Prevalence of Neuropsychiatric Symptoms in Dementia and Mild Cognitive Impairment Results From the Cardiovascular Health Study

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Dementia is a serious public health problem with an increasing prevalence because of the aging of the population.1 Dementia is characterized by global cognitive decline sufficient to affect functioning.2 It is a chronic illness with seriously disabling effects for patients, their families, and society.2 Mild cognitive impairment (MCI) describes cognitive impairment in elderly persons not of sufficient severity to qualify for a diagnosis of dementia.3 Individuals with MCI have complaints of impairment in memory or other areas of cognitive functioning usually noticeable to those around them. In addition, their performance on memory and cognitive tests is below that expected for their age and education. However, their day-to-day functioning is generally preserved. Several operational definitions for MCI have been proposed.4-6 Mild cognitive impairment is a chronic condition and may be a precursor to Alzheimer-type dementia.4 Mild cognitive impairment is often worrisome to patients and families, and is increasingly a presenting complaint for care.

Neuropsychiatric symptoms are a common accompaniment of dementia.7 Neuropsychiatric symptoms are common in MCI, indicating a high prevalence associated with this condition as well. Study of neuropsychiatric symptoms in the context of dementia may improve our understanding of brain-behavior relationships.

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Context Mild cognitive impairment (MCI) may be a precursor to dementia, at least in some cases. Dementia and MCI are associated with neuropsychiatric symptoms in clinical samples. Only 2 population-based studies exist of the prevalence of these symptoms in dementia, and none exist for MCI.

Objective To estimate the prevalence of neuropsychiatric symptoms in dementia and MCI in a population-based study.

Design Cross-sectional study derived from the Cardiovascular Health Study, a longitudinal cohort study.

Setting and Participants A total of 3608 participants were cognitively evaluated using data collected longitudinally over 10 years and additional data collected in 1999-2000 in 4 US counties. Dementia and MCI were classified using clinical criteria and adjudicated by committee review by expert neurologists and psychiatrists. A total of 824 individuals completed the Neuropsychiatric Inventory (NPI); 362 were classified as having dementia, 320 as having MCI; and 142 did not meet criteria for MCI or dementia.

Main Outcome Measure Prevalence of neuropsychiatric symptoms, based on ratings on the NPI in the previous month and from the onset of cognitive symptoms.

Results Of the 682 individuals with dementia or MCI, 43% of MCI participants (n=138) exhibited neuropsychiatric symptoms in the previous month (29% rated as clinically significant) with depression (20%), apathy (15%), and irritability (15%) being most common. Among the dementia participants, 75% (n=270) had exhibited a neuropsychiatric symptom in the past month (62% were clinically significant); 55% (n=199) reported 2 or more and 44% (n=159) 3 or more disturbances in the past month. In participants with dementia, the most frequent disturbances were apathy (36%), depression (32%), and agitation/aggression (30%). Eighty percent of dementia participants (n=233) and 50% of MCI participants (n=139) exhibited at least 1 NPI symptom from the onset of cognitive symptoms. There were no differences in prevalence of neuropsychiatric symptoms between participants with Alzheimer-type dementia and those with other dementias, with the exception of aberrant motor behavior, which was more frequent in Alzheimer-type dementia (5.4% vs 1%; P=.02).

Conclusions Neuropsychiatric symptoms occur in the majority of persons with dementia over the course of the disease. These are the first population-based estimates for neuropsychiatric symptoms in MCI, indicating a high prevalence associated with this condition as well. These symptoms have serious adverse consequences and should be inquired about and treated as necessary. Study of neuropsychiatric symptoms in the context of dementia may improve our understanding of brain-behavior relationships.
These include agitation, depression, apathy, delusions, hallucinations, and sleep impairment. In some cases, they cluster into syndromes, leading to the proposal of operational criteria for specific dementia-associated psychotic or mood disturbances. These symptoms have serious adverse consequences for patients and caregivers, such as greater impairment in activities of daily living, more rapid cognitive decline, worse quality of life, earlier institutionalization, and greater caregiver depression. Thus, the neuropsychiatric accompaniments of dementia are serious conditions that are increasingly becoming a focus of attention.

Several studies have estimated the prevalence of the neuropsychiatric symptoms of dementia. Depending on the method, it has been estimated that they affect 50% to 80% of persons with dementia in the course of the disease. The vast majority of studies were conducted in a clinical setting subject to referral bias that might overestimate the prevalence of neuropsychiatric symptoms.

Only 2 population-based studies have assessed the prevalence of neuropsychiatric symptoms in dementia. The first was conducted in England more than a decade ago and focused only on Alzheimer-type dementia. A more recent US study estimated that in the month before examination 61% of participants with dementia exhibited 1 or more of these symptoms. Apathy (27%), depression (24%), and agitation (24%) were the most common. Because this study was conducted in Utah in a rather homogeneous population, concerns have been raised about its generalizability. There are additional limitations to the population studies of neuropsychiatric symptoms in dementia. First, there has not been a replication of the US estimate. Second, neither study investigated the prevalence of clinically significant symptoms. Third, only the England study estimated the prevalence of symptoms from the onset of cognitive impairment. Fourth, neither study estimated the prevalence of symptoms involving sleeping or eating, both of which are now recognized in clinical settings as being of importance.

No study has assessed the prevalence of neuropsychiatric symptoms in MCI. Such an estimate is important for several reasons. The current definitions of MCI do not mention these symptoms, thus an estimate of prevalence might have definitional implications. Moreover, if MCI is a precursor to Alzheimer-type dementia, the prevalence of neuropsychiatric symptoms in MCI should be intermediate to that in cognitively healthy individuals and in persons with dementia. Such a finding would have implications for the understanding of the pathophysiology of these symptoms in both MCI and dementia.

We undertook the present analyses as part of the Cardiovascular Health Study (CHS) Cognition Study. We sought to estimate the prevalence of neuropsychiatric symptoms, including clinically significant symptoms, in the past month in a population-based panel of persons with dementia, including the prevalence of sleep and eating disturbances; neuropsychiatric symptoms, including clinically significant disturbances, in the past month in MCI; and neuropsychiatric symptoms from the onset of cognitive impairment in MCI or dementia.

**METHODS**

**The CHS Cognition Study and Design Overview**

The CHS and its methods have been described in detail elsewhere. This is a cohort study of individuals at least 65 years old randomly sampled from Medicare lists in 4 US communities, each site overseen by researchers at a nearby university. The communities include Washington County, Maryland (Johns Hopkins University), Forsyth County, North Carolina (Wake Forest University), Allegheny County, Pennsylvania (University of Pittsburgh), and Sacramento County, California (University of California at Davis). A total of 5201 participants were recruited in 1989-1990 and an additional 687 blacks were enrolled in 1992-1993. The institutional review board at each university approved the study, and each participant gave informed consent. Participants completed between 1 and 10 annual clinic visits until 1998-1999. Loss to follow-up in CHS, other than through death, was very low (<5%). The original aims of the CHS were to assess risk factors in elderly persons for cardiovascular outcomes, including angina, myocardial infarction, cardiac death, and stroke.

Data collected longitudinally at each annual visit included information on medical history, blood pressure, medications, physical function, social support, depression, and cognition using the Modified Mini-Mental State Examination, which is a cognitive battery widely used in epidemiologic studies, and the Digit Symbol Substitution Test. If an individual did not receive a clinical evaluation, then attempts were made to evaluate cognition using the Telephone Interview for Cognitive Status. For participants who died between examinations, we obtained further information using the Informant Questionnaire for Cognitive Decline in the Elderly and data concerning circumstances of death. The CHS also collected information for all hospitalizations, including a review of medical records and selected laboratory and clinical evaluations.

Between 1991-1994, 3660 participants received cerebral magnetic resonance imaging (MRI). Differences between those who completed the scan and those who did not have been reported elsewhere. Of the 3660, 3608 participants who completed a Modified Mini-Mental State Examination at the time of the MRI were designated for inclusion in the CHS Cognition Study (Figure 1). Of those who had an MRI, 1492 screened negative for dementia based on the screening procedure that was used. Of the remaining 2116, 707 were classified as having dementia, 577 as MCI, 826 as being cognitively healthy, and 6 unknown based on the CHS Cognition Study evaluation procedures. A subset of participants with dementia (n=362) or MCI (n=320) agreed to be rated on
the Neuropsychiatric Inventory (NPI) and constitute the study sample for these analyses.

**Cognitive Evaluation**

Fieldwork for the CHS Cognition Study, designed to evaluate dementia in a subset of CHS participants, was implemented during 1999–2000. Lopez et al. present further detail on the CHS Cognition Study. In brief, investigators performed a multistage screening and evaluation process on all eligible participants. In the first stage, participants were classified as being at low or high risk for dementia (risk screening), based upon previous cognitive testing during CHS clinic visits and medical history. Using data already collected, individuals at 3 of the centers deemed to be at high risk for dementia, of minority race, or having only limited cognitive data were identified for further evaluation. At 1 center (University of Pittsburgh), attempts to collect additional data were made on all participants regardless of risk. High risk for dementia was based on previous cognitive testing, changes in cognitive scores, nursing home admission, and history of stroke. High risk was defined as a Modified Mini-Mental State Examination score of less than 80 at 1 of their last 2 clinic visits in the study, a 5-point decline in the Modified Mini-Mental State Examination score from the time of MRI to last contact, a Telephone Interview for Cognitive Status score of less than 28 or an Informant Questionnaire for Cognitive Decline in the Elderly score of more than 3.6, an incident stroke, a medical record review recording dementia, or currently residing in a nursing home. Individuals at high risk were recruited for neuropsychological testing. For participants who refused the neuropsychological battery, we collected data from medical records, physician questionnaires, and participant and proxy telephone interviews.

Participants identified for neuropsychological testing underwent a full battery, including tests of premorbid intelligence, memory, language, visuoperceptual and visuoconstructional ability, executive functions, and motor function. The test results of the neuropsychological testing were classified as normal or abnormal by age and levels of education using data that were collected, primarily, from a sample of 250 nondemented controls at the University of Pittsburgh center, where all available participants underwent further evaluation. At the other 3 centers, participants with abnormal tests of memory or of any 2 other domains underwent further evaluation.

Additional evaluation was completed by a neurologist or geriatric psychiatrist and involved a neurological examination and completion of the NPI, a widely used measure of the presence of severity of neuropsychiatric symptoms in dementia. An interview with the participant’s proxy was also done using the Dementia Questionnaire. Using all information, classification of dementia, MCI, or healthy was made locally. The diagnosis of dementia was based on progressive cognitive decline or static cognitive deficit of sufficient severity to affect the participants’ activities of daily living, and history of healthy intellectual function before the onset of cognitive abnormalities. Patients were required to have impairments in 2 cognitive domains, which did not necessarily include memory.

**Classification of Dementia and MCI**

All information was sent to the University of Pittsburgh center regardless of the diagnoses by the local neurologist or psychiatrist. A neurologist with extensive experience in dementia reviewed all cases from every center and reclassified these as dementia, MCI, or healthy. All cases classified as possible dementia locally or at the review were then reviewed by an adjudication committee composed of study neurologists and psychiatrists from all 4 CHS clinics.

Classification was based on *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV)* for dementia and National Institute for Neurologic Diseases and Stroke, Alzheimer Disease and Related Disorders.
Comparison of MCI

Race

one in this study34: (1) MCI amnestic-

Age, mean (SD), y 75 (5.0) 77 (5.0)

Education, mean (SD), y 13.3 (4.8) 12.8 (5.1)

Sex, male 128 (40) 132 (37)

Black 73.3 (5.4) 76.5 (5.7)

White 76.0 (4.6) 77.5 (5.1)

Mean age and younger, No. 197 172

Older than mean age, No. 123 190

Black 32 (27) 43 (23)

White 91 (73) 147 (77)

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Table 1. Demographic Characteristics of Participants

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>MCI (n = 320)</th>
<th>Dementia (n = 362)</th>
<th>Comparison of MCI and Dementia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD), y</td>
<td>75 (5.0)</td>
<td>77 (5.0)</td>
<td>ttest = 5.2, P &lt; .001</td>
</tr>
<tr>
<td>White</td>
<td>76.0 (4.6)</td>
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<tr>
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<td></td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean age and younger.</td>
<td>197</td>
<td>172</td>
<td>χ² = 9.95, P = .002</td>
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* MCI indicates mild cognitive impairment.

Figure 2. Frequency Distribution of Number of Individual Neuropsychiatric Inventory (NPI) Symptoms in the Past Month in the 2 Groups

MCI indicates mild cognitive impairment.

Association33 for Alzheimer-type dementia. Based on results from the University of Pittsburgh center, in which all participants (rather than only high-risk participants) underwent full evaluation, we estimated that overall rates of dementia were about 9% lower than if all participants at all 4 centers were evaluated.

Mild cognitive impairment was defined as cognitive decline not meeting DSM-IV criteria for dementia.32 It was operationalized using results of neuropsychological testing in 2 groups as follows, with both groups considered as one in this study34: (1) MCI amnestic-type: participants with isolated progresive or static memory deficits (delayed-recall verbal memory, nonverbal memory, or both) defined as a score on a standardized test that was 1.5 SD below the mean compared with individuals of the same age and level of education (other tests were healthy); and (2) MCI multiple cognitive deficits-type: participants with a progressive or static deterioration in at least 1 cognitive domain (not including memory), or 1 abnormal test (1.5 SD below the mean adjusted for age and education) in at least 2 other domains, but who had not crossed the threshold for dementia.

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Assessment of Neuropsychiatric Symptoms

We used the NPI10 to define the presence and severity of neuropsychiatric symptoms. The NPI has wide acceptance as a measure of neuropsychiatric symptoms associated with cognitive disorders.33 It rates symptoms in 12 domains: delusions, hallucinations, agitation/aggression, depression, anxiety, euphoria, apathy, disinhibition, irritability, aberrant motor behavior, sleep, and eating. It is a fully structured interview, which obtains its information from an informant knowledgeable about the participant, and it focuses on observable symptoms and behaviors. Within each domain, NPI asks a screening question. If the screening question is answered in the negative, the interviewer moves to the next domain. If it is answered in the affirmative, specific neuropsychiatric symptoms are assessed within each domain. If any of these symptoms are present, they are rated on a 4-point frequency scale and a separate 5-point severity scale. The product of the frequency and severity scales within each domain produces a total domain score (range, 0-20). Individual domain scores are summed to produce a total NPI score. Domain scores of 4 or more or total NPI scores of 4 or more are indicative of clinical significance and are used as entry criteria for treatment trials of dementia-associated neuropsychiatric symptoms.30 In the clinical setting, such scores are associated with need for an intervention to manage the symptoms.

Informants were also asked to note whether neuropsychiatric symptoms had occurred from the onset of cognitive symptoms. The severity of symptoms before the past month was not rated due to concerns that the reliability of such ratings would be low.

The NPI was completed on 824 participants, 362 of whom were ultimately classified as having dementia and 320 classified as having MCI. A total of 142 were rated after the first-phase screening process because of cognitive decline or subnormal cognitive functioning but did not meet criteria for MCI or dementia. This was a sample biased toward individuals with cognitive disturbance of insufficient severity to meet criteria for MCI or dementia. The NPI was also used in the Cache County Study,20 permitting comparisons of the 2 studies.

Analyses

Analyses compared participants with dementia to those with MCI and to published data on NPI symptoms from cognitively healthy elderly persons.20 We compared symptoms in the past month between the study groups with a fre-
Frequency distribution of the number of individual symptoms. Then, we compared the prevalence of any 1 symptom in the past month. In these analyses, we separated mild symptoms within each domain (NPI score = 0-3) from clinically significant symptoms (NPI score = 4). These frequencies were compared using $\chi^2$ tests.

We then compared the prevalence of individual NPI symptoms from the onset of cognitive symptoms between the dementia and MCI groups. These comparisons were made for the presence of any disturbance, regardless of severity, because we did not have severity ratings to differentiate mild disturbances from clinically significant disturbances. These frequencies were also compared using $\chi^2$ tests.

Finally, to assess whether there were differences in NPI symptom prevalence between Alzheimer-type dementia and other dementia, we compared the prevalence of NPI symptoms in the past month in participants with Alzheimer-type dementia with participants with other types of dementia, using $\chi^2$ tests. Statistical analyses were performed using SPSS version 10 (SPSS Inc, Chicago, Ill) and $P<.05$ was the level of significance.

**RESULTS**

Table 1 shows demographic characteristics of the study groups. As expected, those with dementia were older than those with MCI. Among younger participants (mean age and below), those with dementia were less likely to be black compared with those with MCI. There was no difference in sex frequency between the groups and the 2 groups had comparable education.

**NPI Symptoms in the Past Month**

Figure 2 displays a frequency distribution of the number of NPI symptoms in the past month in the 2 study groups, as well as the mean (SD) of each distribution. There was an increase in the number of symptoms from MCI to dementia. Slightly more than half the MCI participants exhibited no neuropsychiatric symptoms. In contrast, only a minority of dementia participants were symptom free. About 55% of the dementia participants reported 2 or more, and 44% reported 3 or more symptoms.

Table 2 compares the prevalence of individual NPI symptoms in the past month by group. We report rates for any symptom (NPI > 0), for clinically significant symptoms (NPI ≥ 4) by domain, and for the NPI as a whole. Using $\chi^2$ tests, the 2 groups were compared on the proportion of participants in each group with NPI scores of 0, 1-3, or 4 and higher. Table 2 also includes prevalence estimates for individual NPI symptoms (NPI > 0) in cognitively healthy participants from the Cache County Study.

Approximately 75% of participants with dementia exhibited 1 or more NPI symp-

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**Table 2. Prevalence of Any NPI Disturbance and of NPI Symptoms Compared With Prevalence Estimates in the Population Without Dementia From the Cache County Study**

<table>
<thead>
<tr>
<th>NPI Symptoms</th>
<th>General Population (Cache County Study, n = 653)</th>
<th>MCI (n = 320)</th>
<th>Dementia (n = 362)</th>
<th>Comparison of MCI and Dementia</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Delusions</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any symptom (NPI &gt; 0)</td>
<td>16 (2.4)</td>
<td>10 (3.1)</td>
<td>65 (18.0)</td>
<td>40.5</td>
</tr>
<tr>
<td>Disturbance score of ≥ 4</td>
<td>NA</td>
<td>2 (0.6)</td>
<td>38 (10.5)</td>
<td></td>
</tr>
<tr>
<td>Hallucinations</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any symptom (NPI &gt; 0)</td>
<td>4 (0.6)</td>
<td>4 (1.3)</td>
<td>38 (10.5)</td>
<td>26.5</td>
</tr>
<tr>
<td>Disturbance score of ≥ 4</td>
<td>NA</td>
<td>4 (1.3)</td>
<td>18 (5)</td>
<td></td>
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<tr>
<td>Agitation/aggression</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Any symptom (NPI &gt; 0)</td>
<td>19 (2.9)</td>
<td>36 (11.3)</td>
<td>110 (30.3)</td>
<td>37.3</td>
</tr>
<tr>
<td>Disturbance score of ≥ 4</td>
<td>NA</td>
<td>15 (4.7)</td>
<td>53 (14.6)</td>
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<tr>
<td>Depression</td>
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<td></td>
</tr>
<tr>
<td>Any symptom (NPI &gt; 0)</td>
<td>47 (7.2)</td>
<td>64 (20.1)</td>
<td>117 (32.3)</td>
<td>18.4</td>
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<tr>
<td>Disturbance score of ≥ 4</td>
<td>NA</td>
<td>20 (6.3)</td>
<td>58 (16)</td>
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<tr>
<td>Anxiety</td>
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<td></td>
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<tr>
<td>Any symptom (NPI &gt; 0)</td>
<td>38 (5.8)</td>
<td>30 (9.9)</td>
<td>78 (21.5)</td>
<td>19.3</td>
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<tr>
<td>Disturbance score of ≥ 4</td>
<td>NA</td>
<td>16 (5)</td>
<td>35 (9.7)</td>
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<tr>
<td>Euphoria</td>
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<tr>
<td>Any symptom (NPI &gt; 0)</td>
<td>2 (0.3)</td>
<td>2 (0.6)</td>
<td>11 (3.1)</td>
<td>6.06</td>
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<tr>
<td>Disturbance score of ≥ 4</td>
<td>NA</td>
<td>0</td>
<td>5 (1.4)</td>
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<td>Apathy</td>
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<tr>
<td>Any symptom (NPI &gt; 0)</td>
<td>21 (3.2)</td>
<td>47 (14.7)</td>
<td>130 (35.9)</td>
<td>52.2</td>
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<tr>
<td>Disturbance score of ≥ 4</td>
<td>NA</td>
<td>20 (6.3)</td>
<td>97 (26.8)</td>
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<tr>
<td>Disinhibition</td>
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<tr>
<td>Any symptom (NPI &gt; 0)</td>
<td>6 (0.9)</td>
<td>10 (3.1)</td>
<td>46 (12.7)</td>
<td>24.5</td>
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<tr>
<td>Disturbance score of ≥ 4</td>
<td>NA</td>
<td>1 (0.3)</td>
<td>25 (6.9)</td>
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</tr>
<tr>
<td>Irritability</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Any symptom (NPI &gt; 0)</td>
<td>30 (4.6)</td>
<td>47 (14.7)</td>
<td>98 (27)</td>
<td>15.2</td>
</tr>
<tr>
<td>Disturbance score of ≥ 4</td>
<td>NA</td>
<td>24 (7.5)</td>
<td>45 (12.4)</td>
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<tr>
<td>Aberrant motor behavior</td>
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</tr>
<tr>
<td>Any symptom (NPI &gt; 0)</td>
<td>3 (0.4)</td>
<td>12 (3.8)</td>
<td>58 (16)</td>
<td>28.4</td>
</tr>
<tr>
<td>Disturbance score of ≥ 4</td>
<td>NA</td>
<td>7 (2.2)</td>
<td>43 (11.9)</td>
<td></td>
</tr>
<tr>
<td>Sleep</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any symptom (NPI &gt; 0)</td>
<td>44 (13.8)</td>
<td>99 (27.4)</td>
<td>20.0</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Disturbance score of ≥ 4</td>
<td>NA</td>
<td>28 (8.8)</td>
<td>72 (19.9)</td>
<td></td>
</tr>
<tr>
<td>Eating</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any symptom (NPI &gt; 0)</td>
<td>NA</td>
<td>33 (10.4)</td>
<td>71 (19.6)</td>
<td>15.3</td>
</tr>
<tr>
<td>Disturbance score of ≥ 4</td>
<td>NA</td>
<td>20 (6.3)</td>
<td>57 (15.7)</td>
<td></td>
</tr>
</tbody>
</table>

Total NPI

Any symptom (NPI > 0) 106 (16.2) 138 (43.1) 270 (74.6) 81.8 <.001

NPI score of ≥ 4 92 (28.7) 223 (61.6) | | | |

*NPI indicates Neuropsychiatric Inventory; MCI, mild cognitive impairment; and NA, not available. Total NPI is not a sum of the columns because many people had more than 1 symptom.
†Data from Lyketsos et al.

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Table 3. Cumulative Prevalence of Individual NPI Symptoms From the Onset of the Cognitive Symptoms in the 2 Groups*

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>MCI (n = 320)</th>
<th>Dementia (n = 362)</th>
<th>χ² Test†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Delusions</td>
<td>15 (4.7)</td>
<td>109 (30.1)</td>
<td>75.6</td>
</tr>
<tr>
<td>Hallucinations</td>
<td>8 (2.5)</td>
<td>59 (16.3)</td>
<td>37.1</td>
</tr>
<tr>
<td>Agitation/aggression</td>
<td>47 (14.7)</td>
<td>145 (40.1)</td>
<td>54.4</td>
</tr>
<tr>
<td>Depression</td>
<td>84 (26.3)</td>
<td>158 (43.6)</td>
<td>23.0</td>
</tr>
<tr>
<td>Anxiety</td>
<td>33 (10.3)</td>
<td>92 (25.4)</td>
<td>27.9</td>
</tr>
<tr>
<td>Euphoria</td>
<td>4 (1.3)</td>
<td>11 (3.0)</td>
<td></td>
</tr>
<tr>
<td>Apathy</td>
<td>58 (18.1)</td>
<td>164 (45.3)</td>
<td>61.2</td>
</tr>
<tr>
<td>Disinhibition</td>
<td>13 (4.1)</td>
<td>66 (18.2)</td>
<td>33.7</td>
</tr>
<tr>
<td>Irritability</td>
<td>53 (16.6)</td>
<td>123 (34.0)</td>
<td>28.3</td>
</tr>
<tr>
<td>Aberrant motor behavior</td>
<td>13 (4.1)</td>
<td>62 (17.1)</td>
<td>31.2</td>
</tr>
<tr>
<td>Sleep</td>
<td>57 (17.8)</td>
<td>109 (30.1)</td>
<td>16.9</td>
</tr>
<tr>
<td>Eating</td>
<td>56 (17.5)</td>
<td>112 (30.9)</td>
<td>16.8</td>
</tr>
<tr>
<td>Any 1 NPI disturbance</td>
<td>139 (49.6)</td>
<td>233 (64.0)</td>
<td>88.8</td>
</tr>
</tbody>
</table>

*NPI indicates Neuropsychiatric Inventory; MCI, mild cognitive impairment. For any 1 NPI disturbance, the total number of symptoms for MCI was 280 and for dementia was 291.
†P < .001 for all symptoms except for euphoria (P = .09, exact test).

Symptoms, with 62% clinically significant. Participants with MCI had lower rates, with 43% exhibiting any 1 symptom and 29% exhibiting clinically significant. There was an incremental increase in frequency of neuropsychiatric symptoms across groups. As expected, the lowest frequency was observed in cognitively healthy participants, intermediate frequency in MCI, and highest frequency in dementia. In all cases, the prevalence of NPI symptoms was significantly higher in participants with dementia than in those with MCI.

Among participants with dementia, the most frequent symptom was apathy (36%), followed by depression (32%), and agitation/aggression (30%). Apathy was the most frequent clinically significant (disturbance score ≥ 4) neuropsychiatric symptom, followed by sleep disturbance and depression. Most symptoms present were clinically significant.

In the MCI group, the frequency of most symptoms was intermediate between the cognitively healthy comparison population and the dementia participants. The most frequent symptom was depression (20%), followed by apathy (15%) and irritability (15%). The most frequent clinically significant symptom (disturbance score ≥ 4) was sleep disturbance (8.8%), followed by irritability (7.5%), depression (6.3%), apathy (6.3%), and eating disturbance (6.3%). Using χ² tests, the rate of neuropsychiatric symptoms in MCI was compared with that among nondemented elderly persons from the Cache County Study, using the published data from the latter study. Given that multiple comparisons were made, we applied the Bonferroni adjustment requiring an α of .001 for statistical significance. The prevalence of any 1 symptom was significantly higher in the MCI participants of CHS than in the elderly population of the Cache County Study (χ² = 81.2, P < .001). When individual disturbances were compared, the prevalence among MCI participants in the CHS was significantly higher for agitation/aggression (χ² = 26.5, P < .001), depression (χ² = 33.5, P < .001), apathy (χ² = 41.7, P < .001), irritability (χ² = 28.6, P < .001), and aberrant motor behavior (χ² = 13.2, P < .001). Differences between the 2 groups were of marginal significance for anxiety (χ² = 3.65, P = .06) and disinhibition (χ² = 5.17, P = .02), and not significant for delusions, hallucinations, or euphoria (in all cases, P > .51). Euphoria was rare in all 3 groups, as expected.

NPI Symptoms From the Onset of Cognitive Impairment

Eighty percent of dementia participants and almost 50% of MCI participants exhibited at least 1 NPI symptom from the onset of cognitive symptoms (Table 3). Apathy and depression were the 2 most common, followed by agitation/aggression. The prevalence of delusions or hallucinations was lower than the most common symptoms. In all cases, there was a significant increase in prevalence from MCI to dementia. The meaning of these data is uncertain because there are no published estimates of the cumulative prevalence of NPI symptoms in cognitively healthy elderly persons aged 65 or older from the Cache County Study or elsewhere. However, the prevalence rates in Table 3 for neuropsychiatric symptoms in both MCI and dementia are much higher than past-month population estimates from the Cache County Study (Table 2) and prevalence estimates for specific mental disorders from the US Epidemiologic Catchment Area study (anxiety disorders, 5.5%; affective disorders, 2.5%; schizophrenia, 0.1%).

Comparison of Alzheimer-Type Dementia and Other Types of Dementia

Table 4 contains the prevalence of symptoms in the past month among participants with National Institute for Neurologic Diseases and Stroke, Alzheimer Disease and Related Disorders Association probable or possible Alzheimer disease compared with those with other dementia. Of the 104 participants with non-Alzheimer disease dementia, the expert consensus panel concluded that 86 had vascular dementia, and 6 had dementia due to Parkinson disease. The remaining 12 had a range of different types of dementia etiologies, such as postanoxic dementia, posttraumatic dementia, frontotemporal degeneration and others. Table 4 compares the frequency of mild symptoms with clinically significant symptoms. There were no significant differences between participants with Alzheimer-type demen-
dementia, and those with other dementia, with the exception of aberrant motor behavior ($P = .02$).

**COMMENT**

These findings confirm previous estimates of high prevalence of neuropsychiatric symptoms in dementia, with 60% of participants with dementia exhibiting clinically significant symptoms in the past month, and more than 80% exhibiting any symptom from the onset of cognitive impairment. Apathy, depression, and agitation were the most frequent. We also report estimates for sleep and eating disturbances, which have not been previously reported. Prevalence estimates were similar in Alzheimer and non-Alzheimer dementia, with the exception of more aberrant motor behavior in Alzheimer-type dementia, consistent with clinical reports that wandering is more frequent in Alzheimer-type dementia. Our findings confirm that the majority of neuropsychiatric symptoms in dementia are of clinical significance based on their severity and because of co-occurrence of multiple symptoms with more than half of participants with dementia exhibiting 2 or more neuropsychiatric symptoms in the past month.

We report the first population-based estimates to our knowledge of neuropsychiatric symptoms in MCI. This is a group of individuals with cognitive impairment not severe enough to warrant a diagnosis of dementia. Recent evidence suggests that many, if not most, eventually develop Alzheimer-type dementia, so that MCI is a precursor syndrome to dementia. The finding that neuropsychiatric symptoms in MCI have a prevalence intermediate to that in healthy participants and those with dementia, further supports this hypothesis. Mild cognitive impairment may not be a separate category of disturbance, such as age-associated or age-appropriate memory loss, but is rather on a continuum between healthy and dementia.

These estimates are comparable with those reported in the other 2 population-based studies. Thus, the epidemiologic evidence supports the findings from clinical studies indicating that neuropsychiatric symptoms afflict almost all patients with dementia over the course of their illness. Similarly, neuropsychiatric symptoms afflict almost 50% of patients with MCI.

Our study limitations include the sampling method in that the participants with dementia were ascertained from the members of an original random sample of elderly individuals in 4 communities who agreed to have an MRI. Those examined were over-sampled for the presence of stroke, minority status, and unknown cognitive scores. Thus, the original sampling frame was not fully representative of the population and may have biased the prevalence estimates for NPI symptoms among those with dementia and MCI. However, any such bias would be.

| Table 4. Prevalence of Individual NPI Symptoms in the Past Month in Participants With Alzheimer-Type Dementia Compared With Other Types of Dementia* |
|---------------------------------|----------------|----------------|----------------|
|                                | No. (%)         | Comparison of Alzheimer-Type Dementia and Other Dementia |
|                                | Alzheimer-Type Dementia (n = 258) | Other Dementia (n = 104) | $\chi^2$ Test | $P$ Value |
| Delusions                       |                  |                |                |                |
| Mild disturbance (0-3)          | 19 (7.4)         | 8 (7.7)        | 2.205          | .33           |
| Disturbance score ≥4           | 31 (12.0)        | 7 (6.7)        |                |                |
| Hallucinations                 |                  |                |                |                |
| Mild disturbance (0-3)          | 13 (5)           | 7 (6.7)        | 1.67           | .43           |
| Disturbance score ≥4           | 15 (5.8)         | 3 (2.9)        |                |                |
| Agitation/Aggression            |                  |                |                |                |
| Mild disturbance (0-3)          | 43 (16.7)        | 14 (13.5)      | 2.05           | .36           |
| Disturbance score ≥4           | 41 (15.9)        | 12 (11.5)      |                |                |
| Depression                      |                  |                |                |                |
| Mild disturbance (0-3)          | 41 (15.9)        | 18 (17.3)      | 0.355          | .84           |
| Disturbance score ≥4           | 40 (15.5)        | 18 (17.3)      |                |                |
| Anxiety                         |                  |                |                |                |
| Mild disturbance (0-3)          | 29 (11.2)        | 14 (13.5)      | 0.352          | .84           |
| Disturbance score ≥4           | 25 (9.7)         | 10 (9.6)       |                |                |
| Euphoria                        |                  |                |                |                |
| Mild disturbance (0-3)          | 5 (1.9)          | 1 (1)          | 0.031          | .73           |
| Disturbance score ≥4           | 4 (1.6)          | 1 (1)          |                |                |
| Apathy                          |                  |                |                |                |
| Mild disturbance (0-3)          | 21 (8.1)         | 12 (11.5)      | 1.35           | .51           |
| Disturbance score ≥4           | 72 (27.9)        | 25 (24)        |                |                |
| Disinhibition                   |                  |                |                |                |
| Mild disturbance (0-3)          | 16 (6.2)         | 5 (4.8)        | 3.215          | .20           |
| Disturbance score ≥4           | 14 (5.4)         | 11 (10.0)      |                |                |
| Irritability                    |                  |                |                |                |
| Mild disturbance (0-3)          | 38 (14.7)        | 15 (14.4)      | 1.18           | .56           |
| Disturbance score ≥4           | 29 (11.2)        | 16 (15.4)      |                |                |
| Aberrant motor behavior         |                  |                |                |                |
| Mild disturbance (0-3)          | 14 (5.4)         | 1 (1)          | 8.02           | .02           |
| Disturbance score ≥4           | 26 (10.0)        | 7 (6.7)        |                |                |
| Sleep                           |                  |                |                |                |
| Mild disturbance (0-3)          | 19 (7.4)         | 8 (7.7)        | 1.65           | .44           |
| Disturbance score ≥4           | 47 (18.2)        | 25 (24.0)      |                |                |
| Eating                          |                  |                |                |                |
| Mild disturbance (0-3)          | 9 (3.5)          | 5 (4.8)        | 1.82           | .40           |
| Disturbance score ≥4           | 37 (14.3)        | 20 (19.2)      |                |                |
| Total NPI                       |                  |                |                |                |
| Mild disturbance (0-3)          | 36 (14.7)        | 11 (10.6)      | 0.75           | .69           |
| NPI score ≥4                    | 157 (60.9)       | 66 (63.5)      |                |                |

*NPI indicates Neuropsychiatric Inventory.

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systematic and lead to an underesti-
mate of the prevalence of disturbance. A
second limitation was that the NPI, while
reliable and valid, did not di-
rectly evaluate participants but rather
relied on information obtained from an
informant interview. Results may have
been different if a clinical diagnosis of
neuropsychiatric symptoms had been
used. However, the agreement be-
tween this study and studies where
clinical evaluations were used is reas-
suring.6-10

What is the significance of the high
prevalence of neuropsychiatric symp-
toms in dementia and MCI? It sup-
ports the status of MCI as an interme-
diate condition between healthy
condition and dementia. With regard
to dementia, there are 2 notable im-
clications. The first involves the patho-
physiology of neuropsychiatric symp-
toms in dementia. These disturbances
may be the consequences of damage to
the brain brought about by underly-
ing brain disease. For example, in Al-
zheimer disease, delusions have been as-
soicated with parietal hyperperfusion on
single-photon emission computed to-
mography,39 depression with damage
to noradrenergic or serotonergic brain nu-
cles,40-43 and aggression with damage
to serotonergic nuclei in the context of
relative preservation of dopaminergic
brain areas.44,45 Thus, the study of
neuropsychiatric symptoms in dementi-
a offers an opportunity for further un-
derstanding of brain-behavior relation-
ships. Studies have focused on clinical
pathologic correlations using brain im-
aging or neuropathology. Recent ad-
ances will also allow us to add ge-
nomic study to estimate the modifying
effect of genes on the expression of
neuropsychiatric symptoms. Already
evidence exists for a link between
Alzheimer-type dementia-associated
psychosis and genetic variation in
dopamine receptors.46

The second implication relates to the
treatment of patients with MCI and de-
mentia. Neuropsychiatric symptoms
compound the disability of patients and
caregivers5,9-11 and are increasingly a
target of treatment. Nonpharmacologi-
cal interventions have efficacy for mild
disturbances.47 Controlled clinical tri-
als have reported efficacy of antipsy-
chotics for agitation or psychosis.48-51
Antidepressants for depression,52-55
anticonvulsants for agitation,56-57 B-
adrenergic blockers for aggression,58
and cholinesterase inhibitors for be-
havioral symptoms.59,61 Careful recogni-
tion and appropriate treatment of the
neuropsychiatric symptoms associ-
ated with MCI and dementia is likely
to provide substantial benefits to pa-
tients and caregivers.5 Dementia and
MCI continue to be poorly recognized
in primary care.62 and neuropsychiatric
symptoms are often not recog-
nized until they have become severe
leading to hospitalization or institu-
tionalization.

In summary, these findings further
confirm the high prevalence of neu-
ropsychiatric symptoms in dementia
and indicate a moderate prevalence in MCI.
Clinical evaluations of patients with
suspected MCI and dementia must in-
clude specific assessment of and treat-
ment for such symptoms. This also has
significant implications for further stud-
ies of the pathophysiology and treat-
ment of neuropsychiatric symptoms in
cognitively impaired elderly people.

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NEUROPSYCHIATRIC SYMPTOMS IN DEMENTIA AND COGNITIVE IMPAIRMENT


