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Predictors of progression from mild cognitive impairment to Alzheimer disease

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ABSTRACT Objective: To determine the occurrence of neuropsychiatric symptomatology and the relation to future development of Alzheimer disease (AD) in persons with and without mild cognitive impairment (MCI). **Method:** We followed 185 persons with no cognitive impairment and 47 with MCI (amnestic and multidomain), ages 75 to 95, from the population-based Kungsholmen Project, Stockholm, Sweden, for 3 years. Three types of neuropsychiatric symptoms were assessed at baseline: mood-related depressive symptoms, motivation-related depressive symptoms, and anxiety-related symptomatology. AD at 3-year follow-up was diagnosed according to Diagnostic and Statistical Manual for Mental Disorders-III-R criteria. **Results:** Psychiatric symptoms occurred more frequently in persons with MCI (36.2% mood, 36.2% motivation, and 46.8% anxiety symptoms) than in cognitively intact elderly individuals (18.4% mood, 13.0% motivation, and 24.9% anxiety). Of persons with both MCI and anxiety symptoms, 83.3% developed AD over follow-up vs 6.1% of cognitively intact persons and 40.9% persons who had MCI without anxiety. Among persons with MCI, the 3-year risk of progressing to AD almost doubled with each anxiety symptom (relative risk [RR] = 1.8 [1.2 to 2.7] per symptom). Conversely, among cognitively intact subjects, only symptoms of depressive mood were related to AD development (RR = 1.9 [1.0 to 3.6] per symptom). **Conclusions:** The predictive validity of mild cognitive impairment (MCI) for identifying future Alzheimer disease (AD) cases is improved in the presence of anxiety symptoms. Mood-related depressive symptoms (dysphoria, suicidal ideation, etc.) in preclinical AD might be related to the neuropathologic mechanism, as they appear preclinically in persons both with and without MCI. **NEUROLOGY 2007;68:1596–1602**

Mild cognitive impairment (MCI) is a syndrome characterized by subjective and objective cognitive impairment in the absence of dementia.[1] MCI subclassifications include an amnestic form, characterized by isolated memory impairments, and one with multiple cognitive deficits.[2] Although it is documented that persons with MCI have an increased risk of Alzheimer disease (AD),[1,3-6] population-based studies have shown that only one-third develop dementia, whereas others improve, reverting to a normal level of cognitive functioning,[5-6] and some die,[5,7] suggesting multiple etiologies for MCI.[8]

Neuropsychiatric disturbances are common in MCI, with a prevalence between 43 and 59%,[9-13] and the same symptoms frequently occur even in the early phases of AD,[14-17] particularly depression. In addition, depression is related to reduced cognitive performance in nondemented elderly individuals[18-21] and has been suggested as a risk factor for incident MCI.[8,22] It remains unclear whether neuropsychiatric disturbances represent independent causes of MCI, symptoms related to an already ongoing neurodegenerative process, or a reaction to cognitive deterioration. Two clinical studies reported contradictory results concerning the role of depressive symptoms in the progression of MCI to AD.[23,24]

To examine the possible role of neuropsychiatric disturbances in MCI, we investigated mood- and motivation-related depressive symptoms as well as anxiety symptomatology in persons with MCI in a longitudinal population-based study. Specific aims include 1) investigating

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the frequency of neuropsychiatric symptomatology in MCI; 2) assessing the contribution of anxiety and depressive symptomatology in progression from MCI to AD over 3 years; and 3) examining whether neuropsychiatric disturbances predict AD in persons without MCI.

METHODS

Study population. Participants were taken from the Kungsholmen Project, a longitudinal population-based study initiated in 1987 to assess the occurrence, risk factors, and evolution of dementia in individuals aged 75+ years living in the Kungsholmen area of Stockholm, Sweden. A two-phase study design was conducted at baseline. First the cognitive status of the 1,810 subjects was assessed by trained nurses using the Mini-Mental State Examination (MMSE),[25] and a sample of 668 individuals underwent a thorough clinical assessment, including both a psychiatric and a neurologic examination by a physician and comprehensive neuropsychological testing. Full description of the study design and data collection has been previously described.[26,27] In brief, all persons scoring less than or equal to 24 on the MMSE and a sample of age- and sex-matched control subjects scoring more than 24 points were selected for the clinical examination.

For the current study, we used the clinical sample of 668 persons. Of them, 225 were excluded due to dementia diagnosed by a physician according to Diagnostic and Statistical Manual of Mental Disorders (DSM) III-R criteria as described in detail later.[26,27] To obtain accurate age- and education-specific normative values for cognitive functioning, 40 persons were excluded due to MMSE <20, unknown educational level, or age over 95 years. Of the remaining persons, 296 underwent comprehensive and complete neuropsychological assessment. Sixty-four persons did not fulfill the criteria for amnestic or multidomain MCI, but they also did not perform at a normal level of cognitive functioning; namely, they had significant impairments (1 SD below age- and education-adjusted norms)[4] on the MMSE (n = 24, 8.1%) or isolated impairment in tasks of visuospatial or language functioning (n = 40, 13.5%). Thus, 47 persons with MCI (amnestic or multidomains) and 185 persons with normal cognitive functioning at baseline constituted the study population.

Baseline characteristics. Information on age, education, and sex was collected at baseline. Education was calculated as the maximum level achieved and dichotomized into low (<8 years) and high (≥8 years).

Psychiatric examination. Symptoms of depression and anxiety were assessed during examination by a geriatric psychiatrist using the Comprehensive Psychopathological Rating Scale (CPRS).[28] The presence and severity of each symptom were reported by the participant and were rated by the psychiatrist on a six-point scale, with a score of 2 to 6 indicating presence of a severe symptom. Based on previous research,[14] we used the findings of principal component analyses on the CPRS to identify symptoms reflecting mood- or motivation-related symptomatology. The mood group included dysphoria, suicidal ideation/thoughts of death, feelings of guilt, and appetite disturbance. The motivation grouping included lack of interest, concentration difficulties, psychomotor disturbances, and loss of energy. Anxiety symptoms included indecision, persistent worrying, anxiety, and social withdrawal.

Subjective memory complaints. At baseline, nurses administered a questionnaire to close informants to detect possible memory decline of the relative. All participants were asked about memory problems both in the nurse interview and during the psychiatric examination. Presence of a memory complaint was defined as a report of problems by either the subject in the nurse interview or psychiatric examination or a report by the informant.

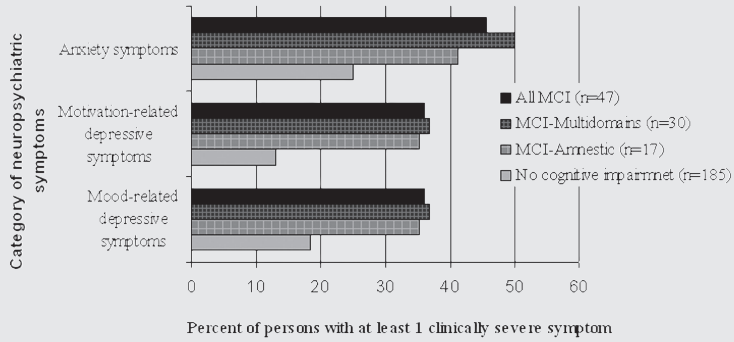
Neuropsychological testing. Cognitive functioning was assessed at baseline by neuropsychologists using an extensive cognitive battery, as described in detail previously.[20] Three specific cognitive domains were the focus of the current study: episodic memory, language fluency, and visuospatial functioning. Impairment was defined as scoring less than 1 SD below the age- and education-specific mean on the respective tests, based on previous studies.[4,5] In brief, episodic memory included a composite score of four word recall tasks: free recall of rapidly presented random words, free recall of slowly presented random words, free recall of organizable words, and cued recall of organizable words. For language, a test of verbal fluency was used where subjects were asked to produce as many grocery items as they could within a 60-second period. Visuospatial functioning was evaluated using a composite score of three tests: block design, clock-setting, and clock-reading.

Criteria for baseline MCI. MCI-amnestic and MCI-multidomains were identified based on previous proposals.[2,29] The definition for both MCI subtypes required 1) subjective memory complaints, 2) no dementia diagnosis, 3) activities of daily living intact or functional impairment not due to cognitive impairment (all subjects underwent a complete neurologic and medical examination by a specialist who excluded that any functional impairment present was not due to memory or cognitive impairments), and 4) objective evidence of cognitive impairment. For MCI-amnestic, objective cognitive impairments included impairment in episodic memory task but normal functioning on visuospatial and language tasks. For MCI-multidomains, impairment was required in two or more of the episodic memory, language, and visuospatial domains.

Diagnosis of AD. Subjects were reassessed 3.4 years (SD 0.6) after baseline. Nineteen (8.2%) subjects did not wish to be re-evaluated or had moved during follow-up. Thirty-three persons (14.2%) died before examination, and their death certificates and medical records were sought. After clinical examination of all subjects, dementia was diagnosed according to DSM-III-R criteria using a three-step procedure[26-27] and made blind to baseline characteristics. Diagnosis of AD was similar to National Institute of Neurological and Communication Disorders and Stroke/Alzheimer's Disease and Related Disorders Association[30] and required gradual onset, progressive deterioration, and lack of any other specific cause of dementia. A preliminary diagnosis was made by the examining physician and independently reviewed by a specialist. In the case of agreement, the diagnosis was accepted; otherwise, a third specialist made a final diagnosis. Dementia diagnoses for deceased subjects were made from extensive review of medical records and death certificates using the same multiple diagnostic procedure. In the current study, progression only to dementia of the Alzheimer type was considered.

Data analyses. First, the frequency of neuropsychiatric symptomatology in each MCI group was assessed. Logistic regression models and χ^2 tests were used to assess differences in the number of neuropsychiatric symptoms between persons with

Figure Proportion of persons with baseline neuropsychiatric symptoms according to cognitive status



MCI and those without cognitive impairments, adjusting for age, sex, and education.

Second, we examined whether the baseline presence of neuropsychiatric symptoms predicted progression to AD over 3 years in subjects with MCI (amnestic or multidomains). Relative risks (RRs) with 95% CI were estimated from hazard ratios computed with Cox proportional hazard models adjusted for age, sex, and education. The onset of AD was assumed as being halfway between the baseline and follow-up examination or the baseline interview and date of death. Finally, Cox models were also used to examine whether the presence of psychiatric symptoms at baseline predicted development of AD in cognitively intact persons. All analyses were also conducted using logistic regression models including adjustments for time of follow-up as well as diagnosis of major depression, and the results remained unchanged (data not shown).

Ethical considerations. Informed consent was provided at baseline by all participants. All parts of the Kungsholmen Project have been approved by the Ethical Committee of the Karolinska Institutet.

RESULTS The mean age of the study population was 84.0 years (SD = 5.1), 84.9% (n = 197) of persons were female, and 39.2% (n = 91) had high education. At baseline, 185 persons had normal cognitive functioning on all tasks, 17 persons had MCI-amnestic, and 30 had MCI-multidomains. Almost all of the MCI-multidomains category were characterized by episodic memory impairment.

The figure shows the distribution of persons with at least one neuropsychiatric symptom in each of the three categories (anxiety and mood- or motivation-related depressive symptoms), for persons with and without MCI at baseline. Logistic regression analyses were conducted to assess whether the odds of exhibiting neuropsychiatric symptomatology was higher among persons with MCI vs those without cognitive impairment for each of the three symptomatic groups (table 1). Persons with MCI-amnestic were four times more likely to have at least one clinically severe psychiatric symptom vs persons without cognitive impairments, and a similar result was seen for MCI-multidomains.

Persons with MCI-amnestic were almost four times more likely to have at least one motivation-related symptom than persons without cognitive impairment. Specifically, lack of interest was severe in 17.6% of persons with MCI-amnestic compared with 0.5% of persons without impairment ($p \leq 0.000$), and concentration difficulties were also more common (17.6 vs 4.9%, $p = 0.033$). Although the group of mood symptoms was not different between MCI-amnestic and no cognitive impairment, one symptom, suicidal ideation, was more frequent in MCI-amnestic (17.6 vs 3.2%, $p = 0.006$). Social withdrawal, from the anxiety category, was more often present in MCI-amnestic compared with cognitively intact subjects (17.6 vs 4.3%, $p = 0.021$).

In all three categories, persons with MCI-multidomains were more likely to have at least one symptom than cognitively intact subjects. The following specific symptoms were independently ele-

Table 1 Proportion of persons who had clinically severe psychiatric symptoms at baseline

	At least one clinically severe symptom of four symptoms for each category									At least one clinically severe symptom of 12 symptoms		
	Mood			Motivation			Anxiety			All three symptomatic groups		
Baseline cognitive status	%	OR	95% CI	%	OR	95% CI	%	OR	95% CI	%	OR	95% CI
No cognitive impairment, n = 185	18.4	1.0		13.0	1.0		24.9	1.0		38.9	1.0	
MCI all types, n = 47	36.2	2.5	1.2-5.0	36.2	3.8	1.8-8.0	46.8	2.5	1.3-5.2	66.0	4.5	2.0-9.8
MCI-amnestic, n = 17	35.3	2.3	0.8-6.8	35.3	3.9	1.3-11.9	41.2	2.1	0.7-6.0	64.7	4.0	1.2-13.8
MCI-multidomains, n = 30	36.7	2.5	1.1-5.7	36.7	3.8	1.6-9.0	50.0	2.9	1.3-6.7	66.7	4.9	1.9-12.7

Odds ratio (ORs) for presence of psychiatric symptoms in persons with different types of mild cognitive impairment (MCI) compared with persons without cognitive impairment, calculated with logistic regression analysis adjusted for age and sex.

Table 2 Follow-up status according to baseline cognitive status: proportion of persons with or without MCI who progressed to dementia after 3 years

	Baseline cognitive status			
	No cognitive impairment		MCI-amnestic and -multidomains	
Status at 3-y follow-up*	n	%	n	%
Alive, without dementia	131	77.1	8	18.6
Dead, without dementia	22	12.9	8	18.6
Alzheimer disease	10	5.9	24	56.2
Other dementias	7	4.1	3	7.0

*Nineteen persons refused to participate or had moved at follow-up examination.
MCI = mild cognitive impairment.

vated in persons with MCI-multidomains: depressed mood and feelings of guilt (26.7 vs 9.2%, $p = 0.006$); suicidal ideation/thoughts of death (16.7 vs 3.2%, $p = 0.002$); lack of interest (23.3 vs 0.5%, $p \leq 0.000$); psychomotor disturbances (6.7 vs 1.1%, $p = 0.036$); persistent worrying (26.7 vs 8.1%, $p = 0.002$); and social withdrawal (20.0 vs 4.3%, $p = 0.001$).

Table 2 shows the follow-up vital and cognitive status of subjects with or without baseline MCI who participated at 3-year follow-up or died during the period (19 persons refused or moved during follow-up). Over half of the persons with MCI-amnestic or MCI-multidomains developed AD over 3 years compared with 5.9% of persons without baseline cognitive impairments. Ten persons received a diagnosis of another dementia type, but these were excluded from the follow-up analyses to focus specifically on dementia of the Alzheimer type.

MCI-amnestic and MCI-multidomains were merged together for further analyses, as almost all persons with MCI-multidomains had episodic memory impairments, MCI-amnestic and MCI-multidomains had similar progression rate to AD, and the pattern of neuropsychiatric symptomatology was comparable. First, we investigated whether the presence of neuropsychiatric symptomatology predicted progression to AD over 3 years among persons with MCI. Mood-related depressive symptoms at baseline were high both in persons with MCI who remained dementia-free (31.3%) and in persons with MCI who developed AD (37.5%) and thus there was no statistically increased risk of developing AD in persons with MCI plus depressive symptoms (table 3). However, anxiety symptomatology predicted AD in subjects with MCI. For each increasing number of anxiety symptoms, the risk of AD almost doubled (RR: 1.8, 95% CI: 1.2 to 2.7). After further adjustment for baseline cognitive status, the results remained unchanged (RR: 1.9, 95% CI: 1.2 to 2.8). Each anxiety symptom was examined individually. Persons with MCI who reported problems with decision making had a fivefold risk of AD vs MCI subjects with no such problems (RR: 5.6, 95% CI: 1.1 to 29.0), and those with persistent worrying also had a fivefold increased risk (RR: 5.3, 95% CI: 1.8 to15.6).

Second, we conducted an additional analysis to calculate the risk of AD in persons with MCI with and without anxiety compared with cognitively intact elderly individuals. Compared with 6% of the cognitive normal elderly individuals, 40.9% of per-

Table 3 Mood-related and motivation-related depressive symptoms and anxiety symptoms in relation to progression to AD in persons with MCI (amnestic or multidomains) and persons with no cognitive impairment: RR for AD per increasing number of clinically severe psychiatric symptoms

	MCI-amnestic or -multidomains, n = 47		No cognitive impairment, n = 185	
Presence of clinically severe symptoms as predictors of AD	RR	95% CI for AD	RR	95% CI for AD
Mood symptoms: 0–4 symptoms	0.9	0.6–1.5	1.9	1.0–3.6
Motivation-related symptoms: 0–4 symptoms	1.1	0.7–1.8	1.9	0.5–7.4
Anxiety symptoms: 0–4 symptoms	1.8	1.2–2.7	1.1	0.5–2.3

Relative risks (RRs) estimated from hazard ratios calculated with Cox proportional hazard models adjusted for age, sex, and education.
AD = Alzheimer disease; MCI = mild cognitive impairment.

sons with MCI without anxiety progressed to AD after 3 years, whereas the progression rate to AD for persons with MCI plus anxiety was 83.3%. This corresponded to a 10-fold higher risk of developing AD among MCI without anxiety (RR: 10.6, 95% CI: 4.2 to 26.8), but a 30 times higher risk among persons with MCI with anxiety (RR: 34.4, 95% CI: 13.9 to 85.8) than cognitively intact persons, after adjustment for age, sex, and education.

We also examined whether the presence of neuropsychiatric symptomatology in persons without cognitive impairment predicted AD (table 3). The risk of AD almost doubled with each increasing number of mood-related depressive symptoms in cognitively intact subjects.

DISCUSSION In this population-based study, neuropsychiatric symptoms were common in persons with MCI. Compared with cognitively intact elderly persons, persons with MCI-multidomains and MCI-amnestic were more likely to have both depression- and anxiety-related symptomatology. Persons with MCI plus anxiety symptomatology had an increased risk of progressing to AD over 3 years compared with persons with MCI without anxiety problems. Furthermore, depressed mood was predictive of AD in persons with normal levels of baseline cognition as well as being frequent in persons with MCI. Together, these findings suggest that anxiety symptoms in MCI may be a response to the initial phases of cognitive deterioration in neurodegeneration, whereas mood-related depressive symptoms may be a preclinical sign of AD related to the neuropathologic mechanism, present even in persons with prodromal AD who have no detectable cognitive impairment.

The results support previous research showing that neuropsychiatric symptoms are prevalent in persons with MCI.[9-11] Consistent with corresponding figures between 47 and 59%, about two-thirds of persons with MCI-amnestic and MCI-multidomains had at least one severe neuropsychiatric symptom. Furthermore, symptoms were most frequent in persons with multiple cognitive impairments, mirroring previous findings[8] that neuropsychiatric symptoms in MCI are associated with more severe levels of cognitive impairment. Alternative explanations are discussed later.

Owing to the longitudinal design of our project, we were able to follow persons with MCI to see whether neuropsychiatric symptoms predicted progression to AD. Indeed, anxiety-related symptomatology was predictive of impending AD in persons with MCI, with an almost twofold increased risk per additional symptom. Specifically, problems with decision making and persistent worrying had high predictivity. The associations remained significant even after adjusting for baseline level of cognitive functioning. Adding anxiety symptoms resulted in higher prediction than simply comparing MCI vs no MCI. Another study on persons with questionable dementia[31] found that those who developed AD over 3 years had more symptoms of personality change, such as agitation, than those who did not develop the disease.

These findings raise the question of whether such symptoms reflect specific neuropathologic changes in the brain or indicate a subjective reaction to the cognitive changes. Anxiety is common in the later stages of AD,[32,33] and some evidence suggests a pathologic mechanism underlying such disturbances. For example, AD patients with agitation have greater neurofibrillary tangle burden in the orbitofrontal cortex.[34] Our finding that milder symptoms of anxiety are present in the prodromal phase could suggest that these particular pathologic mechanisms underlying AD might begin working early in the course of the disease, before current diagnostic criteria for AD are met. However, if anxiety is related to pathologic degeneration, we would expect to see these symptoms occurring in all preclinical AD including AD patients who are cognitively intact 3 years before diagnosis, but that was not the case. The symptomatology in preclinical AD differed depending on whether cognitive impairments were present. In the absence of cognitive impairment, depressive symptoms were elevated in preclinical AD, but in conjunction with memory or multiple cognitive disturbances, anxiety was the predominantly predictive feature. Anxiety can be caused by the awareness of memory loss and cognitive disturbances, but not in all cases, as we found that anxiety was not always present in persons with MCI. It is also plausible that there is a group of persons in the preclinical phase of AD who exhibit anxiety symptoms and progress to clinical AD at a faster rate.

Mood-related depressive symptoms were predictive of future AD in persons without cognitive impairment; the risk of AD almost doubled with each additional symptom. Previous studies have shown that depression is a risk factor for AD, especially when symptoms first occur 1 year before AD diagnosis,[35] and a neuropathologic study found more pronounced neuropathologic changes in the hippocampus in persons with concurrent depression at time of AD diagnosis.[36] Furthermore, one study[23] showed that patients with both MCI and depression had a higher risk of developing AD than those with MCI alone. Together, these findings suggest that

depressive symptomatology could be a precursor, or early symptom, of AD. In the current study, depressive symptoms did not show a statistically significant prediction for AD among persons with MCI because depressive symptoms were high both in persons with MCI who remained dementia-free (31.3%) and in persons with MCI who developed AD (37.5%). It is plausible that in the first group of subjects, MCI was related to an underlying psychiatric disorder, and in the second group, MCI and depression were associated with neurodegeneration. The presence of preclinical depressive symptoms in many cases of AD, including persons with or without MCI, highlights the need to further investigate the role of depression in early AD, also in the absence of clear cognitive disturbances. Further, considering that some individuals do not progress to AD through a clinically identifiable syndrome of cognitive impairment,[4,37] it is valuable to have other predictors that might help identify subjects at risk who would otherwise be undetected.

Some limitations deserve mention. First, because the data derive from a large population-based study, MCI was defined according to performance on neuropsychological tests and self-reported symptoms, rather than based on a clinical diagnosis. However, as our findings indicate that neuropsychiatric symptoms might be helpful in predicting the prognosis of MCI patients, they should be replicated within clinical populations. Second, the relatively small sample may have led to an underestimation of the impact of neuropsychiatric symptomatology in predicting AD. Symptoms such as depression may show higher predictive validity for AD in larger samples. Alternatively, the difference in findings could reflect a complex difference between MCI patients referred to clinics and the wider spectrum of cognitively impaired persons in the general community. Third, as there are no specific recommended tools to diagnose MCI, the operationalization of the criteria may slightly differ from those in other studies. It is also worth noting that prevalent cases of MCI were assessed in the current study, which may include persons with long-term cognitive impairment that remains stable over time. In addition, the crude conversion rates from MCI to AD were quite high in the current study, possibly owing to the high age and large proportion of females in the study population. Therefore, we adjusted analyses for age, education, and sex. Fourth, it is possible that that anxiety in the elderly population, especially if measured with the CPRS, is an indicator of some form of emotional vulnerability, which could be a counterpart of mild depression, or predepression symptoms. However, we identified relevant categories of neuropsychiatric symptoms based on previous research.[14] Finally, our results are based on an extremely old population with a large proportion of women, and it could be argued that the findings may differ from those in younger elderly individuals. For example, vascular disease is related to cognitive impairment, as well as depressive symptoms,[38] particularly motivation-related symptoms.[39] In this older population, vascular disease may be more prevalent and could potentially affect the relationship between MCI and depressive symptoms. However, another study showed an increased risk of MCI due to depressive symptoms is independent of underlying vascular disease.[13]

The current study investigated longitudinally the role of neuropsychiatric symptomatology in MCI in the general population. Our findings suggest that anxiety symptoms in MCI may represent a reaction to the initial phases of cognitive deterioration. In contrast, mood-related depressive symptoms could be considered a preclinical sign of AD, and they might be related to the neuropathologic mechanism. The results also have clinical relevance, as they provide evidence for additional predictors for AD within MCI, as well as in persons without cognitive impairment. Psychiatric symptoms may increase predictive ability and decrease the false-negative rate in identifying future AD cases.

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