

Demographic- and Cohort-Aware Comparison of Alzheimer's Omic Risk Signatures

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BACKGROUND

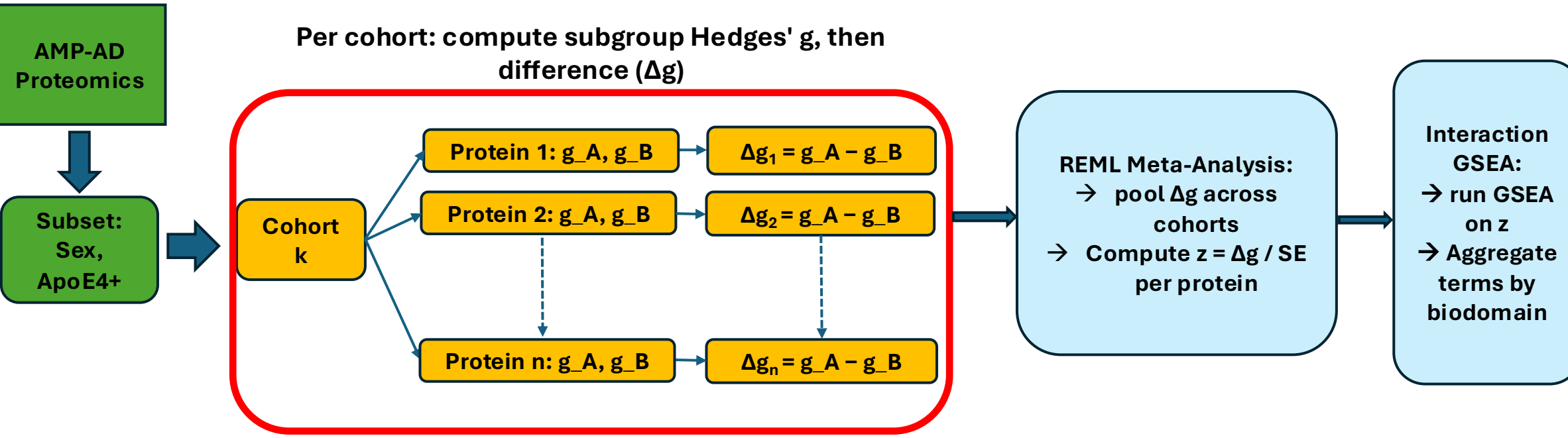
Alzheimer's disease is biologically heterogeneous, and prioritizing therapeutic targets requires methods that resolve disease signals across patient subgroups. The TREAT-AD Target Risk Score (TRS) integrates genetics and multi-omics across AMP-AD cohorts to estimate genome-wide AD-associated effects and map them onto 19 AD biodomains¹. Using the TRS pipeline¹, we recomputed proteomic meta-analytic weights per subgroup across cohorts to characterize subgroup AD signatures. These signatures revealed broadly concordant AD-associated changes, but subgroup-specific differences at the pathway level remained unresolved. Resolving these differences requires direct subgroup comparison, which in meta-analytic settings is vulnerable to aggregation bias, as naive pooling can conflate cohort effects with subgroup effects². To address this, we developed a principled framework that compares subgroups while controlling for cohort-level confounding.

METHODS

Preprocessed protein expression matrices and sample metadata from AMP-AD were subset by user-specified criteria. Initially, for each subset, protein-level AD-associated effects (Hedges' g³, AD vs. control) were estimated using random-effects meta-analysis of standardized mean differences across cohorts. These per-subgroup weights captured each subgroup's independent AD signal to compare to a full-cohort baseline. To compare subgroups, the pipeline computes Hedges' g per subgroup within each cohort first, then differences within cohort ($\Delta g = g_A - g_B$), canceling batch, platform, and population structure effects². Δg is meta-analyzed across cohorts via REML random-effects models, yielding per-protein interaction z-scores ($z = \Delta g / SE$). A high |z| requires the subgroup difference to be both large and consistent across independent cohorts. Pathway discovery uses interaction GSEA^{4,5}, a single gene set enrichment analysis ranked by interaction z-score, mapped to 19 AD biodomains. We applied this pipeline to AMP-AD proteomics across two axes: Sex (Male vs. Female) and APOE4 carrier status (ApoE4+ vs. Non-carrier). Cohorts lacking both subgroups within a comparison were excluded.

For each significant GO term identified by interaction GSEA, subgroup dominance was assigned via a hierarchical majority vote: within each cohort, the subgroup with larger |g| was identified per protein; protein-level dominance was determined by majority across cohorts; term-level dominance was determined by majority across member proteins. This classification partitions enriched pathways into subgroup-dominant sets for visualization.

Comparison	Cohorts (k)	Proteins	AD	CT
Full Cohort	17	9,770	1,267	713
Sex	10	9,384		
Males			510	336
Females			362	228
ApoE4+ Status	9	9,598		
Carrier			522	163
Non-carrier			525	466



Shared AD proteomic signatures across subgroups

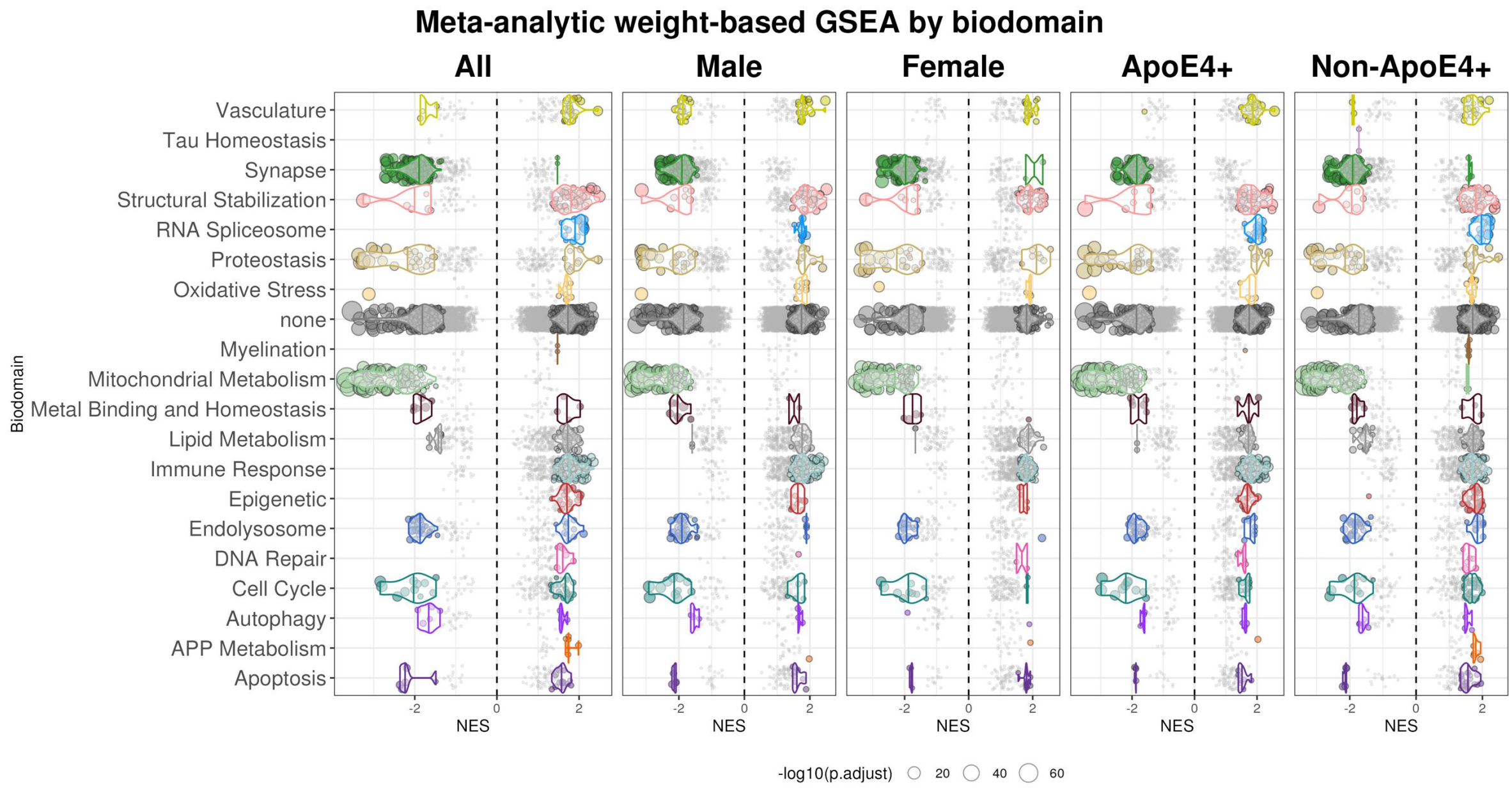


Figure 1: Per-subgroup TE-based GSEA mapped to 19 AD biodomains. Each panel shows enrichment for one subgroup or the full cohort. Colored points: $padj \leq 0.05$; grey: not significant. Point size scales with $-\log_{10}(padj)$.

Sex-stratified signatures diverge across AD-relevant biodomains

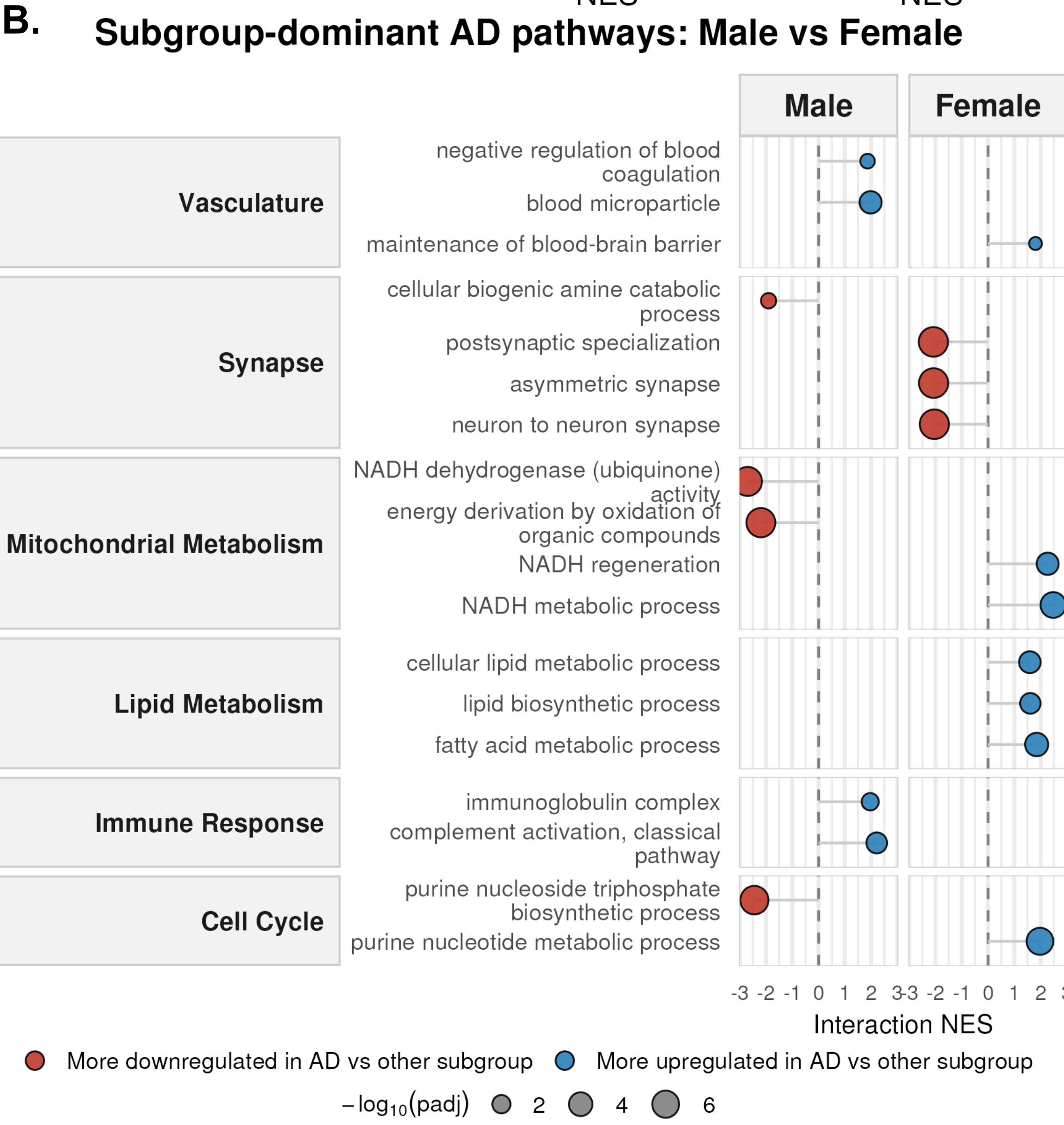
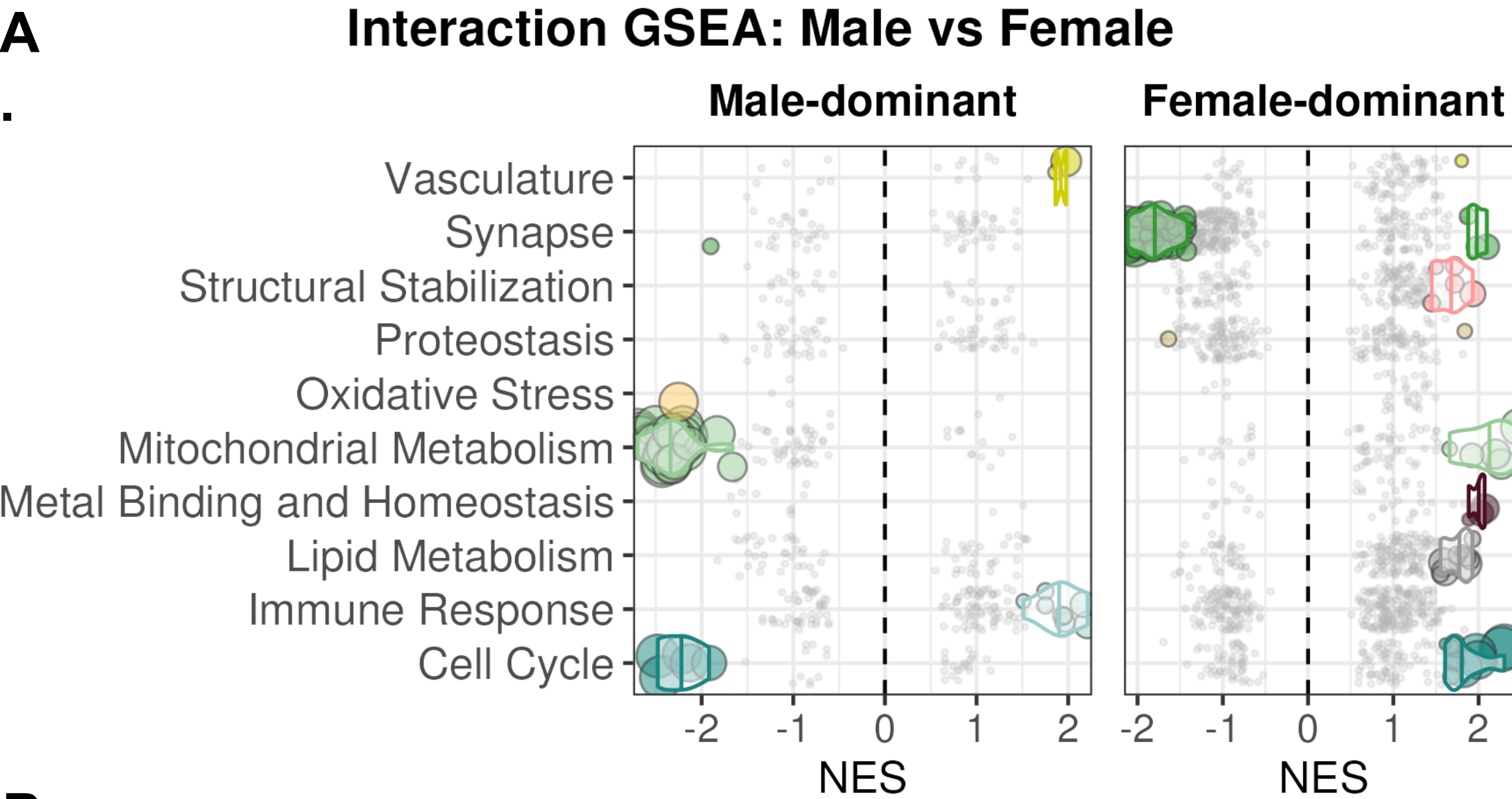


Figure 2: (A) Interaction GSEA results split by within-cohort dominance classification. Proteins ranked by interaction z-score ($\Delta g / SE$). (+) NES: more upregulated in subgroup AD; (-) NES: more downregulated in subgroup AD. (B) Top significant GO terms ($padj \leq 0.05$) per biodomain, classified as male- or female-dominant by cohort-level majority vote. Point color: AD direction; point size: $-\log_{10}(padj)$.

Protein-level validation of sex-specific divergence

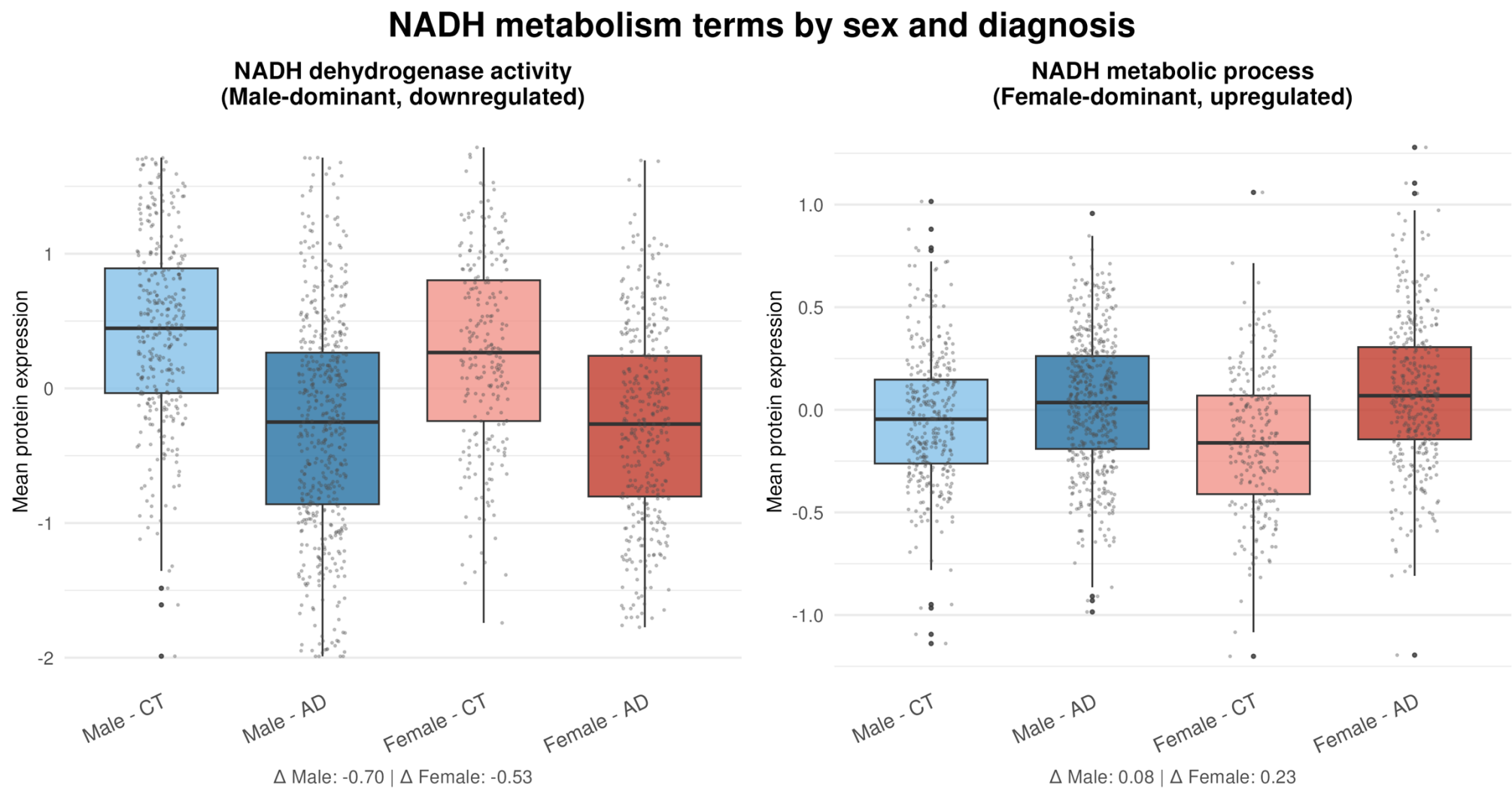


Figure 3: Mean batch-corrected protein expression across GO term members, split by sex and diagnosis. Δ = median difference (AD - CT). Left: NADH dehydrogenase activity (male-dominant, downregulated); right: NADH metabolic process (female-dominant, upregulated).

AD effects are globally stronger in ApoE4+ carriers

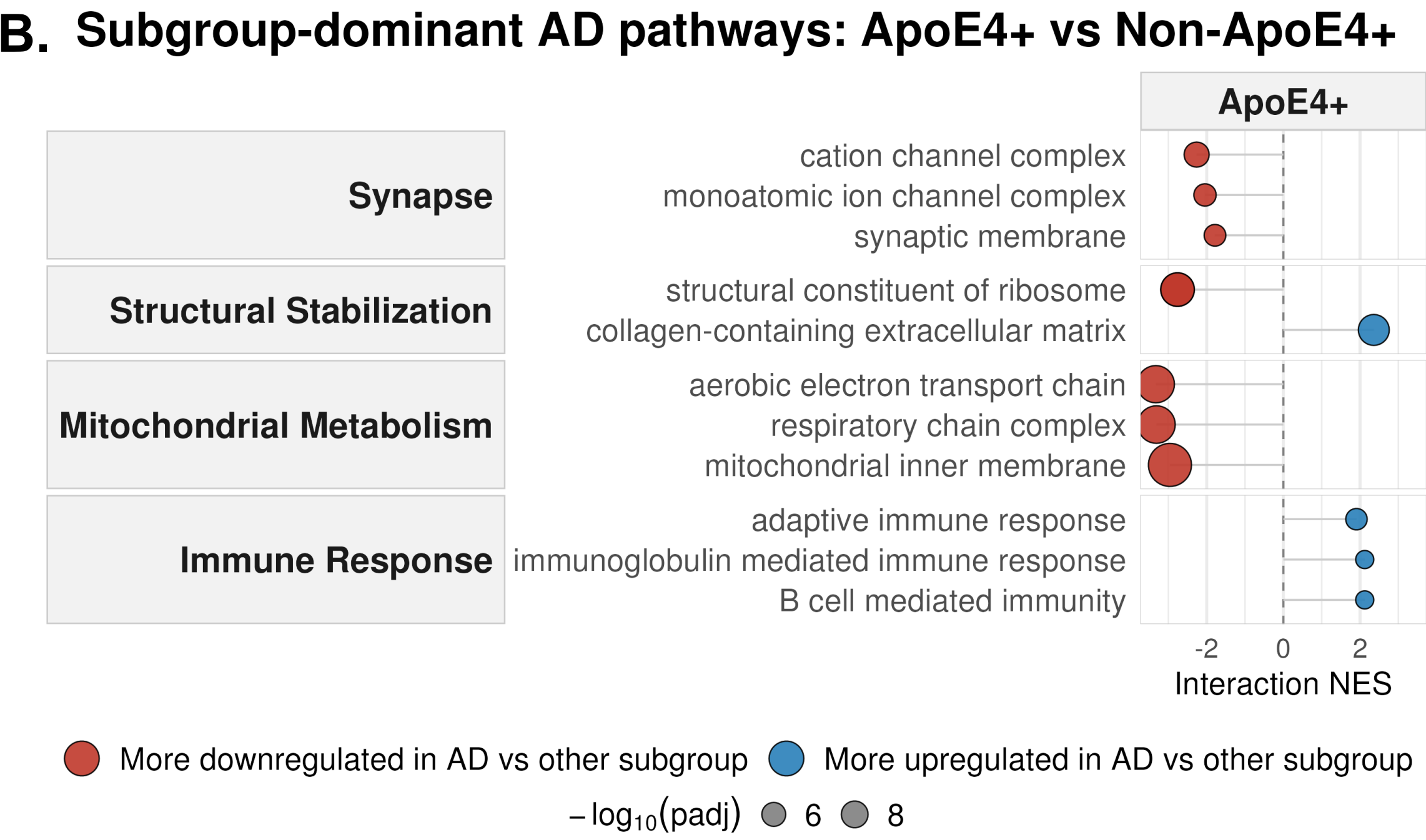
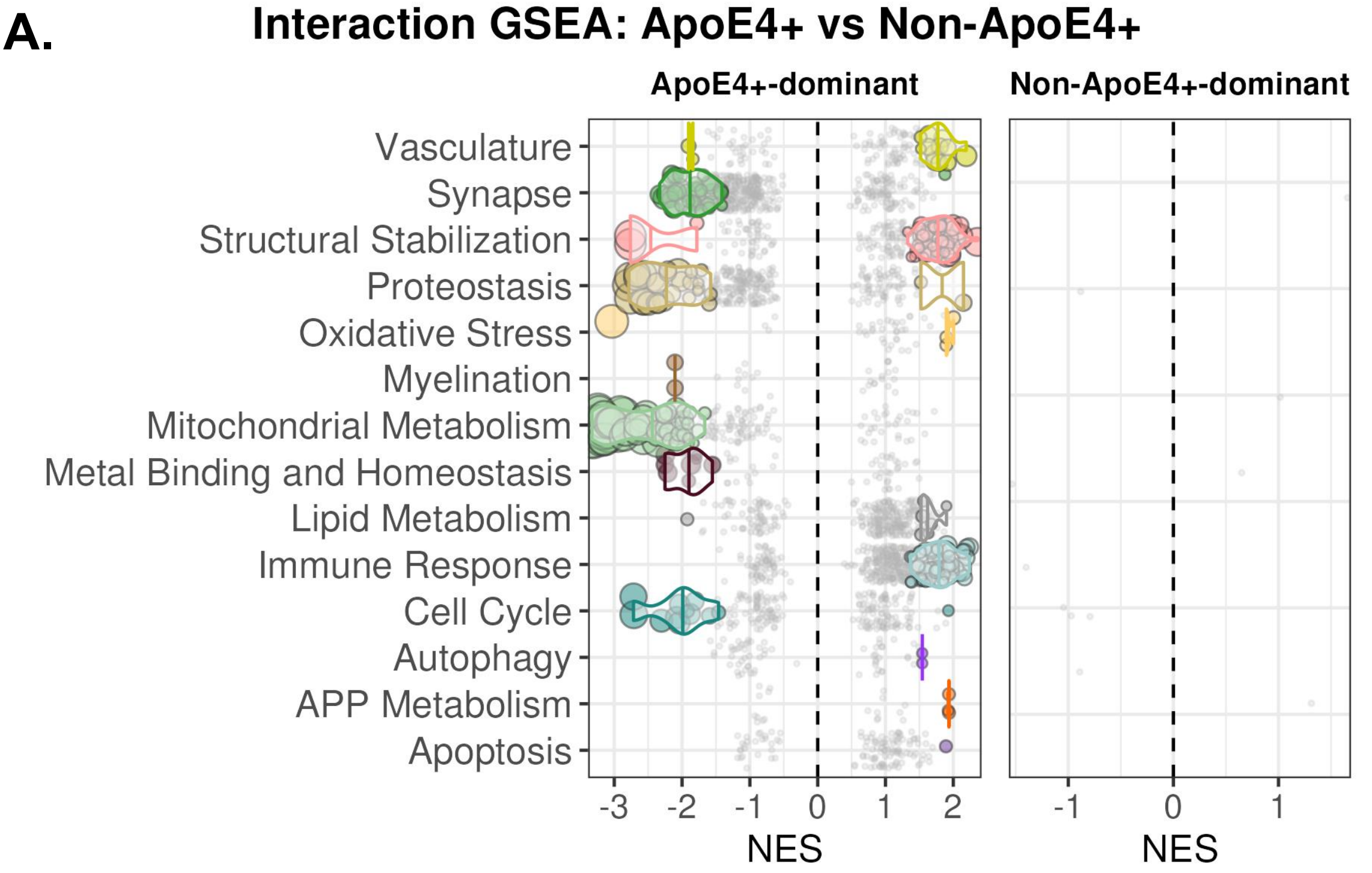


Figure 4: (A) Interaction GSEA results for ApoE4+ -dominant terms only. No significant non-carrier-dominant pathways were identified. (+) NES: more upregulated in ApoE4+ AD; (-) NES: more downregulated. (B) Top significant GO terms ($padj \leq 0.05$) per biodomain, classified as ApoE4+ -dominant. All significant terms were carrier-dominant; non-carrier column omitted.

CONCLUSIONS

- Within-cohort interaction meta-analysis controls for cohort-level confounding and enables principled subgroup comparison of AD proteomic signatures across demographic strata.
- Per-subgroup meta-analytic estimates are broadly concordant, motivating interaction-based approaches to detect relative differences between subgroups.
- All significant ApoE4 interaction pathways show stronger AD effects in carriers versus non-carriers, with no non-carrier-dominant pathways detected.
- Sex-stratified signatures show larger male AD effects in mitochondrial metabolism (NADH dehydrogenase activity) and immune response (complement/immunoglobulin enrichment), and larger female effects in synaptic structure and NADH metabolic processes.
- Protein-level expression confirms the NADH metabolism divergence identified by interaction GSEA.
- Future applications include contrasting AD subtypes, integrating transcriptomic comparisons, and defining subgroup-specific therapeutic hypotheses.

ACKNOWLEDGEMENTS

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For information about data used in this analysis, please visit:
AMP-AD: <https://adknowledgeportal.synapse.org/Explore/Programs/DetailsPage?Program=AMP-AD>

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