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

57 with No-NPS (CI:3.65-27.22, p<0.001). In MCI, the MBI-psychosis-associated dementia incidence

58 was 3.38-fold greater (CI:2.22-5.15, p<0.001). Furthermore, MBI-psychosis-associated dementia

59 incidence in Black participants was 7.44-fold greater than No-NPS (CI:3.54-15.65, p<0.001), while in

60 White participants it was 3.18-fold greater (CI:1.94-5.2, p<0.001). In a secondary analysis, compared

61 to MBI-no-psychosis (n=2260), MBI-psychosis had a 2.47-fold greater incidence of dementia

62 (CI:1.69-3.59, p<0.001).

63

64 **Conclusion**: Although psychosis is an infrequently endorsed MBI domain, when present it is

65 associated with substantial risk for dementia. HRs differed between cognitive strata and these

66 differences were significantly greater when MBI-psychosis emerged in NC as opposed to MCI,

67 emphasizing the importance of cognitive assessment at the time of symptom emergence. Additionally,

68 the relationship between MBI-psychosis and incident dementia was stronger in Black participants than

69 White participants. The emergence of persistent psychotic symptoms in older adults is clinically

70 meaningful, and MBI-psychosis identifies a high-risk group for precision medicine approaches to

71 dementia prevention.

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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.

99   Mild behavioral impairment (MBI) is a syndrome that incorporates psychiatric and behavioral

100   symptoms to identify a high-risk group for incident cognitive decline and dementia[12]. In MBI

101   dementia-free adults older than 50 years of age experience persistent psychiatric and behavioral

102   symptoms, which are of new-onset and reflect a change from longstanding patterns[12-14]. MBI

103   comprises five domains of decreased drive and motivation (apathy), affective dysregulation

104   (mood/anxiety symptoms), impulse dyscontrol (agitation, aggression, impulsivity, impaired reward

105   salience), social inappropriateness (impaired social cognition), and abnormal perception/thought

106   content (psychotic symptoms). Longitudinal studies have determined that MBI is associated with a

107   greater risk of cognitive decline and dementia[15-23]. To our knowledge, only one study has evaluated

108   longitudinal outcomes with MBI-psychosis, in participants with MCI[24]. However, this study

109   incorporated neither the core MBI criterion stipulating new-onset symptomatology, nor the criterion

110   stipulating symptom persistence[12]. Thus, in dementia-free older adults, we assessed progression to

111   dementia in in persons with later-life emergent and persistent psychosis. Furthermore, we explored

112   effect modification by race on the association of MBI-psychosis with incident dementia. Several

113   European studies on dementia patients have indicated a higher incidence and prevalence of psychosis

114   in Black African and Black Caribbean patients compared to White patients[25,26]. We hypothesized that

115   participants with MBI-psychosis would have a greater incidence of dementia compared to participants

116   with no NPS, or those with MBI without psychosis, and this association would differ across racial

117   groups.

118
119
120   **Results**

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

122   The final sample consisted of 3,704 participants with no NPS prior to dementia diagnosis (No-NPS)

123   (mean age=72.8±9.9; 62.7% female), and 66 with new-onset persistent psychosis (*i.e.*, MBI-psychosis)

124   (mean age=75.2±9.8; 53% female) from the National Alzheimer Coordinating Center (NACC). There

125   was a significantly higher percentage of MCI participants within the MBI-psychosis group, compared

126   to No-NPS (p<0.001). No significant differences were found for age (p=0.053) or sex (p=0.14). Years

127   of education were significantly higher in the No-NPS group (p=0.014). Race was significantly

128   different across the NPS groups (p=0.001), with more White participants in the No-NPS group and

129   more racial diversity in the MBI-psychosis group. APOE-ε4 status did not differ between groups

130   (p=0.76). Table 1 demonstrates details of the between-group differences across all covariates.

131

132   Figure 1(A) illustrates the Kaplan-Meier (KM) curve of the dementia-free survival probability and

133   adjusted hazard ratio (HR) for incident dementia over ten years, stratified by NPS group. Compared to

134   the No-NPS group, dementia-free survival was lower in the MBI-psychosis group (p<0.0001). The

135   five-year survival probability for the No-NPS group was 90.5% (CI:89.2%-91.7%), while for the MBI-

136   psychosis group it was only 35.7% (CI:22.8%-55.9%). Compared to No-NPS, MBI-psychosis had

137   3.76-fold greater dementia progression rate (CI:2.53-5.58, p<0.001) (Fig. 1(A)). In total, 303

138   participants progressed to dementia over ten years. Of the 66 participants with MBI-psychosis, 45.5%

139   (n=30) progressed to dementia, consisting of AD (66.7%, n=20), dementia with Lewy Bodies (DLB)

140   (10%, n=3), vascular dementia (3.3%, n=1), and unrecorded dementia subtypes (20%, n=6). Among

141   the 3,704 participants with no NPS, 7.4% (n=273) progressed to dementia, consisting of AD (89%,

142   n=243), behavioral variant of frontotemporal dementia (bvFTD) (1.1%, n=3), DLB (1.1%, n=3),

143   vascular dementia (1.8%, n=5), and unrecorded dementia subtypes (6.9%, n=19).

144

145   While not statistically significant due to sample-size-related imprecision of the estimate, interaction

146   effects were observed for MBI-psychosis and cognitive status with a considerable difference in HRs

147   between cognitive strata (multiplicative interaction test: HR=2.95, CI:0.99-8.72, p=0.05). In MCI,

148   MBI-psychosis had a 3.38-fold greater progression rate than No-NPS (CI:2.22-5.15, p<0.001). In NC,

149   MBI-psychosis had a 9.96-fold greater progression rate than No-NPS (CI:3.65-27.20, p<0.001) (Table

150   2 and Fig. 2(A)). No significant interaction effects were found between MBI-psychosis and sex

151   (p=0.7). Overall, Black participants had lower incidence of dementia compared to White participants

152   (see Fig. 1(B), HR=0.63, CI:0.45-0.87, p=0.005). However, Black participants with MBI-psychosis

153   had a 7.44-fold greater progression rate than the No-NPS participants (CI:3.54-15.65, p<0.001), while

154   among White participants, MBI-psychosis had a 3.18-fold greater progression rate than No-NPS

155   (CI:1.94-5.20, p<0.001). Although non-significant, within the Other races category, MBI-psychosis

156   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)).

157   However, the multiplicative interaction test did not find HRs to significantly differ across race

158   categories (Black vs White: HR=2.34, CI:0.97-5.65, p=0.058; Black vs Other: HR=2.85, CI:0.66-

159   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

160   per race in the Other racial category did not allow the identification of the specific races associated

161   with the risk. Interaction effects were not observed for APOE-ε4 status (p=0.24).

162

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

164   The sample for this secondary analysis consisted of 6,720 individuals with no NPS prior to dementia

165   diagnosis (No-NPS) and 291 with conventionally captured psychosis (Conv-psychosis). Compared to

166   the No-NPS group, the Conv-psychosis group had fewer years of education (p<0.001), fewer females

167   (p<0.001), and fewer Black participants. This group had more participants in Other races (p=0.009),

168   and a higher percentage of MCI (p<0.001) and APOE-ε4 carriers (p=0.004) (supplementary table 1).

169

170   The KM survival curves demonstrated that compared to No-NPS, dementia-free survival was lower in

171   Conv-psychosis (p<0.0001). The five-year dementia-free survival probability for the No-NPS group

172 was 87.3% (CI:86.3-88.4), while for the Conv-psychosis group it was 38.6% (CI:31.7-47.0). The

173 adjusted Cox regression model demonstrated a greater progression rate to dementia in the Conv-

174 psychosis group compared to No-NPS (adjusted HR=1.92, 95%CI:1.58-2.33, p<0.001) (Fig. 1(B)).

175

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

177 Secondary analyses comparing individuals with MBI-psychosis to those with MBI of any type except

178 psychosis (MBI-no-psychosis) yielded similar results. The no-psychosis group consisted of 2,260

179 participants (mean age=75.2±9.1; 48.1% female) with more White participants (85.8%, p<0.001) and

180 lower percentage of MCI diagnosis (42.3%, p<0.001) than the MBI-psychosis group (supplementary

181 table 2).

182

183 KM curves stratified by psychosis group demonstrated that participants with MBI-psychosis had lower

184 dementia-free survival, compared to those with no psychosis (p<0.0001) (Supplementary fig. 1(A)).

185 Five-year survival probability of the no-psychosis group was 70.7% (CI:68.3%-73.1%), while for

186 MBI-psychosis it was only 35.7% (CI:23.8%-55.9%). Adjusted Cox proportional hazards models

187 showed that compared to MBI-no-psychosis, MBI-psychosis had a 2.47-fold greater progression rate

188 (CI:1.69-3.59, p<0.001) (Supplementary fig. 1(B)). In total, 583 participants progressed to dementia

189 over ten years. Among the 2,260 MBI-no-psychosis participants, 24.4% (n=553) progressed to

190 dementia, consisting of AD (86.4%, n=478), bvFTD (1.9%, n=11), DLB (3.2%, n=18), vascular

191 dementia (1.3%, n=7), and unrecorded dementia subtypes (7.1%, n=39).

192

193 No significant interaction of NPS group was found for cognitive status (p=0.61), sex (p=0.55), race

194 (Black vs White: p=0.346, Other vs White: p=0.98), or APOE-ε4 status (p=0.45), however the within-

195 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

220   in MBI-psychosis. Effect modification was observed for cognitive status. In MCI, persistent new-onset

221   psychosis was associated with 3.38-fold greater progression rate compared to No-NPS, but in NC, the

222   relative rate was significantly higher at 9.96. These findings suggest that when psychosis emerges early

223   in the neurodegenerative disease process, the contribution of these symptoms is profound. In MCI,

224   underlying disease burden is theoretically greater, with other factors in play relative to NC, where the

225   impact of psychosis in the modeling is greater. We also investigated dementia incidence in the Conv-

226   psychosis group in which psychosis was assessed with a more conventional approach, *i.e.*, at a single

227   timepoint and without consideration of past psychiatric history. Compared to No-NPS, the Conv-

228   psychosis group had 1.92-fold higher dementia incidence rate, while MBI-psychosis had 3.76-fold

229   higher rate. These findings support the utility of the two core MBI criteria for psychosis and suggest

230   that when psychosis is both emergent and persistent, a considerably greater incidence of dementia is

231   observed.

232

233   The only previous study reporting the association of MBI-psychosis with incident dementia assessed

234   MCI participants alone. All five MBI domains were assessed with NPS based on a single

235   Neuropsychiatric Inventory Questionnaire (NPI-Q) assessment of symptom presence over one month.

236   In that study, psychosis was associated with greater incidence of dementia in two of the three statistical

237   models, with HRs ranging from 1.97-2.71[24]. Of all NPS assessed with this single timepoint measure,

238   psychosis was the only domain demonstrating an association with incident dementia. This finding

239   highlights the impact of psychosis in older adults relative to other NPS, but also the importance of

240   operationalizing MBI criteria to ensure symptom persistence (at two timepoints or with a measure with

241   a reference range of at least six months) to enrich samples with persons at high-risk for incident

242   dementia. Despite the short reference range for MBI case status, psychosis was still associated with

243   dementia. Our study extends this finding, by capturing persistent psychosis across two consecutive

244 timepoints and incorporating No-NPS as well as MBI-no-psychosis comparators into the modeling.

245 While No-NPS participants had a five-year dementia-free survival of 90.5%, MBI-no-psychosis had a

246 70.7% five-year dementia-free survival, and MBI-psychosis had a 35.7% survival. Thus, our study not

247 only highlights the importance of psychosis as a clinically significant symptom, relative to other NPS,

248 but also emphasizes the importance of NPS nosology and measurement in risk assessment and the

249 utility of incorporating MBI criteria into modeling.

250

251 Other longitudinal studies in MCI, using more conventional assessments of psychosis, have assessed

252 progression to dementia with some suggesting greater risk[31-35] and others no greater risk[36-38].

253 Differences in findings may be due to inadequate sample size[36,37], sample heterogeneity[36,38], short

254 follow-up intervals[38,39], psychosis assessed with a shorter-term measure[36], and attrition[37]. A

255 longitudinal study of participants over 17.7 years revealed that psychosis (assessed from ICD codes)

256 had a 2.67-fold greater rate of dementia versus no psychosis. Interestingly, sub-HRs were higher for

257 incident versus prevalent psychosis, and for short-duration versus long-duration psychosis[40]. A similar

258 Swedish health register study demonstrated that VLOSLP diagnosis (ICD codes) versus no VLOSLP

259 had a 4.4-fold greater HR for dementia; incidence was highest in the immediate year following

260 VLOSLP diagnosis[41]. However, cognitive status was not reported in either of these rigorous studies,

261 inherent with the methodological approach of using ICD codes for psychosis, which are only provided

262 when psychotic symptoms are of sufficient severity to prompt clinical attention.[40] Unfortunately, this

263 approach precludes comparisons of natural histories of cognition and psychosis, unless the dataset

264 includes explicit cognitive scores or categories. Nonetheless, these studies clearly support the notion

265 that new-onset symptoms in older persons identify a high-risk group, consistent with the core MBI

266 criterion of symptom emergence in later life. Different reference groups, and different symptom

267 duration/persistence criteria prohibit direct comparisons of HRs with our findings.

268

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].

275

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.

290

291 The social construct of race is often conceptualized as a biological factor to incorrectly relate

292 differences in health outcomes to the biological properties perceived to be associated with race, which

293 has greatly contributed to misdiagnosis and health disparities for Black individuals[47]. Furthermore,

294 socioeconomic status (SES), often measured from income, occupation, and education levels, is

295 associated with earlier and faster pace of aging-related brain changes[48]. The magnitude of the

296 association between SES and biological aging varies across race; wealthier and more highly educated

297 individuals tend to experience less-advanced biological aging[49]. Numerous European studies have

298 demonstrated the significant influence that social inequalities often faced by racial minorities have on

299 the risk of psychosis[26]. The US lags behind Europe in investigating the link between race-related social

300 inequalities and psychosis incidence. A recent review has identified neighborhood, cumulative trauma

301 and stress, and prenatal and perinatal complications as key factors influencing the risk of psychosis,

302 which are disproportionately experienced by Black persons. More extensive studies are required to

303 explore social determinants of psychosis within North America and prospective cohorts need to

304 incorporate more data related to SES and social inequality[50]. As the NACC dataset does not include

305 enough data related to SES, it is unclear if our race-related findings reflect real underlying difference in

306 prevalence, severity, or phenotype of psychosis in Black Americans, or are due to some other

307 epiphenomena.

308

309 Interaction analyses were instructive. Notably, Black participants with MBI-psychosis had a 7.44-fold

310 greater incidence of dementia than those with No-NPS; among White participants, the MBI-psychosis-

311 related incidence of dementia was 3.18-fold greater than No-NPS. While these HRs were not

312 statistically significantly different in the multiplicative interaction test ($p=0.058$), the substantial

313 numerical difference in the measure of effect does provide some pause, and suggests that further

314 research is required. The relative magnitude and direction of effect in the secondary analysis is also

315 supportive. MBI-psychosis in Black participants was also associated with numerically greater rate of

316 dementia than White participants (HR 3.40 vs 2.23). Again, the reason for these findings is not clear -

317 replication of this analysis with a larger sample of MBI-psychosis participants can further evaluate the

318 significance of this interaction, with more precise estimates. Importantly, sampling not only requires

319 broader racial representation of the population at large, but also improved ethnocultural descriptions of

320 participants for better stratification, as the current nomenclature for race is overly simplistic and

321 reductionistic. A recent study of NACC participants assessed associations between depression and

322 incident dementia in five ethnoracial groups, finding that previously established risk factors between

323 depression and dementia were not established in all groups. The authors suggest that the homogenous

324 classification of diverse NACC participants into the restrictive race and ethnicity designations of the

325 US census eschews diversity, life course, and cultural variability that contribute to identity, all of

326 which may impact the development of depression[51]. In our study, whether a cultural component

327 combined with possible genetic variability explains this phenomenon is unknown. However, this signal

328 warrants a closer evaluation of the racial differences of the MBI-psychosis domain in pre-dementia

329 stages.

330

331 We found no association between APOE-ε4 status and NPS groups. Although main effects describe

332 greater dementia incidence for both MBI-psychosis and APOE-ε4 carrier status, the interaction term

333 was non-significant. However, effect modification cannot be ruled out due to a relatively small sample

334 of MBI-psychosis participants. Our results are in contrast to literature showing a relationship between

335 AD genetic risk and psychosis in dementia.[52] [53,54]. Larger samples, and subtyping of psychosis into

336 hallucinations and delusions[55,56] may reconcile these differences.

337

338   In our study, among the MBI-psychosis participants who progressed to dementia, 66.7% developed

339   AD dementia, but ~10% of participants had an unrecorded dementia diagnosis and thus it is difficult to

340   assess between-group differences in dementia diagnoses. However, with respect to DLB, there are

341   numerical differences which are worth discussing. Of the MBI-psychosis participants that progressed

342   to dementia, 10% were given a clinical diagnosis of DLB. Of the MBI-no-psychosis group 3.2% of

343   progressors developed DLB, and of the No-NPS group 1.1% of progressors developed DLB. Studies

344   have found that psychosis in DLB and Parkinson's disease (PD) is more prevalent than in AD[57,58].

345   However, recent clinicopathological studies have illuminated the field further. One study of NACC

346   participants found that when persons experienced psychosis in AD, they were five times more likely to

347   be provided a clinical misdiagnosis of DLB[59]. Another NACC study of NC participants found that 6%

348   with MBI progressed to AD in five years, with MBI a significant predictor of progression to both

349   clinically-diagnosed (HR=1.75) and neuropathology-confirmed AD (HR=1.59). MBI domains were

350   also associated with clinically-diagnosed AD, with psychosis having the greatest effect (HR=6.49)[60].

351   These studies suggest an underdiagnosis of AD in the presence of behavioural symptoms. Furthermore,

352   the past literature indicates that AD co-pathology is quite common in DLB. While the accumulation of

353   pathogenic alpha-synuclein protein in the brain is the characteristic feature of DLB, recent studies have

354   shown that it is often accompanied by amyloid-beta and tau pathology, which are the characteristic

355   hallmarks of AD[61]. Based on reports from a US-based large multi-center cohort, more than 70% of

356   DLB patients had medium to high levels of AD neuropathologic change at autopsy[62]. Therefore, it is

357   possible that many of the participants with DLB in our sample would also develop AD - the psychotic

358   symptoms observed in early dementia stages in these participants may be associated with AD co-

359   pathology, or vice versa. In our sample, among all participants with MBI-psychosis who progressed to

360   dementia, 67% developed AD dementia, 10% developed DLB, 3% developed vascular dementia, 0%

361   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   <u>Source population</u>

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

17

410   Alzheimer's Disease Research Centers (ADRCs) recruiting and collecting data on participants with

411   cognitive functions ranging from normal to dementia. The NACC Uniform Data Set (UDS) is a large

412   longitudinal dataset including demographic and standardized clinical data collected approximately

413   annually. All test centers administered standardized forms, and informed consent was collected from

414   all participants and their informants. All protocols were approved by the University of Washington

415   institutional review board. Detailed information on the cohort and neuropsychological battery of tests

416   included in the UDS is described elsewhere [74-76].

417

418   Participant selection

419   Figure 3 describes participant selection. All NACC participants were initially considered. In order to

420   identify a group with the emergence of *de novo* NPS in later life, not better accounted for by

421   longstanding psychiatric or neurological conditions, participants with a history of chronic and/or

422   recurrent psychiatric disorders (e.g., depression, schizophrenia, bipolar disorder) and

423   neurodevelopmental/neurological disorders (e.g., Down syndrome, autism, Huntington's disease) were

424   excluded.

425

426   As MBI scores were derived from the NPI-Q using a published algorithm[77], only participants with

427   available NPI-Q data were included. The MBI-psychosis domain score was obtained from the sum of

428   scores in NPI-Q delusions and hallucinations domains. To meet the MBI symptom persistence criterion

429   (psychosis present for at least six months), scores from two consecutive visits were used to determine

430   the MBI-psychosis status. This status was determined based on all pre-dementia visits, until the

431   emergence of psychosis (score>0) at two consecutive visits. The latter visit was set as the baseline,

432   marking the onset of MBI-psychosis. The No-NPS group included participants with no NPS prior to

433   dementia diagnosis, with their second visit set as the baseline. For the comparison of MBI-psychosis to

434 No-NPS, participants not fitting into either of these categories were not included in this specific

435 analysis. As a secondary analysis, a group called Conv-psychosis was derived to assess the utility of a

436 conventional approach to incorporating psychosis for dementia prognostication. This group consisted

437 of participants with a baseline single-timepoint NPI-Q psychosis score>0 without consideration of past

438 psychiatric history. Finally, a global MBI group was also derived, consistent with previous research[18],

439 defined as the emergence of any persistent NPS in advance of dementia. From this group of

440 participants with MBI of any type, those with persistent or impersistent psychotic symptoms prior to

441 dementia diagnosis were then removed to generate an additional MBI-no-psychosis comparator group.

442 Using NACC cognitive status at the time when baseline MBI status was assigned, only participants

443 with NC and MCI were included, as MBI is a pre-dementia construct. Participants with no follow-up

444 visits and those missing values on covariates of interest for the longitudinal analysis were excluded

445 from the study. Participants excluded for missing NPI-Q data did not significantly differ from the study

446 sample in terms of education, sex, or race; however, this group was older (73.6 vs 71.6), with lower

447 percentage of APOE-ε4 carriers (13.5% vs 27.2%), and lower percentage of MCI diagnosis (23.2% vs

448 32.6%).

449

450 Statistical analysis

451 Baseline clinical, demographic, and genetic variables across NPS groups included cognitive status,

452 age, sex, years of education, race, and APOE-ε4 status. Race categories were derived from the

453 NACCNIHR item, representing race as defined by the National Institute of Health (NIH) and included

454 White, Black, or Other. The Other races group included Asian, American Indian or Alaska native,

455 native Hawaiian or other Pacific Islanders, and Mixed-Race individuals, merged into one category due

456 to the small sample size per race. Between-group differences for each variable were assessed using

457 two-sample t-tests for continuous variables and Chi-squared tests for categorical variables.

458

459   KM survival curves were generated to compare dementia-free survival over ten years across NPS

460   groups, with a log-rank test applied to assess between-group differences. A Cox proportional hazards

461   regression model was implemented to explore the rates of dementia over ten years across NPS groups,

462   adjusted for cognitive status, baseline age, sex, years of education, race, and APOE-ε4 status.

463   Interaction terms for cognitive status, sex, race, and APOE-ε4 status were further assessed in the

464   model, to explore effect modification between MBI-psychosis and incident dementia at different levels

465   of these covariates. The group with the lowest HR for dementia was set as the reference group. The HR

466   for MBI-psychosis was then assessed within each stratum of cognitive status (MCI or NC), sex (female

467   or male), race (White, Black, or Other), and APOE-ε4 status (noncarrier or carrier), compared to No-

468   NPS. Multiplicative tests of interaction assessed the significance of the observed interactions.

469   Similarly, survival analyses were implemented to examine the association of a conventional measure

470   of psychosis (Conv-psychosis) with incident dementia. Finally, to assess the relative contribution of

471   psychosis to MBI-associated progression, a secondary analysis with an identical set of survival and

472   Cox proportional hazard analyses was performed to compare MBI-psychosis against an MBI-no-

473   psychosis comparator group, in which the participants with MBI-psychosis were removed, leaving

474   only non-psychotic MBI. All hazard ratios (HR) were accompanied by their associated 95%

475   confidence interval (CI) and p-value. The Wald test was used to test for statistical significance in all

476   Cox models.

477

478   Statistical analyses were performed in RStudio v1.3.1093, using the *survival* package v3.2.7 for Cox

479   proportional hazards regression models, and *ggplot2* v3.3.2 and *survminer* v0.4.8 packages for KM

480   curves and forest plots of HR. Assumptions for proportional hazards were assessed using the *cox.zph*

481   function from the *survival* package.

482

Data Availability

Data are available from NACC upon submission of a data access request

(https://naccdata.org/requesting-data/data-request-process).

486

Code Availability

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

489

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511

Author Contributions

513   ZI and MG had major role in study design and conception, data preparation, statistical analysis and

514   interpretation, and drafting and revision of the manuscript. AM, CF, ES, and BC contributed to

515   drafting and revision of the manuscript and interpretation of the data.

516

Competing Interests:

518   Z.I. has received honoraria from Otsuka/Lundbeck outside the submitted work. His institution has

519   received payment in lieu from Acadia, Biogen, and Roche. The remaining authors declare no

520   competing interests.

521

522

523 **Tables**

524 **Table 1.** Baseline demographic, genetic, and cognitive variables of dementia-free participants with no

525 NPS compared to those with MBI-psychosis. p-values were calculated based on two-sided two-sample

526 t-test for continuous variables and Chi-squared test for categorical variables. Bold p-values indicate

527 statistical significance.

528

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%)		

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536   **Table 2.** Hazard ratios for incident dementia associated with the interaction between NPS groups

537   (MBI-psychosis versus No-NPS) and cognitive status categories. The last column represents the risk

538   ratio associated with MBI-psychosis within each stratum of cognitive status. The Wald test was used to

539   test for statistical significance in the Cox model, with bold p-values indicating significance.

540

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**	

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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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Figure legends

559 **Figure 1.** Kaplan-Meier (KM) curve of dementia-free survival and adjusted hazard ratio for incident

560 dementia over ten years stratified by NPS groups: **(A)** MBI-psychosis versus no NPS prior to dementia

561 diagnosis. **(B)** Conventionally measured psychosis (Conv-psychosis) versus no NPS prior to dementia

562 diagnosis. The red dashed line in the KM curve plots represents the median survival probability. The

563 shaded area around the KM curves represents the 95% confidence interval for each group. The log-

564 rank test was applied to test for statistical significance for KM curves. HR refers to the hazard ratio for

565 dementia incidence with the No-NPS group as the reference group. Error bars for HR represent the

566 95% confidence intervals of the mean. The Wald test was used to test for statistical significance in the

567 Cox model, with the star notation indicating significance.

568

569 **Figure 2. (A)** Forest plot of adjusted hazard ratios for incident dementia, across the strata of the

570 interaction between cognitive status (NC, MCI) and NPS groups (No-NPS, MBI-psychosis) **(B)** Forest

571 plot of adjusted hazard ratios for incident dementia, across the strata of the interaction between race

572 (Black, White, Other) and NPS groups (No-NPS, MBI-psychosis). Error bars for HR represent the

573 95% confidence intervals of the mean. The Wald test was used to test for statistical significance in the

574 Cox model, with the star notation indicating significance.

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

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