

Causal inference analysis of the effect of β -amyloid and tau proteins on dementia risk: A Mendelian randomization analysis

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Jacob Apibilla Ayembilla¹, Rachael Osemudiamen Osagie², Adeyemi Timothy Akinade³, Oumar Sako⁴, Oluwafunmbi Ebenezer Ogunmiluyi⁵, Olaitan I. Awe⁶.

¹Department of Science Laboratory Technology, Accra Technical University, Accra, Ghana, ²Faculty of Dental Medicine and Oral Health Sciences, McGill University, Montreal, QC, Canada, ³Department of Genetics and Biochemistry, Clemson University, South Carolina, SC, USA, ⁴African Centre of Excellence in Bioinformatics and Data Intensive Science (ACE-B), University of Sciences Techniques and Technologies of Bamako, Bamako, Mali, ⁵Department of Physiology, University of Medical Sciences, Ondo, Ondo State, Nigeria, ⁶Department of Computer Science, University of Ibadan,, Ibadan, Oyo State, Nigeria.

Highlight

- CSF phosphorylated tau (p-tau) appears to play a causal role in Alzheimer's disease and vascular dementia.
- Amyloid- β and tau exhibit distinct effects across dementia subtypes.
- Biomarker-specific pathways may improve dementia risk stratification and precision medicine.

INTRODUCTION

● Dementia is a growing global health challenge

- Dementia affects more than 55 million people worldwide, with numbers expected to increase substantially due to population ageing.
- Alzheimer's disease (AD), frontotemporal dementia (FTD), and vascular dementia (VaD) are among the most common dementia subtypes.
- Effective disease-modifying therapies remain limited, highlighting the need to identify causal biological mechanisms.

● What is missing in current knowledge

- Amyloid- β (A β), tau, and phosphorylated tau (p-tau) are established biomarkers of neurodegeneration and are widely used in diagnosis and research.
- However, it remains unclear whether these biomarkers are causally involved in dementia pathogenesis or are simply consequences of disease progression.
- Most evidence comes from observational studies, which are vulnerable to confounding and reverse causation.
- The causal effects of CSF and plasma A β , tau, and p-tau across different dementia subtypes remain poorly understood.

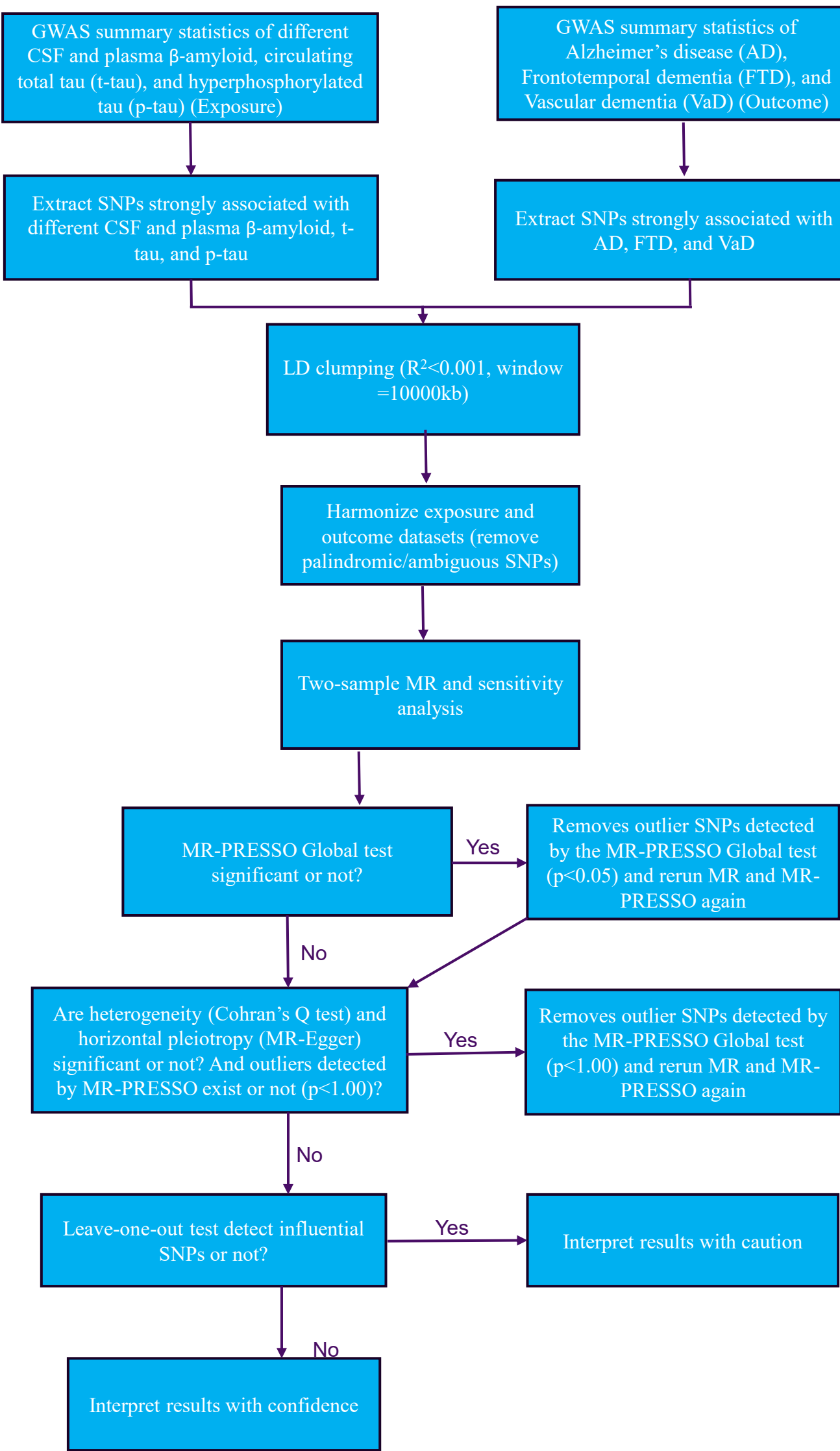
🔗 Why this study is important

- Uses Mendelian randomization (MR) to strengthen causal inference between biomarkers and dementia risk.
- Examines both CSF and plasma biomarkers, providing insights into central and peripheral pathological processes.
- Investigates causal effects across multiple dementia subtypes (AD, FTD, and VaD) rather than focusing on AD alone.
- Identifies biomarker-specific pathways that may improve risk stratification, early detection, and therapeutic target prioritization.
- Provides evidence for precision medicine approaches in dementia prevention and treatment

Aim

To determine whether genetically predicted amyloid- β , tau, and phosphorylated tau levels causally influence the risk of AD, FTD, and VaD.

METHODS



RESULTS

Table 1: MR results of the causal effects between plasma and cerebrospinal fluid amyloid species and dementia

Exposure	Outcome	Method	n SNP	B	se	OR (95%CI)	pval
CSF A β_{1-42} levels	FTD	Inverse variance weighted	92	0.158	0.137	1.17(0.90-1.53)	0.248
CSF A β_{1-42} levels	FTD	MR Egger	92	0.221	0.237	1.25(0.79-1.98)	0.352
CSF A β_{1-42} levels	FTD	Weighted median	92	0.455	0.223	1.58(1.02-2.44)	0.041
CSF A β_{1-42} levels	FTD	Weighted mode	92	0.45	0.217	1.57(1.03-2.40)	0.041
CSF A β_{1-42} levels	FTD	Simple mode	92	0.281	0.571	1.32(0.43-4.05)	0.624
CSF A β_{1-42} levels in <i>APOE4</i> carriers	FTD	Inverse variance weighted	62	0.189	0.116	1.21(0.96-1.52)	0.103
CSF A β_{1-42} levels in <i>APOE4</i> carriers	FTD	MR Egger	62	0.413	0.254	1.51(0.92-2.49)	0.109
CSF A β_{1-42} levels in <i>APOE4</i> carriers	FTD	Weighted median	62	0.215	0.174	1.24(0.88-1.74)	0.217
CSF A β_{1-42} levels in <i>APOE4</i> carriers	FTD	Weighted mode	62	0.644	0.272	1.90(1.12-3.24)	0.021
CSF A β_{1-42} levels in <i>APOE4</i> carriers	FTD	Simple mode	62	-0.046	0.411	0.96(0.43-2.14)	0.912
Plasma A β_{1-42}	FTD	Inverse variance weighted	68	-0.184	0.085	0.83(0.70-0.98)	0.03
Plasma A β_{1-42}	FTD	MR Egger	68	-0.184	0.114	0.83(0.67-1.04)	0.111
Plasma A β_{1-42}	FTD	Weighted median	68	-0.155	0.133	0.86(0.66-1.11)	0.243
Plasma A β_{1-42}	FTD	Weighted mode	68	-0.132	0.106	0.88(0.71-1.08)	0.218
Plasma A β_{1-42}	FTD	Simple mode	68	-0.653	0.292	0.52(0.29-0.92)	0.029

CSF - Cerebrospinal fluid, FTD - Frontotemporal Dementia, A β_{1-42} - Beta amyloid 42

Table 2: MR results of the causal effects between cerebrospinal fluid p-tau species and dementia

Exposure	Outcome	Method	n SNP	B	Se	OR(95%CI)	pval
CSF p-tau levels in abnormal amyloid levels	AD	Inverse variance weighted	33	0.067	0.028	1.07(1.01-1.13)	0.016
CSF p-tau levels in abnormal amyloid levels	AD	MR Egger	33	0.14	0.065	1.15(1.01-1.31)	0.039
CSF p-tau levels in abnormal amyloid levels	AD	Weighted median	33	0.072	0.039	1.07(0.99-1.16)	0.069
CSF p-tau levels in abnormal amyloid levels	AD	Weighted mode	33	0.169	0.083	1.18(1.01-1.39)	0.049
CSF p-tau levels in abnormal amyloid levels	AD	Simple mode	33	0.171	0.089	1.19(1.00-1.41)	0.062
CSF p-tau levels in <i>APOE4</i> non-carriers	AD	Inverse variance weighted	31	0.074	0.03	1.08(1.02-1.14)	0.014
CSF p-tau levels in <i>APOE4</i> non-carriers	AD	MR Egger	31	-0.037	0.083	0.96(0.82-1.13)	0.66
CSF p-tau levels in <i>APOE4</i> non-carriers	AD	Weighted median	31	0.099	0.041	1.10(1.01-1.20)	0.017
CSF p-tau levels in <i>APOE4</i> non-carriers	AD	Weighted mode	31	0.182	0.075	1.20(1.04-1.39)	0.022
CSF p-tau levels in <i>APOE4</i> non-carriers	AD	Simple mode	31	0.174	0.093	1.19(0.99-1.43)	0.071
CSF p-tau levels	VaD	Inverse variance weighted	80	0.107	0.04	1.11(1.03-1.20)	0.008
CSF p-tau levels	VaD	MR Egger	80	0.131	0.098	1.14(0.94-1.38)	0.187
CSF p-tau levels	VaD	Weighted median	80	0.025	0.062	1.03(0.91-1.16)	0.683
CSF p-tau levels	VaD	Weighted mode	80	-0.01	0.115	0.99(0.79-1.24)	0.929
CSF p-tau levels	VaD	Simple mode	80	-0.071	0.142	0.93(0.71-1.23)	0.621

CSF - Cerebrospinal fluid, p-tau - hyperphosphorylated tau, AD - Alzheimer's disease, VaD - Vascular dementia

Table 3: MR results of the causal effects between plasma and cerebrospinal fluid amyloid species and cerebrospinal fluid p-tau species

Exposure	Outcome	Method	n SNP	B	Se	OR (95%CI)	pval
Plasma A β_{1-42}	Circulating total tau	Inverse variance weighted	41	0.031	0.011	1.03(1.01-1.05)	0.004
Plasma A β_{1-42}	Circulating total tau	MR Egger	41	0.027	0.018	1.03(0.99-1.06)	0.13
Plasma A β_{1-42}	Circulating total tau	Weighted median	41	0.025	0.019	1.03(0.99-1.06)	0.182
Plasma A β_{1-42}	Circulating total tau	Weighted mode	41	0.025	0.017	1.03(0.99-1.06)	0.152
Plasma A β_{1-42}	Circulating total tau	Simple mode	41	0.087	0.037	1.09(1.02-1.17)	0.023
Plasma A β_{1-42}	CSF p-tau levels in normal amyloid levels	Inverse variance weighted	64	0.005	0.028	1.00(0.95-1.06)	0.868
Plasma A β_{1-42}	CSF p-tau levels in normal amyloid levels	MR Egger	64	0.002	0.039	1.00(0.92-1.08)	0.951
Plasma A β_{1-42}	CSF p-tau levels in normal amyloid levels	Weighted median	64	0.042	0.042	1.04(0.95-1.08)	0.325
Plasma A β_{1-42}	CSF p-tau levels in normal amyloid levels	Weighted mode	64	0.03	0.038	1.03(0.95-1.11)	0.433
Plasma A β_{1-42}	CSF p-tau levels in normal amyloid levels	Simple mode	64	-0.241	0.088	0.79(0.66-0.95)	0.008
CSF A β_{1-42} levels in normal amyloid levels	CSF p-tau levels in abnormal amyloid levels	Inverse variance weighted	78	-0.019	0.023	0.98(0.94-1.03)	0.397
CSF A β_{1-42} levels in normal amyloid levels	CSF p-tau levels in abnormal amyloid levels	MR Egger	78	-0.041	0.049	0.96(0.87-1.06)	0.407
CSF A β_{1-42} levels in normal amyloid levels	CSF p-tau levels in abnormal amyloid levels	Weighted median	78	-0.036	0.037	0.97(0.90-1.04)	0.326
CSF A β_{1-42} levels in normal amyloid levels	CSF p-tau levels in abnormal amyloid levels	Weighted mode	78	-0.118	0.047	0.89(0.81-0.98)	0.015
CSF A β_{1-42} levels in normal amyloid levels	CSF p-tau levels in abnormal amyloid levels	Simple mode	78	-0.046	0.09	0.96(0.80-1.15)	0.613

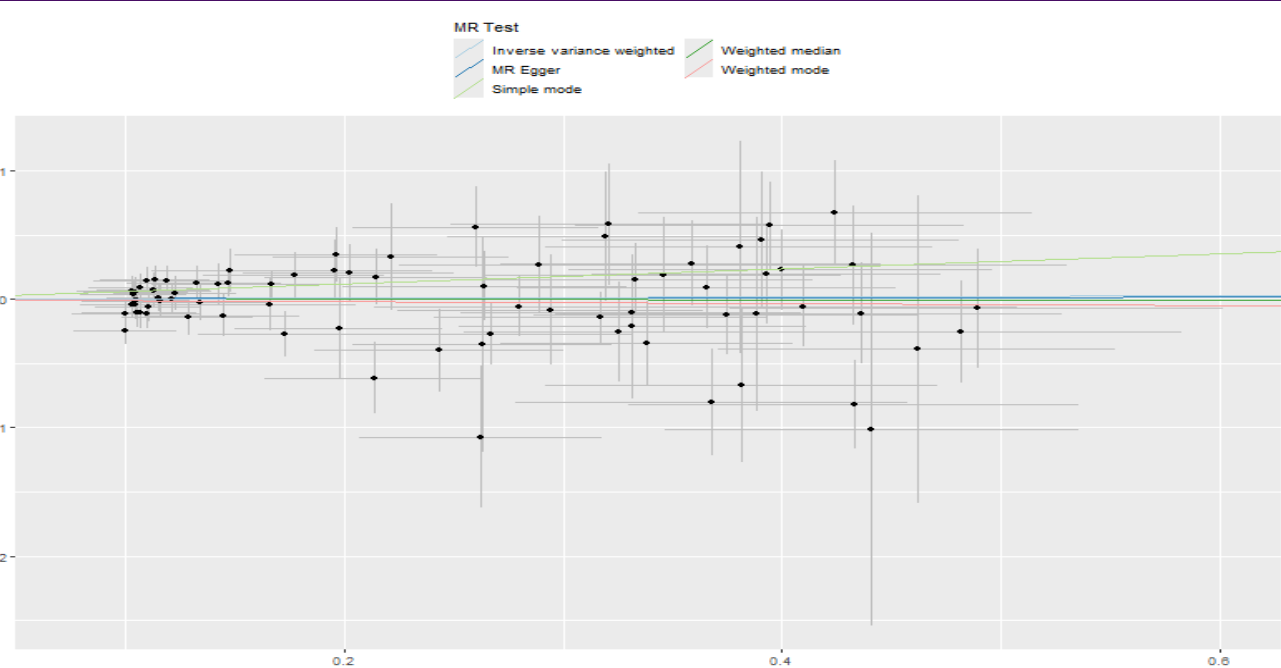


Figure 1: Scatter plot

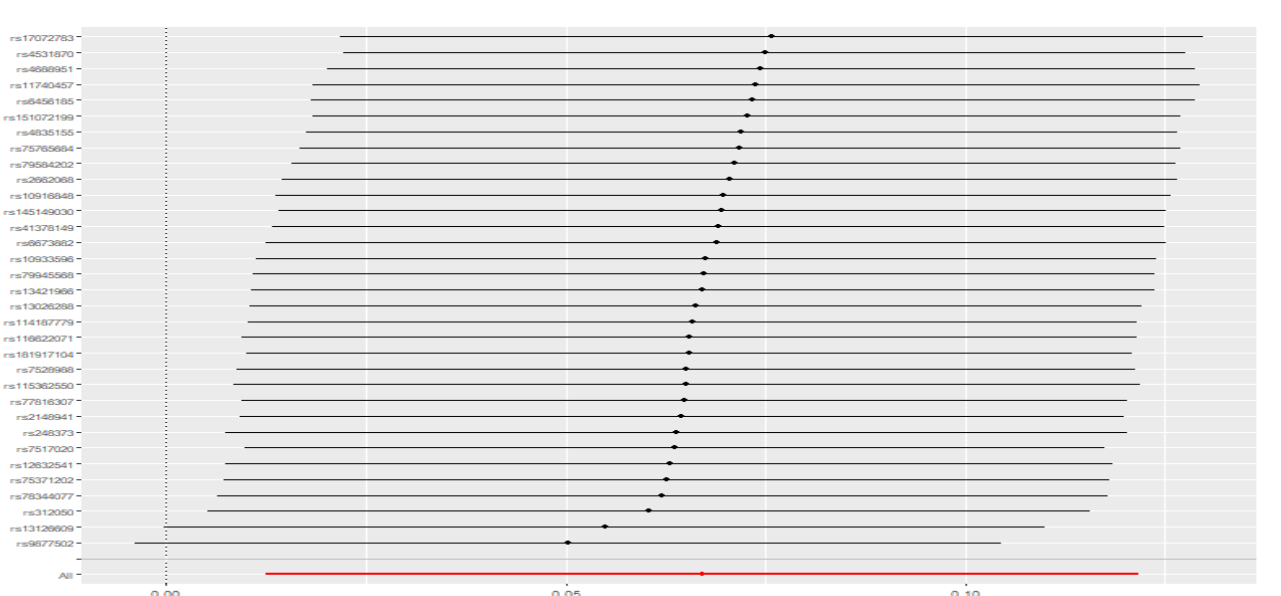


Figure 2: Forest plot

CONCLUSIONS

- CSF phosphorylated tau (p-tau) shows a likely causal role in Alzheimer's disease and vascular dementia, supporting tau pathology as a key disease driver.
- Amyloid- β and tau biomarkers demonstrate differential causal effects across dementia subtypes, indicating distinct underlying disease mechanisms for AD, FTD, and VaD.
- Elevated plasma A β 42 may be protective against FTD, while CSF amyloid and tau effects vary by context and model.
- Findings support the use of genetically informed evidence (Mendelian randomization) to clarify biomarker causality beyond observational associations.
- Results highlight the potential for biomarker-guided risk stratification and targeted therapeutic strategies across dementia subtypes.

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CONTACT



Corresponding:

Jacob A. Ayembilla

Accra Technical University, Ghana.

ayembilla2022@gmail.com

