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## RESEARCH ARTICLE

# Representativeness of samples enrolled in Alzheimer's disease research centers

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## Abstract

To generalize findings on the mechanisms and prognosis in Alzheimer's disease and related dementias (ADRD), it is critical for ADRD research to be representative of the population. Sociodemographic and health characteristics across ethnoracial groups included in the National Alzheimer's Coordinating Center sample (NACC) were compared to the nationally representative Health and Retirement Study (HRS).

Baseline NACC data ( $n = 36,639$ ) and the weighted 2010 HRS wave ( $N = 52,071,840$ ) were included. We assessed covariate balance by calculating standardized mean differences across harmonized covariates (i.e., sociodemographic, health).

NACC participants were older, more educated, with worse subjective memory and hearing, but endorsed fewer depressive symptoms compared to HRS participants. While all racial and ethnic groups in NACC differed from HRS participants in the same way overall, these differences were further amplified between racial and ethnic groups. NACC participants do not represent the U.S. population in key demographic and health factors, which differed by race and ethnicity.

## KEYWORDS

Alzheimer's disease centers, generalizability, racial/ethnic disparities, recruitment

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## HIGHLIGHTS

- We examined selection factors included in NACC studies compared to a nationally representative sample.
- Selection factors included demographic and health factors and self-reported memory concerns.
- Results suggest that NACC participants are not representative of the U.S. population.
- Importantly, selection factors differed across racial and ethnic groups.
- Findings are suggestive of selection bias within NACC studies.

## 1 | INTRODUCTION

By 2050, it is anticipated that 12 million people in the United States will have Alzheimer's disease and related dementias (ADRD).<sup>1</sup> In an effort to clarify mechanisms and identify optimal treatment targets, many public-private partnerships have been created to promote the sharing of ADRD data.<sup>2</sup> These multi-site collaborations and data repositories aim to expand our understanding of the factors associated with ADRD risk, onset, and progression by facilitating larger scale analyses of ADRD clinical and pathological factors than any one site could achieve alone.

Due to rising rates of racial and ethnic disparities in ADRD, future rates of ADRD cases are projected to increase most in minoritized groups.<sup>3</sup> Comprehensive data indicate the prevalence of known ADRD risk factors (e.g., cardiovascular disease, lower educational attainment) disproportionately impact Black and Latinx populations compared to their non-Latinx White counterparts.<sup>4,5</sup> Despite this, underrepresentation of diverse populations in large scale studies of aging persists, bringing the generalizability of ADRD literature into question.

The National Alzheimer's Coordinating Center's (NACC) Uniform Data Set is an example of a large multi-site collaboration that collects rich cognitive and biomarker data that is publicly available.<sup>6-8</sup> Studies using NACC data have been critical to the ADRD field by influencing the latest NIA-AA Research Framework for AD,<sup>9</sup> as well as providing support for racial/ethnic differences in dementia prevalence and presentation,<sup>10</sup> neuropathologic burden,<sup>11</sup> and ADRD biomarkers.<sup>12,13</sup> While these studies have demonstrated key racial and ethnic differences in AD-related predictors and outcomes, they have not examined if the multi-site participant sample comprehensively reflects the demographic makeup of the national population. Delineating the similarity/dissimilarity of the NACC participants to a nationally representative sample of older adults is critical to understanding whether estimates obtained from clinical and biological studies can be accurately applied to a larger target population.

Recent studies utilizing NACC data have demonstrated that factors related to selection for enrollment into studies (i.e., selection factors), such as enrollment strategies and knowledge of family history of dementia, influence ADRD outcomes of interest. A recent study demonstrated that healthy controls recruited from a clinic setting

showed a steeper rate of progression and a higher risk of developing mild cognitive impairment (MCI) compared to those recruited from the community.<sup>14</sup> Another study found that referral source (i.e., clinic vs. community) and prior knowledge of family history of dementia attenuated racial differences in incident MCI.<sup>15</sup> To clarify how racial and ethnic disparities impact aging and ADRD and the magnitude of these effects on incidence and progression, we must better understand how large, multi-site study samples reflect the U.S. population. Determining which sociodemographic and health factors influence participation in clinical research can provide insight into sources of possible bias in large ADRD studies.

In this study, we compared NACC participants to the nationally representative Health and Retirement Study (HRS) sample. The HRS is a study of mortality and health among adults aged 51 and older.<sup>16</sup> By leveraging the nationally weighted HRS data, we sought to compare participants enrolled in the NACC to the U.S. population and determine how these groups differ in key sociodemographic (e.g., age, education, race, and ethnicity) and health (e.g., cardiovascular disease, memory concerns) selection factors. As such, throughout the paper we refer to the nationally representative weighted HRS sample as "U.S. population". Due to reported differences in study design and recruitment strategies between the NACC and HRS, we hypothesized that compared to the older adult U.S. population, NACC participants would be younger, with higher educational attainment and fewer depressive symptoms, and they would endorse worse subjective cognition. Given known racial and ethnic disparities in ADRD research recruitment strategies,<sup>17,18</sup> we also hypothesized minoritized racial and ethnic groups would be underrepresented compared with non-Latinx White NACC participants relative to the older adult U.S. population.

## 2 | METHODS

### 2.1 | Data sources

#### 2.1.1 | NACC

Data from the NACC Uniform Data Set (UDS) were used in this study (data extracted on 09/07/2021). NACC data consist of over 40,000

participants from the 30+ past and present Alzheimer's Disease Core Centers and Alzheimer Disease Research Centers (collectively referred here as ADRCs) funded by the National Institute on Aging.<sup>19</sup> NACC data are described as a case series; there is marked heterogeneity across ADRCs in terms of recruitment, clinical focus, and target populations. Data were collected from 2005 to 2021 by supporting ADRCs. We analyzed baseline visit data for all Latinx, non-Latinx White, and non-Latinx Black participants who were at least age 60 at their initial visit. We selected 60 as our age cut-off due to the higher prevalence of atypical Alzheimer's disease presentations before that age.<sup>20</sup> Similarly, we excluded participants with genetic causes of dementia (autosomal dominant AD mutations, frontotemporal lobar degeneration mutations, Huntington's disease, Down syndrome). These criteria allowed for a total analytic sample of 36,639 individuals (Figure S1).

### 2.1.2 | HRS

Data from the Health and Retirement Study (HRS) 2010 wave were used as the population-representative sample. We chose the 2010 HRS wave as our target population for a couple of reasons. First, 2010 is near the middle of the enrollment period for the NACC data used in this analysis, making it a reasonable "benchmark" year. Second, the 2010 HRS wave is larger than adjacent waves because it included a replenishment sample, which allows us to produce more precise estimates. The HRS (funded by the National Institute on Aging and the U.S. Social Security Administration) is a longitudinal cohort of community-dwelling U.S. adults age 51 and older and their spouses that seeks to examine economic, health, and demographic factors related to aging.<sup>21</sup> HRS was designed to be representative of all community-residing adults in the contiguous United States and included supplemental oversamples of Latinx and Black individuals. We restricted the HRS sample to Latinx, non-Latinx White, and non-Latinx Black participants who were at least 60 years old at their 2010 visit to parallel the NACC data. We excluded HRS participants with a 2010 HRS sampling weight of zero (indicating non-respondents, including those who died, and participants living in nursing homes), resulting in a final analytic sample of  $n = 12,074$  (Figure S1).<sup>22</sup> We applied HRS sampling weights to weight the 2010 HRS up to the non-institutionalized adult U.S. population ages 60+ (weighted  $n = 52,071,840$ ).

## 2.2 | Harmonized selection factors

We harmonized NACC and HRS data using several sociodemographic and health variables comparable across datasets, allowing us to evaluate differences across studies. The following sections summarize our harmonization approach; Table S1 provides additional details.

### 2.2.1 | Sociodemographic factors

Variables included self-reported race and ethnicity (non-Latinx White, non-Latinx Black, Latinx), sex/gender (female, male), age (continuous

### RESEARCH IN CONTEXT

- 1. Systematic Review:** The authors thoroughly reviewed the literature using PubMed. Recent studies using National Alzheimer's Coordinating Center (NACC) data have demonstrated that selection factors (i.e., recruitment strategies, family history of Alzheimer's disease [AD]) can influence AD and related dementias (ADRD) outcomes. It is unclear the extent to which these selection factors impact the representativeness of NACC participants compared to the broad U.S. population.
- 2. Interpretation:** Overall, standardized mean differences showed older age, higher educational attainment, more subjective memory concerns, and more hearing difficulties were strong selection factors into NACC. Importantly, these selection factors differed across racial and ethnic groups. Findings therefore suggest that NACC participants are not representative of the U.S. population across key sociodemographic and health factors.
- 3. Future Directions:** Future studies should assess whether differences in the sociodemographic makeup of the NACC may bias interpretation of ADRD risk factors and outcomes. Studies should also consider mitigating these sources of bias through inclusive recruitment efforts across Alzheimer's Disease Centers to improve generalizability.

years), educational attainment (continuous years), and marital status (married/living as married vs. not). As previously noted, these sociodemographic factors have been associated with both ADRD risk and participants' decisions to enroll in ADRC studies.<sup>14,15,23,24</sup>

### 2.2.2 | Health factors

We examined self-reported history of hypertension or high blood pressure, diabetes or high blood sugar, and hearing/visual functioning. These comorbidities may exclude potential participants from entry into clinical trials.<sup>25,26</sup> Harmonized history of hypertension/high blood pressure ("hypertension") and diabetes/high blood sugar ("diabetes") measures were derived as "Recent/active" or "Remote/inactive" ("yes" in HRS) versus "Absent" in NACC ("no" in HRS). Hearing and vision functioning variables were derived from multiple questions in NACC indicating "functionally normal" hearing/vision (with hearing aid[s] or corrective lenses, if subject uses them) versus "not functionally normal" hearing/vision. HRS participants rated their hearing and vision on a 5-point scale ranging from "poor" to "excellent." The HRS variable was dichotomized with "poor" responses (and "legally blind" for vision) representing difficulties with vision/hearing to be harmonized with NACC respondents reporting their hearing/vision was not functionally normal.

### 2.2.3 | Depressive symptoms

Mood symptoms may also influence selection into NACC studies (e.g., via exclusion criteria related to psychiatric conditions or reduced willingness of potential participants with depression).<sup>26,27</sup> To assess depressive symptoms, NACC included the Geriatric Depression Scale—Short Form (GDS).<sup>28</sup> Scores range from 0 to 15 and higher scores indicate more depressive symptoms. HRS questionnaires included eight items from the Center for Epidemiologic Studies Depression Scale (CES-D), with higher scores indicating more depressive symptoms.<sup>29</sup> A harmonized elevated depressive symptoms measure (yes vs. no; defined as moderate to severe for GDS, and evidence of clinical depression for CES-D short form) was derived using each scale's cut-off score for clinically concerning symptoms ( $\geq 9$  for GDS scores and  $\geq 4$  CES-D scores).

### 2.2.4 | Subjective cognition

Subjective ratings of cognitive function were also a factor of interest due to evidence supporting difference in rates of help-seeking, as well as conversion rates of those with concerns of memory decline.<sup>14</sup> NACC asked respondents to report a decline in memory relative to previously attained abilities (yes vs. no), and HRS asked respondents to rate their memory at present using a 5-point scale. The HRS variable was dichotomized to match the NACC response type by treating “poor” and “fair” responses as endorsement of a decline in memory functioning.

## 2.3 | Missing data

Multiple imputations with chained equations and predictive mean matching<sup>30</sup> was implemented to address covariate missingness, which ranged from 0%-7.3% in NACC and 0%-6.5% in HRS (Table S2).

## 2.4 | Statistical analysis

Descriptive statistics included unweighted means and frequencies in the NACC sample, and weighted means and frequencies in the HRS sample weighted up to the 2010 U.S. population age 60+. To assess differences between the samples, standardized mean differences ( $[\text{mean}(\text{NACC}) - \text{mean}(\text{HRS})] / \text{SD}(\text{HRS})$ ) were calculated for NACC vs. weighted HRS overall and stratified by race and ethnicity. Standardized mean differences greater than +0.25 or less than -0.25 were considered strong selection factors into NACC.<sup>31</sup> However, because standardized mean differences are continuous and multiple threshold values are used, we also discuss relative strengths of standardized mean differences across covariates. Analyses were conducted in R version 4.0.4 with *twang* and *mice* packages.<sup>32,33</sup> Code for this project is available online: <https://github.com/t-mmoble/ADC-sample-representativeness>.

## 3 | RESULTS

Compared to the weighted HRS 2010 sample, NACC participants were older, more likely to be female, with more years of education, and more likely to report subjective cognitive concerns. NACC was also more racially and ethnically diverse than the weighted HRS (8.5% Latinx and 13.7% non-Latinx Black vs. 7.7% and 9.7% in weighted HRS, respectively). Additionally, NACC participants were less likely to report history of hypertension, diabetes, and depressive symptoms compared to the weighted HRS. Lastly, 34% of NACC participants had a diagnosis of dementia at baseline.

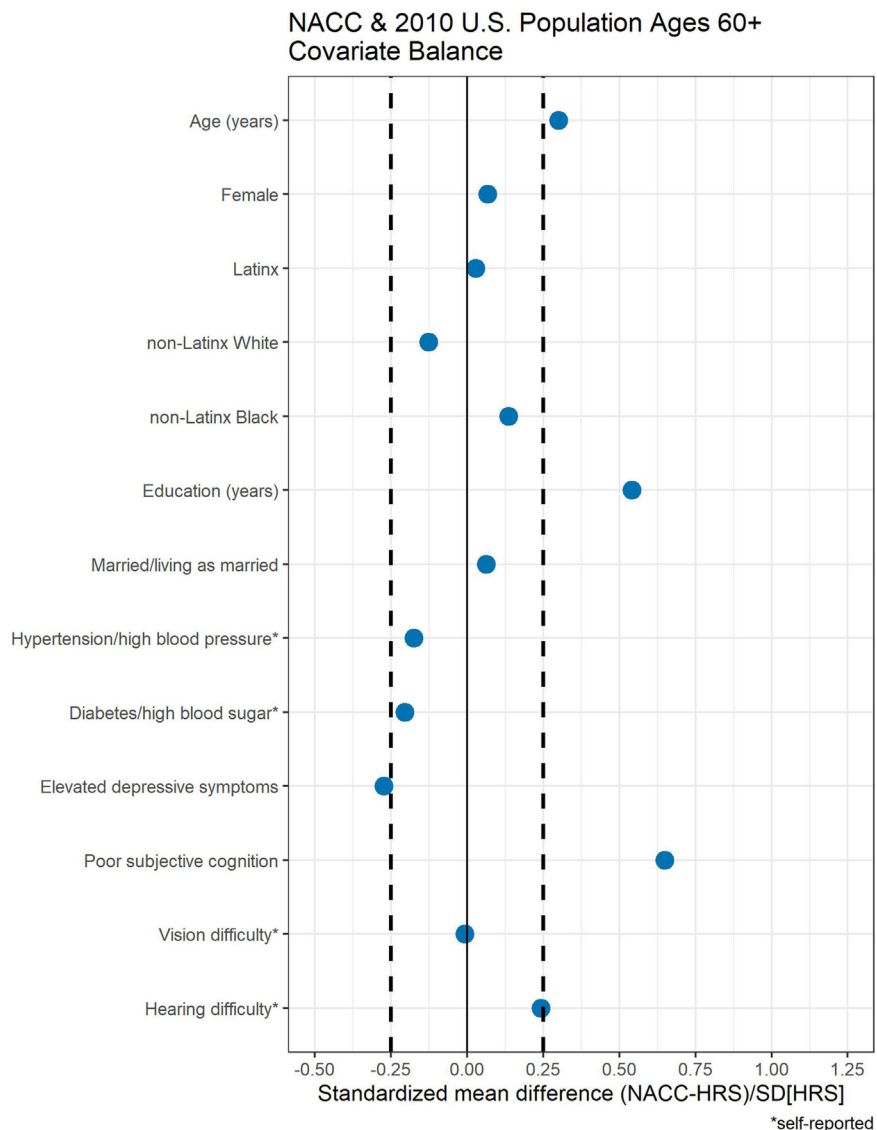
Standardized mean differences between NACC and weighted HRS overall suggested older age, higher educational attainment, worse subjective cognition, greater hearing difficulties, and absence of self-reported depressive symptoms were strong selection factors into NACC (Figure 1). Self-reported history of hypertension and diabetes were less common in NACC compared with weighted HRS, though standardized mean differences were smaller.

Stratified analyses suggested that all racial and ethnic groups in NACC were older, with higher years of education, worse subjective cognition, and absence of self-reported depressive symptoms compared to the weighted HRS sample (Figure 2). Older age was a stronger selection factor among Latinx and non-Latinx Black NACC participants compared to non-Latinx White NACC participants. Higher educational attainment and subjective cognition were stronger selection factors among non-Latinx White NACC participants compared to non-Latinx Black and Latinx NACC participants. Differences from HRS-derived expectations for hearing difficulty were slightly greater for non-Latinx Black NACC participants, and differences for depressive symptoms were greater for Latinx and non-Latinx Black NACC participants compared with differences for non-Latinx White NACC participants. Conversely, differences in lower self-reported cardiovascular risk factors were greater for non-Latinx White NACC participants compared to Latinx and non-Latinx Black NACC participants.

## 4 | DISCUSSION

The advent of large, multi-site studies and data sharing repositories has improved the ADRD research community's ability to address disease-specific questions using well-powered, multi-modal study designs. Important questions have been raised, however, regarding the representativeness of participant samples and the generalizability of results across racial and ethnic groups. We examined selection factors overall and across race/ethnicity included in the NACC compared to the 2010 nationally representative weighted sample of adults age 60+ in the HRS in order to make inferences to the U.S. population more broadly. NACC participants were typically older and more likely to have higher educational attainment, reported worse subjective cognition as well as greater hearing difficulties, but were less likely to report depressive symptoms and cardiovascular risk factors compared to the U.S. older adult population. When looking within each racial and ethnic

**FIGURE 1** Covariate balance (standardized mean differences) between National Alzheimer's Coordinating Center (NACC) and the Health and Retirement Study (HRS) overall.

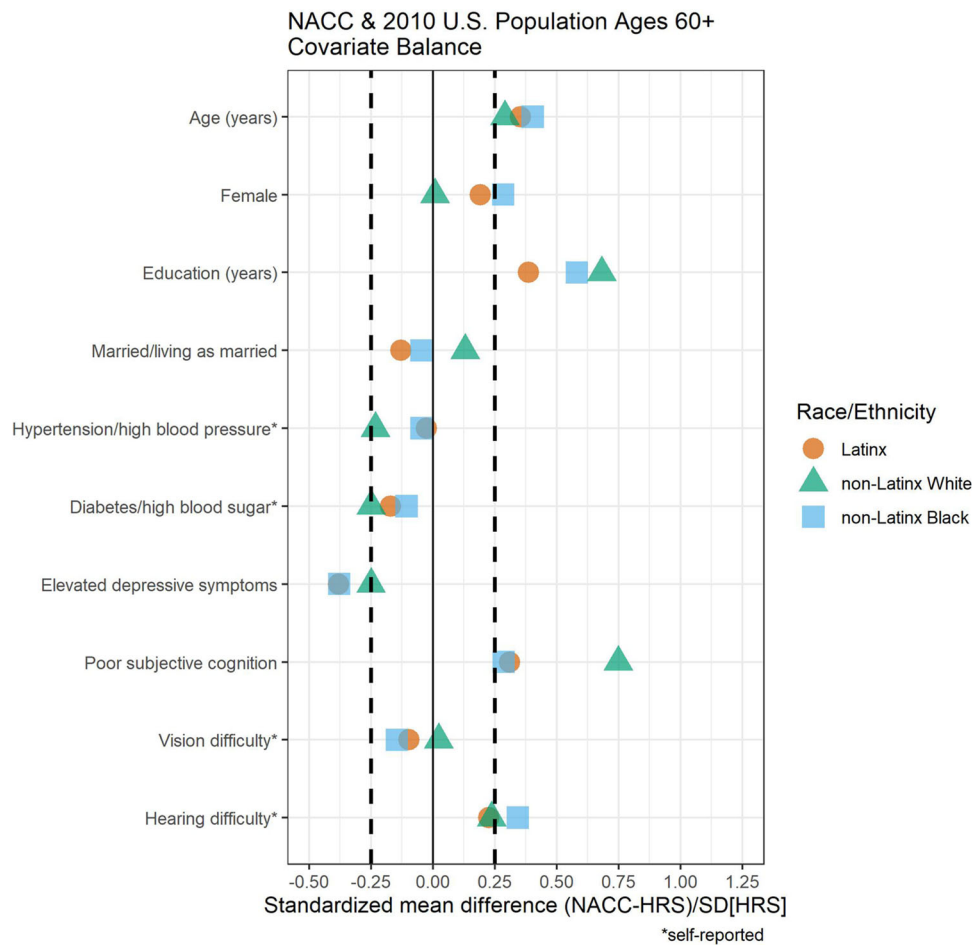


group, standardized mean differences for age were larger for Latinx and non-Latinx Blacks compared to non-Latinx White participants. Furthermore, Latinx and non-Latinx Black NACC participants reported fewer depressive symptoms compared to their national population counterparts. In contrast, differences between educational attainment, subjective cognition, and cardiovascular risk factors were larger for the non-Latinx White participants relative to all other groups when compared to the U.S. population. Overall, our study suggests that NACC participants diverged from the U.S. population in several sociodemographic and health factors. However, it is important to explore each of these factors in detail to better understand their associations with study participation, AD RD risk and resilience, and late-life cognitive decline.

The presence of older age, worse subjective cognition, and higher prevalence of self-reported hearing difficulties is not surprising given that a goal of ADRCs is to study cognitive decline and AD RD and these three factors are associated with increased risk of AD RD.<sup>34</sup> The mechanistic link and directionality between sensory impairment

and cognitive decline remains poorly understood. While there may be shared biological pathways and common etiologies that tie AD RD to sensory loss, studies have indicated that social (e.g., increased loneliness, isolation), mood (e.g., depression), cardiovascular (e.g., reduced physical activity), and neuroanatomical (e.g., diminished input into critical functional networks) factors may serve as underlying mediators of the observed association between sensory loss and cognitive decline.<sup>35,36</sup>

NACC participants had higher levels of education relative to the U.S. population which aligns with the body of evidence indicating a positive association between years of formal education and participation in clinical and biomarker research studies.<sup>37</sup> Generally, higher education is associated with higher socioeconomic status, increased health literacy, and optimal healthcare access and utilization.<sup>38</sup> These socioeconomic factors associated with education may increase the possibility that older adults engage with healthcare facilities such as those in which the ADRCs are generally housed. Additionally, lower educational attainment is associated with increased barriers to engage



**FIGURE 2** Covariate balance (standardized mean differences) between National Alzheimer's Coordinating Center (NACC) and the Health and Retirement Study (HRS) stratified by race/ethnicity.

with healthcare and to participate in research overall.<sup>39</sup> Differences in educational attainment between populations may potentially bias our understanding of AD/DRD disease progression since the relationship between years of formal education and cognitive outcomes in late life is complex. Several studies have reported increased dementia risk with lower education level.<sup>40</sup> Higher education may provide a buffer against cognitive decline, particularly in earlier disease stages; however, once cognitive reserve is "depleted" and more extensive and severe atrophy is present, higher education has been linked to a more rapid cognitive decline.<sup>41,42</sup> These considerations are important when interpreting clinical outcomes in large aging studies. Future studies should determine whether these findings suggest bias toward participants having higher cognitive reserve and, in turn, being further along the AD disease continuum compared to a national population. Moreover, the NACC is currently developing a social determinants of health module with which to characterize in greater detail these socioeconomic factors. Future studies could leverage these additional socioeconomic variables to replicate these analyses to fully tease the associations between education and healthcare utilization. Given the sociocultural, environmental, and economic implications of education level, our understanding of the modifying role of education on symp-

tom severity and progression is likely limited given the narrow level of education represented in research.

Differences between the NACC participant sample composition and the national population were further magnified when appraising how selection factors differ across racial and ethnic groups. We found that differences in age, depressive symptoms, and hearing difficulties were larger among Latinx and non-Latinx Black participants compared to non-Latinx White participants. These results suggest that Latinx and non-Latinx Black participants in NACC were much older and reported fewer depressive symptoms compared to their U.S. population counterparts, and the non-Latinx Black NACC participants had greater hearing difficulties than their U.S. representative Black counterparts. While differences in these factors were also observed among the non-Latinx White participants, the magnitude of these differences was larger among these racial and ethnic groups. Conversely, while all racial/ethnic groups had higher educational attainment and more cognitive concerns compared to the U.S. population, this difference was stronger among the non-Latinx White participants, suggesting that non-Latinx White participants had even higher years of education and worse self-reported cognition compared to their national population counterparts.

**TABLE 1** Characteristics of NACC and 2010 HRS analytic samples.

	NACC (N = 36,639)	HRS (N = 12,074)
Age, years (mean [SD])	74.2 (8.0)	71.5 (8.8)
Female (%)	56.7	53.4
Race/ethnicity (%)		
Latinx	8.5	7.7
non-Latinx White	77.9	82.6
non-Latinx Black	13.7	9.7
Married/living as married (%)	64.2	61.2
Education, years (mean [SD])	14.5 (2.9)	12.8 (3.1)
Hypertension/high blood pressure (%)	53.2	61.7
Diabetes/high blood sugar (%)	13.6	22.2
Elevated depressive symptoms (%)	3.6	12.7
Poor subjective cognition (%)	57.7	28.4
Self-reported vision difficulty (%)	6.0	6.2
Self-reported hearing difficulty (%)	11.9	6.1

Note: Characteristics are averaged across 20 multiply imputed samples. HRS percentages are shown weighted to be representative of the 2010 adult US population aged 60+.

Abbreviations: HRS, Health and Retirement Study; NACC, National Alzheimer's Coordinating Center.

These differences in the distribution of AD RD risk (i.e., older age, subjective cognition, hearing problems) and protective factors (i.e., higher educational attainment, fewer depressive symptoms) across ethn racial groups may impact the inferences and generalizability of study findings. Similarly, these differences in sociodemographic and health factors can limit our understanding of the differential vulnerability to and resilience against AD RD within racial and ethnic groups. For instance, education may not confer the same degree of resilience across racial and ethnic groups<sup>43,44</sup> and environmental factors such as air pollution are associated with disproportionate AD RD risk among minoritized groups.<sup>45</sup> Although Black and Latinx populations are more likely to be adversely impacted by known risk factors for AD RD (e.g., cardiovascular disease, lower educational attainment) compared to their White counterparts; current and projected future prevalence of AD RD disproportionately impact these racial and ethnic groups.<sup>4,5</sup> Despite systematic population differences in known determinants of health, very few studies have examined how well diverse populations are represented in studies of AD RD. It is important to note that simply evaluating percentages (Table 1) might be misleading given that these metrics suggest that NACC could be considered unexpectedly more racially and ethnically diverse than the weighted HRS data (i.e., national population; NACC 14% non-Latinx Black vs. 10% in weighted HRS). However, when moving beyond simple percentage comparisons and more deeply examining the demographics and health characteristics across racial and ethnic groups, the strength of selection factors varied markedly. Thus, although the ethn racial composition of a participant sample may mirror demographic percentages of the national

population, that does not mean that the participants are representative of the national population as our study results suggest.

Our findings demonstrate the need to increase efforts for inclusive recruitment strategies to ensure adequate representation across and within racial and ethnic groups. Raman et al. (2021) demonstrated that site-specific, rather than centralized, recruitment strategies were most successful in recruiting Black, Latinx, and Asian participants for a preclinical AD trial, whereas White participants were more likely to be recruited via media advertisement.<sup>46</sup> Site-specific strategies may involve recruitment from internal sources (e.g., other studies, internal clinic referrals, local research registries) and community outreach. Increased trust established through community engagement is likely central to increasing AD RD research representation of marginalized communities. AD RCs across all sites may consider mitigating sources of selection bias by increasing community engagement through community lectures and presentations at local health centers, conferences, churches, and health fairs and establishing community/participant advisory boards to help guide recruitment and involve the community at all stages of research.<sup>18,46,47</sup>

Dedicated funding to increase diversity and representativeness in AD RCs may also be helpful. As of this publication, all AD RCs are in major urban centers in the United States, with coastal metropolitan regions housing several AD RC sites. Entire regions of the country, however, are represented by having a single AD RC within hundreds of miles. For example, the only AD RC in the Great Plains regions is presently only in the Kansas City metropolitan area: <https://www.nia.nih.gov/health/alzheimers-disease-research-centers>. The location of AD RCs can make it impractical for eligible participants to participate in AD RC studies and, consequently, be included in the NACC database. Moreover, other racial/ethnic groups (e.g., Asians, Indigenous Americans) are not well represented in the NACC. This limits our full understanding of the impact of AD RD across diverse populations. For instance, a recent study leveraging diverse and representative healthcare data of older adults residing in northern California found differences in dementia incidence between racial and ethnic groups such that Asian-American had the lowest risk compared to all other groups.<sup>48</sup> Efforts should be dedicated to not just increase recruitment of these underrepresented populations, but to develop study materials and normative data needed for diagnosis of adults with diverse languages and cultural backgrounds.

A critical factor to consider is that the NACC UDS is designed as a case series, but typically analyzed as a cohort sample. Each site is permitted to use different enrollment criteria that fit with their individual AD RC aims, goals, and budget, which may change over time and with each renewal cycle. Efforts could be directed toward creating a unified inclusion/exclusion criteria across sites. Enrollment criteria should consider selection factors, like those identified by the present study, that may disproportionately exclude minoritized groups. Prospective standardized collection and reporting of key sociodemographic factors<sup>49</sup> across sites would further help characterize selection factors and improve generalizability of results from large datasets like NACC. Future studies should also consider leveraging transportability methods such as weighting and outcome modeling aimed at generalizing



findings to external populations.<sup>50–53</sup> These methods have important assumptions that limit their applicability, but there is some recent work in aging samples.<sup>53</sup> Last, future work evaluating updated recruitment strategies will also want to consider the impact of major historic events on research recruitment and enrollment, like the COVID-19 pandemic. This may be particularly salient to questions related to selective sampling into studies given how the pandemic has exacerbated racial/ethnic health disparities.<sup>54</sup>

Our retrospective study displayed numerous strengths, including the appraisal of a large, widely used, and well-phenotyped database (NACC) and a nationally representative sample (HRS). By characterizing key racial and ethnic differences in selection factors, our study provides an important foundation for future investigations to assess whether these factors ultimately affect –and to what degree– estimates for clinical risk factors, biological and diagnostic outcomes, and rates of symptom progression in ADRD. There are also several limitations that are important to consider. To assess covariate balance across NACC and the weighted HRS data, harmonization of several key variables was conducted. While this is a necessary and well-established method for comparing studies with distinct surveys/questionnaires, it remains possible that some measures may reflect slightly different aspects of a construct. It is also noteworthy that we did not have access to some sociodemographic factors that are known to impact ADRD outcomes (e.g., socioeconomic status). As such, it is likely there are other important convergent and/or divergent characteristics of these samples that could not be adequately assessed in the current study.

In summary, results suggest that participants in NACC are not representative of the U.S. population in key sociodemographic and health factors. Compared to the national population, NACC participants were typically older and more highly educated, reported worse self-reported cognition but fewer depressive symptoms, and endorsed fewer vascular risk factors. Moreover, these selection factors differed across racial and ethnic groups. As large multi-site data are becoming more readily available and used to develop conceptual frameworks for ADRD diagnosis and care, it is incumbent upon the field to assess for and mitigate selection factors through inclusive recruitment efforts. Selection factors that influence enrollment and retention in large scale studies can adversely impact the generalizability of study results to broader populations due to inaccurate estimates and impact co-enrolling studies that use ADRC cohorts for recruitment purposes; as such, it is critical to assess the degree to which these factors may bias current findings and conceptualizations of ADRD clinical and biological outcomes.

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## CONFLICT OF INTEREST STATEMENT

Author disclosures are available in the [supporting information](#).

## CONSENT STATEMENT

All HRS participants provided written informed consent, and all study procedures were approved by the University of Michigan institutional review board. Regarding NACC participants, all contributing ADRCs are required to obtain informed consent from their participants and maintain their own separate IRB reviews and approvals from their institutions prior to submitting data to NACC.

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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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