Title

Toward an Equitable Multidomain Framework: Genomic and Exposomic Contributions to Alzheimer's Disease

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Toward an Equitable Multidomain Framework: Genomic and Exposomic Contributions to Alzheimer's Disease

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Dedication

To my brother and my sister, we have overcome many mountains together, and I'm so glad to always have you by my side.

To my parents, you are the true model for hard work and resilience. I stand here today because of you.

To my grandmother, I dedicate my PhD to you and your spirit, which lives within me.

最初から私達の人生は苦労そのもの、困難な道だったけど、上を向いて走り続けてきた。だからこそ誰よりも逆境を乗り越える力がある。あなた達がいてくれたからこそ、表面的じゃない本当の「愛情」を知り「苦難」を乗り越えてこられた。

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Contributions

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Toward an Equitable Multidomain Framework: Genomic and Exposomic Contributions to Alzheimer's Disease

Meri Okorie

Abstract

Alzheimer's disease (AD) is the most prevalent neurodegenerative disorder, currently affecting more than 7 million Americans aged 65 years and older, with disproportionately higher incidence rates observed among women and Black and Latinx populations. AD is a complex, polygenic, and multifactorial disease that arises through the interaction of genomic susceptibility and exposomic factors, including clinical, lifestyle, and environmental risk exposures experienced across the life course. Recent advances in biomarker research have enabled earlier detection of AD-related processes through plasma and cerebrospinal fluid assays and neuroimaging modalities, supporting preventative intervention during preclinical and prodromal stages. However, the predictive accuracy and generalizability of biomarkers and existing AD risk prediction tools often vary across demographic groups, highlighting the need for analytical validation of these tools in diverse populations. Addressing this gap is critical for developing equitable precision medicine approaches for AD screening and intervention. The present study describes a two-phase investigation aimed at benchmarking genetic, clinical, and environmental measures of AD liability and quantifying the extent to which these risk domains contribute to underlying AD pathology. Collectively, this body of work provides analytical insights into the improvement of risk prediction and assessment strategies in diverse populations while also advancing mechanistic understanding of how genetic, clinical, and environmental factors influence AD pathological processes.

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Chapter 1: Introduction

1.1 Biological and Public Health Imperative of Alzheimer's Disease

Alzheimer's disease (AD) is a progressive neurodegenerative disease characterized by the accumulation of extracellular amyloid-β (Aβ) plaques, intracellular hyperphosphorylated tau neurofibrillary tangles, and neuronal damage and loss that ultimately lead to cognitive and functional decline.[1] AD represents a major global health challenge due to its complex disease etiology, its rising prevalence, and economic burden. The number of people age 65 and older living with AD in the United States is currently estimated at approximately 7.2 million.[2] The prevalence is projected to double by 2060, with the total economic burden of long-term medical care and hospice services for treating AD or other dementias is expected to rise from $196 billion to $1.4 trillion by 2060.[2] Despite evidence showing declining incidence rates across age groups in the United States,[3,4] these improvements have not been felt equally across populations. Historically underrepresented and marginalized populations, including women and Black, Indigenous, and people of color (BIPOC), experience higher lifetime dementia risks and rates compared to their European-descent male counterparts.[2,5] These disparities suggest that the burden of AD is not shared equally across populations, making it critical to understand how emerging screening, prevention, and treatment strategies perform across diverse demographic populations.

Diagnosis for AD is typically made using a combination of patient- or caregiver-reported concerns related to cognition, standardized neuropsychological and cognitive assessments, and neuroimaging measures.[6] A major limitation of the current diagnosis is that clinical diagnosis often occurs after underlying pathology has accumulated, at which point therapeutic interventions are less effective.[7] This underscores the need to determine who is at elevated risk, which pathways to

target for intervention, and when these interventions should occur. Given that AD is highly heterogenous and multifactorial,[8] addressing these questions requires understanding of both genomic susceptibility and exposomic risk burden across the life course. Genome and exposome profiles may influence not only overall disease risk, but also the timing of biomarker abnormality, progression of underlying pathology, transition to clinical symptom onset, and response to intervention.[9–11] Developing equitable and biologically informed risk assessment frameworks is therefore critical for advancing precision medicine approaches for AD prevention, early detection, and treatment.

1.2 Biomarker-Based AD: Changes in Clinical Care

AD is defined by hallmark neuropathological changes involving the extracellular deposition of Aβ into insoluble plaques and intracellular hyperphosphorylation of tau leading to neurofibrillary tangles.[12] These core proteinopathies disrupt cellular homeostasis and spread pathology across regions of brain.[13] Advances in the field have enabled earlier detection of disease-related pathology through blood-based biomarkers, opening a window for therapeutically targeted approaches directed at core AD pathology. Plasma levels of $pTau_{181}$ and recently FDA-cleared plasma $pTau_{217}/A\beta_{42}$ ratio have demonstrated strong concordance with cerebrospinal fluid (CSF) and positron emission tomography (PET) to measure levels of Aβ and tau in the brain,[14–17] offering scalable and less invasive tools for early screening. However, these approaches are still not widely utilized or available at a population level.[18,19] On the therapeutic front, anti-amyloid monoclonal antibodies have provided evidence that targeting core pathological processes can potentially slow disease progression,[20] though their efficacy and safety profiles remain under active debate.[21–23] Complementing these pharmacological advances, multidomain lifestyle intervention trials such as

FINGER and US POINTER have demonstrated that simultaneously targeting modifiable risk factors, including physical activity, diet, cognitive stimulation, and cardiovascular risk monitoring, can protect cognitive function in older adults at elevated risk.[24,25] Together, these advances have transformed the clinical landscape of AD by emphasizing earlier biological detection, preventative intervention, and targeted treatment strategies.

To better characterize the biological continuum of AD, the A/T/N framework has been proposed as a classification framework, in which Aβ (A) and tau (T) pathology are linked to downstream neurodegeneration (N) and cognitive decline, representing the biological continuum of AD.[26–28] Within this framework, each biological construct is typically measured using plasma or CSF levels, PET, and neuroimaging markers such as magnetic resonance imaging (MRI) and fluorodeoxyglucose (FDG)-PET.[27,28] Individuals are then classified into clinically healthy (e.g., A−/T−/N−), probable AD (e.g., A+/T+/N+, A+/T+/N−), or non-AD tauopathies (e.g., A−/T+/N− or A−/T+/N+) based on biological manifestation of the disease.[29] This classification system, which extends beyond traditional diagnosis based on clinical syndrome, allows for more granular identification of individuals at risk before symptom onset and for earlier and more targeted intervention strategies. The biomarkers reflecting these processes have been shown to become abnormal years, and in some cases decades, before clinical symptom onset.[30] This extended preclinical phase signifies the potential window for early detection and intervention. Multimodal approaches that combine fluid biomarkers and neuroimaging measures and targeting modifiable risk factors have shown promises as preventative method for AD.[31,32] However, these studies have largely been conducted in racially and ethnically homogenous populations, and challenges remain in translating precision and accuracy of biomarker-based risk assessments and efficacy of addressing modifiable risk factors equitably across different racial/ethnic populations. Critical

gaps remain in ensuring that biomarkers used in the A/T/N framework are accurate and generalizable across diverse populations.

Genome and exposome factors may influence the trajectory through this AD continuum, including the temporal evolution of biomarker levels, rate of neurodegeneration, and cognitive reserve.[33–35] Some individuals may accumulate substantial amyloid pathology while remaining cognitively unimpaired, whereas others demonstrate more rapid progression toward neurodegeneration and cognitive decline.[36–38] Understanding how multidomain risk burdens influence these transitions is critical for improving individualized risk stratification and identifying biologically meaningful intervention windows across diverse populations. A key strategy for clinical implementation of AD biomarkers is through rigorous analytical validation against neuropathological endpoints, ensuring that the risk factors being targeted influence disease progression at the biological level. In addition to validating these biomarkers as measures of AD risk, it is also necessary to identify risk factors across both genomic and exposomic domains and to determine how these exposures influence levels of AD-related biomarkers.

Because of genetic and cultural diversity that exists among populations,[39,40] there is also a need to develop and validate genomic and exposomic domain-specific risk models that capture population-specific risk profiles and to analytically evaluate how these models relate to Aβ, tau, and neurodegeneration. Addressing this gap is critical in understanding maps onto the pathological cascade and promoting more accurate multidomain intervention framework across diverse populations.

1.3 Genetic Risk Factors

Late-onset AD is highly heritable, with genetic factors estimated to account for approximately 40–60% of disease susceptibility.[41,42] Apolipoprotein E (*APOE*) gene is the strongest genetic risk for the late-onset form of AD, with the ε4 allele conferring increased risk, ε3 considered neutral, and ε2 associated with a protective effect.[43] Globally, the estimated allele frequencies are 7% for ε2, 79% for ε3, and 14% for ε4.[44] Carrying a ε4 allele is associated with a 3–4-fold increase in AD risk, while ε4/ε4 genotype raises the risk to 9-15-fold.[44,45] Notably, the effect size distribution does not translate uniformly across genetic ancestry groups, with individuals of East Asian ancestry having the highest risk and the most attenuated effect in individuals of admixed and African ancestries.[46–48]

Beyond *APOE* regions, genome-wide association studies (GWAS) have expanded and revolutionized our understanding of the genetic architecture of complex polygenic disease like AD. There are now over 5,700 GWAS publications,[49] including recent AD GWAS identifying over 100 risk loci implicated in pathways such as lipid metabolism, immune response, and endosomal trafficking.[50,51] These findings highlight the polygenic architecture of AD, in which many genetic variants cumulatively influence disease risk. Advances in AD GWAS have enabled the development of genomics-based risk prediction approaches that may facilitate early identification of at-risk individuals based on their genetic liability.

1.4 Polygenic Risk Modeling

The growing number of genetic variants associated with AD identified by GWAS have enabled development of AD polygenic risk score (AD-PRS). PRS calculates an individual's genome-wide liability for a given trait or a disease by aggregating all the variants weighted by its effect size

estimates derived from GWAS summary statistics.[52] AD-PRS can differ depending on the GWAS datasets and methodological frameworks used during score construction. For example, some PRS are derived from clinically diagnosed AD GWAS, whereas others incorporate proxy phenotypes such as family history of dementia to increase sample size.[53,54] In addition, PRS may include or exclude the *APOE* region, with some studies modeling *APOE* genotype separately because of its disproportionately large effect on AD risk.[55] These methodological differences can influence downstream associations with diagnostic, biomarker outcomes, and overall predictive performance across populations.

AD-PRS have demonstrated associations with AD pathology and cognitive decline in older adults.[56–58] In clinically adjudicated cases, AD-PRS demonstrates good predictive performance, with an area under the curve (AUC) of ~0.74, improving to ~0.84 in pathologically confirmed cases and controls.[59] Moreover, individuals in the highest quintile of an AD-PRS have a threefold higher risk of dementia compared to the general population.[60] Beyond dementia risk, AD-PRS show stronger associations with downstream biomarkers such as plasma glial fibrillary acidic protein (GFAP), CSF tau, and clinical diagnosis, compared with Aβ-specific measures in plasma, CSF, or neuroimaging.[61,62]

The most accurate PRS models exclude the *APOE* region and treat *APOE* genotypes as separate predictors, showcasing that *APOE* and polygenic burden represent distinct but complementary sources of risk.[63–65] AD-PRS retain their predictive accuracy among pathologically confirmed *APOE**ε3 homozygotes and *APOE**ε4-negative individuals, particularly aged 70 and over.[59,66] In *APOE**ε4 carriers, the higher AD-PRS exacerbates AD risk, accelerates age at onset by about five

years, and exacerbates cognitive decline.[67–69] These findings highlight a vulnerable subgroup with combined genetic burden.

Despite their promise, the clinical translation of AD-PRS is constrained by limited transportability across ancestrally diverse and admixed populations. Because most GWAS have been conducted in predominantly European ancestry cohorts, PRS derived from them often have poor transportability to ancestrally diverse and admixed populations due to differences in linkage disequilibrium (LD), minor allele frequency (MAF), and SNP effect sizes.[70,71] Implementing such models prematurely risks exacerbating existing disparities in AD diagnosis and care.[72] Ongoing efforts aim to address this by expanding GWAS in underrepresented populations, developing cross-ancestry PRS models, and calibrating PRS distributions according to individualized ancestry.[73–76] AD-PRS that explicitly incorporate ancestry and population-specific genetic architecture already show improved performance in diverse cohorts compared with single-ancestry European-based models.[73,77,78]

Nevertheless, methodological diversity further complicates translation. More than 30 methods for deriving PRS have been developed, with little guidance on which are best suited for predicting AD across diverse populations.[79] Early PRS approaches relied on LD clumping and p-value thresholding to select SNPs for constructing a PRS, whereas newer methods incorporate Bayesian shrinkage of effect sizes, restrict variants to only those with functional validation or in specific biological pathways, integrate multiple traits, and include rare variants.[80–82] While advances represent important progress, their improvements are often modest, and model performance remains highly trait- and data-dependent. Consequently, systematic benchmarking is needed to establish analytical and clinical validity and clarify which models are appropriate for AD risk prediction across populations.

Altogether, progress has been made in developing AD-PRS that complements *APOE* in personalized medicine frameworks. However, their use remains confined to research settings until analytical and clinical validity are established. Evaluation of AD-PRS against established AD biomarkers to confirm associations with underlying pathology remains limited, especially in diverse populations. Validation of AD-PRS models in diverse and historically underrepresented populations will be critical not only for improving their accuracy and generalizability, but also for ensuring their equitable and clinically meaningful implementation across diverse patient populations.

1.5 Exposome

Beyond genetic risks, AD risk is increasingly understood as the result of cumulative environmental, lifestyle, and clinical exposures across the life course, conceptualized as the exposome.[33] Two major exposomic domains relevant to the present study are modifiable clinical and lifestyle risk factors and social determinants of health (SDoH). The AD exposome encompasses the totality of non-genetic, modifiable exposures from prenatal development[83] through late-life aging,[84] and has emerged as a critical framework for understanding the multifactorial and temporally complex disease etiology of AD. Unlike the genome, which remains relatively stable throughout life, the exposome is dynamic across one's life and reflects accumulated exposures that interact with biological processes over time.[85] This is especially relevant for AD risk that emerges through the combined effects of genetic susceptibility and lifelong environmental and clinical exposures.[86]

The 2024 Lancet Commission Report has identified 14 modifiable risk factors, including less education during early life, cardiometabolic diseases, smoking and alcohol intake, physical

inactivity, depression, etc., that account for approximately 45% of all dementia cases,[84] increasing to an estimated 65% when SDoH are considered.[87] Many of these exposures are modifiable and may contribute to AD development through pathways like vascular dysfunction, neuroinflammation, oxidative stress, and reduced cognitive reserve rather than directly through Aβ and tau pathways.[88–91] Critically, multidomain intervention trials have begun to demonstrate that targeting these risk factors can meaningfully protect cognitive function. The FINGER trial showed that addressing physical activity, diet, cognitive stimulation, and cardiovascular risk monitoring slowed cognitive decline in at-risk older adults, while US POINTER extended these findings to a larger, more diverse US population, demonstrating efficacy across sex, *APOE* carrier status, and cognitive status.[24,25] Together, these findings highlight the potential for prevention-focused strategies that target non-genetic modifiable risk factors upstream of AD pathology.

Despite increasing recognition of exposomic contributions to AD, many studies investigate these factors independently rather than as interacting risk domains. Furthermore, exposomic risk factors are not distributed equally across populations and are shaped by broader social, environmental, and structural contexts.[92] Addressing these gaps is essential in developing effective AD prevention and screening processes and is dependent on understanding how cumulative environmental and social risk burdens influence disease progression across diverse populations.

1.6 Modifiable Clinical and Lifestyle Risk Burdens

One domain of the exposome is modifiable clinical and lifestyle risk factors that individuals may have as comorbidities or unfavorable clinical profile. A growing body of literature has linked environmental exposures and unfavorable clinical profiles, including air pollution, smoking, chronic stress, built environment like neighborhood greenness, and pesticides, to cognitive decline

and dementia risk.[89,93–95] Subsequent studies have also identified additional modifiable risk factors through systematic reviews and independent studies,[84] leading to the development of composite clinical risk scores (CRS) intended for dementia risk stratification.

Similar to PRS, the number of CRS have expanded rapidly,[96] underscoring the need for validation in diverse populations. However, much of the existing literature relies on its relationship with diagnostic outcomes, and it remains unclear whether elevated CRS are associated with abnormal AD pathology, such investigations have been underexplored. There are two categories of CRS that are interests of the present study; one that is developed through independent cohort and study (e.g., modified Cardiovascular risk factors, Aging, and Incidence of DEmentia [mCAIDE][97] and Washington Heights-Inwood Columbia Aging Project [WHICAP][98]) and another that is developed through systematic reviews (e.g., LIfestyle for BRAin health risk score [LIBRA][99] and Cognitive health and Dementia Risk index [CogDRisk][100]). All are intended to be used for risk assessments during mid-life; however, mCAIDE and WHICAP have been developed through its own independent study whereas LIBRA and CogDRisk were developed through systematic analysis. The gap of understanding the relationship between CRS and AD pathology is salient given that CRS can be administered in community-based settings, independent of primary or specialist care. This underscores the importance of establishing their relationship with AD biomarkers to enhance their utility and adaptation by larger populations.

1.7 Social and Environmental Risk Burdens

A critical, yet often overlooked, risk factor for AD are environmental risks and socioeconomic burdens that individuals face. According to the definition of World Health Organization, SDoH are a non-genetic modifiable factor that influence health outcomes and is “the condition in which

individuals are born, grow, live, work, and age".[101] Psychosocial and socioeconomic exposures represent broader structural contexts that shape risk profiles and disproportionately expose certain populations to adverse living conditions. Bronfenbrenner's ecological systems theory[102] provides a complementary conceptual framework for understanding the complex layers of SDoH, extending beyond structural context to capture how "the social, political, physical, environments, and human behavior combine to influence AD risk".[103]

The theory conceptualizes human development as the result of dynamic interactions between an individual and multiple layers of their environment, ranging from immediate settings (microsystem; e.g., school and food access) to broader societal and cultural contexts (macrosystem; structural racism, ableism, and ageism. Mesosystem describes interactions among microsystems (e.g., family-school system) and exosystem capturing indirect factors influencing health (e.g., climate change). These systems contextualize SDoH as potentially modifiable risk factors that influence physiological processes relevant to AD progression and shape aging trajectories. This perspective is not intended to offer a prescriptive modeling framework, but rather to provide a more nuanced lens through which to conceptualize the interconnectedness of exposome domains and that no domain takes place in isolation. However, studies that assess or integrate these multidomain into risk modeling remain limited in AD research, despite growing recognition of their cumulative impact.[25,104–106]

SDoH encompass multiple domains of individual's lived experience, including access to high quality education and healthcare, neighborhood and environment built, social and community context, and economic stability.[107] It spans from immediate environments within the microsystem to policies and structural forces within the macrosystem, with the mesosystem capturing

interactions across these domains that shape individuals lived experiences. A study has estimated that approximately 20% of non-genetic dementia modifiable risk factors may be attributable SDoH.[87] These factors can contribute to both acute and chronic stresses, and these accumulated stresses could deteriorate one's cognitive reserve overtime.

Moreover, social and health inequity directly and disproportionately affects SDoH profile of low-income, historically marginalized, and rural populations compared to their high-income white counterparts living in urban areas.[108] Individuals from low-income households, those with lower educational attainment (e.g., less than a bachelor's degree), and racial/ethnic minority groups experience lower life expectancy, higher susceptibility to cardiometabolic disease, and poorer overall health.[108] Despite these adverse relationships between one's socioeconomic status and health outcomes, medical mistrust between racial/ethnic minorities and the U.S. medical system complicate clinical engagement and studying representative populations.[109–112] This underscores the need for continuous efforts to investigate the effects of SDoH on overall health and on aging brain, particularly whether adverse SDoH affects the underlying AD pathology.

Despite growing recognition of genetic, clinical, and environmental contributions to AD risk, existing research remains fragmented, with these domains often studied in isolation. PRS and CRS capture individual-level susceptibility, while SDoH captures broader social and environmental risk burdens that are underrepresented and are insufficiently integrated. Moreover, few studies have systematically evaluated how these multidomain risk burdens relate to AD pathology jointly.[25,104,113] This gap is further compounded by the underrepresentation of populations disproportionately affected by adverse SDoH, limiting the generalizability and equity of current risk prediction frameworks for AD.

1.8 Precision Medicine Framework in Diverse Populations

The emergence of blood-based biomarkers and prevention and pharmacological therapies has accelerated the need for precision medicine approaches in AD. Effective screening, prevention, and treatment frameworks require identifying who is at risk based on their genomic and exposomic risk profiles, what biological or environmental pathways are contributing to that risk, and when intervention should occur for maximal benefit. These challenges become more complex in diverse populations, where genetic architecture, environmental exposures, and social contexts differ across and within populations. For example, genetic risk prediction tools like PRS may vary in performance across ancestry groups due to differences in genetic structure,[72] while exposomic risk profiles may differ even among individuals with shared continental ancestry because of variation in lifestyle, environment, and SDoH.[114] Multifactorial and heterogeneous nature of AD requires multidomain risk frameworks that are evaluated in diverse populations. This dissertation addresses this gap by examining how genetic, clinical, and environmental risk domains relate to AD pathology across diverse populations to better inform equitable precision medicine strategies for AD screening, prevention, and treatment across different demographic groups.

1.9 Focus of Dissertation

The overarching objective of this thesis is to provide support towards validating AD risk modeling methods and quantify the effects of genetic, clinical, and environmental risk burdens on AD pathology in diverse populations. Through four main chapters, this work evaluates the analytical validity, biological relevance, and population generalizability of multidomain risk frameworks spanning the genome and exposome.

Chapter 2 evaluates whether single-, multi-, and cross-ancestry AD-PRS approaches improve AD risk prediction and associations with AD endophenotypes across diverse populations. This analysis was necessary because PRS models are traditionally derived primarily from European ancestry GWAS and demonstrate reduced transportability across non-European populations, potentially limiting equitable implementation of genomic risk prediction. This chapter benchmarks PRS performance against cognitive status, neuropathological measures, CSF biomarkers, and plasma biomarkers to assess both predictive utility and biological validity across ancestrally diverse cohorts. This work helps determine whether AD-PRS can serve as clinically meaningful tools for identifying individuals at elevated risk for AD and abnormal AD endophenotype in diverse population.

Chapter 3 evaluates whether CRS developed using modifiable clinical and lifestyle exposures are associated with AD biomarkers and cognitive impairment across diverse populations. This analysis was necessary because existing CRS have largely been validated using diagnostic outcomes rather than AD biomarkers and remain insufficiently evaluated across racially and ethnically diverse cohorts. This chapter examines whether CRS capture abnormal AD endophenotype and whether their predictive performance varies across populations. This work is important because CRS represent scalable and low-cost approaches that may improve early community-based risk identification and help prioritize individuals for biomarker screening, prevention strategies, or further clinical evaluation.

Chapter 4 develops an integrative multidomain framework examining the independent contributions of genetic, clinical, and environmental risk burdens to underlying AD pathology. This chapter was motivated by the observation that genetic, clinical, and environmental risks are

often studied independently despite AD being a multifactorial disease shaped by interacting exposures across the life course. Using latent variable modeling, this chapter evaluates how multidomain risk burdens map onto amyloid/tau, neurodegeneration, and cognition across diverse populations and demographic subgroups. This analysis is important because understanding how different risk domains influence distinct stages of the AD continuum may improve biologically informed risk stratification and support more targeted and equitable precision medicine approaches for AD prevention and treatment.

Chapter 5 summarizes findings across the dissertation and discusses implications for precision medicine, equitable risk assessment, and future directions in AD research. This chapter integrates the findings from the previous chapters to examine how multidomain risk frameworks may improve understanding of AD heterogeneity across diverse populations. This section highlights how integrating genome and exposome risk profiles may help advance more equitable approaches for AD screening, prevention, and therapeutic intervention.

Chapter 2: Cross-Ancestry Polygenic Risk Scores Enhance Alzheimer's Disease Risk Prediction in Multiethnic Cohorts

Abstract

Genome-wide association studies (GWAS) have identified 80+ genetic loci associated with Alzheimer's disease (AD), enabling the development of polygenic risk scores (PRS). However, the predictive accuracy of PRS in diverse populations remains low. Here, we evaluated the predictive accuracy of single-, multi-, and cross-ancestry AD-PRS models across multi-ancestral populations. We used AD GWAS summary statistics from European, African, Admixed American, and East Asian populations to construct AD-PRS for each target population. Model performance was assessed by estimating odds ratios, R^2, and AUC. The cross-ancestry Bayesian PRS model demonstrated the highest predictive performance in non-European populations. It was significantly associated with poorer cognitive function, lower $A\beta_{42}$ CSF levels, and the most severe category of Aβ and tau neuropathological burden, as well as a clinical AD latent variable in a multi-ancestral validation cohort. Inclusive genetic datasets and cross-ancestry PRS models are needed to enhance the transportability of AD-PRS across multi-ancestral populations.

2.1 Introduction

The abundance of GWAS and the growing number of disease-associated genetic variants have enabled the development of polygenic risk scores (PRS). PRSs calculate an individual's genetic liability for a given trait or a disease by aggregating all the variants weighted by their effect size estimates derived from GWAS summary statistics.[1] In some diseases, at-risk individuals identified through PRS exhibit up to 20-fold higher than the carrier frequency of rare monogenic mutations conferring comparable risk.[2] These findings highlight the potential of PRS to identify at-risk

individuals who may not be captured through family history or monogenic variants, creating opportunities to modify risk factors and personalize care before clinical symptoms emerge.[3]

AD GWAS have greatly advanced our understanding of AD genetic architecture, with heritability estimated to be 40-60%,[4–7] and facilitate the development of AD-PRS. AD-PRS show good predictive accuracy, with the best-performing model having an area under the curve (AUC) of 0.74 while adjusting for *APOE* ε2 and ε4 status.[8] The predictive accuracy further increases to 81% when applied to neuropathologically confirmed cases and controls or when using extreme PRS cutoffs.[9,10] The high predictive accuracy of AD-PRS demonstrates its potential utility for risk assessment. However, clinical translation has been slow, partly due to inconsistent performance across studies that raises concerns about generalizability.[11–15]

A major driver of the lack of generalizability of AD-PRS stems from the lack of diversity in GWAS training datasets. Most AD-PRS models have been derived from European ancestry GWAS, given the scarcity of large studies in non-European or admixed populations.[16,17] As a result, AD-PRSs derived from European datasets show markedly reduced predictive accuracy when applied to non-European ancestry populations, with performance declining as genetic distance from the training population increases.[16–18] For instance, AD-PRS derived from African American GWAS datasets outperformed those based on European or multi-ancestry AD-PRS in the African cohort, with some variability across different regions.[13] Similarly, including variants identified specifically in African populations has been shown to improve the accuracy of PRS across ancestrally diverse and admixed populations.[15] In some cases, AD-PRS derived from European GWAS data remains associated with AD risk in non-European populations by careful tuning of pruning and thresholding (P+T) parameters[18]; however, such optimizations may not be practical for routine

clinical use. These trends highlight the limited portability of European-derived PRS and the potential to exacerbate existing health disparities if such models are applied indiscriminately.[16]

The need to address these disparities is particularly urgent given the disproportionate burden of ADRD among older Black and Latinx individuals compared to non-Latinx White individuals.[19] Yet, relatively few studies have systematically evaluated the performance of different AD-PRS models across ancestrally diverse populations, largely due to the limited availability of training and validation datasets. By increasing GWAS sample sizes of historically underrepresented populations and matching the statistical power of European ancestry GWAS, the accuracy of PRS can improve.[15,20–24] Although current non-European AD GWAS are notably smaller than those of European ancestry, multi-ancestry PRS derived from smaller ancestry-matched GWAS have been shown to outperform PRS derived from larger European GWAS.[25] Alternatively, cross-ancestry PRS methods aim to jointly model GWAS summary statistics from multiple ancestry groups to improve PRS prediction within a specified target ancestry.[22,23]

The present study evaluates the predictive accuracy of AD-PRS computed using single-, multi-, and cross-ancestry PRS models in multi-ancestral populations. We expect that AD-PRS will exhibit reduced predictive accuracy in populations not represented in the training data. Beyond disease diagnosis, we also assessed the clinical validity of PRS by examining whether the best-performing model was associated with AD endophenotypes, including biomarkers and cognitive domains within the A/T/N framework.[26,27] This evaluation provides insight into whether PRS can capture early disease-related processes, complementing risk stratification for AD.

2.2 Methods

2.2.1 Genome-Wide Association Study Datasets

We utilized summary statistics from the largest publicly available ancestry-specific GWAS datasets on AD and related dementias (ADRD) to date, including participants of European (Bellenguez et al.[5]: 39,106 cases, 46,828 proxy cases, 401,577 controls; FinnGen Release 6: 7,329 cases, 131,102 controls), African (Kunkle et al.[28]: 2,748 cases, 5,222 controls), East Asian (Shigemizu et al.: 3,962 cases, 4,074 controls[29]), and Caribbean Hispanic descent (Columbia University Study: 1,088 cases, 1,152 controls). We also utilized multi-ancestry meta-analysis (MAMA) GWAS summary statistics, combining data from the five ancestry-specific studies listed above (Lake et al.: 54,233 AD cases, 46,828 proxy cases, 543,127 controls[30]) to construct a multi-ancestry PRS.

2.2.2 Alzheimer's Disease Sequencing Project

Data from the Alzheimer's Disease Sequencing Project (ADSP) Release 4 whole genome sequencing dataset were accessed from the National Institute on Aging Genetics of Alzheimer's Disease Data Storage Site (NIAGADS) (https://dss.niagads.org/). The participants in the ADSP are recruited from large, existing family-based and case/control studies that provide comprehensive phenotypic and genetic data. The ADSP has made a concerted effort to include participants from multi-racial and multi-ethnic groups, as many earlier genetic studies have predominantly involved individuals of European descent. AD diagnosis was harmonized across the cohorts by the ADSP Phenotype Harmonization Consortium (ADSP-PHC).[31] The ADSP-PHC also harmonized AD endophenotype measurements, including cognitive function (language, memory, executive functions; total N = 11,046), cerebrospinal fluid (CSF) biomarkers (Tau,

$pTau_{181}$, $A\beta_{42}$; total N = 815), and neuropathology (CERAD, N = 2,727; Thal Phase, N = 1,186; BRAAK staging, N = 2,725).[32,33] For exclusion, A total of 515 participants diagnosed with mild cognitive impairment (MCI) were excluded from the analysis. An additional 117 participants from a family-based study that overlapped with case/control studies were removed. Additionally, 488 samples were removed due to missing genotype data, and 5,763 participants were removed due to missing diagnosis information.

A standardized Quality Control (QC) pipeline was applied to the WGS datasets using default settings in GenoTools.[34] Variants failing to meet predefined quality thresholds were excluded, including those with a minimum depth of coverage below 10, genotype quality below 20, and minor allele frequency (MAF) below 0.01. Variants with missing rsIDs were assigned a chromosome position ID. To further assess quality, sample-level and variant-level QC were performed using GenoTools to undergo a series of QC checks. Sample-level QC includes call rate (≥ 0.95), sex concordance (male: $F \geq 0.99$, female: $F \geq 0.03$), and relatedness between samples (cutoff = 0.0884). Variant-level QC was performed to examine non-random missingness by haplotypes, Hardy-Weinberg equilibrium ($\leq$ 1e-4), and genotype missingness (< 0.05). 2,743 participants were removed due to sex discrepancy, 359 participants were removed due to heterozygosity pruning, and 3,164 participants were removed due to the relatedness check. The African GWAS summary statistics were derived from participants in the Alzheimer's Disease Genetic Consortium (ADGC), which includes sample overlaps with those from the ADSP. To retain sample independence between the base and the target datasets and avoid PRS inflation caused by sample overlap,[35] relationship inference was performed using software, KING,[36] to identify and exclude samples based on relatedness. Pairwise samples with kinship coefficients $\geq$ 0.354,[36] 2,776 participants, were removed from the ADSP target datasets. After the main

GenoTools filters and excluding participants with missing data, 19,398 participants (7,111 cases and 12,287 controls) remained for the downstream analysis. Additionally, WHICAP participants (N = 442) were excluded from the ADSP to remove potential overlapping participants with the Caribbean Hispanic GWAS. The Stage I Bellenguez et al. GWAS includes European Alzheimer & Dementia Biobank, European Association of Development Research and Training Institutes, GERAD, Bonn, RS1&2, Genome Research at Fundació Ace, DemGene, the CCHS study, NxC, UK Biobank, which do not overlap with the ADSP cohorts.

Genetic ancestry was determined using a principal component analysis (PCA) with the 1000 Genome Project (1KG) + Human Genome Diversity Project (HGDP) as the reference panel, followed by classification via a random forest algorithm implemented in pgsc_calc.[37] Out of 19,398 participants after initial exclusion (eMethods), 8,043 (41.5%) participants were classified as 1KG+HGDP-EUR-like (EUR; European), 1,945 (10.0%) as 1KG+HGDP-AFR-like (AFR; African), 6.901 (35.6%) as 1KG+HGDP-AMR-like (AMR; Admixed American), 2,365 (12.2%) as 1KG+HGDP-CSA-like (CSA; Central/South Asian), 72 (0.37%) as 1KG+HGDP-EAS-like (EAS; East Asian), and 72 (0.37%) participants were assigned as 1KG+HGDP-MID-like (MID; Middle Eastern) ancestry. Participants of EAS and MID were removed due to small sample size, while participants of CSA were excluded due to imbalanced case-control ratios (18 cases: 2,347 controls). Global genetic admixture for each sample was estimated using ADMIXTURE version 1.3.[38] Briefly, we identified a representative reference panel composed of samples distributed by the 1KG. The reference panel and target ADSP dataset were subset to include only overlapping SNPs. We performed an unsupervised admixture analysis of the reference dataset, setting K = 5. The target samples were then projected onto the population structure learned from the reference panel.

2.2.3 Health and Brain Aging Study - Health Disparities

The Health and Aging Brain Study - Health Disparities (HABS-HD) cohort comprises participants from Black, Mexican American, and non-Hispanic White populations recruited at the University of North Texas Health Science Center, Fort Worth, Texas, USA.[39,40] The study collected information on demographics, AD biomarkers, neuroimaging, clinical history, and genomics, providing a comprehensive resource for AD and related dementia research. Eligibility to participate in the study was restricted to generally healthy individuals without serious mental or medical conditions, who were willing to undergo sample collections and neuroimaging procedures. We utilized participant data from the HABS-HD release 5 baseline visit 1. We further applied the exclusion criteria to remove participants younger than 55 years old, those without genetic data, and those with plasma biomarker values identified as outliers. Outliers were detected following the published methodology using the interquartile range approach.[41] All HABS-HD participants (and/or their legal guardians) signed written informed consent to participate in the study.

2.2.4 AD endophenotypes

HABS-HD participants have undergone extensive phenotyping for AD endophenotypes, including plasma A/T/N biomarkers, brain morphometry, amyloid and tau PET, and neuropsychological testing, as previously described.[39,40] For downstream analyses of each endophenotype, we applied the following approaches:

Plasma biomarkers: Fasting blood samples were collected, and the levels of plasma biomarkers (i.e., $A\beta_{42}$, $A\beta_{40}$, $pTau_{217}$, total Tau, NfL) were quantified using commercially available kits, Quanterix, for all the participants of the HABS-HD. $A\beta_{40}$, $A\beta_{42}$, $pTau_{217}$, Tau, and NfL values were natural log-transformed to reduce skewness, and then standardized to z-scores (mean = 0, SD = 1)

across the study samples. *Brain morphometry:* Cortical thickness was defined as the surface area-weighted average of cortical thickness in the right and left entorhinal cortex, fusiform, and inferior and middle temporal cortex. Hippocampal volumes were determined by taking the mean volume of the right and left hippocampal volumes determined on a T1-weighted volume scan. *Neuropsychological testing:* Composite scores for each cognitive domain (memory, language, and executive function) were constructed by averaging z-score-normalized test scores from the neuropsychological battery. The memory domain was assessed using immediate and delayed recall from the Wechsler Memory Scale (WMS-III) Logical Memory and the Spanish English Verbal Learning Test (SEVLT). The language domain was assessed using Letter Fluency and Animal Naming tests. The executive function domain was assessed using the WMS-III Digit Span and the Trail Making Test, Parts A and B. In addition, the Mini-Mental State Examination (MMSE) and Clinical Dementia Rating (CDR) scale were administered to all participants as part of the neuropsychological assessment. *Amyloid PET:* For amyloid positron emission tomography (PET) scan variables, the global standardized uptake value ratio (SUVR) was derived by normalizing tracer uptake to the whole cerebellum. Amyloid PET positivity was defined using a SUVR threshold of 1.08.

2.2.5 Genome-wide Genotyping and QC

Participants were genotyped on the Illumina Global Screening Array (GSA), and genotype data underwent stringent quality control (QC) checks using an in-house Snakemake Pipeline.[42] Variants were excluded if the call rate was <0.95 and not in Hardy–Weinberg equilibrium ($p < 1 \times 10^{-6}$), and samples were excluded if the call rate was <0.95; discordant sex was reported based on X chromosome heterozygosity, excessive/insufficient heterozygosity, and cryptic relatedness. Related individuals were determined within and across cohorts by identity-by-descent (IBD) using

KING,[36] with individuals excluded based on a proportion of IBD < 0.1875, corresponding to less than halfway between second- and third-degree relatives. Single-nucleotide polymorphisms that were not directly genotyped were imputed on the TOPMed Imputation Server.[43] Ancestry groups were imputed separately using all ethnicities of the TOPMed reference panel (Version R3) to allow ancestry-specific imputation quality (R^2) estimation, with Eagle used for phasing and Minimac3 used for imputation. Rather than imputing the joint dataset, ancestry-specific imputation was performed to preserve accuracy and reduce poorly imputed variants in individual ancestry groups.[44] Following imputation, poorly imputed ($R^2 < 0.3$) or rare (MAF < 0.01) variants were removed, and the ancestry groups were merged for joint analysis. Following this merger, variants with low call rate due to differential imputation (< 95%) were removed and then samples with low call rates (< 95%) were removed. To note, different genetic QC software was used for the ADSP and the HABS-HD to accommodate differences in genotyping platforms and data types; accordingly, platform-specific and widely accepted QC thresholds were applied for each cohort. These differences reflect standard best practices for WGS versus array-based data and are not expected to materially affect downstream analyses. The final dataset contained 2,559 samples with ~22M high-quality SNPs per individual.

Of the total of 2,559 participants that were included in the downstream statistical analysis, 1,040 were of European ancestry, 891 were of Admixed American ancestry, and 574 were of African ancestry based on genetic ancestry inference (Refer to ancestry assignment in 2.3.2).

2.2.5 PRS Scorefile Generation

PRSice was used to implement P+T to construct four AD-PRS, stratified by EUR ancestry and MAMA ancestry, at two p-value thresholds. P+T generates scorefiles for SNPs that exceed a given

p-value threshold (P_T) and its corresponding effect size estimated from an independent GWAS. Scorefiles for the single- (EUR) and multi-ancestry (MAMA) PRS models were constructed using SNPs with a p-value < 0.1 ($P_{T0.1}$) and genome-wide significance (GWS) (P_{TGWS}). SNPs from apolipoprotein E (*APOE)* regions ± 500kb (GRCh38, chr19:bp44405791-45409393) were excluded from all the base datasets. A p-value threshold of 0.1 in the construction of PRS has been previously shown to have the best predictive accuracy and will be tested in this study.[8] Linkage disequilibrium (LD) clumping using 1KG + HGDP LD reference panels, with an r^2 threshold of 0.1 and clumping distance of 250kb, was used to select independent SNPs. For the single-ancestry PRS model, the 1KG + HGDP reference panel was filtered for European-only samples, and the whole 1KG + HGDP reference panel was used for the multi-ancestry PRS model.

PRS-CSx was used to construct a scorefile for the cross-ancestry AD-PRS model, a method that improves cross-population polygenic prediction by jointly modeling GWAS summary statistics from multiple populations.[23] The global shrinkage parameter (phi) was set to "auto", which allows for automatic estimation of the effect size from the datasets. Additionally, the "meta" parameter was set to 'true' to combine the SNP effect sizes across populations using an inverse-variance-weighted meta-analysis. For PRS-CSx, SNPs were restricted to the HapMap3 panel as the software was designed for HapMap3 variants, whereas PRSice obtains independent SNPs using a P+T approach. Software used the 1KG reference panel to maintain the LD estimation consistent between the two software. The summary statistics for ancestry-specific AD GWAS were used to construct the scorefile. SNPs from *APOE* regions ± 500kb (GRCh37, chr19:bp44909053-45912650) were excluded from the final scorefile prior to PRS calculation. Liftover was automatically applied during PRS calculation to convert scorefile build to GRCh38. The same

methodology was applied to the HABS-HD cohort with the same parameters and base GWAS datasets.

2.2.6 PRS Calculation and Ancestry Normalization

To mitigate ancestry-related confounding due to differences in PRS distribution and to enable more accurate PRS comparisons across ancestrally diverse populations,[45] we used pgsc_calc[37] to construct PRS and normalize for ancestry differences in the ADSP and the HABS-HD cohort using the PCA method.[46] PCA was performed on the 1KG reference panel to derive principal components (PCs) representing global genetic variation. Target individuals were then projected onto these PCs to determine their position in genetic ancestry space. A RandomForest classifier, trained on the reference panel's PCA loadings (default: 10 PCs), was used to predict the reference population to which each target sample was most similar.[47]

Following PC projection and ancestry assignment, polygenic risk scores (PRS) were normalized by ancestry. First, a regression model predicted PRS from PC loadings, and the residuals were used to center the PRS distribution at zero across ancestry groups (znorm1). A second regression on the squared residuals adjusted for variance, standardizing the PRS spread to approximately one (znorm2). All five PRS models underwent ancestry normalization, and znorm2 scores were used for the downstream analysis. Importantly, phenotypic information (e.g., case-control status) was not used in the normalization process. This approach removes PRS variation attributable to population stratification driven by allele frequency and LD shifts while retaining the GWAS-derived SNP weights and rankings of individual-risks within ancestry groups. This normalization step scales PRS to enable inter-ancestry comparisons, while still capturing disease-relevant genetic risks.

2.2.7 Statistical Analysis

Logistic regression models were used to evaluate the associations of EUR, MAMA, and PRS-CSx PRS models with AD, adjusting for age at baseline, sex, *APOE* genotypes, and 10 PCs. The *APOE* status was encoded as a categorical variable, categorized as *APOE* ε2+ carriers (ε2/ε2, ε2/ε3) and ε4+ carriers (ε2/ε4, ε3/ε4, or ε4/ε4), with the ε3/ε3 allele serving as the reference group. Model performance was evaluated via Area Under the Receiver Operating Curve (AUCROC) to assess model discrimination. R2redux[48] was used to calculate and statistically compare the differences in R^2 for the AD outcome between models. Calibration of AD-PRS was assessed to evaluate the estimated probability of AD against the observed probability using PRS as a predictor.

In the ADSP, multiple linear regression models were fit to assess the relationship between PRS-CSx and (i) cerebrospinal fluid biomarkers (i.e., $pTau_{181}$, total tau, and $A\beta_{42}$), and (ii) cognitive domain scores (i.e., language, memory, and executive function). Models were adjusted for age, sex, *APOE* genotype, PC1-10, and study cohort. Models for cognitive outcomes were additionally adjusted for years of education. Ordinal logistic regression models, performed using the *polr* function in the MASS R package, were fitted for Thal phase, CERAD score, and Braak staging as ordinal outcomes, adjusting for age, sex, *APOE* genotype, PC1-10, and study cohort. All p-values were adjusted for multiple testing at 5% false discovery rate (FDR). Genetic ancestry stratification was performed for cognitive outcomes. CSF biomarkers and other cognitive measures had insufficient sample sizes for ancestry-stratified analyses.

Similarly, in the HABS-HD, multiple linear regression models were fit to assess the associations between PRS-CSx and (i) plasma biomarkers (i.e., $A\beta_{40}$, $A\beta_{42}$, $pTau_{217}$, Tau, and NfL), (ii) neuroimaging variables (i.e., cortical thickness and hippocampal volume), (iii) composite scores

for each domain (i.e., language, memory, and executive function), and (iv) global cognition tests (i.e., CDR and MMSE). Models were adjusted for age, sex, *APOE* genotype, and PC1-4. Additionally, BMI and eGFR were accounted for in the plasma biomarkers. Intracranial volume was accounted for in the neuroimaging variables. Years of education were accounted for in the neuropsychological test battery variables. Both raw and FDR-adjusted p-values (5%) were reported.

Continuous and binary outcomes were modeled using linear and logistic regressions, respectively. PRS effect estimates are interpreted as the change in the outcome per one SD increase in PRS. For ordinal outcomes, ordinal logistic regression was performed, and predicted probabilities represent the estimated likelihood of being in each severity category based on PRS values.

2.3 Results

2.3.1 Patient characteristics

Of 16,461 participants in the ADSP, 9,645 were classified as cognitively normal, and 6,816 were diagnosed with AD (Table 2.1). The cohort had a mean age of 68±10 years and consisted of 60% females. EUR ancestry was the most common (49%), followed by AMR (40%) and AFR participants (11%), respectively. The majority of people with AD were *APOE* ε4 allele carriers (54%). A similar profile is presented in the HABS-HD, with 61% female, with a mean age of 69±8 years. The cohort primarily consists of EUR (41%), AMR (35%), and AFR participants (22%) (Table 2.1, Table S2.1, Table S2.2).

Table 2.1. Descriptive statistics of the study cohorts
Characteristics of the ADSP and the HABSHD cohort, including age, sex, genetic ancestry, APOE genotype, and endophenotypes

Cohort	**ADSP**		**HABS-HD**	
Characteristic	**Cognitively Normal**	**Alzheimer's Disease**	**Cognitively Normal**	**MCI + Dementia**
Sample Size[a]	9,645	6,816	1,855	704
Age, years	68 (11)	73 (9)	67 (7.3)	68 (8.5)
Sex				
Female	6,088 (63%)	3,986 (58%)	1,194 (64%)	371 (53%)
Male	3,557 (37%)	2,830 (42%)	661 (36%)	333 (47%)
Ancestry				
European	3,637 (30%)	4,406 (62%)	845 (47%)	195 (28%)
African	1,377 (11%)	470 (6.8%)	330 (18%)	244 (35%)
Admixed American	4,631 (38%)	1,941 (28%)	637 (35%)	254 (37%)
***APOE* Genotype**				
e3/e3	6,195 (64%)	2,843 (42%)	1,019 (65%)	317 (56%)
e2+	932 (9.7%)	282 (4.1%)	165 (11%)	65 (11%)
e4+	2,518 (26%)	3,691 (54%)	390 (25%)	189 (33%)
Unknown	—	—	281	133
CSF Biomarkers				
Aβ42	0.32 (0.97)	-0.64 (0.87)	—	—
pTau	-0.25 (0.86)	0.62 (0.95)	—	—
Tau	-0.25 (0.90)	0.57 (0.91)	—	—
Plasma Biomarkers				

The PCA projection of the ADSP revealed a high admixture profile among AMR participants. Most of these participants clustered into two distinct patterns, separated from the EUR group, while some overlapped with the AFR group (Fig. 2.1B, Fig. S2.1). Consistent with this, the admixture analysis showed that AMR participants exhibited genetic heterogeneity, with contributions from EUR, Amerindian, and AFR ancestries (Fig. 2.1C). To account for ancestry-related differences in genetic architecture, we examined the distribution of all the PRS models across ancestral groups. Following ancestry normalization, the distributions were well-aligned and approximately normally distributed across groups, confirming that ancestral confounding was mitigated (Fig. S2.2).

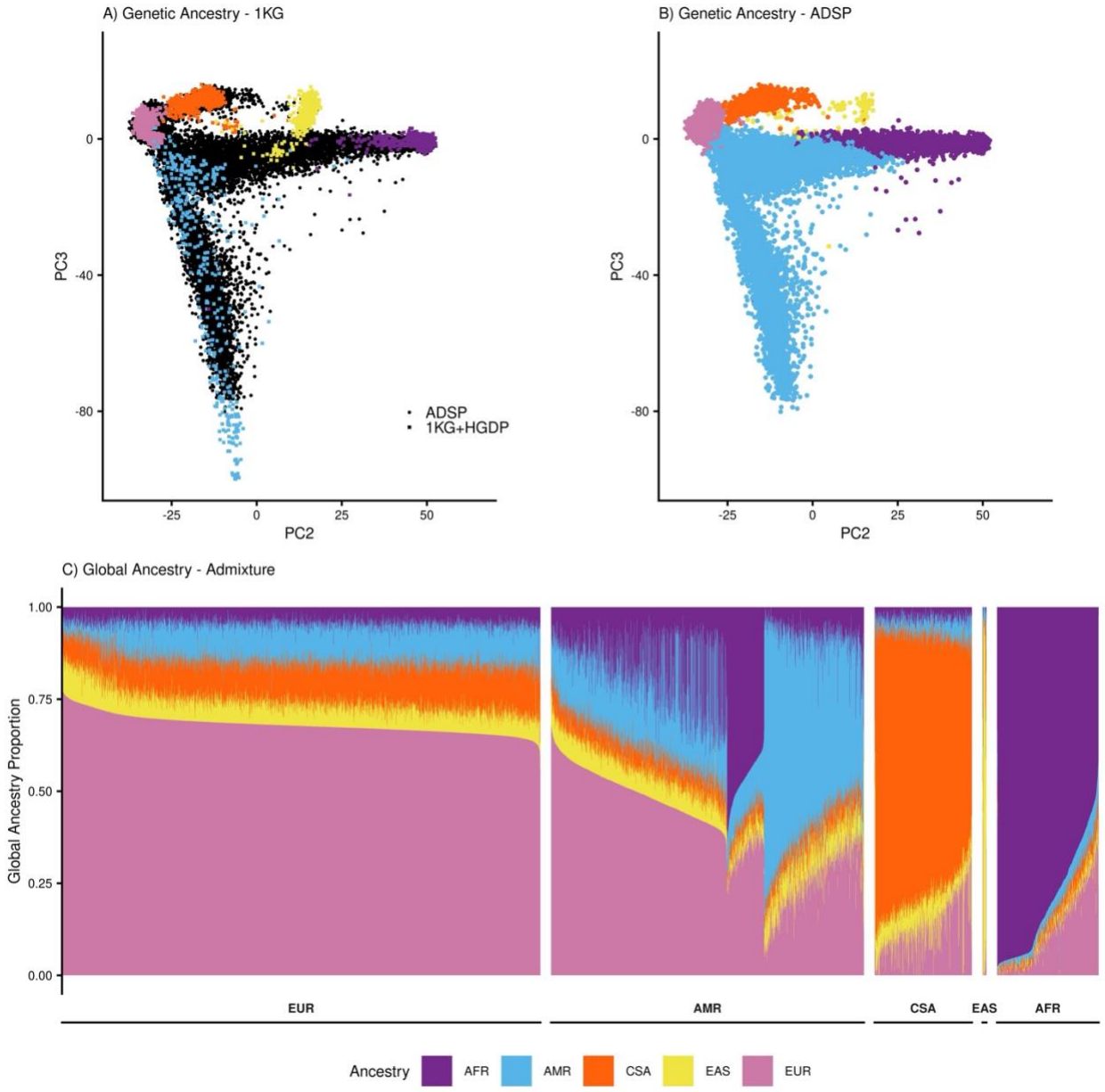


Figure 2.1. Genetic ancestry and global admixture analysis in the ADSP cohort
(A) Principal component analysis (PCA) of genetic ancestry using the 1000 Genomes (1KG) reference panel. ADSP participants (black dots) are overlaid onto 1KG reference populations (square dots). **(B)** PCA of ADSP participants only. **(C)** Global ancestry proportions estimated using admixture analysis, illustrating varying degrees of admixture across ancestry groups.

2.3.2EUR Single-Ancestry PRS

The European-only, single-ancestry PRS model showed robust associations with AD risk in EUR participants at both P_{TGWS} (OR [95% CI] = 1.4 [1.37-1.52], p = $5.53x10^{-42}$) and $P_{T0.1}$ (OR [95% CI] = 1.38 [1.31-1.47], p = 1.69×10^{-27}). R^2 values also declined as the genetic distance for AFR and AMR participants increased from the EUR participants (R^2 = 0.013, 0.018, 0.026, respectively) (Table S2.3). Association of single-ancestry PRS remained statistically significant in the AMR participants at both P_{TGWS} (OR [95% CI] = 1.17 [1.10-1.24], p = $5.59x10^{-7}$) and $P_{T0.1}$ (OR [95%CI] = 1.14 [1.06-1.21], p = $1.69x10^{-4}$) with similar effect sizes. It showed no association with AD risk in the AFR participants, both at P_{TGWS} (OR [95%CI] = 1.08 [0.96-1.21], p = 0.22) and $P_{T0.1}$ (OR [95%CI] = 0.93 [0.81-1.04], p = 0.22) thresholds (Fig. 2.2; Table S2.4).

2.3.3 MAMA Multi-Ancestry PRS

When leveraging the MAMA GWAS summary statistics, multi-ancestry PRS performance improved substantially in the AFR and AMR participants while remaining comparable in the EUR participants. In the EUR participants, the multi-ancestry PRS showed similar associations as EUR PRS with AD risk for P_{TGWS} (OR [95% CI] = 1.44 [1.37-1.52], p = 5.53×10-42) and $P_{T0.1}$ (OR [95% CI] = 1.38 [1.31-1.47], p = 1.69×10^{-27}). $P_{T0.1}$ model showed a stronger association with AD risk than P_{TGWS} model in the AMR participants (P_{TGWS} (OR [95% CI] = 1.17 [1.10-1.24], p = 1.27×10^{-6}) & $P_{T0.1}$ (OR [95% CI] = 1.34 [1.26-1.41], p = 1.71×10^{-23}). The effect was even larger in the AFR participants with $P_{T0.1}$ model, demonstrating 80% increase in the odds of developing AD, while P_{TGWS} model remained nonsignificant (P_{TGWS} (OR [95% CI] = 1.13 [1.00-1.27], p = 0.053) & $P_{T0.1}$ (OR [95% CI] = 1.80 [1.62-2.01], p = 7.30×10^{-27}) (Fig. 2.2; Table S2.4).

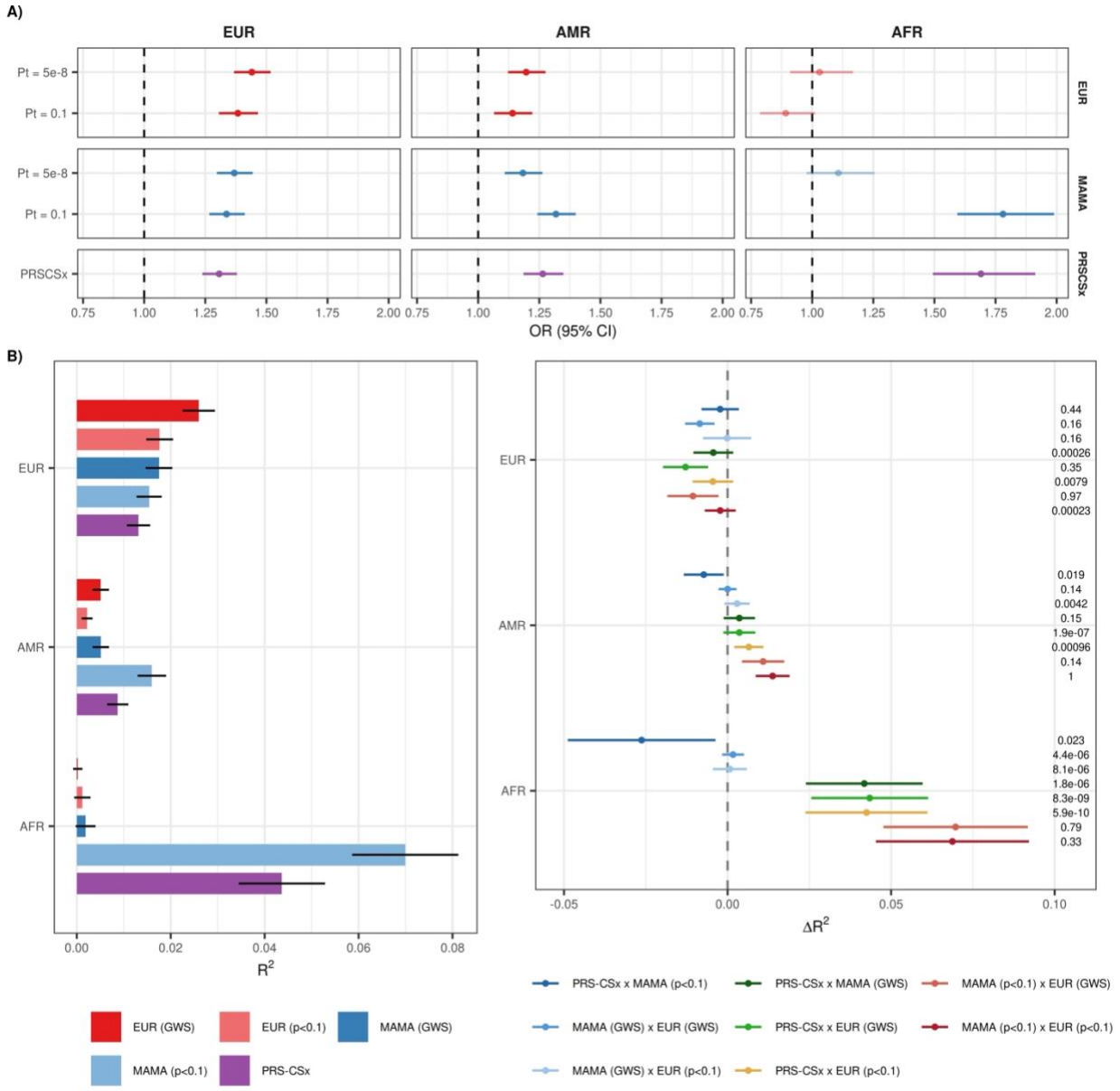


Figure 2.2. Model performance of five PRS models, stratified by genetic ancestry
(A) Odds ratio of ancestry-normalized single- (EUR), multi- (MAMA), and cross-ancestry (PRS-CSx) PRS models (right x-axis) stratified by genetic ancestry (top y-axis). P-values were adjusted for multiple testing using the Benjamini-Hochberg false discovery rate procedure, controlling the false discovery rate (FDR) at 5%. **(B)** Comparison of model performance across ancestry groups. (Left) R2 for EUR PRS (GWS), MAMA PRS (GWS), and PRS-CSx PRS models in the participants of European (EUR), Admixed American (AMR), and African (AFR) ancestry groups. *(Figure caption continues next page)*

(Figure caption continued from previous page) Error bars represent 95% confidence intervals. (Right) Differences in R2 between EUR versus MAMA PRS, EUR versus PRS-CSx PRS, and MAMA versus PRS-CSx PRS models. Error bars represent 95% confidence intervals of the difference.

2.3.4 PRS-CSx Cross-Ancestry PRS

The PRS-CSx cross-ancestry model showed similar trends as PT0,1 MAMA PRS models in regard to the association with AD. It was associated with the highest AD risk in the AFR participants (OR [95% CI] = 1.71 [1.52-1.93], $p = 1.45 \times 10^{-18}$), while remaining significant in the AMR and EUR participants (OR [95% CI] = 1.29 [1.21-1.37], $p = 1.76 \times 10^{-15}$ & OR [95% CI] = 1.31 [1.24-1.38], $p = 7.86 \times 10^{-22}$, respectively) (Fig. 2.2). The model also achieved the highest R^2 values in the AFR and AMR participants ($R^2 = 0.047, 0.010$, respectively) compared to other models (Fig. 2.2; Table S2.3). Differences in R^2 were also significant between PRS-CSx and EUR or MAMA PRS models in the AFR participants (ΔR^2 $p = 4.6 \times 10^{-7}$ & 1.3×10^{-6}, respectively), showcasing PRS-CSx strong predictive performance. A less prominent yet similar trend was seen in the AMR participants (ΔR^2 p = 0.016, 0.023, EUR–PRS-CSx, MAMA–PRS-CSx) (Table S2.3).

Calibration analyses further illustrate that while all models calibrate best in the EUR participants, and maintain high accuracy in the AMR participants, predictive accuracy decays progressively with increasing genetic distance from Europeans, with the greatest calibration gains in AFR participants arising from ancestry-normalized MAMA and PRS-CSx PRS models (Fig. S2.3, Fig. S2.4).

2.3.5 AD endophenotypes: ADSP

To measure PRS performance beyond their established utility in predicting AD risk, we further evaluated the association of the best-predictive PRS model, PRS-CSx, with cognitive domains

(memory, language, and executive function) and CSF biomarkers (Tau, $pTau_{181}$, $A\beta_{42}$). PRS-CSx demonstrated strong associations with poorer cognitive performance across multiple domains (β [95% CI]: Memory = 0.94 [0.93-0.95], p = $6.69x10^{-18}$, Language = 0.95 [0.94-0.97], p = $1.10x10^{-12}$, Executive function = 0.95 [0.94-0.97], p = $1.18x10^{-9}$) in the total cohort (Table S2.5).

PRS-CSx demonstrated significant associations with poorer cognitive functions in participants of European ancestry (Memory (β [95% CI] = -0.08 [-0.099, -0.062], p = $3.71x10^{-17}$); Language (β [95% CI] = -0.059 [-0.077, -0.042], p = $2.87x10^{-10}$); and Executive function (β [95% CI] = -0.056[-0.075, -0.037], p = $1.22x10^{-8}$). In AFR and AMR participants, PRS-CSx was associated with memory language, respectively. Incremental R^2 values were marginal, ranging from $1.8x10^{-4}$ to $8.7x10^{-3}$ in AFR and $3.3x10^{-4}$ to $1.6x10^{-3}$ in AMR participants across the domains (Table S2.5).

Similarly, PRS-CSx was associated with lower $A\beta_{42}$ CSF levels (β [95% CI] = 0.91[0.85-0.98], p = 0.015) (Fig. 2.3) but was not associated with Tau or $pTau_{181}$. Lower CSF levels of $A\beta_{42}$ indicate a worse endophenotype for AD. Furthermore, higher PRS-CSx values were associated with an increased probability of being in the most severe category of CERAD, Thal, and BRAAK classification (e.g., "Frequent/Definite" for CERAD, "Phase 5" for Thal, and "Stage VI" for Braak), suggesting a strong relationship between PRS-CSx and advanced AD pathology (Fig. 2.3; Table S2.5).

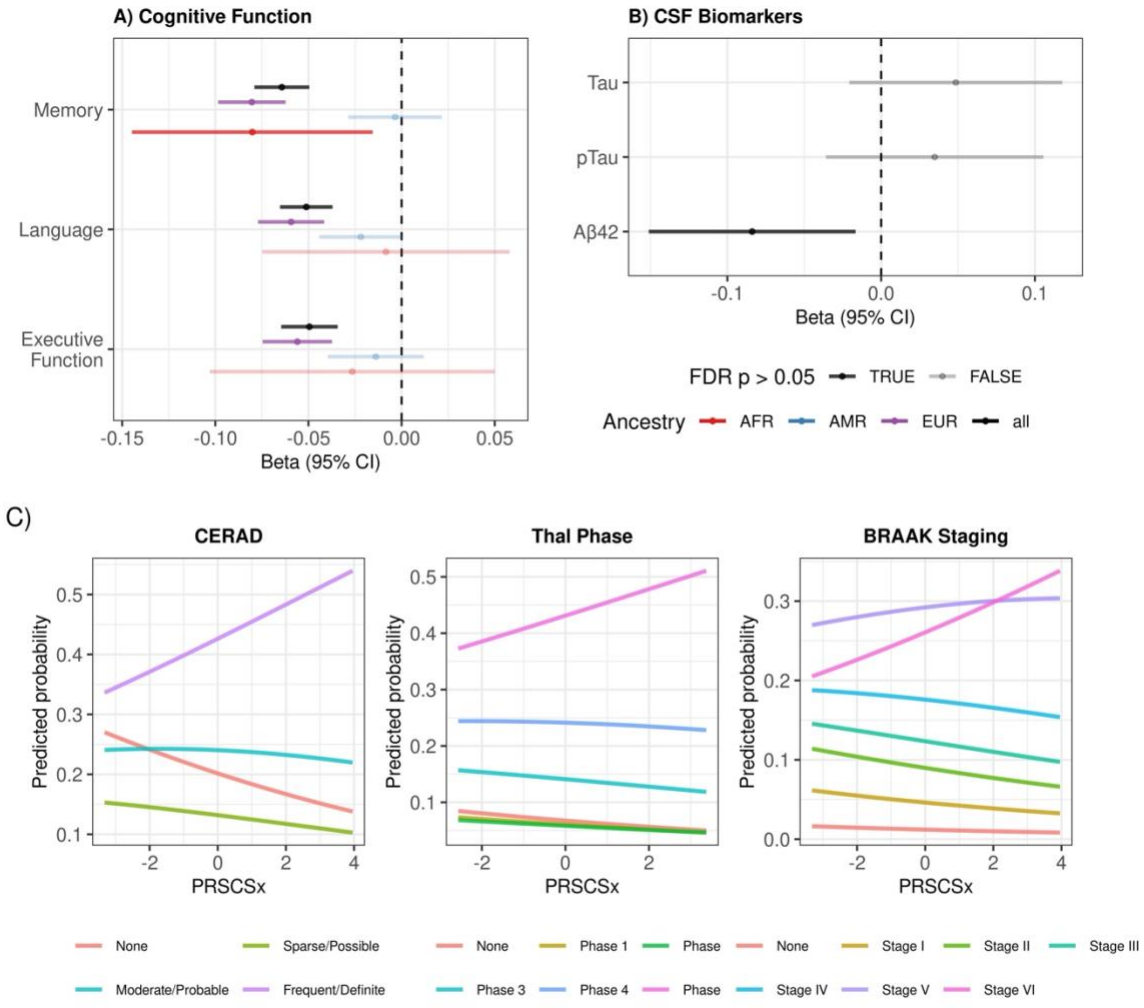


Figure 2.3. Associations of PRS-CSx model with AD endophenotypes
Associations of the best-predictive PRS model, cross-ancestry PRS-CSx, with **(A)** cognitive function and **(B)** cerebrospinal fluid (CSF) biomarkers in the ADSP. The dark blue color represents statistical significance after correction at a 5% false discovery rate (FDR). Cognitive function: N = 10,903 (AFR: 409, AMR: 2,888, EUR: 7,606), CSF biomarkers: N = 808. **(C)** Predicted probabilities of neuropathological staging outcomes by PRS-CSx. CERAD: N = 2,713, Thal Phase: N = 1,175, BRAAK staging: N = 2,711. The sample sizes reported in Table 1 vary, as certain participants contributing to the endophenotype analyses lack an AD diagnosis.

2.3.6 AD endophenotypes: HABS-HD

We further validated the association of the cross-ancestry PRS in HABS-HD using AD endophenotypes. Higher PRS-CSx was significantly associated with lower levels of plasma levels of $A\beta_{42}$, higher levels of $pTau_{217}$, and higher Aβ PET global SUVR in the total cohort. The association with $pTau_{217}$ and Aβ global SUVR was significant in the participants of European ancestry, retaining significance after multiple testing correction. There were no other ancestry-specific effects in the AFR and AMR participants (Table S2.6).

2.4 Conclusion

We evaluated the predictive accuracy of single-, multi-, and cross-ancestry AD-PRS models in participants of African, Admixed American, and European ancestry within the ADSP and the HABS-HD cohort to assess PRS transportability. Single-ancestry PRS showed the strongest performance in participants of European ancestry but declined notably in participants of Admixed American and African ancestry, especially among individuals of African ancestry, consistent with previous reports highlighting ancestry-specific limitations in PRS-based risk stratification.[8,49–51] This highlights reduced accuracy and portability of a single-ancestry PRS model across ancestries, likely driven by differences in LD structure, allele frequency, and genetic architecture.[52–56] In contrast, multi- and cross-ancestry PRS models demonstrated improved predictive accuracy in African and Admixed American ancestry groups. When models incorporated a large number of SNPs from multi-ancestry GWAS (e.g., MAMA $P_{T0.1}$, PRS-CSx), both associations with AD risk and explained variance (R^2) improved, indicating that including more ancestry-matched SNPs capture better risk profiles in African and Admixed populations. The absence of this trend for single-ancestry EUR PRS likely reflects the limited portability of European-derived variants to

non-European populations with more variable genetic architectures. This supports previous findings that PRS constructed from smaller, ancestry-matched GWAS can outperform those derived from larger European datasets.[25]

Although the non-European GWAS datasets used in this study were substantially smaller than the European GWAS dataset, incorporating base datasets that match the ancestry of the target populations improved overall PRS performance. In contrast, one study reported similar performance across single-, multi-, and cross-ancestry AD-PRS models using the MVP data.[57] This discrepancy may be due to differences in SNP selections. For example, their single-ancestry PRS included all GWS SNPs, whereas our approach applied LD pruning to select independent SNPs. As a result, incorporating additional SNPs from multi-ancestry GWAS in their framework may have contributed only marginal effects. Differences in cohort characteristics may also play a role, as AD cases and controls in MVP were defined using ICD codes rather than clinical or biomarker-confirmed diagnoses.

Beyond AD diagnosis, we evaluated the clinical validity of PRS in predicting abnormalities in AD endophenotypes for Aβ, Tau, and cognitive function. The best-performing model, PRS-CSx, was associated with CSF $A\beta_{42}$ levels and cognitive domains of memory, executive function, and language. Notably, PRS-CSx was not associated with CSF $pTau_{181}$ or total tau in the ADSP cohort, which may stem from sampling variability, data harmonization differences, and/or small sample sizes. Higher levels of plasma $pTau_{217}$ were significant in the HABSHD cohort, in addition to associations with lowered levels of plasma $A\beta_{42}$. Significant associations with key plasma biomarkers of AD pathology suggest that polygenic risk prediction may capture upstream pathogenic processes, including Aβ and tau pathways. Higher PRS-CSx was also associated with

the most severe neuropathology burdens across CERAD, Thal phase, and Braak stage in the ADSP cohort. In contrast, associations with lower or intermediate stages were weak or absent, suggesting that PRS-CSx predicts advanced pathology but may be less sensitive to earlier or moderate changes. Although we observed significant associations between AD-PRS and endophenotypes, the effect sizes of PRS still remain modest, explaining only a small fraction of variance in cognitive, neuroimaging, and biomarker outcomes, especially when looking at incremental R^2. This is consistent with previous studies that, while PRS captures cumulative genetic effects, other factors such as age, sex, *APOE* genotype often explain more variance in AD phenotypes than PRS alone.[8,58] However, individuals in the extreme tail of the PRS distribution exhibit substantially elevated disease risk, reportedly as high as a 30-fold increase among those in the top decile.[2,57] By defining thresholds that identify this high-risk group, PRS can still be clinically meaningful for identifying individuals who may benefit from further testing and more regular screenings.

Ancestry normalization emerged as a critical step in improving prediction accuracy for underrepresented groups by accounting for population-specific genetic structures that differ in allele frequency and LD. Although several PRS methods have been developed to include ancestry stratification or ancestry-specific SNP effects to address bias in cross-population prediction,[22,23,30,59–61] explicit normalization of the PRS itself based on global ancestry is still not widely implemented for AD-PRS. Shifts in PRS distributions that arise from differences in MAF and LD complicate the assessment of risks across populations and studies. By employing a reproducible framework such as the pgsc_calc Nextflow pipeline, genetic ancestry estimation and ancestry normalization can be performed effectively and seamlessly. Integrating ancestry normalization into PRS construction enables more equitable genetic prediction tools that better reflect the genetic architecture of ancestrally diverse populations. Given the high degree of genetic

heterogeneity within a single superpopulation[62] (e.g., African and admixed populations), ancestry normalization is a critical step to account for differential risk profiles that arise from ancestral differences rather than true genetic risk.

Several limitations should be acknowledged in our study. First, a lack of representation of people of South and East Asian ancestry limited our ability to assess the cross-ancestry transportability of the PRS models. The dataset is also limited to participants in the US, and how multi- and cross-ancestry perform in non-European populations from other continents is unknown. Furthermore, the currently available GWAS summary statistics from minority populations still don't reflect the full genetic diversity and substructures that exist within one superpopulation. This calls for the necessities to continue expanding and improving the diversity and sample sizes of future GWAS to more fully represent global and intra-ancestry genetic variation. Second, we did not incorporate genotype–environment (GxE) interactions, a framework that explains the interplay of environmental, socioeconomic, and lifestyle factors that can modify genetic risk. These factors are known to contribute additively or multiplicatively to AD susceptibility across populations.[63–65] Third, future iterations of such studies should prioritize larger, more representative cohorts and integrate extensive phenotypic data from biobanks (e.g., All of Us, UK biobanks) to enhance both the calibration and clinical adaptability of risk predictions. Finally, the application of other advanced data-driven models, such as LDpred2,[66] PolyPred+,[69] and BridgPRS,[67] and the incorporation of SNP heritability estimates could further refine the predictive power and cross-population transferability of AD-PRS.[68] With the rapid proliferation of PRS methods,[69] future studies may focus on benchmarking across all the methods in large, diverse cohorts as well as community-based populations.

Despite these limitations, our study demonstrates several key strengths. We systematically evaluated single-, multi-, and cross-ancestry PRS models across participants of African, Admixed American, and European ancestries, providing a comprehensive assessment of PRS transferability in diverse cohorts. By incorporating ancestry-specific normalization and leveraging multi-ancestry GWAS summary statistics, we improved predictive accuracy in underrepresented populations and highlighted the importance of including ancestry-matched SNPs in risk models. Furthermore, by extending the evaluation beyond AD diagnosis to biomarkers and cognitive endophenotypes within the A/T/N framework, we provide evidence for the clinical validity of PRS in capturing biologically relevant AD pathology. The broader implications of our findings align with the objectives of the eMERGE Consortium's Genome Informed Risk Assessment (GIRA) initiative, which emphasizes the integration of PRS into clinical care while ensuring analytical validity and health equity across diverse populations.[70] By leveraging diverse datasets and applying ancestry-specific normalization to PRS calculations, our methodology enhances risk stratification accuracy, supporting the growing consensus that such approaches are crucial for equitable and effective genomic medicine.[16,20,20,60]

In summary, this study highlights methodological innovations of leveraging multi-ancestry base GWAS summary statistics, applying ancestry normalization, and extending evaluation beyond diagnosis to AD endophenotypes that can enhance both the accuracy and clinical relevance of AD-PRS. Importantly, our results call for equitable genomic medicine through increasing genetic representation and moving beyond Eurocentric risk models to reflect the full spectrum of human genetic diversity. By demonstrating practical strategies to improve prediction in underrepresented populations, this work provides a foundation for more inclusive risk assessment tools that can be translated into meaningful clinical applications.

Supplementary Information

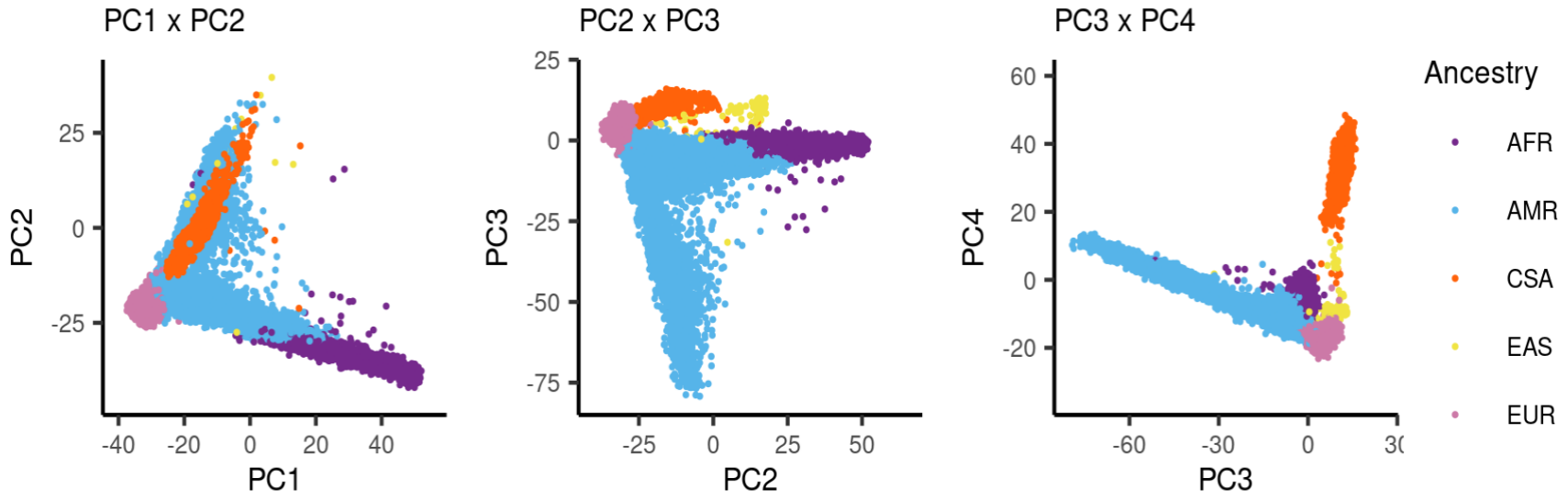


Figure S2.1. Principal component analysis (PCA) of ADSP genetic data
PCA of genetic data reveals global population structure. Scatterplots show the first four principal components (PCs) of genotype data: (left) PC1 vs PC2, (center) PC2 vs PC3, and (right) PC3 vs PC4. Each point represents an individual, colored by population group or inferred ancestry. Clustering patterns reflect genetic differentiation among major continental populations.

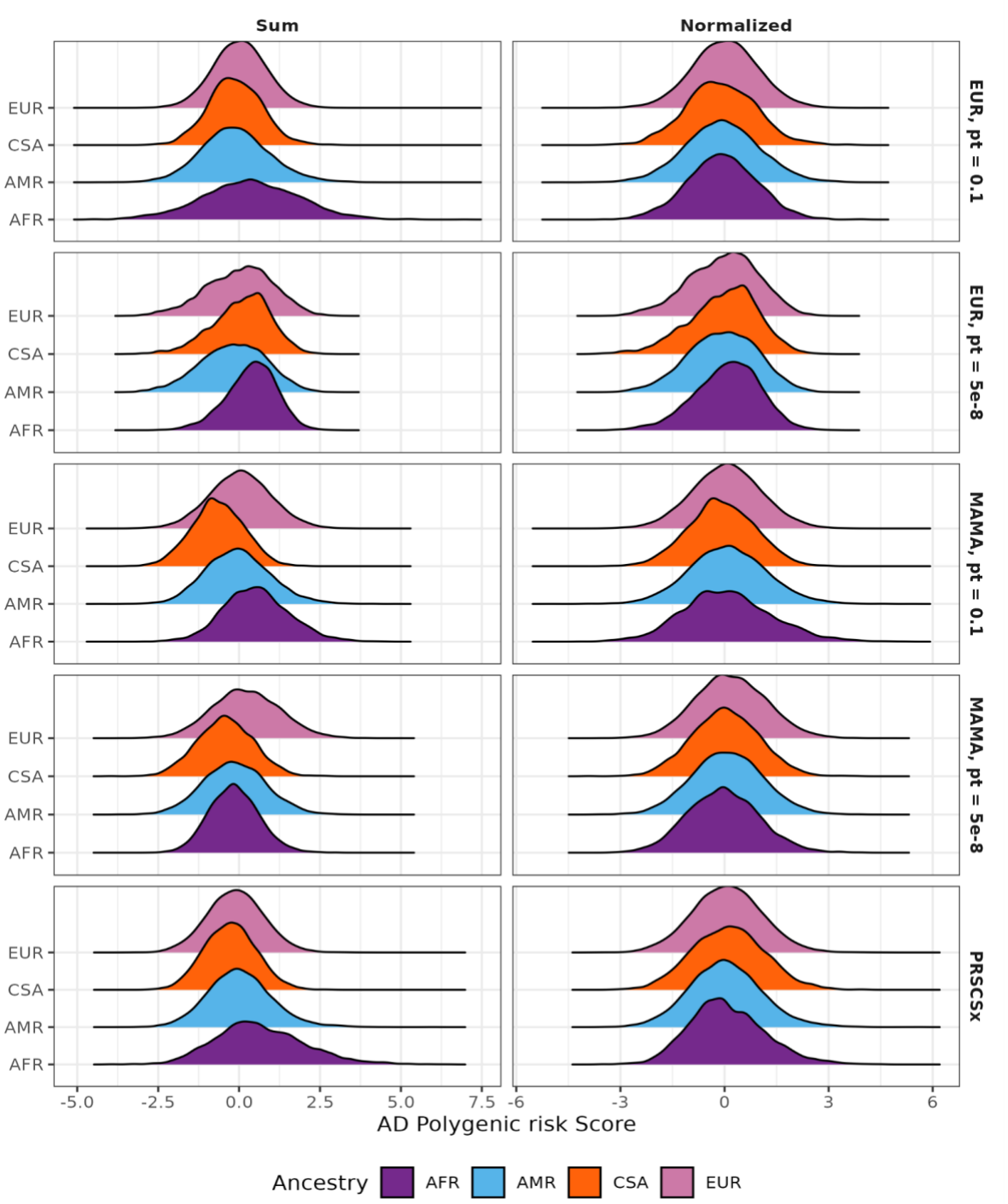


Figure S2.2: Distribution of pre- and post-ancestry normalization for five PRS models, stratified by genetic ancestry

"Sum" indicates raw PRS prior to ancestry normalization, and "Normalized" indicates normalized PRS, stratified by genetic ancestry assignment. CSA participants were included due to a sufficient sample size.

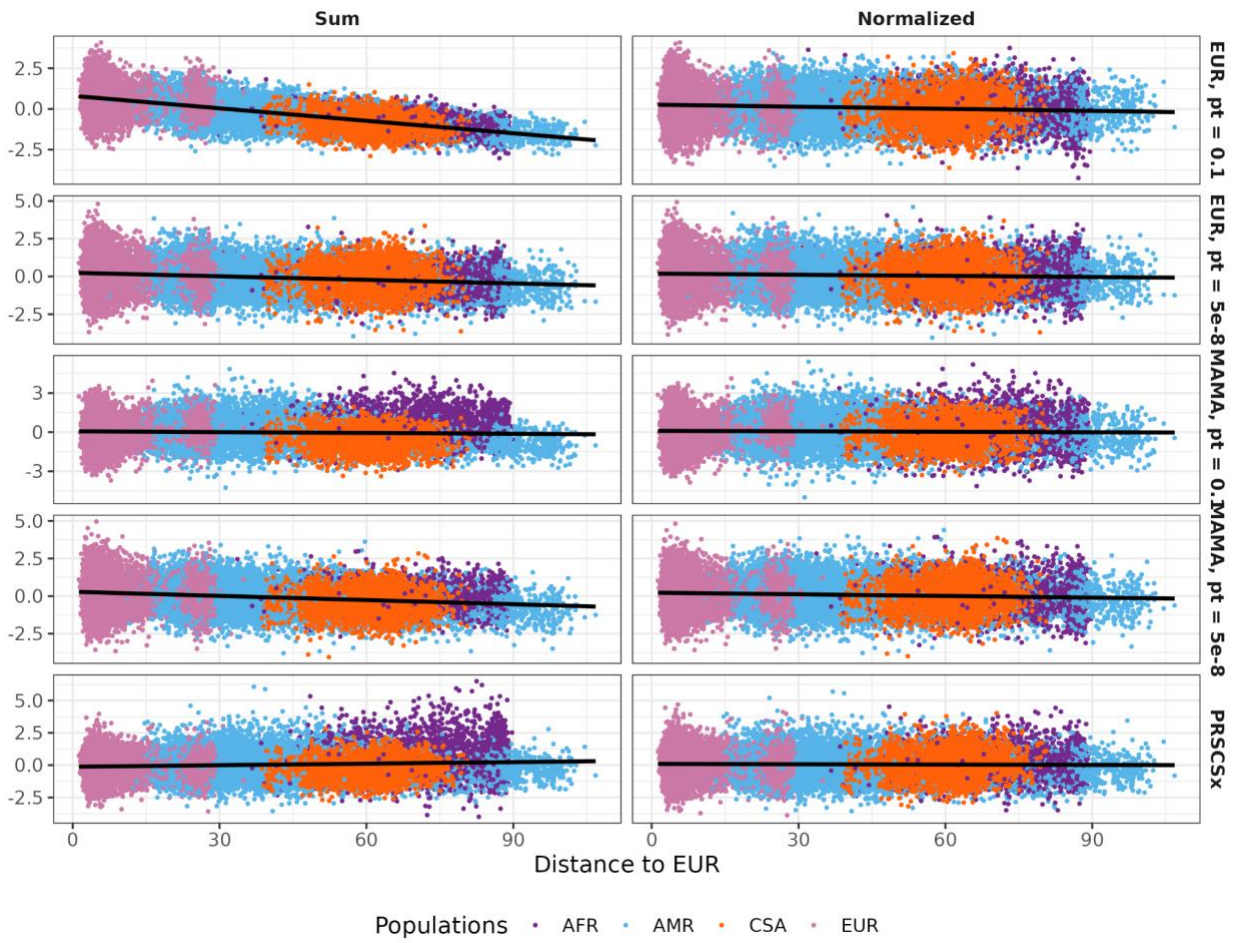
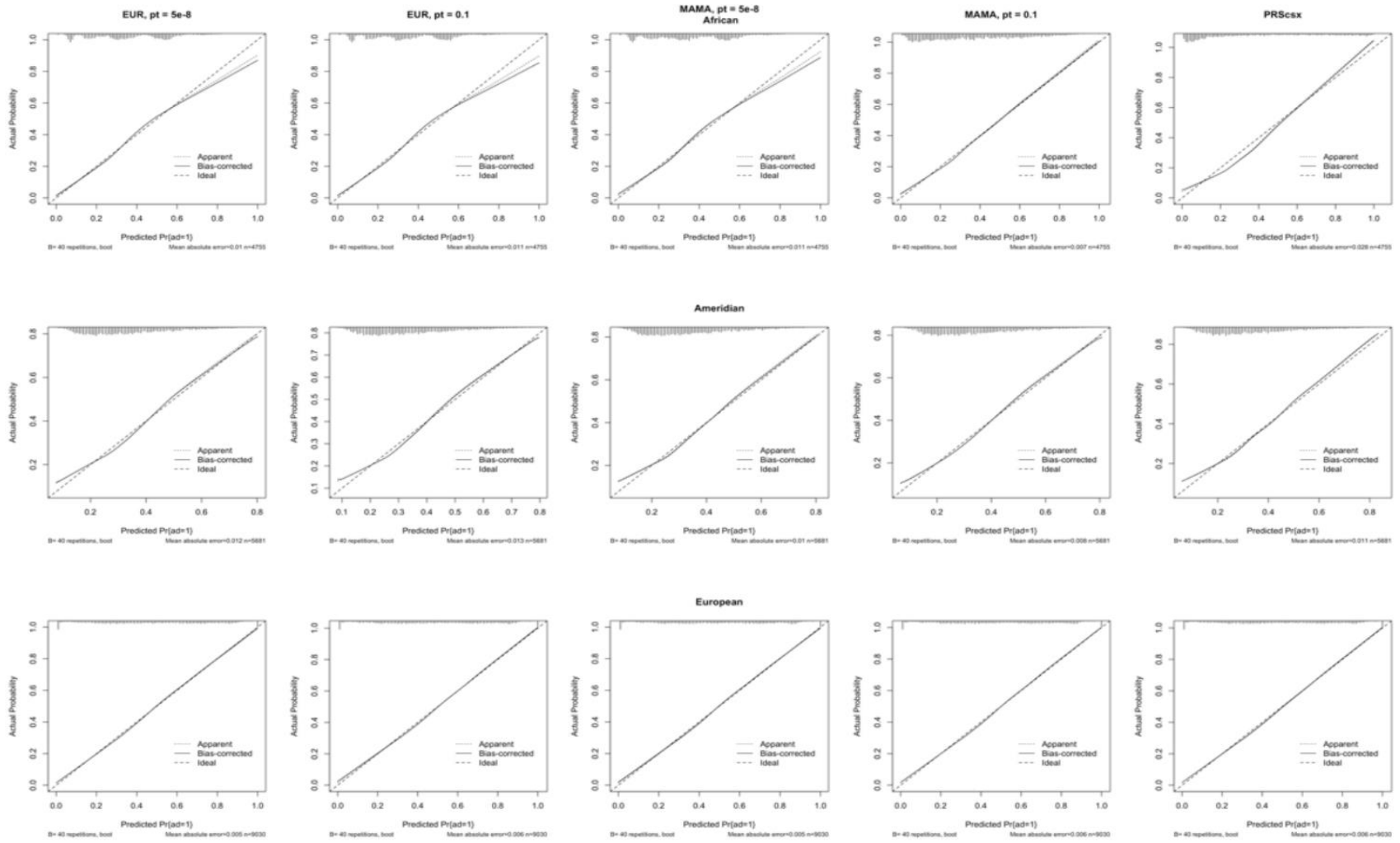


Figure S2.3. Genetic distance analysis of ancestry for the ADSP cohort
Y-axis represents numeric values of PRS, and x-axis represents genetic distance from the European reference population. Lower genetic values represent individuals genetically closer to Europeans, and higher values represent genetically distant populations from the European population. "Sum" represents PRS prior to ancestry normalization, and "Normalized" represents PRS after the ancestry normalization. CSA (Central South Asian) participants were included due to a sufficient sample size.



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Chapter 3: Associations of dementia polyexposure scores to Alzheimer's disease endophenotypes in a diverse population

Abstract

Dementia clinical risk scores (CRS) provide accessible tools for identifying individuals at risk for Alzheimer's disease (AD), yet their performance across diverse populations and relationships to AD endophenotypes remains unclear. We evaluated four CRS, mCAIDE, WHICAP, LIBRA, and CogDRisk, in relation to cognitive impairment (CI) and AD endophenotypes, including $pTau_{217}/A\beta_{42}$ positivity defined using a Youden index–derived cutoff for amyloid PET positivity. Logistic and linear regression models stratified by self-reported race/ethnicity were used to assess the associations of CRS with endophenotypes and CI, and to evaluate predictive performance. CogDRisk showed the strongest and most consistent performance across endophenotypes, $pTau_{217}/A\beta_{42}$ positivity, and CI, with mCAIDE performing the worst and lacking associations with plasma biomarkers. Higher CRS were consistently associated with increased odds of dementia across all races/ethnicities. CRS capture AD-related risk across diverse populations and modestly reflect underlying biological endophenotypes, supporting their utility in community-based risk assessment.

3.1 Introduction

Alzheimer's disease (AD) presents substantial clinical and economic challenges, yet early identification of individuals at risk remains limited in diverse, community-based settings. Current AD risk and diagnostic assessment involve genetic and cognitive screening, cerebrospinal fluid (CSF) and plasma biomarkers of AD pathology, and neuroimaging; however, these approaches, though valuable, remain costly, invasive, and limited to those with access to specialized care in

developed countries.[1–3] Cognitive testing and CSF and plasma biomarkers also only capture risks once pathology has begun, even if clinical symptoms of AD have not yet manifested.[4–6] In addition, many older adults, especially those from underserved populations, are evaluated in primary care contexts where advanced diagnostic resources are unavailable.[7–9] Given these limitations and the growing prevalence and burden of AD, there is a pressing need for effective risk assessment tools that can identify at-risk individuals earlier and support timely preventive interventions.

Clinical risk scores (CRS) have been developed as accessible tools that estimate AD and dementia risks based on demographics, lifestyle, and clinical profiles.[10] Many CRS can be readily implemented in community and primary care settings, often using self-reported information, and can help identify individuals who may benefit from further confirmatory testing with biomarkers or genetic screening.[11,12] CRS are designed to capture modifiable midlife-to-late-life risk factors, enabling individualized prevention strategies and risk stratification. These tools are particularly relevant for individuals with a family history of dementia or known genetic susceptibility, as they provide actionable targets for risk reduction and support precision health approaches. Many CRS have been proposed[13] and validated in mid- and late-life populations across diverse settings, including the modified Cardiovascular Risk Factors, Aging, and Incidence of Dementia (mCAIDE) score,[14] the Washington Heights–Inwood Columbia Aging Project (WHICAP) score,[15] the Lifestyle for Brain Health (LIBRA) index,[16] and the Cognitive Dementia Risk (CogDRisk) score.[17] Among them, mCAIDE and WHICAP were independently developed using U.S.-based cohorts, while LIBRA and CogDRisk were developed based on systematic reviews and meta-analyses. Each integrates slightly different risk domains such as vascular health, lifestyle, psychosocial, and cognitive engagement factors, reflecting distinct methodological approaches and population contexts in which they were developed.[14–20]

External validation studies of CRS have reported variable performance across cohorts and settings. LIBRA and CogDRisk have been validated in multiple independent studies[21–26]; however, most validation studies were conducted in populations of predominantly European descent, limiting their generalizability to other racial and ethnic groups. The WHICAP score, which uniquely incorporates ethnicity-specific weighting, has only been evaluated in a small diverse population.[27] The original CAIDE index has been validated in large, multiethnic samples,[28] but few studies have independently validated mCAIDE. To assess utility in diverse populations, CRS need to be validated across different racial and ethnic groups. Furthermore, only a handful of studies have examined the relationships between these risk indices and AD endophenotypes,[29–31] an important step in determining whether CRS reflect underlying disease pathology. Because abnormalities in AD biomarkers precede clinical syndromes of dementia,[32–34] the growing emphasis on AD pathophysiology highlights the need to validate CRS in detecting early abnormalities in biological endophenotypes.

The present study examines how four widely used CRS relate to dementia diagnosis and to AD endophenotypes within a multiethnic cohort, the Health and Aging Brain Study - Health Disparities (HABS-HD). By investigating the utility of CRS across racial/ethnic groups and their sensitivity to early changes in AD endophenotypes, we aim to clarify the extent to which CRS can serve as equitable and biologically informative tools for AD and dementia risk assessment in real-world, community-based settings.

3.2 Methods

3.2.1 Health & Aging Brain Study - Health Disparities

This study uses cross-sectional data from the HABS-HD cohort. HABS-HD is an ongoing community-based AD study that comprises participants from self-reported Black (AA), Hispanic/Latinx (LA) (Mexican American, Puerto Rican, Dominican Republic, etc.), and non-Hispanic White (NHW) populations recruited at the University of North Texas Health Science Center, Fort Worth, Texas, USA. The study collects data on demographics, AD biomarkers, neuroimaging, clinical history, and genomics, providing a comprehensive resource for AD and related dementia research. The study recruited generally healthy individuals free of serious mental illnesses and medical conditions, and we further excluded participants younger than 55 years old and those without *APOE* genotype information. The visit 1 baseline measurements for all outcomes of interest were used for all downstream analyses. All HABS-HD participants (and/or their legal guardians) signed written informed consent to participate in the study.

3.2.2 Endophenotype Standardization

Plasma biomarkers: Fasting blood samples were collected, and the levels of plasma biomarkers (i.e. $A\beta_{42}$, $A\beta_{40}$, $pTau_{217}$, total Tau, NfL) were quantified using commercially available kits, Quanterix, for all the participants of the HABS-HD.[35] Plasma biomarker levels were log-transformed to reduce the skewness, followed by z-score normalization (mean = 0, standard deviation (SD) = 1) for all participants to standardize and remove any batch effects. $A\beta_{42}/A\beta_{40}$ ratio was calculated by dividing the raw values of $A\beta_{42}$ and $A\beta_{40}$ prior to transformation and normalization.[36] We excluded participants with plasma biomarkers identified as outliers using the interquartile range methodology.[37] *Brain morphometry*: Cortical thickness was defined as the

surface area-weighted average of cortical thickness in the right and left entorhinal cortex, fusiform, and inferior and middle temporal cortex. These regions of interest correspond to brain areas that are especially vulnerable to AD–related neurodegeneration. Hippocampal volume was determined by taking the mean volume of the right and left hippocampal volumes determined on a T1-weighted volume scan.[38] *Cognition*: The memory domain was assessed using immediate and delayed recall from the Wechsler Memory Scale-III (WMS-III) Logical Memory[39] and the Spanish-English Verbal Learning Test (SEVLT).[40] The verbal ability domain was assessed using Letter Fluency and Animal Naming tests.[41] The executive function domain was assessed using the WMS-III Digit Span[39] and the Trail Making Test, Parts A and B.[41] All cognitive test scores were standardized using z-score transformation, and these scores for each domain (memory, verbal ability, and executive function) were averaged to create composite scores. In addition, the Mini-Mental State Examination (MMSE)[42] and Clinical Dementia Rating (CDR) scale[43] were administered to all participants as part of the neuropsychological assessment.

3.2.3 Modifiable Risk Factors

It is important to note that covariate definitions vary across CRS. For example, dyslipidemia is classified through total cholesterol in CogDRisk and LIBRA, HDL in WHICAP, and self-reported high cholesterol in mCAIDE. We retained the covariates as specified by each CRS rather than harmonizing them across models to retain their original scoring scheme.

Education: Years of education were coded as a numeric variable, with values ranging from 0 (kindergarten) to 20 (postgraduate).

Body Mass Index (BMI): BMI at baseline was calculated as weight divided by height squared, kg/m^2. Obesity was classified based on BMI as underweight (<18.5 kg/m^2), normal weight (18.5–24.9 kg/m^2), overweight (25–29.9 kg/m^2), or obese (≥ 30 kg/m^2).

Hypertension: All participants underwent a series of anthropometric measurements to assess blood pressure. Hypertension was defined as a past medical history of the condition or consistently elevated blood pressure, with at least two measurements of systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg at the baseline visit.

Dyslipidemia/High Cholesterol: Hyperlipidemia was defined as meeting any of the following criteria: LDL cholesterol ≥120 mg/dL, total cholesterol ≥240 mg/dL, triglycerides ≥200 mg/dL, or a documented history of high cholesterol.

Diabetes: All participants had measures of hemoglobin A1C from fasting blood samples. Diabetes was defined as an A1C level ≥6.5% at the baseline visit or a documented history of the condition.

Depression: Participants were considered to have depression if they had a past medical history of the condition or scored ≥10 on the 30-item Geriatric Depression Scale (GDS).

Stroke: Participants self-reported (i.e., yes or no) a history of stroke or indicated if they had ever been told by a healthcare professional that they had experienced a stroke.

Traumatic Brain Injury (TBI): TBI with or without loss of consciousness information was collected through self-report data.

Renal Dysfunction: Estimated glomerular filtration rate (eGFR) was calculated using the 2021 Chronic Kidney Disease Epidemiology (CKD-EPI) creatinine equation, which estimates kidney function based on serum creatinine, age, and sex. eGFR values are reported in mL/min/1.73 m^2, and participants with eGFR <60 mL/min/1.73 m^2 were classified as having renal dysfunction, consistent with standard clinical definitions of chronic kidney disease.

Alcohol Intake: Alcohol intake was assessed using a single item from the Alcohol Use Disorders Identification Test (AUDIT): 'How often do you have a drink containing alcohol?' Response options included never, monthly or less, 2–4 times per month, 2–3 times per week, and 4 or more times per week.

Smoking: Smoking was classified as self-reported current smokers, indicating yes or no.

Social Support: Loneliness was approximated using the social support questionnaires in the HABS-HD. The questionnaire consisted of 12 items assessing perceived availability of emotional, neighbourhood-level, and instrumental support.

Physical Activity: Physical activity was assessed using the Rapid Assessment of Physical Activity (RAPA), a questionnaire designed to provide a simple and accessible measure of physical activity among adults aged 50 years and older.[44] RAPA scores were derived according to established guidelines, with higher scores indicating greater levels of physical activity.

3.2.4 Clinical risk scores

For a detailed description of variables for each CRS, refer to Table S3.1.

Modified Cardiovascular Risk Factors, Aging, and Dementia (mCAIDE) was derived from the CAIDE score developed in Finland but modified to better reflect U.S. cohorts and mid-to-late-life risk using two U.S.-based cohorts.[14] mCAIDE incorporates age, sex, education, BMI, systolic blood pressure (SBP), self-reported high cholesterol status, and physical activity measured by the mini Physical Performance Testing (miniPPT). The RAPA was used in place of mPPT to replace the physical activity measure. Participants whose total scores were in the lowest tertile were classified as 'inactive,' and those above this threshold as 'active.'

Washington Heights-Inwood Columbia Aging Project (WHICAP) is a CRS that was developed in an independent cohort of the Washington Heights and Inwood Community Aging project in Manhattan, NY, to create a risk index for late-onset AD.[15] It includes the variables sex, age, education, race/ethnicity, *APOE**ε4 carrier status, BMI, low high-density lipoprotein cholesterol (HDL-C), diabetes, hypertension, and current smoker. Among the four CRS considered in our analysis, WHICAP was the only score that explicitly incorporates race/ethnicity as a predictor. Therefore, we selected WHICAP to assess its transportability within HABS-HD, a multiethnic cohort from a different geographic region of the US. HDL-C was categorized as low or normal based on sex-specific cutoffs: males with HDL-C <50 mg/dL and females with HDL-C <40 mg/dL were classified as low, while values above these thresholds were classified as normal. *APOE**ε4 carrier status was excluded from the scoring to prevent inflation of WHICAP relative to other CRS that do not incorporate *APOE**ε4 information. Additionally, since genetic information is not always readily available in primary clinical settings, CRS that do not incorporate genetic factors may be more practical and more readily adopted.

The Lifestyle for Brain Health (LIBRA) score was developed using an approach that combined a systematic review, meta-analysis, and Delphi consensus studies to identify and weight modifiable lifestyle, cardiovascular, and metabolic risk factors for all-cause dementia.[16,19,45] LIBRA was specifically designed to support primary prevention by focusing purely on modifiable risk factors in mid-to-late life and does not include age, sex, or education. The LIBRA score includes a healthy diet (i.e. Mediterranean diet), physical inactivity, cognitive activity, low to moderate alcohol consumption, current smoker, heart diseases, diabetes, high cholesterol, BMI, hypertension, renal dysfunction, and depression. Participants who reported drinking 2–3 times per week on the AUDIT questionnaire were classified as light to moderate consumers, corresponding to >0 and <14 units of alcohol per week. For the physical activity measure, participants who answered 'yes' to item 1 or item 2 on the RAPA questionnaire were classified as physically inactive. Healthy diet and cognitive activity measures were omitted from the scoring due to the lack of data in the HABS-HD study.

Cognitive Health and Dementia Risk Reduction (CogDRisk) was developed through a systematic review and meta-analysis of studies identified from international databases to quantify the impact of modifiable factors on cognitive decline and dementia.[17,20] The CogDRisk score includes sex-specific age categories (i.e., age effect estimates differ by sex), education, midlife (≤65 yrs) obesity, dyslipidemia, diabetes stratified by sex, history of stroke, history of TBI, hypertension, atrial fibrillation, clinical diagnosis of insomnia, depression, physical inactivity, cognitive engagement, social engagement, diet, and current smoker. Participants who scored at least 1 SD below the mean on the social support questionnaire score were classified as 'lonely,' and those above this threshold were classified as 'not lonely' for the CogDrisk scoring. For physical activity measures, participants who answered 'yes' to item 6 or item 7 on the RAPA questionnaire were

classified as physically active, reflecting an activity level of >150 minutes per week of moderate-to-vigorous activity. Baseline BMI at visit 1 was used in place of midlife obesity/BMI, which was not available in this cross-sectional study. Insomnia, atrial fibrillation, cognitive engagement, and diet measures were excluded from the scoring due to unavailability in the HABS-HD study.

3.2.5 Missingness

Missing data for variables used in the construction of the CRS were imputed using the *missForest* algorithm[46] implemented in R for both continuous and categorical variables. The imputation dataset included relevant demographics, clinical variables, biomarkers, and predictors. Variables with high substantial missingness (> 40%), such as myocardial and heart disease, were excluded from imputation. To verify that imputation did not introduce bias, all analyses were compared against analyses using complete case data.

3.2.6 Mild Cognitive Impairment and Dementia Diagnosis

Cognitive status was assessed using self- and informant-reports, the Clinical Dementia Rating (CDR scale), and a neuropsychological battery covering memory, executive function, and verbal ability (animal naming, FAS, SEVLT, WMS-III Logical Memory, Digit Span, Trail Making, and Digit Symbol Substitution) as previously described.[35,47] Participants without any complaints of cognitive change, either reported by the individual or their informants, with a CDR sum of boxes (CDR-SOB) of 0, were classified as cognitively unimpaired. If a participant has an isolated poor neuropsychological test performance, in the absence of any cognitive complaints and functional decline, they were assigned as cognitively unimpaired. Mild cognitive impairment (MCI) was classified as participants with complaints of cognitive change, either reported by the individual or their informants, with a CDR-SOB score of 0.5-2.0 and performance at or below 1.5 SD below z-

score adjusted norms on at least one cognitive test. Dementia diagnosis was made based on CDR sum of boxes score >=2.5, and cognitive test score at or below 2 SD below the mean on tests in two or more domains.

3.2.7 Statistical analysis

Logistic regression models were used to assess the association of CRS with (i) MCI, (ii) dementia, and (iii) MCI + dementia, using cognitively normal participants as the reference group. Age, sex, *APOE* genotypes, and years of education were adjusted for in LIBRA, and *APOE* genotype was included as a covariate for mCAIDE, WHICAP, and CogDRisk. *APOE* genotype was modelled as a categorical variable at the individual genotype level (ε2/ε2, ε2/ε3, ε2/ε4, ε3/ε4, and ε4/ε4), with ε3/ε3 specified as the reference category. Thus, regression estimates reflect genotype-specific effects relative to the ε3/ε3 group. Model performance was evaluated by calculating the AUC values to assess model discrimination, and the Nagelkerke R-squared (R^2) was calculated to determine the goodness-of-fit of the models. The Delong test was used to assess whether there were statistical differences in the AUC of two models.[48] Self-reported race/ethnicity was used for stratified analysis. P-values were adjusted for multiple hypothesis testing by applying the false discovery rate (FDR) at 5%.

Linear regression models were used to estimate the effects of CRS on AD endophenotypes, including (i) plasma biomarkers ($A\beta_{42}/A\beta_{40}$ ratio, $pTau_{217}$, total Tau, and NfL), (ii) neuroimaging measures (cortical thickness and hippocampal volume), and (iii) clinical function (cognitive severity assessed by MMSE and clinical severity assessed by CDR, and memory, verbal ability, and executive function cognitive domains assessed by composite scores). For associations with plasma biomarkers, models for mCAIDE and WHICAP were adjusted for *APOE* genotype and

eGFR, models for LIBRA were adjusted for age, sex, BMI, and *APOE* genotype, and models for CogDRisk were adjusted for *APOE* genotype, eGFR, and BMI. For neuroimaging associations, models for mCAIDE, WHICAP, and CogDRisk were adjusted for *APOE* genotype and intracranial volume. In contrast, models for LIBRA were adjusted for age, sex, *APOE* genotype, and intracranial volume. For cognitive function associations, models for mCAIDE, WHICAP, and CogDRisk were adjusted for interview language and *APOE* genotype, while models for LIBRA were adjusted for age, sex, years of education, *APOE* genotype, and interview language. P-values were adjusted for multiple hypothesis testing by applying the false discovery rate (FDR) at 5%.

For both logistic and linear regression analyses, we specified two baseline models: (i) a demographics model including age, sex, and years of education, and (ii) a demographics plus *APOE* genotype model. These baseline models were used to evaluate how much each CRS improved prediction beyond demographics alone and beyond demographics combined with *APOE* genotype.

3.2.8 Prediction of pTau$_{217}$/Aβ$_{42}$ amyloid positivity by CRS

To assess whether CRS predict plasma biomarker-derived amyloid positivity, we examined the pTau$_{217}$/Aβ$_{42}$ ratio, an FDA-approved plasma measure[49] that demonstrates high concordance with amyloid PET positivity. Plasma pTau$_{217}$/Aβ$_{42}$ levels were dichotomized using an empirically derived threshold optimized to predict amyloid PET positivity in the HABS-HD cohort. The optimal cutpoint was determined using the Youden index, with stability assessed via bootstrapping (2,000 iterations). Individuals were classified as positive if their pTau$_{217}$/Aβ$_{42}$ value was greater than or equal to the derived threshold.

We evaluated all CRS, including sensitivity models (see Section 3.2.10), as well as two demographic models, to assess predictive performance using OR, AUC, and Nagelkerke R^2. Associations between CRS and dichotomized $pTau_{217}/A\beta_{42}$ were estimated using logistic regression. For mCAIDE, WHICAP, and CogDRisk, models were adjusted for *APOE* genotype. For LIBRA, models additionally included age, sex, years of education, and *APOE* genotype. The same demographic model used in the endophenotype analyses served as the baseline comparison. P-values for odds ratios were adjusted by applying the FDR at 5%.

3.2.9 Racial/Ethnic stratified analysis

To evaluate whether the associations between each CRS and outcomes differed across racial/ethnic groups, we conducted pairwise z-tests comparing regression coefficients between subpopulations. For each score, the difference between standardized coefficients ($\beta_1 - \beta_2$) was divided by the square root of the sum of their squared standard errors to calculate a z-statistic and two-sided p-value. Comparisons were performed for all pairwise combinations of racial/ethnic groups, excluding the overall population, with significant differences highlighted at an FDR-adjusted $p < 0.05$.

3.2.10 Sensitivity analysis

As a sensitivity analysis, demographic variables embedded within the CRS (e.g., age, sex, and education) were removed from the scores and instead included as covariates in the regression models to evaluate the incremental predictive contribution of the clinical risk components beyond demographics and *APOE* genotype. Because these demographic factors are non-modifiable and less clinically actionable, they were excluded from the mCAIDE, WHICAP, and CogDRisk scores when constructing the modified CRS used in these analyses. For a detailed description and the model specification of covariates included in the CRS for both the main and sensitivity analyses,

please refer to the bottom of Table S1. We then conducted regression analyses to assess associations between the modified CRS and both the endophenotypes and the $pTau_{217}/A\beta_{42}$ cutoff and to evaluate model predictive performance. In all linear and logistic regression models, age, sex, years of education, and *APOE* genotype were included as covariates. P-values were adjusted for multiple hypothesis testing using an FDR of 5%.

3.3 Results

3.3.1 Participant characteristics

Of the 2,627 participants, 1,907 were cognitively normal, and 720 were diagnosed with MCI or dementia (Table 1). Female participants (61.4%) comprised the majority in HABS-HD. Non-Hispanic White (NHW) individuals (N = 1,062, 40.4%) were the largest racial/ethnic group, followed by Hispanic/Latinx (LA) (N = 948, 36.1%) and then Black/African American (AA) participants (N = 617, 23.5%). Mean CRS values ranged from 0 to 0.1 in cognitively normal and MCI participants, increasing to 0.3 to 0.5 in those with dementia (Table 3.1).

Table 3.1. Descriptive statistics of the study cohort
Sample characteristics of the Health and Aging Brain Study – Health Disparities (HABS-HD) cohort, stratified by cognitive status.

Characteristics[a]	**Cognitively Normal**	**Mild Cognitive Impairment**	**Dementia**
Sample Size	1855	528	176
Demographics			
Age	66.8 (± 7.3)	66.9 (± 8.2)	70.2 (± 8.9)
Female	1194 (64.4%)	281 (53.2%)	90 (51.1%)
NHW[b]	856 (46.1%)	138 (26.1%)	58 (33.0%)
LA[b]	649 (35.0%)	188 (35.6%)	69 (39.2%)
AA[b]	350 (18.9%)	202 (38.3%)	49 (27.8%)
APOE-ε4 Carrier	406 (25.8%)	132 (31.0%)	43 (29.7%)
Clinical Risk Score			
mCAIDE	-0.069 (± 1.01)	0.14 (± 0.97)	0.32 (± 0.90)
WHICAP	-0.089 (± 0.97)	0.16 (± 0.93)	0.45 (± 1.27)
LIBRA	-0.090 (± 0.98)	0.19 (± 1.00)	0.36 (± 1.06)
CogDRisk	-0.066 (± 0.96)	0.05 (± 1.03)	0.53 (± 1.18)
Cognition			
MMSE	28.20 (± 2.11)	26.63 (± 2.86)	21.52 (± 5.61)
CDR	0.00 (± 0.00)	1.23 (± 0.84)	4.57 (± 2.89)
Executive Function	0.27 (± 0.63)	-0.52 (± 0.78)	-1.21 (± 0.91)
Verbal Ability	0.24 (± 0.75)	-0.40 (± 0.75)	-1.28 (± 0.74)
Memory	0.33 (± 0.67)	-0.62 (± 0.67)	-1.57 (± 0.65)
Neuroimaging			
Cortical Thickness	2.76 (± 0.13)	2.73 (± 0.14)	2.60 (± 0.22)
Hippocampal Volume	0.12 (± 0.92)	-0.14 (± 0.98)	-0.97 (± 1.34)
Plasma Biomarkers			
$A\beta_{42}/A\beta_{40}$	0.012 (± 0.99)	0.055 (± 1.05)	-0.25 (± 0.90)
Total Tau	-0.016 (± 0.98)	-0.009 (± 1.01)	0.24 (± 1.22)
$pTau_{217}$	-0.11 (± 0.90)	0.13 (± 1.06)	0.85 (± 1.43)
$pTau_{217}/A\beta_{42}$	-0.08 (± 0.91)	0.11 (± 1.07)	0.63 (± 1.50)
NfL	-0.078 (± 0.92)	0.055 (± 1.10)	0.66 (± 1.26)

[a]Mean (SD), n (%), [b]Percentages calculated using the total cohort as the denominator for a given diagnosis

For mCAIDE, mean scores for AA, LA, and NHW participants with dementia were 0.25, 0.61, and 0.060, respectively. For WHICAP, NHW participants had a mean of −0.40, AA participants had a mean of 0.1, and LA participants had a mean of 1.20 in participants with dementia. For LIBRA, mean scores were similar between LA and AA participants for MCI (0.30 and 0.20, respectively) and for dementia (0.51 and 0.50, respectively), while NHW participants had a mean of 0 for dementia and MCI diagnosis. For CogDRisk, AA, LA, and NHW participants had mean scores of 0.33, 0.63 and 0.65, respectively, in the dementia group (Table S3.2).

3.3.2 Higher clinical risk burden was associated with worsening AD endophenotypes

Higher mCAIDE scores were associated with increased levels of NfL and total Tau and decreased $A\beta_{42}/A\beta_{40}$ ratios in the total cohort, but not with $pTau_{217}$. In race/ethnicity-stratified analyses, associations with higher NfL and lower $A\beta_{42}/A\beta_{40}$ were only significant in LA participants. For neuroimaging outcomes, mCAIDE was strongly associated with smaller hippocampal volumes across race/ethnicity groups and decreased cortical thickness in LA and NHW participants, but not in AA participants (Fig. 3.1, Table S3.3). The effect sizes for mCAIDE on cortical thickness were statistically different in LA participants compared to NHW participants ($z = -3.79$, $p = 2.10e\text{-}3$) (Table S3.4). For cognitive outcomes, higher mCAIDE scores were associated with lower MMSE performance and poorer verbal ability across racial groups (Fig. 3.1, Table S3.3). There was a statistically significant difference in the effect size for mCAIDE on memory between LA and NHW participants ($z = 2.82$, $p = 0.039$), but no other significant differences were observed (Table S3.4).

The WHICAP score demonstrated similar trends to mCAIDE, with weaker or absent associations among LA and AA participants, specifically for plasma biomarker outcomes. In the total cohort,

higher WHICAP scores were associated with increased NfL, and total Tau, and decreased $A\beta_{42}/A\beta_{40}$. Across racial groups, NfL associations remained consistent, while other biomarkers varied. For neuroimaging outcomes, higher WHICAP was associated with decreased cortical thickness and decreased hippocampal volume (Fig. 3.1, Table S3.3). The magnitude of the effect size was larger in NHW compared to AA and LA (z = AA: 11.6, $p < 1.0e\text{-}5$; LA: 11.9, $p < 1.0e\text{-}5$) (Table S4). For cognitive outcomes, WHICAP was associated with verbal ability and MMSE, both in the total cohort and across all racial/ethnic groups (Fig. 3.1, Table S3.3).

For plasma biomarkers, the LIBRA score was consistently associated with increased levels of total Tau and $pTau_{217}$ and decreased levels of $A\beta_{42}/A\beta_{40}$ in AA participants. The effect of $A\beta_{42}/A\beta_{40}$ significantly differed between AA and NHW participants, with a negative association in AA and a positive association in NHW (z = -3.00, p = 2.54e-2) (Fig. 3.1, Table S3.4). Additionally, a higher LIBRA score was associated with substantially higher NfL levels in LA participants, with a significantly stronger positive association compared to the NHW participants (Table S3.3). For neuroimaging outcomes, a higher LIBRA score was associated with lower hippocampal volume in LA and NHW participants, but not in AA participants. A higher LIBRA score was not associated with either cortical thickness or WMH levels in any population. For clinical outcomes, a higher LIBRA score was associated with higher CDR and decreased executive function across racial/ethnic groups (Fig. 3.1, Table S3.3).

CogDRisk showed consistent associations across all AD endophenotypes, including plasma, neuroimaging, and cognitive domains, in the total cohort. Higher CogDRisk scores were associated with reduced hippocampal volume and cortical thickness, higher levels of plasma biomarkers, including total Tau, $pTau_{217}$, and a lower $A\beta_{42}/A\beta_{40}$ ratio. Higher CogDRisk scores were also

associated with poorer performance across all cognitive domains, including memory, verbal ability, and executive function, as well as with higher CDR scores and lower MMSE scores. (Fig. 3.1, Table S3.3).

For plasma biomarkers, a higher CogDRisk score was associated with increased levels of $pTau_{217}$ in LA participants (Fig. 3.1, Table S3.3). This effect size was significantly greater in LA than in NHW participants ($z = -2.91$, $p = 3.16e\text{-}2$) (Table S3.4). Higher CogDRisk was not associated with levels of $pTau_{217}$ or $A\beta_{42}/A\beta_{40}$ in AA participants. There was a significant difference in the effect size of CogDRisk on hippocampal volume between AA and NHW participants ($z = 3.96$, $p = 1.23e\text{-}3$), with higher CogDRisk showing larger effects in AA than in NHW participants, a pattern not observed for cortical thickness (Table S3.4). For cognitive outcomes, a higher CogDRisk score was consistently associated with decreased MMSE, increased CDR, and decreased executive function across racial/ethnic groups (Fig. 3.1, Table S3.3).

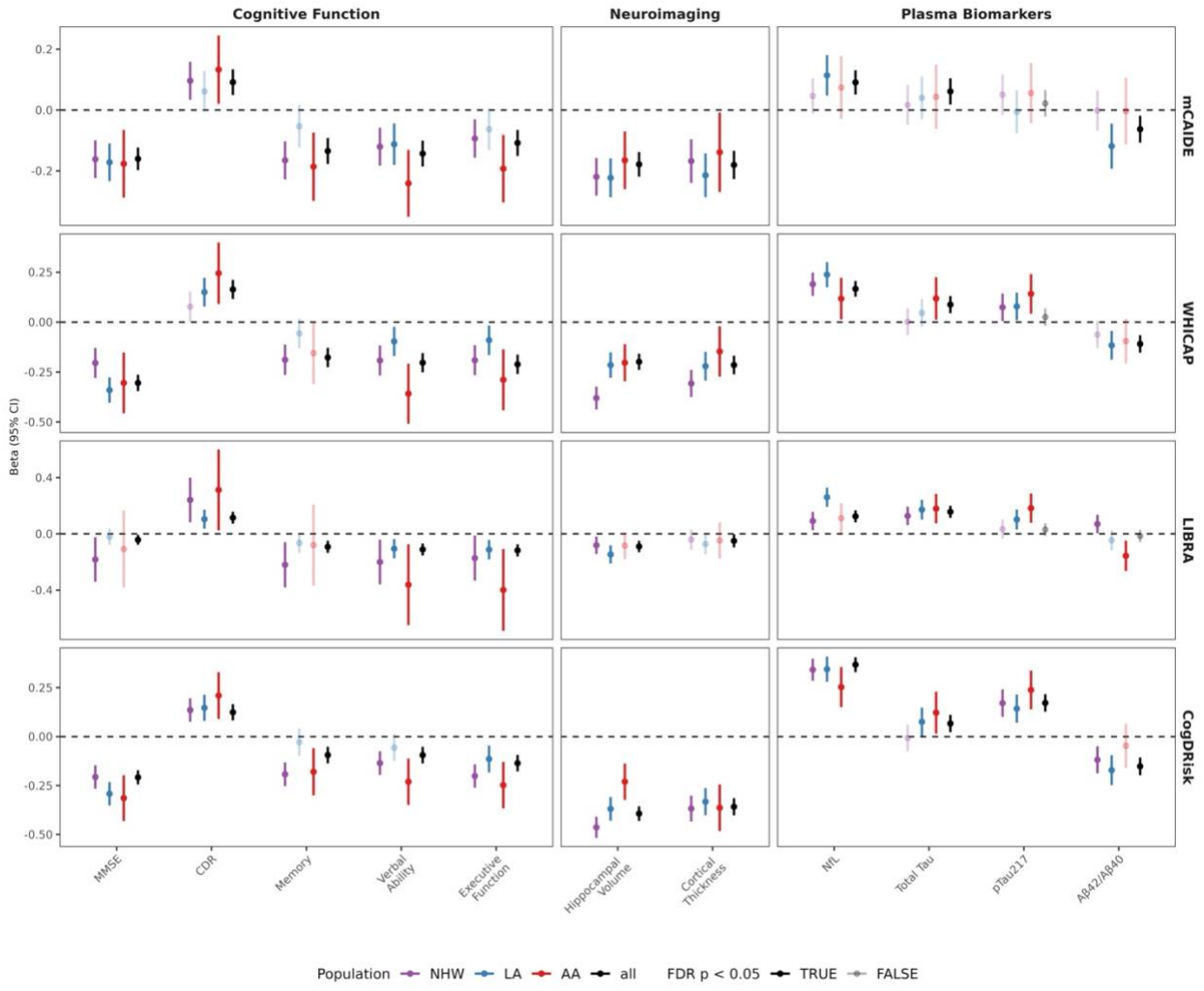

Figure 3.1. Associations of clinical risk score (CRS) with AD endophenotypes
Associations of CRS with cognitive, neuroimaging, and plasma biomarker outcomes in the total cohort and stratified by self-reported race/ethnicity (NHW: Non-Hispanic White, LA: Hispanic/Latinx, AA: Black). Forest plots showing standardized beta coefficients (95% CI) for associations between four CRS (mCAIDE, WHICAP, LIBRA, and CogDRisk) and cognitive function, neuroimaging measures, and plasma biomarkers. The dashed line indicates the null (β = 0).

3.3.3 CogDRisk Score Demonstrates the Strongest and Most Consistent Prediction of pTau$_{217}$/Aβ$_{42}$ Positivity in a diverse cohort

We next assessed the predictive accuracy of CRS for amyloid positivity from pTau$_{217}$/Aβ$_{42}$ levels, using its discriminatory threshold for amyloid PET positivity. Across the total cohort, the CogDRisk score was the only CRS associated with a 63% increase in the odds of pTau$_{217}$/Aβ$_{42}$ positivity, and this association was consistent across all racial/ethnic groups (NHW: 63%, LA: 60%, AA: 76%) (Figure 3.2, Table S3.6). WHICAP was also associated with increased odds of positivity (NHW = 47%, LA = 34%, AA = 61%). mCAIDE was associated with higher odds of positivity in LA and AA groups (31% & 40%, respectively).

The LIBRA score was not associated with pTau$_{217}$/Aβ$_{42}$ positivity; however, when demographic information was added to the score in sensitivity analysis, we observed significant associations across all racial/ethnic groups (all: 37%, NHW: 31%, LA: 51%, AA: 65%). This translated into modest AUC and R^2 for CogDRisk in the total cohort, which are not quite as predictive as those of demographic models, but are better than other CRS (AUC: demographics = 0.72, demographics + APOE = 0.68, CogDRisk = 0.62, LIBRA = 0.52, WHICAP = 0.51, mCAIDE = 0.52; R^2: demographics = 0.15, demographics + APOE = 0.095, CogDRisk = 0.0.047, LIBRA = 1.25×10^{-3}, WHICAP = 8.01×10^{-4}, mCAIDE = 2.56×10^{-3}) (Figure 3.2, Table S3.6).

Addition of the *APOE* genotype to the demographic model improved discrimination for pTau$_{217}$/Aβ$_{42}$ positivity in the total cohort (AUC: 0.740 vs 0.687; ΔAUC = 0.053). However, this improvement was not uniform across ancestry groups and was largely driven by NHW participants (AUC: 0.755 vs 0.658; ΔAUC = 0.097). In contrast, the incremental gain was attenuated in LA participants (AUC: 0.717 vs 0.678; ΔAUC = 0.039) and negligible in AA participants (AUC: 0.691

vs 0.690; ΔAUC = 0.001). A similar pattern was observed for model fit. The inclusion of *APOE* resulted in a notable increase in explained variance in the total cohort and NHW group (total: $\Delta R^2 = 0.08$; NHW: $\Delta R^2 = 0.14$), a more modest improvement in LA participants ($\Delta R^2 = 0.05$), and a negligible change in AA participants ($\Delta R^2 = 0.01$) (Figure 3.2, Table S3.6).

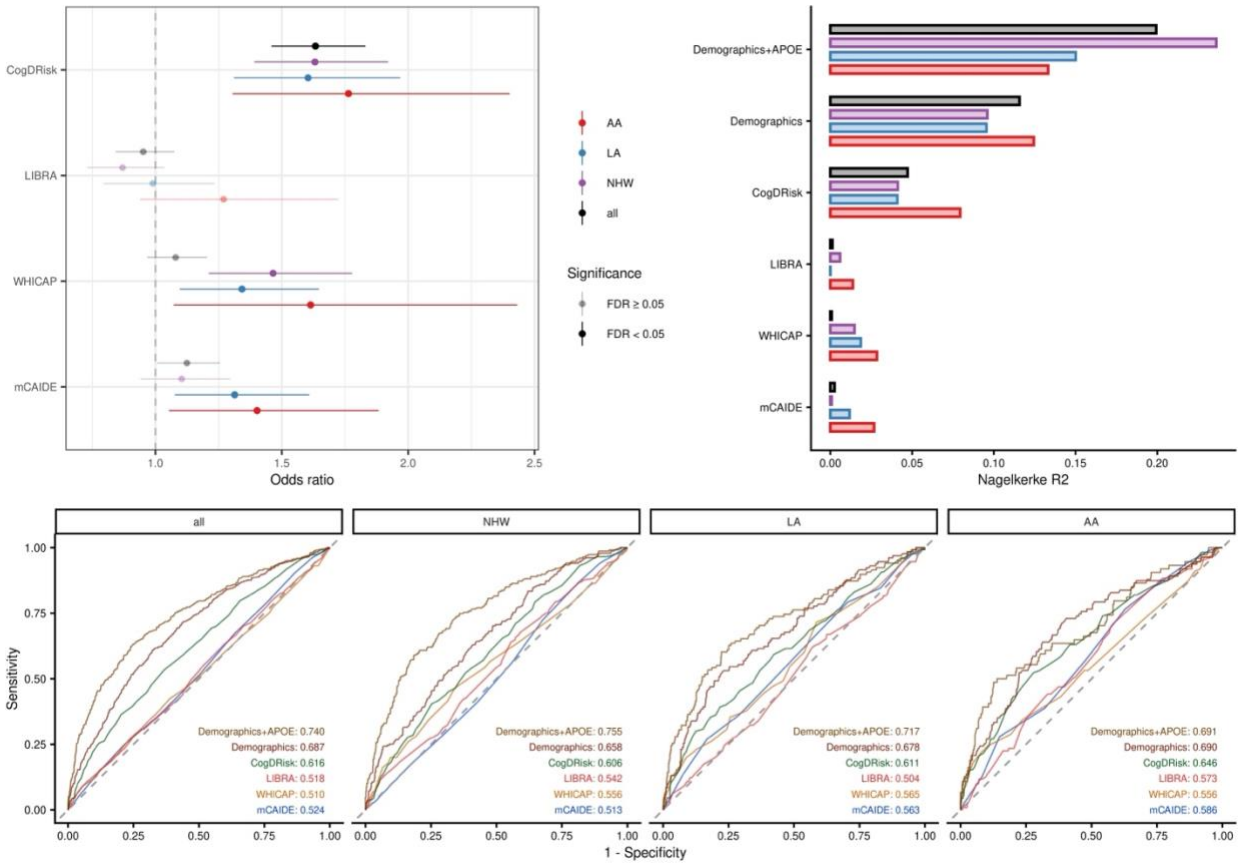

Figure 3.2. Model performance of clinical risk scores for pTau$_{217}$/Aβ$_{42}$ positivity
Predictive performance of CRS for pTau$_{217}$/Aβ$_{42}$ positivity, in the total cohort and stratified by race/ethnicity (NHW: Non-Hispanic White, LA: Hispanic/Latinx, AA: Black). pTau$_{217}$/Aβ$_{42}$ positivity was defined using a cutoff optimized to predict amyloid PET positivity. **(A)** Forest plot of odds ratios (95% CI) for associations between CRS (with and without demographic components) and pTau$_{217}$/Aβ$_{42}$ positivity, stratified by race/ethnicity. The dashed line indicates the null (OR = 1). **(B)** Nagelkerke R^2 values for CRS and demographic models. **(C)** Receiver operating characteristic (ROC) curves and corresponding area under the curve (AUC) values for each model.

3.3.4 Higher clinical risk burdens are associated with increased odds of cognitive impairment across racial/ethnic groups

Across all CRS, higher scores were consistently associated with greater odds of developing dementia in the total cohort. With each SD increase in CRS corresponding to a 35–73% increase in odds of having dementia in the HABS-HD cohort. WHICAP demonstrated the largest effect (73%), followed by CogDRisk (68%) and LIBRA (61%). These observations were consistent across racial/ethnic groups. When MCI and dementia were combined, effect sizes were attenuated across all CRS relative to the dementia-only group, due to a weaker association of CRS with MCI (Fig. S3.1, Table S3.3). These associations translated into only modest predictive performance. For dementia diagnosis, the demographics model had the highest AUC of 0.70 (R^2 = 0.070), which was comparable to the highest AUC achieved by CogDRisk (AUC = 0.65, R^2 = 0.046). All CRS had marginal differences in AUC, with mCAIDE having the lowest performance (AUC = 0.61, R^2 = 0.020) (Fig. S3.2, Table S3.5). Consistent with the overall results, model performance was only modest across racial/ethnic groups. CogDRisk achieved the highest AUC and R^2 across racial/ethnic groups, ranging from 0.70 in AA participants to 0.66 in NHW participants and 0.63 in LA participants. A general pattern of higher AUC and R^2 was observed in AA participants across the four CRS compared to NHW participants, who had the lowest AUC and R^2 (Fig. S3.2, Table S3.5).

3.3.5 Model performance from sensitivity analysis

For the sensitivity analysis, we excluded demographic information (i.e., age, sex, and years of education) from mCAIDE, WHICAP, and CogDRisk scores to assess their contribution to model performance. For diagnostic outcomes, higher CRS was associated with increased odds of

developing dementia in the total cohort across all diagnoses and all CRS, but this association diminished in race/ethnicity-stratified analysis (Table S3.7). This translated into reduced AUC and R^2 values for all CRS (mCAIDE: AUC = 0.55, R^2 = 0.0037; WHICAP: AUC = 0.53, R^2 = 0.032; CogDRisk: AUC = 0.60, R^2 = 0.015) (Table S3.8). The demographic model achieved the highest AUC in the overall cohort and across subgroups, with statistically significant differences compared to both CRS and CRS sensitivity models (Table S3.9).

For endophenotypic outcomes, substantial decreases in the associations of all CRS were observed after excluding demographic information. In the total cohort, significant associations were observed specifically for cognitive outcome measurements but did not translate consistently into neuroimaging and plasma biomarker outcomes. Higher CogDRisk was associated with increased levels of total Tau across all races/ethnicities, but all other associations with endophenotypes for all CRS diminished in sensitivity analysis (Table S3.7). Consistent with the overall results, the sensitivity analysis showcased decreased AUC and R^2 across races/ethnicities. CogDRisk had the highest AUC for all races/ethnicities (AA: 0.63, LA: 0.57, NHW: 0.59) compared to WHICAP and mCAIDE, in which AUC ranged from 0.51 to 0.54 across races/ethnicities (Table S3.8).

3.4 Conclusion

In this study, we evaluated the associations of mCAIDE, WHICAP, LIBRA, and CogDRisk with cognitive impairment and AD endophenotypes in a cross-sectional, multiethnic cohort. Across the total cohort, higher CRS were associated with increased odds of dementia, although effect sizes varied by race/ethnicity. Among these CRS, a higher CogDRisk score was consistently associated with higher odds of dementia, worse AD endophenotypes, and $pTau_{217}/A\beta_{42}$ positivity across racial/ethnic groups. LIBRA also demonstrated consistent associations with AD endophenotypes

despite the absence of demographic information in its scoring. WHICAP and mCAIDE performed similarly overall; however, both CRS lacked associations with plasma biomarkers in stratified racial/ethnic analysis. Across AD endophenotypes, higher CRS were generally associated with more severe pathological abnormalities, particularly among AA participants. These stronger associations may reflect unaccounted environmental factors in the model, such as social determinants of health (SDoH) (e.g. socioeconomic status, neighborhood and built environment, healthcare access) in the population. The wide confidence intervals were also apparent due to a smaller sample size in the AA group. $pTau_{217}/A\beta_{42}$ positivity findings arose as important implications for the clinical implementation of CRS in diverse populations. Although CogDRisk demonstrated consistent associations with $pTau_{217}/A\beta_{42}$ positivity across racial/ethnic groups, its discriminatory power still remained modest and lower than demographic + *APOE* model, limiting its utility as a standalone prediction of $pTau_{217}/A\beta_{42}$ positivity being the proxy to amyloid PET positivity. Together, these findings emphasize the need for replication in larger, racially diverse cohorts with more balanced distributions of group sizes.

Model performance metrics (AUC, R^2) were highest among AA participants and lowest among NHW participants, despite CRS being developed primarily in NHW populations. This likely reflects sample size limitations and more balanced case–control distributions in the AA group (prevalence of MCI + dementia: AA: 41.7%, LA: 28.3%, NHW: 18.6%), which can inflate performance estimates in small samples. Because AUC and R^2 are sensitive to outcome prevalence, the higher prevalence of cognitive impairment among AA participants may have further contributed to optimistic estimates. These findings further highlight the need for larger, more representative datasets to yield stable, generalizable performance estimates.

Consistent with previous studies, mCAIDE was the lowest-performing model, exhibiting weaker discriminatory power and associations.[21,22,25] CogDRisk score, on the other hand, consistently emerged as the best-performing model across cognitive and endophenotypic outcomes, followed closely by LIBRA, which was also observed previously.[21,24,25] Better performance of CogDRisk and LIBRA score is likely reflected by its broader incorporation of mid- to late-life cardiometabolic, lifestyle, and psychosocial risk and protective factors that are strongly linked to dementia risk and are amenable to intervention.[50] Given the associations of these CRS with plasma biomarkers, combining plasma biomarker and CRS screening may be an effective way to identify at-risk individuals in the early preclinical stages. CRS are inexpensive, non-invasive, and largely scalable risk assessments; however, they have limited specificity to AD pathology. With the advancing sensitivity of AD plasma biomarkers, CRS enhance risk identification of individuals who are vulnerable to cognitive impairment based on clinical and lifestyle factors, while biomarkers improve specificity by confirming the presence of AD-related pathology. Genetic factors, such as *APOE*, offer complementary information by capturing underlying susceptibility to AD that is not reflected in clinical or biomarker measures alone. Consistent with this, *APOE* provided incremental predictive value for $pTau_{217}/A\beta_{42}$ positivity compared to the non-*APOE* demographic model. As the field continues to move away from a single-modality approach into multimodal treatments and studies,[51–53] the proposed combined strategies would allow us to have a framework that links risk exposure with biological disease processes. However, successful implementation requires further investigation and consideration of the model performance in large, diverse populations, assay standardization, and the clinical actionability of effective follow-up interventions.

Several limitations should be acknowledged. First, only four CRS were evaluated, which does not capture the full spectrum of both clinically relevant and community-based CRS that have been developed over the years.[13] Even among the four CRS that were evaluated, some CRS components had to be modified due to unavailable information in HABS-HD (e.g. diet, cognitive activity), which could affect the overall results. Second, the cross-sectional study used in this paper limits causal inference and the ability to assess the temporal relationships of CRS and endophenotypes. In particular, reverse causality cannot be excluded for cognitive diagnoses, as early or prodromal disease processes may influence clinical and lifestyle factors captured by CRS. Our results showcasing relationships between CRS and cognitive impairment should be interpreted cautiously. Future studies should examine the longitudinal trajectories of biomarker changes associated with high baseline CRS to strengthen evidence that elevated CRS corresponds to abnormalities in AD pathology. Lastly, this study did not include participants from Native American/Alaska Native, Asian, or Native Hawaiian/Other Pacific Islander groups. Future work should extend these evaluations to cohorts that include these populations that reflect the broader racial and socioeconomic diversity of the US population.

Despite these limitations, this study contributes novel evidence to the development of clinical risk assessment tools. By incorporating racially diverse participants, we were able to evaluate the generalizability of CRS across populations that are often underrepresented in AD research. More importantly, this work advances the field by linking CRS to endophenotypes, particularly plasma biomarkers, which are minimally invasive and increasingly investigated for clinical implementation.[6,49,54–56] This study adds to the growing interest in adopting multimodal dementia prevention and risk identification efforts by supporting the use of CRS as an accessible tool to help identify individuals most likely to benefit from biomarker-based assessment.

In conclusion, the current study found that the CogDRisk score outperformed other CRS for both associations and model performance metrics compared to LIBRA, WHICAP, and mCAIDE, in which all three showed similar performances across different analyses. However, none of the CRS models outperformed the demographics or demographics + *APOE* genotype models, which is expected given that age, sex, years of education, and *APOE**ε4 allele are the strongest predictors of dementia risk. This underscores that CRS are most useful as low-cost, widely accessible tools for preliminary risk screening, rather than as standalone predictors, and highlights the potential value of combining them with other risk measures such as genetic screenings or biomarker assessments to create a multimodal approach that may improve overall accuracy and reliability. Taken together, these findings highlight both the promises and limitations of CRS and clarify the role of CRS as a supportive tool to complement established demographic and genetic predictors in dementia risk assessments.

Supplementary Information

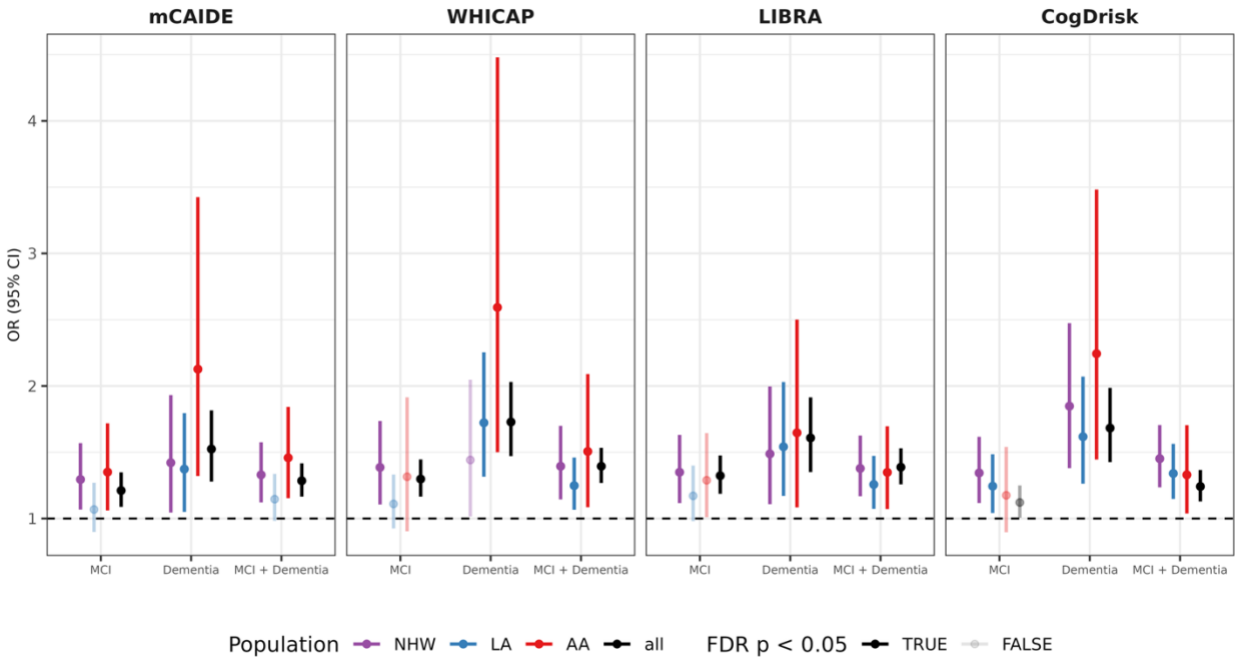

Figure S3.1. Associations of clinical risk score (CRS) with cognitive status
Associations of all CRS with MCI, dementia, and MCI + dementia diagnosis, with cognitively unimpaired participants as the reference group. Logistic regression analysis stratified by self-reported race/ethnicity.

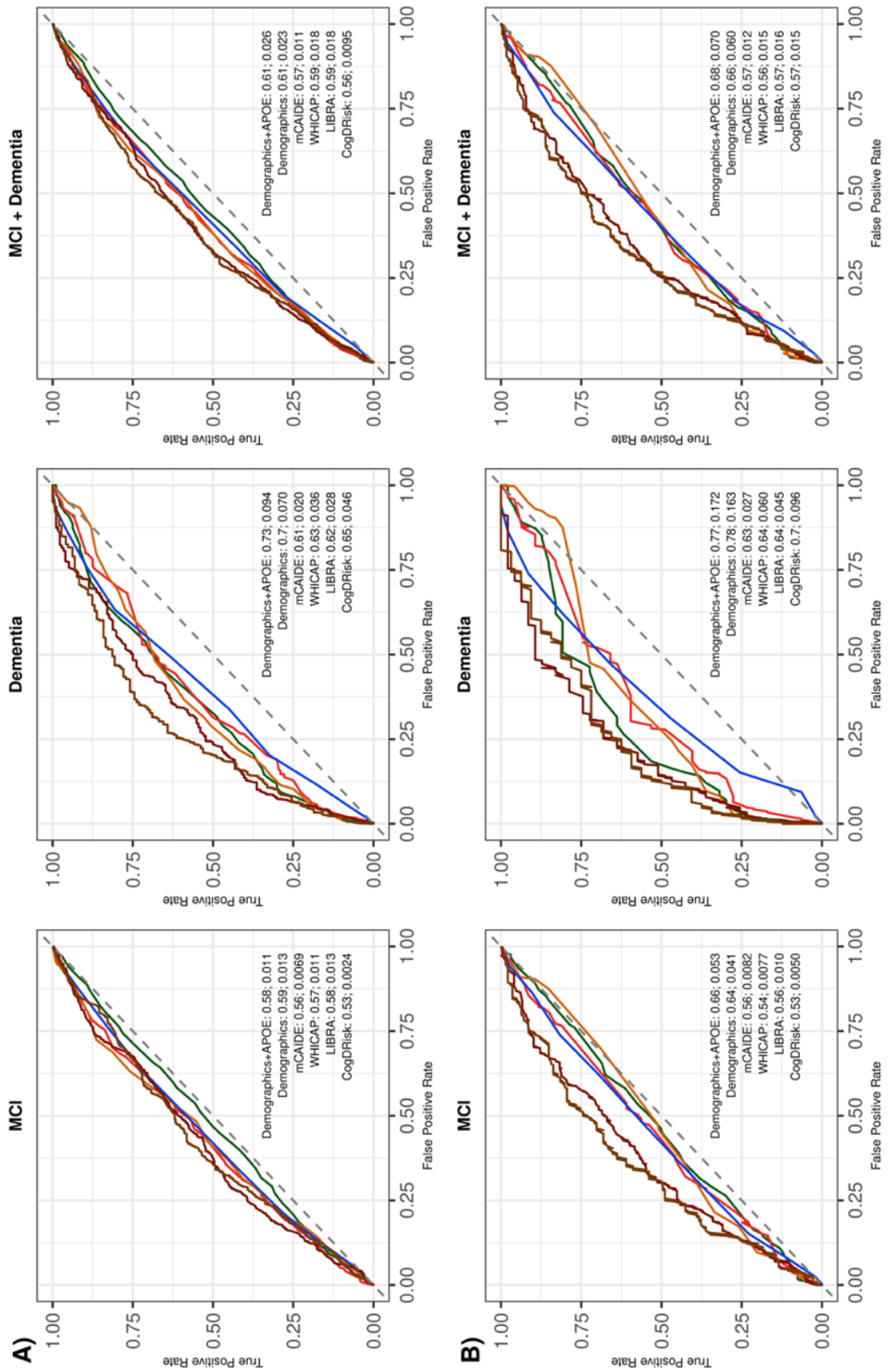

Figure S3.2. Discriminatory power of clinical risk score (CRS) models *(Figure caption continues in two pages)*

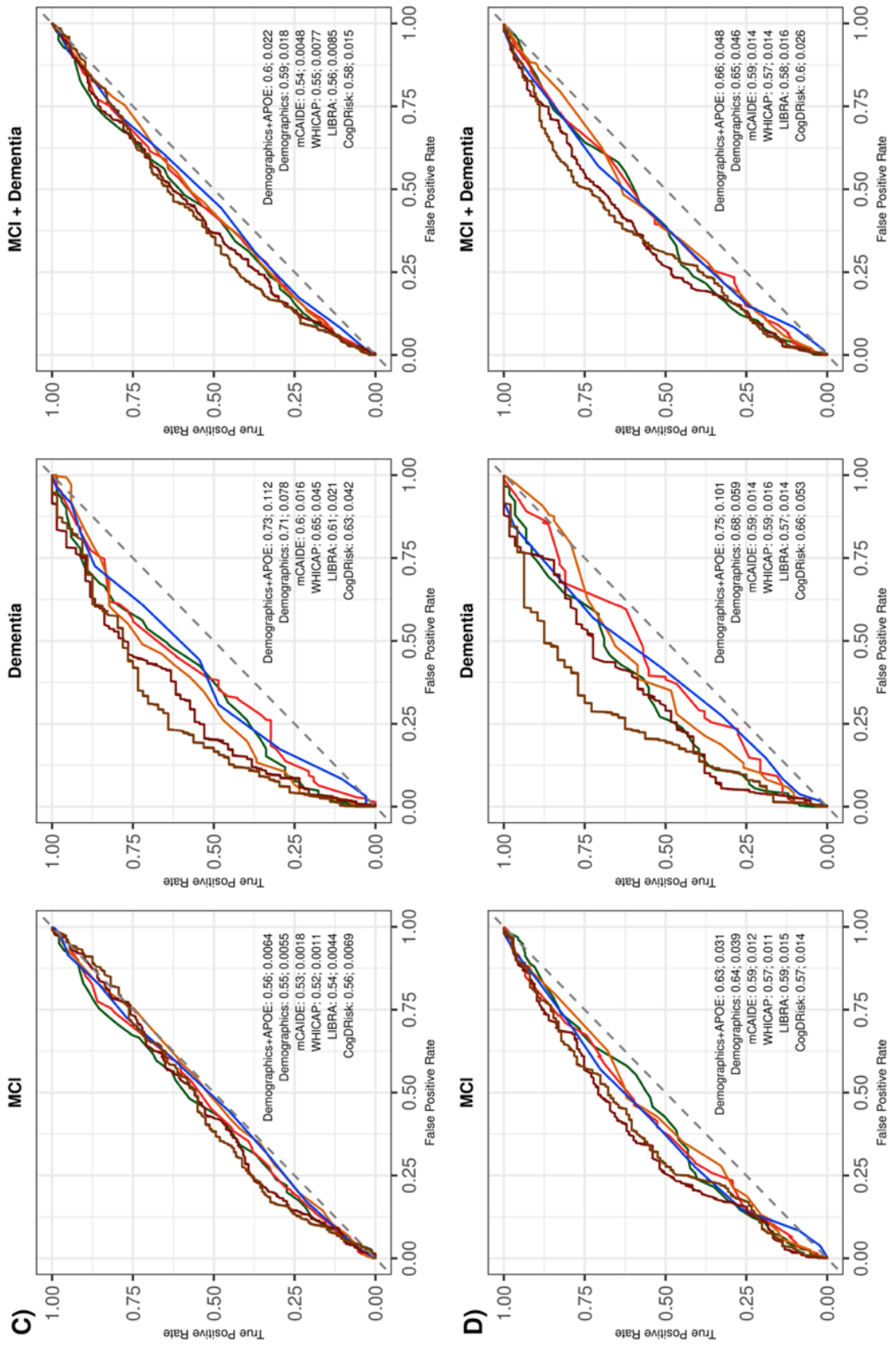

Figure S3.2. Discriminatory power of clinical risk score (CRS) models *(Figure caption continues in next page)*

Figure S3.2. Discriminatory power of clinical risk score (CRS) models
Receiver Operating Characteristic Area Under the Curve (ROCAUC) curve for CRS, demographics, and demographic + *APOE* model, in **(A)** the total cohort and stratified by self-reported race/ethnicity (**B**: Black, **C**: Hispanic/Latinx, and **D**: Non-Hispanic White). The first number next to the model indicates the AUC value, followed by Nagelkerke R^2.

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Chapter 4: Orthogonal Contributions of Genetic, Clinical, and Environmental Risk Burdens on Alzheimer's Disease Pathology

Abstract

Alzheimer's disease (AD) arises from complex interactions among genetic, clinical, and environmental risk factors, yet their independent contributions to underlying AD pathology remain elusive. To quantify the orthogonal associations of risk burdens with latent AD pathology across Aβ/tau, neurodegeneration, and cognition. Cross-sectional analysis using structural equation modeling (SEM). Health and Aging Brain Study–Health Disparities (HABS-HD), a community-based cohort study. A total of 2,173 participants with demographics, genetic, clinical, and biomarker data from visit 1 (release 5&7) of HABS-HD. *APOE**ε4 carrier status, AD polygenic risk score (AD-PRS), clinical risk burden (CogDRisk score), and a latent social determinants of health (SDoH) factor derived using factor analysis. Latent variables representing Aβ/tau pathology (plasma $pTau_{181}$, plasma $pTau_{217}/A\beta_{42}$, amyloid PET positivity, and amyloid PET global standardized uptake value ratio), neurodegeneration (plasma neurofilament light, cortical thickness, hippocampal volume), and cognition (memory, executive, and language tests) were modeled and regressed on latent AD pathology using SEM adjusted for age, sex, and genetic principal components. The total analytic sample included 3,116 participants (non-Hispanic White: 1,194 (38.3%), non-Hispanic Black: 760 (24.4%), and Hispanic/Latinx adults: 1,162 (37.3%)). *APOE**ε4 was strongly associated with worse Aβ/tau latent variable ($\beta = 0.30$; $p < 0.001$), with smaller but significant associations with neurodegeneration ($\beta = 0.082$; $p < 0.01$) and cognition ($\beta = 0.075$; $p < 0.01$). Higher AD-PRS was modestly associated with worse Aβ/tau pathology ($\beta = 0.12$; $p < 0.01$) but was not associated with neurodegeneration or cognition. Higher clinical risk burden was significantly associated with worse neurodegeneration ($\beta = 0.16$; $p < 0.001$) but not

Aβ/tau or cognition. Adverse SDoH was associated with worse neurodegeneration ($\beta = 0.070$; $p < 0.05$) and strongly associated with worse cognition ($\beta = 0.23$; $p < 0.001$), without association with Aβ/tau pathology. The genetic, clinical, and environmental risk domains influence AD through distinct pathways within the AD biological continuum. In the context of multidomain interventions, understanding how diverse risk factors contribute to AD pathogenesis is essential for advancing precision medicine approaches tailored to individuals with heterogeneous risk-exposure profiles.

4.1 Introduction

Alzheimer's disease (AD) is increasingly conceptualized as a biological continuum defined by the Aβ, tau, and neurodegeneration (A/T/N) framework, in which biomarkers are used as more precise characterizations of underlying pathology than syndromal diagnosis alone.[1–3] AD is also etiologically complex, arising from the interplay between the genome and the exposome, spanning genetic, clinical, and environmental domains.[4,5] The ε4 allele of apolipoprotein E (*APOE**ε4) is the strongest genetic risk factor for the late-onset form of AD,[6] with genome-wide polygenic risk scores (PRS) further capturing the highly polygenic architecture of the disease.[4,7] In parallel, 18 modifiable risk factors have been identified that account for up to 65% dementia cases,[8,9] enabling the development of cumulative clinical risk scores (CRS) that capture one dimension of the exposome. Social determinants of health (SDoH) represent a broader set of environmental exposome, encompassing the social, economic, and environmental conditions in which individuals are born, live, work, and age.[10] Approximately 20% of dementia cases are estimated to be attributable to SDoH,[9] and growing evidence implicates disadvantaged SDoH as fundamental drivers of cognitive aging and dementia disparities.[11,12]

These risk domains have largely been identified in relation to cognitive outcomes, with less attention to their associations with pathology, and are studied in isolation.[11–14] Biomarker studies have overlooked social and life-course exposures and have typically focused on a single biological pathway.[15–19] In addition, studies have focused on individual components of SDoH rather than modeling its multidimensional and cumulative effects on cognition and pathology.[20–22] Although some work has linked lifestyle and environmental factors to AD biomarkers, such investigations remain limited, and only a few studies have evaluated the effects of multimodal risk burdens on AD pathology within a unified model.[23–26] Consequently, the field lacks an understanding of the extent to which genetic, clinical, and environmental risk factors affect the underlying AD pathology.

We therefore sought to quantify the orthogonal contributions of genetic (*APOE**ε4, AD-PRS), clinical (CRS), and environmental (SDoH) risk burdens to AD pathology, namely amyloid, tau, neurodegeneration, and cognition, in a racially and ethnically diverse aging cohort, Health and Aging Brain Study–Health Disparities (HABS-HD). We hypothesized that genetic risk burdens would be more strongly associated with amyloid and tau pathology, whereas clinical and environmental risk burdens would relate more closely to neurodegeneration and cognition.

4.2 Methods

4.2.1 Study Populations

The Health and Aging Brain Study – Health Disparities (HABS-HD) cohort was used for this study. The HABS-HD comprises non-Hispanic White (NHW), non-Hispanic Black, and Hispanic participants recruited at the University of North Texas Health Science Center, Fort Worth, Texas.[27,28] The study is an ongoing longitudinal, community-based cohort that has collected

information on demographics, clinical history, lifestyle, SDoH, genetic data, and samples on AD endophenotypes, including plasma biomarkers, neuroimaging, neuropsychological tests, and clinical history, providing extensive resources for AD and related dementia research. Genetic data were obtained by genotyping array on all individuals. Study eligibility was restricted to generally healthy individuals without any major mental or medical conditions, who agreed to undergo sample collection and neuroimaging assessments (N = 3,116). All analyses were conducted using baseline visit 1 data from the HABS-HD release 5 & 7 dataset. Written informed consent was obtained from all HABS-HD participants or their legally authorized representatives before study participation.

4.2.2 Genetic Quality Control

Participants were genotyped on the Illumina Global Screening Array (GSA), and genotype data underwent rigorous quality control (QC) using an in-house Snakemake Pipeline3. Variant-level QC excluded SNPs with call rate < 0.95 or violating Hardy–Weinberg equilibrium ($p < 1 \times 10\text{-}6$). Sample-level QC removed participants with call rates below 0.95, discordant sex based on X chromosome heterozygosity, excessive or insufficient heterozygosity, or cryptic relatedness. Relatedness was evaluated across and within cohorts via identity-by-descent (IBD) using KING,[29] and individuals with an IBD proportion < 0.1875 were excluded, corresponding to less than halfway between second- and third-degree relatives. Non-genotyped SNPs were imputed using the TOPMed Imputation Server,[30] performing ancestry-specific imputation with the full TOPMed reference panel (Version R3) to allow accurate R2 estimation,[31] with Eagle and Minimac3 used for phasing and imputation. After imputation, poorly imputed variants (R2 < 0.3) or rare variants (MAF < 0.01) were removed. Ancestry groups were merged for joint analysis, after which variants and samples with call rates below 95% were removed. The final dataset included 3,116 participants

(~22 million high-quality SNPs per individual), 1,194 are non-Hispanic White, 1,162 are Hispanic/Latinx, and 760 are Black participants.

4.2.3 Biomarker Harmonization and Standardization

To characterize the A/T/N and cognitive measures for AD endophenotypes, the HABS-HD study extensively phenotyped plasma biomarkers (e.g., $A\beta_{42}$, $pTau_{181}$, $pTau_{217}$, and NfL), brain morphometry, Aβ PET, and neuropsychological tests. For downstream analyses, we applied the following harmonization and standardization for each AD endophenotype.

Plasma biomarkers: Fasting blood samples were collected, and the levels of plasma biomarkers were quantified using commercially available kits, Quanterix, for all the participants of the HABS-HD.[27,28] $A\beta_{42}$, $pTau_{181}$, $pTau_{217}$, and NfL values were natural log-transformed and standardized to z-scores (mean = 0, SD = 1) across the study samples. *Brain morphometry*: Cortical thickness was calculated as the surface area-weighted mean of the right and left entorhinal cortex, fusiform gyrus, and inferior and middle temporal cortices. Hippocampal volumes were defined as the mean of the right and left hippocampal volumes derived from T1-weighted MRI scans. *Neuropsychological testing*: Composite scores for memory, language, and executive function were generated by averaging z-score-normalized results from the neuropsychological battery. The memory domain was assessed using immediate and delayed recall from the Wechsler Memory Scale (WMS-III) Logical Memory and the Spanish-English Verbal Learning Test (SEVLT). The language domain was assessed using Letter Fluency and Animal Naming tests. The executive function domain was assessed using the WMS-III Digit Span and the Trail Making Test, Parts A and B. In addition, the Mini-Mental State Examination (MMSE) and Clinical Dementia Rating (CDR) scale were administered to all participants as part of the neuropsychological assessment. Amyloid PET: For

amyloid positron emission tomography (PET) scan variables, the global standardized uptake value ratio (SUVR) was calculated by normalizing tracer uptake to the whole cerebellum. Amyloid PET positivity was defined using a SUVR threshold of 1.08.

4.2.4 Genetics

Participants were genotyped on the Illumina Global Screening Array (GSA), and genotype data underwent rigorous quality control using an in-house Snakemake Pipeline3. The *APOE**ε4 carrier status was encoded as a binary variable of ε4+ carriers (ε2/ε4, ε3/ε4, or ε4/ε4) and non-ε4 carriers.

We leveraged summary statistics from the largest publicly available ancestry-specific genome-wide association studies (GWAS) of Alzheimer's disease and related dementias (ADRD) currently available. These included cohorts of European ancestry (Bellenguez et al.[32]: 39,106 cases, 46,828 proxy cases, 401,577 controls; FinnGen Release 6: 7,329 cases, 131,102 controls), African ancestry (Kunkle et al.[33]: 2,748 cases, 5,222 controls), East Asian ancestry (Shigemizu et al.[34]: 3,962 cases, 4,074 controls), and Caribbean Hispanic ancestry (Columbia University Study: 1,088 cases, 1,152 controls). There are no overlapping participants between the cohorts used in the base GWAS summary statistics and the HABS-HD cohort.

4.2.5 PRS Scorefile Generation

A cross-ancestry PRS was generated using PRS-CSx, which enhances trans-ancestry polygenic prediction by jointly modeling GWAS summary statistics from multiple populations.[35] Based on prior benchmarking of AD-PRS methods (Chapter 2), PRS-CSx demonstrated the strongest predictive performance and was therefore selected for the present analysis.[36] The global shrinkage parameter (phi) was specified as "auto," enabling automatic shrinkage and estimation of SNP

effect sizes from the input datasets. The "meta" option was set to true to aggregate SNP effects across all the GWAS summary statistics through inverse-variance–weighted meta-analysis. Ancestry-specific AD GWAS summary statistics were used as input to construct the scorefile. Prior to PRS computation, SNPs within the APOE locus and surrounding regions (±500 kb; GRCh37, chr19:bp44909053–45912650) were excluded from the final scorefile.

Individual-level PRS was generated for each participant using pgsc_calc.[37] During PRS calculation, liftover was applied automatically to convert the scorefile to the GRCh38 genome build. To reduce ancestry-related confounding arising from differences in PRS distributions and to facilitate more accurate comparisons across ancestrally diverse populations,[38] pgsc_calc was used to normalize PRS by ancestry in the HABS-HD cohorts using a principal components analysis (PCA)-based approach.[39] PCA was first performed on the 1000 Genomes (1KG) reference panel to derive principal components (PCs) capturing global genetic variation. Target individuals were then projected onto these PCs onto the PCA space. A Random Forest classifier trained on the reference panel PCA loadings (default: 10 PCs) was then used to assign each target sample to the most similar reference population.[40]

Following PC projection and ancestry assignment, PRS were normalized within ancestry groups. In the first step, PRS were regressed on PC loadings, and the resulting residuals were used to center the PRS distributions at zero across ancestries (znorm1). In the second step, a regression on the squared residuals was performed to adjust for variance, yielding standardized PRS (znorm2). Notably, phenotypic information, including case–control status, was not incorporated at any stage of the normalization process. This approach removes PRS variation attributable to population stratification driven by allele frequency and linkage disequilibrium differences, while preserving

GWAS-derived SNP weights and relative risk rankings within ancestry groups. As a result, the normalization enables meaningful intra-ancestry comparisons while retaining disease-relevant genetic risk information within PRS.

4.2.6 Clinical Risk Burden

CogDRisk[41] was used to calculated accumulated clinical risk burden associated with AD. We have also previously benchmarked four CRS in Chapter 3, and CogDRisk demonstrated the highest model performance compared to the other CRS.[42] The CogDRisk score includes age stratified by sex, education, midlife (≤ 65 yrs) obesity, dyslipidemia, diabetes stratified by sex, history of stroke, history of TBI, hypertension, atrial fibrillation, clinical diagnosis of insomnia, depression, physical inactivity, cognitive engagement, social engagement, diet, and current smoker. Atrial fibrillation, insomnia, cognitive engagement, and diet variables were excluded as this information was not available in the HABS-HD. Age, sex, and years of education were excluded from the scoring and were instead modeled as independent covariates in the SEM.

Participants who scored at least 1 SD below the mean on the social support questionnaire score were classified as 'lonely,' and those above this threshold were classified as 'not lonely' for the CogDrisk scoring. For physical activity measures, participants who answered 'yes' to item 6 or item 7 on the RAPA questionnaire were classified as physically active, reflecting an activity level of >150 minutes per week of moderate-to-vigorous activity. Baseline BMI at visit 1 was used in place of midlife obesity/BMI, which was not available in this cross-sectional study. Insomnia, atrial fibrillation, cognitive engagement, and diet measures were excluded from the scoring due to unavailability in the HABS-HD study.

4.2.7 Social Determinants of Health

Exploratory Factor Analysis (EFA) was performed to identify latent constructs underlying candidate measures, which included a battery of social support questionnaires, a battery of chronic stress questionnaires, a battery of the Penn State Worry Questionnaire (PSWQ), insurance information, income, years of education, marital status, health status, years lived in the US, and measures of medical visits. Variables with extreme missingness (> 50%) were removed. Everyday Discrimination Scale (EDS) and Women's Health questionnaires were removed due to high missingness. Sampling adequacy and suitability were assessed by the Kaiser-Meyer-Olkin test and Barlett's test of sphericity. Factor retention was determined by assessing the eigenvalue-greater-than-one rule and scree plots. Orthogonal (varimax), oblique (promax), and no rotations were used to examine the correlated factor structures. Variables exhibiting weak loadings (< 0.2), high cross-loadings, or strong multicollinearity were iteratively removed to improve model stability and interpretability. The final EFA solution retained a parsimonious set of indicators reflecting three underlying latent factors.

Confirmatory Factor Analysis (CFA) was performed on the latent structure identified by EFA to formally confirm its structure, with the other 50% of the dataset. Based on the EFA results, a three-factor first-order measurement model was specified, which the latent factor majoritively comprised of PSWQ questionnaire was called Anxiety (AX), the latent factor majorly comprised of social support questionnaire was called Social Adversity (SA), and the latent factor comprised of subset of chronic stress questionnaire, self-rated health status, and medical and economic access was called Healthcare and Economic Adversity (HEA). A second-order latent factor (SDoH) was specified to capture the three first-order domains (AX, SA, and HEA), using weighted least squares mean and variance adjusted (WLSMV) as the estimator. This stepwise framework represents

SDoH as a higher-level construct encompassing multiple domains, and the latent value for SDoH was estimated for each participant for the downstream analysis.

4.2.8 AD Pathology Latent Variables

CFA was used to construct the AD pathology latent variables, namely Aβ/tau, neurodegeneration, and cognition pathology latent variables. Aβ/tau latent variable was indicated by plasma $pTau_{217}/A\beta_{42}$ ratio, Aβ PET positivity, and Aβ PET global SUVR. Neurodegeneration latent variable was indicated by plasma NfL level, cortical thickness, and hippocampal volume, with covariance between cortical thickness and hippocampal volume. Cognition latent variable was indicated by the eight neuropsychological test battery, with covariances among tests within each cognitive function domain (i.e., memory, executive function, language). Prior to CFA, observed indicators were residualized with respect to selected covariates to remove variance attributable to these factors. Aβ PET measures were adjusted for PET scanner type, and plasma $pTau_{217}$ and $A\beta_{42}$ were adjusted for body mass index and estimated glomerular filtration rate to account for the distribution and clearance of the plasma biomarkers. CFA was then conducted on the residualized indicators to evaluate the latent structure independent of covariate effects.

4.2.9 Statistical Analysis

Structural equation modeling (SEM) was used to derive the AD latent pathology and to perform regression analyses to assess the effects of *APOE**ε4, AD-PRS, CogDRisk, and adverse SDoH latent score. AD-PRS, CogDRisk, and SDoH latent score were all treated as numeric variables. SEM was performed using full information maximum likelihood as the estimator, adjusting for age, sex, and population stratification using genetic principal components (4 PCs). Model fit was assessed using the Comparative Fit Index (CFI), Tucker-Lewis Index (TLI), Root Mean Square

Error of Approximation (RMSEA), and Standardized Root Mean Square Residual (SRMR) for all factor analyses. Thresholds of CFI and TLI ≥ 0.95 and RMSEA and SRMR ≤ 0.06 were used to indicate an acceptable/excellent model fit.[43,44] Sex- and racial/ethnic-stratified analyses were conducted to measure the effects of risk domains on AD latent pathology in the subgroups, using self-reported sex and race/ethnicity.

4.2.10 Sensitivity Analysis

FIML estimator in lavaan can be applied to missingness in exogenous variables in the regression models (e.g., age, sex, education). We performed full SEM using FIML for the exogenous variable for both the latent variables and the regression to assess the stability of FIML in the total cohort, as well as for sex- and racial/ethnic-stratification analyses.

All analyses were conducted using R version 4.5.3, with the lavaan package version 0.6.21.

4.3 Results

4.3.1 Samples characteristics for EFA and CFA

The analytic sample (N = 3,116; non-Hispanic White: 1,194 (38.3%), non-Hispanic Black: 760 (24.4%), and Hispanic/Latinx adults: 1,162 (37.3%)) was stratified by sex and race and randomly partitioned for EFA and CFA (N = 1,558, respectively), with comparable demographic distributions across subsamples. Mean age was 65 (±8.75) in the EFA and 65 (±8.67) CFA subsamples. Same sample was used for CFA analysis of AD latent variables (Table 4.1).

4.3.2 Sample characteristics for main analysis

A total of 2,173 participants from the HABS-HD cohort were included in the main analysis. The mean age was 65.4 (±8.7) years; 60.9% were female, and the mean years of education was 13.2 (±4.5) (Table 1, eTable 1). There were 641 participants with missing *APOE* genotype data, 163 with missing genetic data (e.g., PRS, PCs), and 290 excluded from adverse SDoH latent score calculation due to missingness in one or more indicators. An additional 181 participants were excluded due to missingness in one or more CogDRisk variables. 416 participants were diagnosed with MCI, and 119 participants with dementia, with the prevalence of *APOE**ε4 carrier being the highest among participants with dementia (Table 1). A total of 3,116 participants were included in the sensitivity analysis. The mean age was 65.2 (±8.7) years; 62.2% were female, and the mean years of education was 13.3 (±4.3). In both groups, NHW participants were the majority (main: 43.4%; sensitivity: 38.3%), followed by Latinx/Hispanic (main: 41.0%; sensitivity: 37.3%) and Black participants (main: 15.6%; sensitivity: 24.4%) (Table S4.1).

Table 4.1. Descriptive statistics of the HABS-HD cohort
Cohort characteristics of HABS-HD participants used in the main analysis, stratified by cognitive status.

Characteristics	Cognitively Normal	Mild Cognitive Impairment	Dementia
Total	1638	416	119
Age	65.2 (± 8.5)	65.4 (± 9.1)	67.6 (± 10.4)
Female	1041 (63.6%)	226 (54.3%)	56 (47.1%)
Education	780 (47.6%)	123 (29.6%)	41 (34.5%)
APOEε4 Carrier	668 (40.8%)	170 (40.9%)	53 (44.5%)
Non-Hispanic White	190 (11.6%)	123 (29.6%)	25 (21.0%)
Non-Hispanic Black	0.0 (± 1.0)	-0.1 (± 1.0)	-0.5 (± 1.2)
Hispanic/Latinx	409 (25.0%)	114 (27.4%)	50 (42.0%)
CogDRisk	-0.029 (± 0.98)	0.092 (± 1.03)	0.437 (± 1.23)
PRSCSx	0.096 (± 0.97)	-0.070 (± 1.06)	0.075 (± 0.83)
Adverse SDoH Latent Score	-0.015 (± 0.22)	0.068 (± 0.21)	0.133 (± 0.22)
Healthcare and Economic Adversity Latent Score	-0.021 (± 0.34)	0.117 (± 0.29)	0.201 (± 0.29)
Anxiety Latent Score	-0.022 (± 0.45)	0.054 (± 0.45)	0.134 (± 0.55)
Social Adversity Latent Score	-0.035 (± 0.62)	0.150 (± 0.60)	0.313 (± 0.63)
SEVLT Immediate	0.363 (± 0.83)	-0.582 (± 0.81)	-1.408 (± 0.91)
SEVLT Delayed	0.377 (± 0.78)	-0.676 (± 0.88)	-1.477 (± 0.79)
WMS-III Logical Memory I	0.377 (± 0.81)	-0.502 (± 0.87)	-1.354 (± 0.93)
WMS-III Logical Memory II	0.392 (± 0.81)	-0.559 (± 0.87)	-1.395 (± 0.81)
WMS-III Digit Span	0.263 (± 0.93)	-0.396 (± 0.95)	-0.929 (± 0.79)
Trail Making Test A&B	0.328 (± 0.64)	-0.581 (± 1.07)	-1.487 (± 1.54)
FAS	0.242 (± 0.92)	-0.454 (± 0.95)	-1.129 (± 0.76)
Animal Making	0.281 (± 0.89)	-0.374 (± 0.88)	-1.258 (± 0.97)
Cortical Thickness	2.76 (± 0.13)	2.73 (± 0.13)	2.60 (± 0.23)
Hippocampul Volume	0.13 (± 0.92)	-0.11 (± 1.01)	-0.68 (± 1.32)
Aβ PET Positivity	0.12 (± 0.33)	0.16 (± 0.37)	0.30 (± 0.46)
Aβ PET Global SUVR	1.02 (± 0.12)	1.04 (± 0.14)	1.08 (± 0.20)
pTau181	-0.117 (± 0.89)	0.095 (± 1.08)	0.600 (± 1.31)
pTau217/Aβ42	-0.09 (± 0.92)	0.10 (± 1.05)	0.45 (± 1.40)
NfL	-0.082 (± 0.90)	0.084 (± 1.14)	0.521 (± 1.33)

4.3.3 Missingness

For SDoH construction, the percentage of missingness across modeled variables ranged from 0.1% (self-reported health status) to 4.6% (income), with an overall missingness rate of 0.44%.

In the EFA and CFA models, estimation proceeded using complete-case analysis through WLSMV default handling of missing categorical data.

In the full SEM, the extent of missingness varied more substantially across variables, ranging from 0% to 56.2%, with the highest levels observed for amyloid PET global SUVR and amyloid PET positivity. Other variables with notable missingness included the $pTau_{217}/A\beta_{42}$ ratio (31.4%), cortical thickness (23.2%), APOE genotype (20.6%), and plasma NfL (11.6%). Little's test for missing completely at random (MCAR) was statistically significant, indicating that the assumption of MCAR was not met.

To further characterize the missing data mechanism, we conducted logistic regression analyses to evaluate whether missingness was consistent with a missing at random (MAR) assumption. Demographic variables (age, sex, PRS, and years of education) were included as predictors, and a binary indicator of missingness (0 = missing, 1 = observed) was specified as the outcome for those variables with high missigness. Missingness in cortical thickness, *APOE* genotype, and amyloid PET measures was significantly associated with all demographic predictors. In contrast, none of the predictors were associated with missingness in either plasma biomarkers. The absence of associations between demographic variables and plasma biomarker missingness likely reflects measurement and processing variability inherent to the HABS-HD dataset. To mitigate these effects, we applied standardization and harmonization procedures across plasma biomarkers and

restricted analyses to measurements obtained using the Quanterix platform. Despite these steps, residual variability cannot be excluded. Importantly, exclusion of plasma biomarkers from the final model was not pursued, as this could introduce biological bias given their established relevance to AD pathology and the lack of alternative measurements. This consideration represents a limitation of the present analysis. Missing data were handled using full-information maximum likelihood (FIML), which leverages all available observations without imputation and yields parameter estimates under MCAR/MAR assumptions. Prior simulation studies demonstrate that FIML maintains robust performance and outperforms alternative methods even under moderate-to-high levels of missingness (e.g., ~40%).[43]

4.3.4 EFA of SDoH Latent Construct

EFA analysis of SDoH indicators demonstrated excellent sampling adequacy (MSA = 0.93) and a significant Barlett's test of sphericity (χ^2(df = 990) = 23,679.12, p < .001). Medicare insurance status, marital status, and two chronic stress questionnaires were excluded due to low MSA (<0.7). Scree plot inspection supported retention of a three-factor solution. Factor correlations from the EFA showed nontrivial interrelations: Factor1–Factor2 = −0.34, Factor1–Factor3 = 0.045, and Factor2–Factor3 = −0.38, supporting the choice of an oblique rotation given conceptually expected correlations among anxiety, social adversity, and healthcare/economic access. Indicators reflecting routine medical checkup recency, unmet need for physician care, personal primary care provider status, and private, Medicare, and Medicaid insurance coverage were removed due to low primary factor loadings (< 0.2). In addition, years lived in the United States and primary language were removed because of moderate cross-loadings across multiple factors, indicating poor discriminant structure. Inspection of the residual correlation matrix indicated adequate local fit, with no large residuals (max |residual| = 0.20).

4.3.5 CFA of SDoH Latent Construct

The three-factor structure was subsequently evaluated using CFA in the independent subsample. Three first-order latent variables (AX, HEA, SA) were specified, along with a second-order SDoH factor loading on each first-order construct using the weighted least squares mean and variance adjusted (WLSMV) estimator, as variables were majoritively categorical and non-normal. Residual covariances were specified between health status and chronic stress questionnaire item #1 ("Have you had a serious ongoing health problem?"), and between health status and insurance coverage (binary indicator of any coverage vs. uninsured), based on conceptual overlap. Model identification was established using the marker-variable method (one indicator loading fixed to 1.0 per latent variable).

The CFA demonstrated acceptable-to-good global fit: $\chi^2(df = 294) = 1{,}973.11$, $p < 0.001$; CFI = 0.980, TLI = 0.977, RMSEA = 0.057 (90% CI: 0.054–0.060), and SRMR = 0.065. Local fit was adequate; standardized residuals ranged from 0 to 0.21. All standardized factor loadings were statistically significant ($p < 0.001$), and no improper solutions (e.g., negative variances, standardized loadings > 1.0) were observed. Standardized AX loadings ranged roughly from 0.46–0.85 (PSWQ items), HEA loadings ranged from ~0.32–0.93 (chronic stress, income, insurance), and SA loadings ranged from ~0.64–0.74 (social support items). A second-order SDoH factor loaded on HEA, SA, and AX, with standardized first-order loadings of 0.66, 0.87, and 0.44, respectively.

The finalized second-order SDoH model was then re-estimated in the full analytic sample (N = 2,826). Model fit remained close to the thresholds of excellent fit: $\chi^2(df = 522) = 7{,}131.20$; CFI = 0.98, TLI = 0.98, RMSEA = 0.062, 90% CI 0.061–0.064, SRMR = 0.067, and standardized

loadings were consistent with the confirmatory subsample (second-order SDoH loadings: HEA = 0.74, SA = 0.76, AX = 0.43) (Table S4.2). Final SDoH latent factor scores were predicted for each participant and were extracted for the downstream analysis (Figure 4.1).

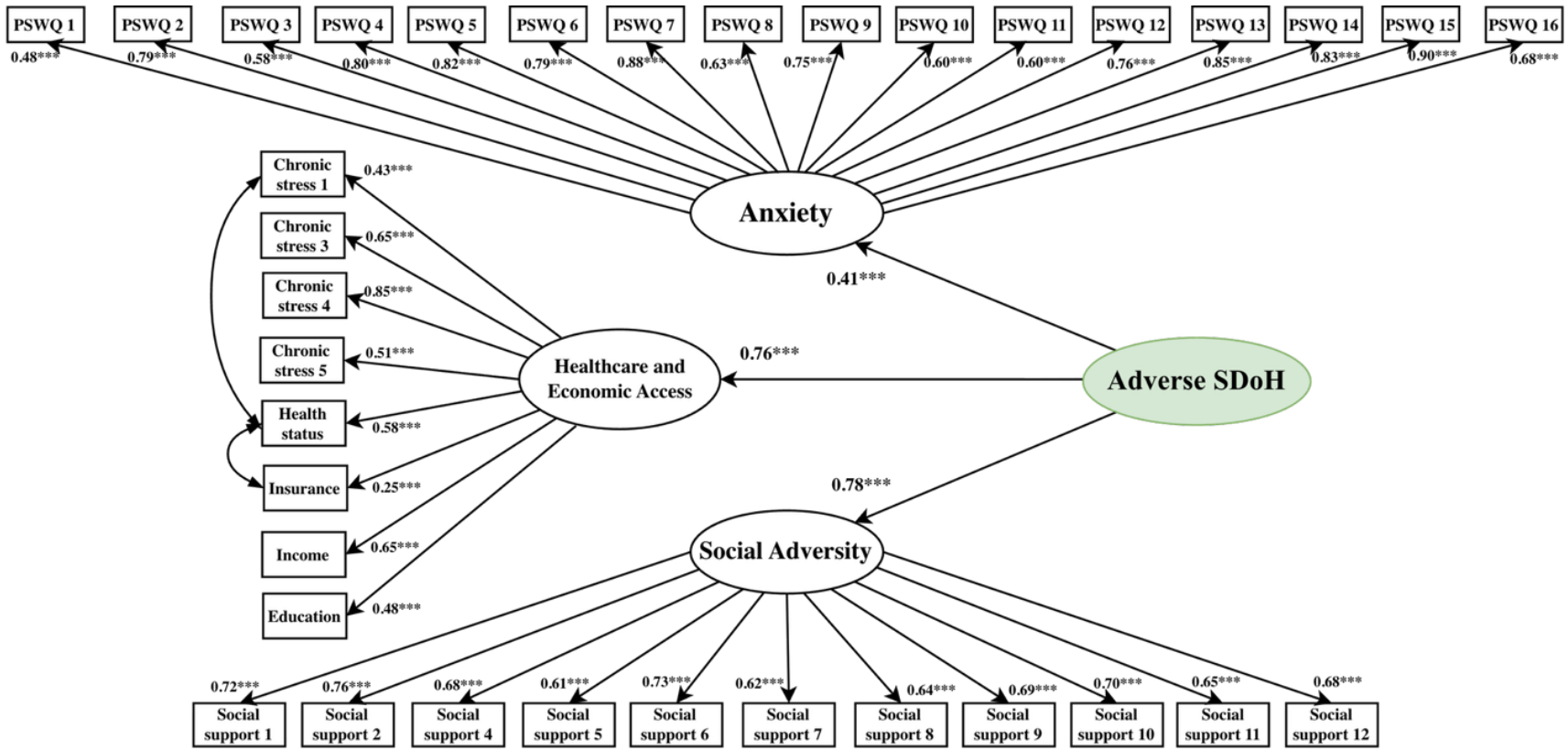

Figure 4.1. Latent structure of social determinants of health

Second-order adverse social determinants of health (SDoH) latent structure was derived from exploratory and confirmatory factor analyses in the full cohort. The weighted least squared mean and variance adjusted (WLSMV) estimator was used for parameter estimation. The adverse SDoH latent score was estimated for 2,826 participants. Scaled CFI = 0.94, scaled TLI = 0.94, scaled RMSEA = 0.062 (90% CI: 0.060-0.063), scaled SRMR = 0.66. The β values indicate standardized path coefficients of indicators to corresponding latent variables. All displayed factor loadings were statistically significant. P-value thresholds: * < 0.05, ** < 0.01, *** < 0.001.

4.3.6 CFA of AD Pathology Latent Variables

Three latent variables, Aβ/tau, neurodegeneration, and cognition, were indicated by corresponding endophenotypes, and were estimated using FIML. The Aβ/tau latent variable was indicated by plasma $pTau_{217}/A\beta_{42}$ level, Aβ PET positivity, and Aβ PET global SUVR, the neurodegeneration latent variable was indicated by plasma NfL level, cortical thickness, and hippocampal volume, and cognition latent variable was indicated by memory, executive function, and language neuropsychological test battery. The total of 3,116 participants were included, and the model demonstrated good global fit: $\chi^2(64) = 344.06$, $p < 0.001$; robust CFI = 0.98; robust TLI = 0.98; robust RMSEA = 0.042 (90% CI: 0.037–0.048); SRMR = 0.030. All indicators loaded significantly onto their respective latent construct, with moderate to strong loadings (Aβ/tau: 0.74–0.83; neurodegeneration: 0.48–0.56; cognition: 0.55–0.65) (Table S4.3).

4.3.7 Structural equation modeling reveals distinct contributions of risk factors across AD pathology latent variables

The full SEM (N = 2,173) was specified to examine the effect sizes of *APOE**ε4, AD-PRS, CogDRisk, and a latent SDoH risk burden on AD latent pathology. The SEM included three endogenous latent outcomes: Aβ/tau, neurodegeneration, and cognition, with covariances specified between Aβ/tau and Neurodegeneration, and between Neurodegeneration and Cognition. All the indicators loaded onto corresponding latent variables strongly and statistically significantly, with loadings ranging from 0.47 (WMS III Digit Span) to 0.82 ($pTau_{217}/A\beta_{42}$). The model demonstrated good global fit: $\chi^2(214) = 1,326.19$, $p < 0.001$; robust CFI = 0.92; robust TLI = 0.90; robust RMSEA = 0.054 (90% CI: 0.050–0.057); SRMR = 0.044 (Table S4.4). Local fit diagnostics

revealed no substantial standardized residuals, and the retained model was selected based on parsimony, theoretical coherence, and model fit.

For the Aβ/tau latent variable, *APOE**ε4 had the highest effect on the latent variable (β = 0.31, SE = 0.035, p < 0.001), whereas AD-PRS showed a modest association (β = 0.075, SE = 0.015, p = 0.002). CogDrisk was not associated, whereas the adverse SDoH was (β = 0.076, SE = 0.069, p = 0.002). For the neurodegeneration latent variable, CogDRisk was strongly associated with worse neurodegeneration (β = 0.16, SE = 0.012, p < 0.001), along with *APOE**ε4 (β = 0.085, SE = 0.025, p = 0.001). The adverse SDoH latent construct was also associated with worse neurodegeneration (β = 0.071, SE = 0.055, p = 0.014), whereas polygenic risk burden was not. For the cognition latent variable, *APOE**ε4 remained significantly associated, with an effect size similar to that observed with the neurodegenerative latent variable (β = 0.083, SE = 0.035, p < 0.001). Adverse SDoH was strongly associated with worse cognition (β = 0.22, SE = 0.077, p < 0.001), whereas polygenic and CogDRisk showed no effect on cognition (Figure 4.2, Table S4.4).

Loadings of indicators onto corresponding latent variables remained consistent across AD pathology in the sensitivity analysis (N = 3,116) (Table S4.5).

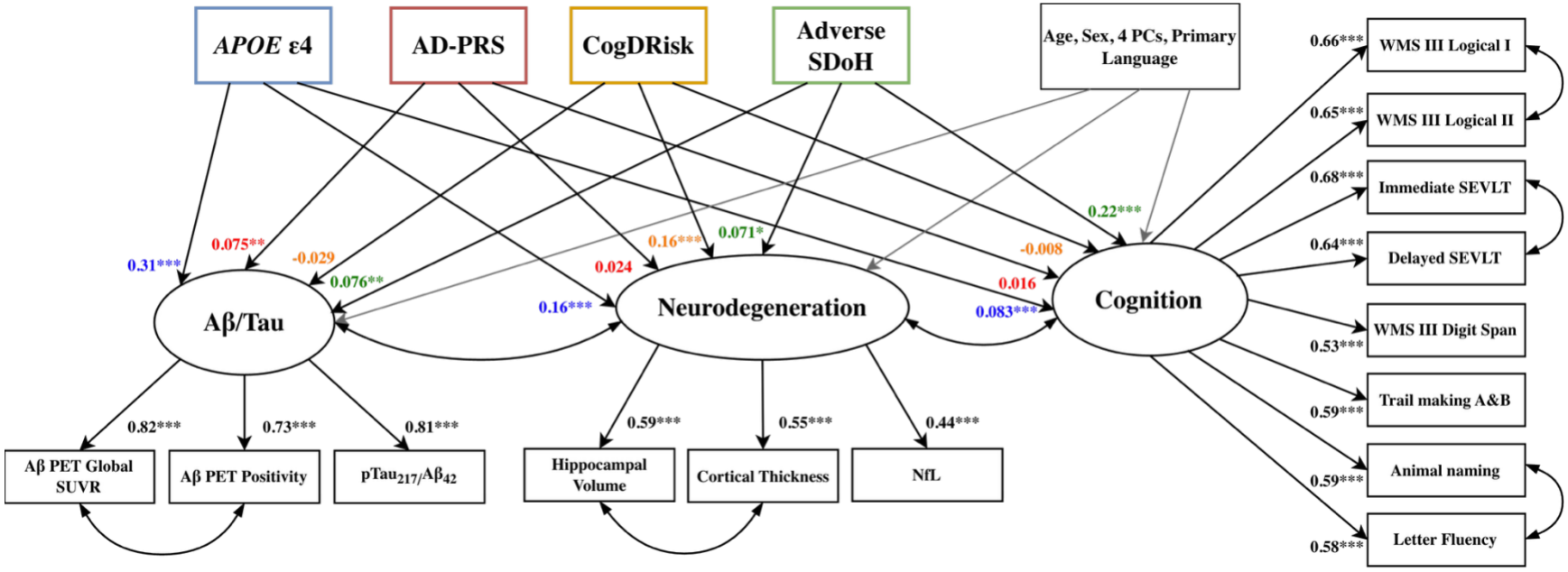

Figure 4.2. Structural equation modeling (SEM) examining the relationship between risk domains and Alzheimer's disease (AD) pathology

The final SEM integrates all risk domains and AD latent variables. *APOE* ε4, AD polygenic risk score (AD-PRS), CogDRisk, and the adverse social determinants of health (SDoH) latent score were modeled as exogenous predictors and regressed on AD latent variables (Aβ/Tau, neurodegeneration, and cognition). All regression paths were adjusted for age, sex, four genetic principal components (PC1–PC4), and primary language. Model fit indices were robust CFI = 0.92, robust TLI = 0.90, robust RMSEA = 0.054 (90% CI: 0.050–0.057), and SRMR = 0.044. Black β values represent standardized factor loadings of indicators onto latent variables, and colored β values represent standardized structural path coefficients from predictors to latent variables. All displayed factor loadings were statistically significant. Significance thresholds: *P < 0.05, **P < 0.01, ***P < 0.001.

4.3.8 Genetic risk contributions to AD pathology differ between sexes

Sex-stratified analysis demonstrated notable differences in genetic effects. For *APOE**ε4, the effects on the Aβ/tau latent variable were concordant between the two groups (female: β = 0.32, SE = 0.041, p < 0.001; male: β = 0.30, SE = 0.064, p < 0.001). The effect of *APOE**ε4 was retained across AD pathology in female participants (neurodegeneration: β = 0.12, SE = 0.036, p < 0.001; cognition: β = 0.13, SE = 0.048, p < 0.001), whereas there were no associations in male participants. The adverse SDoH was associated with the Aβ/tau latent variable only in male participants (β = 0.34, SE = 0.13, p = 0.004) (Table S4.6).

The sensitivity analysis (N = 3,116) did not materially change the loadings of indicators onto the corresponding AD pathology latent variables for both male and female participants (Table S4.7)

4.3.9 Racial/ethnic differences in effect sizes of risk factors on AD pathology

Racial/ethnic-stratified analyses were performed to assess the effect sizes of risk factors on underlying AD pathology, using self-reported race/ethnicity. Among Black participants, *APOE**ε4 and adverse SDoH were associated with the Aβ/tau latent variable (β = 0.19, SE = 0.072, p = 0.002; β = 0.18, SE = 0.16, p = 0.005, respectively). Adverse SDoH was also associated with neurodegeneration and cognition latent variables (β = 0.24, SE = 0.15, p = 0.023; β = 0.32, SE = 0.17, p < 0.001, respectively) (Table S4.8).

Among Latinx/Hispanic participants, *APOE**ε4 was associated with the Aβ/tau latent variable and showed a marginal association with the neurodegeneration latent variable (β = 0.26, SE = 0.059, p < 0.001; β = 0.047, SE = 0.047, p = 0.083, respectively). CogDRisk was associated with the neurodegeneration latent variable, and adverse SDoH was associated with the cognition latent

variable (β = 0.22, SE = 0.021, p < 0.001; β = 0.73, SE = 0.13, p < 0.001, respectively) (Table S4.8).

Lastly, among NHW participants, AD-PRS, *APOE**ε4, and adverse SDoH were all associated with the Aβ/tau latent variable (β = 0.094, SE = 0.025, p = 0.006; β = 0.37, SE = 0.055, p < 0.001; β = 0.085, SE = 0.11, p = 0.015, respectively). Both APOEε4 and adverse SDoH were also associated with neurodegeneration and cognition latent variables (*APOE**ε4: [neurodegeneration] β = 0.089, SE = 0.034, p = 0.013; [cognition] β = 0.11, SE = 0.050, p = 0.001; adverse SDoH: [neurodegeneration] β = 0.094, SE = 0.074, p = 0.012; [cognition] β = 0.23, SE = 0.11, p < 0.001). CogDRisk was associated with the neurodegeneration latent variable (β = 0.12, SE = 0.017, p = 0.002) (Table S4.8).

In sensitivity analysis, CogDRisk was associated with the neurodegeneration latent variable (β = 0.16, SE = 0.029, p = 0.003), and adverse SDoH was no longer associated with the Aβ/tau latent variable among black participants. All other association patterns remained similar across groups (Table S4.9).

4.4 Conclusion

In the community-based cohort of the HABS-HD study, we examined the relationships among genetic, clinical, and environmental risk burdens and the underlying AD pathology, as indicated by the latent variables Aβ/tau, neurodegeneration, and cognition. Examining the standardized estimates, *APOE**ε4 had the strongest effect on the Aβ/tau latent variable among other risk-pathology relationships. Although the magnitude of effect sizes was smaller, the effects of *APOE**ε4 were statistically very strong on both neurodegeneration and cognition latent variables

as well. AD-PRS, on the other hand, also had a strong effect on the Aβ/tau latent variable and a non-significant effect on neurodegeneration and cognition. The strong association of AD genetic risks with more upstream of the disease pathology recapitulates prior reports on the impact of APOE on AD pathology.[45] In contrast, AD-PRS was not significantly associated with the neurodegeneration latent variable in the overall HABS-HD cohort. Given the cohort being generally healthy and cognitively unimpaired, this may reduce the detectable signal in plasma biomarkers. The limited enrichment of neurodegenerative markers and the moderate predictive power for AD-PRS may have attenuated the associations.

Clinical risk burden demonstrated a strong association with the neurodegeneration latent variable. Many CRS, including CogDRisk, are derived using all-type dementia as outcomes, which may explain their stronger effect on neurodegeneration than upstream Aβ/tau or downstream cognition pathways. This pattern is consistent with established links that clinical risk burdens may exert their effect on cognitive impairment through general neuronal injury and neuroinflammation (e.g., vascular comorbidities, metabolic dysfunction, systemic inflammation)[46,47] rather than through non-AD pathology (e.g., Aβ and tau). Similarly, disadvantaged SDoH was associated with neurodegeneration and with cognition much more strongly, but not with Aβ/tau pathology. SDoH, composed of anxiety, chronic stress, social support, and economic and healthcare access, is a cumulative score that measures an individual's stress-related lifestyle exposure, and the large effect on cognition in this study raises the possibility that SDoH influences cognitive reserve and performance independently of canonical AD proteinopathy. These results suggest that interventions targeting social disadvantage and health disparities may therefore yield cognitive benefits even in individuals without elevated amyloid or tau burden. Together, these results suggest that risk domains differently map onto different stages of the AD neuropathological cascade.

Genetic risks appear more etiologically proximal to proteinopathy than to the downstream cognitive phenotype, whereas clinical and environmental risk burdens may operate through non-Aβ/tau, neurodegenerative mechanisms, with a cumulatively disadvantaged SDoH profile that appears to influence the most downstream cognitive expression.

Sex-stratified analyses showed differential associations between genetic risk factors across AD pathology. Specifically, *APOE**ε4 exhibited a stronger association with latent AD pathology in female participants, whereas AD-PRS was significantly associated with Aβ/tau pathology in male participants but not in females. Prior studies have reported sex-specific effects of *APOE**ε4, with female carriers showing higher AD risk, greater tau and amyloid burden, and increased neurodegeneration relative to males,[48–51] although these findings are not entirely consistent across cohorts. The observed sex difference in AD-PRS associations may reflect the composition of AD GWAS signals, which are enriched for lipid metabolism and immune-related pathways that may have differential effects across sexes. Future work should investigate sex-specific genetic susceptibility to AD biomarkers and how *APOE**ε4 and polygenic risks manifest differently in women and men.

Racial/ethnic-stratification analysis revealed different association patterns across groups. The prominent role of adverse SDoH among Black participants may reflect the cumulative impact of social and environmental disadvantage on AD-related biological processes. Chronic exposure to factors such as socioeconomic adversity, stress, and limited healthcare access may contribute to physiological dysregulation, thereby influencing Aβ/tau pathology, neurodegeneration, and cognition; longitudinal analyses are needed to clarify the temporal relationships underlying these associations. The weaker contribution of genetic risk may also reflect the reduced transferability

of genetic risk measures derived primarily from European ancestry populations. However, sample sizes for stratified analyses, particularly among Black participants, were limited, and these findings require validation in larger, more diverse cohorts.

The study includes a few limitations. First, the analyses were cross-sectional analyses restricted our ability to evaluate temporal relationships among multidomain risk factors, AD proteinopathy, and cognitive decline. Second, the construction of both the CRS and the SDoH latent variables was constrained by available data. In particular, the SDoH measure did not include several relevant domains (e.g., neighborhood and built environment, education and healthcare quality, food access), which may have limited the specificity of the environmental risk construct. Finally, although the overall sample size was substantial, larger samples would strengthen model stability, given the complexity of the structural equation model and the inclusion of stratified analyses. Future studies should examine multidomain risk categories and their longitudinal associations with AD pathogenesis in larger, more diverse cohorts.

Despite these limitations, this study has several strengths. Prior work has largely evaluated genetic, clinical, and environmental risk factors in isolation. In contrast, we examined these domains simultaneously within a unified structural model, enabling direct comparison of their associations with underlying AD pathology. Furthermore, we utilized previously benchmarked and validated AD-PRS and CRS and derived the SDoH construct using rigorous exploratory and confirmatory factor analytic methods. Stratified analyses further extend these findings across demographic groups.

In a racially and ethnically diverse aging cohort, HABS-HD, genetic, clinical, and environmental risk burden exhibited distinct associations with AD-related pathology. Genetic risk mapped most

strongly to upstream Aβ/tau pathology, clinical risk to neurodegeneration, and social determinants to cognition. These findings support a multidomain framework of AD vulnerability in which biologic and contextual risks operate at partially independent stages of AD pathogenesis.

Supplementary Information

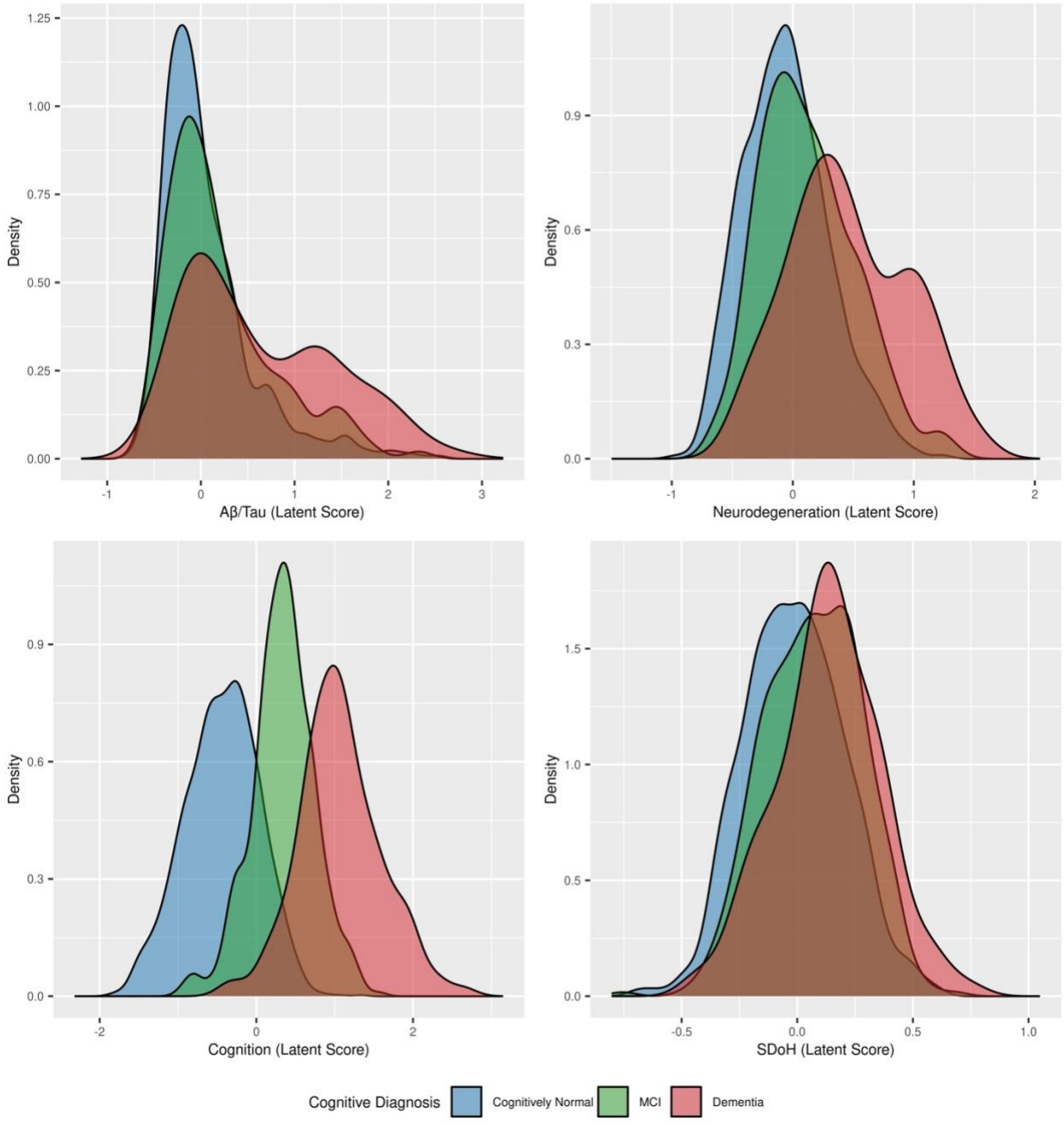

Figure S4.1. Distributions of latent variables, stratified by cognitive diagnosis
Kolmogorov-Smirnov tests confirmed statistically significant deviation of distributions of Aβ/Tau, neurodegeneration, cognition, and adverse SDoH latent scores between MCI vs cognitively normal and dementia vs cognitively normal group. Top left: Aβ/Tau latent score; top right: Neurodegeneration latent score; bottom left: Cognition latent score; bottom right: Adverse SDoH latent score. (N = cognitively normal: 1,638; MCI: 416; dementia: 119)

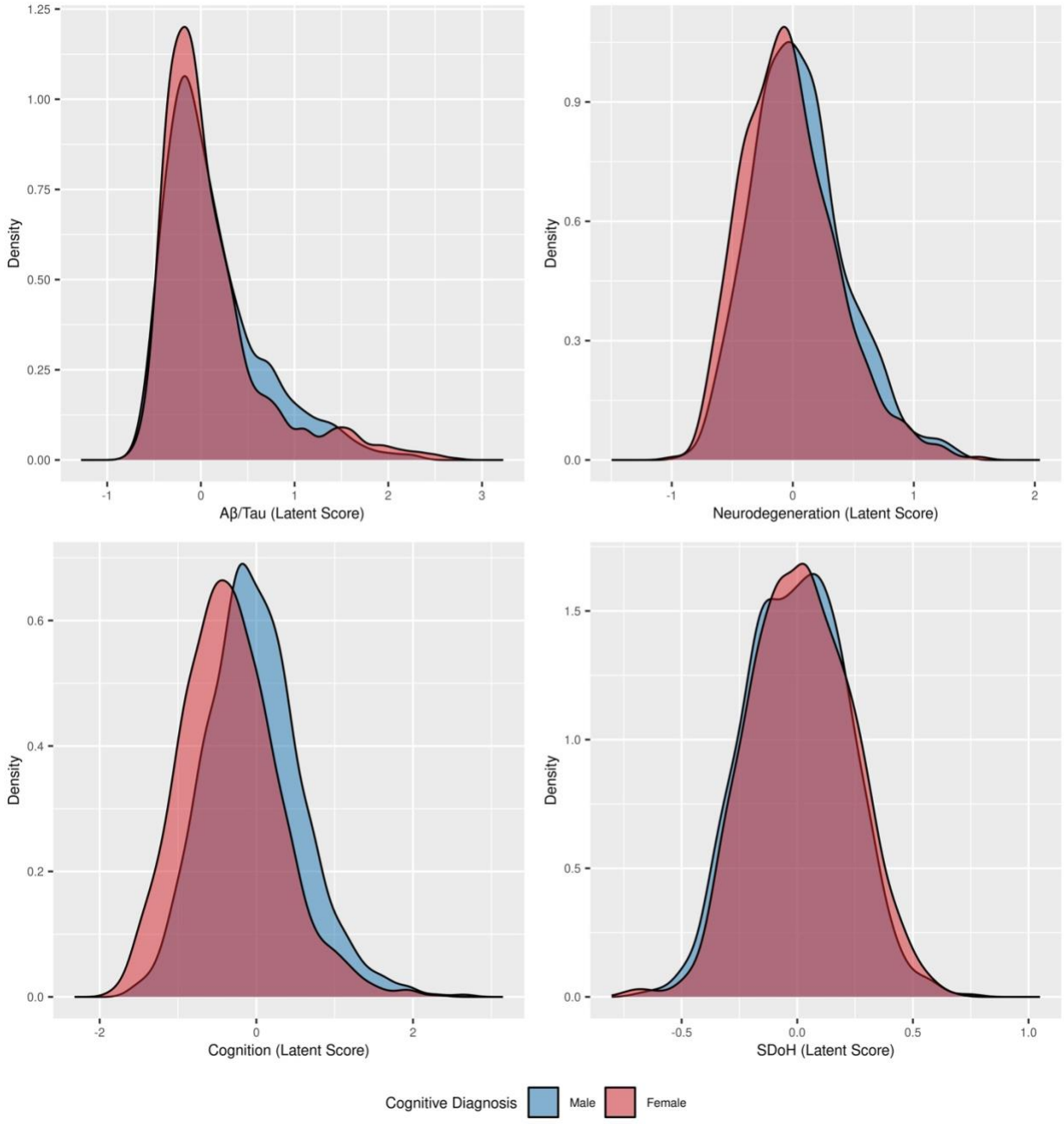

Figure S4.2. Distributions of latent variables, stratified by self-reported sex
Kolmogorov–Smirnov tests indicated statistically significant differences in the distributions of Neurodegeneration and SDoH latent scores between sexes. Top left: Aβ/Tau latent score; top right: Neurodegeneration latent score; bottom left: Cognition latent score; bottom right: Adverse SDoH latent score. (N = Female: 1,323; Male: 850)

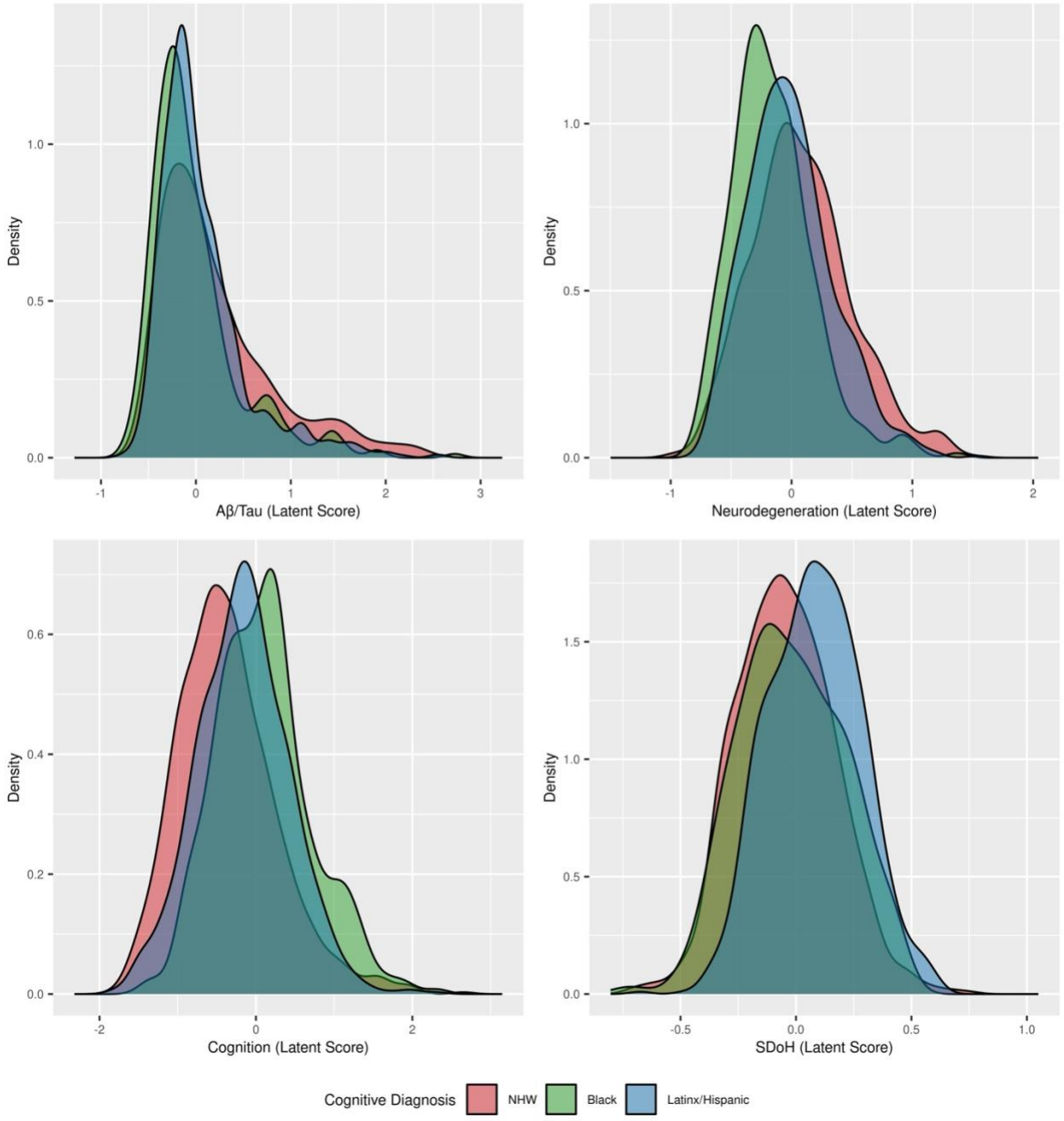

Figure S4.3. Distributions of latent variables, stratified by cognitive diagnosis
Kolmogorov-Smirnov tests confirmed statistically significant deviation of distributions of Aβ/Tau, neurodegeneration, cognition, and adverse SdoH latent scores between NHW vs Black and Black vs Latinx/Hispanic participants. Top left: Aβ/Tau latent score; top right: Neurodegeneration latent score; bottom left: Cognition latent score; bottom right: Adverse SDoH latent score. (N = NHW: 944; Black: 338; Latinx/Hispanic: 891)

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Chapter 5: Conclusion

5.1 Summary of Findings

Alzheimer's disease (AD) remains the most common neurodegenerative disease, and early risk identification is a critical step toward improving disease outcome and building multidomain preventative frameworks. Despite major advances in biomarker development and multi-domain preventative frameworks,[25,27,104,105] effective prevention and treatment strategies remain limited by heterogeneity in disease risk, pathology, and clinical progression across individuals and populations. These challenges are especially important in diverse populations, where differences in genetic architecture, environmental exposures, healthcare access, and social determinants of health (SDoH) may substantially influence disease trajectories and the performance of existing risk assessment tools.[40,114,115]

The overarching objective of this dissertation was to validate AD risk assessment frameworks and quantify how genetic, clinical, and environmental risk burdens relate to underlying AD pathology across diverse populations. This work addressed a gap in the current AD literature, in which genomic, clinical, and environmental risk domains are often studied independently despite AD being a multifactorial disease shaped by cumulative exposures across the life course. Through evaluation of multidomain risk frameworks spanning the genome and exposome, this dissertation examined the analytical validity, biological relevance, and population generalizability of risk assessment tools intended to support more equitable precision medicine approaches for AD screening, prevention, and treatment.

In Chapter 2, we evaluated AD polygenic risk scores (PRS) in relation to cognitive status and AD endophenotypes, including cognitive function, neuropathological measures, and CSF and plasma

biomarkers, across multi-ancestry populations. Moving beyond Eurocentric approaches, we constructed PRS using diverse genome-wide association study (GWAS) summary statistics and applied Bayesian methods to better capture the genetic architecture of AD. These approaches improved the predictive performance of PRS, particularly in African and admixed American ancestry groups. These findings implicate the importance of developing and evaluating equity-centered AD-PRS that incorporate diverse training datasets and leverage advanced statistical methods that capture the complex and heterogenous structure of human genome. Such insights should always be considered for mitigating bias in model outputs. Evaluation of other PRS models remains necessary to establish AD-PRS models that are robust enough for clinical implementation and application in diverse populations.

In Chapter 3, we benchmarked dementia clinical risk scores (CRS) to assess their performance across diverse populations. Among the models evaluated, CogDRisk, which incorporates clinical, lifestyle, and psychosocial factors, demonstrated the most consistent associations with AD endophenotypes and outperformed other CRS. While PRS and CRS represent fundamentally distinct approaches to risk assessment tools, a consistent theme emerged: incorporating diverse sources of information, through increased genetic representation and broader characterization of clinical, lifestyle, and psychosocial factors, improves AD risk assessment and prediction. CRS and PRS operate in different risk domains, but modeling complex, age-related diseases like AD requires an understanding and integration of the diverse factors such as large, diverse training datasets and a consideration of diverse factors that individuals may be exposed to over their life course. No one risk model fit all for diverse populations for AD risk prediction, and it is important to consider all the potential factors that may benefit or bias model performance across different populations.

In Chapter 4, we developed an integrative multidomain framework examining the orthogonal contributions of genetic, clinical, and environmental risk burdens to underlying AD pathology. Using exploratory and confirmatory factor analyses, we constructed a SDoH latent variable, representing an accumulated environmental risk burden. Using exploratory and confirmatory factor analysis, we identified indicators that loaded onto three first-order latent variables, which together formed a second-order SDoH construct. This approach provided an unbiased, data-driven framework to quantify multidimensional environmental risks. We then integrated the SDoH latent score with the best-performing polygenic and clinical risk scores identified in previous chapters to evaluate the independent contributions of genetic, clinical, and environmental factors to underlying AD pathology. We observed that genetic risk was most strongly associated with Aβ/tau pathology, clinical risk with neurodegeneration, and SDoH with cognition. Racial/ethnic- and sex-stratified analyses revealed distinct patterns in how these risk factors map onto each pathway. *APOE**ε4 had a stronger effect across all the pathways among female participants, whereas these effects were attenuated among male participants. Adverse SDoH showed strong associations across all pathways among Black participants, despite this being the smallest subgroup. Notably, these effects were both statistically significant and large in magnitude, highlighting the strength of these relationships even in a limited sample. Higher clinical risk burden was associated with neurodegeneration among Hispanic/Latinx participants, which was not observed among Black participants.

5.2 Expansion of the Findings

Collectively, findings from Chapters 2, 3, and 4 support a multidomain framework for understanding AD vulnerability in which genetic, clinical, and environmental risk domains

influence distinct but interacting pathways of the AD continuum. More importantly, these findings demonstrate that equitable precision medicine frameworks for AD require consideration of both genomic and exposomic risk profiles across diverse populations. Together, this dissertation highlights three central findings that expand the current conceptualization of AD risk assessment, prevention, and disease progression.

1. Risk domains operate through distinct biological AD pathways. As demonstrated in Chapter 4, each risk domain appears to represent a potentially distinct mechanistic pathway through which AD and cognitive decline may manifest. Genetic risk factors exhibited substantially stronger associations with the latent amyloid and tau constructs, suggesting that genetic susceptibility may play a more prominent role in disease initiation and early neuropathological processes rather than in the direct manifestation of cognitive impairment. In contrast, adverse SDoH appeared to exert a greater influence on cognition than on latent amyloid, tau, and neurodegeneration constructs. This emphasizes the multifactorial nature of AD and suggest that distinct domains of risk may differentially contribute to neuropathology and cognitive decline.

2. No single risk domain fully captures AD risks. Polygenic diseases like AD are etiologically complex, with disease manifestation arising from the combined influence of genetic and environmental factors. Accordingly, the phenotypic variance associated with AD can be more comprehensively explained through the integration of both genetic and non-genetic risks. Although PRS were developed to capture genome-wide genetic susceptibility, the ceiling effect of their predictive ability is limited by genetic variance of AD. Consequently, a more complete understanding of AD pathophysiology requires continued investigation into the full spectrum of clinical, environmental, and social risk factors that contribute to disease onset and progression.

3. Risk domains exert differential effects on AD pathology across demographic groups. One of significant findings is the observation that risk domains do not affect all populations uniformly. The United States comprises populations that are culturally, socioeconomically, and genetically diverse, yet AD affects individuals across all demographic groups. These findings emphasize the importance of developing equitable and generalizable risk assessment frameworks that are consider risk weights that are applicable for a given population. Failure to account for demographic heterogeneity in risk prediction models may limit their clinical utility and exacerbate existing disparities in AD research.

While these results are based on cross-sectional data and causal or temporal relationships cannot be established, they support a multi-domain framework for AD risk assessment and highlight the importance of integrating genetic, clinical, and environmental factors in future longitudinal studies. Because each risk domain influences AD risk through distinct biological and social pathways, there is a need for a new paradigm that considers the full spectrum of individuals' backgrounds and lived experiences.

5.3 Implications for Precision Medicine and Clinical Translation

From a precision medicine perspective, the differential risk profiles and their effects on AD pathology have implications on the generalizability of applying current risk assessment tools across demographically diverse populations. Despite evidence from the present study and a growing body of literature on these findings,[72,116,117] we continue to broadly utilize these tools without considering individual's demographics backgrounds. Translation of these tools into clinical practice requires careful consideration of standardization of risk models and biomarkers and rigorous analytical and clinical validation of these tools in large, diverse populations.

Importantly, the use of inadequately optimized risk models can introduce bias and raises bioethical concerns about equity, exacerbating existing health disparities in the medical system. We recognize that genetically representative datasets are essential for the development of genome-wide genetic risk screening tools, as they enable characterization of ancestry-specific variants with distinct effect sizes, linkage disequilibrium structures, and minor allele frequencies unique to that ancestry.[40,118] This consideration should extend to non-genetic modifiable risk factors, like diet, lifestyle, and community-context, which may have impact on shaping individuals' health outcomes. The application of Eurocentric approaches and methodologies to already underrepresented datasets, without taking in the sociocultural contexts of non-White populations, risks reinforcing existing structural biases and fails to identify at-risk individuals not captured by the current risk assessment paradigm.[109,112,119] Ensuring that these tools are developed and validated in diverse populations is essential not only for improving predictive accuracy but also for promoting equitable clinical use. Therefore, future efforts should prioritize methodological validation in the equity framework to support the responsible integration of multi-domain risk models into clinical decision-making.

5.4 Future Directions

The present study has several directions for extending this work to promote health equity in AD research. An important next step is to expand the generalizability and trans-ethnic portability of risk models through benchmarking and SEM analyses in larger biobank-scale datasets. Robust risk prediction and assessment models require large and diverse populations that better reflect real-world patient populations. In the field of PRS, predictive accuracy varies not only across continental ancestry groups but also within them.[72] Moving beyond continental ancestry labels and having more granular subcontinental ancestry stratification is an important step to advance health

equity in genetics and make PRS more portable. However, available GWAS data are limited in non-European populations,[70] and this currently poses as the greatest challenge in PRS advancement.

Second, CRS face similar challenges on generalizability. Our analyses showed that CRS incorporating a broader range of lifestyle and behavioral exposures demonstrated improved predictive performance compared to those more focused on subsets of clinical risk factors (e.g., cardiometabolic profiles). However, variability in lifestyle, diet, and cultural factors across populations makes it challenging to assign consistent weights to individual risk factors across different settings. These challenges highlight the need for systematic evaluation of existing CRS,[96] that have proliferated over the past few decades, alongside population-specific stratification to assess their generalizability and performance across diverse groups.

Third, the cross-sectional design of the present study also points to important opportunities for future longitudinal investigation. Our findings indicate that disadvantaged SDoH are associated with multiple domains of AD pathology, with the strongest effects observed for cognition. However, it remains unclear how early life SDoH exposures influence the longitudinal progression of AD biomarkers and their utility as predictors of future pathological change. In addition, whether cumulative SDoH burden or specific SDoH domains more strongly drive these associations over time warrants further investigation. Among the risk domains examined, SDoH remain comparatively understudied yet it holds potential for clinical actionability. Integrating SDoH into risk assessment frameworks could enable clinicians to identify and address modifiable environmental risk factors alongside genetic and clinical profiles. Furthermore, future studies should incorporate more comprehensive measures of neighborhood environment, structural

disadvantage, healthcare access, environmental toxicants, food security, and life-course adversity to better characterize cumulative exposomic burden. Early efforts in this direction are underway, suggesting that such approaches may be feasible within clinical settings and address health inequity more directly during hospital admissions.[120,121]

5.5 Concluding Remarks

In summary, this work advances a multi-domain framework for understanding AD by integrating genetic, clinical, and environmental risk burdens across the genome and exposome in relation to underlying AD pathology. The present findings underscore that AD risk is not adequately captured by any single domain but rather emerges from the cumulative and orthogonal contributions of multiple risk dimensions across the life course. By leveraging diverse populations and latent variable approaches, this work also highlights the importance of representation and multidimensional measurement in improving risk prediction and advancing health equity.

Importantly, these findings support a growing shift toward precision medicine approaches in AD that extend beyond single-modality biomarker or genetic frameworks alone. Understanding how multidomain risk profiles influence amyloid and tau pathology, neurodegeneration, cognition, and clinical progression may improve identification of individuals most likely to benefit from early screening, prevention strategies, and disease-modifying interventions. This integrative framework provides a foundation for more precise and clinically actionable multidomain risk identification strategies that better inform early detection and intervention in AD.

References for Chapter 1 and Chapter 5

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