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PERSPECTIVE

Recruitment and Retention for Alzheimer's Disease Diversity Genetic Cohorts in the ADSP (READD-ADSP): A global effort to identify genetic factors in Alzheimer's disease

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Abstract

INTRODUCTION: Alzheimer's disease (AD) remains a major neurocognitive disorder of global health significance. Globalizing ancestral diversity in AD genetics is essential to identify causal variants, improve diagnosis, and enable equitable therapeutic interventions across populations. The Recruitment and Retention for Alzheimer's

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Disease Diversity Genetic Cohorts in the ADSP (READD-ADSP) initiative addresses this by including African ancestry and Hispanic/Latinx (HL) ancestry populations.

METHODS: READD-ADSP, a case-control study, aims to recruit, evaluate, and retain 13,000 participants: 5000 Indigenous Africans, 4000 African Americans, and 4000 Hispanic/Latinx individuals. In Africa, recruitment involves nine sub-Saharan African countries under the African Dementia Consortium, and with protocols ensuring standardized data collection, phenotype harmonization, culturally informed diagnostic algorithms, and robust community engagement.

RESULTS: Study participants are recruited, ascertained and retained. Blood samples and fractions (DNA, plasma, RNA) are biobanked for genomic, epigenomic, proteomic, and transcriptomic analyses.

DISCUSSION: This study will advance precision ADRD medicine and establish a model for working with diverse global cohorts of brain disorders.

KEYWORDS

African ancestry, Alzheimer's disease and related dementias, global diversity, Hispanic/Latinx ancestry, precision medicine

Highlights

- Recruitment and Retention for Alzheimer's Disease Diversity Genetic Cohorts in the ADSP (READD-ADSP) addresses critical gaps in Alzheimer's Disease and Related Dementias (ADRD) research by including underrepresented groups.
- The study recruits 13,000 participants of African, African American, and Hispanic/Latinx ancestries.
- Standardized protocols enable rigorous phenotyping and harmonization across diverse populations.
- Findings will inform precision medicine and reduce health disparities in ADRD outcomes.

1 | BACKGROUND

Neurocognitive disorders, particularly Alzheimer's disease (AD), pose a significant and growing global health challenge. Globally, a new case is diagnosed every 3 s,¹ and ≈150 million individuals will be living with dementia by 2050. Low- and middle-income countries (LMICs), including those in Africa, are projected to bear 71% of this burden,²⁻⁴ highlighting the urgency of inclusive research.⁵ AD affects about 6.9 million Americans, with prevalence exceeding 35% among those aged 85 years and older.⁷ AD is characterized by progressive cognitive decline, memory loss, and behavioral changes, with an average of 10 years preceding the clinical expression of the disease, and no effective cure is currently available.⁸ Mortality from AD increased by 47% between the years 2000 and 2006.^{5,6}

Genetic factors significantly influence AD risk, yet much of the landscape remains unexplored, particularly among non-European populations.^{5,9} Mutations in genes such as Amyloid Precursor Protein (*APP*),¹⁰ Presenilin1 (*PSEN1*),¹¹ and Presenilin2 (*PSEN2*)¹² are

linked to familial AD, while the apolipoprotein E (*APOE*) ϵ 4 allele is the strongest genetic risk factor for late-onset AD.¹³ Although genome-wide association studies (GWASs) in European ancestry populations have advanced understanding, under-representation of diverse populations may worsen genomic disparities, thereby affecting AD diagnosis, treatment, and outcomes.¹⁴⁻¹⁶ Recent studies, notably the largest AD genetic meta-analysis (111,326 cases, 677,663 controls)¹⁷ identified 42 novel risk loci. However, findings predominantly involved European ancestry populations.⁵ African (AF) and Hispanic/Latinx (HL) population groups have, respectively, 2- and 1.5-fold higher AD risk than non-Hispanic Whites (NHWs) but remain underrepresented.¹⁸ African American (AA) and HL individuals, who constitute 12.6% and 16.3% of the U.S. population, respectively,¹⁹ face significant barriers to research participation, including mistrust and inadequate representation in study designs. Addressing these disparities is vital for equitable outcomes.^{15,20,21} Expanding research to diverse global populations is critical for identifying population-specific genetic variants, understanding environmental and sociocultural influences, and developing personalized therapies.⁵

Collaborative initiatives like the Alzheimer's Disease Sequencing Project (ADSP)²² and the African Dementia Consortium (AfDC)²³ help bridge disparities in AD research. Launched in 2012 by the National Institutes of Health (NIH), the ADSP uses advanced genomic tools to identify rare and common AD risk variants.²² The AfDC ensures equitable representation of diverse African populations by integrating genetics and non-medical drivers of health, complementing the ADSP's objectives. Together, these efforts highlight the importance of global collaboration in understanding the complex AD genetics.^{5, 24}

Our project, the Recruitment and Retention for Alzheimer's Disease Diversity Genetic Cohorts in the ADSP (READD-ADSP) initiative,¹⁹ branded as DAWN (Diverse Alzheimer's Workforce and Networks),¹⁸ builds on ADSP and AfDC achievements. READD-ADSP aims to recruit, evaluate, and retain a diverse cohort of participants, including 5000 AF, 4000 AA, and 4000 HL individuals. It addresses historical gaps in genomic research, emphasizing inclusion and diversity to ensure findings are applicable to a broader spectrum of populations.^{15, 16}

The main goal of the READD-ADSP is to increase the diversity of the ADSP and make it a global resource by including historically understudied groups such as African (AA and AF) and HL ancestries in large-scale efforts aimed at unraveling the genetic architecture of AD across diverse populations.

DAWN fosters a global, multidisciplinary network of researchers, clinicians, and community stakeholders to advance scientific knowledge and support the development of personalized therapeutics for AD. By integrating diverse datasets into newer phases of the ADSP, the initiative will enhance understanding of how ancestral genetic variations influence AD risk.

This study provides an overview of the specific aims, strategies and activities, innovations, and unique features of READD-ADSP in bridging critical gaps in global dementia genetics research.

2 | AIMS AND RESEARCH STRATEGY

2.1 | Specific aims and overall study design

The READD-ADSP, a case-control study, was designed to achieve five specific aims, which are summarized in Table 1, whereas the overall study design and activities being undertaken to achieve the specific aims are summarized in Figure 1.

Specific Aim 1: To develop a large genomics resource for the study of AD in individuals of AF and HL ancestries. Two major cores—an administrative (Core A) and ascertainment (Core B)—were established for the recruitment, clinical assessment, and sampling of 13,000 individuals (6500 cases and 6500 controls), which includes 5000 AF, 4000 AA, and 4000 U.S. HL. Core A (administrative) provides regulatory oversight for the entire study including maintaining ethical standards with due consideration of cultural differences among participant populations and ensuring protection of human subjects across all study sites. Core B (ascertainment) provides oversight for the recruitment and clinical evaluation procedures for obtaining clinical and neurocognitive datasets as well as collection and management of biological samples

(including whole blood, plasma, and blood in PAXgene RNA tubes) from the study participants. The biobanking processes including shipments in READD-ADSP are described elsewhere.²⁵

Specific Aim 2: To adjudicate (Core C) and harmonize clinical and neurocognitive datasets (Figure 2). A key goal of the READD-ADSP is to develop a harmonized and consistent phenotypic dataset. We clinically adjudicate and harmonize neurocognitive and clinical data from the study participants through consensus diagnosis to determine the clinical diagnosis (control, mild cognitive impairment, AD, or non-AD dementia). The clinical adjudication committee operates at the level of individual study sites, national level, and a central adjudication, comprising key investigators from the United States and AfDC. Any diagnostic discordance at one level is resolved at a higher level of adjudication and finally by the central adjudication committee through consensus. An overview of the clinical data and adjudication workflow is shown in Figure 2. In addition, the central adjudication committee is developing and applying culturally informed algorithms for AD and related dementias. The final consensus clinical diagnoses constitute datasets that are triangulated with other datasets generated under subsequent specific aims, all of which are utilized in the analytic phase of the study (Projects 1 and 2) and are also deposited at the National Institute on Aging (NIA) Genetics of Alzheimer's Disease Data Storage Site (NIAGADS) to facilitate broad access including contributions to the AD Phenotype Harmonization Consortium of the ADSP (ADSP-PHC).

Specific Aim 3: To process, store, and assay biological materials obtained from study participants. These specimens include whole blood, plasma, and RNA for future expression studies. Guided by robust protocols and standard operating procedures co-developed by both U.S. and AfDC teams, biospecimens are collected, processed, and stored at individual study sites for periods not more than 3 months. The samples are then shipped on dry ice to the African coordinating center at the College of Medicine, University of Ibadan, where DNA extraction from whole blood samples is done and all biosamples are further stored in solar powered -80° ultralow freezers. Aliquoted specimens are then shipped to the University of Miami, USA, for storage in a centralized, automated, state-of-the-art biorepository. From this facility, samples are transferred to the National Centralized Repository for Alzheimer's Disease and Related Dementia (NCRAD). Genomic DNA is utilized for genome-wide single nucleotide polymorphism (SNP) genotyping, whole genome sequencing (WGS), while plasma is processed for AD-related biomarker discovery effort. These activities under Specific Aim 3 are organized into the Core D framework of the project.

Specific Aim 4: To manage multilevel phenotypic, genomic, and biomarker datasets. The process involves the use of electronic data management systems and activities, which are organized into the Core E framework of the project. All datasets are consolidated into a centralized database infrastructure to ease access and transmission to NIAGADS and enable access to the broader research community. Furthermore, Core E provides the necessary infrastructure for high-performance computing and large-scale genomic analyses to support the initial genomic characterization of the resource under Specific Aim 5.

TABLE 1 Summary of Study Aims, Design, and Innovations for a Multi-Ancestry Genomics Resource in Alzheimer's Disease Research.

Aim	Description	Innovation and expected outcomes
1	To develop a large genomics resource of individuals with AF and HL ancestry. Two major cores, an administrative (Core A) and ascertainment (Core B) were established both in the United States and in Africa for the recruitment, clinical assessment, and sampling of 13,000 individuals (6500 cases and 6500 controls) of diverse race/ethnicity, including 5000 AFs, 4000 AAs, and 4000 U.S. HLs. Biological samples such as whole blood and plasma are obtained from the study participants for DNA sequencing, AD biomarkers, and future gene expression studies, respectively. Likewise, using comparable evaluation procedures, clinical and neurocognitive data are being obtained on all participants. Regulatory oversight is being provided that puts cultural differences across participant populations into perspective to ensure consistency in the protection of human subjects across all the study sites.	<ul style="list-style-type: none"> • Filling a critical resource gap in AD genetics research and creating a novel resource for the field. • Harmonize phenotypic information collected across diverse geographic and cultural backgrounds. Ascertainment includes engagement with the AA, HL, and AF communities to ensure trust, higher levels of participation and retention. • Global partnership with AfDC will ensure a comprehensive framework.
2	To adjudicate (Core C) and harmonize clinical and neurocognitive data (Figure 2). Critical to the value of this resource is a well-documented and consistent phenotypic data. We will adjudicate cases and controls from U.S. and AfDC sites as well as harmonize multi-domain clinical data from these cohorts. A clinical adjudication committee of investigators from U.S. and AfDC sites will develop and apply culturally informed algorithms for AD and related disorders. Data generated would be transferred to NIAGADS for broad sharing, including the AD Phenotype Harmonization Consortium of the ADSP (ADSP-PHC).	<ul style="list-style-type: none"> • Analyze AA and HL datasets with sufficient power to allow for the first-ever large-scale GWAS for AD in these ancestry groups
3	To process, store, and assay biological materials for the genomics resource, including DNA isolation, plasma, and RNA for future gene expression studies. All materials will be aggregated into a single resource at a single site and stored in a state-of-the-art automated biospecimen resource for transfer to NCRAD. DNA will be extracted for genomic analyses and genome-wide SNP array data and plasma biomarker data will be generated (Core D).	<ul style="list-style-type: none"> • Translating association results into an understanding of population-specific mechanisms for AD risk. • Identify biological networks and pathways that harbor genetic variants contributing to AD risk within AA and HL ancestry groups. <p>Synthesize a biological portrait of AD pathogenesis within each population and identify the common underlying biology of AD. Generating AD biomarker data (total tau, Aβ40, and Aβ42, p-tau181, and neurofilament light) on a subset of the AF, AA, and HL samples to provide, for the first time, benchmark data for comparisons across these populations.</p>
4	Data management for all phenotypes, genomics, and biomarkers using electronic data capture systems, where possible. Data to be collected into a single database system to ease access and transmission to NIAGADS, which will provide access to the broader research community. In addition, infrastructure for high-performance computation and large-scale genomic analyses will be provided for the initial genomic characterization of the resource (Core E).	<ul style="list-style-type: none"> • Employing novel statistical methodology to assess the impact of local ancestry on AD risk. This approach will provide insights about the risk factors correlated with different genetic ancestries.
5	Perform genomic sequence analyses. We will provide initial characterization of this resource through tests of genomic and phenotypic hypotheses within cohorts (Project 1) and tests of ancestry-based hypotheses across populations (Project 2). These projects make extensive use of the data generated as part of this resource, as well as taking advantage of existing data from the ADSP Follow-up Study (ADSP-FUS).	<ul style="list-style-type: none"> • Developing and applying novel analytical approaches to include ancestry-aware transcriptome wide association study (TWAS) methods, new kernel-based association tests that account for the ancestry of rare variants and haplotypes and new approaches for scoring regulatory variants that will eliminate the need for ancestry-specific TWAS reference panels. • Broaden applicability of TWAS and rare-variant association tests by directly modeling the predicted impact of genetic variants on transcription factor binding, eliminating the need for population-specific eQTL reference panels. • Examine patterns of African divergence and potential roles of other groups such as Amerindians.

Abbreviations: AA, African American; A β , Amyloid beta; AD, Alzheimer's disease; ADSP-FUS, ADSP Follow-up Study; ADSP, Alzheimer's Disease Sequencing Project; AF, African; AfDC, African Dementia Consortium; eQTL, Expression quantitative trait loci; GWAS, Genome-wide association study; HL, Hispanic/Latinx; NCRAD, National Centralized Repository for Alzheimer's Disease and Related Dementias; NIAGADS, The National Institute on Aging Genetics of Alzheimer's Disease Data Storage Site; SNP, Single-nucleotide polymorphism; TWAS, Transcriptome wide association study.

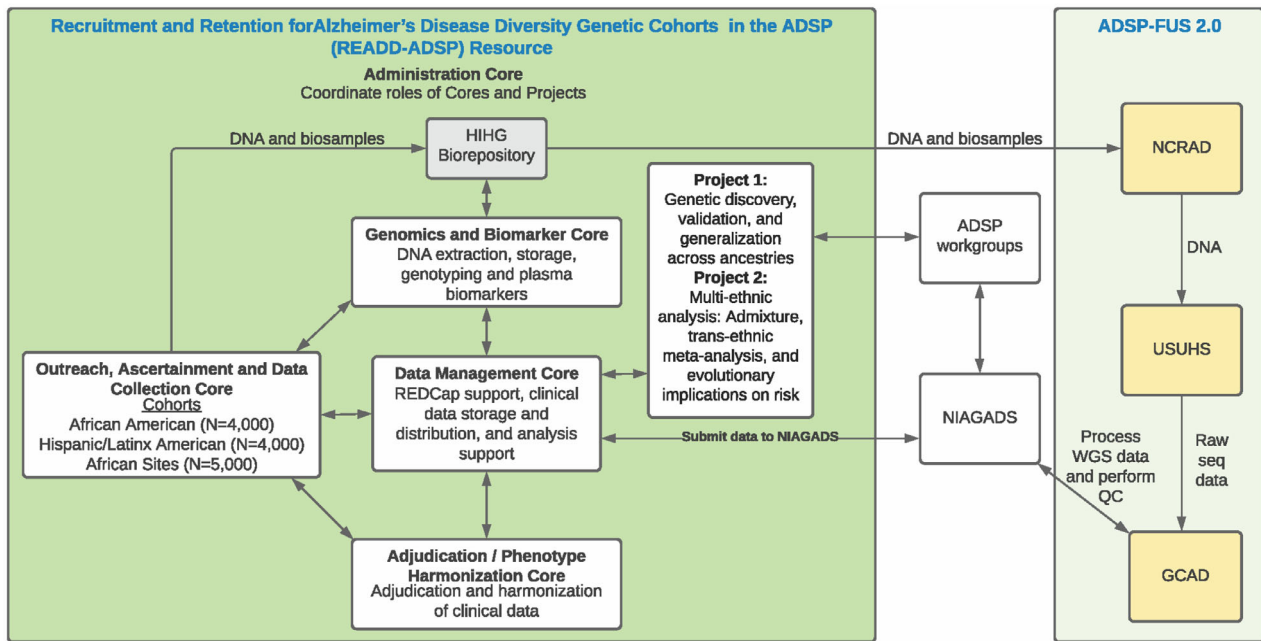


FIGURE 1 Overview of the READD-ADSP activities necessary to build required resource and fulfill aims. GCAD, Genome Center for Alzheimer's Disease; HIHG, Hussmann Institute for Human Genomics; NIAGADS, National Institute on Aging Genetics of Alzheimer's Disease Data Storage Site; USUHS, Uniformed Services University of the Health Sciences.

Specific Aim 5: To perform genomic sequence analyses for the initial characterization of study participants through tests of genomic and phenotypic hypotheses within cohorts (Project 1) and tests of ancestry-based hypotheses across populations (Project 2). These projects make extensive use of the phenotypic, genomic, and biomarker datasets generated in Core E under Specific Aim 4 and also take advantage of existing data from the ADSP Follow-up Study (ADSP-FUS).

2.2 | Eligibility

Participants 65 years of age or older without any obvious other neurological or psychiatric disorders are recruited into READD-ADSP, which was carefully designed to ascertain eligible participants while minimizing recruitment bias. With robust community engagement strategies uniquely fitted to the context of each participating site, eligible participants are recruited from health facilities including general and specialty clinics (geriatrics, neurology, and psychiatry) as well as through patient referrals from primary and secondary-level facilities. In some study sites, participants are recruited primarily from established demographic surveillance sites in rural areas of the country. The community engagement programs, including community advisory boards (CABs), are further supported by awareness strategies through social, print, and electronic media and mobile telephony. These multi-layer strategies ensure a fair sampling of the population in recruiting participants into the READD-ADSP. Furthermore, control participants are recruited from the same geographic regions from which cases are recruited to ensure appropriate matching for ethnicity and geographic origin.

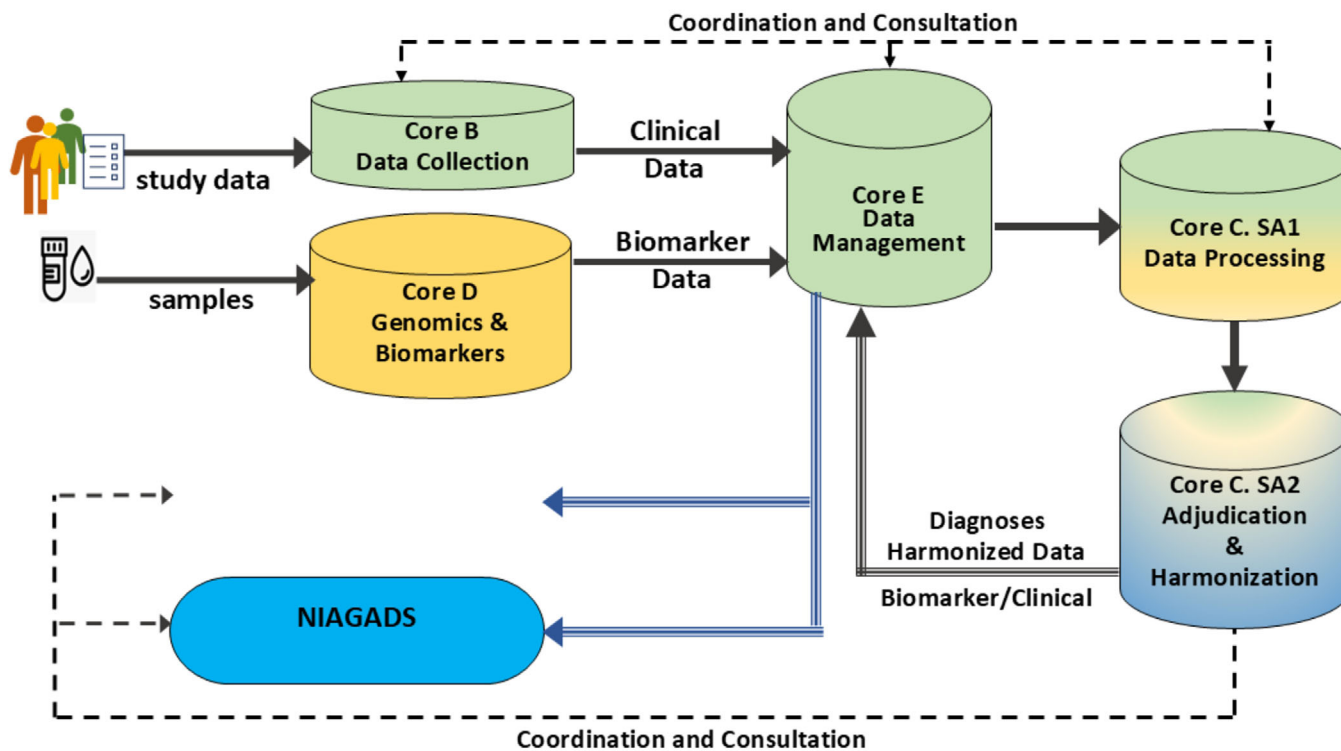
2.3 | Ethical considerations and procedure

Ethical and regulatory approval was sought and secured from relevant national and site-based health research ethics committees in each participating country site. Each site also has a CAB to provide local oversight and facilitate community understanding of the study processes. For each study participant, the consenting process involves detailed explanation of the study protocols to the prospective participant in the language best understood to ensure full understanding before consenting to participate. The informed consent form also includes a witness who may be a family member. For participants who may have lost capacity due to severe cognitive impairment, consent is provided by a proxy who is often a family member (spouse or offspring) of the study participant. Broad consent is obtained from participants, and each participant is at liberty to opt out at any stage of the study. To ensure confidentiality, each participant is assigned a unique coded identifier, and all data collected are de-identified and handled in accordance with international data protection standards. Individuals are informed of their right to decline or withdraw from the study at any time without consequence.

2.4 | Study setting and approach

The READD-ADSP collaborative group includes five U.S. sites, the prime site being the John P. Hussman Institute for Human Genomics (HIHG) at the University of Miami Miller School of Medicine. Other sites are Case Western Reserve University, Columbia University, Wake Forest University (WFU), and the University of Pennsylvania. In Africa,

Overview of Clinical Data Flow



Adjudication Workflow

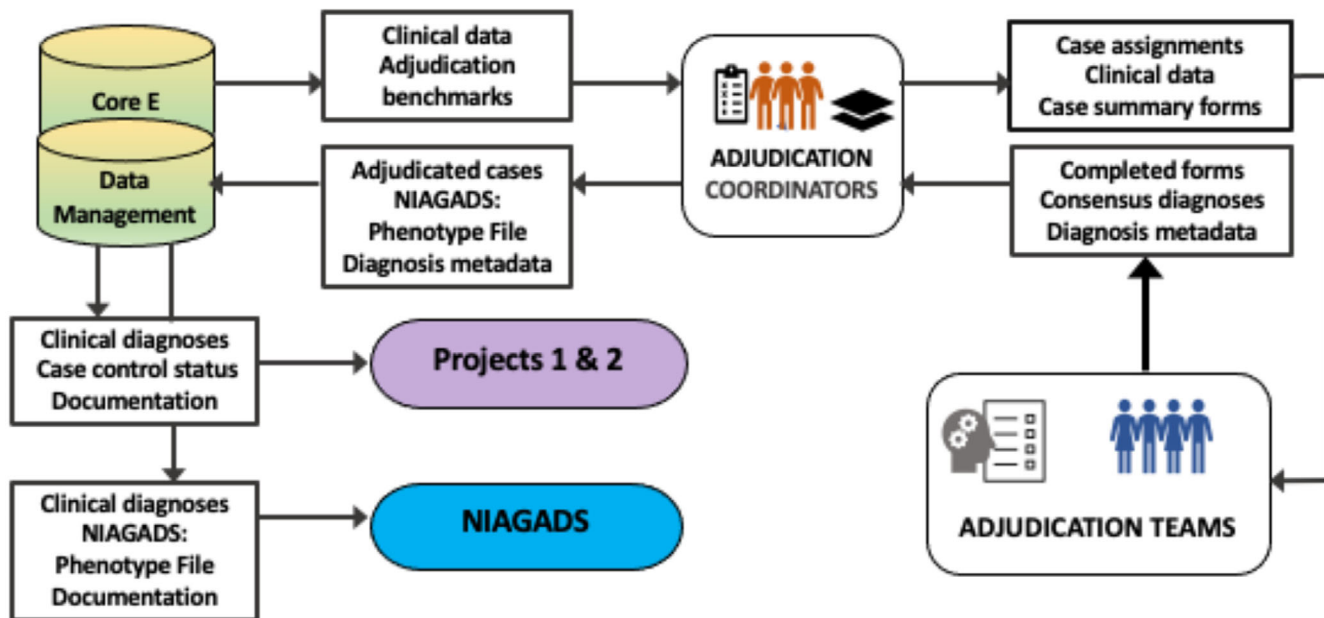


FIGURE 2 The overview of clinical data flow (A) and adjudication workflow (B) for READD-ADSP. NIAGADS, National Institute on Aging Genetics of Alzheimer’s Disease Data Storage Site; SA, Specific Aim.

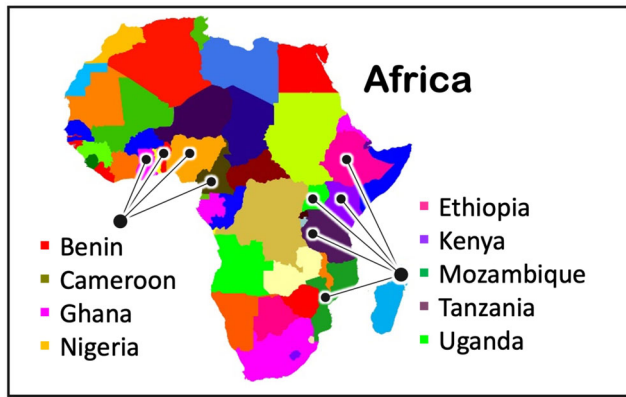


FIGURE 3 Map of Africa showing READD-ADSP country sites operating under the African Dementia Consortium (AfDC).

nine countries are involved including Benin, Ghana, Nigeria, Cameroon, Ethiopia, Kenya, Uganda, Tanzania, and Mozambique (Figure 3). A number of institutions in these countries are participating, including the University of Ibadan; University of Lagos; University of Ilorin; Neuropsychiatric Hospital, Aro, Abeokuta; Ahmadu Bello University, Zaria; University of Port Harcourt; Rivers State University Port Harcourt; Nnamdi Azikiwe University; Federal Teaching Hospital Ido – Ekiti; Benue State University Makurdi; University of Ghana College of Health Sciences; Korle-Bu Teaching Hospital; Kwame Nkrumah University of Science and Technology; Makerere University; University of Parakou; Brain Research Africa Initiative/University of Yaounde; Africa Institute of Mental and Brain Health / University of Nairobi; Eduardo Mondlane University; Kilimanjaro Christian Medical University College; and Addis Ababa University. Under the aegis of the AfDC, the College of Medicine, University of Ibadan hosts the African Coordinating Center and leads other African institutions to achieve the READD-ADSP set objectives. These under-represented populations are chosen to bridge the global genomic data gap and to better understand the AD genetic landscape among local ancestries.

Protocol-guided evaluation procedures, which were designed to accommodate diverse cultural contexts, are implemented to ensure harmonized phenotyping and facilitate deeper exploration of the biological and social contexts associated with AD in diverse under-represented settings to enhance better understanding of the genetic architecture of AD and the development of ancestry-informed interventions.^{5, 11, 12, 17}

2.5 | READD-ADSP Africa Activation Training

In June 2023, a two-day hybrid training program was conducted to activate the READD-ADSP across participating African sites. The training brought together over 100 site leads and team members, providing hands-on instruction in standardized, protocol-driven procedures for patient and community engagement, as well as participant recruitment and retention. The protocols were very clear about informed consent, confidentiality, and eligibility. The READD-ADSP

participant recruitment form (PRF) was reviewed with emphasis on comprehensive sociodemographic and clinical data collection, and culturally-sensitive cognitive assessment. The training also addressed adequate resource allocation to study sites, adjudication, consensus clinical diagnosis, and strategies for phenotype harmonization across sites.

Additional sessions covered protocols for biological sample collection, processing, storage, and shipment, alongside the use of electronic databases for secure data entry, upload, and quality assurance. Community engagement strategies, outreach models, and ascertainment protocols were discussed extensively to ensure culturally responsive implementation.

Participants were also introduced to the African Neurocognitive Disorders Registry. All phenotypic, genomic, and biomarker data would be stored in a centralized database, enabling robust hypothesis-driven analyses within and across ancestry-defined cohorts. The team developed a pocket protocol to facilitate the ascertainment and clinical diagnostic procedure (Supplementary File 1). This integrated model serves as a prototype for globally coordinated ascertainment of complex neurocognitive phenotypes.

2.6 | Innovation

The READD-ADSP initiative integrates several novel strategies. These include:

1. Addressing a critical resource gap in AD genetics research that has historically remained largely unaddressed until now. Creating this critical and novel resource is an innovation for the field.
2. Harmonizing phenotypic data across diverse geographic and cultural backgrounds. This will be done in full coordination with the ascertainment objectives, making this by far the largest harmonized AD dataset of diverse ancestries globally. For downstream analysis, this will reduce substantial sources of “nuisance parameters” and background heterogeneity, to the benefit of all who will access this resource.
3. Comprehensive and community-sensitive approach toward ascertainment that includes mutual engagement with the AA, AF, and HL communities to boost participation and retention.
4. Enabling the first-ever large-scale GWAS for AD in AA, AF, and HL ancestry groups.
5. Global collaboration with AfDC for joint case-control ascertainment and data analyses.
6. Generating AD biomarker data (glial fibrillary acidic protein [GFAP], amyloid beta [A β]40 and A β 42, phosphorylated tau-181 [p-tau181], and neurofilament light [NfL]) on a subset of the AA, AF, and HL samples to provide, for the first time, benchmark data for comparisons across these populations.
7. Applying novel analytical methods, including ancestry-aware transcriptome-wide association study (TWAS) approaches, kernel-based association tests that account for the ancestry of rare variants and haplotypes, and regulatory variant scoring methods

that eliminate the need for ancestry-specific TWAS reference panels.

This approach will broaden the applicability of TWAS and rare-variant association tests by directly modeling the predicted impact of genetic variants on transcription factor binding, eliminating the need for population-specific expression quantitative trait loci (eQTL) reference panels.

1. Translating genetic association findings into meaningful biological insights through pathway analysis to define AD mechanisms across populations.
2. Using statistical methodology to analyze local ancestry effects. This approach will provide insights into the risk factors correlated with different genetic ancestries. Ancestry inference and admixture analysis will be performed using principal component analysis (PCA), ADMIXTURE, and deconvolution tools to understand ancestry-specific risk.
3. Developing local ancestry-based association methods, boosting detection power in admixed individuals.
4. Studying selection pattern and evolutionary divergence and similarity across diverse populations, especially Africans, representing global genetic diversity.
5. Examining the potential role of the Amerindian (AI) population. AI are among the least included groups in AD research. We will explore the admixed HL populations to analyze the AI genetic component.
6. Exploring the association of Social, Behavioral, and Environmental Determinants of Health (SBEDOH) and AD risk providing a basis for integrative studies of biological and social risks of AD. In addition to the primary focus of our study on genetics, we recognize the powerful influence of SBEDOH on cognitive trajectories as recently shown by the report of the Lancet Commission, which showed that 45% of dementia risk is due to 14 modifiable risk factors.²⁶ Hence, READD-ADSP also has a section (Supplementary File 2) with relevant questions and tools interrogating the SBEDOH in all study participants and with adaptation to local contexts. This will allow for integrative analyses of modifiable risk factors as well as robust exploration of gene–environment interactions in the study population.

The sample collection timeline is shown in Figure 4. READD-ADSP has been scheduled to run for 5 years.

2.7 | Recruitment strategies and retention efforts

From our experience in previous projects,^{27,28} we identified common barriers to participation in long-term studies, and developed effective, ancestry-informed strategies. Our successful ascertainment and research efforts to date have led to multiple studies of AAs^{29,30} and HLs.³¹ From these studies, we have discovered notable differences across ancestries in the genetic architecture of AD. Notably, HLs are

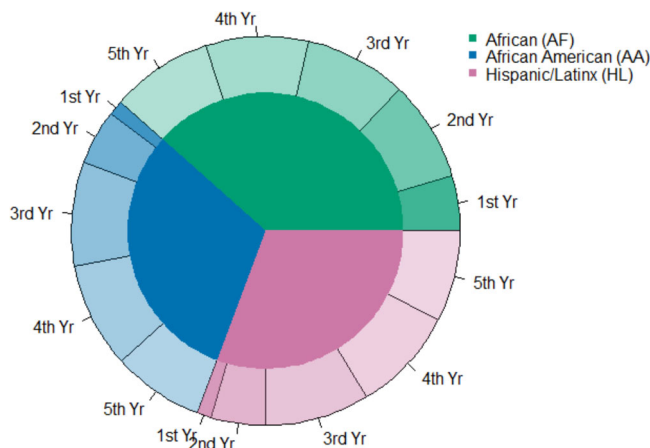


FIGURE 4 Timeline for sample collection.

twice as likely as NHWs to develop AD,³² with Caribbean HL families showing triple the incidence compared to NHW families.³³

We employ the following recruitment strategies: (1) Leverage Participant and Community Input to Assure Recruitment Success: We are using the Perceived Research Burden Assessment (PeRBA) and the Ultra-Short Research Participant Perception Survey to assess participant impressions of our recruitment process³⁴ and obtain community input to our recruitment practices. We also created an AA AD recruitment tool kit of best practices that is being used across our AD research sites, as well as national large-scale projects. (2) We created a Cross-Site Community Participant Advisory Team (CPAT) of three to four community members from each of our four sites that assisted in material development and effective recruitment strategies. An example of bi-directional learning, the CPAT has been useful in giving us ongoing and direct feedback, thereby enhancing participant recruitment and retention. (3) Increase Genomics Awareness: We work with our communications and marketing teams to customize project materials for each site. (4) Virtual and Faith-based Outreach: During the coronavirus disease 2019 (COVID-19) pandemic, e.g., the WFU team hosted 13 COVID-19 awareness and COVID-19 vaccine webinars through the Triad Pastors Network (TPN),³⁵ reaching more than 30,000 AAs. We are currently leveraging this faith-based platform where we created congregational aging hubs, established and trained congregational health ambassadors to assist with AD awareness and recruitment. We already have 21 churches that have agreed to participate. AA men have the worst overall health outcomes.³⁵ Yet, they are routinely missing from trials and studies. We emphasize recruitment in this population through the TPN (100 AA faith leaders, the majority are male), which gives us the platform to target this population. (5) Physician Engagement: We are engaging groups of physicians and community stakeholders who are trusted voices in the AA communities to assist with messaging and trust building. (6) Community Leadership: Local community leaders are engaged to strengthen grassroots outreach.

All participants undergo culturally tailored ascertainment, including (1) collection of sociodemographic information, detailed medical and family history, and information to establish age-at-onset, course, and evidence of decline; (2) self- or informant-reported vascular risk

factors and other comorbidities and measurement of blood pressure (Project 1); (3) evaluation of neurocognitive abilities across several domains using validated screening tools; and (4) evaluation of functional performance based on report from a knowledgeable informant such as a spouse, sibling, or caregiver.

For participants recruited from U.S. sites, the AD Uniform Data Set version 3 (UDS3) is used as the primary tool for neurocognitive assessment. However, due to differences in education, literacy, and cultural contexts,³⁶ some components of the UDS3 measures have shown limited applicability in sub-Saharan African populations. Evidence from pilot studies revealed that certain adaptations of the UDS3 allowed for more culturally appropriate and accurate assessments of cognitive decline in African participants. As a result, a modified version of the UDS3 has been implemented across AfDC sites. In addition, the Identification and Intervention for Dementia in Elderly Africans (IDEA) cognitive screening tool has been incorporated to further enhance cognitive assessments.³⁷ To evaluate the functional consequences of cognitive impairment (Supplementary File 2), the IDEA Instrumental Activities of Daily Living (IDEA-IADL) scale is also employed. This tool complements the IDEA and the Cognitive Screening Instrument for Dementia (CSID).^{4,38}

All sites have institutional review board approval. Informed broad consent was obtained from all participants or proxies when needed.

2.8 | Our approaches and limitations

A major global limitation to the participation of AA and HL groups in biomedical research has been the reluctance of the research community to include these populations. This is in part due to the tradition of recruiting through large health care systems that under-represent these groups and concerns about data heterogeneity. In addition, mistrust in research, rooted in historical mistreatment, has contributed to participant hesitancy. To address these barriers, our teams has built trust through transparent communication. The 13,000 participants being recruited into the present study represent a major improvement over prior studies. Diversity within AF and HL populations is substantial and with moderate sample size. Findings from our previous work^{39,40} underscore that even with moderate sample sizes, regionally enriched variants can be detected through ancestry-aware approaches. Furthermore, our data will be combined with other AF and HL ancestry genetic data available in the ADSP, allowing for increased sample sizes and a broader diversity of genetic data.

Through collaboration with community advisors, families, and individuals, we have identified and addressed common barriers to participation, including transportation, site accessibility, diverse staffing, and limited information flow to families. Our multi-site team addresses these challenges continually through weekly calls and bi-annual meetings. The inclusion of team members from AA, AF, and HL population groups is a key strength, enhancing trust, cultural sensitivity, and communication with the communities we serve. Their shared backgrounds foster rapport and ensure that our strategies are culturally aligned. This has enabled us to adopt recruitment and engagement approaches to

better reflect community needs, thereby promoting greater inclusivity and sustained participation.

We also leverage the AfDC network²³ and past success stories²⁹⁻³¹ to overcome known challenges. Recruited participants will be longitudinally followed up under an additional funding mechanism.

3 | DISCUSSION

3.1 | Rationale for diversity in genetic cohorts

Genomic research^{15,16} has historically focused on European (EU) populations, with AF and HL populations underrepresented. This disparity is concerning, with data showing that Caribbean HL individuals have a 2- to 3-fold higher risk of late-onset AD³³ and dementia is more prevalent among AAs.⁴¹ These disparities stem from a complex interplay of genetic, environmental, socioeconomic, and systemic health care inequities.⁴² We opine that this disparity is also partly due to differences in genetic architectures across populations. Limited representation may mask ancestry-specific variants influencing AD risk.²¹ Including diverse populations is essential for identifying such variants and understanding gene-environment interactions.⁵

Current evidence suggests that variation in AD prevalence across ancestral populations is due in part to differences in population genetic structure. To fully understand the genetic architecture of AD, it is essential to investigate a broad array of genetic variants across ancestries. Including diverse populations enables the discovery of both universal and population-specific risk alleles. Some variants may be unique to a specific ancestry, yet they offer key insights into disease biology and health disparities.⁴³ For instance, *PCSK9* polymorphisms identified in AA populations have informed lipid-lowering therapies for broader populations.⁴⁴

A second advantage of studying diverse ancestries lies in identifying risk variants that are universal but exhibit differing effect sizes due to contextual or modifying factors. These may include interactions with other genetic variants, or environmental contexts. For example, *APOE* genotypes that alter the risk of AD have smaller effect sizes in AA.²⁴ Understanding such contextual differences helps identify both shared and ancestry-specific biological mechanisms underlying AD.

Allelic and locus heterogeneity shaped by historical evolutionary and environmental factors influence disease susceptibility directly or through pleiotropic effects. A major goal of this study is to recruit participants from diverse populations to better understand the shared and population-specific biological mechanisms of AD. By recruiting AF, AA, and HL individuals, our study aims to reveal these patterns and advance precision medicine for all.

3.2 | Incorporating diverse cohorts for inclusive research

Incorporating diverse cohorts in AD research, as facilitated by READD-ADSP, offers numerous advantages. It enables the discovery of

population-specific genetic variants, supports tailored approaches to diagnosis and treatment, and promotes equity in research. It contributes to the development of global standards for AD care that are culturally sensitive and relevant across populations. It also enhances community engagement, strengthens research impact, and ensures that findings have global relevance.⁴⁵

3.3 | Implications for Alzheimer's disease research

The READD-ADSP initiative is the largest genetic study of AD in African ancestry populations to date. This will undoubtedly enhance global diversity and inclusion in AD genetics research. We will, for the first time, be able to analyze AA, AF, and HL datasets with sufficient power to allow for the first-ever large-scale GWAS for AD in these ancestry groups.

By enlisting diverse genetic cohorts from populations underrepresented in past large-scale genomic efforts, READD-ADSP will enrich the existing knowledge base with a more comprehensive understanding of AD genetics. This includes exploring rare and common genetic variants, their prevalence, and their potential contributions to AD susceptibility and progression.^{5,46}

The insights gained through READD-ADSP are poised to have transformative implications for AD diagnosis, prevention, and treatment. Understanding genetic diversity across diverse populations can lead to the identification of population-specific risk factors, the development of more tailored and well-structured diagnostic tools, informed and targeted prevention strategies, and improved accuracy of genetic risk assessments and personalized treatment approaches.

3.4 | Community benefits

Diversifying genetic data in AD research is critical for unraveling the complex interplay of genetics and disease manifestation across different populations. Incorporating a broad spectrum of diverse genetic backgrounds, specifically from underrepresented groups, can lead to the development of a more comprehensive understanding of AD pathogenesis. This inclusivity ensures that diagnostic tools, preventive measures, and treatments are effective across the full mosaic of human genetics, rather than just a subset. In doing so, we not only enhance the precision of medical interventions for AD but also address historical health inequities, thereby improving outcomes and quality of life for all communities affected by AD.

3.5 | Translational science—Bench to bedside

One of the primary ways in which READD-ADSP benefits the community is through its commitment to translational science. The wealth of genetic data generated by the project is not limited to academic or research communities but is intended for practical application. This initiative drives scientific discoveries from the laboratory bench to the bedside—and ultimately to the community—ensuring that insights

gained directly influence health care practices, improve patient outcomes, shape policy, and support community-based disease prevention efforts.⁴⁷

3.6 | Tailored and structured community advocacy

READD-ADSP is committed to community advocacy that is tailored toward addressing the specific cultural biases and genetic needs of diverse populations. A notable example is the TPN initiative.³⁵ By understanding the genetic landscape of AD across different ancestries, we have launched targeted and structured advocacy efforts within local communities. These initiatives ensure that community engagement is not a generic exercise but a culturally-sensitive approach aimed at raising awareness, dispelling harmful myths that may delay early detection and treatment, and addressing prevalent misconceptions surrounding AD—particularly among individuals of African ancestry.⁴⁸ Some commonly held beliefs include attributing AD symptoms to bewitchment, witchcraft, spirit possession, or divine punishment.⁴⁸ Our advocacy strategies have taken these beliefs into account, ensuring the delivery of accurate, accessible, and tailored information on AD susceptibility, prevention, early detection, management, and treatment. This culturally informed approach fosters trust, promotes informed health-seeking behaviors, and encourages participation in genomic research.

3.7 | A step further in genomic data equitable representation

Genomic studies have long been dominated by data from populations of EU ancestry, thereby limiting the relevance of findings for other ancestry groups. By integrating data from ancestrally diverse cohorts, the project enhances our ability to detect both shared and population-specific risk and protective variants, ultimately contributing to a more inclusive and globally relevant understanding of AD.²⁰

3.8 | Advances in precision and personalized medicine

READD-ADSP will drive progress in precision medicine by identifying ancestry-specific genetic risk factors, enabling tailored interventions. Moving beyond one-size-fits-all approaches based on European data, this shift promotes equity, enhances treatment efficacy, reduces side effects, and improves outcomes. Ultimately, precision medicine will become accessible to all, ensuring inclusive health care benefits.^{49–51}

3.9 | Collaborative successes and future directions

The project builds on collaborative models from AfDC and ADSP, demonstrating the feasibility of large-scale research through multidisciplinary partnership across African countries. These efforts integrate

genetics, neurology, neuropsychology, statistics, health education, and epidemiology.

Future goals include expanding cohort integration, improving data-sharing frameworks, and strengthening genomics and bioinformatics capacity in LMICs. While focused on AF, AA, and HL populations, future collaborations should extend to other underserved regions such as Asia and the Middle East, promoting global equity and accelerating translation of research into health benefits.

4 | CONCLUSION

The READD-ADSP initiative is a groundbreaking effort to diversify AD genetic research. By addressing disparities and ensuring equitable representation, it advances knowledge of AD across ancestries and supports precision medicine. Outcomes from this study will inform better diagnostics, therapies, and equitable global care. Through collaboration and community engagement, READD-ADSP sets a model for inclusive research in complex phenotypes.

AUTHOR CONTRIBUTIONS

Rufus Akinyemi conceptualized and developed the outline of the manuscript. Rufus Akinyemi and Olabode Omotoso wrote the first draft of the manuscript. Rufus Akinyemi, Olabode Omotoso, Lwera Kamada, David Ndeti, Michael Cuccaro, Albert Akpalu, Larry D. Adams, Stephen F. Sarfo, Alfred K. Njamnshi, Patrice Whitehead, Njideka Okubadejo, Mena Pedro Ramon, Albertino Damasceno, Scott Williams, Biniyam Ayele, Yared Zenebe, Thierry Adokounou, Jean Ikanga, Judith Boshe, Joshua Akinyemi, Olufisayo Elugbadebo, Reginald Obiako, Kolawole Wahab, Emmanuel Iwuozo, Kazeem Akinwande, Stella-Marie Paddick, Mayowa Ogunronbi, Christine Musyimi, Anyamele Ibuchim, Gabriel Ogunde, Motunrayo Coker, Olaleye Adeniji, Eniola Cadmus, Oladotun Olalusi, Timothy Ciesielski, Paul Nwani, Susan Halloran Blanton, Paul Olowoyo, Oluwadamilola Ojo, Rasaq Durodoye, Godwin Osaigbovo, Noeline Nakasujja, Mlaki Damas Andrea, Akinsola Ojagbemi, Godwin Ogbole, Temitope Farombi, Adefolakemi T. Ogundele, Azizi Seixas, Lawrence Adebusoye, Michelle Nichols, Ernest O. Nwazor, Nosakhare Osemwegie, Maeleen Guerchet, Farid Rajabli, Olufemi Olowookere, Jacob L. McCauley, Oyedunni Arulogun, Sudha Seshadri, Mayowa Owolabi, Guiseppe Tosto, Goldie Byrd, Richard Walker, Christiane Reitz, William Bush, Olusegun Baiyewu, Anthony J. Griswold, Brian W. Kunkle, Jonathan Haines, Rajesh N. Kalaria, Jeffery M. Vance, Adesola Ogunniyi, Margaret Pericak-Vance provided substantial intellectual inputs into, and revised drafts of the manuscript and approved the final version of the manuscript. MPV obtained funding for the READD-ADSP Study.

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CONFLICT OF INTEREST STATEMENT

The authors report no conflicts of interest. Any author disclosures are available in the [supporting information](#).

ETHICS STATEMENT

READD-ADSP is approved by the institutional review boards of each national study lead and participating sites.

DATA AVAILABILITY STATEMENT

Not applicable.

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SUPPORTING INFORMATION

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

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