Offspring Study of Racial and Ethnic Disparities in Alzheimer's Disease: Objectives and Design

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Running Title: Offspring Study of Alzheimer's Disparities

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Abstract

Alzheimer's Disease (AD) is a neuropathologically heterogeneous clinical syndrome, which disproportionately affects Non-Latinx Black and Latinx older adults. There are likely to be multiple mechanistic pathways to AD, and these pathways may be racially patterned and may account for racial/ethnic disparities in AD. Our research suggests that lifecourse social forces, such as discrimination, policy-driven investment in schooling, and early life SES are drivers of these different pathways and promote resilience or confer risk for cognitive decline. Intergenerational studies provide insight into these mechanisms so that we can inform preventive strategies and interventions to narrow disparities in cognitive decline and AD. The Offspring Study of Racial and Ethnic Disparities in Alzheimer's Disease began in 2017 to identify biological and sociocultural mechanisms of disparities in cognitive function among middle-aged people with and without a parent with AD. Partnering with the multi-ethnic, neighborhood-based Washington Heights Inwood Columbia Aging Project (WHICAP) study as the parent cohort, the Offspring study assesses neuropsychological, psychosocial, and medical function, reading level, health literacy, and bilingualism. Lifecourse social and environmental exposures are surveyed through, in part, lifetime residential, educational, and occupational histories. Participants provide blood for biomarker and genetic analysis, and structural and functional MRI neuroimaging and PET imaging of cerebral amyloid and tau pathology is conducted. This article outlines the objectives and design of this prospective cohort study aimed at advancing the understanding of risk factors among middle aged offspring in order to clarify pathways to AD, and provides background on recruitment and retention of this diverse cohort.

Key Words: Alzheimer Disease, Health Status Disparities, Minority Health, Cognitive Aging, Social Determinants of Health, Neuroimaging, Biomarkers

INTRODUCTION

Racial/Ethnic Disparities in AD

There are racial/ethnic disparities in AD prevalence^{1–11} and incidence^{12,13}; non-Latinx Black and Latinx older adults have elevated rates of clinical AD history of clinical AD (hereafter referred to as AD) compared with non-Latinx Whites^{14,15}. These racial disparities are more consistently observed in community-based studies than in clinic-based studies^{14,16–20}. The causal pathways of racial/ethnic disparities in risk for AD dementia are not well understood. The prevalence of many cardiovascular and demographic risk factors for AD is higher, and educational attainment lower, among African Americans and Latinxs than among Whites. Cardiovascular conditions such as hypertension, diabetes, insulin resistance, obesity/overweight, and hyperlipidemia^{21–29}, as well as cerebrovascular disease including stroke, silent infarcts, and white matter hyperintensities (WMH)³⁰ have also been associated with higher risk for developing cognitive decline and AD. Educational quality and quantity are associated with AD risk, independent of race^{21,23,24,26,31–36}. The contribution of these factors to risk of AD may differ across racial/ethnic groups. Indeed, secular trends reveal that later birth cohorts have lower AD risk, underrepresented racial/ethnic groups have not benefitted equally^{37,38}. There is evidence that social inequalities in early and midlife lead to vascular, inflammatory, and neurodegenerative changes, which in turn fuel disparities in cognitive aging and dementia. Studies that integrate biological, psychosocial, and clinical methods in diverse, representative cohorts are needed to understand the biopsychosocial causes of AD disparities.

AD Disparities must be studied before the age of 65

There are three primary lines of reasoning for studying AD disparities before the age of 65. First, the time from earliest pathological change to clinical AD can span over 20 years^{39,40}. This long preclinical phase is crucial for intervention and timely diagnosis⁴¹. Second, midlife health is associated with cognitive decline and AD in late life, which is particularly relevant for Black and Latinx people. Midlife vascular risk factors are associated with risk of incident dementia in all groups,⁴² but their impact differs by race/ethnicity. Systemic inflammation during midlife is associated with steeper memory decline⁴³, and with white matter damage, particularly in Black people, which, in turn, is associated with AD in late life^{44,45}. In fact, the strength of the relationship between late-onset AD and hypertension, diabetes, insulin resistance, obesity/overweight, and hyperlipidemia appears to be strongest if these risks are assessed in middle age^{21,31,32,46,47}. Black people show evidence of accelerated biological aging compared with Whites^{48–50}. Racial/ethnic differences in biological aging widen through midlife until late-life, when this gap narrows⁵⁰. Third, the mechanisms underlying late-life cognitive outcomes are difficult to study if samples are limited to old age because of bias related to differential survival⁵¹, particularly in Black and Latinx men.^{51–53} Prior studies with AD biomarkers have been limited by selection bias and small samples among non-White groups.^{30,31}

Intergenerational studies of the transmission of parental AD risk to their offspring can clarify pathways to AD

Risk of sporadic AD increases 4-10 times with a first-degree family history of AD^{54–56}. Family history is related to earlier dementia onset^{57,58}, to lower cognitive performance⁵⁹, and to biofluidic and neuroimaging AD biomarkers^{40,60–62}, amyloid and tau pathology⁶³, and cerebrovascular disease^{64–66}. However, the mechanisms underlying AD risk through heritability of environmental and health risk factors are not well understood^{67,68}. There is evidence that effect of family history differs across race/ethnicity, as familial risk of AD is higher among Black than White individuals⁶⁹.

Several studies of middle-aged asymptomatic offspring who report a parent with AD found impairments in multiple cognitive domains, including memory, visuospatial function, and language^{70,71}, measures of brain atrophy^{72–77}, amyloid burden in the brain⁷⁸, and brain metabolism⁷⁹; however, some studies have found weak or no relationships^{80–82}. Family history of AD was usually determined by self-report alone. Biomarkers were not consistently evaluated in parents, and familial aggregation of risk factors was not determined. Only few large-scale cohort studies have prospectively-collected data of both parental and offspring generations^{70,83–85} and most research on increased risk of family history of AD is performed among volunteer-based, well-educated, White parents and offspring.

In addition to familial risk, secular changes in AD risk should be considered to place the effects of family history on development of AD in context. Our group showed that later birth year is associated with better cognitive abilities and slower decline over time, but that these changes were attributable to increases in early childhood socioeconomic status (SES) and education³⁸. The impact of secular trends related to education, prevalence of risk factors, medical care and lifestyle factors can be clarified by comparing parent and offspring generations. There is evidence

that state and local investment in schooling, exposure to cognitively challenging tasks (through work or leisure activities), nutrition, economic status, and access and quality of health care may explain secular improvements in cognitive test performance among older adults.

Rationale for the Offspring Study

Research on middle-aged offspring of well-characterized older adults with and without AD is a powerful tool to identify biological pathways, early biomarkers, and genetic risk factors for AD. Intergenerational studies can identify the earliest changes in cognitive, brain, and blood biomarkers among asymptomatic children of people with AD, which can help inform the earliest sources of risk and be used as outcomes for interventions, or to identify people for clinical trials. As research and clinical diagnostic criteria for AD evolve, there is a growing consensus that the AD continuum is broader than previously thought⁸⁶, including clinical and pathological heterogeneity⁸⁷. Especially among Black and Latinx people, middle age is the ideal time to examine etiologies related to AD development; it is when impactful pathologies begin⁸⁸ and when risk factors have the greatest predictive power⁸⁹. There is evidence that there are different pathways to AD and cognitive impairment in old age that are patterned by race and ethnicity. Our research suggests that lifecourse social forces, such as discrimination and early life SES, are drivers of these different pathways. An intergenerational design provides insight into these mechanisms so that we may inform interventions to narrow disparities in cognitive decline and AD. Our data suggest that transmission of risk for cognitive decline and ADRD in Whites is mediated more by traditional AD-related neurodegenerative pathways than among Black and

Latinx people and that, conversely, inflammatory, vascular, and accelerated biological aging mechanisms may play a relatively greater role among Black and Latinx people. We are not proposing that AD is a different disease by race or ethnicity, but that social forces drive differential relative contributions of biological factors to the disease process.

In the Offspring study, race/ethnicity is used as a marker of risk, not as a risk factor or proxy for genetic variation^{90,91}. Following the multiple levels of analysis in the NIA Health Disparities Framework⁹², the design of the study incorporates measurement of structural racism, interpersonal experiences of discrimination, lifecourse educational and socioeconomic exposures, psychosocial function, medical conditions, and health behaviors.

The potential impact of the Offspring study is two-fold. First, integration of social forces and biological factors can lead to more rigorous standards for understanding the relationships between racially patterned risk factors and brain health. Second, data gathered in partnership with the community can inform and drive policy change to reduce disparities.

STUDY DESIGN

The procedures of this study are approved by the Institutional Review Board of Columbia University.

The Parent Cohort

The parental cohort is derived from participants in the Washington Heights/Hamilton Heights Inwood Columbia Aging Project (WHICAP) a multi-ethnic community-based, epidemiological study of aging and dementia in Northern Manhattan, NY (P01AG07232, R.

Mayeux, PI, R01AG037212 R. Mayeux, N. Schupf, Co-PIs, and RF1AG054023 R. Mayeux, PI). The Offspring Study leverages a well-characterized parent cohort, the Washington Heights Inwood Columbia Aging Project (WHICAP^{9,37,93,94}; XXXref), Parents were originally recruited in 1992, between 1999 and 2001, between 2009 and 2014, and beginning in 2017, ongoing recruitment maintains the current cohort at approximately 2000 older adults. Objective data from this parent generation, including incident AD diagnosis, cognitive function, cardiovascular disease, socioeconomic status, and brain imaging in a subset of participants are available for analysis. WHICAP parents are followed at approximately 24-month intervals with similar assessments at each interval. Each assessment wave includes an in-person interview of medical history, a physical and neurological exam, a neuropsychological battery, and an assessment of functional capacity. Historically, 8% of the non-demented participants develop dementia each year (93% of those with dementia are diagnosed with AD), annual mortality has averaged approximately 10%, and 80% return for follow-up at each follow-up wave. Follow-up rates do not differ by ethnicity or educational level, but mortality is highest for African American men and lowest for Latinx women. Blood for genetic and biomarker studies have been collected at multiple intervals. Since 2005, a total of 1,800 WHICAP participants have had MRI imaging (32% White, 33% Hispanic/Latinx, and 35% African American); currently, 350 have undergone repeat scans. A total of 161 WHICAP participants have undergone amyloid PET imaging. About 77% of participants have at least one child.

To date, we have successfully enrolled offspring from 872 WHICAP parents; Table 1 shows characteristics of the parents whose offspring were recruited. Average age at onset of AD was 81

years (23% were prevalent and 77% were incident AD). Established criteria were used to diagnose parents with AD⁹⁵ or MCI^{94,96,97}

Table 1. Characteristics of WHICAP Parent of Offspring Participants

	Parents with AD	Parents with MCI	Parents with normal cognition	X ² or F statistic	range
N	234	240	398		
Age	78.3	74.4	73.9	40.2***	63 - 103
% women	79%	78%	79%	0.188	
Race/Ethnicity				73.1***	
Latinx	84%	62%	52%		
Non-Latinx Black	11%	24%	27%		
Non-Latinx-White	5%	15%	18%		
# of children	5.0	3.9	3.4	32.2***	1 - 14
# Offspring participating	2.1	1.5	1.5	37.7***	1 - 10
Years of school	5.6	9.3	11.0	97.2***	0 - 20
% with HTN	75%	75%	69%	3.2	
% with diabetes	42%	30%	28%	13.1***	
Years of follow-up	8.6	7.4	5.7	22.9***	0 - 26
Dead	33.8	19.2	19.4	18.5***	

***p <.001

The Offspring cohort

Offspring are adult children of WHICAP participants, age 28 or older, fluent in English or Spanish, willing to donate a sample of blood, and willing to be followed longitudinally. To date, we have enrolled 1,469 Offspring. Table 2 displays the characteristics of Offspring at the time of the last data freeze (n=1,384). While almost 98% of the people who identify as Hispanic/Latinx in the parent cohort are primarily Spanish speakers, 32% of their offspring felt most comfortable in English. Compared to Spanish-speaking Latinx, the English-speaking Latinx were younger, had more years of school, were less likely to have a parent with AD, and were more likely to be assessed

remotely. Although we originally proposed three racial/ethnic groups to be the focus in the Offspring Study, we did not take into account this major source of heterogeneity within the Latinx group.

Table 2. Offspring Cohort Characteristics

	Non-Latinx White	Non-Latinx Black	Latinx Tested in English	Latinx Tested in Spanish	X ² or F statistic
N	139	245	321	679	
Age (mean)	56.1	56.1	51.0	59.6	35.9***
Gender (% female)	65	63	66	70	7.9
Years of school (mean)	16.7	13.9	13.9	10.9	149.9***
APOE E4 allele present (%)	29.4	39.1	26.0	26.9	7.5*
Parent with MCI (%)	31	30	24	25	4.9
Parent with AD (%)	7	16	22	49	168.3***
Parent yrs of school (mean)	14.6	12.9	8.2	5.6	360.6***
Parent with HTN (%)	42	75	76	78	74.4***
Parent with diabetes (%)	6	28	40	42	72.9***
Assessed remotely (%)	50	21	25	10	49.4***

Characteristics of Offspring MRI subsample. All participants are offered participation in the MRI aspect of the study. To date, we have successfully scanned 38% of the cohort (n=549). MRI participants were a random subset of the overall study cohort, with the goal of scanning one participant per family. Approximately 18% approached about MRI scanning indicated that they were not interested. Of those indicating interest, 12% were deemed ineligible based on initial screening. Of the participants who indicated that they were eligible and passed initial screening, we successfully scanned 84%. Compared with individuals who were not approached and not scanned, those who received MRI scans were younger (54.5±10.7 vs. 57.8±11.7, t=5.26, p<0.001), had a higher proportion of Black participants (21% vs. 14%) and lower proportion of White

participants (6% vs. 12%; $\chi^2=30.1$, $p<0.001$), but were similar in sex/gender distribution ($\chi^2=2.95$, $p=0.23$).

PROCEDURES

The Offspring Study Team

The majority of the staff is bilingual (English-Spanish) and bicultural (e.g., Dominican-American), and were born and raised in the area. We require prospective research assistants to undergo two to three weeks of training and certification to demonstrate their language fluency, abilities in the interview setting, and facility with standard procedures. During these weeks of training, a bilingual/bicultural neuropsychology postdoctoral fellow (MAR), under the supervision of senior neuropsychologists (JJM/AMB), assisted in training and supervision of standardized administration of the neuropsychological battery. Similarly, all staff members complete thorough training and certification on the administration of the medical evaluation and sociocultural questionnaires under the supervision of the study coordinator (MNM).

Recruitment

Offspring who agree to be seen for the study are scheduled for an in-person visit in their home or in an office on the campus of Columbia University Irving Medical Center to obtain informed consent and to determine whether inclusion/exclusion criteria are met. Participants are paid for their participation and costs incurred from travel to the testing site are reimbursed.

Language of Administration

Language of test administration is assessed at scheduling but can be modified once the participant is observed by a bilingual examiner. First, participants are contacted by an English-Spanish bilingual staff member to determine interest in participating in the study and for scheduling. Before administration of measures, our interviewers describe the cognitive testing and survey activities in general terms, and ask the participants to decide which language they would feel most comfortable using for the evaluation. This choice determines the language used for follow-up evaluations as well.

Community Engagement and Social Work Services

We encounter high levels of unmet medical, social, psychological, and financial needs among our participant population and their families. Emergent medical and psychosocial conditions are rarely encountered during the parent WHICAP study. It has been rare for WHICAP participants to have conditions such as dangerously high blood pressure and suicidality requiring emergency psychiatric care, to request help for dealing with domestic abuse or substance dependence, or to have difficulty scheduling visits due to recent loss of jobs or homelessness. Yet these examples are daily occurrences in the Offspring study. WHICAP parents are all covered by Medicare – in fact, they were recruited via CMS lists of Medicare beneficiaries. In contrast, many of their middle-age children have no medical insurance and are reluctant to seek medical follow-up when necessary because of concerns of financial burden; this situation has been further exacerbated by the COVID-19 pandemic.

To improve research engagement, and following the example of Dr. Lisa Barnes in the MARS Study at Rush University Medical Center⁹⁸, we successfully engaged bilingual staff with social work expertise in the Washington Heights community who provides culturally-tailored assessment and links to services among our participants, and developed culturally tailored family-based health education and outreach activities. Engagement of the offspring generation in research requires additional assessment of individual needs, experience with assigning levels of care and linkages for services, and consistent follow-up to ensure that participants are connected with culturally and linguistically appropriate social and medical services. The provision of culturally tailored information and support for basic life needs demonstrates reciprocal gain from participation in the study among WHICAP families, increasing research engagement among WHICAP families, increasing recruitment of all offspring within a family, and aiding retention over time.

The social worker has the opportunity to meet with every participant during or after their evaluation and makes house calls if needed. The social worker assesses the needs of each participant and assigns levels of care and determine linkages for services, ensuring that every participant is connected with appropriate services that are responsive to their financial and health insurance status. These encounters and connection to services are documented, tracked, and coded. The social worker has also tailored informational materials for our research staff, including social services and COVID-19 specific services guides, and collaborate with the recruitment specialist to design community engagement activities. Social work engagement enriches the participatory experience, leading to stronger community engagement and partnership. Ultimately, the effort improves recruitment and retention, maximizes the quality

and fidelity of the data collected, and leads to greater trust and partnership between the investigators and community.

Measures

Race and ethnicity

Race and ethnicity are self-identified, using methods identical to the according to the Precision Medicine Initiative All of Us Research Program (PMI-AURP; Precision Medicine Initiative Working Group Report⁹⁹. Participants self-identify racial and ethnic categories that apply to them (i.e., American Indian or Alaskan Native, Asian, Black or African American or African, Hispanic/Latino or Spanish, Middle Eastern or North African, Native Hawaiian or other Pacific Islander, and White). Participants will also select from any subgroup within each of the race/ethnic identification above (e.g., South African, Costa Rican, Jamaican, Mexican, Senegalese).

Sex and Gender

Information on sex (e.g., male, female, intersex/other) and gender (e.g., man, woman, transman, transwoman, genderqueer/gender non-conforming, different, identified as: [specify]) are also collected.

Educational Experience

The following variables are assessed separately for elementary, high school, and post-high school phases of education: years completed, age or date of first year attended, location, name of school, setting (public vs. private), class size, and estimated ethnic composition of student body and teachers. Participants are asked whether they were ever “left back or had to repeat a grade”, and whether they completed a GED. For those born in the US, information on per pupil

expenditures, teacher salaries, pupil/teacher ratios, and length of school year have been obtained^{100–106} by state, and where available by county, city, and district.

Family history

Family History has already been collected from the parent cohort, but we extend and enrich the information in offspring. The structured interview¹⁰⁷ queries about family structure, birth order, vital status, education, history of cognitive impairment, dementia, and other medical, neurologic and psychiatric disorders among first-degree relatives.

Lifetime Socioeconomic Status

Measures of childhood SES include: maternal and paternal education and occupation, childhood financial hardship, subjective childhood SES¹⁰⁸, and number of siblings (this information is collected directly from both parents and children). Current SES is determined via collection of income, assets, debts, and material hardship¹⁰⁹ data. Occupational history. We collect information about longest-held job: job title, duties, and start and end year, and industry type. These data are used to determine a Standard Occupation Code¹¹⁰, which is linked to U.S. Department of Labor Occupational Information Network (O*NET)¹¹¹, which can be used to derive indices of job characteristics such as substantive complexity and interpersonal communication.

Residential History

The location (city, state) of all the places lived for at least 1 year and ages at each move from birth to study enrollment are recorded. Current residential address is documented and verified over the follow-up period, geocoded to latitude and longitude, and then can be assigned to census tracts or linked to databases with neighborhood level SES indicators like the Area Deprivation Index¹¹².

Social Network Size and Social Support

Current social situation (e.g., marital/partner status, with whom the participant resides) is collected. Participants are asked how many children, friends, and other relatives they talk to at least once a month¹¹³. Total network size will be calculated by summing these items¹¹⁴. *Social Support*. Emotional and Instrumental Social support will be measured using the Social Provisions Scale¹¹⁵, the 3-item UCLA Loneliness Scale¹¹⁶, and the Social Support Scale from the NIH Toolbox Emotion Battery.

Positive and Negative Psychosocial Factors

Depressive symptoms in the past week are assessed with the CES-D¹¹⁷. The DSM 5 Cross-Cutting Symptom measure^{118,119} is used to measure symptoms of depression, anger, mania, anxiety, somatic symptoms, sleep disturbance, psychosis, obsessive thoughts/behaviors, suicidality, and substance use. Life satisfaction¹²⁰, positive well-being¹²¹, self-esteem¹²², and perceived control¹²³ are assessed.

Experiences of Discrimination and Vigilance

Everyday discrimination is assessed with a modified version of the Everyday Discrimination Scale^{124,125}. This 10-item scale asks participants about experiences of general interpersonal mistreatment such as “You are treated with less respect than other people” and “You are treated as if you are not smart” over the course of the last 12 months. Responses to each item are rated on a 1 to 4 scale (1 = never, 2 = rarely, 3 = sometimes, 4 = often). Each item/example of mistreatment does not refer to race/ethnicity, gender, or other individual characteristics and thus has been validated for use among participants of many ethnic and educational backgrounds^{126–129} and has excellent internal consistency and convergent and divergent validity^{126,130}.

Major experiences of discrimination are determined by asking about perceived discrimination and experiences of violations of civil rights¹²⁴. This 9-item scale includes items such as “Do you think you have ever been unfairly fired or denied a promotion?” and “Have you ever been unfairly discouraged by a teacher or advisor from continuing your education?” Participants are asked when the last time each event happened (1 = within the last week, 2 = within the last month, 3 = within the last year, 4 = more than a year ago), and how many times each event happened in their lifetime. Finally, the perceived reason for this experience is assessed (1 = ancestry/national origins, 2 = gender, 3 = race, 4 = age, 5 = height/weight, 6 = skin color, 7 = other). The Vigilant Anticipatory Coping measure¹³¹ assesses racism-related vigilance.

Stress and Lifetime Trauma

The Perceived Stress measure from the NIH Toolbox is administered. Participants are asked whether they experienced any of 12 potentially adverse events before the age of 18¹¹⁴. We added a COVID-19 questionnaire in May 2020 that examines health, financial, housing, and psychosocial events that participants may be facing due to the pandemic.

Bilingualism

The Offspring study presents a unique cohort to characterize bilingualism and investigate its associations to cognition and neuroanatomical structures. The parental cohort are primarily immigrants and generally reside within the Washington Heights and Inwood neighborhoods within Northern Manhattan. These neighborhoods are rich in bilingual experiences due to multi-generational homes, and the community businesses and services are available in both English and Spanish. Bilingualism is assessed with both self-report and objective measures. Self-reported bilingualism is obtained through a Language History Questionnaire (LHQ). The LHQ represents a

modified and expanded version of the Bilingual Language Profile (BLP). The Offspring LHQ measures language history (i.e., age of exposure and acquisition, number of exposed languages, method of acquisition), language use (i.e., frequency of use across different contexts, language dominance), language proficiency (i.e., reading, writing, speaking, understanding), frequency of code-switching, and language attitudes (i.e., “it is important to me to use English like a native speaker”, “it bothers me when speakers mix languages”). The Offspring LHQ is available in both English and Spanish and allows for endorsing more than 2 languages (i.e., multilingualism). A subsample of the participants is administered the 68-item Multilingual Naming Test (MINT; Gollan et al., 2012), a well-validated objective measure of bilingualism. The administration of the extended MINT consists of presenting the participant with the items (6 per page) and asking them to name as many as possible in their dominant language, and then in their non-dominant language. Through the extended MINT one can compute bilingualism indices (i.e., degree of bilingualism, language dominance), correlates strongly with self-report and language surveys (Gollan et al., 2012), and is only administered to participants that identify as Latinx in both English and Spanish.

Neuropsychological Examination

Offspring participants undergo an extensive neuropsychological evaluation as part of their study visit. The neuropsychological battery is comprised of elements from three standardized and validated batteries: the WHICAP neuropsychological battery (Stern, 1992; Siedlecki 2010), the University of Washington’s National Alzheimer’s Coordinating Center battery (NACC; Weintraub 2018), and the NIH Toolbox (NIHTB; Gershon et al., 2013; Weintraub, et al., 2013). These three batteries were combined in order to compliment domains already being assessed in the WHICAP

study (i.e., memory, language, visuospatial functioning) and provide a more comprehensive assessment of other cognitive domains (executive functioning) as well as an assessment of motor and sensation functioning.

The WHICAP neuropsychological test battery has been validated (Stern et al., 92), administered over 16,000 times in Spanish and English since 1992, and used in hundreds of analyses and publications. This battery continues to be administered to parents at each assessment wave. The NACC neuropsychological battery was developed as part of the of Uniform Data Set (UDS) data collection protocols used across NIA-Alzheimer's Disease Centers (ADC) designed to differentiate between normal cognition, mild cognitive impairment (MCI), and dementia among adults over the age of 60, and has undergone three revisions (Weintraub et al., 2018). The NIH Toolbox was developed with a similar goal to collect information on aspects of neurologic and behavioral function in a uniformed manner among individuals spanning the age range from 3 to 85 years (Gershon et al., 2013). The WHICAP, NACC, and NIH Toolbox batteries have been translated and validated for use among Spanish-speakers^{132–134}.

The cognitive battery includes measures of **learning and memory** (the Selective Reminding Test¹³⁵, Craft Story Memory¹³⁶, and Benson Complex Figure Delayed Recall¹³⁷), **visuospatial ability** (Benson Complex Figure Copy¹³⁷) **language** (Multilingual Naming Test¹³⁸, Controlled Oral Word Association Test¹³⁹, Category Fluency Test¹⁴⁰, NIH Toolbox Vocabulary), **psychomotor speed** (Color Trails Test, Part 1¹⁴¹, WAIS-R Digit Symbol subtest¹⁴², and NIH Toolbox Pattern Comparison¹⁴³) and **executive functioning** (NIH Toolbox Flanker and Dimensional Change Card Sort¹⁴³, Color Trails 2). **English and Spanish reading level** is assessed using the NIH Toolbox Oral Reading Recognition Test¹⁴⁴, the WRAT-IV¹⁴⁵, and the Word Accentuation Test^{146,147}. Table X

lists each of the neuropsychological tests by cognitive domain. The Color Trails Test was selected instead of the Trail Making Test (TMT) because it is more appropriate for this population, many of whom do not have enough knowledge of the alphabet for satisfactory completion of TMT Trial B^{141,148}. Additionally, we have included an additional letter to the verbal fluency tasks in order to match the measure given in the WHICAP study (i.e., from F/L only to C/F/L). Lastly, we have included the 12-item Brief Smell Identification Test¹⁴⁹ which was developed as an abridged test of olfaction and validated across cross-cultural settings.

Medical history interview and physiological and anthropometric measures

The medical/neurological examination records current weight, height, visual acuity with and without glasses, hearing impairment with and without a hearing aid, and systolic and diastolic BP. Extrapyramidal signs are rated^{150–152}. Reproductive history is recorded for women and men. Current medications, vitamin, and nutritional supplement use are queried. Presence of physician-diagnosed conditions, such as hypertension, diabetes, elevated cholesterol, cancer, myocardial infarction (MI) or angina, other heart disease, stroke, transient ischemic attack (TIA), migraine, arthritis, thyroid disorder, osteoporosis, chronic obstructive pulmonary disease (COPD), seizure, HIV infection, head injury with loss of consciousness, depression, anxiety, neurological illness including Parkinson's disease and AD is queried. We use WHO diagnostic criteria for stroke¹⁵³ and collect information on individual symptoms of stroke and TIA. History of head injury, smoking, alcohol abuse, and use of anti-inflammatory drugs is queried. For each condition named, we ascertain age at onset, duration, treatment history and whether there has been any change in the last 12 months. Self-reported sleep quality is recorded using the Pittsburgh Sleep Questionnaire¹⁵⁴.

Depression and neuropsychiatric status

Depressive symptoms in the past week are assessed using the 30-item Center for Epidemiologic Studies Depression (CES-D) scale¹⁵⁵. Neuropsychiatric status was measured with the self- and informant-based DSM 5 Cross-Cutting Psychiatric Symptom Measures^{118,119}. The Cross-Cutting Measures, which can be administered online, have been demonstrated to be a valid, reliable, brief, adaptive instrument designed to assess all major domains of psychopathology with good psychometric properties¹¹⁹.

Daily Function and Subjective Cognitive Complaints

The Disability and Functional Limitation Instrument is^{156,157} and contains self- and observer ratings in instrumental activities, personal self-maintenance activities, perceived difficulty with memory, mobility, and activities and social participation¹⁵⁸. The Clinical Dementia Rating^{159,160} score is used to rate impairment caused by cognitive dysfunction. Participants are administered 3 different questionnaires that measured subjective cognitive complaint (SCC): (1) the self-report version of the Everyday Cognition (E-Cog) scale^{161,162}, which contains 6 domain-specific factors that include Everyday Memory, Language, Visuospatial Abilities, Planning, Organization, and Divided Attention; (2) the Memory Functioning Questionnaire¹⁶³ (MFQ), which is divided into several subscales that include the General Frequency of Forgetting, Seriousness of Forgetting, Retrospective Functioning, and Mnemonics Usage; and (3) participants were administered a set of 7 questions that were adapted from the Structured Telephone Interview for Dementia Assessment¹⁶⁴ (STIDA). Research staff is trained in the administration based on the Washington University protocol¹⁵⁹.

Diagnostic endpoints

Diagnosis of MCI and dementia are established by a review of all available clinical information (i.e., neuropsychological, medical, neurological, and functional but not including radiological data). A consensus group of expert diagnosticians review available data to assign a research diagnosis. Diagnosis of MCI is based on Petersen criteria as it has been adapted and validated for this diverse, community-based setting^{94,97}. Diagnosis of all-cause dementia is based on standard criteria² and dementia subtype is based on research criteria for AD², Lewy body dementia¹⁶⁵, vascular dementia¹⁶⁶, etc.

Structural MRI

A subset of participants undergoes brain MRI acquisition on a Siemens 3 Tesla scanner. The MRI protocol acquires data in a single 1.25 hour session that has been generally tolerated well. Table 3 displays the MRI acquisition protocol used in Offspring for primary imaging outcome measures and those that are part of ancillary or secondary efforts.

Table 3. MRI sequences proposed for the current study. Primary MRI outcomes will be derived with the first three sequences. Sequences shaded in grey are collected as part of ancillary or exploratory studies.

Sequence	TE/TR (ms)	Voxel size (mm)	Flip angle (degrees)	Acquisition time	Resolution (mm ³)	Slice thickness (mm)
3DT1	2.26/2300	1x1x1	8	5:21	192x256x256	1
FLAIR	387/5000	.4x.4x.9	n/a	5:42	192x512x512	0.9
SWI	20/27	.9x.9x1.5	15	6:13	104x232x256	1.5
DTI	70/5500	2x2x2	n/a	7:16	51x114x114	2
MRS	20/200	30x20x20	90	4:26	n/a	n/a
T2 TSE	74/6650	.4x.4x2	n/a	6:47	448x448x41	2
ASL	13.36/4600	1.9x1.9x4	n/a	5:36	36x128x128	4
MRA	3.42/21	.3x.3x.5	18	5:33	136x696x768	0.5
Resting State	30/2040	2x2x3	90	10:24	37x94x94	3

Primary neuroimaging outcome variables include regional volumetry and cortical thickness; regional white matter hyperintensity volume; presence, number, and region of cerebral

microbleeds; and number and distribution of infarcts. Regional cortical thickness/volumetry. Measures of regional brain volume and cortical thickness are derived with FreeSurfer (<http://surfer.nmr.mgh.harvard.edu/>). We also derive regional diffusion metrics, metabolite concentrations, regional blood flow, resting state connectivity, hippocampal subfield anatomy, perivascular spaces, and large vessel morphology.

PET Scanning

A subset of 150 offspring participants undergoes amyloid and tau PET scans (within 4 months of each other) on a Siemens Biograph mCT PET scanner. This subset must also be willing and eligible for MRI. As with the MRI, our staff will be available throughout the PET scan procedure to provide support, reduce anxiety, optimize the comfort of the subject and remove the subject from the machine if requested.

First, an intravenous (IV) catheter is placed, followed by slow bolus injection (over 10-20 sec) of ^{18}F -Florbetaben (fibrillar amyloid- β plaques) or ^{18}F -MK6240 (hyperphosphorylated tau in paired helical filaments). The amyloid scans are acquired in 5-minute frames from 50-70 minutes post-injection, while the tau scans are acquired in 5-minute frames from 80-110 minutes post-injection in order to reach pseudo-equilibrium. A low-dose CT scan is also acquired in the Siemens Biograph mCT PET scanner at the time of each PET scan for attenuation correction of annihilation photons. PET data are also corrected for radioactive decay, scanner normalization, detector deadtime, and random or scatter events.

T1-weighted brain MRIs are used for anatomical localization of the amyloid and tau PET signal. Briefly, dynamic PET frames are aligned to the crude mean of all frames. The structural T1 in FreeSurfer space is co-registered to the participant's mean PET image. PET data are quantified

as the standard uptake value ratio (SUVR), using PET data at pseudo-equilibrium for each radiotracer and an inferior cerebellar gray matter reference region (derived from FreeSurfer).

Analyses for amyloid includes regions involved in Thal phasing of amyloid plaque deposition at autopsy in cases with AD (citation). A visual rating method similar to that of Barthel and colleagues¹⁶⁷ is used for the visual classification of amyloid- β deposition as amyloid negative or amyloid positive. Analyses for tau includes regions involved in Braak staging of neurofibrillary tangle deposition at autopsy in cases with AD.

Follow-up

Longitudinal follow-up of this offspring cohort will be important to further illuminate mechanisms of disparities. From the Dominantly Inherited Alzheimer Network³⁹ (DIAN) study in which the parental age of dementia onset can be used to reliably predict the offspring age of dementia onset, hippocampal volume changes do not begin until approximately 15 years prior to dementia, while memory changes do not begin until approximately 5-10 years prior to dementia. Given that dementia onset due to AD occurs in late life (4% <65 years old, 16% 65-74 years old, 44% 75-84 years old, 37% >85 years old)¹⁶⁸, we can expect to observe changes in amyloid and tau, which begin decades prior to dementia onset, but not changes in neurodegeneration or cognition. As a result, the recruitment plan was structured so that there will be sufficient sample size and power for a 5-year follow-up, taking conservative estimates of attrition into account.

DISCUSSION

There is a critical need to identify people at risk for developing AD before they are symptomatic, or at the preclinical phase. There have been several groundbreaking studies, such

as the Wisconsin Registry for Alzheimer's Prevention, Adult Children Study, BIOCARD, and Framingham, that have identified cognitive and other markers among asymptomatic people at higher familial risk for AD. The Offspring Study is unique due to its enrollment of large numbers of middle-aged Latinx and African American offspring of educationally and racially/ethnically diverse parents, allowing for increased knowledge about groups who are at higher risk for cognitive decline and racial differences in etiologic pathways to AD. WHICAP parents have been diagnosed detailed in-person assessment, longitudinal cognitive data, risk factors, and date of onset, and most with dementia were incident cases during the course of their follow-up, allowing for more precise age-at-onset dates and risk factor information collected prior to dementia onset.

Mechanisms of disparities are difficult to study if samples are limited to age 65 and older because several factors attenuate the relationships of these risk factors with AD when measured in old age. Our group found that racial disparities in cognitive function narrow with age due to selective survival. In addition, there is increasing evidence for the importance of cardiovascular and cerebrovascular risk factors for AD, but these relationships appear to be strongest when cardiovascular factors are measured in middle age. The stronger association between mid-life risk factors and later life AD may be because AD pathology begins in the brain decades before the onset of clinical symptoms. This is particularly relevant for studying racial disparities in AD because cardiovascular risk factors are more prevalent and have an earlier age of onset among minorities, in whom the potential influence of inflammatory, accelerated aging, and cardiovascular factors on the development of AD may take place at an earlier age.

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