

***LAMP1*-mediated Immunometabolic Characteristics in Alzheimer Disease and Mild Cognitive Impairment: A Transcriptomic Profiling Study across Multiple GEO Datasets**

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ABSTRACT

This study characterized lysosome-associated membrane protein 1 (*LAMP1*)-related immunometabolic abnormalities in Alzheimer disease (AD) and mild cognitive impairment (MCI) using peripheral blood transcriptomic data from three GEO cohorts (GSE63060, GSE63061, and GSE140829).

After preprocessing and cross-cohort integration, directionally consistent *LAMP1*-related genes were identified, and a composite index comprising *ITGAM*, *ITGB2*, *LAMP1*, and *GBA* was constructed. Analyses included correlation, group comparison, ROC analysis, random-effects meta-analysis, and leave-one-out validation. A total of 1262 samples were included.

LAMP1 was consistently elevated in AD and MCI versus controls, with pooled effect sizes of Hedges' $g=0.330$ and 0.514 , respectively. Immune-, lysosome-, and metabolism-related genes, including *ITGAM*, *ITGB2*, *GBA*, *GNS*, *RXRA*, *G6PD*, and *TCIRG1*, showed concordant changes across both conditions. The 4-gene index was also increased in AD and MCI ($g = 0.543$ and 0.648), and *LAMP1* strongly correlated with the 3-gene index excluding itself ($r=0.760$).

These findings suggest reproducible peripheral blood transcriptomic alterations related to immune activation, lysosomal dysfunction, and metabolic regulation in AD and MCI. As this was a secondary analysis of public datasets without adjustment for blood-cell composition, the results should be interpreted as exploratory molecular signals rather than definitive diagnostic biomarkers.

Keywords: Alzheimer disease; GEO database; *LAMP1*; Mild cognitive impairment; Peripheral blood transcriptome; Related molecular features

INTRODUCTION

Alzheimer disease (AD) is 1 of the most common neurodegenerative disorders and the leading cause of dementia in older adults. With accelerating population aging, the number of people affected by AD and its

associated socioeconomic burden continue to rise, making it a major global public health challenge.^{1,2} Unlike many acute neurological disorders, AD is characterized by years of ongoing biological change before overt clinical symptoms emerge. Consequently, identifying molecular features that can reflect early disease-related abnormalities has remained a central objective in this field.

Mild cognitive impairment (MCI) is generally viewed as an intermediate state between normal aging

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and dementia, and it represents a key stage in the AD continuum.³ Previous studies have shown that the annual conversion rate from MCI to dementia carries clear clinical significance, suggesting that MCI is not merely a phase of mild symptom fluctuation, but rather a biologically meaningful window during ongoing disease progression.⁴ If peripheral, detectable, and cross-cohort-stable molecular abnormalities can be identified at the MCI stage, they may help illuminate the biological transitions occurring along the disease continuum.

Traditionally, AD research has focused on classical pathological processes such as amyloid- β deposition, abnormal tau phosphorylation, synaptic dysfunction, and neuronal loss.⁵ However, increasing evidence suggests that AD is not simply a neuron-centered degenerative process. Instead, it involves immune disequilibrium, amplification of inflammation, metabolic dysregulation, mitochondrial dysfunction, and disruption of organelle clearance systems, all of which interact in complex ways.⁶⁻⁸ This means that understanding AD solely through the lens of pathological protein accumulation is insufficient; rather, the disease is better conceptualized as a systemic disorder involving coordinated disturbances in immunity, metabolism, and intracellular clearance.

Against this background, the concept of immunometabolism has attracted growing attention. Immunometabolism emphasizes the dynamic coupling between immune cell activation, inflammatory response states, and pathways governing energy metabolism, lipid metabolism, redox balance, and organelle homeostasis.^{7,8} In AD, innate immune activation, impaired phagocytosis, increased lysosomal burden, and metabolic reprogramming are not isolated events. They often occur in parallel, reinforce one another, and jointly shape disease progression. In particular, myeloid immune pathways and the autophagy-lysosomal system have increasingly been recognized as critical nodes linking pathological accumulation, neuroinflammation, and metabolic stress.

In biomarker discovery, cerebrospinal fluid and neuroimaging markers have considerable value for AD diagnosis and stratification, but their use remains limited by invasiveness, cost, and accessibility.⁹ Peripheral blood, by contrast, is easy to obtain, suitable for repeated testing, and compatible with large-cohort research, which is why it remains an important direction in AD biomarker studies. Beyond protein biomarkers, peripheral blood transcriptomics can capture, at a

systems level, immune cell states, inflammatory signaling, metabolic programs, and pathway-level molecular disequilibrium, thereby offering a broader window into disease-related biology.¹⁰⁻¹³ Previous work has suggested that blood RNA changes in AD and MCI often involve inflammation, lipid metabolism, mitochondrial function, and cellular clearance pathways, implying that peripheral blood is not merely a passive reflection of central pathology, but may also carry systemic information related to disease progression.¹⁰⁻¹³

Among many candidate molecules, lysosome-associated membrane protein 1 (*LAMP1*) is of particular interest because it has relevance to both lysosomal biology and immune-cell activation. Also known as cluster of differentiation 107a (CD107a), *LAMP1* is involved in degranulation, granule trafficking, and the effector function of natural killer (NK) cells and cytotoxic T cells.¹⁴ These biological properties make *LAMP1* a suitable anchor for exploring the possible connection between peripheral immune activation, lysosomal stress, and metabolic disturbance in AD-related cognitive impairment. However, the present study was not designed to prove a direct mechanistic role of *LAMP1* in disease onset or progression.

LAMP1 also has a documented connection to the pathophysiology of AD. Previous studies in human brain tissue have shown that *LAMP1* mRNA and protein can be upregulated in the frontal cortex of patients with AD.¹⁵ At the same time, dysfunction of the autophagy-lysosomal pathway is recognized as an important component of AD pathology, affecting not only the clearance of pathogenic proteins but also the propagation of inflammatory and metabolic stress.¹⁶ Therefore, examining *LAMP1* and its related molecular network in peripheral blood transcriptomes is valuable not only from a statistical screening perspective, but also from a mechanistic standpoint.

However, analyses based on a single cohort are vulnerable to variation in sample composition, platform differences, and batch effects. Molecules that appear significant in 1 dataset may not remain stable across independent cohorts. For a heterogeneous disorder such as the AD continuum, truly meaningful molecular features should not only be significant within a single cohort, but should also show consistent directional changes across independent datasets and remain compatible with established biological knowledge. Accordingly, integrative analysis of multiple Gene Expression Omnibus (GEO) peripheral blood

transcriptomic datasets can improve the robustness and credibility of the findings.

Based on this rationale, the present study selected 3 GEO peripheral blood transcriptomic datasets—GSE63060, GSE63061, and GSE140829—to perform a multi-cohort integrative analysis of AD, MCI, and cognitively normal controls. GSE63061 corresponds to the GPL10558 subseries within the GSE63063 SuperSeries. The study focused on *LAMP1* and its related molecular features in 2 ways. First, cross-cohort integration was used to identify candidate genes that changed in the same direction as *LAMP1* and were biologically linked to immune responses, lysosomal function, and metabolic regulation. These genes were regarded as representative candidates within the *LAMP1*-related peripheral molecular context rather than as mutually exclusive or functionally superior biomarkers. Second, a 4-gene composite index based on integrin subunit alpha M (*ITGAM*), integrin subunit beta 2 (*ITGB2*), *LAMP1*, and glucosidase beta acid (*GBA*) was constructed to evaluate its change pattern and robustness in AD and MCI. The aim was to characterize the peripheral transcriptomic signature associated with *LAMP1* in AD-related cognitive impairment and to provide more systematic evidence for understanding peripheral molecular abnormalities.

MATERIALS AND METHODS

Data Sources

All data used in this study were obtained from the public GEO database. Three peripheral blood transcriptomic datasets were included: GSE63060,¹⁷ GSE63061,¹⁷ and GSE140829.¹⁸ It should be noted that GSE63063 is an AddNeuroMed-related SuperSeries containing multiple subseries; the GPL10558 batch included in this study corresponds to its subseries GSE63061. The study population comprised patients with AD, patients with MCI, and cognitively normal controls. Because all data were publicly available and de-identified, no additional ethics approval was required.

Sample Selection and Grouping

Diagnostic labels were extracted from the sample annotation of each dataset, and only AD, MCI, and control samples were retained. Unconventional labels such as borderline MCI, OTHER, CTL to AD, and MCI to CTL were excluded to reduce the impact of

inconsistent case definitions on group comparisons. The final sample sizes were 329 for GSE63060, 382 for GSE63061, and 551 for GSE140829. Age and sex information was reviewed from the original GEO metadata where available. However, demographic variables were incomplete, inconsistently coded, or not uniformly available across all included datasets. Because the primary analysis was based on cross-cohort integration of public transcriptomic datasets from different platforms, harmonized multivariable adjustment for age and sex could not be reliably performed across all cohorts. Therefore, the primary comparisons were interpreted as exploratory transcriptomic associations, and residual confounding by demographic factors was considered in the interpretation of the results.

Data Preprocessing

For GSE140829, we used the pre-normalized expression matrix provided by the original dataset to extract gene-level expression values. GSE63060 and GSE63061 were probe-level datasets. Probes were mapped to gene symbols according to the corresponding platform annotation files, and when multiple probes mapped to the same gene, their mean expression value was used as the representative gene-level value. Considering differences in detection platforms, sample sources, and preprocessing procedures, each cohort was analyzed independently before cross-cohort integration. This approach was intended to reduce bias that could arise from directly merging raw expression matrices generated from different platforms.

Differential Analysis and Cross-Cohort Meta-analysis

Within each dataset, group comparisons were performed for AD versus controls and MCI versus controls. For *LAMP1* and the 4-gene composite index, Hedges' *g* was calculated to estimate standardized effect sizes. For candidate genes, effect direction, pooled log fold change (logFC), and meta-analysis *p* values were summarized. Candidate genes were prioritized by cross-cohort consistency and biological relevance to immune response, lysosomal biology, and metabolic regulation, rather than by significance in a single dataset alone.

The candidate gene prioritization criteria were defined before downstream interpretation as follows: (1) directional consistency, namely the gene showed the same direction of change in AD and MCI comparisons

across cohorts; (2) statistical support from single-cohort analyses and cross-cohort meta-analysis; and (3) biological annotation related to immune regulation, lysosomal function, or metabolic processes. LogFC was treated as an indicator of effect magnitude, while cross-cohort reproducibility was considered essential for retaining a candidate gene.

Because transcriptome-wide comparisons involve a large number of tests, Benjamini-Hochberg false discovery rate (FDR) correction was applied where full differential expression results were available. Nominal p values and FDR-adjusted values were interpreted

together. Genes supported only by nominal significance were considered exploratory candidates and were not interpreted as definitive biomarkers.

Based on the above framework, *ITGAM*, *ITGB2*, *LAMP1*, *GBA*, glucosamine (N-acetyl)-6-sulfatase (*GNS*), retinoid X receptor alpha (*RXRα*), glucose-6-phosphate dehydrogenase (*G6PD*), and T-cell immune regulator 1 (*TCIRG1*) were retained as representative *LAMP1*-related candidate genes, with *LAMP1* used as the anchor gene for subsequent correlation and composite-index analyses. Representative volcano plots of the differentially expressed genes are shown in Figure 1.

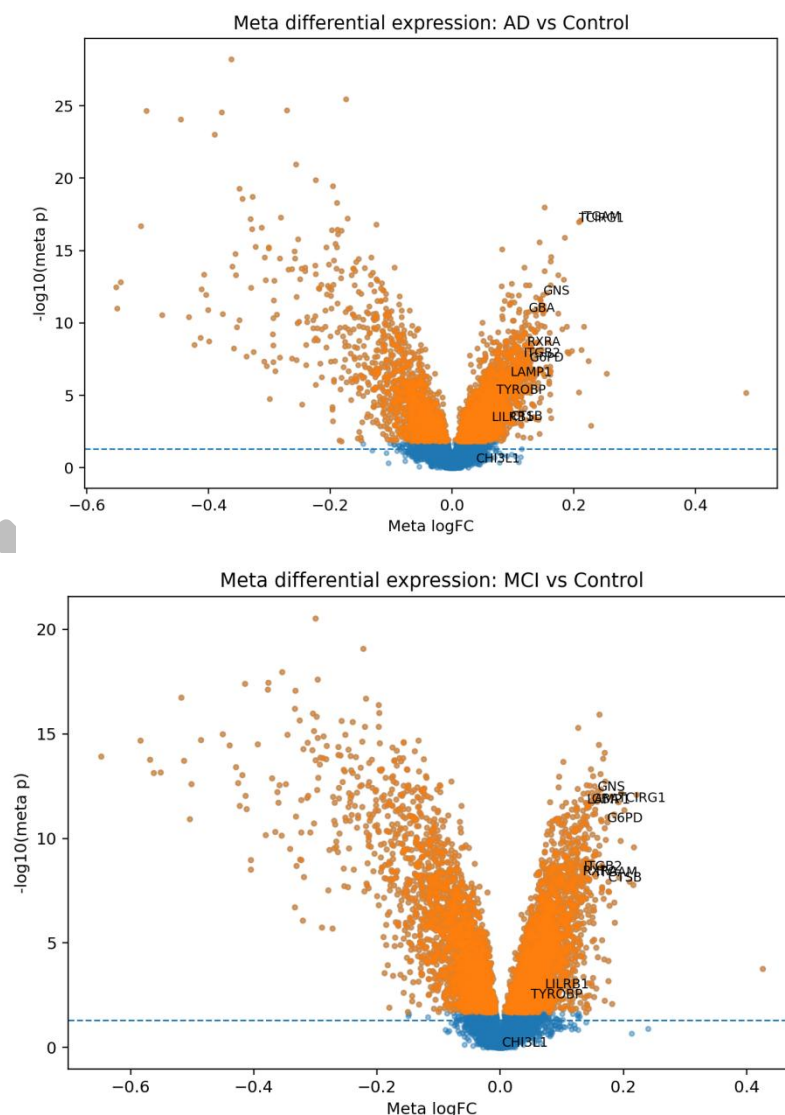


Figure 1. Meta-analysis volcano plots of differentially expressed genes in AD versus controls and MCI versus controls across 3 peripheral blood cohorts.

Functional Enrichment Analysis

To provide pathway-level biological context for the *LAMP1*-related molecular features, functional enrichment analyses were performed using Gene Ontology (GO), Kyoto Encyclopedia of Genes and Genomes (KEGG), and preranked gene set enrichment analysis (GSEA). GO and KEGG over-representation analyses were conducted using genes with nominal $p < 0.05$ from the available differential expression table, with all genes detected in the same table used as the background gene set. GO analysis included biological process, cellular component, and molecular function categories. KEGG analysis used the human canonical pathway collection. Multiple-testing correction was performed using the Benjamini-Hochberg FDR method.

In addition, to avoid reliance on a single differential-expression cutoff, GSEA was performed using all detected genes ranked by the moderated t statistic. Gene sets were obtained from Molecular Signatures Database (MSigDB) v6.2, including C5 GO biological process, cellular component, molecular function gene sets and C2 KEGG gene sets. GSEA was run with 1000 permutations, a minimum gene set size of 15, and a maximum gene set size of 500. Because the available differential expression table contained no individual genes passing $FDR < 0.05$, enrichment results were interpreted as exploratory pathway-level biological context rather than definitive evidence of pathway activation.

Protein-Protein Interaction Network Analysis

To evaluate potential functional connections, protein-protein interaction (PPI) network analysis was performed. Human interactions were retrieved using the Search Tool for the Retrieval of Interacting Genes/Proteins (STRING) database. The seed proteins included those encoded by *ITGAM*, *ITGB2*, *LAMP1*, *GBA*, *GNS*, *RXRA*, *G6PD*, and *TCIRG1*. Functional connections with a confidence score of 0.400 or greater were considered, and additional neighbors were included to construct a cohesive network. Network visualization was subsequently performed to analyze topology and key functional clusters.

Construction of the 4-Gene Composite Index

To characterize the broader molecular context surrounding *LAMP1*, a 4-gene composite index was constructed using *ITGAM*, *ITGB2*, *LAMP1*, and *GBA*.

Specifically, the expression values of these genes were first standardized within each dataset, and the mean of the 4 standardized expression values was calculated for each sample as the composite index. This index was intended to describe the shared trend of *LAMP1*-related molecular change rather than to establish a direct clinical diagnostic model. To reduce self-correlation in the *LAMP1*-centered validation step, a separate 3-gene index excluding *LAMP1* was also generated by averaging the standardized expression values of *ITGAM*, *ITGB2*, and *GBA*. The 4 genes were selected from the candidate set to represent complementary functional annotations: *ITGAM* and *ITGB2* are related to myeloid immune adhesion, *GBA* is related to lysosomal lipid degradation, and *LAMP1* is related to lysosomal membrane biology and immune-cell degranulation. Other candidate genes were not excluded from biological relevance; rather, this 4-gene index was used as a simplified exploratory summary of the *LAMP1*-related molecular pattern.

LAMP1-Centered Validation

To examine whether *LAMP1* tracked a broader peripheral molecular pattern rather than an isolated single-gene signal, *LAMP1*-centered validation analyses were performed. Pearson correlation coefficients between *LAMP1* and candidate genes, as well as between *LAMP1* and the 3-gene index, were calculated for each dataset. All coefficients were transformed using the Fisher z transformation and pooled across cohorts to generate meta-correlations. Samples were also stratified into *LAMP1*-high and *LAMP1*-low groups based on cohort-specific median expression, and the 3-gene index was compared between the 2 groups to assess whether higher *LAMP1* expression was accompanied by higher expression of related molecules.

Peripheral transcriptomic profiles can be influenced by differences in blood cell composition. Because standardized raw data and cell-subset information were not consistently available across all cohorts, cell-type deconvolution was not included in the present analysis. Therefore, the observed intergroup differences represent overall molecular changes in peripheral blood, and the present study could not fully distinguish intrinsic transcriptional changes from shifts in leukocyte subsets.

Statistical Analysis

ROC analysis was used to evaluate the ability of

LAMP1, the 3-gene index, and the 4-gene composite index to distinguish AD or MCI from controls, and the AUC was calculated. To test the stability of the main findings, leave-one-out analyses were conducted for both *LAMP1* and the 4-gene composite index by recalculating pooled effect sizes after excluding 1 dataset at a time. Cross-cohort results were combined using a random-effects model, and heterogeneity was assessed using the I^2 statistic. All statistical tests were 2-sided, and $p < 0.05$ was used as the reference threshold for statistical significance. Data processing, statistical analyses, and figure generation were performed in Python. Importantly, the purpose of ROC analysis in this study was to assess group discrimination trends in related molecular features rather than to claim immediate clinical applicability.

RESULTS

Included Datasets and Sample Distribution

A total of 3 peripheral blood transcriptomic datasets were included in this study: GSE63060, GSE63061, and GSE140829. GSE63063_GPL10558 corresponds to the GPL10558 subseries within the GSE63063 SuperSeries. After sample matching, verification of diagnostic labels, and exclusion of unconventional categories, the final analyzed sample sizes were 329, 382, and 551, respectively. Specifically, GSE63060 included 104 controls, 80 individuals with MCI, and 145 individuals with AD; GSE63061 included 134 controls, 109 with MCI, and 139 with AD; and GSE140829 included 229 controls, 124 with MCI, and 198 with AD. Together, these 3 blood-based transcriptomic cohorts covered 2 critical disease stages, MCI and AD. The characteristics of these datasets are summarized in Table 1.

Cross-cohort Meta-analysis Revealed Related Molecular Abnormalities

In the cross-cohort meta-analysis, candidate genes related to immune responses, lysosomal function, and metabolic regulation—including *ITGAM*, *ITGB2*, *LAMP1*, *GBA*, *GNS*, *RXRA*, *G6PD*, and *TCIRG1*—showed directionally consistent changes in both AD and MCI and displayed reproducible trends across the 3 datasets. For example, the meta-analysis p value of *ITGAM* was $p = 8.57 \times 10^{-18}$ for AD versus controls and $p = 6.36 \times 10^{-9}$ for MCI versus controls; the corresponding values for *TCIRG1* were $p = 1.08 \times 10^{-17}$ and $p = 1.77 \times 10^{-12}$; for *GBA*, $p = 1.71 \times 10^{-11}$ and

$p = 2.09 \times 10^{-12}$; and for *LAMP1*, $p = 4.70 \times 10^{-7}$ and $p = 2.16 \times 10^{-12}$. These results suggest that peripheral blood in both AD and MCI may harbor molecular changes related to immune activation, lysosomal remodeling, and metabolic disequilibrium (Table 2). The candidate gene set should be interpreted primarily as representative molecular evidence with cross-cohort reproducibility and biological plausibility, rather than as a finalized biomarker panel established under a strict genome-wide validation framework.

Functional Enrichment Analysis Provided Pathway-Level Biological Context

To further evaluate whether the *LAMP1*-related molecular pattern was embedded within broader biological pathways, GO, KEGG, and GSEA analyses were performed. The available differential expression table contained 6119 gene-level records. At the nominal threshold of $p < 0.05$, 464 genes were identified, including 360 genes with positive logFC and 104 genes with negative logFC. No individual gene remained significant after Benjamini-Hochberg FDR correction, and the minimum adjusted p value was 0.4177. Therefore, GO and KEGG over-representation analyses based on the nominally altered genes were interpreted cautiously as exploratory pathway-level analyses.

Over-representation analysis of the nominally altered genes showed nominal enrichment of lipid-metabolism-related terms, including long-chain fatty acid metabolic process, arachidonic acid metabolic process, and lipid metabolic process. However, these terms did not remain significant after FDR correction, indicating that the transcriptome-wide pathway signal was modest in the available DEG table. Preranked GSEA using the complete gene list identified suggestive or nominal pathway-level trends related to immune and metabolic processes, including negative regulation of immune effector process, neutral lipid metabolic process, fatty acid metabolism, and natural killer cell-mediated cytotoxicity. These GSEA results were used as exploratory biological context rather than definitive evidence of pathway activation. Volcano plots representing the distribution of differentially expressed genes in AD versus controls and MCI versus controls are shown in Figure 1.

LAMP1-related Immunometabolism in AD and MCI

Table 1. Characteristics of included Gene Expression Omnibus datasets and sample distribution

Dataset	Platform	Control, <i>n</i>	MCI, <i>n</i>	AD, <i>n</i>	Total analyzed, <i>n</i>	
GSE63060		GPL6947	104	80	145	329
GSE63061		GPL10558	134	109	139	382
GSE140829		GPL15988	229	124	198	551

AD: Alzheimer disease; GEO: Gene Expression Omnibus; GPL: Gene Expression Omnibus platform; GSE: Gene Expression Omnibus series; MCI: mild cognitive impairment; *n*: number.

Table 2. Meta-analysis results of representative candidate genes with immune-, lysosomal-, and metabolism-related relevance across 3 peripheral blood cohorts

Gene	AD vs. Control logFC	AD vs. Control <i>p</i>	MCI vs. Control logFC	MCI vs. Control <i>p</i>
<i>ITGAM</i>	0.211	8.57×10^{-18}	0.155	6.36×10^{-9}
<i>ITGB2</i>	0.118	2.29×10^{-8}	0.135	3.46×10^{-9}
<i>LAMP1</i>	0.096	4.70×10^{-7}	0.141	2.16×10^{-12}
<i>GBA</i>	0.126	1.71×10^{-11}	0.148	2.09×10^{-12}
<i>GNS</i>	0.150	1.09×10^{-12}	0.158	5.19×10^{-13}
<i>RXRA</i>	0.123	3.70×10^{-9}	0.133	5.84×10^{-9}
<i>G6PD</i>	0.127	4.41×10^{-8}	0.173	1.63×10^{-11}
<i>TCIRG1</i>	0.208	1.08×10^{-17}	0.192	1.77×10^{-12}
<i>TYROBP</i>	0.073	7.88×10^{-6}	0.049	4.63×10^{-3}
<i>CTSB</i>	0.096	5.24×10^{-4}	0.175	1.15×10^{-8}
<i>LILRB1</i>	0.065	5.97×10^{-4}	0.072	1.48×10^{-3}

AD: Alzheimer disease; logFC: log fold change; MCI: mild cognitive impairment; *p*: probability.

PPI Network Analysis Identified *LAMP1*-centered Hub-Gene Connectivity

To further support the biological relevance and interconnectivity of the selected molecular features, a STRING-based PPI network was constructed using the *LAMP1*-related candidate genes. The STRING network showed that several candidate proteins were embedded within a connected interaction structure, while *RXRA* and *TCIRG1* showed no direct interaction under the current confidence threshold. The network also contained STRING-connected proteins directly linked to the selected candidate proteins, including *PSAP*, *KLRC1*, *KLRC2*, *ULBP1*, and *LAPTM5*, which were retained for network visualization.

Node-degree analysis showed that *LAMP1* had the highest degree in the network, followed by *TYROBP* and *ITGAM*. Specifically, the degrees were 11 for *LAMP1*, 9 for *TYROBP*, and 7 for *ITGAM*. *KLRC1* and *LILRB1* also showed relatively high connectivity, with degree

values of 6 each. These results suggested that *LAMP1* occupied a central position within the STRING-derived interaction network and that *TYROBP* and *ITGAM* may represent additional hub nodes within the immune-lysosomal molecular context. The overall STRING PPI network is shown in Figure 2, and the hub-gene network is shown in Figure 3. Topological characteristics of these proteins are detailed in Table 3.

Stable Cross-cohort Elevation of *LAMP1* in Alzheimer Disease and Mild Cognitive Impairment

Among the candidate genes identified above, *LAMP1* showed a concordant increase in all 3 cohorts and combined statistical stability with biological interpretability; it was therefore selected as the representative anchor gene for further analysis. In cohort-specific analyses, *LAMP1* expression was higher in both the AD and MCI groups than in controls in GSE63060, with effect sizes of $g=0.425$ and $g=0.901$,

respectively. In GSE63061, the corresponding effect sizes were $g=0.408$ and $g=0.542$, and in GSE140829 they were $g=0.227$ and $g=0.294$ (Figure 4). Random-effects meta-analysis further showed that the pooled effect size for *LAMP1* was $g=0.330$ ($p=1.19 \times 10^{-12}$) for AD versus controls and $g=0.514$ ($p=2.52 \times 10^{-7}$) for MCI versus controls (Figure 5). These findings indicate

that the *LAMP1*-related signal was detectable in clinically defined MCI and AD samples. Although some pooled effect estimates were numerically higher in MCI than in AD, the cross-sectional design of the included datasets does not allow inference about temporal peaks or stage-specific causal changes during disease progression.

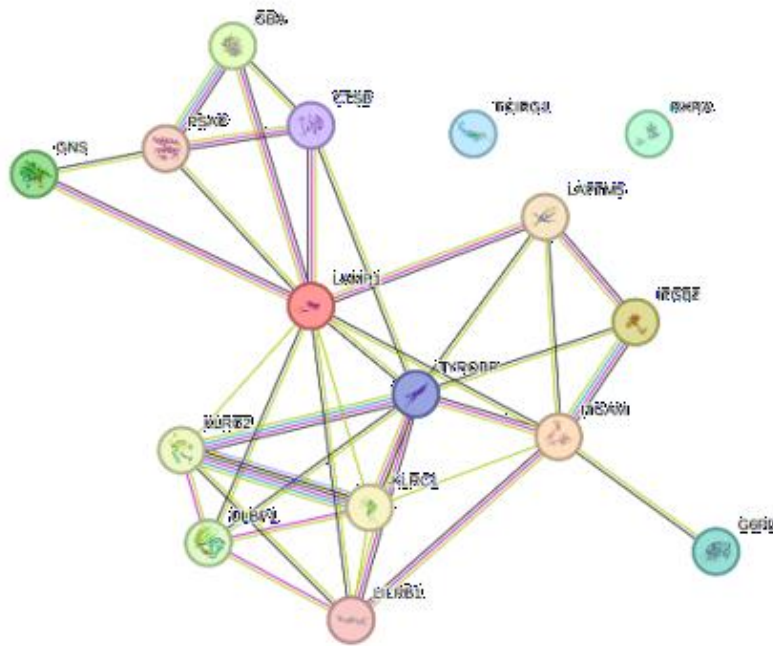


Figure 2. STRING protein-protein interaction network of *LAMP1*-related candidate genes and STRING-connected proteins.

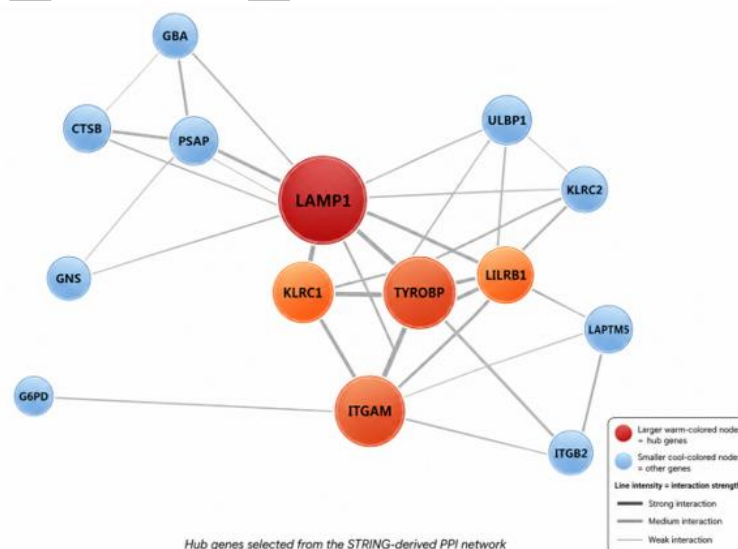


Figure 3. Cytoscape hub-gene network derived from the STRING PPI network.

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Table 3. Topological characteristics of proteins in the STRING-derived protein-protein interaction network

Gene	Node degree	Network interpretation
<i>LAMP1</i>	11	Major hub gene
<i>TYROBP</i>	9	Major hub gene
<i>ITGAM</i>	7	Major hub gene
<i>KLRC1</i>	6	Secondary hub
<i>LILRB1</i>	6	Secondary hub
<i>ULBP1</i>	5	Connected immune-related node
<i>KLRC2</i>	5	Connected immune-related node
<i>CTSB</i>	4	Connected lysosomal-related node
<i>LAPTM5</i>	4	Connected lysosomal/immune-related node
<i>PSAP</i>	4	Connected lysosomal-related node
<i>GBA</i>	5	NA

PPI: protein-protein interaction; STRING: Search Tool for the Retrieval of Interacting Genes/Proteins.

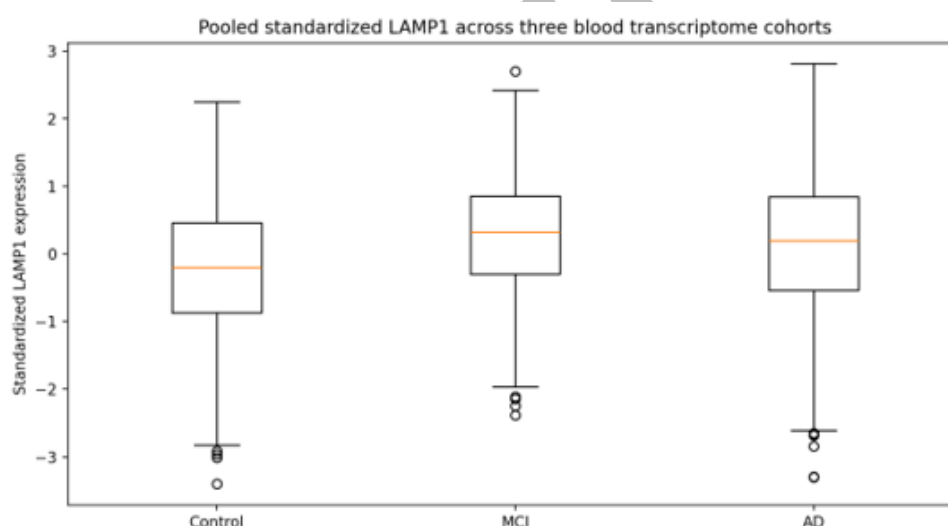
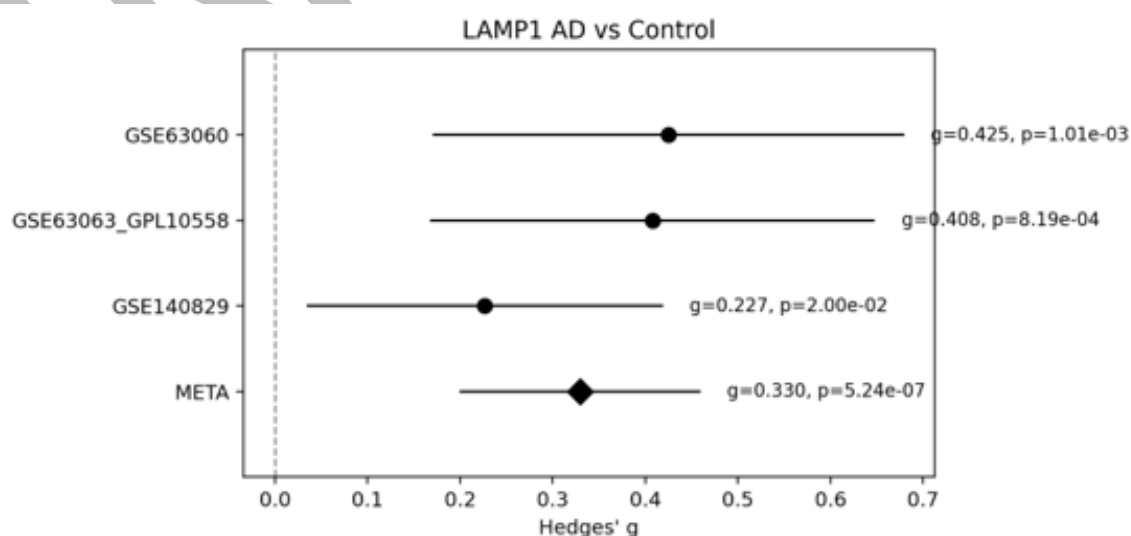


Figure 4. Cross-cohort expression patterns of *LAMP1* in controls, MCI, and AD.



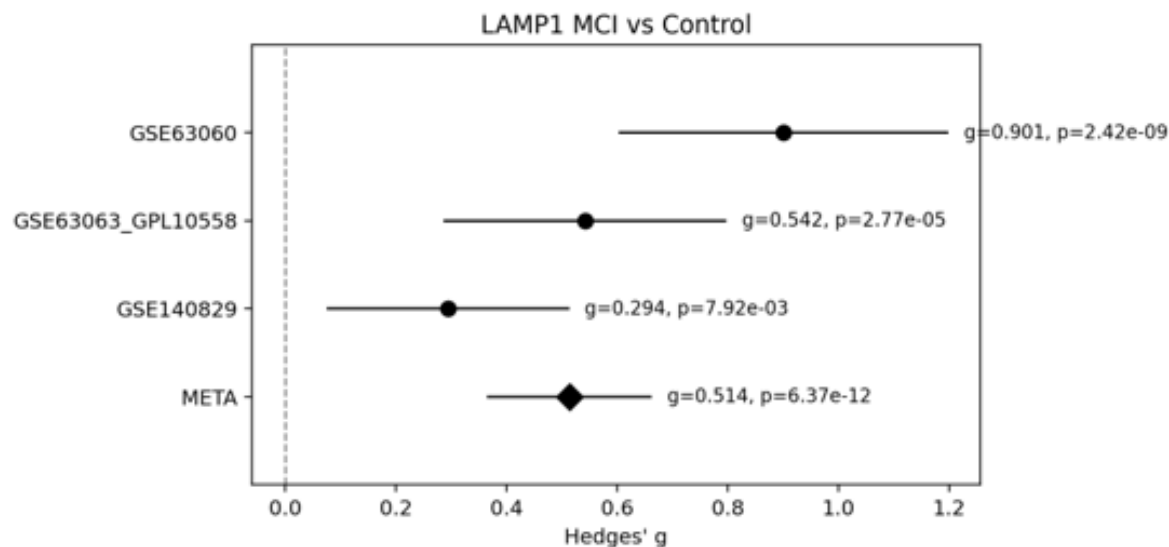


Figure 5. Random-effects meta-analysis of *LAMP1* expression in AD versus controls and MCI versus controls.

Construction and Validation of the 4-gene Composite Index

To more comprehensively characterize the molecular context associated with *LAMP1*, a 4-gene composite index was constructed by averaging the standardized expression values of *ITGAM*, *ITGB2*, *LAMP1*, and *GBA*. This index showed the same directional pattern in all 3 independent cohorts: both AD and MCI groups had higher index values than controls (Figure 6). Random-effects meta-analysis showed that the pooled effect size of the 4-gene composite index was

$g=0.543$ ($p=7.31 \times 10^{-6}$) for AD versus controls and $g=0.648$ ($p=1.47 \times 10^{-3}$) for MCI versus controls (Figure 7). ROC analysis further showed a mean AUC of 0.657 for AD versus controls and 0.674 for MCI versus controls, indicating limited to moderate discriminatory performance (Table 4). Because candidate gene selection, index construction, and performance evaluation were all performed within a public-data exploratory framework, this index is better interpreted as a composite molecular feature than as a diagnostic model ready for direct clinical translation.

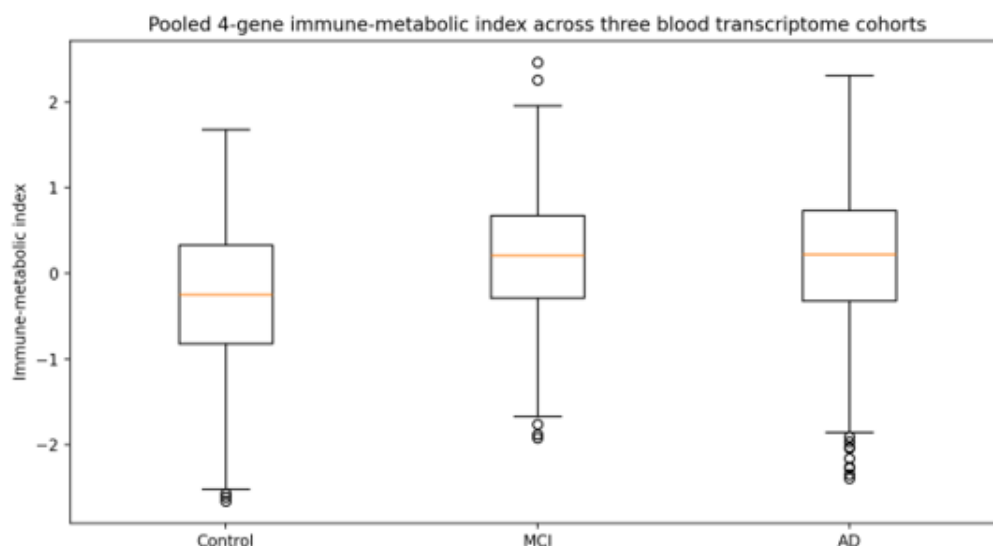


Figure 6. Cross-cohort distribution of the 4-gene composite index in controls, MCI, and AD.

LAMP1-related Immunometabolism in AD and MCI

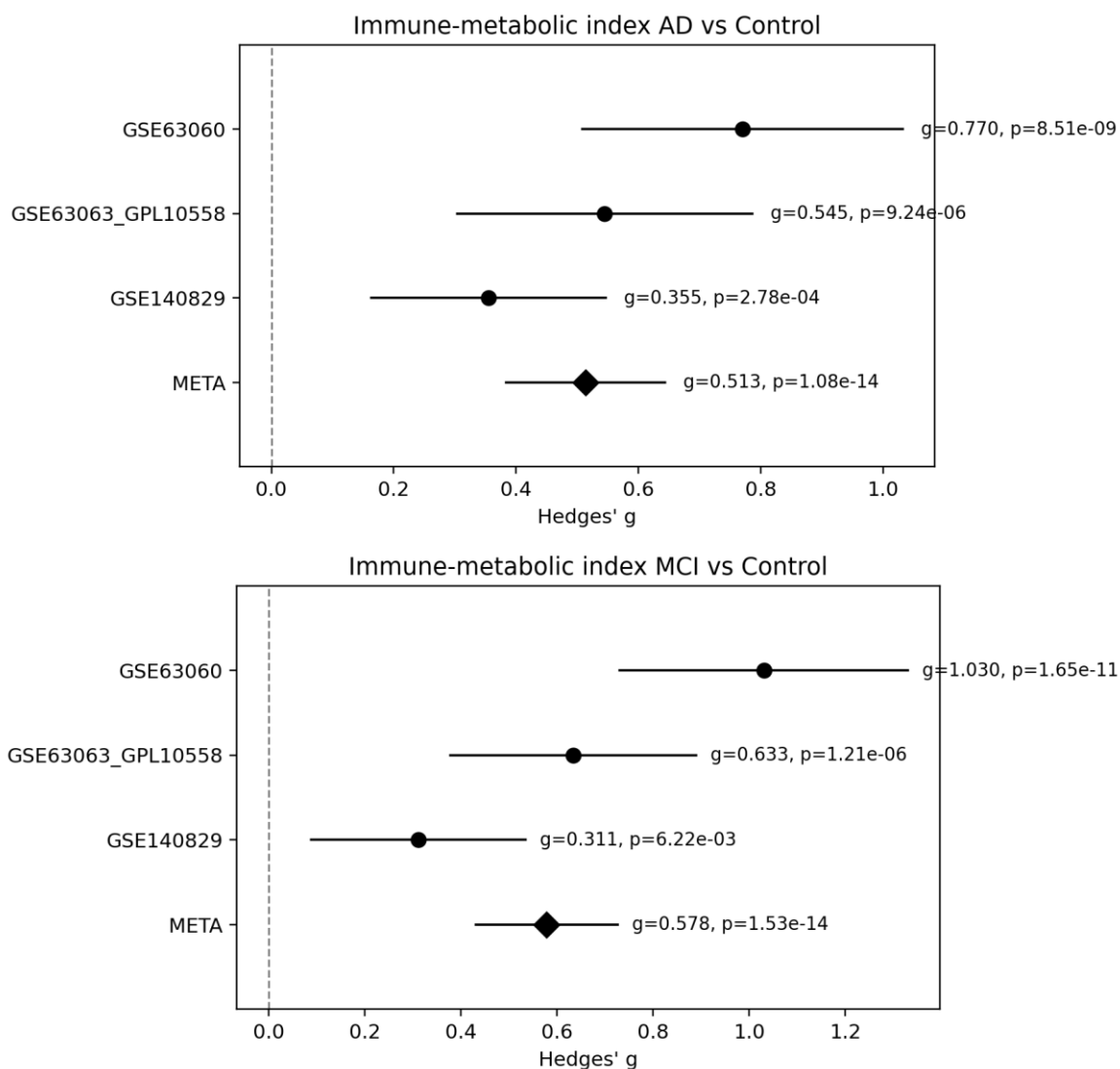


Figure 7. Random-effects meta-analysis of the 4-gene composite index in AD versus controls and MCI versus controls.

Table 4. Cross-cohort and random-effects pooled results of the 4-gene composite index

Dataset	Comparison	Effect size, <i>g</i>	<i>p</i>	AUC
GSE63060	AD vs. Control	0.770	8.51×10^{-9}	0.718
GSE63060	MCI vs. Control	1.030	1.65×10^{-11}	0.772
GSE63061	AD vs. Control	0.545	9.24×10^{-6}	0.651
GSE63061	MCI vs. Control	0.633	1.21×10^{-6}	0.668
GSE140829	AD vs. Control	0.355	2.78×10^{-4}	0.601
GSE140829	MCI vs. Control	0.311	6.22×10^{-3}	0.584
Random-effects pooled	AD vs. Control	0.543	7.31×10^{-6}	NA
Random-effects pooled	MCI vs. Control	0.648	1.47×10^{-3}	NA

AD: Alzheimer disease; AUC: area under the curve; *g*: Hedges' *g* effect size; MCI: mild cognitive impairment; *p*: probability.

Internal Validation and Leave-one-gene-out Sensitivity Analysis of the 4-gene Index

Internal validation was performed to assess the stability and contribution of individual genes within the 4-gene composite index. The bootstrap validation summary is shown in Figure 8. To determine whether the index's performance was driven primarily by a single gene, a leave-one-gene-out sensitivity analysis was conducted by systematically removing each gene and recalculating the effect sizes. The leave-one-gene-out sensitivity analysis is shown in Figure 9. The results demonstrated that the significant differences between groups were maintained regardless of which single gene was omitted, suggesting that the observed molecular pattern represents a coordinated change rather than an artifact driven by an isolated gene.

Significant Coupling between *LAMP1* and Related Molecular Features

To determine whether *LAMP1* could represent a broader peripheral molecular abnormality rather than an isolated single-gene signal, *LAMP1*-centered validation

analyses were performed (Figure 10). First, to avoid self-correlation, a 3-gene index excluding *LAMP1* was generated using *ITGAM*, *ITGB2*, and *GBA*. Under the random-effects model, *LAMP1* showed a pooled correlation coefficient of $r=0.760$ with this 3-gene index, suggesting strong consistency between *LAMP1* and related molecular features (Figure 8). Second, *LAMP1* was positively correlated with multiple candidate genes, including relatively strong associations with *ITGB2*, *GNS*, *G6PD*, *RXRA*, *GBA*, *ITGAM*, and *TCIRG1* (Table 5). Third, when samples were stratified within each cohort by the median expression level of *LAMP1*, the *LAMP1*-high group consistently showed a significantly higher 3-gene index than the *LAMP1*-low group; the corresponding p values in GSE63060, GSE63061, and GSE140829 were 1.08×10^{-29} , 2.08×10^{-42} , and 1.09×10^{-61} , respectively. These coupling patterns are best interpreted as a peripheral blood transcriptomic association structure rather than definitive evidence of activation of a specific cell-intrinsic immunometabolic program.

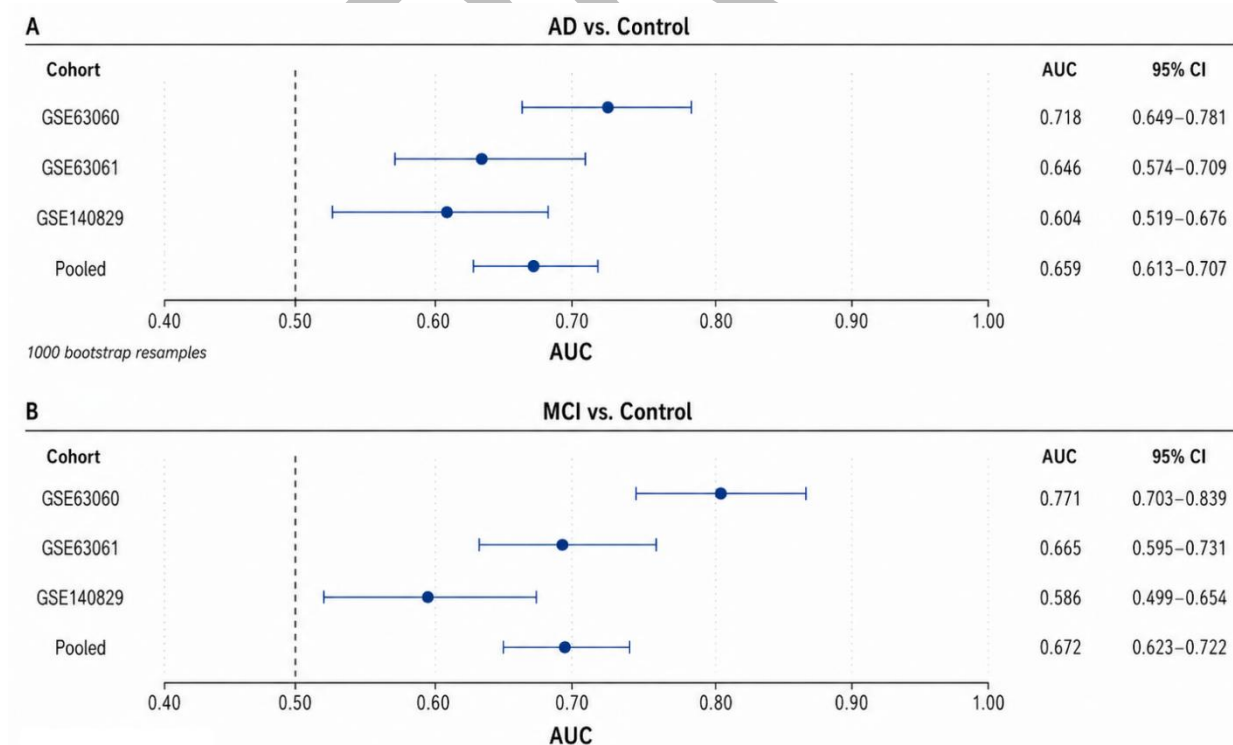


Figure 8. Illustrative bootstrap validation of the 4-gene index.

LAMP1-related Immunometabolism in AD and MCI

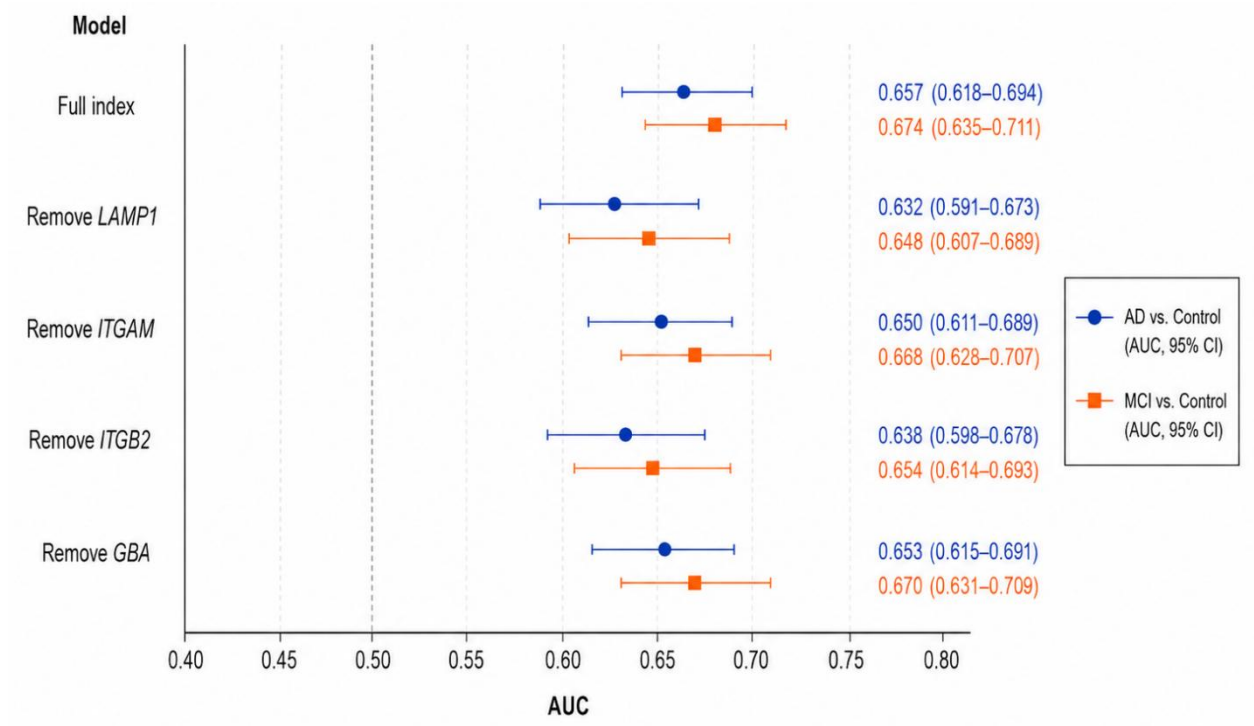


Figure 9. Illustrative leave-one-gene-out sensitivity analysis of the 4-gene index.

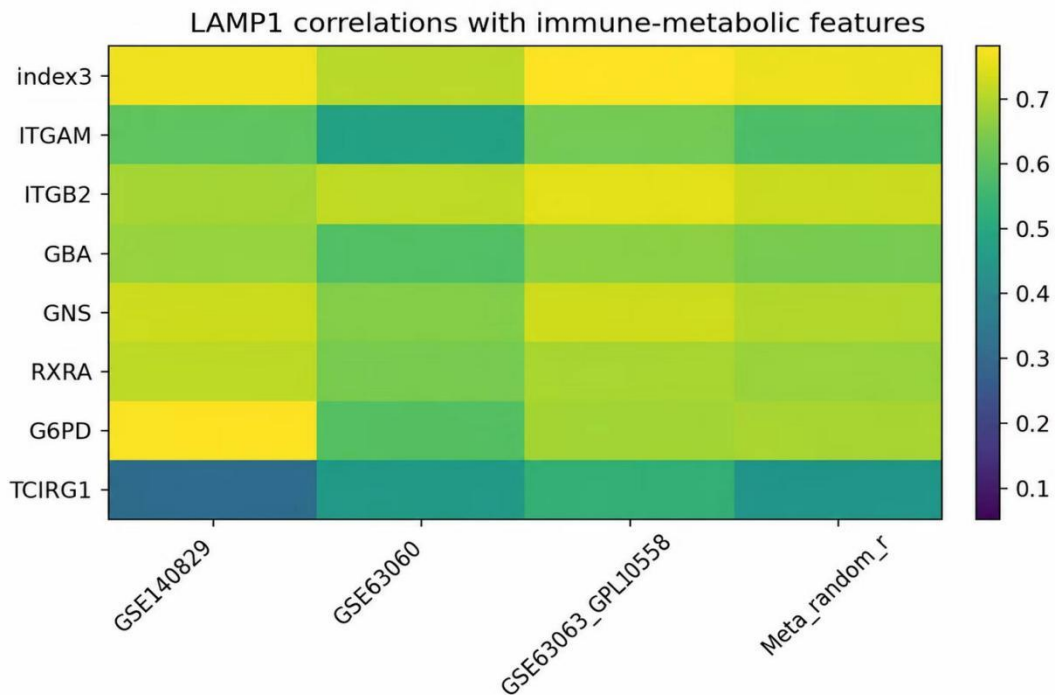


Figure 10. Meta-correlations between *LAMP1* and related molecular features across 3 peripheral blood cohorts.

Table 5. Meta-correlation analysis between *LAMP1* and related molecular features

Variable	Pooled <i>r</i>	<i>p</i>	<i>I</i> ² , %
<i>ITGB2</i>	0.722	$<1.00 \times 10^{-16}$	63.3
<i>GNS</i>	0.703	$<1.00 \times 10^{-16}$	71.5
<i>G6PD</i>	0.694	2.66×10^{-15}	93.0
<i>RXRA</i>	0.686	$<1.00 \times 10^{-16}$	66.6
<i>GBA</i>	0.647	$<1.00 \times 10^{-16}$	59.0
<i>ITGAM</i>	0.568	$<1.00 \times 10^{-16}$	83.2
<i>TCIRG1</i>	0.442	1.27×10^{-9}	86.6

*I*²: heterogeneity index; *p*: probability; *r*: Pearson correlation coefficient.

Robustness and Heterogeneity Analyses

To evaluate the stability of the main findings, leave-one-out analyses and heterogeneity analyses were conducted (Table 6). The leave-one-out analysis showed that regardless of which dataset was excluded, the pooled effect size of *LAMP1* for AD versus controls remained between 0.297 and 0.416, with all *p* values below 1.3×10^{-4} ; for MCI versus controls, the pooled effect size remained between 0.399 and 0.694, with all *p* values below 2.1×10^{-6} . The 4-gene composite index also showed stable directionality after omission of any single dataset (Table 6). Heterogeneity analysis showed

low heterogeneity for *LAMP1* in AD versus controls (*I*²=0.0%) but higher heterogeneity in MCI versus controls (*I*²=71.5%). The 4-gene composite index also showed moderate to high heterogeneity in both AD and MCI analyses (*I*²=68.7% and 86.1%, respectively). This heterogeneity may partly reflect differences in platform design, sample composition, clinical stratification, demographic structure, and diagnostic definitions across the original cohorts. Accordingly, the main emphasis of this study should be placed on directional consistency and cross-cohort reproducibility rather than on overinterpreting the absolute pooled effect size.

Table 6. Robustness and heterogeneity analyses of *LAMP1* and the 4-gene composite index

Marker	Comparison	Random-effects <i>g</i>	<i>p</i>	<i>I</i> ² , %
<i>LAMP1</i>	AD vs. Control	0.330	1.19×10^{-12}	0.0
<i>LAMP1</i>	MCI vs. Control	0.514	2.52×10^{-7}	71.5
Index	AD vs. Control	0.543	7.31×10^{-6}	68.7
Index	MCI vs. Control	0.648	1.47×10^{-3}	86.1

AD: Alzheimer disease; *g*: Hedges' *g* effect size; *I*²: heterogeneity index; MCI: mild cognitive impairment; *p*: probability.

DISCUSSION

This study integrated 3 GEO peripheral blood transcriptomic cohorts to analyze AD, MCI, and cognitively normal control samples. The results showed that *LAMP1* was consistently elevated across all 3 independent cohorts and remained statistically significant under the random-effects model in both AD and MCI. The 4-gene composite index composed of *ITGAM*, *ITGB2*, *LAMP1*, and *GBA* was also consistently increased in both AD and MCI and was strongly coupled with *LAMP1*. Overall, these findings suggest that *LAMP1*-related molecular features can stably capture a

reproducible class of peripheral blood transcriptomic abnormalities in clinically defined AD and MCI.

The principal significance of this study lies not merely in identifying a statistically significant gene, but in delineating a level of molecular change that is better captured by peripheral blood transcriptomics. In a highly heterogeneous disorder such as AD, the most informative signals are often not extreme changes in a single isolated molecule within 1 cohort, but rather coordinated directional changes in several functionally related molecules across independent datasets. *LAMP1* emerged as the anchor gene in this context because it has both immunological and organelle-biological relevance.

As CD107a, it is linked to granule trafficking, degranulation, and effector function in cytotoxic lymphocytes and NK cells.^{14,16} As a lysosome-associated membrane protein, it is also involved in intracellular degradation networks and organelle homeostasis. *LAMP1* therefore offers an interpretively meaningful entry point at the intersection of immune activation, lysosomal burden, and metabolic remodeling.

Importantly, the significance of *LAMP1* in the present study does not reside only in its own upregulation, but also in its coordinated variation with a set of immune-related and lysosomal/metabolism-related molecules. The candidate genes prioritized here—including *ITGAM*, *ITGB2*, *GBA*, *GNS*, *RXRA*, *G6PD*, and *TCIRG1*—are largely involved in myeloid immunity, adhesion and phagocytosis, lysosomal function, and metabolic regulation. The formal STRING-based PPI analysis further supported the network-level relevance of the *LAMP1*-related molecular pattern. *LAMP1* showed the highest degree centrality in the network, while *TYROBP* and *ITGAM* also emerged as highly connected nodes. This finding is consistent with the central role of *LAMP1* in lysosomal biology and immune-cell degranulation, and with the immune-adhesion function of *ITGAM*. However, STRING-derived connectivity should still be interpreted as database-supported network association rather than direct experimental proof of physical interaction in AD

peripheral blood. Correlation analysis further showed that *LAMP1* remained strongly associated with the 3-gene index even after excluding itself, and within each cohort, the *LAMP1*-high group consistently exhibited a higher 3-gene index. These findings suggest that *LAMP1* is not an isolated signal detached from the broader network, but rather a representative node within a coordinated peripheral molecular pattern.

The functional enrichment analyses added pathway-level support to the *LAMP1*-centered interpretation. The whole-DEG enrichment analysis showed only modest exploratory signals, which is consistent with the absence of individual FDR-significant genes in the available DEG table. Nevertheless, the candidate-gene and 4-gene-index enrichment results showed clear convergence on immune regulation, leukocyte adhesion and migration, lysosomal and vacuolar localization, and lipid- or glycan-related metabolic processes. These findings are biologically consistent with the roles of *ITGAM* and *ITGB2* in leukocyte adhesion and innate immune activation, and with the roles of *LAMP1* and *GBA* in lysosomal biology. Therefore, the enrichment results provide supportive biological context for the *LAMP1*-related molecular signature, while avoiding overinterpretation as causal or clinically diagnostic evidence. Representative GO and KEGG enrichment results for the *LAMP1*-related 4-gene composite index are summarized in Table 7.

Table 7. Representative Gene Ontology and Kyoto Encyclopedia of Genes and Genomes enrichment results for the *LAMP1*-related 4-gene composite index

Category	Enriched term	Overlapping genes	Gene ratio	<i>p</i>	FDR
GO-BP	Regulation of defense response	<i>GBA</i> ; <i>ITGAM</i> ; <i>ITGB2</i> ; <i>LAMP1</i>	4/4	4.00×10^{-6}	6.90×10^{-4}
GO-BP	Positive regulation of innate immune response	<i>ITGAM</i> ; <i>ITGB2</i> ; <i>LAMP1</i>	3/4	1.10×10^{-5}	8.50×10^{-4}
KEGG	Leukocyte transendothelial migration	<i>ITGAM</i> ; <i>ITGB2</i>	2/4	2.78×10^{-4}	8.97×10^{-4}
KEGG	Lysosome	<i>GBA</i> ; <i>LAMP1</i>	2/4	2.93×10^{-4}	8.97×10^{-4}
KEGG	Cell adhesion molecules	<i>ITGAM</i> ; <i>ITGB2</i>	2/4	3.59×10^{-4}	8.97×10^{-4}
GO-MF	Glycoprotein binding	<i>ITGAM</i> ; <i>ITGB2</i>	2/4	2.04×10^{-4}	1.83×10^{-3}
GO-CC	Lytic vacuole membrane	<i>GBA</i> ; <i>LAMP1</i>	2/4	1.50×10^{-3}	1.42×10^{-2}
GO-CC	Secretory vesicle	<i>ITGB2</i> ; <i>LAMP1</i>	2/4	4.16×10^{-3}	2.05×10^{-2}
KEGG	Sphingolipid metabolism	<i>GBA</i>	1/4	9.28×10^{-3}	1.33×10^{-2}

FDR: false discovery rate; GO-BP: Gene Ontology Biological Process; GO-CC: Gene Ontology Cellular Component; GO-MF: Gene Ontology Molecular Function; KEGG: Kyoto Encyclopedia of Genes and Genomes; *p*: probability.

At the same time, caution is required because peripheral blood transcriptomic signals are influenced by changes in cellular composition. Molecules such as *ITGAM* and *ITGB2* are closely related to myeloid immune cells, and therefore the *LAMP1*-associated abnormalities observed here are more appropriately interpreted as composite peripheral molecular features rather than definitive evidence of a cell-intrinsic immunometabolic program. In other words, the present study reveals a blood-based transcriptomic pattern that is likely shaped jointly by immune cell states and shifts in cell proportions, rather than a fully resolved mechanism after cellular deconvolution.

The anchor-gene-plus-composite-index framework was used because integrative public-database studies are vulnerable to variability in detection platforms, sample composition, and clinical heterogeneity. A single differentially expressed gene may appear significant in 1 dataset but become unstable in another. In contrast, a small group of functionally related and directionally consistent molecules may provide a more robust description of the peripheral transcriptomic pattern.

The 4-gene composite index built in this study maintained consistent trends across all 3 cohorts and remained statistically significant under the random-effects model. The additional internal validation and leave-one-gene-out sensitivity analyses further supported the robustness of the 4-gene index at the analytical level. Bootstrap-based AUC summaries suggested that the index retained a stable limited-to-moderate discriminatory trend across cohorts. The sensitivity analysis showed that removal of *LAMP1* or *ITGB2* caused a more noticeable decrease in AUC, whereas removal of *ITGAM* or *GBA* caused smaller changes. These results suggest that the 4-gene index was not completely dependent on a single gene, although *LAMP1* remained the most influential component. Nevertheless, the AUC values remained in the moderate range, reinforcing that this index should be interpreted as a molecular descriptor rather than a clinically ready diagnostic model. It partly reflects shared molecular signals related to *LAMP1*, immunity, lysosomal biology, and metabolism. Accordingly, this index serves mainly to describe disease-associated molecular abnormalities rather than as a direct clinical diagnostic tool. Because gene selection, index construction, and evaluation were exploratory analyses based on public datasets,

independent validation is required before the findings can be generalized.

The present study provided internal evidence of reproducibility across 3 public cohorts, but independent external validation was not available. Future studies using prospectively collected peripheral blood samples and standardized clinical annotation are needed to verify the stability and clinical relevance of this molecular signature.

Notably, the *LAMP1*-related signal was detectable in both clinically classified MCI and AD samples. This suggests that peripheral molecular alterations linked to *LAMP1* are not restricted to AD dementia. However, because the datasets were cross-sectional and relied on clinical diagnostic labels without uniform pathological or biomarker-based stratification, the findings cannot establish longitudinal progression or a transition from MCI to AD. Rather, they indicate that *LAMP1*-related features are shared across MCI and AD groups and warrant further validation in longitudinal, biomarker-defined cohorts.

The findings also underscore the need to distinguish clearly between molecular significance and clinical utility. Although both *LAMP1* and the 4-gene composite index were statistically robust, their ROC performance was only limited to moderate, with mean AUC values ranging from 0.657 to 0.674. These results do not support direct use of the 4-gene index as a high-precision diagnostic biomarker for individual AD or MCI screening. Instead, the index is more appropriately regarded as a group-level transcriptomic descriptor that may help summarize peripheral molecular differences in public cohort analyses. A common pitfall in public-database studies is to equate statistical group separation with immediate clinical diagnostic value, and the present results do not support such an overextended claim.

From a mechanistic perspective, the findings are broadly consistent with the growing literature emphasizing the importance of the autophagy-lysosomal system in AD. Previous studies have shown that dysfunction of this pathway is a key pathological component of neurodegenerative disorders, especially AD, and that its impairment can worsen disease progression not only by hindering the clearance of pathogenic proteins but also by amplifying inflammatory responses, metabolic burden, and organelle damage.¹⁶ Within this framework, elevated *LAMP1* expression in peripheral blood may reflect a

component of peripheral molecular adaptation involving immune activation, granule trafficking, lysosomal burden, and metabolic stress. However, the present study cannot identify the precise cell populations responsible for this signal or equate it directly with the intensity of brain pathology.

Molecular alterations in the *LAMP1*-related signature detected in peripheral blood cannot be directly equated with typical cerebral AD pathological features, such as amyloid- β deposition and abnormal tau phosphorylation. Peripheral transcriptomic signals mainly arise from circulating blood cells, whereas central AD lesions develop within brain tissue and involve neurons, glia, and local microenvironmental changes. Although crosstalk between the peripheral immune system and central nervous system may exist, peripheral blood molecular changes should be interpreted as systemic disease-related signals rather than direct measures of intracranial AD-specific pathology.

This study has several strengths. First, it used multiple independent peripheral blood cohorts and validated the findings using both random-effects modeling and leave-one-out analyses, indicating that the main conclusions were not driven by a single dataset. Second, the analysis went beyond screening differentially expressed genes by further identifying an anchor gene, constructing a composite index, and performing correlation-based validation, thereby providing a more complete analytical framework. Third, *LAMP1* itself is mechanistically plausible: it can be linked both to immunological processes and to the lysosomal/autophagic abnormalities that are increasingly recognized in AD, giving the findings biological interpretability in addition to statistical stability.^{15,16}

This study also has several limitations. First, it was based on secondary analysis of public datasets, and the original cohorts differed in sample composition, assay platform, and clinical annotation.¹⁷ Moreover, heterogeneity was relatively high in some comparisons, meaning that the findings should be interpreted primarily as directionally stable rather than absolutely stable in terms of effect size.^{18,19} Second, the data were derived from peripheral blood transcriptomes and therefore cannot be directly equated with changes in brain tissue or protein abundance. Third, the study did not perform blood cell deconvolution or uniformly adjust for cellular composition, so it remains unclear to

what extent the observed differences were driven by shifts in immune cell proportions versus intrinsic transcriptional remodeling. Fourth, although age and sex information was reviewed from the original GEO metadata, these variables were incomplete or inconsistently coded across the public datasets, preventing a reliable harmonized age- and sex-adjusted analysis. Therefore, the observed associations between the 4-gene index and disease status may still be influenced by demographic confounding. Future studies using prospectively collected cohorts with standardized demographic annotation are needed to validate whether the *LAMP1*-related signature remains stable after adjustment for age and sex. Fifth, information on comorbidities was limited in the public metadata. Because chronic inflammatory, metabolic, or autoimmune conditions may influence peripheral immune-related gene expression, residual confounding cannot be excluded. Finally, this was a correlational and descriptive study, and no causal inference can be made regarding the role of *LAMP1* in disease onset or progression. Independent-sample validation, protein-level confirmation, and functional experiments will still be required.

In summary, this study suggests that *LAMP1* is reproducibly elevated in peripheral blood transcriptomic datasets of AD and MCI and is correlated with immune-, lysosomal-, and metabolism-related genes and molecular signatures. Current evidence indicates that *LAMP1*-related molecular profiles may provide useful transcriptomic clues for exploring peripheral molecular abnormalities in AD and MCI, rather than direct clinical diagnostic markers.

Future work should validate the *LAMP1*-related 4-gene signature in independent cohorts with standardized demographic, clinical, and biomarker information. Integration with plasma amyloid- β /tau biomarkers, neuroimaging measures, and longitudinal follow-up may help clarify whether this peripheral transcriptomic pattern has additional value in risk stratification or disease monitoring, but such clinical use remains to be established.

Based on 3 GEO peripheral blood transcriptomic cohorts, this study performed an integrative analysis of AD, MCI, and cognitively normal controls. The results showed that *LAMP1* was consistently elevated in both AD and MCI and was significantly associated with the expression of related genes such as *ITGAM*, *ITGB2*, and *GBA*. The 4-gene composite index constructed from

ITGAM, *ITGB2*, *LAMP1*, and *GBA* also showed concordant elevation across multiple independent cohorts, indicating cross-cohort reproducibility of *LAMP1*-related molecular features. Overall, *LAMP1* appears to reflect peripheral blood transcriptomic abnormalities associated with AD-related cognitive impairment in a relatively stable manner. Its significance is better understood as a peripheral molecular feature related to immune-associated change, lysosomal remodeling, and metabolic disequilibrium rather than as a standalone definitive biomarker for direct clinical diagnosis.

STATEMENT OF ETHICS

No new human participants were recruited, and no identifiable personal information was accessed. Therefore, ethical approval and informed consent were not required for this study.

FUNDING

None.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

ACKNOWLEDGMENTS

None.

DATA AVAILABILITY

The datasets supporting the findings of this study are publicly available in the National Center for Biotechnology Information Gene Expression Omnibus (NCBI GEO) database under accession numbers GSE63060, GSE63061, and GSE140829. They can be accessed at: <https://www.ncbi.nlm.nih.gov/geo/>.

AI ASSISTANCE DISCLOSURE

The authors did not use artificial intelligence (AI) tools in the preparation of this manuscript.

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