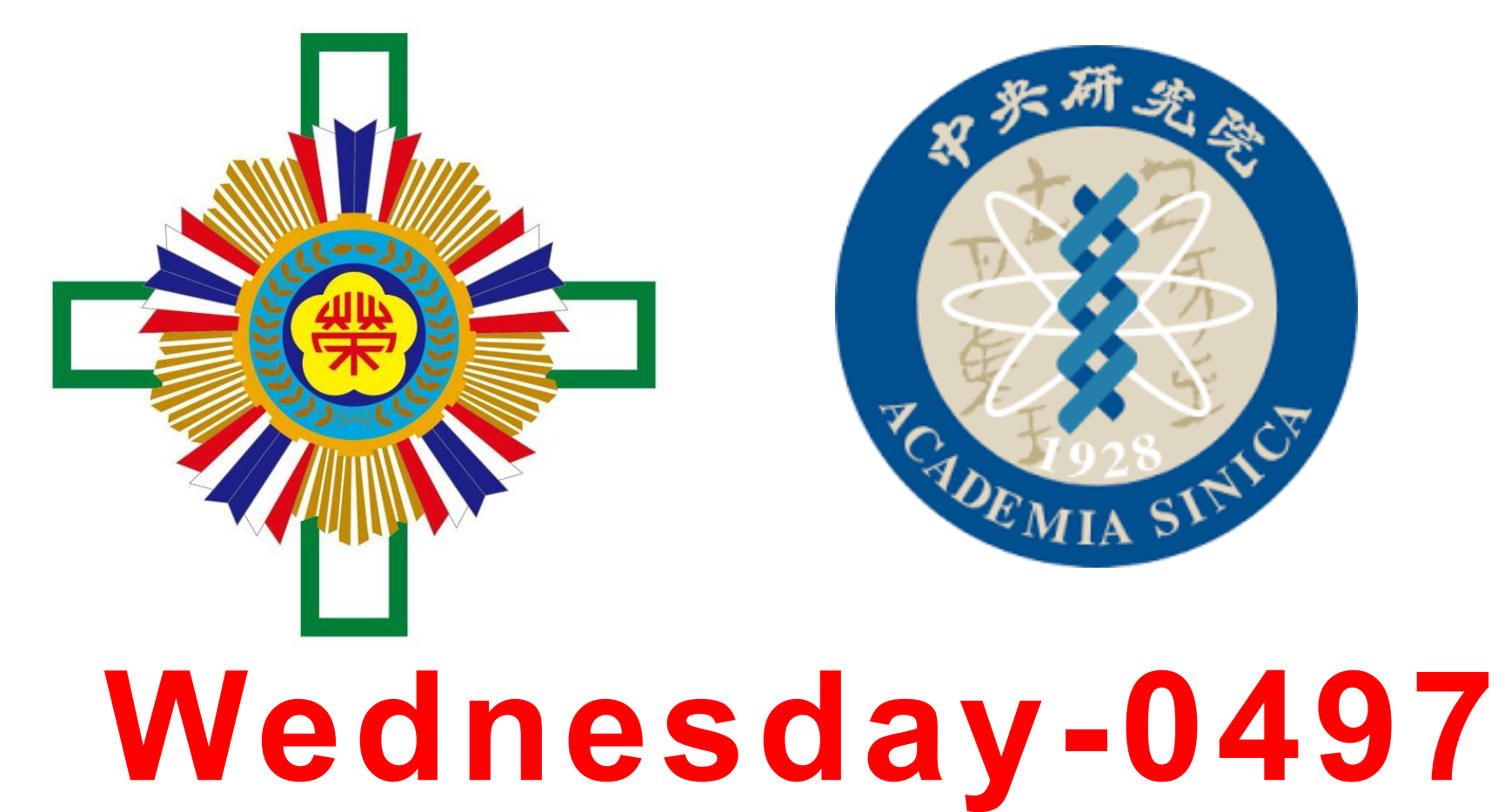


Multi-Dimensional Risk Profiling of Alzheimer’s Disease: Integrating Genetic, Environmental, and Neuroimaging Insights



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- *APOE*-region genetic variation is the primary driver of Alzheimer’s disease susceptibility in Taiwanese population.
- Long-term exposure to PM_{2.5} air pollution multiplies this genetic risk, creating an exceptionally vulnerable subgroup among individuals who are *APOE* ε4 homozygotes.
- This specific genetic vulnerability is directly linked to reduced hippocampal volume.

INTRODUCTION

Alzheimer’s disease (AD) reflects genetic, environmental, and neurobiological influences, but integrated East Asian data remain limited. We aimed to build a Taiwanese multidimensional risk-profiling framework integrating GWAS, functional microglial assays, polygenic risk score (PRS), *APOE*-PM_{2.5} interaction, Mendelian randomization, and imaging genetics.

METHODS

We analyzed three Taiwanese cohorts using GWAS meta-analysis, PRS validation, *APOE*-region–PM_{2.5} interaction testing, Mendelian randomization (MR), and exploratory imaging GWAS. Clinical AD cases from TPMI and VGHTPE (n = 5105) were combined with Taiwan Biobank AD-by-proxy cases (n = 7750) and controls.

RESULTS

The strongest association localized to the chromosome 19 *APOE*-region. TPMI showed candidate signals near *SHARPIN* and *KMO*. The PRS provided modest discrimination and partial external transportability (AUC 0.59 vs AUC 0.6-0.66). Long-term PM_{2.5} exposure showed additive interaction with *APOE*-region susceptibility, especially among *APOE* ε4 homozygotes (OR 11.87), whereas MR did not support a robust marginal causal effect of genetically predicted PM_{2.5}. *APOE*-region variation was associated with reduced hippocampal volume.

Figure 1. Manhattan plots show the dominant *APOE*-region peak across Taiwanese AD analyses.\

CONCLUSIONS

APOE-region variation is the major common genetic determinant of AD susceptibility in Taiwanese cohorts. PM_{2.5} exposure identifies an environmentally susceptible high-risk subgroup, especially *APOE* ε4 homozygotes. *SHARPIN* and *KMO* are candidate non-*APOE* loci but require independent replication and variant-to-gene validation. *APOE*-region variants were associated with reduced hippocampal volume, linking genetic risk to neurodegeneration. The integrated framework supports East Asian precision prevention linking genetics, exposure, and neurodegeneration.

Figure 2. ROC and quartile analyses indicate partial external transportability but limited gain over *APOE*-region information

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Table 1. Demographics and comorbidities of the 3 cohorts analyzed

Characteristic	TPMI Clinical Cohort		VGHTPE AD-Taiwan Biobank Cohort		Taiwan Biobank Proxy-AD Cohort	
	AD (n=3979)	Controls (n=39,790)	AD (n=1126)	Controls (n=14,512)	AD (n=7750)	Controls (n=52,700)
Age (years)	77.9 ± 6.7	78.0 ± 6.9	75.8 ± 7.7	62.5 ± 7.2	56.0 ± 8.1	42.7 ± 9.1
Female, n (%)	2563 (64.4)	25,630 (64.4)	552 (49.0)	7091 (48.9)	5012 (64.8)	32,974 (62.6)
<i>APOE</i> ε4 carrier*, n (%)	1200 (30.3)	6286 (15.8)	445 (39.5)	2336 (16.3)	1817 (23.5)	8451 (16.1)
Hypertension, n (%)	1849 (46.5)	17,660 (44.4)	576 (59.4)	3676 (25.33)	1305 (16.8)	3403 (6.5)
Type 2 diabetes, n (%)	1060 (26.6)	10,885 (27.4)	263 (27.2)	1592 (11.0)	521 (6.7)	1497 (2.8)
Hyperlipidemia, n (%)	1484 (37.3)	14,920 (37.5)	215 (22.3)	2121 (14.6)	1045 (13.5)	2201 (4.2)

Table 2. Additive Interaction Between High PM_{2.5} Exposure and *APOE* ε4 Homozygosity on Alzheimer’s Disease Risk

PM _{2.5} exposure†	<i>APOE</i> genotype	ε4 carrier status*	AD cases n (%)	Controls n (%)	Adj. OR (95% CI)	RERI (95% CI)
Low	ε2/ε2, ε3/ε3	Non-carrier	1703 (34.8)	10076 (51.5)	1 (ref)	
Low	ε2/ε4, ε3/ε4	1 ε4	741 (15.2)	1901 (9.7)	2.31 (2.09-2.55)	
Low	ε4/ε4	2 ε4	87 (1.8)	81 (0.4)	6.28 (4.61-8.55)	
High	ε2/ε2, ε3/ε3	Non-carrier	1617 (33.1)	6381 (32.6)	1.46 (1.35-1.57)	
High	ε2/ε4, ε3/ε4	1 ε4	664 (13.6)	1076 (5.5)	3.58 (3.21-4.00)	
High	ε4/ε4	2 ε4	75 (1.5)	37 (0.2)	11.87 (7.97-17.67)	5.04 (0.04-10.04)

RERI, relative excess risk due to interaction (additive scale). An interaction was considered significant if the 95% CI of RERI did not contain 0.