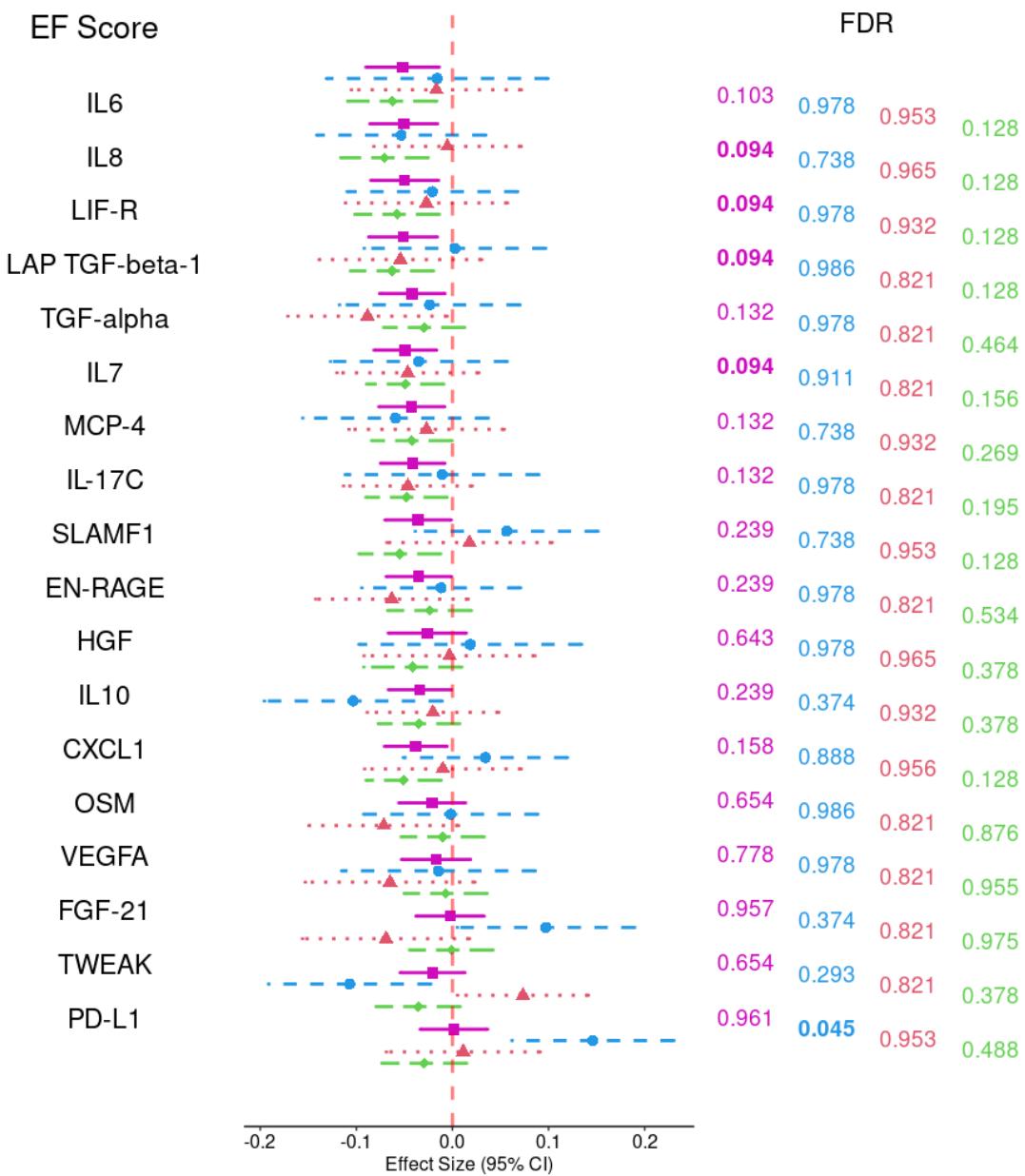
For Association of NP cognitive scores with inflammatory proteins

EF domain

Model 1



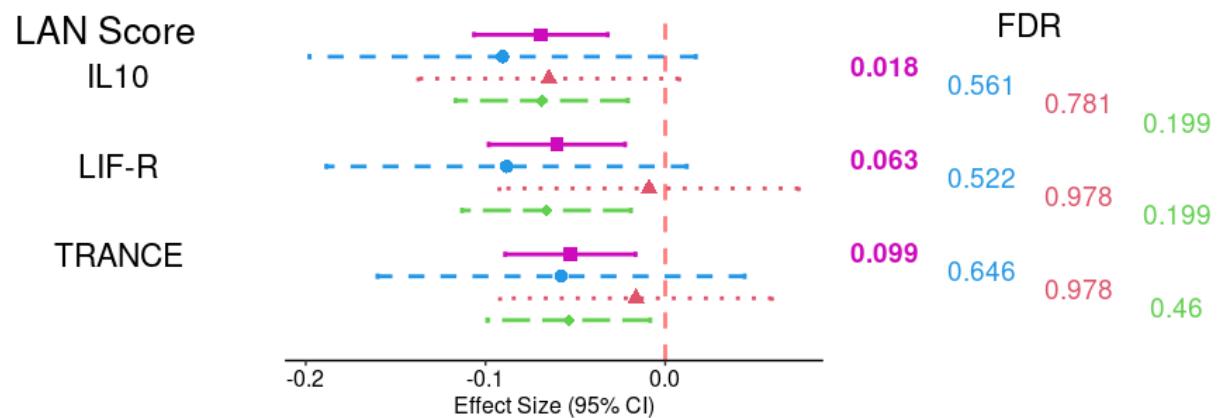
Model 2 (also include significant proteins in model 1)



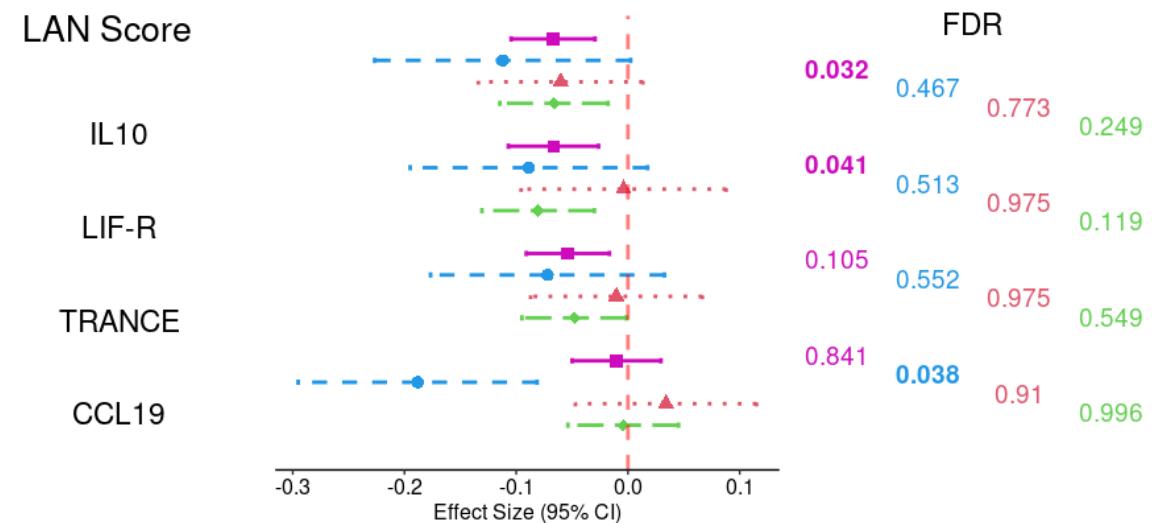
LAN domain

- Combined (n=708)
- E2 Carrier (n=87)
- ▲ E4 Carrier (n=133)
- ◆ E3E3 (n=468)

Model 1



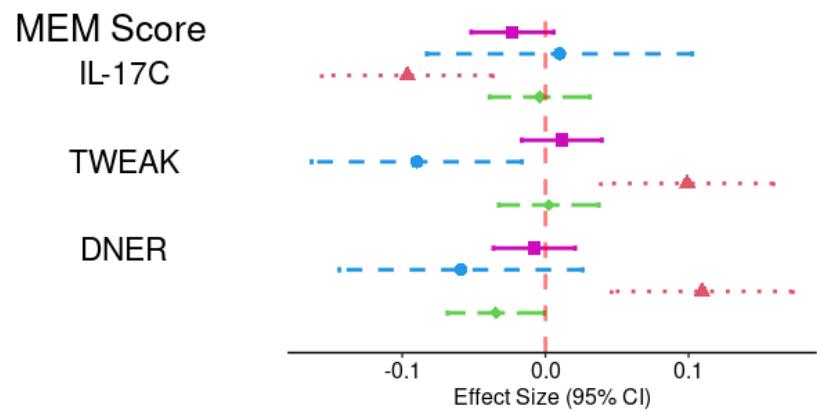
Model 2 (also include significant proteins in model 1)



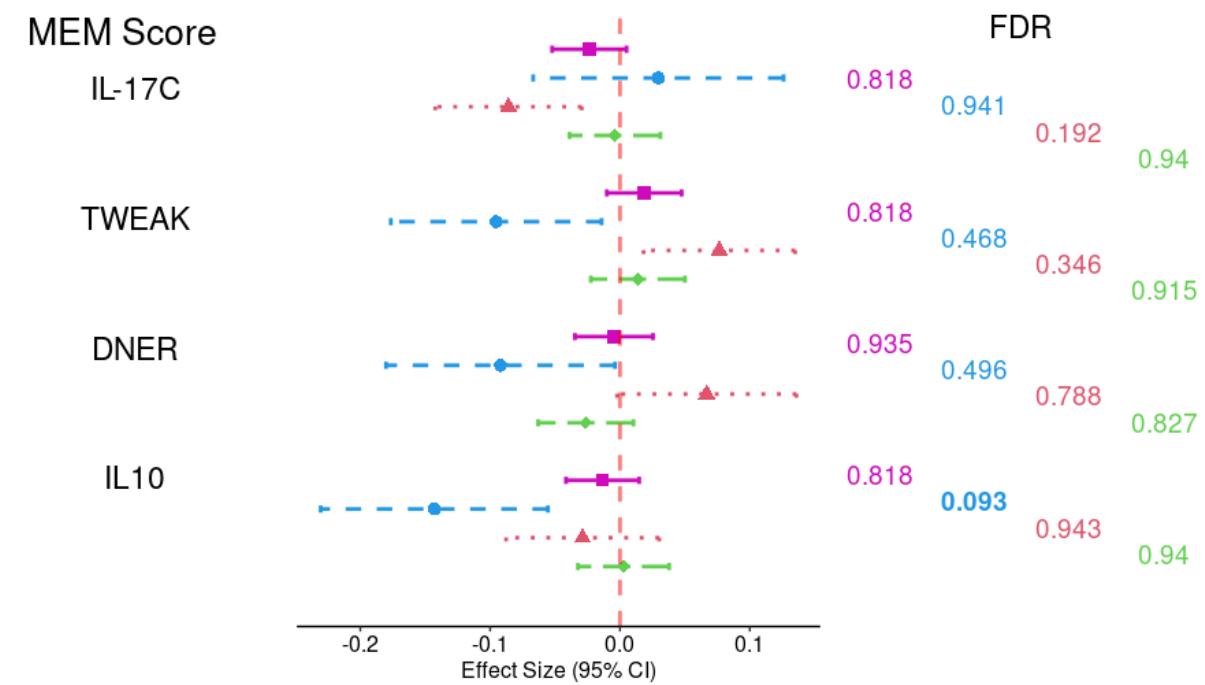
MEM domain

- Combined (n=708)
- E2 Carrier (n=87)
- ▲ E4 Carrier (n=133)
- ◆ E3E3 (n=468)

Model 1

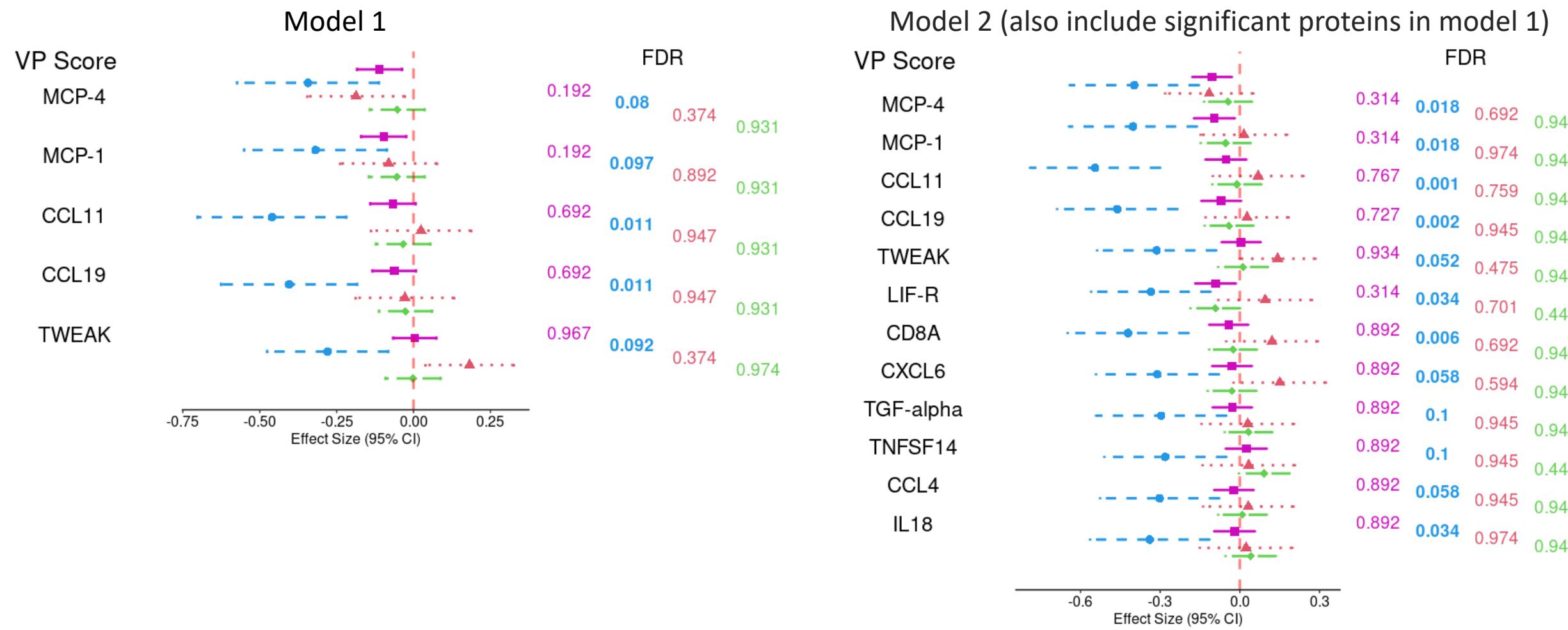


Model 2 (also include significant proteins in model 1)



VP domain

- Combined (n=708)
- E2 Carrier (n=87)
- ▲ E4 Carrier (n=133)
- ◆ E3E3 (n=468)



Results

Association of dementia-related outcomes with the inflammatory proteins (Model 1)

Higher levels of TNFB popped up as associated with higher risks of dementia, AD, and MCI.

Outcome	Follow-up Time	Stratum	Protein	Hazard Ratio	95% CI	p-value	FDR	
Incident dementia	10 years	Combined	TNFB	1.90	(1.38, 2.62)	<=0.001	0.006	
			TNFB	1.65	(1.33, 2.03)	<=0.001	<=0.001	
			CDCP1	1.66	(1.28, 2.16)	<=0.001	0.005	
		Full	TNF	1.94	(1.37, 2.75)	<=0.001	0.013	
			TNFB	1.87	(1.30, 2.70)	0.001	0.026	
			CCL19	1.70	(1.18, 2.45)	0.004	0.096	
			TNFRSF9	1.80	(1.16, 2.78)	0.008	0.099	
			MCP-1	1.63	(1.13, 2.37)	0.010	0.099	
			TGF-alpha	1.65	(1.13, 2.42)	0.010	0.099	
			IL18	1.50	(1.10, 2.07)	0.011	0.099	
		E3E3	CCL3	1.84	(1.15, 2.94)	0.012	0.099	
			CDCP1	1.74	(1.27, 2.40)	0.001	0.047	
Incident AD	10 years	Combined	TNFB	1.75	(1.25, 2.44)	0.001	0.081	
		Full	Combined	TNFB	1.67	(1.30, 2.14)	<=0.001	0.004
			E4	TNFB	2.11	(1.44, 3.09)	<=0.001	0.008
MCI	10 years	Combined	TNFB	1.52	(1.23, 1.88)	<=0.001	0.008	
	Full	Combined	TNFB	1.45	(1.21, 1.73)	<=0.001	0.003	

Cross-sectional associations of proteins with dementia-related outcomes for the combined and stratified analyses using Model 1(FDR ≤ 0.1)