

Impact of Angiotensin Receptor Blockers on Biomarkers in Alzheimer’s Disease and Mild Cognitive Impairment

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Introduction

The Global Challenge

- Alzheimer’s Disease (AD): Neurodegeneration marked by amyloid- β plaques and tau accumulation.
- Epidemiology: Global cases of AD are projected to hit 13.8 million by 2060.¹
- Early Detection: Critical 20-year prodromal window (pre-symptomatic phase) exists before onset.²

Metabolomics

- Biofluids: Saliva and urine offer cost-effective alternatives to invasive Cerebrospinal Fluid (CSF) or Positron Emission Tomography (PET).
- Diagnostics: Building on Yilmaz et al. (2017, 2020), this study utilizes validated metabolite panels to identify unique chemical signatures that distinguish Healthy Controls (NC), Mild Cognitive Impairment (MCI), and Alzheimer’s Disease (AD) cohorts.^{3,4}

Medication Confounding

- Hypertension Link: Hypertension is a primary modifiable risk factor for neurodegeneration.
- ARB Usage: High prevalence of Angiotensin II Receptor Antagonists (ARBs) in aging populations.
- The Gap: Determining if ARB-induced metabolic shifts invalidate established biomarker panels.

Aims and Objectives

Aim 1: Determine how (if at all) ARBs alter the general urinary and salivary metabolome.

- Objective: Profile the salivary and urinary metabolites of individuals treated with ARBs using ¹H NMR and mass spectrometry.
- Objective: Determine if ARB administration results in statistically significant concentration shifts compared to healthy controls.

Aim 2: Determine how ARBs alter urinary and salivary biomarkers of AD or MCI.

- Objective: Verify the diagnostic stability of the Yilmaz et al. biomarkers across AD, MCI, and healthy control groups.
- Objective: Confirm that ARB use does not confound the stratification of individuals into their respective experimental groups.
- Objective: Support the validation of existing diagnostic biomarkers by ensuring they remain isolated from the metabolic effects of a common antihypertensive therapy.

Methods

Study Design & Cohorts

- Type: Retrospective Case-Control Study.
- Groups: Alzheimer’s Disease (AD), Mild Cognitive Impairment (MCI), and Healthy Controls (NC).
- Participants:
 - Urine Cohort: N = 159 (68 Controls, 38 AD, 53 MCI).
 - Saliva Cohort: N = 378 (190 Controls, 102 AD, 86 MCI).
- Focus: Assessing the impact of Angiotensin II Receptor Antagonists (ARBs) on diagnostic accuracy.

Biofluid Analysis

- Specimens: Saliva and Urine
- NMR: ¹H NMR Spectroscopy for primary metabolite quantification.
- Mass Spec: High-sensitivity MS for comprehensive urinary profiling.

Targeted Biomarker Validation

- Source: Analysis focused on validated metabolite panels identified in Yilmaz et al. (2017, 2020).^{3,4}
- Salivary/Urinary Assessment: Comparison of established biomarkers across ARB-treated and untreated groups.
- Objective: Determine if antihypertensive therapy acts as a metabolic confounder for AD/MCI diagnostic signatures.

Statistical Rigor

- Model: Linear modeling to isolate medication-specific effects from disease pathology.
- Correction: Significance determined via q-values (FDR corrected) to ensure statistical robustness.
- Goal: Resolving the "confounding dichotomy" in polypharmacy patient populations.

Table 1. Study subjects for urine metabolomics analysis, grouped by disease status. Demographic variables displayed below.

	Controls	MCI	AD	p
N	68	53	38	
Age, mean (SD)	77.91 (8.76)	81.52 (7.43)	81.15 (7.72)	0.62 ^a
Gender				
Male	35	21	13	
Female	33	32	25	0.73 ^b
Race				
Caucasian/white	59	48	33	0.58
Black American/Indian/Alaska Native	7	5	5	
MMSE	28.70 (1.21)	23.43 (2.05)	20.11 (4.07)	0.00009
Geriatric Depression SCORE	2.33 (2.42)	2.41 (2.18)	2.28 (2.44)	0.37

Table 2. Study subjects for saliva metabolomics analysis, grouped by disease status. Demographic variables displayed below.

	Controls	MCI	AD	p
N	190	86	102	
Age, mean (SD)	80.34 (9.06)	83.09 (8.04)	83.86 (7.72)	0.69 ^a
Gender				
Male	79	35	31	
Female	111	51	71	0.54 ^b
Race				
Caucasian/white	164	72	85	0.61
Black American/Indian/Alaska Native	23	12	16	
MMSE	27.56 (2.36)	23.05 (2.18)	18.92 (5.44)	0.00003
Geriatric Depression SCORE	2.41 (2.68)	2.57 (2.35)	2.75 (2.64)	2.45

Results

1. Urinary Metabolome: ARB Impact

- Global Stability: No significant metabolic profile differences across the total population due to ARB use.
- AD-Specific Shift: Within the Alzheimer’s Disease cohort, Tryptophan levels were significantly lower in patients taking an ARB compared to those who were not (q = 0.001).

2. Salivary Metabolome: ARB Impact

- Cross-Cohort Elevations: Linear modeling revealed significant increases in Acetone and Isopropyl Alcohol across all groups (AD, MCI, and Controls) receiving ARB treatment (q = 0.001).

Metabolite Ratios:

- AD vs. Control: Asymmetric arginine methylation was significantly higher in AD patients on ARBs (q = 0.021).
- MCI vs. Control: Citrulline synthesis was significantly lower in the MCI group on ARBs compared to the Control group on ARBs (q = 0.024)

Pathway Enrichment: The Carnitine metabolic pathway was significantly upregulated in AD patients on ARB therapy (p < 0.01).

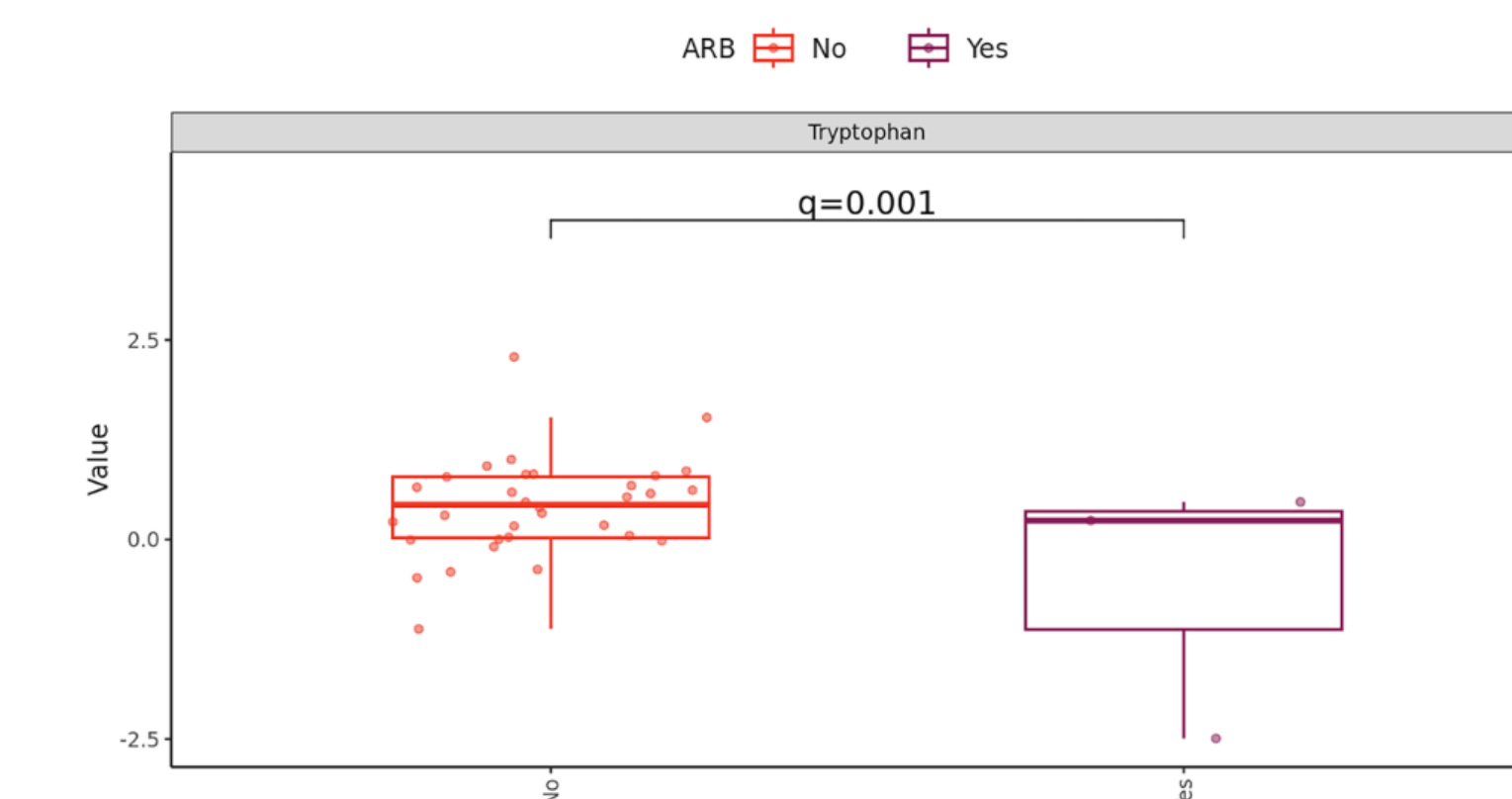


Figure 1. Distributions of statistically significant urinary metabolite changes associated with ARB usage among individuals with AD.

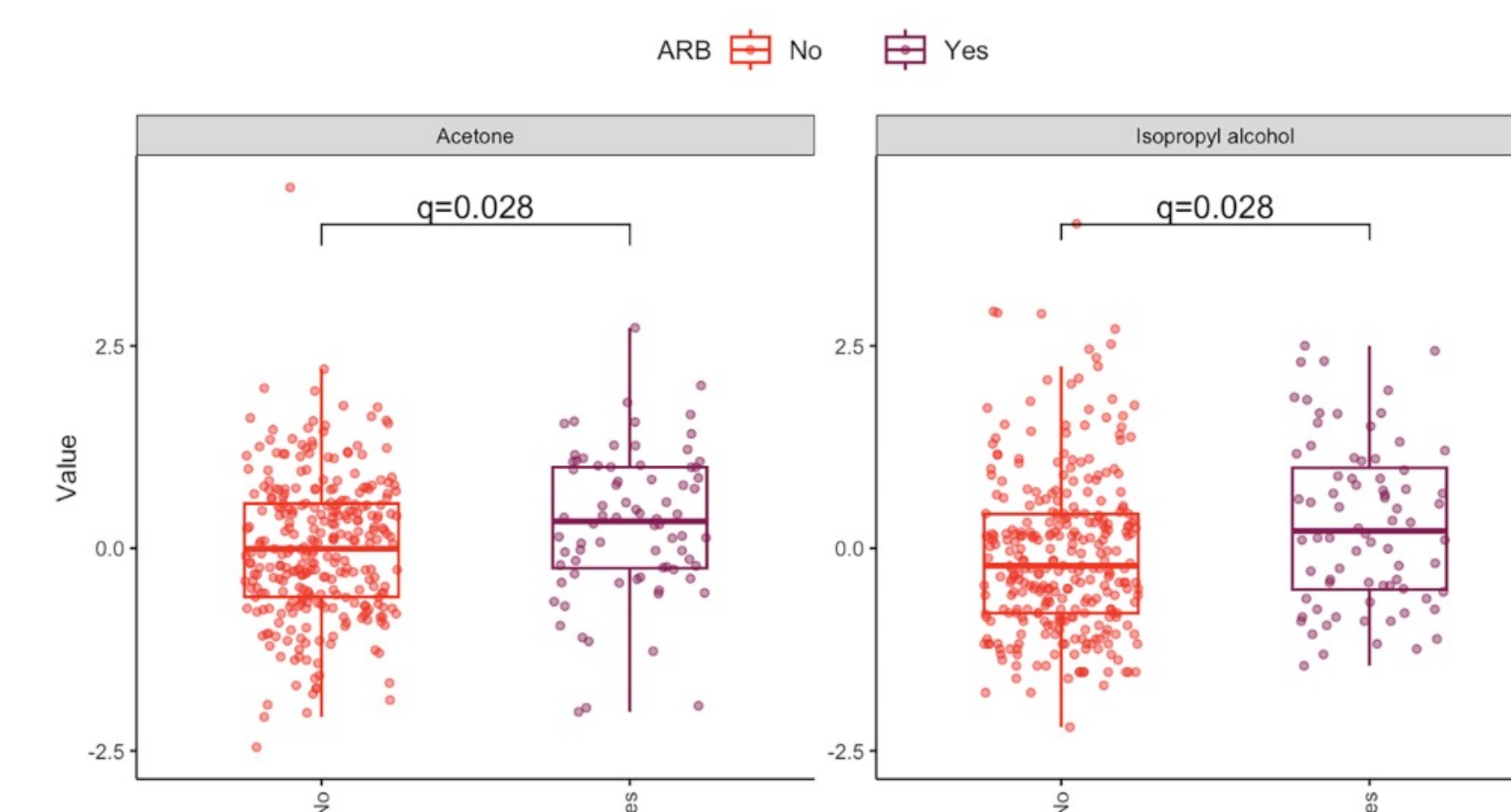


Figure 2. Distributions of statistically significant salivary metabolite changes associated with ARB usage among individuals with AD.

Conclusions

Clinical Significance

- Diagnostic Integrity: Salivary/urinary biomarkers remain stable and reliable despite antihypertensive polypharmacy.
- Viable Screening: Validates saliva and urine as low-cost, non-invasive alternatives to CSF and PET imaging.

Key Findings

- Pathological Independence: ARB-induced shifts (e.g., L urinary tryptophan, 1 salivary acetone) are distinct from neurodegenerative signatures.
- Resolving Confounders: Research successfully isolates drug-induced shifts, clearing the path for clinical metabolomic diagnostics.

Future Directions

- Comorbidities: Investigating how conditions like Type 2 Diabetes affect diagnostic stability.
- Progression Prediction: Longitudinal studies to determine if these stable markers predict the rate of MCI to AD conversion.

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