Acute $PM_{2.5}$ Intervention on Cognition and Underlying Mechanisms: Evidence from Integrating Alternative Splicing into Multi-Omics

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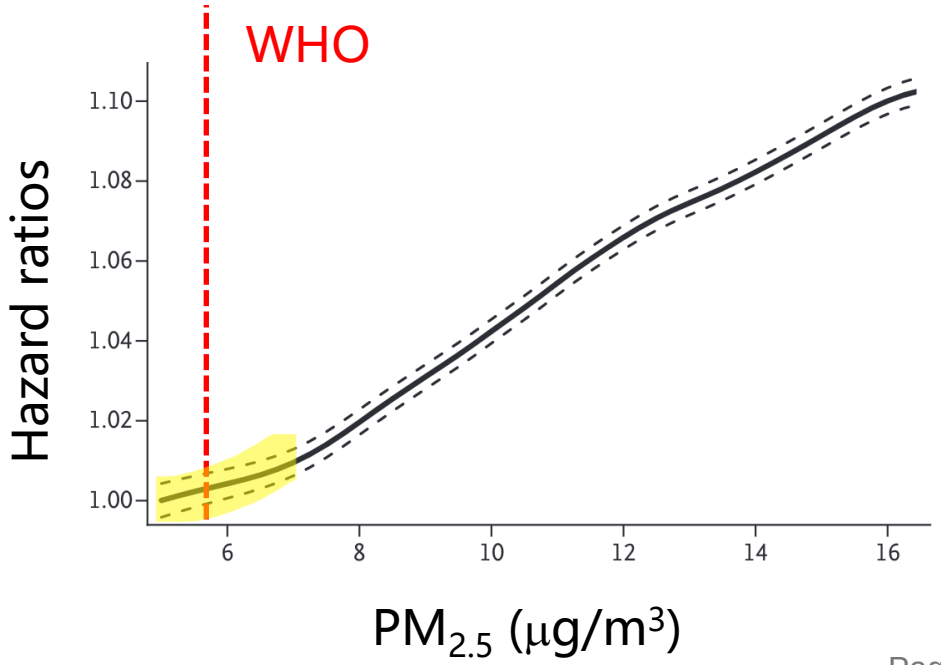
Background of $PM_{2.5}$ and Brain Cognition

Fine Particulate Matter (PM2.5) and Health Threatens

- Adverse effects at much lower levels of PM2.5 had previously been studied;
- Almost the entire global population (99%) breathes air that exceeds WHO air quality limits.
  —— Importance of air purifiers

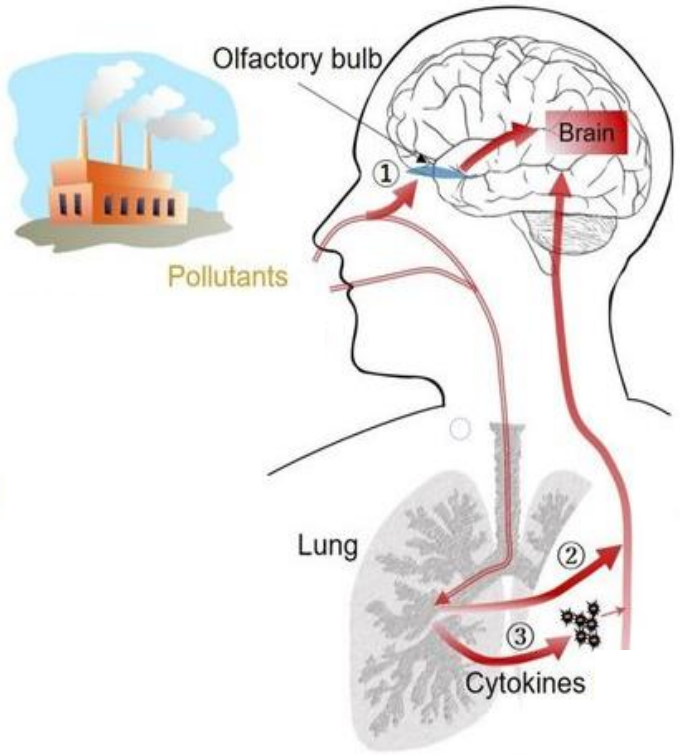


WHO's Air Quality Guidelines, 2021.
Di Q, Wang Y, Zanobetti A, *et al.* Air Pollution and Mortality in the Medicare Population. *N Engl J Med* 2017; **376**: 2513–22.

Background of $PM_{2.5}$ and Brain Cognition

$PM_{2.5}$ and Cognition Decline

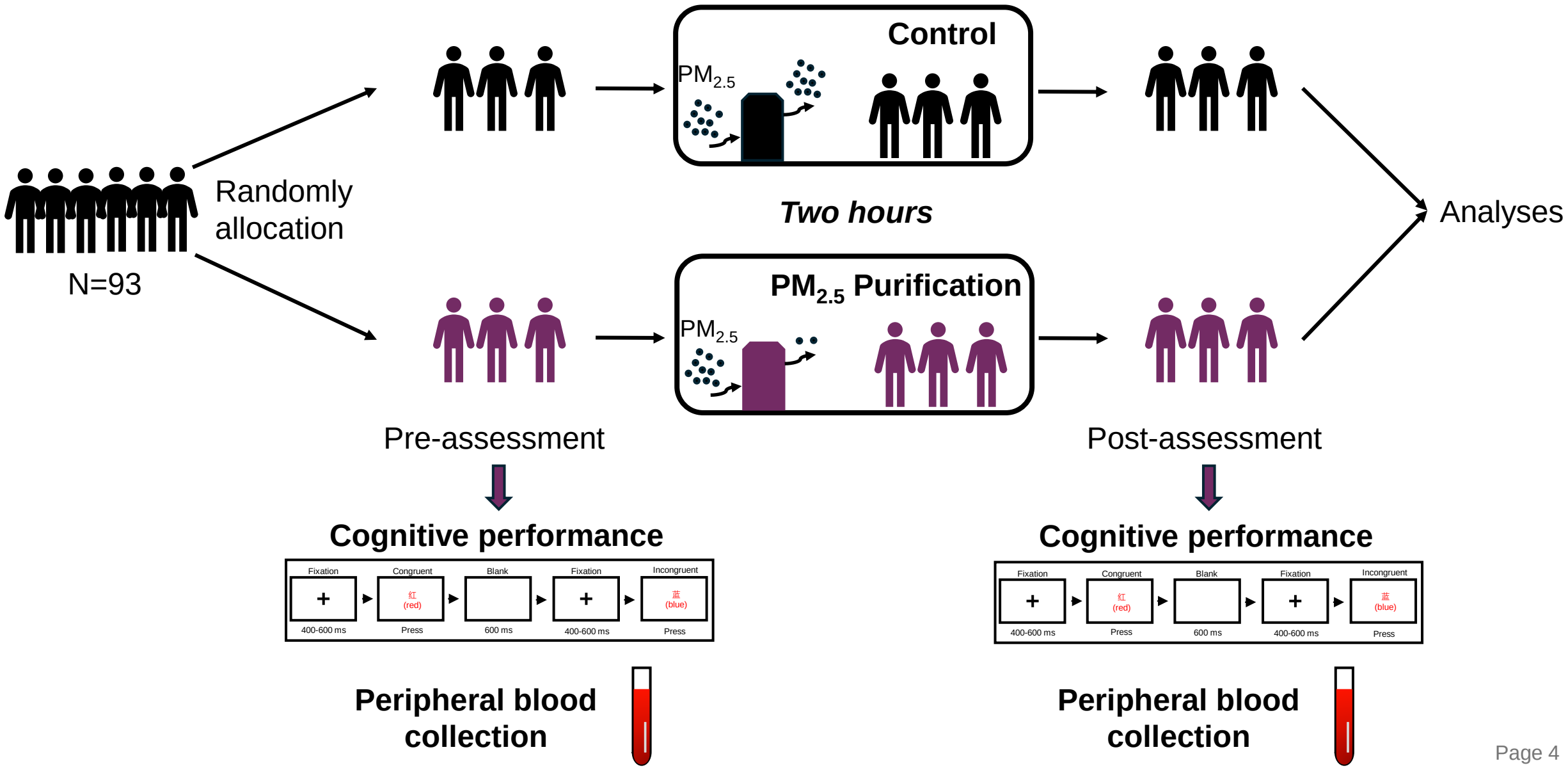
- Exposure to $PM_{2.5}$ caused adverse effects on brain structure and cognitive function;
- Even daily- and hourly-level pollution exposures could have impacts on brain functions.



- ☐ Dose acute $PM_{2.5}$ purification intervention help to improve $PM_{2.5}$-induced cognition decline?
- ☐ What is the underlying mechanisms of $PM_{2.5}$ purification intervention and cognition improvement?

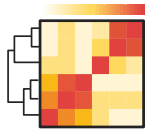
Ranft, U., Schikowski, T., Sugiri, D., Krutmann, J. & Krämer, U. Long-term exposure to traffic-related particulate matter impairs cognitive function in the elderly. Environmental Research 109, 1004–1011 (2009).
Thompson, R. *et al.* Air pollution and human cognition: A systematic review and meta-analysis. *Science of The Total Environment* **859**, 160234 (2023).

Methods —— Acute $PM_{2.5}$ Purification Intervention



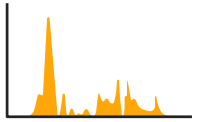
Methods —— Acute $PM_{2.5}$ Purification Intervention

Peripheral blood collection

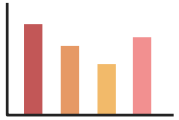


Transcriptomics from PBMCs → Transcripts

Alternative splicing events

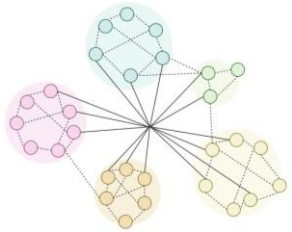


Proteomics from Plasma → Proteins



Metabolomics from Plasma → Metabolites

ELISA、Biochemical assay → BDNF, Tau



Linear Mixed-Effect Models

↓

Differentially expressed components

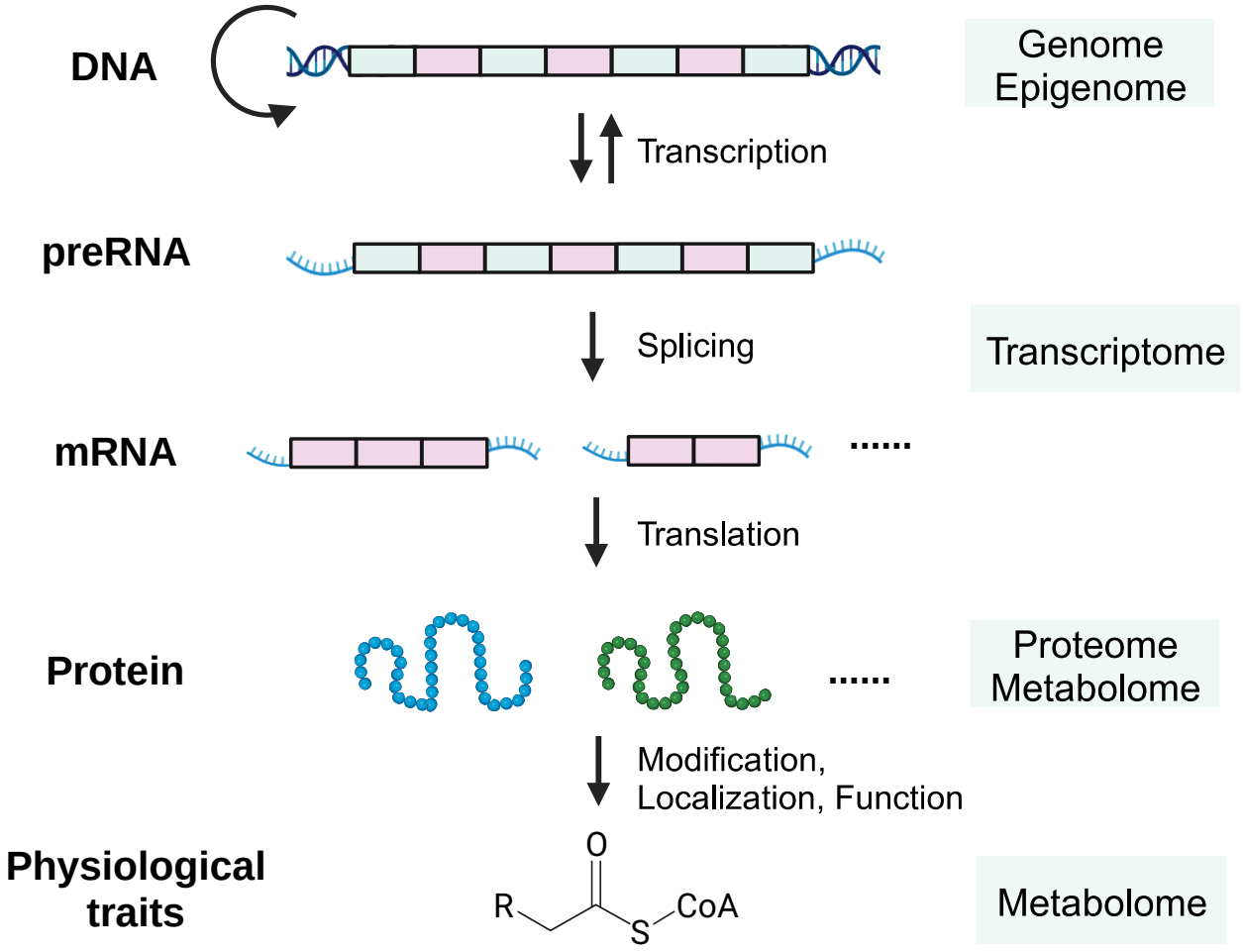
← *Reactome/ KEGG*

↓

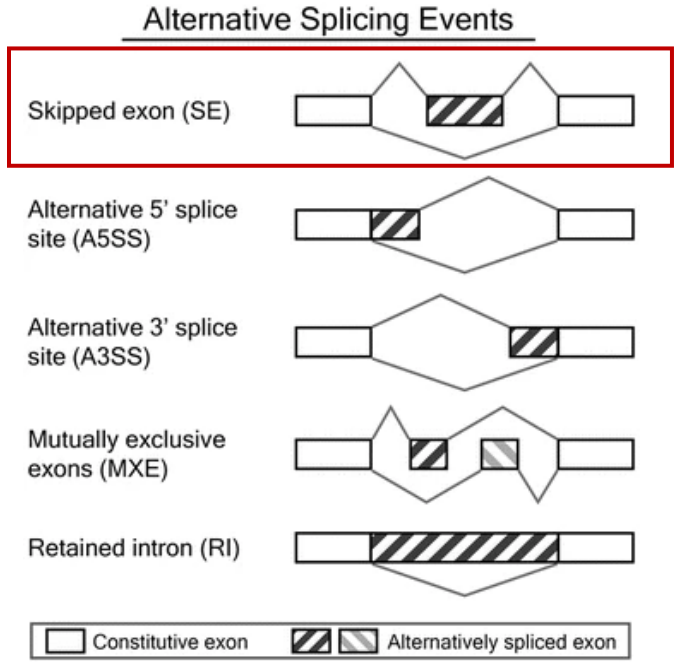
Cellular functional/pathway analysis

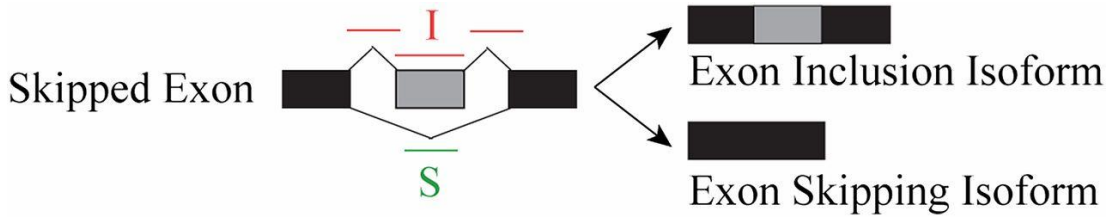
Methods —— Acute $PM_{2.5}$ Purification Intervention

The central dogma of genetics



Replicate multivariate analysis of transcript splicing (rMATS)

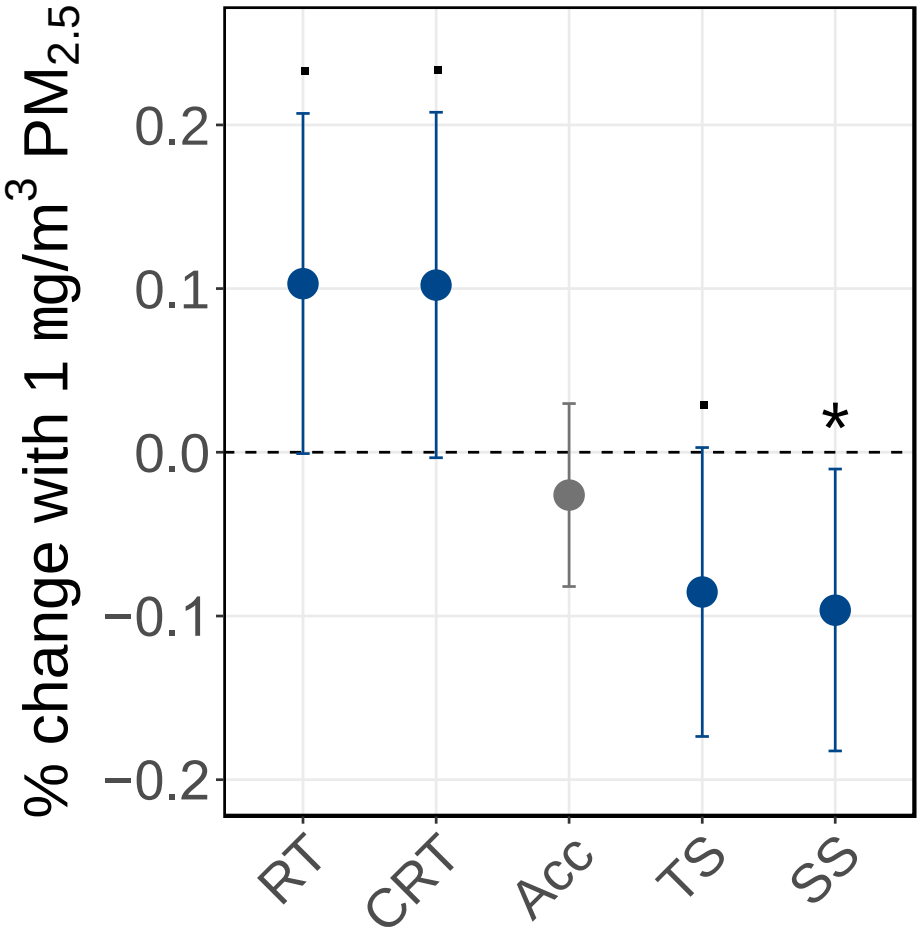




Shen, S. *et al.* rMATS: Robust and flexible detection of differential alternative splicing from replicate RNA-Seq data. *Proc. Natl. Acad. Sci. U.S.A.* **111**, (2014).

Results —— Acute $PM_{2.5}$ Purification Intervention

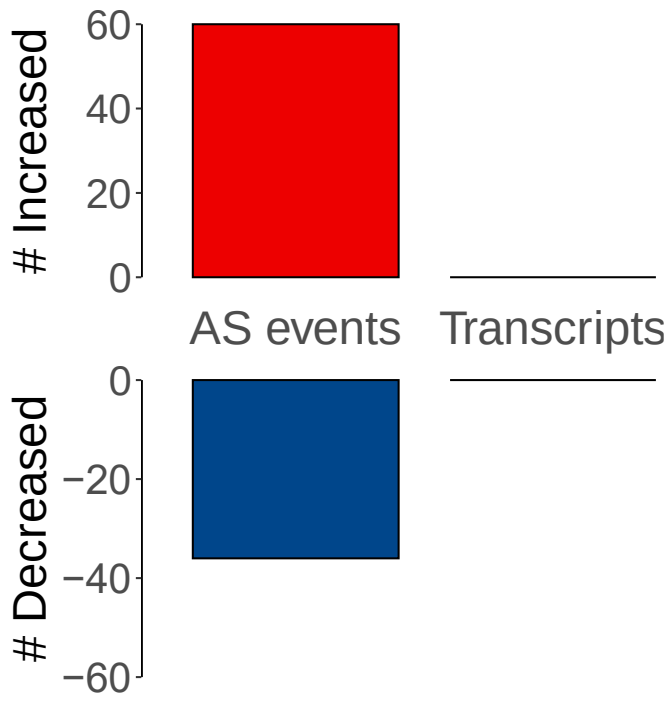
Improved Cognitive Function Induced by Acute $PM_{2.5}$ Purification Intervention

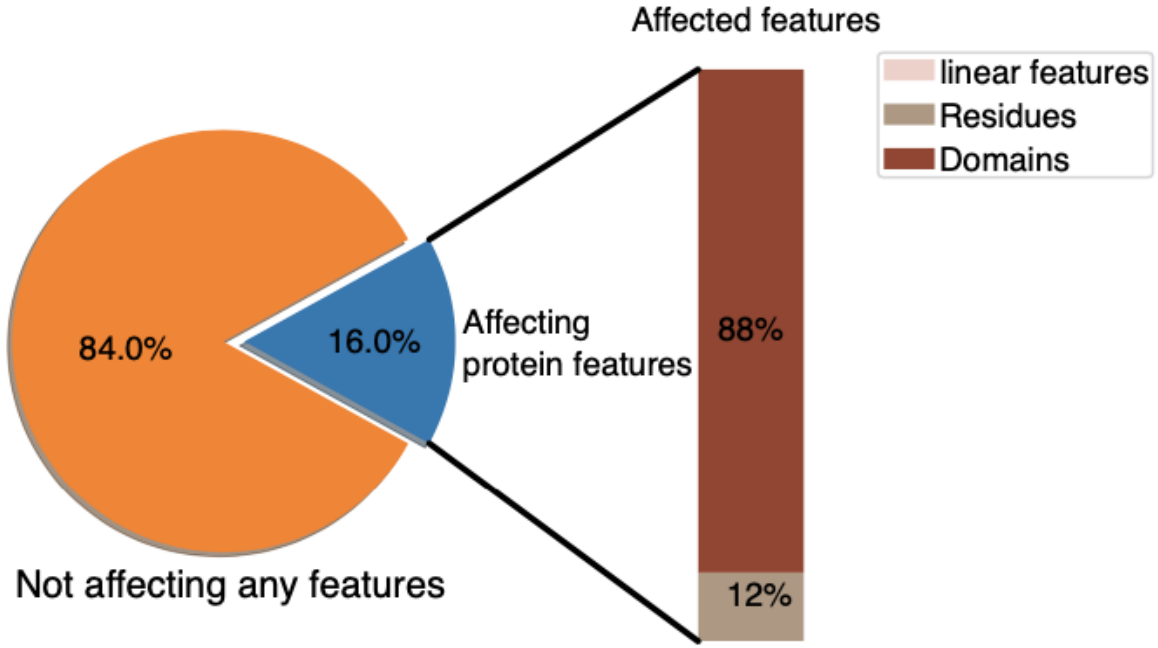


- Increased levels of $PM_{2.5}$ led to higher response time (RT) (p = 0.055) and correct response time (CRT) (p = 0.061)
- Increased levels of $PM_{2.5}$ led to lower total score (TS) (p = 0.062) and standard score (SS) (p = 0.031)

Results —— Acute $PM_{2.5}$ Purification Intervention

Alternative Splicing (AS) Events and Transcripts in Relation to $PM_{2.5}$





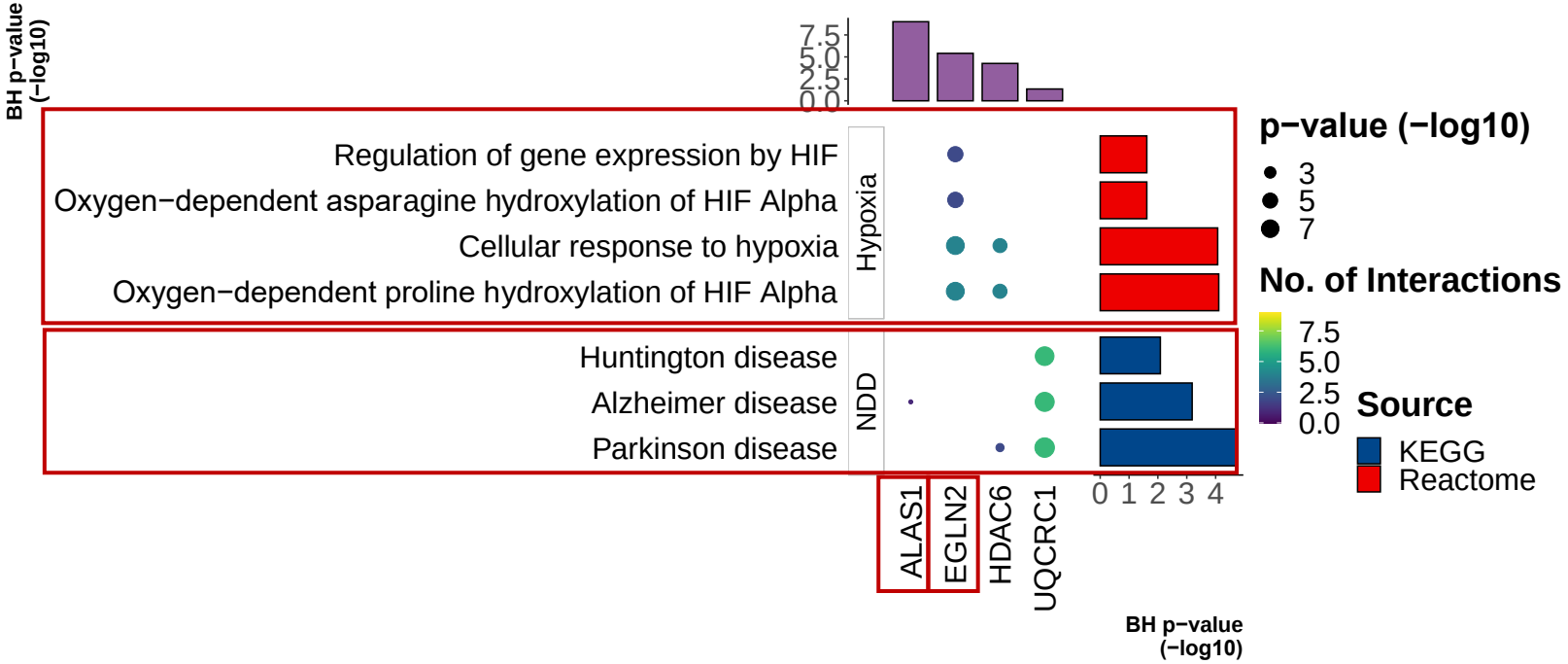
- No differential expressed transcripts associated with acute $PM_{2.5}$ intervention
- 96 skipping-exon events that displayed significant variations

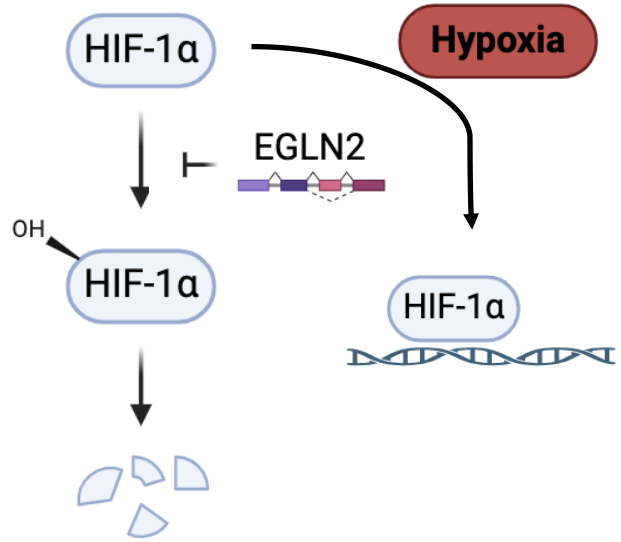
- Network-based Enrichment method for AS Events (NEASE) enrichment analysis by mapping genes on the significant AS events to the Reactome and KEGG databases

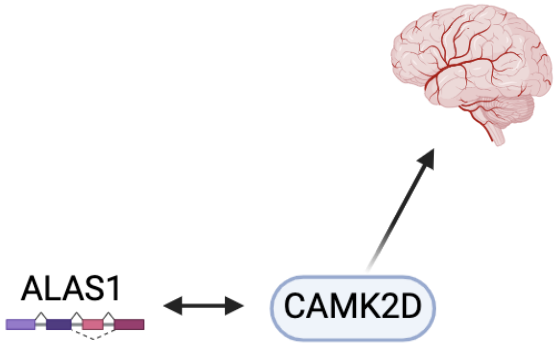
Louadi, Z. et al. Functional enrichment of alternative splicing events with NEASE reveals insights into tissue identity and diseases. Genome Biol 22, 327 (2021).

Results —— Acute $PM_{2.5}$ Purification Intervention

Molecular Mechanisms due to Acute PM2.5 Intervention from Alternative Splicing



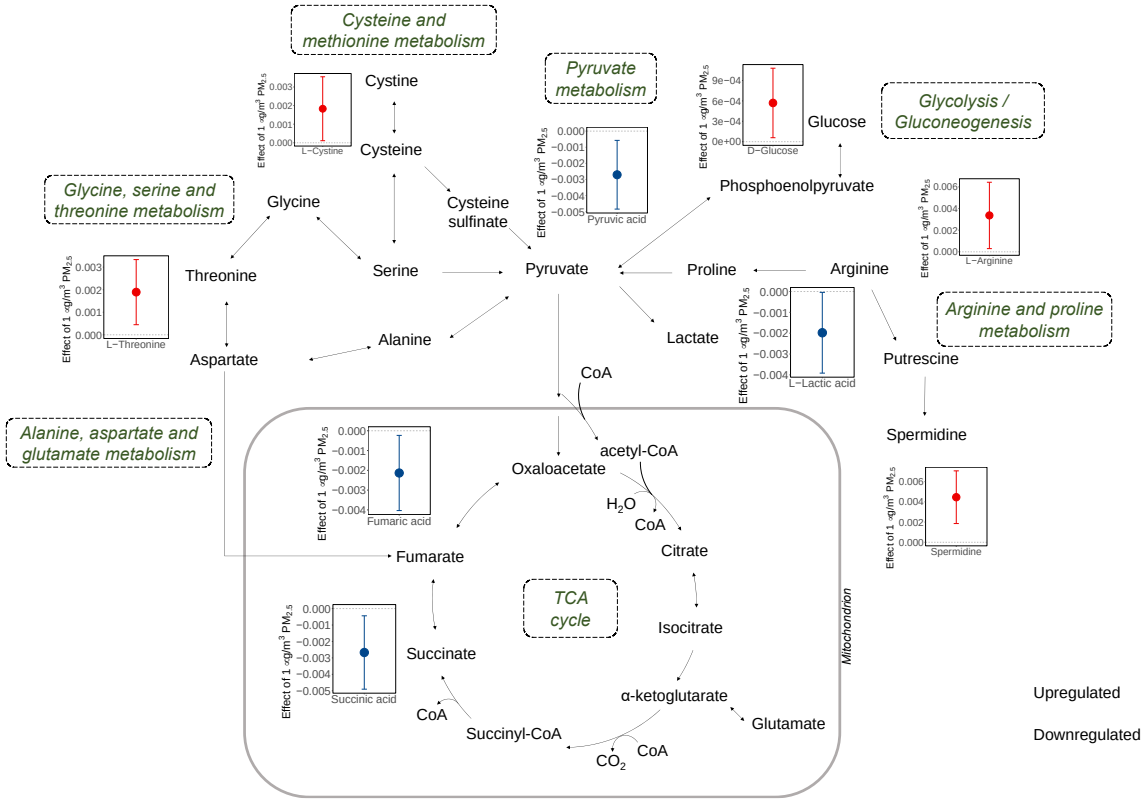


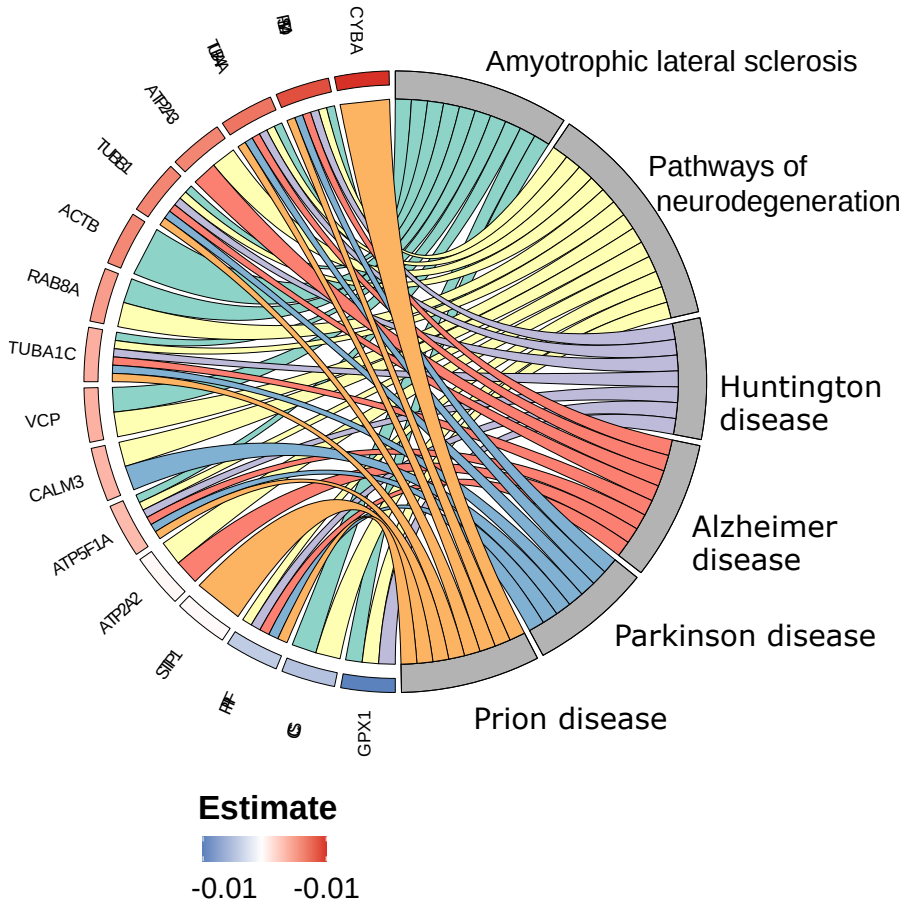


- Shift in hypoxia-related processes —— EGLN2 (Egl-9 Family Hypoxia Inducible Factor 2) gene
- Enriched pathways in the neurodegenerative diseases —— ALAS1 (5'-Aminolevulinate Synthase 1) gene

Results —— Acute $PM_{2.5}$ Purification Intervention

Molecular Mechanisms due to Acute PM2.5 Intervention from Metabolomics and Proteomics

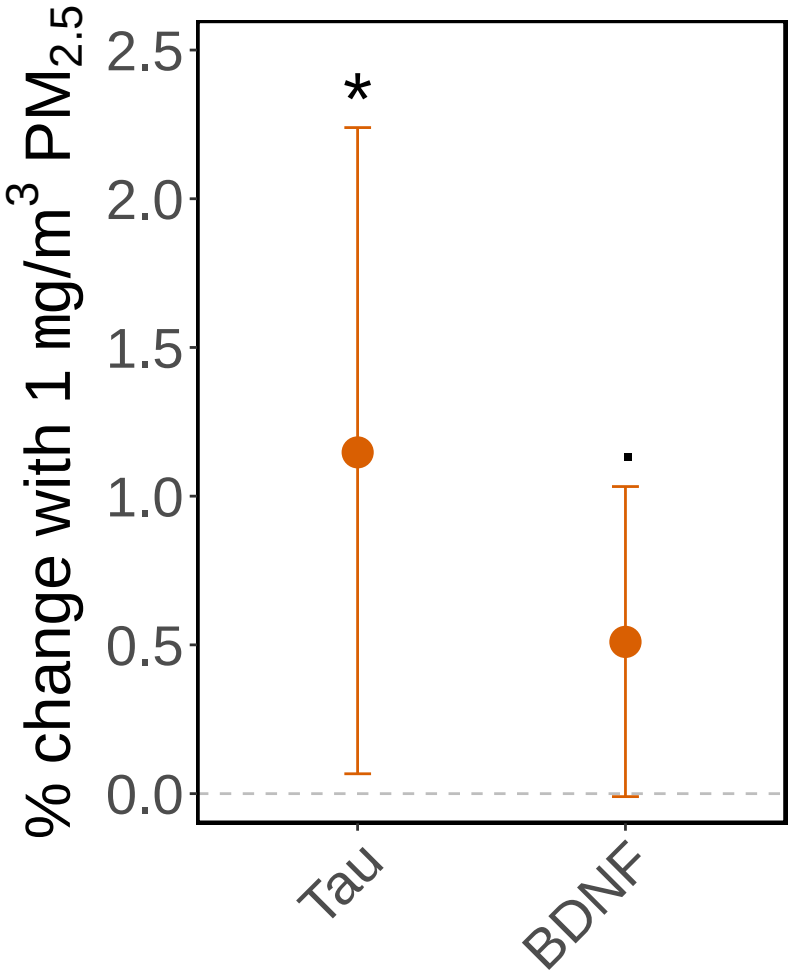




- Significant differences in metabolites related to energy metabolism
- Proteomics data mainly involved in pathways related to neurodegenerative diseases

Results —— Acute $PM_{2.5}$ Purification Intervention

Serum Biomarkers Changes due to Acute PM2.5 Intervention



- Changes of PM2.5 levels induced significantly increased levels of total Tau and Brain-derived neurotrophic factor (BDNF) in serum;
- Tau and BDNF played major roles in central nervous system.

Take home message

- Acute PM2.5 purification intervention induced temporary improvements in cognitive functions;
- We explained the mechanisms by which acute PM2.5 purification improved cognitive function, especially from the way of Alternative Splicing;
- We emphasized the significance of Alternative Splicing into multi-omics analyses to decode complex molecular interactions.

Acknowledgements

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Thank you for Listening

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