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Neuropsychiatric Symptoms and *In Vivo* Alzheimer's Biomarkers in Mild Cognitive Impairment

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Abstract.
Background: Neuropsychiatric symptoms (NPS) carry an increased risk of progression from mild cognitive impairment (MCI) to Alzheimer's disease (AD). There is a need to understand how to integrate NPS into the paradigm outlined in the 2018 NIA-AA Research Framework.
Objective: To evaluate a prediction model of MCI-AD progression using a collection of variables, including NPS, cognitive testing, apolipoprotein E4 status (*APOE4*), imaging and laboratory AD biomarkers.
Methods: Of 300 elderly subjects, 219 had stable MCI and 81 MCI-AD progression over a 5-year follow-up. NPS were measured using the Neuropsychiatric Inventory (NPI). A multivariate Cox Proportional Hazards Regression Analysis assessed the effects of *APOE4*, baseline NPI, baseline CSF amyloid-β, phosphorylated and total tau, baseline AD-signature MRI biomarker, baseline memory and executive function on MCI-AD progression.
Results: 27% progressed to dementia (median follow-up = 43 months). NPS were found in stable MCI (62.6%) and MCI-AD converters (70.3%). The Cox model exhibited a good fit ($p < 0.001$), and NPS (HR = 1.033, $p = 0.027$), phosphorylated tau (HR = 1.011, $p = 0.025$), total tau (HR = 1.005, $p = 0.024$), AD-signature MRI biomarker (HR = 0.111, $p = 0.002$), executive function (HR = 0.727, $p = 0.045$), and memory performance (HR = 0.387, $p < 0.001$) were significantly associated with dementia.
Conclusions: NPS may inform dementia risk assessment in conjunction with cognitive testing and imaging and laboratory AD biomarkers. NPS is independently associated with the risk of MCI-dementia progression, over and beyond the contributions of CSF biomarkers.

Keywords: Alzheimer's disease, amyloid, cerebrospinal fluid, cognitive dysfunction, magnetic resonance imaging, neuropsychiatric symptoms

INTRODUCTION

Alzheimer's disease (AD) has been traditionally defined as a probable clinical diagnosis in patients with multidomain amnestic dementia after exclusion of other potential etiologies, with a definitive

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diagnosis only being made at autopsy [1]. Mild cognitive impairment (MCI) of the Alzheimer-type is characterized by memory complaints and amnestic syndrome on exam, normal or only mildly impaired complex activities of daily living, and exclusion of other disorders [2, 3]. Amnestic MCI is considered a prodromal state of AD. In the last two decades our understanding of AD has evolved from a purely clinical definition of the diagnosis to the introduction of a growing array of imaging and cerebrospinal fluid (CSF) biomarkers allowing for early detection of extracellular deposition of amyloid-β (Aβ) plaques and tau intracellular neurofibrillary tangles [4]. In 2018, the NIA-AA launched a novel research framework which defined AD by its underlying pathology, as determined by biological biomarkers [5]: Aβ biomarkers, as indicated by low CSF Aβ or abnormal amyloid imaging with positron emission tomography (PET); tau biomarkers, as indicated by elevated CSF hyperphosphorylated tau (p-tau) or cortical tau PET ligand binding; biomarkers of neurodegeneration aiming to stage disease severity, as indicated by CSF total tau (t-tau), fluorodeoxyglucose (FDG) PET hypometabolism, or magnetic resonance imaging (MRI) atrophy.

Neuropsychiatric symptoms are highly prevalent in MCI and AD [6, 7]. A meta-analysis has shown that the prevalence of apathy, depression, and anxiety in AD are respectively 49%, 42%, and 39% [8]. Neuropsychiatric symptoms may manifest in the early stages of AD, even preceding cognitive decline [9]. Studies have shown an association between apathy, anxiety, depression, presence of any neuropsychiatric symptoms, and risk of progression to AD-type dementia in patients with MCI [10–12]. The presence of more than one NPS is associated with worse and faster cognitive decline in MCI [13]. In a longitudinal study, MCI subjects with any neuropsychiatric symptoms had an approximately 40% increased risk of any type of dementia and AD-type dementia in comparison to subjects not exhibiting these symptoms [6]. In another longitudinal study, the progression rate to dementia was about double in elderly individuals with at least two neuropsychiatric symptoms [14]. Studies have also demonstrated an association between neuropsychiatric symptoms and AD pathological changes in the elderly population [15–17]. Mah et al. have studied the effects of anxiety in amnestic MCI, and found an association between the severity of anxiety and the rate of conversion from MCI to probable AD [18]. Furthermore, they found that the association remained significant after controlling for depression, cognitive decline, and measures of mesial temporal atrophy.

While a significant body of literature exists on the relationship between NPS and MCI-AD progression, a critical issue requires further determination: the integration of NPS within the paradigm provided by the 2018 NIA-AA Research Framework. Studies have shown that Aβ deposition may have an association with NPS in cognitively unimpaired subjects and in preclinical AD, and tau pathology may be linked to NPS in MCI and early in the course of AD, although there is conflicting evidence concerning the relationship between tau deposition and NPS [19–21]. Previous studies have also acknowledged the high prevalence of NPS in MCI and AD, noting their potential as predictive markers for progression. Our study aims to bridge the gap between these observations and the latest advances in AD research. Our purpose is to evaluate the role of NPS in the prediction of MCI-dementia progression not in isolation, but within the broader context of other well-established predictors, including *in vivo* imaging and laboratory AD biomarkers, apolipoprotein E status (*APOE4*), and cognitive testing. The rationale for examining the role of NPS in conjunction with other predictors serves a dual purpose. First, it allows us to disentangle potential confounding effects and understand the distinct influence of NPS on MCI-dementia progression, particularly in relation to Aβ/tau pathology. Additionally, the integration of established predictors aligns our study with existing research, potentially enhancing the relevance of our findings. Understanding the relative contributions of various predictors, including NPS, holds promise for guiding future research and intervention strategies. For instance, if NPS are found to have an independent predictive effect, it would underscore the importance of addressing and managing these symptoms in future clinical trials and clinical practice. We hypothesized that the total burden of NPS would be greater in individuals with progression to dementia, and that NPS would be significantly associated with progression to dementia in a prediction model also including *in vivo* AD biomarkers, *APOE4*, and cognitive testing.

METHODS

Data used in the preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (http://adni.loni.usc.edu). ADNI was launched in

2003 as a public-private partnership, led by Principal Investigator Michael W. Weiner, MD. The primary goal of ADNI has been to test whether serial MRI, PET, other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of MCI and early AD. For up-to-date information, see http://www.adni-info.org. Procedures involving experiments on human subjects were done in accord with the ethical standards of the Committee on Human Experimentation of the institution in which the experiments were done in accord with the Helsinki Declaration of 1975. This retrospective study was approved by the Institutional Review Board and was compliant with Health Insurance Portability and Accountability Act regulations.

Study population

Data collected for this study were obtained from the Alzheimer's Disease Neuroimaging Initiative 2 (ADNI 2) database. The ADNI 2 cohort was followed for 5 years and included cognitively unimpaired elderly subjects, MCI, and AD patients. At baseline, 659 had a diagnosis of MCI. Clinical criteria for amnestic MCI included: MMSE score of 24–30, objective memory loss tested by delayed recall of the Wechsler Memory Scale Logical Memory II, normal activities of daily living; a CDR score of 0.5, and absence of dementia [2]. Major depression was an exclusion criterion and study participants were required to have a Geriatric Depression Scale (GDS) < 6 to be eligible for the study.

Cognitive and neuropsychiatric testing

Patients participated in the research study for 5 years. In ADNI 2 NPS were measured using the Neuropsychiatric Inventory (NPI) (ranging from 0, for no NPS, to 144, for severe NPS), a caregiver-based report of NPS, including ratings of the severity and frequency of the following symptoms: delusions, hallucinations, agitation/aggression, depression/dysphoria, anxiety, elation/euphoria, apathy/indifference, disinhibition, irritability/lability, aberrant motor activity, sleep disturbances, and changes in appetite and eating behaviors [22]. For all subjects, we recorded the total NPI rating collected during the study baseline visit. We also collected baseline ADNI Memory and ADNI Executive Function scores, which are composite scores created to address site-to-site variability in neuropsychological test versions [23, 24]. Cognitive assessments were scheduled at baseline, at a three-month follow-up visit, and then annually. These serial assessments were used by the ADNI investigators to define whether patients were clinically stable or had progressed from MCI to dementia.

Inclusion and exclusion criteria

Inclusion criteria were as follows: MCI at baseline; brain MRI study obtained during the baseline study visit; baseline neuropsychiatric assessment with the NPI, lumbar puncture with concentrations of CSF Aβ, p-tau and t-tau, and apolipoprotein E genotype. *APOE* genotype was determined from peripheral blood DNA at the ADNI Biomarker Core Laboratory. Subjects were classified as *APOE4* carriers (at least one ε4 allele) and noncarriers (no ε4 allele). CSF samples were obtained as described in the ADNI procedures manual (http://www.adni-info.org/) [25]. We excluded all subjects with missing laboratory or imaging data. We recorded conversion from MCI to AD documented by the ADNI investigators during study participation.

Imaging

Brain MRI included a 3D T1-weighted MPRAGE volumetric sequence collected using standardized protocols across multiple sites [26]. The AD-signature MRI biomarker was calculated using FreeSurfer V5.1 software (http://surfer.nmr.mgh.harvard.edu) as previously described [27]. In brief, we calculated the average cortical thickness in nine regions of interest that have been previously linked to AD, collectively known as the "cortical signature" of AD [28, 29]. In this study, we used a single summary measure, the "AD-signature measure", which is the average thickness of all nine regions of interest, as our primary imaging biomarker. This measure is highly sensitive to subtle changes in the cortical network affected by AD pathology, even before the onset of clinical symptoms. In summary, baseline total NPI, baseline ADNI Memory and ADNI Executive Function, baseline CSF biomarkers, *APOE4* status, and baseline MRI data were collected and utilized in the statistical analyses.

Statistical analyses

The outcome measure was the progression from MCI to probable dementia during study participation,

as documented by the ADNI investigators. Subjects were divided into the following two groups: 1) MCI with stable cognition during the course of the study; 2) MCI with cognitive worsening leading to the diagnosis of probable AD. Comparisons between the stable and progressed groups were computed with independent samples *t*-tests for age, education (years), baseline ADNI Memory, baseline ADNI Executive function, and baseline AD-signature MRI biomarker, and were described with means (*M*) and standard deviations (*SD*). Mann-Whitney U tests were used for group comparisons of baseline NPI, Aβ, phosphorylated tau, and total tau and were described with medians (*Mdn*) and median absolute deviations (*MAD*). The dispersion of NPI scores was described with interquartile ranges (*IQR = Q3-Q1*), which contains the second and third quartiles where the middle 50% of scores lie. Chi-square tests were used to evaluate potential group differences in the distributions of sex, % Caucasian, and % *APOE4*, with Fisher's Exact Test used for cases in which there are < 5 data points in a case. A multivariate Cox Proportional Hazards Regression Analysis model was used to evaluate the association between genetic status (*APOE4* positivity), total burden of neuropsychiatric symptoms (Baseline NPI), cognitive function (ADNI Memory and ADNI Executive Function), CSF biomarkers (Aβ, phosphorylated tau, and total tau), and AD-related regional cortical thinning (AD-signature MRI biomarker) with the likelihood of MCI subjects progressing to AD. All participants were right censored with the final follow up visit as the last time point for stable MCI subjects, and the visit at which conversion was observed as the last time point for probable AD subjects. Hazard ratios (HR) and 95% confidence intervals (95% CI) are reported for each variable. Two-sided *p*-values are reported, and statistical significance was set at the $\alpha < 0.05$ threshold. Analyses were conducted with SPSS version 27 (IBM: Armonk, NY).

RESULTS

Three hundred subjects were eligible for inclusion. 27% of individuals progressed from MCI to a diagnosis of dementia during study participation (81/300 of subjects). Seventy-eight patients were diagnosed with dementia likely due to AD, two with dementia likely secondary to other etiology, and one with dementia of unknown type. The median follow-up was of 43 months (IQR = 25.5–50 months) for individuals with stable MCI and 42 months (IQR = 31–50 months) with patients with MC-AD conversion. The demographic and clinical characteristics of the study cohort are displayed in Table 1. Data regarding the use of psychotropic medications during study participation are included in Table 2. This information provides valuable clinical context about treatment regimens of participants in stable MCI and MCI-AD group. The median baseline NPI was 2 (IQR = 0–6, range = 0–33) for the stable MCI group, and 3 (IQR = 0–9, range = 0–32) for the MCI-AD conversion group. In the stable MCI group, 137 subjects

Table 1
Demographic and Clinical Characteristics

		Stable MCI ($n = 219$)	MCI-AD progression ($n = 81$)	*p*
Demographics	Age*	71.54 (7.47)	72.24 (6.72)	0.46
	Education* (y)	16.11 (2.72)	16.32 (2.62)	0.54
	Gender (% male)	53.0%	55.6%	0.70
	Caucasian (%)	93.2%	98.8%	0.08
Neuropsychiatric Evaluation	Neuropsychiatric Symptoms***	62.6 %	70.3%	0.13
	Baseline Total Neuropsychiatric Inventory§	2 (0 – 6)	3 (0–9)	0.08
Genetics	*APOE4* (%) [a]	40.6%	69.1%	< 0.001
Cognition	ADNI Memory*	0.52 (0.63)	–0.20 (0.54)	< 0.001
	ADNI Executive Function*	0.49 (0.84)	–0.08 (0.84)	< 0.001
CSF Biomarkers	Aβ**	187.00 (43.00)	136.00 (19.00)	< 0.001
	Phosphorylated tau**	32.00 (11.90)	57.90 (15.40)	< 0.001
	Total tau**	66.10 (22.50)	119.00 (48.90)	< 0.001
MRI	AD-signature MRI biomarker (mm)*	2.66 (0.16)	2.54 (0.18)	< 0.001

NPI, Neuropsychiatric Inventory. *Mean (standard deviation). [a]*APOE4*: At least one copy of apolipoprotein E epsilon 4. §Median (interquartile range). **Median (median absolute deviation). ***Percent of subjects with any neuropsychiatric symptoms at baseline (Baseline NPI > 0).

Table 2
Use of Psychotropic Medications During the Study

	Stable MCI ($n=219$)	MCI-AD progression ($n=81$)
Selective Serotonin Reuptake Inhibitors	56/219	32/81
Tricyclic Antidepressants	1/219	1/81
Serotonin-Norepinephrine Reuptake Inhibitors	13/219	5/81
Norepinephrine-Dopamine Reuptake Inhibitors	13/219	8/81
Atypical Antidepressants	2/219	6/81
Benzodiazepine	14/219	6/81
Non-Benzodiazepine Sedative-Hypnotic Medications	2/219	5/219

Table 3
Neuropsychiatric Symptoms by Neuropsychiatric Inventory Domains

	Stable MCI ($n=219$)	MCI-AD progression ($n=81$)
Delusions	3 (1.3)*	3 (3.7)
Hallucinations	0 (0)	3 (3.7)
Agitation and Aggression	41 (18.7)	19 (23.5)
Depression and Dysphoria	64 (29.2)	28 (34.6)
Anxiety	27 (12.3)	16 (19.8)
Elation and Euphoria	9 (4.1)	2 (2.5)
Apathy and Indifference	25 (11.4)	17 (20.1)
Disinhibition	28 (12.8)	7 (8.6)
Irritability and Lability	56 (25.6)	29 (35.8)
Aberrant Motor Behavior	5 (2.3)	1 (1.2)
Sleep Disturbances	54 (24.7)	18 (22.2)
Appetite and eating disorder	14 (6.4)	12 (14.8)

*Number of subjects (percent) presenting with symptoms in each domain of the Neuropsychiatric Inventory.

had neuropsychiatric symptoms at baseline (NPI > 0, 62.6%, 137/219). In the MCI-AD conversion group, 57 subjects had neuropsychiatric symptoms at baseline (NPI > 0, 70.3%, 57/81). The numbers of subjects presenting symptoms in each of the 12 domains of the NPI are reported in Table 3.

The overall fit of the Cox Proportional Hazards Regression Analysis model was assessed using the –2 Log-Likelihood and the Likelihood Ratio Chi-Square test statistic, and the *p*-value indicated that the model provided a good fit to the data (–2 Log-Likelihood = 721.18, Chi-square 128.78, $p < 0.001$). The Hazard Ratios and corresponding 95% confidence intervals (CI) were estimated for each of the independent variables (Table 4). Baseline total NPI (HR = 1.033, 95%CI: 1.004–1.063, $p = 0.027$) was associated with an increased risk of progressing to AD. Greater cortical thickness in the baseline

Table 4
Multivariate Prediction Model of Progression to Dementia

	HR*	95% CI**	Sig.
CSF Aβ	0.996	0.990–1.003	0.241
CSF t-tau	1.005	1.001–1.010	0.024
CSF p-tau	1.011	1.001–1.021	0.025
APOE4+	1.421	0.774–2.610	0.258
ADNI Memory	0.387	0.248–0.606	<0.001
ADNI Executive Function	0.727	0.532–0.993	0.045
Baseline Total NPI	1.033	1.004–1.063	0.027
AD-signature MRI biomarker	0.111	0.027–0.462	0.002

*HR, Hazard Ratio; **CI, Confidence Interval.

AD-signature MRI biomarker was associated with a decreased risk of progressing to AD (HR = 0.111, 95%CI: 0.027–0.462, $p = 0.002$). Higher ADNI memory scores (HR = 0.387, 95%CI: 0.248–0.606, $p < 0.001$) and ADNI executive function scores (HR = 0.727, 95%CI: 0.532–0.993, $p = 0.045$) were associated with a decreased risk of progressing to AD. Higher levels of t-tau (HR = 1.005, 95%CI: 1.001–1.010, $p = 0.024$) and p-tau (HR = 1.011, 95%CI: 1.001–1.021, $p = 0.025$) were associated with an increased risk of progressing to AD. Aβ (HR = 0.996, 95%CI: 0.990–1.003, $p = 0.241$) and *APOE4* status (HR = 1.421, 95%CI: 0.774–2.610, $p = 0.258$) were not significantly associated with progression from MCI to AD.

DISCUSSION

Our aim was to investigate the contribution of NPS to the prediction of progression to dementia in MCI, in a prediction model including cognitive testing, NPS, *APOE4*, and *in vivo* AD biomarkers. The burden of NPS was associated with progression to dementia in a model including well-known predictors of AD-type dementia, such as executive function and memory performance, CSF AD biomarkers (total tau and phosphorylated tau), and an imaging biomarker (AD-signature MRI biomarker). Our findings provide further evidence for the role of neuropsychiatric symptoms as a marker of cognitive decline in MCI. Notably, we have found that the burden of NPS is independently linked to progression from MCI to dementia, even after considering the influence of CSF biomarkers.

NPS, including anxiety, depression, delusions, hallucinations, aberrant motor behavior, and sleep disorders, have been described as early symptoms of preclinical AD and risk factors for dementia [11, 14, 30, 31]. Several possible biological explanations have been proposed for the association between NPS

and AD-type dementia [32]. AD-related cognitive decline may cause the development or exacerbation of NPS as a psychological response to being aware of incipient and progressive cognitive impairment. NPS may represent direct non-cognitive manifestations of Aβ/tau pathology, secondary to the involvement of brain areas responsible for behavior and emotion processing, such as the limbic system and the prefrontal cortex [33, 34]. In this context, NPS may be caused or exacerbated by neurotransmitter deficits secondary to AD pathology, for example by the reduction of dopamine and serotonin in several cortical and subcortical brain regions [33, 35]. Anxiety is associated with abnormal CSF Aβ and t-tau concentration and symptoms of agitation and irritability are associated with abnormal CSF Aβ concentration, as well as with an increased risk of AD-type dementia in MCI [36]. The onset of neuropsychiatric symptoms may overlap with findings of preclinical AD-related pathology in the limbic system. A population based clinicopathological study has shown an association between neuropsychiatric symptoms (including agitation, anxiety, depression, appetite changes and sleep disturbances) and early neurofibrillary tangle deposition typical of the presymptomatic stages of AD in the entorhinal cortex and regions of the hippocampus (Braak stages I/II) [15]. In addition to autopsy studies, research studies using *in vivo* AD biomarkers have shown an association between neuropsychiatric symptoms and AD pathologic changes. Donovan et al. found that higher Aβ burden on Pittsburgh compound B (PiB) PET was associated with worsening anxiety and depression over time in cognitively unimpaired individuals [17]. Bensamoun et al. found an association between anxiety, irritability and frontal as well as global Aβ deposition measured by ^{18}F-Florbetapir-PET [16]. Conversely, Tissot et al. found that neuropsychiatric symptoms are associated to *in vivo* tau pathology as measured using tau PET, but not to Aβ deposition as measured by amyloid PET [37]. These findings support the hypothesis that NPS are associated with greater Aβ and tau deposition in the neurodegenerative process leading to AD. Despite these observations, we have found that the burden of NPS is independently associated with the risk of cognitive decline to dementia, over and beyond the contribution of CSF t-tau and p-tau. In fact, higher NPI scores were associated with an increase in the risk of progressing to dementia, when holding all other variables including CSF biomarkers constant. Our findings favor a more complex interplay between Aβ/tau pathology and NPS in the progression from MCI to AD, rather than a direct causal relationship. Various factors, for example NPS, environmental influences, genetic profile, and medical comorbidities may collectively increase the risk for MCI-AD progression. The pathophysiology and genetic basis of NPS in dementia remains a topic of ongoing investigation. NPS could develop as the result of genetic characteristics and lifestyle choices, but could also be related to neurotransmitter deficits, brain regional atrophy, and disconnection [38]. The genetic profile predisposing to NPS is polygenic in nature, involving a combination of common and more rare genetic variants [38]. The effects of NPS on cognition could also be mediated by the effects of NPS on the neuroendocrine system or other metabolic pathways [39, 40]. In summary, the relationships between NPS and other risk factors for MCI-AD progression require further determination. It is conceivable that NPS increase the risk of AD via mechanisms other than a direct link to Aβ/tau deposition, and a combination of multiple mechanisms likely play a role.

In this study 81 (27%) of 300 patients with MCI converted to dementia during a mean follow-up of 40 months. The overall frequency of NPS in this cohort was 64.7%, consistent with frequencies ranging from 59% to 76% reported in memory clinic studies [41–43], although lower frequencies of NPS are reported in population-based studies [44–46]. In the regression model, for each 1-point increase in NPI score, there was a 3% increase in the risk of cognitive decline leading to the diagnosis of dementia. Our study builds upon previous work by evaluating the association between NPS severity and conversion to dementia. We found that NPS are significantly associated with cognitive decline in MCI in a model including *in vivo* AD biomarkers of Aβ and tau deposition and a measure of AD pathology-related cortical thinning, in addition to traditional predictors as memory performance. In our study, the role of Aβ in the prediction model was not found to be statistically significant, which may appear to contradict previous reports. However, it is important to interpret this finding within the specific context of our study sample, consisting of individuals with amnestic MCI. While abnormal Aβ deposition in the brain is a characteristic feature of AD, biomarker evidence of Aβ deposition without concurrent pathologic tauopathy can be observed in presymptomatic patients, indicating the presence of "Alzheimer's pathologic change", which represents an earlier stage along the AD continuum [5]. The abnormal accumulation of Aβ in the brain may initiate 10–20 years prior to the onset

of AD-type dementia, and progresses slowly from the presymptomatic stages to dementia [47]. However, the definition of AD necessitates the presence of biomarker evidence for both Aβ and pathologic tau deposition [5]. In this study, the prognostic significance of pathologic tau deposition surpassed that of amyloid deposition in our amnestic MCI cohort. This likely arises from the closer temporal relationship between the onset or progression of pathologic tauopathy and cognitive decline leading to dementia. Furthermore, our findings did not reveal a significant association between *APOE4* status and the progression to dementia, which may appear inconsistent with previous studies. Although *APOE4* has been known to impact the age of onset of AD and has been associated with an increased risk of MCI, as well as a slightly increased rate of progression of cognitive decline in both MCI and AD dementia, other studies have indicated that the *APOE4* allele does not influence the speed of cognitive decline in early AD [48–50]. Overall, the impact of *APOE4* on the rate of cognitive decline is likely to be modest small, and it is possible that our study lacked sufficient statistical power to detect this effect.

A controversial point is whether NPS are merely a result of cognitive impairment, or they are independent of cognitive status. We found that the contribution of NPS to the prediction model was independent of cognitive function, including memory and executive function performance. This is in agreement with findings of a study by Palmer et al. [11]. Conversely, Gallagher et al. found that anxiety and activity disturbance were predictive of dementia but the association did not survive correction for baseline cognitive status [41]. Discrepancies between our findings and those of previous studies may reflect differences between community-based and memory clinic samples, and the use of different scales to assess neuropsychiatric symptoms and cognition. Differences in study design and in the duration of longitudinal assessments may also play a role. Our study highlights a prevalence of NPS in MCI of about 65%, in agreement with the literature [8], and suggest the potential role of NPS on the trajectory from MCI to dementia.

Our findings highlight the role of NPS as early markers of MCI and risk factors for cognitive decline. Determining the role of NPS in the progression of cognitive decline has important implications, for example in the design of clinical trials targeting prodromal AD stages. Furthermore, if NPS are closely associated and coexists with MCI, potential treatments targeting underlying neuropathologic changes may have a stronger effect on disease severity and course than symptomatic treatments of NPS alone [51]. A comprehensive investigation of neuropsychiatric symptoms in cognitively unimpaired elderly individuals and individuals with MCI may lead to better strategies to diagnose and treat preclinical AD.

Our study has several limitations. The hazard ratio suggests a small effect of baseline NPI scores on the probability of progression from MCI to dementia. Any new or worsening neuropsychiatric symptoms that may have emerged after the initial study visit were not considered in the analysis, as only baseline symptoms were accounted for in the model. Future studies should evaluate longitudinal changes in the burden of neuropsychiatric symptoms and their relationship to the progression towards dementia. Another limitation of our study is the fact that we did not account for demographic characteristics in the regression model. However, it is worth noting that stable MCI and MCI-dementia progression groups did not exhibit significant differences in age, gender, and education level (Table 1), which might partially mitigate this limitation. NPI is an informant-based measure of NPS, and caregivers' interpretation of the patient symptoms may introduce biases. However, NPI is widely used in the literature to assess neuropsychiatric symptoms in MCI and AD [22]. Given the cognitive impairment present in MCI and AD, patients may lack the metacognitive ability to report on their own NPS levels. Our findings reflect observations made in the ADNI cohort, consisting of predominantly Caucasian MCI subjects, with higher education level than the general population, recruited from memory clinics, and may not be representative of the general MCI population. On the other hand, a strength of the study is subject retention with a median follow-up of about 40 months, allowing us to characterize the effects of NPS on the incidence of dementia. All MCI participants recruited had GDS less than 6, which limits the ability to generalize our results. We have not examined the effect of NPS on cognitive decline in cognitively unimpaired subjects, and this topic should be the subject of future investigations. Our focus was to examine the association between total burden of NPS, AD pathology, and cognitive decline in amnestic MCI. Thus, we have not evaluated the impact of the different types of NPS. Due to the limitations of our study, our results should be considered preliminary and the effect of NPS on progression from MCI to dementia should be further

evaluated in future studies with larger sample sizes and external patient cohorts.

NPS, commonly observed in MCI, were associated with a mildly increased risk of progression to dementia, in conjunction with cognitive performance, and *in vivo* imaging and laboratory AD biomarkers. Of particular significance, NPS were independently associated with the risk of dementia, even when factoring in the contribution of CSF biomarkers to that risk. Our findings provide further evidence for the association between NPS and cognitive decline in MCI. Given that approximately 65% of the study population exhibited neuropsychiatric symptoms and considering the mildly increased risk of dementia associated with these symptoms, our results emphasize the importance of a psychiatric evaluation as part of the workup for cognitive impairment in the elderly.

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CONFERENCE PRESENTATION

This work has been presented in part at the 106th Radiological Society of North America Meeting, November 29 – December 5, 2020, Chicago, IL.

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CONFLICT OF INTEREST

Maria V. Spampinato has received research grants from Siemens and Bayer, but neither are not related to the subject of the paper.

All other authors have no conflict of interest to report.

DATA AVAILABILITY

The data supporting the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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