Article

Baseline Neuropsychiatric Symptoms and the Risk of Incident Mild Cognitive Impairment: A Population-Based Study

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Objective: The authors conducted a prospective cohort study to estimate the risk of incident mild cognitive impairment in cognitively normal elderly (aged ≥70 years) individuals with or without neuropsychiatric symptoms at baseline. The research was conducted in the setting of the population-based Mayo Clinic Study of Aging.

Method: A classification of normal cognitive aging, mild cognitive impairment, and dementia was adjudicated by an expert consensus panel based on published criteria. Hazard ratios and 95% confidence intervals were computed using Cox proportional hazards model, with age as a time scale. Baseline Neuropsychiatric Inventory Questionnaire data were available for 1,587 cognitively normal persons who underwent at least one follow-up visit.

Results: The cohort was followed to incident mild cognitive impairment (N=365) or censoring variables (N=179) for a median of 5 years. Agitation (hazard ratio=3.06, 95% CI=1.89–4.93), apathy (hazard ratio=2.26, 95% CI=1.49–3.41), anxiety (hazard ratio=1.87, 95% CI=1.28–2.73), irritability (hazard ratio=1.84, 95% CI=1.31–2.58), and depression (hazard ratio=1.63, 95% CI=1.23–2.16), observed initially, increased risk for later mild cognitive impairment. Delusion and hallucination did not. A secondary analysis, limited in significance by the small number of study participants, showed that euphoria, disinhibition, and nighttime behaviors were significant predictors of nonamnestic mild cognitive impairment but not amnestic mild cognitive impairment. By contrast, depression predicted amnestic mild cognitive impairment (hazard ratio=1.74, 95% CI=1.22–2.47) but not nonamnestic mild cognitive impairment.

Conclusions: An increased incidence of mild cognitive impairment was observed in community-dwelling elderly adults who had nonpsychotic psychiatric symptoms at baseline. These baseline psychiatric symptoms were of similar or greater magnitude as biomarkers (genetic and structural MRI) in increasing the risk of incident mild cognitive impairment.

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Mild cognitive impairment is the intermediate stage between normal cognitive aging and dementia (1–3). Individuals with mild cognitive impairment constitute a high-risk group because they develop dementia at a rate of 10%−15% per year compared with 1%−2% per year in the general population (4). Therefore, it is critical to understand the risk factors for mild cognitive impairment in order to intervene where possible.

Investigators have examined the outcome of incident dementia as determined by baseline neuropsychiatric symptoms in subjects with prevalent mild cognitive impairment (5–9). However, few studies have examined the risk of incident mild cognitive impairment in a cognitively normal cohort by neuropsychiatric status at baseline (10–12). Therefore, we conducted a population-based study to estimate the risk of incident mild cognitive impairment among cognitively normal individuals with or without baseline neuropsychiatric symptoms.

Method

Setting

The Mayo Clinic Study of Aging is a population-based study (13) designed to estimate the prevalence (14) and incidence (15) of mild cognitive impairment in elderly individuals in Olmsted County, Minnesota. Briefly, October 1, 2004, was selected as the prevalence date, and elderly individuals were recruited using a stratified random sampling from the target population of nearly 10,000 elderly people residing in Olmsted County (16). After complete description of the study, written informed consent was obtained. The study was conducted with the approval of the institutional review boards of the Mayo Clinic and Olmsted Medical Center in Rochester, Minnesota.

Cognitive Evaluation

Each participant underwent the following three face-to-face evaluations: 1) neurological evaluation by a physician, 2) risk factor assessment by a nurse or study coordinator, and 3) neuropsychological testing that was interpreted by a neuropsychologist. The interview by the nurse or study coordinator included administration of the Clinical Dementia Rating Scale (17) to the participant and to an informant. The neurological evaluation was performed by a physician and included administration of the Short Test of Mental Status (18), medical history review, and a complete neurological examination.

Neuropsychological testing was performed to assess four cognitive domains: 1) memory (assessed with the Logical Memory-II and Visual Reproduction-II [delayed recall for both] subtests from the Wechsler Memory Scale-Revised and with the Auditory Verbal Learning Test [delayed recall] [19–22]); 2) executive function

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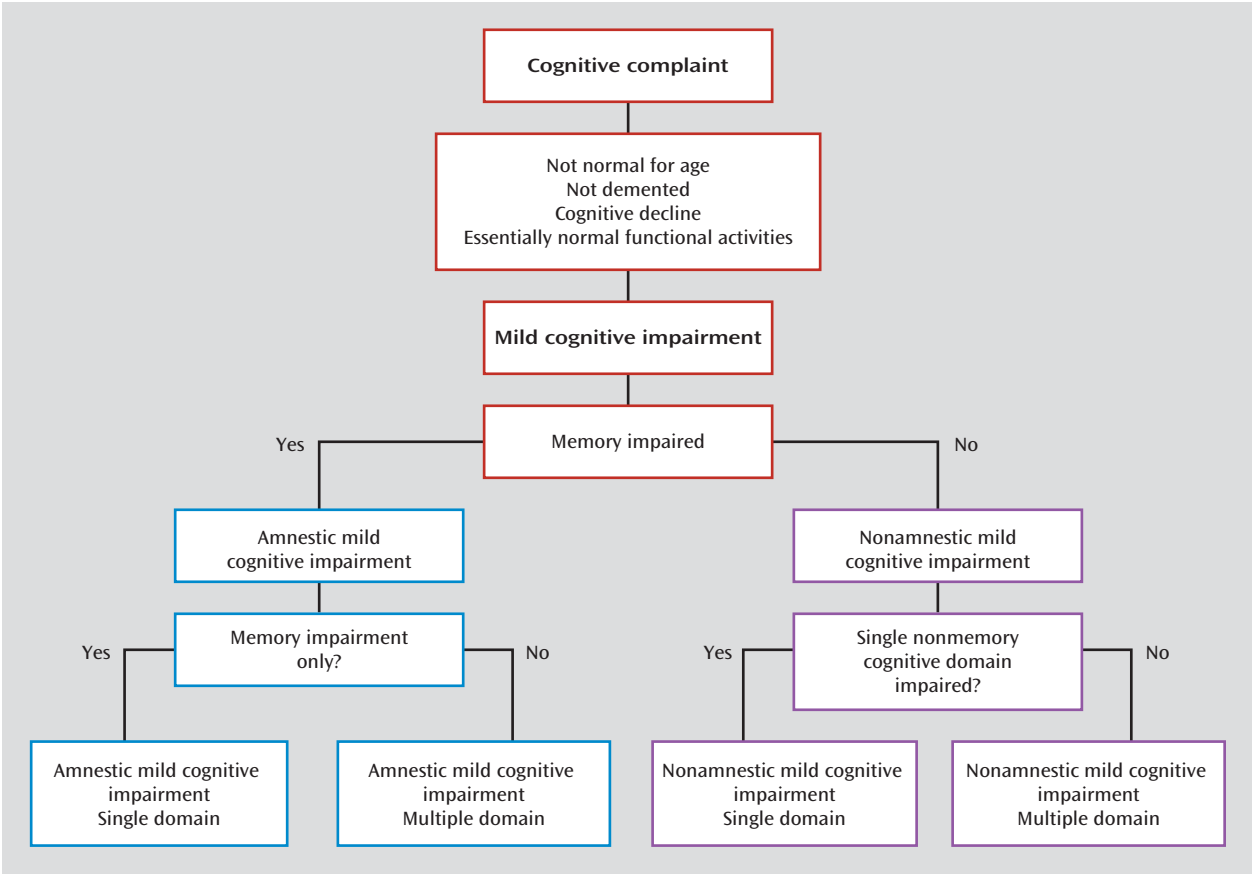
FIGURE 1. Mild Cognitive Impairment Criteria and Subtypes[a]



[a] Adapted/modified with permission from Petersen RC, "Mild Cognitive Impairment" [Continuum 2004; 10:9–28]. Copyright © 2004 American Academy of Neurology.

(assessed with the Trail Making Test, Part B [23], and the Digit Symbol Substitution subtest from WAIS-R); 3) language (assessed with the Boston Naming Test [24]) and category fluency task [25]); and 4) visuospatial skills (assessed with the Picture Completion and Block Design from WAIS-R). The raw neuropsychological test scores were transformed to age-adjusted scores and were scaled to have a mean of 10 and a standard deviation of 3 in reference to normative data of Mayo's Older Americans Normative Studies (26). Cognitive domain scores were obtained for each participant. Additionally, we calculated z scores in order to make comparisons across the four cognitive domains. Each person's domain score was compared with the mean (standard deviation) from Mayo's Older Americans Normative Studies. Thus, a z score ≥1.0 below the mean in a specific domain (e.g., memory) indicated memory impairment. However, the final decision about impairment in any cognitive domain was made during the weekly consensus panel of research team members that included physicians, neuropsychologists, and research nurses.

Mild Cognitive Impairment Criteria

We used the following revised Mayo Clinic criteria for mild cognitive impairment: 1) cognitive concern expressed by a physician, an informant, a participant, or nurse; 2) cognitive impairment in one or more domains (executive function, memory, language, or visuospatial); 3) normal functional activities; and 4) absence of dementia (27, 28). Participants with mild cognitive impairment could have a Clinical Dementia Rating Scale score of 0 or 0.5; however, the final diagnosis was not based exclusively on the clinical dementia rating but rather on all available data. The diagnosis of normal cognition, mild cognitive impairment, dementia, or Alzheimer's disease was made by an expert consensus panel of physicians, psychologists, and nurses based on published criteria (1, 13, 28–30). The panel met once per week and reviewed three independent sources of data (i.e., the clinical data collected by behavioral neurologists and physicians of other specialties with expertise in dementia and mild cognitive impairment, neuropsychological data collected by psychometrists who are supervised by neuropsychologists, and nursing data gathered by research nurses) (13).

Mild Cognitive Impairment Subtypes

Participants that met criteria for mild cognitive impairment were further classified as having either the amnestic or the nonamnestic form of the disorder based on whether memory domain was impaired or not. Additionally, participants were further classified as having single- or multiple-domain impairment according to the number of domains that were impaired (27) (e.g., an individual with impairment of the memory domain only as defined by a z score ≥1.0 below the mean would be classified to have amnestic mild cognitive impairment, single-domain type, whereas an individual with impairments in both memory and executive function would be classified as having amnestic mild cognitive impairment, multiple-domain type). Furthermore, an individual with impairment in executive function only would be classified as having nonamnestic mild cognitive impairment, single-domain type. If both executive function and language were impaired, then the person would be classified as having nonamnestic mild cognitive impairment, multiple-domain type (Figure 1).

TABLE 1. Demographic Characteristics of the Study Participants by Baseline Nonpsychotic Neuropsychiatric Symptoms

Characteristic	Total (N=1,408)		Depression Cohort (N=153)		Apathy Cohort (N=57)		Anxiety Cohort (N=66)	
	N	%	N	%	N	%	N	%
Male	704	50.0	72	47.1	33	57.9	28	42.4
	Median	Interquartile Range	Median	Interquartile Range	Median	Interquartile Range	Median	Interquartile Range
Age (years)	79.3	75.0–83.4	79.8	75.2–83.6	79.1	76.2–82.7	81.3	75.9–83.9
	N	%	N	%	N	%	N	%
70–79	741	52.6	79	51.6	31	54.4	30	45.5
80–91	667	47.4	74	48.4	26	45.6	36	54.5
	Median	Interquartile Range	Median	Interquartile Range	Median	Interquartile Range	Median	Interquartile Range
Education (years)	13	12–16	12	12–15	13	12–16	13	12–16
	N	%	N	%	N	%	N	%
>12	801	56.9	74	48.4	29	50.9	36	54.5
	Median	Interquartile Range	Median	Interquartile Range	Median	Interquartile Range	Median	Interquartile Range
Charlson comorbidity index score	3	1–5	3	2–5	4	2–8	3	2–5
Time in study (years)	5.03	5.3–8.0	4.5	2.9–5.2	4.1	2.7–5.2	4.5	3.2–5.2
	N	%	N	%	N	%	N	%
Incident mild cognitive impairment	364	25.9	59	38.6	25	43.9	30	45.5
	Incidence Rate	95% CI	Incidence Rate	95% CI	Incidence Rate	95% CI	Incidence Rate	95% CI
Incidence rate[b]	68	61–76	109	83–141	142	92–210	138	93–197

[a] Nighttime behaviors assessment data were not available for 271 participants (the informant was unable to assess).
[b] Data represent the age- and sex-standardized incidence rate of mild cognitive impairment (per 1,000 person-years).

Neuropsychiatric Assessment

We assembled a cohort of cognitively normal persons for whom Neuropsychiatric Inventory Questionnaire data were available. The exposed cohort consisted of cognitively normal persons with one or more neuropsychiatric symptoms at baseline. The outcome of interest was incident mild cognitive impairment as measured by modified Mayo Clinic criteria (27). The baseline administration of the Neuropsychiatric Inventory Questionnaire took place between October 1, 2004, and September 1, 2007. Previously, we reported the population-based prevalence of baseline neuropsychiatric symptoms in mild cognitive impairment and normal cognitive aging (31). For the present incidence study, individuals with mild cognitive impairment were excluded at baseline. There were 1,640 cognitively normal persons in the cohort; however, data from the Neuropsychiatric Inventory Questionnaire were not available for 53 individuals. Thus, baseline data were available for 1,587 cognitively normal persons. Because 35 individuals died and 144 were lost to follow-up before the first follow-up visit, our analyses included a total of 1,408 participants.

The Neuropsychiatric Inventory Questionnaire was administered as a structured interview to a spouse or an informant of each study participant (32). The questionnaire is a shorter version of the Neuropsychiatric Inventory, which is a structured interview with established reliability and validity (33). Both the Neuropsychiatric Inventory and the Neuropsychiatric Inventory Questionnaire measure 12 emotional behavioral domains. We used the Neuropsychiatric Inventory Questionnaire because it was selected by the Uniform Data Set initiative of the National Institute on Aging (34).

The structured interview addressed 12 neuropsychiatric domains (agitation, delusion, hallucination, depression, anxiety, euphoria, apathy, disinhibition, irritability, aberrant motor behavior, sleep, and eating/appetite). The categorical outcome of the presence or absence of a neuropsychiatric symptom was documented and served as the exposure of interest of the study. Our primary goal was to determine the risk of incident mild cognitive impairment based on the presence or absence of baseline neuropsychiatric symptoms, not to determine the severity of neuropsychiatric symptoms. This goal was generated from our previous study derived from a clinical sample (10) (wherein we examined whether the presence or absence of baseline depression predicted the risk of incident mild cognitive impairment). Therefore, we sought to estimate a population-based risk of incident mild cognitive impairment by baseline presence or absence of neuropsychiatric symptoms, and we did not investigate the severity of neuropsychiatric symptoms.

Statistical Analyses

We conducted cohort analyses to determine the risk of incident mild cognitive impairment in cognitively normal individuals with or without a specific neuropsychiatric symptom at baseline. We computed hazard ratios and 95% confidence intervals using Cox proportional hazards model. The hazard ratio (95% confidence interval) for each neuropsychiatric symptom quantified the risk of developing incident mild cognitive impairment associated with a specific symptom at baseline after adjusting for age, sex, education, and medical comorbidity (35). The Charlson comorbidity

Agitation Cohort (N=33)		Irritability Cohort (N=96)		Appetite/Eating Cohort (N=67)		Motor Disturbance Cohort (N=7)		Nighttime Behaviors Cohort[a] (N=122)	
N	%	N	%	N	%	N	%	N	%
20	60.6	62	64.6	3	64.2	4	57.1	68	55.7
Median	Interquartile Range	Median	Interquartile Range	Median	Interquartile Range	Median	Interquartile Range	Median	Interquartile Range
79.1	75.3–82.7	79.3	75.1–83.3	81.5	76.9–84.3	79.4	72.8–83.1	80.2	75.2–82.6
N	%	N	%	N	%	N	%	N	%
20	60.6	52	54.2	27	40.3	4	57.1	61	50.0
13	39.4	44	45.8	40	59.7	3	42.9	61	50.0
Median	Interquartile Range	Median	Interquartile Range	Median	Interquartile Range	Median	Interquartile Range	Median	Interquartile Range
13	12–16	13	12–16	13	12–16	12	12–17	13	12–16
N	%	N	%	N	%	N	%	N	%
20	60.6	50	52.1	38	56.7	3	42.9	70	57.4
Median	Interquartile Range	Median	Interquartile Range	Median	Interquartile Range	Median	Interquartile Range	Median	Interquartile Range
4	2–6	3	1–5	4	2–7	2	2–6	3	2–6
4.3	3.1–5.2	4.6	2.9–5.2	4.5	3.6–5.3	4.1	3.9–5.3	5.1	3.1–5.3
N	%	N	%	N	%	N	%	N	%
18	54.5	38	39.6	25	37.3	3	42.9	38	31.1
Incidence Rate	95% CI	Incidence Rate	95% CI	Incidence Rate	95% CI	Incidence Rate	95% CI	Incidence Rate	95% CI
186	110–295	119	85–164	103	67–152	116	24–338	86	61–118

index was calculated using Deyo's method, wherein numeric values were assigned to comorbid medical conditions (e.g., a score of 1 was assigned for congestive heart failure, and a score of 6 was assigned for malignant tumor). A composite index was then calculated using Deyo's method of the Charlson index (35, 36). Adjusting for age, sex, education, and medical comorbidity ensured that baseline neuropsychiatric symptoms predicted incident mild cognitive impairment over and above that which can be explained by these potential confounders. We also conducted secondary analyses for mild cognitive impairment subtypes by separating amnestic and nonamnestic impairment.

Statistical testing was performed at the conventional two-tailed alpha level of 0.05. All analyses were performed using SAS (SAS Institute, Cary, N.C.).

Results

Demographic characteristics of the sample are presented in Table 1. We followed the cohort of cognitively normal persons with available data from the Neuropsychiatric Inventory Questionnaire (N=1,587), to the outcome of incident mild cognitive impairment (N=365) or censoring events (death, N=35; lost to longitudinal follow-up, N=144), for a median of 5.0 years (interquartile range: 3.8–5.3). At baseline, there were differences in the frequency of neuropsychiatric symptoms by sex. There were more men than women in the agitation, apathy, irritability, and disinhibition groups, whereas there were more women than men in the depression, anxiety, and euphoria groups. The median age of the cohort members was 79.3 years (interquartile range: 75.0–83.4). The median level of education was 13 years (interquartile range: 12–16). The median number of comorbid medical conditions was 3 (interquartile range: 1–5), as measured by the Charlson comorbidity index.

We used person-years and survival analyses to calculate the incidence of mild cognitive impairment as predicted by baseline neuropsychiatric status. Thus, the age-sex standardized incidence rate of impairment was 68 per 1,000 person-years. After adjusting for age, sex, education, and medical comorbidity, we observed that the following baseline neuropsychiatric symptoms significantly predicted incident mild cognitive impairment: agitation (hazard ratio=3.06, 95% CI [confidence interval]=1.89–4.93, $p<0.001$); apathy (hazard ratio=2.26, 95% CI=1.49–3.41, $p<0.001$); anxiety (hazard ratio=1.87, 95% CI=1.28–2.73, $p<0.001$); irritability (hazard ratio=1.84, 95% CI=1.31–2.58, $p<0.001$); and depression (hazard ratio=1.63, 95% CI=1.23–2.16, $p<0.001$). Baseline delusion and hallucination did not predict incident impairment. There were substantial missing data for nighttime behavior (N=271). Therefore, the hazard ratio of nighttime behavior (1.46, 95% CI=1.03–2.06, p=0.03)

TABLE 2. Demographic Characteristics of the Study Participants by Baseline Psychotic Symptoms and Other Emotional Behaviors

Characteristic	Disinhibition Cohort (N=22)		Euphoria Cohort (N=7)		Delusions Cohort (N=5)		Hallucinations Cohort (N=5)	
	N	%	N	%	N	%	N	%
Male	12	54.5	3	42.9	2	40.0	3	60.0
	Median	Interquartile Range	Median	Interquartile Range	Median	Interquartile Range	Median	Interquartile Range
Age (years)	80.3	76.2–84.3	81.3	78.0–82.0	80.9	78.4–83.5	86.2	82.7–86.8
	N	%	N	%	N	%	N	%
70–79	9	40.9	3	42.9	2	40.0	0	0.0
80–91	13	59.1	4	57.1	3	60.0	5	100.0
	Median	Interquartile Range	Median	Interquartile Range	Median	Interquartile Range	Median	Interquartile Range
Education (years)	12	12–14	16	13–16	13	13–15	13	13–14
	N	%	N	%	N	%	N	%
>12	10	45.5	6	85.7	4	80.0	4	80.0
	Median	Interquartile Range	Median	Interquartile Range	Median	Interquartile Range	Median	Interquartile Range
Charlson comorbidity index score	3.5	2–5	4	3–4	3	1–5	4	4–5
Time in study (years)	3.0	2.6–5.2	5.4	3.1–5.4	2.7	2.7–5.2	2.9	2.7–4.2
	N	%	N	%	N	%	N	%
Incident mild cognitive impairment	11	50.0	6	85.7	1	20.0	2	40.0
	Incidence Rate	95% CI	Incidence Rate	95% CI	Incidence Rate	95% CI	Incidence Rate	95% CI
Incidence rate[a]	177	89–317	265	97–576	55	1–308	162	20–583

[a] Data represent the age- and sex-standardized incidence rate of mild cognitive impairment (per 1,000 person-years).

should be interpreted with caution. Even though euphoria (hazard ratio=5.10, 95% CI=2.24–11.6, p<0.001) and disinhibition (hazard ratio=2.59, 95% CI=1.42–4.73, p=0.002) were significant predictors of incident impairment, these analyses were based on relatively small events. For example, there were only seven cognitively normal persons with baseline euphoria, of whom six developed incident mild cognitive impairment during subsequent follow-up. Similarly, there were only 22 cognitively normal persons with baseline disinhibition, of whom 11 developed incident impairment. Details of these findings are summarized in Table 2. The four most frequent neuropsychiatric symptoms at baseline were agitation, apathy, depression, and anxiety. At baseline, none of the participants had all four symptoms simultaneously. Only one participant had apathy, agitation, and anxiety at the same time at baseline. This person developed incident mild cognitive impairment during follow-up. Twenty-eight persons had comorbid depression and apathy, and 10 of these developed incident impairment during the subsequent follow-up.

Secondary Analyses

The primary outcome of interest was incident mild cognitive impairment. We conducted secondary analyses to examine whether neuropsychiatric symptoms differentially predicted amnestic or nonamnestic impairment (Tables 3 and 4). Euphoria (hazard ratio=11.3, 95% CI=3.44–37.2, p<0.001) and disinhibition (hazard ratio=5.18, 95% CI=2.24–12.0, p<0.001) were significant predictors of nonamnestic impairment. However, neither disinhibition nor euphoria significantly predicted amnestic impairment. Nighttime behavior was a significant predictor of nonamnestic impairment (hazard ratio=2.04, 95% CI=1.11–3.76, p=0.02) but not amnestic impairment. Depression predicted amnestic impairment (hazard ratio=1.74, 95% CI=1.22–2.47, p=0.002) but not nonamnestic impairment. Apathy predicted both amnestic (hazard ratio=1.93, 95% CI=1.09–3.41, p=0.02) and nonamnestic (hazard ratio=3.19, 95% CI=1.62–6.26, p<0.001) impairment.

Discussion

We reported the population-based risk of incident mild cognitive impairment as predicted by baseline neuropsychiatric symptoms in cognitively normal persons. At baseline, there were sex differences in the frequency of neuropsychiatric symptoms (i.e., more men than women were observed to have agitation, apathy, irritability, and disinhibition, whereas more women than men were observed to have depression, anxiety, and euphoria). These findings were largely consistent with previously reported observations (e.g., a study conducted in Helsinki reported a slightly higher rate of apathy in men than in women [37]; a Japanese study reported that physical agitation but not verbal agitation was higher in men than in women [38]; several studies, including the Cache County Study [39] and large-scale epidemiological studies [40, 41], have reported that depression is higher in women than in men).

TABLE 3. Risk of Incident Mild Cognitive Impairment by Baseline Nonpsychotic Neuropsychiatric Symptoms

	Risk Adjusted for Age (Time Scale), Sex, and Education			Risk Additionally Adjusted for Medical Comorbidity		
Psychiatric Symptom	Hazard Ratio	95% CI	p	Hazard Ratio	95% CI	p
Total mild cognitive impairment						
Depression	1.68	1.27–2.22	<0.001	1.63	1.23–2.16	<0.001
Apathy	2.46	1.63–3.70	<0.001	2.26	1.49–3.41	<0.001
Anxiety	1.91	1.31–2.78	<0.001	1.87	1.28–2.73	0.001
Agitation	3.13	1.94–5.05	<0.001	3.06	1.89–4.93	<0.001
Irritability	1.85	1.32–2.60	<0.001	1.84	1.31–2.58	<0.001
Appetite/eating	1.44	0.96–2.17	0.08	1.34	0.89–2.02	0.16
Motor disturbance	1.63	0.52–5.11	0.40	1.60	0.51–5.00	0.42
Nighttime behaviors[a]	1.48	1.05–2.08	0.03	1.46	1.03–2.06	0.03
Amnestic mild cognitive impairment						
Depression	1.75	1.23–2.48	0.002	1.74	1.22–2.47	0.002
Apathy	1.98	1.13–3.47	0.02	1.93	1.09–3.41	0.02
Anxiety	1.65	0.99–2.76	0.05	1.64	0.98–2.74	0.06
Agitation	2.18	1.07–4.44	0.03	2.16	1.06–4.41	0.03
Irritability	1.69	1.09–2.64	0.02	1.69	1.08–2.63	0.02
Appetite/eating	1.09	0.61–1.95	0.78	1.06	0.59–1.91	0.85
Motor disturbance	0.84	0.12–6.01	0.86	0.84	0.12–5.97	0.86
Nighttime behaviors[a]	1.44	0.93–2.24	0.11	1.44	0.93–2.25	0.10
Nonamnestic mild cognitive impairment						
Depression	1.26	0.68–2.31	0.46	1.18	0.64–2.16	0.60
Apathy	3.81	1.97–7.38	<0.001	3.19	1.62–6.26	<0.001
Anxiety	2.84	1.50–5.35	0.001	2.74	1.45–5.16	0.002
Agitation	5.14	2.46–10.7	<0.001	4.92	2.36–10.3	<0.001
Irritability	2.18	1.18–4.02	0.01	2.18	1.18–4.03	0.01
Appetite/eating	1.52	0.70–3.30	0.29	1.31	0.60–2.85	0.50
Motor disturbance	4.12	1.00–16.9	<0.05	3.89	0.94–16.0	0.06
Nighttime behaviors[a]	2.11	1.15–3.88	0.02	2.04	1.11–3.76	0.02

[a] Nighttime behaviors assessment data were not available for 271 participants (the informant was unable to assess).

TABLE 4. Risk of Incident Mild Cognitive Impairment by Baseline Psychotic Symptoms and Other Emotional Behaviors

	Risk Adjusted for Age (Time Scale), Sex, and Education			Risk Additionally Adjusted for Medical Comorbidity		
Psychiatric Symptom	Hazard Ratio	95% CI	p	Hazard Ratio	95% CI	p
Total mild cognitive impairment						
Disinhibition	2.60	1.42–4.75	0.002	2.59	1.42–4.73	0.002
Euphoria	5.07	2.23–11.5	<0.001	5.10	2.24–11.6	<0.001
Delusions	0.60	0.08–4.27	0.61	0.55	0.08–3.95	0.55
Hallucinations	1.57	0.39–6.37	0.52	1.48	0.37–5.99	0.58
Amnestic mild cognitive impairment						
Disinhibition	1.49	0.55–4.01	0.43	1.48	0.55–4.00	0.44
Euphoria	2.42	0.59–9.84	0.22	2.41	0.59–9.83	0.22
Delusions	1.02	0.14–7.34	0.98	1.00	0.14–7.15	1.00
Hallucinations	1.32	0.18–9.52	0.78	1.30	0.18–9.34	0.80
Nonamnestic mild cognitive impairment						
Disinhibition	5.22	2.26–12.0	<0.001	5.18	2.24–12.0	<0.001
Euphoria	10.7	3.27–35.1	<0.001	11.3	3.44–37.2	<0.001
Delusions[a]			0.99			0.99
Hallucinations	3.10	0.42–22.7	0.27	2.76	0.38–20.3	0.32

[a] Values for hazard ratios and 95% confidence intervals were not applicable.

We observed that nonpsychotic symptoms strongly increased the risk for incident mild cognitive impairment. How do these neuropsychiatric symptoms compare with genetic, biomarker, and demographic predictors of incident mild cognitive impairment? Such comparisons are best done with studies that use methods that are similar, if not identical, to those of our study. Therefore, we compared our findings with the biomarker predictors of incident

mild cognitive impairment reported by our colleagues who specialize in the imaging work of the Mayo Clinic Study of Aging. Our colleagues reported that the hazard ratio for hippocampal volume (as measured by brain MRI) in predicting incident impairment was 1.8 (95% CI=1.4–2.20) (42), whereas here we report that the hazard ratio for apathy in predicting incident impairment is 2.26 (95% CI=1.49–3.41), and it is even higher for agitation (3.06, 95% CI=1.89–4.93). This is an informative comparison because the difference in the strength of predicting incident mild cognitive impairment by a biomarker compared with a neuropsychiatric symptom cannot simply be attributed to methodological difference because both the imaging and neuropsychiatric research took place in the context of the Mayo Clinic Study of Aging. Similarly, the risk of incident mild cognitive impairment given exposure to baseline neuropsychiatric symptoms was as strong as, or even stronger than, the risk given exposure to apolipoprotein ε4 (10), comorbid medical conditions (43), or demographic variables, such as lower education (15).

Delusions and hallucinations did not predict incident mild cognitive impairment. Even though euphoria and disinhibition were significant predictors of incident impairment, their risk estimates were based on few participants. There were only seven cognitively normal persons with baseline euphoria, of whom six developed incident impairment. Similarly, there were 22 cognitively normal persons with baseline disinhibition, of whom 11 developed incident impairment. A secondary analysis showed that euphoria and disinhibition were significant predictors of nonamnestic but not amnestic impairment. Given the small number of participants that reported these symptoms, at best we can only hypothesize that disinhibition and euphoria at baseline in a cognitively normal elderly person may increase the risk of nonamnestic impairment that may progress to fronto-temporal dementia. Similarly, nighttime behavior was a significant predictor of nonamnestic but not amnestic impairment, and this may lead to progression of dementia with Lewy bodies (44).

Few studies have investigated the prediction of incident mild cognitive impairment by baseline neuropsychiatric symptoms (10–12). Most studies have examined the prediction of incident dementia by baseline neuropsychiatric symptoms (7, 45). The Sydney Memory and Ageing Study reported the prediction of cognitive impairment by baseline neuropsychiatric symptoms in 873 individuals aged 70–90 years (46). Consistent with our study, the investigators measured baseline neuropsychiatric symptoms using the Neuropsychiatric Inventory (34). They defined cognitive impairment by diagnostic category (prevalent mild cognitive impairment or incident dementia) or by neuropsychological performance. They followed the cohort of cognitively normal persons and individuals with prevalent mild cognitive impairment over a 2-year period to the outcomes of cognitive decline (defined as worse neuropsychological performance) or incident dementia. They observed that agitation and anxiety predicted cognitive decline (12). These investigators also observed that agitation, apathy, irritability, and anxiety were associated with prevalent impairment. A study examining the outcome of incident mild cognitive impairment by baseline neuropsychiatric symptoms would be ideal to compare with our study. The Chicago Health and Aging Project examined the outcome of incident mild cognitive impairment as predicted by baseline status of proneness to chronic psychological distress measured by the NEO Personality Inventory (47, 48). The investigators observed that a "distress prone" elderly person at baseline was 40% more likely to develop incident mild cognitive impairment than a person who reported to be less distress prone (11). The construct of chronic proneness to psychological distress is not identical to the neuropsychiatric construct as measured by the Neuropsychiatric Inventory Questionnaire; however, both instruments measured emotional behavior in a cohort of elderly persons that were recruited for cognitive research. Thus, we can suggest that emotional behavior at baseline in a cognitively normal person may be associated with increased risk of mild cognitive impairment.

We did not investigate the possible mechanisms linking baseline neuropsychiatric symptoms with incident mild cognitive impairment. Previously, we proposed possible explanations for the link between baseline depression and the outcome of incident mild cognitive impairment (10, 49). It is possible that baseline neuropsychiatric symptoms could be the noncognitive manifestation of the underlying neurodegenerative disorder (reverse causality). Alternatively, an underlying neuropathology may be causing both cognitive and emotional behavior manifestations (shared etiology model). The third possibility is that a synergistic interaction between neuropsychiatric symptoms and a biological factor (e.g., apolipoprotein ε4 genotype) may lead to clinical outcomes such as mild cognitive impairment.

Our study findings consist of several strengths. First, we conducted our study in a population-based setting involving a large cohort that was followed for several years. Thus, our findings are less prone to referral bias (50–52). Second, we were able to examine a spectrum of emotional behavior by investigating several neuropsychiatric symptoms as predictors of incident mild cognitive impairment. Third, we measured impairment using a face-to-face evaluation adjudicated by an expert consensus panel at a center that has a well established reputation for measuring mild cognitive impairment. On the other hand, our findings should be interpreted in light of some limitations. The Neuropsychiatric Inventory/Neuropsychiatric Inventory Questionnaire gathers information from an informant who is knowledgeable about the participant. In our sample, 90% of the informants were spouses. Even though such data have the advantage of being observed behaviors, the informant may not be able to recognize subtle signs. However, other studies (e.g., the Sydney Memory and

Ageing Study) that used the Neuropsychiatric Inventory also reported similar results (e.g., agitation and anxiety predicted cognitive decline in both the Sydney study and our study). While our study's goal of examining the presence or absence of a baseline neuropsychiatric symptom in predicting incident mild cognitive impairment addresses a clinically relevant question, it is also possible that factoring in severity of symptoms might have added more depth to our findings.

In summary, in this population-based study, we assembled a cohort of cognitively normal persons for whom we acquired baseline neuropsychiatric symptoms data. We then followed the cognitively normal cohort forward in time to the outcomes of incident mild cognitive impairment or censoring events. Nonpsychotic neuropsychiatric symptoms at baseline were significant positive predictors of incident mild cognitive impairment. Euphoria, disinhibition, and nighttime behavior predicted incident nonamnestic but not amnestic impairment. Psychotic symptoms (delusions and hallucinations) predicted neither amnestic nor nonamnestic impairment.

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Clinical Guidance: Psychiatric Risk Factors for Mild Cognitive Impairment in Older Adults

Agitation, apathy, anxiety, irritability, and depression in elderly persons are associated with greater risk for development of mild cognitive impairment, the intermediate stage between normal cognitive aging and dementia. As reported by Geda et al., 1,587 cognitively normal community-dwelling adults and their spouses or other informants were interviewed at age 70–90 and again 4–5 years later. Although nonpsychotic symptoms at baseline were related to mild cognitive impairment at follow-up, baseline delusions and hallucinations were not.