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RESEARCH ARTICLE

Neuropsychiatric Symptoms and Trajectories of Dependence and Cognition in a Sample of Community-dwelling Older Adults with Dementia

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Abstract: ***Background and Objectives*:** Neuropsychiatric symptoms (NPS), including psychotic symptoms (hallucinations, illusions, delusions), agitation/aggression, and depressed mood, are common in individuals with Alzheimer's disease (AD) and predict poorer outcomes, including faster disease progression. We aimed to evaluate associations between NPS and cognition and dependence in a multi-ethnic sample of community-dwelling older adults with AD.

***Methods*:** Predictors 3 (P3) is a cohort study of AD disease courses recruiting older adults aged 65 and above residing in upper Manhattan. A total of 138 of 293 participants had probable AD at the study baseline. We fit linear mixed models to examine longitudinal associations of time-varying NPS (psychotic symptoms, agitation/aggression, and depressed mood) with dependence and cognition, adjusted for race-ethnicity, sex, education, age, clinical dementia rating score, APOE-ϵ4, and comorbidity burden; separate interaction models were fit for age, Hispanic ethnicity, and sex.

***Results*:** Psychotic symptoms were associated with faster rates of increasing dependence and declining cognition over time, agitation/aggression with faster rates of declining cognition, and depressed mood with faster rates of increasing dependence. Among psychotic symptoms, delusions, but not hallucinations or illusions, were associated with worse outcome trajectories. Depressed mood predicted an accelerated increase in dependence in males but not females.

***Conclusion*:** Our results confirm and extend prior results in clinic-based samples. The presence of NPS was associated with worse trajectories of dependence and cognition in this muti-ethnic sample of older adults with AD. Importantly, sex modified the association between depressed mood and dependence. Our results on NPS as predictors of differential AD progression in a community-dwelling, ethnically diverse sample serve to better inform the clinical care of patients and the future development of AD therapies.

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1. INTRODUCTION

Neuropsychiatric symptoms (NPS) are common in Alzheimer's disease (AD) and are present in up to 75% of individuals with AD [1-4]. NPS include psychotic symptoms, such as hallucinations, delusions, and illusions, agitation and aggression, and depressed mood [1, 2]. Prior studies have found that the presence of NPS in AD is associated with a faster course of disease progression and predicts a faster progression to mortality, institutionalization, functional impairment, and dependence, as well as faster rates of cognitive and functional decline in AD [5-11]. Furthermore, NPS contribute to the societal impact of AD, resulting in a higher burden of stress for caretakers and increased costs of care [12-15]. Evidence for the association between psychotic symptoms and cognitive decline and institutionalization is particularly strong, while evidence for associations between

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other NPS and AD outcomes, such as functional decline or increase in dependence, is mixed due to differences in study design and follow-up period across studies [6, 7, 9]. Furthermore, while the presence of NPS may fluctuate over time [16], many prior studies have only examined NPS as baseline predictors of AD progression.

To date, most studies of NPS in AD have focused on clinic-based and/or predominately White samples of older adults, potentially limiting the generalizability of these results to the wider U.S. population. Prevalence of AD and risk factors for AD, course of disease progression, and patterns of healthcare utilization differ by race and ethnicity, with Black and Hispanic older adults having worse AD outcomes on average [17-20]. Additionally, participants in clinic-based cohorts have relatively high levels of educational attainment. Education may relate to differences in AD progression *via* differences in cognitive reserve [21], with higher levels of educational attainment being associated with faster rates of cognitive decline in incident AD cases [22]. For these reasons, researchers are increasingly recognizing the importance of including community-dwelling, multiethnic cohorts in AD research [7]. Furthermore, while cognitive decline, risk of AD, and dynamics of AD progression differ by important demographic factors, such as age, sex, race, and ethnicity [7, 23-27], many AD studies treat these as covariates in analyses rather than investigating and reporting potential subgroup effects [28, 29]. As the aging population of the U.S. is growing more racially and ethnically diverse [30], further research is needed to better understand the relationships between NPS and AD disease courses in samples that better reflect the racial, ethnic, and educational profile of the broader population of older adults. Investigation of potential risk subgroups can help to shed light on differences in AD outcomes by demographic risk factors, with implications for clinical care and the development of interventions [31].

The present study investigates relationships between time-varying NPS and trajectories of cognition and dependence in a multiethnic community-based sample of older adults aged 65 and older with probable AD. We aimed to confirm results from prior research conducted in a clinic-based, predominately White sample of patients that found that NPS was related to greater declines in cognition and independence over time [6]. To investigate potentially disparate associations between specific NPS and trajectories of cognition and dependence, we explored associations between the presence of psychotic symptoms, agitation/aggression, and depressed mood in separate models for cognitive and dependence scores. To better describe associations between psychotic symptoms and outcomes, we also explored trajectories of cognition and dependence by individual psychotic symptoms: hallucinations, illusions, and delusion. To investigate potential risk subgroups for NPS in AD progression, we explored whether associations between NPS and trajectories of cognition and dependence differed by age, sex, and Hispanic ethnicity. We hypothesized that NPS would predict lower average cognitive performance, higher average dependence, faster rates of cognitive decline, and an increase in dependence over time. We further hypothesized that associations between NPS and outcome trajectories would differ by age, sex, and Hispanic ethnicity.

2. METHODS

2.1. Data Sources

Predictors 3 (P3) is a multiethnic, predominately Hispanic, community-based cohort study of dementia among older adults residing in the upper Manhattan area of New York City. The aim of P3 is to extend findings on predictors of differential AD disease course and outcomes from the prior clinic-based Predictors 1 and 2 studies to a community-dwelling sample of older adults [32]. At recruitment, P3 participants included those aged 65 and older with incident dementia, recently identified prevalent dementia, or identified as at risk for imminent conversion to dementia who were concurrently enrolled in the Washington Heights-Hamilton Heights-Inwood Columbia Aging Project (WHICAP). WHICAP is an ongoing prospective aging study following randomized samples of English or Spanish-speaking Medicare recipients aged 65 and older in upper Manhattan [26, 33]. Details regarding P3 recruitment and assessment methods were previously published [32].

P3 participants were evaluated annually by trained, bilingual interviewers with a comprehensive set of neuropsychological instruments and neurological, functional, psychiatric, medical, and demographic questionnaires and assessments. At each annual visit, interviewers also conducted interviews with a study partner, who may be a family member, close friend, or home health attendant of the participant. Consensus diagnoses of dementia status were made by a team of clinicians after each visit, following the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association criteria for probable dementia [34]. Data used in this study were collected between 2011 and 2020.

2.2. Analytical Sample

The base population for this study consisted of 293 participants recruited from 2011 to 2019. As the goal of the study was to examine AD trajectories, we excluded 135 participants who were at risk of dementia conversion but had no dementia diagnosis at baseline. Eligible participants for the present study were those who had a baseline diagnosis of dementia, were not missing NPS, cognitive, or dependence data at baseline, and had at least one follow-up visit. Twenty participants not meeting these criteria were also excluded, yielding an analytical sample of 138 participants (Fig. **1**). Follow-up for this analysis was capped at 6 years from the study baseline, as fewer than 10% of participants had follow-up greater than 6 years.

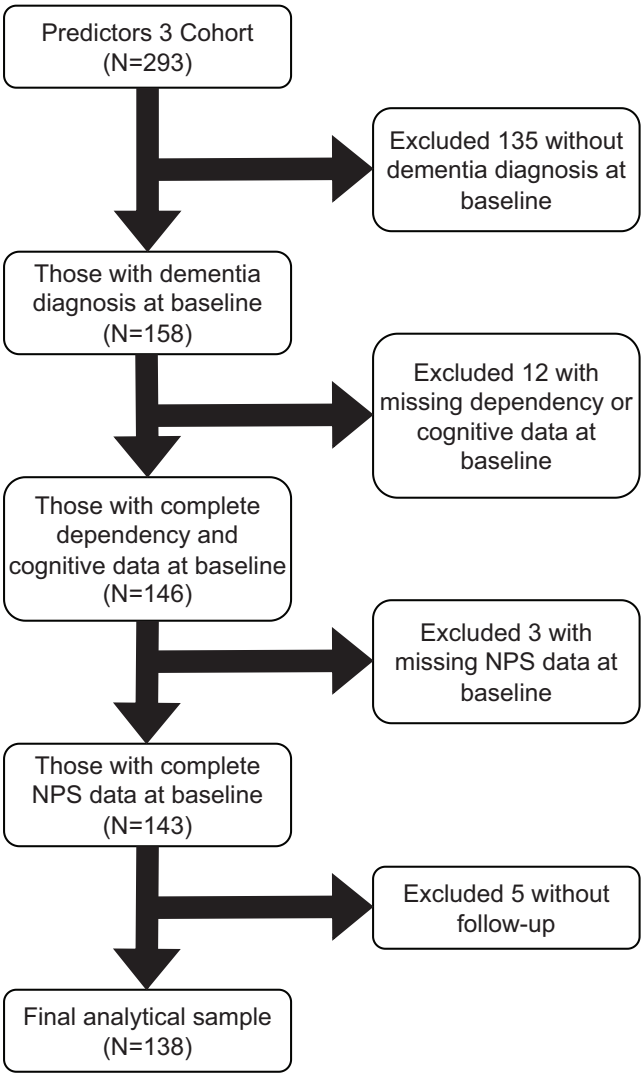

Fig. (1). Population flow chart for analytical sample. *(A higher resolution / colour version of this figure is available in the electronic copy of the article).*

2.3. Outcomes

Dependence, as a unified representation of AD disease severity, was measured using the Dependence Scale (DS). The DS is composed of 13 items administered to a participant's study partner annually to assess the degree to which the participant is functionally dependent on others. Of these, 11 items are dichotomous, yielding yes/no responses (*e.g.,* need for frequent help with finding objects and other common tasks), while two items use a three-point scale for frequency of care (*e.g.,* needs reminders or advice for routine tasks). Summing all 13 items provides the dependence sum score, ranging from 0 to 15, with a higher score representing more severe dependence. The psychometric properties of the DS range from good to excellent [35]. In the present study, the dependence sum score was modeled as a continuous outcome measure.

Cognition was measured using the Modified Mini-Mental State Examination (mMMS), an instrument for assessing cognitive impairment in dementia [36]. The mMMS ranges from 0 to 57, with a lower score representing greater cognitive impairment. In the present study, we modeled the mMMS as a continuous outcome measure.

2.4. Predictors

At baseline and each follow-up visit, we measured NPS using the Columbia University Scale for Psychopathology in Alzheimer's Disease (CUSPAD), a semi-structured interview administered to the participant's study partner annually to assess the presence of various psychiatric symptoms during the previous month [37]. For the present study, we recorded the presence of psychotic symptoms if any hallucinations, illusions, or delusions were present and recorded the presence of agitation/aggression and depressed mood. Based on prior research, we defined psychotic symptoms broadly to include illusions along with hallucinations and delusions [6, 7, 38]. Psychotic symptoms and their subtypes (hallucinations, illusions, and delusions), agitation/aggression, and depressed mood were modeled as dichotomous predictor variables. These specific NPS are included in the present study for consistency with prior investigation in the predictors study [6, 7].

2.5. Covariates

Information on participant race, Hispanic ethnicity, language, age, sex, years of education, Clinical Dementia Rating (CDR) score, Apolipoprotein E (APOE)-ϵ4 polymorphism, and presence of cardiometabolic comorbidities was collected at study enrollment. Age at enrollment and education in years were determined *via* self/informant reports and operationalized as continuous variables. Racial and Hispanic ethnic identity were determined *via* self/informant-report following the 2000 US Census format and operationalized for analyses as a categorical variable (non-Hispanic White, non-Hispanic Black, Hispanic of any race). Due to the small number of non-Hispanic participants in our sample, we used a dichotomous indicator for Hispanic ethnicity (Hispanic vs. non-Hispanic, of any race) in interaction analyses. The presence of APOE-ϵ4 polymorphism was defined as the presence of at least one APOE-ϵ4 risk allele. CDR score was operationalized as a dichotomous variable (1, >1). To assess cardiometabolic comorbidities, we determined the presence of stroke, cardiovascular disease, diabetes, and hypertension *via* self-report, review of medical records, and medication usage. We scored the presence of each comorbidity as 1 point, summed these to create a comorbidities burden score ranging from 0 to 4, and operationalized the comorbidities burden as a dichotomous variable (<3, ≥3) [39]. We used *a priori* model specification to select covariates for multivariable analyses according to previous studies of NPS and dementia outcomes [7, 40]. Language was not included as a covariate in analyses as it is highly correlated with Hispanic ethnicity in our sample.

2.6. Statistical Analyses

We reported distributions of baseline sample characteristics as median (interquartile range) for continuous variables and number (%) for categorical variables and stratified sample characteristics by baseline dichotomized NPS status. We set statistical significance for all tests *a priori* at the 0.05 level and performed all analyses using the *R* statistical package v. 4.1.0 and *RStudio* v. 1.4.177 [41, 42].

To account for potential selection bias due to differential attrition, models were weighted with stabilized inverse probability of censoring weights (IPCW) for participants who contributed less than 4 years of follow-up time [43]. IPCW aims to create an unbiased pseudo-population wherein attrition is marginally independent of exposure by more heavily weighting those with a higher level of exposure and higher odds of attrition. We computed IPCW by fitting pooled logistic regression models predicting attrition at each visit timepoint for each NPS predictor and outcome combination using a set of predictive covariates (age at enrollment, race-ethnicity, sex, education, APOE-ϵ4 polymorphism, CDR, and comorbidities burden score) using the *ipw* package [44].

Missing data were handled using k-nearest neighbors imputation with the *caret* package [45]. Fourteen participants were missing comorbidities data at baseline. Missing comorbidities burden scores were imputed using a full set of predictive covariates (age at enrollment, race-ethnicity, sex, education, APOE-ϵ4 polymorphism, CDR, and comorbidities burden score). We conducted secondary sensitivity analyses by fitting unweighted models using complete cases without missing comorbidities data (N=124).

We fit separate IPCW-weighted linear mixed-effects models to estimate the associations between each NPS predictor variable as a time-varying predictor and dependence and mMMS scores over time using the *lme4* package [46]. Models were fitted with random intercepts for participants using an unstructured covariance matrix [47]. Time was modeled as time since study enrollment rounded to the nearest year. For each NPS predictor and outcome, we fit unadjusted models with a *time X predictor* cross-product term. The coefficient for the predictor is the average association between the predictor and outcome score across time points, while the coefficient for the cross-product term is the association between the predictor and the rate of change in the outcome score over time. Next, we fit models adjusting for potential confounders (race-ethnicity, sex, age at enrollment, education, comorbidities burden score).

This study investigated potential interaction on the additive scale by fitting unadjusted models with three-way interaction terms for time X predictor X modifier for Hispanic ethnicity (dichotomous), sex, and age at enrollment (dichotomized at the median value of 86 years). If a three-way interaction term was statistically significant, we then fit adjusted models as above for each subgroup defined by the levels of the modifier in question.

3. RESULTS

3.1. Sample Characteristics

Table **1** presents baseline characteristics for the study sample. Participants with a median age of 86 years and median educational attainment of 5 years (range = 0 - 20) were more likely to be female and Hispanic and less likely to have the APOE-ϵ4 allele or to have a CDR greater than 1. While all non-Hispanic participants were tested in English, all Hispanic participants except one were tested in Spanish. Sixty-two percent of participants had psychotic symptoms (30% had hallucinations, 3.6% illusions, and 58% delusions), while 40% and 54% had agitation/aggression and depressed mood, respectively. The median mMMS score was 29, and the median DS score was 7. Participants contributed a total of 524.6 person-years of follow-up time, and the median follow-up time was 4.36 years.

Table 1. Baseline sample characteristics.

Characteristic	N = 138[1]
Follow-up (years)	4.36 (2.09, 5.79)
Age at Enrollment	86 (81, 90)
CDR (>1)	20 (14.5%)
Race-Ethnicity	-
Hispanic	118 (86%)
Non-Hispanic Black	13 (9.4%)
Non-Hispanic White	7 (5.1%)
Language	-
Spanish	117 (85%)
English	21 (15%)
Sex	-
Female	116 (84%)
Male	22 (16%)
Education (Years)	5 (2, 9)
APOE-ϵ4	49 (36%)
Comorbidities Burden (>=3)	104 (75%)
Psychotic Symptoms (Any)	85 (62%)
Hallucinations	42 (30%)
Illusions	5 (3.6%)
Delusions	80 (58%)
Agitation/Aggression	55 (40%)
Depressed Mood	75 (54%)
DS (0-15)	7 (5, 9)
mMMS (0-57)	29 (24, 34)

Note:[1]Median (IQR); n (%) Continuous variables were summarized using Median (IQR), as these variables were not normally distributed. Abbreviations: APOE=Apolipoprotein E, CDR=Clinical Dementia Rating, IQR=Interquartile range, DS=Dependence Scale, mMMS=Modified Mini Mental Status Exam.

At visit 6, 67% of participants had psychotic symptoms (33% had hallucinations, 17% had illusions, and 58% had delusions), 42% had agitation/aggression, and 42% depressed mood. The median mMMS score at visit 6 was 24, and the median DS score was 12. Over the course of 6 years of follow-up, 20% of participants did not have psychotic symptoms at baseline but developed psychotic symptoms at

a later visit, while 15% had psychotic symptoms at baseline but did not have psychotic symptoms at a later visit. These proportions were 28% and 17% and 17% and 21% for agitation/aggression and depressed mood, respectively.

3.2. Main Effects Models for NPS and Outcomes

Table **2** presents associations between NPS and dependence and cognition from adjusted linear mixed-effects models. Participants with psychotic symptoms had, on average, a 1.1-point higher DS score (95% CI= 0.37, 1.8) and an additional 0.29-point increase in DS scores per year of follow-up (95% CI= 0.02, 0.55) compared to those without psychotic symptoms, while those with depressed mood had an additional 0.30-point increase in DS scores per year of follow-up (95% CI= 0.06, 0.54) compared to those without depressed mood. Participants with psychotic symptoms had, on average, a 0.57-point lower cognitive score (95% CI= -2.3, 1.2) and an additional 0.92-point decline in cognitive scores per year of follow-up (95% CI= -1.5, -0.30) compared to those without psychotic symptoms, while those with agitation/aggression had, on average, a 0.89-point lower cognitive score (95% CI= -2.5, 0.75) and an additional 0.68-point decrease in cognitive scores per year of follow-up (95% CI= -1.3, -0.09) compared to those without agitation/aggression. Among specific psychotic symptoms, delusions were significantly associated with worse trajectories of change in both DS scores and cognition, while associations with hallucinations and illusions were not statistically significant.

In sensitivity analyses, fitting unweighted models, excluding the 14 participants with missing comorbidities data, had small to moderate effects on model parameters and statistical significance, indicating that results from the primary analyses were robust to the use of IPCW and imputed data. Model diagnostics for linear mixed-effects model assumptions did not provide evidence for departure from linearity.

Fig. (**2**) shows model-predicted trajectories for statistically significant NPS/outcome associations over 6 years of follow-up. Model-predicted effects for psychotic symptoms on cognitive score were equivalent to an additional decline of approximately 5.52 points on the 57-point mMMS instrument over 6 years of follow-up as compared to those without psychotic symptoms, while predicted effects for agitation/aggression on cognitive score were equivalent to an additional decline of approximately 4.08 points as compared to those without agitation/aggression. Predicted effects for psychotic symptoms on the DS were equivalent to an additional 1.74-point increase on the 15-point DS, while predicted effects for depressed mood were equivalent to an additional 1.80-point increase on the DS.

3.3. Subgroup Analyses

Table **3** presents results from unadjusted linear mixed-effects models fitted with three-way interaction terms for dichotomized age, Hispanic ethnicity, and sex. Sex modified the relationship between depressed mood and dependence, while other interactions were not statistically significant. Table **4** presents results from an adjusted model for the relationship between depressed mood and dependence fitted with a three-way interaction term for *time X depressed mood X sex* and separate adjusted models for males and females. Compared to males without depressed mood, males with depressed mood had an additional 0.89-point increase in dependence scores per year of follow-up (95% CI= 0.12, 1.7). Among females, the relationship between depressed mood and dependence was not statistically significant.

Fig. (**3**) shows separate model-predicted trajectories of dependence by depressed mood for females and males. Among males, the predicted effects of depressed mood on dependence scores were equivalent to an additional increase of approximately 5.34 points on the 15-point DS over 6 years of follow-up compared to males without depressed mood.

Table 2. Adjusted Linear Mixed-Effects Model Results (n=138).

Outcome	Model	Time	Predictor	Predictor X Time
DS	Psychotic Symptoms	0.48 (0.27, 0.70)***	1.1 (0.37, 1.8)**	0.29 (0.02, 0.55)*
	Agitation/Aggression	0.65 (0.49, 0.82)***	0.36 (-0.36, 1.1)	0.15 (-0.10, 0.40)
	Depressed Mood	0.58 (0.41, 0.75)***	-0.08 (-0.80, 0.65)	0.30 (0.06, 0.54)*
	Hallucinations	0.64 (0.48, 0.79)***	1.1 (0.35, 1.8)**	0.13 (-0.12, 0.38)
	Illusions	0.72 (0.59, 0.85)***	1.6 (-0.06, 3.3)	-0.24 (-0.69, 0.21)
	Delusions	0.48 (0.28, 0.68)***	0.84 (0.11, 1.6)*	0.32 (0.07, 0.57)*
mMMS	Psychotic Symptoms	-0.66 (-1.2, -0.16)**	-0.57 (-2.3, 1.2)	-0.92 (-1.5, -0.30)**
	Agitation/Aggression	-1.0 (-1.4, -0.64)***	-0.89 (-2.5, 0.75)	-0.68 (-1.3, -0.09)*
	Depressed Mood	-1.2 (-1.6, -0.80)***	-0.78 (-2.4, 0.88)	-0.34 (-0.89, 0.22)
	Hallucinations	-1.1 (-1.4, -0.71)***	-1.0 (-2.7, 0.74)	-0.53 (-1.1, 0.06)
	Illusions	-1.2 (-1.5, -0.91)***	-2.5 (-6.5, 1.5)	-0.35 (-1.4, 0.74)
	Delusions	-0.69 (-1.1, -0.23)**	-0.87 (-2.5, 0.81)	-0.92 (-1.5, -0.33)**

Note: *p<0.05; **p<0.01; ***p<0.001. All models adjusted for age at enrollment, race-ethnicity, sex, education, apolipoprotein E-ϵ4 polymorphism, Clinical Dementia Rating score, and dichotomized comorbidities burden score. Results are shown as beta coefficients with 95% confidence intervals. **Abbreviations:** DS=Dependence Scale, mMMS=Modified Mini Mental Status Exam.

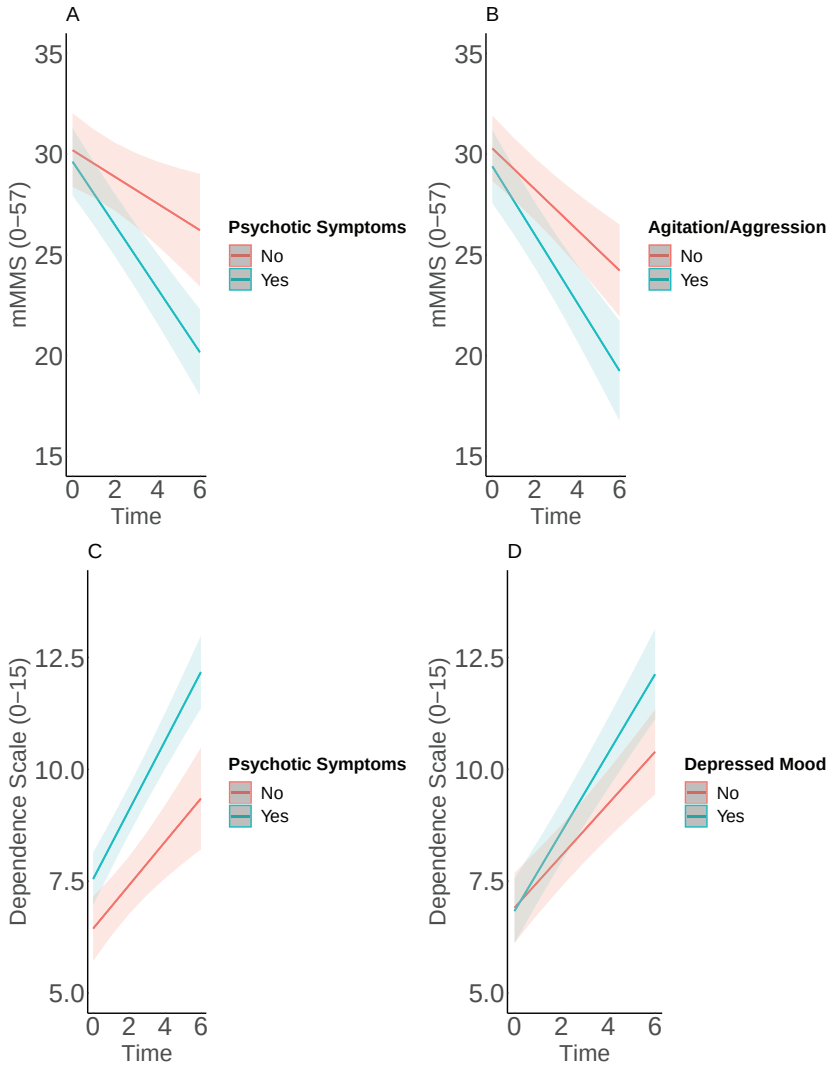

Fig. (2). Predicted trajectories over 6 years of follow-up for adjusted mixed-effects models (n=138). Plot "**A**" depicts model predicted trajectories for cognition by psychotic symptoms. Plot "**B**" depicts model predicted trajectories for cognition by agitation/aggression. Plot "**C**" depicts model predicted trajectories for dependence by psychotic symptoms. Plot "**D**" depicts model predicted trajectories for dependence by depressed mood. Predicted trajectories calculated for Hispanic females, 86 years old, with 5 years of education, clinical dementia rating score of 1, no Apolipoprotein E-ϵ4 polymorphism, and 3 or more comorbidities. Shaded areas represent 95% confidence bands. *(A higher resolution / colour version of this figure is available in the electronic copy of the article).*

Table 3. Unadjusted linear mixed-effects models for interaction analyses (n=138).

Effect Modifier	Interaction Model	DS Outcome	mMMS Outcome
Age >86	Time X Psychotic Symptoms X Age	-0.31 (-0.85, 0.24)	1.3 (-0.02, 2.6)
	Time X Agitation/Aggression X age	-0.42 (-0.94, 0.10)	0.92 (-0.32, 2.2)
	Time X Depressed Mood X Age	-0.16 (-0.68, 0.36)	0.81 (-0.39, 2.0)
Hispanic Ethnicity	Time X Psychotic Symptoms X Ethnicity	0.46 (-0.39, 1.3)	1.3 (-0.84, 3.3)
	Time X Agitation/Aggression X Ethnicity	0.35 (-0.56, 1.3)	1.4 (-0.69, 3.6)
	Time X Depressed Mood X Ethnicity	0.73 (-0.67, 2.1)	-0.41 (-3.7, 2.9)
Sex=Male	Time X Psychotic Symptoms X Sex	0.20 (-0.48, 0.88)	-1.3 (-3.0, 0.32)
	Time X Agitation/Aggression X Sex	-0.09 (-0.83, 0.64)	-1.5 (-3.2, 0.30)
	Time X Depressed Mood X Sex	0.85 (0.14, 1.6)*	-0.19 (-2.0, 1.6)

Note: *p<0.05; **p<0.01; ***p<0.001. **Abbreviations:** DS=Dependence Scale, mMMS=Modified Mini Mental Status Exam. Results are shown as beta coefficients with 95% confidence intervals.

Table 4. Adjusted linear mixed-effects models for depressed mood and dependence outcome; interaction and subgroup analyses by sex.

Model	Time	Depressed Mood	Depressed Mood X Time	Depressed Mood X Time X Sex
Total (n=138)	0.67 (0.47, 0.86)***	0.04 (-0.77, 0.84)	0.17 (-0.09, 0.44)	0.82 (0.11, 1.5)*
Males (n=22)	0.41 (-0.01, 0.82)	0.04 (-2.0, 2.1)	0.89 (0.12, 1.7)*	N/A
Females (n=116)	0.69 (0.50, 0.88)***	0.02 (-0.76, 0.81)	0.15 (-0.11, 0.41)	N/A

Note: *p<0.05; **p<0.01; ***p<0.001. All models adjusted for age at enrollment, race-ethnicity, education, apolipoprotein E-ϵ4 polymorphism, Clinical Dementia Rating score, and dichotomized comorbidities burden score. Results are shown as beta coefficients with 95% confidence intervals.

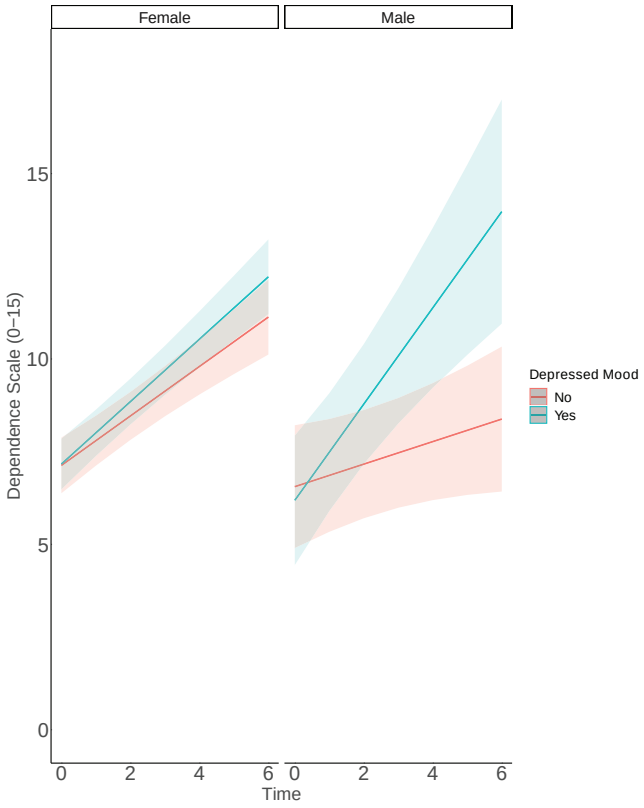

Fig. (3). Predicted trajectories of dependence over 6 years of follow-up for adjusted mixed-effects models. Predicted trajectories depicted separately for females (n=116) and males (n=22): calculated for Hispanic participants, 86 years old, with 5 years of education, Clinical dementia rating score of 1, no Apolipoprotein E-ϵ4 polymorphism, and 3 or more comorbidities. *(A higher resolution / colour version of this figure is available in the electronic copy of the article).*

4. DISCUSSION

In a community-based, multiethnic sample of older adults with probable AD, we found evidence that NPS are related to changes in cognitive and dependence scores over time. The presence of psychotic symptoms, defined broadly to include illusions as well as hallucinations, and agitation/aggression predicted lower average cognitive scores and a greater rate of decline in cognition over time, while the presence of depressed mood was related to a greater rate of increase in dependence over time. The association between psychotic symptoms and trajectories of cognition and dependence was driven by the presence of delusions rather than hallucinations or illusions. Furthermore, we found evidence that the association between depressed mood and dependence varied by sex, with depressed mood predicting trajectories of dependence in males but not in females. These results partially confirm and extend findings from prior studies that found that NPS was related to an increased risk of poorer AD outcomes in both clinic-based and community-based samples [6, 7, 48].

Our results help to build the body of evidence on associations between AD risk factors and outcomes in multiethnic, educationally diverse, community-dwelling samples of older adults. A prior study using a sample from the P3 cohort found that the baseline presence of psychotic symptoms predicted an increased risk of reaching functional and dependence, but not cognitive, endpoints in a Cox proportional hazards analysis [7]. The present study adds to these findings by exploring longitudinal associations between time--varying NPS and continuous outcome scores, modeling effects of agitation/aggression and depressed mood in addition to psychotic symptoms on outcomes, and exploring whether associations between NPS and outcomes vary by potential effect modifiers. The presence of NPS has been shown to fluctuate for AD [16], and in our sample, approximately 40% of participants had fluctuations in NPS compared to their baseline status over follow-up. For this reason, time-varying indicators of NPS may better capture dynamic associations between NPS and AD outcomes over time.

To frame the magnitude of associations that we found, it is illustrative to compare the association between NPS and cognitive decline and increase in dependence to an increased rate of cognitive aging equivalent to increased age at baseline. The associations between psychotic symptoms and agitation/aggression and the rate of decline in cognitive scores were equivalent to the unadjusted effects of an 18.4-year and a 13.6-year increase in age at baseline, respectively. The associations between psychotic symptoms and depressed mood and DS scores were equivalent to the unadjusted effects of a 29-year and a 30-year increase in age at baseline, respectively. To give the reader a sense of the magnitude of these predicted effects, the interquartile range for baseline age in our sample was 9 years.

In a study of longitudinal associations between NPS and cognitive and dependence scores in the clinic-based Predictors 1 and 2 cohorts, agitation/aggression was associated with accelerated rates of cognitive decline and increased dependence over time, while neither psychotic symptoms nor depressed mood was associated with rates of change in ei-

ther outcome [6]. As in many other clinic-based samples, those recruited in these previous cohorts were predominately White non-Hispanic with relatively high levels of education [6, 10, 11, 48], while our sample was predominately Hispanic, Spanish-speaking, and had median educational attainment of 5 years. Demographic differences between samples may account for differential findings for specific NPS in the present study. Prior research related to the theory of cognitive reserve has indicated that those with higher levels of educational attainment exhibit higher levels of cognitive reserve and consequently tend to not show clinical signs of AD sufficient for diagnosis until a relatively later stage of underlying neuropathology [21, 49], which may explain observations that those with higher educational attainment show a faster rate of cognitive decline following AD diagnosis [22]. While previous research on cognitive reserve has shown that educational attainment may influence the course and presentation of AD in older age, studies have shown that racial and ethnic identity relates to both AD incidence and disease progression [27, 50], with African American and Hispanic older adults having an elevated risk of AD and presenting with greater disease severity compared to non-Hispanic Whites [25, 26]. Furthermore, education, race, and ethnicity may interact in complex ways concerning AD risk and progression, as years of education may not be comparable between White and non-White older adults given average differences in schooling environment and resources in early life [51], potentially modifying observed associations between educational attainment and cognitive aging. As the US population continues to both age and grow more racially and ethnically diverse, non-White older adults and their caregivers are projected to put an increasing burden of AD incidence and disease severity in coming years as compared to the past [52]. For these reasons, it is critical to better understand the roles that risk factors for increased AD severity and disease progression may play within samples of older adults that better represent the diversity of the broader aging population.

As the incidence of AD, rates of cognitive decline, and presence and severity of NPS have been shown to vary by ethnicity, sex, and age [9, 23-27, 29], research exploring potential subgroup differences in the effects of predictors of differential AD outcomes can help us to better understand the heterogeneity of AD disease progression both within and across important risk groups. While the AD research community has increasingly recognized the importance of including diverse samples of older adults in research, many studies have modeled age, sex, and ethnicity as covariates in analyses to estimate population average effects on AD outcomes rather than exploring and reporting differences in associations within potential risk subgroups [28]. While we did not find differences in associations between NPS and cognition and dependence by age or Hispanic ethnicity, we did find that the association between depressed mood and the trajectory of dependence differed by sex, with an association among males but not females. Heterogeneity in this association by sex may be related to underlying sex differences in neuropathology. A pathway for sex differences in NPS associations with AD progression may lie in sex hormone effects on brain and cognitive aging, as estradiol has been previously linked to both increased risk of AD and depression *via* effects on neurotransmitter signaling and mitochondrial function [53]. Our results support further research on etiologic mechanisms for sex differences in associations between NPS and AD progression, potentially examining neuroimaging and other biomarker correlates of depressed mood and dependence in AD.

The study has several limitations. Without "gold standard" neuropathological confirmation of AD, we were limited to the use of clinical diagnosis of probable AD. It is thus possible that the inclusion of participants in our sample was subject to selection bias if the likelihood of clinical diagnosis was associated with either NPS or differences in outcome scores. The clinical consensus diagnosis method used in P3, however, has shown high reliability and consistency of diagnosis over time [54]. While we used IPCW and imputation to mitigate bias from attrition and missing data, these methods produce unbiased results only if the models used to generate IPCW and imputed data include all factors predictive of differential attrition and patterns of missingness. In an observational dataset, these assumptions may not be warranted, and results may be affected by residual bias. Furthermore, our study made use of a relatively small sample of participants, potentially limiting statistical power to detect small to moderate differences in outcome scores, particularly in models fitted with three-way interaction terms. While we did find that sex modified the association between depressed mood and the rate of change in dependence, our sample only included 22 males, limiting the ability to draw firm conclusions about these relationships among males. As the CUSPAD instrument used in this study to record the presence of NPS does not measure the severity of individual symptoms, we were unable to investigate potential relationships between symptom severity and rates of change in outcome measures. Additionally, while treatment of NPS might influence relationships between NPS and outcome measures, the P3 study did not collect information on NPS treatment, and we were thus unable to investigate the potential role of treatment.

This study has several strengths. We modeled NPS as time-varying predictors to better capture dynamic relationships between potential changes in NPS and trajectories of AD outcomes. While some prior studies have only investigated individual NPS domains, we explored outcome trajectories by psychotic symptoms, agitation/aggression, and depressed mood. A relatively long follow-up window of 6 years with frequent annual visits allowed us to capture changes in cognition and dependence that might not be evident with a shorter follow-up window and less frequent visits. Furthermore, we investigated subgroup effects by age, sex, and Hispanic ethnicity rather than treating what may be important risk group factors only as covariates in adjusted models. Lastly, we investigated associations of NPS with trajectories of AD progression in a multiethnic, community-dwelling cohort composed predominately of Hispanic older adults, a historically understudied population.

CONCLUSION

We found that the presence of specific NPS was related to greater rates of decline in cognitive scores and greater rates of increase in dependence scores over time in a community-dwelling cohort of older adults with probable AD. Furthermore, we found that depressed mood was related to greater rates of increased dependence, but only in males. While prior research has found robust evidence for associations between NPS and greater AD disease severity and course of progression, comparatively less is understood about how these relationships may hold in community-dwelling, educationally, and ethnically diverse samples. With a US population that is both aging and growing more racially and ethnically diverse, a better understanding of predictors of differential AD progression in diverse populations is needed to inform the clinical care of patients and the development of effective therapies [31]. Our results add to a growing body of literature on predictors of AD progression in community-dwelling samples that better reflect an increasingly diverse aging population in the US.

LIST OF ABBREVIATIONS

AD	=	Alzheimer's Disease
APOE	=	Apolipoprotein E
CDR	=	Clinical Dementia Rating
CUSPAD	=	Columbia University Scale for Psychopathology in Alzheimer's Disease
DS	=	Dependence Scale
IPCW	=	Inverse Probability of Censoring Weights
mMMS	=	Modified Mini-Mental Examination
NPS	=	Neuropsychiatric Symptoms
P3	=	Predictors 3

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The predictors 3 study protocol was approved by the Institutional Review Board of the New York State Psychiatric Institute.

HUMAN AND ANIMAL RIGHTS

All human subjects-based research for this study was conducted under the Helsinki Declaration of 1975, as revised in 2013 (http://ethics.iit.edu/ecodes/node/3931).

CONSENT FOR PUBLICATION

All predictors 3 study participants and study partners provided informed consent for participation.

STANDARDS FOR REPORTING

STROBE guidelines and methodology were followed.

AVAILABILITY OF DATA AND MATERIAL

Data used in this study can be made available upon reasonable request.

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CONFLICT OF INTEREST

Dr. Yian Gu is the Editorial Board Member of Current Alzheimer Research.

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REFERENCES

[1] Lyketsos, C.G.; Carrillo, M.C.; Ryan, J.M.; Khachaturian, A.S.; Trzepacz, P.; Amatniek, J.; Cedarbaum, J.; Brashear, R.; Miller, D.S. Neuropsychiatric symptoms in Alzheimer's disease. *Alzheimers Dement.,* **2011**, *7*(5), 532-539. http://dx.doi.org/10.1016/j.jalz.2011.05.2410 PMID: 21889116

[2] Lyketsos, C.G.; Lopez, O.; Jones, B.; Fitzpatrick, A.L.; Breitner, J.; DeKosky, S. Prevalence of neuropsychiatric symptoms in dementia and mild cognitive impairment: Results from the cardiovascular health study. *JAMA,* **2002**, *288*(12), 1475-1483. http://dx.doi.org/10.1001/jama.288.12.1475 PMID: 12243634

[3] Cummings, J. The role of neuropsychiatric symptoms in research diagnostic criteria for neurodegenerative diseases. *Am. J. Geriatr. Psychiatry,* **2021**, *29*(4), 375-383. http://dx.doi.org/10.1016/j.jagp.2020.07.011 PMID: 32819825

[4] Papma, JM; Franzen, S; Swieten, JC; Ossenkoppele, R; Coesmans, M; Berg, E [P1–311]: The role of neuropsychiatric symptoms in ad differential diagnosis. *Alzheimers Dement.,* **2017**, *13*(7S_Part_7), P372-P373.

[5] Spalletta, G.; Long, J.D.; Robinson, R.G.; Trequattrini, A.; Pizzoli, S.; Caltagirone, C.; Orfei, M.D. Longitudinal neuropsychiatric predictors of death in alzheimer's disease. *J. Alzheimers Dis.,* **2015**, *48*(3), 627-636. http://dx.doi.org/10.3233/JAD-150391 PMID: 26402103

[6] Zahodne, L.B.; Ornstein, K.; Cosentino, S.; Devanand, D.P.; Stern, Y. Longitudinal relationships between Alzheimer disease progression and psychosis, depressed mood, and agitation/aggression. *Am. J. Geriatr. Psychiatry,* **2015**, *23*(2), 130-140. http://dx.doi.org/10.1016/j.jagp.2013.03.014 PMID: 23871118

[7] Gottesman, R.T.; Kociolek, A.; Fernandez, K.; Cosentino, S.; Devanand, D.P.; Stern, Y.; Gu, Y. Association between early psychotic symptoms and alzheimer's disease prognosis in a community-based cohort. *J. Alzheimers Dis.,* **2021**, *81*(3), 1131-1139. http://dx.doi.org/10.3233/JAD-200729 PMID: 33896840

[8] Forester, B.P.; Vahia, I. Behavioral and psychological symptoms—an emerging crisis of the alzheimer dementia epidemic. *JAMA Netw. Open,* **2019**, *2*(3), e190790. http://dx.doi.org/10.1001/jamanetworkopen.2019.0790 PMID: 30901037

[9] Gottesman, R.T.; Stern, Y. Behavioral and psychiatric symptoms of dementia and rate of decline in alzheimer's disease. *Front. Pharmacol.,* **2019**, *10*, 1062. http://dx.doi.org/10.3389/fphar.2019.01062 PMID: 31616296

[10] Wilson, R.S.; Tang, Y.; Aggarwal, N.T.; Gilley, D.W.; McCann, J.J.; Bienias, J.L.; Evans, D.A. Hallucinations, cognitive decline, and death in Alzheimer's disease. *Neuroepidemiology.,* **2006**, *26*(2), 68-75. http://dx.doi.org/10.1159/000090251 PMID: 16352909

[11] Connors, M.H.; Ames, D.; Woodward, M.; Brodaty, H. Psychosis and clinical outcomes in alzheimer disease: A longitudinal study. *Am. J. Geriatr. Psychiatry,* **2018**, *26*(3), 304-313.

http://dx.doi.org/10.1016/j.jagp.2017.10.011 PMID: 29174998

[12] Hallikainen, I.; Koivisto, A.M.; Välimäki, T. The influence of the individual neuropsychiatric symptoms of people with Alzheimer disease on family caregiver distress-A longitudinal ALSOVA study. *Int. J. Geriatr. Psychiatry,* **2018**, *33*(9), 1207-1212. http://dx.doi.org/10.1002/gps.4911 PMID: 29851148

[13] Herrmann, N.; Lanctôt, K.L.; Sambrook, R.; Lesnikova, N.; Hébert, R.; McCracken, P.; Robillard, A.; Nguyen, E. The contribution of neuropsychiatric symptoms to the cost of dementia care. *Int. J. Geriatr. Psychiatry,* **2006**, *21*(10), 972-976. http://dx.doi.org/10.1002/gps.1594 PMID: 16955429

[14] Murman, D.L.; Chen, Q.; Powell, M.C.; Kuo, S.B.; Bradley, C.J.; Colenda, C.C. The incremental direct costs associated with behavioral symptoms in AD. *Neurology,* **2002**, *59*(11), 1721-1729. http://dx.doi.org/10.1212/01.WNL.0000036904.73393.E4 PMID: 12473759

[15] Iravani, B.; Abdollahi, E.; Eslamdoust-Siahestalkhi, F.; Soleimani, R. Neuropsychiatric symptoms of alzheimer's disease and caregiver burden. *Front. Neurol.,* **2022**, *13*, 877143. http://dx.doi.org/10.3389/fneur.2022.877143 PMID: 35968317

[16] Devanand, D.P. The interrelations between psychosis, behavioral disturbance, and depression in Alzheimer disease. *Alzheimer Dis. Assoc. Disord.,* **1999**, *13*(S2), S3-S8. PMID: 10622673

[17] Dilworth-Anderson, P.; Hendrie, H.C.; Manly, J.J.; Khachaturian, A.S.; Fazio, S.; Social, B. Diagnosis and assessment of Alzheimer's disease in diverse populations. *Alzheimers Dement.,* **2008**, *4*(4), 305-309. http://dx.doi.org/10.1016/j.jalz.2008.03.001 PMID: 18631983

[18] Morris, J.C.; Schindler, S.E.; McCue, L.M.; Moulder, K.L.; Benzinger, T.L.S.; Cruchaga, C.; Fagan, A.M.; Grant, E.; Gordon, B.A.; Holtzman, D.M.; Xiong, C. Assessment of racial disparities in biomarkers for alzheimer disease. *JAMA Neurol.,* **2019**, *76*(3), 264-273. http://dx.doi.org/10.1001/jamaneurol.2018.4249 PMID: 30615028

[19] Gottesman, R.F.; Schneider, A.L.C.; Zhou, Y.; Chen, X.; Green, E.; Gupta, N.; Knopman, D.S.; Mintz, A.; Rahmim, A.; Sharrett, A.R.; Wagenknecht, L.E.; Wong, D.F.; Mosley, T.H., Jr The ARIC-PET amyloid imaging study. *Neurology,* **2016**, *87*(5), 473-480. http://dx.doi.org/10.1212/WNL.0000000000002914 PMID: 27371485

[20] Gavett, B.E.; Fletcher, E.; Harvey, D.; Farias, S.T.; Olichney, J.; Beckett, L.; DeCarli, C.; Mungas, D. Ethnoracial differences in brain structure change and cognitive change. *Neuropsychology.,* **2018**, *32*(5), 529-540. http://dx.doi.org/10.1037/neu0000452 PMID: 29648842

[21] Stern, Y. Cognitive reserve in ageing and Alzheimer's disease. *Lancet Neurol.,* **2012**, *11*(11), 1006-1012. http://dx.doi.org/10.1016/S1474-4422(12)70191-6 PMID: 23079557

[22] Scarmeas, N.; Albert, S.M.; Manly, J.J.; Stern, Y. Education and rates of cognitive decline in incident Alzheimer's disease. *J. Neurol. Neurosurg. Psychiatry,* **2005**, *77*(3), 308-316. http://dx.doi.org/10.1136/jnnp.2005.072306 PMID: 16484637

[23] Levine, D.A.; Gross, A.L.; Briceño, E.M.; Tilton, N.; Giordani, B.J.; Sussman, J.B.; Hayward, R.A.; Burke, J.F.; Hingtgen, S.; Elkind, M.S.V.; Manly, J.J.; Gottesman, R.F.; Gaskin, D.J.; Sidney, S.; Sacco, R.L.; Tom, S.E.; Wright, C.B.; Yaffe, K.; Galecki, A.T. Sex differences in cognitive decline among US adults. *JAMA Netw. Open,* **2021**, *4*(2), e210169. http://dx.doi.org/10.1001/jamanetworkopen.2021.0169 PMID: 33630089

[24] Bernick, C.; Cummings, J.; Raman, R.; Sun, X.; Aisen, P. Age and rate of cognitive decline in Alzheimer disease: Implications for clinical trials. *Arch. Neurol.,* **2012**, *69*(7), 901-905. http://dx.doi.org/10.1001/archneurol.2011.3758 PMID: 22431834

[25] Lennon, J.C.; Aita, S.L.; Bene, V.A.D.; Rhoads, T.; Resch, Z.J.; Eloi, J.M. Black and White individuals differ in dementia prevalence, risk factors, and symptomatic presentation. *Alzheimers Dement.,* **2021**, *18*(8), 1461-1471. PMID: 34854531

[26] Tang, M.X.; Cross, P.; Andrews, H.; Jacobs, D.M.; Small, S.; Bell, K.; Merchant, C.; Lantigua, R.; Costa, R.; Stern, Y.; Mayeux, R. Incidence of AD in African-Americans, caribbean hispanics, and caucasians in northern Manhattan. *Neurology.,* **2001**, *56*(1), 49-56. http://dx.doi.org/10.1212/WNL.56.1.49 PMID: 11148235

[27] Chen, C.; Zissimopoulos, J.M. Racial and ethnic differences in trends in dementia prevalence and risk factors in the United States. *Alzheimers Dement.,* **2018**, *4*(1), 510-520. http://dx.doi.org/10.1016/j.trci.2018.08.009 PMID: 30364652

[28] Schwartz, J.B.; Weintraub, S. Treatment for alzheimer disease-sex and gender effects need to be explicitly analyzed and reported in clinical trials. *JAMA Netw. Open,* **2021**, *4*(9), e2124386. http://dx.doi.org/10.1001/jamanetworkopen.2021.24386 PMID: 34515788

[29] Babulal, G.M.; Quiroz, Y.T.; Albensi, B.C.; Arenaza-Urquijo, E.; Astell, A.J.; Babiloni, C.; Bahar-Fuchs, A.; Bell, J.; Bowman, G.L.; Brickman, A.M.; Chételat, G.; Ciro, C.; Cohen, A.D.; Dilworth-Anderson, P.; Dodge, H.H.; Dreux, S.; Edland, S.; Esbensen, A.; Evered, L.; Ewers, M.; Fargo, K.N.; Fortea, J.; Gonzalez, H.; Gustafson, D.R.; Head, E.; Hendrix, J.A.; Hofer, S.M.; Johnson, L.A.; Jutten, R.; Kilborn, K.; Lanctôt, K.L.; Manly, J.J.; Martins, R.N.; Mielke, M.M.; Morris, M.C.; Murray, M.E.; Oh, E.S.; Parra, M.A.; Rissman, R.A.; Roe, C.M.; Santos, O.A.; Scarmeas, N.; Schneider, L.S.; Schupf, N.; Sikkes, S.; Snyder, H.M.; Sohrabi, H.R.; Stern, Y.; Strydom, A.; Tang, Y.; Terrera, G.M.; Teunissen, C.; Melo van Lent, D.; Weinborn, M.; Wesselman, L.; Wilcock, D.M.; Zetterberg, H.; O'Bryant, S.E. Perspectives on ethnic and racial disparities in Alzheimer's disease and related dementias: Update and areas of immediate need. *Alzheimers Dement.,* **2019**, *15*(2), 292-312. http://dx.doi.org/10.1016/j.jalz.2018.09.009 PMID: 30555031

[30] Vespa, J; Armstrong, DM; Medina, L; Bureau, USC Demographic turning points for the United States: Population projections for 2020 to 2060 *Report Number P25-1144,* **2018**.

[31] Devi, G.; Scheltens, P. Heterogeneity of Alzheimer's disease: Consequence for drug trials? *Alzheimers Res. Ther.,* **2018**, *10*(1), 122. http://dx.doi.org/10.1186/s13195-018-0455-y PMID: 30567585

[32] Stern, Y.; Gu, Y.; Cosentino, S.; Azar, M.; Lawless, S.; Tatarina, O. The predictors study: Development and baseline characteristics of the Predictors 3 cohort. *Alzheimers Dement.,* **2017**, *13*(1), 20-27. http://dx.doi.org/10.1016/j.jalz.2016.04.004 PMID: 27219818

[33] Manly, J.J.; Bell-McGinty, S.; Tang, M.X.; Schupf, N.; Stern, Y.; Mayeux, R. Implementing diagnostic criteria and estimating frequency of mild cognitive impairment in an urban community. *Arch. Neurol.,* **2005**, *62*(11), 1739-1746. http://dx.doi.org/10.1001/archneur.62.11.1739 PMID: 16286549

[34] McKhann, G.; Drachman, D.; Folstein, M.; Katzman, R.; Price, D.; Stadlan, E.M. Clinical diagnosis of Alzheimer's disease: Report of the NINCDS-ADRDA work group under the auspices of department of health and human services task force on alzheimer's disease. *Neurology.,* **1984**, *34*(7), 939-944. http://dx.doi.org/10.1212/WNL.34.7.939 PMID: 6610841

[35] Zhu, C.W.; Bruinsma, B.G.; Stern, Y. Utility of the dependence scale in dementia: Validity, meaningfulness, and health economic considerations. *Alzheimers Res. Ther.,* **2018**, *10*(1), 78. http://dx.doi.org/10.1186/s13195-018-0414-7 PMID: 30103820

[36] Stern, Y.; Sano, M.; Paulson, J.; Mayeux, R.P. Modified mini--mental state examination: Validity and reliability. *Neurology,* **1987**, 37.

[37] Devanand, D.P. Use of the columbia university scale to assess psychopathology in alzheimer's disease. *Int. Psychogeriatr.,* **1997**, *9*(S1), 137-142. http://dx.doi.org/10.1017/S104161029700481X PMID: 9447437

[38] Stern, Y.; Albert, M.; Brandt, J.; Jacobs, D.M.; Tang, M-X.; Marder, K.; Bell, K.; Sano, M.; Devanand, D.P.; Bylsma, F.; Lafleche, G. Utility of extrapyramidal signs and psychosis as predictors of cognitive and functional decline, nursing home admission, and death in Alzheimer's disease: Prospective analyses from the Predictors Study. *Neurology,* **1994**, *44*(12), 2300-2307. http://dx.doi.org/10.1212/WNL.44.12.2300 PMID: 7991116

[39] Gu, Y.; Gutierrez, J.; Meier, I.B.; Guzman, V.A.; Manly, J.J.; Schupf, N.; Brickman, A.M.; Mayeux, R. Circulating inflammato-

ry biomarkers are related to cerebrovascular disease in older adults. *Neurol. Neuroimmunol. Neuroinflamm.,* **2019**, *6*(1), e521. http://dx.doi.org/10.1212/NXI.0000000000000521 PMID: 30568999

[40] Kociolek, A.J.; Fernandez, K.K.; Jin, Z.; Cosentino, S.; Zhu, C.W.; Gu, Y.; Stern, Y. Extrapyramidal signs and Alzheimer's disease prognosis in a multiethnic, community-based sample of demented elders. *Alzheimers Dement.,* **2021**, *17*(9), 1465-1473. http://dx.doi.org/10.1002/alz.12309 PMID: 33710771

[41] Team, R.C. A language and environment for statistical computing. In: *R Foundation for Statistical Computing, Vienna, Austria*; , **2020**.

[42] Team, R.S.; Allaire, J. *RStudio: Integrated Development for R, Boston, MA.,* **2012**, *770*(394), 165-71.

[43] Cole, S.R.; Hernán, M.A. Constructing inverse probability weights for marginal structural models. *Am. J. Epidemiol,* **2008**, *168*(6), 656-664.

[44] van der Wal, W.M.; Geskus, R.B. {ipw}: An {R} package for inverse probability weighting. *J. Stat. Softw.,* **2011**, *43*(13), 1-23.

[45] Kuhn, M. *caret: Classification and Regression Training*; Astrophysics Source Code Library, **2021**.

[46] Bates, D.; Mächler, M.; Bolker, B.; Walker, S. Fitting linear mixed-effects models using lme4. *J. Stat. Softw.,* **2015**, *67*(1), 1-48. http://dx.doi.org/10.18637/jss.v067.i01

[47] Twisk, J.W.R. *Applied longitudinal data analysis for epidemiology: a practical guide*; Cambridge University Press: Cambridge, New York, **2015**.

[48] Scarmeas, N.; Brandt, J.; Albert, M.; Hadjigeorgiou, G.; Papadimitriou, A.; Dubois, B.; Sarazin, M.; Devanand, D.; Honig, L.; Marder, K.; Bell, K.; Wegesin, D.; Blacker, D.; Stern, Y. Delusions and hallucinations are associated with worse outcome in Alzheimer disease. *Arch. Neurol.,* **2005**, *62*(10), 1601-1608. http://dx.doi.org/10.1001/archneur.62.10.1601 PMID: 16216946

[49] Stern, Y. Cognitive reserve and Alzheimer disease. *Alzheimer Dis. Assoc. Disord.,* **2006**, *20*(2), 112-117. http://dx.doi.org/10.1097/01.wad.0000213815.20177.19 PMID: 16772747

[50] Manly, J.M.R. Ethnic differences in dementia and Alzheimer'sdisease. In: *Critical Perspectives on Racial and Ethnic Differences in Health in Late Life*; National Academies Press, **2004**.

[51] Sisco, S.; Gross, A.L.; Shih, R.A.; Sachs, B.C.; Glymour, M.M.; Bangen, K.J.; Benitez, A.; Skinner, J.; Schneider, B.C.; Manly, J.J. The role of early-life educational quality and literacy in explaining racial disparities in cognition in late life. *J. Gerontol. B Psychol. Sci. Soc. Sci.,* **2015**, *70*(4), 557-567. http://dx.doi.org/10.1093/geronb/gbt133 PMID: 24584038

[52] Matthews, K.A.; Xu, W.; Gaglioti, A.H.; Holt, J.B.; Croft, J.B.; Mack, D.; McGuire, L.C. Racial and ethnic estimates of Alzheimer's disease and related dementias in the United States (2015–2060) in adults aged ≥65 years. *Alzheimers Dement.,* **2019**, *15*(1), 17-24. http://dx.doi.org/10.1016/j.jalz.2018.06.3063 PMID: 30243772

[53] Russell, J.K.; Jones, C.K.; Newhouse, P.A. The role of estrogen in brain and cognitive aging. *Neurotherapeutics,* **2019**, *16*(3), 649-665. http://dx.doi.org/10.1007/s13311-019-00766-9 PMID: 31364065

[54] Schofield, P.W.; Tang, M.; Marder, K.; Bell, K.; Dooneief, G.; Lantigua, R.; Wilder, D.; Gurland, B.; Stern, Y.; Mayeux, R. Consistency of clinical diagnosis in a community-based longitudinal study of dementia and Alzheimer's disease. *Neurology,* **1995**, *45*(12), 2159-2164. http://dx.doi.org/10.1212/WNL.45.12.2159 PMID: 8848185