

Mapping The Egyptian Neuroexposome: Integrative Multiomics Of Genetic, Metabolic, And Environmental Dementia Risk

Mai Othman¹, Mohamed Salama^{1,2,3}

1. Institute of Global Health and Human Ecology (I-GHHE), The American University in Cairo, Cairo, Egypt. 2. Faculty of Medicine, Mansoura University, Mansoura, Egypt. 3. Global Brain Health Institute (GBHI), Trinity College Dublin, Dublin, Ireland.

AAIC 2026 | aaic2026.83e0f40



BACKGROUND & RATIONALE

- Dementia affects **57 million globally** and is projected to reach **153 million by 2050**, with the fastest growth in LMICs
- Egypt** — the most populous Arab nation — faces a rising dementia burden yet is severely underrepresented in neuroepidemiology research
- Existing evidence on genetic, environmental, and metabolic dementia risk factors derives almost entirely from high-income, Western populations — **limiting generalisability and equity**
- The **neuroexposome framework** integrates internal susceptibility (genetics, metabolism) with external exposures (metals, agrochemicals) to characterise AD and AD/VD risk holistically
- Heavy metals** (arsenic, lead, mercury) and **trace elements** (lithium) are plausible modifiable contributors to AD pathogenesis via oxidative stress, tau hyperphosphorylation, and amyloid processing — yet blood metal biomonitoring in Egyptian dementia cohorts has never been performed
- Metabonomics** provides a biochemical fingerprint bridging environmental exposures and disease pathology, with potential to distinguish AD from VaD in resource-limited settings
- The **Egyptian Dementia Network (EDN)**, a multi-centre registry spanning six governorates, was established to enable population-representative dementia research in Egypt for the first time

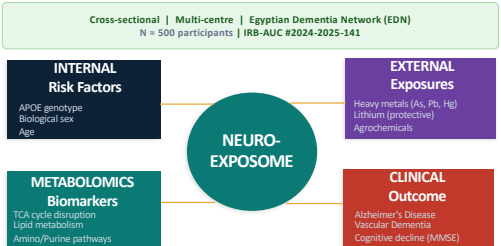
OBJECTIVES

Study 1: Characterise APOE ε2/ε3/ε4 allele and genotype frequencies in a multi-centre Egyptian AD cohort and assess their association with AD risk, adjusting for age, sex, and geographical region; explore sex-specific interactions

Study 2: Quantify blood arsenic, lead, mercury, and lithium concentrations by ICP-OES in AD patients vs. cognitively healthy controls; evaluate associations with AD diagnosis and MMSE cognitive scores using KM-imputed regression and binary detection sensitivity analyses

Study 3: Characterise serum metabolomic profiles of clinically diagnosed AD and VaD patients vs. controls by untargeted LC-ESI-MS/MS; identify significantly altered metabolites, environmental contaminants, and enriched pathways; explore discriminatory metabolites between dementia subtypes

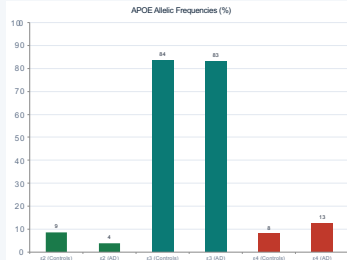
METHODS



RESULTS

Study 1: APOE Genomics

APOE allele frequencies & association with AD risk in Egyptian population



Key Findings

- ε3/ε3 most common genotype AD: 71.4% - Controls: 70.1%
- ε4 trend toward AD risk aOR = 1.62 (95% CI: 0.76–3.38) p = 0.20 (non-significant)
- ε2 trend toward protection aOR = 0.70 (95% CI: 0.23–1.77) p = 0.46 (non-significant)
- ♀ No significant sex-specific APOE effects detected
- ~25% power - Needs >500 per group for 80% power
- ♂ Egyptian ε4 freq (8%) aligns with European populations

ACKNOWLEDGEMENTS & CONTACT

Supported by: Davos Alzheimer's Collaborative (DAC) Global Cohorts Program

Mai Othman* Mai.saadzaghloul@aucegypt.edu
www.linkedin.com/in/mai-zaghloul



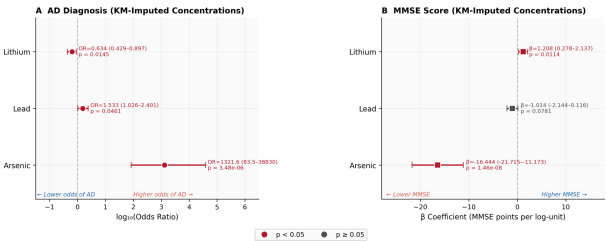
RESULTS

Study 2: Metal-AD Associations & Cognitive Correlations

Regression models adjusted for age and sex

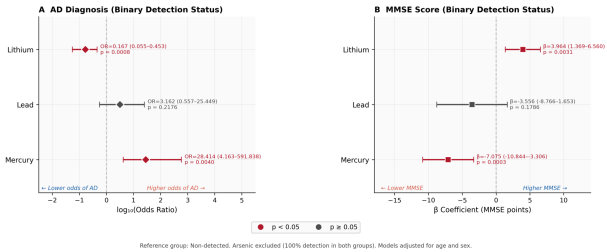
PRIMARY ANALYSIS: KM-IMPUTED CONCENTRATIONS (ADJUSTED FOR AGE & SEX)

Statistical method: Group-stratified Kaplan-Meier imputation → log-transform → logistic/linear regression



SENSITIVITY ANALYSIS: BINARY DETECTION (DETECTED VS. NON-DETECTED)

Avoids imputation assumptions — treats detectable exposure itself as the exposure metric



Reference group: Non-detected. Arsenic excluded (100% detection in both groups). Models adjusted for age and sex.

DETECTED CONCENTRATIONS AMONG DETECTED SAMPLES (PPB)

Metal	Ctrl mean±SD (ppb)	Ctrl median	AD mean±SD (ppb)	AD median	MWU / p
Arsenic	10.21±2.09	9.83	13.41±2.26	13.93	U=342 p<0.0001
Lead	68.98±78.77	49.13	138.96±115.59	118.30	U=634 p=0.0006
Lithium	24.40±26.03	17.91	11.35±12.45	7.02	U=253 p=0.200
Mercury	20.83 (n=1)	—	84.15±55.84	85.14	U=— ‡ insufficient

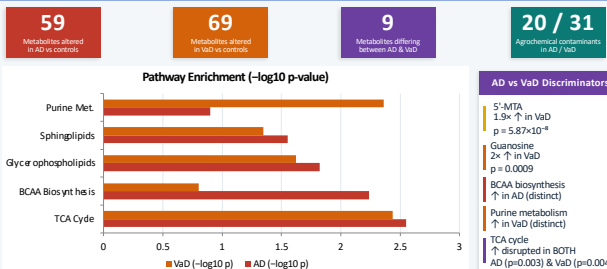
PROPOSED MECHANISMS

Based on the literature



Study 3: Metabonomics Results

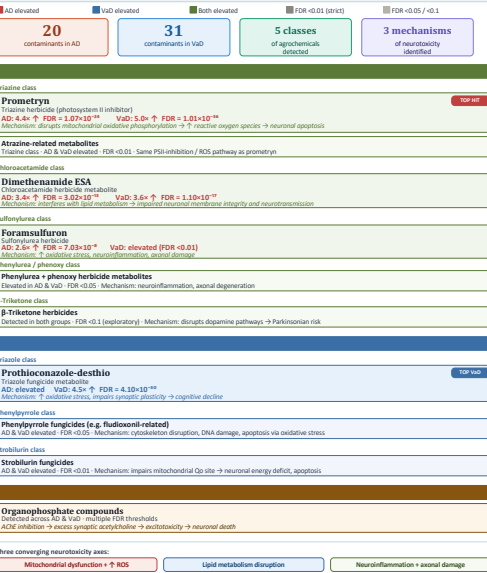
Significant metabolic alterations in AD and VaD vs healthy controls



RESULTS

Study 3: Metabonomics Results

Agrochemical Contaminants in Dementia Serum



CONCLUSIONS

- Arsenic is the strongest and most robust environmental finding:** OR = 1321.61 per log-unit (>7x increased odds per doubling of concentration); β = -16.44 points on MMSE per log-unit. Both associations survive Benjamini-Hochberg FDR correction, making arsenic the leading modifiable environmental AD risk factor identified in this cohort.
- Lithium shows a consistent neuroprotective signal across both analytical approaches:** KM-imputed OR = 0.634 (FDR = 0.022) and binary detection OR = 0.167 (FDR = 0.002). Lithium was detectable in only 28% of AD patients vs. 58% of controls, suggesting a genuine depletion in disease — consistent with GSK-3β inhibition as a neuroprotective mechanism.
- Mercury presents a striking detection asymmetry:** detectable in 24% of AD patients vs. only 2% of controls (Fisher OR = 15.14, p = 0.002). Binary sensitivity analysis yields OR = 28.41 and β = -7.08 for MMSE — large FDR-significant effects, though preliminary given only n = 1 control detected; warrants dedicated high-sensitivity assays.
- Lead shows a borderline but directionally consistent association:** OR = 1.53, p = 0.046, which does not survive FDR correction. Detected concentrations are significantly higher in AD (median 118 vs. 49 ppb, p = 0.0006), supporting biological plausibility via APP/BACE1 upregulation and amyloid plaque formation.
- The tiered censored-data strategy is methodologically essential:** the combination of KM imputation (primary) and binary detection sensitivity analysis demonstrates that the choice of method for left-censored environmental data materially affects statistical conclusions — a critical consideration for environmental epidemiology in LMIC settings.
- This is the first rigorous blood metal biomonitoring study in a clinically characterised Egyptian AD cohort,** filling a critical LMIC- and MENA data gap. The Egyptian Dementia Network infrastructure enables scalable, multi-centre research in an underrepresented population.
- Multi-omics findings converge on two core pathogenic axes:** (1) mitochondrial dysfunction — evidenced by TCA cycle disruption in both AD and VaD, and FAD as a super-hub (+7 degree) in the AD metabolic network; (2) lipid dysregulation — agrochemical contaminants, APOE ε4-associated downregulation of oleic and linoleic acids, and disrupted glycerophospholipid profiles.
- Actionable public health implications emerge for Egypt and LMIC settings:** arsenic source control (water supply, food chain), lithium adequacy monitoring as a potentially protective dietary/environmental factor, and mercury exposure surveillance represent evidence-informed targets for dementia risk reduction.
- 20-31 serum agrochemical contaminants** (triazine herbicides, chloroacetamide metabolites, sulfonamide herbicides, triazole and phenylpyrazole fungicides, organophosphates) are elevated in dementia patients, suggesting that environmental pesticide exposure contributes to neurodegeneration through mitochondrial disruption, lipid metabolism interference, and neuroinflammation.

FUTURE DIRECTIONS

- Longitudinal EDN follow-up** — repeat metal and metabolomic measurements in the same participants to establish temporal precedence and move from association to causal inference
- Metal mixture analysis** — apply WQS and BMR regression to model the joint neurotoxic effect of As + Pb + Hg + Li and their interaction with agrochemical co-exposures
- Expanded multi-omics** — integrate epigenomics, proteomics, and microbiome profiling to build a comprehensive neuroexposome map, including APOE-stratified epigenetic signatures
- Larger APOE-stratified cohorts** — >500 participants per genotype group to achieve 80% power for definitive ε4/ε2 risk conclusions in the Egyptian genetic background (current power ~25%)
- Pesticide exposure characterisation** — prospective collection of agrochemical histories, dietary records, agricultural proximity data, and urinary pesticide metabolites to quantify exposure beyond serum detection
- Biomarker validation** — prospective replication of S'-methylthioadenosine and guanosine as serum AD vs. VaD discriminators in an independent EDN cohort, with assessment of clinical utility in resource-limited settings