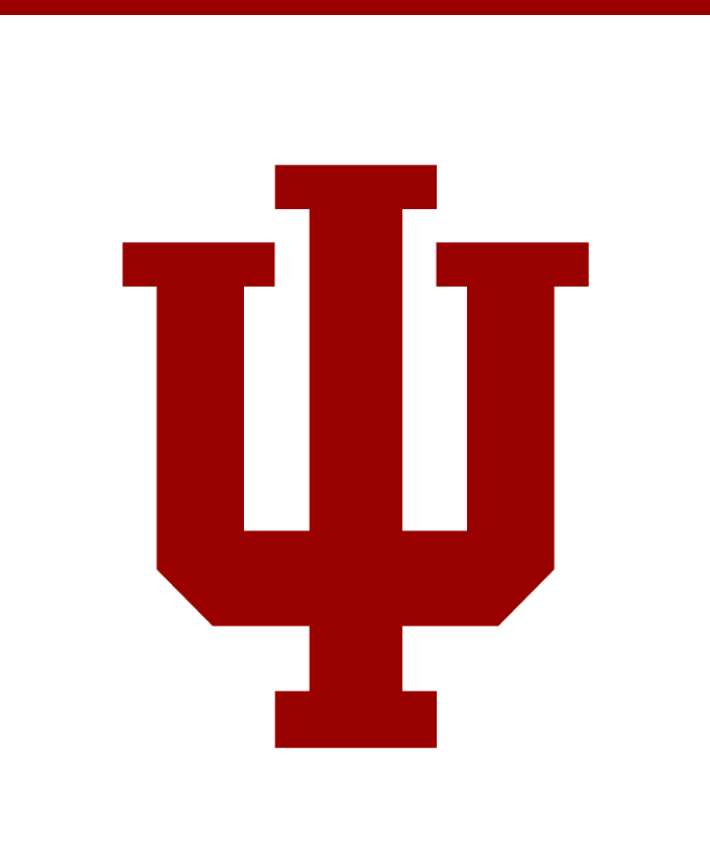




Association Between Lifetime Total Physical Activity, Blood Transcriptome, and Neurodegeneration

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INTRODUCTION

- Physical activity (PA) is known to lower the risk for Alzheimer's disease (AD).¹
- In patients with AD, PA slows cognitive decline and improves functional performance and independence.¹
- However, the molecular mediators underlying this association remain understudied using transcriptomics approaches.
- In this study, we aim to replicate the association between PA and AD biomarkers, identify gene expression signatures as associated with PA using transcriptomics data, and determine potential molecular mediators of the association between PA and AD biomarkers in a well-characterized Korean cohort, Korean Brain Aging Study for the Early Diagnosis and Prediction of Alzheimer's Disease (KBASE).

METHODS

Study Sample

Physical activity (PA), MRI scans, and blood transcriptomics data from the Korean Brain Aging Study for the Early Diagnosis and Prediction of Alzheimer's Disease (KBASE) cohort were used (Table 1).^{2,3}

Data Modalities Analyzed

- Physical activity:** Physical activity (PA) was assessed using the Lifetime Total Physical Activity Questionnaire (LTPAQ) across three domains, occupational, household, and leisure activities, and encompassing three parameters, activity frequency, duration, and intensity.
- High versus Low LTPAQ groups** were defined using the median LTPAQ score as threshold.
- Neuroimaging-based biomarker for AD:** Hippocampal volume and entorhinal cortical thickness (EntCtx_Thick; Neurodenegeneration biomarkers) were calculated from 3T MRI scans. Global cortical A β deposition and A β positivity (Amyloid biomarkers) were calculated from PIB PET scans.
- Blood transcriptome data:** RNA sequencing was performed on blood samples. The conditional quantile normalized (CQN) gene expression data was used to perform Weighted Gene Co-expression Network Analysis (WGCNA) to construct network-based co-expression modules, producing 18 network modules.

Statistical Analyses Performed

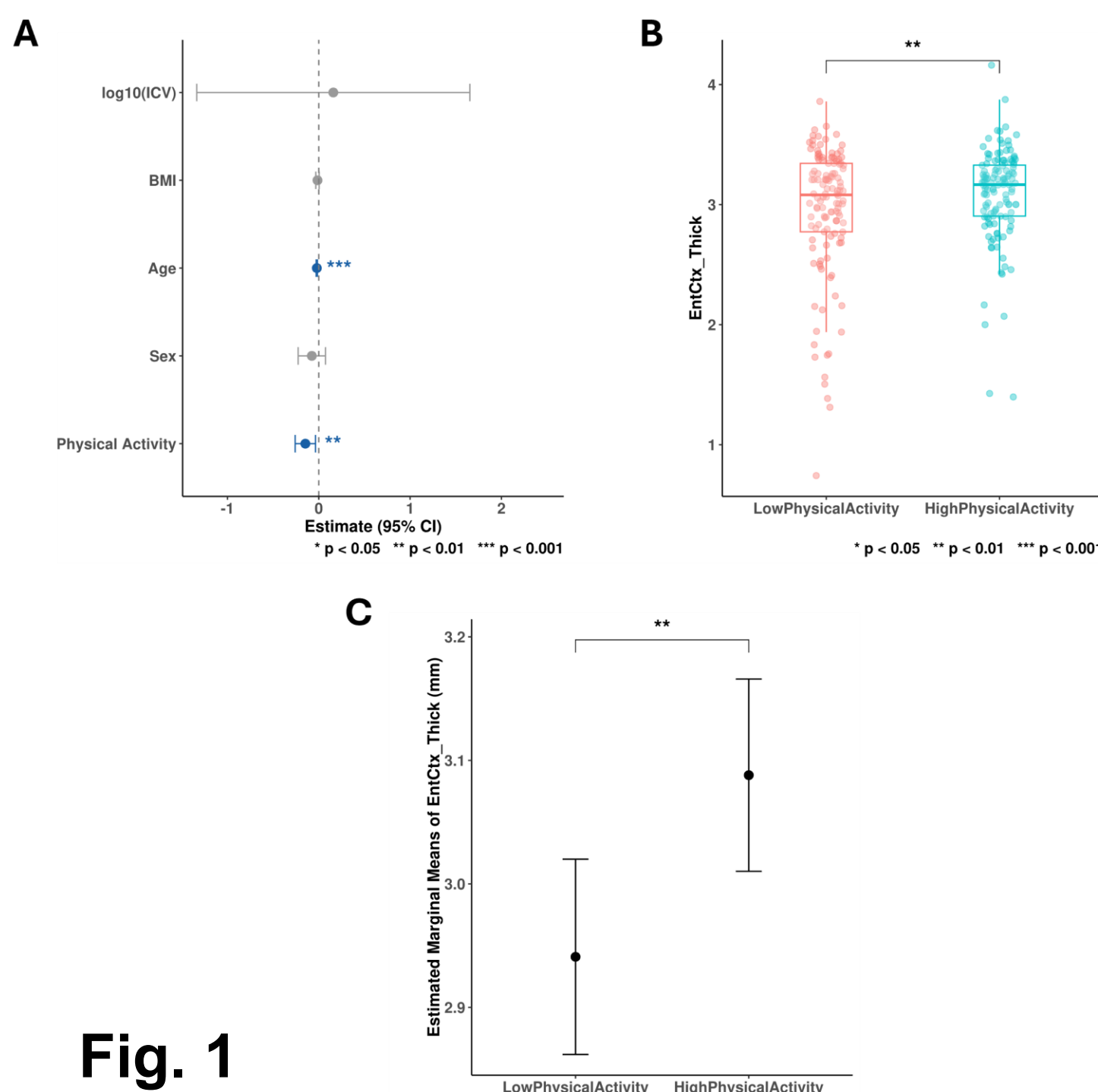
- Cross-sectional linear regression analyses were performed to identify significant associations (a) between LTPAQ groups and AD biomarkers and (b) between LTPAQ groups and network modules.
- Gene-set enrichment analysis was performed using Metascape to identify significantly enriched pathways in network modules.
- Mediation analysis was performed to identify potential mediators on hub genes of significant network modules of physical activity's association with AD biomarkers.
- METAFlux was used to infer metabolic reaction fluxes from RNA-Seq data.

Table 1. Participant Characteristics.

	High Physical Activity (N=129)	Low Physical Activity (N=129)
Age, Median (IQR)	68 (63, 75)	69 (59, 76)
Female, No. (%)	60 (47%)	79 (61%)
Clinical Diagnosis, No. (%)		
CN	109 (84%)	95 (74%)
MCI	20 (16%)	34 (26%)
A β positivity, No. (%)	12 (9.4%)	18 (14%)

RESULTS: EntCtx_Thick ~ LTPAQ groups

- Lower PA was significantly associated with smaller entorhinal cortical thickness (EntCtx_Thick), after adjusting for age, sex, body mass index (BMI), and intracranial volume ($\beta = -0.147$; $p = 0.01$) [Fig. 1A and 1B].
- Estimated marginal means of entorhinal cortical thickness after adjusting for covariates in the Low PA group was 2.94 mm [95% CI: 2.86 – 3.02], while that for the High PA group was 3.09 mm [95% CI: 3.01 – 3.17] (Fig. 1C).



RESULTS: Network modules ~ LTPAQ groups

- Three of 18 network modules tested were significantly associated with PA groups: ME1 ($\beta = 0.017$; FDR-corrected $p = 0.038$), ME2 ($\beta = -0.017$; FDR-corrected $p = 0.038$), and ME9 ($\beta = -0.018$; FDR-corrected $p = 0.038$) [Fig. 2A].
- Genes in ME1 were enriched for pathways related to translation regulation [Fig. 2B], whereas genes in ME2 were enriched for pathways related to immunity [Fig. 2C], and genes in ME9 were enriched for pathways related to autophagy and clearance [Fig. 2D].

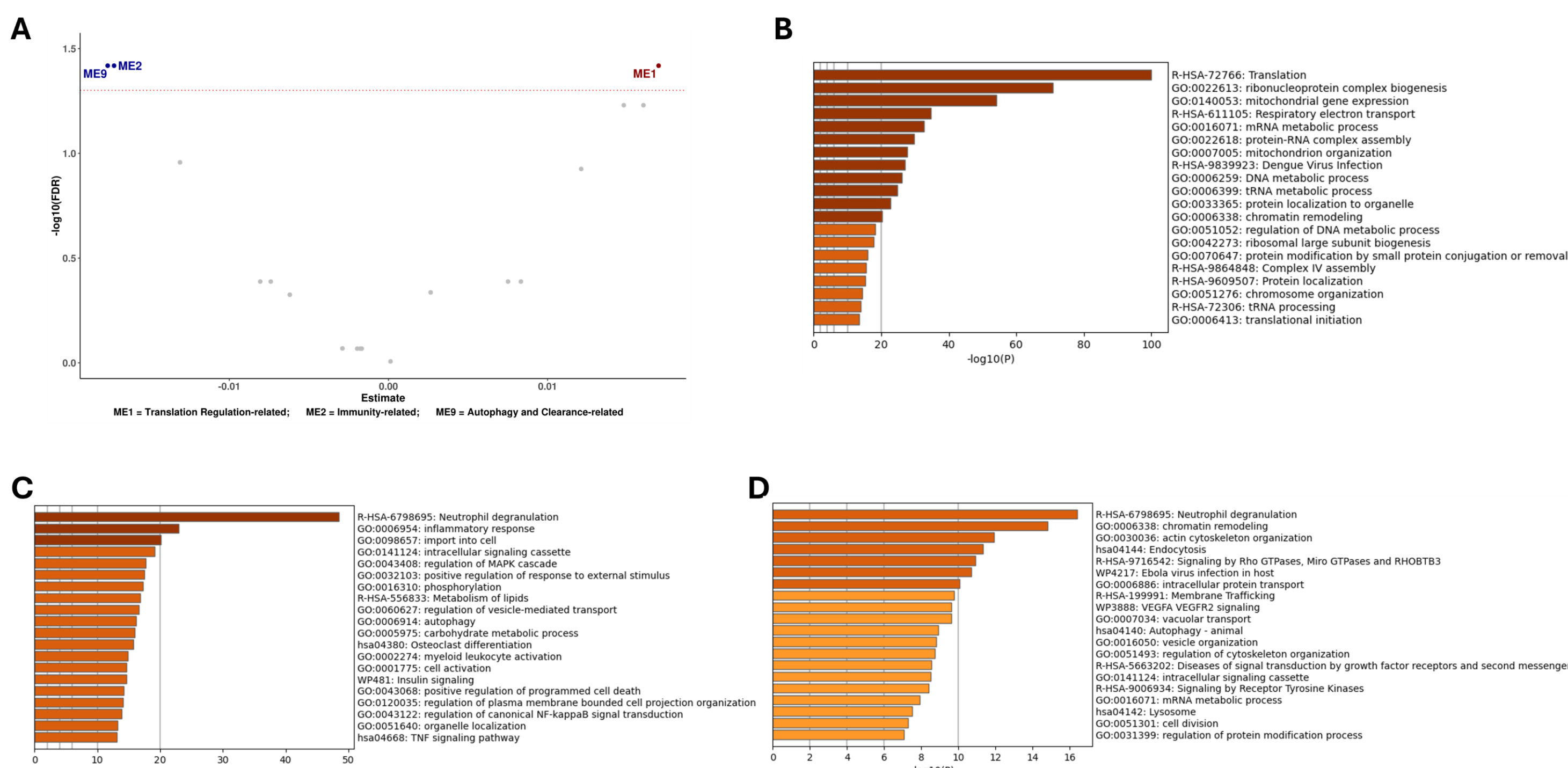


Fig. 2

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RESULTS: Hub genes ~ LTPAQ groups or EntCtx_Thick

- Of the top 25% most connected (Hub) genes in ME1, ME2, and ME9 (N=1200 genes in total), 500 were significantly associated with PA groups [Fig. 3A].
- Of the 500 physical activity-associated hub genes, 6 genes were also significantly associated with entorhinal cortical thickness (EntCtx_Thick) [Fig. 3B].

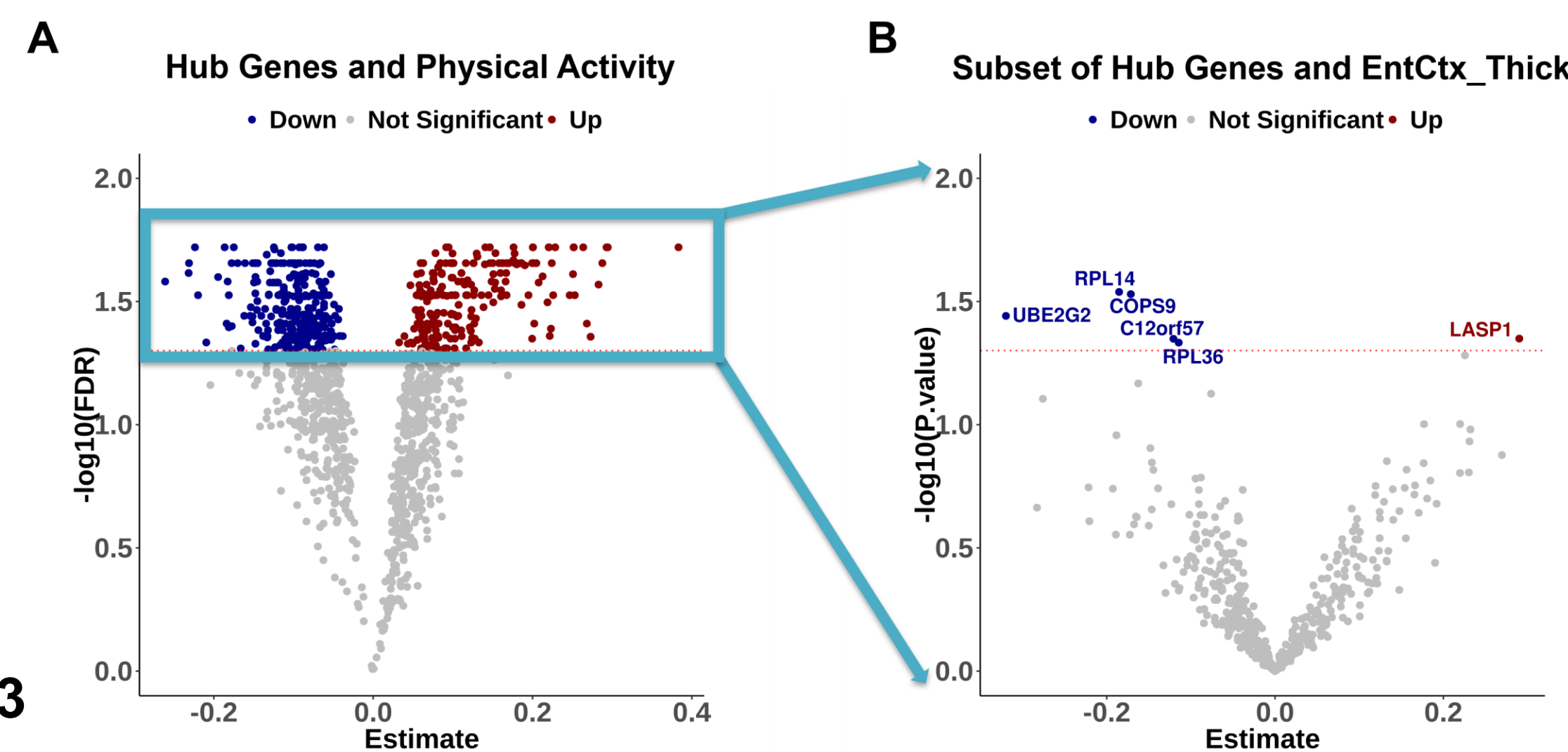


Fig. 3

RESULTS: Mediation analysis

- Of the 6 genes significantly associated with both PA groups and entorhinal cortical thickness (EntCtx_Thick) [Fig. 3A and 3B above], *UBE2G2* was a significant potential mediator of association between the Low PA group and entorhinal cortical thickness (EntCtx_Thick) [Fig. 4A].
- RNA-Seq-informed genome-scale metabolic flux inference analysis using METAflux identified a significantly higher flux of ubiquitination reaction in the Low PA group compared to the High PA group [Fig. 4B].

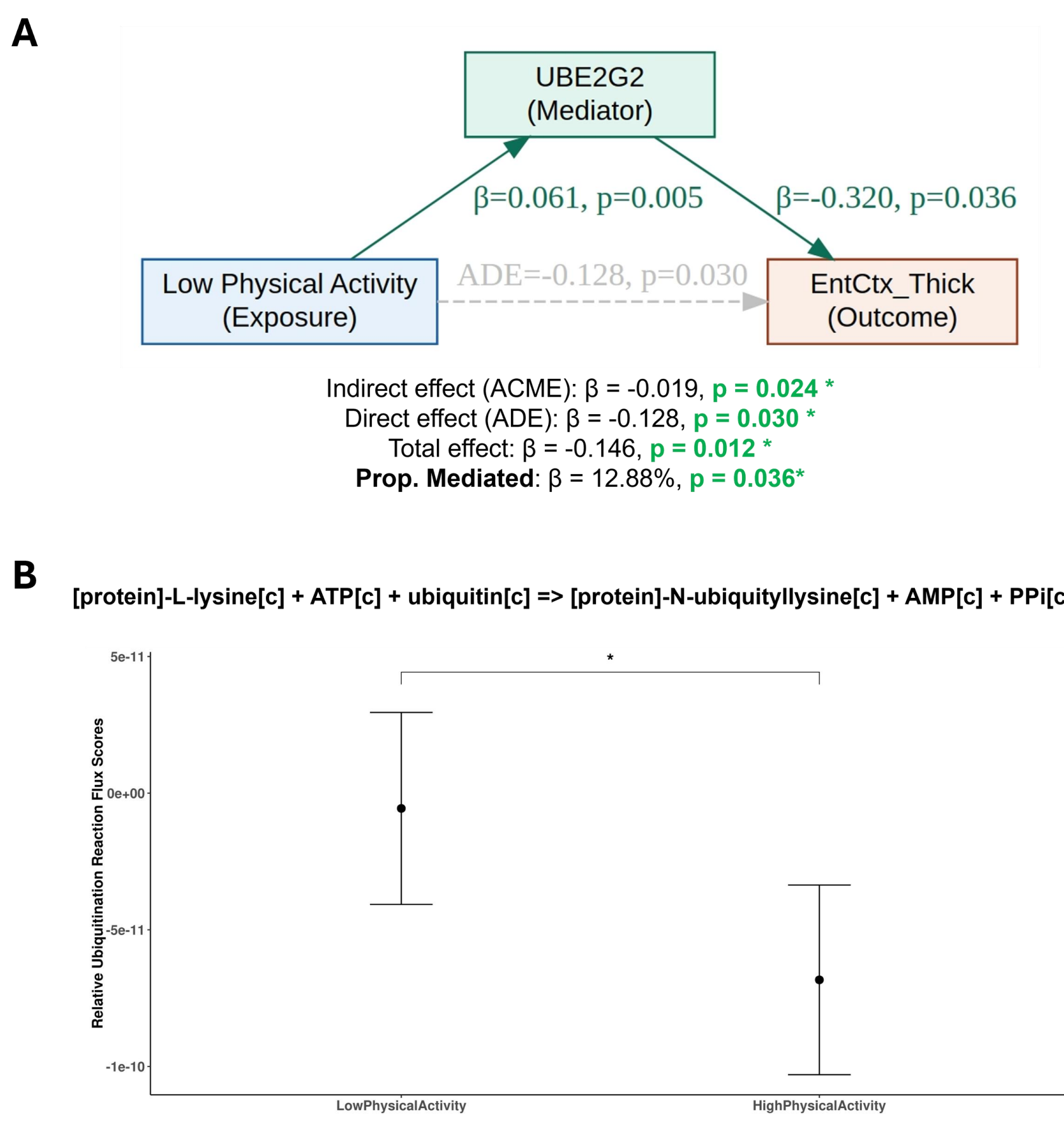


Fig. 4

CONCLUSIONS

- Lower lifetime total physical activity is associated with significantly smaller entorhinal cortical thickness in a Korean population.
- Lifetime total physical activity is associated with peripheral blood expression levels of genes related to pathways including translation regulation, immunity, and autophagy and clearance.
- Ubiquitination, specifically, *UBE2G2* may be a potential mediator of the association between physical activity and neurodegeneration biomarker for AD.