Examining Kidney Function and Obesity Influences on AD/ADRD Plasma Biomarker Associations with Amyloid Burden and Incident Dementia: the ARIC Study

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Background

- Blood-based biomarkers have emerged as promising tools for Alzheimer's disease (AD), and AD Related Dementias (ADRD) diagnosis and prognosis.
- Limited studies have examined the potential modifying effects of kidney function or obesity on AD/ADRD plasma biomarker associations with PET-measured amyloid burden or future dementia risk.

Objectives

- Examine whether kidney function and obesity measures modify the associations of AD/ADRD plasma biomarkers, namely p-tau$_{181}$, Aβ_{42}/Aβ_{40} ratio, GFAP and NfL, with concurrent PET-measured amyloid burden and incident dementia in the community-based Atherosclerosis Risk in Communities (ARIC) Study
- Evaluate whether these modifying effects differ between Black and White participants.

Methods

Study population:
- Subset of the ARIC study, a prospective cohort of adults from Washington County, MD; Forsyth, NC; Jackson, MS; & Minneapolis, MN (enrolled 1987–1989), with plasma biomarkers measured at Visit 5 (2011-2013, n=1828)
- N=1,534 participants included in the incident dementia analysis (Visit 5 to 2023)
- N=306 participants included in the cross-sectional analysis with Visit 5 amyloid PET

Amyloid burden: Measured using florbetapir PET and calculated as a weighted average global SUVR across multiple cortical regions

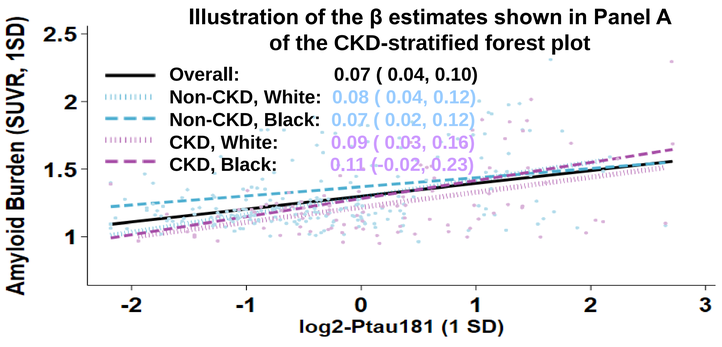
Dementia: Ascertained through 2023 using in-person evaluations, informant interviews, and hospital and death records.

Plasma biomarkers: Measured using Quanterix Simoa® assays

Kidney function: eGFR: calculated using the 2021 CKD-EPI creatinine–cystatin C combined equation; Chronic kidney disease (CKD): eGFR < 60 ml/min/1.73m^2

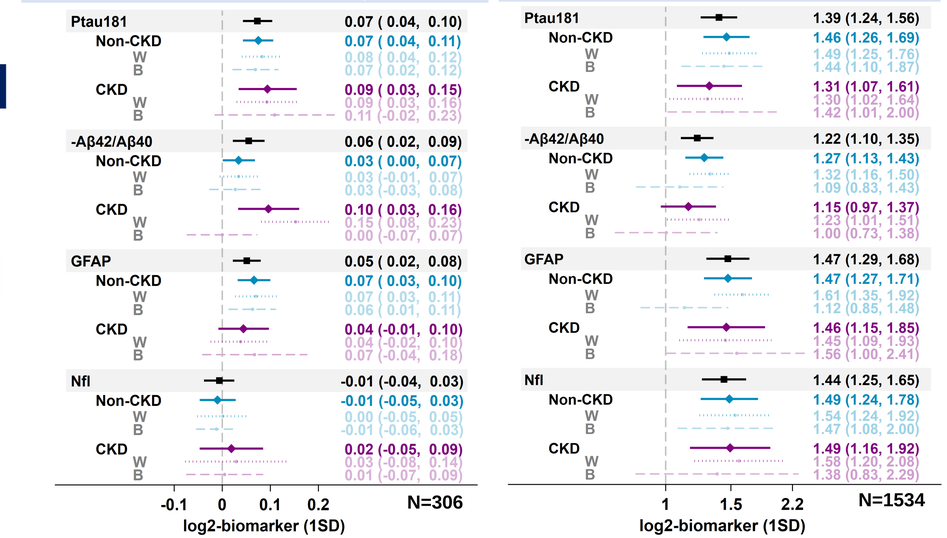
Obesity: BMI ≥30 kg/m^2

Statistical analysis
- Linear regression models examined associations between plasma AD/ADRD biomarkers and amyloid burden, while Cox models examined associations with incident dementia; interaction terms tested effect modification by kidney function, obesity, and race.
- Adjusted for age, sex, education, APOE ε4 status, Area Deprivation Index, smoking status, BMI (excluded for obesity analyses), hypertension, coronary heart disease, diabetes, and total cholesterol.
- Inverse probability weights were applied to all analyses to ensure that weighted estimates reflect associations in the eligible Visit 5 population.



Results

Forest Plots of Visit 5 Plasma Biomarkers Associations with (A) Concurrent Amyloid Burden and (B) Incident Dementia, Overall and by CKD Status and Race



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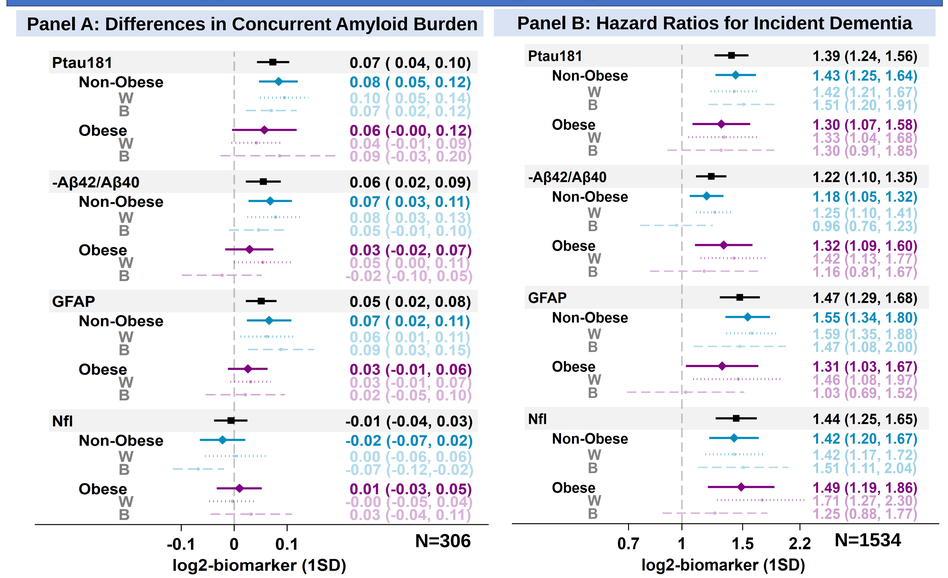
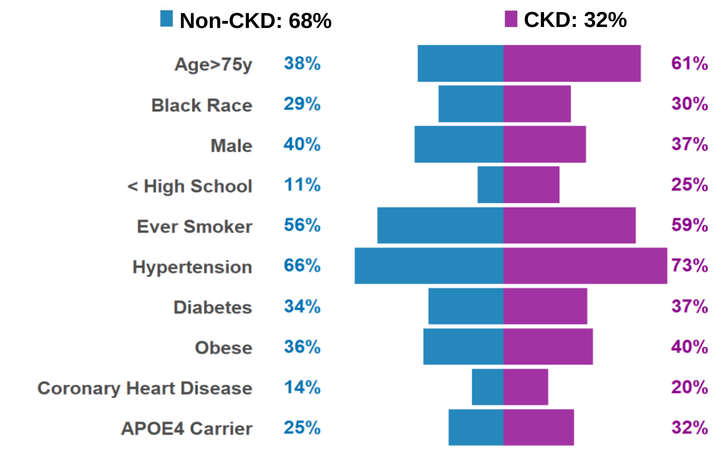


The standardized log$_2$(Aβ42/Aβ40) was multiplied by -1 to align β estimate direction across biomarkers. Panel A indicates the SD difference in amyloid burden per 1-SD increase in the log2-biomarker. Panel B indicates the relative hazard of incident dementia per 1-SD increase in the log2-biomarker. For each biomarker, the first row shows the overall estimate; subsequent rows show estimates by CKD/obesity status and race, with all subgroup estimates obtained using post-estimation marginal standardization. Abbreviations: W: White participants; B, Black participants.

Weighted Characteristics of Amyloid PET Analysis Sample by CKD at Visit 5 (unweighted N=306; mean age: 75 ± 6 years)



Discussion

- Higher p-tau181 and GFAP, and lower Aβ42/Aβ40 were associated with elevated amyloid burden and dementia risk, whereas higher NfL was associated only with increased dementia risk. These associations were generally consistent across CKD/obesity strata and continuous eGFR and BMI.
- Limited race-specific differences were observed, and were inconsistent across biomarkers, warranting further investigation.
- Although CKD and obesity were associated with biomarker concentrations, they were not associated with amyloid-PET burden or dementia risk in this study.
- Our findings suggest that kidney function and obesity may influence absolute biomarker levels, but do not substantially alter AD/ADRD biomarker associations with amyloid burden or dementia risk.
- Future studies should validate these findings in larger populations with greater representation of advanced CKD and in younger populations.

Strengths:
- Rigorous dementia case ascertainment;
- Inclusion of Black and White participants from a community-based cohort with long-term follow-up.
- Comprehensive information on potential confounders

Limitations:
- The amyloid-PET subsample was modest in size, potentially limiting the statistical power and precision for detecting interaction effects
- Race and study site are highly confounded in ARIC
- No participants had an eGFR < 30 ml/min/1.73m^2

Acknowledgements

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