Title: A longitudinal study of late-life psychosis and incident dementia and the potential effects of race and cognition

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Abstract

Background: Later-life psychotic symptoms are meaningful and are associated with adverse outcomes. Psychosis is an important domain in mild behavioral impairment (MBI), a syndrome that incorporates later-life emergent and persistent neuropsychiatric symptoms (NPS) in dementia-free individuals into dementia prognostication. However, MBI-psychosis-associated risk and its interaction with race has not been well quantified. Here, we determined risk of incident dementia in dementia-free participants with MBI-psychosis, and effect modification by race as an important factor in assessing the risk of psychosis.

Methods: Data for participants with normal cognition (NC) or mild cognitive impairment (MCI) from the National Alzheimer Coordinating Centre (NACC) were utilized. Participants with neurodevelopmental, neurological and/or longstanding psychiatric disorders were excluded. MBI-psychosis was defined by persistence of delusions and hallucinations across two consecutive visits. Kaplan-Meier curves of ten-year dementia-free survival were generated for MBI-psychosis versus no NPS prior to dementia diagnosis. Cox proportional hazard models were implemented to assess relative incidence rates, adjusted for cognitive status, age, sex, education, race, and APOE-ε4 status. Interaction terms were included for relevant demographic variables. Similar secondary analyses utilized MBI-no-psychosis as reference.

Results: The sample consisted of 3,704 No-NPS (age=72.8±9.9; 62.7% female; 13.4% MCI), and 66 MBI-psychosis participants (age =75.2±9.8; 53% female; 72.7% MCI). For MBI-psychosis, in reference to No-NPS, the hazard ratio (HR) for incident dementia was 3.76 (CI:2.53-5.58, $p<0.001$), while for conventionally captured psychosis the HR was 1.92 (CI:1.58-2.33, $p<0.001$). Interaction analysis revealed that in NC, those with MBI-psychosis had a 9.96-fold greater incidence than those

with No-NPS (CI:3.65-27.22, p<0.001). In MCI, the MBI-psychosis-associated dementia incidence was 3.38-fold greater (CI:2.22-5.15, p<0.001). Furthermore, MBI-psychosis-associated dementia incidence in Black participants was 7.44-fold greater than No-NPS (CI:3.54-15.65, p<0.001), while in White participants it was 3.18-fold greater (CI:1.94-5.2, p<0.001). In a secondary analysis, compared to MBI-no-psychosis (n=2260), MBI-psychosis had a 2.47-fold greater incidence of dementia (CI:1.69-3.59, p<0.001).

Conclusion: Although psychosis is an infrequently endorsed MBI domain, when present it is associated with substantial risk for dementia. HRs differed between cognitive strata and these differences were significantly greater when MBI-psychosis emerged in NC as opposed to MCI, emphasizing the importance of cognitive assessment at the time of symptom emergence. Additionally, the relationship between MBI-psychosis and incident dementia was stronger in Black participants than White participants. The emergence of persistent psychotic symptoms in older adults is clinically meaningful, and MBI-psychosis identifies a high-risk group for precision medicine approaches to dementia prevention.

Main

Neuropsychiatric symptoms (NPS) are non-cognitive psychiatric and behavioural symptoms experienced by patients with neurodegenerative diseases. These symptoms are core dementia features, with a period prevalence of approximately 97% in Alzheimer's disease dementia (AD) in the first five years after diagnosis[1]. Psychotic symptoms (hallucinations and delusions) are clinically meaningful NPS, common in AD dementia, with a prevalence of 41%[2]. Psychosis in AD is associated with poor outcomes including cognitive and functional impairment, higher mortality, and greater caregiver burden[3-6]. However, psychotic symptoms are also observed before syndromic dementia and signal a group at high risk for incident cognitive decline and dementia[7,8]. Accordingly, the revised International Psychogeriatric Association (IPA) criteria for psychosis in neurocognitive disorders have expanded to include mild neurocognitive disorder[9], whereas previous criteria stipulated that psychotic symptoms must emerge after dementia diagnosis[10]. The International Society to Advance Alzheimer's Research and Treatment (ISTAART) research criteria for psychosis in AD extend even further to include cognitively normal (NC) persons, to include all older adults with new-onset psychosis for further epidemiological, biomarker, and genetic research, irrespective of cognitive status[11]. Thus, given the implications of late-life psychosis for dementia incidence, a systematic approach for prediction and prognostication is required, as the first step towards investigating targeted therapy[8]. What remains unclear, is whether late-life psychosis (LLP) is a risk factor or a disease marker. For the former, LLP would represent a psychiatric disorder labelled using current nosology (e.g., schizophrenia, delusional disorder). For the latter, however, LLP would represent behavioural sequelae of neurodegenerative disease changes, labelled by symptoms (e.g., hallucinations, delusions). Cross-sectionally, one cannot rely on phenomenology alone to distinguish between the two; neuropathology and biomarker studies would be required to clarify. However, symptom natural history may also offer insights.

Mild behavioral impairment (MBI) is a syndrome that incorporates psychiatric and behavioral symptoms to identify a high-risk group for incident cognitive decline and dementia[12]. In MBI dementia-free adults older than 50 years of age experience persistent psychiatric and behavioral symptoms, which are of new-onset and reflect a change from longstanding patterns[12-14]. MBI comprises five domains of decreased drive and motivation (apathy), affective dysregulation (mood/anxiety symptoms), impulse dyscontrol (agitation, aggression, impulsivity, impaired reward salience), social inappropriateness (impaired social cognition), and abnormal perception/thought content (psychotic symptoms). Longitudinal studies have determined that MBI is associated with a greater risk of cognitive decline and dementia[15-23]. To our knowledge, only one study has evaluated longitudinal outcomes with MBI-psychosis, in participants with MCI[24]. However, this study incorporated neither the core MBI criterion stipulating new-onset symptomatology, nor the criterion stipulating symptom persistence[12]. Thus, in dementia-free older adults, we assessed progression to dementia in in persons with later-life emergent and persistent psychosis. Furthermore, we explored effect modification by race on the association of MBI-psychosis with incident dementia. Several European studies on dementia patients have indicated a higher incidence and prevalence of psychosis in Black African and Black Caribbean patients compared to White patients[25,26]. We hypothesized that participants with MBI-psychosis would have a greater incidence of dementia compared to participants with no NPS, or those with MBI without psychosis, and this association would differ across racial groups.

Results

Primary analysis: dementia incidence across MBI-psychosis and No-NPS groups

The final sample consisted of 3,704 participants with no NPS prior to dementia diagnosis (No-NPS) (mean age=72.8±9.9; 62.7% female), and 66 with new-onset persistent psychosis (*i.e.*, MBI-psychosis)

(mean age=75.2±9.8; 53% female) from the National Alzheimer Coordinating Center (NACC). There was a significantly higher percentage of MCI participants within the MBI-psychosis group, compared to No-NPS ($p<0.001$). No significant differences were found for age ($p=0.053$) or sex ($p=0.14$). Years of education were significantly higher in the No-NPS group ($p=0.014$). Race was significantly different across the NPS groups ($p=0.001$), with more White participants in the No-NPS group and more racial diversity in the MBI-psychosis group. APOE-ε4 status did not differ between groups ($p=0.76$). Table 1 demonstrates details of the between-group differences across all covariates.

Figure 1(A) illustrates the Kaplan-Meier (KM) curve of the dementia-free survival probability and adjusted hazard ratio (HR) for incident dementia over ten years, stratified by NPS group. Compared to the No-NPS group, dementia-free survival was lower in the MBI-psychosis group ($p<0.0001$). The five-year survival probability for the No-NPS group was 90.5% (CI:89.2%-91.7%), while for the MBI-psychosis group it was only 35.7% (CI:22.8%-55.9%). Compared to No-NPS, MBI-psychosis had 3.76-fold greater dementia progression rate (CI:2.53-5.58, $p<0.001$) (Fig. 1(A)). In total, 303 participants progressed to dementia over ten years. Of the 66 participants with MBI-psychosis, 45.5% (n=30) progressed to dementia, consisting of AD (66.7%, n=20), dementia with Lewy Bodies (DLB) (10%, n=3), vascular dementia (3.3%, n=1), and unrecorded dementia subtypes (20%, n=6). Among the 3,704 participants with no NPS, 7.4% (n=273) progressed to dementia, consisting of AD (89%, n=243), behavioral variant of frontotemporal dementia (bvFTD) (1.1%, n=3), DLB (1.1%, n=3), vascular dementia (1.8%, n=5), and unrecorded dementia subtypes (6.9%, n=19).

While not statistically significant due to sample-size-related imprecision of the estimate, interaction effects were observed for MBI-psychosis and cognitive status with a considerable difference in HRs between cognitive strata (multiplicative interaction test: HR=2.95, CI:0.99-8.72, $p=0.05$). In MCI,

MBI-psychosis had a 3.38-fold greater progression rate than No-NPS (CI:2.22-5.15, p<0.001). In NC, MBI-psychosis had a 9.96-fold greater progression rate than No-NPS (CI:3.65-27.20, p<0.001) (Table 2 and Fig. 2(A)). No significant interaction effects were found between MBI-psychosis and sex (p=0.7). Overall, Black participants had lower incidence of dementia compared to White participants (see Fig. 1(B), HR=0.63, CI:0.45-0.87, p=0.005). However, Black participants with MBI-psychosis had a 7.44-fold greater progression rate than the No-NPS participants (CI:3.54-15.65, p<0.001), while among White participants, MBI-psychosis had a 3.18-fold greater progression rate than No-NPS (CI:1.94-5.20, p<0.001). Although non-significant, within the Other races category, MBI-psychosis had a 2.61-fold greater progression rate than No-NPS (CI:0.74-9.18, p=0.136) (Table 3 and Fig. 2(B)). However, the multiplicative interaction test did not find HRs to significantly differ across race categories (Black vs White: HR=2.34, CI:0.97-5.65, p=0.058; Black vs Other: HR=2.85, CI:0.66-12.31, p=0.159; Other vs White: HR=0.82, CI:0.21-3.13, p=0.772) (Table 3). The small sample size per race in the Other racial category did not allow the identification of the specific races associated with the risk. Interaction effects were not observed for APOE-ε4 status (p=0.24).

Secondary analysis: dementia incidence across Conv-psychosis and No-NPS groups

The sample for this secondary analysis consisted of 6,720 individuals with no NPS prior to dementia diagnosis (No-NPS) and 291 with conventionally captured psychosis (Conv-psychosis). Compared to the No-NPS group, the Conv-psychosis group had fewer years of education (p<0.001), fewer females (p<0.001), and fewer Black participants. This group had more participants in Other races (p=0.009), and a higher percentage of MCI (p<0.001) and APOE-ε4 carriers (p=0.004) (supplementary table 1).

The KM survival curves demonstrated that compared to No-NPS, dementia-free survival was lower in Conv-psychosis (p<0.0001). The five-year dementia-free survival probability for the No-NPS group

was 87.3% (CI:86.3-88.4), while for the Conv-psychosis group it was 38.6% (CI:31.7-47.0). The adjusted Cox regression model demonstrated a greater progression rate to dementia in the Conv-psychosis group compared to No-NPS (adjusted HR=1.92, 95%CI:1.58-2.33, p<0.001) (Fig. 1(B)).

Secondary analysis: dementia incidence across MBI-psychosis and MBI-no-psychosis groups

Secondary analyses comparing individuals with MBI-psychosis to those with MBI of any type except psychosis (MBI-no-psychosis) yielded similar results. The no-psychosis group consisted of 2,260 participants (mean age=75.2±9.1; 48.1% female) with more White participants (85.8%, p<0.001) and lower percentage of MCI diagnosis (42.3%, p<0.001) than the MBI-psychosis group (supplementary table 2).

KM curves stratified by psychosis group demonstrated that participants with MBI-psychosis had lower dementia-free survival, compared to those with no psychosis (p<0.0001) (Supplementary fig. 1(A)). Five-year survival probability of the no-psychosis group was 70.7% (CI:68.3%-73.1%), while for MBI-psychosis it was only 35.7% (CI:23.8%-55.9%). Adjusted Cox proportional hazards models showed that compared to MBI-no-psychosis, MBI-psychosis had a 2.47-fold greater progression rate (CI:1.69-3.59, p<0.001) (Supplementary fig. 1(B)). In total, 583 participants progressed to dementia over ten years. Among the 2,260 MBI-no-psychosis participants, 24.4% (n=553) progressed to dementia, consisting of AD (86.4%, n=478), bvFTD (1.9%, n=11), DLB (3.2%, n=18), vascular dementia (1.3%, n=7), and unrecorded dementia subtypes (7.1%, n=39).

No significant interaction of NPS group was found for cognitive status (p=0.61), sex (p=0.55), race (Black vs White: p=0.346, Other vs White: p=0.98), or APOE-ε4 status (p=0.45), however the within-stratum effects did follow similar trends to those of the primary analysis. In MCI, those with MBI-

196 psychosis had a 2.38-fold greater progression rate than those with no psychosis (CI:1.59-3.57,
197 p<0.001). Among NC participants, MBI-psychosis had a 3.14-fold greater progression rate than MBI-
198 no-psychosis (CI:1.16-8.53, p=0.024). (Supplementary table 3). For race, among Black participants,
199 those with MBI-psychosis had a 3.40-fold greater progression rate than MBI-no-psychosis (CI:1.62-
200 7.10, p<0.001). Among White participants, MBI-psychosis had a 2.23-fold greater rate (CI:1.39-3.60,
201 p<0.001). Although non-significant, within the Other races category, those with MBI-psychosis had a
202 2.30-fold greater incidence than those with no psychosis (CI:0.67-7.60, p=0.189) (supplementary table
203 4).
204
205 **Discussion**
206 Although psychotic symptoms occur relatively infrequently in advance of dementia, these are
207 meaningful symptoms. A recent meta-analysis estimated the pooled prevalence of MBI-psychosis as
208 4.83% in MCI and 1.84% in NC[27]. However, different approaches to NPS measurement and
209 inconsistent use of MBI symptom emergence and persistence criteria result in substantial estimate
210 heterogeneity in these types of analyses. Studies using the MBI checklist (MBI-C)[28], developed
211 explicitly for MBI case ascertainment, have also reported psychosis prevalence. In the community
212 sample of participants in the PROTECT study, MBI-psychosis prevalence was 6% via informant report
213 and 3% via self-report[29]. In a memory clinic-based sample, MBI-psychosis prevalence was 5.4% in
214 patients with subjective cognitive decline and 17% in MCI[30]. These are not trivial frequencies for what
215 are very impactful symptoms, ultimately occurring in 41% in patients with AD dementia and 75% with
216 DLB[8].
217
218 We demonstrated that incidence of dementia was 3.76-fold higher in MBI-psychosis versus No-NPS.
219 When compared to MBI-no-psychosis in secondary analyses, dementia incidence was 2.47-fold higher

in MBI-psychosis. Effect modification was observed for cognitive status. In MCI, persistent new-onset psychosis was associated with 3.38-fold greater progression rate compared to No-NPS, but in NC, the relative rate was significantly higher at 9.96. These findings suggest that when psychosis emerges early in the neurodegenerative disease process, the contribution of these symptoms is profound. In MCI, underlying disease burden is theoretically greater, with other factors in play relative to NC, where the impact of psychosis in the modeling is greater. We also investigated dementia incidence in the Conv-psychosis group in which psychosis was assessed with a more conventional approach, *i.e.*, at a single timepoint and without consideration of past psychiatric history. Compared to No-NPS, the Conv-psychosis group had 1.92-fold higher dementia incidence rate, while MBI-psychosis had 3.76-fold higher rate. These findings support the utility of the two core MBI criteria for psychosis and suggest that when psychosis is both emergent and persistent, a considerably greater incidence of dementia is observed.

The only previous study reporting the association of MBI-psychosis with incident dementia assessed MCI participants alone. All five MBI domains were assessed with NPS based on a single Neuropsychiatric Inventory Questionnaire (NPI-Q) assessment of symptom presence over one month. In that study, psychosis was associated with greater incidence of dementia in two of the three statistical models, with HRs ranging from 1.97-2.71[24]. Of all NPS assessed with this single timepoint measure, psychosis was the only domain demonstrating an association with incident dementia. This finding highlights the impact of psychosis in older adults relative to other NPS, but also the importance of operationalizing MBI criteria to ensure symptom persistence (at two timepoints or with a measure with a reference range of at least six months) to enrich samples with persons at high-risk for incident dementia. Despite the short reference range for MBI case status, psychosis was still associated with dementia. Our study extends this finding, by capturing persistent psychosis across two consecutive

timepoints and incorporating No-NPS as well as MBI-no-psychosis comparators into the modeling. While No-NPS participants had a five-year dementia-free survival of 90.5%, MBI-no-psychosis had a 70.7% five-year dementia-free survival, and MBI-psychosis had a 35.7% survival. Thus, our study not only highlights the importance of psychosis as a clinically significant symptom, relative to other NPS, but also emphasizes the importance of NPS nosology and measurement in risk assessment and the utility of incorporating MBI criteria into modeling.

Other longitudinal studies in MCI, using more conventional assessments of psychosis, have assessed progression to dementia with some suggesting greater risk[31-35] and others no greater risk[36-38]. Differences in findings may be due to inadequate sample size[36,37], sample heterogeneity[36,38], short follow-up intervals[38,39], psychosis assessed with a shorter-term measure[36], and attrition[37]. A longitudinal study of participants over 17.7 years revealed that psychosis (assessed from ICD codes) had a 2.67-fold greater rate of dementia versus no psychosis. Interestingly, sub-HRs were higher for incident versus prevalent psychosis, and for short-duration versus long-duration psychosis[40]. A similar Swedish health register study demonstrated that VLOSLP diagnosis (ICD codes) versus no VLOSLP had a 4.4-fold greater HR for dementia; incidence was highest in the immediate year following VLOSLP diagnosis[41]. However, cognitive status was not reported in either of these rigorous studies, inherent with the methodological approach of using ICD codes for psychosis, which are only provided when psychotic symptoms are of sufficient severity to prompt clinical attention.[40] Unfortunately, this approach precludes comparisons of natural histories of cognition and psychosis, unless the dataset includes explicit cognitive scores or categories. Nonetheless, these studies clearly support the notion that new-onset symptoms in older persons identify a high-risk group, consistent with the core MBI criterion of symptom emergence in later life. Different reference groups, and different symptom duration/persistence criteria prohibit direct comparisons of HRs with our findings.

Few studies have described progression to dementia in samples where cognitively normal status at baseline was explicit [37,42-44], with two of four demonstrating an association.[42,43] Methodological differences and small sample sizes limit interpretation and comparison of results. This limited, disparate, and heterogeneous evidence base further reinforces the inclusion of cognitively normal status in the ISTAART research criteria for psychosis in AD, in order to generate more consistent data across the whole cognitive spectrum[11].

The incorporation of race as a covariate was an important contributor to the modeling. We found that dementia-free participants with psychosis were more racially diverse compared to participants with no NPS. The MBI-psychosis group consisted of 63.6% White participants, 18.2% Black, and 18.2% Other races. The No-NPS group in comparison, had 75.5% White participants, 17.8% Black, and 6.7 Other races. Similar trends were observed when comparing participants with MBI-psychosis to those with MBI-no-psychosis (no-psychosis group: 85.8% White, 8.4% Black, 5.8% Other). These findings are consistent with previous literature highlighting racial differences of psychosis in pre-dementia stages[2,45,46]. Black Americans are 3-4-fold more likely to show symptoms of psychosis compared to White Americans and are more likely to be diagnosed with psychosis[2]. Similar findings have been reported in European studies, where a higher incidence and prevalence of psychosis was reported in Black African and Black Caribbean patients compared to White patients[25,26]. These results raise questions about whether there are ethnoracial differences in the expression of MBI symptomatology, or if specific groups are diagnosed with psychosis more often based on external issues like differential access to specialized care or the use of culturally insensitive measures.

The social construct of race is often conceptualized as a biological factor to incorrectly relate differences in health outcomes to the biological properties perceived to be associated with race, which has greatly contributed to misdiagnosis and health disparities for Black individuals[47]. Furthermore, socioeconomic status (SES), often measured from income, occupation, and education levels, is associated with earlier and faster pace of aging-related brain changes[48]. The magnitude of the association between SES and biological aging varies across race; wealthier and more highly educated individuals tend to experience less-advanced biological aging[49]. Numerous European studies have demonstrated the significant influence that social inequalities often faced by racial minorities have on the risk of psychosis[26]. The US lags behind Europe in investigating the link between race-related social inequalities and psychosis incidence. A recent review has identified neighborhood, cumulative trauma and stress, and prenatal and perinatal complications as key factors influencing the risk of psychosis, which are disproportionately experienced by Black persons. More extensive studies are required to explore social determinants of psychosis within North America and prospective cohorts need to incorporate more data related to SES and social inequality[50]. As the NACC dataset does not include enough data related to SES, it is unclear if our race-related findings reflect real underlying difference in prevalence, severity, or phenotype of psychosis in Black Americans, or are due to some other epiphenomena.

Interaction analyses were instructive. Notably, Black participants with MBI-psychosis had a 7.44-fold greater incidence of dementia than those with No-NPS; among White participants, the MBI-psychosis-related incidence of dementia was 3.18-fold greater than No-NPS. While these HRs were not statistically significantly different in the multiplicative interaction test ($p=0.058$), the substantial numerical difference in the measure of effect does provide some pause, and suggests that further research is required. The relative magnitude and direction of effect in the secondary analysis is also

supportive. MBI-psychosis in Black participants was also associated with numerically greater rate of dementia than White participants (HR 3.40 vs 2.23). Again, the reason for these findings is not clear - replication of this analysis with a larger sample of MBI-psychosis participants can further evaluate the significance of this interaction, with more precise estimates. Importantly, sampling not only requires broader racial representation of the population at large, but also improved ethnocultural descriptions of participants for better stratification, as the current nomenclature for race is overly simplistic and reductionistic. A recent study of NACC participants assessed associations between depression and incident dementia in five ethnoracial groups, finding that previously established risk factors between depression and dementia were not established in all groups. The authors suggest that the homogenous classification of diverse NACC participants into the restrictive race and ethnicity designations of the US census eschews diversity, life course, and cultural variability that contribute to identity, all of which may impact the development of depression[51]. In our study, whether a cultural component combined with possible genetic variability explains this phenomenon is unknown. However, this signal warrants a closer evaluation of the racial differences of the MBI-psychosis domain in pre-dementia stages.

We found no association between APOE-ε4 status and NPS groups. Although main effects describe greater dementia incidence for both MBI-psychosis and APOE-ε4 carrier status, the interaction term was non-significant. However, effect modification cannot be ruled out due to a relatively small sample of MBI-psychosis participants. Our results are in contrast to literature showing a relationship between AD genetic risk and psychosis in dementia.[52] [53,54]. Larger samples, and subtyping of psychosis into hallucinations and delusions[55,56] may reconcile these differences.

In our study, among the MBI-psychosis participants who progressed to dementia, 66.7% developed AD dementia, but ~10% of participants had an unrecorded dementia diagnosis and thus it is difficult to assess between-group differences in dementia diagnoses. However, with respect to DLB, there are numerical differences which are worth discussing. Of the MBI-psychosis participants that progressed to dementia, 10% were given a clinical diagnosis of DLB. Of the MBI-no-psychosis group 3.2% of progressors developed DLB, and of the No-NPS group 1.1% of progressors developed DLB. Studies have found that psychosis in DLB and Parkinson's disease (PD) is more prevalent than in AD[57,58]. However, recent clinicopathological studies have illuminated the field further. One study of NACC participants found that when persons experienced psychosis in AD, they were five times more likely to be provided a clinical misdiagnosis of DLB[59]. Another NACC study of NC participants found that 6% with MBI progressed to AD in five years, with MBI a significant predictor of progression to both clinically-diagnosed (HR=1.75) and neuropathology-confirmed AD (HR=1.59). MBI domains were also associated with clinically-diagnosed AD, with psychosis having the greatest effect (HR=6.49)[60]. These studies suggest an underdiagnosis of AD in the presence of behavioural symptoms. Furthermore, the past literature indicates that AD co-pathology is quite common in DLB. While the accumulation of pathogenic alpha-synuclein protein in the brain is the characteristic feature of DLB, recent studies have shown that it is often accompanied by amyloid-beta and tau pathology, which are the characteristic hallmarks of AD[61]. Based on reports from a US-based large multi-center cohort, more than 70% of DLB patients had medium to high levels of AD neuropathologic change at autopsy[62]. Therefore, it is possible that many of the participants with DLB in our sample would also develop AD - the psychotic symptoms observed in early dementia stages in these participants may be associated with AD co-pathology, or vice versa. In our sample, among all participants with MBI-psychosis who progressed to dementia, 67% developed AD dementia, 10% developed DLB, 3% developed vascular dementia, 0% developed bvFTD, while 20% had an unrecorded diagnosis. Thus, while psychosis is an early

362 manifestation of DLB, as is well appreciated in the literature, most with MBI-psychosis still go on to
363 develop AD, attendant with the substantially higher population prevalence of AD and the frequency of
364 psychosis in AD. Our AD-predominant sample provides additional insight into the NPS of AD[59], such
365 that psychosis can be an early manifestation of all dementias including AD, and represents a more
366 severe dementia phenotype. These findings are supported by the burgeoning literature linking MBI
367 with AD biomarkers[63-70]. Future studies should explore these biomarkers in MBI-psychosis
368 specifically.
369
370 **Limitations**
371 While study strengths include exploration of the novel MBI framework, with explicit inclusion of new-
372 onset and persistent psychotic symptoms, several limitations are worth noting. The type of psychotic
373 symptom (i.e., hallucination or delusion) was not distinguished due to the low prevalence of these
374 symptoms in advance of dementia, notwithstanding the fact that these symptoms can have different
375 risks, trajectories, and neurobiological underpinnings[52,55,56]. Findings from the PROTECT study have
376 demonstrated that in the sample of mostly cognitively intact individuals, persecutory delusions
377 comprise the majority of psychotic symptoms[29]. Larger samples will be needed to explore differences
378 in risk between hallucinations and delusions. Our sample of MBI-psychosis is relatively small as many
379 participants with persistent psychosis had dementia at baseline (n>1000), potentially underestimating
380 the association of psychosis and cognitive impairment. The possible exclusion of those with late onset
381 delusional disorder, LOS, and VLOSLP (whether through study recruitment and sampling, or
382 exclusion criteria for analysis) may have resulted in an underestimation of the effect. Addressing this
383 issue is fundamental to better dementia prognostication and earlier detection, as well as targeted
384 assessment, workup, and implementation of preventative therapies, both pharmacological and non-
385 pharmacological. Self-awareness, anosognosia, or lack of insight are important constructs in

386 neurodegenerative disease and were not included in our analysis due to difficulties operationalizing
387 them as a variable. Poor self-awareness for cognitive symptoms may be related to NPS, as cause or
388 consequence, or may be common to both even, manifesting secondary to neurodegenerative disease
389 changes[18,71-73]. Our study design did not allow for exploration of this very important issue.
390 Furthermore, the use of antipsychotic medications was not accounted for in our models. The only
391 available item regarding the use of antipsychotics is the self-reported NACCAPSY item, in which
392 antipsychotic exposure was inconsistently recorded across all participant visits. Future studies using
393 cohorts with a full account of antipsychotic medication exposure are required to clarify any
394 confounding effects of medication use in the model.
395
396 **Conclusions**
397 Our study highlights the importance of assessment for emergence and persistence of psychosis in
398 dementia-free older adults, which captures a group with a high dementia incidence relative to non-
399 psychotic older adults. Future studies should embrace the IPA and ISTAART psychosis criteria to
400 standardize the evidence base. Importantly, the study also highlights potential racial differences in the
401 association between MBI-psychosis and incident dementia. That Black participants with MBI-
402 psychosis had substantially numerically greater dementia incidence rates than White participants is a
403 fascinating finding that needs further exploration, with larger sample sizes of diverse populations, with
404 better descriptions of ethnoracial groups.
405
406 **Methods**
407 Source population
408 Data were obtained from the NACC database (https://naccdata.org), with a December 2021 data freeze.
409 NACC was established by the National Institute on Aging (NIA) and consists of multiple NIA-funded

Alzheimer's Disease Research Centers (ADRCs) recruiting and collecting data on participants with cognitive functions ranging from normal to dementia. The NACC Uniform Data Set (UDS) is a large longitudinal dataset including demographic and standardized clinical data collected approximately annually. All test centers administered standardized forms, and informed consent was collected from all participants and their informants. All protocols were approved by the University of Washington institutional review board. Detailed information on the cohort and neuropsychological battery of tests included in the UDS is described elsewhere [74-76].

Participant selection

Figure 3 describes participant selection. All NACC participants were initially considered. In order to identify a group with the emergence of *de novo* NPS in later life, not better accounted for by longstanding psychiatric or neurological conditions, participants with a history of chronic and/or recurrent psychiatric disorders (e.g., depression, schizophrenia, bipolar disorder) and neurodevelopmental/neurological disorders (e.g., Down syndrome, autism, Huntington's disease) were excluded.

As MBI scores were derived from the NPI-Q using a published algorithm[77], only participants with available NPI-Q data were included. The MBI-psychosis domain score was obtained from the sum of scores in NPI-Q delusions and hallucinations domains. To meet the MBI symptom persistence criterion (psychosis present for at least six months), scores from two consecutive visits were used to determine the MBI-psychosis status. This status was determined based on all pre-dementia visits, until the emergence of psychosis (score>0) at two consecutive visits. The latter visit was set as the baseline, marking the onset of MBI-psychosis. The No-NPS group included participants with no NPS prior to dementia diagnosis, with their second visit set as the baseline. For the comparison of MBI-psychosis to

No-NPS, participants not fitting into either of these categories were not included in this specific analysis. As a secondary analysis, a group called Conv-psychosis was derived to assess the utility of a conventional approach to incorporating psychosis for dementia prognostication. This group consisted of participants with a baseline single-timepoint NPI-Q psychosis score>0 without consideration of past psychiatric history. Finally, a global MBI group was also derived, consistent with previous research[18], defined as the emergence of any persistent NPS in advance of dementia. From this group of participants with MBI of any type, those with persistent or impersistent psychotic symptoms prior to dementia diagnosis were then removed to generate an additional MBI-no-psychosis comparator group. Using NACC cognitive status at the time when baseline MBI status was assigned, only participants with NC and MCI were included, as MBI is a pre-dementia construct. Participants with no follow-up visits and those missing values on covariates of interest for the longitudinal analysis were excluded from the study. Participants excluded for missing NPI-Q data did not significantly differ from the study sample in terms of education, sex, or race; however, this group was older (73.6 vs 71.6), with lower percentage of APOE-ε4 carriers (13.5% vs 27.2%), and lower percentage of MCI diagnosis (23.2% vs 32.6%).

Statistical analysis

Baseline clinical, demographic, and genetic variables across NPS groups included cognitive status, age, sex, years of education, race, and APOE-ε4 status. Race categories were derived from the NACCNIHR item, representing race as defined by the National Institute of Health (NIH) and included White, Black, or Other. The Other races group included Asian, American Indian or Alaska native, native Hawaiian or other Pacific Islanders, and Mixed-Race individuals, merged into one category due to the small sample size per race. Between-group differences for each variable were assessed using two-sample t-tests for continuous variables and Chi-squared tests for categorical variables.

KM survival curves were generated to compare dementia-free survival over ten years across NPS groups, with a log-rank test applied to assess between-group differences. A Cox proportional hazards regression model was implemented to explore the rates of dementia over ten years across NPS groups, adjusted for cognitive status, baseline age, sex, years of education, race, and APOE-ε4 status. Interaction terms for cognitive status, sex, race, and APOE-ε4 status were further assessed in the model, to explore effect modification between MBI-psychosis and incident dementia at different levels of these covariates. The group with the lowest HR for dementia was set as the reference group. The HR for MBI-psychosis was then assessed within each stratum of cognitive status (MCI or NC), sex (female or male), race (White, Black, or Other), and APOE-ε4 status (noncarrier or carrier), compared to No-NPS. Multiplicative tests of interaction assessed the significance of the observed interactions. Similarly, survival analyses were implemented to examine the association of a conventional measure of psychosis (Conv-psychosis) with incident dementia. Finally, to assess the relative contribution of psychosis to MBI-associated progression, a secondary analysis with an identical set of survival and Cox proportional hazard analyses was performed to compare MBI-psychosis against an MBI-no-psychosis comparator group, in which the participants with MBI-psychosis were removed, leaving only non-psychotic MBI. All hazard ratios (HR) were accompanied by their associated 95% confidence interval (CI) and p-value. The Wald test was used to test for statistical significance in all Cox models.

Statistical analyses were performed in RStudio v1.3.1093, using the *survival* package v3.2.7 for Cox proportional hazards regression models, and *ggplot2* v3.3.2 and *survminer* v0.4.8 packages for KM curves and forest plots of HR. Assumptions for proportional hazards were assessed using the *cox.zph* function from the *survival* package.

Data Availability

Data are available from NACC upon submission of a data access request (https://naccdata.org/requesting-data/data-request-process).

Code Availability

Custom R codes are available online (https://github.com/mghahrem/psychosis_and_incidentdementia).

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Author Contributions

ZI and MG had major role in study design and conception, data preparation, statistical analysis and interpretation, and drafting and revision of the manuscript. AM, CF, ES, and BC contributed to drafting and revision of the manuscript and interpretation of the data.

Competing Interests:

Z.I. has received honoraria from Otsuka/Lundbeck outside the submitted work. His institution has received payment in lieu from Acadia, Biogen, and Roche. The remaining authors declare no competing interests.

Tables

Table 1. Baseline demographic, genetic, and cognitive variables of dementia-free participants with no NPS compared to those with MBI-psychosis. p-values were calculated based on two-sided two-sample t-test for continuous variables and Chi-squared test for categorical variables. Bold p-values indicate statistical significance.

Variable	No-NPS (N=3704)	MBI-psychosis (N=66)	t/χ2	p-value
Age				
Mean (SD)	72.8 (9.85)	75.2 (9.80)	1.97	0.0529
Median [Min, Max]	73.0 [23.0, 101]	74.5 [54.0, 93.0]		
Years of education				
Mean (SD)	15.9 (2.93)	14.8 (3.42)	-2.54	**0.0136**
Median [Min, Max]	16.0 [1.00, 29.0]	15.0 [3.00, 21.0]		
Sex				
Male	1382 (37.3%)	31 (47.0%)	2.19	0.139
Female	2322 (62.7%)	35 (53.0%)		
Race				
White	2797 (75.5%)	42 (63.6%)	13.63	**0.0011**
Black	659 (17.8%)	12 (18.2%)		
Other	248 (6.7%)	12 (18.2%)		
APOE-ε4 status				
Noncarrier	2488 (67.2%)	46 (69.7%)	0.09	0.763
Carrier	1216 (32.8%)	20 (30.3%)		
Clinical diagnosis				
NC	3208 (86.6%)	18 (27.3%)	180.12	**<0.001**
MCI	496 (13.4%)	48 (72.7%)		

Table 2. Hazard ratios for incident dementia associated with the interaction between NPS groups (MBI-psychosis versus No-NPS) and cognitive status categories. The last column represents the risk ratio associated with MBI-psychosis within each stratum of cognitive status. The Wald test was used to test for statistical significance in the Cox model, with bold p-values indicating significance.

Cognitive status	**No-NPS**	**MBI-psychosis**	**Effect of psychosis within the strata of cognitive status**
	HR [95% CI] **p-value**	**HR [95% CI]** **p-value**	**HR [95% CI]** **p-value**
NC	1 [Reference]	9.96 [3.65, 27.22] **p<0.001**	9.96 [3.65, 27.22] **p<0.001**
MCI	13.34 [10.32, 17.24] **p<0.001**	45.09 [28.68, 70.91] **p<0.001**	3.38 [2.22, 5.15] **p<0.001**
Multiplicative interaction test		HR= 2.95, CI: 0.99-8.72, **p=0.05**	

552 **Table 3.** Hazard ratios for incident dementia associated with the interaction between NPS groups
553 (MBI-psychosis versus No-NPS) and racial categories. The Wald test was used to test for statistical
554 significance in the Cox model, with bold p-values indicating significance.
555

Race	No-NPS	MBI-psychosis	Effect of psychosis within the strata of race
	HR [95% CI] **p-value**	**HR [95% CI]** **p-value**	**HR [95% CI]** **p-value**
Black	1 [Reference]	7.44 [3.54, 15.65] **p<0.001**	7.44 [3.54, 15.65] **p<0.001**
White	1.79 [1.25, 2.56] **p=0.002**	5.68 [3.19, 10.12] **p<0.001**	3.18 [1.94, 5.20] **p<0.001**
Other	1.51 [0.82, 2.77] p=0.187	3.93 [1.18, 13.04] **p=0.026**	2.61 [0.74, 9.18] p=0.136
Multiplicative interaction:		**Black vs White:** HR=2.34, CI: 0.97-5.65, p=0.058 **Black vs Other:** HR=2.85, CI: 0.66-12.31, p=0.159 **Other vs White:** HR= 0.82, CI: 0.21-3.13, p=0.772	

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557

Figure legends

Figure 1. Kaplan-Meier (KM) curve of dementia-free survival and adjusted hazard ratio for incident dementia over ten years stratified by NPS groups: **(A)** MBI-psychosis versus no NPS prior to dementia diagnosis. **(B)** Conventionally measured psychosis (Conv-psychosis) versus no NPS prior to dementia diagnosis. The red dashed line in the KM curve plots represents the median survival probability. The shaded area around the KM curves represents the 95% confidence interval for each group. The log-rank test was applied to test for statistical significance for KM curves. HR refers to the hazard ratio for dementia incidence with the No-NPS group as the reference group. Error bars for HR represent the 95% confidence intervals of the mean. The Wald test was used to test for statistical significance in the Cox model, with the star notation indicating significance.

Figure 2. (A) Forest plot of adjusted hazard ratios for incident dementia, across the strata of the interaction between cognitive status (NC, MCI) and NPS groups (No-NPS, MBI-psychosis) **(B)** Forest plot of adjusted hazard ratios for incident dementia, across the strata of the interaction between race (Black, White, Other) and NPS groups (No-NPS, MBI-psychosis). Error bars for HR represent the 95% confidence intervals of the mean. The Wald test was used to test for statistical significance in the Cox model, with the star notation indicating significance.

Figure 3. Flowchart illustrating the step-by-step process of the participant inclusion/exclusion criteria

References

1. Steinberg M, Shao H, Zandi P, et al. Point and 5-year period prevalence of neuropsychiatric symptoms in dementia: the Cache County Study. *International Journal of Geriatric Psychiatry.* 2008;23(2):170-177.
2. Ropacki SA, Jeste DV. Epidemiology of and risk factors for psychosis of Alzheimer's disease: a review of 55 studies published from 1990 to 2003. *Am J Psychiatry.* 2005;162(11):2022-2030.
3. Fischer CE, Ismail Z, Schweizer TA. Delusions increase functional impairment in Alzheimer's disease. *Dement Geriatr Cogn Disord.* 2012;33(6):393-399.
4. Wilson R, Tang Y, Aggarwal N, et al. Hallucinations, cognitive decline, and death in Alzheimer's disease. *Neuroepidemiology.* 2006;26(2):68-75.
5. Scarmeas N, Brandt J, Albert M, et al. Delusions and hallucinations are associated with worse outcome in Alzheimer disease. *Arch Neurol.* 2005;62(10):1601-1608.
6. Zahodne LB, Ornstein K, Cosentino S, Devanand DP, Stern Y. Longitudinal relationships between Alzheimer disease progression and psychosis, depressed mood, and agitation/aggression. *The American Journal of Geriatric Psychiatry.* 2015;23(2):130-140.
7. Fischer CE, Agüera-Ortiz L. Psychosis and dementia: risk factor, prodrome, or cause? *Int Psychogeriatr*. 2018:209-219.
8. Ismail Z, Creese B, Aarsland D, et al. Psychosis in Alzheimer disease - mechanisms, genetics and therapeutic opportunities. *Nat Rev Neurol.* 2022;18(3):131-144.
9. Cummings J, Pinto LC, Cruz M, et al. Criteria for Psychosis in Major and Mild Neurocognitive Disorders: International Psychogeriatric Association (IPA) Consensus Clinical and Research Definition. *Am J Geriatr Psychiatry.* 2020;28(12):1256-1269.

10. Jeste DV, Finkel SI. Psychosis of Alzheimer's disease and related dementias: diagnostic criteria for a distinct syndrome. *The American Journal of Geriatric Psychiatry.* 2000;8(1):29-34.
11. Fischer CE, Ismail Z, Youakim JM, et al. Revisiting criteria for psychosis in Alzheimer's disease and related dementias: toward better phenotypic classification and biomarker research. *J Alzheimers Dis.* 2020;73(3):1143-1156.
12. Ismail Z, Smith EE, Geda Y, et al. Neuropsychiatric symptoms as early manifestations of emergent dementia: provisional diagnostic criteria for mild behavioral impairment. *Alzheimer's & Dementia.* 2016;12(2):195-202.
13. Creese B, Ismail Z. Mild behavioral impairment: measurement and clinical correlates of a novel marker of preclinical Alzheimer's disease. *Alzheimers Res Ther.* 2022;14(1):2.
14. Mortby ME. Mild behavioral impairment: challenges facing a quickly developing evidence base. *Int Psychogeriatr.* 2021;33(3):209-212.
15. Creese B, Brooker H, Ismail Z, et al. Mild Behavioral Impairment as a Marker of Cognitive Decline in Cognitively Normal Older Adults. *Am J Geriatr Psychiatry.* 2019;27(8):823-834.
16. Matsuoka T, Ismail Z, Narumoto J. Prevalence of mild behavioral impairment and risk of dementia in a psychiatric outpatient clinic. *J Alzheimers Dis.* 2019;70(2):505-513.
17. Tsunoda K, Yamashita T, Osakada Y, et al. Early Emergence of Neuropsychiatric Symptoms in Cognitively Normal Subjects and Mild Cognitive Impairment. *J Alzheimers Dis.* 2020;73(1):209-215.
18. Ismail Z, McGirr A, Gill S, Hu S, Forkert ND, Smith EE. Mild Behavioral Impairment and Subjective Cognitive Decline Predict Cognitive and Functional Decline. *J Alzheimers Dis.* 2021;80(1):459-469.
19. Wolfova K, Creese B, Aarsland D, et al. Sex differences in the association of mild behavioral impairment with cognitive aging. *medRxiv.* 2021:2021.2005.2020.21257514.

20. McGirr A, Nathan S, Ghahremani M, Gill S, Smith EE, Ismail Z. Progression to Dementia or Reversion to Normal Cognition in Mild Cognitive Impairment as a Function of Late-Onset Neuropsychiatric Symptoms. *Neurology.* 2022;98(21):e2132-e2139.

21. Taragano FE, Allegri RF, Heisecke SL, et al. Risk of Conversion to Dementia in a Mild Behavioral Impairment Group Compared to a Psychiatric Group and to a Mild Cognitive Impairment Group. *J Alzheimers Dis.* 2018;62:227-238.

22. Kan CN, Cano J, Zhao X, Ismail Z, Chen CL-H, Xu X. Prevalence, Clinical Correlates, Cognitive Trajectories, and Dementia Risk Associated With Mild Behavioral Impairment in Asians. *The Journal of Clinical Psychiatry.* 2022;83(3):40123.

23. Vellone D, Ghahremani M, Goodarzi Z, Forkert ND, Smith EE, Ismail Z. Apathy and APOE in mild behavioral impairment, and risk for incident dementia. *Alzheimer's & Dementia: Translational Research & Clinical Interventions.* 2022.

24. Yokoi Y, Takano H, Sakata M, Maruo K, Nakagome K, Matsuda H. Discrete effect of each mild behavioural impairment category on dementia conversion or cognitive decline in patients with mild cognitive impairment. *Psychogeriatrics.* 2019;19(6):591-600.

25. Tsamakis K, Gadelrab R, Wilson M, et al. Dementia in People from Ethnic Minority Backgrounds: Disability, Functioning, and Pharmacotherapy at the Time of Diagnosis. *J Am Med Dir Assoc.* 2021;22(2):446-452.

26. Selten JP, van der Ven E, Termorshuizen F. Migration and psychosis: a meta-analysis of incidence studies. *Psychol Med.* 2020;50(2):303-313.

27. Pan Y, Shea YF, Ismail Z, et al. Prevalence of mild behavioural impairment domains: a meta-analysis. *Psychogeriatrics.* 2022;22(1):84-98.

28. Ismail Z, Aguera-Ortiz L, Brodaty H, et al. The Mild Behavioral Impairment Checklist (MBI-C): A Rating Scale for Neuropsychiatric Symptoms in Pre-Dementia Populations. *J Alzheimers Dis.* 2017;56(3):929-938.

29. Creese B, Griffiths A, Brooker H, et al. Profile of mild behavioral impairment and factor structure of the Mild Behavioral Impairment Checklist in cognitively normal older adults. *Int Psychogeriatr.* 2020;32(6):705-717.

30. Hu S, Patten S, Charlton A, et al. Validating the Mild Behavioral Impairment Checklist in a Cognitive Clinic: Comparisons With the Neuropsychiatric Inventory Questionnaire. *J Geriatr Psychiatry Neurol.* 2022:8919887221093353.

31. Dietlin S, Soto M, Kiyasova V, et al. Neuropsychiatric symptoms and risk of progression to Alzheimer's disease among mild cognitive impairment subjects. *J Alzheimers Dis.* 2019;70(1):25-34.

32. Brodaty H, Sachdev P, Koschera A, Monk D, Cullen B. Long-term outcome of late-onset schizophrenia: 5-year follow-up study. *The British Journal of Psychiatry.* 2003;183(3):213-219.

33. Kohler S, Allardyce J, Verhey FR, et al. Cognitive decline and dementia risk in older adults with psychotic symptoms: a prospective cohort study. *Am J Geriatr Psychiatry.* 2013;21(2):119-128.

34. Liew TM. Symptom clusters of neuropsychiatric symptoms in mild cognitive impairment and their comparative risks of dementia: a cohort study of 8530 older persons. *J Am Med Dir Assoc.* 2019;20(8):1054. e1051-1054. e1059.

35. Rosenberg PB, Mielke MM, Appleby BS, Oh ES, Geda YE, Lyketsos CG. The association of neuropsychiatric symptoms in MCI with incident dementia and Alzheimer disease. *The American Journal of Geriatric Psychiatry.* 2013;21(7):685-695.

36. Peters M, Rosenberg P, Steinberg M, et al. Neuropsychiatric symptoms as risk factors for progression from CIND to dementia: the Cache County Study. *The American Journal of Geriatric Psychiatry.* 2013;21(11):1116-1124.
37. Pink A, Stokin GB, Bartley MM, et al. Neuropsychiatric symptoms, APOE epsilon4, and the risk of incident dementia: a population-based study. *Neurology.* 2015;84(9):935-943.
38. Valero S, Marquié M, De Rojas I, et al. Interaction of neuropsychiatric symptoms with APOE ε4 and conversion to dementia in MCI patients in a Memory Clinic. *Sci Rep.* 2020;10(1):1-10.
39. Palmer BW, Bondi MW, Twamley EW, Thal L, Golshan S, Jeste DV. Are late-onset schizophrenia spectrum disorders neurodegenerative conditions? Annual rates of change on two dementia measures. *The Journal of neuropsychiatry and clinical neurosciences.* 2003;15(1):45-52.
40. Almeida OP, Ford AH, Hankey GJ, Yeap BB, Golledge J, Flicker L. Risk of dementia associated with psychotic disorders in later life: the health in men study (HIMS). *Psychol Med.* 2019;49(2):232-242.
41. Stafford J, Dykxhoorn J, Sommerlad A, Dalman C, Kirkbride JB, Howard R. Association between risk of dementia and very late-onset schizophrenia-like psychosis: a Swedish population-based cohort study. *Psychol Med.* 2021:1-9.
42. Liew TM. Neuropsychiatric symptoms in cognitively normal older persons, and the association with Alzheimer's and non-Alzheimer's dementia. *Alzheimers Res Ther.* 2020;12(1):35.
43. Burke SL, Maramaldi P, Cadet T, Kukull W. Neuropsychiatric symptoms and Apolipoprotein E: Associations with eventual Alzheimer's disease development. *Arch Gerontol Geriatr.* 2016;65:231-238.
44. Nagendra J, Snowdon J. An Australian study of delusional disorder in late life. *Int Psychogeriatr.* 2020;32(4):453-462.

45. Schwartz RC, Blankenship DM. Racial disparities in psychotic disorder diagnosis: A review of empirical literature. *World J Psychiatry.* 2014;4(4):133-140.
46. Barnes LL, Bennett DA. Alzheimer's disease in African Americans: risk factors and challenges for the future. *Health Aff (Millwood).* 2014;33(4):580-586.
47. Bryant BE, Ayana J, Uraina SC. Race as a Social Construct in Psychiatry Research and Practice. *JAMA Psychiatry.* 2021;79(2):93-94.
48. Steptoe A, Zaninotto P. Lower socioeconomic status and the acceleration of aging: An outcome-wide analysis. *Proc Natl Acad Sci U S A.* 2020;117(26):14911-14917.
49. Avila-Rieger J, Turney IC, Vonk JMJ, et al. Socioeconomic Status, Biological Aging, and Memory in a Diverse National Sample of Older US Men and Women. *Neurology.* 2022;99(19):e2114-e2124.
50. Anglin DM, Ereshefsky S, Klaunig MJ, et al. From Womb to Neighborhood: A Racial Analysis of Social Determinants of Psychosis in the United States. *Am J Psychiatry.* 2021;178(7):599-610.
51. Babulal GM, Zhu Y, Roe CM, et al. The complex relationship between depression and progression to incident cognitive impairment across race and ethnicity. *Alzheimers Dement.* 2022;in press.
52. Qian W, Fischer CE, Schweizer TA, Munoz DG. Association Between Psychosis Phenotype and APOE Genotype on the Clinical Profiles of Alzheimer's Disease. *Curr Alzheimer Res.* 2018;15(2):187-194.
53. Demichele-Sweet MA, Lopez OL, Sweet RA. Psychosis in Alzheimer's disease in the national Alzheimer's disease coordinating center uniform data set: clinical correlates and association with apolipoprotein e. *Int J Alzheimers Dis.* 2011;2011:926597.

54. DeMichele-Sweet MAA, Sweet RA. Genetics of Psychosis in Alzheimer Disease. *Curr Genet Med Rep.* 2014;2(1):30-38.
55. Ismail Z, Nguyen MQ, Fischer CE, Schweizer TA, Mulsant BH. Neuroimaging of delusions in Alzheimer's disease. *Psychiatry Res.* 2012;202(2):89-95.
56. Ismail Z, Nguyen MQ, Fischer CE, Schweizer TA, Mulsant BH, Mamo D. Neurobiology of delusions in Alzheimer's disease. *Curr Psychiatry Rep.* 2011;13(3):211-218.
57. Vik-Mo AO, Giil LM, Borda MG, Ballard C, Aarsland D. The individual course of neuropsychiatric symptoms in people with Alzheimer's and Lewy body dementia: 12-year longitudinal cohort study. *Br J Psychiatry.* 2020;216(1):43-48.
58. Cummings J, Ballard C, Tariot P, et al. Pimavanserin: Potential Treatment For Dementia-Related Psychosis. *J Prev Alzheimers Dis.* 2018;5(4):253-258.
59. Fischer CE, Qian W, Schweizer TA, et al. Determining the impact of psychosis on rates of false-positive and false-negative diagnosis in Alzheimer's disease. *Alzheimers Dement (N Y).* 2017;3(3):385-392.
60. Ruthirakuhan M, Ismail Z, Herrmann N, Gallagher D, Lanctot KL. Mild behavioral impairment is associated with progression to Alzheimer's disease: A clinicopathological study. *Alzheimers Dement.* 2022;18(11):2199-2208.
61. Irwin DJ, Hurtig HI. The Contribution of Tau, Amyloid-Beta and Alpha-Synuclein Pathology to Dementia in Lewy Body Disorders. *J Alzheimers Dis Parkinsonism.* 2018;8(4).
62. Irwin DJ, Grossman M, Weintraub D, et al. Neuropathological and genetic correlates of survival and dementia onset in synucleinopathies: a retrospective analysis. *Lancet Neurol.* 2017;16(1):55-65.
63. Gill S, Mouches P, Hu S, et al. Using Machine Learning to Predict Dementia from Neuropsychiatric Symptom and Neuroimaging Data. *J Alzheimers Dis.* 2020;75(1):277-288.

64. Gill S, Wang M, Mouches P, et al. Neural correlates of the impulse dyscontrol domain of mild behavioral impairment. *Int J Geriatr Psychiatry.* 2021;36(9):1398-1406.
65. Johansson M, Stomrud E, Insel PS, et al. Mild behavioral impairment and its relation to tau pathology in preclinical Alzheimer's disease. *Transl Psychiatry.* 2021;11(1):76.
66. Lussier FZ, Pascoal TA, Chamoun M, et al. Mild behavioral impairment is associated with β-amyloid but not tau or neurodegeneration in cognitively intact elderly individuals. *Alzheimer's & Dementia.* 2020;16(1):192-199.
67. Matuskova V, Ismail Z, Nikolai T, et al. Mild behavioral impairment is associated with atrophy of entorhinal cortex and hippocampus in a memory clinic cohort. *Frontiers in Aging Neuroscience.* 2021;13:236.
68. Miao R, Chen HY, Gill S, et al. Plasma beta-Amyloid in Mild Behavioural Impairment - Neuropsychiatric Symptoms on the Alzheimer's Continuum. *J Geriatr Psychiatry Neurol.* 2021:8919887211016068.
69. Naude J, Gill S, Hu S, et al. Plasma Neurofilament Light: a marker of cognitive decline in Mild Behavioural Impairment. *J Alzheimers Dis.* 2020;76(3):1017-1027.
70. Ghahremani M, Nathan S, Smith EE, McGirr A, Goodyear B, Ismail Z. Functional connectivity and mild behavioral impairment in dementia-free elderly. *Alzheimer's & Dementia: Translational Research & Clinical Interventions.* 2023;9(1):e12371.
71. Mograbi DC, Morris RG. On the relation among mood, apathy, and anosognosia in Alzheimer's disease. *J Int Neuropsychol Soc.* 2014;20(1):2-7.
72. Tagai K, Nagata T, Shinagawa S, Shigeta M. Anosognosia in patients with Alzheimer's disease: current perspectives. *Psychogeriatrics.* 2020;20(3):345-352.

73. Nosheny RL, Amariglio R, Sikkes SAM, et al. The role of dyadic cognitive report and subjective cognitive decline in early ADRD clinical research and trials: Current knowledge, gaps, and recommendations. *Alzheimers Dement (N Y).* 2022;8(1):e12357.

74. Weintraub S, Salmon D, Mercaldo N, et al. The Alzheimer's disease centers' uniform data set (UDS): The neuropsychological test battery. *Alzheimer Dis Assoc Disord.* 2009;23(2):91.

75. Beekly DL, Ramos EM, Lee WW, et al. The National Alzheimer's Coordinating Center (NACC) database: the uniform data set. *Alzheimer Dis Assoc Disord.* 2007;21(3):249-258.

76. Morris JC, Weintraub S, Chui HC, et al. The Uniform Data Set (UDS): clinical and cognitive variables and descriptive data from Alzheimer Disease Centers. *Alzheimer Dis Assoc Disord.* 2006;20(4):210-216.

77. Sheikh F, Ismail Z, Mortby ME, et al. Prevalence of mild behavioral impairment in mild cognitive impairment and subjective cognitive decline, and its association with caregiver burden. *Int Psychogeriatr.* 2018;30(2):233-244.