

Blood Markers of the Renin-Angiotensin System and Brain Volumes in a Longitudinal Study



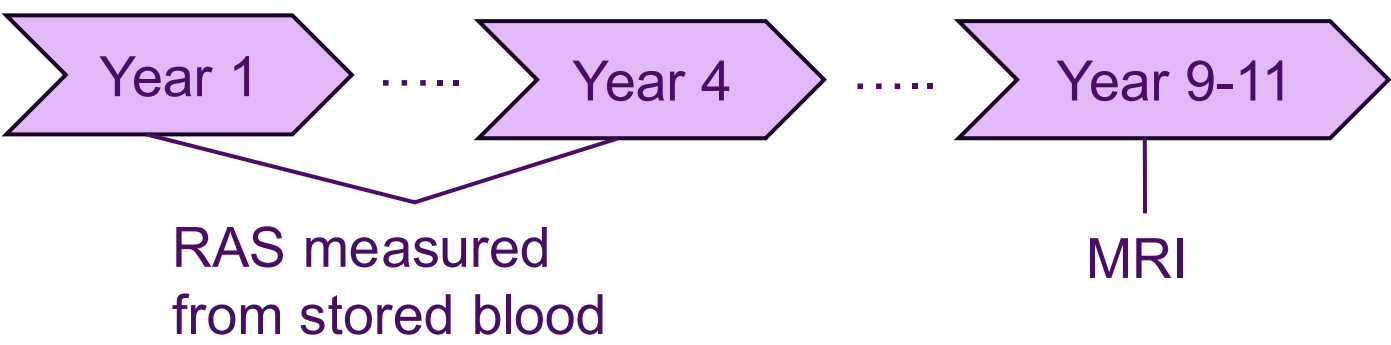
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INTRODUCTION

- 2024 Lancet Commission on dementia reported hypertension as one of the risk factors
- Mechanisms linking vascular dysfunction to neurodegeneration are still not fully understood
- Dysregulation of the vascular system, specifically renin-angiotensin system (RAS), has been proposed as a potential modifier of Alzheimer’s disease (AD) pathogenesis, but longitudinal human data are limited.

”We examined whether circulating renin-angiotensin system (RAS) biomarkers measured in mid-life are associated with late-life MRI brain volumes implicated in dementia pathogenesis, and whether these relationships are modified by amyloid-β and vascular endothelial growth factor (VEGF).”



METHODS

Data	Community-dwelling, cognitively intact patients with overweight/obesity and type 2 diabetes in LOOK AHEAD study
Participants	71 adults (≥40 years old at baseline); Individuals taking RAS-affecting medications were excluded
Predictors	Plasma angiotensin-converting-enzyme-1 (ACE1), ACE2, angiotensin II (ANGII), and angiotensin 1-7 (ANG1-7) were measured at year 1 and 4
Outcomes	T1-weighted brain MRI images were acquired at 10-12 years from baseline
Covariables	Age, Biologic Sex, Race, Education, Intracranial Volume, Blood Pressure (YR1, YR4), Creatinine (YR1, YR4), MCI/Dementia status. Randomization Arm, History of Cardiovascular and Neurologic comorbidities, Apolipoprotein ε4 (APOE ε4)
Interaction variables	• Amyloid β (Aβ42/40) • Vascular Endothelial Growth Factor (VEGF)
Statistical analyses	Multivariable linear regression in R

RESULTS

Variables	N (%) or Mean (SD)	Variables	N (%) or Mean (SD)
Randomization Arm		Race/Ethnicity	
Lifestyle Intervention	38 (53%)	API	1 (1%)
Diabetes Support and Education	33 (46%)	Non-Hisp Black	15 (21%)
		Non-Hisp White	55 (77%)
Age (10-yr bands, yr)	58.4 (6.89)	Education	
40-49	10 (13%)	Bachelor’s or more	30 (42%)
50-59	34 (45%)	Some College	20 (28%)
60-69	21 (33%)	HS or less	14 (19%)
70-79	6 (9%)	(Missing)	3 (4%)
Sex		APOE4 allele carrier	12 (17%)
Female	57 (80%)	Plasma Aβ42 (units)	4.32 (1.15)
Male	14 (20%)		

Fig 2. RAS biomarker x Amyloid

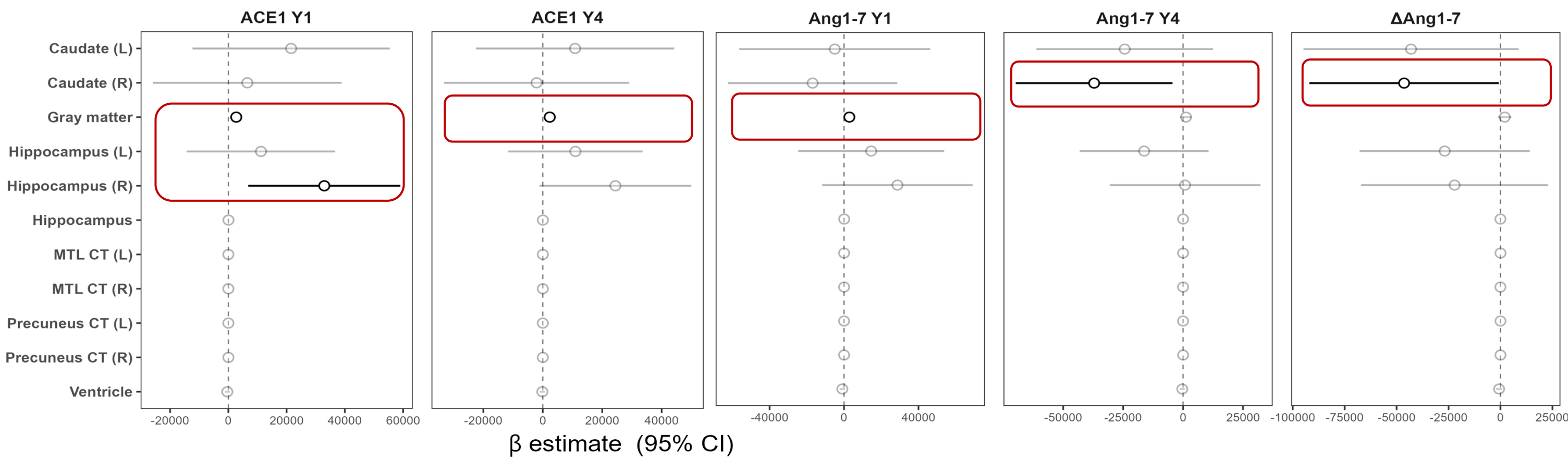
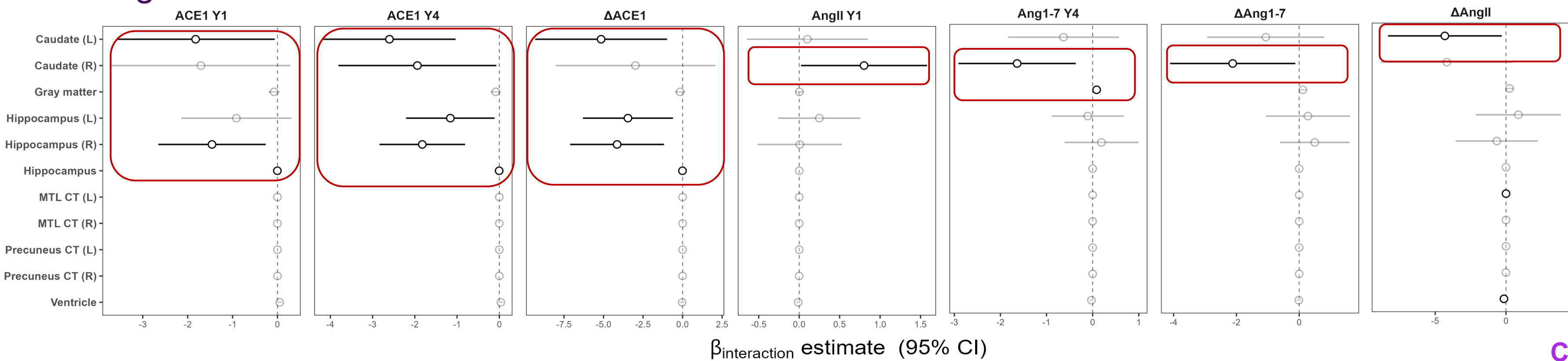


Fig 3. RAS biomarker x VEGF



CONCLUSIONS

- Individuals with type 2 diabetes and obesity are at increased risk for AD/ADRD.
- Higher ACE-1 levels were associated with smaller hippocampal and MTL volumes years later.
- Amyloid and VEGF modified several RAS & MRI associations, supporting both neurodegenerative and vascular mechanisms.
- These findings support the RAS as a potential target for early intervention in populations at high risk for AD/ADRD.

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