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Diagnostic Accuracy and Differential Associations Between Ratings of Functioning and Neuropsychological Performance in Non-Hispanic Black and White Older Adults

Lisa V. Graves[a,b], **Emily C. Edmonds**[a,b], **Kelsey R. Thomas**[a,b], **Alexandra J. Weigand**[c], **Shanna Cooper**[a,b], **Ariana M. Stickel**[d], **Zvinka Z. Zlatar**[b], **Alexandra L. Clark**[a,b], **Mark W. Bondi**[a,b]

[a]VA San Diego Healthcare System, San Diego, CA, USA

[b]Department of Psychiatry, University of California San Diego, La Jolla, CA, USA

[c]San Diego State University/University of California San Diego Joint Doctoral Program in Clinical Psychology, San Diego, CA, USA

[d]Department of Neurosciences, University of California San Diego, La Jolla, CA, USA

Abstract

Objective: We recently demonstrated that relative to consensus-based methods, actuarial methods may improve diagnostic accuracy across the continuum of cognitively normal (CN), mild cognitive impairment (MCI), and dementia in the overall National Alzheimer's Coordinating Center (NACC) cohort. However, the generalizability and comparative utility of current methods of diagnosing MCI and dementia due to Alzheimer's disease and related disorders (ADRD) are significantly understudied in non-Hispanic Black (NHB) older adults. Thus, we extended our previous investigation to more specifically explore the utility of consensus-based and actuarial diagnostic methods in NHB older adults.

Method: We compared baseline consensus and actuarial diagnostic rates, and associations of ratings of functioning with neuropsychological performance and diagnostic outcomes, in NHB (n=963) and non-Hispanic White (NHW; n=4577) older adults in the NACC cohort.

Results: 60.0% of the NHB subsample, versus 29.2% of the NHW subsample, included participants who met actuarial criteria for MCI despite being classified as CN or impaired-not-MCI per consensus. Additionally, associations between ratings of functioning and neuropsychological performance were less consistent in NHB participants than in NHW participants.

Conclusions: Our results provide evidence of differential degrees of association between reported functioning and neuropsychological performance in NHB and NHW older adults, which may contribute to racial group differences in diagnostic rates, and prompt consideration of the

Please address correspondence to: Mark W. Bondi, PhD, ABPP/CN, Psychology Service (116B), VA San Diego Healthcare System, 3350 La Jolla Village Drive, San Diego, CA 92161, USA. Phone: (858) 552-8585 Ext. 2809; mbondi@health.ucsd.edu.

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strengths and weaknesses of consensus-based and actuarial diagnostic approaches in assessing neurocognitive functioning in NHB older adults.

Keywords

mild cognitive impairment; dementia; Alzheimer's disease and related disorders; non-Hispanic Black older adults; diagnostic approaches

Black individuals comprise the second largest racial/ethnic minority group in the U.S. and are projected to outpace the growth of the non-Hispanic White (NHW) population in coming decades (with estimated increases of 172% for Black individuals versus 75% for NHW individuals by 2060; Bernstein, 2015; Colby et al., 2017; Matthews et al., 2019). Moreover, Black adults are twice as likely as NHW adults to develop Alzheimer's disease (AD) and related dementias (ADRD; Matthews et al., 2019; Mayeda et al., 2016; Potter et al., 2009; Rajan et al., 2019; Steenland et al., 2015). Given these current and projected estimates, significant efforts are needed to increase the representation of Black participants in ADRD research, which remains largely based on NHW samples, in an effort to promote brain health equity in the Black population (Dotson & Duarte, 2020).

Racial disparities in ADRD have been linked to a number of health, sociocultural, and environmental inequities driven by systemic racism. For example, greater cardiovascular disease burden, poorer educational quality, and neighborhood disadvantage help to explain racial differences that contribute to increased prevalence of ADRD among Black participants (Barnes & Bennett, 2014). However, our understanding of the epidemiology and clinical presentation of ADRD has been further complicated by a lack of understanding of the extent to which commonly utilized methods of ADRD diagnosis—primarily developed on racially homogenous samples—generalize to more racially/ethnically diverse groups (Chin et al., 2011). Thus, there is an essential need to critically examine the utility of current methods of diagnosing MCI and dementia due to ADRD in the Black population, and to identify culturally-informed and -appropriate diagnostic approaches, which in turn may help to optimize the treatment, health, and well-being of Black individuals at risk for ADRD.

Actuarial diagnostic methods (e.g., the use of regression-based norming to generate demographically-adjusted *z*-scores on neuropsychological tests [i.e., to account for factors such as age, sex/gender, and education, shown to influence neuropsychological performance in older adults; van Hooren et al., 2007], coupled with criteria contingent upon patterns of *z*-scores within and across cognitive domains to classify cognitive status) have been shown to improve diagnostic accuracy, predict progression, and strengthen AD biomarker associations in individuals with MCI or dementia in several large-scale, racially homogenous cohort studies of cognitive aging (Bondi et al., 2014; Edmonds et al., 2016; Graves et al., 2020; Jak et al., 2009; Thomas et al., 2019). These studies suggest that conventional or other consensus-based diagnostic methods (e.g., those implemented by the Alzheimer's Disease Neuroimaging Initiative [ADNI; Petersen & Morris, 2005; Petersen et al., 2010] and the National Alzheimer's Coordinating Center [NACC; Beekly et al., 2007; Morris et al., 2006; Weintraub et al., 2009; Weintraub et al., 2018]) that incorporate clinician judgment, subjective complaints of cognitive and functional decline, and cognitive and functional

screening measures (and in some cases, a single memory score) may be prone to diagnostic errors.

Our group recently reported evidence for the diagnostic utility of actuarial methods across the continuum of cognitively normal (CN), MCI, and dementia due to ADRD in the NACC cohort (Graves et al., 2020). We found that approximately one-third (34%) of participants classified as CN and more than one-fifth (22%) of participants diagnosed with dementia per NACC consensus met actuarial criteria for MCI (these were thought to reflect possible false negative MCI and false positive dementia cases, respectively). Additionally, many participants with consensus MCI diagnoses appeared to represent possible diagnostic errors in that they were classified as CN or diagnosed with dementia per actuarial criteria (these were thought to reflect possible false positive MCI and false negative dementia cases, respectively). Actuarial diagnoses were corroborated by group comparisons of apolipoprotein E (APOE) ε4 carrier status. Specifically, groups that shared the same actuarial diagnosis, despite having different consensus diagnoses, had comparable percentages of ε4 carriers. Moreover, scores on the CDR® Dementia Staging Instrument (a global assessment tool that is based in part on clinician judgment [rather than purely on objective performance] and therefore open to some degree of subjectivity) were more consistent with consensus diagnoses than with performance on comprehensive neuropsychological testing and corresponding actuarial diagnoses. Taken together, these findings suggested that actuarial methods may enhance diagnostic accuracy relative to consensus-based methods across the continuum of CN, MCI, and dementia due to ADRD (Graves et al., 2020).

While our actuarial diagnostic methods statistically adjusted for race/ethnicity in previous analyses (Graves et al., 2020), we did not directly assess whether the degree of consensus and actuarial diagnostic agreement/discrepancy differed across racial/ethnic groups, nor did we explore factors that might have contributed to any observed differences in diagnostic agreement/discrepancy across racial/ethnic groups. Further, a notable limitation of actuarial diagnostic methods is that the existing corpus of studies demonstrating their utility is largely based on findings within NHW samples. Furthermore, the actuarial approach is purely data-driven, leaving open the impact of other (e.g., sociocultural) factors that are not always well-captured but may be pertinent in the diagnosis of MCI or dementia in racially/ethnically diverse groups. Taken together, whether the utility of actuarial diagnostic methods generalizes to non-Hispanic Black (NHB) older adults and other racially/ethnically diverse samples currently remains unclear.

Reported concerns of cognitive and functional decline are a key component of conventional and other consensus-based methods of MCI and dementia diagnosis. Notably, in both research and clinical settings, consideration of functional capacity is essential for differentiating between MCI and dementia (e.g., the Diagnostic and Statistical Manual for Mental Disorders, 5th Edition [DSM-5] states that major neurocognitive disorder [i.e., dementia] involves significant decline in one or more cognitive domains that interferes with the ability to independently carry out daily activities). However, research has yielded inconsistent support for a relationship between reported cognitive and functional difficulties and performance on comprehensive neuropsychological testing (Edmonds et al., 2014;

Edmonds et al., 2018; Lenehan et al., 2012; Thomas et al., 2019). While few studies have examined these relationships in primarily NHB samples, those that have suggest that reported cognitive concerns are not necessarily associated with neuropsychological (e.g., memory) performance in these groups (Jackson et al., 2017; Sims et al., 2011). Additionally, emotional factors including depressive symptoms have been shown to contribute to higher ratings of cognitive and functional difficulties (Edmonds et al., 2014). While several large epidemiologic studies have reported lower prevalence of mental health disorders in NHB individuals than in NHW individuals (Burnett-Zeigler et al., 2018), other studies suggest that individuals from racial/ethnic minority groups experience more chronic and disruptive psychiatric distress (Breslau et al., 2006; Williams et al., 2007), and are exposed to unique stressors (e.g., systemic racism and discrimination) that independently predict negative health outcomes. Thus, exploring the potential influence of emotional factors when examining relationships between reported functioning and neuropsychological performance in NHB samples is imperative.

Research suggests that experiences and meanings associated with dementia vary across cultural groups, which in turn can contribute to heterogeneity in reporting of changes or difficulties with various aspects of daily living (Barnes & Bennett, 2014; Chui & Gatz, 2005; Dilworth-Anderson & Gibson, 2002; Mis et al., 2019; Rovner et al., 2013). In a recent study of participants with MCI in the NACC cohort, Hackett et al. (2020) found that after controlling for participant age, sex, cognition, and depression, Black informants reported significantly lower Functional Activity Questionnaire (FAQ) scores (reflecting better ratings of functioning) compared to informants of other racial backgrounds. Similarly, Tappen et al. (2010) found that compared to European-American and Hispanic-American individuals, African-American and Afro-Caribbean individuals had nominally lower mean FAQ scores, although these differences did not reach statistical significance. However, it is worth noting that the aforementioned analyses by Hackett and colleagues focused specifically on participants with MCI, and did not include a direct examination of whether FAQ scores varied by *participant* race. In our recent study of consensus and actuarial diagnostic agreement/discrepancy in the NACC cohort (Graves et al., 2020), we incorporated FAQ scores into our actuarial criteria as an index of daily functioning specifically to help differentiate between MCI and dementia. However, we did not directly assess whether ratings of functioning, nor the degree to which reported functioning corresponded with neuropsychological performance and diagnostic outcomes, differed across racial groups.

In the present study, we extended our previous investigation to examine whether baseline consensus and actuarial diagnostic rates, and associations of ratings of functioning with neuropsychological performance and diagnostic outcomes, differed for NHB and NHW older adults in the NACC cohort. Given evidence in the literature of potential racial/ethnic differences on reporting of cognitive and functional difficulties as well as on associations between reported functioning and neuropsychological performance, we hypothesized that differential associations between ratings of functioning and neuropsychological performance would be observed with the NHB and NHW subsamples. This differential association may help to (at least partly) explain any observed differences in the degree of consensus and actuarial diagnostic agreement/discrepancy across the two subsamples.

Method

The NACC Uniform Data Set (UDS) was implemented in 2005 by the National Institute on Aging (NIA) Alzheimer's Disease Research Centers (ADRCs) program with the intention of longitudinally assessing cognitive and other clinical changes in MCI and dementia due to ADRD (e.g., frontotemporal lobar degeneration, Lewy body disease). Consent is obtained at the individual ADRCs, as approved by individual Institutional Review Boards (IRBs). As determined by the University of Washington Human Subjects Division, the NACC database itself is exempt from IRB review and approval because it does not involve human subjects, as defined by federal and state regulations. The present study utilized data from Version 3.0 of the UDS, collected at baseline visits conducted across 32 ADRCs from March 2015 to March 2021 (alz.washington.edu). The study was conducted in accord with the Helsinki Declaration of 1975.

Participants

There were 5540 total participants in the present study, including 963 NHB (17.4% of total sample) and 4577 NHW (82.6% of total sample) adults aged 50 years or older (M_{age} = 70.24 years, SD_{age} = 8.13; 61.6% female, 38.4% male; $M_{education}$ = 16.28 years, $SD_{education}$ = 2.51). Both NHB and NHW participants were represented across all 32 ADRCs. All study participants: (1) completed at least 6 years of formal education; (2) reported English as their primary language; (3) underwent neuropsychological testing in English; (4) completed all neuropsychological and functional measures required (see below) to render reclassification of baseline cognitive status using actuarial diagnostic methods; and (5) had data available regarding their referral source and family history of cognitive impairment (Gleason et al., 2019).

Diagnostic Methods

NACC Consensus Diagnostic Method—The NACC UDS includes: demographic information; history of medical conditions and medication use; clinical and neurological examination findings; behavioral and functional measures (e.g., FAQ); clinical ratings of dementia severity (CDR); and neuropsychological test scores. Clinician judgment is based on a review of all available information. Clinical diagnosis (CN, impaired-not-MCI [defined by the NACC as cognitive impairment that neither fully meets MCI criteria nor represents normal aging; Beekly et al., 2004], MCI, or dementia) is made by the evaluating physician or a consensus team, and this process varies according to each ADRC's protocol (e.g., use of informal NACC-derived norms [published mean/standard deviation values], algorithm-based approaches and normative calculators, or local norms; Beekly et al., 2007; Morris et al., 2006; Weintraub et al., 2009; Weintraub et al., 2018).

Actuarial Diagnostic Method—A regression-based norming approach using data from participants identified in the NACC UDS as those who maintained a consensus diagnosis of CN across all ADRC visits was used to transform neuropsychological raw scores into *z*-scores adjusting for demographic variables (age, sex/gender, education) as well as enrollment factors (referral source [personal (e.g., self, family, friend), professional (e.g., clinician or clinic-based), other (e.g., community-based), unknown]; family history

of cognitive impairment [no, yes, unknown]) that have been shown to influence observed differences between NHB and NHW NACC participants in MCI and dementia incidence (Gleason et al., 2019). Norming was conducted separately for the NHB and NHW subsamples, given that the NHB reference group (n=562) had significantly lower scores than the NHW reference group (n=2470) on all neuropsychological measures (ps < .001; see Table 1 for descriptive statistics associated with neuropsychological performance in the NHB and NHW normative reference groups; note: primary analyses were also stratified by racial group when appropriate). Criteria for assigning actuarial diagnoses were then applied (see Table 2). These criteria were adapted from guidelines put forth by Jak et al. (Bondi et al., 2014; Jak et al., 2009) and incorporated performance on comprehensive neuropsychological testing as well as ratings of daily functioning on the FAQ. A neuropsychological z-score was considered reflective of impairment if it fell more than one standard deviation below the corresponding adjusted normative mean. FAQ scores of 6 or higher were considered indicative of significant functional impairment in differentiating between MCI and dementia (Teng et al., 2010).

Neuropsychological and Functional Measures

Raw neuropsychological test scores were derived from measures available in the NACC UDS Version 3.0, encompassing domains of: (1) verbal memory (Craft Story Immediate Recall, Craft Story Delayed Recall, Benson Complex Figure Recall); (2) language (Multilingual Naming Test [MINT], Category Fluency [sum of Animals and Vegetables trials], Letter Fluency [sum of F and L trials]); (3) attention (Trail Making Test [TMT] Part A, Number Span Forward); and (4) executive functioning/processing speed (TMT Part B, Number Span Backward, Benson Complex Figure Copy). TMT scores were transformed to be reverse-scored such that higher numbers reflected better performance, consistent with other neuropsychological measures examined in the present study. (Note: while there is inherently some degree of overlap in the neuropsychological tests that were considered in assigning NACC consensus diagnoses and those that were incorporated into the actuarial method for reclassifying cognitive status, there is no standard application of these tests in assigning consensus diagnoses.)

Ratings of functioning were derived from the FAQ and CDR. The FAQ is an informant-based measure that assesses an individual's level of independence (with higher scores reflecting worse ratings of functioning, or higher dependence) with respect to various daily activities, including managing finances (e.g., paying bills, managing financial records), shopping, playing games, cooking (e.g., using kitchen appliances, meal preparation), keeping track of current events, paying attention, remembering dates, and traveling (Pfeffer et al., 1982).

The CDR characterizes six domains of cognition and daily functioning, including memory, orientation, judgment and problem solving, community affairs, home and hobbies, and personal care (Morris, 1993). The information required to assign a rating in each domain is obtained through a semi-structured interview of the patient and a reliable informant (if available). Each rating is ultimately assigned by the evaluating clinician (and is therefore based in part on clinician judgment). While global CDR and CDR Sum of Boxes (CDR-SB)

scores are highly related, CDR-SB scores encompass a wider range of values to provide a more detailed, quantitative general index of cognition and functioning, and have increased utility in tracking changes within and between stages of dementia severity (Berg et al., 1988; Lynch et al., 2006; O'Bryant et al., 2008). Thus, CDR-SB scores were deemed more suitable for analysis in the present study. CDR scores were available on all study participants.

Both the FAQ and CDR showed high levels of internal consistency, in the whole study sample (Cronbach's alpha = .94 for FAQ and .92 for CDR), and within the NHB (Cronbach's alpha = .93 for FAQ and .87 for CDR) and NHW (Cronbach's alpha = .94 for FAQ and .92 for CDR) subsamples. Moreover, FAQ and CDR-SB scores showed strong correlations within the NHB ($r = .84$, $p < .001$) and NHW ($r = .88$, $p < .001$) subsamples.

Statistical Analysis

Statistical analysis was performed using the IBM SPSS® software platform (Version 27). Preliminary independent *t*-tests and chi-square tests were conducted to examine whether NHB and NHW participants differed on demographic variables (age [years], sex/gender [female, male], education [years]) and enrollment factors (referral source [personal, professional, other, unknown], family history of cognitive impairment [no, yes, unknown]). Additionally, given evidence for the effects of these risk factors/conditions on cognitive outcomes, and/or reported differences in prevalence among NHB and NHW groups (Breslau et al., 2006; Kulshreshtha et al., 2019; Kurian et al., 2007), NHB and NHW participants were also characterized with respect to: APOE ε4 carrier status (non-carrier, carrier; these data were available on 58.6% [n=564] and 65.2% [n=2982] of the NHB and NHW subsamples, respectively); cardiovascular disease burden (cumulative presence [recent or remote history] of heart attack, atrial fibrillation, congestive heart failure, angina, stroke, transient ischemic attack, hypertension, or hypercholesterolemia; possible range: 0-8; these data were available on 95.0% [n=915] and 97.4% [n=4459] of the NHB and NHW subsamples, respectively); and depressive symptoms (Geriatric Depression Scale [GDS] scores; possible range: 0-15; these data were available on 99.4% [n=957] and 99.0% [n=4530] of the NHB and NHW subsamples, respectively). Moreover, multivariate analysis of covariance (MANCOVA) tests were conducted to examine whether NHB and NHW participants differed on neuropsychological performance and ratings of functioning, after controlling for demographic, enrollment, and clinical variables.

Consensus and Actuarial Diagnostic Rates—Chi-square tests were conducted to examine whether percentages of consensus and actuarial diagnoses varied by racial group. Chi-square tests (with Bonferroni-corrected post-hoc comparisons), stratified by racial group, were then conducted to examine associations between diagnosis and APOE ε4 carrier status using both diagnostic classifications.

Associations of Ratings of Functioning with Diagnostic Outcomes and Neuropsychological Performance—Given that both FAQ and CDR scores are considered in the NACC consensus diagnostic method, MANCOVA tests (with follow-up univariate tests and Bonferroni-corrected post-hoc comparisons) were conducted to examine whether ratings of functioning (FAQ and CDR-SB scores) varied across consensus

diagnostic groups, after controlling for demographic, enrollment, and clinical variables; these analyses were stratified by racial group. To assess the convergent validity among the various key components of *each* diagnostic method, bivariate correlations between ratings of functioning and neuropsychological performance were examined; these analyses were also stratified by racial group. First, correlations between FAQ and neuropsychological test scores were examined, using both consensus and actuarial diagnostic classifications, given FAQ scores are incorporated in both consensus and actuarial diagnostic methods (see supplementary Table S3). Second, correlations between CDR-SB and neuropsychological test scores were examined, using the consensus diagnostic classification only, given CDR scores are only incorporated in the consensus diagnostic method (see supplementary Table S4). To account for multiple tests, an adjusted alpha level of .01 was applied to correlation analyses.

The following cutoffs were used to facilitate interpretation of effect size values from analyses (Cohen, 1992): for φ_c and r, values of 0.1, 0.3, and 0.5 represent small, medium, and large effect sizes, respectively; for d, values of 0.2, 0.5, and 0.8 represent small, medium, and large effect sizes, respectively; and for $\eta^2_{p,}$ values of 0.01, 0.06, and 0.14 represent small, medium, and large effect sizes, respectively.

Assumptions of chi-square, ANOVA, and correlation were tested. All chi-square assumptions were met. With regard to ANOVA, histograms showed normal distributions of scores on most neuropsychological and functional measures, although some were skewed due to inherent floor and/or ceiling effects (e.g., MINT, TMT, Benson Figure Copy). Additionally, Levene's tests showed that several measures (except Craft Story, Benson Figure Recall, Category and Letter Fluency, and TMT Parts A and B) demonstrated homogeneity of variance across racial groups. There were no violations of independence. With regard to correlations, assumptions regarding level of measurement (continuous), related pairs (of variables), and linearity were generally met. No scores were observed to fall outside the possible or expected range of measurement.

Results

Descriptive statistics associated with demographic, enrollment, and clinical variables and performance on neuropsychological and functional measures, by racial group, are presented in Table 3. Compared to NHW participants, NHB participants: (1) were significantly younger, $t(1507.52) = 3.33$, $p = .001$, $d = 0.11$; (2) had a significantly higher percentage of female participants, $\chi^2(1, N = 5540) = 147.44$, $p < .001$, $\varphi_c = .16$; (3) completed significantly fewer years of education, $t(1360.18) = 13.07$, $p < .001$, $d = 0.48$; (4) had significantly higher percentages of referrals from personal or other (e.g., community-based) sources, but a significantly lower percentage of referrals from professional or unknown sources, $\chi^2(3, N = 5540) = 118.39$, $p < .001$, $\varphi_c = .15$; (5) were less likely to have a positive, and more likely to have an unknown, family history of cognitive impairment, $\chi^2(2, N = 5540) = 47.73$, $p < .001$, $\varphi_c = .09$; (6) had significantly higher cardiovascular disease burden, $t(5372) = 8.45$, $p < .001$, $d = 0.31$; and (7) reported significantly lower depressive symptoms, $t(5485) = 2.07$, $p = .039$, $d = 0.07$. NHB and NHW participants did not differ significantly on APOE ε4 carrier status, $\chi^2(1, N = 5540) = 2.31$, $p > .05$, $\varphi_c = .03$.

Neuropsychological performance significantly differed between NHB and NHW participants (after controlling for demographic and enrollment factors), $F(11, 5523) = 31.69$, $p < .001$, Wilks' $\lambda = .94$, $\eta^2_p = .06$. NHB participants had significantly lower scores than NHW participants on all measures of language, attention, and executive functioning/processing speed (ps < .001). NHB participants had significantly lower ratings of functioning than NHW participants, $F(2, 5532) = 39.13$, $p < .001$, Wilks' $\lambda = .99$, $\eta^2_p = .014$, which appeared to be driven by racial group differences among participants with consensus MCI diagnoses in particular (NHB: FAQ *EMM* = 1.25, *SE* = 0.24, CDR-SB *EMM* = 0.86, *SE* = 0.06; NHW: FAQ *EMM* = 2.70, *SE* = 0.11, CDR-SB *EMM* = 1.28, *SE* = 0.03). Racial group differences on neuropsychological performance and ratings of functioning were retained after accounting for cardiovascular disease burden and depressive symptoms.

Consensus and Actuarial Diagnostic Rates

Diagnostic rates significantly differed between NHB and NHW participants using both consensus and actuarial classifications (consensus: χ^2 [3, N = 5540] = 92.77, $p < .001$, $\varphi_c = .13$; actuarial: χ^2 [2, N = 5540] = 235.58, $p < .001$, $\varphi_c = .21$). Using consensus classifications, there were significantly higher percentages of CN and impaired-not-MCI diagnoses and a significantly lower percentage of dementia diagnoses among NHB participants than among NHW participants (ps < .05). Using actuarial classifications, there were significantly lower percentages of CN and dementia diagnoses and a significantly higher percentage of MCI diagnoses among NHB participants than among NHW participants (ps < .05).

Frequencies and relative percentages of actuarial diagnoses across consensus diagnostic groups are shown in Figure 1. Among individuals with a consensus CN diagnosis, the percentage with a concordant actuarial CN diagnosis was significantly lower among NHB participants (41.9%) than among NHW participants (72.8%; $p < .05$). This corresponded to a significantly higher percentage of individuals with an actuarial MCI diagnosis, despite their consensus CN diagnosis, among NHB participants (57.8%) than among NHW participants (27.1%; $p < .05$).

Among participants with a consensus impaired-not-MCI diagnosis, there was a significantly higher percentage of actuarial MCI diagnoses among NHB participants (78.1%) than among NHW participants (57.7%; $p < .05$). Additionally, there was a significantly lower percentage of actuarial CN diagnoses among NHB participants (16.4%) than among NHW participants (40.8%; $p < .05$). Taken together, 60.0% of the NHB subsample ([352+57]/[609+73]x100=60.0; see Figure 1) and 29.2% of the NHW subsample ([713+113]/[2629+196]x100=29.2) consisted of participants with an actuarial MCI diagnosis despite a consensus CN or impaired-not-MCI diagnosis.

Among individuals with a consensus MCI diagnosis, the percentage with a concordant actuarial MCI diagnosis was significantly higher among NHB participants (87.4%) than among NHW participants (71.0%; $p < .05$). This corresponded to significantly lower percentages of individuals with an actuarial CN or dementia diagnosis, despite their consensus MCI diagnosis, among NHB participants (12.6%) than among NHW participants (28.9%; $p < .05$).

Among individuals with a consensus dementia diagnosis, the percentage with a concordant actuarial dementia diagnosis was comparable between NHB (67.4%) and NHW (66.0%) participants, and this corresponded to comparable percentages of individuals with an actuarial CN or MCI diagnosis, despite their consensus dementia diagnosis, among NHB participants (32.5%) and NHW participants (34.1%; *p*s > .05).

Associations Between Diagnosis and APOE ε4 Carrier Status—Percentages of APOE ε4 carriers, stratified by racial and diagnostic group, are presented in supplementary Tables S1 (consensus diagnoses) and S2 (actuarial diagnoses) and illustrated in Figure 2.

In the NHB subsample, a significant association between consensus diagnosis and ε4 carrier status was observed, χ^2 (3, N = 564) = 9.35, $p = .025$, $\varphi_c = .13$. However, while percentages of ε4 carriers nominally increased across CN, MCI, and dementia groups, these post-hoc comparisons did not reach statistical significance (*p*s > .05). No association between actuarial diagnosis and ε4 carrier status was observed, χ^2 (2, N = 564) = 0.96, $p > .05$, $\varphi_c = .04$.

In the NHW subsample, significant associations between diagnosis and ε4 carrier status were observed using both consensus and actuarial classifications (consensus: χ^2 [3, N = 2982] = 93.48, $p < .001$, $\varphi_c = .18$; actuarial: χ^2 [2, N = 2982] = 65.55, $p < .001$, $\varphi_c = .15$). Using both classifications, percentages of ε4 carriers significantly increased across CN, MCI, and dementia groups (*p*s < .05). Additionally, using consensus classifications, the dementia group had a significantly higher percentage of ε4 carriers than the impaired-not-MCI group ($p < .05$).

Associations of Ratings of Functioning with Diagnostic Outcomes and Neuropsychological Performance

Descriptive statistics associated with performance on neuropsychological and functional measures, stratified by racial and diagnostic groups, are presented in supplementary Tables S1 (consensus diagnoses) and S2 (actuarial diagnoses).

Consensus Diagnostic Group Differences on Ratings of Functioning—Consensus diagnostic group differences on FAQ and CDR-SB scores, stratified by racial group, are illustrated in Figure 3. In the NHB subsample, ratings of functioning significantly differed across consensus diagnostic groups, after controlling for demographic factors, $F(6, 1910) = 233.99$, $p < .001$, Wilks' $\lambda = .33$, $\eta^2_p = .42$. FAQ and CDR-SB scores significantly increased across the CN, MCI, and dementia groups, and were significantly higher in the dementia group than in the impaired-not-MCI group (*p*s < .001). CDR-SB scores (but not FAQ scores) were also significantly higher in the MCI group than in the impaired-not-MCI group ($p < .001$).

In the NHW subsample, ratings of functioning significantly differed across consensus diagnostic groups, after controlling for demographic factors, $F(6, 9138) = 1096.27$, $p < .001$, Wilks' $\lambda = .34$, $\eta^2_p = .42$. FAQ and CDR-SB scores significantly increased across CN, impaired-not-MCI, MCI, and dementia groups (*p*s < .005). Results observed within both

the NHB and NHW subsamples were retained after accounting for enrollment and clinical variables.

An exploratory analysis of GDS scores within the actuarial CN and MCI diagnostic groups showed that scores significantly increased across consensus classifications (CN, impaired-not-MCI, MCI, dementia) in NHW participants, but not in NHB participants. Relatedly, GDS scores were more robustly correlated with ratings of functioning *and* neuropsychological performance in the NHW subsample than in the NHB subsample. Specifically, GDS scores were significantly correlated with scores on both functional measures and all 11 neuropsychological measures in the NHW subsample (rs = .23 to .24 on functional measures and −.19 to −.08 on all neuropsychological measures [ps < .001]), but were significantly correlated with scores on both functional measures and only 2 of the 11 neuropsychological measures in the NHB subsample (rs = .11 to .14 for functional measures and −.13 to −.14 for Craft Story Immediate and Delayed Recall [ps < .001]).

Correlations Between Ratings of Functioning and Neuropsychological Performance—Coefficients derived from analyses of correlations between ratings of functioning and neuropsychological performance are presented in supplementary Tables S3 (FAQ) and S4 (CDR-SB).

FAQ scores and neuropsychological performance.: In the NHB subsample, there were significant negative correlations between FAQ scores and performance on all neuropsychological measures except Number Span Forward (rs = −.08 to −.36, ps < .01). In analyses that were further stratified by consensus or actuarial diagnosis, most of the correlations did not retain significance, particularly within the MCI and dementia groups. For example, FAQ scores did not retain significant correlations with scores on any neuropsychological measures within the consensus MCI group (ps > .01), and were significantly correlated with scores on TMT Part B only within the consensus dementia group (p < .01).

In the NHW subsample, there were significant negative correlations between FAQ scores and performance on all neuropsychological measures (rs = −.19 to −.52, ps < .01). In analyses that were further stratified by consensus or actuarial diagnosis, most correlations retained significance, particularly within the MCI and dementia groups. For example, FAQ scores were significantly correlated with scores on all measures except MINT, Letter Fluency, Number Span, and Benson Figure Copy within the consensus MCI group, and on all measures except MINT and Number Span within the consensus dementia group (ps < .01).

CDR-SB scores and neuropsychological performance.: In the NHB subsample, there were significant negative correlations between CDR-SB scores and performance on all neuropsychological measures (rs = −.13 to −.42, ps < .01). Most of the correlations did not retain significance in analyses that were further stratified by consensus diagnosis.

In the NHW subsample, there were significant negative correlations between CDR-SB scores and performance on all neuropsychological measures (rs = −.21 to −.55, ps < .01).

Most of these correlations retained significance in analyses that were further stratified by consensus diagnosis. Furthermore, these associations were retained after partialing out effects of GDS scores.

Taken together, these results mirrored those from analyses of correlations between FAQ scores and neuropsychological performance, which is not surprising given the aforementioned, strong correlations observed between FAQ and CDR-SB scores. In order to determine whether the observed racial group differences in correlations were meaningful, we conducted two MANCOVAs to test race x FAQ and race x CDR-SB interaction effects on neuropsychological performance (while accounting for potential main effects of race, FAQ and CDR-SB scores, and age, sex/gender, and education). Significant race x FAQ and race x CDR-SB interactions were observed (race x FAQ: $F[275, 54621.99] = 1.63$, $p < .001$, Wilks' $\lambda = .92$, $\eta^2_p = .01$; race x CDR-SB: $F[176, 49459.50] = 2.19$, $p < .001$, Wilks' $\lambda = .93$, $\eta^2_p = .01$).

Discussion

In the present study, we examined whether baseline consensus and actuarial diagnostic rates, and associations of ratings of functioning with neuropsychological performance and diagnostic outcomes, differed for NHB and NHW older adults in the NACC cohort. Overall, findings demonstrated that relative to the NHW subsample, the NHB subsample had nearly double (60.0% among NHBs versus 29.2% among NHWs) the percentage of participants with an actuarial MCI diagnosis despite their consensus CN or impaired-not-MCI diagnosis, and exhibited less consistent associations between ratings of functioning and neuropsychological performance.

Percentages of consensus and actuarial diagnoses of CN, MCI, and dementia significantly differed between NHB and NHW participants. As noted above, relative to the NHW subsample, the NHB subsample had nearly double the percentage of participants with an actuarial MCI diagnosis despite a consensus CN or impaired-not-MCI diagnosis. This could reflect higher rates of false negative MCI cases using the consensus diagnostic method (i.e., assigning consensus CN or impaired-not-MCI diagnoses when participants truly have MCI), particularly for NHB older adults. However, without a definitive gold standard of MCI and dementia diagnosis, we cannot rule out the possibility that the actuarial method is prone to false *positive* MCI diagnostic errors (i.e., assigning actuarial MCI diagnoses when participants are truly CN or impaired-not-MCI). Furthermore, we compared associations of APOE ε4 carrier status with consensus and actuarial diagnoses to assess the comparative utility of the two diagnostic methods. We found that significant associations with ε4 carrier status were consistently observed, using either diagnostic classification, in the NHW subsample, such that higher percentages of ε4 carriers corresponded to greater severity of cognitive impairment. In contrast, a significant association between ε4 carrier status and consensus diagnosis, but not actuarial diagnosis, was observed in the NHB subsample, although post-hoc comparisons did not reach statistical significance. Previous studies investigating the effects of the ε4 allele on cognition have produced mixed findings (O'Donoghue et al., 2018; El Haj et al., 2016), and have been largely based on NHW samples. Moreover, while prevalence of the ε4 allele is consistently found to be higher in

the Black population than in the White population (note: NHB participants had a nominally higher percentage of ε4 carriers, on average, in the present study), it is inconsistently related to Alzheimer's dementia and cognition in the former (Barnes & Bennett, 2014), and this was corroborated by the present study findings. However, other research suggests that the ε4 allele is related to faster episodic memory decline in both NHB and NHW individuals, whereas its effect on decline in other cognitive abilities (e.g., working memory, semantic memory) differs across these groups (Barnes et al., 2013). Therefore, with regard to the present study, it is worth considering whether the observed discrepancies between NHB and NHW participants in the degree of association between diagnosis and ε4 carrier status could be at least partly driven by the specific cognitive tests or domains represented in the NACC UDS. Broadly speaking, the variability in the literature on APOE and cognition that is focused on NHB samples may be partly due to differences in diagnostic methods utilized across studies.

The NHB subsample had a higher degree of cardiovascular disease burden relative to the NHW subsample (although this effect was small), thus, it is also important to consider the possibility that the differential associations of APOE ε4 carrier status with consensus and actuarial diagnoses observed across racial groups may reflect differences in underlying etiologies of cognitive impairment, with MCI or dementia due to cerebrovascular versus AD-related pathology being more prevalent among NHB versus NHW participants, respectively (Miles et al., 2001; Hou et al., 2006). Thus, identifying and incorporating appropriate biomarkers for validating diagnostic approaches, particularly with NHB other underrepresented racial/ethnic groups, remains imperative.

Differential associations of ratings of functioning with neuropsychological performance and diagnostic outcomes were observed in the present study. FAQ and CDR-SB scores significantly increased across consensus diagnostic groups in the NHW subsample (and this effect was large). In the NHB subsample, similar patterns were observed, although with some exceptions (i.e., the impaired-not-MCI group was comparable to both the CN and MCI groups on FAQ scores, and to the CN group on CDR-SB scores; refer to Figure 3). These findings extend those of previous studies demonstrating the FAQ's ability to discriminate between CN, MCI, and dementia stages (Brown et al., 2011; Pfeffer et al., 1982; Teng et al., 2010) by highlighting that both the FAQ and the CDR-SB index are able to discriminate between CN, MCI, and dementia stages in both NHB and NHW samples. Additionally, while ratings of functioning were significantly lower, on average, for NHB participants than for NHW participants, this effect was small, and appeared to be driven by racial group differences on reported functioning among participants with MCI in particular. These findings suggest that there may be differences between racial groups in appraisals of functional status and decline during the MCI stage of ADRD; this presents a possible, important area of further study in efforts to improve diagnostic accuracy and detection for NHB older adults and other culturally diverse groups at risk for ADRD. Additionally, consistent with findings reported previously by Edmonds et al. (2014), GDS scores were shown to correlate with reported functioning – which may have at least partly contributed to observed diagnostic discrepancies – and this was despite the fact that NHB participants had lower GDS scores, on average, relative to NHW participants (although this effect was small).

These findings reiterate the importance of evaluating depressive symptoms in assessments of neurocognitive functioning.

Ratings of functioning were shown to be associated with neuropsychological performance less consistently in NHB participants than in NHW participants. These findings corroborate those from previous studies focused on primarily NHB samples (Jackson et al., 2017; Sims et al., 2011), and help to clarify discrepancies in the broader literature reflecting inconsistent support for a relationship between reported cognitive and functional difficulties and performance on comprehensive neuropsychological testing. Specifically, the current results present the possibility that the degree of convergent validity among the various key components of the NACC consensus diagnostic method (e.g., CDR, FAQ, and neuropsychological test scores) may be lower for NHB individuals than for NHW individuals. However, it is worth highlighting that according to NACC diagnostic protocols, clinician judgment of cognitive status is based on a review of *all* available information, and interpreting any components or measures in isolation may compromise diagnostic accuracy in some cases. Relatedly, it is important to consider the possibility that the consensus-based method captures additional information (e.g., education quality, past or current life stressors, other psychosocial factors) above and beyond scores on functional and neuropsychological measures that is important for appropriately determining one's cognitive status. In this sense, consensus methods may have more utility relative to actuarial approaches that are based primarily on neuropsychological test scores, particularly when assessing neurocognitive functioning in NHB individuals. Taken together, while both consensus-based and actuarial methods come with inherent strengths and weaknesses, perhaps shifting away from any "one-size-fits-all" approach to assessment and diagnosis, and adapting diagnostic protocols to be more culturally-informed and -appropriate is paramount to improving the assessment and diagnosis of NHB individuals at risk for ADRD, especially given that there is currently no definitive gold standard for MCI and dementia diagnosis. These considerations are especially relevant in efforts to improve diagnostic accuracy in large-scale multisite studies of cognitive aging (e.g., NACC), particularly given the variable representation of NHB individuals across sites within these studies.

Several additional factors may play a role in consensus-based diagnostic methods in particular, and are important to take into consideration when interpreting the present findings and identifying directions for future research. These factors may include, but are not limited to, explicit and/or implicit examiner/provider bias, and hesitancy in reporting of symptoms and/or seeking medical attention among NHB individuals as a result of fear or mistrust due to historical injustices within academic and medical institutions (e.g., based on past experiences of racism and discrimination in research and healthcare settings; Chapman et al., 2013; Cory, 2020; Rivera Mindt et al., 2010; Romano, 2018). Additional studies using larger NHB samples are needed to: (1) more comprehensively assess the measurement invariance of various functional and neuropsychological measures, including those that are currently used in large-scale studies of cognitive aging (e.g., while FAQ ratings are purportedly minimally influenced by socioeconomic status [Pfeffer et al., 1982], the potential influence of other sociocultural factors on FAQ ratings and their relationship with neuropsychological performance requires further investigation); and (2) elucidate the manner in which additional

factors (e.g., those noted above) may help to explain varying degrees of correspondence between ratings of functioning and neuropsychological performance.

The present study is not free of limitations. For instance, NACC participants do not accurately represent the general population given their substantially higher average level of education and predominantly NHW composition. The present results also only apply to participants who were able to tolerate/complete the full NACC UDS Version 3.0 neuropsychological battery (i.e., systematic differences in the determination of missingness on measures with discontinuation criteria [e.g., TMT Part B] may have resulted in some participants, particularly those demonstrating higher degrees of cognitive impairment, being excluded from the study sample). Additionally, as was previously noted, there is inherently some degree of overlap in the neuropsychological tests that were considered in assigning NACC consensus diagnoses and those that were incorporated into the actuarial method for reclassifying cognitive status. Relatedly, participants in the normative reference groups that were used in the present study to facilitate assignment of actuarial diagnoses were those identified in the NACC UDS as those who maintained a *consensus* diagnosis of CN across all ADRC visits. Taken together, these issues inherently cause some degree of redundancy between the consensus and actuarial diagnostic approaches. Moreover, it is worth considering that some ADRCs may utilize algorithm-based approaches that are similar to those reflected in our actuarial diagnostic method. Nevertheless, one particular strength of the present study is that the actuarial diagnostic method that was utilized adjusted for enrollment factors (referral source, family history of cognitive impairment) that are likely unaccounted for in NACC-based normative algorithms or calculators. In addition, it is worth noting that we adopted a relatively inclusive approach to selecting the present study sample, which allowed us to maintain a robust NHB subsample, highlighting that successfully increasing NHB representation in large-scale studies of cognitive aging will require critical (re)evaluation of study inclusion/exclusion criteria that are commonly employed yet resulting in disproportionately reduced recruitment, retention, and overall representation of NHB adults in this research.

The present findings prompt consideration of the strengths and weaknesses of consensus-based and actuarial diagnostic methods, and underscore the critical need to identify and implement more culturally-informed and -appropriate methods for assessing NHB individuals, including in large-scale multisite studies of cognitive aging. We believe our findings further highlight the inconsistencies surrounding the relationship between ratings of functioning and neuropsychological performance, which may be particularly implicated in assessments of neurocognitive functioning in NHB older adults. We hope that these findings and corresponding points of consideration will encourage researchers to engage in related efforts to address and mitigate disparities in the assessment and diagnosis of MCI and dementia due to ADRD in NHB older adults. Such efforts may include (but are not limited to): (1) the development and implementation of strategies for significantly increasing recruitment and retention of NHB older adults in large-scale studies of cognitive aging (in line with the aims of the recently formed ADNI Diversity Taskforce); and (2) more conscious and consistent efforts to apply valuable insights from existing, ongoing initiatives such as the Minority Aging Research Study (e.g., Barnes et al., 2012) and Washington Heights-Inwood Community Aging Project (e.g., Jacobs et al., 1996; Manly et al., 1998)

to amplify the use of inclusive, community-based approaches for elucidating and mitigating ADRD risk, and promoting brain health equity, in NHB and other racially/ethnically diverse older adults.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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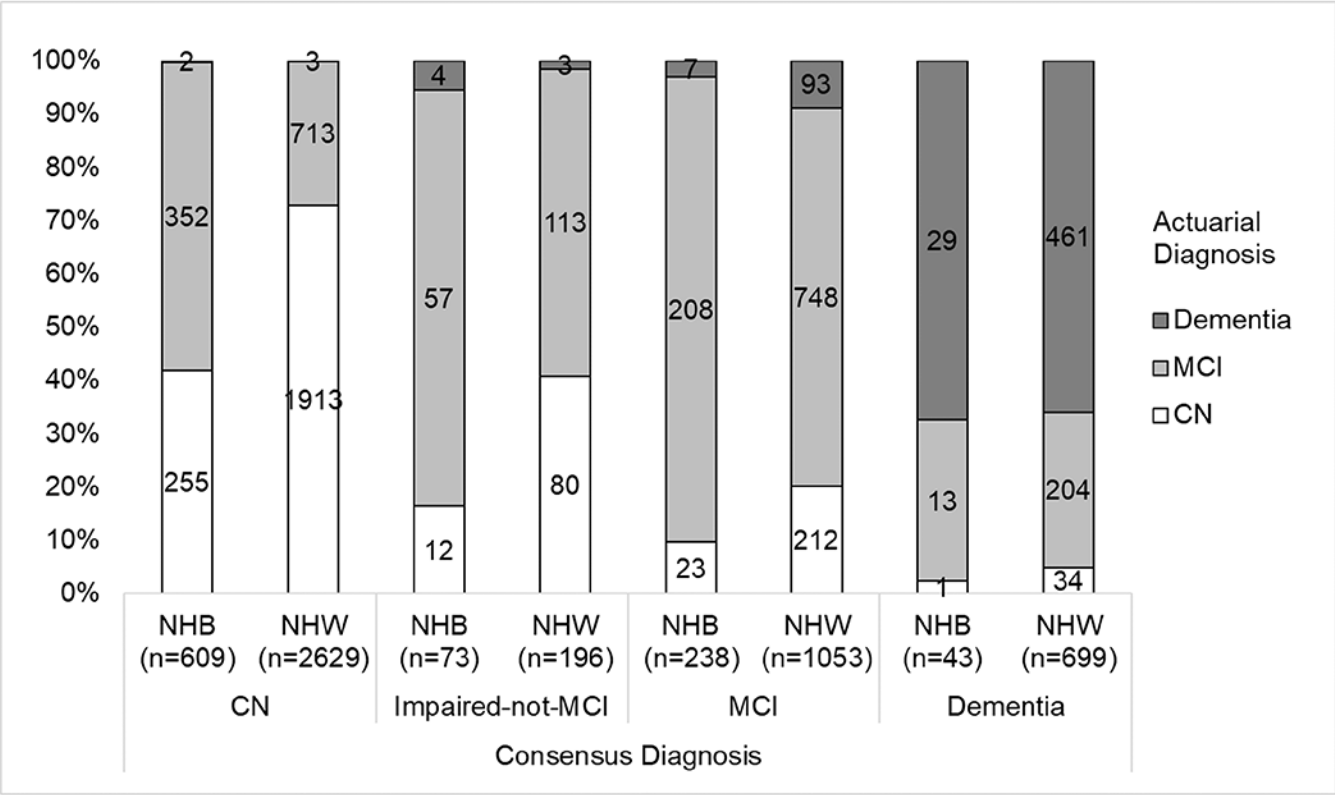

Figure 1.

Frequencies and relative percentages of actuarial diagnoses across consensus diagnostic groups in NHB and NHW participants. Note: NHB = non-Hispanic Black; NHW = non-Hispanic White; CN = cognitively normal; MCI = mild cognitive impairment.

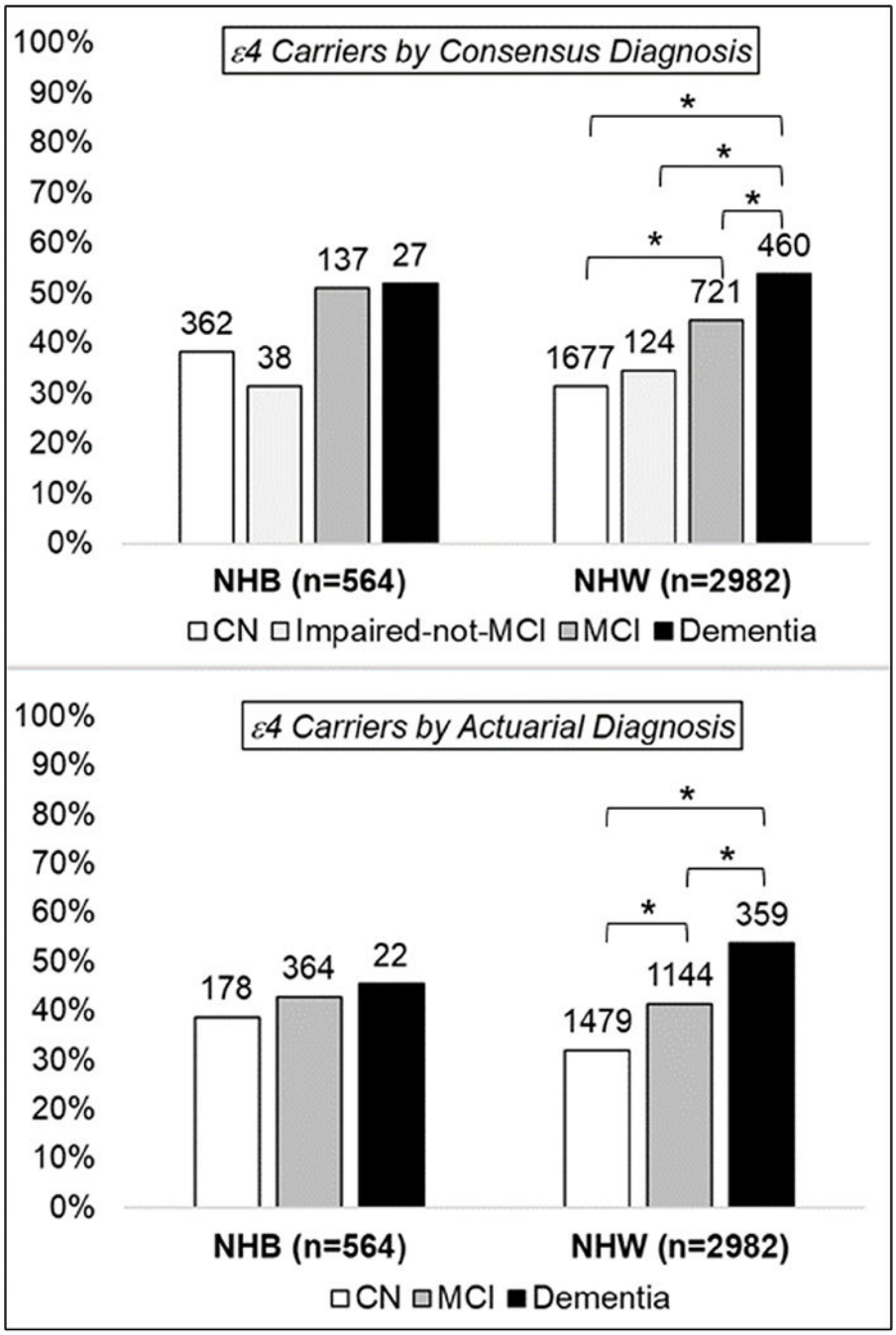

Figure 2.

Percentages of APOE ε4 carriers across consensus (top) and actuarial (bottom) diagnostic groups in NHB and NHW participants. Note: NHB = non-Hispanic Black; NHW = non-Hispanic White; CN = cognitively normal; MCI = mild cognitive impairment; total numbers of NHB and NHW participants with APOE data are noted in parentheses, and numbers of participants with APOE data in each diagnostic group are noted above each bar; *p-value significant after Bonferroni correction.

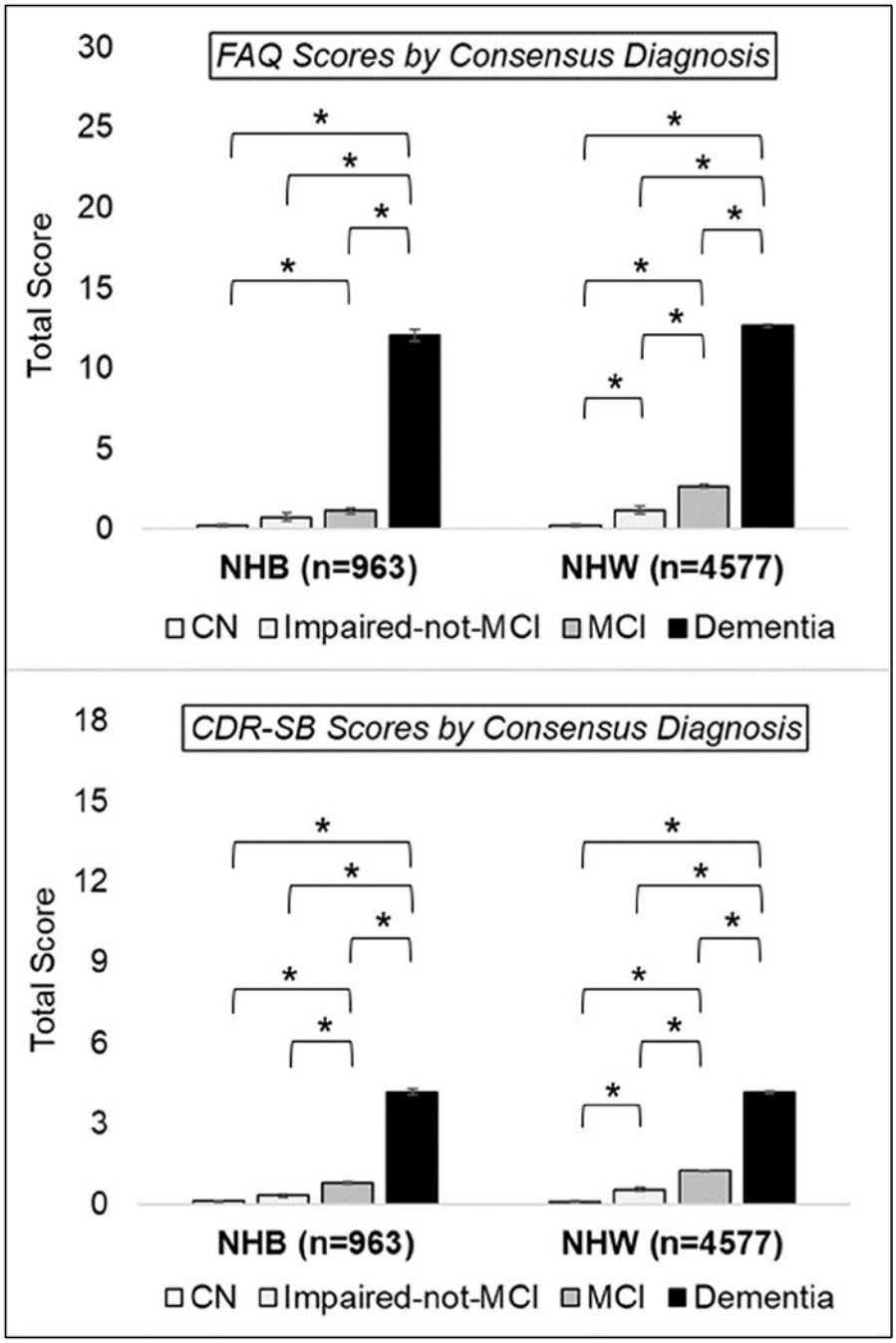

Figure 3.

Estimated marginal means for FAQ (top) and CDR-SB (bottom) scores across consensus diagnostic groups in NHB and NHW participants. Note: NHB = non-Hispanic Black; NHW = non-Hispanic White; CN = cognitively normal; MCI = mild cognitive impairment; *p-value significant after Bonferroni correction.

Table 1.

Descriptive statistics associated with performance on neuropsychological measures in the NHB and NHW normative reference groups.

	Normative Reference Group				
	NHB (n=562)		**NHW (n=2470)**		
Demographic, Enrollment, and Clinical Variables	***M***	***SD***	***M***	***SD***	***d***
Age (years) *	68.58	7.01	69.84	8.03	0.16
Sex (% female) *	81.3%		65.3%		
Education (years) *	15.50	2.48	16.73	2.28	0.53
Referral source (%)					
Personal	58.0%		53.9%		
Professional *	32.4%		38.1%		
Other *	9.4%		5.5%		
Unknown *	0.2%		2.4%		
Family history of cognitive impairment (%)					
No *	37.4%		31.2%		
Yes *	45.0%		55.2%		
Unknown *	17.6%		13.6%		
APOE ε4 carrier status (% carriers) *	37.8%		31.1%		
Cardiovascular disease burden *	1.36	0.95	0.99	0.96	0.38
GDS score *	1.27	1.81	1.09	1.64	0.11
Neuropsychological Measures	**M**	**SD**	**M**	**SD**	**d**
Craft Story Immediate Recall *	20.92	6.22	22.75	6.30	0.29
Craft Story Delayed Recall *	17.82	6.29	19.96	6.36	0.34
Benson Figure Recall *	10.91	2.86	11.54	2.78	0.23
MINT *	28.39	2.53	30.66	1.51	1.30
Category Fluency *	33.18	7.40	37.84	8.17	0.58
Letter Fluency *	26.29	7.75	29.48	8.04	0.40
TMT Part A *	−37.13	14.63	−29.70	10.16	0.67
Number Span Forward *	7.77	2.17	8.62	2.24	0.38
TMT Part B *	−103.68	50.77	−73.89	31.41	0.83
Number Span Backward *	6.25	2.02	7.43	2.12	0.56
Benson Figure Copy *	15.16	1.44	15.59	1.23	0.33

Note: NHB = non-Hispanic Black; NHW = non-Hispanic White; M = mean; SD = standard deviation; APOE = apolipoprotein E; GDS = Geriatric Depression Scale; MINT = Multilingual Naming Test; TMT = Trail Making Test;

* significant racial group differences were observed on these indices.

Table 2.

Criteria for assigning actuarial diagnoses.

CN	MCI	Dementia
Criterion of ≥2 impaired scores in ≥1 cognitive domains not met (regardless of FAQ score)	≥2 impaired scores in 1 cognitive domain (regardless of FAQ score), or, ≥2 impaired scores in ≥2 cognitive domains + FAQ score < 6	≥2 impaired scores in ≥2 cognitive domains + FAQ score ≥ 6

Note: CN = cognitively normal; MCI = mild cognitive impairment; FAQ = Functional Activities Questionnaire.

Table 3.

Descriptive statistics associated with demographic, enrollment, and clinical variables, and performance on neuropsychological and functional measures, by racial group.

	Racial Group				
	NHB (n=963)		**NHW (n=4577)**		
Demographic, Enrollment, and Clinical Variables	***M***	***SD***	***M***	***SD***	***d***
Age (years) *	69.51	7.42	70.40	8.26	0.11
Sex (% female) *	78.9%		58.0%		
Education (years) *	15.31	2.55	16.48	2.45	0.48
Referral source (%)					
Personal *	50.6%		44.3%		
Professional *	35.5%		48.6%		
Other *	13.0%		5.1%		
Unknown *	0.9%		2.0%		
Family history of cognitive impairment (%)					
No	37.5%		31.9%		
Yes *	43.4%		55.0%		
Unknown *	19.1%		13.2%		
APOE ε4 carrier status (% carriers)	41.7%		38.3%		
Cardiovascular disease burden *	1.39	0.96	1.08	1.01	0.31
GDS score *	1.49	2.08	1.65	2.19	0.07
Neuropsychological and Functional Measures	**M**	**SD**	**M**	**SD**	**d**
Craft Story Immediate Recall	18.73	6.79	19.03	7.93	0.04
Craft Story Delayed Recall	15.29	7.14	15.68	8.49	0.05
Benson Figure Recall	9.61	3.66	9.50	4.26	0.03
MINT *	27.74	2.89	29.49	3.63	0.50
Category Fluency *	30.90	7.90	32.87	10.21	0.20
Letter Fluency *	24.33	8.20	26.73	9.00	0.27
TMT Part A *	−40.85	18.37	−35.03	17.82	0.33
Number Span Forward *	7.51	2.17	8.10	2.33	0.25
TMT Part B *	−124.82	68.87	−101.68	66.59	0.35
Number Span Backward *	5.74	2.07	6.74	2.26	0.45
Benson Figure Copy *	14.91	1.79	15.25	1.79	0.19
FAQ *	1.02	3.38	2.74	5.61	0.33
CDR-SB *	0.50	1.07	1.02	1.80	0.31

Note: NHB = non-Hispanic Black; NHW = non-Hispanic White; M = mean; SD = standard deviation; APOE = apolipoprotein E; GDS = Geriatric Depression Scale; MINT = Multilingual Naming Test; TMT = Trail Making Test; FAQ = Functional Activities Questionnaire; CDR-SB = CDR Dementia Staging Instrument Sum of Boxes;

*significant racial group differences were observed on these indices.