

Association Between Early Psychotic Symptoms and Alzheimer's Disease Prognosis in a Community-Based Cohort

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Handling Associate Editor: Gad Marshall

Accepted 15 March 2021

Pre-press 19 April 2021

Abstract.

Background: Psychotic symptoms are an important and increasingly recognized aspect of Alzheimer's disease (AD). They have been shown to contribute to faster disease progression in clinic-based, demographically homogenous samples with high educational attainment.

Objective: We studied the association between baseline psychotic symptoms and disease progression among individuals with incident AD or 'at risk' of developing AD, from a demographically heterogeneous, community-based cohort with minimal educational attainment.

Methods: 212 participants received the Columbia University Scale of Psychopathology in Alzheimer's Disease scale. Participants had psychotic symptoms with any of: visual illusions, delusions, hallucinations, or agitation/aggression. Disease progression was measured yearly and defined by meeting cognitive (≤ 10 on the Folstein MMSE) or functional endpoints (≥ 10 on the Blessed Dementia Rating Scale or ≥ 4 on the Dependence Scale).

Results: The mean age was 85 years old. The cohort was 78.3% female, 75.9% Hispanic, and had a mean 6.96 years of education. Within the follow-up period (mean: 3.69 years), 24 met the cognitive endpoint, 59 met the functional endpoint, and 132 met the cutoff for dependence. The presence of at least one psychotic symptom was initially associated with an increased risk of reaching the functional endpoint (HR 3.12, 95% CI 1.67–5.86, $p < 0.001$) and the endpoint of dependence (HR = 1.498, 95% CI 1.05–2.13, $p = 0.03$). However, these associations were attenuated and non-significant when adjusted for baseline functional status. Psychotic symptoms were not associated with the cognitive endpoint.

Conclusion: Psychotic symptoms may predict functional decline in patients of non-Caucasian ethnicity and with lower educational attainment.

Keywords: Alzheimer's disease, ethnic groups, neurobehavioral manifestations, prognosis

INTRODUCTION

Neuropsychiatric symptoms (NPS) are an important aspect of Alzheimer's disease (AD) care and management [1]. These symptoms contribute to

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caregiver stress [2] and increased medical resource use [3] and costs [4]. Additionally, these symptoms may impact disease course. Apathy and night-time behavioral disturbances were shown to contribute to increased mortality [5], and symptoms of psychosis [6], agitation, and aggression [7] have been shown to contribute to increased risk of institutionalization and functional and cognitive decline. The ability to identify risk factors for faster decline is important for patient and caregiver education, as well as for improved advance care planning.

There is increasing recognition of the importance of including non-white populations in the body of research around AD. In general, AD is more prevalent among Blacks and Hispanics [8] and some studies have demonstrated that molecular [9, 10] and structural [11] biomarkers for AD may differ by race/ethnicity. In the U.S., individuals from racial/ethnic minorities tend to have different patterns of healthcare utilization [8] and may come to diagnosis later than non-Hispanic whites. Similarly, individuals with low socio-economic status might also have limited access to timely AD diagnosis and care.

In addition, education, as a proxy for cognitive reserve, might have an important impact on cognitive trajectory in AD patients. According to the cognitive reserve theory, those with higher education have faster decline after disease onset, possibly due to the higher pathological burden in the brain [12]. This has implications when predicting disease progression. For example, it has been demonstrated that community-dwelling patients with AD in the Washington Heights and Inwood Aging Project (WHICAP) who have higher levels of education experience faster rates of cognitive decline [13].

A better understanding of whether behavioral and neuropsychiatric symptoms affect the course of AD when the patient is already moderately demented would provide valuable clinical information. In addition, research in this area may apply better to real-world conditions where patients are from diverse backgrounds. Hence, the association between neuropsychiatric symptoms and AD progression may need to be evaluated in the context of ethnicity, education background, and socioeconomic status.

However, much research to date has been focused primarily on clinic-based, Caucasian cohorts with relatively high levels of education, which may not be optimally generalizable to the increasingly diverse U.S. population. Participants in the Predictors 1 and 2 studies [14, 15], when combined for a study of

hallucinations and delusions [6], had a mean level of education of 13 years. Similarly, when Wilson et al [16] studied the effects of NPS on cognitive decline, their cohort was 70.1% white with a mean education of 11.7 years and Connors et al. [17] in their study of hallucinations and delusions had a cohort in which over a third had post-secondary education. Factors such as ethnic and racial background and level of education likely influence nearly every aspect of research in AD and related dementias, yet individuals from diverse populations with lower educational attainment are sorely under-represented in the literature. A recent white paper suggested several steps to address this knowledge gap [18]. Therefore, we analyzed data collected from a subset of the Predictors 3 cohort, which is a community-based cohort that is predominantly non-Caucasian. This is a community-based cohort that was developed for the purpose of testing whether observations in the Predictors 1 and 2 cohorts, two clinic-based studies with predominantly Caucasian participants, are generalizable to the community [19]. We selected patients with either recently (within the prior 2 years) diagnosed probable AD patients or deemed likely to be at high risk of converting to AD while being followed over time (either with a diagnosis of mild cognitive impairment, or with neuropsychological testing scores close to pre-determined cut-points that would indicate impairment). We hypothesized that in this community-based cohort, as in the Predictors 1 and 2 cohorts, the presence of psychotic symptoms at baseline would predict faster cognitive and functional decline.

METHODS

Participants

This study was conducted using data from the Predictors 3 cohort. The cohort development, inclusion criteria, and assessment procedures of the Predictors 3 cohort have been described in detail [19]. In brief, this cohort was developed to study a community-based and more ethnically diverse cohort than those of the clinic-based Predictors 1 and Predictors 2 cohorts, which was recruited from memory disorder practices at specialized research centers and was racially homogenous. For the Predictors 3 cohort, patients with incident and recently identified prevalent AD were recruited from the Washington Heights-Inwood Columbia Aging Project (WHICAP) study, which has been following randomly sampled Medicare recipients in North Manhattan since 1992. Patients were

recruited to the Predictors 3 study if, at a follow-up visit, they were diagnosed with probable AD based on the 2011 National Institute of Aging criteria [20] or if they were identified as being ‘high risk’ of conversion to AD based on a comprehensive neuropsychological evaluation. Because the interval between visits for the parent WHICAP study is 1.5–2 years, [19] this method of recruitment made it highly likely that the development of probable AD or ‘at risk’ of conversion had occurred within that time frame. Once recruited to Predictors 3, patients are assessed on a yearly basis. For purposes of this study, all participants with follow up visits and with neuropsychiatric data at baseline were included in the analysis. The Predictors 3 study was approved by the Institutional Review Board of the New York State Psychiatric Institution.

Evaluation

At every Predictors 3 visit, a detailed neuropsychological assessment, including questions on presence or absence of delusions, hallucinations, visual illusions, agitation/aggression, and depression is completed by an informant using the Columbia University Scale for Psychopathology in Alzheimer’s Disease (CUSPAD) [21]. We chose to focus on psychotic symptoms based on prior evidence that symptoms of psychosis predict adverse clinical outcomes in AD, both in the Predictors 1 and 2 cohorts [6, 7] as well as in other studies [16, 17, 22–24]. We created a composite variable to indicate the presence of any psychotic symptom. While the CUSPAD is administered at every Predictors 3 visit, we chose to restrict our analysis to the score at the initial Predictors 3 visit, to mimic as best as possible the real-world condition of a patient or caregiver desiring a prognosis at the first assessment by a clinician.

Outcomes

Assessment of functional ability was done using the Blessed Dementia Rating Scale (BDRS) [25] which can be scored on a scale of 0–17. Higher scores reflect lower functional status. We chose a cutoff score of 10 as a marker of severe disease, as in previous studies [6]. Assessment of dependency was completed using the Dependence Scale [26], which is a 13-item scale used to assess the degree of assistance required by participants. A dependence level is then assigned, which may range from 0 (completely independent) to 5 (completely dependent). The scale is able to demonstrate changes in

functional dependency independently of cognitive decline, although in the Predictors 3 cohort it was found to associate with other markers of disease severity, independent of demographic factors [27]. We chose a cutoff of dependence level 4 as a marker of moderate to severe disease as previously described [28]. Assessment of cognitive ability was performed using the Folstein Mini-Mental State Exam (MMSE) [29] which can be scored on a scale of 0–30, with higher scores reflecting better cognitive ability. We chose a cutoff score of 10 on the MMSE as similar cutoff scores have been identified in previous studies [6, 22]. We also conducted sensitivity analyses with a MMSE cutoff of 8 based on the possible educational and socioeconomic effects on test performance among primarily Hispanic-Latino populations [30], as well as restricted our analyses to those with milder disease (defined as MMSE \geq 16).

All of the above scores were converted into dichotomous variables to indicate the status of first time point of reaching the undesirable endpoints or not, with \leq 10 on MMSE, \geq 10 on BDRS, or \geq 4 on dependence scale coded as 1 (i.e., meeting endpoints), and the other scores coded as 0.

Statistical analysis

For comparing baseline characteristics, *t*-tests were used for continuous variables and Chi-square tests for categorical variables, unless greater than 20% of cells had expected counts of $<$ 5, in which case Fischer’s exact test was used. We calculated Cox proportional hazards models to compare the risk of reaching the cognitive, functional, and dependence endpoints. The predictor was a binary variable indicating the presence of at least one of the four selected symptoms on the CUSPAD, with the reference category being the absence of any of the selected symptoms. The time scale was the time from baseline to the first time point of reaching each of the undesirable endpoints or to the last visit for those who did not meet the endpoint. We ran a crude model (Model 1) without any adjustment, and then adjusted for demographic variables (sex, age at study entry, ethnicity, level of education in years) in Model 2, and additionally adjusted for baseline scale performance in BDRS, MMSE, or Dependence in Model 3. The assumption of proportionality was confirmed by visual inspection of the Kaplan-Meier curves. Five participants endorsed using antipsychotics upon enrollment. Since all of these 5 participants were also identified as having behavioral symptoms,

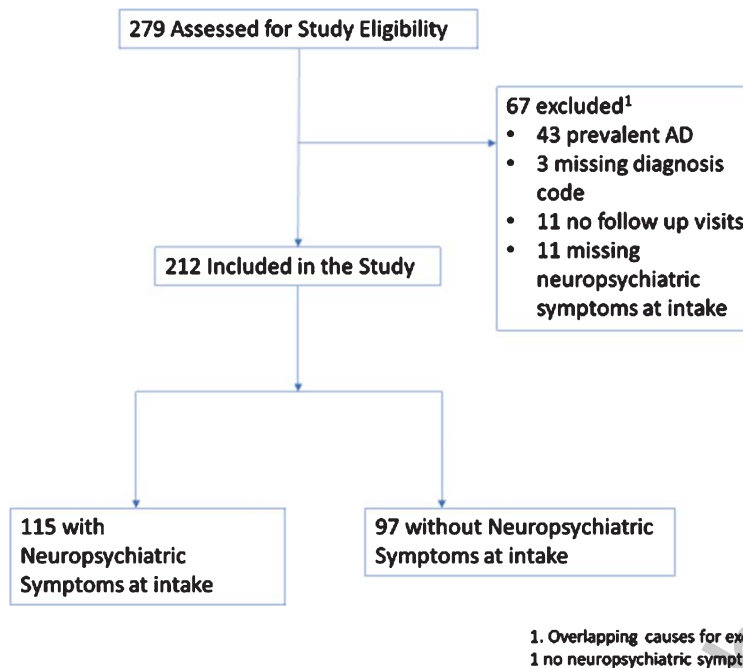


Fig. 1. Population Flow Diagram.

antipsychotic use was not used as an additional covariate in the primary analyses; however, sensitivity analyses were done with only those individuals who denied taking antipsychotics. Sensitivity analyses were also performed among individuals with milder disease state (separately for CDR < 1, MMSE < 16, or BDRS < 14) only. Analyses were performed using SPSS Statistics v.25.

RESULTS

There were 279 participants in the study (Fig. 1). After excluding 47 prevalent AD cases, 3 cases with no diagnosis, 11 cases who had no follow-up, and 11 cases with no neuropsychiatric data at baseline, 212 participants were included in the current analyses (4 excluded cases had both prevalent AD and no follow up, and 1 excluded case had both no psychiatric data at baseline and no follow up). There were 101 with incident AD and 111 'at risk' of conversion to AD, defined as those with MCI or with neuropsychological test performance near pre-defined cut scores which are not norms-based [19]. Within the 'at-risk' group, 36 converted to a clinical diagnosis of dementia during the follow-up period. The mean age was 85 years old (range 69–105 years, SD 6.56 years). The cohort was 78.3% female, 75.9% Hispanic, had a mean of 6.96 years of education (range 0–20 years,

SD 4.78 years), and had an average of 3.69 years of follow up (range 0.97–7.93 years, SD 1.59 years). There were 115 (54.2%) with the psychotic symptoms at baseline, and 152 (71.7%) with depression.

For the overall cohort, the mean baseline MMSE was 20.83 (range 8–29, SD 4.28), the mean dependence level was 3 (range 0–5, SD 1.61), and the mean BDRS was 4.53 (range 0–15, SD 3.43). The mean time to the functional cutoff was 2.23 years (range 0–6.59, SD 1.71). The mean time to the dependency cutoff was 2.45 years (range 0.66–6.89, SD 1.19). The mean time to the cognitive cutoff was 3.72 years (range 0.97–7.93, SD 1.57).

Participants with psychotic NPS at baseline performed more poorly on the MMSE ($p < 0.001$), were more functionally impaired ($p < 0.001$) and had higher levels of dependence ($p < 0.001$) (Table 1).

Within the study period, 53 met the functional cutoff and 132 met the dependency cutoff. In a crude analysis, those with psychotic NPS at baseline were at higher risk to reach the functional endpoint than those without (HR 3.12, 95% CI 1.67–5.86, $p < 0.001$), and remained so (HR 3.31, 95% CI 1.74–6.30, $p < 0.001$) after adjusting for demographics. In this model, female sex was a predictor of increased risk of reaching the functional endpoint as well (HR 2.44, 95% CI 1.02–5.85, $p = 0.045$). However, when the model was controlled for baseline functional status, this

Table 1
Baseline Cohort Characteristics

	With NPS (n = 115)	Without NPS (n = 97)	
Mean follow-up, y (SD)	3.71 (1.67)	3.66 (1.49)	p = 0.82
Mean age, y (SD)	85.20 (6.72)	84.98 (6.52)	p = 1.00
Mean education, y (SD)	6.51 (4.60)	7.44 (4.93)	p = 0.14
%female	82.60	73.20	p = 0.07
Ethnicity%:			p = 0.07
non-Hispanic white	8	15	
Hispanic	93	68	
African American	12	14	
Other	2	0	
Mean MMSE at baseline (SD)	19.73 (4.44)	22.13 (3.70)	p < 0.001
Met MMSE cutoff at initial visit, N (%)	2 (1.74)	1 (1.03)	p = 1.00
Mean BDRS at baseline (SD)	5.62 (3.41)	3.24 (2.98)	p < 0.001
Met BDRS cutoff at initial visit, N (%)	13 (11.30)	4 (4.12)	p = 0.06
Antipsychotic use, %	4.67	0	p = 0.063
Delusions, N (%)	90 (78.26)	**	**
Hallucinations, N (%)	43 (37.39)	**	**
Agitation/Aggression, N (%)	68 (59.13)	**	**
Visual Illusions, N (%)	5 (4.35)	**	**

effect was attenuated and no longer statistically significant (Table 2, model 3). Similar results were found when predicting dependency. Crude analysis demonstrated increased likelihood of becoming moderately-severely dependent (HR = 1.50, 95% CI 1.05–2.13, p = 0.03) and this association remained significant when adjusted for demographics; however, this was mitigated by baseline dependency. Age was a predictor of slightly increased risk of reaching the dependency endpoint (HR = 1.05, 95% CI 1.03–1.08, p < 0.001) as well. When assessing individual symptoms, all symptoms were independently associated with higher risk of reaching the functional cutoff in unadjusted models although these, too, became nonsignificant when adjusted for baseline functional status. Delusions and hallucinations, but not aggression or illusions, were independently associated with higher risk of reaching the dependency cutoff in unadjusted models and when adjusting for demographics and baseline levels of function, hallucinations remained a significant predictor (HR 1.58, 95% CI 1.04–2.41, p = 0.03) (Table 3). In sensitivity

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Table 2

Cox Models Predicting Occurrence of the Outcomes by Psychotic NPS (any of Delusions, Hallucinations, Agitation/Aggression, and Visual Illusions)

	Functional (BDRS)		Cognitive (MMSE)		Dependence (Dependence Scale)	
	HR	95% CI	HR	95% CI	HR	95% CI
Psychotic NPS	3.12	(1.67–5.86)* p < 0.001	1.59	(0.69–3.68) p = 0.28	1.49	(1.05–2.13)* p = 0.03
	Model 1					
	3.31	(1.74–6.30)* p < 0.001	1.84	(0.76–4.41) p = 0.18	1.5	(1.05–2.46)* p = 0.03
Model 2: Adjusted for Demographics**						
Model 3: Adjusted for Demographics and Baseline Status***						
	1.58	(0.79–3.15) p = 0.20	0.89	(0.34–2.31) p = 0.81	1.01	(0.70–1.46) p = 0.96

HR, hazard ratio; CI, confidence interval. *Denotes significant hazard ratios (p < 0.05). **Adjusted for age, gender, ethnicity, education. ***Adjusted for demographics as well as baseline measure status.

Table 3
Associations for Individual NPS

	Functional (BDRS)		Cognitive (MMSE)		Dependence (Dependence Scale)	
	HR	95% CI	HR	95% CI	HR	95% CI
Crude Models						
Hallucinations	2.42	(1.33–4.39)* p = 0.004	1.79	(0.74–4.32) p = 0.20	1.63	(1.10–2.43)* p = 0.02
Agitation/ Aggression	2.44	(1.41–4.20)* p = 0.01	0.99	(0.41–2.39) p = 0.97	1.35	(0.95–1.93) p = 0.10
Delusions	2.79	(1.60–4.86)* p < 0.001	2.46	(1.09–5.55)* p = 0.03	1.47	(1.04–2.07)* p = 0.03
Visual Illusions	5	(1.52–16.42)* p = 0.008	–	–	1.4	(0.52–3.78) p = 0.51
Adjusted Models**						
Hallucinations	1.29	(0.69–1.42) P = 0.42	1.52	(0.61–3.82) p = 0.37	1.58	(1.04–2.41)* p = 0.03
Agitation/ Aggression	1.17	(0.65–2.13) p = 0.60	0.47	(0.17–1.30) p = 0.15	1.00	(0.69–1.45) p = 0.99
Delusions	1.24	(0.66–2.32) p = 0.50	1.86	(0.69–5.02) p = 0.22	0.92	(0.64–1.34) p = 0.92
Visual Illusions	2.19	(0.65–7.38) p = 0.21	–	–	1.82	(0.65–5.15) p = 0.26

HR, hazard ratio; CI, confidence interval. *Denotes significant hazard ratios (p < 0.05). **Adjusted for demographics as well as baseline measure status.

analysis of individuals who denied taking antipsychotics, the risk of reaching the functional cutoff among those with psychotic NPS was similar and significant (HR 2.89, 95% CI 1.53–5.46, $p=0.001$) and the risk of reaching the dependency cutoff was similar as well, with a trend toward statistical significance (HR 1.43, 95% CI 0.995–2.05, $p=0.053$).

Within the study period, 24 participants met the cutoff for the MMSE. Psychotic NPS at baseline did not significantly predict the endpoint (HR 1.59, 95% CI 0.69–3.68, $p=0.28$), although in unadjusted secondary analysis, delusions was an independent predictor of the outcome (Table 3).

Sensitivity analysis of a subgroup of 182 participants with milder disease (defined as MMSE ≥ 16) yielded similar results (unadjusted analysis HR 0.98, 95% CI 0.35–2.73, $p=0.97$). Exploratory analysis of a different endpoint for the MMSE (≤ 8) did not suggest a different effect (unadjusted analysis HR 0.86, 95% CI 0.32–2.32, $p=0.76$). In stratified analysis by subgroup ('at risk' versus 'incident AD'), similar results were found for the functional cutoff. Analyses were no longer significant for the dependence cutoff except in one analysis, and not at all in the 'incident AD' group. (Supplementary Tables 1–4).

In order to compare the effect of psychotic symptoms to the effect of depression, secondary analyses were run to assess the association between depression and risk of decline, using the same cohort however the requirement of no missing psychotic data was shifted to requiring no missing depression data. Depression did not predict any of the endpoints, however, neared significance for the functional endpoint (HR 1.87, 95% CI 0.94–3.74, $p=0.07$).

DISCUSSION

We found that in a cohort of multiethnic patients with either recently diagnosed dementia or at risk for incipient dementia, symptoms of delusions, hallucinations, visual illusions, and agitation/aggression may be associated with functional decline and dependency, but not cognitive decline. However, a large component of this effect seems to be attributable to baseline function and dependence level. Additionally, these associations were driven by frank hallucinations, delusions, and with regards to function, aggression as well with regards to unadjusted models. Hallucinations remained an independent predictor of dependency when adjusted for baseline status. We also found that female sex was an independent predictor of functional decline.

There are several possible reasons for the different findings on cognitive endpoints in the current study and in the Predictor 1 and 2 cohorts, which found that symptoms of psychosis and disruptive behavior were associated with increased risks of cognitive decline, functional decline, and institutionalization [6, 7]. First, the Predictor 3 study participants have lower levels of educational attainment. The cognitive reserve theory suggests that decline may be delayed initially and then accelerated later in those with higher educational attainment, whereas in subjects with lower education attainment, the major change in cognition and function might occur earlier. Therefore, at the time of diagnosis, patients may have limited room for further decline. Additionally, markers of cognitive reserve such as education level have been shown to amplify the effect of depression on cognition among patients with AD, which may be related in part to increased [31] awareness of deficits among patients with high cognitive reserve [32]. Among our participants, educational attainment and therefore cognitive reserve was low, and the lack of this moderating factor may have contributed to the non-significant results in the adjusted analyses. Second, the current study population has a different ethnic makeup compared to the Predictor 1 and 2 studies, which could suggest that cultural factors play a role. One study found that community-dwelling African Americans and Latinos with dementia may have behavioral symptoms more frequently than non-Hispanic whites [33], and non-Caucasian ethnicity has been associated with psychosis in patients with AD [34].

Finally, despite limiting our study to participants with recently diagnosed AD or at high risk for converting to AD, in the current study subjects were more impaired cognitively and functionally at the baseline visit compared with previous Predictor Study cohorts, which were comprised exclusively of patients with mild dementia. In the Predictor 1 and 2 cohorts, the baseline mMMSE, MMSE, and BDRS were 40, 21, and 3.5, respectively. In the current study, the overall averages were 32, 20, and 5.62, respectively. However, it is important to note that the Predictors 3 cohort includes those considered at-risk for converting to AD and less impaired cognitively; the incident AD subgroup of the cohort has a mean MMSE score of 19.1 and the at-risk subgroup has a mean score of 22.7 [19], which is similar to the Predictor 1 and 2 cohorts. Within the 'at-risk' group, 33% of individuals converted to dementia during the study period. It is possible that in later stages of disease there is

416 less room for decline, limiting the power for any
417 factor to predict the decline. In fact, a study of a
418 VA/community cohort of mild AD found that after
419 2 years, rates of cognitive and functional decline
420 slowed and became non-linear [35].

421 An additional plausible explanation for our find-
422 ings is that psychotic symptoms are a marker of a
423 worse cognitive state in this patient population, and
424 if so, would imply that it is the worse cognitive state
425 at baseline that is associated with the decline rather
426 than the psychotic symptoms. However, when we
427 attempted sensitivity analyses of less impaired par-
428 ticipants, the results did not change, suggesting that
429 psychotic symptoms may indeed be an independent
430 factor. This is consistent with the findings of Del-
431 gato et al. [36] which showed that neuropsychiatric
432 symptoms had a greater cross-sectional impact on
433 functional impairment in earlier stages but less of
434 an impact in more advanced stages of disease. Thus,
435 we could reasonably postulate that it could be possi-
436 ble that psychotic symptoms had been related to the
437 MMSE and BDRS decline even prior to the base-
438 line of the study. Finally, while the exact mechanism
439 is unclear, evidence suggests that there is increased
440 accumulation of neurofibrillary tangles in neocortical
441 areas among AD patients with psychotic symptoms
442 independently of disease severity [37], which might
443 potentially explain the observed association.

444 We included models that both did and did not
445 include adjustment for the baseline measure. Both
446 approaches have the potential to introduce bias, par-
447 ticularly in a prolonged process where the beginning
448 is difficult to determine. Indeed, Glymour et al. [38]
449 demonstrated that baseline-adjusted estimates can
450 be biased when a measured 'baseline' occurs after
451 change has already started due, in part, to unmea-
452 sured causes. One unmeasured cause in our study is
453 the pathological protein deposition of AD. Patholog-
454 ical proteins begin accumulating in the brain long
455 before cognitive and functional decline emerge [39]
456 and it is therefore very difficult to identify a true 'base-
457 line.' This is particularly true in a community-based
458 setting. Several studies have found an association
459 between amyloid [40] and/or tau [37, 41] deposi-
460 tion and the presence of neuropsychiatric symptoms,
461 however in some clinical trials of anti-amyloid drugs,
462 removal of amyloid exacerbated neuropsychiatric
463 symptoms rather than ameliorating them [42]. We
464 did find that after adjusting for baseline function,
465 the association between psychotic symptoms and
466 functional decline was attenuated and no longer sig-
467 nificant. Another possible explanation could be that

468 the baseline performance serves as a mediator for
469 the association between psychotic symptoms and the
470 degree of change, as psychotic symptoms may lead
471 to baseline difference in function which in turn leads
472 to differential trajectories.

473 Our population had an average age of 85 years,
474 which is older than many others studied [14, 43, 44].
475 Age may have influenced our results, as functional
476 impairment and dependency may plausibly be related
477 to age-related frailty. However, it has been previ-
478 ously demonstrated in this cohort that dependency
479 correlates with disease severity and not demographic
480 factors such as age [27].

481 Our study has several strengths. It is a community-
482 based cohort, which is more likely to reflect clinical
483 conditions in the community. Additionally, we
484 focused on a traditionally understudied population.
485 This is a reflection of real-world conditions in our
486 patient population. Both of these factors make our
487 results more generalizable than those from clinic-
488 based cohorts and expand current knowledge about
489 factors that affect patient decline.

490 There are also several limitations to our study.
491 Our participants were more cognitively and function-
492 ally impaired at baseline compared with participants
493 in the previous Predictor Study cohorts, which may
494 make longitudinal data collection more difficult. We
495 also had few patients reach the cognitive endpoint
496 and a high amount of censoring in our data, which
497 if it is related to worsening severity of disease could
498 have introduced bias into our results. Additionally,
499 our sample size was relatively small which made it
500 difficult to run adequately powered stratified analy-
501 ses across education levels. It is also possible that the
502 relatively short duration of follow up influenced how
503 many patients reached the endpoints by the end of
504 the study, particularly for those participants in the 'at-
505 risk' group. It is also possible that dichotomizing our
506 end-points affected the ability of our study to detect
507 associations; however, defining end-points is useful
508 clinically and our chosen metrics and end-points have
509 been previously utilized [6, 22, 28]. Few participants
510 had visual illusions, yet this was included in order to
511 be inclusive of all psychotic symptoms and to account
512 for the possibility that distinguishing visual illusions
513 from hallucinations may be difficult for informants.
514 Finally, we could not rule out the possibility of resid-
515 ual confounding by other neuropsychiatric symptoms
516 such as apathy and irritability, which are not measured
517 in the CUSPAD.

518 In sum, our work is consistent with previous re-
519 search suggesting that psychotic symptoms may be

associated with future decline in AD. Although it is different in that in our cohort, with the exceptions of hallucinations and dependency, this relationship was accounted for by the baseline worsened status and we found a relationship with functional decline and dependency only. It is important in the clinical encounter to ask about these symptoms, as they are useful for discussions of prognosis, caretaker decisions, and advance care planning. While current research focuses heavily on early stages of disease for purposes of increasing the likelihood of disease-modifying therapy, our results are important for those patients who have already advanced by the time new therapies are validated and approved.

ACKNOWLEDGMENTS

The authors wish to thank the participants of the Predictors 3 study and their caregivers.

Support was provided by NIH grants R01AG007370, R01AG059013, R01AG061008, and 5T32NS007153.

Columbia University licenses the Dependence Scale, and in accordance with University policy. Dr. Stern is entitled to royalties through this license.

Authors' disclosures available online (<https://www.j-alz.com/manuscript-disclosures/20-0729r2>).

SUPPLEMENTARY MATERIAL

The supplementary material is available in the electronic version of this article: <https://dx.doi.org/10.3233/JAD-200729>.

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