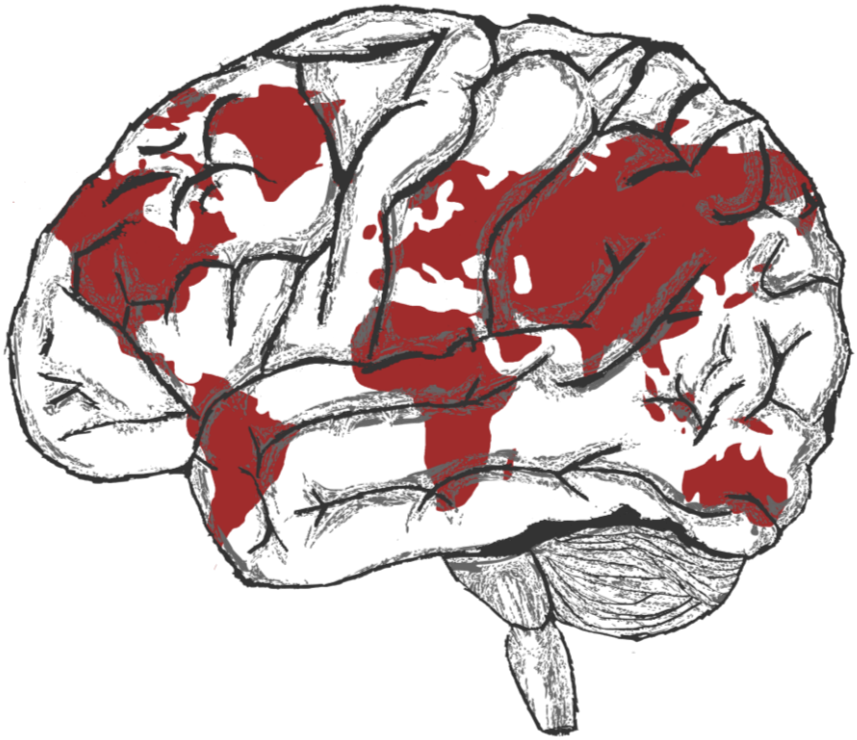
UNIVERSITY OF COPENHAGEN
FACULTY OF HEALTH AND MEDICAL SCIENCES

Diagnostic assessment of culturally diverse memory clinic patients

Clinical utility of blood biomarkers and cross-cultural cognitive tests



PhD thesis

Daniel Kjaergaard

DANISH DEMENTIA RESEARCH CENTRE

Rigshospitalet
Copenhagen University Hospital

This thesis has been submitted to the graduate School of Health and Medical Sciences, University of Copenhagen on the 30th of April 2026

Diagnostic assessment of culturally diverse memory clinic patients

Clinical utility of blood biomarkers and cross-cultural cognitive tests

PhD thesis

Daniel Kjaergaard

Danish Dementia Research Centre

Department of Neurology

Copenhagen University Hospital – Rigshospitalet

"A fair test does not advantage or disadvantage some individuals because of characteristics irrelevant to the intended construct"

- Standards for Educational and Psychological Testing, APA 2014

PhD thesis

Diagnostic assessment of culturally diverse memory clinic patients

Clinical utility of blood biomarkers and cross-cultural cognitive tests

Author	Daniel Kjaergaard, MSc, Danish Dementia Research Centre, Department of Neurology, Copenhagen University Hospital – Rigshospitalet, Copenhagen, Denmark
Supervisors	
Principal supervisor	Professor Gunhild Waldemar, MD, DMSc, Danish Dementia Research Centre, Department of Neurology, Copenhagen University Hospital – Rigshospitalet, and Department of Clinical Medicine, University of Copenhagen, Copenhagen, Denmark
Primary co-supervisor	Associate Professor T. Rune Nielsen, MSc, PhD Danish Dementia Research Centre, Department of Neurology, Copenhagen University Hospital – Rigshospitalet, and Department of Psychology, University of Copenhagen, Copenhagen, Denmark
Co-supervisor	Anja Hviid Simonsen, MSc, PhD, Danish Dementia Research Centre, Department of Neurology, Copenhagen University Hospital – Rigshospitalet, Copenhagen, Denmark

This thesis has been submitted to the Graduate School of Health and Medical Sciences, University of Copenhagen on the 30th of April 2026.

Assessment committee

Chairperson	Associate Professor Peter Høgh, MD, PhD, Department of Clinical Medicine, University of Copenhagen, and Regional Dementia Research Centre, Department of Neurology, Zealand University Hospital, Roskilde, Denmark
Assessor	Professor Silke Kern, MD, PhD, Institute of Neuroscience and Physiology, Sahlgrenska Academy, University of Göthenburg, Göthenburg, Sweden
Assessor	Professor Jonathan Evans, MSc, PhD, School of Health and Wellbeing, University of Glasgow, Glasgow, United Kingdom

Preface and acknowledgements

This PhD thesis was carried out at the Danish Dementia Research Centre (DDRC), Copenhagen University Hospital – Rigshospitalet in Copenhagen, Denmark. I am sincerely grateful of our consortium partners in *Early and accurate diagnostic and prognostic markers for Alzheimer's disease (EDAP-AD)*, supported financially by the Innovation Fund Denmark (grant number 1099-00022B), under the frame of ERA PerMed (reference number ERAPERMED2021-184). This collaboration included participating institutions at Lund University (Sweden), Fundació Institut Hospital del Mar d'Investigacions Mediques (Spain), Toulouse University Hospital (France), Klinikum der Universität München (Germany), and Helmholtz Zentrum München (Germany). I am also very appreciative of the funding from the Danish Alzheimer Association, Beckett Fonden, Aase and Ejnar Danielsens Fond, and Frimodt-Heineke Fonden, which made it possible to explore new biomarkers in the BlooDiv cohort as part of ongoing studies.

These past three years have been inspiring, motivating, and life-changing. I am deeply thankful for the opportunity to have worked in a research environment that fosters confidence and curiosity, while maintaining a consistent focus on improving patient care.

To Gunhild Waldemar, I cannot begin to express my profound appreciation for being welcomed into the research team and into the house that you built. Your approach to research is something that has truly inspired me, particularly your unwavering focus on work that makes a difference in the lives of our patients and caregivers. Despite having the busiest schedule I have ever witnessed, you always took the time to guide me. This is something I cannot thank you enough for. Thank you for teaching me the *frikadelle* recipe, keeping a somewhat distracted mind on track. I will carry your lessons with me in all my future endeavors and remind myself – what would Gunhild say to this?

To Rune Nielsen, I offer my heartfelt thanks for dedicating so much time and energy to training me in every aspect that a PhD entails. I deeply appreciate you always making yourself available to any question, large or small, I have had. Your dedication to improving diagnostic conditions and promoting fairness for minoritized groups has inspired me, as it has many others. I am proud to have contributed research that stands on the shoulders of all the hard work you have done. Thank you for your kindness throughout these three years. I have always felt your involvement and your motivation to help me reach my goals.

To Anja Hviid Simonsen, I feel incredibly fortunate to have had such a warm, engaged, and insightful supervisor. Throughout the PhD process, I always felt understood and respected, whether I was navigating ethical approval applications or managing the inevitable ups and downs that a PhD entails. You continue to impress me with your ability to juggle countless responsibilities, while still having the energy to pursue new ideas together. I entered the biomarker field knowing next to nothing, and thanks to you, I feel

confident and enthusiastic about our work. Your authenticity, down-to-earthiness, and the genuine care for your students are deeply inspirational. Thank you.

Thank you to my collaborators and co-authors from Lund University for your invaluable guidance and contributions to the BlooDiv studies. A special thanks to Erik Stomrud and Oskar Hansson for your time and effort with patient inclusion and your hospitality in hosting me for a few months, and to Shorena Janelidze and Divya Bali for your immense effort in plasma analyses. Thank you to all my co-authors from the DDRC, with whom I feel fortunate to have worked, each contributing unique expertise to our shared work.

I am also deeply grateful to my co-authors and collaborators who shared their data and expertise on the Multicultural Cognitive Examination (MCE), contributing to what became the largest cohort to date on the MCE. I am especially grateful to Sanne Franzen and Alfonso Delgado-Álvarez, with whom I have found considerable support throughout this journey. The European Consortium on Cross-Cultural Neuropsychology (ECCroN) has been an invaluable network for me to discuss ideas and receive guidance.

I had the pleasure of spending a four-month research stay with Marco Canevelli, Marco Toccaceli Blasi, Simona Buscarnera, and Filippo Nuti at Sapienza University in Rome – thank you for your exceptional hospitality and kindness. Rome has since felt like a second home because of you. I am thankful for the financial support for this research stay from the University of Copenhagen and Knud Højgaards Fond.

My time working on the PhD has been especially memorable thanks to my wonderful colleagues at the DDRC. I am so happy to have met and learned from each one of you. I am especially grateful to the senior researchers who always had their doors open for advice, and to the younger researchers whose dedication and genuine curiosity were contagious. In particular, I want to thank Oskar Hoffmann McWilliam for getting me out of the office to work out, and Janet Janbek for being a great friend and sparring partner on our many walks. Thanks to the social committee for younger researchers, Cecilie Madsen and Emma Kjær Pedersen, for fostering a great social environment.

Finally, and most importantly, I thank my wonderful wife. You have listened patiently to endless hours of statistics and science talk and made me believe that I could succeed. Thank you for being my anchor, without you, I would not have reached this milestone. I also owe the deepest gratitude to my friends and family for helping me remember there is a world outside and for bearing with me throughout these three years.

List of publications

This thesis is based on five original studies:

Study 1 **Kjaergaard, D**., Delgado-Álvarez, A., Waldemar, G., Beinhoff, U., Bekkhus-Wetterberg, P., Franzen, S., Illingworth, C., Laks, J., Lozano-Ruiz, Á., Lueschow, A., Matias-Guiu, J. A., Pomati, S., Segers, K., Torkpoor, R., Wagle, J., & Nielsen, T. R. (2026). Diagnostic accuracy of the Multicultural Cognitive Examination (MCE) for detection of MCI and dementia in a diverse international cohort. *The Clinical Neuropsychologist*. 1-16. Advance online publication. https://doi.org/10.1080/13854046.2026.2652032 [1]

Study 2 **Kjaergaard, D**., Simonsen, A. H., Waldemar, G., & Nielsen, T. R. (2025). Ethnic and racial influences on blood biomarkers for Alzheimer's disease: A systematic review. *Journal of Alzheimer's disease: JAD*, *103*(1), 81–91. https://doi.org/10.1177/13872877241299047 [2]

Study 3 **Kjaergaard, D**., Nielsen, T. R., Stomrud, E., Palmqvist, S., Bali, D., Dolado, A. O., Janelidze, S., Hansson, O., Waldemar, G., & Simonsen, A. H. (2025). Influence of ethnicity on the diagnostic accuracy of plasma p-tau217 for the identification of Alzheimer's disease: A consecutive mixed memory clinic cohort study. *Alzheimer's & dementia : the journal of the Alzheimer's Association*, *21*(6), e70315. https://doi.org/10.1002/alz.70315 [3]

Study 4 **Kjaergaard, D**., Simonsen, A. H., Stomrud, E., Bali, D., Janelidze, S., Hansson, O., Waldemar, G., & Nielsen, T. R. (2025). Combining plasma p-tau217 and cross-cultural cognitive tests to identify Alzheimer's Disease in an ethnically diverse mixed memory clinic cohort. *Journal of Neurological Sciences, 478, 123739, https://doi.org/10.1016/j.jns.2025.123739* [4]

Study 5 **Kjaergaard, D**., Nielsen, T. R., Stomrud, E., Bali, D., Clemmensen, F. K., Frederiksen, K. S., Gleerup, H. S. C., Hasselbalch, S. G., Janelidze, S., Hansson, O., Waldemar, G., & Simonsen, A. H. Plasma phosphorylated tau217 discordance in an ethnically diverse mixed memory clinic cohort. *Under review with Journal of the Neurological Sciences (submitted 16th of March 2026).*

Abbreviations

Aβ	Amyloid beta
ACE	Addenbrooke's Cognitive Examination
AD	Alzheimer's Disease
ADAS-Cog	Alzheimer's Disease Assessment Scale – Cognitive subscale
ADL	Activities of Daily Living
ALS	Amyotrophic Lateral Sclerosis
ALT	Alanine aminotransferase
APP	Amyloid Precusor Protein
AUC	Area Under the Receiver Operating Characteristics Curve
BMI	Body Mass Index
CCD	Cross-Cultural Dementia Screening
CNTB	European Cross-Cultural Neuropsychological Test Battery
CRT	Clock Reading Test
CSF	Cerebrospinal Fluid
CT	Computed Tomography
DLB	Dementia with Lewy Bodies
DSM	Diagnostic and Statistical Manual of Mental Disorders
ECL	Electrochemiluminescence
ECCroN	European Consortium on Cross-Cultural Neuropsychology
EDAP-AD	Early and Accuracy Diagnostic and Prognostic Markers for Alzheimer's Disease
EDTA	Ethylenediaminetetraacetic Acid
eGFR	Estimated Glomerular Filtration Rate
ELISA	Enzyme-Linked Immunosorbent Assay
FDG	Fluorodeoxyglucose
FDR	False Discovery Rate
GFAP	Glial Fibrillary Acidic Protein
HABS-HD	Health and aging brain study – Health disparities
HbA1c	Hemoglobin A1c
HC	Healthy Control
IWG	International Working Group
LATE	Limbic-Predominant Age-related TDP-43 Encephalopathy

MAPT	Microtubule associated protein tau
MCE	Multicultural Cognitive Examination
MCI	Mild Cognitive Examination
MMSE	Mini-Mental State Examination
MoCA	Montreal Cognitive Assessment
MR	Magnetic Resonance
MSD	Meso Scale Discovery
NfL	Neurofilament Light
NIA-AA	National Institute of Aging – Alzheimer's Association
NPH	Normal Pressure Hydrocephalus
PET	Position Emission Tomography
PiB	Pittsburgh Compound B
PICOS	Population, Intervention, Comparison, Outcome, Study design
PPA	Primary Progressive Aphasia
P-tau	Phosphorylated Tau
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-analyses
ROC	Receiver Operating Characteristic
RPT	Recall of Pictures Test
RUDAS	Rowland Universal Dementia Assessment Scale
SCD	Subjective Cognitive Decline
SD	Semantic Dementia
SFT	Supermarket Fluency Test
Simoa	Single Molecule Array
TDP-43	Transactive Response DNA-binding Protein 43 kDa
TSH	Thyroid Stimulating Hormone
TULIPA	Towards a Universal Language: Intervention and Psychodiagnostics Assessment
VaD	Vascular Dementia

English summary

Culturally, linguistically, and educationally diverse memory clinic patients encounter substantial barriers in their diagnostic evaluation and are underrepresented in most areas of research. This growing patient population is at higher risk of misdiagnosis and delayed diagnosis, with serious consequences for early intervention. One cause of this imbalance arises from most diagnostic tools being developed for homogeneous populations and may therefore be biased in patients with diverse backgrounds. As a response to this challenge, cross-cultural cognitive tests have been developed, but bias, clinical applicability, and accuracy of these are not adequately established in diverse cohorts. Similarly, blood biomarkers for Alzheimer's disease (AD) are not sufficiently examined across patients with diverse ethnic or racial backgrounds. To address this challenge, this thesis aimed to examine the influence of sociodemographic factors and medical conditions on the blood biomarker plasma phosphorylated tau217 (p-tau217) and on the cross-cultural cognitive test, Multicultural Cognitive Examination (MCE). We also investigated the diagnostic accuracy of these diagnostic tools in a memory clinic setting. Five studies were included to address this overall aim.

We found no influence of having immigrant background on the MCE, but only an effect of age and education. The MCE was accurate in identifying dementia (AUC 0.95) and Mild Cognitive Impairment (MCI) (AUC 0.84) in a large and diverse cohort. The MCE was equally accurate for identifying AD dementia as non-AD dementia. Supplementing the MCE with plasma p-tau217 significantly improved the ability to differentiate between AD and non-AD conditions.

There is a disagreement in the field regarding whether ethnicity or race affects blood biomarkers. In our cohort, we found no influence of geographic origin on plasma p-tau217 concentration or accuracy in identifying AD. We also found a strong ability of plasma p-tau217 to identify AD and amyloid pathology (AUC > 0.89). However, we discovered that 13.6% of the cohort had positive p-tau217 results despite negative cerebrospinal fluid (CSF) and amyloid-β positron emission tomography (Aβ-PET) biomarkers, but the cause of this discordance could not be identified in our cohort.

Our results may aid in improving the diagnostic accuracy and differential diagnosis of dementia disorders for culturally, linguistically, and educationally diverse memory clinic patients and limit potential misinterpretations of blood biomarkers. I urge researchers and clinicians to include underrepresented populations in research and ensure that new tests and tools are fair for everyone. Representative diagnostic tools are essential, especially as migration rises and more people grow up in bilingual and bicultural households.

Danish summary | Dansk resumé

Kulturelt, sprogligt og uddannelsesmæssigt diverse patienter i hukommelsesklinikker møder betydelige barrierer i deres demensudredning, og samtidigt er de underrepræsenterede inden for de fleste forskningsområder. Dette medfører betydelige konsekvenser i form af højere risiko for forsinket diagnosticering samt fejldiagnosticering. En årsag til denne skævvridning er, at de fleste diagnostiske redskaber er udviklet til homogene populationer, og de kan derfor være mindre valide for patienter med andre baggrunde. Som et svar på denne udfordring, er der udviklet tværkulturelle kognitive tests, men bias, klinisk brugbarhed og præcision af disse er ikke tilstrækkeligt undersøgt. Tilsvarende er nye blodbiomarkører for Alzheimers sygdom (AD) heller ikke tilstrækkeligt undersøgt på tværs af etniske grupper. For at belyse denne problematik, søgte denne afhandling at undersøge indflydelsen af sociodemografiske faktorer og medicinske tilstande på blodbiomarkøren plasma fosforyleret tau217 (p-tau217) samt på den tværkulturelle kognitive test, Multicultural Cognitive Examination (MCE). Derudover har vi undersøgt den diagnostiske præcision af disse redskaber i en hukommelsesklinik. Fem studier indgår for at besvare dette overordnede formål.

Vi fandt ingen indflydelse af immigrationsbaggrund på MCE, men kun en effekt af alder og uddannelse. MCE var god til at identificere demens (AUC 0.95) og mild kognitiv svækkelse (AUC 0.84) i en stor alsidig kohorte. MCE var lige god til at identificere AD demens og non-AD demens. Ved at supplere MCE med plasma p-tau217 øgede den diagnostiske præcision i differentieringen mellem AD og non-AD sygdomme.

Der er uenighed i feltet om, hvorvidt etnicitet eller race påvirker blodbiomarkører. I vores kohorte var der ingen indflydelse af etnicitet på plasma p-tau217 koncentrationer eller præcision i identifikation af AD. Plasma p-tau217 var desuden nøjagtig til at identificere AD og amyloidpatologi (AUC > 0.89). Vi fandt dog, at 13.6% af kohorten var positive på plasma p-tau217, men var negative på cerebrospinalvæske (CSV) og amyloid-β positron emission tomografi (Aβ-PET) biomarkører. Vi kunne dog ikke identificere årsagen til denne diskordans.

Vores fund kan bidrage til at forbedre den diagnostiske præcision og differentialdiagnoser af demenslidelser for kulturelt, sprogligt, og uddannelsesmæssigt diverse hukommelsesklinikpatienter, samt reducere potentielle fejlfortolkninger af blodbiomarkører. Jeg opfordrer forskere og klinikere til at inkludere underrepræsenterede grupper i forskningsprojekter og sikre, at vores diagnostiske redskaber er lige præcise for alle. Repræsentative diagnostiske redskaber er essentielle, især da migrationen stiger og flere personer vokser op i flersprogede og multikulturelle hjem.

Table of contents

1. INTRODUCTION **12**

1.1. TERMINOLOGY AND CLASSIFICATION OF DIVERSITY **12**

2. BACKGROUND **14**

2.1. DEMENTIA AND MILD COGNITIVE IMPAIRMENT **14**

2.1.1. Diagnostic evaluations in the memory clinic 14

2.1.2. Epidemiology 15

2.2. DIAGNOSTIC BARRIERS **17**

2.2.1. Diagnostic barriers for patients with diverse backgrounds 17

2.2.2. Diagnostic evaluations in culturally, linguistically, and educationally diverse patients 19

2.3. ALZHEIMER'S DISEASE **22**

2.3.1. Epidemiology 22

2.3.2. Pathogenesis 23

2.3.3. Co-pathology 25

2.4. BIOMARKERS **26**

2.4.1. Currently established biomarkers 26

2.4.2. Blood biomarkers 28

2.4.3. Bias and variability 31

3. AIMS **33**

3.1. OVERALL AIM **33**

3.2. STUDY-SPECIFIC AIMS **33**

4. METHODS **34**

4.1. STUDY DESIGNS **34**

4.2. ELIGIBILITY CRITERIA **34**

4.2.1. The MCE cohort 34

4.2.2. Systematic review 36

4.2.3. The BlooDiv cohort 36

4.3. PRIMARY PREDICTORS AND OUTCOMES **38**

4.3.1. Ethnic/racial/geographic diversity 38

4.3.2. Plasma p-tau217 39

4.3.3. Multicultural Cognitive Examination (MCE) 40

4.4. STATISTICAL SOFTWARE AND STATISTICAL APPROACH **41**

4.5. ETHICS AND APPROVALS **41**

4.6. STUDY SPECIFIC METHODS **42**

4.6.1. Study 1 42

4.6.2. Study 2 42

4.6.3. Study 3 43

4.6.4. Study 4 44

4.6.5. Study 5 45

5. SUMMARY OF RESULTS **46**

5.1. STUDY 1 ..... **46**

5.2. STUDY 2 ..... **48**
5.3. STUDY 3 ..... **50**
5.4. STUDY 4 ..... **52**
5.5. STUDY 5 ..... **53**

6. DISCUSSION **55**

6.1. SUMMARY OF MAIN FINDINGS **55**
6.2. OVERCOMING DIAGNOSTIC BARRIERS FOR DIVERSE PATIENTS **56**
6.2.1. MCE vs. other cognitive tests 57
6.2.2. Language and interpreter-mediated assessment 58
6.2.3. Cultural bias 59
6.2.4. Education and age 60
6.3. ETHNICITY AND BLOOD BIOMARKERS **63**
6.3.1. Evidence for ethnicity and race influencing blood biomarkers 63
6.3.2. Evidence against ethnicity and race influencing blood biomarkers 65
6.3.3. Synthesis 66
6.4. DISCORDANT BIOMARKER PROFILES **68**
6.4.1. Medical conditions influence discordance 68
6.4.2. Findings from longitudinal studies 70
6.4.3. Plasma p-tau217 is not pathognomonic 71
6.5. METHODOLOGICAL CONSIDERATIONS **72**
6.5.1. Strengths 72
6.5.2. Limitations 73

7. CONCLUSION AND PERSPECTIVES **76**

7.1. CONCLUSIONS **76**
7.2. CLINICAL IMPLICATIONS **76**
7.3. FUTURE RESEARCH **78**

8. REFERENCES **80**

9. APPENDIX **100**

9.1. STUDY 1. ..... **102**
9.2. STUDY 2. ..... **132**
9.3. STUDY 3. ..... **152**
9.4. STUDY 4. ..... **180**
9.5. STUDY 5. ..... **194**
9.6. DATA EXTRACTION FROM ONGOING SYSTEMATIC REVIEW ON PLASMA P-TAU217 STUDIES. **212**

1. INTRODUCTION

In almost every discipline of science, there is a history of underrepresentation of huge groups of people, skewing the effects of targeted medicine and diagnostic tools. Within the cancer field, this has become abundantly clear, with women having been systematically excluded from trials, skewing diagnostic tools and treatments to the male biology, which led to delayed diagnoses and poorer outcomes [5, 6]. This underrepresentation and skewedness are also present in the dementia field in lower- and middle-income countries and for people with minority ethnic backgrounds. Most cognitive tests and novel biomarkers are disproportionally tailored to and examined in patients from Western cultures and with high education levels, leaving all other patients at higher risk of misdiagnoses, mismanagement of symptoms, and delayed treatment. As the world is becoming increasingly diverse, the need for robust and less biased diagnostic tools is an urgent priority. This thesis sheds light on the clinical utility of blood biomarkers and cross-cultural cognitive tests in underrepresented patient groups.

1.1. Terminology and classification of diversity

Throughout this thesis, I will refer to diversity, ethnicity, and race, however no agreement exists on the terminology and classification of these terms. In the literature, these terms and more are applied interchangeably. I will elaborate on the terms in the context of this thesis.

Ethnicity refers to people with shared cultural, geographical, religious, and linguistic backgrounds [7, 8]. Being from a minority ethnic group implies that the person's background is different from that of the people in the country in which they live. What is often of interest is whether the patients are culturally or linguistically diverse from the majority ethnic group. This is regularly operationalized in research by country of birth or by self-identified ethnic group. In our cohort studies, we used

country of birth, but the limitations of this categorization will be discussed. One perspective is that today cultures and languages mix more and more, implying that the binary classification of minority vs. majority ethnic groups may not be completely representative.

Race and racial groups are often distinguished based on how people look rather than where they are from (e.g., the color of their skin, eyes, and hair, and facial structure). Classification usually includes groupings directly tied with appearance such as White, Black, or directly with geographic region such as Asian.

2. BACKGROUND

2.1. Dementia and Mild Cognitive Impairment

Dementia is a debilitating syndrome characterized by cognitive impairment and loss of independence in activities of daily living (ADL) [9]. Dementia is divided into severities (mild, moderate, severe) based on the extent of cognitive impairment, ADL impairment, and the degree of self-reliance. Meanwhile, cognitively impaired patients with spared functional independence and ADL function can be characterized as Mild Cognitive Impairment (MCI) or Mild Neurocognitive Disorder [9–12]. Common for dementia and MCI is that symptoms are not caused by normal aging, but one or more underlying diseases affecting brain function [9, 12].

The causes of dementia and MCI are multifactorial and include different neurodegenerative diseases, vascular disease, and other causes such as those related to metabolic, infectious, and toxic factors. Some of the most common etiologies underlying dementia and MCI are Alzheimer's Disease (AD), Vascular Dementia (VaD), Dementia with Lewy Bodies (DLB), and Frontotemporal Lobar Degeneration [13]. These more common etiologies can lead to neurological injury and disruption through the spread of pathological proteins and/or through vascular injury. This thesis will primarily focus on AD.

2.1.1. Diagnostic evaluations in the memory clinic

A diagnostic evaluation in a memory clinic typically includes medical history uptake, physical and neurological examination, cognitive screening, assessment of ADL functioning, and standard laboratory blood work [14, 15]. These procedures are typically supplemented by one or more additional investigations, including structural brain imaging with computerized tomography (CT) or magnetic resonance (MR), neuropsychological evaluation, cerebrospinal fluid (CSF) biomarkers, and

18F-Fluorodeoxyglucose (FDG) or amyloid-β (Aβ) Positron Emission Tomography (PET) scans. These investigations provide clinicians with a comprehensive view of patients' clinical phenotype and information on the pathophysiology.

Cognitive impairment is consistently listed in the core criteria for dementia and MCI, making it a central element in the diagnostic evaluation [12, 15, 16]. Cognitive functions can be divided into the following domains: attention, episodic and semantic memory, language, visuospatial abilities, and executive functions, with many additional subdivisions within each domain. In memory clinic settings, clinicians will typically first administer cognitive screening tests meant to examine overall cognitive function, with tests such as the Mini-Mental State Examination (MMSE) [17], the Montreal Cognitive Assessment (MoCA) [18], or Addenbrooke's Cognitive Examination (ACE) [19]. Following, the patient may be referred for a more comprehensive neuropsychological evaluation. The neuropsychological evaluation uses tests intended to assess the extent of cognitive impairment across specific cognitive domains. Most test results are compared to normative data, allowing characterization of how well a specific patient scores relative to healthy individuals of comparable age and education. The result of the neuropsychological evaluation can be a specific cognitive profile corresponding to specific disease processes. Therefore, neuropsychological evaluations aid the overall diagnostic process and can, in some cases, detect subtle cognitive impairment that cognitive screening tests are not sensitive enough to capture.

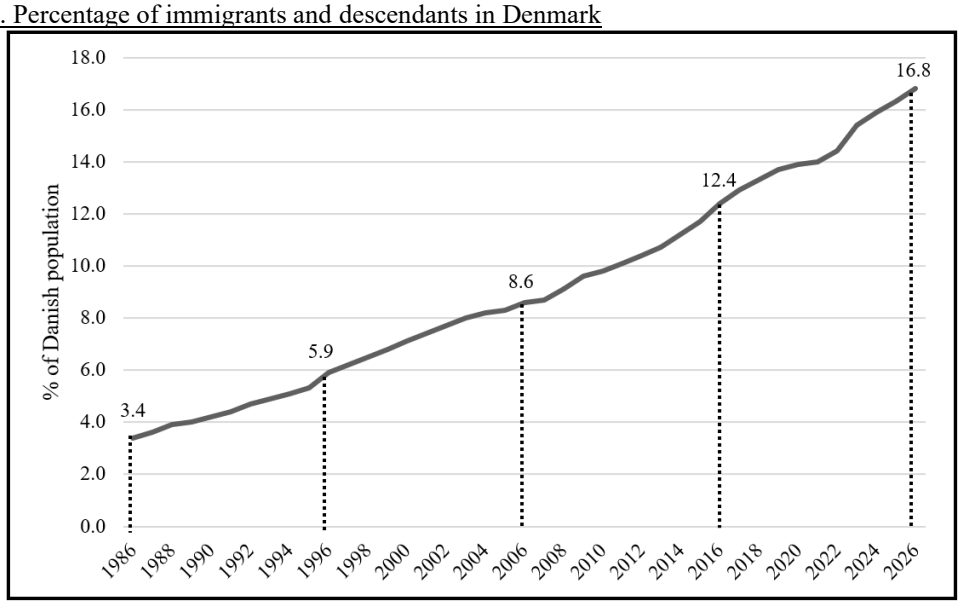
2.1.2. Epidemiology

More than dementia being a debilitating syndrome, it also constitutes a global health crisis. The number of people diagnosed with dementia is expected to rise globally by 166% from 2019 to 2050 [20]. In Denmark alone, there were 6,560 people who received a dementia diagnosis in 2020

compared to 7,765 in 2024 - an 18.4% increase in just four years [13, 21]. This increase creates an imminent challenge that must be addressed before memory clinics worldwide reach capacity.

Patients with immigrant backgrounds may be a particularly vulnerable group in this health crisis. In 2026, 16.8% of the Danish population either had immigrant backgrounds or were descendants of people who immigrated to Denmark [22] (Figure 2.1.2). Many of these people may develop neurodegenerative diseases and need an evaluation in a memory clinic. A study across the European Union countries found that patients with immigrant backgrounds constitute around 6.5% of all dementia cases [23]. Other studies have furthermore suggested that dementia incidence may differ between majority and minority ethnic populations. A study in the United Kingdom found a higher incidence of dementia among Black individuals, along with a younger age of diagnosis and shorter survival time [24]. Similar patterns are found in memory clinics across Europe, which see more and more patients with immigration backgrounds for diagnostic evaluations [20, 25–27]. However, diagnostic tools and procedures are mainly tailored to the majority population in the country where people are being examined, leaving patients who are culturally, linguistically or educationally diverse at a disadvantage.

Figure 2.1.2. Percentage of immigrants and descendants in Denmark



Note: Data from Statistics Denmark [22]

2.2. Diagnostic barriers

2.2.1. Diagnostic barriers for patients with diverse backgrounds

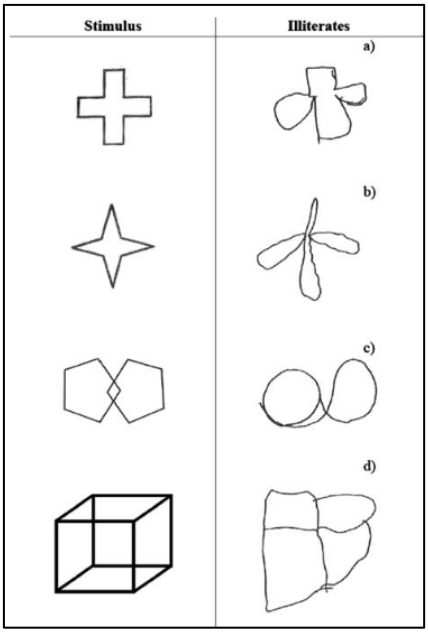
Perceptions about one's health and symptoms are shaped by culture and the words used to express it. Therefore, the way each patient experiences and talks about their symptoms is unique and can lead to misinterpretations when cultures meet. One example is that in some cultures, caregivers may underreport symptoms out of respect for the elderly, because cognitive changes are not considered problematic, or that cognitive impairment is not considered to be due to disease [28], while in countries like Denmark, clinicians would expect a more direct reporting. Since memory clinic patients with immigrant backgrounds are prevalent, improved cultural knowledge and sensitivity on the part of clinicians have become crucial. This also includes rethinking how diagnostic evaluations are carried out. Indeed, a survey across memory clinics in Europe explored clinicians' perceived influence of patients having minority ethnic background on different areas of the clinical evaluation [29, 30]. This survey showed that clinicians experienced substantial barriers in examining patients with minority ethnic backgrounds, including the clinical interview, psychiatric evaluation, and cognitive testing, but also in other areas such as lumbar puncture [29]. Specifically, diagnostic barriers can be divided into those related to culture, language, or education.

Culture shapes our values, knowledge, and ways of communicating [31]. In the context of dementia evaluations, many studies have found influences of cultural background on cognitive tests and scales, such as those assessing ADL functioning [32–34]. A very simple but clear example of cultural influences was a study using the commonly used test *Alzheimer's Disease Assessment Scale – Cognitive* (ADAS-Cog) in Sub-Saharan Africa [32]. One of the subtests in the ADAS-Cog requires the patient to name parts of the body, including the names of fingers. However, in Swahili, the names of fingers are more descriptive, such as "finger of the middle", instead of having a distinct name, making the naming task less appropriate in a cultural context such as this one.

Language is central in expressing internal thoughts and feelings and in communication between caregivers and clinicians. In dementia evaluations, all procedures, whether cognitive testing or lumbar puncture, require communicating instructions through words. However, both receiving and giving verbal information is limited by language, even with an interpreter present [35]. Linguistic bias can also be seen on cognitive tests. One study administered a verbal fluency test to an Arabic, Kurdish, and Turkish speaking patient with limited reading ability and little formal schooling, asking her to produce words starting with the letter 'F' [36]. The woman produced words based on phonology, such as words starting with 'ef' rather than the actual letter 'F'. A case study like this demonstrates how linguistic barriers and the extent of knowledge of the Latin alphabet can affect test administration and results in everyday clinical evaluations.

Education, understood as formal schooling, develops our ability to read, write, calculate, draw, and much more. Education has a significant impact on most cognitive tests, likely because many cognitive tests rely on school-learned abilities [37, 38]. Therefore, when asking patients to draw or copy something, education often influences the result. For example, in healthy persons who have never attended school, their drawing of even simple figures can be misinterpreted as an indication of impaired cognition – see Figure 2.2.1. [39]. In this figure, the healthy person copying the figures had clear challenges, particularly with the three-dimensional aspects.

Figure 2.2.1. Educational bias in cognitive tests



Note: Figure snippet from Nielsen & Jørgensen, 2013 [39]. Left side shows the stimulus, and the right side shows how a cognitively healthy person who had never attended school copied the figures.

This thesis will use the term *diversity* referring to cultural, linguistic, and educational diversity. As seen in the examples given above, it can be difficult to distinguish what difficulties may be caused by differences in culture, language, and education. Other areas, such as referral patterns, healthcare structure, racism, and discrimination, will not be addressed in our studies, although they are relevant in addressing diagnostic barriers for patients with diverse backgrounds [40].

2.2.2. Diagnostic evaluations in culturally, linguistically, and educationally diverse patients

The barriers described above limit the clinical utility of diagnostic tools and scales and the quality of information from clinical evaluations when examining patients with diverse backgrounds. It is, however, encouraging how much attention research and clinical initiatives this topic has gained lately, for example, with the creation and growth of the European Consortium on Cross-Cultural Neuropsychology (ECCroN), the International Neuropsychological Society hosting their 52nd annual meeting on *Culture & Connectivity – Neuropsychology without borders* in 2024, and the 1st Global

Neuropsychology Congress in 2025 with a major focus on cross-cultural neuropsychology. In the following, I will touch upon some of the main challenges and developments across the different parts of the clinical evaluation.

The clinical interview and psychiatric evaluation are primarily limited by linguistic barriers as the source of information is the conversation with the patient. However, diagnosing dementia requires accurate knowledge about cognitive complaints and symptomology to set an accurate and unbiased diagnosis. Hence, communication is a clinical priority. Ideally, the clinical evaluation can be carried out by a clinician with a similar cultural background and who speaks the same language as the patient [35]. In Europe, this is often unachievable because of immensely diverse immigration patterns, resulting in patients speaking many different languages [35]. Therefore, interpreters may be utilized not only to interpret, but also to (sometimes) offer specific cultural knowledge, influencing local idioms of distress relevant for the evaluation [35, 41]. Gaining knowledge of cultural aspects such as social norms, religion, and traditions is emphasized as a main recommendation among clinicians [42].

ADL evaluation, frequently examined using questionnaires, often poses as challenging because the items in the questionnaires or scales are highly culture-bound [34]. This is problematic as assessment of ADL functioning is a key criterion across diagnostic criteria for dementia. These questionnaires typically concern everyday activities related to judgment, problem solving, hobbies, house activities, and finances [28, 34]. However, many of these activities are inherently context-bound and differ depending on cultural background, gender, and preference [34]. Therefore, what may be interpreted as impairment on the scales may, in fact, reflect normal variation due to factors unrelated to cognitive impairment, and it is left to clinicians to interpret the results.

Cognitive testing is essential in the diagnostic evaluation, however some of the most widely used cognitive screening tests [17–19] are prone to cultural, linguistic, and educational bias leaving

patients with diverse backgrounds at a disadvantage [43–45]. These tests, and many other neuropsychological tests, are developed for a specific cultural context and require countless cultural adaptations and validations in each culture and language around the globe. Adapting and validating appear extremely challenging simply because of the sheer number of countries, cultures, and languages in the world, but also since cultures and languages mix more and more [30, 38, 42]. In response to this, cross-cultural cognitive tests have been developed that intend to reduce bias from cultural, linguistic, and educational factors.

One of the first cross-cultural cognitive tests to gain international recognition is the *Rowland Universal Dementia Assessment Scale* (RUDAS) [46]. Storey and colleagues believed that cognition can be assessed independently of culture, and therefore developed a scale intended to be valid across culturally diverse populations [46]. This short cognitive screening test has repeatedly proven to be as accurate as other short cognitive screening tests in the majority ethnic population, more accurate in minority ethnic populations, and less influenced by educational factors compared to other cognitive screening tests [43, 47, 48]. Cross-cultural cognitive tests aim to avoid imposing cultural ideas, use globally recognized items, incorporate colored images, and avoid tasks that rely heavily on school-learned skills [49]. Other cross-cultural cognitive tests have been developed including longer cognitive screening tests such as the *Cross-Cultural Dementia screening test* (CCD) [50], *Multicultural Cognitive Examination* (MCE) [51], neuropsychological test batteries such as the *European Cross-Cultural Neuropsychological Test Battery* (CNTB) [52, 53] and the *Towards a Universal Language: Intervention and Psychodiagnostic Assessment* (TULIPA) battery [54] to mention a few. Common to these cognitive tests and batteries is their ability to be administered directly with an interpreter, a limited need for adaptation across languages and cultures, and relatively little influence of education. Development, translation, and adaptation of neuropsychological tests should follow international guidelines such as those proposed by the International Test Commission,

to ensure valid and reliable psychometric properties [55]. Studies 1 and 4 concern cross-cultural cognitive tests applied in culturally, linguistically, and educationally diverse groups.

2.3. Alzheimer's disease

AD is characterized by a gradual symptom onset, worsening cognition over time, and by prominent episodic memory loss in the amnestic presentation, which is the most common presentation [15]. Other less common presentations of AD include a primary language presentation, a primarily visuospatial presentation, and a primarily executive presentation [15, 56]. These presentations differ because different brain areas are affected, but they share the same underlying pathophysiology. As the disease progresses, the cognitive impairment spreads to the other cognitive functions, leading to increasing loss of independence and functional decline.

Different diagnostic criteria for AD exist that emphasize clinical or underlying biological aspects. Our understanding of AD is in line with the description by the National Institute on Aging – Alzheimer's Association (NIA-AA) and the International Working Group (IWG) [15, 57, 58]. These require a diagnosis of dementia or MCI, an identifiable clinical AD phenotype, and can be further supported by biomarkers reflecting underlying AD pathology.

2.3.1. Epidemiology

AD accounts for up to 60 to 70% of all dementia cases [59]. Global estimates approximate that 32 million people lived with AD dementia in 2021, and prevalence rates are predicted to continue to rise across the globe [20, 60, 61]. In 2019, AD dementia and other dementia disorders were estimated as the fourth leading cause of lost healthy life years among people aged 75 years and older, making

diagnosing and treating an urgent healthcare priority [62]. The burden of disease, however, disproportionately affects Lower- and Middle-Income Countries [62, 63].

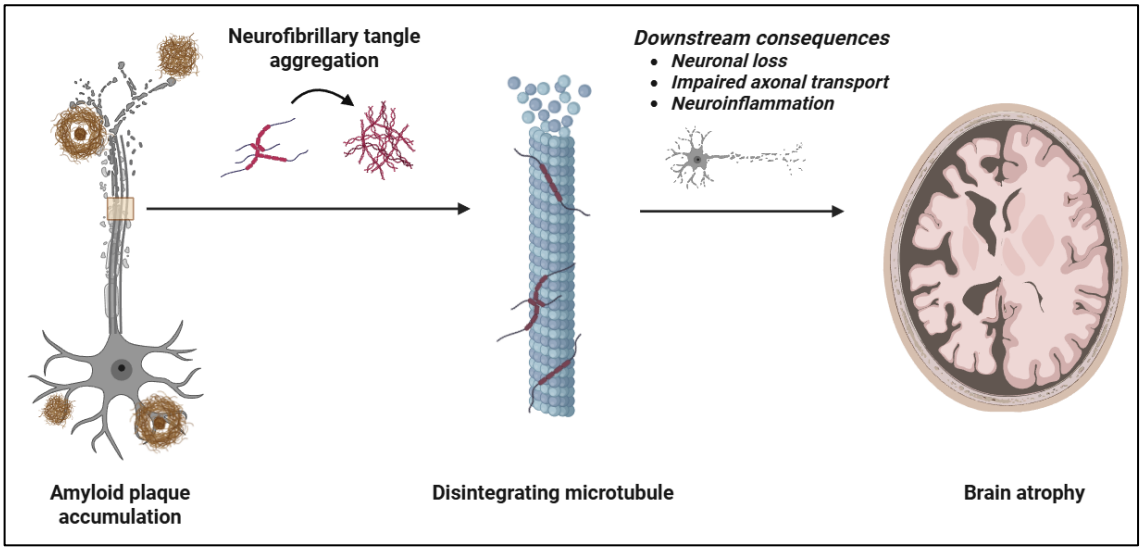
While these numbers reflect the clinical diagnosis of AD, the disease starts much earlier, with protein accumulation already decades before the onset of clinical symptoms [64]. Indeed, when examining cognitively intact participants in Sweden, Kern and colleagues found that 46% of 70-year-olds presented with abnormal levels of CSF AD biomarkers [65]. So, although the number of people with a clinical AD diagnosis is already high, many more people have underlying AD pathology that may develop into a clinical syndrome, especially as populations continue to age.

2.3.2. Pathogenesis

The exact initiating cause of AD pathology is unknown, but many risk factors have been identified [66, 67]. However, the dominating hypothesis is the *amyloid cascade hypothesis* proposed by Hardy and Higgins in 1992 [68]. This hypothesis proposes that the first peptide to accumulate and misfold is Aβ, leading to the formation of amyloid plaques. This is believed to trigger hyperphosphorylation of tau proteins, which, when accumulated, creates neurofibrillary tangles. Amyloid plaques aggregate mainly extracellularly, while neurofibrillary tangles accumulate intracellularly and cause neurodegeneration and atrophy, resulting in loss of cognitive functioning [64, 68, 69]. See Figure 2.3.2. for visual representation.

Understanding the pathogenesis of AD is essential to recognize the role of biomarkers, which will be elaborated on in section 2.4. However, first, a detailed description of the individual processes in the brain is necessary. This description concerns (1) the peptide Aβ, (2) the protein tau, and (3) neuroinflammation processes.

Figure 2.3.2. AD pathogenesis



Note: Figure displaying the amyloid cascade hypothesis. Created in BioRender.

Aβ peptides: Amyloid Precursor Protein (APP) found in the cellular membrane of neurons plays a central role in neuronal growth, formation of synapses, and transport within the cells [70]. Normally, APP is cleaved by α-secretase and γ-secretase, leaving soluble peptides that are released and cleared from the extracellular matrix and are not considered pathological. However, when APP is cleaved by β-secretase and γ-secretase the peptide Aβ is created. γ-secretase cleaves APP at different sites, resulting in different lengths of Aβ [70]. The shorter Aβ variants (such as Aβ40) are considered less aggregation-prone, whereas the longer variant, Aβ42, is more prone to aggregation and is closely associated with AD pathology. This aggregation occurs when monomers of Aβ group together creating oligomers, then fibrils, and later extracellular amyloid plaques. Such amyloid plaques occupy the extracellular matrix and likely contribute to later hyperphosphorylation of tau.

Tau proteins: Tau is an intracellular protein that helps stabilize microtubules, which in turn stabilize the cell and facilitate the transport of molecules. During normal functioning, tau is activated when a phosphate group is added to it. However, if tau is hyperphosphorylated (p-tau), the protein becomes pathological. The phosphate causes tau to change shape (misfold) and, in turn, destabilizes the

microtubules. As more tau proteins become hyperphosphorylated, they aggregate, creating neurofibrillary tangles that lead to apoptosis [71].

Neuroinflammation: Aβ and p-tau are considered the hallmarks of AD pathology, however the accumulation of these proteins also coincides with other pathological processes [70]. For example, glial cells, including microglia and astrocytes, that are normally considered 'helper' cells that help with clearance, regulate inflammation, and can be considered part of the immune system of the brain become pathological. During the accumulation of plaques and tangles, the glial cells activate to attempt to regulate the presence of plaques and tangles. This makes the glial cells chronically active, promoting inflammation of the brain [72].

2.3.3. Co-pathology

While the above description of AD pathogenesis represents our current understanding of AD, isolated, many patients with AD will have concurrent pathologies, such as transactive response DNA-binding protein 43 kDa (TDP-43) pathology, vascular pathology, and *α*-synuclein pathology [73–77]. TDP-43 pathology, similar to AD, is characterized by pathological protein aggregation, which can result in a clinical presentation of *limbic-predominant age-related TDP-43 encephalopathy* (LATE) [78]. Clinically, patients with LATE have similar cognitive profiles as those with AD, which is further complicated by a neuropathological overlap of up to 57% [76]. Another co-pathology caused by *α*-synuclein, the hallmark protein of DLB and Parkinson's disease, is commonly found in AD patients. Neuropathological studies have found that up to 50% of patients with AD pathology also have *α*-synuclein pathology [79, 80]. Lastly, vascular pathology, such as microbleeds, white matter lesions, and stroke, also frequently overlaps with AD pathology [74, 75]. Co-pathology generally exacerbates cognitive decline, underscoring the need to understand the complex interplay between the diseases

[74, 76, 77]. This is not an exhaustive list of co-pathologies in AD, but it demonstrates that co-pathology is common and central to consider. These biological processes can be measured neuropathologically or using different biomarkers.

2.4. Biomarkers

A biomarker can be defined as any measure of biological processes in the body. Biomarkers can, for example, be used to quantify pathological proteins (Aβ, tau, α-synuclein, TDP-43), inflammation, or vascular burden. Biomarkers can be measured through different modalities, assays, and technologies. These biomarkers can be used for various purposes, including diagnosis, prognosis, and monitoring, although this thesis will primarily focus on their diagnostic properties.

In the following, I will first describe the biomarkers currently used in clinical practice and then turn to the novel blood biomarkers that are the focus of this thesis.

2.4.1. Currently established biomarkers

Imaging biomarkers: The first in vivo biomarker used to aid the clinical diagnosis of AD was structural brain imaging. Structural brain imaging has two purposes in the diagnostic procedure, first to exclude other pathologies such as tumors, second to identify patterns associated with diseases such as temporoparietal and hippocampal atrophy in AD, and third to quantify vascular burden [81, 82]. The structural brain imaging technologies most commonly used are CT and MR, with MR offering better resolution but it is more time consuming and expensive. While structural brain imaging provides essential diagnostic information, it is less disease-specific, as for example, patients with AD and LATE both have hippocampal atrophy [83].

The invention of PET opened up the possibility of visualizing brain metabolism or proteins using radioactive tracers that bind to their targets and emit positrons, which are detected and quantified. The first paper successfully quantifying Aβ using PET was published in 2004 [84], using the tracer Pittsburgh Compound-B. This discovery was revolutionary for the AD field, as Aβ could be detected and quantified within the brain. Later, tau-PET tracers were successfully invented, with the most commonly used today being flortaucipir [85–87]. Aβ-PET and tau-PET have quickly become important for AD trials, research, and clinical work, as they can both quantify protein burden and visualize its distribution in the brain.

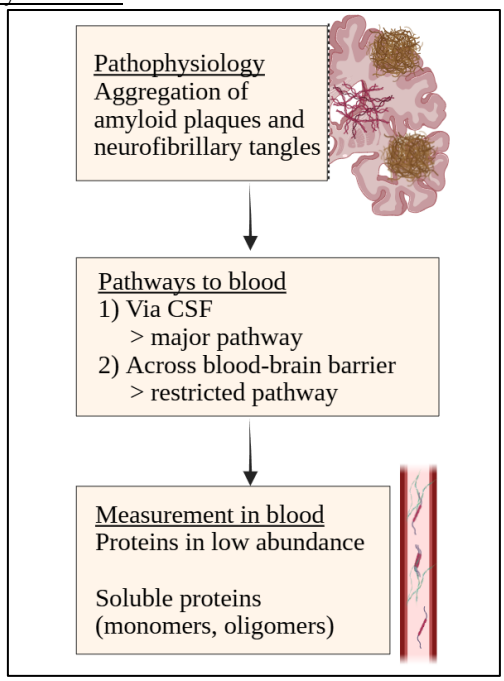
Cerebrospinal fluid: Before the invention of Aβ-PET and tau-PET tracers, CSF biomarkers were the only way to measure AD proteins in vivo. AD proteins present in the brain are released into the extracellular matrix and into the CSF in the ventricles, subarachnoid space, and spinal cord. In turn, a lumbar puncture collects CSF, which contains proteins that reflect AD pathology in the brain. Targeted biomarkers can be quantified using different assays and technologies, with the most widespread being based on an enzyme-linked immunosorbent assay (ELISA). ELISA uses an immunoassay 'sandwich' approach with capture and detection antibodies binding to the targeted protein. The capture antibody immobilizes the targeted protein. The detection antibody is linked to an enzyme that produces a signal (colorimetric/fluorescent/chemiluminescent) when adding a substrate for the enzyme. This signal is quantified and reflects the concentration of the protein. In 1995, the first successful measurements of Aβ42 [88] and total tau [89] in CSF were described. Following this, the use of CSF AD biomarkers, including Aβ, t-tau, and p-tau, has become widespread and is part of many clinical examinations. Indeed, CSF biomarkers are used diagnostically either as supportive or standalone, according to different criteria [15, 57, 90]. Such CSF biomarkers reflecting AD pathology correlate with clinical measures such as brain atrophy and cognitive symptoms [91, 92].

Novel targets, immunoassays, and technologies have made it possible to measure many other biomarkers than Aβ and tau, including Neurofilament light (NfL) and Glial Fibrillary Acidic Protein (GFAP), reflecting neurodegeneration and inflammation through axonal injury and astrocytic activation [93, 94]. However, CSF biomarkers require lumbar puncture performed by specialized personnel and are often perceived as invasive, which has encouraged the development of other scalable, less invasive, and easy-to-use biomarkers [95, 96].

2.4.2. Blood biomarkers

Historically, measuring proteins associated with neurodegeneration through peripheral biomarkers, such as in blood, has been met with skepticism and poor results in its early days. The main challenge was that the proteins measurable in CSF are present in much lower concentrations in blood, requiring more sensitive instruments. Several pathways have been proposed for how AD proteins enter the blood, with the main pathway being from the CSF to the blood (Figure 2.4.2.A).

Figure 2.4.2.A. Brain protein pathways to blood



Note: Illustration of how aggregation of plaques and tangles can be reflected in blood. Created in BioRender.
Abbreviations: CSF = Cerebrospinal fluid

The development of new and more sensitive technologies overcame this challenge. Among these are Single Molecule Array (Simoa) and Meso Scale Discovery (MSD), which have become central to blood biomarker research and can detect proteins in low abundance.

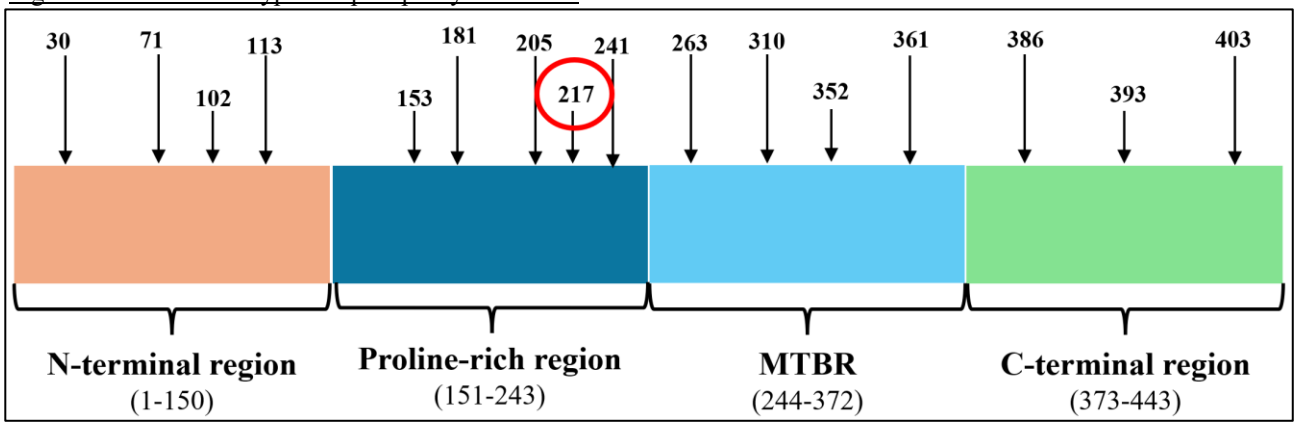
- **Simoa** takes the traditional ELISA approach one step further by adding magnetic beads capturing the targeted individual molecules. Each bead is added to separate wells, and fluorescent signals are captured digitally by the Simoa technology [97].
- **MSD** technology is also based on the ELISA principles but utilizes electrochemiluminescence (ECL) to detect protein concentrations. Plasma is combined with a capture antibody and a detector antibody with an ECL tag, such as ruthenium. When electricity is applied, the ECL tag emits light, reflecting the concentration of the measured protein as described previously [98]. Plasma concentrations for the manuscripts in this thesis are based on an MSD approach, and our specific methodological approach is described in the methods section.

Several blood biomarker studies have aimed to measure the same proteins as in CSF, such as Aβ42, p-tau at different phosphorylation sites, and NfL. The earliest plasma studies examined Aβ42 and Aβ42/40 ratio and found that biomarker concentrations were reduced in patients with AD and amyloid pathology [99–102]. Surprisingly, plasma p-tau was also found to primarily reflect amyloid pathology, and to a lesser extent tau aggregation, although disagreement does exist among researchers [103–107]. It is hypothesized that p-tau in blood signals early tau dysregulation before neurofibrillary tangles form [106, 108]. As both plasma Aβ and p-tau reflect amyloid pathology, other biomarkers of neurodegeneration may be beneficial to improve diagnostic and prognostic performance and better reflect the extent of cognitive impairment and neural injury. For these purposes, NfL may be particularly useful, especially for clinical purposes. One study compared the predictive role and the ability to track cognitive change of plasma- and CSF NfL, and found equal ability to predict cognitive decline and imaging burden [109]. Furthermore, they found that plasma NfL levels changed with

cognitive impairment, indicating that it can be used as a marker of progression [109]. These findings are supported by other studies [110–112].

Plasma p-tau can be phosphorylated at different threonines (e.g., 181, 217, 231), and these can be specifically targeted (See Figure 2.4.2.B). This thesis focuses specifically on the biomarker plasma p-tau217, which has been found to better classify and predict Aβ pathology than p-tau181, p-tau231, and Aβ42/40 [113–115]. Plasma p-tau217 is sensitive to the accumulation of Aβ both when comparing to post-mortem plaques, and to CSF and Aβ-PET biomarkers [107, 116, 117]. But it also reflects tau accumulation on tau-PET and in autopsy studies [118], albeit it is uncertain whether the tau-PET correlation is due to the underlying Aβ pathology. Furthermore, plasma p-tau217 can predict future decline in patients without cognitive impairment [119]. Importantly, with many existing technologies and assays, studies have explored the accuracy of the different approaches head-to-head [117, 120, 121]. Overall, the studies do not find any differences between the immunoassay used (e.g. WashU, Lilly, Janssen, ALZpath), but the technologically complex mass spectrometry approach may be slightly superior when predicting Aβ-PET and tau-PET status. The above indicates that plasma p-tau217 is an accurate biomarker of Aβ pathology, with comparable performance to CSF biomarkers and Aβ-PET.

Figure 2.4.2.B. Tau isotype and phosphorylation sites



Note: Illustration of the 2N4R tau isoform. Phosphorylation sites are indicated with site 217 encircled in red. Whether it is a serine or threonine phosphorylation is not marked.
Abbreviations: MTBR = Microtubule Binding Region Tau.

2.4.3. Bias and variability

The cohorts from the studies mentioned above consist primarily of homogeneous patients, both in terms of representation of sociodemographic variables, but also in represented medical conditions. Indeed, in a systematic review of participant characteristics in blood biomarker p-tau217 studies, Blasi and colleagues (under preparation – see data extraction table in section 9.6) found that among 131 published papers on plasma p-tau217, around 25% included participants with minority ethnic or racial backgrounds, but these participants with minority ethnic or racial backgrounds generally represented less than 10% of each cohort. This issue will be one of the main focuses of this thesis.

The influence of race and ethnicity on biomarkers is heavily debated, with roots dating back to CSF and Aβ-PET studies. Some CSF and Aβ-PET studies indicated that biomarker concentration and precision differ based on ethnicity or race [122–128]. Whether these differences were driven by genetic predispositions or specific susceptibility to disease from certain haplotypes, diet, and diseases over generations or by other societal factors, barriers in healthcare, and differing referral patterns is unknown [129–134]. If race/ethnicity indeed influences biomarkers, it is essential to understand the underlying reasons and incorporate them into our interpretation of the biomarkers. However, if race/ethnicity does not influence biomarkers, it is crucial to focus on the factors that do have an influence. If race/ethnicity adjusted biomarker concentrations or cutoffs should be implemented, it should be proven without a shred of doubt that no other factors could be underlying the influence to avoid misdiagnosing specific populations. Studies 2 and 3 precisely address this issue in the context of blood biomarkers, and the discussion will further elaborate on our findings and compare them with other studies.

Most researchers in the blood biomarker field agree that body mass index (BMI) and kidney function impact blood biomarkers [135–138]. Most studies that have explored the association find that a higher BMI is associated with lower biomarker concentrations and that worse kidney function is associated

with higher biomarker concentrations. BMI reflects an increase in blood volume, which may dilute proteins in blood, resulting in lower concentrations [138]. Reduced kidney function, often represented by low estimated glomerular filtration rate (eGFR), may increase biomarker concentration through worse filtration of blood [135]. While BMI and kidney function have received most attention in research, other studies are emerging demonstrating associations between plasma biomarkers and other non-AD diseases, such as amyotrophic lateral sclerosis (ALS), stroke, and even in newborns, to mention a few [139–141]. Study 5 will address whether any sociodemographic or medical variables can explain discordance rates within our cohort and the discussion.

3. AIMS

3.1. Overall aim

The overarching aim of this PhD thesis was to investigate influences of sociodemographic factors and medical conditions on plasma p-tau217 and the MCE, and to examine the diagnostic accuracy of these diagnostic tools in a memory clinic setting.

3.2. Study-specific aims

Study 1	To (a) determine the influence of demographic variables on the MCE, (b) create normative data for the MCE, (c) determine the diagnostic accuracy of the MCE for differentiating cognitively intact participants from patients with MCI and dementia, and (d) examine the ability of the MCE to distinguish cognitively intact participants from patients with AD dementia and non-AD dementia.
Study 2	To investigate ethnic and racial influences on blood biomarker concentrations and diagnostic and prognostic accuracy for AD.
Study 3	To examine the influence of ethnicity on the diagnostic accuracy of plasma p-tau217 in identifying AD and CSF/Aβ-PET-verified AD pathology in a mixed memory clinic cohort.
Study 4	To examine the added value of combining routine cross-cultural cognitive assessments with plasma p-tau217 in identifying MCI and dementia due to AD in a consecutive mixed memory clinic cohort of culturally and linguistically diverse patients.
Study 5	To characterize patients with discordant plasma p-tau217 and CSF or Aβ-PET biomarker profiles in an ethnically diverse mixed memory clinic cohort

4. METHODS

The thesis is based on five studies. Study 1 focused on the MCE, Study 2 is a systematic review on ethnicity and blood biomarkers, and studies 3 to 5 utilized the BlooDiv cohort focusing on plasma p-tau217. I will first present our study designs, eligibility criteria, define our main covariates, statistical software and approach, and ethics and approvals. Lastly, I will present study-specific methods for studies 1 to 5.

4.1. Study designs

Our studies are based on retrospective cross-sectional study designs and one systematic review. The MCE cohort created the basis for Study 1. The BlooDiv cohort created the basis for studies 3 to 5.

4.2. Eligibility criteria

4.2.1. The MCE cohort

Participant data was included of ongoing and finalized research projects across inclusion sites in Belgium, Brazil, Denmark, France, Germany, Italy, the Netherlands, Norway, Spain, Sweden, and the United Kingdom [53, 142–147]. Patients were recruited in memory clinics, while cognitively healthy control participants (HC) were recruited through relatives, registries, senior centers, local districts, voluntary organizations, advertisements in newspapers, and social networks of researchers. Study participants were included from September 2009 to August 2024. See Table 4.2.1 for inclusion and exclusion criteria.

Table 4.2.1. Eligibility criteria for the MCE cohort

Inclusion criteria	Exclusion criteria
Available data on the MCE	Motor, physical, neurological, hearing, vision, or psychiatric impairment interfering with cognitive testing.
Known age, sex, years of school, and country of birth	Missing data on more than one MCE subtest.
Known syndrome diagnosis (HC, SCD, MCI, dementia)	

Note: Table from the eligibility criteria described in Kjaergaard et al., 2026 [1]
Abbreviations: HC = Healthy controls, MCE = Multicultural Cognitive Examination, MCI = Mild Cognitive Impairment, SCD = Subjective Cognitive Decline

Memory clinic patients and HC were examined with the MCE across the included sites. We grouped the participants in cognitively intact (HC and subjective cognitive decline (SCD)), MCI, and dementia. Syndrome diagnoses were determined according to official criteria of MCI [11, 57, 148, 149], dementia [15, 148–151]. (see supplementary table 2 in Kjaergaard et al., 2026 for specification [1] or in Appendix 1 of this thesis)

Memory clinic patients had all completed a comprehensive clinical evaluation, and their syndrome diagnoses and etiological diagnoses were established by a multidisciplinary team. The clinical workup typically comprised interviews with the patient and an informant, alongside physical, neurological, cognitive, and psychiatric examinations, routine laboratory blood testing, and structural neuroimaging using CT or MR imaging. When clinically indicated, most centers additionally performed CSF biomarker analyses, PET, or detailed neuropsychological or psychiatric assessments. The MCE was part of the clinical evaluation in the Netherlands, where it was part of the neuropsychological test battery TULIPA, which also replaced SFT with food fluency (N = 111) [54].

4.2.2. Systematic review

Study 2 is a systematic review and followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [152]. We identified published manuscripts through PubMed and Web of Science until the 15th of June 2023.

Selection criteria were chosen to identify studies with appropriate participants, intervention/measurement, comparison, outcomes, and study design (PICOS) [152]. Our inclusion and exclusion criteria are specified in Table 4.2.2.

Table 4.2.2. Eligibility criteria of the systematic review

Inclusion criteria	Exclusion criteria
Determined AD by clinical criteria or amyloid-pathology by CSF/Aβ-PET.	In vitro studies, intervention studies, case reports, editorials, commentaries, reviews, studies in non-human subjects.
Included >1 ethnic or racial group.	Studies not published in English.
Longitudinal studies must have minimum 2 years follow-up, and required any participants to be diagnosed with clinical AD at follow-up.	Including participants younger than 18 years of age.
Assessed Aβ, t-tau, p-tau, NfL, and/or GFAP in plasma or serum.	
Clinical AD must be compared to a cognitively intact control group.	
Analyses must include a comparison between the ethnic/racial groups and report a measurement of the influence of ethnicity/race on biomarker concentration, diagnostic accuracy, and/or prognostic value.	
Have an observational study design.	

Note: Table from eligibility criteria in Kjaergaard et al., 2025 [2].
Abbreviations: Aβ = Amyloid-β, Alzheimer's disease, CSF = Cerebrospinal fluid, GFAP = Glial Fibrillary Acidic Protein, NfL = Neurofilament light, PET = Positron Emission Tomography, p-tau = phosphorylated tau, t-tau = total tau

4.2.3. The BlooDiv cohort

Studies 3 to 5 all used data from the same cohort – the BlooDiv cohort. The BlooDiv studies were part of the *Early and Accurate Diagnostic and Prognostic Markers for Alzheimer's disease* (EDAP-

AD) project. The BlooDiv cohort identified memory clinic patients through medical records at the Copenhagen University Hospital – Rigshospitalet (Denmark) and Skåne University Hospital (Sweden). Patients with complete diagnostic evaluations between January 2020 to December 2023 in Denmark, and June 2017 to March 2024 in Sweden were eligible for inclusion. First, all patients with immigrant backgrounds across the two clinics were identified and matched one-to-one to Danish-born patients on age and sex. See Table 4.2.3.A for inclusion and exclusion criteria.

Table 4.2.3.A. Eligibility criteria of the BlooDiv cohort

Inclusion criteria	Exclusion criteria
Complete diagnostic evaluation in a memory clinic.	Hereditary neurogenetic disorders.
Consent for research use of plasma samples and information from medical records.	No stored plasma available for biomarker analyses.
Known country of birth.	Danish or Swedish origin for patients with immigrant backgrounds.

Note: Eligibility criteria described in Kjaergaard et al., 2025 [3].

In the memory clinic in Copenhagen University Hospital – Rigshospitalet, patients were diagnosed with a cognitive syndrome diagnosis and an etiological diagnosis following a multidisciplinary consensus conference. The cognitive syndrome diagnoses were SCD, MCI, or mild to severe dementia [11, 15, 57, 148, 153]. AD was diagnosed following NIA-AA criteria [15, 57], and other diagnoses followed official criteria, including those for DLB [154], VaD [155], behavioral variant Frontotemporal dementia [156], non-fluent Primary progressive aphasia (PPA) or semantic dementia (SD) [157], and Normal Pressure Hydrocephalus (NPH) [158]. Meanwhile, in the memory clinic at Skåne University Hospital, patients with a typical disease presentation who had supportive biomarkers were diagnosed by the individual physician. In this clinic, AD was diagnosed following the Diagnostic and Statistical Manual of Mental Disorders (DSM) fifth edition criteria [12, 149].

When deemed necessary, the diagnostic evaluations were supplemented with AD biomarkers, including CSF biomarkers and/or Aβ-PET (Table 4.2.3.B). While the clinical use and interpretation of these methods differed between the clinics, the BlooDiv studies operationalized Aβ-PET using the evaluation from the clinical radiologist and CSF using p-tau181/Aβ42 ratios.

Table 4.2.3.B. CSF and Aβ-PET description

CSF / Aβ-PET	Assay/ligand	Method	Center	Time period
CSF	Innotest	ELISA	Copenhagen University Hospital - Rigshospitalet	2020 to July 2022
CSF	Elecsys (v.2)	ECLIA	Copenhagen University Hospital - Rigshospitalet	July 2022 to 2023
Aβ-PET	^{11}C-PiB		Copenhagen University Hospital - Rigshospitalet	2020 to 2023
CSF	MSD	ECL	Skåne University Hospital	2017 to October 2019
CSF	Lumipulse	CLEIA	Skåne University Hospital	November 2019 to 2024
Aβ-PET	[^{18}]F-Flutemetamol		Skåne University Hospital	2017 to 2023

Note: Table adapted from Kjaergaard et al., (2025) [3].
Abbreviations: Aβ = Amyloid-β, CLEIA = Chemiluminescent enzyme immunoassay, CSF = Cerebrospinal fluid, ECL = Electrochemiluminescence, ECLIA = Electrochemiluminescence immunoassay, ELISA = Enzyme-linked immunosorbent assay, MSD = Meso Scale Discover, PET = Positron emission tomography, PiB = Pittsburgh compound B.

4.3. Primary predictors and outcomes

4.3.1. Ethnic/racial/geographic diversity

All five manuscripts include a diversity variable. We operationalized this diversity variable based on immigrant status in studies 1 and 3 to 5. If patients were examined in their country of birth, they were characterized as non-immigrants, and if they were examined in a different country than their country of birth, they were characterized as immigrants. The rationale for this grouping was to include a covariate to capture cultural, linguistic, and geographic diversity. Moreover, geographic origin may

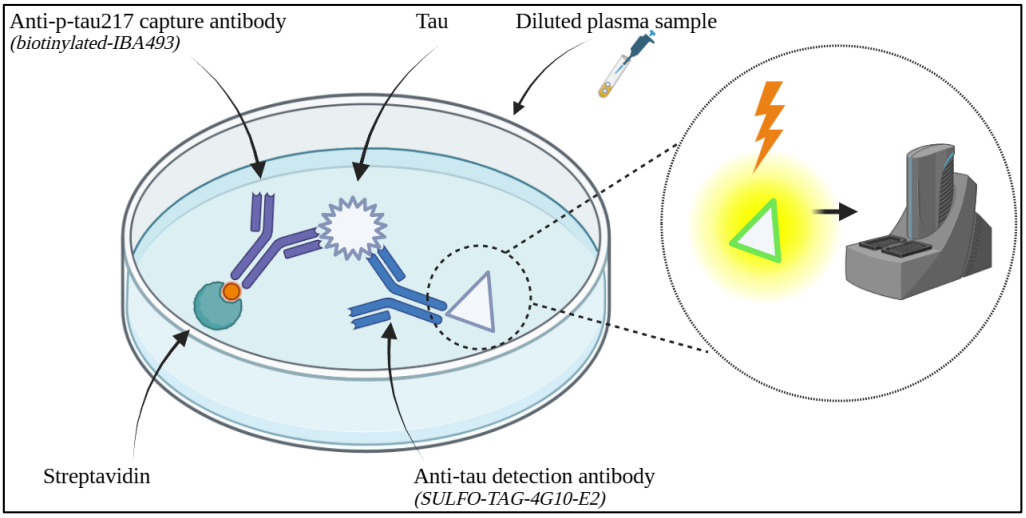
reflect specific climates, haplotypes, diet, and diseases, possibly affecting genetic predispositions and susceptibility to disease relevant for Study 3 [129–134]. Study 2, being a systematic review, allowed a broader definition also including racial groupings (e.g. White/Black) and ethnic groupings without knowledge of exact geographic origin (e.g. Hispanic/Asian). The studies included in the review primarily relied on self-identified racial and/or ethnic group.

4.3.2. Plasma p-tau217

The blood biomarker plasma p-tau217 was the most central variable in studies 3-5. Blood was collected as part of the diagnostic evaluation, if informed consent was given. Blood was collected in ethylenediaminetetraacetic acid (EDTA) plasma tubes and processed within 2 hours of sampling, and the resulting plasma was stored at minus 80 degrees Celsius. EDTA-plasma samples were transported on dry ice to the memory research unit at Lund University, Sweden, to be analyzed.

The plasma samples were thawed at room temperature and centrifuged [159]. Following, plasma p-tau217 was assessed in a single-batch analysis on the MSD platform using a Lilly Research Laboratories immunoassay [159]. This method of analysis uses an ECL approach. The analysis followed the following steps: First, the capture antibody (biotinylated-IBA493) was added to a streptavidin-coated MSD plate. Second, diluted plasma samples were added to the plates. Third, the detector (SULFO-TAG-4G10-E2) was added to the plate. Lastly, the MSD SQ120 analyzed each plate by adding electricity, causing the emission of light from the SULFO-TAG labels. Light intensity was quantified to determine the concentration of p-tau217 in each sample. See Figure 4.3.2. for a graphic overview.

Figure 4.3.2. Electrochemiluminescence on a Meso Scale Discovery platform



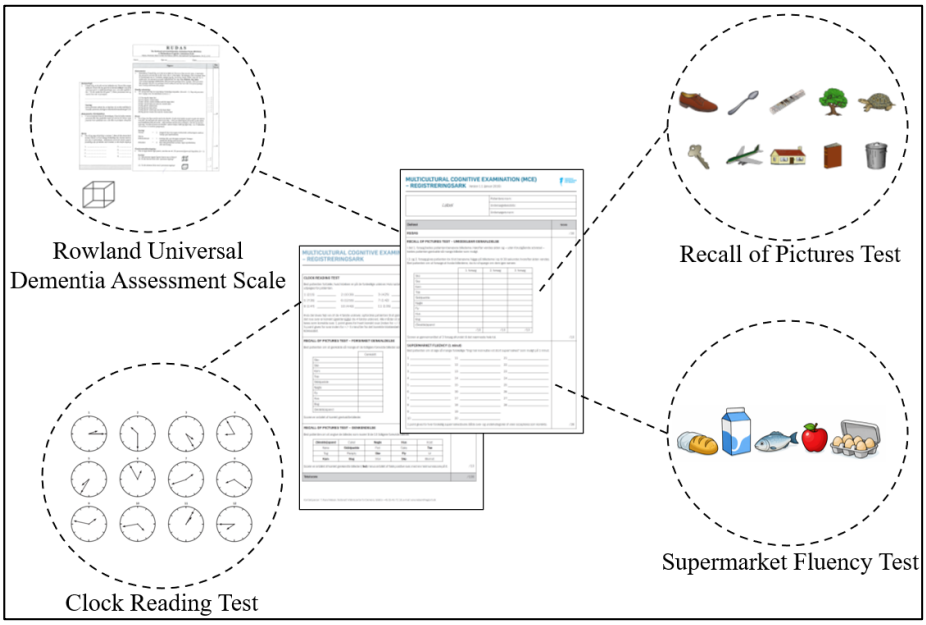
Note: Illustration of the electrochemiluminescence approach to measure phosphorylated tau217. Created in BioRender.

All patient samples in the BlooDiv cohort (studies 3 to 5) were analyzed in duplicates by staff blinded to all patient information. The samples were analyzed in batches randomized by age, sex, ethnicity, and AD diagnosis.

4.3.3. Multicultural Cognitive Examination (MCE)

The MCE was used as a main predictor in studies 1 and 4. The MCE is a cross-cultural cognitive test consisting of the RUDAS [46], Recall of Pictures Test (RPT) [160], Supermarket Fluency Test (SFT) [161], and Clock Reading Test (CRT) [162]. Of a 100 potential points on the MCE, 30 potential points come from the RUDAS, 30 from the RPT tasks, 28 from the SFT, and 12 from the CRT (Figure 4.3.3). The MCE subtests were originally selected from the CNTB and prioritized easily administered materials without needing to change stimuli, was created with interpreter-mediated administration in mind, and appropriate for people with little or no education [51, 53, 142].

Figure 4.3.3. The Multicultural Cognitive Examination



Note: Figure adapted from Nielsen et al., 2019, displaying the MCE and its subtests [51].

4.4. Statistical software and statistical approach

All statistical analyses were carried out using the statistical software R and RStudio (versions 4.4.1 to 4.4.2). Analyses were considered statistically significant at $\alpha = p < 0.05$ (two-tailed). All statistical code is shared openly on GitHub (MCE: https://github.com/dkja0031/MCE. BlooDiv files for matching, and studies 3-5: https://github.com/dkja0031/BlooDiv).

4.5. Ethics and approvals

All studies including participant data (studies 1, 3-5), were approved by the Danish Data Protection Agency (p-2024-15786, p-2023-14275), and studies 3-5 were also approved by the Swedish Ethical Review Authority (2023-07108-01) and by the Regional Ethics Committee in the Capital Region of Denmark (H-23035053). Study 1 only included fully anonymized data and did not require ethical approval. All patients in studies 3-5 gave written informed consent for using information from their medical records and stored blood samples for research purposes.

4.6. Study specific methods

4.6.1. Study 1

The statistical approach is described in depth in the published manuscript (Appendix 1). In brief, the cognitive syndrome diagnosis constituted the main reference standard, and the clinical etiological diagnoses (AD or non-AD dementia) constituted a secondary reference standard. Participant characteristics and group differences were first examined. Then, to examine the influence of sociodemographic variables on the MCE, a multiple linear regression model was created in the cognitively intact participants with MCE score as the dependent variable, and age, sex, years of school, and immigrant background as predictors. Following, we created regression-based normative using the significant variables in the regression model by using the predicted mean MCE score and residual standard deviation. Lastly, diagnostic accuracy was examined using Receiver operating characteristic (ROC) models with the cognitive syndrome diagnosis as the reference standard for both the MCE and RUDAS scores. Importantly, participants younger than 65 years of age were excluded from diagnostic accuracy analyses as they were almost exclusively cognitively intact, and including them would likely have falsely inflated our accuracy. Differences between the Area under the ROC curve (AUC) of RUDAS and MCE were established using DeLong's method. Results were summarized with accuracy, sensitivity, specificity, and likelihood ratios across Youden's threshold, the original MCE cutoff, and the generated regression-based percentile cutoffs. A subanalysis examined the ability of the MCE and RUDAS to differentiate AD dementia from non-AD dementia using ROC models as described above.

4.6.2. Study 2

Our systematic review aimed to investigate ethnic and racial influences on blood biomarker concentrations and diagnostic and prognostic accuracy for AD.

Following PRISMA guidelines [152], we created a search string and selection criteria to identify relevant studies, including search words for blood biomarkers, AD, and ethnicity/race (search string is detailed in Kjaergaard et al., (2025)) [2] and Appendix 2). The databases PubMed and Web of Science were used to identify relevant studies. Each study was screened by two independent assessors.

We extracted data from each study, including sample size of ethnic/racial groups, biomarker concentrations, accuracy/prognostic effects, and the authors' interpretations of their findings. We compared the evidence in a qualitative synthesis and summarized the findings in three tables (concentrations, diagnostic accuracy, prognostic value).

We used the *Quality Assessment of Diagnostic Accuracy Studies* framework to evaluate the quality of the studies [163]. Two researchers assessed each study independently as having low/high/unclear risk across seven categories covering risk of bias and applicability concerns.

4.6.3. Study 3

The reference standard in this study was (1) a probable or possible clinical diagnosis of AD-MCI or AD-dementia, and (2) CSF/Aβ-PET-verified AD pathology. The main predictor was plasma p-tau217, and we were specifically interested in the variables immigrant status and geographic region of birth. The statistical approach is described in depth in the published manuscript (Appendix 3). In brief, we examined the influence of ethnicity on plasma p-tau217 concentrations first by group comparisons across the included covariates (age, sex, education, AD status, CSF/Aβ-PET-verified AD pathology, BMI, eGFR, Alanine aminotransferase (ALT), Hemoglobin A1c (HbA1c), Thyroid-stimulating hormone (TSH), and cumulative comorbidities). Second, multiple linear regression models were created with plasma p-tau217 as the dependent variable, and AD or CSF/Aβ-PET-verified AD status

and other covariates as predictors. Using this approach, we sought to identify any variables that influenced plasma p-tau217 that were not explained by AD. Lastly, logistic regression models and ROC analyses were used to examine the influence of ethnicity and other covariates on diagnostic accuracy.

4.6.4. Study 4

In this study, we assessed the added value of combining the MCE with plasma p-tau217 in identifying AD-MCI and AD-dementia. This study selected patients from the BlooDiv cohort who (1) were born outside of the Nordic countries, and (2) were examined with the MCE during their routine clinical evaluation. We excluded patients with unknown cognitive status. The reference standard was a possible or probable diagnosis of AD-dementia or AD-MCI.

The statistical approach is described in depth in the published manuscript (Appendix 4). Briefly, we created four models (logistic regression and five-fold cross-validated ROCs), all adjusted for age, sex, and education. The four models were an MCE model, an MCE subtest model, an MCE with p-tau217 model, and an MCE subtest with p-tau217 model. The added value of combining MCE and plasma p-tau217 was examined using measures of model fit (Akaike Information Criterion) and measures of diagnostic accuracy (AUC, sensitivity, specificity, predictive values, and likelihood ratios). DeLong's statistics compared the AUCs between the models. Subanalyses were performed comparing AD to other specific dementia disorders, and in patients with known CSF or Aβ-PET status.

4.6.5. Study 5

Study 5 characterized sociodemographic factors and medical conditions across patients with concordant and discordant biomarker profiles using a subset of the BlooDiv cohort [3]. These patients were selected if they had CSF results on the biomarkers Aβ42 and p-tau181 or Aβ-PET. Amyloid status was established using established cutoffs of a ratio between Aβ42 and p-tau181 (see Supplementary Table 1 in Kjaergaard et al., 2025 [3]) or Aβ-PET. Aβ-PET took priority in cases of disagreement. Plasma p-tau217 was dichotomized using a single cutoff from a pre-established cutoff developed at Lund University using Youden's index (0.308 pg/ml).

The statistical approach is described in depth in the submitted manuscript (Appendix 5). We created four groups based on patients' amyloid status (Aβ+/-) and plasma p-tau217 status (p-tau217+/-). Group differences were examined between Aβ+/p-tau217+ and Aβ+/p-tau217- and between Aβ-/p-tau217- and Aβ-/p-tau217+. Statistical significance was set at $p < 0.05$ for False Discovery Rate (FDR) corrected adjusted comparisons. Effect sizes were interpreted as negligible, small, medium, and large (Cohen's D: 0.0-0.2 = negligible, 0.2-0.5 = small, 0.5-0.8 = medium, >0.8 = large. Cliff's Delta: 0.0-0.147 = negligible, 0.147-0.33 = small, 0.33-0.474 = medium, >0.474 = large. Cramer's V: 0.0-0.1 = negligible, 0.1-0.3 small, 0.3-0.5 medium, >0.5 large).

5. SUMMARY OF RESULTS

This section will present the main findings from studies 1 to 5 [1–4] (Appendix 1-5). The full manuscripts of the studies are available in the Appendices for comprehensive descriptions.

5.1. Study 1

A total of 1,449 participants were included. Of these, 786 (54.2%) had immigrant backgrounds. The participants were born across 63 countries, with most being from Europe (N = 640), followed by South America (N = 414), Middle East and North Africa (N = 370), South, East, and Southeast Asia (N = 14), and Sub-Saharan Africa (N = 11). In total, 1001 participants were cognitively intact, while 140 patients had MCI, and 308 had dementia (Table 5.1.A).

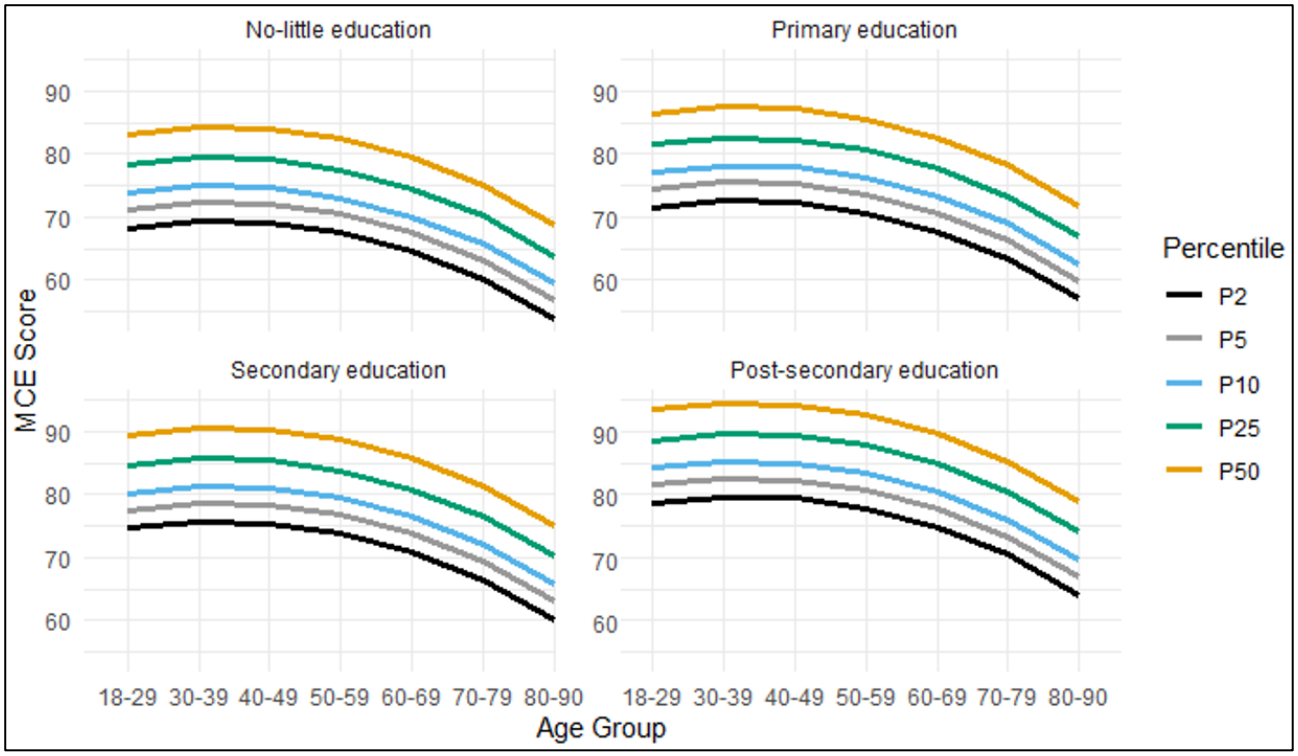
Table 5.1.A. Descriptive characteristics

	Cognitively intact	**Cognitively intact *(≥ 65 years old)***	**MCI**	**Dementia**	**P-value**
N	1001	364	140	308	-
Age, years	59.0 [47.0, 69.0]	73.0 [68.0, 78.0]	72.0 [65.0, 77.0]	77.0 [73.0, 82.0]	< .001[c,d]
Female sex (%)	593 (59.2%)	224 (61.5%)	68 (48.6%)	171 (55.5%)	.025 [b]
Education, years	12.0 [6.0, 15.0]	10.0 [5.0, 14.0]	9.0 [6.0, 12.0]	7.5 [4.0, 11.0]	< .001[c,d]
No formal education (%)	60 (6.0%)	38 (10.5%)	4 (3.0%)	25 (8.4%)	.03 [b,d]
Immigrant status (%)	610 (60.9%)	150 (41.2%)	63 (45.0%)	113 (36.7%)	.20
MCE score	89.0 [81.0, 94.0]	82.0 [79.0, 89.0]	67.0 [60.0, 76.5]	51.0 [43.0, 61.0]	< .001 [a]
RUDAS score	28.0 [27.0, 30.0]	27.0 [26.0, 28.0]	24.0 [22.0, 26.0]	20.0 [17.0, 23.0]	< .001 [a]

Note: Pairwise comparisons (corrected p-values) between cognitively intact ≥65 years old, MCI, and dementia (a = Significant differences between all groups, b = difference between cognitively intact and MCI, c = difference between cognitively intact and dementia, d = difference between MCI and dementia). Table from Kjaergaard et al., 2026 [1]
Abbreviations: MCE = Multicultural Cognitive Examination, MCI = Mild Cognitive Impairment, RUDAS = Rowland Universal Dementia Assessment Scale

We found a significant effect of age (β = -0.21, p < 0.001) and years of school (β = 0.80, p < 0.001), but not sex (p = 0.10) or immigrant background (p = 0.63) on the MCE score in cognitively intact participants. Based on these findings, we created regression-based normative data using age, age^2, and education. The age^2 variable was added because of the quadratic effect of age on the MCE and a significantly improved model fit. We then summarized the normative data in percentile thresholds (2nd percentile (P2), P5, P10, P25, P50) as displayed in Figure 5.1.

Figure 5.1. Percentile thresholds of normative MCE data



Note: Figure displaying the estimated percentile thresholds (p50, p25, p10, p5, p2) across age and education groups. Figure created from the normative data in Kjaergaard et al., 2026 [1].

Diagnostic accuracy analyses found that the MCE was significantly more accurate compared to the RUDAS in differentiating cognitively intact from dementia (AUC 0.95 vs. 0.92, p < 0.001), and cognitively intact from MCI (AUC 0.84 vs. 0.78, p = 0.01). We provided accuracy metrics across Youden's index, the original MCE cutoff [51], and the different generated percentile scores in Table 5.1.B.

Table 5.1.B. Diagnostic accuracies for dementia and MCI

Dementia vs. cognitively intact						
Cutoff	**Original** [51] *70/71*	**Youden** *68/69*	**25th percentile**	**10th percentile**	**5th percentile**	**2nd percentile**
Accuracy	0.88	0.88	0.83	0.89	0.89	0.88
Sensitivity	0.94	0.91	0.96	0.92	0.87	0.82
Specificity	0.83	0.86	0.73	0.86	0.90	0.93
MCI vs. cognitively intact						
Cutoff	**Original** [51] *70/71*	**Youden** *73/74*	**25th percentile**	**10th percentile**	**5th percentile**	**2nd percentile**
Accuracy	0.80	0.78	0.75	0.82	0.82	0.82
Sensitivity	0.70	0.78	0.81	0.65	0.52	0.43
Specificity	0.83	0.79	0.73	0.86	0.90	0.93

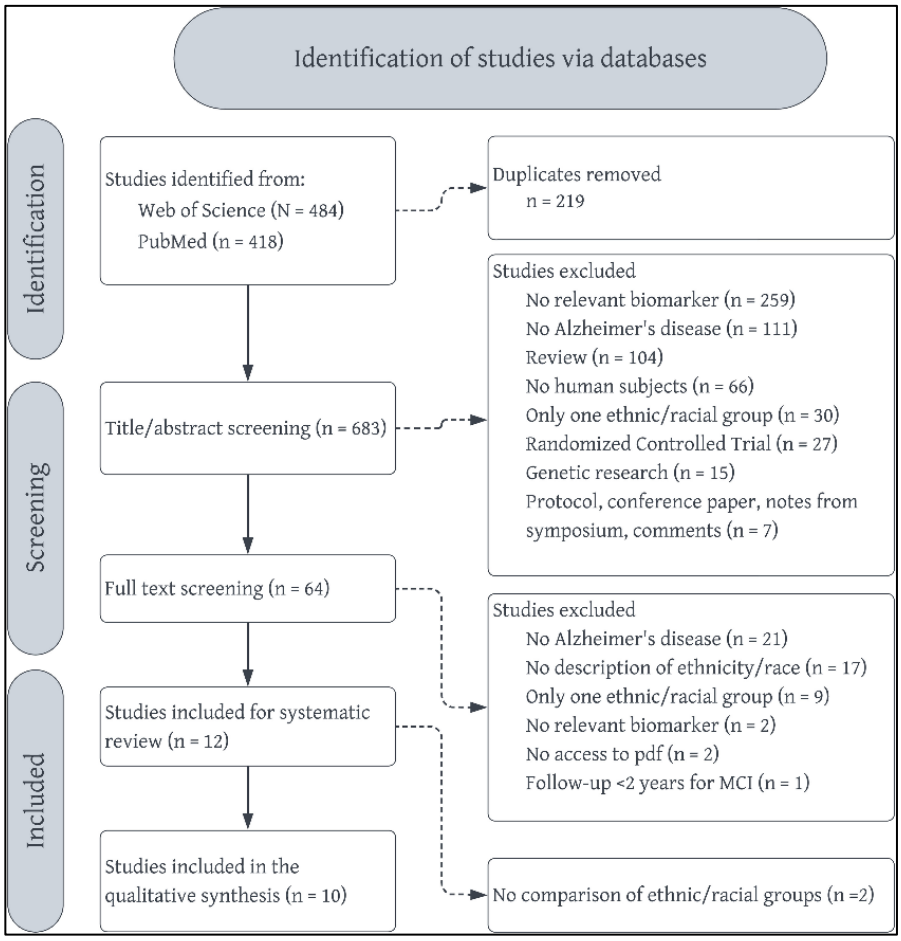
Note: Table presenting accuracy, sensitivity, and specificity across the original MCE cutoff, Youden's index cutoff, and percentile cutoffs from our normative data. Table from Kjaergaard et al., 2026 [1].
Abbreviations: MCI = Mild cognitive impairment.

The AUCs of the MCE did not significantly differ in separating AD dementia or non-AD dementia from cognitively intact participants (AUC 0.97 vs. 0.94, $p = 0.06$). Of the MCE subtests, RPT delayed recall best differentiated patients with AD dementia and non-AD dementia (median: 1.0 vs. 4.0, $p < 0.001$).

5.2. Study 2

We included 10 of the 683 screened studies in this systematic review on ethnic and racial influences on blood biomarkers for AD (Figure 5.2.A) [110, 164–172]. The studies characterized their participants as White, Black/African American, and Hispanic. White participants were present in all 10 studies, Hispanic participants in 8 studies, and Black participants in 7 studies. 9 different blood biomarkers were examined across the studies, including NfL, p-tau variants, and Aβ.

Figure 5.2.A. Flow-chart for systematic review

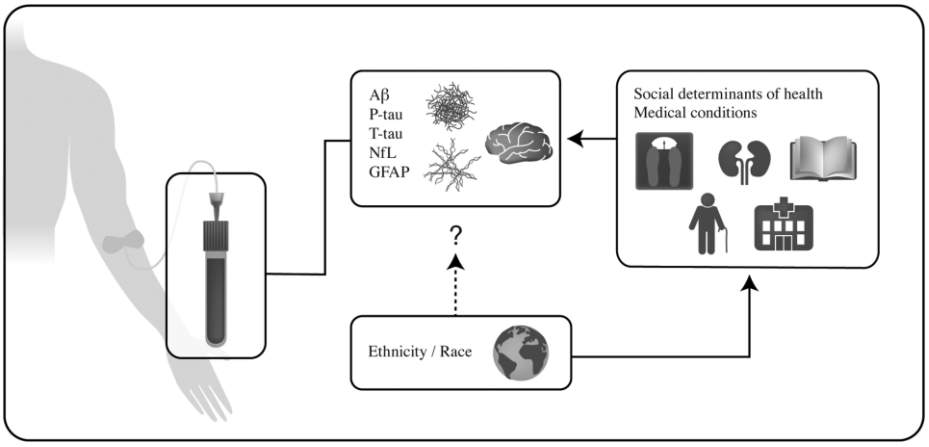


Note: Figure from Kjaergaard et al., (2025) [2]. Figure created using Lucidchart.

The results were grouped in three sections: Concentrations, diagnostic accuracy, and prognostic accuracy. The studies generally found differences between ethnic/racial groups on biomarker concentrations, although the significance became non-significant in two of five studies when adjusting for covariates [168, 171]. For diagnostic and prognostic accuracy, similar patterns were found in which some studies found differences between ethnic/racial groups, but the effects became non-significant in some studies after adjusting or matching on covariates [165, 171].

No clear pattern emerged across the studies regarding whether there are differences in blood biomarker concentrations or in diagnostic or prognostic accuracies between participants from different ethnic/racial groups. We found it most plausible that ethnicity/race was acting as a mediating factor rather than having a direct influence on the biomarkers (Figure 5.2.B).

Figure 5.2.B Interpretation of the results from the systematic review



Note: Figure displaying our interpretation that ethnicity/race may be a mediating factor, but itself may not have an influence on blood biomarkers. Figure from Kjaergaard et al., (2025) [2]. Created in Adobe Illustrator 2024.
Abbreviations: Aβ = Amyloid beta, GFAP = Glial fibrillary acidic protein, NfL = Neurofilament light, p-tau = phosphorylated tau, t-tau = total tau.

5.3. Study 3

In study 3, we included 1,170 memory clinic patients of whom 50% had immigrant backgrounds. Most foreign-born patients originated from the Greater Middle East (N = 236), followed by Europe (N = 191), and Africa (N = 59). Overall, the foreign-born patients had fewer years of education, lower prevalence of clinical AD and CSF/Aβ-PET-verified AD pathology, higher BMI and HbA1c, and more cumulative comorbidities (Table 5.3).

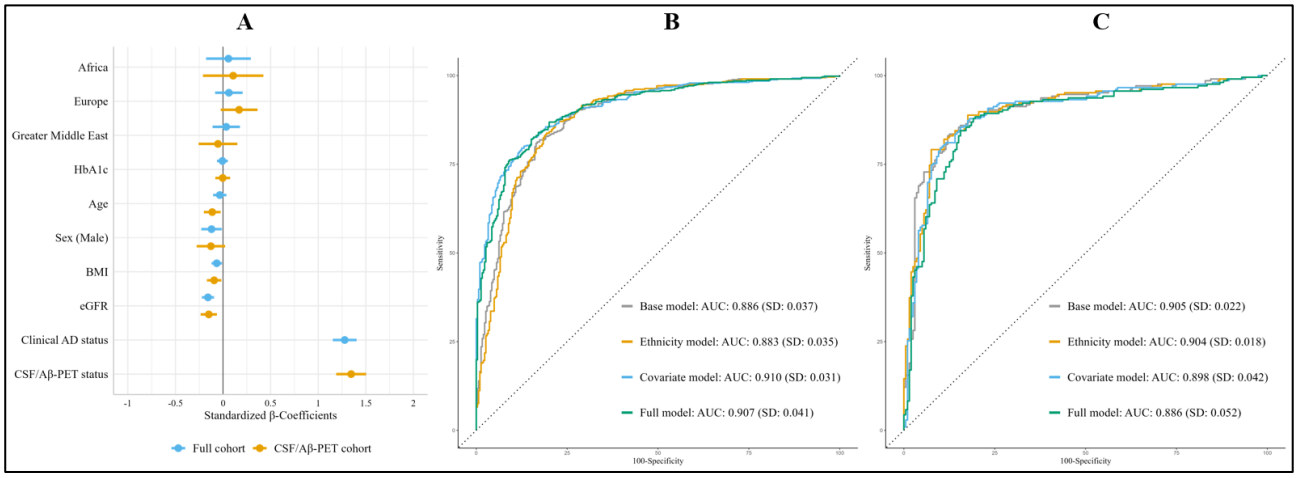
Plasma p-tau217 concentrations were examined using a linear regression. The results showed that AD-status, eGFR, sex, and BMI had significant influences on plasma p-tau217 concentrations ($p < 0.05$) (Figure 5.3.A). Geographic origin did not influence the plasma p-tau217 concentrations (p ranged from 0.40 to 0.64). Across four ROC models, we found no differences in diagnostic accuracies when adjusting for covariates, including geographic origin, compared to plasma p-tau217 alone (Figure 5.3.B and Figure 5.3.C).

Table 5.3. Characteristics of the BlooDiv cohort

	Native-born	Foreign-born	Greater Middle East	Europe	Africa	P-value
N	585	585	236	191	59	-
Copenhagen/Malmö clinic	585 / 0	448 / 137	186 / 50	136 / 55	55 / 4	< .001
Age, years	68.5 (10.7)	68.6 (10.6)	65.9 (9.9)	70.8 (11.0)	67.7 (9.3)	< .001
Sex (% female)	53.0%	51.5%	47.5%	55.0%	50.8%	.409
Education, years	11.7 (3.3)	10.1 (4.9)	9.4 (5.4)	10.5 (3.9)	7.9 (5.3)	< .001
Plasma p-tau217 pg/ml	0.404 [0.273; 0.701]	0.347 [0.256; 0.585]	0.319 [0.242; 0.475]	0.416 [0.275; 0.721]	0.300 [0.240; 0.477]	< .001
AD or Mixed AD (%)	230/585 (39.3%)	162/585 (27.7%)	40/236 (16.9%)	73/191 (38.2%)	11/59 (23.7%)	< .001
CSF/Aβ-PET-verified AD pathology (%)	151/258 (58.5%)	113/281 (40.2%)	31/108 (28.7%)	46/97 (47.4%)	10/28 (35.7%)	< .001
Standard bloodwork and BMI						
Body mass index (kg/m^2)	25.3 [22.5; 28.9]	26.4 [23.4; 30.0]	27.5 [24.6; 31.1]	25.8 [22.9; 28.9]	27.6 [24.5; 29.4]	< .001
eGFR (mL/min/1.73m^2)	82 [69;91]	85 [72; 94]	87 [75;96]	84 [69;93]	87.5 [76;94]	.004
ALT (IU/L)	22 [17;29]	21 [16.8; 29]	22 [17;30]	20.7 [15.6;27]	21 [18;29]	.146
HbA1c (IFCC: mmol/mol)	38.3 [34.9; 41.7]	40.4 [36.9; 47.9]	42.4 [38.3; 53.1]	39 [35.5; 44]	41 [37.1; 45]	< .001
TSH (mIE/L)	1.5 [1.1; 2.2]	1.5 [1.0; 2.3]	1.6 [1; 2.5]	1.6 [1; 2.2]	1.4 [1; 2.3]	.774
Medical conditions						
Cumulative comorbidities (%) (0-1 / 2-3 / 4-6)	61.9 / 32.0 / 6.2	46.7 / 40.3 / 13.0	39.8 / 42.4 / 17.8	48.7 / 41.9 / 9.4	54.2 / 35.6 / 10.2	< .001

Note: Cohort characteristics of the BlooDiv cohort. Modified from Kjaergaard et al., (2025) [3]. P-value compared native-born patients with the three geographic areas. Cumulative comorbidities include diabetes, hypertension, hypercholesterolemia, history of stroke, thyroid disease, kidney disease, liver disease, ischemic heart disease, atrial fibrillation, depression, neuropathy, head trauma within one year, and sleep disorder.
Abbreviations: Aβ = Amyloid beta, AD = Alzheimer's disease, ALT = alanine transaminase, CSF = cerebrospinal fluid, eGFR = estimated glomerular filtration rate, HbA1c = hemoglobin A1c, IFCC = International Federation of Clinical Chemistry, PET = positron emission tomography, p-tau = phosphorylated tau, TSH = thyroid-stimulating hormone.

Figures 5.3. (A) Forestplot of standardized beta-coefficients, (B) AUC for clinical AD, (C) AUC for CSF/Aβ-PET-verified AD pathology



Note: Figures modified from Kjaergaard et al. (2025) [3]
Abbreviations: Aβ = amyloid beta, AD = Alzheimer's disease, AUC = Area under the receiver operating characteristics curve, BMI = body mass index, CSF = cerebrospinal fluid, eGFR = estimated glomerular filtration rate, HbA1c = hemoglobin A1c, PET = positron emission tomography, SD = standard deviation.

5.4. Study 4

In study 4, we included 201 memory clinic patients with immigrant backgrounds from the BlooDiv cohort. 51 had AD, 45 had other specific dementia disorders, 83 had SCD, affective or somatic disorders, and 22 needed further follow-up to set a certain diagnosis (Table 5.4). 101 patients had available data on CSF or Aβ-PET biomarkers, of these, 41 were classified as Aβ positive and 60 as Aβ negative.

Table 5.4. Cohort characteristics

	AD and mixed AD	Other specific dementia disorders *	SCD/Affective/ Somatic †	Uncertain	p-value
N	51	45	83	22	
Age, years	76.0 [71.0, 79.0]	73.0 [65.0, 77.0]	63.0 [57.0, 69.0]	71.5 [63.0, 75.0]	< 0.001
Female sex (%)	31 (60.8%)	16 (35.6%)	51 (61.4%)	14 (63.6%)	0.018
Education, years	9.0 [5.0, 12.0]	9.0 [5.0, 12.0]	8.0 [5.0, 12.0]	10.0 [5.0, 12.0]	0.8
Syndrome diagnosis					< 0.001
SCD	0 (0%)	0 (0%)	53 (63.9%)	1 (4.5%)	
MCI	6 (11.8%)	8 (17.8%)	26 (31.3%)	12 (54.5%)	
Dementia (mild/moderate/severe)	24/20/1 (88.3%)	20/16/1 (82.2%)	2/2/0 (4.8%)	8/1/0 (40.9%)	
P-tau217, pg/ml	0.7 [0.5, 1.1]	0.3 [0.2, 0.4]	0.3 [0.2, 0.4]	0.3 [0.2, 0.4]	< 0.001
MCE score	50.5 [37.5, 65.5]	54.5 [36.0, 65.5]	73.0 [62.0, 82.0]	65.8 [62.0, 69.0]	< 0.001
RUDAS	20.0 [15.0, 24.0]	21.0 [16.0, 24.0]	26.0 [22.0, 28.0]	23.0 [21.0, 26.0]	< 0.001
RPT immediate recall	4.3 [2.3, 5.7]	4.7 [3.0, 5.3]	7.0 [5.7, 8.0]	6.0 [5.0, 7.0]	< 0.001
RPT delayed recall	2.0 [0.0, 5.0]	4.0 [1.0, 6.0]	7.0 [6.0, 9.0]	6.0 [4.0, 7.0]	< 0.001
RPT recognition	8.0 [5.0, 10.0]	8.0 [5.0, 10.0]	10.0 [9.0, 10.0]	9.5 [9.0, 10.0]	< 0.001
SFT	10.0 [6.0, 13.0]	8.0 [5.0, 10.0]	14.0 [10.0, 17.0]	12.0 [9.0, 16.0]	< 0.001
CRT	9.0 [4.0, 11.0]	9.0 [5.5, 11.5]	11.0 [8.5, 12.0]	10.0 [9.0, 12.0]	< 0.001

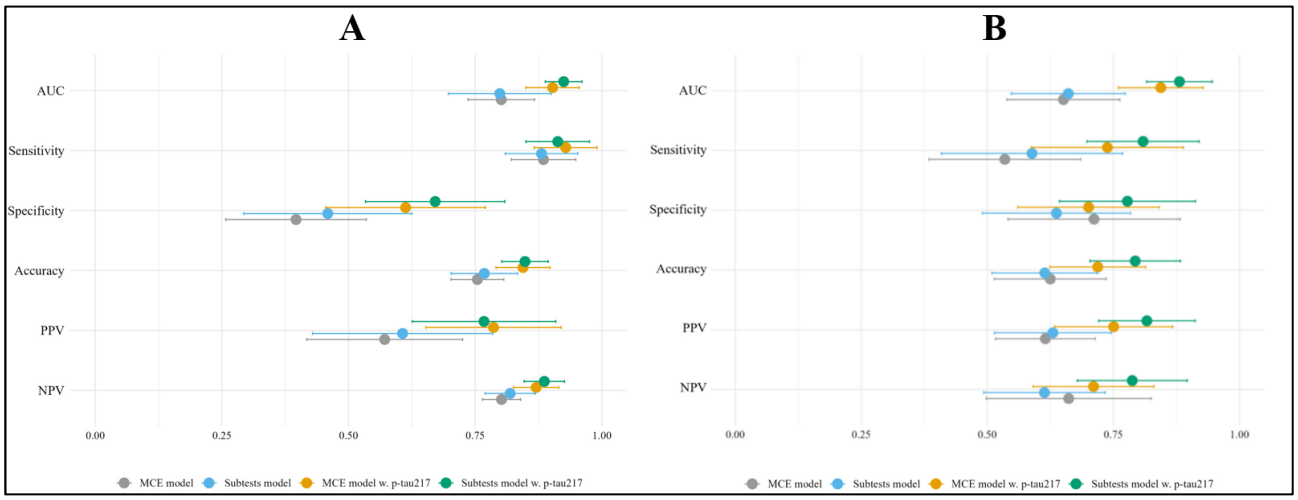
Note: Table adapted from Kjaergaard et al., 2025 [4].
Abbreviations: AD = Alzheimer's disease, CRT = Clock Reading Test, MCE = Multicultural Cognitive Examination, MCI = Mild Cognitive Impairment, p-tau = phosphorylated tau, SCD = Subjective Cognitive Decline, RPT = Recall of Pictures Test, RUDAS = Rowland Universal Dementia Assessment Scale, SFT = Supermarket Fluency Test.

The four logistic regression models for identifying AD in the mixed memory clinic cohort progressively explained more variance and displayed a better model fit when the MCE subtests and plasma p-tau217 were included (R^2: 0.223 to 0.544, AIC: 174.6 to 118.59). These improvements were also found in the cross-validated ROC models, with each model having significantly higher AUC

than the previous (AUCs improved from 0.798 to 0.925) (Figure 5.4.A). These improvements in particular reflected higher specificities and negative predictive values.

Meanwhile, in differentiating AD from other specific dementia disorders, the MCE and its subtests were less accurate with AUCs from 0.651 to 0.661 (Figure 5.4.B). However, adding plasma p-tau217 significantly improved AUCs (0.844 and 0.881) (Figure 5.4.B).

Figure 5.4. (A) Diagnostic accuracy metrics for identifying AD in a mixed memory clinic cohort. (B) Diagnostic accuracy for differentiating AD from other dementia disorders.



Note: Figure from Kjaergaard et al., 2025 [4].
Abbreviations: AUC = area under the receiver operating characteristic curve, MCE = Multicultural Cognitive Examination, NPV =Negative Predictive Value, PPV = Positive Predictive Value, p-tau = phosphorylated tau.

5.5. Study 5

In study 5, we included 539 memory clinic patients from the BlooDiv cohort, of whom 249 were classified as Aβ+/p-tau217+, 203 Aβ-/p-tau217-, 72 Aβ-/p-tau217+, and 15 Aβ+/p-tau217-. Comparing the groups, we only found differences in the proportion of clinical AD diagnoses in all comparisons and syndrome diagnosis among Aβ+ patients. There were no statistically significant differences in any sociodemographic variables or medical conditions (Table 5.5). All the non-significant variables had negligible effect sizes except for eGFR (Cohen's D = 0.27) and BMI

(Cohen's D = 0.32) among the Aβ- patients, which showed small effect sizes, and BMI among Aβ+ patients, which revealed a moderate to large effect size (Cohen's D = 0.67).

Table 5.5. Descriptive characteristics and comparison of concordant with discordant patients

	Aβ-/ p-tau217-	**Aβ-/ p-tau217+**	**P-value**	**Effect size**	**Aβ+/ p-tau217-**	**Aβ+/ p-tau217+**	**P-value**	**Effect size**
N	203	72			15	249		
Age, years	66.8 (9.3)	68.7 (8.5)	0.37	Small	69.1 (9.0)	69.9 (7.8)	0.89	Negligible
Female sex	94 (46.3%)	34 (47.2%)	>0.9	Negligible	5 (33.3%)	148 (59.4%)	0.18*	Small
Immigrant status	126 (62.1%)	42 (58.3%)	0.65	Negligible	8 (53.3%)	105 (42.2%)	0.56	Negligible
Syndrome diagnosis			0.56	Negligible			0.005*	Medium
SCD	26 (12.8%)	10 (13.9%)			2 (13.3%)	3 (1.2%)		
MCI	81 (39.9%)	21 (29.2%)			8 (53.3%)	51 (20.5%)		
Dementia	76 (37.4%)	36 (50.0%)			5 (33.3%)	190 (76.3%)		
undecided	20 (9.9%)	5 (6.9%)			0 (0.0%)	5 (2.0%)		
Etiological diagnoses			<0.001*	Medium			<0.001*	Medium
AD and mixed AD	10 (4.9%)	20 (27.8%)			6 (40.0%)	214 (85.9%)		
Non-neurodegenerative	36 (17.7%)	8 (11.1%)			1 (6.7%)	6 (2.4%)		
NPH	21 (10.3%)	11 (15.3%)			0 (0%)	9 (3.6%)		
Other neurodegenerative	31 (15.3%)	10 (13.9%)			1 (6.7%)	7 (2.8%)		
Non neurological	49 (24.1%)	15 (20.8%)			2 (13.3%)	4 (1.6%)		
Unknown	56 (27.6%)	8 (11.1%)			5 (33.3%)	9 (3.6%)		
Diabetes	67 (33.0%)	20 (27.8%)	0.64	Negligible	2 (13.3%)	49 (19.7%)	0.89	Negligible
Hypertension	100 (49.3%)	32 (44.4%)	0.64	Negligible	6 (40.0%)	103 (41.4%)	>0.9	Negligible
Hyperlipidemia	43 (21.2%)	18 (25.0%)	0.64	Negligible	6 (40.0%)	62 (24.9%)	0.47	Negligible
Clinical history of stroke	15 (7.4%)	7 (9.7%)	0.64	Negligible	2 (13.3%)	17 (6.8%)	0.51	Negligible
eGFR, mL/min/1.73m^2	83.8 (18.4)	78.6 (21.0)	0.24	Small	81.2 (14.8)	81.1 (14.6)	>0.9	Negligible
BMI, kg/m^2	27.7 (5.2)	26.1 (4.4)	0.12*	Small	28.5 (4.2)	25.5 (4.5)	0.10*	Medium-large
Fazeka's score			0.39	Negligible			>0.9	Negligible
0-1	83 (60.1%)	36 (72.0%)			9 (81.8%)	151 (74.4%)		
2-3	55 (39.9%)	14 (28.0%)			2 (18.2%)	52 (25.6%)		
MMSE/RUDAS (0-30)	23.0 [20.0, 27.0]	24.0 [20.0, 28.0]	0.64	Negligible	25.0 [22.0, 28.0]	23.0 [18.0, 26.0]	0.35	Small

Note: Adapted from Kjaergaard et al., (under review) (Appendix 5). Effect sizes interpretation (Cohen's D: 0.0-0.2 Negligible, 0.2-0.5 Small, 0.5-0.8 Medium, >0.8 Large. Cliff's Delta: 0.0-0.147 Negligible, 0.147-0.33 Small, 0.33-0.474 Medium, >0.474 Large. Cramer's V: 0.0-0.1 Negligible, 0.1-0.3 Small, 0.3-0.5 Medium, >0.5 Large).
Abbreviations: Aβ = Amyloid beta, AD = Alzheimer's disease, BMI = Body Mass Index, eGFR = estimated Glomerular Filtration Rate, MCI = Mild Cognitive Impairment, MMSE = Mini Mental State Examination, NPH = Normal Pressure Hydrocephalus, p-tau = phosphorylated tau, RUDAS = Rowland Universal Dementia Assessment Scale, SCD = Subjective Cognitive Decline.

6. DISCUSSION

6.1. Summary of main findings

This thesis addressed the overarching aim to investigate influences of sociodemographic factors and medical conditions on plasma p-tau217 and the MCE, and to examine the diagnostic accuracy of these diagnostic tools in a diverse memory clinic setting.

Concerning the **MCE** (Study 1), we did not identify any influence of sex or having immigrant background, but we did find an influence of age and education. The age and education-related influences were addressed by creating normative data, which was then applied to explore diagnostic performance. Overall, the MCE was significantly more accurate compared to the RUDAS, both for dementia and MCI, and was equally accurate for identifying AD dementia as non-AD dementia. Study 4 replicated the overall accuracies in the BlooDiv cohort, which were supplemented by discovering that the MCE is less accurate for differential diagnostic purposes among cognitively impaired patients. For differential diagnostic purposes among cognitively impaired patients, plasma p-tau217 significantly improved diagnostic accuracy.

Studies 2 to 5 explored covariate influences and accuracies for **plasma p-tau217**. Study 2 set the scene by summarizing the results from previous studies on ethnicity/race and blood biomarkers. This systematic review revealed a clear lack of knowledge and consensus in the field concerning whether patients' ethnic or racial background influences biomarker concentrations and accuracy. Study 3 adds to the knowledge base on ethnicity and plasma p-tau217, providing evidence that ethnicity does not influence plasma p-tau217 concentrations or diagnostic accuracy. This result was consistent whether using clinical diagnoses or CSF/Aβ-PET-verified AD pathology as the outcome. As plasma p-tau217 would not be used as the sole component of the diagnostic evaluation, study 4 more closely reflects the clinical reality, by examining if and how plasma p-tau217 contributes to the diagnostic accuracy after cognitive testing with the MCE. Indeed, plasma p-tau217 improved accuracy metrics, especially

specificities and differential diagnostics. As we did not find an influence of ethnicity, I was curious if there were other causes that influenced plasma p-tau217 by characterizing discordant biomarker profiles. Study 5 characterized patients with discordant biomarker profiles but found no significant differences, except for dementia severity and etiological diagnosis, as expected. It was surprising to us that the results were not clearer for kidney function and BMI, as previous studies have suggested.

In the following, I critically discuss our results in relation to other studies and evaluate methodological limitations. The discussion is divided into three parts. One focusing on overcoming diagnostic barriers for diverse patients, a second dedicated to ethnicity and blood biomarkers, and a third discussing possible causes of discordant biomarker profiles and implications for clinical practice

6.2. Overcoming diagnostic barriers for diverse patients

Culturally, linguistically, and educationally diverse memory clinic patients encounter substantial barriers in their dementia evaluations, particularly concerning cognitive testing [29]. Some consequences of these barriers may include higher rates of misdiagnosis and delayed diagnosis [25, 173, 174]. Indeed, a systematic review that collected evidence of delayed diagnoses and misdiagnoses found that ethnicity was the most frequent factor associated with delayed diagnosis or misdiagnosis [173]. Furthermore, the patients with minority ethnic backgrounds had more cognitive and functional decline at the time of diagnosis compared to the majority ethnic population. So, there are clear risks and challenges that these patients face, but the causes are less clear. Qualitative evidence among patients with dementia, carers, health care professionals, and interpreters points to challenges associated with social and structural barriers to care as well as stigma and mistrust, leading to avoidance of the medical system [175]. Our studies address one aspect of these barriers, validating cognitive tests that are less influenced by culture, language, and education. This may be beneficial for patients who enter the medical system and, hopefully, can help build trust as healthcare

professionals become better equipped for cross-cultural situations. However, focus on outreach, community engagement, and knowledge sharing should be a top priority.

6.2.1. MCE vs. other cognitive tests

In our study, we demonstrated that the MCE was equally accurate for native-born participants as for those with immigrant backgrounds, suggesting that the MCE can overcome a key barrier in cognitive screening (Study 1). However, identifying cognitive impairment in multicultural settings is not unique to the MCE, as similar diagnostic accuracies are found among other cross-cultural screening tests, test batteries, and case-finding instruments [37, 53, 143, 176].

Identifying MCI has been a longstanding challenge, also in traditional cognitive tests, but this is particularly challenging in diverse populations. In our cohort, we were enthusiastic about the ability of the MCE to identify MCI. We found that the MCE differentiated cognitively intact participants from those with MCI with an AUC of 0.84, significantly higher than that of the RUDAS (AUC 0.78, $p = 0.01$). Also relevant is whether the MCE is better than other clinically implemented tests, such as the MMSE, MoCA, and ACE [17–19]. A meta-analysis of the ability of these three tests in differentiating controls from MCI ranges from 0.76 to 0.85 [177], which would place the MCE in the uppermost estimates. Importantly, the accuracy of the MCE in Study 1 was determined in a diverse cohort, emphasizing its clinical utility and generalizability, while the other tests were examined in more homogeneous cohorts. Another well-known cross-cultural cognitive screening test is the CCD, for which the AUCs of its subtests range from 0.85 to 0.95 in identifying dementia in a diverse cohort [50]. However, less is known about the CCD's ability to identify MCI in diverse mixed memory clinic cohorts, but one study in a majority Spanish population found AUCs for AD-MCI ranging from 0.72 to 0.84 [178].

The context of use should always be considered, including whether the tests are accurate across typical diagnoses in a memory clinic. Some screening tests are designed to be disease-specific, with, for example, an emphasis on episodic memory when targeting AD. Both in Studies 1 and 4 we demonstrated an equal ability of the MCE to identify AD and non-AD dementia, suggesting it may be appropriate for the initial screening or triaging in a memory clinic setting. However, our evidence does not support using the MCE as a differential diagnostic tool, although patients with AD were particularly impaired on RPT delayed recall. In practice, the MCE may identify most patients with dementia and MCI, whereas evidence from other parts of the clinical evaluation may be more useful for differential diagnostic purposes (clinical history, subjective symptoms, neurological exam, structural and functional imaging, biomarkers, neuropsychological assessment). For example, study 4 supports plasma p-tau217 as a strong aid for differential diagnostic purposes.

6.2.2. Language and interpreter-mediated assessment

Our operationalization of being culturally and linguistically diverse by country of origin may have missed important nuances of clinical importance. We did not include language parameters in our analyses, including the administration language, whether this language was the patient's native, dominant, or preferred language, nor whether it was an interpreter-mediated assessment. As touched upon in the background, being examined in a non-native language may lead to lower scores on cognitive tests, especially on verbal tasks [179]. The difficulty of cognitive tests and scales may vary with spoken language because of differences in phonology, lexicon, and grammar. Cross-cultural tests attempt to limit these factors by choosing words/images with similar difficulties and lengths across languages, and limit complex test instructions.

Interpreter-mediated assessment may diminish linguistic bias, reduce miscommunication, improve patient satisfaction, and improve clinical outcomes [35, 41]. Although using an interpreter is

recommended by several national neuropsychological societies and ECCroN, this service is not always available, and the quality varies between clinics and countries. An additional caveat is that several tests are not validated for interpreter-mediated administration, so linguistic bias may remain in interpreter-mediated assessment if not using appropriate cognitive tests [35, 41, 42, 49]. When possible, the MCE was administered with an interpreter to minimize linguistic bias [3, 53, 142–147]. Within the BlooDiv cohort, we noted whether the MCE was administered with an interpreter (professional or informal). 238 patients were assessed with an interpreter (160 with a professional interpreter, 78 with an informal interpreter). However, analyses comparing the impact of having an interpreter are less meaningful in our cohort, as there is no fair comparison group and likely substantial selection bias in who is offered interpreting services.

6.2.3. Cultural bias

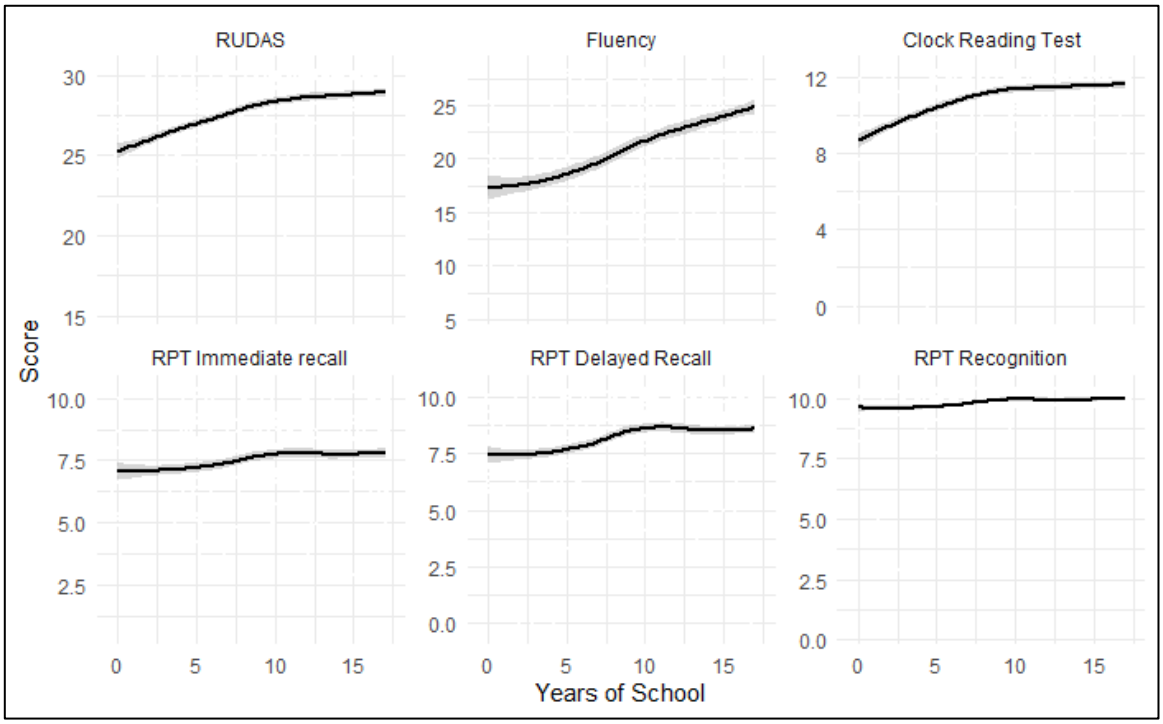
Interpreters serve not only as language translators, but also often as cultural mediators with relevant knowledge of history and local idioms of distress. We all grow up in specific cultural contexts and develop our cognitive skills within these contexts. Therefore, differences in test performance can be expected among patients from different countries, but also between subcultures within the same country [180]. Reducing cultural bias is an essential step in adopting a new cognitive test, which should be done following official translation and adaptation guidelines, for example, the International Test Commission Guidelines [55]. Following these guidelines, problematic test items should be identified, which include words that do not exist in the other language and items that are not equally difficult in the adopting culture (for example, pictures related to snow in tropical countries) [55, 180]. The benefit of cross-cultural cognitive tests is that they generally have simple and clear test instructions that are easily translated and have less need for adaptation or even do not need adaptation of test items at all [35, 38, 42]. However, even if tests have been validated and adapted properly, it

does not imply that testing all cultural groups is free of bias, as including every cultural group and language in research studies is unrealistic. Clinicians should consider each patient's cultural and linguistic background. It is likely impossible for all tests to be free of cultural influences, especially in areas such as social cognition, where the cognitive ability is closely linked with the cultural context [181].

6.2.4. Education and age

While the MCE may overcome some barriers related to culture and language, the MCE was influenced by age and education. The effect of **education** was equivalent to a person with 10 years of formal schooling scoring 8 points higher (8% difference) on the MCE compared to someone who never attended school. While this effect is clinically relevant, it is relatively low compared to that of other cognitive screening tests such as the MMSE, MoCA, and ACE [43, 44, 182, 183]. Cognitive tasks resemble school-related tasks and build on skills learned in school (e.g., calculating, planning, sustained attention, reading, writing). For the MCE specifically, a sub-analysis found the RPT subtasks to be relatively free of educational bias (R^2 ranged from 0.6% to 2.2%), but that RUDAS, CRT, and SFT were the ones more influenced (R^2 ranged from 11.4% to 15.5%) (See Figure 6.2.4.A). The RPT is not speeded, includes colored and widely known pictures, and the patients can answer in whatever language they prefer, which likely limits the influence of education, culture, and language. The educational bias in the other subtests is likely related to visual tests having strong associations with education, biasing both RUDAS and CRT [49, 184]. Meanwhile, SFT puts demand on executive functions (switching, planning) and speed, in addition to its focus on language. Executive functions and processing speed have often been shown to be strongly associated with formal schooling, as many Western cultures rely on speeded exams and tests [33, 185].

Figure 6.2.4.A. Influence of education on MCE subtests



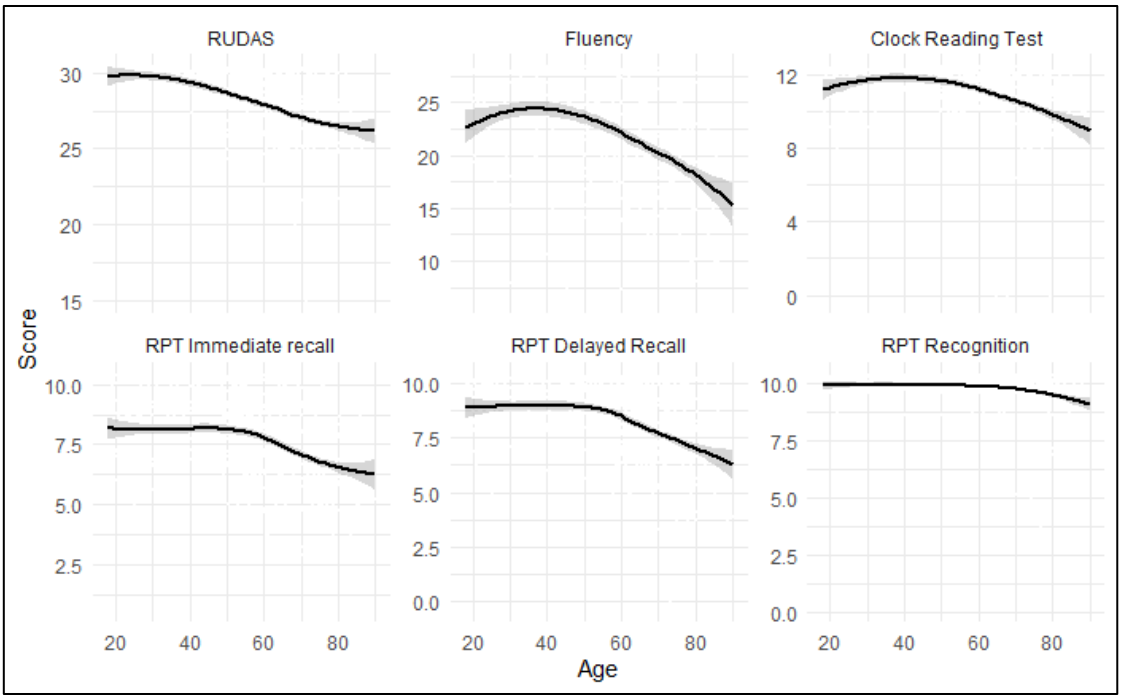
Note: MCE subtest scores by years of formal schooling for the cognitively intact participants in the MCE cohort (Study 1). The line represents a nonparametric smoothing function (Locally Estimated Scatterplot Smoothing). Data for the figure is from Kjaergaard et al., 2026 [1].
Abbreviations: RPT = Recall of Pictures Test, RUDAS = Rowland Universal Dementia Assessment Scale.

Recently, more focus has been given to the **quality of education**, rather than crude years of formal schooling, as we included in our studies. Quality of education may be a better measure of educational attainment, as there are major differences between educational systems, and years of schooling may therefore not capture educational experience equally [180]. Educational quality can be captured through reading ability tests, information on teacher-student ratios, time spent in class, and access to a library, books, or computers [180]. A systematic review by Metcalfe and colleagues on the quality of education and neuropsychological tests found that educational quality may be a better estimate, especially in minoritized groups [186]. These findings encourage caution when interpreting results against age and education-based normative data to avoid misclassifications.

Age exhibited a non-linear effect on the MCE, with greater influence as a person ages. Most cognitive tests display an inverted U slope, gaining cognitive ability during childhood and adolescence,

plateauing sometime during adulthood, and declining towards older age [187, 188]. We only included adults in our sample, and therefore do not see the increasing cognitive ability, but only the decline towards old age (Study 1). However, it is also well known that cognitive domains do not develop and decline at the same time [188]. For example, I would expect a similar decline for episodic memory, working memory, and processing speed, but expect vocabulary and semantic memory to be relatively stable throughout the lifespan [188, 189]. This may explain some of the results we found when examining the MCE subtests, where age explains a substantial proportion of the variance for RUDAS, RPT recall (immediate and delayed), and fluency, but less for CRT and RPT recognition (Figure 6.2.4.B). As presented in Figure 6.2.4.B, all fitted regression lines drop with older age, although the curve is less steep for CRT and RPT recognition. These results may encourage normative data for each subtest, however for a cognitive screening test, this is likely not beneficial for clinical practice when time is short.

Figure 6.2.4.B. Influence of age on MCE subtests



Note: MCE subtest scores by age for the cognitively intact participants in the MCE cohort (Study 1). The line represents a nonparametric smoothing function (Locally Estimated Scatterplot Smoothing). Data for the figure is from Kjaergaard et al., 2026 [1].
Abbreviations: RPT = Recall of Pictures Test, RUDAS = Rowland Universal Dementia Assessment Scale.

6.3. Ethnicity and blood biomarkers

The one aspect that most blood biomarker studies mention in their limitations is the lack of representative cohorts, which limits the generalizability of their findings. We sought to both address this critical representativity issue and shed light on whether patients' ethnic background is an essential covariate in interpreting blood biomarkers. Our systematic review revealed a divided field, with some studies finding differences and others not finding them. Study 3 presented results against geographic origin being an important factor in interpreting plasma p-tau217 across group comparisons, regression models, and diagnostic accuracy models. However, to this day, the field remains divided, with evidence both for and against the impact of ethnicity and race on blood biomarker concentrations and accuracy. In the following, I will first present both the evidence for and against the influence of ethnicity and race on blood biomarkers. The potential impact of this debate is deciding whether different population-specific cutoffs should be used in clinical practice.

6.3.1. Evidence for ethnicity and race influencing blood biomarkers

The debate on whether biomarkers act similarly across ethnic and racial groups started in studies in CSF and PET [122–128]. Many of these studies suggested that biomarker concentrations and accuracies varied by ethnic or racial group, but the debate was never settled. With the rapid development of blood biomarkers and the increasing focus on underrepresented populations, the debate continued in the field of blood biomarkers, with some authors proposing ethnicity or race-adjusted cutpoints [126].

Among the studies that find ethnicity influenced biomarker expression, the studies based on the *Health and Aging Brain Study – Health Disparities (HABS-HD)* cohort is probably the most influential. HABS-HD is a community-based cohort with studies focusing on AD in Hispanic, non-Hispanic Black, and non-Hispanic White individuals in the US [190]. This cohort included more than

1,000 individuals from each of the mentioned ethnic/racial groups. One recent study examining disparities in plasma p-tau217 in the HABS-HD cohort found that p-tau217 performed better in non-Hispanic White individuals compared to the other groups, and the non-Hispanic White group had higher p-tau217 concentrations [191]. Similarly, other studies have found higher p-tau217 concentrations in White Americans compared to Black Americans, and an effect of racial group on biomarker concentrations [192, 193]. Indeed, more than half of the studies in our systematic review (Study 2) found differences in blood biomarker concentrations, although these studies did not include plasma p-tau217. Among these studies, the Black or African American group had lower biomarker concentrations generally [2]. These studies that found differences disagree whether the cause of the ethnic/racial differences is biological/genetic or a problem related to minoritazation/racialization [2, 192, 194].

To explore inherent biological or genetic variation by race or ethnicity, we must look to studies that include genetic evidence rather than self-identified race/ethnicity. Young-onset AD is known to have stronger links to genetic predispositions in *APP,* or *presenilin* 1 or 2, representing around 11% of all young-onset AD patients [195]. Asken and colleagues compared Hispanic and White individuals with early-onset AD and found similar biomarker concentrations, but ethnicity moderated the association between the biomarkers and age and sex [196]. The authors suggest that ethnicity may influence how blood biomarkers relate to age and sex. However, this study did not include genetic testing. If genetic or biological differences are present, it would likely be because of generational exposure to specific climates, diet, specific disease exposure, leading to genetic predispositions and susceptibility to disease [129–134]. Indeed, by examining haplotypes (specific DNA constellations on specific chromosomes), it is possible to identify geographic origin and lineage. Several studies have found that the microtubule-associated protein tau (*MAPT*) *H2* haplotype, an AD risk factor gene, is primarily found in European and Middle Eastern populations [131, 197, 198]. In addition, several studies have

found differences across ethnic/racial groups in both incidence and expression of the *APOE* genotypes [132, 133, 199]. The importance of these findings is that the underlying biology of AD may be expressed differently due to genetic variation.

Alternatively, the differences are driven by selection bias, problems with cognitive tests, access to health care, referral patterns, help-seeking behavior, comorbidity burden, structural racism, and stigma [200, 201]. The HABS-HD cohort found racial differences, with the non-Hispanic Black individuals having more cognitive impairment and lower mean p-tau217 [191]. However, the Black individuals were also younger (63.2 vs 68.5 years), had less kidney disease and less cardiovascular disease. And perhaps most importantly, all participants are assessed using the Clinical Dementia Rating scale, MMSE, and Trail Making Test. These are all tests that several studies have found to be biased in culturally, linguistically, and educationally diverse individuals, likely resulting in the racialized non-Hispanic Black group having lower cognitive scores [28, 34, 42, 202, 203]. What exactly the underlying reasons are for the biomarker studies finding differences between ethnic and racial groups remains unresolved, but perhaps examining the studies that do not find differences would help illuminate the potential causes.

6.3.2. Evidence against ethnicity and race influencing blood biomarkers

Study 3 did not replicate the findings from the studies mentioned above, but found no differences in plasma p-tau217 concentrations or accuracies across people from different geographic regions [3]. Our study, however, differs from most other studies on ethnicity and biomarkers, as it was based in Europe and operationalized ethnicity by country of birth and not self-identified racial or ethnic category. Importantly, the lack of influence of ethnicity and race has been found in other studies using self-identified racial or ethnic groups [165, 204–207]. Our results were consistent when using clinical diagnosis or CSF/PET biomarker evidence as the reference standard.

What generally differentiates studies that do not find differences from those that do may be related to how the cohort is selected. The studies that either age-match or recruit demographically similar groups also seem to be the ones that do not find differences [3, 204–207]. With age being the single greatest risk factor of AD, it is not surprising to find differences between groups where one is significantly older [208].

Including minoritized individuals does not equal representation. Indeed, by not including patients or populations representatively, the study results may not generalize [205]. Selection bias can be present even without one noticing it, but maybe there are structural issues that lead to only certain select individuals wanting to participate in a research study. Considering AD trials, for example, a lot of effort is being put into including underrepresented populations by, for example, refunding economic costs and reducing travel strain to central complexes [209]. By simply sampling the nearby community, which one hopes is more or less random, there is a risk of selection bias if there are geographical disparities, which is the case in the US [200, 205, 209].

There may also exist an issue in our operationalization of ethnicity or race. In our study (Study 3), we grouped people based on where they were born and then by larger geographic areas for statistical analyses. We did not include any genetic evidence or knowledge about prior migration patterns from our patients' history. If we had included this information, I could have attempted analyses based on specific geographically linked haplotypes. The country of birth can be argued to be a proxy for geographic descent, but we could not group people by underlying biology/genetics. However, as genetic risk genes are rare, especially in late-onset AD, I doubt that such a grouping would have been meaningful.

6.3.3. Synthesis

Based on the above evidence, I do not find race or ethnicity cutoffs or adjustments appropriate as suggested by, for example, Morris and colleagues [126]. There should be no doubt that genetics can

and do play a role in AD pathophysiology and expression, and that some genetic mutations are more prevalent in some geographic regions than others [131–133]. However, essentially no studies group based on genetics, in fact, most studies use the same three minoritized or racialized categories non-Hispanic White, Black, or Hispanic. These are groupings primarily based on US history and immigration patterns, but they rarely specify where people are from. To put it into perspective, the non-Hispanic White grouping covers North America, Europe, the Middle East, North Africa, and Russia, which is an incredibly large area representing different climates, diets, immigration patterns, and cultures. These racialized and minoritized categorizations are unlikely to represent geographically linked mutations. Even if a study included and analyzed patients country-by-country, genetic mutations and risk (or protective) alleles, such as APOE, would likely be represented in only a minority of patients [132]. If researchers or clinicians seek to adjust for genetic or biological differences, they should look at exactly that, genetics or biology, not surrogates such as ethnicity or race.

It is more likely that different selection strategies and statistical approaches caused the divergent results and interpretations in the field of ethnicity and biomarkers. Minoritized individuals are known to face more barriers in the health care sector (access to care, structural racism, lack of trust), are at a higher risk of misdiagnosis or delayed diagnosis because of less appropriate diagnostic tools, including cognitive testing and functional ability, and generally represent a group who are disproportionally affected by medical conditions. Such medical conditions may, in fact, be among the factors that affect biomarker concentrations, such as BMI and kidney function.

6.4. Discordant biomarker profiles

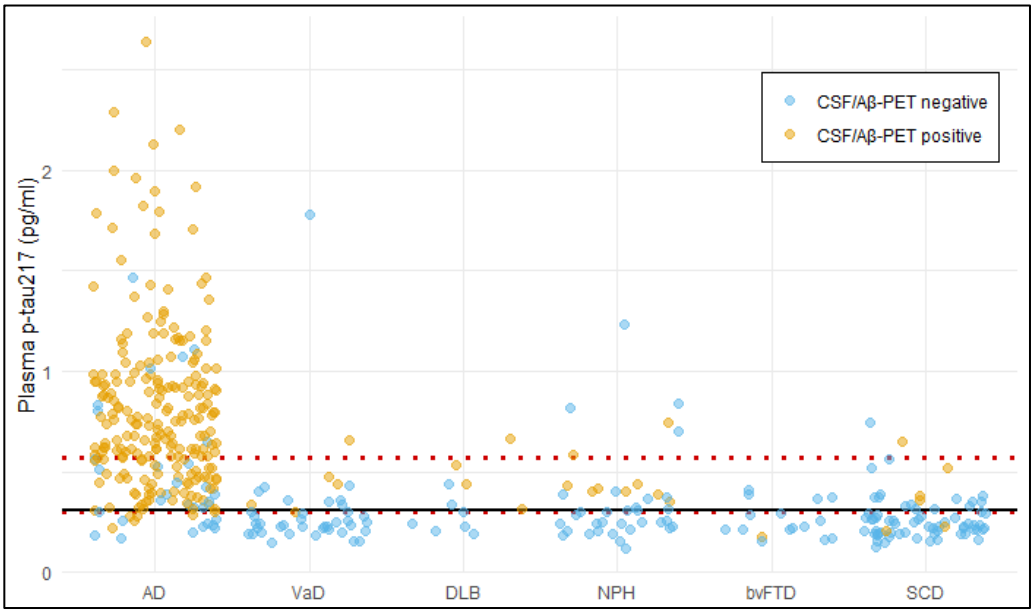
Despite the high accuracy of plasma p-tau217 found in our studies and others [3, 206, 210], applying a single cutoff, we still found a discordance rate of 16.1% in study 5. The discordance particularly concerned patients who were plasma p-tau217 positive and CSF/Aβ-PET negative. Based on previous studies, we expected to find this discordant group having worse kidney function and perhaps lower BMI [138, 206, 211], but we found no statistically significant differences, only higher effect sizes compared to other covariates. This was surprising, given our well phenotyped cohort, which included a range of medical conditions, yet we found no clear explanation for the high discordance rate. However, the explanation may be found from other studies employing other covariates or a longitudinal study design.

6.4.1. Medical conditions influence discordance

As touched upon in the Background section, kidney function and BMI are some of the most frequently found factors that influence plasma biomarker concentrations [135–138]. While we do not find significant groupwise differences in Study 5, there are numeric differences in the expected directions, with more kidney dysfunction in the p-tau217 positive/Aβ negative group, and higher BMI in the p-tau217 negative /Aβ positive group. Additionally, we found BMI and eGFR to significantly influence biomarker concentrations in Study 3 using the same cohort, suggesting that BMI (or blood volume) and kidney function do play an important role, but that these factors do not explain the entire picture in a mixed memory clinic cohort. In our analyses on covariate influences on plasma p-tau217 (Study 3, Study 5), we included a wide range of variables, including hypertension, hyperlipidemia, diabetes, HbA1c, liver, and thyroid function. But none of these were statistically significant. However, other studies found statistical significance for, for example, diabetes [205].

To overcome discordance, one approach gaining popularity is the dual cutoff approach, which allows for a statistically defined intermediate zone in which other diagnostic procedures are warranted [211–213]. These dual cutoffs can be established using different methods, one using 95% sensitivity and 95% specificity, allowing more certainty in negative and positive results. We examined our single cutoff approach to a dual cutoff (95% sensitivity, 95% specificity) in the BlooDiv cohort from Study 5. Using the dual cutoff, 182 (33.8%) were above the upper threshold of 0.5682 pg/ml, while 210 (39.0%) were below the lower threshold of 0.299 pg/ml. This, however, left 147 (27.3%) in the intermediate zone between 0.300 and 0.5681 (Figure 6.4.1). This categorization classified CSF/Aβ-PET positive patients as plasma p-tau217 positive in 64.0% of cases, while 30.7% remained in the intermediate zone. Similarly, for CSF/Aβ-PET negative patients, 71.3% were also plasma p-tau217 negative, but 24% were in the intermediate zone. Within the BlooDiv cohort, a dual cutoff would move many non-AD diagnoses from the positive to the intermediate zone. For example, 20 of 41 NPH patients were positive using the single cutoff, but only 6 remained using the dual cutoff. On the one hand, the dual cutoff approach may reduce bias, but on the other hand, it leaves approximately one-third of a mixed memory clinic cohort in an intermediate zone. Especially in heterogeneous mixed memory clinic cohorts, diagnostic accuracies are generally lower, but they do represent the clinical context-of-use of the biomarkers [214]. Additionally, a dual cutoff may give clinicians a false sense of security if a patient is not in the intermediate zone. Clinically, if a patient has an AD clinical phenotype and is high in the intermediate zone, I will argue that the patient likely has AD pathology.

Figure 6.4.1. Plasma p-tau217 concentration across diagnostic groups in the BlooDiv cohort



Note: Plasma p-tau217 concentration shown on the y-axis, and diagnostic groups on the x-axis. Single cutoff is illustrated with the black line, and the dual cutoffs (95% sensitivity, 95% specificity) are illustrated with the red dotted lines.
Abbreviations: Aβ-PET = Amyloid-β Positron Emission Tomography, AD = Alzheimer's disease, bvFTD = behavioral variant frontotemporal dementia, CSF = Cerebrospinal fluid, DLB = Dementia with Lewy Bodies, NPH = Normal Pressure Hydrocephalus, P-tau = Phosphorylated tau, SCD = Subjective Cognitive Decline, VaD = Vascular Dementia.

6.4.2. Findings from longitudinal studies

Unexplained effects or lack thereof can sometimes be understood using longitudinal studies, these are, however, sparse compared to the abundance of cross-sectional studies. It is doubtful that our large discordance in Study 5 can be explained solely by medical conditions influencing biomarker concentrations. But it is possible that the discordance rate should be viewed in a prognostic light rather than conditions causing false positive and false negative results. Perhaps the large proportion of patients who are positive on plasma p-tau217 but negative on CSF/Aβ-PET reflects that the biomarkers capture AD pathology differently.

Studies assessing the prognostic value of plasma p-tau217 have indeed found that increased concentration of plasma p-tau217 in cognitively healthy individuals is predictive of future cognitive decline and AD pathology [119, 215, 216]. For example, Yakoub and colleagues assessed the ability of plasma p-tau217 in predicting which cognitively healthy individuals will be diagnosed with MCI

in a span of 10 years [216]. They found that almost all individuals with increased plasma p-tau217 concentrations were diagnosed with MCI in a 10-year span. These findings are in line with other studies suggesting plasma p-tau217 is increased early in the amyloid cascade, already with amyloid plaque load, or may reflect early tau dysregulation not yet captured by tau-PET [217, 218]. This early spike of plasma p-tau217 before presentation of clinical syndromes may explain some of the discordance in our BlooDiv cohort. Our reference standard was determined with a CSF ratio reflecting both amyloid and tau pathology or with Aβ-PET for amyloid pathology, potentially the plasma p-tau217 biomarker became positive before the other biomarkers. We performed a subanalysis in the patients with CSF results and examined discordance for Aβ42 and p-tau181 individually with plasma p-tau217. As expected, more patients had negative CSF p-tau181 and positive p-tau217 (28.0%) compared to CSF Aβ42 negative and plasma p-tau217 positive (10.2%). These findings suggest that plasma p-tau217 increases early in the amyloid cascade, whether this increase primarily reflects amyloid pathology or signals early tau dysregulation remains a subject of discussion.

Using the novel plasma eMTBR-tau243 biomarker, Mattsson-Carlgren and colleagues found eMTBR-tau243 to reflect symptomatic AD and tau tangle burden, while plasma p-tau217 was a strong amyloid pathology marker [219]. Their suggestion is that cognitively impaired patients who are positive on plasma p-tau217 but negative on plasma eMTBR-tau243 do not experience cognitive impairment due to AD but due to other co-pathologies.

6.4.3. Plasma p-tau217 is not pathognomonic

Many researchers and clinicians are moving toward biological definitions of AD, giving less attention to the clinical presentation [220]. Other researchers have expressed concerns about this direction, as we currently do not know whether the patient will experience symptoms and are therefore against

labeling biomarker positive individuals as having AD [58]. Additionally, our biomarkers, including plasma p-tau217, are unlikely to be pathognomonic.

Several studies have found plasma or serum p-tau217 increased compared to controls in well-defined non-AD related conditions such as ALS [139, 140]. These studies point to p-tau217 also being secreted in other parts of the body, such as muscle fibers, in patients without AD. Similarly, plasma p-tau217 has been found to be increased in Creutzfeldt-Jakob Disease [221], and even among newborns, particularly preterm babies [140]. The p-tau217 level in the newborns had a clear downward curve from birth, potentially signaling another role of p-tau in early development [140]. Additionally, tau phosphorylation is also increased in prostate cancer [222], pneumonia [223], cardiac arrest [224], and severe traumatic brain injury [225]. Based on this evidence, it is not unlikely that discordance rates can be explained by other non-AD conditions that affect production, secretion, or clearance of p-tau.

Many of these conditions mentioned above can be easily distinguished from AD from their clinical presentation, but I hope to have emphasized that p-tau217 should not be used as a standalone biomarker believed to be pathognomonic of AD. Additionally, when using p-tau217 in clinical practice, even with the clinical presentation, it is important to remember that there could be other causes of increased p-tau217.

6.5. Methodological considerations

6.5.1. Strengths

Our main consideration across the studies was to produce research that was representative and clinically relevant. In turn, this was also the main strength across the MCE and BlooDiv studies, which had large, diverse, and well-defined cohorts. The MCE and BlooDiv cohorts included participants from 63 and 91 different countries, respectively, which was made possible through our

cross-country collaboration with other memory clinics and research institutions. Our large sample sizes spanned most of the world and enabled us to examine biomarkers and cognitive tests across diverse contexts. Altogether, these factors promote the generalizability of our results.

Across studies, we focused on diagnostic equity, including whether accuracy changed depending on patient characteristics. We also aimed to provide direct ties to clinical applicability, as we did with creating normative data in Study 1. After our systematic review (Study 2), it became clear that research on ethnicity and race cannot be considered isolated from its political context. The results revealed a divided field, with different approaches and interpretations concerning the influence of ethnicity or race on biomarkers. Our study 3 contributed to one side of this ongoing debate. In these contexts, where science and politics become intertwined, methodological rigor is particularly crucial. Therefore, for all the studies, we started with agreeing on a protocol including a specified plan of analysis to limit the risk of confirmation bias.

6.5.2. Limitations

Our focus on big representative cohorts came at the cost of not examining the biomarkers or cognitive tests longitudinally. We do not know whether plasma p-tau217 or MCE varies over time, meaning the stability of our results within our cohorts. Therefore, I cannot draw any conclusions about the ability to track or predict decline. This includes clinically relevant information, such as at what point in their disease do patients start to decline, and when they cross the detection threshold.

The reference standard across studies introduced different limitations. In both the MCE and BlooDiv cohorts, patients were diagnosed clinically based on different diagnostic criteria, using different diagnostic tools, and in different contexts (see Study 1 and Study 3). This includes differing criteria for MCI, dementia, and AD, which were our main reference standards. For MCI and dementia, the content of the clinical criteria did not differ much, but for AD there was a different weighing of

biomarker evidence. The weight of this biomarker evidence also varied between sites in the BlooDiv cohort. First, in terms of selection bias, the patients selected for CSF/Aβ-PET examinations represent a different group of patients suspected of AD, and this also implied that the clinical AD group was not blinded to the CSF results that were likely part of the diagnostic decision. Second, the CSF evidence was based on different assays that were not equally accurate (supplementary table 10 in Study 3), but in our main analysis, the patients were pooled. We implemented individual cutoffs for each assay, but if our cohort had only used one reference standard, it would likely have influenced our results. Furthermore, clinically, the CSF biomarkers were interpreted individually for some patients (e.g., low Aβ42 and high p-tau181 indicative of AD), but our study only applied the ratio between the two, possibly overlooking important nuances. Patients were examined by different clinicians in different contexts, where, particularly in the MCE cohort, each site represents unique cultural, historical, and political characteristics. Altogether, these limitations may have influenced our results and interpretations in various ways. By enlarging the effects of the identification of clinical AD with p-tau217, as many patients were diagnosed with knowledge of CSF or Aβ-PET results, and the differing criteria may have obscured the true effect of our predictors.

A last essential limitation concerns residual confounding. We chose to define culturally and linguistically diverse populations by their country of birth, which we believe is a better categorization than racialized and minoritized categories such as non-Hispanic White, Black, and Hispanic as studies otherwise typically use. However, I argue that our categorization represents exactly culture, language, and maybe even biological/genetic differences, but did not include any information about genetics, acculturation, spoken languages, language fluency, nor about quality of education or comorbidities (in the MCE cohort). It is possible that plasma p-tau217 or MCE would have been influenced by *APOE* genotype, geographically linked mutations, and/or on specific measures of culture or language. Additionally, we included patients from many countries, but there was an overrepresentation of

patients from certain areas reflecting European migration patterns, leaving other areas of the world underrepresented in our studies. So, our interpretation that there are no influences of ethnicity may be true, but it does leave out important nuances for clinical practice. Whether plasma p-tau217 behaves differently in specific groups and whether the MCE is equally accurate independent of interpreter use, language fluency, or in specific languages cannot be answered from our studies.

7. CONCLUSION AND PERSPECTIVES

7.1. Conclusions

In conclusion, this thesis suggests that MCE and plasma p-tau217 are viable and accurate diagnostic tools for memory clinic patients, independent of country of birth. The accuracy of the MCE was comparable to other cognitive screening tests, and the accuracy of the MCE did not decrease in our culturally, linguistically, and educationally diverse cohort. Plasma p-tau217 was accurate for AD and amyloid pathology and was unaffected by geographic origin. There was a slight influence of kidney function and BMI, but this did not appear to affect discordance rates significantly.

Specifically, Study 1 demonstrated that the MCE is an accurate cross-cultural cognitive screening test for identifying dementia and MCI, but not for differential diagnostic purposes. Study 4 supplemented these findings by showing that diagnostic accuracy improved when combining MCE with plasma p-tau217, particularly for differentiating AD from non-AD dementia. Study 2 found mixed results concerning the influence of ethnicity or race on blood biomarkers, while Study 3 found that plasma p-tau217 is not affected by geographic origin. Lastly, Study 5 found a high proportion of plasma p-tau217 positive but CSF/Aβ-PET negative patients, and unlike previous studies, did not find clear patterns explaining this discordance.

Together, these results may improve the diagnostic conditions for ethnically, culturally, linguistically, and educationally diverse memory clinic patients and limit potential misinterpretations of blood biomarkers.

7.2. Clinical implications

As mentioned repeatedly throughout this thesis, the world is becoming increasingly diverse, emphasizing a need for less biased diagnostic tools. However, more than increased immigration, more and more people grow up in bilingual households, with one culture at home and another at school and

at work. Mixing cultures and languages will only become more normal, and the current health care system is underprepared, as most research focuses on homogeneous groups that are not representative of the patients entering a clinic. All five of our studies encourage researchers to include representative samples, this does not mean to have 50% of their cohorts to consist of minority ethnic populations, but not exclude patients if they do not speak the dominant language or are born abroad. It could be a normal limitation for researchers to consider in their studies.

Furthermore, our results encourage the clinical implementation and use of the MCE. The implication would be a fairer cognitive screening, without the need to consider which test is most appropriate for this patient. Hopefully, fewer patients would be misdiagnosed or have delays in their diagnostic assessment, as cognitive impairment can be identified in most patients, thereby limiting the need to consider whether the patients' background skewed the test results. In addition, the normative data gives each individual clinician the possibility to interpret the result based on their unique context of use.

Plasma p-tau217 could be an additional diagnostic tool to supplement the clinical evaluation and cognitive testing. While plasma p-tau217 is not pathognomonic for AD, it is increased in most patients with AD and would constitute a strong and less invasive alternative to CSF biomarkers. Currently, there are also other conditions than AD that affect the implemented CSF biomarkers, such as NPH, and clinicians must be aware of them to avoid misinterpretations. This way of thinking should continue in interpreting plasma biomarkers. Studies of bias in plasma p-tau217 biomarkers should continue, but our results encourage their use in a mixed memory clinic setting.

7.3. Future research

Improving diagnostic conditions for underrepresented populations should remain a priority in research. Including minoritized populations and ensuring that diagnostic tools and treatment serves a representative population will improve the real-world impact and prevent creating gaps based on factors that should not be relevant to the test, diagnosis, or treatment. Additionally, patients' cognitive phenotype may differ between countries, impacting the applicability of diagnostic criteria [226, 227]. Investigating the cross-linguistic or cross-cultural applicability of diagnostic criteria should be a priority to avoid misdiagnosing patients.

The MCE was unable to differentiate dementia syndromes and identify specific cognitive profiles, creating a need for cross-cultural neuropsychological tests that can do exactly this. Cross-cultural neuropsychological tests specific to certain cognitive domains are limited, meaning that while patients may be identified, we have limited resources to go further. Future research should focus on developing these new cross-cultural neuropsychological tests, but also examine cross-cultural cognitive tests in a longitudinal perspective.

Plasma p-tau217 was accurate for AD, but much remains unknown about potential pitfalls from medication use, and neurological and somatic disorders. At the same time, research is already moving into even less invasive and more scalable biomarker alternatives, including dried blood spots and saliva [228, 229]. All the above considerations remain relevant as the field moves into new biomarkers, assays, and technologies. Representativeness should be a focus in all research, whether it is regarding sex, ethnicity, frailty, or any of the aspects that may be relevant for the intended use of a test.

8. References

[1] Kjaergaard D, Delgado-Álvarez A, Waldemar G, et al. Diagnostic accuracy of the Multicultural Cognitive Examination (MCE) for detection of MCI and dementia in a diverse international cohort. *Clin Neuropsychol* 2026; 1–16.

[2] Kjaergaard D, Simonsen AH, Waldemar G, et al. Ethnic and racial influences on blood biomarkers for Alzheimer's disease: A systematic review. *J Alzheimers Dis* 2025; 103: 81–91.

[3] Kjaergaard D, Nielsen TR, Stomrud E, et al. Influence of ethnicity on the diagnostic accuracy of plasma p-tau217 for the identification of Alzheimer's disease: A consecutive mixed memory clinic cohort study. *Alzheimers Dement*; 21. Epub ahead of print 12 June 2025. DOI: 10.1002/ALZ.70315.

[4] Kjaergaard D, Simonsen AH, Stomrud E, et al. Combining plasma p-tau217 and cross-cultural cognitive tests to identify Alzheimer's Disease in an ethnically diverse mixed memory clinic cohort. *J Neurol Sci*; 478. Epub ahead of print 15 November 2025. DOI: 10.1016/j.jns.2025.123739.

[5] Weisman CS, Cassard SD. Health Consequences of Exclusion or Underrepresentation of Women in Clinical Studies (I). In: Mastroianni AC, Faden R, Federman D (eds) *Women and Health Research: Ethical and Legal Issues of Including Women in Clinical Studies: Volume 2: Workshop and Commissioned Papers.* Washington (DC): National Academies Press (US), https://www.ncbi.nlm.nih.gov/books/NBK236583/ (1999, accessed 14 April 2026).

[6] Lee E, Wen P. Gender and sex disparity in cancer trials. *ESMO Open* 2020; 5: e000773.

[7] Smedley A, Smedley BD. Race as biology is fiction, racism as a social problem is real: Anthropological and historical perspectives on the social construction of race. *Am Psychol* 2005; 60: 16–26.

[8] Alzheimer Europe. *The development of intercultural care and support for people with demen-tia from minority ethnic groups*. 2018.

[9] World Health Organization (WHO). International Statistical Classification of Diseases and Related Health Problems, Eleventh Revision (ICD-11). *World Health Organization (WHO)*.

[10] Petersen RC. Mild Cognitive Impairment. *Continuum : Lifelong Learning in Neurology* 2016; 22: 404.

[11] Winblad B, Palmer K, Kivipelto M, et al. Mild cognitive impairment - Beyond controversies, towards a consensus: Report of the International Working Group on Mild Cognitive Impairment. *J Intern Med* 2004; 256: 240–246.

[12] American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. Fifth edition, Text Revision. *Diagnostic and Statistical Manual of Mental Disorders*. Epub ahead of print 18 March 2022. DOI: 10.1176/APPI.BOOKS.9780890425787.

[13] Sundhedsvæsenets Kvalitetsinstitut. *Dansk Klinisk Kvalitetsdatabase for Demens (DanDem) - National årsrapport 2024*. Aarhus, 2024.

[14] Hasselbalch SG, Andersen BB, Ejlerskov P, et al. The Danish Dementia Research Centre: Integrating patient care, clinical research, and national educational services. *J Alzheimers Dis*. Epub ahead of print 8 August 2025. DOI: 10.1177/13872877251365195.

[15] McKhann GM, Knopman DS, Chertkow H, et al. The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement* 2011; 7: 263–269.

[16] World Health Organization. International statistical classification of diseases and related health problems (11th ed.). *WHO*.

[17] Folstein MF, Folstein SE, McHugh PR. 'Mini-mental state'. A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res* 1975; 12: 189–198.

[18] Nasreddine ZS, Phillips NA, Bédirian V, et al. The Montreal Cognitive Assessment, MoCA: A brief screening tool for mild cognitive impairment. *J Am Geriatr Soc* 2005; 53: 695–699.

[19] Mathuranath PS, Nestor PJ, Berrios GE, et al. A brief cognitive test battery to differentiate Alzheimer's disease and frontotemporal dementia. *Neurology* 2000; 55: 1613–1620.

[20] Nichols E, Steinmetz JD, Vollset SE, et al. Estimation of the global prevalence of dementia in 2019 and forecasted prevalence in 2050: an analysis for the Global Burden of Disease Study 2019. *Lancet Public Health*; 7. Epub ahead of print 2022. DOI: 10.1016/S2468-2667(21)00249-8.

[21] Regionernes Kliniske Kvalitetsudviklingsprogram (RKKP). *Dansk Klinisk Kvalitetsdatabase for Demens (DanDem) - Årsrapport 2020* . 2020.

[22] Indvandrere og efterkommere - Danmarks Statistik, https://www.dst.dk/da/Statistik/emner/borgere/befolkning/indvandrere-og-efterkommere (accessed 15 April 2026).

[23] Canevelli M, Lacorte E, Cova I, et al. Estimating dementia cases amongst migrants living in Europe. *Eur J Neurol* 2019; 26: 1191–1199.

[24] Mukadam N, Marston L, Lewis G, et al. Incidence, age at diagnosis and survival with dementia across ethnic groups in England: A longitudinal study using electronic health records. *Alzheimers Dement* 2023; 19: 1300–1307.

[25] Nielsen TR, Vogel A, Phung TKT, et al. Over- and under-diagnosis of dementia in ethnic minorities: a nationwide register-based study. *Int J Geriatr Psychiatry* 2011; 26: 1128–1135.

[26] Segers K, Benoit F, Colson C, et al. Pioneers in migration, pioneering in dementia: first generation immigrants in a European metropolitan memory clinic. *Acta Neurol Belg* 2013; 113: 435–440.

[27] Van Mol C, de Valk H. Migration and Immigrants in Europe: A Historical and Demographic Perspective. *IMISCOE Research Series* 2016; 31–55.

[28] Wee SL, Mei SC, Sahadevan S. Utility of the clinical dementia rating in Asian populations. *Clin Med Res* 2007; 5: 61–70.

[29] Nielsen TR, de Mendonça A, Frölich L, et al. Assessment of Dementia in Minority Ethnic Groups in Europe: A 14-Year Follow-Up Survey. *Int J Geriatr Psychiatry*; 39. Epub ahead of print 1 December 2024. DOI: 10.1002/GPS.70034.

[30] Nielsen TR, Vogel A, Riepe MW, et al. Assessment of dementia in ethnic minority patients in Europe: A European Alzheimer's Disease Consortium survey. *Int Psychogeriatr* 2011; 23: 86–95.

[31] Ardila A. Cross-Cultural Neuropsychology: History and Prospects. *RUDN Journal of Psychology and Pedagogics* 2020; 17: 64–78.

[32] Paddick SM, Kisoli A, Mkenda S, et al. Adaptation and validation of the Alzheimer's Disease Assessment Scale - Cognitive (ADAS-Cog) in a low-literacy setting in sub-Saharan Africa. *Acta Neuropsychiatr* 2017; 29: 244–251.

[33] Agranovich A V., Panter AT, Puente AE, et al. The culture of time in neuropsychological assessment: exploring the effects of culture-specific time attitudes on timed test performance in Russian and American samples. *J Int Neuropsychol Soc* 2011; 17: 692–701.

[34] Slachevsky A, Grandi F, Thumala D, et al. A Multidimensional, Person-Centered Framework for Functional Assessment in Dementia: Insights from the 'What', 'How', 'To Whom', and 'How Much' Questions. *J Alzheimers Dis* 2024; 99: 1187–1205.

[35] Nielsen TR, Franzen S, Watermeyer TJ, et al. Interpreter-mediated neuropsychological assessment: Clinical considerations and recommendations from the European Consortium on Cross-Cultural Neuropsychology (ECCroN). *Clinical Neuropsychologist*. Epub ahead of print 2024. DOI: 10.1080/13854046.2024.2335113.

[36] Plejert C, Antelius E, Yazdanpanah M, et al. 'There's a letter called ef' on Challenges and Repair in Interpreter-Mediated Tests of Cognitive Functioning in Dementia Evaluations: A Case Study. *J Cross Cult Gerontol* 2015; 30: 163–187.

[37] Franzen S, Van Den Berg E, Goudsmit M, et al. A Systematic Review of Neuropsychological Tests for the Assessment of Dementia in Non-Western, Low-Educated or Illiterate Populations. *J Int Neuropsychol Soc* 2020; 26: 331–351.

[38] Franzen S, Watermeyer TJ, Pomati S, et al. Cross-cultural neuropsychological assessment in Europe: Position statement of the European Consortium on Cross-Cultural Neuropsychology (ECCroN). *Clin Neuropsychol* 2022; 36: 546–557.

[39] Nielsen TR, Jørgensen K. Visuoconstructional abilities in cognitively healthy illiterate turkish immigrants: A quantitative and qualitative investigation. *Clinical Neuropsychologist* 2013; 27: 681–692.

[40] Nong P, Raj M, Creary M, et al. Patient-Reported Experiences of Discrimination in the US Health Care System. *JAMA Netw Open* 2020; 3: e2029650.

[41] Fujii D, Santos O, Malva L Della. INTERPRETER-ASSISTED NEUROPSYCHOLOGICAL ASSESSMENT: CLINICAL CONSIDERATIONS. *Understanding Cross-Cultural Neuropsychology: Science, Testing, and Challenges* 2022; 135–147.

[42] Franzen S, Papma JM, Van Den Berg E, et al. Cross-cultural neuropsychological assessment in the European Union: a Delphi expert study. *Arch Clin Neuropsychol* 2021; 36: 815–830.

[43] Goudsmit M, Van Campen J, Schilt T, et al. One Size Does Not Fit All: Comparative Diagnostic Accuracy of the Rowland Universal Dementia Assessment Scale and the Mini Mental State Examination in a Memory Clinic Population with Very Low Education. *Dement Geriatr Cogn Dis Extra* 2018; 8: 290–305.

[44] Chithiramohan T, Santhosh S, Threlfall G, et al. Culture-Fair Cognitive Screening Tools for Assessment of Cognitive Impairment: A Systematic Review. *J Alzheimers Dis Rep* 2024; 8: 289–306.

[45] O'Driscoll C, Shaikh M. Cross-Cultural Applicability of the Montreal Cognitive Assessment (MoCA): A Systematic Review. *J Alzheimers Dis* 2017; 58: 789–801.

[46] Storey JE, Rowland JTJ, Conforti DA, et al. The Rowland Universal Dementia Assessment Scale (RUDAS): a multicultural cognitive assessment scale. *Int Psychogeriatr* 2004; 16: 13–31.

[47] Nielsen TR, Andersen BB, Gottrup H, et al. Validation of the Rowland Universal Dementia Assessment Scale for multicultural screening in Danish memory clinics. *Dement Geriatr Cogn Disord* 2013; 36: 354–362.

[48] Nielsen TR, Jorgensen K. Cross-cultural dementia screening using the Rowland Universal Dementia Assessment Scale: a systematic review and meta-analysis. *Int Psychogeriatr* 2020; 32: 1031–1044.

[49] Nielsen TR. Cognitive Assessment in Culturally, Linguistically, and Educationally Diverse Older Populations in Europe. *Am J Alzheimers Dis Other Demen*; 37. Epub ahead of print 1 July 2022. DOI: 10.1177/15333175221117006.

[50] Goudsmit M, Uysal-Bozkir Ö, Parlevliet JL, et al. The Cross-Cultural Dementia Screening (CCD): A new neuropsychological screening instrument for dementia in elderly immigrants. *J Clin Exp Neuropsychol* 2017; 39: 163–172.

[51] Nielsen TR, Segers K, Vanderaspoilden V, et al. Validation of a brief Multicultural Cognitive Examination (MCE) for evaluation of dementia. *Int J Geriatr Psychiatry* 2019; 34: 982–989.

[52] Nielsen TR. Effects of Illiteracy on the European Cross-Cultural Neuropsychological Test Battery (CNTB). *Arch Clin Neuropsychol* 2019; 34: 713–720.

[53] Nielsen TR, Segers K, Vanderaspoilden V, et al. Validation of a European Cross-Cultural Neuropsychological Test Battery (CNTB) for evaluation of dementia. *Int J Geriatr Psychiatry* 2019; 34: 144–152.

[54] Franzen S, van den Berg E, Bossenbroek W, et al. Neuropsychological assessment in the multicultural memory clinic: Development and feasibility of the TULIPA battery. *Clin Neuropsychol* 2023; 37: 60–80.

[55] Nguyen CM, Rampa S, Staios M, et al. Neuropsychological application of the International Test Commission Guidelines for Translation and Adapting of Tests. *J Int Neuropsychol Soc* 2024; 30: 621–634.

[56] Schott JM, Lehmann M, Primativo S, et al. Consensus classification of posterior cortical atrophy. *Alzheimers Dement* 2017; 13: 870.

[57] Albert MS, DeKosky ST, Dickson D, et al. The diagnosis of mild cognitive impairment due to Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement* 2011; 7: 270.

[58] Dubois B, Villain N, Schneider L, et al. Alzheimer Disease as a Clinical-Biological Construct-An International Working Group Recommendation. *JAMA Neurol*. Epub ahead of print 1 November 2024. DOI: 10.1001/JAMANEUROL.2024.3770.

[59] World Health Organization. World Health Organization - Dementia, https://www.who.int/news-room/fact-sheets/detail/dementia (2025, accessed 4 February 2026).

[60] Gustavsson A, Norton N, Fast T, et al. Global estimates on the number of persons across the Alzheimer's disease continuum. *Alzheimers Dement* 2023; 19: 658–670.

[61] Li X, Feng X, Sun X, et al. Global, regional, and national burden of Alzheimer's disease and other dementias, 1990-2019. *Front Aging Neurosci*; 14. Epub ahead of print 10 October 2022. DOI: 10.3389/FNAGI.2022.937486.

[62] Abbafati C, Abbas KM, Abbasi M, et al. Global burden of 369 diseases and injuries in 204 countries and territories, 1990-2019: a systematic analysis for the Global Burden of Disease Study 2019. *Lancet* 2020; 396: 1204–1222.

[63] Liu W, Deng W, Gong X, et al. Global burden of Alzheimer's disease and other dementias in adults aged 65 years and over, and health inequality related to SDI, 1990-2021: analysis of data from GBD 2021. *BMC Public Health*; 25. Epub ahead of print 1 December 2025. DOI: 10.1186/s12889-025-22378-z.

[64] Jack CR, Knopman DS, Jagust WJ, et al. Hypothetical model of dynamic biomarkers of the Alzheimer's pathological cascade. *Lancet Neurol* 2010; 9: 119–128.

[65] Kern S, Zetterberg H, Kern J, et al. Prevalence of preclinical Alzheimer disease: Comparison of current classification systems. *Neurology* 2018; 90: E1682–E1691.

[66] Mukadam N, Marston L, Lewis G, et al. South Asian, Black and White ethnicity and the effect of potentially modifiable risk factors for dementia: A study in English electronic health records. *PLoS One*; 18. Epub ahead of print 1 October 2023. DOI: 10.1371/JOURNAL.PONE.0289893.

[67] Livingston G, Huntley JD, Liu KY, et al. Potentially modifiable risk factors for dementia putting the evidence together: Total population attributable fraction. *Alzheimer's & Dementia* 2025; 20: e085063.

[68] Hardy JA, Higgins GA. Alzheimer's disease: the amyloid cascade hypothesis. *Science* 1992; 256: 184–185.

[69] Karran E, Mercken M, Strooper B De. The amyloid cascade hypothesis for Alzheimer's disease: an appraisal for the development of therapeutics. *Nat Rev Drug Discov* 2011; 10: 698–712.

[70] Hampel H, Hardy J, Blennow K, et al. The Amyloid-β Pathway in Alzheimer's Disease. *Mol Psychiatry* 2021; 26: 5481–5503.

[71] Gong C-X, Iqbal K. Hyperphosphorylation of Microtubule-Associated Protein Tau: A Promising Therapeutic Target for Alzheimer Disease. *Curr Med Chem* 2008; 15: 2321.

[72] Al-Ghraiybah NF, Wang J, Alkhalifa AE, et al. Glial Cell-Mediated Neuroinflammation in Alzheimer's Disease. *Int J Mol Sci* 2022; 23: 10572.

[73] Josephs KA, Whitwell JL, Weigand SD, et al. TDP-43 is a key player in the clinical features associated with Alzheimer's disease. *Acta Neuropathol* 2014; 127: 811–824.

[74] Eisenmenger LB, Peret A, Famakin BM, et al. Vascular contributions to Alzheimer's disease. *Translational Research* 2023; 254: 41–53.

[75] Kalaria RN, Ballard C. Overlap between pathology of Alzheimer disease and vascular dementia. *Alzheimer Dis Assoc Disord*; 13 Suppl 3. Epub ahead of print 1999. DOI: 10.1097/00002093-199912003-00017.

[76] Meneses A, Koga S, O'Leary J, et al. TDP-43 Pathology in Alzheimer's Disease. *Mol Neurodegener*; 16. Epub ahead of print 1 December 2021. DOI: 10.1186/s13024-021-00503-x.

[77] Almeida FC, Santos A, Jesus T, et al. Lewy body co-pathology in Alzheimer's disease and primary age-related tauopathy contributes to differential neuropathological, cognitive, and brain atrophy patterns. *Alzheimers Dement*; 21. Epub ahead of print 1 January 2025. DOI: 10.1002/alz.14191.

[78] Nag S, Schneider JA. Limbic-predominant age-related TDP43 encephalopathy (LATE) neuropathological change in neurodegenerative diseases. *Nat Rev Neurol* 2023; 19: 525–541.

[79] Franzmeier N, Roemer-Cassiano SN, Bernhardt AM, et al. Alpha synuclein co-pathology is associated with accelerated amyloid-driven tau accumulation in Alzheimer's disease. *Mol Neurodegener* 2025; 20: 31.

[80] Robinson JL, Lee EB, Xie SX, et al. Neurodegenerative disease concomitant proteinopathies are prevalent, age-related and APOE4-associated. *Brain* 2018; 141: 2181–2193.

[81] Frisoni GB, Fox NC, Jack CR, et al. The clinical use of structural MRI in Alzheimer disease. *Nat Rev Neurol* 2010; 6: 67–77.

[82] Vemuri P, Jack CR. Role of structural MRI in Alzheimer's disease. *Alzheimers Res Ther*; 2. Epub ahead of print 2010. DOI: 10.1186/alzrt47.

[83] Wolk DA, Nelson PT, Apostolova L, et al. Clinical criteria for limbic-predominant age-related TDP-43 encephalopathy. *Alzheimers Dement*; 21. Epub ahead of print 1 January 2025. DOI: 10.1002/alz.14202.

[84] Klunk WE, Engler H, Nordberg A, et al. Imaging brain amyloid in Alzheimer's disease with Pittsburgh Compound-B. *Ann Neurol* 2004; 55: 306–319.

[85] Ossenkoppele R, Coomans EM, Apostolova LG, et al. Tau PET positivity in individuals with and without cognitive impairment varies with age, amyloid-β status, APOE genotype and sex. *Nat Neurosci* 2025; 28: 1610–1621.

[86] Fodero-Tavoletti MT, Okamura N, Furumoto S, et al. 18F-THK523: a novel in vivo tau imaging ligand for Alzheimer's disease. *Brain* 2011; 134: 1089–1100.

[87] Cassinelli Petersen G, Roytman M, Chiang GC, et al. Overview of tau PET molecular imaging. *Curr Opin Neurol* 2022; 35: 230–239.

[88] Motter R, Vigo-Pelfrey C, Kholodenko D, et al. Reduction of beta-amyloid peptide42 in the cerebrospinal fluid of patients with Alzheimer's disease. *Ann Neurol* 1995; 38: 643–648.

[89] Blennow K, Wallin A, Ågren H, et al. Tau protein in cerebrospinal fluid: a biochemical marker for axonal degeneration in Alzheimer disease? *Mol Chem Neuropathol* 1995; 26: 231–245.

[90] Jack CR, Bennett DA, Blennow K, et al. NIA-AA Research Framework: Toward a biological definition of Alzheimer's disease. *Alzheimers Dement* 2018; 14: 535–562.

[91] Seidu NM, Kern S, Sacuiu S, et al. Association of CSF biomarkers with MRI brain changes in Alzheimer's disease. *Alzheimers Dement (Amst)*; 16. Epub ahead of print 1 January 2024. DOI: 10.1002/DAD2.12556.

[92] Römer M, Lange-Asschenfeldt C, Müller-Schmitz K, et al. Cerebrospinal Fluid Biomarkers and Neuropsychological Abnormalities in Dementia: A Monocentric Study of Consecutive Patients. *J Clin Med*; 14. Epub ahead of print 1 February 2025. DOI: 10.3390/JCM14030710.

[93] Benedet AL, Milà-Alomà M, Vrillon A, et al. Differences Between Plasma and Cerebrospinal Fluid Glial Fibrillary Acidic Protein Levels Across the Alzheimer Disease Continuum. *JAMA Neurol* 2021; 78: 1471–1483.

[94] Meeker KL, Butt OH, Gordon BA, et al. Cerebrospinal fluid neurofilament light chain is a marker of aging and white matter damage. *Neurobiol Dis*; 166. Epub ahead of print 1 May 2022. DOI: 10.1016/j.nbd.2022.105662.

[95] Bonomi S, Gupta MR, Schindler SE. Inadequate reimbursement for lumbar puncture is a potential barrier to accessing new Alzheimer's disease treatments. *Alzheimers Dement* 2023; 19: 5849–5851.

[96] Moulder KL, Besser LM, Beekly D, et al. Factors Influencing Successful Lumbar Puncture in Alzheimer Research. *Alzheimer Dis Assoc Disord* 2017; 31: 287–294.

[97] Rissin DM, Kan CW, Campbell TG, et al. Single-molecule enzyme-linked immunosorbent assay detects serum proteins at subfemtomolar concentrations. *Nat Biotechnol* 2010; 28: 595–599.

[98] Palmqvist S, Janelidze S, Quiroz YT, et al. Discriminative Accuracy of Plasma Phospho-tau217 for Alzheimer Disease vs Other Neurodegenerative Disorders. *JAMA* 2020; 324: 772–781.

[99] Janelidze S, Stomrud E, Palmqvist S, et al. Plasma β-amyloid in Alzheimer's disease and vascular disease. *Sci Rep*; 6. Epub ahead of print 31 May 2016. DOI: 10.1038/srep26801.

[100] Verberk IMW, Slot RE, Verfaillie SCJ, et al. Plasma Amyloid as Prescreener for the Earliest Alzheimer Pathological Changes. *Ann Neurol* 2018; 84: 648–658.

[101] Schindler SE, Bollinger JG, Ovod V, et al. High-precision plasma β-amyloid 42/40 predicts current and future brain amyloidosis. *Neurology* 2019; 93: E1647–E1659.

[102] Ovod V, Ramsey KN, Mawuenyega KG, et al. Amyloid β concentrations and stable isotope labeling kinetics of human plasma specific to central nervous system amyloidosis. *Alzheimers Dement* 2017; 13: 841–849.

[103] Tatebe H, Kasai T, Ohmichi T, et al. Quantification of plasma phosphorylated tau to use as a biomarker for brain Alzheimer pathology: pilot case-control studies including patients with Alzheimer's disease and down syndrome. *Mol Neurodegener*; 12. Epub ahead of print 4 September 2017. DOI: 10.1186/s13024-017-0206-8.

[104] Mielke MM, Hagen CE, Xu J, et al. Plasma phospho-tau181 increases with Alzheimer's disease clinical severity and is associated with tau- and amyloid-positron emission tomography. *Alzheimers Dement* 2018; 14: 989–997.

[105] Leuzy A, Mattsson-Carlgren N, Palmqvist S, et al. Blood-based biomarkers for Alzheimer's disease. *EMBO Mol Med*; 14. Epub ahead of print 11 January 2022. DOI: 10.15252/emmm.202114408.

[106] Pichet Binette A, Franzmeier N, Spotorno N, et al. Amyloid-associated increases in soluble tau relate to tau aggregation rates and cognitive decline in early Alzheimer's disease. *Nat Commun* 2022; 13: 6635.

[107] Salvadó G, Ossenkoppele R, Ashton NJ, et al. Specific associations between plasma biomarkers and postmortem amyloid plaque and tau tangle loads. *EMBO Mol Med*; 15. Epub ahead of print 8 May 2023. DOI: 10.15252/emmm.202217123.

[108] Cogswell PM, Lundt ES, Therneau TM, et al. Modeling the temporal evolution of plasma p-tau in relation to amyloid beta and tau PET. *Alzheimers Dement* 2024; 20: 1225–1238.

[109] Mielke MM, Syrjanen JA, Blennow K, et al. Plasma and CSF neurofilament light: Relation to longitudinal neuroimaging and cognitive measures. *Neurology* 2019; 93: E252–E260.

[110] Barker W, Quinonez C, Greig MT, et al. Utility of Plasma Neurofilament Light in the 1Florida Alzheimer's Disease Research Center (ADRC). *J Alzheimers Dis* 2021; 79: 59–70.

[111] Simonsen AH, Gleerup HS, Musaeus CS, et al. Neurofilament light chain levels in serum among a large mixed memory clinic cohort: Confounders and diagnostic usefulness. *Alzheimers Dement (Amst)*; 15. Epub ahead of print 1 October 2023. DOI: 10.1002/DAD2.12512.

[112] Verberk IMW, Laarhuis MB, van den Bosch KA, et al. Serum markers glial fibrillary acidic protein and neurofilament light for prognosis and monitoring in cognitively normal older people: a prospective memory clinic-based cohort study. *Lancet Healthy Longev* 2021; 2: e87–e95.

[113] Anastasi F, Fernández-Lebrero A, Ashton NJ, et al. A head-to-head comparison of plasma biomarkers to detect Alzheimer's disease in a memory clinic. *Alzheimers Dement*; 21. Epub ahead of print 1 February 2025. DOI: 10.1002/alz.14609.

[114] Kwon HS, Hwang M, Koh SH, et al. Comparison of plasma p-tau217 and p-tau181 in predicting amyloid positivity and prognosis among Korean memory clinic patients. *Sci Rep*; 15. Epub ahead of print 1 December 2025. DOI: 10.1038/s41598-025-90232-8.

[115] Schindler SE, Petersen KK, Saef B, et al. Head-to-head comparison of leading blood tests for Alzheimer's disease pathology. *Alzheimers Dement* 2024; 20: 8074–8096.

[116] Ashton NJ, Brum WS, Molfetta G Di, et al. Diagnostic Accuracy of a Plasma Phosphorylated Tau 217 Immunoassay for Alzheimer Disease Pathology. *JAMA Neurol* 2024; 81: 255–263.

[117] Warmenhoven N, Salvadó G, Janelidze S, et al. A comprehensive head-to-head comparison of key plasma phosphorylated tau 217 biomarker tests. *Brain* 2025; 148: 416–431.

[118] Feizpour A, Doecke JD, Doré V, et al. Detection and staging of Alzheimer's disease by plasma pTau217 on a high throughput immunoassay platform. *EBioMedicine*; 109. Epub ahead of print 1 November 2024. DOI: 10.1016/j.ebiom.2024.105405.

[119] Ossenkoppele R, Salvadó G, Janelidze S, et al. Plasma p-tau217 and tau-PET predict future cognitive decline among cognitively unimpaired individuals: implications for clinical trials. *Nat Aging* 2025; 5: 883–896.

[120] Anastasi F, Fernández-Lebrero A, Ashton NJ, et al. A head-to-head comparison of plasma biomarkers to detect Alzheimer's disease in a memory clinic. *Alzheimer's and Dementia*; 21. Epub ahead of print 1 February 2025. DOI: 10.1002/ALZ.14609,.

[121] Deek RA, Balogun WG, Zeng X, et al. Head-to-head comparison of plasma p-tau217 immunoassays for incipient Alzheimer's disease in community cohorts. *Alzheimers Res Ther* 2026; 18: 61.

[122] Lebrun L, Hanseeuw B, van Pesch V, et al. Alzheimer disease's cerebrospinal fluid biomarkers differences between immigrants and natives in a Belgian memory clinic. *Acta Neurol Belg* 2023; 123: 537–544.

[123] Gleason CE, Zuelsdorff M, Gooding DC, et al. Alzheimer's disease biomarkers in Black and non-Hispanic White cohorts: A contextualized review of the evidence. *Alzheimers Dement* 2022; 18: 1545–1564.

[124] Modeste ES, Ping L, Watson CM, et al. Quantitative proteomics of cerebrospinal fluid from African Americans and Caucasians reveals shared and divergent changes in Alzheimer's disease. *Mol Neurodegener*; 18. Epub ahead of print 1 December 2023. DOI: 10.1186/S13024-023-00638-Z.

[125] Chaudhry A, Rizig M. Comparing fluid biomarkers of Alzheimer's disease between African American or Black African and white groups: A systematic review and meta-analysis. *J Neurol Sci*; 421. Epub ahead of print 15 February 2021. DOI: 10.1016/J.JNS.2020.117270.

[126] Morris JC, Schindler SE, McCue LM, et al. Assessment of Racial Disparities in Biomarkers for Alzheimer Disease. *JAMA Neurol* 2019; 76: 264–273.

[127] Howell JC, Watts KD, Parker MW, et al. Race modifies the relationship between cognition and Alzheimer's disease cerebrospinal fluid biomarkers. *Alzheimers Res Ther*; 9. Epub ahead of print 2 November 2017. DOI: 10.1186/S13195-017-0315-1.

[128] Deters KD, Napolioni V, Sperling RA, et al. Amyloid PET Imaging in Self-Identified Non-Hispanic Black Participants of the Anti-Amyloid in Asymptomatic Alzheimer's Disease (A4) Study. *Neurology* 2021; 96: E1491–E1500.

[129] Hunter P. The genetics of human migrations: Our ancestors migration out of Africa has left traces in our genomes that explain how they adapted to new environments. *EMBO Rep* 2014; 15: 1019.

[130] Karlsson EK, Kwiatkowski DP, Sabeti PC. Natural selection and infectious disease in human populations. *Nat Rev Genet* 2014; 15: 379–393.

[131] Evans W, Fung HC, Steele J, et al. The tau H2 haplotype is almost exclusively Caucasian in origin. *Neurosci Lett* 2004; 369: 183–185.

[132] Le Guen Y, Raulin AC, Logue MW, et al. Association of African Ancestry-Specific APOE Missense Variant R145C With Risk of Alzheimer Disease. *JAMA* 2023; 329: 551–560.

[133] Qin W, Li W, Wang Q, et al. Race-Related Association between APOE Genotype and Alzheimer's Disease: A Systematic Review and Meta-Analysis. *J Alzheimers Dis* 2021; 83: 897–906.

[134] Templeton AR. Haplotype trees and modern human origins. *Am J Phys Anthropol* 2005; Suppl 41: 33–59.

[135] Arslan B, Brum WS, Pola I, et al. The impact of kidney function on Alzheimer's disease blood biomarkers: implications for predicting amyloid-β positivity. *Alzheimers Res Ther*; 17. Epub ahead of print 1 December 2025. DOI: 10.1186/S13195-025-01692-Z.

[136] Janelidze S, Barthélemy NR, He Y, et al. Mitigating the Associations of Kidney Dysfunction With Blood Biomarkers of Alzheimer Disease by Using Phosphorylated Tau to Total Tau Ratios. *JAMA Neurol* 2023; 80: 516–522.

[137] Wu J, Xiao Z, Wang M, et al. The impact of kidney function on plasma neurofilament light and phospho-tau 181 in a community-based cohort: the Shanghai Aging Study. *Alzheimers Res Ther*; 16. Epub ahead of print 1 December 2024. DOI: 10.1186/S13195-024-01401-2.

[138] Jacobs T, Brien CO, Figueredo L, et al. Body mass index and blood volume influence plasma biomarkers and positron emission tomography classification in preclinical Alzheimer's disease. *Alzheimers Dement* 2025; 21: e70765.

[139] Abu-Rumeileh S, Scholle L, Mensch A, et al. Phosphorylated tau 181 and 217 are elevated in serum and muscle of patients with amyotrophic lateral sclerosis. *Nat Commun*; 16. Epub ahead of print 1 December 2025. DOI: 10.1038/S41467-025-57144-7.

[140] Gonzalez-Ortiz F, Vávra J, Payne E, et al. The potential dual role of tau phosphorylation: plasma phosphorylated-tau217 in newborns and Alzheimer's disease. *Brain Commun*; 7. Epub ahead of print 2025. DOI: 10.1093/BRAINCOMMS/FCAF221.

[141] Gundersen JK, Gonzalez-Ortiz F, Karikari T, et al. Neuronal plasma biomarkers in acute ischemic stroke. *J Cereb Blood Flow Metab* 2025; 45: 77–84.

[142] Nielsen TR, Segers K, Vanderaspoilden V, et al. Performance of middle-aged and elderly European minority and majority populations on a Cross-Cultural Neuropsychological Test Battery (CNTB). *Clin Neuropsychol* 2018; 32: 1411–1430.

[143] Nielsen TR, Jørgensen K, Delgado-Álvarez A, et al. Comparison of the diagnostic accuracy of five cross-cultural cognitive screening instruments for dementia and mild cognitive impairment in a multicultural memory clinic sample. *J Alzheimers Dis*. Epub ahead of print 22 June 2025. DOI: 10.1177/13872877251351037.

[144] Torkpoor R, Frolich K, Londos E, et al. Diagnostic Accuracy of the Swedish Version of the Multicultural Cognitive Examination for Cognitive Assessment in Swedish Memory Clinics. *J Alzheimers Dis* 2024; 97: 715–726.

[145] Araujo NB, Nielsen TR, Barca ML, et al. Brazilian version of the European Cross-Cultural Neuropsychological Test Battery (CNTB-BR): diagnostic accuracy across schooling levels. *Braz J Psychiatry* 2020; 42: 286–294.

[146] Delgado-Álvarez A, Delgado-Alonso C, Valles-Salgado M, et al. Normative Data in Cross-Cultural Neuropsychological Instruments in Spaniards and Colombians Living in Spain. *Journal of Alzheimer's Disease* 2023; 96: 1231–1241.

[147] Delgado-Álvarez A, Nielsen TR, Delgado-Alonso C, et al. Validation of the European Cross-Cultural Neuropsychological Test Battery (CNTB) for the assessment of mild cognitive impairment due to Alzheimer's disease and Parkinson's disease. *Front Aging Neurosci*; 15. Epub ahead of print 2023. DOI: 10.3389/FNAGI.2023.1134111/PDF.

[148] World Health Organization. *The ICD-10 Classification of Mental and Behavioural Disorders: diagnostic criteria for research*. Geneva: World Health Organization, 1993.

[149] American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition. *Diagnostic and Statistical Manual of Mental Disorders*. Epub ahead of print 22 May 2013. DOI: 10.1176/APPI.BOOKS.9780890425596.

[150] American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders. Fourth Edition, Text Revision ed.* Washington DC: Arlington: American Psychiatric Publishing, 2000.

[151] American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders. Fourth Edition (DSM-IV)*. Washington DC: Arlington: American Psychiatric Publishing, 1994.

[152] Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med*; 6. Epub ahead of print 1 July 2009. DOI: 10.1371/JOURNAL.PMED.1000097.

[153] Jessen F, Amariglio RE, Van Boxtel M, et al. A conceptual framework for research on subjective cognitive decline in preclinical Alzheimer's disease. *Alzheimers Dement* 2014; 10: 844–852.

[154] McKeith IG, Boeve BF, Dickson DW, et al. Diagnosis and management of dementia with Lewy bodies: Fourth consensus report of the DLB Consortium. *Neurology* 2017; 89: 88–100.

[155] Sachdev P, Kalaria R, O'Brien J, et al. Diagnostic criteria for vascular cognitive disorders: a VASCOG statement. *Alzheimer Dis Assoc Disord* 2014; 28: 206–218.

[156] Rascovsky K, Hodges JR, Kipps CM, et al. Diagnostic criteria for the behavioral variant of frontotemporal dementia (bvFTD): current limitations and future directions. *Alzheimer Dis Assoc Disord*; 21. Epub ahead of print October 2007. DOI: 10.1097/WAD.0B013E31815C3445.

[157] Gorno-Tempini ML, Hillis AE, Weintraub S, et al. Classification of primary progressive aphasia and its variants. *Neurology* 2011; 76: 1006.

[158] Relkin N, Marmarou A, Klinge P, et al. Diagnosing idiopathic normal-pressure hydrocephalus. *Neurosurgery* 2005; 57: S24–S216.

[159] Bali D, Hansson O, Janelidze S. Effects of certain pre-analytical factors on the performance of plasma phospho-tau217. *Alzheimers Res Ther*; 16. Epub ahead of print 1 December 2024. DOI: 10.1186/S13195-024-01391-1.

[160] Nielsen TR, Vogel A, Waldemar G. Comparison of performance on three neuropsychological tests in healthy Turkish immigrants and Danish elderly. *Int Psychogeriatr* 2012; 24: 1515–1521.

[161] Ph.D. DAC. E. Strauss, E. M. S. Sherman, & O. Spreen, A Compendium of Neuropsychological Tests: Administration, Norms, and Commentary. *Appl Neuropsychol* 2007; 14: 62–63.

[162] Schmidtke K, Olbrich S. The Clock Reading Test: validation of an instrument for the diagnosis of dementia and disorders of visuo-spatial cognition. *Int Psychogeriatr* 2007; 19: 307–321.

[163] Whiting PF, Rutjes AWS, Westwood ME, et al. QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. *Ann Intern Med* 2011; 155: 529–536.

[164] Luchsinger JA, Tang MX, Miller J, et al. Relation of plasma homocysteine to plasma amyloid beta levels. *Neurochem Res* 2007; 32: 775–781.

[165] Brickman AM, Manly JJ, Honig LS, et al. Plasma p-tau181, p-tau217, and other blood-based Alzheimer's disease biomarkers in a multi-ethnic, community study. *Alzheimers Dement* 2021; 17: 1353–1364.

[166] Brickman AM, Manly JJ, Honig LS, et al. Correlation of plasma and neuroimaging biomarkers in Alzheimer's disease. *Ann Clin Transl Neurol* 2022; 9: 756–761.

[167] Hall JR, Petersen M, Johnson L, et al. Characterizing Plasma Biomarkers of Alzheimer's in a Diverse Community-Based Cohort: A Cross-Sectional Study of the HAB-HD Cohort. *Front Neurol*; 13. Epub ahead of print 18 August 2022. DOI: 10.3389/FNEUR.2022.871947.

[168] O'Bryant S, Petersen M, Hall J, et al. Characterizing plasma NfL in a community-dwelling multi-ethnic cohort: Results from the HABLE study. *Alzheimers Dement* 2022; 18: 240–250.

[169] Schindler SE, Karikari TK, Ashton NJ, et al. Effect of Race on Prediction of Brain Amyloidosis by Plasma Aβ42/Aβ40, Phosphorylated Tau, and Neurofilament Light. *Neurology* 2022; 99: E245–E257.

[170] Rajan KB, McAninch EA, Aggarwal NT, et al. Longitudinal Changes in Blood Biomarkers of Clinical Alzheimer Disease in a Biracial Population Sample. *Neurology* 2023; 100: E874–E883.

[171] Gonzales MM, Short MI, Satizabal CL, et al. Blood biomarkers for dementia in Hispanic and non-Hispanic White adults. *Alzheimers Dement (N Y)*; 7. Epub ahead of print 2021. DOI: 10.1002/TRC2.12164.

[172] O'Bryant SE, Petersen M, Hall J, et al. Depression is differentially related to cognitive and biomarker outcomes among Mexican Americans. *Front Psychiatry*; 13. Epub ahead of print 23 August 2022. DOI: 10.3389/FPSYT.2022.901403.

[173] Giebel C, Silva-Ribeiro W, Watson J, et al. A Systematic Review on the Evidence of Misdiagnosis in Dementia and Its Impact on Accessing Dementia Care. *Int J Geriatr Psychiatry*; 39. Epub ahead of print 1 October 2024. DOI: 10.1002/gps.6158.

[174] Trudel L, Therriault J, Macedo AC, et al. Estimated prevalence of underdiagnosed dementia in a multiethnic community-based study. *J Prev Alzheimers Dis*; 13. Epub ahead of print 1 April 2026. DOI: 10.1016/j.tjpad.2026.100510.

[175] Carter C, Roche M, Whitfield E, et al. Equality of opportunity for timely dementia diagnosis (EQUATED): a qualitative study of how people from minoritised ethnic groups experience

the early symptoms of dementia and seek help. *Age Ageing*; 53. Epub ahead of print 1 November 2024. DOI: 10.1093/ageing/afae244.

[176] Rune Nielsen T, Jørgensen K, Canevelli M, et al. Validation of the Brief Assessment of Impaired Cognition and Brief Assessment of Impaired Cognition Questionnaire in a multicultural memory clinic sample across six European countries. *J Alzheimers Dis* 2025; 104: 823–834.

[177] Breton A, Casey D, Arnaoutoglou NA. Cognitive tests for the detection of mild cognitive impairment (MCI), the prodromal stage of dementia: Meta-analysis of diagnostic accuracy studies. *Int J Geriatr Psychiatry* 2019; 34: 233–242.

[178] Delgado-Álvarez A, Delgado-Alonso C, Goudsmit M, et al. Validation of the cross-cultural dementia screening test in Alzheimer's disease and Parkinson's disease. *Front Psychol*; 13. Epub ahead of print 4 January 2023. DOI: 10.3389/FPSYG.2022.1043721.

[179] Stålhammar J, Hellström P, Eckerström C, et al. Neuropsychological Test Performance Among Native and Non-Native Swedes: Second Language Effects. *Archives of Clinical Neuropsychology* 2020; 37: 826.

[180] Evans J. THE INFLUENCE OF CULTURE ON THE ASSESSMENT OF EXECUTIVE FUNCTIONING. *Understanding Cross-Cultural Neuropsychology: Science, Testing, and Challenges* 2022; 110–121.

[181] Bourdage R, Franzen S, Palisson J, et al. The TIE-93: a Facial Emotion Recognition Test Adapted for Culturally, Linguistically, and Educationally Diverse Alzheimer's Dementia Patients in France. *Arch Clin Neuropsychol*. Epub ahead of print 20 February 2025. DOI: 10.1093/ARCLIN/ACAF012.

[182] Matallana D, De Santacruz C, Cano C, et al. The relationship between education level and Mini Mental State Examination domains among older Mexican Americans. *J Geriatr Psychiatry Neurol* 2010; 24: 9.

[183] Tsoi KKF, Chan JYC, Hirai HW, et al. Cognitive Tests to Detect Dementia: A Systematic Review and Meta-analysis. *JAMA Intern Med* 2015; 175: 1450–1458.

[184] Franzen S, Van Den Berg E, Kalkisim Y, et al. Assessment of Visual Association Memory in Low-Educated, Non-Western Immigrants with the Modified Visual Association Test. *Dement Geriatr Cogn Disord* 2019; 47: 345–354.

[185] Narme P, Maillet D, Palisson J, et al. How to Assess Executive Functions in a Low-Educated and Multicultural Population Using a Switching Verbal Fluency Test (the TFA-93) in Neurodegenerative Diseases? *Am J Alzheimers Dis Other Demen* 2019; 34: 469–477.

[186] Metcalfe T, Nielsen TR, O'Donald F, et al. A Systematic Review of the Measurement and Influence of Quality of Education on Neuropsychological Test Performance in Later Life. *Neuropsychol Rev*. Epub ahead of print 2026. DOI: 10.1007/s11065-025-09689-z.

[187] Craik FIM, Bialystok E. Cognition through the lifespan: mechanisms of change. *Trends Cogn Sci* 2006; 10: 131–138.

[188] Heiskanen MA, Nevalainen J, Pahkala K, et al. Cognitive performance from childhood to old age and intergenerational correlations in the multigenerational Young Finns Study. *J Neurol* 2024; 271: 7294–7308.

[189] Murman DL. The Impact of Age on Cognition. *Semin Hear* 2015; 36: 111.

[190] Petersen ME, Zhou Z, Hall JR, et al. Health and Aging Brain Study-Health Disparities (HABS-HD) methods and partner characteristics. *Alzheimers Dement (N Y)*; 11. Epub ahead of print 1 July 2025. DOI: 10.1002/TRC2.70140.

[191] Hayes CA, Najmi Z, Contreras JA, et al. Plasma p-tau217 and cognitive impairment: Evaluating biomarker equity across racial/ethnic groups in HABS-HD. *Alzheimers Dement (Amst)*; 18. Epub ahead of print 1 January 2026. DOI: 10.1002/dad2.70269.

[192] DuBois KN, Pal S, Reader JM, et al. Evaluation of a panel of plasma biomarkers for Alzheimer's disease in a diverse research cohort. *J Alzheimers Dis* 2026; 109: 247–265.

[193] Nayyar A, Li M ling, Sotelo V, et al. Influence of cognitive impairment and race on plasma p-Tau217 in two diverse cohorts. *Alzheimers Dement*; 21. Epub ahead of print 1 February 2025. DOI: 10.1002/alz.14585.

[194] Brodman ST, Heaton N, Triana-Baltzer G, et al. Plasma biomarkers, brain amyloid-beta pathology, and cortical thickness in a non-Hispanic White and Black/African American middle-aged community cohort: The HCP-CoBRA study. *Alzheimers Dement*; 21. Epub ahead of print 1 December 2025. DOI: 10.1002/alz.70985.

[195] Mendez MF. Early-onset Alzheimer Disease and Its Variants. *Continuum (Minneap Minn)* 2019; 25: 34.

[196] Asken BM, Wang WE, Arias F, et al. Sex and ethnicity in early-onset Alzheimer's disease biomarkers and global function. *Alzheimers Dement (Amst)*; 17. Epub ahead of print 1 July 2025. DOI: 10.1002/dad2.70157.

[197] Stefansson H, Helgason A, Thorleifsson G, et al. A common inversion under selection in Europeans. *Nat Genet* 2005; 37: 129–137.

[198] Boettger LM, Handsaker RE, Zody MC, et al. Structural haplotypes and recent evolution of the human 17q21.31 region. *Nat Genet* 2012; 44: 881–885.

[199] Belloy ME, Andrews SJ, Le Guen Y, et al. APOE Genotype and Alzheimer Disease Risk Across Age, Sex, and Population Ancestry. *JAMA Neurol* 2023; 80: 1284.

[200] Clement S, Schauman O, Graham T, et al. What is the impact of mental health-related stigma on help-seeking? A systematic review of quantitative and qualitative studies. *Psychol Med* 2015; 45: 11–27.

[201] McGrath RP, Snih S Al, Markides KS, et al. The burden of health conditions across race and ethnicity for aging Americans: Disability-adjusted life years. *Medicine* 2019; 98: e17964.

[202] Fernández AL, Marcopulos BA. A comparison of normative data for the Trail Making Test from several countries: equivalence of norms and considerations for interpretation. *Scand J Psychol* 2008; 49: 239–246.

[203] Dodge HH, Meguro K, Ishii H, et al. Cross-cultural comparisons of the Mini-mental State Examination between Japanese and U.S. cohorts. *Int Psychogeriatr* 2009; 21: 113–122.

[204] Cousins KAQ, Korecka M, Wan Y, et al. Comparison of plasma p-tau217/Aβ42, p-tau217, and Aβ42/Aβ40 biomarkers by race to detect Alzheimer's disease. *Alzheimers Dement*; 21. Epub ahead of print 1 August 2025. DOI: 10.1002/alz.70469.

[205] Brickman AM, Muller C, Warren JR, et al. Alzheimer Disease Blood Biomarker Concentrations Across Race and Ethnicity Groups in Middle-Aged Adults. *JAMA Netw Open* 2025; 8: e2545046.

[206] Asken BM, DeSimone JC, Wang WE, et al. Plasma p-tau217 concordance with amyloid PET among ethnically diverse older adults. *Alzheimers Dement (Amst)*; 16. Epub ahead of print 1 July 2024. DOI: 10.1002/DAD2.12617.

[207] Gogola A, Zeng X, Williams LA, et al. Impact of racialization on neuroimaging and plasma biomarkers of Alzheimer's disease. *Alzheimers Dement*; 21. Epub ahead of print 1 July 2025. DOI: 10.1002/alz.70463.

[208] Hou Y, Dan X, Babbar M, et al. Ageing as a risk factor for neurodegenerative disease. *Nat Rev Neurol* 2019; 15: 565–581.

[209] Raman R, Quiroz YT, Langford O, et al. Disparities by Race and Ethnicity Among Adults Recruited for a Preclinical Alzheimer Disease Trial. *JAMA Netw Open* 2021; 4: e2114364.

[210] Groot C, Cicognola C, Bali D, et al. Diagnostic and prognostic performance to detect Alzheimer's disease and clinical progression of a novel assay for plasma p-tau217. *Alzheimers Res Ther*; 14. Epub ahead of print 1 December 2022. DOI: 10.1186/S13195-022-01005-8.

[211] Yun J, Lee J, Shin D, et al. Plasma Phosphorylated Tau 217 Cutoffs for Amyloid Pathology and Kidney Function, Body Mass Index, and Anemia. *JAMA Neurol* 2026; 83: 269.

[212] Schindler SE, Galasko D, Pereira AC, et al. Acceptable performance of blood biomarker tests of amyloid pathology - recommendations from the Global CEO Initiative on Alzheimer's Disease. *Nat Rev Neurol*; 20. Epub ahead of print 1 July 2024. DOI: 10.1038/S41582-024-00977-5.

[213] Palmqvist S, Warmenhoven N, Anastasi F, et al. Plasma phospho-tau217 for Alzheimer's disease diagnosis in primary and secondary care using a fully automated platform. *Nat Med* 2025; 31: 2036–2043.

[214] Gleerup HS, Simonsen AH, Grötschel L, et al. Plasma biomarkers of amyloid, tau, astrogliosis, and axonal injury in a mixed memory clinic cohort. *Alzheimers Dement (Amst)*; 17. Epub ahead of print 1 January 2025. DOI: 10.1002/DAD2.70073.

[215] Gonzalez-Ortiz F, Kirsebom BE, Yakoub Y, et al. Associations Between Changes in Levels of Phosphorylated Tau and Severity of Cognitive Impairment in Early Alzheimer Disease. *Neurology*; 104. Epub ahead of print 15 May 2025. DOI: 10.1212/WNL.0000000000213676.

[216] Yakoub Y, Gonzalez-Ortiz F, Ashton NJ, et al. Plasma p-tau217 identifies cognitively normal older adults who will develop cognitive impairment in a 10-year window. *Alzheimers Dement*; 21. Epub ahead of print 1 February 2025. DOI: 10.1002/ALZ.14537.

[217] Wennström M, Janelidze S, Nilsson KPR, et al. Cellular localization of p-tau217 in brain and its association with p-tau217 plasma levels. *Acta Neuropathol Commun*; 10. Epub ahead of print 1 December 2022. DOI: 10.1186/S40478-021-01307-2.

[218] Salvadó G, Janelidze S, Bali D, et al. Plasma Phosphorylated Tau 217 to Identify Preclinical Alzheimer Disease. *JAMA Neurol* 2025; 82: 1122–1134.

[219] Mattsson-Carlgren N, Palmqvist S, Horie K, et al. Integration of plasma eMTBR-tau243 and p-tau217 in the diagnosis and stratification of Alzheimer's disease: a prospective cohort study. *Lancet Neurol* 2026; 25: 357–367.

[220] Jack CR, Andrews JS, Beach TG, et al. Revised criteria for diagnosis and staging of Alzheimer's disease: Alzheimer's Association Workgroup. *Alzheimers Dement*. Epub ahead of print 27 June 2024. DOI: 10.1002/alz.13859.

[221] Bentivenga GM, Gonzalez-Ortiz F, Baiardi S, et al. Clinical value of novel blood-based tau biomarkers in Creutzfeldt-Jakob disease. *Alzheimers Dement*; 21. Epub ahead of print 1 February 2025. DOI: 10.1002/ALZ.14422.

[222] Clementi L, Sabetta S, Zelli V, et al. Mitotic phosphorylation of Tau/MAPT modulates cell cycle progression in prostate cancer cells. *J Cancer Res Clin Oncol* 2023; 149: 7689–7701.

[223] Balczon R, Choi CS, deWeever A, et al. Infection promotes Ser-214 phosphorylation important for generation of cytotoxic tau variants. *FASEB J*; 37. Epub ahead of print 1 July 2023. DOI: 10.1096/FJ.202300620RR.

[224] Ashton NJ, Moseby-Knappe M, Benedet AL, et al. Alzheimer Disease Blood Biomarkers in Patients With Out-of-Hospital Cardiac Arrest. *JAMA Neurol* 2023; 80: 388–396.

[225] Gonzalez-Ortiz F, Dulewicz M, Ashton NJ, et al. Association of Serum Brain-Derived Tau With Clinical Outcome and Longitudinal Change in Patients With Severe Traumatic Brain Injury. *JAMA Netw Open*; 6. Epub ahead of print 1 July 2023. DOI: 10.1001/JAMANETWORKOPEN.2023.21554.

[226] Mazzeo S, Hardy CJD, Jiang J, et al. Primary Progressive Aphasia in Italian and English: A Cross-Linguistic Cohort Study. *Neurology* 2024; 103: e210058.

[227] Nielsen TR, Kjaergaard D. Primary Progressive Aphasia Across Languages: Prevalence and Presentation of Phenotypes Are Shaped by Language-Specific Features. *Neurology* 2024; 103: e210165.

[228] Gleerup HS, Sanna F, Koutarapu S, et al. Saliva phosphorylated tau concentration is not associated with Alzheimer's disease, cerebrospinal fluid or blood biomarkers. *Front Neurosci*; 19. Epub ahead of print 2025. DOI: 10.3389/fnins.2025.1718237.

[229] Huber H, Montoliu-Gaya L, Brum WS, et al. A minimally invasive dried blood spot biomarker test for the detection of Alzheimer's disease pathology. *Nat Med*; 32. Epub ahead of print 1 February 2026. DOI: 10.1038/s41591-025-04080-0.

9. Appendix

9.1. Kjaergaard, D., Delgado-Álvarez, A., Waldemar, G., Beinhoff, U., Bekkhus-Wetterberg, P., Franzen, S., Illingworth, C.H., Laks, J., Lozano-Ruiz, A., Lueschow, A., Matias-Guiu, J.A., Pomati, S., Segers, K., Torkpoor, R., Wagle, J., & Nielsen, T. R. (2026). Diagnostic accuracy of the Multicultural Cognitive Examination (MCE) for detection of MCI and dementia in a diverse international cohort. *The Clinical Neuropsychologist*, Online ahead of publication, 1–16. https://doi.org/10.1080/13854046.2026.2652032

9.2. Kjaergaard, D., Simonsen, A. H., Waldemar, G., & Nielsen, T. R. (2025). Ethnic and racial influences on blood biomarkers for Alzheimer's disease: A systematic review. *Journal of Alzheimer's disease : JAD*, *103*(1), 81–91. https://doi.org/10.1177/13872877241299047

9.3. Kjaergaard, D., Nielsen, T. R., Stomrud, E., Palmqvist, S., Bali, D., Dolado, A. O., Janelidze, S., Hansson, O., Waldemar, G., & Simonsen, A. H. (2025). Influence of ethnicity on the diagnostic accuracy of plasma p-tau217 for the identification of Alzheimer's disease: A consecutive mixed memory clinic cohort study. *Alzheimer's & dementia : the journal of the Alzheimer's Association*, *21*(6), e70315. https://doi.org/10.1002/alz.70315

9.4. Kjaergaard, D., Simonsen, A. H., Stomrud, E., Bali, D., Janelidze, S., Hansson, O., Waldemar, G., & Nielsen, T. R. (2025). Combining plasma p-tau217 and cross-cultural cognitive tests to identify Alzheimer's Disease in an ethnically diverse mixed memory clinic cohort. *Journal of the neurological sciences*, *478*, 123739. https://doi.org/10.1016/j.jns.2025.123739

9.5. Kjaergaard, D., Nielsen, T. R., Stomrud, E., Bali, D., Clemmensen, F. K., Frederiksen, K. S., Gleerup, H. S., Hasselbalch, S.G., Janelidze, S., Hansson, O., Waldemar, G., & Simonsen, A. H. Plasma phosphorylated tau217 discordance with amyloid status in an ethnically diverse mixed memory clinic cohort. Under review with *Journal of the neurological sciences*. Submitted the 16th of March 2026.

9.6 Data extraction table for: Blasi, M.T., Buscarnera, S., Salzillo, M., Bruno, G., Nuti, F., Simonsen, A.H., Nielsen, T.R., Kjaergaard, D., & Canevelli, M. Participant characteristics in blood p-tau217 studies for Alzheimer's disease: A systematic review. Manuscript in preparation (Prospero ID: CRD420251000147)

9.1. Study 1.

Diagnostic accuracy of the Multicultural Cognitive Examination (MCE) for detection of MCI and dementia in a diverse international cohort

Daniel Kjaergaard, Alfonso Delgado-Álvarez, Gunhild Waldemar, Ulrike Beinhoff, Peter Bekkhus-Wetterberg, Sanne Franzen, Caitlin H. Illingworth, Jerson Laks, Alvaro Lozano-Ruiz, Andreas Lueschow, Jordi A. Matias-Guiu, Simone Pomati, Kurt Segers, Rozita Torkpoor, Jørgen Wagle & T. Rune Nielsen

The Clinical Neuropsychologist (2026). https://doi.org/10.1080/13854046.2026.2652032

THE CLINICAL NEUROPSYCHOLOGIST
https://doi.org/10.1080/13854046.2026.2652032

Routledge
Taylor & Francis Group

OPEN ACCESS Check for updates

Diagnostic accuracy of the Multicultural Cognitive Examination (MCE) for detection of MCI and dementia in a diverse international cohort

Daniel Kjaergaard[a], Alfonso Delgado-Álvarez[b,c], Gunhild Waldemar[a,d], Ulrike Beinhoff[e], Peter Bekkhus-Wetterberg[f], Sanne Franzen[g], Caitlin H. Illingworth[h], Jerson Laks[i], Alvaro Lozano-Ruiz[j], Andreas Lueschow[e], Jordi A. Matias-Guiu[b], Simone Pomati[k], Kurt Segers[l], Rozita Torkpoor[m], Jørgen Wagle[n] and T. Rune Nielsen[a,o]

[a]Danish Dementia Research Centre, Department of Neurology, Copenhagen University Hospital - Rigshospitalet, Copenhagen, Denmark; [b]Department of Neurology. Hospital Clinico San Carlos. San Carlos Institute for Health Research (IdiSSC), Universidad Complutense. Madrid, Spain; [c]Department of Psychobiology & Behavioral Sciences Methods, Faculty of Psychology, Universidad Complutense de Madrid, Madrid, Spain; [d]Department of Clinical Medicine, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark; [e]Neurology, Ambulantes Gesundheitszentrum der Charité GmbH, Berlin, Germany; [f]Department of Geriatric Medicine, Oslo University Hospital, Oslo, Norway; [g]Department of Neurology & Alzheimer Center, Erasmus MC University Medical Center, Rotterdam, the Netherlands; [h]Department of Neuroscience, University of Sheffield, Sheffield, United Kingdom; [i]Institute of Psychiatry, Federal University of Rio de Janeiro, Rio de Janeiro, Brazil; [j]Department of Health Sciences, Valencian International University – VIU, Valencia, Spain; [k]Istituti Clinici Scientifici Maugeri IRCCS, Pavia, Italy; [l]Memory clinic neurology Dpt, Brugmann Hospital, Belgium; [m]Memory Clinic, Skåne University Hospital, Malmö, Sweden; [n]The Norwegian National Centre for Ageing and Health, Vestfold Hospital Trust, Tønsberg, Norway; [o]Department of Psychology, University of Copenhagen, Copenhagen, Denmark

ABSTRACT

Objective: Accurate cognitive screening tests for culturally, linguistically, and educationally diverse populations remain scarce, contributing to diagnostic inequities. To address this, we examined the cross-cultural properties and diagnostic accuracy of the Multicultural Cognitive Examination (MCE) in classifying mild cognitive impairment (MCI), dementia, Alzheimer's disease (AD) dementia, and non-AD dementia in participants with diverse backgrounds. Method: In this retrospective cross-sectional study, we aggregated data from 1,449 participants across 11 countries. Multiple linear regression models were used to determine the influence of demographic variables on MCE scores, which informed the creation of regression-based normative data. Diagnostic accuracies were examined using Receiver Operating Characteristics (ROC) curves. Results: The cohort consisted of 1001 cognitively intact participants, 140 patients with MCI, and 308 patients with dementia. 54.2% had immigrant backgrounds and originated from 63 different countries. MCE scores were significantly influenced by education and age,

ARTICLE HISTORY
Received 27 November 2025
Accepted 23 March 2026
Published online 09 April 2026

KEYWORDS
Alzheimer's disease; cognitive tests; dementia; ethnic groups; culture; cross-cultural comparison; education; mild cognitive impairment; minority groups; neuropsychological tests

CONTACT Daniel Kjaergaard daniel.kjaergaard.01@regionh.dk Danish Dementia Research Centre, Department of Neurology, Neuroscience Centre, Copenhagen University Hospital – Rigshospitalet, section 8008, Blegdamsvej 9, 2100, Copenhagen, Denmark.

Supplemental data for this article can be accessed online at https://doi.org/10.1080/13854046.2026.2652032.

© 2026 The Author(s). Published by Informa UK Limited, trading as Taylor & Francis Group
This is an Open Access article distributed under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/4.0/), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited. The terms on which this article has been published allow the posting of the Accepted Manuscript in a repository by the author(s) or with their consent.

but not by sex or immigrant status. The MCE demonstrated high accuracy in differentiating cognitively intact participants from patients with dementia (AUC: .95) and MCI (AUC: .84). The MCE was both accurate for classifying AD dementia (AUC: .97) and non-AD dementia (AUC: .94). Conclusions: This study supports the clinical utility of the MCE as a culturally robust and highly accurate cognitive screening test. Future studies should examine the ability of the MCE to monitor cognitive decline.

Introduction

Global immigration is at an all-time high, with an estimated 3.6% of the world population being migrants in 2024 (McAuliffe & Oucho, 2024). This increase is also found in memory clinics across the world as the number of patients with immigrant backgrounds referred for diagnostic assessment is increasing (Nichols et al., 2022; Nielsen et al., 2011; Segers et al., 2013; Van Mol & de Valk, 2016). However, clinicians frequently encounter barriers when examining patients with immigrant backgrounds because of cultural and linguistic differences (Nielsen, 2022; Nielsen et al., 2024; Nielsen & Kjaergaard, 2024). Such barriers include difficulty communicating medical history, biases in cognitive testing, and the inappropriateness of diagnostic criteria (Franzen et al., 2021; Mazzeo et al., 2024; Nielsen & Kjaergaard, 2024). To address these challenges, several initiatives, including the European Consortium of Cross-cultural Neuropsychology (ECCroN), promote knowledge and develop tools for fair assessment of people with diverse cultural, linguistic, and educational backgrounds (Ardila, 2020; Franzen et al., 2020; 2021; 2022).

The most widely used cognitive screening tests in memory clinic settings are prone to cultural and linguistic biases (Nielsen, 2022). These include the Mini-Mental Status Examination (MMSE), Montreal Cognitive Assessment (MoCA), and the Addenbrooke's Cognitive Examination (ACE) (Tsoi et al., 2015). Examples of bias include confrontation naming of black-and-white drawings in the MoCA and ACE, which disfavors individuals with lower levels of education and require specific cultural knowledge of objects and animals, that may be specific to certain parts of the world (Franzen et al., 2020; Nielsen, 2022; Reis et al., 2006). In addition, literacy and school dependent skills influence most aspects of the MMSE, including reading, writing, copying, orientation, subtractions, and repetitions (Brucki & Nitrini, 2010; Mandyla & Kosmidis, 2023; Milman et al., 2018). Solely translating the tests into different languages would be unfeasible in clinical practice, as comprehensive cultural adaptations and validations would be required for each language and cultural context (Franzen et al., 2020; Nielsen, 2022). Therefore, there is a pressing need for accurate and easy-to-use cross-cultural cognitive screening tests in memory clinics. Such tests already exist, including the Rowland Universal Dementia Assessment Scale (RUDAS) (Storey et al., 2004), the Cross-Cultural Dementia screening (CCD) (Goudsmit et al., 2017), the Multicultural Cognitive Examination (MCE) (Nielsen et al., 2019; Torkpoor et al., 2024), and the European Cross-cultural Neuropsychological Test Battery (CNTB) (Nielsen et al., 2018; 2019). However, cross-cultural cognitive tests, such as these, are so far not widely implemented (Nielsen et al., 2019; 2024; 2025). In particular, the MCE may be one of the

most accurate cross-cultural cognitive tests for identifying cognitive impairment. Additionally, the MCE can be administered across languages without changing the content, includes visual stimuli, low verbal load, fit for interpreter-mediated administration, and has little influence of education (Chithiramohan et al., 2024; Matias-Guiu & Delgado-Álvarez, 2023). In head-to-head comparisons, the MCE demonstrated superior diagnostic properties in multicultural populations compared to other screening tests, including the MMSE, RUDAS, CCD, and the Category Cued Memory Test (CCMT), and showed comparable performance to the Brief Assessment of Impaired Cognition (BASIC), although these findings are based on smaller samples (Delgado-Álvarez et al., 2026; Nielsen et al., 2025). Furthermore, the MCE can potentially also inform clinicians about cognitive profiles as it makes a broad assessment of several cognitive functions. Cross-cultural cognitive tests that reliably identify MCI and dementia across diverse populations, and for which clear evidence of their clinical applicability exists, are essential especially given the rising global prevalence of dementia and increasing diversity of world populations (McAuliffe & Oucho, 2024; Nichols et al., 2022; Nielsen et al., 2011; Segers et al., 2013; Van Mol & de Valk, 2016).

This paper extends prior research on the MCE conducted in smaller samples (Kjaergaard et al., 2025; Nielsen et al., 2019; 2025; Torkpoor et al., 2024), by examining the MCE on a large scale across sites in multiple countries with a culturally, linguistically, and educationally diverse cohort with mild cognitive impairment (MCI) and dementia. To support the cross-cultural properties and clinical applicability of the MCE, this study aimed to: (a) determine the influence of demographic variables on the MCE, (b) create normative data for the MCE, (c) determine the diagnostic accuracy of the MCE for differentiating cognitively intact participants from patients with MCI and dementia, and (d) examine the ability of the MCE to distinguish cognitively intact participants from patients with AD dementia and non-AD dementia.

Materials and methods

Study design and participants

We conducted a retrospective cross-sectional study, in which we aggregated existing participant data from sites in 11 countries. Participant data was obtained from published and ongoing studies across Belgium, Brazil, Denmark, France, Germany, Italy, the Netherlands, Norway, Spain, Sweden, and the United Kingdom (Araujo et al., 2020; Delgado-Álvarez et al., 2023; 2023; Nielsen et al., 2018; 2019; Nielsen et al., 2025; Torkpoor et al., 2024). Anonymized participant data was pooled and analyzed at the Danish Dementia Research Center. See participant characteristics stratified by country of inclusion in Supplementary Table 1.

Study participants included cognitively intact participants consisting of healthy controls (HC) and memory clinic patients with subjective cognitive decline (SCD). The cognitively impaired patients were memory clinic patients diagnosed with MCI or dementia. Participants were eligible for inclusion if they had available data on the MCE, demographic information (age, sex, education, country of birth), and syndrome diagnosis (HC, SCD, MCI, dementia). Patients' syndrome diagnosis was determined using different clinical criteria for MCI (Albert et al., 2011; American Psychiatric

Association, 2013; Winblad et al., 2004; World Health Organization, 1993) and dementia (American Psychiatric Association, 1994; 2000; 2013; McKhann et al., 2011; World Health Organization, 1993) across the participating sites (see Supplementary Table 2 for specifications). Across sites, diagnostic criteria required evidence of objective cognitive impairment, preserved functional independence in MCI, and functional decline in dementia. Differences primarily concerned terminology (for example major cognitive disorder vs. dementia) and emphasis on biomarker evidence. Diagnoses in memory clinics were set by multidisciplinary teams following comprehensive assessments. HC and SCD participants were pooled in this study, forming a cognitively intact group. Participants were excluded if they had significant physical, motor, neurological, vision, hearing, or psychiatric conditions that could interfere with cognitive testing. Furthermore, participants with missing data on more than one subtest of the MCE were excluded.

All memory clinic patients had undergone a comprehensive clinical examination, and the diagnoses were determined by a multidisciplinary team. The clinical assessment generally included a patient and informant interview, physical, neurological, cognitive, and psychiatric evaluation, standard laboratory blood tests, and structural brain imaging (computerized tomography or magnetic resonance imaging). At most sites, cerebrospinal fluid biomarkers, positron emission tomography, and neuropsychological or psychiatric evaluation were included when needed. The MCE was not part of the diagnostic evaluation, except for some patients included in the Netherlands ($N = 111$), where it was administered as part of an extensive culture-sensitive neuropsychological test battery (the TULIPA battery (Franzen et al., 2023)). HC participants were recruited from local districts, population registries, relatives of patients in memory clinics, senior centers, voluntary organizations, social networks of bilingual researchers, and advertisements in local newspapers.

Participants born in a different country than their country of examination were classified as having immigrant backgrounds, while participants born in their country of examination were classified as native-born.

The multicultural cognitive examination

The MCE consists of four subtests (Table 1): RUDAS (Storey et al., 2004), Recall of Pictures Test (RPT) (Nielsen et al., 2012), Supermarket Fluency Test (SFT) (Strauss et al., 2007), and Clock Reading Test (CRT) (Schmidtke & Olbrich, 2007). The total MCE score ranges from 0 to 100 points.

Table 1. The multicultural cognitive examination.

Cognitive test	Cognitive domain	Score range
MCE	General cognitive function	0–100
RUDAS	General cognitive function	0–30
RPT immediate recall	Episodic memory	0–10
RPT delayed recall	Episodic memory	0–10
RPT recognition	Episodic memory	0–10
SFT	Language function Executive function	0–28
CRT	Visuospatial function	0–12

Abbreviations: CRT = Clock Reading Test, MCE = Multicultural Cognitive Examination, RPT = Recall of Pictures Test, RUDAS = Rowland Universal Dementia Assessment Scale, SFT = Supermarket Fluency Test.

RUDAS is a brief cognitive screening test assessing orientation, praxis, drawing, judgment, memory, and language (Storey et al., 2004). The RUDAS ranges from 0 to 30 points. RPT is a measure of episodic memory with immediate- and delayed recall, and recognition of ten colored pictures (Nielsen et al., 2012). In the immediate recall, the ten pictures are learned over three trials, while the delayed recall task is performed after distraction interval. The recognition task requires the participant to correctly identify the original ten pictures among a set consisting of ten previously learned and ten new pictures. The three RPT subtests each have a score range from 0 to 10 points. The whole RPT ranges from 0 to 30 points. SFT is a measure of semantic fluency, requiring participants to name as many different things as possible that can be bought in a supermarket within one minute (Strauss et al., 2007). The SFT score was capped at 28 points, resulting in a score range of 0 to 28. CRT is a measure of visuospatial function which requires participants to correctly read the time on 12 clock faces without numbering (Schmidtke & Olbrich, 2007). The CRT score ranges from 0 to 12 points. In the current study, at the Dutch site, supermarket fluency was replaced by food fluency ($N = 111$).

Data analysis

The aggregated data was checked for errors and accuracy by checking distributions and outliers. Missing data were dealt with by creating imputed values using multiple imputations by chained equations (MICE) applying predictive mean matching, based on age, education and the other MCE subtests when maximum one subtest was missing. The primary outcome was the syndrome diagnosis of the participants (HC/SCD, MCI, dementia), while a secondary outcome was the clinical etiological diagnosis of AD dementia and non-AD dementia. Overall group differences were determined by the Kruskal-Wallis rank sum test for non-normally distributed continuous variables and by the Chi-squared test for categorical variables. Pairwise comparisons were examined using the Mann-Whitney U test for non-normally distributed continuous variables and Fisher's exact test for categorical variables. Rank-biserial correlations were used for effect sizes (very small < .10, small .10-.29, moderate .30-.49, large ≥ .50.

A multiple linear regression model in cognitively intact participants was used to estimate and quantify the influence of the following predictors on MCE scores: Years of education, age, sex, and immigrant background. Regression-based normative data for the MCE were calculated based on significant predictors and presented as percentile scores (50^{th}, 25^{th}, 10^{th}, 5^{th}, 2^{nd} percentile). The percentiles were calculated using the predicted mean MCE score and the residual standard deviation (subtracting the actual MCE score from the predicted score). The median ages (24, 34, 44, 54, 64, 74, 85) and median years of education (2, 6, 10, 12) were used to calculate the percentile scores in the summarized groups.

Receiver Operating Characteristic (ROC) analyses were utilized to compare the Area Under the ROC Curve (AUC) of the MCE and RUDAS using the consensus diagnosis established by the multidisciplinary team as reference standard. Significant differences were determined using DeLong's method. Accuracy, sensitivity, specificity, and likelihood ratios were estimated based on the original MCE cutoff, Youden's J statistic, and the 25^{th}, 10^{th}, 5^{th}, and 2^{nd} percentile cutoffs from the generated normative data.

Participants younger than 65 years old were excluded from all accuracy analyses as younger participants were highly under-represented among memory clinic patients.

All analyses were conducted using the statistical software R (version 4.4.1). The R code used is available on GitHub (https://github.com/dkja0031/MCE/blob/main/Accuracy). $p < .05$ (two-tailed) was considered significant.

Results

Participant characteristics

Data from 1,449 participants were included in the study. The participants were born in 63 different countries ($n = 640$ from Europe, $n = 414$ from South America, $n = 370$ from the Middle East and North Africa, $n = 14$ from South, East, and Southeast Asia, and $n = 11$ from Sub-Saharan Africa), 54.2% had immigrant backgrounds (Supplementary Table 3). In the cognitively intact group, participants with immigrant backgrounds were younger ($p < .001$), less likely to be female ($p < .001$), had fewer years of education ($p = .004$), and higher scores on RUDAS ($p = .002$) but not on MCE ($p = .084$) (Supplementary Table 4). Of the 308 participants with dementia, 188 were diagnosed with Alzheimer's disease (AD), 42 with mixed AD with vascular pathology, 28 with vascular dementia (VaD), 11 with behavioral variant frontotemporal dementia, 8 with dementia with Lewy bodies or Parkinson's disease dementia, 21 with unspecified dementia, and 10 with other specified dementias (3 normal pressure hydrocephalus, 2 semantic dementia, 1 HIV-associated neurocognitive disorder, 1 other organic dementia, 1 Gerstmann-Sträussler-Scheinker disease, 1 post traumatic dementia, and 1 multifactorial decline). Across inclusion sites, 1,434 participants had complete data on all subscales of the MCE. A total of 15 participants were missing data for one MCE subtest, which was handled by creating imputed values. Participant characteristics are presented in Table 2.

Impact of demographic variables

A linear regression model measuring the effect of age, sex, education, and immigrant background on the MCE score in cognitively intact participants showed significant effects of education ($p < .001$, $R^2 = .20$) and age ($p < .001$, $R^2 = .16$), but not sex ($p = .10$) or having immigrant background ($p = .63$) (Table 3, Figure 1).

All MCE subtests were significantly affected by age and education ($p < .001$), however the RPT subtests were less influenced by education (R^2 range = .6%-2.2%) compared to RUDAS, CRT and SFT (R^2 range = 11.4%-15.5%). The RPT recognition subtests was least affected by age ($R^2 = 2.0\%$) followed by CRT, SFT, and the other RPT subtests (R^2 range = 4.7%-9.3%) and lastly by the RUDAS ($R^2 = 17.5\%$).

Normative data

Normative data were based on the 1001 cognitively intact participants. The MCE showed a slightly negatively skewed normal distribution and had a low ceiling effect (scoring max points on the MCE) of 1.1%. The above multiple linear regression

Table 2. Cohort characteristics.

	Cognitively intact	Cognitively intact *(≥ 65 years old)*	MCI	Dementia	P-value
N	1001	364	140	308	–
Age, years	59.0 [47.0, 69.0]	73.0 [68.0, 78.0]	72.0 [65.0, 77.0]	77.0 [73.0, 82.0]	< .001[c,d]
Female sex (%)	593 (59.2%)	224 (61.5%)	68 (48.6%)	171 (55.5%)	.025[b]
Education, years	12.0 [6.0, 15.0]	10.0 [5.0, 14.0]	9.0 [6.0, 12.0]	7.5 [4.0, 11.0]	< .001[c,d]
No formal education (%)	60 (6.0%)	38 (10.5%)	4 (3.0%)	25 (8.4%)	.03 [b,d]
Immigrant status (%)	610 (60.9%)	150 (41.2%)	63 (45.0%)	113 (36.7%)	.20
MCE score	89.0 [81.0, 94.0]	82.0 [79.0, 89.0]	67.0 [60.0, 76.5]	51.0 [43.0, 61.0]	< .001[a]
RUDAS score	28.0 [27.0, 30.0]	27.0 [26.0, 28.0]	24.0 [22.0, 26.0]	20.0 [17.0, 23.0]	< .001[a]
RPT immediate recall	8.0 [7.0, 9.0]	7.0 [6.0, 8.0]	5.0 [4.0, 7.0]	4.0 [2.5, 5.0]	< .001[a]
RPT delayed recall	9.0 [7.0, 10.0]	8.0 [6.0, 9.0]	5.0 [3.0, 6.0]	2.0 [0.0, 4.0]	< .001[a]
RPT recogniton	10.0 [10.0, 10.0]	10.0 [10.0, 10.0]	10.0 [8.0, 10.0]	8.0 [6.0, 10.0]	< .001[a]
CRT	12.0 [11.0, 12.0]	11.0 [10.0, 12.0]	11.0 [9.0, 12.0]	8.0 [4.0, 10.0]	< .001[c,d]
SFT	23.0 [18.0, 27.0]	19.0 [15.0, 24.0]	15.0 [12.0, 19.0]	10.0 [7.0, 14.0]	< .001[a]

Note: Continuous variables presented as median [Q1, Q3]; categorical variables are presented as n (%). Overall p-values are determined by Kruskal-Wallis rank sum test for continuous variables and by Chi-squared test for categorical variables. Pairwise comparisons were determined by Mann-Whitney U test and Fisher's exact test. Pairwise comparisons used Benjamini–Hochberg adjusted $p < .05$ (a = All are significantly different from each other, b = cognitively intact/MCI, c = cognitively intact/dementia, d = MCI/dementia).

Abbreviations: MCI = Mild Cognitive Impairment, MCE = Multicultural Cognitive Examination, RPT = Recall of Pictures Test, RUDAS = Rowland Universal Dementia Assessment Scale, SFT = Supermarket Fluency Test.

Table 3. Linear regression.

	Beta	95% CI	SE	P-value	R^2
Education	.80	.70, .90	.05	< .001	.20
Age	−0.21	−0.25, −0.18	.02	< .001	.16
Immigrant status	.26	−0.78, 1.3	.53	.63	< .01
Female sex	.81	−0.16, 1.8	.49	.10	< .01

Note: N = 1,001.

Abbreviations: CI = Confidence interval, SE = Standard Error.

identified age and education as significant predictors of the MCE score and these were therefore used to calculate the normative data. Age^2 was included in the regression model as it significantly improved the model fit as age and MCE score did not follow a strict linear relationship (R^2: .40 to .45, Akaike Information Criterion (AIC): 6903 to 6818, $p < .001$). The best model fit was therefore: Predicted MCE score = MCE score intercept + .504(Age) − .007(Age^2) + .791(Years of education). Model assumptions were checked and were not violated including linearity, homoscedasticity, normality of residuals, and multicollinearity. The normative data are presented as 50th, 25th, 10th, 5th, and 2nd percentiles in Supplementary Table 5.

Classification accuracy

ROC curves showed that the raw MCE was highly accurate in differentiating cognitively intact participants from patients with dementia (AUC .95, 95% CI .94-.97) and MCI

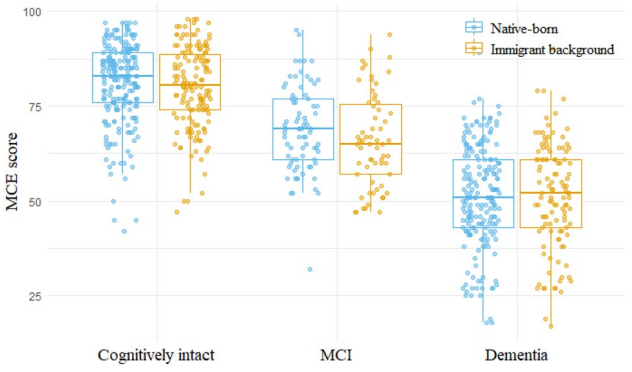


Figure 1. MCE scores stratified by syndrome diagnosis and immigrant background.
Note: Orange = Participants with immigrant backgrounds, Blue = Native-born participants. Cognitively intact participants are ≥ 65 years old. N = 812.
Abbreviations: MCE = Multicultural Cognitive Examination, MCI = Mild Cognitive Impairment.

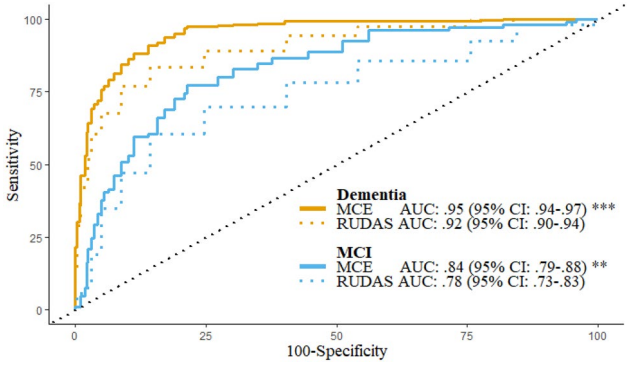


Figure 2. Classification accuracy of dementia and MCI using the MCE or RUDAS.
Note: * = P < .05, ** = P < .01, *** = P < .001. All participants are ≥ 65 years old. N = 755.
Abbreviations: AUC = Area under the Receiver Operating Characteristics curve, CI = Confidence Interval, MCE = Multicultural Cognitive Examination, MCI = Mild Cognitive Impairment, RUDAS = Rowland Universal Dementia Assessment Scale.

(AUC .84, 95% CI .79-.88). The MCE was significantly more accurate using DeLong's test compared to the RUDAS for dementia (AUC .95 vs. .92, $p < .001$) and MCI (AUC .84 vs. .78, $p = .01$) (Figure 2). Sub-analyses revealed no differences in AUCs when stratifying by immigrant/native-born backgrounds (AUC .92 vs .93, $p = .50$).

In the present sample, Youden's index cutoff for separating cognitively intact participants from patients with dementia was 68/69 (sensitivity .91, specificity .86), and for MCI 73/74 (sensitivity .78, specificity .79) (Table 4). The original MCE cutoff to differentiate dementia from cognitively intact participants was 70/71 (sensitivity .94, specificity .83) (Nielsen et al., 2019). Utilizing the generated normative data cutoffs at 25th, 10th, 5th, and 2nd percentiles, generally changed the weighing of sensitivity and specificity. For example, the 5th percentile specificity for MCI was .90 compared to .79 at Youden's cutoff.

The MCE was equally accurate in differentiating cognitively intact participants from AD dementia (AUC .97, 95% CI .95-.98) and non-AD dementia (AUC .94, 95% CI .91-.96, $p = .06$). Additionally, the MCE was significantly more accurate than the RUDAS

Table 4. Diagnostic accuracy of the MCE in differentiating dementia and MCI from no cognitive impairment.

Dementia						
Cutoff	Original (Nielsen et al., 2019) 70/71	Youden 68/69	25th percentile	10th percentile	5th percentile	2nd percentile
Accuracy	.88	.88	.83	.89	.89	.88
Sensitivity	.94	.91	.96	.92	.87	.82
Specificity	.83	.86	.73	.86	.90	.93
LR+	5.51	6.49	3.57	6.71	8.82	11.5
LR-	.08	.11	.05	.09	.14	.20
MCI						
Cutoff	Original (Nielsen et al., 2019) 70/71	Youden *73/74*	25th percentile	10th percentile	5th percentile	2nd percentile
Accuracy	.80	.78	.75	.82	.82	.82
Sensitivity	.70	.78	.81	.65	.52	.43
Specificity	.83	.79	.73	.86	.90	.93
LR+	4.05	3.62	3.01	4.75	5.24	6.11
LR-	.38	.29	.26	.40	.53	.61

Note: All included participants were ≥ 65 years old. $N = 755$.
Abbreviations: LR = Likelihood ratio, MCI = Mild Cognitive Impairment, MCE = Multicultural Cognitive Examination.

Table 5. MCE subtests by AD dementia and non-AD dementia.

	AD dementia	Non-AD dementia	p-value	Rank-biserial correlation
N	177	48	–	–
Age, years	78.0 [74.0, 83.0]	77.5 [74.5, 81.5]	.50	.07
Education, years	6.0 [4.0, 11.0]	8.0 [5.0, 12.0]	.20	−0.12
RUDAS score	20.0 [17.0, 23.0]	21.5 [18.0, 24.0]	.03	−0.21
RPT immediate recall	3.0 [2.0, 5.0]	4.0 [3.0, 5.0]	.01	−0.23
RPT delayed recall	1.0 [0.0, 3.0]	4.0 [2.0, 5.5]	<.001	−0.46
RPT recognition	8.0 [6.0, 10.0]	9.0 [8.0, 10.0]	.001	−0.30
CRT	7.0 [4.0, 10.0]	8.0 [6.0, 10.0]	.04	−0.20
SFT	11.0 [8.0, 14.0]	10.0 [6.5, 14.5]	.50	.07

Note: Continuous variables presented as median [Q1, Q3]. P-values are determined by Mann-Whitney U test. Rank-biserial correlation reported as the effect size. The non-AD dementia disorders were Vascular dementia ($N = 24$), Lewy Body Dementia/Parkinsons Disease dementia ($N = 8$), Frontotemporal dementia ($N = 9$), Normal Pressure Hydrocephalus ($N = 3$), Semantic dementia ($N = 2$), Other organic dementia ($N = 1$), Multifactorial decline ($N = 1$).
Abbreviations: AD = Alzheimer's disease, CRT = Clock Reading Test, RPT = Recall of Pictures Test, RUDAS = Rowland Universal Dementia Assessment Scale, SFT = Supermarket Fluency Test.

in differentiating cognitively intact participants from AD (AUC .92, 95% CI .90-.95, $p < .001$) and non-AD dementia (AUC .89, 95% CI .84-.93, $p = .01$). Across MCE subtests, RPT delayed recall was the subtest that best distinguished between AD and non-AD dementia being the only variable with a moderate effect size (rank-biserial

correlation = −0.46, $p < .001$) (Table 5). Among dementia patients scoring ≤ 1 on RPT delayed recall, 57.1% had AD (101/177) compared to 20.8% of the non-AD patients (10/48). Whereas of the patients scoring 2 or above, 42.9% had AD (76/177) and 79.2% had non-AD (38/48).

Discussion

We examined the cross-cultural properties and diagnostic accuracy of the MCE in a large international sample of 1,449 participants originating from 63 different countries. We found that the MCE was influenced by education and age, but not by sex or having immigrant background, suggesting that it is relatively unaffected by participant's cultural and linguistic backgrounds. Next, we created regression-based normative data for the MCE to provide clinicians with a better method for interpreting the performance of individual patients. Comparable to previous studies (Nielsen et al., 2019; 2025; Torkpoor et al., 2024), we found that the MCE was highly accurate in differentiating patients with dementia (AUC .95) and MCI (AUC .84) from cognitively intact participants, also when using the original MCE cutoff (Nielsen et al., 2019). By applying regression-based normative data we could slightly improve overall diagnostic accuracy metrics, giving clinicians a better possibility to evaluate the cognitive performance of memory clinic patients depending on the specific context. Lastly, we found that the MCE was equally accurate for differentiating cognitively intact participants from AD dementia and non-AD dementia indicating that the MCE is not only relevant for AD but also for other dementia disorders. Although scoring 1 or below on RPT delayed recall was indicative of AD dementia, but further assessment would be encouraged. To our knowledge, this is the largest study to examine a cross-cultural cognitive test for memory clinic settings.

Distinguishing individuals with MCI from cognitively intact individuals with brief cognitive screening tests has long been a challenge in research and clinical settings, particularly in culturally diverse populations. We found an AUC of .84 for identifying MCI, which was significantly higher compared to the RUDAS with an AUC of .78 ($p = .01$). These results are comparable to the upper estimates of a meta-analysis of cognitive screening tests such as MMSE, MoCA, and ACE that found AUCs ranging from .758 to .847 in identifying MCI (Breton et al., 2019). In contrast to these cognitive screening tests, the MCE was evaluated in a culturally, linguistically, and educationally diverse cohort while retaining high diagnostic accuracy. Although education significantly influenced MCE performance in the present study, evidence from the broader literature indicates that educational bias may be less pronounced for the MCE than for commonly used screening instruments such as the MMSE and MoCA (Chithiramohan et al., 2024; Goudsmit et al., 2018; Steis & Schrauf, 2009). Compared with other cross-cultural cognitive tests such as the CCD and CNTB, the MCE shows comparable or superior diagnostic accuracy for MCI (AUC: 0.72–0.82 vs. .84) and dementia (AUC: 0.80–0.99 vs. .95) (Delgado-Álvarez et al., 2022; Nielsen et al., 2019). The combination of strong cross-cultural validity, multidomain cognitive assessment, and brief administration time makes the MCE well suited for both research and clinical settings where populations are culturally, linguistically, and educationally diverse. Altogether, these results suggest that the MCE is a highly accurate cognitive test that is appropriate for culturally, linguistically, and educationally diverse

populations. Our results encourage clinicians to consider implementing the MCE, particularly in culturally, linguistically, and educationally diverse populations, as it is less culturally biased while retaining high accuracy.

This large multicultural study represents participants originating from Europe, the Middle East, North Africa, South Asia, and South America, supporting the generalizability of the results. However, other major geographic regions are less represented including Oceania, Southeast- and East Asia, and Sub-Saharan Africa encouraging future studies to include participants from these regions. Other limitations of this study should be considered. While the clinical evaluations included a comprehensive assessment and consensus diagnosis, the adopted clinical criteria differed between sites (see Supplementary Table 2), which may have affected the classification of specific cognitive disorders. In addition, linguistic and cultural differences between inclusion sites may have influenced how the same diagnostic criteria were interpreted and implemented (Mazzeo et al., 2024; Nielsen & Kjaergaard, 2024). Immigrant status does not directly capture differences in language fluency, bi/multilingualism, acculturation, and quality of education, but it served as a proxy for these in the current study. Patients' immigrant background reflects the complex interplay between these factors, but future studies are needed to reflect the direct influences on the cross-cultural cognitive tests as acknowledged by ECCroN (Franzen et al., 2022). Each inclusion site represents unique characteristics, reflecting its local cultural, economic, educational, linguistic, and geographic context. These differences include differences in educational quality, structure, and curricular content, which may have led to over- or underestimation of the influence of education on the MCE. Although this reflects the clinical reality where large differences are present across countries, our study generalized results across multiple sites where certain country-specific aspects would be clinically relevant to consider. For example, the Brazilian inclusion site is unique as all participants were born in Brazil, but also had few years of schooling in general. However, a post-hoc sensitivity analysis where we excluded participants from the Brazilian site in a multiple linear regression found similar beta-coefficients as the original regression model (Supplementary Table 6). Pooling HC participants and patients with SCD in a cognitively intact group may influence outcomes by reducing diagnostic accuracy, as some patients with SCD may represent preclinical stages of neurodegenerative disease. However, inclusion of SCD reflects a more realistic memory clinic population. Sensitivity analyses excluding patients with SCD revealed results consistent with the primary analyses (Supplementary Tables 7–9).

In conclusion, as the world is becoming increasingly more culturally and linguistically diverse, diagnostic tools must be accurate and unbiased to fight health disparities and diagnostic inequities. Our study suggests that the MCE is highly accurate in identifying MCI and dementia in culturally, linguistically, and educationally diverse populations. Future studies should explore the ability of the MCE to monitor cognitive decline longitudinally and to capture effects of interventions.

Acknowledgments

The authors express our sincere gratitude to the participants and clinics staff involved. We would like to acknowledge the important contributions with participant inclusion by Esther van den

Berg, Lize Jiskoot, and Judy van Hemmen (all Erasmus MC University Medical Center), Lotte van de Wiel (Maasstad Ziekenhuis), Naaheed Mukadam (University College London), Juliette Palisson (Avicenne University Hospital), Nieves Méndez and Marina Gavilán (University of Granada), and the Israac Sheffield Somali community champions: Muse Jama and Sahra Abdi, and Sheffield Biomedical Research Centre. Furthermore, we would like to thank research assistants and students at relevant sites for their contributions to data collection.

Consent statement

The study was approved by the Danish Data Protection Agency (p-2024-15786).

Disclosure statement

No potential conflict of interest was reported by the authors.

Funding

The study was supported by the Innovation Fund Denmark [grant number 1099-00022B], under the frame of ERA PerMed [reference number: ERAPERMED2021-184] and the Instituto de Salud Carlos III (PI19/01260). JAMG is supported by Instituto de Salud Carlos III through the project INT20/00079 and INT23/00017 (co-funded by European Regional Development Fund "A way to make Europe"). SF is supported by ZonMW (#73305095007, #10510032120004) and Health Holland, Topsector Life Sciences & Health (PPP-allowance; #LSHM20106). Data collected from the University of Sheffield is independent research funded by the NIHR i4i NIHR202911/CognoSpeak: a Cognitive Health Assessment Tool (CcHAT). The views expressed are those of the author(s) and not necessarily those of the NIHR i4i, the NIHR or the Department of Health and Social Care. The Memory Clinic at Skåne University Hospital was supported by the Swedish federal government under the ALF agreement, and by the Kockska foundation and Vinnova (grant No. 583 2021–02680). The funding sources had no involvement in the design or reporting of the study.

ORCID

Daniel Kjaergaard http://orcid.org/0000-0001-9955-8220
Sanne Franzen http://orcid.org/0000-0002-4461-5109
Jordi A. Matias-Guiu http://orcid.org/0000-0001-5520-2708

Data availability statement

The data that support the findings of this study originate from multiple centers who each hold the ownership of their data. Data can be made available upon reasonable request and consent from the respective centers.

References

Albert, M. S., DeKosky, S. T., Dickson, D., Dubois, B., Feldman, H. H., Fox, N. C., Gamst, A., Holtzman, D. M., Jagust, W. J., Petersen, R. C., Snyder, P. J., Carrillo, M. C., Thies, B., & Phelps, C. H. (2011). The diagnosis of mild cognitive impairment due to Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimer's & Dementia: The Journal of the Alzheimer's Association*, *7*(3), 270–279. https://doi.org/10.1016/j.jalz.2011.03.008

American Psychiatric Association. (1994). *Diagnostic and Statistical manual of mental disorders*. 4th edition (DSM-IV). American Psychiatric Publishing.

American Psychiatric Association. (2000). *Diagnostic and Statistical Manual of Mental Disorders*. 4th ed., Text Revision ed. American Psychiatric Publishing.

American Psychiatric Association. (2013). *Diagnostic and Statistical Manual of Mental Disorders*. 5th ed. Diagnostic and Statistical Manual of Mental Disorders. https://doi.org/10.1176/APPI.BOOKS.9780890425596

Araujo, N. B., Nielsen, T. R., Barca, M. L., Engedal, K., Marinho, V., Deslandes, A. C., Coutinho, E. S., & Laks, J. (2020). Brazilian version of the European Cross-Cultural Neuropsychological Test Battery (CNTB-BR): Diagnostic accuracy across schooling levels. *Revista Brasileira De Psiquiatria (Sao Paulo, Brazil: 1999)*, *42*(3), 286–294. https://doi.org/10.1590/1516-4446-2019-0539

Ardila, A. (2020). Cross-cultural neuropsychology: History and prospects. *RUDN Journal of Psychology and Pedagogics*, *17*(1), 64–78. https://doi.org/10.22363/2313-1683-2020-17-1-64-78

Breton, A., Casey, D., & Arnaoutoglou, N. A. (2019). Cognitive tests for the detection of mild cognitive impairment (MCI), the prodromal stage of dementia: Meta-analysis of diagnostic accuracy studies. *International Journal of Geriatric Psychiatry*, *34*(2), 233–242. https://doi.org/10.1002/GPS.5016

Brucki, S. M. D., & Nitrini, R. (2010). Mini-mental state examination among lower educational levels and illiterates: Transcultural evaluation. *Dementia & Neuropsychologia*, *4*(2), 120–125. https://doi.org/10.1590/S1980-57642010DN40200008

Chithiramohan, T., Santhosh, S., Threlfall, G., Hull, L., Mukaetova-Ladinska, E. B., Subramaniam, H., & Beishon, L. (2024). Culture-fair cognitive screening tools for assessment of cognitive impairment: A systematic review. *Journal of Alzheimer's Disease Reports*, *8*(1), 289–306. https://doi.org/10.3233/ADR-230194

Delgado-Álvarez, A., Delgado-Alonso, C., Goudsmit, M., García-Ramos, R., Gil-Moreno, M. J., Valles-Salgado, M., Díez-Cirarda, M., Zamarrón-Cassinello, M. D., Matías-Guiu, J., & Matias-Guiu, J. A. (2022). Validation of the cross-cultural dementia screening test in Alzheimer's disease and Parkinson's disease. *Frontiers in Psychology*, *13*, 1043721. https://doi.org/10.3389/FPSYG.2022.1043721

Delgado-Álvarez, A., Delgado-Alonso, C., Valles-Salgado, M., Gil-Moreno, M. J., Fernández-Romero, L., Matías-Guiu, J., & Matias-Guiu, J. A. (2023). Normative data in cross-cultural neuropsychological instruments in spaniards and colombians living in Spain. *Journal of Alzheimer's Disease: JAD*, *96*(3), 1231–1241. https://doi.org/10.3233/JAD-230866

Delgado-Álvarez, A., Delgado-Alonso, C., Valles-Salgado, M., González-Baz, V., Gil-Moreno, M. J., Palacios-Sarmiento, M., Matías-Guiu, J., & Matías-Guiu, J. A. (2026). Diagnostic performance of the mini-mental state examination and three cross-cultural screening tests in majority and diverse populations. *Journal of Alzheimer's Disease: JAD*, *109*(4), 1615–1620. https://doi.org/10.1177/13872877251407704

Delgado-Álvarez, A., Nielsen, T. R., Delgado-Alonso, C., Valles-Salgado, M., López-Carbonero, J. I., García-Ramos, R., Gil-Moreno, M. J., Díez-Cirarda, M., Matías-Guiu, J., & Matias-Guiu, J. A. (2023). Validation of the European Cross-Cultural Neuropsychological Test Battery (CNTB) for the assessment of mild cognitive impairment due to Alzheimer's disease and Parkinson's disease. *Frontiers in Aging Neuroscience*, *15*, 1134111. https://doi.org/10.3389/FNAGI.2023.1134111/PDF

Franzen, S., Papma, J. M., Van Den Berg, E., & Nielsen, T. R. (2021). Cross-cultural neuropsychological assessment in the European Union: A Delphi expert study. *Archives of Clinical Neuropsychology: The Official Journal of the National Academy of Neuropsychologists*, *36*(5), 815–830. https://doi.org/10.1093/ARCLIN/ACAA083

Franzen, S., van den Berg, E., Bossenbroek, W., Kranenburg, J., Scheffers, E. A., van Hout, M., van de Wiel, L., Goudsmit, M., van Bruchem-Visser, R. L., van Hemmen, J., Jiskoot, L. C., & Papma, J. M. (2023). Neuropsychological assessment in the multicultural memory clinic: Development and feasibility of the TULIPA battery. *The Clinical Neuropsychologist*, *37*(1), 60–80. https://doi.org/10.1080/13854046.2022.2043447

Franzen, S., van den Berg, E., Goudsmit, M., Jurgens, C. K., van de Wiel, L., Kalkisim, Y., Uysal-Bozkir, Ö., Ayhan, Y., Nielsen, T. R., & Papma, J. M. (2020). A systematic review of neuropsychological tests for the assessment of dementia in non-western, low-educated or illiterate populations.

Journal of the International Neuropsychological Society: JINS, *26*(3), 331–351. https://doi.org/10.1017/S1355617719000894

Franzen, S., Watermeyer, T. J., Pomati, S., Papma, J. M., Nielsen, T. R., Narme, P., Mukadam, N., Lozano-Ruiz, Á., Ibanez-Casas, I., Goudsmit, M., Fasfous, A., Daugherty, J. C., Canevelli, M., Calia, C., van den Berg, E., & Bekkhus-Wetterberg, P, European Consortium on Cross-Cultural Neuropsychology (ECCroN). (2022). Cross-cultural neuropsychological assessment in Europe: Position statement of the European consortium on cross-cultural neuropsychology (ECCroN). *Clin Neuropsychol*, *36*(3), 546–557. https://doi.org/10.1080/13854046.2021.1981456

Goudsmit, M., Uysal-Bozkir, Ö., Parlevliet, J. L., van Campen, J. P. C. M., de Rooij, S. E., & Schmand, B. (2017). The Cross-Cultural Dementia Screening (CCD): A new neuropsychological screening instrument for dementia in elderly immigrants. *Journal of Clinical and Experimental Neuropsychology*, *39*(2), 163–172. https://doi.org/10.1080/13803395.2016.1209464

Goudsmit, M., Van Campen, J., Schilt, T., Hinnen, C., Franzen, S., & Schmand, B. (2018). One size does not fit all: Comparative diagnostic accuracy of the rowland universal dementia assessment scale and the mini mental state examination in a memory clinic population with very low education. *Dementia and Geriatric Cognitive Disorders Extra*, *8*(2), 290–305. https://doi.org/10.1159/000490174

Kjaergaard, D., Simonsen, A. H., Stomrud, E., Bali, D., Janelidze, S., Hansson, O., Waldemar, G., & Nielsen, T. R. (2025). Combining plasma p-tau217 and cross-cultural cognitive tests to identify Alzheimer's Disease in an ethnically diverse mixed memory clinic cohort. *Journal of the Neurological Sciences*, *478*, 123739. https://doi.org/10.1016/j.jns.2025.123739

Mandyla, M.-A., & Kosmidis, M. H. (2023). Limitations and recommendations regarding the Mini-Mental State Examination (MMSE) in illiterate and low educated older adults. *Psychology: The Journal of the Hellenic Psychological Society*, *28*(2), 141–157. https://doi.org/10.12681/psy_hps.31694

Matias-Guiu, J. A., & Delgado-Álvarez, A. (2023). Novel cognitive screening tests to address new clinical priorities and cultural diversity. *European Journal of Neurology*, *30*(4), 799–801. https://doi.org/10.1111/ene.15653

Mazzeo, S., Hardy, C. J. D., Jiang, J., Morinelli, C., Moschini, V., Brooks, E., Johnson, J. C. S., Chokesuwattanaskul, A., Giacomucci, G., Volkmer, A., Rohrer, J. D., Ingannato, A., Bagnoli, S., Padiglioni, S., Nacmias, B., Sorbi, S., Bessi, V., & Warren, J. D. (2024). primary progressive aphasia in Italian and English: A cross-linguistic cohort study. *Neurology*, *103*(12), e210058. https://doi.org/10.1212/WNL.0000000000210058

McAuliffe, M., & Oucho, L. A. (2024). *World migration report 2024*. International Organization for Migration (IOM).

McKhann, G. M., Knopman, D. S., Chertkow, H., Hyman, B. T., Jack, C. R., Kawas, C. H., Klunk, W. E., Koroshetz, W. J., Manly, J. J., Mayeux, R., Mohs, R. C., Morris, J. C., Rossor, M. N., Scheltens, P., Carrillo, M. C., Thies, B., Weintraub, S., & Phelps, C. H. (2011). The diagnosis of dementia due to Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimer's & Dementia: The Journal of the Alzheimer's Association*, *7*(3), 263–269. https://doi.org/10.1016/J.JALZ.2011.03.005

Milman, L. H., Faroqi-Shah, Y., Corcoran, C. D., & Damele, D. M. (2018). Interpreting mini-mental state examination performance in highly proficient bilingual Spanish-English and Asian Indian-English speakers: Demographic adjustments, item analyses, and supplemental measures. *Journal of Speech, Language, and Hearing Research: JSLHR*, *61*(4), 847–856. https://doi.org/10.1044/2017_JSLHR-L-17-0021

Nichols, E., Steinmetz, J. D., Vollset, S. E., Fukutaki, K., Chalek, J., Abd-Allah, F., Abdoli, A., Abualhasan, A., Abu-Gharbieh, E., Akram, T. T., Al Hamad, H., Alahdab, F., Alanezi, F. M., Alipour, V., Almustanyir, S., Amu, H., Ansari, I., Arabloo, J., Ashraf, T., … Vos, T. (2022). Estimation of the global prevalence of dementia in 2019 and forecasted prevalence in 2050: An analysis for the Global Burden of Disease Study 2019. *The Lancet Public Health*, *7*(2), e105–e125. https://doi.org/10.1016/S2468-2667(21)00249-8

Nielsen, T. R. (2022). Cognitive assessment in culturally, linguistically, and educationally diverse older populations in Europe. *American Journal of Alzheimer's Disease and Other Dementias*, *37*, 15333175221117006. https://doi.org/10.1177/15333175221117006

Nielsen, T. R., & Kjaergaard, D. (2024). Primary progressive aphasia across languages: prevalence and presentation of phenotypes are shaped by language-specific features. *Neurology*, *103*(12), e210165. https://doi.org/10.1212/WNL.0000000000210165

Nielsen, T. R., de Mendonça, A., Frölich, L., Engelborghs, S., Gove, D., Lamirel, D., Calia, C., & Waldemar, G. (2024). Assessment of dementia in minority ethnic groups in Europe: A 14-year follow-up survey. *International Journal of Geriatric Psychiatry*, *39*(12), e70034. https://doi.org/10.1002/GPS.70034

Nielsen, T. R., Franzen, S., Watermeyer, T., Jiang, J., Calia, C., Kjærgaard, D., Bothe, S., & Mukadam, N. (2024). Interpreter-mediated neuropsychological assessment: Clinical considerations and recommendations from the European Consortium on Cross-Cultural Neuropsychology (ECCroN). *The Clinical Neuropsychologist*, *38*(8), 1775–1805. https://doi.org/10.1080/13854046.2024.2335113

Nielsen, T. R., Jørgensen, K., Delgado-Álvarez, A., Franzen, S., Lozano-Ruiz, A., Özden, M., Palisson, J., Mukadam, N., & Waldemar, G. (2025). Comparison of the diagnostic accuracy of five cross-cultural cognitive screening instruments for dementia and mild cognitive impairment in a multicultural memory clinic sample. *Journal of Alzheimer's Disease: JAD*, *106*(3), 1143–1152. https://doi.org/10.1177/13872877251351037

Nielsen, T. R., Segers, K., Vanderaspoilden, V., Beinhoff, U., Minthon, L., Pissiota, A., Bekkhus-Wetterberg, P., Bjørkløf, G. H., Tsolaki, M., Gkioka, M., & Waldemar, G. (2019). Validation of a brief Multicultural Cognitive Examination (MCE) for evaluation of dementia. *International Journal of Geriatric Psychiatry*, *34*(7), 982–989. https://doi.org/10.1002/GPS.5099

Nielsen, T. R., Segers, K., Vanderaspoilden, V., Beinhoff, U., Minthon, L., Pissiota, A., Bekkhus-Wetterberg, P., Bjørkløf, G. H., Tsolaki, M., Gkioka, M., & Waldemar, G. (2019). Validation of a european cross-cultural neuropsychological test battery (CNTB) for evaluation of dementia. *International Journal of Geriatric Psychiatry*, *34*(1), 144–152. https://doi.org/10.1002/GPS.5002

Nielsen, T. R., Segers, K., Vanderaspoilden, V., Bekkhus-Wetterberg, P., Minthon, L., Pissiota, A., Bjørkløf, G. H., Beinhoff, U., Tsolaki, M., Gkioka, M., & Waldemar, G. (2018). Performance of middle-aged and elderly European minority and majority populations on a Cross-Cultural Neuropsychological Test Battery (CNTB). *The Clinical Neuropsychologist*, *32*(8), 1411–1430. https://doi.org/10.1080/13854046.2018.1430256

Nielsen, T. R., Vogel, A., & Waldemar, G. (2012). Comparison of performance on three neuropsychological tests in healthy Turkish immigrants and Danish elderly. *International Psychogeriatrics*, *24*(9), 1515–1521. https://doi.org/10.1017/S1041610212000440

Nielsen, T. R., Vogel, A., Phung, T. K. T., Gade, A., & Waldemar, G. (2011). Over- and under-diagnosis of dementia in ethnic minorities: A nationwide register-based study. *International Journal of Geriatric Psychiatry*, *26*(11), 1128–1135. https://doi.org/10.1002/GPS.2650

Reis, A., Faísca, L., Ingvar, M., & Petersson, K. M. (2006). Color makes a difference: Two-dimensional object naming in literate and illiterate subjects. *Brain and Cognition*, *60*(1), 49–54. https://doi.org/10.1016/j.bandc.2005.09.012

Schmidtke, K., & Olbrich, S. (2007). The clock reading test: Validation of an instrument for the diagnosis of dementia and disorders of visuo-spatial cognition. *International Psychogeriatrics*, *19*(2), 307–321. https://doi.org/10.1017/S104161020600456X

Segers, K., Benoit, F., Colson, C., Kovac, V., Nury, D., & Vanderaspoilden, V. (2013). Pioneers in migration, pioneering in dementia: First generation immigrants in a European metropolitan memory clinic. *Acta Neurologica Belgica*, *113*(4), 435–440. https://doi.org/10.1007/s13760-013-0245-z

Steis, M. R., & Schrauf, R. W. (2009). A review of translations and adaptations of the Mini-Mental State Examination in languages other than English and Spanish. *Research in Gerontological Nursing*, *2*(3), 214–224. https://doi.org/10.3928/19404921-20090421-06

Storey, J. E., Rowland, J. T. J., Basic, D., Conforti, D. A., & Dickson, H. G. (2004). The Rowland Universal Dementia Assessment Scale (RUDAS): A multicultural cognitive assessment scale. *International Psychogeriatrics*, *16*(1), 13–31. https://doi.org/10.1017/S1041610204000043

Strauss, E., Sherman, E. M. S., & Spreen, O. (2007). A compendium of neuropsychological tests: Administration, norms, and commentary. *Appl Neuropsychol*, *14*, 62–63. https://doi.org/10.1080/09084280701280502

Torkpoor, R., Frolich, K., Londos, E., & Nielsen, T. R. (2024). Diagnostic accuracy of the swedish version of the multicultural cognitive examination for cognitive assessment in Swedish memory clinics. *Journal of Alzheimer's Disease: JAD*, *97*(2), 715–726. https://doi.org/10.3233/JAD-230998

Tsoi, K. K. F., Chan, J. Y. C., Hirai, H. W., Wong, S. Y. S., & Kwok, T. C. Y. (2015). Cognitive tests to detect dementia: A systematic review and meta-analysis. *JAMA Internal Medicine*, *175*(9), 1450–1458. https://doi.org/10.1001/JAMAINTERNMED.2015.2152

Van Mol, C., de Valk, H. (2016). Migration and Immigrants in Europe: A Historical and Demographic Perspective. In: Garcés-Mascareñas, B., Penninx, R. (eds), *Integration Processes and Policies in Europe. IMISCOE Research Series*. Cham: Springer. https://doi.org/10.1007/978-3-319-21674-4_3

Winblad, B., Palmer, K., Kivipelto, M., Jelic, V., Fratiglioni, L., Wahlund, L.-O., Nordberg, A., Bäckman, L., Albert, M., Almkvist, O., Arai, H., Basun, H., Blennow, K., de Leon, M., DeCarli, C., Erkinjuntti, T., Giacobini, E., Graff, C., Hardy, J., … Petersen, R. C. (2004). Mild cognitive impairment - Beyond controversies, towards a consensus: Report of the International Working Group on Mild Cognitive Impairment. *Journal of Internal Medicine*, *256*(3), 240–246. https://doi.org/10.1111/J.1365-2796.2004.01380.X

World Health Organization. (1993). *The ICD-10 Classification of Mental and Behavioural Disorders: Diagnostic criteria for research.* WHO.

Supplementary materials – Study 1

Supplementary Table 1. Syndrome diagnosis by country of examination.

	Cognitively intact	MCI	Dementia
Belgium (Brussels)	90	0	0
Brazil (Rio de Janeiro)	65	0	70
Denmark (Copenhagen)	205	23	52
France (Paris)	0	0	4
Germany (Berlin)	11	6	29
Italy (Milan)	2	5	5
Netherlands (Rotterdam)	92	16	18
Norway (Oslo)	60	0	0
Spain (Madrid, Granada)	395	54	62
Sweden (Malmö)	31	36	67
United Kingdom (Sheffield, London)	50	0	1

Abbreviations: MCI = Mild Cognitive Impairment.

Supplementary Table 2. Applied diagnostic criteria

Country/partner	MCI criteria	Dementia criteria	AD criteria	Other criteria
Inclusion site/project: CNTB (Denmark, Germany, Belgium, Norway, Sweden) DOI: https://doi.org/10.1080/13854046.2018.1430256, https://doi.org/10.1002/GPS.5002	Winblad [1]	DSM-IV-TR [6]	NINCDS-ADRDA [5]	VaD: NINDS-AIREN [9] FTD: McKhann [11] DLB: McKeith [12]
Inclusion site/project: TIMING (Denmark, Netherlands, Spain, UK, France) DOI: https://doi.org/10.1177/13872877251351037.	Winblad [1]	DSM-5 [4]	NIA-AA [8]	VaD: VASCOG [13] FTD: Rscovsky [10] DLB: McKeith [14]
Inclusion site/project: Brazil DOI: https://doi.org/10.1590/1516-4446-2019-0539.	Not relevant	DSM-IV [7]	NINCDS-ADRDA [5]	Not relevant
Inclusion site/project: Sweden DOI: https://doi.org/10.3233/JAD-230998.	ICD-10 [2]	ICD-10 [2]	ICD-10 [2]	VaD: ICD-10 [2] FTD: ICD-10 [2] DLB: McKeith [14]
Inclusion site/project: Netherlands Note: Data from the TULIPA study (https://doi.org/10.1080/13854046.2022.2043447) and unpublished data	Albert [3]	NIA-AA [8] NINDS-AIREN [9] Rascovsky [10]	NIA-AA [8]	VaD: NINDS-AIREN [9] FTD: Rascovsky [10]
Inclusion site/project: Italy Note: Unpublished data	DSM-5 [4]	DSM-5 [4]	NIA-AA [8]	VaD: NINDS-AIREN [9] FTD: Rascovsky [10]
Inclusion site/project: Spain, Madrid DOI: https://doi.org/10.3233/JAD-230866, https://doi.org/10.3389/FNAGI.2023.1134111/PDF.	NINCDS-ADRDA [5] + CDR = 0.5	NINCDS-ADRDA [5] + CDR = 1.0	NINCDS-ADRDA [5] + CDR + supporting biomarkers	Not relevant

Note: CNTB = Cross-Cultural Neuropsychological Test Battery; DLB = Dementia with Lewy Bodies; DSM = Diagnostic and Statistical Manual of Mental Disorders; FTD = Frontotemporal Dementia; ICD = International Classification of Diseases; NIA-AA = National Institute on Aging–Alzheimer's Association; NINCDS-ADRDA = National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer's Disease and Related Disorders Association; NINDS-AIREN = National Institute of Neurological Disorders and Stroke–Association Internationale pour la Recherche et l'Enseignement en Neurosciences; TIMING = Timely diagnosis of dementia in minority ethnic groups in Europe; VASCOG = Vascular Cognitive Disorders Group; VaD = Vascular Dementia.

References to Supplementary Table 2

[1] Winblad B, Palmer K, Kivipelto M, Jelic V, Fratiglioni L, Wahlund LO, et al. Mild cognitive impairment - Beyond controversies, towards a consensus: Report of the International Working Group on Mild Cognitive Impairment. J Intern Med 2004;256:240–6. https://doi.org/10.1111/J.1365-2796.2004.01380.X,.

[2] Health Organization W. The ICD-10 Classification of Mental and Behavioural Disorders: Clinical descriptions and diagnostic guidelines 1992.

[3] Albert MS, DeKosky ST, Dickson D, Dubois B, Feldman HH, Fox NC, et al. The diagnosis of mild cognitive impairment due to Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement 2011;7:270. https://doi.org/10.1016/J.JALZ.2011.03.008.

[4] American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition. Diagnostic and Statistical Manual of Mental Disorders 2013. https://doi.org/10.1176/APPI.BOOKS.9780890425596.

[5] Dubois B, Feldman HH, Jacova C, DeKosky ST, Barberger-Gateau P, Cummings J, et al. Research criteria for the diagnosis of Alzheimer's disease: revising the NINCDS-ADRDA criteria. Lancet Neurol 2007;6:734–46. https://doi.org/10.1016/S1474-4422(07)70178-3.

[6] American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. Fourth Edition, Text Revision ed. Washington DC: 2000.

[7] American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. Fourth Edition (DSM-IV). Washington DC: Arlington: American Psychiatric Publishing; 1994.

[8] McKhann GM, Knopman DS, Chertkow H, Hyman BT, Jack CR, Kawas CH, et al. The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement 2011;7:263–9. https://doi.org/10.1016/J.JALZ.2011.03.005.

[9] Román GC, Tatemichi TK, Erkinjuntti T, Cummings JL, Masdeu JC, Garcia JH, et al. Vascular dementia: diagnostic criteria for research studies. Report of the NINDS-AIREN International Workshop. Neurology 1993;43:250–60. https://doi.org/10.1212/WNL.43.2.250.

[10] Rascovsky K, Hodges JR, Knopman D, Mendez MF, Kramer JH, Neuhaus J, et al. Sensitivity of revised diagnostic criteria for the behavioural variant of frontotemporal dementia. Brain 2011;134:2456–77. https://doi.org/10.1093/BRAIN/AWR179.

[11] McKhann GM, Albert MS, Grossman M, Miller B, Dickson D, Trojanowski JQ. Clinical and pathological diagnosis of frontotemporal dementia: report of the Work Group on Frontotemporal Dementia and Pick's Disease. Arch Neurol 2001;58:1803–9. https://doi.org/10.1001/ARCHNEUR.58.11.1803.

[12] McKeith IG, Galasko D, Kosaka K, Perry EK, Dickson DW, Hansen LA, et al. Consensus guidelines for the clinical and pathologic diagnosis of dementia with Lewy bodies (DLB): report of the consortium on DLB international workshop. Neurology 1996;47:1113–24. https://doi.org/10.1212/WNL.47.5.1113.

[13] Sachdev P, Kalaria R, O'Brien J, Skoog I, Alladi S, Black SE, et al. Diagnostic criteria for vascular cognitive disorders: a VASCOG statement. Alzheimer Dis Assoc Disord 2014;28:206–18. https://doi.org/10.1097/WAD.0000000000000034.

[14] McKeith IG, Boeve BF, Dickson DW, Halliday G, Taylor JP, Weintraub D, et al. Diagnosis and management of dementia with Lewy bodies: Fourth consensus report of the DLB Consortium. Neurology 2017;89:88–100. https://doi.org/10.1212/WNL.0000000000004058.

Supplementary Table 3. Country of birth

Country	N	Country	N	Country	N
Afghanistan	2	Guatemala	2	Somalia	50
Albania	2	Honduras	2	Spain	231
Algeria	2	India	2	Suriname	6
Antilles	2	Indonesia	1	Sweden	101
Argentina	5	Iran	4	Switzerland	1
Azerbaijan	1	Iraq	7	Syria	2
Belgium	76	Italy	1	Thailand	2
Bolivia	2	Laos	1	Türkiye	193
Bosnia	5	Lebanon	1	Uganda	2
Brazil	139	Mexico	7	Ukraine	6
Cameroon	1	Morocco	41	Venezuela	17
Cape Verde	5	Netherlands	15	Vietnam	2
Chile	2	Nicaragua	1	(ex)Yugoslavia	31
China	4	Norway	16		
Colombia	179	Pakistan	59		
Congo	1	Palestine	1		
Cuba	1	Peru	25		
Curaçao	1	Philippines	2		
Denmark	74	Poland	51		
Dominican Republic	7	Portugal	1		
Ecuador	15	Romania	2		
Ethiopia	2	Russia	2		
Finland	1	El Salvador	1		
Germany	22	Saudi Arabia	7		
Greece	1	Serbia	1		

Supplementary Table 4. Characteristics of cognitively intact participants by immigrant/native-born background

	Native-born	Immigrant background	p-value
N	391	610	
Age, years	66.0 [53.0, 76.0]	56.0 [43.0, 64.0]	< .001
Female sex (%)	257 (65.7%)	336 (55.1%)	< .001
Education, years	12.0 [8.0, 16.0]	10.5 [6.0, 14.0]	.004
RUDAS score	28.0 [26.0, 30.0]	29.0 [27.0, 30.0]	.002
MCE score	88.0 [80.0, 94.0]	89.0 [82.0, 94.0]	.084

Note: Continuous variables presented as median [Q1, Q3]; categorical variables are presented as n (%). P-values are determined by Mann-Whitney U test and Chi-squared test.

Abbreviations: MCE = Multicultural Cognitive Examination, RUDAS = Rowland Universal

Dementia Assessment Scale

Supplementary Table 5. Regression-based normative data for the MCE test

Age	Years of education	N	P2	P5	P10	P25	P50
18-29	0-3	2	68	71	74	78	83
	4-7	6	71	74	77	81	86
	8-12	29	75	78	80	85	90
	13+	54	79	82	84	89	93
30-39	0-3	1	69	72	75	79	84
	4-7	3	73	76	78	83	87
	8-12	37	76	79	81	86	91
	13+	47	80	83	85	90	95
40-49	0-3	1	69	72	75	79	84
	4-7	15	72	75	78	82	87
	8-12	32	75	78	81	85	90
	13+	47	79	82	85	89	94
50-59	0-3	21	67	70	73	77	82
	4-7	66	71	74	76	81	86
	8-12	68	74	77	79	84	89
	13+	74	78	81	83	88	93
60-69	0-3	41	64	67	70	75	79
	4-7	61	68	71	73	78	83
	8-12	68	71	74	76	81	86
	13+	87	75	78	80	85	90
70-79	0-3	27	60	63	66	70	75
	4-7	45	63	66	69	73	78
	8-12	40	66	69	72	76	81
	13+	59	70	73	76	80	85
80-90	0-3	13	54	57	59	64	69
	4-7	26	57	60	63	67	72
	8-12	11	60	63	66	70	75
	13+	20	64	67	70	74	79

Note: Normative data presented across the 2nd (P2), 5th percentile (P5), 10th percentile (P10), 25th percentile (P25), and 50th percentile (P50) based on age and education.

Supplementary Table 6: Linear regression excluding the Brazilian site (post-hoc sensitivity analysis)

	Beta	95% CI	SE	P-value	R^2
Education	.72	.62, .82	.05	< .001	.18
Age	-.21	-.24, -.18	.02	< .001	.16
Immigrant status	-.80	-1.8, 0.23	.52	.13	<.01
Female sex	.98	.04, 1.9	.48	.04	<.01

Note: N = 936.

Abbreviations: CI = Confidence interval, SE = Standard Error.

Supplementary Table 7. Linear regression excluding SCD

	Beta	95% CI	SE	P-value	R^2
Education	.79	.69, .88	.05	< .001	.22
Age	-.19	-.22, -.16	.02	< .001	.15
Immigrant status	1.05	.03, 2.1	.52	.043	< .01
Female sex	.73	-.22, 1.7	.48	.13	< .01

Note: N = 939.

Abbreviations: CI = Confidence interval, SCD = Subjective Cognitive Decline, SE = Standard error

Supplementary Table 8. Regression-based normvative data for the MCE test excluding subjective cognitive decline

Age	Years of education	N	P2	P5	P10	P25	P50
18-29	0-3	2	69	72	75	79	83
	4-7	6	72	75	78	82	87
	8-12	29	76	78	81	85	90
	13+	54	79	82	85	89	93
30-39	0-3	1	71	73	76	80	85
	4-7	3	74	77	79	83	88
	8-12	37	77	80	82	86	91
	13+	47	81	83	86	90	95
40-49	0-3	1	71	73	76	80	85
	4-7	15	74	76	79	83	88
	8-12	32	77	79	82	86	91
	13+	47	80	83	86	90	95
50-59	0-3	21	69	72	74	78	83
	4-7	66	72	75	77	82	86
	8-12	68	75	78	80	85	89
	13+	74	79	82	84	88	93
60-69	0-3	41	66	69	71	76	80
	4-7	61	69	72	74	79	83
	8-12	68	72	75	78	82	86
	13+	87	76	79	81	85	90

Age	Years of education	N	P2	P5	P10	P25	P50
70-79	0-3	27	62	65	67	71	76
	4-7	45	65	68	70	74	79
	8-12	40	68	71	73	77	82
	13+	59	72	75	77	81	86
80-90	0-3	13	55	58	61	65	70
	4-7	26	59	61	64	68	73
	8-12	11	62	64	67	71	76
	13+	20	65	68	71	75	79

Note: Normative data presented across the 2nd (P2), 5th percentile (P5), 10th percentile (P10), 25th percentile (P25), and 50th percentile (P50) based on age and education

Supplementary Table 9. Diagnostic accuracy of the MCE in differentiating dementia and MCI from no cognitive impairment excluding subjective cognitive decline

Dementia						
Cutoff	**Original** [51] *70/71*	**Youden** *68/69*	**25th percentile**	**10th percentile**	**5th percentile**	**2nd percentile**
Accuracy	.90	.90	.84	.90	.91	.89
Sensitivity	.94	.91	.97	.94	.89	.84
Specificity	.87	.88	.73	.86	.92	.94
MCI						
Cutoff	**Original** [51] *70/71*	**Youden** *73/74*	**25th percentile**	**10th percentile**	**5th percentile**	**2nd percentile**
Accuracy	.83	.81	.76	.83	.84	.83
Sensitivity	.70	.78	.85	.72	.60	.47
Specificity	.87	.82	.73	.86	.92	.94

Note: All included participants were ≥ 65 years old. N = 720.

Abbreviations: LR = Likelihood ratio, MCI = Mild Cognitive Impairment, MCE = Multicultural Cognitive Examination.

9.2. Study 2.

Ethnic and racial influences on blood biomarkers for Alzheimer's disease: A systematic review

Daniel Kjaergaard, Anja Hviid Simonsen, Gunhild Waldemar, T Rune Nielsen

Journal of Alzheimer's Disease (2025). https://doi.org/10.1177/13872877241299047

Check for updates

Systematic review

Ethnic and racial influences on blood biomarkers for Alzheimer's disease: A systematic review

Journal of Alzheimer's Disease
1–11
© The Author(s) 2025
Article reuse guidelines:
sagepub.com/journals-permissions
DOI: 10.1177/13872877241299047
journals.sagepub.com/home/alz



Daniel Kjaergaard[1], Anja Hviid Simonsen[1], Gunhild Waldemar[1,2] and T Rune Nielsen[1,3]

Abstract

Background: Little is known about confounding factors influencing Alzheimer's disease (AD) blood biomarker concentrations.

Objective: The objective of this systematic review was to explore the available evidence for the influences of ethnicity and race on AD blood biomarker concentrations.

Methods: We conducted a comprehensive systematic search in PubMed and Web of Science databases spanning from inception until 15 June 2023. We included studies that utilized plasma or serum biomarkers (amyloid-β [Aβ], total tau [t-tau], phosphorylated tau [p-tau], neurofilament light [NfL], and glial fibrillary acidic protein [GFAP]), compared individuals with AD to healthy controls, and included a minimum of two ethnic or racial groups for comparison. A total of 10 studies were included in the qualitative synthesis. All studies were conducted in the US.

Results: Seven studies reported differences in blood biomarker concentrations between ethnic or racial groups. However, after adjusting for medical conditions and social determinants of health, the differences became non-significant in two of the studies. The included studies differed in their included covariates and their statistical approaches, which complicated the interpretation of the observed differences.

Conclusions: The available evidence suggests that ethnicity and race may influence blood biomarker concentrations. However, it remains unclear to what extent these differences are mediated by differences in social determinants of health and medical conditions. Future studies are needed to explore ethnic and racial differences in blood biomarkers, including studies in diverse samples outside the US.

Keywords

Alzheimer's disease, biomarkers, blood-based biomarkers, dementia, diversity, ethnicity, plasma, racial groups, review, serum

Received: 24 June 2024; accepted: 25 September 2024

Introduction

Blood biomarkers may serve as novel tools contributing to early and accurate detection of Alzheimer's disease (AD). Blood biomarkers have demonstrated their relevance from extensive evidence of their diagnostic- and prognostic value.[1–8] However, this evidence is almost exclusively based on studies in Western White individuals, and little is known about how the results generalize to ethnically and racially diverse individuals. Under-representation of diverse populations is a general issue in dementia research[9] that also applies to research on AD blood biomarkers. This under-representation may be related to barriers for ethnic and racial minority populations, including language barriers in migrants, difficulty accessing the healthcare system, financial or logistic barriers to participate in research, and insufficient community engagement. Similar challenges have been described in including ethnically and racially diverse populations in AD

[1]Danish Dementia Research Centre, Department of Neurology, Copenhagen University Hospital - Rigshospitalet, Copenhagen, Denmark
[2]Department of Clinical Medicine, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark
[3]Department of Psychology, University of Copenhagen, Copenhagen, Denmark

Corresponding author:
Daniel Kjærgaard, Danish Dementia Research Centre, Department of Neurology, Neuroscience Centre, Copenhagen University Hospital – Rigshospitalet, section 8008, 2100, Copenhagen, Denmark.
Email: daniel.kjaergaard.01@regionh.dk

drug trials.[10] Research on ethnic and racial influences on blood biomarker concentrations, and related diagnostic and prognostic accuracy, is crucial before wider clinical implementation.[2,11]

Biomarker concentrations have previously been found to differ between ethnic or racial groups in cerebrospinal fluid (CSF)[12–15] and in positron emission tomography (PET) measuring amyloid deposition.[14] The reasons behind these differences are unclear but may in part be due to genetic differences. It is well-established that genetic variation between individuals belonging to different ethnic or racial groups can lead to different disease expressions or disease trajectories, for instance in the *apolipoprotein E (APOE)* ϵ4 gene[16,17] and the *tau H2 haplotype* associated with the *microtubule-associated protein tau (MAPT)*[18] that has a direct impact on CSF tau concentrations.[19] However, in some studies, racial or ethnic differences in CSF concentrations persist even after adjusting for *APOE* ϵ4.[20,21]

Biomarker concentrations may also differ based on medical conditions and social determinants of health. At the present stage, studies have found some evidence that age, sex, kidney function, cholesterol metabolism, and body mass index (BMI) may influence blood biomarker concentrations such as neurofilament light (NfL) and glial fibrillary acidic protein (GFAP).[22–24] Concurrently, there are well-established differences between ethnic and racial groups in the prevalence of these medical conditions and AD, with higher prevalence typically being reported for minority and racialized groups.[25–35] Therefore, it is imperative to understand if blood biomarker concentrations vary by ethnicity and race and if these potential differences reflect genetic differences or differences in medical conditions and/or social determinants of health.[36,37]

The objective of this systematic review was to investigate ethnic and racial influences on blood biomarker concentrations and diagnostic and prognostic accuracy for AD. Ethnicity is understood as a term referring to shared cultural attributes, including geographic region, language, and social identity. Ethnicity in research studies typically focus on geographic regions, such as country of origin. Meanwhile, race typically refers to physical characteristics such as skin color. As the reviewed studies generally, did not consistently differentiate between race and ethnicity, we will generally refer to ethnicity/race for clarity.

Methods

Search strategy

This systematic review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[38] Studies were identified from PubMed and Web of Science databases from inception until 15 June 2023. The search strategy for identification of studies was: (blood OR plasma OR serum) AND (alzhei* OR dement*) AND (race OR ethnic* OR black OR Hispanic OR Latin* OR Asia*) AND (amyloid OR tau OR NfL OR neurofilament OR GFAP OR "Glial fibril*" OR β). After the removal of duplicates, all studies were assessed for eligibility by title/abstract screening. Potentially relevant studies proceeded to full-text screening and were evaluated for eligibility by two independent researchers (DK and TRN). Any disagreements were settled by consensus.

Selection criteria

Eligibility criteria were established in accordance with the PRISMA guidelines.[38] The criteria were: (1) Studies that included either participants with clinical AD or AD by CSF/PET confirmation of amyloid pathology and included participants from more than one ethnic/racial group. For longitudinal studies, a minimum follow-up period of 2 years was required, and participants were required to be diagnosed with clinical AD at follow-up; (2) studies that examined plasma or serum amyloid-β (Aβ), total tau (t-tau), phosphorylated tau (p-tau), NfL, or GFAP; (3) studies that compared a cognitively unimpaired healthy control group to the AD group and compared the included ethnic/racial groups; (4) studies with any measurement of the influence of ethnic/racial group on plasma or serum biomarker concentrations, diagnostic accuracy, and/or prognostic value; and (5) studies with an observational study design.

In vitro studies, intervention studies, case reports, editorials, commentaries, reviews, studies in non-human subjects, studies not published in English, longitudinal studies with less than 2 years of follow-up, and studies in participants aged less than 18 years were excluded.

Data analysis

A qualitative synthesis of the included studies was performed, focusing on the influence of ethnicity/race on blood biomarker concentrations as well as differences in sociodemographic factors and medical conditions. The reviewed studies used various ethnic and racial categories, hence for the sake of clarity the terms 'Black', 'Hispanic', 'White' are used throughout the review.

Quality assessment

Each study was assessed for risk of bias and applicability concerns using the *Quality Assessment of Diagnostic Accuracy Studies* (QUADAS-2) tool.[39] Each study was evaluated independently on participant selection, index test, reference standard, and flow and timing. Risk of bias and applicability was independently evaluated as high risk, low risk, or unclear risk by two researchers (DK and TRN), and any disagreement was settled by consensus. The individual assessments can be found in Supplemental Table 2.

Results

Study selection

After the removal of duplicates, 683 studies were screened. Of these, 619 were excluded following title/abstract screening with reasons noted in Figure 1. Full-text screening of the remaining 64 studies resulted in the identification of 12 studies fulfilling the inclusion criteria. Careful examination of each study resulted in the exclusion of another two studies as no comparisons or analyses of ethnic/racial groups were reported.[40,41] Thus, a total of 10 studies were included in the qualitative synthesis in the present systematic review.[42–51]

Study characteristics

Study characteristics can be found in Supplemental Table 1. Importantly, all studies originated from the United States (US). Of which two studies included the same participant samples from The Washington Height-Hamilton Heights-Inwood Community Aging Project (WHICAP) cohort,[43,44] and three included participants from the Health and Aging Brain among Latino Elders (HABLE)/Health & Aging Brain Study-Health Disparities (HABS-HD) cohort.[45,47,51] Of these, two studies included the same participant sample.[47,51]

Regarding ethnic/racial groups, White participants were included in all studies, Hispanic participants in

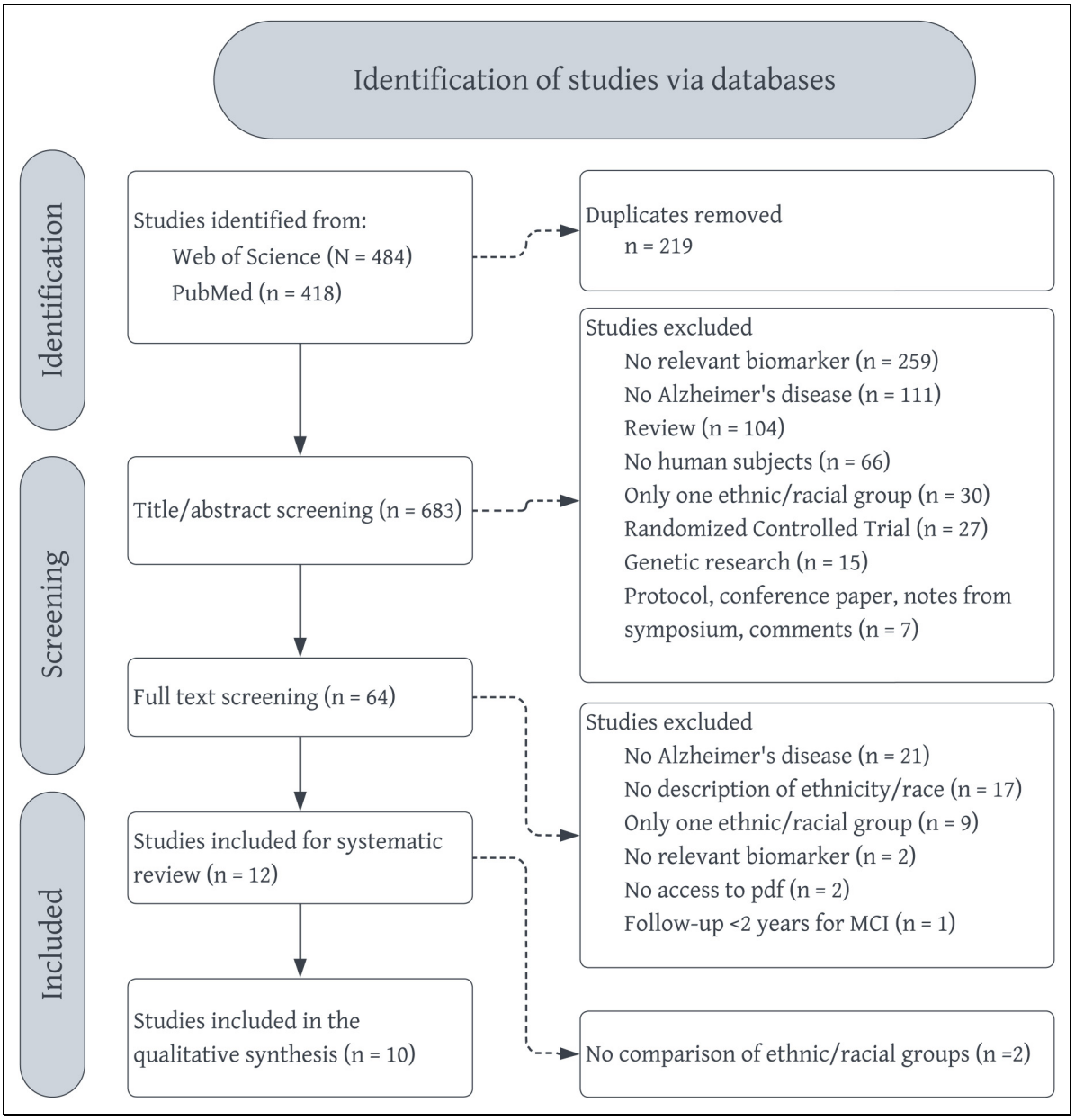


Figure 1. PRISMA flowchart. Flowchart created with Lucidchart.com.

Table 1. Blood biomarker concentrations and ethnicity/race

Study	Influence of ethnic/racial group on biomarker concentration	Biomarker platform	Authors' interpretation(s)
Luchsinger et al. [42]	**Plasma concentration (across HC and clinical AD dementia)** ***Aβ40*** *(pg/mL)* ***White (N=69)*** 134.6 ***Hispanic (N=141)*** 136.0 ***Black (N=117)*** 153.0 *Difference* * (*unadjusted*)	**Plasma (ELISA)** $A\beta_{40}$ $A\beta_{42}$	$A\beta_{40}$ concentration varied by Black race compared to White and Hispanic participants.
Barker et al. [46]	**Plasma concentration (across HC, MCI, and clinical AD dementia)** NfL No significant differences between Hispanics and non-Hispanics in NfL for either HC or AD adjusted for age (data not reported) (Total N=309).	**Plasma (SIMOA)** NfL	NfL concentration was not related to Hispanic ethnicity when adjusting for age.
Brickman et al. [43]	**Plasma concentration (across HC and clinical AD dementia)** $A\beta_{42/40}$, t-tau, p-tau181, p-tau217, and NfL No significant differences for any biomarker between the White (N=100), Black (N=100), and Hispanic group (N=100). *Difference: p range 0.11 - 0.54 (unadjusted)*	**Plasma (SIMOA)** $A\beta_{42/40}$ T-tau NfL **Plasma (MSD)** P-tau181 P-tau217	Biomarker concentrations were similar across race/ethnicity
Gonzales et al. [50]	**Serum concentration (across HC, MCI, and clinical AD dementia)** ***t-tau*** *(pg/mL)* ***NfL*** *(pg/mL)* ***GFAP*** *(pg/mL)* ***White (N=650)*** *0.3 (0.2; 0.6)* 28 (20; 39) 344 (203; 488) ***Hispanic (N=1193)*** 0.3 (0.1; 0.4) 17 (12; 26) 155 (110; 224) *Difference* *NS* *NS* *NS*	**Serum (SIMOA)** t-tau NfL GFAP	Biomarker concentrations were not different across ethnicity when matching on demographics.
Brickman et al. [44]	**Distribution of ethnic/racial groups in plasma / symptomatic defined groups** No differences in the proportions of ethnic/racial groups across p-tau positive/negative and symptomatic/asymptomatic groups (Total N = 300). *p range: 0.43 - 0.47.*	**Plasma (SIMOA)** Aβ42/40 T-tau NfL **Plasma (MSD)** P-tau181 P-tau217	Biomarker concentrations were not different across ethnic/racial groups.
Hall et al. [45]	**Plasma concentration** ***HC*** ***Aβ40*** *(pg/mL)* ***Aβ42*** *(pg/mL)* ***Aβ42/40*** *(ratio)* ***t-tau*** *(pg/mL)* ***NfL*** *(pg/mL)* ***White (N=644)*** 266.01±62.66 12.24±3.12 0.047±0.013 2.31±1.07 20.10±12.69 ***Hispanic (N=642)*** 237.73±66.41 11.86±3.35 0.051±0.022 2.56±1.07 16.75±12.97 ***Black (N=142)*** 163.38±41.83 8.87±3.03 0.065±0.029 1.71±0.64 12.58±10.45 *Difference* *** *** *** *** ***	**Plasma (SIMOA)** $A\beta_{40}$ $A\beta_{42}$ $A\beta_{42}/A\beta_{40}$ T-tau NfL	Biomarker concentrations vary across racial/ethnic groups.

(continued)

Table 1. Continued.

Study	Influence of ethnic/racial group on biomarker concentration	Biomarker platform	Authors' interpretation(s)
	Clinical AD ***Aβ40*** (pg/mL) ***Aβ42*** (pg/mL) ***Aβ42/40*** (ratio) ***t-tau*** (pg/mL) ***NfL***(pg/mL) ***White (N=45)*** 262.64±62.11 11.92±3.10 0.0457±0.011 2.63±0.71 25.98±1.87 ***Hispanic (N=64)*** 245.04±67.46 11.28±3.40 0.0491±0.018 2.76±0.71 26.11±1.65 ***Black (N=19)*** 174.79±49.56 10.13±3.49 0.0580±0.028 2.03±0.74 21.85±2.41 *Difference* *** *NS* * * ***		
O'Bryant et al. [47]	**Plasma concentration (across HC, MCI, and clinical AD dementia)** ***NfL*** (pg/mL) ***White (N=813)*** 20.87±11.29 ***Hispanic (N=890)*** 17.43±11.97 *Difference* *NS*	**Plasma (SIMOA)** NfL	NfL concentrations were not different across ethnic groups when adjusting for covariates.
Schindler et al. [48]	**Plasma concentration (across HC and biomarker defined AD)** ***Aβ40*** (pg/mL) ***Aβ42*** (pg/mL) ***Aβ42/40*** (ratio) ***p-tau181*** (pg/mL) ***p-tau231*** (pg/mL) ***NfL*** (pg/mL) ***White (N=76)*** 425 (390; 482) 40.9 (37.8; 46.3) 0.096 (0.090; 0.103) 14.2 (10.6; 19.3) 9.1 (6.6; 13.1) 11.8 (8.9; 16.7) ***Black (N=76)*** 409 (380; 470) 41.9 (39.3; 49.6) 0.105 (0.099; 0.110) 12.3 (10.2; 16.2) 8.2 (4.4; 11.3) 11.1 (7.6; 15.5) *Difference* *NS* * *** *NS* *NS* *NS*	**Plasma (IP/MS)** $A\beta_{40}$ $A\beta_{42}$ $A\beta_{42}/A\beta_{40}$ **Plasma (SIMOA)** P-tau181 P-tau231 NfL	Some biomarker concentrations vary across racial group, but these differences more likely reflect differences in comorbidities, social determinants of health, or effects of systematic racism.
Rajan et al. [49]	**Serum concentration (across HC and clinical AD dementia)** ***t-tau*** (pg/mL) ***NfL***(pg/mL) ***GFAP*** (pg/mL) ***White (N=516)*** 0.83±3.04 40.2±64.2 288.7±251.9 ***Black (N=811)*** 0.76±2.67 33.4±38.6 271.9±278.6 *Difference* *NS* * *NS*	**Serum (SIMOA)** t-tau NfL GFAP	Baseline NfL concentrations differed between racial groups, but not t-tau and GFAP, when adjusting for covariates.

Aβ: amyloid-beta; AD: Alzheimer's disease; ELISA: enzyme-linked immunosorbent assay; GFAP: glial fibrillary acidic protein; HC: healthy controls; IP/MS: immunoprecipitation mass spectrometry assay; MSD: Meso Scale Discovery; MCI: mild cognitive impairment; NfL: neurofilament light; NS: non-significant; p-tau: phosphorylated tau; SIMOA: Single Molecule Array; t-tau: total tau.
*p<0.05; **p<0.01; ***p<0.001.
O'Bryant and colleagues[51] is not reported in the table as they do not report on their biomarker concentrations.

Table 2. Diagnostic accuracy

Study	Diagnostic accuracy					Authors' interpretation(s)
Brickman et al. [43]	**AUC from plasma (clinical AD versus HC)**‡					There was generally lower accuracy for the biomarkers in Hispanic participants, while the biomarkers were comparable among White and Black participants.
		Aβ42/40	***t-tau***	***p-tau181***	***p-tau217*** ***NfL***	
	White	0.50	0.53	0.69	0.71 0.65	
	Hispanic	0.45	0.58	0.51	0.52 0.48	
	Black	0.50	0.56	0.63	0.68 0.64	
Gonzales et al. [50]	**Risk of AD/MCI (OR) with interaction from serum**					No interactions were present for NfL and GFAP, while significant interactions in t-tau odds-ratios were found. Interactions based on ethnicity generally dissipated in a subset of demographically matched participants.
		t-tau	***NfL***	***GFAP***		
	White	1.59	1.57	1.83		
	Hispanic	1.22	1.43	1.42		
	Difference	*	*NS*	*NS*		
Schindler et al. [48]	**AUC of CSF confirmed AD with significance of race as covariate from plasma**					Accuracy based on plasma $A\beta_{42}/A\beta_{40}$ was not affected by self-identified race. However, differences across p-tau181, p-tau231, and NfL were found, suggesting that applying cut-offs based on White participants would be problematic.
		$A\beta_{42/40}$	***p-tau181***	***p-tau231***	***NfL***	
	AUC	0.90	0.85	0.85	0.81	
	Race as covariate	*NS*	**	**	**	

Aβ: amyloid-beta; AD: Alzheimer's disease; AUC: area under the ROC curve; GFAP: glial fibrillary acidic protein; HC: healthy controls; MCI: mild cognitive impairment: NfL: neurofilament light; NS: non-significant; OR: odds-ratio; p-tau: phosphorylated tau; t-tau: total tau.
*p < 0.05; **p < 0.01; ***p < 0.001.
‡No statistical comparison of AUCs were performed.

eight studies,[42–47,50,51] and Black participants in seven studies.[42–46,48,49] Ethnicity/race was self-reported in all included studies except for one study[42] in which the Health Care Financing Administration records were used. Six studies reported sociodemographic characteristics and/or medical covariates stratified by ethnic/racial group (see Supplemental Table 1).[45,47–51] White participants were older in five of the six studies, had more years of education compared to Hispanic participants, but not the Black participants, and had lower proportions of medical conditions compared to Black and Hispanic participants except for one study in which Hispanic participants had a lower proportion of diabetes.[47] Nine studies included patients with clinically diagnosed AD,[42–47,49–51] and five studies included patients with amyloid-PET or CSF-confirmed AD.[43,46–48,51] NfL was the most examined biomarker (n = 9), followed by t-tau (n = 6), $A\beta_{42/40}$ (n = 5), $A\beta_{42}$ (n = 3), $A\beta_{40}$ (n = 3), p-tau181 (n = 3), p-tau217 (n = 2), GFAP (n = 2), and p-tau231 (n = 1).

Risk of bias and applicability

QUADAS-2 risk of bias and applicability concerns are presented in Supplemental Table 2. Overall risk of bias was low across the included studies. However, in several studies, it was unclear if the index test and reference standard were interpreted independently as this was not explicitly reported. In one study,[44] there was applicability concern regarding participant selection as the division of participant groups and comparison of ethnic/racial groups did not fully match our research question.

Influence of ethnicity/race on blood biomarkers

Biomarker concentrations. Seven of the 10 included studies reported differences in blood biomarker concentrations between ethnic/racial groups (see Table 1).[42,45,47–51] However, in two of five studies that adjusted for covariates,[45,47–50] these differences became non-significant.[47,50]

Among the studies in which differences in biomarker concentrations were found, Luchsinger and colleagues found significantly higher plasma $A\beta_{40}$ concentrations in Black participants compared to Hispanic and White participants in unadjusted comparisons.[42] While Hall and colleagues also found differences in plasma $A\beta_{40}$, $A\beta_{42}$, $A\beta_{42/40}$, t-tau, and NfL concentrations across the White, Hispanic, and Black participants after adjusting for age and sex differences.[45] Differences were also found on concentrations of plasma $A\beta_{42/40}$ and $A\beta_{42}$, but not on $A\beta_{40}$, p-tau181, p-tau231, and NfL concentrations by Schindler and colleagues when matching Black and White participants one-to-one on *APOE* ϵ4 status, cognitive status, and time of plasma extraction.[48] Rajan and colleagues found differences in NfL, GFAP, and t-tau concentrations between Black and White participants in unadjusted comparisons.[49] However, after adjusting for age, only differences in NfL remained significant. Meanwhile, O'Bryant and colleagues found that concentrations of plasma $A\beta_{42}$ were related to the Geriatric Depression Scale (GDS) for Hispanic, but not White, participants in analyses adjusting for age, education, and cognitive diagnosis (Table 1).[51]

When adjusting for covariates, the influence of Hispanic ethnicity disappeared in two studies. Gonzales and

Table 3. Prognostic accuracy

Study	Prognostic accuracy	Authors' interpretation(s)
Brickman et al. [43]	**Risk of development of clinical AD ~4 years later from plasma (*White participants as reference*)** ***p-tau181*** ***OR (95%CI)*** ***Hispanic*** 1.09 (0.58-2.04) ***Black*** 0.82 (0.43-1.59) ***p-tau217*** ***OR (95%CI)*** ***Hispanic*** 0.66 (0.34-1.29) ***Black*** 0.80 (0.42-1.54)	The results support the use of blood biomarkers in diverse cohorts.
Rajan et al. [49]	**Annual change in serum concentration** ***t-tau*** ***NfL*** ***GFAP*** ***White*** 5.4% 5.6% 3.5% ***Black*** 4.0% 6.1% 4.4% *Difference* - - *	The annual change may not differ between Black and White patients for NfL and t-tau. A difference in the annual change for GFAP between Black and White patients may suggest higher amount of progressive atrophy in Black patients.

AD: Alzheimer's disease; GFAP: glial fibrillary acidic protein; NfL: neurofilament light; p-tau: phosphorylated tau; t-tau: total tau.
*p < 0.05; **p < 0.01; ***p < 0.001.

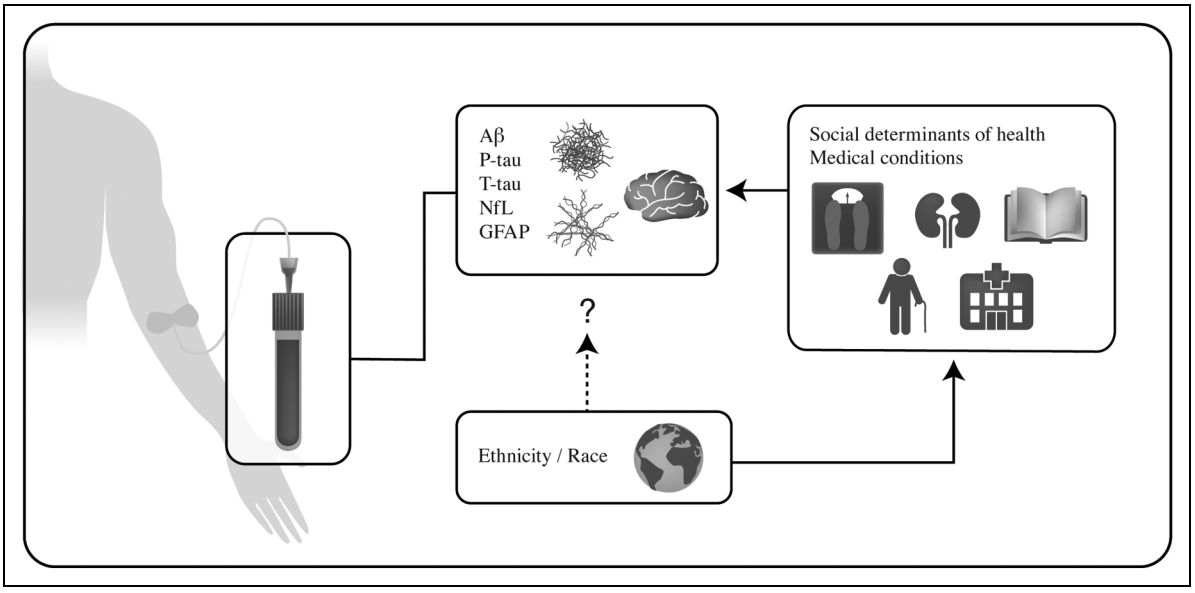


Figure 2. Hypothetical model visualizing race/ethnicity as a possible mediating factor for medical conditions and social determinants of health influencing blood biomarkers. Figure created with Adobe Illustrator 2024.

colleagues found higher concentrations of serum GFAP, NfL, and t-tau among White compared to Hispanic participants in unadjusted comparisons.[50] However, when adjusting for all included covariates (age, sex, *APOE* ϵ4 status, education, and diagnostic group), these differences became non-significant. The same pattern was reported by O'Bryant and colleagues who found higher plasma NfL concentrations in White compared to Hispanic participants in an unadjusted comparison.[47] But, after adjusting for the covariates age, sex, education, and ethnicity, only age remained a statistically significant predictor of NfL concentrations.

Three studies did not find ethnic/racial differences in biomarker concentrations.[43,44,46] Brickman and colleagues found no significant biomarker concentration differences between White, Hispanic, and Black participants.[43] Another study by Brickman and colleagues found that the proportions of White, Hispanic, and Black participants did not significantly differ when comparing plasma p-tau positive/negative and symptomatic/non-symptomatic participants.[44] In a comparison adjusted for age, Barker and colleagues found no differences in plasma NfL concentrations between Hispanic and non-Hispanic groups.[46]

Diagnostic accuracy. Three studies examined the influence of ethnicity/race on diagnostic accuracy as presented in Table 2.[43,48,50] Brickman and colleagues found a lower area under the receiver operating characteristic curves

(AUCs) for separating clinical AD from controls in Hispanic compared to White and Black participants across most of the included blood biomarkers (Table 2).[43] Schindler and colleagues reported that the precision of the included plasma biomarkers to predict CSF $A\beta_{42/40}$ positivity increased when including the covariates race, sex, age, *APOE* ϵ4 status, and cognitive status.[48] Of these covariates, race was a significant covariate for plasma p-tau181, p-tau23, and NfL, but not $A\beta_{42/40}$. Gonzales and colleagues explored the risk of dementia or mild cognitive impairment (MCI) and found that serum t-tau concentration, but not NfL and GFAP concentrations, significantly interacted with ethnicity/race.[50] However, this interaction became non-significant after matching the ethnic/racial groups on age, sex, *APOE* ϵ4 status, education, and diagnostic group.

Prognostic accuracy. Two studies examined the influence of ethnicity/race on prognostic accuracy of blood biomarkers as presented in Table 3.[43,49] Brickman and colleagues found no effect of including race as a covariate in the prediction of developing clinical AD during a four-year period (using p-tau181 and p-tau217).[43] Rajan and colleagues found that GFAP, not NfL and t-tau, concentrations had a significantly greater annual increase among Black compared to White participants after adjusting for age, sex, education, and *APOE* ϵ4.[49]

Discussion

To our knowledge, this is the first systematic review exploring the influence of ethnicity/race on AD blood biomarker concentrations. Although the review found some evidence for ethnic/racial differences in blood biomarker concentrations, it remains unclear whether these differences are mediated by differences in social determinants of health and medical conditions rather than ethnicity/race per se.

Regarding blood biomarker concentrations, seven of the ten reviewed studies reported ethnic/racial differences.[42,45,47–51] After adjusting for sociodemographic covariates, including age, sex, and education, differences were no longer significant in two of the studies,[47,50] whereas differences persisted in three studies after adjusting for age and sex,[45,49] or matching on *APOE* ϵ4, cognitive status, and time of plasma extraction.[48] These results generally align with previous studies reporting racial/ethnic differences in CSF AD biomarker concentrations.[12–15] However, the reason behind the differences remains unresolved. For instance, it is unclear if differences in medical conditions or genetic variation in *APOE* ϵ4[16,17] and *MAPT*[18,19] are sufficient to explain ethnic/racial differences as such deep phenotyping was not included in the reviewed studies. Importantly, the term 'race' is socially defined and it can be argued that 'race' does not necessarily refer to any specific genetic characteristics or geographic origin but rather to the skin color of people who may have lived in the country of examination for generations. Therefore, operating with such racialized groups, differences in blood biomarker concentrations may reflect individuals' socio-economic status and access to healthcare, which in turn affect the prevalence of medical conditions. Considering medical conditions, especially the ones affecting kidney function and thus blood filtration, may be crucial for our understanding of blood biomarkers. Therefore, it is surprising that measures of kidney function were not considered more in the included studies. However, the current evidence does not provide any conclusive answers to the reasons behind the observed ethnic/racial differences in blood biomarker concentrations, hence further research is needed.

For clinical practice, however, it may be more relevant to understand if the observed differences in blood biomarker concentrations affect diagnostic and prognostic accuracy. Three of the included studies did report an influence of ethnicity/race on accuracy measures.[43,48,49] However, in two other studies the effect of ethnicity/race either disappeared when matching on age, sex, *APOE* ϵ4 status, education, and diagnostic group,[50] or no effect of ethnicity/race was found for prognostic accuracy.[43] Thus, it remains uncertain whether race/ethnicity influences the diagnostic and prognostic accuracy of AD blood biomarkers. However, as several studies do report an influence, it seems paramount to explore this further before widespread implementation. Nevertheless, it has been suggested to use different cut-off values for CSF based on race.[52] However, applying different cut-off values of blood, CSF, or amyloid-PET based on ethnicity/race seems premature. Firstly, the number of studies including diverse samples remains sparse. This is problematic as it may lead to misinterpretations and poorer diagnostic outcomes if biomarkers are applied in populations in which they have not been sufficiently examined. Secondly, the reasons behind ethnic/racial differences in AD blood biomarker concentrations remain unknown. Therefore, identification and quantification of important influencing factors on blood biomarker concentrations need to be identified first.

No definite proof of influencing factors on blood biomarker concentrations or accuracy measures is currently available, hence unmeasured covariates may affect the results from blood biomarkers. Furthermore, when identifying effects, it is challenging to distinguish between confounding, mediating, or indirect effects of covariates. This challenge becomes clear as studies disagree on whether ethnicity/race, certain medical conditions, BMI, education, or other variables should be considered when analyzing or interpreting the results of blood biomarkers.

Interestingly, across the included studies White participants were generally older, had more years of education, and had lower prevalence of medical conditions compared with Black and Hispanic participants, especially concerning diabetes, hypertension, and dyslipidemia (Supplemental Table 1). This is in line with the Centers for Disease Control and Prevention (CDC) which reports higher rates

of diabetes and obesity among Black and Hispanic compared to White Americans as well as higher rates of hypertension in Black compared to White Americans.[35] Three of the included studies demonstrated possible effects of hypertension, diabetes, dyslipidemia,[47] BMI,[43] and depression[51] on blood biomarkers. Other studies in primarily White populations have also shown effects of BMI, kidney function, and diabetes.[22–24,53] Potentially, higher BMI leads to higher blood volume diluting protein concentrations, while kidney function, measured through creatinine or estimated glomerular filtration rate, affects blood filtration causing protein build-up.[23] For example, a study by Simonsen and colleagues recommends accompanying serum NfL with data on age and kidney function as the influence on NfL concentrations was significant.[24] As social determinants of health and medical conditions are known to differ across ethnic/racial groups possible interactions between ethnicity/race and other factors require further exploration.[32]

Based on the available evidence it is not possible to rule out that a lack of adjustment for important covariates may have influenced reported results. Importantly, the ethnic/racial groups included in the current review differ in medical conditions that have been demonstrated to impact blood biomarker concentrations and differ in known risk factors of AD. Therefore, ethnic/racial differences in blood biomarker concentrations may reflect that ethnicity/race is a mediating factor for medical conditions which have a direct influence on blood biomarker concentrations through for example kidney function (Figure 2).

Limitations

This systematic review has several limitations that should be considered. First, all included studies originated from the US and adopted US-specific racialized categories, limiting the generalizability of the findings to other world regions and contexts. These categories are not readily applicable to other parts of the world, as the migration histories, languages, and geographic origins of people with minority ethnic backgrounds vary significantly between countries and world regions.[54] Moreover, the same cohorts were used across several studies, which further limits the generalizability of the findings. Second, the included studies examined different covariates, possibly leading to different results regarding which social determinants of health and medical conditions influence blood biomarkers. Third, only studies published in English were included, with the risk of overlooking relevant studies published in other languages. Fourth, the only social determinant of health included in the reviewed studies was education. However, many other variables such as socioeconomic status and access to healthcare could be relevant to examine. The results of this systematic review should be interpreted with these limitations in mind.

Conclusions

As blood biomarkers may change the landscape for diagnosing AD, it is paramount to identify factors that need to be taken into consideration in the interpretation of the biomarker results. This review provides some evidence for ethnic/racial differences in blood biomarker concentrations. Importantly, when working with diverse populations in terms of medical conditions and social determinants of health, previously rejected factors may become relevant since the prevalence of medical conditions may differ. Before wider clinical implementation of AD blood biomarkers, there is a need to further explore confounding or mediating influences on blood biomarker concentrations and their diagnostic and prognostic accuracy. As the identified studies in this review exclusively originated from the US, it also seems relevant to conduct studies in other cultural contexts and ethnic/racial groups. For instance, to better understand associations between ethnicity and blood-based biomarkers, it would be valuable to conduct studies using geographic region of origin as a basis for defining ethnic groups, rather than relying on socially constructed racialized categories. This approach would enhance the global generalizability of studies, whether they are conducted within or outside the US. Blood biomarkers may revolutionize the way neurodegenerative disorders are diagnosed, nonetheless, they are still in the early stages of exploration.

Acknowledgments

We would like to thank visual designer Amalie Frimann Friis-Andersen for her valuable contribution in designing Figure 2 for this article.

ORCID iD


Daniel Kjaergaard https://orcid.org/0000-0001-9955-8220

Statements and declarations

Author contributions

Daniel Kjaergaard (Conceptualization; Formal analysis; Methodology; Writing – original draft); Anja Hviid Simonsen (Conceptualization; Supervision; Writing – review & editing); Gunhild Waldemar (Conceptualization; Methodology; Writing – review & editing); T. Rune Nielsen (Conceptualization; Methodology; Project administration; Supervision; Writing – review & editing).

Funding

The authors disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This work was supported by the Innovation Fund Denmark [grant number 1099-00022B], under the frame of ERA PerMed [reference number ERAPERMED2021-184]. AHS was supported by the Absalon Foundation founded 1st of May 1978. These funding sources had no involvement in the formulation of this review.

Declaration of conflicting interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Data availability

The data supporting the findings of this study are available on reasonable request from the corresponding author.

Supplemental material

Supplemental material for this article is available online.

References

1. Teunissen CE, Verberk IMW, Thijssen EH, et al. Blood-based biomarkers for Alzheimer's disease: towards clinical implementation. *Lancet Neurol* 2022; 21: 66–77.
2. Hansson O, Edelmayer RM, Boxer AL, et al. The Alzheimer's association appropriate use recommendations for blood biomarkers in Alzheimer's disease. *Alzheimers Dement* 2022; 18: 2669–2686.
3. Leuzy A, Mattsson-Carlgren N, Palmqvist S, et al. Blood-based biomarkers for Alzheimer's disease. *EMBO Mol Med* 2022; 14: e14408.
4. Brand AL, Lawler PE, Bollinger JG, et al. The performance of plasma amyloid beta measurements in identifying amyloid plaques in Alzheimer's disease: a literature review. *Alzheimers Res Ther* 2022; 14: 195.
5. Salvadó G, Ossenkoppele R, Ashton NJ, et al. Specific associations between plasma biomarkers and postmortem amyloid plaque and tau tangle loads. *EMBO Mol Med* 2023; 15: e17123.
6. Aguillon D, Langella S, Chen Y, et al. Plasma p-tau217 predicts in vivo brain pathology and cognition in autosomal dominant Alzheimer's disease. *Alzheimers Dement* 2023; 19: 2585–2594.
7. Mattsson-Carlgren N, Salvadó G, Ashton NJ, et al. Prediction of longitudinal cognitive decline in preclinical Alzheimer disease using plasma biomarkers. *JAMA Neurol* 2023; 80: 360–369.
8. Palmqvist S, Stomrud E, Cullen N, et al. An accurate fully automated panel of plasma biomarkers for Alzheimer's disease. *Alzheimers Dement* 2023; 19: 1204–1215.
9. Gilmore-Bykovskyi AL, Jin Y, Gleason C, et al. Recruitment and retention of underrepresented populations in Alzheimer's disease research: a systematic review. *Alzheimers Dement (N Y)* 2019; 5: 751–770.
10. Franzen S, Smith JE, van den Berg E, et al. Diversity in Alzheimer's disease drug trials: the importance of eligibility criteria. *Alzheimers Dement* 2022; 18: 810–823.
11. Karikari TK. Blood tests for Alzheimer's disease: increasing efforts to expand and diversify research participation is critical for widespread validation and acceptance. *J Alzheimers Dis* 2022; 90: 967–974.
12. Chaudhry A and Rizig M. Comparing fluid biomarkers of Alzheimer's disease between African American or black African and white groups: a systematic review and meta-analysis. *J Neurol Sci* 2021; 421: 117270.
13. Modeste ES, Ping L, Watson CM, et al. Quantitative proteomics of cerebrospinal fluid from African Americans and caucasians reveals shared and divergent changes in Alzheimer's disease. *Mol Neurodegener* 2023; 18: 48.
14. Gleason CE, Zuelsdorff M, Gooding DC, et al. Alzheimer's disease biomarkers in Black and non-Hispanic White cohorts: a contextualized review of the evidence. *Alzheimers Dement* 2022; 18: 1545–1564.
15. Lebrun L, Hanseeuw B, van Pesch V, et al. Alzheimer disease's cerebrospinal fluid biomarkers differences between immigrants and natives in a Belgian memory clinic. *Acta Neurol Belg* 2023; 123: 537–544.
16. Qin W, Li W, Wang Q, et al. Race-related association between APOE genotype and Alzheimer's disease: a systematic review and meta-analysis. *J Alzheimers Dis* 2021; 83: 897–906.
17. Le Guen Y, Raulin AC, Logue MW, et al. Association of African ancestry-specific APOE missense variant R145C with risk of Alzheimer disease. *JAMA* 2023; 329: 551–560.
18. Evans W, Fung HC, Steele J, et al. The tau H2 haplotype is almost exclusively Caucasian in origin. *Neurosci Lett* 2004; 369: 183–185.
19. Kauwe JS, Cruchaga C, Mayo K, et al. Variation in MAPT is associated with cerebrospinal fluid tau levels in the presence of amyloid-beta deposition. *Proc Natl Acad Sci U S A* 2008; 105: 8050–8054.
20. Howell JC, Watts KD, Parker MW, et al. Race modifies the relationship between cognition and Alzheimer's disease cerebrospinal fluid biomarkers. *Alzheimers Res Ther* 2017; 9: 88.
21. Morris JC, Schindler SE, McCue LM, et al. Assessment of racial disparities in biomarkers for Alzheimer disease. *JAMA Neurol* 2019; 76: 264–273.
22. Syrjanen JA, Campbell MR, Algeciras-Schimnich A, et al. Associations of amyloid and neurodegeneration plasma biomarkers with comorbidities. *Alzheimers Dement* 2022; 18: 1128–1140.
23. Pichet Binette A, Janelidze S, Cullen N, et al. Confounding factors of Alzheimer's disease plasma biomarkers and their impact on clinical performance. *Alzheimers Dement* 2023; 19: 1403–1414.
24. Simonsen AH, Gleerup HS, Musaeus CS, et al. Neurofilament light chain levels in serum among a large mixed memory clinic cohort: confounders and diagnostic usefulness. *Alzheimers Dement (Amst)* 2023; 15: e12512.
25. Rosselli M, Uribe IV, Ahne E, et al. Culture, ethnicity, and level of education in Alzheimer's disease. *Neurotherapeutics* 2022; 19: 26–54.
26. Mayeda ER, Glymour MM, Quesenberry CP, et al. Inequalities in dementia incidence between six racial and ethnic groups over 14 years. *Alzheimers Dement* 2016; 12: 216–224.
27. Green RC, Cupples LA, Go R, et al. Risk of dementia among white and African American relatives of patients with Alzheimer disease. *JAMA* 2002; 287: 329–336.
28. Cooper C, Tandy AR, Balamurali TB, et al. A systematic review and meta-analysis of ethnic differences in use of

dementia treatment, care, and research. *Am J Geriatr Psychiatry* 2010; 18: 193–203.
29. Chin AL, Negash S and Hamilton R. Diversity and disparity in dementia: the impact of ethnoracial differences in Alzheimer disease. *Alzheimer Dis Assoc Disord* 2011; 25: 187–195.
30. Ma'u E, Cullum S, Cheung G, et al. Differences in the potential for dementia prevention between major ethnic groups within one country: a cross sectional analysis of population attributable fraction of potentially modifiable risk factors in New Zealand. *Lancet Reg Health West Pac* 2021; 13: 100191.
31. Mukadam N, Marston L, Lewis G, et al. South Asian, black and white ethnicity and the effect of potentially modifiable risk factors for dementia: a study in English electronic health records. *PLoS One* 2023; 18: e0289893.
32. Chen C and Zissimopoulos JM. Racial and ethnic differences in trends in dementia prevalence and risk factors in the United States. *Alzheimers Dement (N Y)* 2018; 4: 510–520.
33. McGrath RP, Snih SA, Markides KS, et al. The burden of health conditions across race and ethnicity for aging Americans: disability-adjusted life years. *Medicine (Baltimore)* 2019; 98: e17964.
34. Teagle WL, Norris ET, Rishishwar L, et al. Comorbidities and ethnic health disparities in the UK biobank. *JAMIA Open* 2022; 5: ooac057.
35. Akinbami LJ, Chen T-C, Davy O, et al. National health and nutrition examination survey, 2017–march 2020 prepandemic file: sample design, estimation, and analytic guidelines. *Vital Health Stat* 2022; (190): 1–36.
36. Livingston G, Sommerlad A, Orgeta V, et al. Dementia prevention, intervention, and care. *Lancet* 2017; 390: 2673–2734.
37. Livingston G, Huntley J, Sommerlad A, et al. Dementia prevention, intervention, and care: 2020 report of the Lancet Commission. *Lancet* 2020; 396: 413–446.
38. Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med* 2009; 6: e1000097.
39. Whiting PF, Rutjes AW, Westwood ME, et al. QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. *Ann Intern Med* 2011; 155: 529–536.
40. Yamashita K, Miura M, Watanabe S, et al. Fully automated and highly specific plasma β-amyloid immunoassays predict β-amyloid status defined by amyloid positron emission tomography with high accuracy. *Alzheimers Res Ther* 2022; 14: 86.
41. Cosentino SA, Stern Y, Sokolov E, et al. Plasma β-amyloid and cognitive decline. *Arch Neurol* 2010; 67: 1485–1490.
42. Luchsinger JA, Tang MX, Miller J, et al. Relation of plasma homocysteine to plasma amyloid beta levels. *Neurochem Res* 2007; 32: 775–781.
43. Brickman AM, Manly JJ, Honig LS, et al. Plasma p-tau181, p-tau217, and other blood-based Alzheimer's disease biomarkers in a multi-ethnic, community study. *Alzheimers Dement* 2021; 17: 1353–1364.
44. Brickman AM, Manly JJ, Honig LS, et al. Correlation of plasma and neuroimaging biomarkers in Alzheimer's disease. *Ann Clin Transl Neurol* 2022; 9: 756–761.
45. Hall JR, Petersen M, Johnson L, et al. Characterizing plasma biomarkers of Alzheimer's in a diverse community-based cohort: a cross-sectional study of the HAB-HD cohort. *Front Neurol* 2022; 13: 871947.
46. Barker W, Quinonez C, Greig MT, et al. Utility of plasma neurofilament light in the 1Florida Alzheimer's disease research center (ADRC). *J Alzheimers Dis* 2021; 79: 59–70.
47. O'Bryant S, Petersen M, Hall J, et al. Characterizing plasma NfL in a community-dwelling multi-ethnic cohort: results from the HABLE study. *Alzheimers Dement* 2022; 18: 240–250.
48. Schindler SE, Karikari TK, Ashton NJ, et al. Effect of race on prediction of brain amyloidosis by plasma Aβ42/Aβ40, phosphorylated tau, and neurofilament light. *Neurology* 2022; 99: e245–e257.
49. Rajan KB, McAninch EA, Aggarwal NT, et al. Longitudinal changes in blood biomarkers of clinical Alzheimer disease in a biracial population sample. *Neurology* 2023; 100: e874–e883.
50. Gonzales MM, Short MI, Satizabal CL, et al. Blood biomarkers for dementia in hispanic and non-hispanic white adults. *Alzheimers Dement (N Y)* 2021; 7: e12164.
51. O'Bryant S, Petersen M, Hall J, et al. Depression is differentially related to cognitive and biomarker outcomes among Mexican Americans. *Front Psychiatry* 2022; 13: 901403.
52. Garrett SL, McDaniel D, Obideen M, et al. Racial disparity in cerebrospinal fluid amyloid and tau biomarkers and associated cutoffs for mild cognitive impairment. *JAMA Netw Open* 2019; 2: e1917363.
53. Koini M, Pirpamer L, Hofer E, et al. Factors influencing serum neurofilament light chain levels in normal aging. *Aging (Albany NY)* 2021; 13: 25729–25738.
54. Nielsen TR. Assessment in culturally, linguistically, and educationally diverse older populations in Europe. *Am J Alzheimers Dis Other Demen* 2022; 37: 15333175221117006.

Supplementary materials – Study 2

Supplemental Table 1. Study characteristics

Study	Participants	Demographics (across diagnostic categories)			Medical conditions and genetic risk factors (across diagnostic categories)				AD biomarker(s)	Relevant study objective
		Age	% Female	Education	Diabetes	Hypertension	Dyslipidemia	*APOE ε4*		
Luchsinger et al. [1]	**Ethnicity/race** White (n = 69) Hispanic (n = 141) Black (n = 117) **Diagnostic categories** Clinical AD and HC	***Not reported per ethnicity/race***			***Not reported per ethnicity/race***				**Plasma (ELISA)** $A\beta_{40}$ $A\beta_{42}$	To explore plasma homocysteine levels and $A\beta_{40}$ and $A\beta_{42}$ levels and their association with risk of AD and MCI.
Barker et al. [2]	**Ethnicity/race** White (n = 188) Black (n = 7) ~58% of total sample have Hispanic ethnicity[§] **Diagnostic categories** Clinical AD, amyloid-PET confirmed AD, and HC	***Not reported per ethnicity/race***			***Not reported per ethnicity/race***				**Plasma (SIMOA)** NfL	To examine the association of NfL with different covariates such as ethnicity and age.
Brickman et al. [3]	**Ethnicity/race** White (n = 100) Hispanic (n = 100) Black (n = 100) **Diagnostic categories** Clinical AD, PET-amyloid confirmed AD, and HC	***Not reported per ethnicity/race***			***Not reported per ethnicity/race***				**Plasma (SIMOA)** $A\beta_{42/40}$ T-tau NfL **Plasma (MSD)** P-tau181 P-tau217	To compare plasma biomarker concentrations and their differences by race/ethnicity.
Gonzales et al. [4]	**Ethnicity/race** White (n = 535) Hispanic (n = 868) *Difference* **Diagnostic categories** Clinical AD, MCI, and HC	74±8 67±9 *	55% 70% *	15±3 10±5 *	10% 33% *	- - -	- - -	48% 21% *	**Serum (SIMOA)** t-tau NfL GFAP	To evaluate blood biomarker diagnostic accuracy in a bi-ethnic cohort.
Brickman et al. [5]	**Ethnicity/race** White (n = 100) Hispanic (n = 100) Black (n = 100)	***Not reported per ethnicity/race***			***Not reported per ethnicity/race***				**Plasma (SIMOA)** $A\beta_{42/40}$ T-tau	To examine demographic and other variables in a

	Diagnostic categories Four groups divided by clinical AD and HC, and plasma p-tau181 and p-tau217 positivity.								NfL **Plasma (MSD)** P-tau181 P-tau217	multi-ethnic cohort.
Hall et al. [6]	**Ethnicity/race** White (n = 686) Hispanic (n = 706) Black (n = 161) *Difference* **Diagnostic categories** Clinical AD, MCI, and HC	69.30±8.68 63.07±7.98 63.09±7.71 ***	57% 67% 71% NS	15.49±2.57 9.17±4.59 15.29±2.65 ***	13% 37% 25% ***	59% 66% 77% ***	40% 67% 63% ***	- - - -	**Plasma (SIMOA)** $A\beta_{40}$ $A\beta_{42}$ $A\beta_{42}/A\beta_{40}$ T-tau NfL	To investigate the influence of ethnicity/race on plasma biomarker concentrations.
O'Bryant et al. [7]	**Ethnicity/race** White (n = 813) Hispanic (n = 890) *Difference* **Diagnostic categories** Clinical AD, MCI, and HC (subset with amyloid-PET confirmed AD)	69.34±8.65 63.87±8.02 ***	54% 66% ***	15.49±2.55 9.48±4.61 ***	61% 36% ***	55% 63% ***	61% 64% NS	- - -	**Plasma (SIMOA)** NfL	To characterize the influence of demographic factors and comorbidities on NfL concentrations.
O'Bryant et al. [8]	**Ethnicity/race** White (n = 781) Hispanic (n = 853) *Difference* **Diagnostic categories** Clinical AD, MCI, and HC (subset with amyloid-PET confirmed AD)	69.35±8.65 63.84±7.98 ***	54% 66% ***	15.50±2.55 9.51±4.61 ***	***Not reported***				**Plasma (SIMOA)** $A\beta_{40}$ $A\beta_{42}$ t-tau NfL	To examine the associations between biomarker outcomes, depressive symptoms and neuropsychological tests across Hispanic ethnicity.
Schindler et al. [9]	**Ethnicity/race** White (n = 76) Black (n = 76) *Difference* **Diagnostic categories** CSF-determined AD and HC	68.4 (64.1-73.1) 68.4 (64.9-73.2) NS	51% 58% NS	16 (14-18) 16 (12-18) NS	4% 21% ***	33% 51% ***	- - -	42% 42% NS	**Plasma (IP/MS)** $A\beta_{40}$ $A\beta_{42}$ $A\beta_{42/40}$ **Plasma (SIMOA)** P-tau181 P-tau231 NfL	To examine the relationship between plasma biomarkers and reference measures of brain amyloidosis.

Rajan et al. [10] ¶	**Ethnicity/race**								**Serum (SIMOA)**	To investigate longitudinal biomarker changes over 17 years in a biracial sample.
	White (n = 516)	80.0±6.1	61%	14.0±3.2	14%	45%	-	29%	t-tau	
	Black (n = 811)	77.8±6.1	63%	11.4±3.5	29%	68%	-	37%	NfL	
	Diagnostic categories								GFAP	
	Clinical AD and HC									

Aβ: amyloid-beta; AD, Alzheimer's disease; *APOE*: apolipoprotein; ELISA: enzyme-linked immunosorbent assay; GFAP: glial fibrillary acidic protein; HC: healthy controls; IP/MS: immunoprecipitation mass spectrometry assay; MSD: Meso Scale Discovery; MCI: mild cognitive impairment; NfL: neurofilament light; NS: non-significant; p-tau: phosphorylated tau; SIMOA: Single Molecule Array; t-tau: total tau.

*p<0.05; **p<0.01; ***p<0.001.

‡Medical conditions reported in two or more studies are noted.

§Barker and colleagues[2] report sample size per racial group (white/black/other), but only Hispanic ethnicity by percentage of the total sample.

¶Statistical differences on age, sex, education, and medical covariates is not described.

S**upplemental Table 2.** QUADAS-2

	RISK OF BIAS				APPLICABILITY CONCERNS		
STUDY	**PATIENT SELECTION**	**INDEX TEST**	**REFERENCE STANDARD**	**FLOW AND TIMING**	**PATIENT SELECTION**	**INDEX TEST**	**REFERENCE STANDARD**
Barker et al. [2]	✓	✓	✓	✓	✓	✓	✓
Brickman et al. [3]	✓	?	✓	✓	✓	✓	✓
Brickman et al. [5]	✓	?	✓	✓	!	✓	✓
Gonzales et al. [4]	✓	✓	?	✓	✓	✓	✓
Hall et al. [6]	✓	?	✓	?	✓	✓	?
Luchsinger et al. [1]	✓	?	?	✓	✓	✓	✓
O'Bryant et al. [7]	✓	?	?	✓	✓	✓	✓
O'Bryant et al. [8]	✓	?	?	✓	✓	✓	✓
Rajan et al. [10]	✓	?	?	✓	✓	✓	✓
Schindler et al. [9]	✓	✓	?	✓	✓	✓	✓

✓ = Low Risk; ! = High Risk; ? = Unclear Risk

References

1. Luchsinger JA, Tang MX, Miller J, et al. Relation of plasma homocysteine to plasma amyloid beta levels. *Neurochem Res* 2007; 32: 775-781.
2. Barker W, Quinonez C, Greig MT, et al. Utility of plasma neurofilament light in the 1Florida Alzheimer's Disease Research Center (ADRC). *J Alzheimers Dis* 2021; 79: 59-70.
3. Brickman AM, Manly JJ, Honig LS, et al. Plasma p-tau181, p-tau217, and other blood-based Alzheimer's disease biomarkers in a multi-ethnic, community study. *Alzheimers Dement* 2021; 17: 1353-1364.
4. Gonzales MM, Short MI, Satizabal CL, et al. Blood biomarkers for dementia in Hispanic and non-Hispanic White adults. *Alzheimers Dement (N Y)* 2021; 7: e12164.
5. Brickman AM, Manly JJ, Honig LS, et al. Correlation of plasma and neuroimaging biomarkers in Alzheimer's disease. *Ann Clin Transl Neurol* 2022; 9: 756-761.
6. Hall JR, Petersen M, Johnson L, et al. Characterizing plasma biomarkers of Alzheimer's in a diverse community-based cohort: A cross-sectional study of the HAB-HD cohort. *Front Neurol* 2022; 13: 871947.
7. O'Bryant S, Petersen M, Hall J, et al. Characterizing plasma NfL in a community-dwelling multi-ethnic cohort: Results from the HABLE study. *Alzheimers Dement* 2022; 18: 240-250.
8. O'Bryant S, Petersen M, Hall J, et al. Depression is differentially related to cognitive and biomarker outcomes among Mexican Americans. *Front Psychiatry* 2022; 13: 901403.
9. Schindler SE, Karikari TK, Ashton NJ, et al. Effect of race on prediction of brain amyloidosis by plasma Aβ42/Aβ40, phosphorylated tau, and neurofilament light. *Neurology* 2022; 99: e245-e257.
10. Rajan KB, McAninch EA, Aggarwal NT, et al. Longitudinal changes in blood biomarkers of clinical Alzheimer disease in a biracial population sample. *Neurology* 2023; 100: e874-e883.

9.3. Study 3.

Influence of ethnicity on the diagnostic accuracy of plasma p-tau217 for the identification of Alzheimer's disease: A consecutive mixed memory clinic cohort study

Daniel Kjaergaard, T. Rune Nielsen, Erik Stomrud, Sebastian Palmqvist, Divya Bali, Anna Orduña Dolado, Shorena Janelidze, Oskar Hansson, Gunhild Waldemar, Anja Hviid Simonsen

Alzheimer's & Dementia (2025). https://doi.org/10.1002/alz.70315

Received: 19 March 2025 | Revised: 23 April 2025 | Accepted: 30 April 2025

DOI: 10.1002/alz.70315

Alzheimer's & Dementia®
THE JOURNAL OF THE ALZHEIMER'S ASSOCIATION

RESEARCH ARTICLE

Influence of ethnicity on the diagnostic accuracy of plasma p-tau217 for the identification of Alzheimer's disease: A consecutive mixed memory clinic cohort study

Daniel Kjaergaard[1] | **T. Rune Nielsen**[1,2] | **Erik Stomrud**[3,4] | **Sebastian Palmqvist**[3,4] | **Divya Bali**[3] | **Anna Orduña Dolado**[3] | **Shorena Janelidze**[3] | **Oskar Hansson**[3] | **Gunhild Waldemar**[1,5] | **Anja Hviid Simonsen**[1]

[1]Danish Dementia Research Centre, Department of Neurology, Neuroscience Centre, Copenhagen University Hospital - Rigshospitalet, Copenhagen, Denmark

[2]Department of Psychology, University of Copenhagen, Copenhagen, Denmark

[3]Clinical Memory Research Unit, Department of Clinical Sciences Malmö, Lund University, Lund, Sweden

[4]Memory Clinic, Skåne University Hospital, Malmö, Sweden

[5]Department of Clinical Medicine, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark

Correspondence
Daniel Kjaergaard, Danish Dementia Research Centre, Department of Neurology, Neuroscience Centre, Copenhagen University Hospital–Rigshospitalet, Section 8008, Blegdamsvej 9, 2100, Copenhagen, Denmark.
Email: daniel.kjaergaard.01@regionh.dk

Funding information
Innovation Fund Denmark, Grant/Award Number: 1099-00022B; ERA PerMed, Grant/Award Number: ERAPERMED2021-184; Danish Ministry of Health; Absalon Foundation founded 1st of May 1978; European Research Council, Grant/Award Number: ADG-101096455; Alzheimer's Association, Grant/Award Numbers: ZEN24-1069572, SG-23-1061717; GHR Foundation; Swedish Research Council, Grant/Award Number: 2022-00775; Knut and Alice Wallenberg foundation, Grant/Award Number: 2022-0231; Strategic Research Area MultiPark; Swedish Alzheimer Foundation, Grant/Award Number: AF-980907; Swedish Brain Foundation, Grant/Award Number: FO2021-0293; Parkinson foundation of Sweden, Grant/Award Number: 1412/22; Cure Alzheimer's fund; Rönström Family Foundation; Konung Gustaf V:s och Drottning Victorias Frimurarestiftelse; Skåne University Hospital Foundation, Grant/Award Number:

Abstract

INTRODUCTION: Blood-based biomarkers have demonstrated high accuracy for identifying Alzheimer's disease (AD) pathology. However, the lack of representative cohorts creates a knowledge gap regarding their real-world applicability. We examined the influence of ethnicity on the diagnostic accuracy of plasma tau phosphorylated at threonine 217 (p-tau217) in identifying AD.

METHODS: A total of 1170 mixed memory clinic patients originating from 91 different countries were included. Cerebrospinal fluid or amyloid positron emission tomography supplemented the diagnostic evaluation for 539 patients. Plasma was analyzed for p-tau217.

RESULTS: Plasma p-tau217 concentrations did not differ between ethnic groups, and there was no influence of ethnicity on the diagnostic accuracy of plasma p-tau217. Plasma p-tau217 demonstrated strong discriminative ability for AD and AD-pathology in our ethnically diverse cohort.

DISCUSSION: Our study suggests that ethnicity does not influence the diagnostic accuracy of plasma p-tau217. Nonetheless, medical conditions influencing plasma biomarkers may disproportionally affect minoritized groups because of social determinants of health.

KEYWORDS
Alzheimer's disease, amyloid pathology, blood-based biomarkers, cerebrospinal fluid, confounders, dementia, diversity, ethnicity, phosphorylated tau, plasma biomarkers, racial groups

This is an open access article under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.
© 2025 The Author(s). *Alzheimer's & Dementia* published by Wiley Periodicals LLC on behalf of Alzheimer's Association.

2020-O000028; Regionalt Forskningsstöd, Grant/Award Number: 2022-1259; Swedish federal government under the ALF agreement, Grant/Award Number: 2022-Projekt0080

Highlights

- Plasma tau phosphorylated at threonine 217 (p-tau217) was highly accurate in the identification of Alzheimer's disease.
- Geographic origin did not influence the precision of plasma p-tau217.
- Kidney function may influence p-tau217 concentrations.
- Representative inclusion in studies and trials should be a priority.

1 | BACKGROUND

The emerging approval of anti-amyloid beta (Aβ) disease-modifying therapies in reducing the load of Aβ[1–3] and slowing the rate of cognitive decline in early symptomatic Alzheimer's disease (AD)[1–4] underscores the importance of developing scalable measures to identify patients with AD pathology early, cost-effectively, and without bias. However, currently used bmeasures to identify AD pathology such as cerebrospinal fluid (CSF) analysis and Aβ positron emission tomography (Aβ-PET) are limited by their costliness and perceived invasiveness.[5,6]

Blood-based biomarkers (BBMs) present a new avenue of cost-effective, accurate, and scalable measures for identifying and predicting AD and AD pathology,[7–15] although depending on the clinical context of use, BBMs at their current stage of validation, may pose a higher cost compared to the current standard of care.[16] Indeed, BBMs performing as accurately as Aβ-PET have been incorporated into the revised AD criteria from the National Institute on Aging and the Alzheimer's Association (NIA-AA).[17] An abundance of BBMs have been examined, including the Aβ42/40 ratio, neurofilament light (NfL), and glial fibrillary acidic protein (GFAP), but especially tau phosphorylated at threonine 217 (p-tau217) has gained attention as an AD-specific biomarker.[5,18] Plasma p-tau217 is highly accurate in detecting AD pathology[19–22] and in distinguishing AD from non-AD neurodegenerative disorders,[12,23] and has proven to be more precise compared to p-tau181, p-tau231, and Aβ42/40 ratio.[13,19,24,25] It is important to note that certain non-AD conditions may also display increased concentrations of plasma p-tau217, such as amyotrophic lateral sclerosis, emphasizing the need to explore BBMs broadly.[26] Indeed, BBMs may be susceptible to being affected by different confounders complicating the interpretation, such as specific medical conditions, atypical disease presentations, or patients with uncertain etiologies, and certain ethnic or racial groups. Medical conditions such as reduced kidney function, diabetes, high blood pressure, and body mass may to some extent affect the BBMs, since these biomarkers are not limited to the central nervous system as in the case of the CSF.[27–36] This opens up a variety of potential effects on the BBMs that need to be explained and understood before clinical implementation. One potential confounder that needs to be understood is the effect of ethnicity and race.

Previous studies on CSF biomarkers and Aβ-PET have found differences in biomarker levels and diagnostic accuracies by ethnic or racial group.[37–43] However, what could drive these differences remains unknown, and the question continues in blood biomarker research as pointed out by several experts in the field.[17,18,44] According to a new systematic review, no agreement on whether ethnicity or race influences BBMs exists, as only a limited number of studies examined the influence of ethnicity or race.[45] Furthermore, the included studies originated exclusively from the United States and used mainly U.S.-specific racialized or minoritized categorizations such as Black and Non-Hispanic White.[45] Such socially defined racialized/minoritized categorizations may not be appropriate if potential biological or genetic aspects are attempted to be uncovered as such influences would more likely be related to geographic origin. Defining ethnicity by country of birth may be more suitable for a scientific basis of genetic influences.[46,47] This approach may reflect specific climates, haplotypes, diet, and diseases over generations, which could affect genetic predispositions and special susceptibility patterns to diseases such as AD.[48–51] To our knowledge, the influence of ethnicity on BBMs has never been examined in patients outside of the United States.

This study aimed to examine the influence of ethnicity on the diagnostic accuracy of plasma p-tau217 in identifying AD and CSF/Aβ-PET-verified AD pathology in a mixed memory clinic cohort.

2 | METHODS

2.1 | Patients

We retrospectively included consecutive foreign-born patients with complete diagnostic evaluations, including blood collection, at the memory clinic at Copenhagen University Hospital–Rigshospitalet, Denmark from January 1, 2020 to December 31, 2023, and at the memory clinic at Skåne University Hospital, Sweden from June 9, 2017 to March 5, 2024. All foreign-born patients were matched one-to-one on age and sex to random Danish-born memory clinic patients (Rigshospitalet, Denmark) with complete diagnostic evaluations between January 1, 2020 and December 31, 2023. The foreign-born patients have lived on average 39.6 (SD: 14.2) years in Denmark and 28.1 (SD: 15.0) years in Sweden. Memory clinic patients with hereditary neurogenetic disorders (e.g., Huntington's disease and spinocerebellar ataxia), without available plasma or with concurrent brain cancer were excluded. Table 1 displays the clinical characteristics of the cohort.

The diagnostic evaluations included medical history; neurological, physical, and cognitive examination; informant-based history when possible, standard laboratory blood work; and, for most patients, structural brain imaging (magnetic resonance imaging [MRI] or computer-

ized tomography [CT]) was also part of the evaluation. The diagnostic evaluations were often carried out with an interpreter. When deemed necessary, CSF biomarkers, [^{18}F]-fluorodeoxyglucose PET (FDG-PET), or Aβ-PET ([^{11}C] Pittsburgh compound B (PiB) or [^{18}F]-flutemetamol in Denmark and Sweden, respectively) aided the diagnostic evaluation. The Aβ-PET results were evaluated by a radiologist as normal or abnormal informed by the standardized uptake value ratio (SUVR).[52] CSF was analyzed in clinical routine as part of the diagnostic evaluation, and values were defined as abnormal or normal dependent on established cutoffs (Table S1). In the current study, patients were defined as having CSF/Aβ-PET-verified AD pathology if the Aβ-PET was abnormal or the CSF p-tau181/Aβ42 ratio was abnormal (Table S1). In cases of discrepancy, Aβ-PET took priority.

In Denmark, a multidisciplinary consensus conference established the diagnosis according to diagnostic criteria. The diagnosis of AD (possible/probable) followed the criteria by the NIA-AA for patients with mild cognitive impairment (MCI) and dementia.[53,54] Vascular dementia (VaD) was diagnosed using the criteria of the International Society of Vascular Behavioral and Cognitive Disorders (VasCog),[55] and patients with mixed AD with vascular pathology fulfilled the same criteria of possible AD and had significant cerebrovascular injury.[53] Frontotemporal dementia (FTD) was diagnosed according to the criteria for the behavioral variant,[56] the Gorno-Tempini criteria for the semantic variant, or the non-fluent aphasia variant of FTD.[57] Dementia with Lewy bodies (DLB) was diagnosed according to the fourth consensus report of the DLB consortium,[58] whereas Parkinson's disease with dementia and atypical Parkinson's syndromes (progressive supranuclear palsy and corticobasal degeneration) was diagnosed according to diagnostic criteria by the International Parkinson and Movement Disorder Society.[59,60]

In Sweden, the individual physician determined the diagnosis in case of typical disease presentation accompanied by supportive biomarkers. A consensus conference was held in cases of uncertainty or atypical presentation. The fifth edition and the revised version of the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders was used for clinical diagnoses.[61,62]

Patients were defined as "unspecified" if the initial diagnostic evaluation did not result in a clear diagnosis and further follow-up was needed. All clinical diagnoses were determined without knowledge of the plasma p-tau217 result.

The primary outcome in our study was the possible or probable clinical diagnosis of AD for both MCI and dementia; supplementary analyses used the CSF/Aβ-PET-verified AD pathology as the outcome. Information on the diagnostic techniques used by geographic origin, patient characteristics by memory clinics, and an overview of all diagnoses in the cohort can be found in Tables S2 and S4, respectively.

2.2 | Plasma collection and analysis

Blood was collected as part of the normal diagnostic evaluation at the memory clinics. Plasma was stored at −80°C within 2 hours of sampling. Single-batch analysis of plasma p-tau217 was carried out at Lund University on a Mesoscale Discovery (MSD) platform using an immuno-assay developed by Lilly Research Laboratories as described previously.[63]

The analyses were run in duplicate and randomized by AD diagnosis, age, sex, and ethnicity to minimize run-to-run variability. Plasma analyses were performed by personnel who were blinded to participant information.

RESEARCH IN CONTEXT

1. **Systematic review**: Studies on blood-based biomarkers for Alzheimer's disease (AD) have primarily examined homogeneous Western populations, leaving a gap in the real-world applicability of these novel biomarkers. Some U.S.-based studies have included ethnic or racial minority groups.
2. **Interpretation**: We found high diagnostic accuracy of plasma tau phosphorylated at threonine 217 (p-tau217) in identifying AD irrespective of geographic origin. Influences of certain medical conditions such as kidney function were found for all patient groups. Such medical conditions, however, may disproportionally affect minority ethnic groups as they are often more prevalent due to social determinants of health.
3. **Future directions**: These findings in a large diverse mixed memory clinic cohort indicate that the precision of plasma p-tau217 is unchanged across patients with different geographic origins. Future studies should prioritize broad representativeness in blood-based biomarker research as advancing knowledge on real-world applicability will aid in clinical implementation.

2.3 | Operationalization of ethnicity

To understand the influence of ethnicity on plasma p-tau217, patients were grouped into four geographic regions according to their country of birth, inspired by the United Nations division[64]: (1) Danish native-born as the reference group, (2) Geographic Greater Middle East, (3) Geographic Europe, and (4) Geographic Africa. Patients from geographic North America, South America, Oceania, East Asia, and most of South Asia were excluded from analyses of ethnicity because of small sample sizes. (See Table S5 for country specifications.)

2.4 | Covariates

Extensive sociodemographic information and information from the dementia evaluation were included in the current study. Information about the patients' age, sex, years of education, country of birth, cognitive status, and dementia syndrome was retrieved at the first

TABLE 1 Clinical characteristics by geographic origin.

	Native-born	Foreign-born	Greater Middle East	Europe	Africa	*p*-value
N	585	585	236	191	59	-
Copenhagen/Malmö clinic, n	585/0	448/137	186/50	136/55	55/4	< 0.001
Age, years, mean	68.5 (10.7)	68.6 (10.6)	65.9 (9.9)	70.8 (11.0)	67.7 (9.3)	< 0.001
Female sex, (%)	53.0%	51.5%	47.5%	55.0%	50.8%	0.409
Education, years, mean (SD)	11.7 (3.3)	10.1 (4.9)	9.4 (5.4)	10.5 (3.9)	7.9 (5.3)	< 0.001
Plasma p-tau217, pg/mL, median (IQR)	0.404 (0.273; 0.701)	0.347 (0.256; 0.585)	0.319 (0.242; 0.475)	0.416 (0.275; 0.721)	0.300 (0.240; 0.477)	< 0.001
AD or mixed AD, n (%)	230/585 (39.3%)	162/585 (27.7%)	40/236 (16.9%)	73/191 (38.2%)	11/59 (23.7%)	< 0.001
CSF/Aβ-PET-verified AD pathology, n (%)	151/258 (58.5%)	113/281 (40.2%)	31/108 (28.7%)	46/97 (47.4%)	10/28 (35.7%)	< 0.001
CSF Aβ42 pg/mL, median (IQR)	*N* = 233 748.0 (586.0; 960.0)	*N* = 256 842.5 (633.0; 1208.0)	*N* = 91 1020.0 (741.5; 1372.0)	*N* = 92 694.0 (560.0; 1051.0)	*N* = 26 875.0 (766.5; 1153.8)	< 0.001
CSF t-tau pg/mL, median (IQR)	*N* = 230 290.5 (200.0; 463.5)	*N* = 255 288.0 (206.5; 415.5)	*N* = 90 278.0 (203.5; 402.5)	*N* = 92 317.0 (225.0; 498.3)	*N* = 26 264.0 (179.5; 343.3)	0.286
CSF p-tau181 pg/mL, median (IQR)	*N* = 233 38.0 (21.0; 59.0)	*N* = 256 35.5 (23.0; 59.3)	*N* = 91 35.0 (22.5; 54.5)	*N* = 92 35.5 (24.0; 63.5)	*N* = 28 34.0 (21.5; 50.3)	0.732
CSF NfL pg/mL, median (IQR)	*N* = 139 1275.0 (934.8; 1809.5)	*N* = 184 1105.0 (678.3; 1870.0)	*N* = 70 930.0 (621.0; 1467.5)	*N* = 69 1400.0 (930.0;2230.0)	*N* = 11 1057.0 (505.0; 1323.0)	0.001
Standard bloodwork and BMI						
Body mass index, kg/m^2, median (IQR)	25.3 (22.5; 28.9)	26.4 (23.4; 30.0)	27.5 (24.6; 31.1)	25.8 (22.9; 28.9)	27.6 (24.5; 29.4)	< 0.001
eGFR, mL/min/1.73m^2, median (IQR)	82 (69;91)	85 (72; 94)	87 (75;96)	84 (69;93)	87.5 (76;94)	0.004
ALT, U/L, median (IQR)	22 (17;29)	21 (16.8; 29)	22 (17;30)	20.7 (15.6;27)	21 (18;29)	0.146
HbA1c, IFCC: mmol/mol, median (IQR)	38.3 (34.9; 41.7)	40.4 (36.9; 47.9)	42.4 (38.3; 53.1)	39 (35.5; 44)	41 (37.1; 45)	< 0.001
TSH, IU/L, median (IQR)	1.5 (1.1; 2.2)	1.5 (1.0; 2.3)	1.6 (1; 2.5)	1.6 (1; 2.2)	1.4 (1; 2.3)	0.774
Medical conditions						
Cumulative comorbidities, (%) (0–1/2–3/4–6)	61.9/32.0/6.2	46.7/40.3/13.0	39.8/42.4/17.8	48.7/41.9/9.4	54.2/35.6/10.2	< 0.001

Note: *p*-values are displayed for comparing native-born with the Greater Middle East, Europe, and Africa. Significance levels for continuous measures were established with the Kruskal–Wallis *H* test for non-normally distributed values and analysis of variance for normally distributed values; chi-square was used for categorical variables.

Abbreviation: AD, Alzheimer's disease; ALT, alanine transaminase; CSF, cerebrospinal fluid; eGFR, estimated glomerular filtration rate; HbA1c, hemoglobin A1c; IFCC, International federation of Clinical Chemistry; IQR, interquartile range; IU, international units; NfL, neurofilament Light; PET, positron emission tomography; p-tau, phosphorylated tau; SD, standard deviation; t-tau, total tau; TSH, thyroid-stimulating hormone.

TABLE 2 Clinical characteristics of the CSF/Aβ-PET examined patients.

	Aβ negative	Aβ positive	Differences
N	275	264	–
Plasma p-tau217, pg/mL, median (IQR)	0.286 (0.240; 0.374)	0.772 (0.531; 1.092)	< 0.001
Age, years, mean (SD)	67.3 (9.1)	69.9 (7.8)	< 0.001
Female sex, (%)	46.5%	58.0%	0.008
Geographic region, n (%)			
Native-born	107 (42.3%)	151 (63.4%)	
Geographic Africa	18 (7.1%)	10 (4.2%)	< 0.001
Geographic Europe	51 (20.2%)	46 (19.3%)	
Geographic Greater Middle East	77 (30.4%)	31 (13.0%)	
AD or Mixed AD, n (%)	30 (10.9%)	220 (83.3%)	< 0.001
Body mass index, kg/m^2, median (IQR)	26.6 (23.4; 30.4)	25.0 (22.5; 28.0)	< 0.001
eGFR, mL/min/1.73m^2, median (IQR)	86.0 (73.0; 95.5)	84.0 (72.0; 91.8)	0.041
ALT, U/L, median (IQR)	22.0 (17.0; 31.0)	22.0 (17.7; 28.8)	0.329
HbA1c, IFCC: mmol/mol, median (IQR)	39.7 (36.2; 48.1)	38.3 (35.5; 41.7)	< 0.001
Cumulative comorbidities, (%) (0–1/2–3/4–6)	52.7/38.2/9.1	64.0/32.2/3.8	0.006

Note: Significance levels for continuous measures were established with the Kruskal–Wallis *H* test for non-normally distributed values and analysis of variance for normally distributed values; chi-square was used for categorical variables.
Abbreviations: Aβ, amyloid beta; AD, Alzheimer's disease; ALT, alanine transaminase; CSF, cerebrospinal fluid; eGFR, estimated glomerular filtration rate; HbA1c, hemoglobin A1c; IFCC, international federation of Clinical Chemistry; IQR, interquartile range; p-tau, phosphorylated tau; PET, positron emission tomography; SD, standard deviation.

visit. A comorbidity burden index (0–13) was created from the presence/absence of diabetes, hypertension, hypercholesterolemia, stroke, kidney disease, liver disease, thyroid disease, ischemic heart disease, atrial fibrillation, depression, neuropathy, head trauma within 1 year, and sleep disorder. Furthermore, body mass index (BMI), creatinine, estimated glomerular filtration rate (eGFR), hemoglobin A1c (HbA1c), alanine transaminase (ALT), and thyroid-stimulating hormone (TSH) were included from the first visit.

2.5 | Statistics

The one-to-one matching of ethnic groups (native-born and foreign-born) on age and sex was performed via propensity scores to the nearest neighbor using the R package "MatchIt." The success of the matching was determined by a mean empirical cumulative distribution function below 0.1.

Differences between the native-born and foreign-born were determined by Wilcoxon rank-sum test or analysis of variance for continuous variables, and by chi-squared for categorical variables. All covariates included in the statistical analyses were selected a priori.

We performed linear regression with log-10 transformed plasma p-tau217 concentration as the dependent variable, AD as the main predictor, and medical conditions and sociodemographic information as covariates (excluding patients with unknown clinical diagnosis). The same analysis was also run in the CSF/Aβ-PET-examined patients. The standardized β-coefficients were used as an effect measure of the relative weight of each covariate. A forest plot was produced with the standardized β-coefficients with 95% confidence intervals (CIs) demonstrating the effect of each covariate on the plasma p-tau217 concentrations. The forest plot includes the coefficients for patients with AD and with CSF/Aβ-PET-verified AD pathology, respectively.

The ability of p-tau217 to identify AD was determined by 10-fold cross-validated logistic regression models to calculate the area under the receiver-operating characteristics (ROC) curve (AUC) in the whole cohort (excluding patients with unknown clinical diagnoses) and in the CSF/Aβ-PET-examined patients. The accuracies for these comparisons were estimated with and without the identified covariates from the linear regression. DeLong's test was used to determine the significance of differences between AUCs.

Post hoc analyses explored possible differences in plasma p-tau217 concentrations by geographic origin. To address this, we compared plasma p-tau217 concentration across geographic origins stratified by AD status. Furthermore, we examined the possible differences in diagnostic accuracies, sensitivities, and specificities across geographic origins using a pre-established plasma p-tau217 threshold developed at Lund University using Youden's index.

Statistical analyses were performed with RStudio (version 4.4.1). The full R script is freely available on Github (https://github.com/dkja0031/BlooDiv). Results were deemed statistically significant at $p < 0.05$.

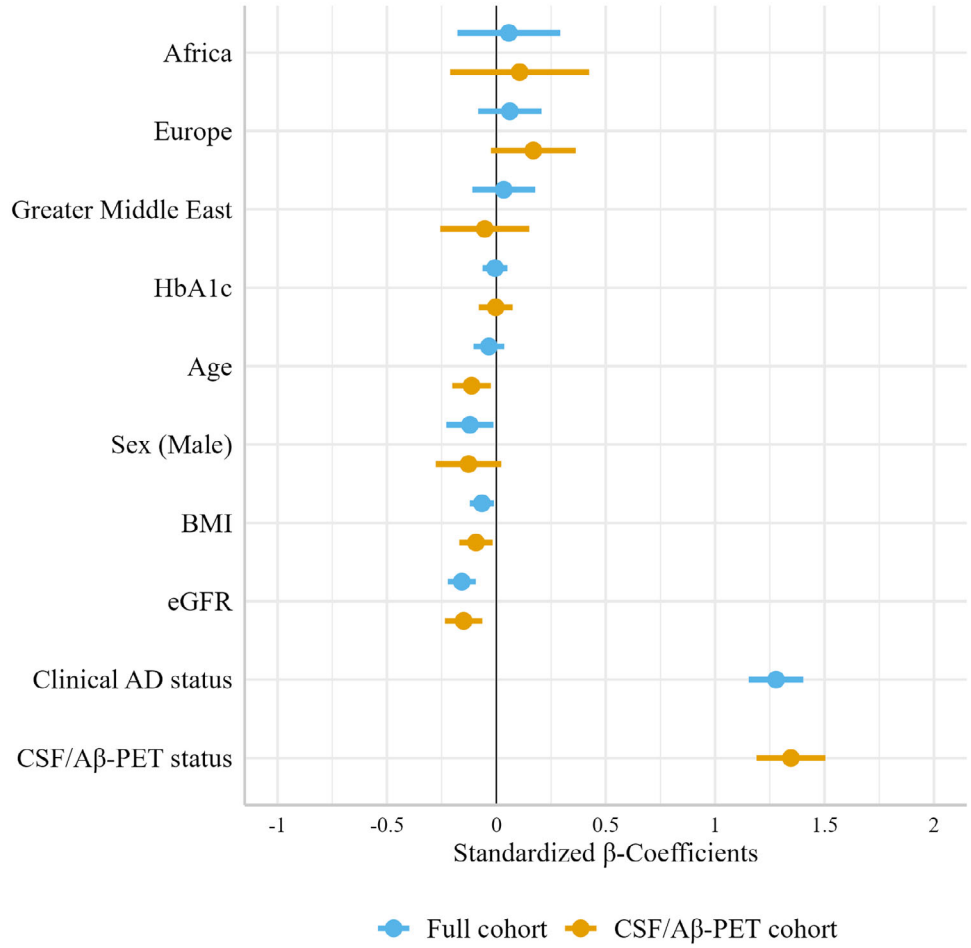


FIGURE 1 Covariate influences on plasma p-tau217 concentrations. Patients with unknown clinical diagnoses were excluded from the full cohort. Standardized β-coefficients of numeric variables were included as predictors (blue = AD; orange = CSF/Aβ-PET-examined). Plasma p-tau217 was log-transformed. Aβ-PET, amyloid beta; AD, Alzheimer's disease; BMI, body mass index; CSF, cerebrospinal fluid; eGFR, estimated glomerular filtration rate; HbA1c, hemoglobin A1c; p-tau217, phosphorylated tau-217; PET, positron emission tomography.

3 | RESULTS

3.1 | Demographics and clinical characteristics

The total cohort consisted of 1170 patients, of which 1033 were recruited from the memory clinic in Denmark and 137 from the memory clinic in Sweden. The one-to-one matching was successful, with mean empirical cumulative distribution functions below 0.1 for age and sex. There were no significant differences in age ($p > 0.05$) or sex ($p > 0.05$) between foreign-born and native-born patients.

Dividing the foreign-born patients into the four geographic regions (Table 1) revealed differences in age but not in sex (Table 1). Furthermore, significant differences were found for education, and AD frequency. Several medical conditions and standard clinical metrics differed by geographic region, such as BMI, eGFR, HbA1c, and cumulative diseases per patient. In contrast, no differences were found for ALT or TSH.

In an unmatched subset of patients ($N = 539$) the diagnostic evaluation was supported by data on CSF or Aβ-PET. The Aβ-positive patients differed significantly from the Aβ-negative patients in plasma p-tau217 concentrations (Table 2). The biomarker-positive group was older, included more females and more native-born patients, and differed in BMI, HbA1c, eGFR, and cumulative comorbidities (Table 2).

3.2 | Association between plasma p-tau217 concentrations and ethnicity

A multiple linear regression with log-transformed plasma p-tau217 concentrations as the dependent variable found statistically significant influences of AD status ($p < 0.001$), eGFR ($p < 0.001$), sex ($p = 0.028$), and BMI ($p = 0.019$), but not geographic origin (p-range = 0.402–0.643), HbA1c ($p = 0.832$), or age ($p = 0.342$) (Figure 1 and Table S6).

The same pattern emerged from the same statistical analysis in the CSF/Aβ-PET-examined patients. This analysis found statistically significant influences of CSF/Aβ-PET-verified AD pathology ($p < 0.001$), eGFR ($p < 0.001$), age ($p = 0.012$), and BMI ($p = 0.017$), but not geographic origin (p-range = 0.087 TO 0.609), HbA1c ($p = 0.944$), and sex ($p = 0.096$) on log-transformed plasma p-tau217 concentrations. Figure 1 displays

TABLE 3 Logistic regression models for AD identification.

	β	95% CI	p-value	OR (95% CI)
Base model				
Plasma p-tau217	5.112	4.487–6.022	< 0.001	185.883 (88.822; 412.552)
Ethnicity model				
Plasma p-tau217	5.112	4.368–5.916	< 0.001	166.063 (78.869; 371.069)
Africa	−0.757	−1.753–0.107	0.107	0.469 (0.173; 1.113)
Europe	−0.012	−0.493–0.461	0.961	0.988 (0.611; 1.586)
Greater Middle East	−0.996	−1.531 to -0.490	< 0.001	0.369 (0.216; 0.613)
Covariate model				
Plasma p-tau217	5.112	4.003–5.535	< 0.001	114.167 (54.779; 253.450)
BMI	−0.055	−0.098 to −0.012	0.013	0.947 (0.906; 0.988)
eGFR	0.012	0.005–0.032	0.006	1.019 (1.005; 1.033)
Age	0.105	0.079–0.132	< 0.001	1.110 (1.082; 1.141)
Sex	−0.301	−0.694–0.090	0.133	0.740 (0.499; 1.095)
Full model				
Plasma p-tau217	5.112	3.921–5.452	< 0.001	105.063 (50.447; 233.236)
Africa	−0.706	−1.727–0.207	0.149	0.494 (0.178; 1.230)
Europe	−0.239	−0.765–0.278	0.368	0.787 (0.465; 1.321)
Greater Middle East	−0.773	−1.345–-0.225	0.007	0.462 (0.260; 0.798)
BMI	−0.045	−0.089–-0.002	0.044	0.956 (0.915; 0.998)
eGFR	0.019	0.005–0.033	0.007	1.019 (1.005; 1.033)
Age	0.103	0.077–0.130	< 0.001	1.108 (1.080; 1.139)
Sex	−0.276	−0.673–0.119	0.171	0.759 (0.510; 1.127)

Note: Excluding one patient with extreme eGFR level (eGFR concentration = 6) did not change the results significantly.
Abbreviations: β, log-odds; BMI, body mass index; CI, confidence interval; eGFR, estimated glomerular filtration rate; OR, odds ratio; p-tau, phosphorylated tau.

the standardized β-coefficients with 95% CIS for the full cohort and the CSF/Aβ-PET-examined cohort. See Table S6 for numeric values.

3.3 | Influence of ethnicity on the diagnostic accuracy of plasma p-tau217

We created four logistic regression models to understand the possible influence of geographic region and other covariates on the diagnostic accuracy of plasma p-tau217: (1) Base model with only plasma p-tau217, (2) Ethnicity model with plasma p-tau217 and geographic origin, (3) Covariate model with plasma p-tau217, age, sex, eGFR, and BMI but excluding geographic origin, and (4) Full model with plasma p-tau217, age, sex, eGFR, BMI, and geographic origin. Other than the influence of plasma p-tau217, we also found significant influences of eGFR, BMI, age, and being from the Middle East, on the identification of AD (Table 3). For CSF/Aβ-PET-examined patients, plasma p-tau217, Middle Eastern origin, European origin, and age were statistically significant (Table S7).

Four corresponding k-fold cross-validated models based on logistic regression were created for the full cohort and the CSF/Aβ-PET-examined cohort with 10- and 5-folds, respectively. All AUCs had excellent accuracies for the whole cohort (AUC range: 0.883–0.910) and the CSF/Aβ-PET-examined cohort (AUC range: 0.886–0.905) (Figure 2). DeLong's test revealed no significant differences between the models within the whole cohort or the CSF/Aβ-PET-examined cohort. The metrics from each fold are reported in Table S8.

The prevalence of AD or mixed AD was significantly lower in the Middle East group (16.9%) compared to the native-born group (39.3%); this could explain the small but statistically significant effect of being from the Middle East on identification of AD in the logistic regression. Indeed, when comparing plasma p-tau217 concentrations within the AD and non-AD groups, there were no significant differences when stratified by geographic regions (*p*-range = 0.132–0.746) (Figure 3). Furthermore, when using a pre-established threshold from Lund University based on Youden's index no significant differences were found in accuracies, sensitivities, or specificities across geographic regions (Figure S1; Table S9).

4 | DISCUSSION

Our study suggests that ethnicity does not influence the diagnostic accuracy of plasma p-tau217 in identifying AD or amyloid pathology.

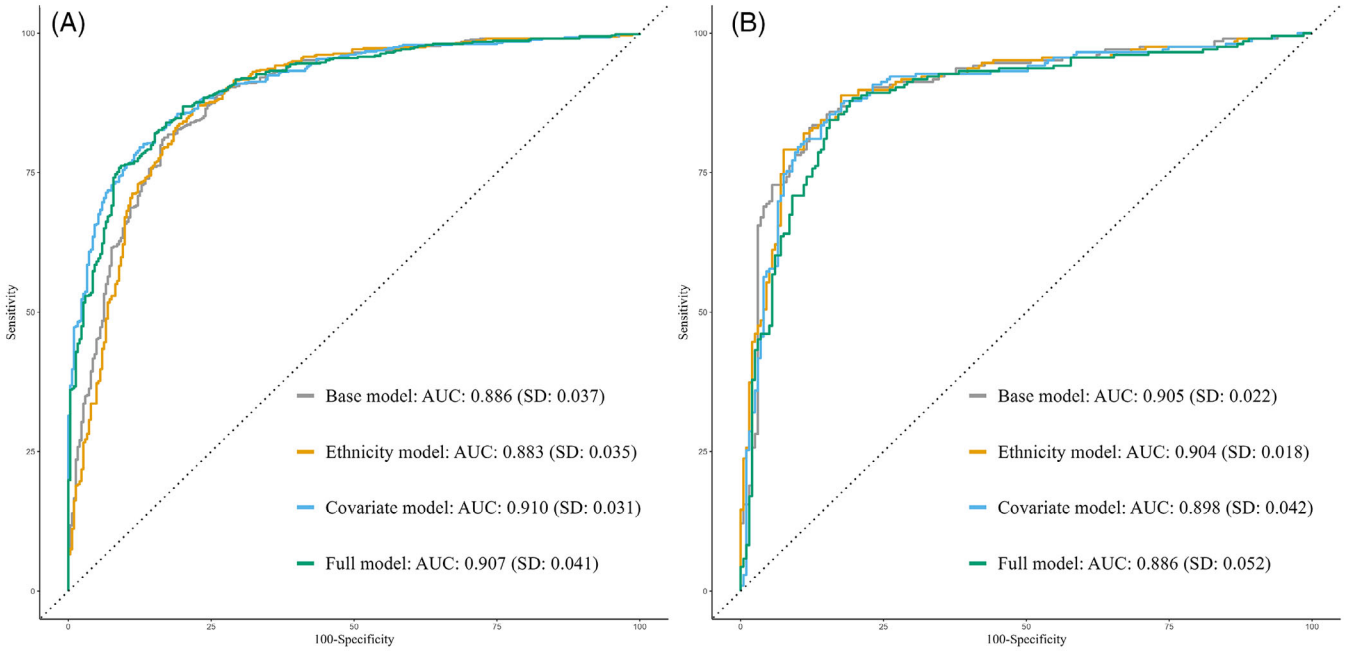


FIGURE 2 Diagnostic accuracy. Graph A = Full cohort, Graph B = CSF/Aβ-PET examined cohort. Base model: p-tau217. Ethnicity model: p-tau217 + geographic origin. Covariate model: p-tau217 + age + sex + BMI + eGFR. Full model: p-tau217 + geographic origin + age + sex + BMI + eGFR. Aβ, amyloid beta; AUC, area under the receiver-operating characteristic (ROC) curve; BMI, body mass index; CSF, cerebrospinal fluid; eGFR, estimated glomerular filtration rate; p-tau217, phosphorylated tau-217; PET, positron emission tomography; SD, standard deviation.

Furthermore, even in this large ethnically diverse mixed memory clinic cohort, we found high diagnostic accuracy irrespective of ethnicity and medical conditions. Indeed, p-tau217 displayed comparable high accuracies in our cohort in line with previous more homogeneous studies of plasma p-tau217 on an MSD platform.[12,13,22,23,25] This convincing precision in an ethnically diverse, mixed memory clinic cohort has been sought after by leading experts in the field.[5,17] It is important to note that although plasma p-tau217 is highly sensitive and identifies almost all patients with AD, the specificities are lower, implying worse positive predictive values. The results from the current paper using a single cut-off would, therefore, support plasma p-tau217 as a rule-out rather than a rule-in instrument of AD or amyloid pathology. To our knowledge, this is the largest study in a European setting to examine plasma biomarkers for AD and ethnicity.

Contradictory to our finding, previous studies indicated that ethnicity or race may influence the concentrations and accuracies of different plasma biomarkers.[45] For example, Brickman and colleagues found lower diagnostic accuracies for Hispanic compared to Non-Hispanic White and Black participants in identifying AD for plasma Aβ42/40, p-tau181, p-tau217, and NfL.[65] Similarly, Schindler and colleagues found race to be a significant covariate for p-tau181, p-tau231, and NfL in a logistic regression model with amyloid status as the outcome.[66] Both of these studies attribute the differences between ethnic and racial groups to societal factors rather than inherent biological or genetic differences, meaning that minoritized ethnic and racial groups represent certain social determinants of health that impact medical conditions. Other studies argue that ethnicity or race itself is the driving factor of differences in BBM concentrations and accuracies.[67,68] This would suggest that there are differences dependent on people's origin that cause AD to manifest differently. We find the former theory to be more likely, that it is the social consequences associated with ethnicity or racial group rather than genetic or inherent biological differences that promote differences. Supportive of this, Hajjar et al.,[69] who included both self-identified race and genetic ancestry in their analysis of plasma biomarkers, found that only self-identified race is influential, not genetic ancestry. Thus, including race or ethnic group may be misleading, as it was more likely the social determinants of health that the ethnic or racial group represent, rather than ethnicity and race in itself, that in turn affects medical conditions or research cohorts' composition, which influence plasma biomarkers.

Including representative minoritized groups is often a challenge in research. For example, our memory clinic cohort showed differences in disease distribution, with patients originating from the Middle East having a lower prevalence of AD or mixed AD (16.9% vs 39.3%) and a higher prevalence of affective disorder (23.7% vs 8.2%) and subjective cognitive decline (22.9% vs 14.2%) compared to the native-born patients. These differences were likely related to referral patterns, patients' help-seeking behavior, perceived stigma, and knowledge of dementia.[70,71]

In line with previous research, we found significant influences of reduced kidney function, BMI, and age on plasma p-tau217 concentrations.[27,35] Measures of kidney function especially had a significant influence; therefore extremely low renal function may be important to consider for correct interpretation to avoid false-positive interpretations. The influence of BMI and age are statistically significant, but their clinical relevance appears to be

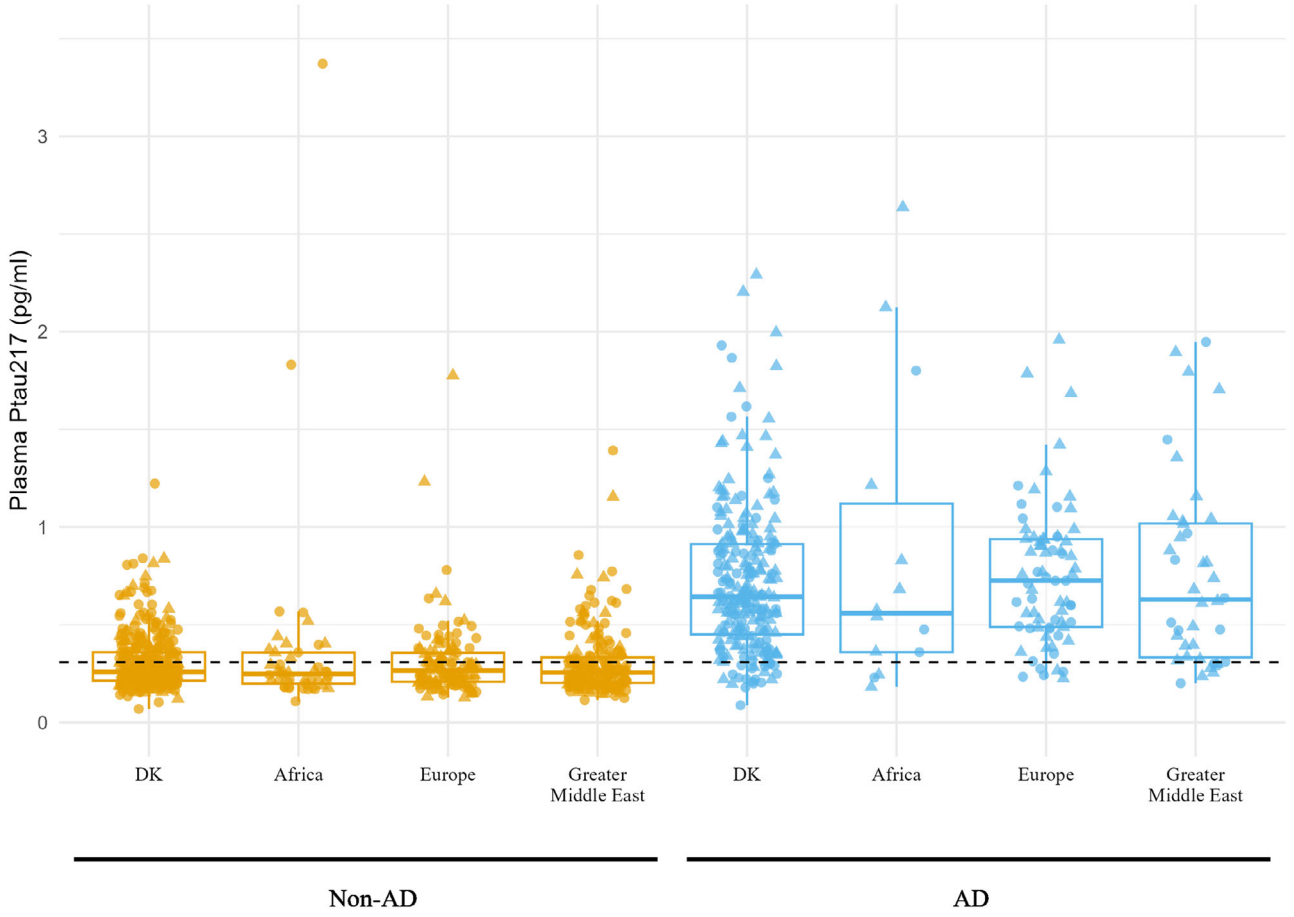


FIGURE 3 Plasma concentrations stratified by AD status and geographic origin. Orange = non-AD, Blue = AD. Circles = Clinically examined patients, Triangles = CSF/Aβ-PET examined patients. The horizontal line signifies the pre-established threshold of 0.308 pg/mL from Lund University based on Youden's index. The boxplot represents the interquartile range and median within the box, whereas the whiskers show the data range from 1.5 of the interquartile range value. Outliers are defined as the data points extending beyond the whiskers. AD, Alzheimer's disease; DK, Denmark; p-tau217, phosphorylated tau-217.

limited. It is notable that medical conditions potentially leading to reduced renal function are more frequently reported in ethnic and racial minority populations.[72] Therefore, false-positive results may be more frequently experienced in minority populations, making it even more important to include minority populations in BBM studies.

4.1 | Strengths and limitations

The primary strength of our study lies in the representativeness of our cohort. Five hundred eighty-five of the patients were foreign born originating from 91 different countries, making it possible to create geographic regions of origin to elude possible effects of ethnicity defined by geographic origin. Furthermore, to encompass a broader view of ethnicity, we included comprehensive sociodemographic and health-related information, as well as patients with severe or multiple health conditions. Indeed, ethnicity may represent differences in health care–seeking behavior and stigma, resulting in differences in severity and amount of health conditions. Finally, patients were included from two sites in different countries (Denmark and Sweden) to further promote representativeness.

Limitations arose primarily from the retrospective and observational study design. Selection bias through referral patterns or in who were selected by the clinician for CSF analysis or Aβ-PET may have influenced the results. Overcoming the potential selection bias is a challenging task, although we selected the patients in our cohort consecutively, there may be inherent selection bias regarding who is referred for dementia assessment by the general practitioner to secondary care in the first place. If a cultural or language barrier is present, the referring physician may have difficulty interpreting the patient's symptoms, and therefore could more likely refer patients without cognitive impairment or with psychiatric symptoms. Another limitation was the use of four different assays for the CSF reference standard. We performed supplementary analyses, splitting the cohort by which method was used, and generally found higher accuracies using the Aβ-PET and Lumipulse sub-cohort (Table S10). Using eGFR, sex, and age in statistical analyses may skew the coefficients because of multicollinearity, as age and sex are used in the calculation of eGFR. Finally, although we obtained extensive information about the patients,

genetic information such as apolipoprotein E (*APOE*) ε4 or haplotype was not available.

5 | CONCLUSIONS

In conclusion, ethnicity does not appear to influence the diagnostic accuracy of plasma p-tau217 in identifying AD or amyloid pathology in our mixed memory clinic cohort. AUCs were consistently above 0.88 for both AD diagnosis and amyloid pathology, demonstrating excellent diagnostic accuracy irrespective of ethnicity and medical conditions. We did find a small but significant effect of kidney function, BMI, and age on plasma p-tau217 concentrations, although severely low kidney function may be the only clinically significant variable to consider for the correct interpretation of plasma p-tau217. Our study implies that plasma p-tau217 can be interpreted independently of ethnicity defined by geographic origin. Moreover, the possible selection bias arising from our observational study design resulting in differing AD prevalence rates may be a shared challenge in other studies and clinical trials. Ensuring representativeness in BBM research should continue to be a priority to identify potential pitfalls from somatic and neurological disorders, certain medications, and specific ethnic groups.

ACKNOWLEDGMENTS

The authors would like to express our sincere gratitude to Theis Hornshøj Mouritsen and Jette Pedersen for their invaluable help with biobank procedures. We also thank the patients and clinical staff who have made this study possible. This work was supported by the Innovation Fund Denmark (grant number 1099-00022B), under the frame of ERA PerMed (reference number ERAPERMED2021-184). The Danish Dementia Research Centre (DDRC) is supported by the Danish Ministry of Health. A.H.S. was supported by the Absalon Foundation founded May 1, 1978. Work at Lund University was supported by the European Research Council (ADG-101096455), Alzheimer's Association (ZEN24-1069572, SG-23-1061717), GHR Foundation, Swedish Research Council (2022-00775), ERA PerMed (ERAPERMED2021-184), Knut and Alice Wallenberg foundation (2022-0231), Strategic Research Area MultiPark (Multidisciplinary Research in Parkinson's disease) at Lund University, Swedish Alzheimer Foundation (AF-980907), Swedish Brain Foundation (FO2021-0293), Parkinson foundation of Sweden (1412/22), Cure Alzheimer's fund, Rönström Family Foundation, Konung Gustaf V:s och Drottning Victorias Frimurarestiftelse, Skåne University Hospital Foundation (2020-O000028), Regionalt Forskningsstöd (2022-1259), and Swedish federal government under the ALF agreement (2022-Projekt0080). The funding sources had no role in the design and conduct of the study; in the collection, analysis, interpretation of the data; or in the preparation, review, or approval of the manuscript.

CONFLICT OF INTEREST STATEMENT

A.H.S. declares no conflicts of interest. A.O.D. declares no conflicts of interest. D.B. declares no conflicts of interest. D.K. declares no conflicts of interest. E.S. declares no conflicts of interest. G.W. declares no conflicts of interest. O.H. is an employee of Lund University and Eli Lilly. S.J. declares no conflicts of interest. S.P. has acquired research support (for the institution) from Avid and ki elements through ADDF. In the past 2 years, he has received consultancy/speaker fees from Bioartic, Biogen, Eisai, Eli Lilly, Novo Nordisk, and Roche. T.R.N. declares no conflicts of interest. Author disclosures are available in the Supporting Information.

CONSENT STATEMENT

The study was designed in accordance with the Declaration of Helsinki, and all patients provided written informed consent for their samples and clinical data to be used for research. The study was approved by the Regional Ethics Committee in the Capital Region Denmark (H-23035053), the Danish Data Protection Agency (p-2023-14275), and the Swedish Ethical Review Authority (2023-07108-01).

ORCID

Daniel Kjaergaard https://orcid.org/0000-0001-9955-8220

REFERENCES

1. Sims JR, Zimmer JA, Evans CD, et al. Donanemab in early symptomatic Alzheimer disease: the TRAILBLAZER-ALZ 2 randomized clinical trial. *JAMA*. 2023;330:512-527. doi:10.1001/jama.2023.13239
2. Budd Haeberlein S, Aisen PS, Barkhof F, et al. Two randomized phase 3 studies of aducanumab in early Alzheimer's disease. *J Prev Alzheimers Dis*. 2022;9:197-210. doi:10.14283/jpad.2022.30
3. van Dyck CH, Swanson CJ, Aisen P, et al. Lecanemab in early Alzheimer's disease. *N Engl J Med*. 2023;388:9-21. doi:10.1056/NEJMoa2212948
4. Mintun MA, Lo AC, Duggan Evans C, et al. Donanemab in early Alzheimer's disease. *N Engl J Med*. 2021;384:1691-1704. doi:10.1056/NEJMOA2100708
5. Schindler SE, Galasko D, Pereira AC, et al. Acceptable performance of blood biomarker tests of amyloid pathology—recommendations from the Global CEO Initiative on Alzheimer's Disease. *Nat Rev Neurol*. 2024;20:426-439. doi:10.1038/S41582-024-00977-5
6. Bonomi S, Gupta MR, Schindler SE. Inadequate reimbursement for lumbar puncture is a potential barrier to accessing new Alzheimer's disease treatments. *Alzheimers Dement*. 2023;19:5849-5851. doi:10.1002/ALZ.13473
7. Verberk IMW, Thijssen E, Koelewijn J, et al. Combination of plasma amyloid beta(1-42/1-40) and glial fibrillary acidic protein strongly associates with cerebral amyloid pathology. *Alzheimers Res Ther*. 2020;12:118. doi:10.1186/S13195-020-00682-7
8. Verberk IMW, Laarhuis MB, van den Bosch KA, et al. Serum markers glial fibrillary acidic protein and neurofilament light for prognosis and monitoring in cognitively normal older people: a prospective memory clinic-based cohort study. *Lancet Healthy Longev*. 2021;2:e87-e95. doi:10.1016/S2666-7568(20)30061-1
9. Pereira JB, Janelidze S, Stomrud E, et al. Plasma markers predict changes in amyloid, tau, atrophy and cognition in non-demented subjects. *Brain*. 2021;144:2826-2836. doi:10.1093/BRAIN/AWAB163
10. Pereira JB, Janelidze S, Smith R, et al. Plasma GFAP is an early marker of amyloid-β but not tau pathology in Alzheimer's disease. *Brain*. 2021;144:3505-3516. doi:10.1093/BRAIN/AWAB223
11. Palmqvist S, Tideman P, Cullen N, et al. Prediction of future Alzheimer's disease dementia using plasma phospho-tau combined with other accessible measures. *Nat Med*. 2021;27:1034-1042. doi:10.1038/S41591-021-01348-Z

12. Palmqvist S, Janelidze S, Quiroz YT, et al. Discriminative accuracy of plasma phospho-tau217 for Alzheimer disease vs other neurodegenerative disorders. *JAMA*. 2020;324:772-781. doi:10.1001/JAMA.2020.12134
13. Janelidze S, Palmqvist S, Leuzy A, et al. Detecting amyloid positivity in early Alzheimer's disease using combinations of plasma Aβ42/Aβ40 and p-tau. *Alzheimers Dement*. 2022;18:283-293. doi:10.1002/ALZ.12395
14. Karikari TK, Pascoal TA, Ashton NJ, et al. Blood phosphorylated tau 181 as a biomarker for Alzheimer's disease: a diagnostic performance and prediction modelling study using data from four prospective cohorts. *Lancet Neurol*. 2020;19:422-433. doi:10.1016/S1474-4422(20)30071-5
15. Den Braber A, Verberk IMW, Tomassen J, et al. Plasma biomarkers predict amyloid pathology in cognitively normal monozygotic twins after 10 years. *Brain Commun*. 2023;5:fcad024. doi:10.1093/BRAINCOMMS/FCAD024
16. Wimo A, Handels R, Blennow K, et al. Cost-effectiveness of diagnosing and treating patients with early Alzheimer's disease with anti-amyloid treatment in a clinical setting. *J Alzheimers Dis*. 2025;104(4):1167-1184. doi:10.1177/13872877251323231
17. Jack CR, Andrews JS, Beach TG, et al. Revised criteria for diagnosis and staging of Alzheimer's disease: Alzheimer's Association Workgroup. *Alzheimers Dement*. 2024;20(8):5143-5169. doi:10.1002/alz.13859
18. Hansson O, Edelmayer RM, Boxer AL, et al. The Alzheimer's Association appropriate use recommendations for blood biomarkers in Alzheimer's disease. *Alzheimers Dement*. 2022;18:2669-2686. doi:10.1002/ALZ.12756
19. Kivisäkk P, Fatima HA, Cahoon DS, et al. Clinical evaluation of a novel plasma pTau217 electrochemiluminescence immunoassay in Alzheimer's disease. *Sci Rep*. 2024;14:629. doi:10.1038/S41598-024-51334-X
20. Ashton NJ, Brum WS, Di Molfetta G, et al. Diagnostic accuracy of a plasma phosphorylated tau 217 immunoassay for Alzheimer disease pathology. *JAMA Neurol*. 2024;81:255-263. doi:10.1001/JAMANEUROL.2023.5319
21. Barthélemy NR, Salvadó G, Schindler SE, et al. Highly accurate blood test for Alzheimer's disease is similar or superior to clinical cerebrospinal fluid tests. *Nat Med*. 2024;30:1085-1095. doi:10.1038/S41591-024-02869-Z
22. Groot C, Cicognola C, Bali D, et al. Diagnostic and prognostic performance to detect Alzheimer's disease and clinical progression of a novel assay for plasma p-tau217. *Alzheimers Res Ther*. 2022;14:67. doi:10.1186/S13195-022-01005-8
23. Vandevrede L, La Joie R, Thijssen EH, et al. Evaluation of plasma phosphorylated tau217 for differentiation between Alzheimer disease and frontotemporal lobar degeneration subtypes among patients with corticobasal syndrome. *JAMA Neurol*. 2023;80:495-505. doi:10.1001/JAMANEUROL.2023.0488
24. Barthélemy NR, Horie K, Sato C, Bateman RJ. Blood plasma phosphorylated-tau isoforms track CNS change in Alzheimer's disease. *J Exp Med*. 2020;217:e20200861. doi:10.1084/JEM.20200861
25. Janelidze S, Bali D, Ashton NJ, et al. Head-to-head comparison of 10 plasma phospho-tau assays in prodromal Alzheimer's disease. *Brain*. 2023;146:1592-1601. doi:10.1093/BRAIN/AWAC333
26. Abu-Rumeileh S, Scholle L, Mensch A, et al. Phosphorylated tau 181 and 217 are elevated in serum and muscle of patients with amyotrophic lateral sclerosis. *Nat Commun*. 2025;16:2019. doi:10.1038/S41467-025-57144-7
27. Pichet Binette A, Janelidze S, Cullen N, et al. Confounding factors of Alzheimer's disease plasma biomarkers and their impact on clinical performance. *Alzheimers Dement*. 2023;19:1403-1414. doi:10.1002/ALZ.12787
28. Simonsen AH, Gleerup HS, Musaeus CS, et al. Neurofilament light chain levels in serum among a large mixed memory clinic cohort: confounders and diagnostic usefulness. *Alzheimers Dement*. 2023;15:e12512. doi:10.1002/DAD2.12512
29. Koini M, Pirpamer L, Hofer E, et al. Factors influencing serum neurofilament light chain levels in normal aging. *Aging*. 2021;13:25729-25738. doi:10.18632/AGING.203790
30. O'Bryant SE, Petersen M, Hall J, Johnson LA. Medical comorbidities and ethnicity impact plasma Alzheimer's disease biomarkers: important considerations for clinical trials and practice. *Alzheimers Dement*. 2023;19:36-43. doi:10.1002/ALZ.12647
31. Fitzgerald KC, Sotirchos ES, Smith MD, et al. Contributors to serum NfL levels in people without neurologic disease. *Ann Neurol*. 2022;92:688-698. doi:10.1002/ANA.26446
32. Wu J, Xiao Z, Wang M, et al. The impact of kidney function on plasma neurofilament light and phospho-tau 181 in a community-based cohort: the Shanghai Aging Study. *Alzheimers Res Ther*. 2024;16:32. doi:10.1186/S13195-024-01401-2
33. Sarto J, Esteller-Gauxax D, Tort-Merino A, et al. Impact of demographics and comorbid conditions on plasma biomarkers concentrations and their diagnostic accuracy in a memory clinic cohort. *J Neurol*. 2024;271:1973-1984. doi:10.1007/S00415-023-12153-8
34. Hayden KM, Mielke MM, Evans JK, et al. Association between Modifiable Risk Factors and Levels of Blood-Based Biomarkers of Alzheimer's and Related Dementias in the Look AHEAD Cohort. *JAR Life*. 2024;13:1-21. doi:10.14283/JARLIFE.2024.1
35. Syrjanen JA, Campbell MR, Algeciras-Schimnich A, et al. Associations of amyloid and neurodegeneration plasma biomarkers with comorbidities. *Alzheimers Dement*. 2022;18:1128-1140. doi:10.1002/ALZ.12466
36. Janelidze S, Barthélemy NR, He Y, Bateman RJ, Hansson O. Mitigating the associations of kidney dysfunction with blood biomarkers of Alzheimer disease by using phosphorylated tau to total tau Ratios. *JAMA Neurol*. 2023;80:516-522. doi:10.1001/JAMANEUROL.2023.0199
37. Lebrun L, Hanseeuw B, van Pesch V, Ivanoiu A. Alzheimer disease's cerebrospinal fluid biomarkers differences between immigrants and natives in a Belgian memory clinic. *Acta Neurol Belg*. 2023;123:537-544. doi:10.1007/S13760-022-02143-4
38. Gleason CE, Zuelsdorff M, Gooding DC, et al. Alzheimer's disease biomarkers in Black and non-Hispanic White cohorts: a contextualized review of the evidence. *Alzheimers Dement*. 2022;18:1545-1564. doi:10.1002/ALZ.12511
39. Modeste ES, Ping L, Watson CM, et al. Quantitative proteomics of cerebrospinal fluid from African Americans and Caucasians reveals shared and divergent changes in Alzheimer's disease. *Mol Neurodegener*. 2023;18:48. doi:10.1186/S13024-023-00638-Z
40. Chaudhry A, Rizig M. Comparing fluid biomarkers of Alzheimer's disease between African American or Black African and white groups: a systematic review and meta-analysis. *J Neurol Sci*. 2021;421:117270. doi:10.1016/J.JNS.2020.117270
41. Morris JC, Schindler SE, McCue LM, et al. Assessment of racial disparities in biomarkers for Alzheimer disease. *JAMA Neurol*. 2019;76:264-273. doi:10.1001/JAMANEUROL.2018.4249
42. Howell JC, Watts KD, Parker MW, et al. Race modifies the relationship between cognition and Alzheimer's disease cerebrospinal fluid biomarkers. *Alzheimers Res Ther*. 2017;9:88. doi:10.1186/S13195-017-0315-1
43. Deters KD, Napolioni V, Sperling RA, et al. Amyloid PET imaging in self-identified Non-Hispanic Black participants of the anti-amyloid in asymptomatic Alzheimer's disease (A4) study. *Neurology*. 2021;96:E1491-E1500. doi:10.1212/WNL.0000000000011599
44. Karikari TK. Blood tests for Alzheimer's disease: increasing efforts to expand and diversify research participation is critical for widespread validation and acceptance. *J Alzheimers Dis*. 2022;90:967-974. doi:10.3233/JAD-215730

45. Kjaergaard D, Simonsen AH, Waldemar G, Nielsen TR. Ethnic and racial influences on blood biomarkers for Alzheimer's disease: a systematic review. *J Alzheimers Dis*. 2025;103:81-91. doi:10.1177/13872877241299047
46. Hunter P. The genetics of human migrations: our ancestors migration out of Africa has left traces in our genomes that explain how they adapted to new environments. *EMBO Rep*. 2014;15:1019. doi:10.15252/EMBR.201439469
47. Karlsson EK, Kwiatkowski DP, Sabeti PC. Natural selection and infectious disease in human populations. *Nat Rev Genet*. 2014;15:379-393. doi:10.1038/NRG3734
48. Evans W, Fung HC, Steele J, et al. The tau H2 haplotype is almost exclusively Caucasian in origin. *Neurosci Lett*. 2004;369:183-185. doi:10.1016/J.NEULET.2004.05.119
49. Le Guen Y, Raulin AC, Logue MW, et al. Association of African Ancestry-Specific APOE missense variant R145C with risk of Alzheimer disease. *JAMA*. 2023;329:551-560. doi:10.1001/JAMA.2023.0268
50. Qin W, Li W, Wang Q, et al. Race-related association between APOE genotype and Alzheimer's disease: a systematic review and meta-analysis. *J Alzheimers Dis*. 2021;83:897-906. doi:10.3233/JAD-210549
51. Templeton AR. Haplotype trees and modern human origins. *Am J Phys Anthropol*. 2005;Suppl 41:33-59. doi:10.1002/AJPA.20351
52. Ladefoged CN, Anderberg L, Madsen K, et al. Estimation of brain amyloid accumulation using deep learning in clinical [11C]PiB PET imaging. *EJNMMI Phys*. 2023;10:44. doi:10.1186/S40658-023-00562-7
53. McKhann GM, Knopman DS, Chertkow H, et al. The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement*. 2011;7:263-269. doi:10.1016/J.JALZ.2011.03.005
54. Albert MS, DeKosky ST, Dickson D, et al. The diagnosis of mild cognitive impairment due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement*. 2011;7:270. doi:10.1016/J.JALZ.2011.03.008
55. Sachdev P, Kalaria R, O'Brien J, et al. Diagnostic criteria for vascular cognitive disorders: a VASCOG statement. *Alzheimer Dis Assoc Disord*. 2014;28:206-218. doi:10.1097/WAD.0000000000000034
56. Rascovsky K, Hodges JR, Knopman D, et al. Sensitivity of revised diagnostic criteria for the behavioural variant of frontotemporal dementia. *Brain*. 2011;134:2456-2477. doi:10.1093/BRAIN/AWR179
57. Gorno-Tempini ML, Hillis AE, Weintraub S, et al. Classification of primary progressive aphasia and its variants. *Neurology*. 2011;76:1006. doi:10.1212/WNL.0B013E31821103E6
58. McKeith IG, Boeve BF, Dickson DW, et al. Diagnosis and management of dementia with Lewy bodies: fourth consensus report of the DLB Consortium. *Neurology*. 2017;89:88-100. doi:10.1212/WNL.0000000000004058
59. Emre M, Aarsland D, Brown R, et al. Clinical diagnostic criteria for dementia associated with Parkinson's disease. *Mov Disord*. 2007;22:1689-1707. doi:10.1002/MDS.21507
60. Höglinger GU, Respondek G, Stamelou M, et al. Clinical diagnosis of progressive supranuclear palsy: the movement disorder society criteria. *Mov Disord*. 2017;32:853-864. doi:10.1002/MDS.26987
61. American Psychiatric Association. Diagnostic and statistical manual of mental disorders. *Diagnostic and Statistical Manual of Mental Disorders*. 2013. doi:10.1176/APPI.BOOKS.9780890425596
62. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. *Diagnostic and Statistical Manual of Mental Disorders* 2022. doi:10.1176/APPI.BOOKS.9780890425787
63. Bali D, Hansson O, Janelidze S. Effects of certain pre-analytical factors on the performance of plasma phospho-tau217. *Alzheimers Res Ther*. 2024;16:31. doi:10.1186/S13195-024-01391-1
64. United Nations Statistics Division. *Methodology: Standard Country or Area Codes for Statistical Use (M49)*. United Nations; 1997. https://unstats.un.org/unsd/methodology/m49/
65. Brickman AM, Manly JJ, Honig LS, et al. Plasma p-tau181, p-tau217, and other blood-based Alzheimer's disease biomarkers in a multiethnic, community study. *Alzheimers Dement*. 2021;17:1353-1364. doi:10.1002/ALZ.12301
66. Schindler SE, Karikari TK, Ashton NJ, et al. Effect of race on prediction of brain amyloidosis by plasma Aβ42/Aβ40, phosphorylated tau, and neurofilament light. *Neurology*. 2022;99:E245-E257. doi:10.1212/WNL.0000000000200358
67. O'Bryant SE, Petersen M, Hall J, Johnson LA. Medical comorbidities and ethnicity impact plasma Alzheimer's disease biomarkers: important considerations for clinical trials and practice. *Alzheimers Dement*. 2023;19:36-43. doi:10.1002/ALZ.12647
68. Hall JR, Petersen M, Johnson L, O'Bryant SE. Characterizing plasma biomarkers of Alzheimer's in a diverse community-based cohort: a cross-sectional study of the HAB-HD cohort. *Front Neurol*. 2022;13:871947. doi:10.3389/FNEUR.2022.871947
69. Hajjar I, Yang Z, Okafor M, et al. Association of plasma and cerebrospinal fluid Alzheimer disease biomarkers with race and the role of genetic ancestry, vascular comorbidities, and neighborhood factors. *JAMA Netw Open*. 2022;5:E2235068. doi:10.1001/JAMANETWORKOPEN.2022.35068
70. Nielsen TR, de Mendonça A, Frölich L, et al. Assessment of dementia in minority ethnic groups in Europe: a 14-year follow-up survey. *Int J Geriatr Psychiatry*. 2024;39:e70034. doi:10.1002/GPS.70034
71. Nielsen TR, Vogel A, Phung TKT, Gade A, Waldemar G. Over- and under-diagnosis of dementia in ethnic minorities: a nationwide register-based study. *Int J Geriatr Psychiatry*. 2011;26:1128-1135. doi:10.1002/GPS.2650
72. Lopez-Neyman SM, Davis K, Zohoori N, Broughton KS, Moore CE, Miketinas D. Racial disparities and prevalence of cardiovascular disease risk factors, cardiometabolic risk factors, and cardiovascular health metrics among US adults: nHANES 2011-2018. *Sci Rep*. 2022;12:19475. doi:10.1038/S41598-022-21878-X

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Kjaergaard D, Nielsen TR, Stomrud E, et al. Influence of ethnicity on the diagnostic accuracy of plasma p-tau217 for the identification of Alzheimer's disease: A consecutive mixed memory clinic cohort study. *Alzheimer's Dement*. 2025;21:e70315. https://doi.org/10.1002/alz.70315

Supplementary materials – Study 3

Supplementary Table 1

Copenhagen University Hospital	Assay	Platform	P-tau181/Aβ^{42} ratio cut-off	Source
2020-2022	Innotest	Enzyme-linked immunosorbent assay (ELISA)	17.7 (reversed)	Keshavan et al., 2020 *(DOI: 10.1002/dad2.12131)*
July 2022 - 2023	Elecsys version 2	Electrochemiluminescence immunoassay (ECLIA)	0.023	Blennow et al., 2022 *(DOI: 10.1515/cclm-2022-0516)*

Skåne University Hospital	Assay	Platform	P-tau181/Aβ^{42} ratio cut-off	Source
2017- Oct. 2019	MSD assay	Electrochemiluminescence (ECL)	9.89 (reversed)	Janelidze et al., 2017 *(DOI: 10.1001/jamaneurol.2017.2814)*
Nov 2019 – 2024	Lumipulse	Chemiluminescent enzyme immunoassay (CLEIA)	0.072	Willemse et al., 2021 *(DOI: 10.1002/dad2.12182)*

Note: CSF values above or below the limits of quantification were handled by imputing the threshold values. Innotest (N=233), Elecsys (N=172), MSD (N=37), Lumipulse (N=97).
Abbreviations: Aβ = Amyloid-β, CLEIA = Chemiluminescent enzyme immunoassay, ECL = Electrochemiluminescence, ECLIA = Electrochemiluminescence immunoassay, ELISA = Enzyme-linked immunosorbent assay, MSD = Meso Scale Discover, p-tau = phosphorylated tau.

Supplementary Table 2: Diagnostic techniques used by geographic origin

	Native-born	Foreign-born	Greater Middle East	Europe	Africa
N	585	585	236	191	59
CSF or Aβ-PET used	261 (44.6%)	284 (48.5%)	110 (46.6%)	98 (51.3%)	28 (47.5%)
Structural brain scan					
MTA reported	431 (73.7%)	453 (77.4%)	176 (74.6%)	148 (77.5%)	52 (88.1%)
GCA reported	426 (72.8%)	409 (69.9%)	170 (72.0%)	127 (66.5%)	45 (76.3%)
Fazekas reported	494 (84.4%)	447 (76.4%)	179 (75.8%)	143 (74.9%)	49 (83.1%)
Interpreter used (% Yes)	0 (0%)	238 (40.8%)	115 (48.7%)	72 (37.7%)	19 (32.8%)

Note: Most patients do have a structural brain scan, but MTA, GCA, or Fazekas were not reported for all patients.

Abbreviations: Aβ-PET = Amyloid-β Positron Emission Tomography, CSF = Cerebrospinal fluid, GCA = Global Cortical Atrophy, MTA = Medial Temporal Atrophy.

Supplementary Table 3: Characteristics by memory clinic

	Copenhagen clinic (N = 1033)	Malmö clinic (N = 137)	P-value
Geographic origin (N)			
Native-born	585	0	< .001
Greater Middle East	186	50	
Europe	136	55	
Africa	55	4	
Age, years	68.6 (10.8)	68.7 (9.6)	.920
Sex (% female)	51.7%	56.2%	.321
Education, years	11.0 (4.1)	9.9 (4.9)	.004
Diagnosis after assessment			
AD or mixed	343/1033 (33.2%)	49/137 (35.8%)	< .001
VaD	108/1033 (10.5%)	15/137 (10.9%)	
DLB	26/1033 (2.5%)	3/137 (2.2%)	
FTD, SD, nfPPA	22/1033 (2.1%)	8/137 (5.9%)	
SCD	178/1033 (17.2%)	11/137 (8.0%)	
Affective disorder	125/1033 (12.1%)	18/137 (13.1%)	
Other	231/1033 (22.4%)	33/137 (24.1%)	
CSF/Aβ-PET AD pathology (%)	213/405 (52.6%)	51/134 (38.1%)	.004
Body mass index (kg/m^2)	25.9 [22.8; 29.2]	27.1 [23.8; 31.6]	.008
eGFR ($mL/min/1.73m^2$)	83 [69;92]	89 [73; 97]	.001
HbA1c (IFCC: mmol/mol)	39.0 [35.5; 43.3]	40.0 [36.0; 46.8]	.028

Abbreviations: Aβ-PET = Amyloid-β Positron Emission Tomography, AD = Alzheimer's Disease, CPH = Copenhagen, CSF = Cerebrospinal Fluid, DK = Denmark, DLB = Dementia with Lewy Bodies, FTD = Frontotemporal Dementia, eGFR = Estimated Glomerular Filtration Rate, HbA1c = Hemoglobin A1c, nfPPA = Non-fluent Primary Progressive Aphasia, SCD = Subjective Cognitive Decline, SD = Semantic dementia, VaD = Vascular Dementia.

Supplementary Table 4: Diagnoses in the cohort

	N (%)
Clinical diagnoses	
AD	336 (28.7%)
SCD	189 (16.2%)
Affective disorder	143 (12.2%)
VaD	123 (10.5%)
Unknown	110 (9.4%)
*Other-specified**	57 (4.9%)
NPH	57 (4.9%)
Mixed AD	56 (4.8%)
DLB	29 (2.5%)
Alcohol	27 (2.3%)
bvFTD	18 (1.5%)
aPD†	8 (0.7%)
SD	7 (0.6%)
nfPPA	5 (0.4%)
PD	5 (0.4%)
Cognitive status	
SCD	241 (20.6%)
MCI	350 (29.9%)
Mild dementia	320 (27.4%)
Moderate dementia	200 (17.1%)
Severe dementia	13 (1.1%)
Undecided	46 (3.9%)

Note: *****Other-specified: Multifactorial somatic (N=30), TBI/hemorrhage/meningioma (N=8), Other neurological disorders (N=6), Neurodevelopmental disorders (N=5), Drug abuse/vitamin deficiency (N=5), Sleep disorders (N=3).

† Progressive Supranuclear paresis (N=7), corticobasal degeneration (N=1).

Abbreviations: AD = Alzheimer's disease, aPD = atypical Parkinson's Disease, bvFTD = behavioral variant Frontotemporal Dementia, DLB = Dementia with Lewy Bodies, MCI = Mild Cognitive Impairment, nfPPA = Non-fluent Primary Progressive Aphasia, NPH = Normal Pressure Hydrocephalus, PD = Parkinson's Disease, SD = Semantic Dementia, SCD = Subjective Cognitive Decline, VaD = Vascular Dementia.

Supplementary Table 5: Country of birth

Geographic region	Country	N
Native-born	Denmark	585
Geographic Greater Middle East	Türkiye	59
	Pakistan	46
	Iran	41
	Iraq	37
	Afghanistan	15
	Syria	14
	Lebanon	10
	Israel	4
	Yemen	4
	Palestine	2
	Armenia	1
	Azerbaijan	1
	Georgia	1
	Qatar	1
Geographic Africa	Morocco	25
	Somalia	9
	Algeria	5
	Egypt	4
	Tunisia	4
	Gambia	2
	Ghana	2
	Uganda	2
	Eritrea	1
	Ethiopia	1
	Guinea	1
	Rwanda	1
	South Africa	1
	Sudan	1
Geographic Europe	North Macedonia	24
	Poland	24
	Bosnia	17
	Faroe Islands	12
	Germany	10
	England	8
	Kosovo	7
	Former Yugoslavia	7
	Finland	6
	Greenland	6
	Norway	6
	Ukraine	6
	Albania	4

	Hungary	5
	Romania	5
	Russia	5
	Serbia	4
	Austria	4
	Greece	4
	Croatia	3
	France	3
	Iceland	3
	Italy	3
	Ireland	2
	Lithuania	2
	Netherlands	2
	Spain	2
	Belarus	1
	Bulgaria	1
	Czechoslovakia	1
	Montenegro	1
	Portugal	1
	Slovakia	1
	Slovenia	1

Note: The following countries and their sample size were not grouped into larger geographic regions*: Argentina (3), Australia (3), Barbados (1), Bolivia (3), Brazil (4), Central America (1), Chile (11), China (9), Colombia (2), Cuba (2), El Salvador (1), India (13), Indonesia (2), Jamaica (1), Japan (4), Korea (1), Malaysia (1), Mexico (1), New Zealand (1), Papua New Guinea (1), Philippines (4), Sri Lanka (2), Taiwan (2), Thailand (8), Trinidad (1), Uruguay (2), USA (7), Vietnam (8).*

Supplementary Table 6: Linear regression of plasma p-tau217 with standardized coefficients

	Full cohort				CSF/Aβ-PET-examined cohort			
	B	**B^{std}**	**95% CI^{std}**	**p-value**	**B**	**B^{std}**	**95% CI^{std}**	**p-value**
AD status	0.796	1.278	1.153 to 1.403	< .001	0.879	1.347	1.189 to 1.504	< .001
eGFR	-0.005	-0.158	-0.222 to -0.094	< .001	-0.006	-0.150	-0.235 to -0.064	< .001
BMI	-0.008	-0.066	-0.121 to -0.011	.019	-0.013	-0.093	-0.169 to -0.017	.017
Sex	-0.075	-0.121	-0.228 to -0.013	.028	-0.083	-0.127	-0.277 to 0.023	.096
Age	0.002	-0.034	-0.104 to 0.036	.342	-0.009	-0.113	-0.202 to -0.025	.012
HbA1c	-0.0008	-0.006	-0.063 to 0.051	.832	-0.001	-0.003	-0.080 to 0.075	.944
Africa	0.029	0.057	-0.178 to 0.292	.633	0.075	0.107	-0.211 to 0.424	.509
Europe	0.021	0.062	-0.083 to 0.207	.402	0.083	0.169	-0.025 to 0.263	.087
Greater Middle East	0.012	0.034	-0.110 to 0.178	.643	-0.038	-0.053	-0.256 to 0.150	.609

Note: We excluded patients with unknown clinical diagnoses from the full cohort. Standardized B-coefficients were included as predictors. Plasma p-tau217 was log-transformed.

Abbreviations: AD = Alzheimer's Disease, B^{std} = Standardized Beta Coefficients, BMI = Body Mass Index, CI = Confidence Interval, eGFR = Estimated Glomerular Filtration Rate, HbA1c = Hemoglobin A1

Supplementary Table 7: Logistic regression models for AD pathology identification in CSF/Aβ-PET-examined patients

Base model		**B**	**95% CI**	**p-value**	**OR (95% CI)**
	Plasma p-tau217	5.714	4.613 to 6.954	< .001	303.138 (100.794; 1047.901)
Geographic model		**B**	**95% CI**	**p-value**	**OR (95% CI)**
	Plasma p-tau217	5.546	4.448 to 6.784	< .001	256.275 (85.415; 883.616)
	Africa	-0.516	-1.671 to 0.547	.357	0.597 (0.188; 1.728)
	Europe	-0.768	-1.484 to -0.081	.031	0.464 (0.227; 0.922)
	Greater Middle East	-0.916	-1.610 to -0.252	.008	0.400 (0.200; 0.777)
Covariate model		**B**	**95% CI**	**p-value**	**OR (95% CI)**
	Plasma p-tau217	5.569	4.475 to 6.804	< .001	262.192 (87.826; 901.620)
	BMI	-0.021	-0.078 to 0.035	.465	0.979 (0.925; 1.035)
	eGFR	0.013	-0.006 to 0.033	.179	1.013 (0.994; 1.033)
	Age	0.056	0.017 to 0.096	.005	1.057 (1.017; 1.100)
	Sex	-0.207	-0.731 to 0.318	.439	0.813 (0.481; 1.374)
Full model		**B**	**95% CI**	**p-value**	**OR (95% CI)**
	Plasma p-tau217	5.435	4.346 to 6.665	< .001	229.236 (77.179; 784.288)
	Africa	-0.464	-1.648 to 0.637	.422	0.629 (0.192; 1.891)
	Europe	-0.920	-1.656 to -0.213	.012	0.399 (0.191; 0.808)
	Greater Middle East	-0.858	-1.572 to -0.172	.016	0.424 (0.208; 0.842)
	BMI	-0.014	-0.072 to 0.042	.625	0.986 (0.930; 1.043)
	eGFR	0.015	-0.072 to 0.035	.129	1.015 (0.996; 1.036)
	Age	0.060	0.020 to 0.101	.004	1.062 (1.020; 1.107)
	Sex	-0.215	-0.751 to 0.320	.430	0.806 (0.472; 1.377)

Abbreviations: B = Log-odds, BMI = Body Mass Index CI = Confidence Interval, eGFR = Estimated Glomerular Filtration Rate, OR = Odds ratio.

Supplementary Table 8: AUC for each fold from Figure 2

	Full cohort				CSF/Aβ cohort			
FOLD	**Base model**	**Ethnicity model**	**Covariate model**	**Full model**	**Base model**	**Ethnicity model**	**Covariate model**	**Full model**
1	0.898	0.914	0.928	0.905	0.878	0.886	0.894	0.880
2	0.813	0.860	0.930	0.935	0.910	0.897	0.890	0.815
3	0.862	0.875	0.882	0.872	0.925	0.897	0.919	0.962
4	0.855	0.891	0.898	0.954	0.928	0.900	0.952	0.888
5	0.946	0.880	0.941	0.882	0.891	0.934	0.838	0.889
6	0.889	0.885	0.940	0.822				
7	0.927	0.907	0.917	0.880				
8	0.896	0.799	0.872	0.935				
9	0.893	0.919	0.859	0.940				
10	0.878	0.899	0.944	0.930				

Note: Base model = plasma p-tau217 alone, Ethnicity model = plasma p-tau217 + geographic origin, Covariate model = plasma p-tau217 + age + sex + eGFR + body mass index, Full model = plasma p-tau217 + geographic origin + age + sex + eGFR + body mass index.

Supplementary Table 9: P-tau217 accuracy by preestablished cutoff stratified by geographic region

	Full cohort			
	Denmark	**Greater Middle East**	**Europe**	**Africa**
Accuracy	0.756 (0.721-0.791)	0.720 (0.665-0.775)	0.754 (0.702-0.806)	0.729 (0.610-0.831)
Sensitivity	0.909 (0.870-0.943)	0.825 (0.700-0.925)	0.918 (0.849-0.973)	0.786 (0.571-1.0)
Specificity	0.656 (0.606-0.707)	0.699 (0.633-0.760)	0.653 (0.568-0.737)	0.711 (0.578-0.844)
	CSF/Aβ-PET cohort			
	Denmark	**Greater Middle East**	**Europe**	**Africa**
Accuracy	0.857 (0.818-0.895)	0.861 (0.787-0.926)	0.835 (0.763-0.897)	0.679 (0.500-0.857)
Sensitivity	0.954 (0.914-0.980)	0.968 (0.903-1.0)	1.0 (1.0-1.0)	0.800 (0.500-1.0)
Specificity	0.720 (0.636-0.804)	0.818 (0.714-0.909)	0.686 (0.549-0.804)	0.611 (0.389-0.833)

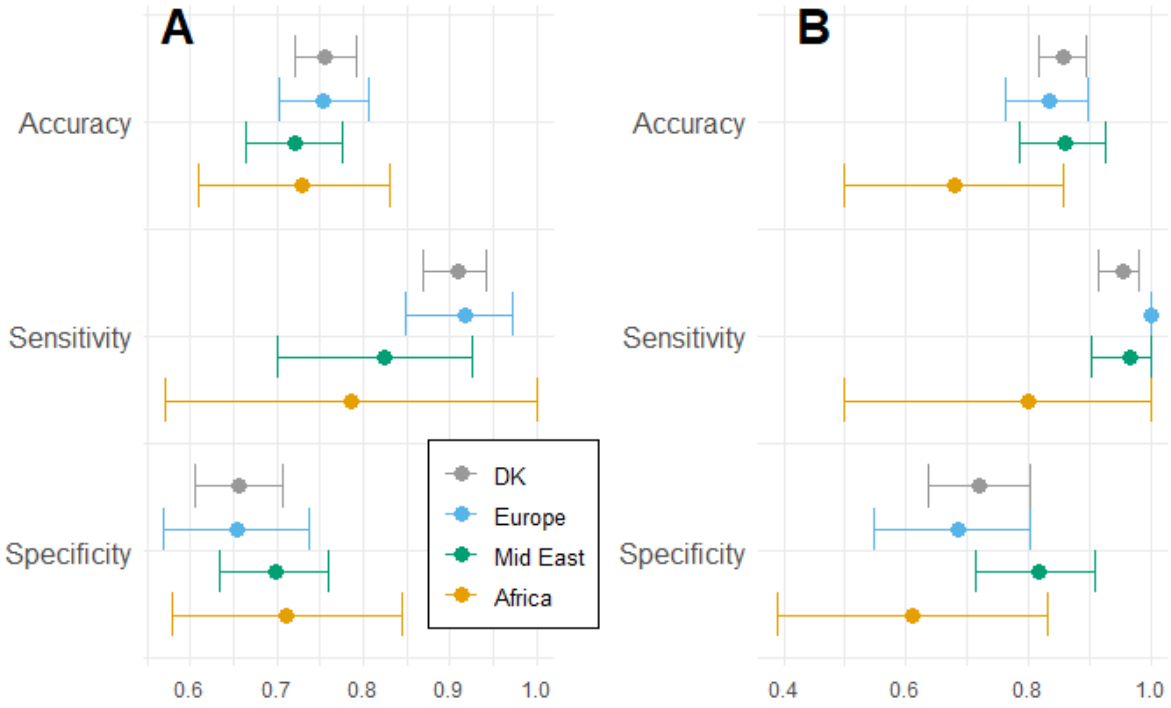
Note: The pre-established cutoff (0.308 pg/ml) of the normalized high plasma p-tau217 was used. 95% CI were estimated by bootstrapping with 1000 iterations. This has been visualized in Supplementary Figure 1.

Supplementary Table 10: Diagnostic accuracy for subsets of the CSF/Aβ-PET examined patients (5-fold logistic regression)

	N	AD pathology (%)	Geographic region	AUC	SD
Aβ-PET	77	38 (49.4%)	Native: 46 Africa: 3 Europe: 7 Middle East: 20	0.959	0.063
Elecsys	144	81 (56.3%)	Native-born: 82 Africa: 8 Europe: 24 Middle East: 19	0.896 (2)	0.045
Innotest	185	94 (50.8%)	Native: 130 Africa: 13 Europe: 12 Middle East: 22	0.859 (1, 2)	0.051
Lumipulse	96	41 (42.7%)	Native: 0 Africa: 2 Europe: 37 Middle East: 35	0.977	0.036
MSD	37	10 (27.0%)	Native: 0 Africa: 2 Europe: 17 Middle East: 12	0.847	0.206

Note: (1) = significantly lower AUC than Aβ-PET, (2) = significantly lower AUC than Lumipulse

Supplementary Figure 1: Graphical representation of plasma p-tau217 accuracy by preestablished cutoff stratified by geographic region



Note: Figure A = Identification of AD in the full cohort. Figure B = Identification of amyloid pathology in the CSF/Aβ-PET examined sub cohort. The pre-established cutoff (0.308 pg/ml) of the normalized high plasma p-tau217 was used. 95% CI was estimated by bootstrapping with 1000 iterations. See Supplementary Table 9 for numeric values.

Supplementary methodology

Identifying patients

In the Danish Dementia Research Centre, 5324 patients were screened by first and last name and we excluded Danish names. Of these, 1005 patients with non-Danish sounding names were checked in the clinical database, and 502 patients were not born in Denmark, of these, 450 had consented to participate in research and had plasma available. Screening by name has previously been used (Mateos, 2007; Fiscella & Fremont, 2006). We applied the approach conservatively by over-selecting patients who were possibly born outside the country of examination. Importantly, 50.05 percent of patients were misclassified with a name search only therefore scouring the clinical database was necessary.

In the memory clinic in Malmö, probable foreign-born patients were initially selected if they had results from the RUDAS during their diagnostic evaluation and gave consent to participate in research. A total of 181 patients were screened, and 147 fulfilled the inclusion criteria. Of these, only 137 had available plasma samples in the biobank.

The complete cohort was then 587 foreign-born and 587 native-born patients. However, four patients were removed during/after the plasma analysis, one because of mislabeling and one because of inconclusive results (CV > 20%) and their matches (N=2). Therefore, the total cohort size was 1170.

Literature list for supplementary methodology

Fiscella, K., & Fremont, A. M. (2006). Use of geocoding and surname analysis to estimate race and ethnicity. Health services research, 41(4 Pt 1), 1482–1500. https://doi.org/10.1111/j.1475-6773.2006.00551.x

Mateos, P. (2007), A review of name-based ethnicity classification methods and their potential in population studies. Popul. Space Place, 13: 243-263. https://doi.org/10.1002/psp.457

9.4. Study 4.

Combining plasma p-tau217 and cross-cultural cognitive tests to identify Alzheimer's Disease in an ethnically diverse mixed memory clinic cohort

Daniel Kjaergaard, Anja Hviid Simonsen, Erik Stomrud, Divya Bali, Shorena Janelidze, Oskar Hansson, Gunhild Waldemar, T. Rune Nielsen

Journal of the Neurological Sciences (2025). https://doi.org/10.1016/j.jns.2025.123739

Journal of the Neurological Sciences 478 (2025) 123739



Contents lists available at ScienceDirect

Journal of the Neurological Sciences

journal homepage: www.elsevier.com/locate/jns





Combining plasma p-tau217 and cross-cultural cognitive tests to identify Alzheimer's Disease in an ethnically diverse mixed memory clinic cohort

Daniel Kjaergaard [a,*], Anja Hviid Simonsen [a], Erik Stomrud [b,c], Divya Bali [b], Shorena Janelidze [b], Oskar Hansson [b], Gunhild Waldemar [a,d], T. Rune Nielsen [a,e]

[a] Danish Dementia Research Centre, Department of Neurology, Copenhagen University Hospital - Rigshospitalet, Copenhagen, Denmark
[b] Clinical Memory Research Unit, Department of Clinical Sciences Malmö, Lund University, Lund, Sweden
[c] Memory Clinic, Skåne University Hospital, Malmö, Sweden
[d] Department of Clinical Medicine, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark
[e] Department of Psychology, University of Copenhagen, Copenhagen, Denmark

ARTICLE INFO

Keywords:
Alzheimers disease
plasma biomarkers
phosphorylated tau
ethnicity
Neuropsychological test
diversity

ABSTRACT

Objective: To determine whether combining routine cross-cultural cognitive assessments with plasma phosphorylated tau217 (p-tau217) increases diagnostic accuracy in identifying Alzheimer's disease (AD) in a consecutive mixed memory clinic cohort of ethnically diverse patients.
Methods: We included 201 memory clinic patients originating from 42 different countries. Patients were examined with the Multicultural Cognitive Examination (MCE) as part of their routine cognitive assessment. Plasma p-tau217 levels were analyzed blinded to the results of the clinical evaluation. Repeated cross-validated models assessed the added diagnostic value of plasma p-tau217 through change in accuracy metrics, including sensitivity, specificity, predictive values, and likelihood ratios. The primary outcome was clinically established AD. In subgroup analyses, accuracy metrics were evaluated for differentiating AD from other dementia disorders and patients with and without AD pathology determined by cerebrospinal fluid biomarkers or Amyloid-β PET.
Results: Routine cognitive assessment with the MCE alone demonstrated high diagnostic accuracy for identifying AD (AUC: 0.80–0.81). However, combining the MCE with plasma p-tau217 significantly increased diagnostic accuracy (AUC: 0.91–0.93), which mainly reflected an increased ability to rule-out AD. When differentiating AD from other dementia disorders, the MCE alone was less accurate (AUC: 0.64–0.65), and accuracies increased by including plasma p-tau217 (AUC: 0.85–0.89).
Conclusions: Combining routine cross-cultural cognitive tests with an accurate plasma biomarker increased the accuracy of identifying AD in a diverse mixed memory clinic cohort. These results demonstrate the value of using appropriate diagnostic tools in culturally, linguistically, and ethnically diverse patients, who are known to face barriers in their clinical evaluation.

1. Background

Patients with culturally, linguistically, and educationally diverse backgrounds frequently encounter barriers in their dementia evaluations, leaving them at a disadvantage [1]. These barriers are present across medical history taking, cognitive testing, assessment of activities of daily living, and even appropriateness of diagnostic criteria [2–5]. Such barriers especially affect people with minority ethnic backgrounds and may result in more misdiagnoses in memory clinics or primary care in these populations [6]. With increasing migration and globalization, it is essential that these barriers are addressed by developing diagnostic methods that are less prone to bias in culturally, linguistically, and educationally diverse patients [6–9].

Cross-cultural cognitive tests are developed to be less influenced by cultural, linguistic, and educational factors, while retaining the accuracy of traditional cognitive tests [4,10–18]. Cross-cultural cognitive tests overcome the barriers by for example using globally known color pictures for naming tasks [12,19], and using culturally appropriate words

* Corresponding author at: Danish Dementia Research Centre, Department of Neurology, Neuroscience Centre, Copenhagen University Hospital – Rigshospitalet, section 8008, Blegdamsvej 9, 2100 Copenhagen, Denmark.
E-mail address: daniel.kjaergaard.01@regionh.dk (D. Kjaergaard).

https://doi.org/10.1016/j.jns.2025.123739
Received 26 August 2025; Received in revised form 16 October 2025; Accepted 22 October 2025
Available online 25 October 2025
0022-510X/© 2025 The Authors. Published by Elsevier B.V. This is an open access article under the CC BY-NC license (http://creativecommons.org/licenses/by-nc/4.0/).

with similar difficulty and frequency across languages [20]. While cognitive tests can identify clinical phenotypes for diseases such as Alzheimer's disease (AD), biomarkers provide essential information about the underlying pathology. To this end, blood-based biomarkers have emerged as a scalable, less invasive, and accurate diagnostic tool, especially for identifying AD pathology [21–25]. The plasma biomarker tau phosphorylated at threonine 217 (p-tau217) has proven to be one of the most precise plasma biomarkers of AD pathology [22,23,26–30]. However, little is known about the diagnostic accuracy of plasma p-tau217 for AD in diverse populations as people with minority ethnic backgrounds are often underrepresented in blood biomarker research [31,32]. In a recent study in 1170 ethnically diverse memory clinic patients, we found no influence of geographic origin on the concentration or accuracy of plasma p-tau217 [33]. Hence, plasma p-tau217 appears to be equally accurate in identifying AD regardless of ethnic backgrounds and could constitute an efficient tool for overcoming some of the barriers that culturally, linguistically, and educationally diverse patients encounter.

Previous studies have indicated that a combination of blood-based biomarkers and information from the standard clinical evaluation, including brief cognitive tests, may increase accuracy in the prediction [34,35] and classification of AD [36–38]. However, the generalizability of these results is limited as the cognitive tests used did not involve cross-cultural cognitive tests and few studies included ethnically diverse patients.

This study aimed to examine the added value of combining routine cross-cultural cognitive assessments with plasma p-tau217 in identifying mild cognitive impairment (MCI) and dementia due to AD in a consecutive mixed memory clinic cohort of culturally and linguistically diverse patients.

2. Methods

2.1. Patients

This study included a subset of mixed memory clinic patients from a larger study [33]. This subset was selected by including only culturally and linguistically diverse patients, defined as patients born outside the Nordic countries (Denmark, Sweden, Norway, and Finland), who had been assessed with the 'Multicultural Cognitive Examination' (MCE) as part of their routine clinical evaluation. All patients had complete diagnostic evaluations, known cognitive status, and available plasma for research purposes. Patient data and plasma were included from the Copenhagen University Hospital Memory Clinic, Rigshospitalet, Denmark from 1st of January 2020 to 31st of December 2023, and from Skåne University Hospital Memory Clinic, Sweden from 9th of June 2017 to 5th of March 2024 (see Supplementary Table 1 for number of patients by country of origin). We excluded patients that were diagnosed with hereditary neurogenetic disorders, did not have available plasma for research purposes, were born in Scandinavia, or had concurrent brain cancer.

The routine diagnostic evaluations consisted of medical history taking, neurological and physical examination, cognitive testing with the MCE, informant-based history taking when available, and routine laboratory blood tests. Often, the routine diagnostic evaluation involved an interpreter. For most patients, their evaluation also included structural brain imaging (Magnetic Resonance Imaging or Computerized Tomography). The individual physician evaluated the need for supplementing the diagnostic evaluation with cerebrospinal fluid (CSF) biomarkers, ^{18}fluorodeoxyglucose positron emission tomography (FDG-PET) or amyloid-PET (MBq C-11 PiB). The amyloid-PET and CSF biomarkers were classified as abnormal or normal according to pre-defined cutoffs as described previously [33].

The primary outcome was a clinical diagnosis of AD, using implemented clinical criteria for possible/probable AD with MCI or dementia in the memory clinic in Copenhagen [39,40] and Malmö [41,42] as the gold standard. Other dementia disorders were diagnosed according to clinical consensus criteria [41–46] as described in detail previously [47]. In Copenhagen, diagnoses were established through a multidisciplinary consensus conference. In Malmö, diagnoses were determined by individual physicians when the disease presentation was typical and supported by biomarkers. However, in cases of uncertainty or an atypical presentation, a consensus conference was held. Patient characteristics by inclusion site are presented in Supplementary Table 2.

Patients were classified as 'uncertain' if the initial complete diagnostic evaluation did not yield a clear diagnosis, requiring further follow-up.

2.2. Plasma collection and analysis

Blood samples were obtained during routine diagnostic evaluation at the memory clinics. Extracted ethylenediaminetetraacetic acid (EDTA) plasma was stored within two hours of sampling at −80 °C. We performed a single batch analysis of plasma p-tau217 on an immuno-assay developed by Eli Lilly on the Mesoscale Discovery (MSD) platform at Lund University as described in detail previously [48].

We ran analyses randomized by age, sex, dementia diagnosis, and geographic origin and in duplicates. Plasma analyses were performed by personnel who were blind to participant information, and clinical personnel were blinded to the plasma p-tau217 results.

2.3. Cognitive tests

The MCE was part of the routine diagnostic evaluation for all included patients. The MCE [14] consists of four subtests; Recall of Pictures Test (RPT), Supermarket Fluency Test (SFT), Clock Reading Test (CRT), and Rowland Universal Dementia Assessment Scale (RUDAS) [49]. RUDAS is a cross-cultural cognitive screening test comparable to the Mini-Mental Status Examination (MMSE) [50] and Montreal Cognitive Assessment (MoCA) [51] assessing general cognition. The RPT measures episodic memory with immediate- and delayed recall, and recognition of ten pictures. The SFT requires participants to name as many things as possible that you can buy in a supermarket within 1 min. The CRT requires participants to correctly read the time on 12 clock faces. The total MCE score ranges from 0 to 100.

2.4. Statistical analysis

The significance of group differences was determined by the Wilcoxon rank sum test for continuous variables and by the Chi-squared test for categorical variables.

Two logistic regression models were created for differentiating clinical AD from the other patients in the mixed memory clinic cohort. One model included the total MCE score as the predictor, and the other included individual MCE subtest scores as predictors. Both models were adjusted for age, sex, and education. The model fit was deemed to be similar if the difference in the Akaike Information Criterion (AIC) was $\leq$2. Multicollinearity was examined using variance inflation factors (VIF).

To estimate the added value of plasma p-tau217 beyond cross-cultural cognitive tests for identifying AD, we compared the change in performance metrics in the models mentioned above when adding plasma p-tau217 as a predictor. The added value of plasma p-tau217 was examined through repeated 5-fold cross-validated models looking at the Area Under the Receiver Operating Characteristic (AUC) curves, sensitivity, specificity, positive and negative predictive values (PPV / NPV), and positive and negative likelihood ratios (LR+ / LR-). Comparisons of the AUCs were performed using DeLongs statistics. To further explore the added value of adding p-tau217 to the MCE, subanalyses compared the accuracy metrics in patients with AD to patients with other specific dementia disorders. A sensitivity analysis in CSF/Amyloid-PET examined patients was performed with amyloid-β (Aβ) status as the

dependent variable.

Statistical analyses were performed with RStudio (version 4.4.2). Results were deemed statistically significant at a two-sided *p*-value <0.05. The R script is available on Github (https://github.com/dkja0031/BlooDiv/blob/main/Combining%20plasma%20p-tau217%20and%20MCE).

3. Results

A total of 201 patients were included in the final cohort, of which 51 were diagnosed with AD or mixed AD, 45 with other neurological or neurodegenerative disorders, 83 with SCD/affective/somatic conditions, and 22 needed further follow-up and therefore were classified as 'uncertain'. Patient characteristics are presented in Table 1. Overall, the AD and mixed AD group was older ($p < 0.001$), had higher plasma p-tau217 concentrations ($p < 0.001$), and had lower MCE total and subtests scores ($p < 0.001$) (See Table 1).

A subsample of 101 patients were examined with CSF ($N = 87$), amyloid-PET ($N = 12$), or both ($N = 2$) as part of their clinical evaluation. Of these, 41 were classified as Aβ-positive and 60 as Aβ-negative. Compared to Aβ-negative patients, Aβ-positive patients were older ($p = 0.003$) and had higher plasma p-tau217 concentrations ($p < 0.001$). There were no differences in sex distribution ($p = 0.8$) or education ($p = 0.10$). Regarding cognitive tests, the Aβ-positive group had significantly lower MCE total ($p = 0.010$), RPT immediate recall ($p = 0.001$), RPT delayed recall ($p = 0.002$), and CRT ($p = 0.012$) scores, while there were no significant differences on SFT ($p = 0.5$), RPT recognition ($p = 0.3$), or RUDAS ($p = 0.052$). See Table 2.

In the MCE model, both MCE total score ($p = 0.030$) and age ($p < 0.001$) were significantly associated with AD. In the subtests model, only RPT delayed recall score ($p < 0.001$) and age ($p < 0.001$) were significantly associated with AD. The subtests model had a better model fit and explained a larger amount of variance (AIC: 171.21, R2: 28.7%) compared to the MCE model (AIC: 174.6, R2: 22.3 %). The AICs further improved by including plasma p-tau217, and the explained variance increased to 46.5 % and 54.4 % (Table 3). VIF across models were all <3.

We used cross-validated models to identify the added diagnostic value of including plasma p-tau217 in the four models mentioned above. The MCE model was accurate in identifying AD within a mixed memory clinic cohort (AUC: 0.801), similar to the subtests model (AUC: 0.798; DeLong $z = 0.331$, $p < 0.001$). Both models significantly improved by adding plasma p-tau217 (MCE model with p-tau217: AUC: 0.902, DeLong $z = -7.326$, $p < 0.001$. Subtests model with p-tau217: AUC: 0.925, DeLong $z = -9.595$, $p < 0.001$). These improvements primarily reflected improved specificities as more patients without AD were classified correctly (Fig. 1, Table 3, Supplementary Table 3).

We assessed whether adding plasma p-tau217 to the models also improved the ability to distinguish patients with AD from patient with other specific dementia disorders. The ability to distinguish the two groups based solely on cognitive tests was lower (AUC: 0.651 to 0.661) compared to the AUCs in the full cohort. However, adding plasma p-tau217 to the two models significantly improved the diagnostic accuracies (MCE model with p-tau217: AUC: 0.844, DeLong $z = -9.096$, $p < 0.001$. Subtests model with p-tau217: AUC 0.881, DeLong $z = -10.711$, $p < 0.001$). In contrast to the analysis in the full mixed cohort, all diagnostic accuracy metrics improved by including plasma p-tau217, not primarily the specificity (Fig. 2, Supplementary Table 3).

We performed a sensitivity analysis in patients examined with CSF or amyloid-PET as part of their diagnostic evaluation. There was a significant association between the Aβ status determined by CSF/Amyloid-PET and plasma p-tau217 at the cutoff 0.308 pg/ml ($\chi^2 = 44$, $p <$

Table 2
Characteristics of the CSF and Aβ-PET examined patients.

	Aβ-	Aβ+	p-value
N	60	41	
Age, years	69.0 [62.0, 74.0]	74.0 [70.0, 77.0]	0.003
Female sex (%)	31 (51.7 %)	22 (53.7 %)	0.8
Education, years	8.0 [5.0, 12.0]	11.5 [6.0, 12.0]	0.10
Cognitive status			< 0.001
SCD	13	1	
MCI	20	6	
Dementia severity (Mild/moderate/severe)	18/8/1	20/14/0	
AD or Mixed AD	5 (8.3 %)	32 (78.05 %)	< 0.001
P-tau217, pg/ml	0.3 [0.2, 0.4]	0.7 [0.5, 1.1]	< 0.001
MCE score	62.0 [51.3, 70.5]	51.0 [39.0, 65.0]	0.010
RUDAS	22.0 [20.0, 26.0]	20.0 [15.0, 24.0]	0.052
RPT immediate recall	5.3 [4.0, 7.2]	4.3 [3.0, 5.7]	0.001
RPT delayed recall	5.0 [3.0, 6.5]	2.0 [0.0, 5.0]	0.002
RPT recognition	9.0 [6.0, 10.0]	8.0 [5.0, 10.0]	0.3
SFT	10.5 [7.0, 14.0]	10.0 [6.0, 13.0]	0.5
CRT	10.3 [7.5, 12.0]	8.0 [4.0, 10.5]	0.012

Abbreviations: Aβ-PET = Amyloid-β Positron Emission Tomography; AD = Alzheimer's Disease; CRT = Clock Reading Test; CSF = Cerebrospinal Fluid; MCE = Multicultural Cognitive Examination; MCI = Mild Cognitive Impairment; P-tau = Phosphorylated tau; RPT = Recall of Pictures Test; RUDAS = Rowland Universal Dementia Assessment Scale; SCD = Subjective Cognitive Decline; SFT = Supermarket Fluency Test

Note: Groupwise differences were determined by Kruskal-Wallis rank sum test for continuous variables, and by Chi-squared test for categorical variables.

Table 1
Clinical characteristics.

	AD and mixed AD	Other specific dementia disorders *	SCD/Affective/Somatic †	Uncertain	p-value
N	51	45	83	22	
Age, years	76.0 [71.0, 79.0]	73.0 [65.0, 77.0]	63.0 [57.0, 69.0]	71.5 [63.0, 75.0]	< 0.001
Female sex (%)	31 (60.8 %)	16 (35.6 %)	51 (61.4 %)	14 (63.6 %)	0.018
Education, years	9.0 [5.0, 12.0]	9.0 [5.0, 12.0]	8.0 [5.0, 12.0]	10.0 [5.0, 12.0]	0.8
P-tau217, pg/ml	0.7 [0.5, 1.1]	0.3 [0.2, 0.4]	0.3 [0.2, 0.4]	0.3 [0.2, 0.4]	< 0.001
MCE score	50.5 [37.5, 65.5]	54.5 [36.0, 65.5]	73.0 [62.0, 82.0]	65.8 [62.0, 69.0]	< 0.001
RUDAS	20.0 [15.0, 24.0]	21.0 [16.0, 24.0]	26.0 [22.0, 28.0]	23.0 [21.0, 26.0]	< 0.001
RPT immediate recall	4.3 [2.3, 5.7]	4.7 [3.0, 5.3]	7.0 [5.7, 8.0]	6.0 [5.0, 7.0]	< 0.001
RPT delayed recall	2.0 [0.0, 5.0]	4.0 [1.0, 6.0]	7.0 [6.0, 9.0]	6.0 [4.0, 7.0]	< 0.001
RPT recognition	8.0 [5.0, 10.0]	8.0 [5.0, 10.0]	10.0 [9.0, 10.0]	9.5 [9.0, 10.0]	< 0.001
SFT	10.0 [6.0, 13.0]	8.0 [5.0, 10.0]	14.0 [10.0, 17.0]	12.0 [9.0, 16.0]	< 0.001
CRT	9.0 [4.0, 11.0]	9.0 [5.5, 11.5]	11.0 [8.5, 12.0]	10.0 [9.0, 12.0]	< 0.001

Abbreviations: AD = Alzheimer's Disease; CRT = Clock Reading Test; MCE = Multicultural Cognitive Examination; P-tau = Phosphorylated tau; RPT = Recall of Pictures Test; RUDAS = Rowland Universal Dementia Assessment Scale; SCD = Subjective Cognitive Decline; SFT = Supermarket Fluency Test

Note: Groupwise differences were determined by Kruskal-Wallis rank sum test for continuous variables, and by Chi-squared test for categorical variables.

*: Vascular dementia ($N = 22$), Lewy Body Dementia ($N = 5$), Normal Pressure Hydrocephalus (N = 2), behavioral variant frontotemporal dementia ($N = 6$), Semantic dementia (N = 2), non-fluent primary progressive aphasia ($N = 1$), Parkinson's dementia (N = 1), progressive supranuclear palsy (N = 2), sequala from gunshot/meningioma/cardiac arrest or traumatic brain injury ($N = 4$).

†: SCD ($N = 39$), Affective disorder ($N = 36$), Somatic ($N = 8$).

Table 3
Logistic regression results and diagnostic accuracy.

Model	Variable	OR	AUC	AIC	R^2 (McFadden)
MCE model	MCE	0.630 (0.412; 0.948) *	0.801 (0.066)	174.6	0.223
	Age	3.466 (2.123; 6.063) ***			
	Education	1.186 (0.806; 1.766)			
	Sex	0.552 (0.247; 1.195)			
Subtests model	RUDAS	1.239 (0.646; 2.406)	0.798 (0.101)	171.21	0.287
	RPT immediate recall	1.088 (0.540; 2.211)			
	RPT delayed recall	0.281 (0.134; 0.562) ***			
	RPT recognition	1.281 (0.805; 2.095)			
	Clock Reading Test	0.855 (0.493; 1.531)			
	Supermarket Fluency Test	1.255 (0.731; 2.172)			
	Age	2.875 (1.671; 5.303) ***			
	Education	1.100 (0.709; 1.722)			
	Sex	0.619 (0.253; 1.474)			
	P-tau217	6.169 (3.415; 12.585) ***			
MCE model w. p-tau217	MCE	0.794 (0.472; 1.334)	0.903 (0.053)	125.41	0.465
	Age	2.962 (1.622; 5.851) ***			
	Education	0.859 (0.524; 1.398)			
	Sex	0.731 (0.276; 1.897)			
	P-tau217	10.377 (4.746; 28.104) ***			
Subtests model w. p-tau217	RUDAS	0.871 (0.360; 2.112)	0.925 (0.036)	118.59	0.544
	RPT immediate recall	1.588 (0.662; 4.130)			
	RPT delayed recall	0.222 (0.083; 0.547) **			
	RPT recognition	1.182 (0.625; 2.280)			
	Clock Reading Test	2.372 (1.106; 5.674) *			
	Supermarket Fluency Test	1.116 (0.566; 2.154)			
	Age	2.770 (1.358; 6.183) **			
	Education	0.525 (0.259; 1.011)			
	Sex	0.825 (0.276; 2.439)			

Abbreviations: AIC = Akaike Information Criterion; AUC = Area under the Receiver Operating Characteristics curve; MCE = Multicultural Cognitive Examination; OR = Odds ratio; P-tau = Phosphorylated tau; RPT = Recall of Pictures Test; RUDAS = Rowland Universal Dementia Assessment Scale
Note: *** = $p < 0.001$, ** = $p < 0.01$, * = $p < 0.05$.

0.001). A confusion matrix had an accuracy of 0.832, a sensitivity of 0.927, and a specificity of 0.767.

4. Discussion

We examined whether adding plasma p-tau217 to routine cognitive assessment with the cross-cultural cognitive screening test MCE improved the diagnostic accuracy for identifying AD in a consecutive mixed memory clinic cohort of culturally and linguistically diverse patients. We found that the MCE and its subtests were highly accurate in identifying AD, however, adding plasma p-tau217 to the cognitive assessment significantly improved the overall diagnostic accuracies in this diverse mixed memory clinic cohort. Importantly, the MCE did not sufficiently differentiate AD from other specific dementia disorders as all were cognitively impaired. However, classification of these patients greatly improved by adding plasma p-tau217. To our knowledge, this is the first study to examine whether combining cross-cultural cognitive tests and plasma p-tau217 increases the diagnostic accuracy of clinical AD in a culturally, linguistically, and educationally diverse patient cohort.

Our findings are similar to previous studies exploring integrated diagnostic approaches of combining plasma biomarkers with cognitive tests [37,38]. For example, in a Chinese cohort Pan and colleagues [38] found that the MMSE, plasma p-tau181, and plasma Aβ42/40 were the most influential variables in classifying AD pathology, while other biomarkers such as neurofilament light (NfL) were less influential. An integrated approach also improved predictions of conversion from MCI to AD dementia [34,35]. Indeed, considering evidence of the clinical phenotype and of the underlying pathology is beneficial for correct classification of memory clinic patients.

It is possible to overcome some of the barriers that culturally, linguistically, and educationally diverse patients encounter in their diagnostic evaluations by using a suitable approach. Using appropriate cognitive tests at their initial evaluation will identify most patients with cognitive impairment, while using traditional cognitive screening tests in diverse individuals would most likely result in a bias towards classifying more cognitively unimpaired patients as cognitively impaired because of the larger influences of education, language, and culture [11,52]. Combining a culture sensitive cognitive assessment followed by an AD biomarker would give the individual clinician sufficient knowledge to decide which other procedures are necessary to establish a diagnosis. Importantly, the ability to rule-out AD was stronger than the ability to rule-in AD. With these considerations we hope to advance knowledge on diagnostic approaches in patients who are known to face barriers in their diagnostic evaluations [1]. Alongside our findings promoting the use of cross-cultural cognitive tests, there are several international initiatives that drive change in cross-cultural assessments, such as the European Consortium on Cross-Cultural Neuropsychology (ECCroN) [10], the Diversity and Disparities PIA under the AAIC, and the International Network for Cross-Linguistic Research on Brain Health (INCLUDE).

There are important limitations to keep in mind when interpreting our results. Interpreting the true classification accuracy of the MCE is limited as this test was part of the clinical work-up. Furthermore, all patients were included based on whether the MCE was used in the routine diagnostic evaluation which may give rise to selection bias. Also, the culturally and linguistically diverse patients may vary in socioeconomic status, degrees of acculturation, and other unmeasured variables.

In conclusion, adding plasma p-tau217 to routine cognitive assessments in culturally and linguistically diverse patients improved the diagnostic accuracy for AD in a mixed memory clinic cohort. Our findings are generally in line with previous studies combining plasma biomarkers and cognitive testing but extents results to patients with diverse backgrounds increasing the real-world representativeness. These results encourage wider use of scalable cross-cultural cognitive tests and plasma

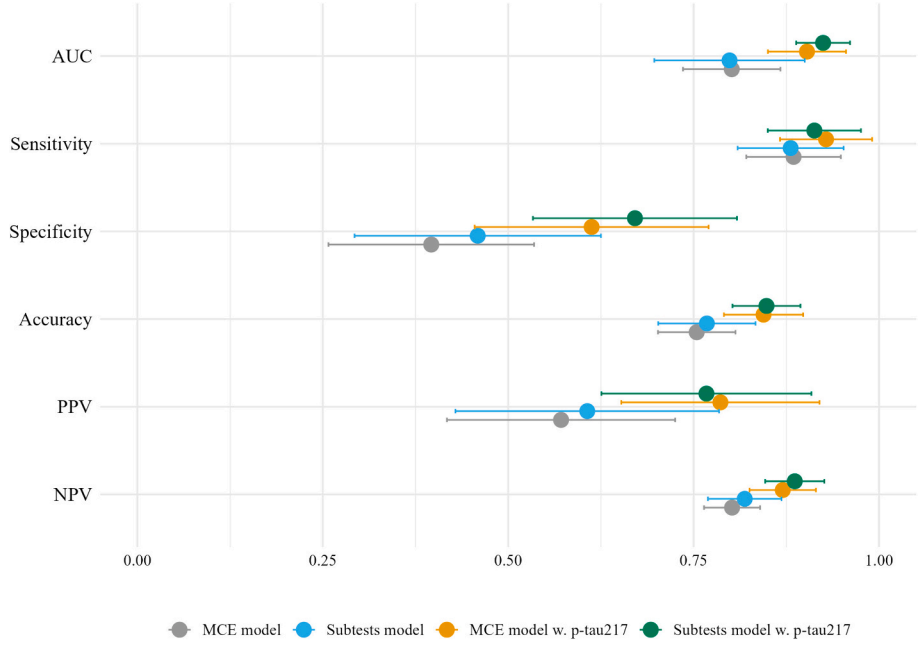


Fig. 1. Identification of AD in a mixed memory clinic cohort. Abbreviations: AD = Alzheimers disease, AUC = Area under the Receiver Operating Characteristics curve, MCE = Multicultural Cognitive Examination, NPV = Negative Predictive Values, PPV = Positive Predictive Values, P-tau = Phosphorylated tau.
Note: Forest plot displays AUC, sensitivity, specificity, accuracy, PPV, and NPV in identifying AD in a mixed memory clinic cohort. Results are plotted as mean ± 1 standard deviation.

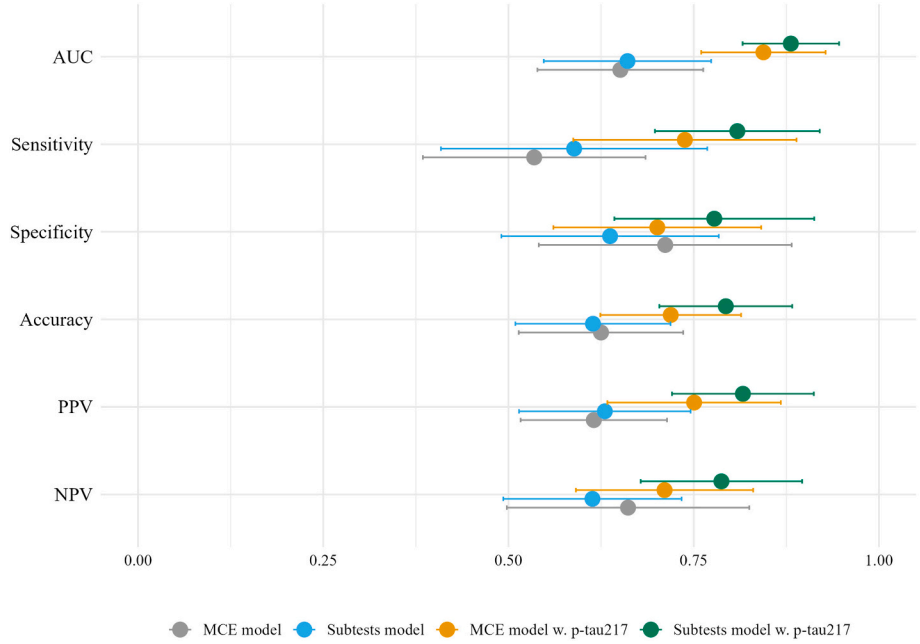


Fig. 2. AD vs. other specific dementia disorders. Abbreviations: AD = Alzheimers disease, AUC = Area under the Receiver Operating Characteristics curve, MCE = Multicultural Cognitive Examination, NPV = Negative Predictive Values, PPV = Positive Predictive Values, P-tau = Phosphorylated tau.
Note: Forest plot displays AUC, sensitivity, specificity, accuracy, PPV, and NPV in differentiating AD and other specific dementia disorders. Results are plotted as mean ± 1 standard deviation.

biomarkers in diverse population and perhaps even to primary care settings. Future studies should explore the added value of plasma biomarkers on clinical decision-making in culturally and linguistically diverse participants to continue to move the field forward and improve the diagnostic conditions for people with diverse backgrounds.

Potential conflicts of interest

AHS has received a one-time consultancy fee (for the institution) from Eisai and BioArtic in 2025.

DB declares no conflicts of interest.

DK declares no conflicts of interest.

ES has acquired research support (for the institution) from C2N Diagnostics, Fujirebio, GE Healthcare and Roche Diagnostics.

GW declares no conflicts of interest.
OH is an employee of Lund University and Eli Lilly.
SJ declares no conflicts of interest.
TRN declares no conflicts of interest.

Data availablity

The data that support the findings of this study are available from the corresponding author upon reasonable request. The R-script is available on GitHub (https://github.com/dkja0031/BlooDiv/blob/main/Combining%20plasma%20p-tau217%20and%20MCE).

CRediT authorship contribution statement

Daniel Kjaergaard: Writing – review & editing, Writing – original draft, Visualization, Validation, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Anja Hviid Simonsen:** Writing – review & editing, Supervision, Resources, Project administration, Data curation, Conceptualization. **Erik Stomrud:** Writing – review & editing, Supervision, Resources, Data curation. **Divya Bali:** Writing – review & editing, Resources, Formal analysis, Data curation. **Shorena Janelidze:** Writing – review & editing, Resources, Formal analysis, Data curation. **Oskar Hansson:** Writing – review & editing, Supervision, Funding acquisition, Data curation. **Gunhild Waldemar:** Writing – review & editing, Supervision, Resources, Project administration, Funding acquisition, Data curation, Conceptualization. **T. Rune Nielsen:** Writing – review & editing, Supervision, Project administration, Methodology, Funding acquisition, Formal analysis, Data curation, Conceptualization.

Consent statement

The study was designed in accordance with the Declaration of Helsinki, and all patients gave written consent for their samples and clinical data to be used for research. The study was approved by the Regional Ethics Committee in the Capital Region Denmark (H-23035053), the Danish Data Protection Agency (p-2023-14,275), and the Swedish Ethical Review Authority (2023–07108-01).

Acknowledgments

The authors would like to thank the patients and clinical staff who made this study possible.

This work was supported by the Innovation Fund Denmark [grant number 1099-00022B], under the frame of ERA PerMed [reference number ERAPERMED2021-184]. The Danish Dementia Research Centre (DDRC) is supported by the Danish Ministry of Health. AHS was supported by the Absalon Foundation founded 1st of May 1978. Work at Lund University was supported by the European Research Council (ADG-101096455), Alzheimer's Association (ZEN24-1069572, SG-23-1061717), GHR Foundation, Swedish Research Council (2022-00775), ERA PerMed (ERAPERMED2021-184), Knut and Alice Wallenberg foundation (2022−0231), Strategic Research Area MultiPark (Multidisciplinary Research in Parkinson's disease) at Lund University, Swedish Alzheimer Foundation (AF-980907), Swedish Brain Foundation (FO2021-0293), Parkinson foundation of Sweden (1412/22), Cure Alzheimer's fund, Rönström Family Foundation, Konung Gustaf V:s och Drottning Victorias Frimurarestiftelse, Skåne University Hospital Foundation (2020-O000028), Regionalt Forskningsstöd (2022-1259) and Swedish federal government under the ALF agreement (2022-Projekt0080).

The funding sources had no role in the design and conduct of the study; in the collection, analysis, interpretation of the data; or in the preparation, review, or approval of the manuscript.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jns.2025.123739.

References

[1] T.R. Nielsen, A. de Mendonça, L. Frölich, S. Engelborghs, D. Gove, D. Lamirel, et al., Assessment of dementia in minority ethnic groups in Europe: a 14-year follow-up survey, Int. J. Geriatr. Psychiatry (2024) 39, https://doi.org/10.1002/GPS.70034.
[2] T.R. Nielsen, Cognitive assessment in culturally, linguistically, and educationally diverse older populations in Europe, Am. J. Alzheimers Dis. Other Dement. (2022) 37, https://doi.org/10.1177/15333175221117006.
[3] S. Mazzeo, C.J.D. Hardy, J. Jiang, C. Morinelli, V. Moschini, E. Brooks, et al., Primary progressive aphasia in Italian and English: a cross-linguistic cohort study, Neurology 103 (2024) e210058, https://doi.org/10.1212/WNL.0000000000210058.
[4] T.R. Nielsen, S. Franzen, T.J. Watermeyer, J. Jiang, C. Calia, D. Kjærgaard, et al., Interpreter-mediated neuropsychological assessment: clinical considerations and recommendations from the European consortium on cross-cultural neuropsychology (ECCroN), Clin. Neuropsychol. (2024), https://doi.org/10.1080/13854046.2024.2335113.
[5] T.R. Nielsen, D. Kjaergaard, Primary progressive aphasia across languages: prevalence and presentation of phenotypes are shaped by language-specific features, Neurology 103 (2024) e210165, https://doi.org/10.1212/WNL.0000000000210165.
[6] T.R. Nielsen, A. Vogel, T.K.T. Phung, A. Gade, G. Waldemar, Over- and under-diagnosis of dementia in ethnic minorities: a nationwide register-based study, Int. J. Geriatr. Psychiatry 26 (2011) 1128–1135, https://doi.org/10.1002/GPS.2650.
[7] E. Nichols, J.D. Steinmetz, S.E. Vollset, K. Fukutaki, J. Chalek, F. Abd-Allah, et al., Estimation of the global prevalence of dementia in 2019 and forecasted prevalence in 2050: an analysis for the global burden of disease study 2019. Lancet, Public Health (2022) 7, https://doi.org/10.1016/S2468-2667(21)00249-8.
[8] K. Segers, F. Benoit, C. Colson, V. Kovac, D. Nury, V. Vanderaspoilden, Pioneers in migration, pioneering in dementia: first generation immigrants in a European metropolitan memory clinic, Acta Neurol. Belg. 113 (2013) 435–440, https://doi.org/10.1007/S13760-013-0245-Z.
[9] C. Van Mol, H. de Valk, Migration and immigrants in Europe: a historical and demographic perspective, IMISCOE Res. Ser. (2016) 31–55, https://doi.org/10.1007/978-3-319-21674-4_3/FIGURES/6.
[10] S. Franzen, T.J. Watermeyer, S. Pomati, J.M. Papma, T.R. Nielsen, P. Narme, et al., Cross-cultural neuropsychological assessment in Europe: position statement of the European consortium on cross-cultural neuropsychology (ECCroN), Clin. Neuropsychol. 36 (2022) 546–557, https://doi.org/10.1080/13854046.2021.1981456.
[11] S. Franzen, J.M. Papma, E. Van Den Berg, T.R. Nielsen, Cross-cultural neuropsychological assessment in the European Union: a Delphi expert study, Arch. Clin. Neuropsychol. 36 (2021) 815–830, https://doi.org/10.1093/ARCLIN/ACAA083.
[12] T.R. Nielsen, B.U. Grollenberg, S.P. Ringkøbing, M. Özden, B. Weekes, G. Waldemar, The Copenhagen cross-linguistic naming test (C-CLNT): development and validation in a multicultural memory clinic population, J. Int. Neuropsychol. Soc. 29 (2023) 911–921, https://doi.org/10.1017/S1355617723000437.
[13] R. Bourdage, S. Franzen, J. Palisson, D. Maillet, C. Belin, C. Joly, et al., The TIE-93: a facial emotion recognition test adapted for culturally, linguistically, and educationally diverse Alzheimer's dementia patients in France, Arch. Clin. Neuropsychol. (2025), https://doi.org/10.1093/ARCLIN/ACAF012.
[14] T.R. Nielsen, K. Segers, V. Vanderaspoilden, U. Beinhoff, L. Minthon, A. Pissiota, et al., Validation of a brief multicultural cognitive examination (MCE) for evaluation of dementia, Int. J. Geriatr. Psychiatry 34 (2019) 982–989, https://doi.org/10.1002/GPS.5099.
[15] R. Torkpoor, K. Frolich, E. Londos, T.R. Nielsen, Diagnostic accuracy of the Swedish version of the multicultural cognitive examination for cognitive assessment in Swedish memory clinics, J Alzheimer's Dis 97 (2024) 715–726, https://doi.org/10.3233/JAD-230998.
[16] T.R. Nielsen, K. Segers, V. Vanderaspoilden, U. Beinhoff, L. Minthon, A. Pissiota, et al., Validation of a European cross-cultural neuropsychological test battery (CNTB) for evaluation of dementia, Int. J. Geriatr. Psychiatry 34 (2019) 144–152, https://doi.org/10.1002/GPS.5002.
[17] T.R. Nielsen, K. Segers, V. Vanderaspoilden, P. Bekkhus-Wetterberg, L. Minthon, A. Pissiota, et al., Performance of middle-aged and elderly European minority and majority populations on a cross-cultural neuropsychological test battery (CNTB), Clin. Neuropsychol. 32 (2018) 1411–1430, https://doi.org/10.1080/13854046.2018.1430256.
[18] S. Franzen, E. van den Berg, W. Bossenbroek, J. Kranenburg, E.A. Scheffers, M. van Hout, et al., Neuropsychological assessment in the multicultural memory clinic: development and feasibility of the TULIPA battery, Clin. Neuropsychol. 37 (2023) 60–80, https://doi.org/10.1080/13854046.2022.2043447.
[19] S. Franzen, E. Van Den Berg, Y. Ayhan, D.D. Satoer, Genç Akpulat G.E. Türkoğlu, et al., The naming assessment in multicultural Europe (NAME): development and validation in a multicultural memory clinic, J. Int. Neuropsychol. Soc. 29 (2023) 92–104, https://doi.org/10.1017/S135561772100148X.

[20] V. Fyndanis, M. Lind, S. Varlokosta, M. Kambanaros, E. Soroli, K. Ceder, et al., Cross-linguistic adaptations of the comprehensive aphasia test: challenges and solutions, Clin. Linguist. Phon. 31 (2017) 697–710, https://doi.org/10.1080/02699206.2017.1310299.
[21] I.M.W. Verberk, E. Thijssen, J. Koelewijn, K. Mauroo, J. Vanbrabant, A. De Wilde, et al., Combination of plasma amyloid beta(1-42/1-40) and glial fibrillary acidic protein strongly associates with cerebral amyloid pathology, Alzheimer's Res Ther (2020) 12, https://doi.org/10.1186/S13195-020-00682-7.
[22] S. Palmqvist, S. Janelidze, Y.T. Quiroz, H. Zetterberg, F. Lopera, E. Stomrud, et al., Discriminative accuracy of plasma Phospho-tau217 for Alzheimer disease vs other neurodegenerative disorders, JAMA 324 (2020) 772–781, https://doi.org/10.1001/JAMA.2020.12134.
[23] S. Janelidze, S. Palmqvist, A. Leuzy, E. Stomrud, I.M.W. Verberk, H. Zetterberg, et al., Detecting amyloid positivity in early Alzheimer's disease using combinations of plasma Aβ42/Aβ40 and p-tau, Alzheimers Dement. 18 (2022) 283–293, https://doi.org/10.1002/ALZ.12395.
[24] A. Den Braber, I.M.W. Verberk, J. Tomassen, B. Den Dulk, E. Stoops, J.L. Dage, et al., Plasma biomarkers predict amyloid pathology in cognitively normal monozygotic twins after 10 years, Brain Commun (2023) 5, https://doi.org/10.1093/BRAINCOMMS/FCAD024.
[25] F. Anastasi, A. Fernández-Lebrero, N.J. Ashton, P. Ortiz-Romero, J. Torres-Torronteras, A. González-Escalante, et al., A head-to-head comparison of plasma biomarkers to detect Alzheimer's disease in a memory clinic, Alzheimer's and Dementia (2025) 21, https://doi.org/10.1002/ALZ.14609.
[26] P. Kivisäkk, H.A. Fatima, D.S. Cahoon, B. Otieno, L. Chacko, F. Minooei, et al., Clinical evaluation of a novel plasma pTau217 electrochemiluminescence immunoassay in Alzheimer's disease, Sci. Rep. (2024) 14, https://doi.org/10.1038/S41598-024-51334-X.
[27] N.R. Barthélemy, K. Horie, C. Sato, R.J. Bateman, Blood plasma phosphorylated-tau isoforms track CNS change in Alzheimer's disease, J. Exp. Med. (2020) 217, https://doi.org/10.1084/JEM.20200861.
[28] L. Vandevrede, R. La Joie, E.H. Thijssen, B.M. Asken, S.A. Vento, T. Tsuei, et al., Evaluation of plasma phosphorylated Tau217 for differentiation between Alzheimer disease and frontotemporal lobar degeneration subtypes among patients with Corticobasal syndrome, JAMA Neurol. 80 (2023) 495–505, https://doi.org/10.1001/JAMANEUROL.2023.0488.
[29] S.E. Schindler, D. Galasko, A.C. Pereira, G.D. Rabinovici, S. Salloway, M. Suárez-Calvet, et al., Acceptable performance of blood biomarker tests of amyloid pathology - recommendations from the global CEO initiative on Alzheimer's disease, Nat. Rev. Neurol. (2024) 20, https://doi.org/10.1038/S41582-024-00977-5.
[30] O. Hansson, R.M. Edelmayer, A.L. Boxer, M.C. Carrillo, M.M. Mielke, G. D. Rabinovici, et al., The Alzheimer's Association appropriate use recommendations for blood biomarkers in Alzheimer's disease, Alzheimers Dement. 18 (2022) 2669–2686, https://doi.org/10.1002/ALZ.12756.
[31] T.K. Karikari, Blood tests for Alzheimer's disease: increasing efforts to expand and diversify research participation is critical for widespread validation and acceptance, J Alzheimer's Dis 90 (2022) 967–974, https://doi.org/10.3233/JAD-215730.
[32] D. Kjaergaard, A.H. Simonsen, G. Waldemar, T.R. Nielsen, Ethnic and racial influences on blood biomarkers for Alzheimer's disease: a systematic review, J Alzheimer's Dis 103 (2025) 81–91, https://doi.org/10.1177/13872877241299047.
[33] D. Kjaergaard, T.R. Nielsen, E. Stomrud, S. Palmqvist, D. Bali, A.O. Dolado, et al., Influence of ethnicity on the diagnostic accuracy of plasma p-tau217 for the identification of Alzheimer's disease: a consecutive mixed memory clinic cohort study, Alzheimers Dement. (2025) 21, https://doi.org/10.1002/ALZ.70315.
[34] S. Palmqvist, P. Tideman, N. Cullen, H. Zetterberg, K. Blennow, J.L. Dage, et al., Prediction of future Alzheimer's disease dementia using plasma phospho-tau combined with other accessible measures, Nat. Med. 27 (2021) 1034–1042, https://doi.org/10.1038/S41591-021-01348-Z.
[35] A. Pichet Binette, S. Palmqvist, D. Bali, G. Farrar, C.J. Buckley, D.A. Wolk, et al., Combining plasma phospho-tau and accessible measures to evaluate progression to Alzheimer's dementia in mild cognitive impairment patients, Alzheimer's Res Ther (2022) 14, https://doi.org/10.1186/S13195-022-00990-0.
[36] S. Toniolo, S. Zhao, A. Scholcz, B. Amein, A. Ganse-Dumrath, A.J. Heslegrave, et al., Relationship of plasma biomarkers to digital cognitive tests in Alzheimer's disease, Alzheimers Dement (Amst) 16 (2024), https://doi.org/10.1002/DAD2.12590.
[37] M. Petersen, J. Hall, T. Parsons, L. Johnson, S. O'Bryant, Combining select blood-based biomarkers with neuropsychological assessment to detect mild cognitive impairment among Mexican Americans, J Alzheimer's Dis 75 (2020) 739–750, https://doi.org/10.3233/JAD-191264.
[38] F. Pan, Y. Huang, X. Cai, Y. Wang, Y. Guan, J. Deng, et al., Integrated algorithm combining plasma biomarkers and cognitive assessments accurately predicts brain β-amyloid pathology, Commun. Med. (2023) 3, https://doi.org/10.1038/S43856-023-00295-9.
[39] G.M. McKhann, D.S. Knopman, H. Chertkow, B.T. Hyman, C.R. Jack, C.H. Kawas, et al., The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease, Alzheimers Dement. 7 (2011) 263–269, https://doi.org/10.1016/J.JALZ.2011.03.005.
[40] M.S. Albert, S.T. DeKosky, D. Dickson, B. Dubois, H.H. Feldman, N.C. Fox, et al., The diagnosis of mild cognitive impairment due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease, Alzheimers Dement. 7 (2011) 270, https://doi.org/10.1016/J.JALZ.2011.03.008.
[41] American Psychiatric Association, Diagnostic and Statistical Manual of Mental Disorders. Diagnostic and statistical manual of mental disorders, 2013, https://doi.org/10.1176/APPI.BOOKS.9780890425596.
[42] American Psychiatric Association, Diagnostic and Statistical Manual of Mental Disorders. Diagnostic and statistical manual of mental disorders, 2022, https://doi.org/10.1176/APPI.BOOKS.9780890425787.
[43] P. Sachdev, R. Kalaria, J. O'Brien, I. Skoog, S. Alladi, S.E. Black, et al., Diagnostic criteria for vascular cognitive disorders: a VASCOG statement, Alzheimer Dis. Assoc. Disord. 28 (2014) 206–218, https://doi.org/10.1097/WAD.0000000000000034.
[44] K. Rascovsky, J.R. Hodges, D. Knopman, M.F. Mendez, J.H. Kramer, J. Neuhaus, et al., Sensitivity of revised diagnostic criteria for the behavioural variant of frontotemporal dementia, Brain 134 (2011) 2456–2477, https://doi.org/10.1093/BRAIN/AWR179.
[45] M.L. Gorno-Tempini, A.E. Hillis, S. Weintraub, A. Kertesz, M. Mendez, S.F. Cappa, et al., Classification of primary progressive aphasia and its variants, Neurology 76 (2011) 1006, https://doi.org/10.1212/WNL.0B013E31821103E6.
[46] I.G. McKeith, B.F. Boeve, D.W. Dickson, G. Halliday, J.P. Taylor, D. Weintraub, et al., Diagnosis and management of dementia with Lewy bodies: fourth consensus report of the DLB consortium, Neurology 89 (2017) 88–100, https://doi.org/10.1212/WNL.0000000000004058.
[47] A.H. Simonsen, H.S. Gleerup, C.S. Musaeus, F. Sellebjerg, M.B. Hansen, H. B. Søndergaard, et al., Neurofilament light chain levels in serum among a large mixed memory clinic cohort: confounders and diagnostic usefulness, Alzheimers Dement (Amst) (2023) 15, https://doi.org/10.1002/DAD2.12512.
[48] D. Bali, O. Hansson, S. Janelidze, Effects of certain pre-analytical factors on the performance of plasma phospho-tau217, Alzheimer's Res Ther 16 (2024), https://doi.org/10.1186/S13195-024-01391-1.
[49] J.E. Storey, J.T.J. Rowland, D.A. Conforti, H.G. Dickson, The Rowland universal dementia assessment scale (RUDAS): a multicultural cognitive assessment scale, Int. Psychogeriatr. 16 (2004) 13–31, https://doi.org/10.1017/S1041610204000043.
[50] M.F. Folstein, S.E. Folstein, P.R. McHugh, "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician, J. Psychiatr. Res. 12 (1975) 189–198, https://doi.org/10.1016/0022-3956(75)90026-6.
[51] Z.S. Nasreddine, N.A. Phillips, V. Bédirian, S. Charbonneau, V. Whitehead, I. Collin, et al., The Montreal cognitive assessment, MoCA: a brief screening tool for mild cognitive impairment, J. Am. Geriatr. Soc. 53 (2005) 695–699, https://doi.org/10.1111/J.1532-5415.2005.53221.X.
[52] M. Goudsmit, J. Van Campen, T. Schilt, C. Hinnen, S. Franzen, B. Schmand, One size does not fit all: comparative diagnostic accuracy of the Rowland universal dementia assessment scale and the Mini mental state examination in a memory clinic population with very low education, Dement Geriatr Cogn Dis Extra 8 (2018) 290–305, https://doi.org/10.1159/000490174.

Supplementary material – Study 4

Supplementary Table 1. Countries of origin

Country of birth	N (%)
Afghanistan	7 (3.5%)
Albania	2 (1.0%)
Algeria	1 (0.5%)
Belarus	1 (0.5%)
Bolivia	2 (1.0%)
Bosnia and Herzegovina	9 (4.5%)
Brazil	1 (0.5%)
Chile	2 (1.0%)
China	7 (3.5%)
Colombia	1 (0.5%)
Cuba	1 (0.5%)
Eritrea	1 (0.5%)
Gambia	1 (0.5%)
Greece	1 (0.5%)
Hungary	3 (1.5%)
India	2 (1.0%)
Iran	11 (5.5%)
Iraq	8 (4.0%)
Kosovo	2 (1.0%)
Lebanon	6 (3.0%)
Lithuania	1 (0.5%)
Morocco	14 (7.0%)
North Macedonia	9 (4.5%)
Pakistan	30 (15%)
Palestine	2 (1.0%)

Philippines	3 (1.5%)
Poland	7 (3.5%)
Romania	1 (0.5%)
Russia	2 (1.0%)
Serbia	2 (1.0%)
Slovakia	1 (0.5%)
Somalia	6 (3.0%)
Sri Lanka	1 (0.5%)
Syria	6 (3.0%)
Taiwan	1 (0.5%)
Thailand	6 (3.0%)
Tunisia	2 (1.0%)
Türkiye	29 (14%)
Uganda	1 (0.5%)
Ukraine	3 (1.5%)
Vietnam	3 (1.5%)
Yemen	2 (1.0%)

Supplementary Table 2. Descriptives by Memory Clinic

	Memory clinic Copenhagen	Memory clinic Malmö	p-value
N	162	39	
Age, years	69.5 [62.0, 75.0]	70.0 [63.0, 76.0]	0.5
Female sex (%)	89 (54.9%)	23 (59.0%)	0.6
Education, years	8.0 [5.0, 12.0]	11.0 [7.0, 15.0]	0.006
Cognitive status			
SCD	49 (29.3%)	5 (12.8%)	
MCI	37 (22.2%)	15 (38.5%)	
Dementia (Mild/moderate/severe)	81 (48.5%)	19 (48.7%)	
AD or Mixed AD	37 (22.2%)	14 (35.9%)	
P-tau217 concentration, pg/ml	0.3 [0.3, 0.5]	0.4 [0.3, 0.7]	0.3
MCE score	64.0 [50, 74]	65 [42, 73]	0.7
RUDAS score	23 [18, 26]	23 [19, 26]	0.9
RPT immediate recall	5.7 [4.3, 7.0]	5.0 [4.0, 8.0]	0.2
RPT delayed recall	6 [3, 7]	4 [1, 8]	0.3
RPT recognition	9 [7, 10]	9 [5, 10]	0.8
SFT	11 [8, 15]	10 [8, 14]	0.6
CRT	10 [6, 12]	11 [8.5, 12]	0.3

Abbreviations: AD = Alzheimer's Disease, MCE = Multicultural Cognitive Examination, MCI = Mild Cognitive Impairment, P-tau = Phosphorylated tau, RUDAS = Rowland Universal Dementia Assessment Scale, SCD = Subjective Cognitive Decline.

Note: Groupwise comparison by Kruskal-Wallis rank sum test and Chi-squared test.

Supplementary Table 3. Likelihood ratios

	LR+	LR-
Whole cohort		
MCE model	1.47	0.29
Subtests model	1.63	0.26
MCE model w. p-tau217	2.40	0.12
Subtests model w. p-tau217	2.77	0.13
AD vs. other specific dementia disorders		
MCE model	1.85	0.65
Subtests model	1.62	0.65
MCE model w. p-tau217	2.47	0.37
Subtests model w. p-tau217	3.64	0.25

Abbreviations: AD = Alzheimer's Disease, LR = Likelihood Ratio, MCE = Multicultural Cognitive Examination, P-tau = Phosphorylated tau.

9.5. Study 5.

Plasma phosphorylated tau217 discordance with amyloid status in an ethnically diverse mixed memory clinic cohort

Daniel Kjaergaard, T. Rune Nielsen, Erik Stomrud, Divya Bali, Frederikke Kragh Clemmensen, Kristian Steen Frederiksen, Helena Sophia Gleerup, Steen Gregers Hasselbalch, Shorena Janelidze, Oskar Hansson, Gunhild Waldemar, & Anja Hviid Simonsen

Under review with Journal of the neurological sciences (Submitted the 16th of March, 2026)

Title: Plasma phosphorylated tau217 discordance with amyloid status in an ethnically diverse mixed memory clinic cohort

Running head: Plasma p-tau217 discordance

Daniel Kjaergaard[1], T. Rune Nielsen[1, 2], Erik Stomrud[3, 4], Divya Bali[3], Frederikke Kragh Clemmensen[1], Kristian Steen Frederiksen[1, 5], Helena Sophia Gleerup[1], Steen Gregers Hasselbalch[1, 5], Shorena Janelidze[3], Oskar Hansson[3], Gunhild Waldemar[1, 5], & Anja Hviid Simonsen[1]

[1] Danish Dementia Research Centre, Department of Neurology, Copenhagen University Hospital - Rigshospitalet, Copenhagen, Denmark

[2] Department of Psychology, University of Copenhagen, Copenhagen, Denmark

[3] Clinical Memory Research Unit, Department of Clinical Sciences Malmö, Lund University, Lund, Sweden

[4] Memory Clinic, Skåne University Hospital, Malmö, Sweden

[5] Department of Clinical Medicine, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark

Corresponding author *:
Daniel Kjaergaard
Danish Dementia Research Centre,
Department of Neurology, Neuroscience Centre
Copenhagen University Hospital – Rigshospitalet, section 8008
Blegdamsvej 9, 2100, Copenhagen, Denmark.
Phone: +45 35 45 69 22
Email: daniel.kjaergaard.01@regionh.dk
Word count of the manuscript: 1.842

Abstract

We characterized patients with discordant plasma p-tau217 results and amyloid status determined by the Aβ42/p-tau181 CSF ratio or Aβ-PET biomarkers in an ethnically diverse mixed memory clinic cohort. Among 539 patients, 83.9% had concordant biomarker profiles, while 13.4% were amyloid negative and plasma p-tau217 positive discordant, and 2.8% were amyloid positive and plasma p-tau217 negative discordant. Discordant groups differed in cognitive syndrome severity and etiological diagnosis, but no other variables reached significance. However, analyses indicated small effects of BMI, kidney function, and certain neurological conditions. Amyloid negativity and plasma p-tau217 positivity discordance may reflect plasma p-tau217 detecting early amyloid pathology not detected by CSF or Aβ-PET. Further research is needed to clarify mechanisms underlying discordant biomarker profiles.

Keywords

Alzheimer's disease, biomarker, confounders, discordance, diversity, phosphorylated tau, plasma

INTRODUCTION

Plasma tau phosphorylated at threonine 217 (p-tau217) is moving from research into clinical practice as an amyloid specific biomarker [1–5]. However, several factors may influence plasma p-tau217 concentrations, including kidney function, body mass index (BMI), age, and ethnicity or race [6–12]. Furthermore, plasma p-tau217 levels have been found to be increased in other conditions than Alzheimer's disease (AD), such as amyotrophic lateral sclerosis (ALS) [13,14] and acute ischemic stroke [15], and even in newborns [16]. These findings call into question how many patients may be misclassified from plasma biomarkers due to factors other than those related to amyloid pathology, and whether the misclassification can be mitigated, especially in real-world cohorts where patients have high rates of comorbidities and concurrent pathologies.

Previous studies focusing on discordance between brain amyloid and plasma biomarkers primarily compared plasma p-tau217 to Amyloid-β Positron Emission Tomography (Aβ-PET) results as the reference standard. These studies found a higher rate of Aβ-PET-/p-tau217+ results compared to Aβ-PET+/p-tau217- results [17–19]. The studies also explored the potential causes for discordance and found that the Aβ-PET-/p-tau217+ patients were older [17,19] and had higher rates of comorbidities such as hypertension, diabetes, hyperlipidemia, and chronic kidney disease [19], while Aβ-PET+/p-tau217- patients had higher BMI [19]. The evidence base for the causes of discordant results remains scarce especially in ethnically diverse cohorts as most studies on plasma p-tau217 have been carried out in ethnically homogeneous cohorts [20]. Additionally, studies exploring discordance generally include patients with low rates of comorbidities or consider only few comorbidities [21]. In this study, we aimed to characterize patients with discordant plasma p-tau217 results and amyloid status, defined from cerebrospinal fluid (CSF) Aβ42/p-tau181 ratio or Aβ-PET biomarkers, in an ethnically diverse mixed memory clinic cohort. Applied thresholds for CSF Aβ42/p-tau181 ratio and Aβ-PET are previously described [6]. Sub analyses explored whether discordance rates differed dependent on immigrant status.

METHODS

Patients

The analyses were conducted in a subset of patients from the BlooDiv mixed memory clinic cohort [6]. Briefly, the BlooDiv cohort consists of one-to-one matched Danish-born patients to patients with immigrant backgrounds on age and sex, leading to a high representation of patients with immigrant backgrounds. The subset used in the current study consists of 539 memory clinic patients selected based on the following inclusion criteria: Patients had undergone a complete diagnostic evaluation in a specialized memory clinic in Copenhagen (Denmark) or in Malmö (Sweden), provided consent for research use of existing plasma samples, had results from the CSF biomarkers p-tau181 and Aβ42 or from Aβ-PET. For those with immigrant

backgrounds, information on country of birth was required. Exclusion criteria comprised age under 18 years, presence of hereditary neurogenetic disorders, lack of plasma samples, Danish patients examined in Sweden or Swedish patients examined in Denmark, or concurrent brain cancer. The memory clinic in Copenhagen is a tertiary referral center for Normal Pressure Hydrocephalus (NPH), leading to a high representation of this patient group in our cohort. Of the 539 patients, 489 were examined with CSF biomarkers and 77 with Aβ-PET (27 of these had both CSF and Aβ-PET) as part of their clinical evaluation. Aβ-PET took priority for amyloid status determination in cases of discordance.

Plasma p-tau217 was analyzed using an immunoassay developed by Lilly Research Laboratories on a Meso Scale Discovery (MSD) platform in September 2024 as described previously [6]. A pre-established and previously published threshold of 0.308 pg/ml was used to categorize p-tau217 data into normal/abnormal [6].

Patients were grouped into four groups dependent on their amyloid status (Aβ-/+) and plasma p-tau217 status (p-tau217+/-). The groups were (1) Aβ-/p-tau217-, (2) Aβ-/p-tau217+, (3) Aβ+/p-tau217-, (4) Aβ+/p-tau217+.

Covariates

We examined differences between the discordant and concordant groups on sociodemographic information (age, sex, and immigrant status), medical conditions (diabetes, hypertension, hyperlipidemia, clinical history of stroke, estimated Glomerular Filtration Rate (eGFR), BMI, Fazekas score), cognitive test scores (mini-mental status examination (MMSE) and Rowland Universal Dementia Assessment Scale (RUDAS)), cognitive syndrome severity, and etiological diagnosis.

Data analysis

We compared group differences between Aβ+/p-tau217+ and Aβ+/p-tau217-, and Aβ-/p-tau217- and Aβ-/p-tau217+ on all included covariates. For continuous variables independent samples t-test or Mann-Whitney U test was used, and for categorical variables Chi-squared test or Fisher's exact test was used. P-values were adjusted for multiple comparisons using False Discovery Rate (FDR) and deemed statistically significant at $p < 0.05$. A sub analysis stratified by whether the patient was examined with Aβ-PET or CSF explored if the group comparisons differed between Aβ-PET or CSF (Supplementary Tables 1 and 2). Statistical analyses were performed using RStudio.

RESULTS

Concordance between plasma p-tau217 and Aβ status was 83.9% (452 of 539). Group sizes were: Aβ+/p-tau217+ 249 (46.2%), Aβ-/p-tau217- 203 (37.7%), Aβ-/p-tau217+ 72 (13.4%), and Aβ+/p-tau217- 15 (2.8%). There were no significant differences between the Aβ-/p-tau217- and Aβ-/p-tau217+ groups, or between Aβ+/p-tau217- and Aβ+/p-tau217+ groups on age, sex, or immigrant status (Table 1). The most frequent

etiological diagnoses were AD (42.1%), followed by vascular dementia (VaD) (8.0%), and NPH (7.6%). Within each etiological diagnosis group, the NPH patients had the highest Aβ-/p-tau217+ discordance of 26.8% (11 of 41).

TABLE 1. Cohort characteristics

	Aβ-/ p-tau217-	Aβ-/ p-tau217+	P-value	Effect size	Aβ+/ p-tau217-	Aβ+/ p-tau217+	P-value	Effect size
N	203	72			15	249		
Age, years	66.8 (9.3)	68.7 (8.5)	0.37	Small	69.1 (9.0)	69.9 (7.8)	0.89	Negligible
Female sex (%)	94 (46.3%)	34 (47.2%)	>0.9	Negligible	5 (33.3%)	148 (59.4%)	0.18*	Small
Immigrant status	126 (62.1%)	42 (58.3%)	0.65	Negligible	8 (53.3%)	105 (42.2%)	0.56	Negligible
Syndrome diagnosis			0.56	Negligible			0.005*	Medium
SCD	26 (12.8%)	10 (13.9%)			2 (13.3%)	3 (1.2%)		
MCI	81 (39.9%)	21 (29.2%)			8 (53.3%)	51 (20.5%)		
Dementia	76 (37.4%)	36 (50.0%)			5 (33.3%)	190 (76.3%)		
Undecided	20 (9.9%)	5 (6.9%)			0 (0.0%)	5 (2.0%)		
Etiological diagnoses			<0.001*	Medium			<0.001*	Medium
AD and mixed AD	10 (4.9%)	20 (27.8%)			6 (40.0%)	214 (85.9%)		
Non-neurodegenerative	36 (17.7%)	8 (11.1%)			1 (6.7%)	6 (2.4%)		
NPH	21 (10.3%)	11 (15.3%)			0 (0%)	9 (3.6%)		
Other neurodegenerative	31 (15.3%)	10 (13.9%)			1 (6.7%)	7 (2.8%)		
Non neurological	49 (24.1%)	15 (20.8%)			2 (13.3%)	4 (1.6%)		
Unknown	56 (27.6%)	8 (11.1%)			5 (33.3%)	9 (3.6%)		
Diabetes	67 (33.0%)	20 (27.8%)	0.64	Negligible	2 (13.3%)	49 (19.7%)	0.89	Negligible
Hypertension	100 (49.3%)	32 (44.4%)	0.64	Negligible	6 (40.0%)	103 (41.4%)	>0.9	Negligible
Hyperlipidemia	43 (21.2%)	18 (25.0%)	0.64	Negligible	6 (40.0%)	62 (24.9%)	0.47	Negligible
Clinical history of stroke	15 (7.4%)	7 (9.7%)	0.64	Negligible	2 (13.3%)	17 (6.8%)	0.51	Negligible
eGFR, mL/min/1.73m^2	83.8 (18.4)	78.6 (21.0)	0.24	Small	81.2 (14.8)	81.1 (14.6)	>0.9	Negligible
BMI, kg/m^2	27.7 (5.2)	26.1 (4.4)	0.12*	Small	28.5 (4.2)	25.5 (4.5)	0.10*	Medium-large
Fazekas score			0.39	Negligible			>0.9	Negligible
0-1	83 (60.1%)	36 (72.0%)			9 (81.8%)	151 (74.4%)		
2-3	55 (39.9%)	14 (28.0%)			2 (18.2%)	52 (25.6%)		
MMSE/RUDAS (0-30)	23.0 [20.0, 27.0]	24.0 [20.0, 28.0]	0.64	Negligible	25.0 [22.0, 28.0]	23.0 [18.0, 26.0]	0.35	Small

Note: Pairwise comparisons were based on independent samples t-test, Mann-Whitney U test, Chi-Squared test, or Fisher's exact test. Effect sizes: Cohen's D (0.0-0.2 Negligible, 0.2-0.5 Small, 0.5-0.8 Medium, >0.8 Large), Cliff's Delta (0.0-0.147 Negligible, 0.147-0.33 Small, 0.33-0.474 Medium, >0.474 Large), and Cramer's V (0.0-0.1 Negligible, 0.1-0.3 Small, 0.3-0.5 Medium, >0.5 Large). * = p-value was significant before adjustment for multiple comparisons.

Abbreviations: Aβ = Amyloid-β, AD = Alzheimer's disease, BMI = Body Mass Index, eGFR = estimated Glomerular Filtration Rate, MCI = Mild Cognitive Impairment, MMSE = Mini-Mental State Examination, NPH = Normal Pressure Hydrocephalus, p-tau217 = phosphorylated tau 217, RUDAS = Rowland Universal Dementia Assessment Scale, SCD = Subjective Cognitive Decline.

The Aβ-/p-tau217+ group differed in proportion of etiological diagnoses and included more patients with a clinical AD diagnosis compared to the Aβ-/p-tau217- group (27.8% vs 4.9%, p<0.001), but no other variables reached significance after FDR correction. Similarly, the Aβ+/p-tau217+ had more patients with a clinical AD diagnosis (85.9% vs. 40.0%, p = 0.001) and had more patients diagnosed with dementia (76.3% vs. 33.3%, p = 0.005) compared to the Aβ+/p-tau217- group.

While no medical conditions were statistically significant after FDR correction, we observed small effect sizes for eGFR and BMI between the Aβ-/p-tau217- and Aβ-/p-tau217+ groups, in which the discordant group had numerically lower eGFR (83.8 vs. 78.6, p = 0.2, Cohen's D = 0.27) and numerically lower BMI (27.7 vs. 26.1, p = 0.1, Cohen's D = 0.32). Meanwhile, between the Aβ+/p-tau217- and Aβ+/p-tau217+ groups we observed a medium-large effect size for BMI in which the discordant group had higher BMI (28.5 vs. 25.5, p = 0.08, Cohen's D = 0.67). We found no significant differences in diabetes, hypertension, hyperlipidemia, clinical history of stroke, Fazekas score or cognitive scores on the MMSE or RUDAS. Results were similar when stratified by whether the patients were examined with Aβ-PET (Supplementary Table 1) or CSF (Supplementary Table 2). However, since too few patients were examined with Aβ-PET little can be inferred about the Aβ-PET+/p-tau217- group.

When stratifying patients based on eGFR, concordance rate was 85.1% among patients with an eGFR >60 mL/min/1.73m2, while it dropped to 73.2% among patients with an eGFR<60 mL/min/1.73m2 (X2 = 4.27, p = 0.04). Analyses stratified by immigrant status revealed no differences in concordance rates (X2 = 0.94, p = 0.33), with a concordance rate of 85.7% for the Danish participants, and 82.2% for patients with immigrant backgrounds.

DISCUSSION

We aimed to characterize patients with discordant plasma p-tau217 results and amyloid status determined by CSF or Aβ-PET in an ethnically diverse mixed memory clinic cohort. A total of 87 patients (16.1%) displayed discordant biomarker profiles, which is slightly higher compared to previous studies with discordance rate ranging from 9.5% to 14.6% [17,19]. In our cohort, most discordant patients were Aβ-/p-tau217+ (13.4%), while only few patients were Aβ+/p-tau217- (2.8%). As expected, the groups differed in the proportion of patients who had received an AD diagnosis, with Aβ+/p-tau217+ having the highest proportion. Patients were more likely to have dementia when both CSF and plasma biomarkers were positive, as previously seen [22]. Importantly, CSF biomarkers and Aβ-PET were used as part of the diagnostic evaluation. We found no distinctive patterns in sociodemographic or medical conditions that differentiated the groups.

While not statistically significant, our results are in line with previous studies exploring discordant biomarker profiles on BMI and eGFR [5,10,11,23]. Across all groups we found numerically higher BMI in the p-tau217

negative groups, with a mean difference between Aβ+/p-tau217- and Aβ+/p-tau217+ of 3.0 kg/m2. Studies have hypothesized that increased BMI may dilute protein concentrations because of increased blood volume [10,23]. Furthermore, previous studies have found an influence of eGFR as reduced kidney function may increase AD biomarker concentrations through reduced clearance of proteins [5,11]. We found a small effect size of eGFR for which the Aβ-/p-tau217+ group had worse kidney function than the Aβ-/p-tau217- group. Although the effects of BMI and eGFR were not statistically significant in our cohort, we cannot rule out that they have an influence as previous studies have demonstrated [10]. Indeed, in our stratified analyses concordance was higher among those with an eGFR >60 mL/min/1.73m2 compared to those below. Unlike other studies on discordance there were no age differences between the compared groups in our cohort, suggesting that the influence of BMI and eGFR in previous studies could at least partly be driven by age. Another possible explanation is that some discordant biomarker profiles are the result of expected short-term intra-individual variability [24].

Interestingly, 20 of 41 patients diagnosed with NPH had positive plasma p-tau217 results, 11 of those 41 had discordant results. Only one patient had abnormal CSF p-tau181 but 32 had abnormal CSF Aβ42. NPH typically display reduced levels of Aβ42 in CSF, possibly because of reduced metabolism in the brain, underlying amyloid pathology, or reduced clearance [25,26]. To our knowledge, no studies have been carried out on plasma p-tau217 in NPH, making it relevant to explore in future research.

The group with the highest discordance rate was the Aβ-/p-tau217+ group, which may be due to several factors. One explanation is that medical conditions increase the plasma p-tau217 concentration, resulting in false-positive results [8]. This is, however, not clearly supported by our data. Another explanation is that plasma p-tau217 is an earlier biomarker of AD pathology compared to CSF or Aβ-PET suggesting that patients who were Aβ-/p-tau217+ may have amyloid pathology that is not yet detected by CSF or Aβ-PET [18,19]. This is supported by a study reporting the Aβ-PET-/p-tau217+ group to have faster cognitive decline compared to their Aβ-PET-/p-tau217- group [19].

A strength of our study is the two center mixed memory clinic design and large, deeply phenotyped, and ethnically diverse sample as this represents a real-world memory clinic cohort, promoting the generalizability of the results. However, several limitations must be considered. First, there were no longitudinal measures to examine if the groups have different cognitive trajectories. Second, few patients were classified as Aβ+/p-tau217-, which limits interpretations about this group, although it speaks to a strong negative predictive value of plasma p-tau217. Lastly, some clinical AD diagnoses were supported by individual cutoffs on CSF Aβ42, p-tau181, and total tau, and not always by the p-tau181/Aβ42 ratio used in this study. Therefore, some Aβ-/p-tau217+ patients could initially have been interpreted as positive in the clinic.

In conclusion, there were no distinctive differences in sociodemographic or medical conditions that could explain the discordant biomarker profiles. However, there were some indications that BMI, kidney function,

certain etiologies, and cognitive syndrome severity may influence plasma p-tau217 concentrations. More research is needed on the causes of positive plasma p-tau217 and negative CSF or Aβ-PET biomarker profiles.

Supplemenmtary materials – Study 5

Supplementary Table 1. Aβ-PET / Plasma p-tau217 comparisons

	PET-/ p-tau217-	PET-/ p-tau217+	P-value	PET+/ p-tau217-	PET+/ p-tau217+	P-value
N	30	9		1	37	
Age, years	66.1 (8.7)	65.8 (9.8)	>0.9	NA	67.0 (6.0)	NA
Female sex (%)	14 (46.7%)	6 (66.7%)	0.9	NA	25 (67.6%)	NA
Immigrant status	15 (50.0%)	6 (66.7%)	0.9	NA	10 (27.0%)	NA
Syndrome diagnosis			0.9	NA		NA
SCD	1 (3.3%)	1 (11.1%)		NA	0 (0.0%)	NA
MCI	13 (43.3%)	3 (33.3%)		NA	7 (18.9%)	NA
Dementia	16 (53.3%)	5 (55.6%)		NA	30 (81.1%)	NA
undecided	0 (0.0%)	0 (0.0%)		NA	0 (0.0%)	NA
Etiological diagnoses			0.8			NA
AD and mixed AD	0 (0.0%)	1 (11.1%)		NA	36 (97.3%)	
Non-neurodegenerative	7 (23.3%)	1 (11.1%)		NA	1 (2.7%)	
NPH	1 (3.3%)	0 (0%)		NA	0 (0.0%)	
Other neurodegenerative	6 (20.0%)	1 (11.1%)		NA	0 (0.0%)	
Non neurological	5 (16.7%)	4 (44.4%)		NA	0 (0.0%)	
Unknown	11 (36.7%)	2 (22.2%)		NA	0 (0.0%)	
Diabetes	9 (30.0%)	3 (33.3%)	>0.9	NA	6 (16.2%)	NA
Hypertension	19 (63.3%)	1 (11.1%)	0.06	NA	19 (51.4%)	NA
Hyperlipidemia	9 (30.0%)	2 (22.2%)	>0.9	NA	11 (29.7%)	NA
Clinical history of stroke	2 (6.7%)	2 (22.2%)	0.8	NA	4 (10.8%)	NA
eGFR, mL/min/1.73m^2	82.3 (14.9)	81.1 (21.1)	>0.9	NA	83.5 (11.2)	NA
BMI, kg/m^2	29.6 (6.2)	25.3 (6.5)	0.5	NA	25.5 (4.3)	NA
Fazekas score			>0.9			NA
0-1	16 (69.6%)	5 (62.5%)		NA	22 (73.3%)	NA
2-3	7 (30.4%)	3 (37.5%)		NA	8 (26.7%)	NA
MMSE/RUDAS (0-30)	22.0 [21.0, 24.0]	21.0 [11.0, 26.0]	0.9	NA	23.0 [19.0, 26.0]	NA

Note: Pairwise comparisons were based on independent samples t-test, Mann-Whitney U test, Chi-Squared test, or Fisher's exact test. No results are reported for the PET+/plasma- group and no p-values reported as N = 1.

Abbreviations: AD = Alzheimer's disease, BMI = Body Mass Index, eGFR = estimated Glomerular Filtration Rate, MCI = Mild Cognitive Impairment, MMSE = Mini-Mental State Examination, NPH = Normal Pressure Hydrocephalus, PET = Positron Emission Tomography, p-tau217 = phosphorylated tau 217, RUDAS = Rowland Universal Dementia Assessment Scale, SCD = Subjective Cognitive Decline

Supplementary Table 2. CSF / Plasma p-tau217 comparisons

	CSF-/ p-tau217-	CSF -/ p-tau217+	p-value	CSF +/ p-tau217-	CSF +/ p-tau217+	p-value
N	188	66		14	221	
Age, years	66.6 (9.4)	68.5 (8.8)	0.3	69.4 (9.3)	70.1 (8.0)	>0.9
Female sex (%)	86 (45.7%)	31 (47.0%)	>0.9	4 (28.6%)	129 (58.4%)	0.08*
Immigrant status	115 (61.2%)	37 (56.1%)	0.6	8 (57.1%)	96 (43.4%)	0.5
Syndrome diagnosis			0.4			0.001
SCD	25 (13.3%)	9 (13.6%)		2 (14.3%)	3 (1.4%)	
MCI	76 (40.4%)	20 (30.3%)		8 (57.1%)	45 (20.4%)	
Dementia	67 (35.6%)	32 (48.5%)		4 (28.6%)	168 (76.0%)	
undecided	20 (10.6%)	5 (7.6%)		0 (0.0%)	5 (2.3%)	
Etiological diagnoses			<0.001			<0.001
AD and mixed AD	10 (5.3%)	20 (30.3%)		5 (35.7%)	186 (84.2%)	
Non-neurodegenerative	33 (17.6%)	7 (10.6%)		1 (7.1%)	6 (2.7%)	
NPH	20 (10.6%)	11 (16.7%)		1 (7.1%)	7 (3.2%)	
Other neurodegenerative	28 (14.9%)	9 (13.6%)		0 (0.0%)	9 (4.1%)	
Non neurological	45 (23.9%)	12 (18.2%)		5 (35.7%)	9 (4.1%)	
Unknown	52 (27.7%)	7 (10.6%)		2 (14.3%)	4 (1.8%)	
Diabetes	62 (33.0%)	17 (25.8%)	0.4	2 (14.3%)	44 (19.9%)	>0.9
Hypertension	89 (47.3%)	31 (47.0%)	>0.9	5 (35.7%)	87 (39.4%)	>0.9
Hyperlipidemia	37 (19.7%)	16 (24.2%)	0.6	5 (35.7%)	53 (24.0%)	0.5
Clinical history of stroke	13 (6.9%)	6 (9.1%)	0.7	2 (14.3%)	13 (5.9%)	0.4
eGFR, mL/min/1.73m^2	84.2 (18.4)	79.2 (21.1)	0.3	81.9 (15.1)	80.8 (15.1)	>0.9
BMI, kg/m^2	27.5 (5.2)	25.9 (4.2)	0.1*	28.6 (4.4)	25.5 (4.6)	0.08*
Fazekas score			0.3			>0.9
0-1	74 (59.2%)	33 (73.3%)		8 (80.0%)	135 (75.4%)	
2-3	51 (40.8%)	12 (26.7%)		2 (20.0%)	44 (24.6%)	
MMSE/RUDAS (0-30)	23.0 [20.0, 27.0]	25.0 [21.0, 28.0]	0.4	25.0 [22.0, 28.0]	23.0 [18.0, 26.0]	0.3

Note: Pairwise comparisons were based on independent samples t-test, Mann-Whitney U test, Chi-Squared test, or Fisher's exact test. * = p-value was significant before adjustment for multiple comparisons.

Abbreviations: AD = Alzheimer's disease, BMI = Body Mass Index, CSF = Cerebrospinal Fluid, eGFR = estimated Glomerular Filtration Rate, MCI = Mild Cognitive Impairment, MMSE = Mini-Mental State Examination, NPH = Normal Pressure Hydrocephalus, p-tau217 = phosphorylated tau 217, RUDAS = Rowland Universal Dementia Assessment Scale, SCD = Subjective Cognitive Decline.

ACKNOWLEDGEMENTS

We are thankful to the patients and clinical staff from the memory clinics at the Copenhagen University Hospital – Rigshospitalet and Skåne University Hospital.

DISCLOSURE STATEMENT

A.H.S. has received a one-time consultancy fee (for the institution) from Eisai and BioArtic in 2025.

D.B. declares no conflicts of interest.

D.K. declares no conflicts of interest.

E.S. has acquired research support (for the institution) from Beckman Coulter, Bristol Myers Squibb, C2N Diagnostics, Eisai, Fujirebio, GE Healthcare and Roche Diagnostics.

F.K.C. declares no conflicts of interest.

G.W. declares no conflicts of interest.

H.S.G. declares no conflicts of interest.

K.S.F. is or has been member of advisory boards or acts or has acted as consultant for Eisai, Novo Nordisk, Roche Diagnostics, Eli Lilly, AbbVie, BioArctic, Roche (remuneration paid to institution), Imprint Medicine (no renumeration), has speaking engagement for Eisai, BioArctic, Eli Lilly, Novo Nordisk, Roche Diagnostics (remuneration paid to institution), Best Practice Nordic (personal renumeration) is or has been principal investigator in clinical trials for Biogen, Novo Nordisk, Roche, Roche Diagnostics (remuneration paid to institution), has produced educational material for Medscape (personal remuneration), has provided consultation for Guidepoint and Neurocode (personal remuneration), is Editor-in-Chief for Alzheimer's Research and Therapy (Springer - Nature) (personal remuneration) and has received research funding from Aase og Ejner Danielsens Fond, Alzheimer Forskningsfonden, A.P. Møller fonden, Beckett fonden, C2N, DANMODIS, Ellen Mørch Fonden, ERA-PERMED, Fonden for Neurologisk Forskning, Grosserer F.L.Foghts Fond, Harboefonden, Hertzfonden, IHI, Innovationsfonden, Jascha Fonden, KID fonden, Kong Christian den Tiendes Minde-fond, Overretssagfører L. Zeuthens Mindefond, Parkinsonforeningen, Rigshospitalets Forskningspulje.

O.H. is an employee of Lund University and Eli Lilly.

S.G.H. declares no conflicts of interest.

S.J. declares no conflicts of interest.

T.R.N. declares no conflicts of interest.

CONSENT STATEMENT

The study was conducted in accordance with the Declaration of Helsinki, and all patients gave written consent for their samples and clinical data to be used for research. The study was approved by the Regional Ethics Committee in the Capitol Region Denmark (H-23035053), the Danish Data Protection Agency (p-2023-14275), and the Swedish Ethical Review Authority, Sweden (2023-07108-01).

FUNDING STATEMENT

This work was supported by the Innovation Fund Denmark [grant number 1099-00022B, under the frame of ERA PerMed [reference number ERAPERMED2021-184]. The Danish Dementia Research Centre (DDRC) is supported by the Danish Ministry of Health. AHS was supported by the Absalon Foundation founded 1st of May 1978 and Frimodt-Heineke Fonden. KSF was supported by Aase og Ejner Danielsens Fond, Alzheimer Forskningsfonden, A.P. Møller fonden, Beckett fonden, C2N, DANMODIS, Ellen Mørch Fonden, ERA-PERMED, Fonden for Neurologisk Forskning, Grosserer F.L.Foghts Fond, Harboefonden, Hertzfonden, IHI, Innovationsfonden, Jascha Fonden, KID fonden, Kong Christian den Tiendes Minde-fond, Overretssagfører L. Zeuthens Mindefond, Parkinsonforeningen, and Rigshospitalets Forskningspulje.

Work at Lund University and Skåne University Hospital was supported by the National Institute of Aging (R01AG083740), the Alzheimer's Association, (22AARF-1029663, ZEN24-1069572) the Alzheimer's Association in collaboration with the GHR Foundation (ALZSI-26-1523522), the European Research Council (ADG-101096455), European Commission/Horizon Europe (101108819, 101153323), ERA PerMed (ERAPERMED2021-184), The Michael J Fox Foundation (MJFF-025507, MJFF-025741), Global Research Platform LLC, the Cure Alzheimer's fund (F2025/1066), Swedish Research Council (2021-02219, 2022-00775, 2023-06428), the Swedish Alzheimer Foundation (AF-981132, AF-980907 and AF-968598, AF-1011949, AF-1011799), the

Swedish Brain Foundation (FO2023-0163, FO2024-0133-HK-46, FO2024-0284,FO2024-0385, FO2025-0055), The Swedish Parkinson Foundation (1485/23, 1589/24), the Strategic Research Area MultiPark (Multidisciplinary Research in Parkinson's disease) at Lund University, WASP and DDLS Joint call for research projects (WASP/DDLS22-066), the Skåne University Hospital Foundation, Regional research support (2025-2024-2925, 2025-2024-2862), the Swedish federal government under the ALF agreement (2022-Project0080, 2022-Project0107, 2022-Project0062, 2022-YF0017, 2024-YF0048, 2024-ST0026), Lilly Research Award Program (F2025/932), Avid Pharmaceuticals, F Hoffman-la Roche AG (F2025/453), Biogen, Bristol Myers Squibb, CellInvent (F2025/1321), Eisai, Fujirebio, GE Healthcare, the Knut and Alice Wallenberg foundation (2017-0383), Konung Gustaf V:s och Drottning Victorias Frimurarestiftelse, the Kamprad Foundation (20243058), Bundy Academy, Greta and Johan Kock Foundation (F2024/228, F2024/2330, F2024/197, F2025/160, F2024/198, F2024/2332, F2025/319), the Crafoord Foundation (20240888), the Rönström Family Foundation (AF1011799, FRS 0013, FRS-0003, FRS-0004, AF-1011949), the Royal Physiographic Society (F2025/1092), Stiftelsen för Gamla Tjänarinnor (2024-250), Thorsten and Elsa Segerfalk's Foundation (F2024/1053, F2025/1320), and Fredrik and Ingrid Thuring's Foundation (2024-099).

The funding sources had no role in the design and conduct of the study; in the collection, analysis, interpretation of the data; or in the preparation, review, or approval of the manuscript.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study originate from two centers who each hold the ownership of their data. Data can be made available upon reasonable request and consent from the respective centers.

REFERENCES

[1] Kivisäkk P, Fatima HA, Cahoon DS, Otieno B, Chacko L, Minooei F, et al. Clinical evaluation of a novel plasma pTau217 electrochemiluminescence immunoassay in Alzheimer's disease. Sci Rep 2024;14. https://doi.org/10.1038/S41598-024-51334-X.

[2] Ashton NJ, Brum WS, Molfetta G Di, Benedet AL, Arslan B, Jonaitis E, et al. Diagnostic Accuracy of a Plasma Phosphorylated Tau 217 Immunoassay for Alzheimer Disease Pathology. JAMA Neurol 2024;81:255–63. https://doi.org/10.1001/JAMANEUROL.2023.5319.

[3] Barthélemy NR, Salvadó G, Schindler SE, He Y, Janelidze S, Collij LE, et al. Highly accurate blood test for Alzheimer's disease is similar or superior to clinical cerebrospinal fluid tests. Nat Med 2024;30:1085–95. https://doi.org/10.1038/S41591-024-02869-Z.

[4] Schindler SE, Galasko D, Pereira AC, Rabinovici GD, Salloway S, Suárez-Calvet M, et al. Acceptable performance of blood biomarker tests of amyloid pathology - recommendations from the Global CEO Initiative on Alzheimer's Disease. Nat Rev Neurol 2024;20. https://doi.org/10.1038/S41582-024-00977-5.

[5] Palmqvist S, Warmenhoven N, Anastasi F, Pilotto A, Janelidze S, Tideman P, et al. Plasma phospho-tau217 for Alzheimer's disease diagnosis in primary and secondary care using a fully automated platform. Nat Med 2025;31:2036–43. https://doi.org/10.1038/S41591-025-03622-W.

[6] Kjaergaard D, Nielsen TR, Stomrud E, Palmqvist S, Bali D, Dolado AO, et al. Influence of ethnicity on the diagnostic accuracy of plasma p-tau217 for the identification of Alzheimer's disease: A consecutive mixed memory clinic cohort study. Alzheimers Dement 2025;21. https://doi.org/10.1002/ALZ.70315.

[7] Janelidze S, Barthélemy NR, He Y, Bateman RJ, Hansson O. Mitigating the Associations of Kidney Dysfunction With Blood Biomarkers of Alzheimer Disease by Using Phosphorylated Tau to Total Tau Ratios. JAMA Neurol 2023;80:516–22. https://doi.org/10.1001/JAMANEUROL.2023.0199.

[8] Pichet Binette A, Janelidze S, Cullen N, Dage JL, Bateman RJ, Zetterberg H, et al. Confounding factors of Alzheimer's disease plasma biomarkers and their impact on clinical performance. Alzheimers Dement 2023;19:1403–14. https://doi.org/10.1002/ALZ.12787.

[9] Kjaergaard D, Simonsen AH, Stomrud E, Bali D, Janelidze S, Hansson O, et al. Combining plasma p-tau217 and cross-cultural cognitive tests to identify Alzheimer's Disease in an ethnically diverse mixed memory clinic cohort. J Neurol Sci 2025;478. https://doi.org/10.1016/j.jns.2025.123739.

[10] Jacobs T, Brien CO, Figueredo L, Gogola A, Gaggi NL, Hurwitz B, et al. Body mass index and blood volume influence plasma biomarkers and positron emission tomography classification in preclinical Alzheimer's disease. Alzheimers Dement 2025;21:e70765. https://doi.org/10.1002/ALZ.70765.

[11] Arslan B, Brum WS, Pola I, Therriault J, Rahmouni N, Stevenson J, et al. The impact of kidney function on Alzheimer's disease blood biomarkers: implications for predicting amyloid-β positivity. Alzheimers Res Ther 2025;17. https://doi.org/10.1186/S13195-025-01692-Z.

[12] Mielke MM, Dage JL, Frank RD, Algeciras-Schimnich A, Knopman DS, Lowe VJ, et al. Performance of plasma phosphorylated tau 181 and 217 in the community. Nat Med 2022;28:1398–405. https://doi.org/10.1038/S41591-022-01822-2.

[13] Abu-Rumeileh S, Scholle L, Mensch A, Großkopf H, Ratti A, Kölsch A, et al. Phosphorylated tau 181 and 217 are elevated in serum and muscle of patients with amyotrophic lateral sclerosis. Nat Commun 2025;16. https://doi.org/10.1038/S41467-025-57144-7.

[14] Janelidze S, Ashton NJ, Orduña Dolado A, Nordström U, Bali D, Forsberg KME, et al. A comparison of p-tau assays for the specificity to detect tau changes in Alzheimer's disease. Alzheimers Dement 2025;21. https://doi.org/10.1002/ALZ.70208.

[15] Gundersen JK, Gonzalez-Ortiz F, Karikari T, Kirsebom BE, Mertes K, Zetterberg H, et al. Neuronal plasma biomarkers in acute ischemic stroke. J Cereb Blood Flow Metab 2025;45:77–84. https://doi.org/10.1177/0271678X241293537.

[16] Gonzalez-Ortiz F, Vávra J, Payne E, Kirsebom BE, Sjöbom U, Santos C, et al. The potential dual role of tau phosphorylation: plasma phosphorylated-tau217 in newborns and Alzheimer's disease. Brain Commun 2025;7. https://doi.org/10.1093/BRAINCOMMS/FCAF221.

[17] Asken BM, DeSimone JC, Wang WE, McFarland KN, Arias F, Levy SA, et al. Plasma p-tau217 concordance with amyloid PET among ethnically diverse older adults. Alzheimers Dement (Amst) 2024;16. https://doi.org/10.1002/DAD2.12617.

[18] Cody KA, Du L, Studer RL, Jonaitis EM, Asthana S, Christian BT, et al. Accuracy of plasma biomarkers to detect Alzheimer's disease proteinopathy prior to dementia. Alzheimers Dement 2025;21. https://doi.org/10.1002/ALZ.14570.

[19] Yun J, Shin D, Lee EH, Kim JP, Ham H, Gu Y, et al. Temporal Dynamics and Biological Variability of Alzheimer Biomarkers. JAMA Neurol 2025;82:384. https://doi.org/10.1001/JAMANEUROL.2024.5263.

[20] Kjaergaard D, Simonsen AH, Waldemar G, Nielsen TR. Ethnic and racial influences on blood biomarkers for Alzheimer's disease: A systematic review. J Alzheimers Dis 2025;103:81–91. https://doi.org/10.1177/13872877241299047.

[21] Valletta M, Canevelli M, Gasparini F, Buscarnera S, Salzillo M, Triolo F, et al. Multimorbidity and fluid biomarkers of Alzheimer's disease: a systematic review. Eur Geriatr Med 2025. https://doi.org/10.1007/S41999-025-01222-Y,.

[22] Feizpour A, Doecke JD, Doré V, Krishnadas N, Huang K, Bourgeat P, et al. Detection and staging of Alzheimer's disease by plasma pTau217 on a high throughput immunoassay platform. EBioMedicine 2024;109. https://doi.org/10.1016/j.ebiom.2024.105405.

[23] Ahn J, Lee EH, Yoo H, Shin D, Kang H, Yim S, et al. Tailoring thresholds for interpreting plasma p-tau217 levels. J Neurol Neurosurg Psychiatry 2025;96:722–7. https://doi.org/10.1136/JNNP-2025-335830.

[24] Clemmensen FK, Gramkow MH, Simonsen AH, Ashton NJ, Huber H, Blennow K, et al. Short-term variability of Alzheimer's disease plasma biomarkers in a mixed memory clinic cohort. Alzheimers Res Ther 2025;17:26. https://doi.org/10.1186/S13195-024-01658-7,.

[25] Manniche C, Simonsen AH, Hasselbalch SG, Andreasson U, Zetterberg H, Blennow K, et al. Cerebrospinal Fluid Biomarkers to Differentiate Idiopathic Normal Pressure Hydrocephalus from Subcortical Ischemic Vascular Disease. J Alzheimers Dis 2020;75:937–47. https://doi.org/10.3233/JAD-200036.

[26] Manniche C, Hejl AM, Hasselbalch SG, Simonsen AH. Cerebrospinal Fluid Biomarkers in Idiopathic Normal Pressure Hydrocephalus versus Alzheimer's Disease and Subcortical Ischemic Vascular Disease: A Systematic Review. J Alzheimers Dis 2019;68:267–79. https://doi.org/10.3233/JAD-180816.

9.6. Data extraction from ongoing systematic review on plasma p-tau217 studies.

Preliminary title: Participant characteristics in blood p-tau217 studies for Alzheimer's disease: A systematic review

Marco Toccaceli Blasi, Simona Buscarnera, Martina Salzillo, Giuseppe Bruno, Filippo Nuti, Anja Hviid Simonsen, T. Rune Nielsen, Daniel Kjaergaard & Marco Canevelli

Status: Under preparation

Prospero ID: CRD420251000147

Data extraction table the ethnicity variable

The review extracted data on all the following variables: Title, authors, year, journal, aim, study design, single/multicenter, study location, cohort, study setting, assay/platform, plasma/serum used, AD definition, sample size including biomarker confirmed AD, cognitive status, sex, age, ethnicity/race, education, BMI, kidney function, comorbidities, cumulative health measures, medication use, vascular damage, inclusion and exclusion criteria.

Title	**Ethnicity, n (%)**
Blood Biomarkers to Detect Alzheimer Disease in Primary Care and Secondary Care.	/
Diagnostic Accuracy of a Plasma Phosphorylated Tau 217 Immunoassay for Alzheimer Disease Pathology.	/
Discriminative Accuracy of Plasma Phospho-tau217 for Alzheimer Disease vs Other Neurodegenerative Disorders.	/
Head-to-head comparison of 10 plasma phospho-tau assays in prodromal Alzheimer's disease.	/
Plasma phosphorylated tau 217 and phosphorylated tau 181 as biomarkers in Alzheimer's disease and frontotemporal lobar degeneration: a retrospective diagnostic performance study.	White 507/593 (85%), Asian 23/593 (4%), Black 5/593 (<1%), Pacific Islander 1/593 (<1%), Unknown ethnic origin 57/593 (10%)
Plasma phosphorylated tau 217 in preclinical Alzheimer's disease.	White 158/165 (96%), Black 4/165 (2%), Native American 3/165 (2%)
Plasma p-tau181, p-tau217, and other blood-based Alzheimer's disease biomarkers in a multi-ethnic, community study.	Autopsy cohort: White 52/113 (46%), Black 32/113 (28%), Hispanic 29/113 (26%). Clinical cohort: White 100/300 (33%), Black 100/300 (33%), Hispanic 100/300 (33%)
Plasma p-tau231 and p-tau217 as state markers of amyloid-β pathology in preclinical Alzheimer's disease.	/
Performance of plasma phosphorylated tau 181 and 217 in the community.	Non-Hispanic 1311/1329 (98.6%), White 1287/1329 (96.8%), Black 10/1329 (0.8%), Other 32/1329 (2.4%)
Predicting amyloid PET and tau PET stages with plasma biomarkers.	/
Highly accurate blood test for Alzheimer's disease is similar or superior to clinical cerebrospinal fluid tests.	Biofinder: NA. ADRC: White 308/337 (91.4%), Black 24/337 (7.1%), other 5/337 (1.5%)
Blood plasma phosphorylated-tau isoforms track CNS change in Alzheimer's disease.	/
Differential roles of Aβ42/40, p-tau231 and p-tau217 for Alzheimer's trial selection and disease monitoring.	/

Plasma and CSF biomarkers in a memory clinic: Head-to-head comparison of phosphorylated tau immunoassays.	/
Plasma p-tau217 in Alzheimer's disease: Lumipulse and ALZpath SIMOA head-to-head comparison.	/
An accurate fully automated panel of plasma biomarkers for Alzheimer's disease.	/
Equivalence of plasma p-tau217 with cerebrospinal fluid in the diagnosis of Alzheimer's disease.	/
Association of Phosphorylated Tau Biomarkers With Amyloid Positron Emission Tomography vs Tau Positron Emission Tomography.	Hispanic/Latinx 1/171 (0.6%), Not Hispanic/Latinx 161/171 (94.2%)
Comparison of two plasma p-tau217 assays to detect and monitor Alzheimer's pathology.	Race: Asian 14/294 (4.8%), Black or African American 1/294 (0.3%), White 277/294 (94.2%). Ethnicity: Hispanic or Latino 2/294 (0.68%), Not Hispanic or Latino 292/294 (99.3%)
Prediction of future Alzheimer's disease dementia using plasma phospho-tau combined with other accessible measures.	/
Prediction of Longitudinal Cognitive Decline in Preclinical Alzheimer Disease Using Plasma Biomarkers.	/
Comparison of Plasma Phosphorylated Tau Species With Amyloid and Tau Positron Emission Tomography, Neurodegeneration, Vascular Pathology, and Cognitive Outcomes.	White 198/200 (99.0%), Multiracial 2/200 (1.0%)
Plasma Aβ42/Aβ40 and phospho-tau217 concentration ratios increase the accuracy of amyloid PET classification in preclinical Alzheimer's disease.	Ethnicity: Hispanic/Latino: 146/1080 (13.5%), Not Hispanic/Latino: 934/1080 (86.5%). Race: White 1011/1080 (93.6%), Black/African American 39/1080 (3.6%), Asian 9/1080 (0.8%), Multiracial 10/1080 (0.9%), Other 9/1080 (0.8%), Unknown/not reported 1/1080 (0.1%)
Combining plasma Aβ and p-tau217 improves detection of brain amyloid in non-demented elderly.	Japanese 474 (72.8%), Caucasian 177 (27.2%) *
Plasma Biomarker Strategy for Selecting Patients With Alzheimer Disease for Antiamyloid Immunotherapies.	/
Clinical validation of the PrecivityAD2 blood test: A mass spectrometry-based test with algorithm combining %p-tau217 and Aβ42/40 ratio to identify presence of brain amyloid.	Hispanic or Latino 177 (30.4%); Not Hispanic or Latino 392 (67.2%); Not Reported 3 (0.5%); Unknown 11 (1.9%)
Plasma Phosphorylated Tau 217 and Aβ42/40 to Predict Early Brain Aβ Accumulation in People Without Cognitive Impairment.	Knight ADRC: White 255/283 (90.1%), Black 24/283 (8.5%), Other 4/283 (1.4%) *
Head-to-head comparison of leading blood tests for Alzheimer's disease pathology.	Black 14/392 (3.6%), White 366/392 (93.4%), Other 12/392 (3.1%) *
A two-step workflow based on plasma p-tau217 to screen for amyloid β positivity with further confirmatory testing only in uncertain cases.	/
Clinical and analytical comparison of six Simoa assays for plasma P-tau isoforms P-tau181, P-tau217, and P-tau231.	/

Diagnostic performance of plasma pTau 217, pTau 181, Aβ 1-42 and Aβ 1-40 in the LUMIPULSE automated platform for the detection of Alzheimer disease.	/
A novel ultrasensitive assay for plasma p-tau217: Performance in individuals with subjective cognitive decline and early Alzheimer's disease.	/
The Bio-Hermes Study: Biomarker database developed to investigate blood-based and digital biomarkers in community-based, diverse populations clinically screened for Alzheimer's disease.	Non-Hispanic White 720/956 (75.3%), Hispanic 110/956 (11.5%), Non-Hispanic Black 108/956 (11.3%), Other 18/956 (1.9%) *
Plasma p-tau231 and p-tau217 inform on tau tangles aggregation in cognitively impaired individuals.	/
P-tau217 and other blood biomarkers of dementia: variation with time of day.	/
Plasma pTau181 and pTau217 predict asymptomatic amyloid accumulation equally well as amyloid PET.	/
Head-to-head comparison between plasma p-tau217 and flortaucipir-PET in amyloid-positive patients with cognitive impairment.	Race: White 83/87 (95.4%), Black/African American 1/87 (1.1%), Asian 3/87 (3.4%). Ethnicity: Hispanic or Latino 6/87 (6.9%), Non-Hispanic or Latino 81/87 (93.1%) *
Plasma Alzheimer's disease biomarker variability: Amyloid-independent and amyloid-dependent factors.	/
A blood-based biomarker workflow for optimal tau-PET referral in memory clinic settings.	TRIAD: White 172/179 (96.1%), Asian 3/179 (1.7%), Black 1/179 (0.6%)
Comparison of plasma biomarkers and amyloid PET for predicting memory decline in cognitively unimpaired individuals.	/
Longitudinal plasma phosphorylated-tau217 and other related biomarkers in a non-demented Alzheimer's risk-enhanced sample.	Non-Hispanic White 402/424 (94.8%)
Clinical value of plasma ALZpath pTau217 immunoassay for assessing mild cognitive impairment.	/
A comprehensive head-to-head comparison of key plasma phosphorylated tau 217 biomarker tests.	/
Detecting amyloid positivity in early Alzheimer's disease using combinations of plasma Aβ42/Aβ40 and p-tau.	/
Evaluation of Plasma Phosphorylated Tau217 for Differentiation Between Alzheimer Disease and Frontotemporal Lobar Degeneration Subtypes Among Patients With Corticobasal Syndrome.	Asian: 20/386 (5.2%), Black: 9/386 (2.3%), Hispanic: 3/386 (0.8%), Native American: 1/386 (0.3%), White: 317/386 (82.1%) *
Optimal blood tau species for the detection of Alzheimer's disease neuropathology: an immunoprecipitation mass spectrometry and autopsy study.	White: 113/123 (91.9%), Black or African American 6/123 (4.9%), American Indian/Alaska Native 2/123 (1.6%), Asian 1/123 (0.8%), Other 1/123 (0.8%)
Detection and staging of Alzheimer's disease by plasma pTau217 on a high throughput immunoassay platform.	/
Longitudinal plasma p-tau217 is increased in early stages of Alzheimer's disease.	/

Association Between Plasma Biomarkers of Amyloid, Tau, and Neurodegeneration with Cerebral Microbleeds.	/
Specific associations between plasma biomarkers and postmortem amyloid plaque and tau tangle loads.	/
Plasma p-tau181 and p-tau217 in discriminating PART, AD and other key neuropathologies in older adults.	/
Optimizing cutpoints for clinical interpretation of brain amyloid status using plasma p-tau217 immunoassays.	White: 415/427 (97%), Black: 4/427 (<1%), Asian: 2/427 (<1%), Hispanic or Latino 1/427 (<1%), More than one race: 3/427 (<1%)
Diagnosis of Alzheimer's disease using plasma biomarkers adjusted to clinical probability.	ADNI: Race: Asian: 8/1559 (0.5%), Black: 6/1559 (0.4%), More than one: 15/1559 (1.0%), White 1523/1559 (97.7%); Ethnicity: Hispanic / Latinx: 6/1559 (0.4%), Not Hispanic / Latinx: 1543/1559 (99.0%) HABS-HD: Race: American Indian / Alaskan Native: 3/598 (0.5%), Asian: 1/598 (0.2%), Black: 277/598 (46.3%), Hawaiian / Pacific Islander: 2/598 (0.3%), More than one: 17/598 (2.8%), White: 298/598 (49.8%); Ethnicity: Hispanic/Latinx: 127/598 (21.2%), Not Hispanic/Latinx: 471/598 (78.8%) BICWALZS: Race: Asian: 727/727 (100%) (reported in the paper) BioDEGMAR: Race: Asian: 1/210 (0.5%), More than one / Other 1/210 (0.5%), White: 208/210 (99.0%) McGill Memory Clinic: Race: Asian: 1/54 (1.8%), More than one: 1/54 (1.8%), White: 52/54 (96.3%)
Identification of late-stage tau accumulation using plasma phospho-tau217.	/
Performance of plasma p-tau217 for the detection of amyloid-β positivity in a memory clinic cohort using an electrochemiluminescence immunoassay.	/
Temporal Dynamics and Biological Variability of Alzheimer Biomarkers.	/
Where Do Plasma Biomarkers fit in With Current Alzheimer's Disease Detection?	Race: White 69/74 (93.2%), Black or African American 4/74 (5.4%), Asian 1/74 (1.4%).

	Ethnicity: Hispanic 1/74 (1.4%), Not Hispanic 73/74 (98.6%).
Plasma phosphorylated tau-217 exhibits sex-specific prognostication of cognitive decline and brain atrophy in cognitively unimpaired adults.	Non-Hispanic White: CU males 41/44 (93.2%), CU females 36/41 (87.8%), MCI males 34/37 (94.4%), MCI females 37/41 (90.2%)
Associations of Plasma Phospho-Tau217 Levels With Tau Positron Emission Tomography in Early Alzheimer Disease.	/
Plasma p-tau217 concordance with amyloid PET among ethnically diverse older adults.	Hispanic/Latino White 115/239 (48.1%), Non-Hispanic/Latino White 112/239 (46.9%), Black/African American 10/239 (4.2%), Black/Hispanic 2/239 (0.8%) *
Modeling the temporal evolution of plasma p-tau in relation to amyloid beta and tau PET.	/
Performance of plasma p-tau217 and NfL in an unselected memory clinic setting.	/
Confounding factors of Alzheimer's disease plasma biomarkers and their impact on clinical performance.	/
Correlation of plasma and neuroimaging biomarkers in Alzheimer's disease.	White (non-Latinx) 100/300 (33.3%), Black/African American (non-Latinx) 100/300 (33.3%), Hispanic/Latinx 100/300 (33.3%) *
Effects of time of the day at sampling on CSF and plasma levels of Alzheimer' disease biomarkers.	/
Plasma p-tau217 identifies cognitively normal older adults who will develop cognitive impairment in a 10-year window.	White 211/215 (98.1%)
Plasma p-tau217, p-tau181, and NfL as early indicators of dementia risk in a community cohort: The Shanghai Aging Study.	/
Plasma p217+tau versus NAV4694 amyloid and MK6240 tau PET across the Alzheimer's continuum.	/
Biomarker-Based Prediction of Longitudinal Tau Positron Emission Tomography in Alzheimer Disease.	/
Diagnostic accuracy of automated Lumipulse plasma pTau-217 in Alzheimer's disease: a real-world study.	/
Serum neurofilament light chain and inflammatory cytokines as biomarkers for early detection of mild cognitive impairment.	/
Significance of plasma p-tau217 in predicting long-term dementia risk in older community residents: Insights from machine learning approaches.	/
Soluble P-tau217 reflects amyloid and tau pathology and mediates the association of amyloid with tau.	/
Personalized whole-brain neural mass models reveal combined Aβ and tau hyperexcitable influences in Alzheimer's disease.	NA
Diagnostic performance of plasma pTau(217), pTau(181), Aβ(1-42) and Aβ(1-40) in the LUMIPULSE automated platform for the detection of Alzheimer disease.	/
Disentangling relationships between Alzheimer's disease plasma biomarkers and established biomarkers in patients of tertiary memory clinics.	/

Plasma biomarkers of Alzheimer's disease improve prediction of cognitive decline in cognitively unimpaired elderly populations.	/
Plasma Phosphorylated Tau 217 as a Discriminative Biomarker for Cerebral Amyloid Angiopathy.	/
Diagnostic and prognostic performance to detect Alzheimer's disease and clinical progression of a novel assay for plasma p-tau217.	/
Plasma Alzheimer's disease biomarker relationships with incident abnormal amyloid PET.	/
Longitudinal trajectory of plasma p-tau217 in cognitively unimpaired subjects.	/
Plasma phosphorylated tau217 strongly associates with memory deficits in the Alzheimer's disease spectrum.	/
Assessing cognitive impairment and disability in older adults through the lens of whole brain white matter patterns.	NA
Mitigating the Associations of Kidney Dysfunction With Blood Biomarkers of Alzheimer Disease by Using Phosphorylated Tau to Total Tau Ratios.	/
Global neuropathologic severity of Alzheimer's disease and locus coeruleus vulnerability influences plasma phosphorylated tau levels.	NA
Test-retest variability of plasma biomarkers in Alzheimer's disease and its effects on clinical prediction models.	/
Machine learning prediction of tau-PET in Alzheimer's disease using plasma, MRI, and clinical data.	
Influence of medical conditions on the diagnostic accuracy of plasma p-tau217 and p-tau217/Aβ42	White 302/357 (85%), Black 45/357 (13%), Asian 3/357 (0.8%), Biracial 4/357 (1.1%), Native Hawaiian or other Pacific Islander 2/357 (0.6%)
How well do plasma Alzheimer's disease biomarkers reflect the CSF amyloid status?	/
Evaluation of plasma p-tau217 for detecting amyloid pathology in a diverse and heterogeneous community-based cohort.	White 462/598 (77.3%), Black or African American 124/598 (20.7%), Asian 6/598 (1.0%), American Indian or Alaska Native 4/598 (0.7%) *
Strong diagnostic performance of plasma ptau217 for CSF biomarker-defined young-onset Alzheimer disease in a diagnostically heterogeneous clinical cohort.	/
Tau PET correlates with different Alzheimer's disease-related features compared to CSF and plasma p-tau biomarkers.	/
Combining plasma phospho-tau and accessible measures to evaluate progression to Alzheimer's dementia in mild cognitive impairment patients.	/
Quantitative Assessment of the Effect of Chronic Kidney Disease on Plasma P-Tau217 Concentrations.	Non-Hispanic White 199/202 (90%), Black 2/202 (1%), Asian 1/202 (0.5%)
Tau-PET is superior to phospho-tau when predicting cognitive decline in symptomatic AD patients.	/
Differential roles of Alzheimer's disease plasma biomarkers in stepwise biomarker-guided diagnostics.	/
Clinical decision points for two plasma p-tau217 laboratory developed tests in neuropathology confirmed samples.	/

Visual read of [F-18]florquinitau PET that includes and extends beyond the mesial temporal lobe is associated with increased plasma pTau217 and cognitive decline in a cohort that is enriched with risk for Alzheimer's disease.	American Indian or Alaskan Native 21/728 (2.9%), Asian 1/728 (0.1%), Black or African American 52/728 (7.1%), White, Hispanic 7/728 (1.0%), White, non-Hispanic 644/728 (88.5%)
Plasma phospho-tau217 as a predictive biomarker for Alzheimer's disease in a large south American cohort.	Native American ancestry 80%, European ancestry 18%, African ancestry 2%
The Hippocampal Subfield Volume Reduction and Plasma Biomarker Changes in Mild Cognitive Impairment and Alzheimer's Disease.	NA
Exploring the ability of plasma pTau217, pTau181 and beta-amyloid in mirroring cerebrospinal fluid biomarker profile of Mild Cognitive Impairment by the fully automated Lumipulse(®) platform.	/
Diagnostic Accuracy of Plasma p-tau217 for Detecting Pathological Cerebrospinal Fluid Changes in Cognitively Unimpaired Subjects Using the Lumipulse Platform.	/
The Bayesian approach for real-world implementation of plasma p-tau217 in tertiary care memory clinics in Thailand.	/
Plasma pTau-217 and N-terminal tau (NTA) enhance sensitivity to identify tau PET positivity in amyloid-β positive individuals.	/
MRI-Derived AD Signature of Cortical Thinning and Plasma P-Tau217 for Predicting Alzheimer Dementia Among Community-Dwelling Older Adults.	/
Immunoassay detection of multiphosphorylated tau proteoforms as cerebrospinal fluid and plasma Alzheimer's disease biomarkers.	/
Differences of longitudinal plasma biomarkers between single memory domain and multidomain subject cognitive decline: Evidence from SILCODE.	/
Influence of cognitive impairment and race on plasma p-Tau(217) in two diverse cohorts.	Chinese American 38/221 (17.2%), Black or African American 66/221 (29.9%), Non-Hispanic White 112/221 (50.7%)
The impact of kidney function on Alzheimer's disease blood biomarkers: implications for predicting amyloid-β positivity.	/
Association and multimodal model of retinal and blood-based biomarkers for detection of preclinical Alzheimer's disease.	/
Diagnostic and discriminative accuracy of plasma phosphorylated tau 217 for symptomatic Alzheimer's disease in a Chinese cohort.	/
Harnessing cognitive trajectory clusterings to examine subclinical decline risk factors.	/
The Alzheimer's Association Global Biomarker Standardization Consortium (GBSC) plasma phospho-tau Round Robin study.	White 12/40 (30.0%), Other 4/40 (10.0%) *
Comparison of Plasma p-tau217 and [(18)F]FDG-PET for Identifying Alzheimer Disease in People With Early-Onset or Atypical Dementia.	/
Comparative performance of plasma pTau181/Aβ42, pTau217/Aβ42 ratios, and individual measurements in detecting brain amyloidosis	/
Core blood biomarkers of Alzheimer's disease: A single-center real-world performance study.	/

Accuracy and clinical applicability of plasma tau 181 and 217 for Alzheimer's disease diagnosis in a memory clinic cohort.	Caucasian 465/468 (99.36%), Chinese 1/468 (0.2%), Arabic 2/468 (0.4%)
Clinical performance of the fully automated Lumipulse plasma p-tau217 assay in mild cognitive impairment and mild dementia.	/
The Taiwan-ADNI workflow toward integrating plasma p-tau217 into prediction models for the risk of Alzheimer's disease and tau burden.	/
Detection of Alzheimer Neuropathology in Alzheimer and Non-Alzheimer Clinical Syndromes With Blood-Based Biomarkers.	American Indian 2/349 (0.6%), Asian 6/349 (1.7%), Black 3/349 (0.9%), Hispanic 15/349 (4.3%), Non-Hispanic White 308/349 (88.3%)
Analytical and clinical performance of eight Simoa(®) and Lumipulse(®) assays for automated measurement of plasma p-tau181 and p-tau217.	/
Plasma p-tau217 and p-tau217/Aβ1-42 are effective biomarkers for identifying CSF- and PET imaging-diagnosed Alzheimer's disease: Insights for research and clinical practice.	/
Clinical utility of plasma p-tau217 in identifying abnormal brain amyloid burden in an Asian cohort with high prevalence of concomitant cerebrovascular disease.	/
Short-term variability of Alzheimer's disease plasma biomarkers in a mixed memory clinic cohort.	/
Cross-cultural validation of plasma p-tau217 and p-tau181 as precision biomarkers for amyloid PET positivity: An East Asian study in Taiwan and Korea.	/
Remote and unsupervised digital memory assessments can reliably detect cognitive impairment in Alzheimer's disease.	NA
A head-to-head comparison of plasma biomarkers to detect Alzheimer's disease in a memory clinic.	/
Plasma p-tau217 and neurofilament/p-tau217 ratio in differentiating Alzheimer's disease from syndromes associated with frontotemporal lobar degeneration	/
Diagnostic performance of plasma pTau217, pTau181, Aβ1-42 and Aβ1-40 in the LUMIPULSE automated platform for the detection of Alzheimer disease	/
Head-to-head study of diagnostic accuracy of plasma and cerebrospinal fluid ptau217 versus ptau181 and ptau231 in a memory clinic cohort	/
APOE ε4 potentiates amyloid β effects on longitudinal tau pathology	NA