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Poor cardiovascular health has been linked to structural brain changes, including brain atrophy, cerebral microbleeds, total brain volume, and white matter hyperintensities, which have also been shown to play a role in dementia.

Govindarajan et al. (2025) created machine learning derived MRI Spatial Patterns of Abnormalities for Recognition (SPARE) scores for the cardiometabolic and vascular risk factors (CVMs) of **diabetes**, **hyperlipidemia**, **hypertension**, **obesity**, and **smoking**.

- Scores reflect how strongly one's brain structure expresses the risk-factor–related patterns of brain atrophy.

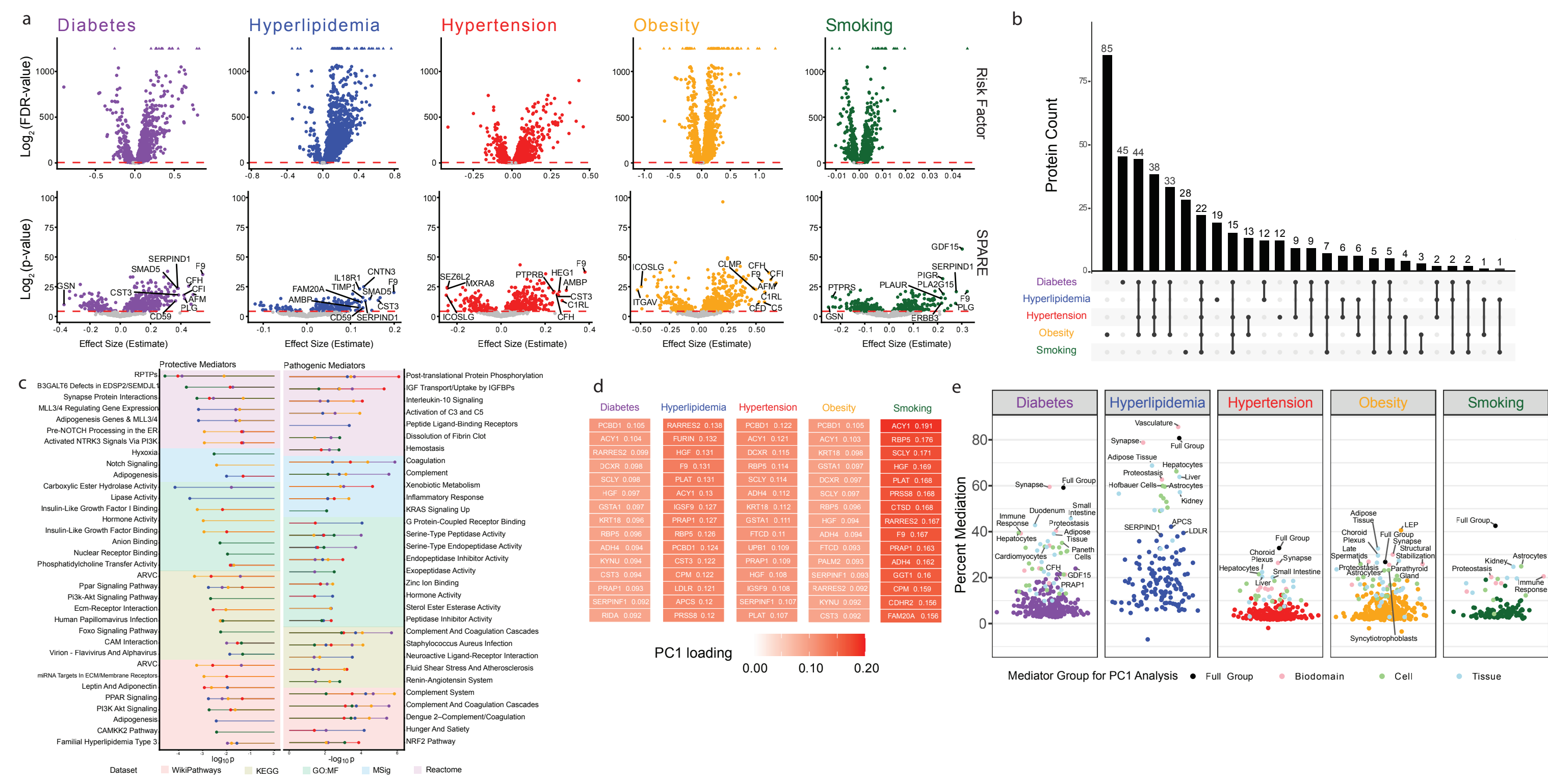
The proteome's role in mediating the relationship between CVMs and brain atrophy patterns requires further investigation.

In this study, we identified protein mediators of the CVM-specific brain atrophy, leveraging proteomic and MRI data from multiple cohorts including the UK Biobank (UKB), Global Neurodegeneration Proteomics Consortium (GNPC), and the Baltimore Longitudinal Study of Aging (BLSA).

Mediators were found for all five CVMs, with most mediating multiple CVMs.

- Diabetes (250 mediators):** Synaptic function and lipid/cholesterol metabolism and maintenance.
- Hyperlipidemia (123):** Adipogenesis regulation and PPAR signaling.
- Hypertension (183):** Epithelial–mesenchymal transition and IGF transport.
- Obesity (271):** mTORC1 pathway regulation, metabolic and detoxification stress.
- Smoking (94):** Hemostasis, RAAS, GAG synthesis and cellular senescence.

All five risk factors: ECM integrity, complement/coagulation pathways, chronic inflammation, and oxidative stress.

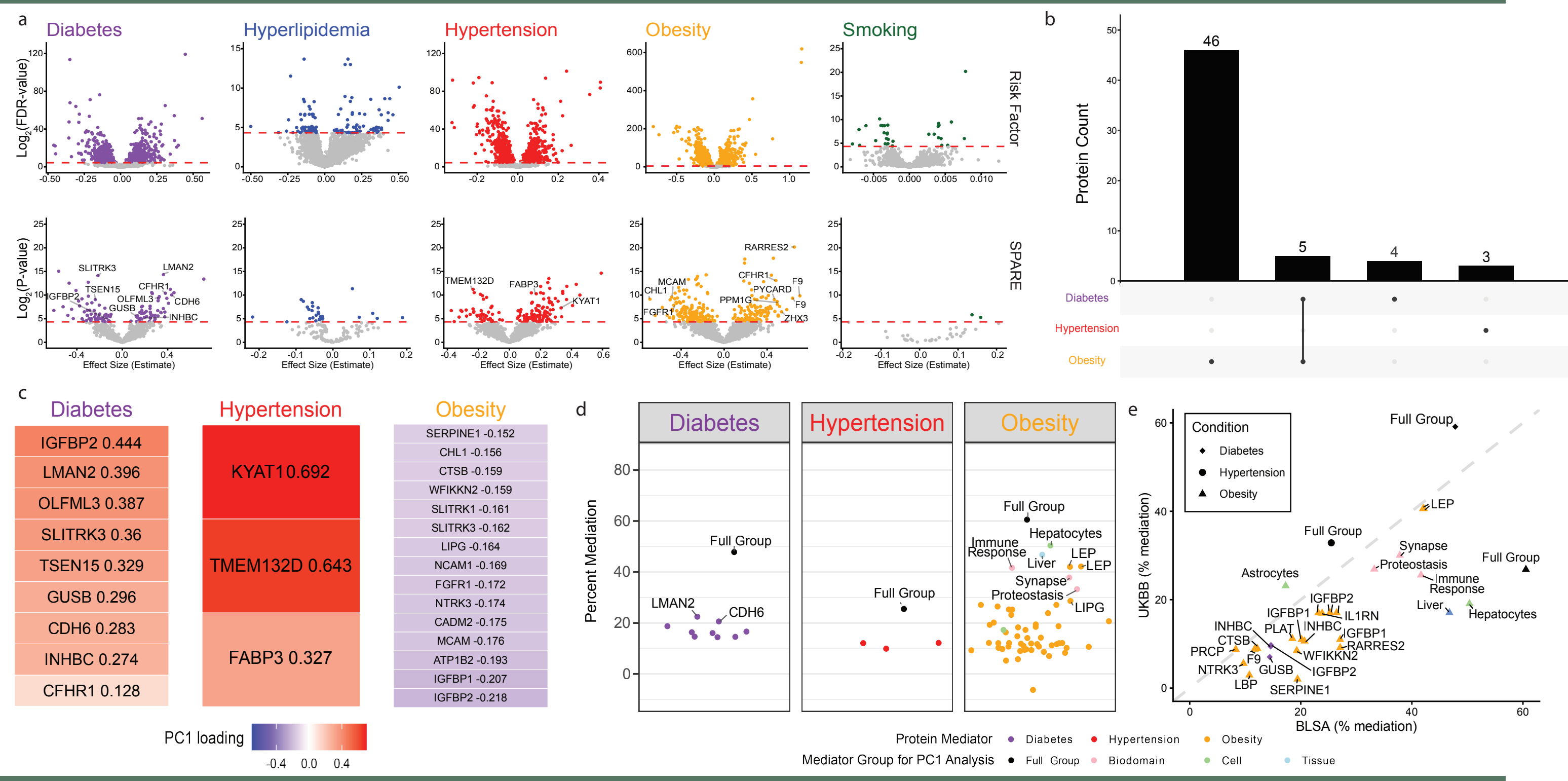


Mediators were identified for **diabetes**, **hypertension** and **obesity** with there being some overlap between mediators for diabetes and obesity.

Diabetes (9): 47.8% mediation as a group, with immune response and synapse-specific proteins as the strongest mediators.

Hypertension (3): 25.5% mediation as a group.

Obesity (51): 60.5% mediation as a group, with hepatocyte- and liver-specific proteins as the strongest mediators.



a

Cardiometabolic risk factors

Type 2 Diabetes

Hyperlipidemia

Hypertension

Obesity

Smoking

Plasma proteome

Olink
(~3k proteins)
n=45-53k participants

SomaScan
(~7k proteins)
n=12k participants

FDR < 0.05

b

Cardiometabolic-associated proteins
(n = 34-1174 proteins)

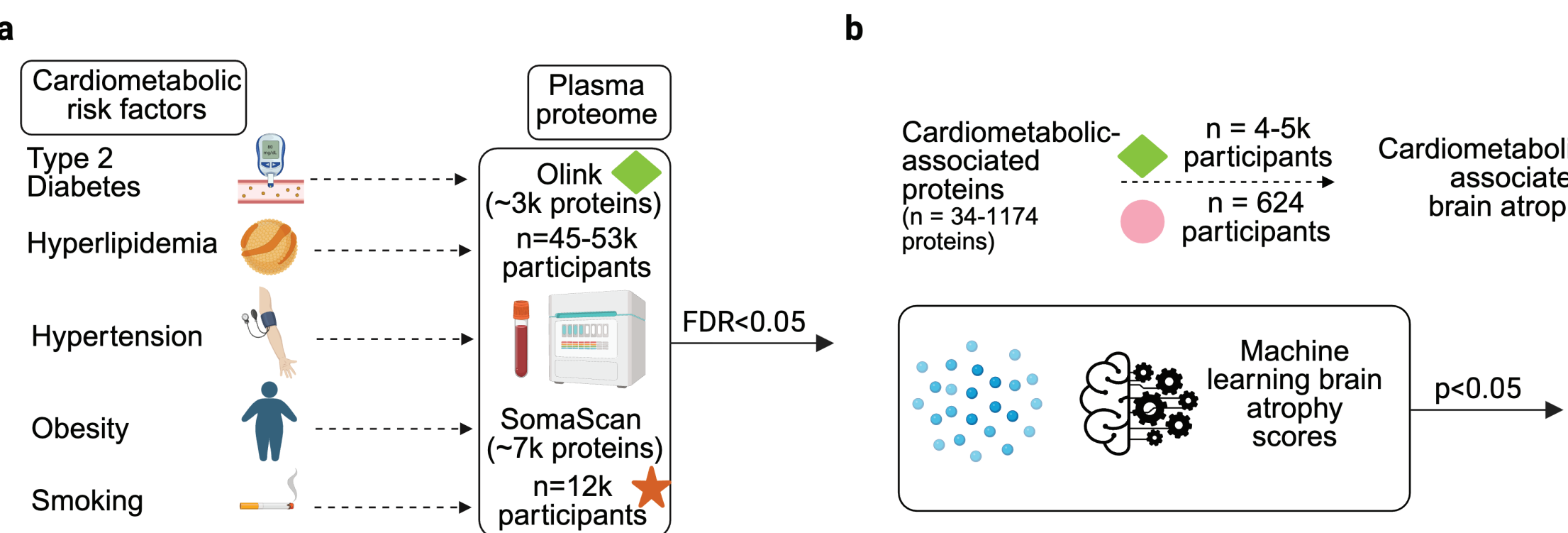
n = 4-5k participants

n = 624 participants

Cardiometabolic-associated brain atrophy

Machine learning brain atrophy scores

p < 0.05



A. Proteins were required to be significantly associated with the CVM (FDR < 0.05) in UKB (Olink) and GNPC (SomaScan).
B. These proteins also had to be associated with the corresponding SPARE score from a subsequent visit at nominal significance ($p < 0.05$) in UKB (Olink) and BLSA (SomaScan).

c

Mediation analyses

Protein (n = 306-809 proteins)
(n = 2-288 proteins)

Cardiometabolic risk factors

Brain atrophy

p < 0.05

d

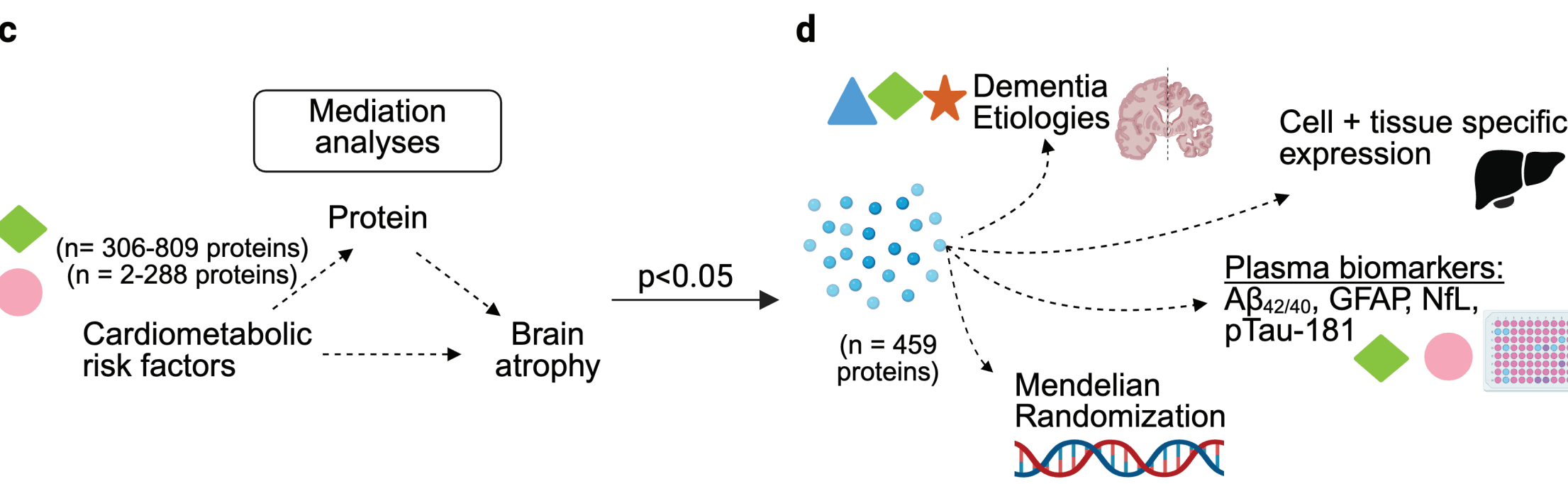
Dementia Etiologies

Cell + tissue specific expression

Plasma biomarkers: Aβ_{42/40}, GFAP, NFL, pTau-181

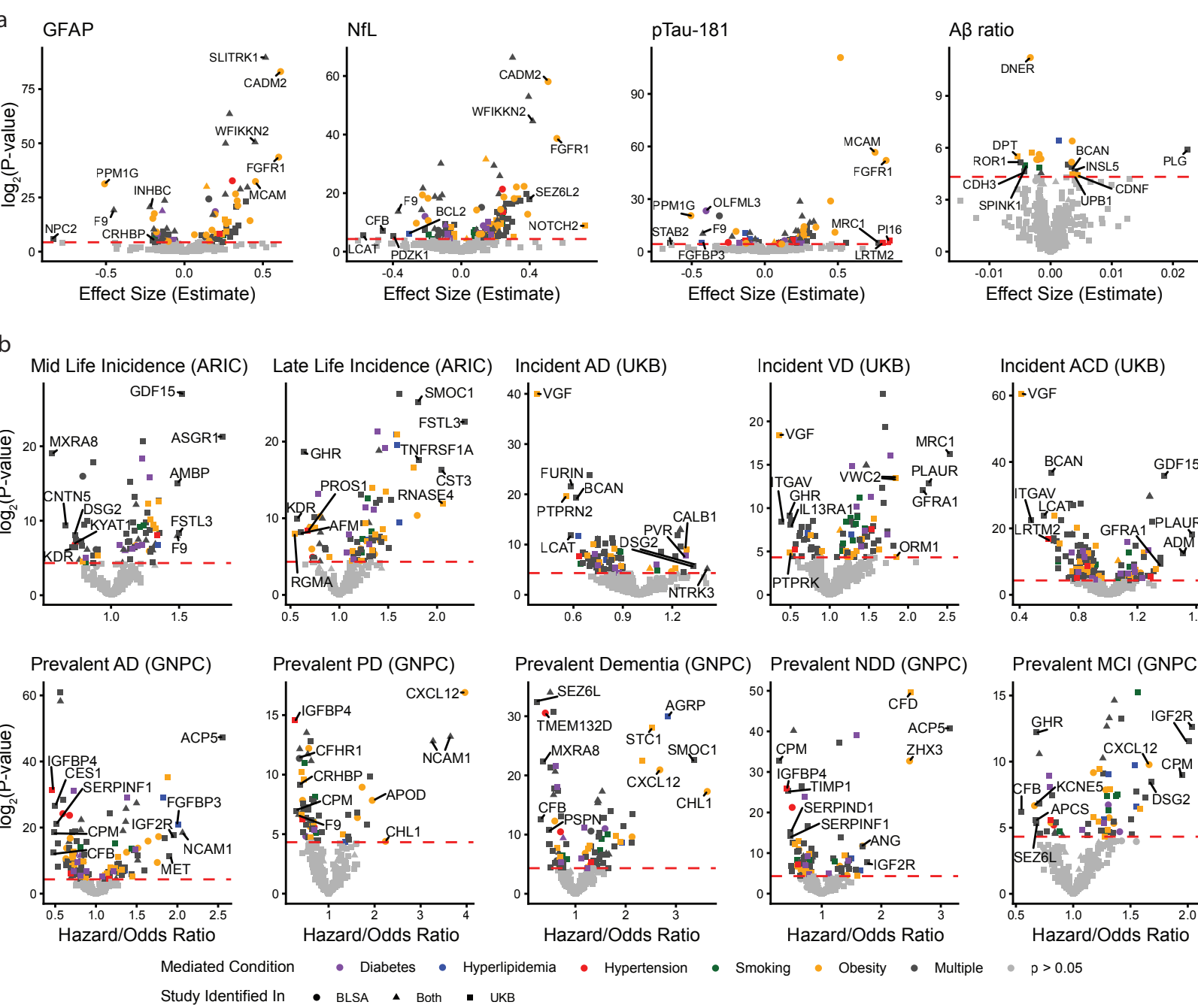
Mendelian Randomization

(n = 459 proteins)



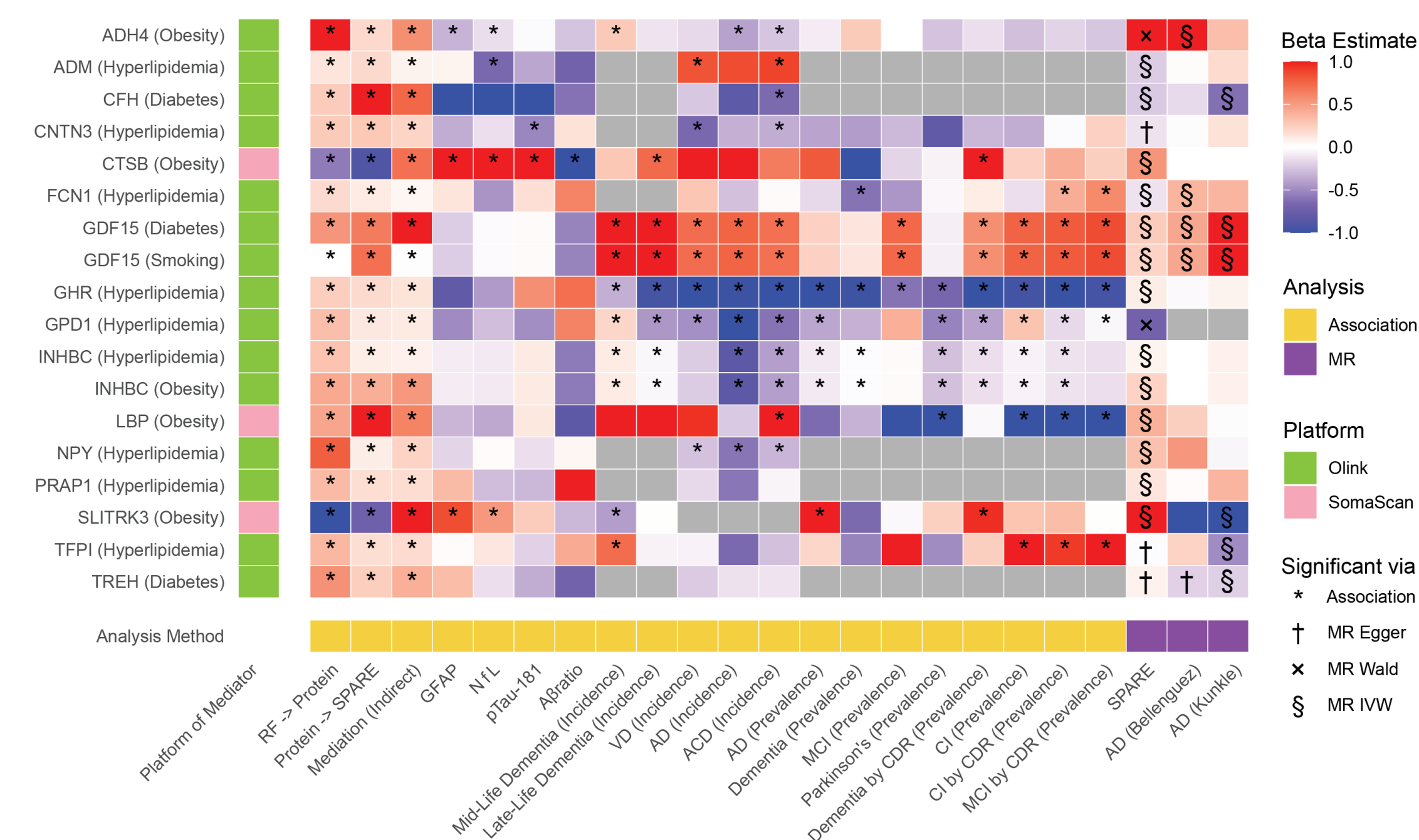
C. Proteins meeting both criteria were evaluated using structural equation modeling (SEM) to confirm mediation effects.

D. Confirmed mediators were further characterized based on their cell and tissue-specific expression patterns, associations with Alzheimer's disease plasma biomarkers, and relationships with dementia and other neurodegenerative outcomes. Mendelian randomization was used to evaluate for causal relationships between mediators and SPARE-CVM.



Associations with AD/ADRD biomarkers:

- NFI In UKB: 16.3% - 24.5% of mediators per condition
- NFI in BLSA: 88.9% Diabetes and 81.8% Obesity
- GFAP in BLSA: 88.9% Diabetes and 84.1% Obesity
- pTau-181 in BLSA: 66.7% Hypertension, 61.4% Obesity, 44.4% Diabetes



Associations with neurodegenerative diseases:

- 72.5% were associated with ≥ 1 prevalent outcome.
- 56.7% were associated with $\geq$ incident outcome.

- 18 Protein -> SPARE-CVM pairs were identified in MR analyses.
- 8 proteins were causally implicated with AD.
- 4 proteins exhibited consistent associations with SPARE and AD.

STRENGTHS AND LIMITATIONS:

- This study leverages data from multiple cohorts and uses a combination of analytical techniques to verify results including the inclusion of genetic techniques to indicate causality.
 - The BLSA is a healthy, relatively small cohort in comparison to other studies in the consortium used to train SPARE scores, limiting the robustness of analyses.
 - Due to the limited number of overlap between the GWAS for proteins and SPARE-CVM/ AD outcomes, not all mediators could be evaluated for causal relationships.
- FUTURE DIRECTIONS:
- Evaluate the 4 proteins for their potential role as therapeutics/ drug targets.

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