ORIGINAL ARTICLE

Prediction of Dementia by Subjective Memory Impairment

Effects of Severity and Temporal Association With Cognitive Impairment

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Context: Subjective memory impairment (SMI) is receiving increasing attention as a pre-mild cognitive impairment (MCI) condition in the course of the clinical manifestation of Alzheimer disease (AD).

Objectives: To determine the risk for conversion to any dementia, dementia in AD, or vascular dementia by SMI, graded by the level of SMI-related worry and by the temporal association of SMI and subsequent MCI.

Design: Longitudinal cohort study with follow-up examinations at 1½ and 3 years after baseline.

Setting: Primary care medical record registry sample.

Participants: A total of 2415 subjects without cognitive impairment 75 years or older in the German Study on Aging, Cognition and Dementia in Primary Care Patients.

Main Outcome Measures: Conversion to any dementia, dementia in AD, or vascular dementia at follow-up 1 or follow-up 2 predicted by SMI with or without worry at baseline and at follow-up 2 predicted by different courses of SMI at baseline and MCI at follow-up 1.

Results: In the first analysis, SMI with worry at baseline was associated with greatest risk for conversion to any dementia (hazard ratio [HR], 3.53; 95% confidence interval [CI], 2.07-6.03) or dementia in AD (6.54; 2.82-15.20) at follow-up 1 or follow-up 2. The sensitivity was 69.0% and the specificity was 74.3% conversion to dementia in AD. In the second analysis, SMI at baseline and MCI at follow-up 1 were associated with greatest risk for conversion to any dementia (odds ratio [OR], 8.92; 95% CI, 3.69-21.60) or dementia in AD (19.33; 5.29-70.81) at follow-up 2. Furthermore, SMI at baseline and amnestic MCI at follow-up 1 increased the risk for conversion to any dementia (OR, 29.24; 95% CI, 8.75-97.78) or dementia in AD (60.28; 12.23-297.10), with a sensitivity of 66.7% and a specificity of 98.3% for conversion to dementia in AD.

Conclusion: The prediction of dementia in AD by SMI with subsequent amnestic MCI supports the model of a consecutive 3-stage clinical manifestation of AD from SMI via MCI to dementia.

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THE IDENTIFICATION OF at-risk and prodromal syndromes for dementia is a major research goal driven in part by the anticipated advent of disease-modifying treatment for Alzheimer disease (AD).[1] Mild cognitive impairment (MCI) has been identified as an at-risk condition, with an annual conversion rate to dementia of 10% to 20%.[2] Mild cognitive impairment represents neuropsychological test performance below age-, sex-, and education-adjusted normal ranges and activities of daily living (ADL) that are largely intact.[2] In contrast, the diagnosis of dementia requires cognitive impairment plus impaired ADL. The concept of MCI as a predementia manifestation of AD is substantiated by studies[3,4] providing biologic evidence for the presence of AD in patients with MCI.

However, AD-related pathologic changes in the brain evolve several years before the onset of MCI.[5,6] Longitudinal studies[7,8] have reported subtle cognitive decline, not yet exceeding age-, sex-, and education-adjusted normal ranges, before MCI. Recently, the temporal association of this pre-MCI cognitive decline with the occurrence of cognitive complaints in subjects with subsequent dementia has been demonstrated,[9] suggesting that initial worsening of cognitive performance is already experienced by affected individuals. This

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may qualify subjective memory impairment (SMI) as a clinical indicator of pre-MCI cognitive decline. Support for this concept is the slightly poorer performance on memory tests among subjects with SMI compared with control subjects without cognitive complaints that is observed in large cross-sectional cohorts,[10-12] as well as in the first studies[13-15] on biologic evidence of AD (eg, mediotemporal lobe atrophy) in SMI. Furthermore, longitudinal cohort studies[16,17] among older subjects without cognitive impairment identified SMI as a predictor of cognitive decline and dementia.

The particular wealth of SMI is the implicit information on the longitudinal course of subtle cognitive decline in a subject that is not obtained by cross-sectional testing and might not be discovered by longitudinal testing because of variation in task performance and the effects of successive testing. However, SMI is frequent in older subjects[18] and by itself might have insufficient sensitivity and specificity to predict dementia or to justify extended diagnostic testing for AD. This limitation may be overcome by a refinement of the characterization of SMI. One approach is the grading of severity. Subjective memory impairment is a personal judgment suggesting that the extent of SMI-related worry caused by the experienced decline may serve as a grading variable.

A second approach to increase the predictive power of SMI for dementia in older subjects without impairment is the assessment of SMI in temporal association with the occurrence of cognitive impairment (such as MCI), defined by below-normal performance on testing. Under the hypothesis that SMI is a correlate of pre-MCI decline in progressive deterioration to dementia, SMI plus MCI later should be associated with greatest risk for subsequent dementia.

Within the German Study on Aging, Cognition and Dementia in Primary Care Patients of the German Competence Network Dementia, a longitudinal investigation in subjects initially without dementia, we tested the association of SMI with or without worry and future dementia. Second, we tested different sequences of SMI and MCI at follow-up with regard to the prediction of dementia. We tested these effects separately for conversion to any dementia, dementia in AD, or vascular dementia. Other relevant predictors of SMI and dementia such as age, sex, education, depressive symptoms, and apolipoprotein E 4 (*ApoE4*) genotype were included as independent variables.

METHODS

PARTICIPANTS

This study was performed within the German Study on Aging, Cognition and Dementia in Primary Care Patients of the German Competence Network Dementia. The subjects were recruited at 6 study sites (Bonn, Düsseldorf, Hamburg, Leipzig, Mannheim, and Munich) via medical record registry of general practitioners (GPs). Inclusion criteria were age 75 years or older, absence of dementia according to judgment of GP, and at least 1 contact with the GP within the last 12 months. Exclusion criteria were GP consultation by home visits only, residence in a nursing home, severe illness with an anticipated fatal outcome within 3 months, German-language insufficiency, deafness or blindness, and lack of ability to provide informed consent. About 95% of the subjects in this age group are registered at an office of a GP. Because we used a medical record registry approach rather than a waiting-room recruitment strategy, the participants in this study are unselected and can be considered representative of community-dwelling older subjects. Detailed recruitment figures have been given elsewhere.[12] All subjects gave written informed consent before the study. The protocol was approved by the ethics committees at all participating sites.

A total of 3327 subjects were included in the baseline sample of the German Study on Aging, Cognition and Dementia in Primary Care Patients. Two follow-up waves were performed at 1½ and 3 years after the baseline investigation. A total of 2820 subjects were personally interviewed at follow-up 1. Information was obtained from informants for 482 subjects, who were excluded from follow-up 2. No information was available for 25 subjects (0.8% of the baseline cohort). A total of 2478 subjects were personally interviewed at follow-up 2. Information was obtained from informants for 341 subjects. No information was available for 508 subjects (15.3% of the baseline cohort).

ASSESSMENT

Subjects were interviewed in their home environment by trained psychologists (S.E.-G., F.H., T.L., E.M., A.W., T.Z., and M.P.) or physicians (C.B. and H.K.). In the initial phase of the interview, the following question was asked to assess SMI (from a 1999 study by Geerlings et al[19]): "Do you feel like your memory is becoming worse?" Possible answers were "no," "yes, but this does not worry me," or "yes, this worries me."

Neuropsychological assessment included the Structured Interview for Diagnosis of Dementia of Alzheimer Type, Multi-infarct Dementia and Dementia of Other Etiology According to *DSM-IV*[20] and *ICD-10* (SIDAM).[20] The SIDAM is specifically designed to diagnose dementia according to the named criteria. It contains (1) a neuropsychological test battery, (2) a 14-item scale for the assessment of ADL (SIDAM ADL Scale), and (3) the Hashinski-Rosen Scale.[21] The neuropsychological battery is composed of 55 items (SIDAM cognitive [SISCO] score), including the Mini-Mental State Examination.[22] The SISCO score is subdivided into 1 memory domain and 3 nonmemory domains (orientation; language, perception, and praxis; and reasoning and problem solving). German age- and education-specific norms for the SISCO score are published.[23] Depressive symptoms were assessed using the 15-item version of the Geriatric Depression Scale.[24] Education was categorized as low, middle, or high using the Comparative Analysis of Social Mobility in Industrial Nations educational classification.[25]

The SIDAM interview, including the SISCO score and the Geriatric Depression Scale score, was performed at baseline and follow-ups 1 and 2. Medical history was also obtained from the subjects and their GP at baseline and follow-ups 1 and 2. For subjects who could not be interviewed in person, the Global Deterioration Scale[26] and 2 subscales of the Blessed Dementia Scale (the changes in performance of everyday activities subscale and the changes in habits subscale)[27] were completed by the interviewer with an informant. Apolipoprotein E4 genotyping was performed in almost all subjects.

DEFINITIONS OF MCI AND DEMENTIA

In accord with the current guidelines,[2] MCI was defined (1) by 1-SD performance below age- and education-adjusted normal ranges in any of 4 SISCO score domains,[23] (2) by a lack of impairment in ADL (score of <2 on the SIDAM ADL Scale),

Table 1. Baseline Characteristics of the Study Subjects

Characteristic	No SMI (n=1027)	SMI Without Worry (n=1006)	SMI With Worry (n=382)	Statistic	*P* Value
Sex, No. (%)				χ^2=24.56	<.001
Female	685 (66.7)	591 (58.7)	273 (71.5)		
Male	342 (33.3)	415 (41.3)	109 (28.5)		
Age, mean (SD), y	79.4 (3.4)	79.8 (3.6)	79.8 (3.5)	*F*=2.87	.06
Education status, No. (%)[a]				χ^2=18.44	.001
Low	697 (67.9)	641 (63.7)	271 (70.9)		
Middle	252 (24.5)	247 (24.6)	68 (17.8)		
High	78 (7.6)	118 (11.7)	43 (11.3)		
ApoE4 genotype, No. (%)/total subpopulation	195/990 (19.7)	200/962 (20.8)	78/369 (21.1)	χ^2=0.51	.77
SISCO score, mean (SD)[b]	49.4 (3.2)	49.7 (3.2)	49.4 (3.3)	*F*=2.42	.09
Geriatric Depression Scale score, mean (SD)[c]	1.8 (2.0)	2.1 (2.1)	3.2 (2.7)	*F*=63.22	<.001

Abbreviations: *ApoE4*, apolipoprotein E4; SISCO, cognitive domain of the Structured Interview for Diagnosis of Dementia of Alzheimer Type, Multi-Infarct Dementia and Dementia of Other Etiology according to *DSM-IV* and International Classification of Diseases, 10th edition. SMI, subjective memory impairment.

[a] Comparative Analysis of Social Mobility in Industrial Nations educational classification.

[b] Cognitive domain of the Structured Interview for Diagnosis of Dementia of Alzheimer Type, Multi-Infarct Dementia and Dementia of Other Etiology According to *DSM-IV* and *ICD-10*, with a maximum score of 55.

[c] Scores exceeding 6 indicate evidence of a clinically relevant depressive episode.

and (3) by the absence of dementia. Although SMI is a criterion in the most widely used MCI definition,[2] it was not included herein because we used MCI to describe all subjects with cognitive impairment and not just those with cognitive impairment plus SMI. Mild cognitive impairment was only diagnosed in subjects who were personally interviewed and tested.

Dementia was diagnosed according to the criteria of the *DSM-IV*, which comprise a diagnostic algorithm in the SIDAM, including cognitive impairment on the SISCO score and impairment in ADL (score of ≥2 on the SIDAM ADL Scale). The diagnosis of dementia in AD was established according to the National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer's Disease and Related Disorders Association criteria for probable AD.[28] Vascular dementia diagnosis was guided by the National Institute of Neurological Disorders and Stroke–Association Internationale pour la Recherché et l'Enseignement en Neurosciences criteria[29] (ie, evidence of a cerebrovascular event [Hashinski-Rosen Scale and medical history] and temporal association of the cerebrovascular event with cognitive decline). Mixed dementia was diagnosed in the absence of temporal association of the cerebrovascular event with cognitive decline. For all analyses, subjects with mixed dementia and dementia in AD were combined. Dementia diagnosis in subjects who were not personally interviewed was based on the Global Deterioration Scale and the Blessed Dementia Scale subscales. A score of at least 4 on the Global Deterioration Scale represented a diagnosis of dementia. The diagnosis was established in these cases if the causal information provided was sufficient for judgment using the aforementioned criteria. All diagnoses were made in consensus conferences that included the interviewer and experienced geriatric psychiatrists (F.J. and S.G.-R.H.) or geriatricians (S.W. and H.B.).

BASELINE SAMPLE FOR PREDICTION OF DEMENTIA BY SMI

We were interested in the prediction of dementia by SMI in subjects without cognitive impairment. Therefore, we excluded all subjects with MCI at baseline or with a lack of information at follow-up. We also excluded 85 subjects with dementia, age younger than 75 years, or with grossly incomplete data at baseline. The baseline population for the present analyses consisted of 2415 subjects. Descriptive data are given in **Table 1**.

DEFINITIONS OF SMI AND MCI COURSES

We aimed to test the prediction of dementia by different sequences of SMI and MCI. For this purpose, we classified the subjects into those who developed MCI at follow-up 1 and those who remained without cognitive impairment. These 2 groups were categorized with regard to the presence of SMI at baseline. For this analysis, subjects having SMI with or without worry were combined. Subjects with dementia at follow-up 1 and subjects without personal cognitive testing at follow-up 1 were excluded from this analysis. The 4 temporal sequences of SMI at baseline and MCI at follow-up 1 are as follows: (1) no SMI at baseline and no MCI at follow-up 1, (2) SMI at baseline and no MCI at follow-up 1, (3) no SMI at baseline and MCI at follow-up 1, and (4) SMI at baseline and MCI at follow-up 1. **Table 2** gives the characteristics of subjects in the 4 temporal sequences.

In an additional analysis, we grouped subjects with SMI at baseline and MCI at follow-up 1 as those with amnestic MCI (impairment on the SISCO score memory domain) and those with nonamnestic MCI. For further exploratory analyses, subjects with amnestic MCI at follow-up 1 were grouped as those with SMI and those without SMI at baseline.

STATISTICAL ANALYSIS

Using multivariate-adjusted Cox proportional hazards regression models, we analyzed the effect of SMI at baseline on the time to conversion to any dementia, dementia in AD, or vascular dementia separately at follow-up 1 or follow-up 2. Subjects with SMI were grouped into those with or without SMI-related worry at baseline. Covariates were age, sex, education, baseline SISCO score, Geriatric Depression Scale score, and *ApoE4* genotype. The hazard ratios (HRs) with 95% confidence intervals (CIs) were determined. Sensitivity and specificity were calculated for the condition with greatest risk for dementia in AD.

Multivariate logistic regression analysis was performed to evaluate the risk for any dementia, dementia in AD, or vascular dementia separately at follow-up 2 by the different courses of SMI at baseline (absent or present) and by the presence or absence of MCI at follow-up 1. Covariates were again age, sex, education, baseline SISCO score, Geriatric Depression Scale score, and *ApoE4* genotype. The odds ratios (ORs) and 95% CIs were calculated.

Table 2. Baseline Characteristics of 2075 Subjects in 4 Temporal Sequences

Characteristic	No SMI at Baseline and no MCI at Follow-up 1 (n=766)	SMI at Baseline and no MCI at Follow-up 1 (n=1025)	No SMI at Baseline and MCI at Follow-up 1 (n=108)	SMI at Baseline and MCI at Follow-up 1[a]		Statistic	*P* Value
				Amnestic (n=21)	Nonamnestic (n=155)		
Sex, No (%)						χ^2=4.91	.29
Female	514 (67.1)	642 (62.6)	71 (65.7)	14 (66.7)	94 (60.6)		
Male	252 (32.9)	383 (37.4)	37 (34.3)	7 (33.3)	61 (39.4)		
Age, mean (SD), y	79.3 (3.3)	79.5 (3.7)	79.8 (3.1)	79.8 (4.1)	80.4 (3.7)	*F*=3.84	.004
Education status, No. (%)[b,c]						χ^2=131.00	.001
Low	545 (71.1)	709 (69.2)	43 (39.8)	13 (61.9)	57 (36.8)		
Middle	169 (22.1)	189 (18.4)	48 (44.4)	5 (23.8)	77 (49.7)		
High	52 (6.8)	127 (12.4)	17 (15.7)	3 (14.3)	21 (13.5)		
ApoE4 genotype, No. (%)	139 (18.8)	201 (20.4)	20 (19.2)	10 (47.6)	34 (22.7)	χ^2=11.33	.02
SISCO score, mean (SD)[d]	49.7 (3.0)	50.1 (3.0)	48.9 (3.6)	46.3 (3.4)	49.3 (3.3)	*F*=12.28	<.001
Geriatric Depression Scale score, mean (SD)[d]	1.7 (1.9)	2.3 (2.3)	1.8 (1.9)	2.6 (1.8)	2.3 (1.2)	*F*=10.23	<.001

Abbreviations: *ApoE4*, apolipoprotein E 4; MCI, mild cognitive impairment; SISCO, cognitive domain of the Structured Interview for Diagnosis of Dementia of Alzheimer Type, Multi-Infarct Dementia and Dementia of Other Etiology According to *DSM-IV* and *International Classification of Diseases, 10th edition*; SMI, subjective memory impairment.

[a] These subjects had greatest risk for dementia and were subcategorized into those having amnestic vs nonamnestic MCI for further analyses.

[b] Cognitive domain of the Structured Interview for Diagnosis of Dementia of Alzheimer Type, Multi-Infarct Dementia and Dementia of Other Etiology According to *DSM-IV* and *ICD-10*, with a maximum score of 55.

[c] Due to rounding, percentages do not total 100.

[d] Scores exceeding 6 indicate evidence of a clinically relevant depressive episode.

Additional models were calculated for SMI at baseline and for amnestic vs nonamnestic MCI at follow-up 1, and with regard to the risk for any dementia, for dementia in AD at follow-up 2. Again, sensitivity and specificity were calculated for the condition with greatest risk for dementia in AD.

Among subjects with SMI at baseline, the numbers with incident vascular dementia relative to amnestic vs nonamnestic MCI at follow-up 1 are given. Because of few subjects, no statistical analyses were performed.

Among subjects with or without SMI at baseline, there were also few with any dementia, dementia in AD, or vascular dementia among subjects with amnestic MCI at follow-up 1. Therefore, these incidence rates are also only reported descriptively.

Dementia diagnosis was based only on an informant and judgment of a GP in some subjects. Therefore, all analyses were repeated for exploratory purposes after exclusion of these subjects.

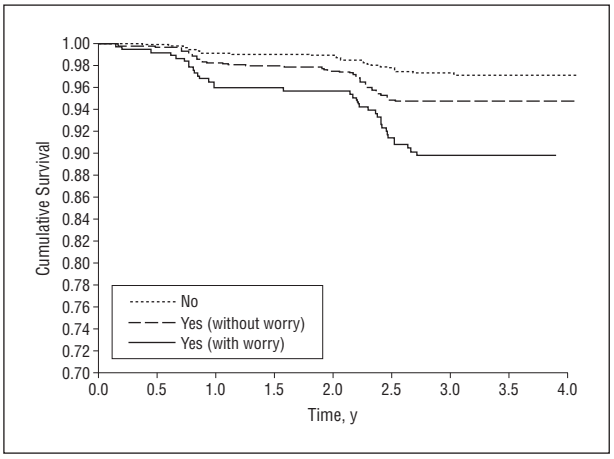

Figure. Kaplan-Meier survival curves showing the conversion to dementia in Alzheimer disease relative to the presence of subjective memory impairment with or without worry at baseline.

RESULTS

DEMENTIA RISK BY SMI AT BASELINE

In the multivariate Cox proportional hazards regression model, SMI with worry ($P<.001$) and SMI without worry ($P=.02$) were associated with increased risk for dementia at follow-up 1 or follow-up 2. Other significant risk factors were age ($P=.003$), *ApoE4* genotype ($P=.04$), and baseline SISCO score ($P<.001$). Sex, education, and Geriatric Depression Scale score were not associated with increased risk for dementia.

Incident dementia in AD at follow-up 1 or follow-up 2 was associated with SMI with worry ($P<.001$), SMI without worry ($P=.007$), age ($P=.003$), and baseline SISCO score ($P<.001$). Sex, education, Geriatric Depression Scale score, and *ApoE4* genotype were not associated with incident dementia in AD. The **Figure** shows the Kaplan-Meier survival curves. With a sensitivity of 69.0% and a specificity of 74.3%, SMI with worry at baseline predicted conversion to dementia in AD at follow-up 1 or follow-up 2. Incident vascular dementia was not associated with any variable. **Table 3** lists all HRs and CIs in the first analysis.

After exclusion of subjects with dementia diagnosis based on an informant and GP judgment only, exploratory analyses revealed similar HRs and no changes in significance. These data are not shown.

DEMENTIA RISK BY SMI AT BASELINE WITH SUBSEQUENT MCI

Subjects without SMI at baseline and without MCI at follow-up 1 served as the reference category in the second analysis. Compared with this group, subjects with SMI at baseline and without MCI at follow-up 1 had a trend

Table 3. First Analysis Among 2415 Subjects

Variable	Hazard Ratio (95% Confidence Interval) of Conversion at Follow-up 1 or Follow-up 2		
	Any Dementia (n=110)	Dementia in AD (n=54)	Vascular Dementia (n=26)
No SMI at baseline (n=1027)	1 [Reference]	1 [Reference]	1 [Reference]
No. (%)	26 (2.5)	9 (0.9)	9 (0.9)
SMI without worry at baseline (n=1006)	1.83 (1.12-2.99)[a]	3.04 (1.36-6.81)[a]	1.12 (0.44-2.84)
No. (%)	49 (4.9)	25 (2.5)	10 (1.0)
SMI with worry at baseline (n=382)	3.53 (2.07-6.03)[a]	6.54 (2.82-15.20)[a]	2.68 (0.96-7.46)
No. (%)	35 (9.2)	20 (5.2)	7 (1.8)
SISCO score at baseline, per point	0.76 (0.71-0.82)[a]	0.76 (0.69-0.83)[a]	0.96 (0.80-1.14)
Female sex	1.35 (0.88-2.06)	1.09 (0.58-2.06)	1.35 (0.58-3.15)
Age, per y	1.08 (1.03-1.13)[a]	1.12 (1.04-1.19)[a]	1.05 (0.95-1.17)
ApoE4 genotype	1.57 (1.03-2.41)[a]	1.65 (0.91-3.04)	0.53 (0.16-1.78)
Geriatric Depression Scale score, per point	1.04 (0.97-1.13)	1.03 (0.92-1.15)	0.96 (0.80-1.14)
Education status[b]			
Low	1 [Reference]	1 [Reference]	1 [Reference]
Middle	1.66 (0.94-2.93)	1.36 (0.58-3.19)	2.06 (0.76-5.55)
High	1.92 (0.83-4.42)	1.47 (0.39-5.51)	0.72 (0.08-6.14)

Abbreviations: AD, Alzheimer disease; *ApoE4*, apolipoprotein E4; SISCO, cognitive domain of the Structured Interview for Diagnosis of Dementia of Alzheimer Type, Multi-Infarct Dementia and Dementia of Other Etiology According to *DSM-IV* and *International Classification of Diseases, 10th edition*; SMI, subjective memory impairment.

[a] Statistically significant.

[b] Cognitive domain of the Structured Interview for Diagnosis of Dementia of Alzheimer Type, Multi-infart Dementia and Dementia of Other Etiology According to *DSM-IV* and *ICD-10*, with a maximum score of 55.

toward increased risk for any dementia ($P=.06$) and dementia in AD ($P=.06$) but not vascular dementia ($P=.48$) at follow-up 2. Subjects without SMI at baseline but with MCI at follow-up 1 had increased risk for any dementia ($P=.009$) and dementia in AD ($P=.04$) but not vascular dementia ($P=.14$). Subjects with SMI at baseline and with MCI at follow up 1 had increased risk for any dementia ($P<.001$) and dementia in AD ($P<.001$) but not vascular dementia ($P=.96$) at follow-up 2. Baseline SISCO score was also associated with the risk for any dementia ($P<.001$) and dementia in AD ($P=.005$) but not vascular dementia ($P=.45$) at follow-up 2. Sex, age, education, *ApoE4* genotype, and Geriatric Depression Scale score were not associated with any dementia, dementia in AD, or vascular dementia at follow-up 2 (**Table 4**).

After exclusion of subjects with dementia diagnosis based on an informant and GP judgment only, exploratory analyses revealed higher ORs and greater CIs. In subjects with SMI at baseline and with MCI at follow-up 1, the risk became significant for any dementia (OR, 7. 29; 95% CI, 1.68-31.63) and dementia in AD (8. 23; 1.05-64.53). In subjects without SMI at baseline and without MCI at follow-up 1, the OR for dementia in AD was also higher in this analysis (OR, 10.42; 95% CI, 0.89-121.70) but did not achieve significance because of few subjects. In all other exploratory analyses, no change in significance occurred (data not shown).

DEMENTIA RISK BY SMI AT BASELINE WITH SUBSEQUENT AMNESTIC VS NONAMNESTIC MCI

The model was recalculated after division of subjects with SMI at baseline and with MCI at follow-up 1 into those with amnestic vs nonamnestic MCI. Compared with subjects without SMI at baseline and without MCI at follow-up, subjects with SMI at baseline and with amnestic vs nonamnestic MCI at follow-up 1 had increased risk for any incident dementia and dementia in AD ($P<.001$ for both) at follow-up 2 (Table 4). With a sensitivity of 66.7% and a specificity of 98.3%, SMI at baseline and amnestic MCI at follow-up 1 predicted conversion to dementia in AD at follow-up 2.

After exclusion of subjects with dementia diagnosis based on an informant and GP judgment only, exploratory analyses revealed higher ORs and greater CIs, without change in significance. These data are not shown.

DEMENTIA RISK BY AMNESTIC MCI WITH VS WITHOUT SMI AT BASELINE

The total number of subjects in this analysis was 33. Of 21 subjects with SMI at baseline and with amnestic MCI at follow-up 1, a total of 8 developed dementia. Of these, 6 subjects had developed dementia in AD at follow-up 2, and none had developed vascular dementia. Of 12 subjects with amnestic MCI at follow-up, only 1 subject without SMI at baseline (8.3%) developed dementia (AD) at follow-up 2. None developed vascular dementia.

COMMENT

We identified SMI as a risk factor for dementia in older subjects without cognitive impairment after adjustment for known confounding variables of SMI such as age, sex, education, symptoms of depression, baseline cognitive performance, and *ApoE4* genotype. Theses results support the findings of earlier studies[17,30] with large cohorts and long observation periods. In addition to the presence of SMI, we assessed the association of SMI with or

Table 4. Second Analysis Among 2075 Subjects

Variable	Odds Ratio (95% Confidence Interval) of Conversion at Follow-up 2		
	Any Dementia (n=61)	Dementia in AD (n=36)	Vascular Dementia (n=14)
No SMI at baseline and no MCI at follow-up 1 (n=766)	1 [Reference]	1 [Reference]	1 [Reference]
No. (%)	8 (1.0)	3 (0.4)	3 (0.4)
SMI at baseline and no MCI at follow-up 1 (n=1025)	2.22 (0.97-4.97)	3.44 (0.97-12.16)[a]	1.64 (0.41-6.53)
No. (%)	27 (2.6)	15 (1.5)	8 (0.8)
No SMI at baseline and MCI at follow-up 1 (n=108)	4.41 (1.44-13.48)[a]	5.74 (1.09-30.16)[a]	4.09 (0.64-26.38)
No. (%)	6 (5.6)	3 (2.8)	2 (1.9)
SMI at baseline and MCI at follow-up 1 (n=176)	8.92 (3.69-21.60)[a]	19.33 (5.29-70.81)[a]	1.05 (0.10-11.08)
No. (%)	20 (11.3)	15 (8.5)	1 (0.6)
Amnestic (n=21)[b]	29.24 (8.75-97.78)[a]	60.28 (12.23-297.10)[a]	. . .
No. (%)	8 (38.1)	6 (28.6)	. . .
Nonamnestic (n=155)[b]	6.26 (2.41-16.28)[a]	13.80 (3.53-53.99)[a]	. . .
No. (%)	12 (7.7)	9 (5.8)	. . .
SISCO score at baseline, per point	0.83 (0.75-0.92)[a]	0.83 (0.73-0.95)[a]	0.93 (0.76-1.13)
Female sex	1.12 (0.62-2.03)	0.88 (0.40-1.94)	1.99 (0.63-6.25)
Age, per y	1.06 (0.98-1.14)	1.05 (0.95-1.15)	1.11 (0.96-1.29)
ApoE4 genotype	1.61 (0.89-2.94)	1.81 (0.86-3.84)	0.32 (0.41-2.50)
Geriatric Depression Scale score, per point	1.13 (1.00-1.24)	1.13 (0.99-1.29)	1.17 (0.95-1.44)
Education[c,d]			
Low	1 [Reference]	1 [Reference]	1 [Reference]
Middle	1.00 (0.44-2.27)	0.86 (0.29-2.48)	1.64 (0.39-6.87)
High	1.29 (0.42-3.99)	0.85 (0.16-4.53)	0.79 (0.08-7.83)

Abbreviations: AD, Alzheimer disease; *ApoE4*, apolipoprotein E4; ellipsis, not applicable; MCI, mild cognitive impairment; SISCO, cognitive domain of the Structured Interview for Diagnosis of Dementia of Alzheimer Type, Multi-Infarct Dementia and Dementia of Other Etiology According to *DSM-IV* and *International Classification of Diseases, 10th edition*; SMI, subjective memory impairment.

[a] Statistically significant.

[b] Subjects with SMI at baseline and MCI at follow-up 1 had greatest risk for dementia and were subcategorized into those having amnestic vs nonamnestic MCI for further analyses.

[c] Cognitive domain of the Structured Interview for Diagnosis of Dementia of Alzheimer Type, Multi-Infarct Dementia and Dementia of Other Etiology According to *DSM-IV* and *ICD-10*, with a maximum score of 55.

[d] Scores exceeding 6 indicate evidence of a clinically relevant depressive episode.

without worry. Subjective memory impairment without worry was independently associated with increased risk for dementia. This risk was roughly doubled by the presence of SMI-related worry. These results extend findings of an earlier study[19] that combined subjects having SMI with or without worry in its prediction models. The associated risk of SMI with or without worry was approximately twice as great for dementia in AD compared with any dementia. Our data suggest that beyond factors affecting one's own experience of memory decline (such as depression and education[17]), SMI may reflect initial impairment specifically related to the clinical manifestations of AD. Because subjects with impairment on baseline testing were excluded in this study, our data support the concept of SMI as a pre-MCI condition in AD. Furthermore, the risk increase associated with SMI-related worry indicates that this early memory decline in AD may vary and may be more subjectively dramatic than memory decline related to other factors such as normal aging even among subjects with equal performance on testing. The risk increase with SMI-related worry is in agreement with reports on severity of impairment associated with cognitive decline.[31,32] The sensitivity and specificity for conversion to dementia in AD among subjects having SMI with worry at baseline were 69.0% and 74.3%, respectively, in our study. Therefore, cross-sectional evaluation of SMI in association with appraisal of worry improves the risk assessment for dementia in AD but might be insufficient to predict the first clinical manifestation of AD.

In the second analysis of this study, a priori–defined temporal sequences of SMI and later MCI were tested with regard to the risk for subsequent dementia. Compared with no SMI at baseline and no impairment at follow-up, SMI at baseline and no impairment at follow-up (reflecting stable cognitive function) was associated with a trend toward increased risk for dementia. Development of MCI at follow-up 1 without SMI at baseline was associated with increased risk for dementia at follow-up 2, which is in agreement with other findings on MCI as a predictor of dementia.[33] However, greatest risk for dementia was observed in subjects with SMI at baseline and with MCI at follow-up 1. At follow-up 2, the risk for conversion to any dementia was increased by an OR of 8.92, while the risk for conversion to dementia in AD was increased by an OR of 19.33. Results of MCI studies[34,35] suggested that amnestic MCI is more predictive of future dementia in AD than nonamnestic MCI. Therefore, we classified the group of subjects with SMI at baseline into those with amnestic vs nonamnestic MCI at follow-up 1. Greatest risk for conversion to any dementia (OR, 29.24) was observed in subjects with SMI at baseline and with amnestic MCI at follow-up 1. The risk was even greater (OR, 60.28) for conversion to dementia in AD at follow-up 2.

The number of subjects developing incident dementia in AD was much greater among subjects with SMI at

baseline and with amnestic MCI than among those without SMI at baseline. However, the significance of this finding could not be tested because of few subjects in the analysis. The overrepresentation of subjects with predementia AD among those with SMI at baseline and with amnestic MCI at follow-up is further evidenced by the high frequency of the *ApoE4* genotype in this group. Overall, these data provide strong empiric support for the recently suggested model of SMI as a pre-MCI syndrome in the clinical manifestation of AD.[30,36]

The hypothesis that SMI is the correlate of mild pre-MCI cognitive decline is supported in our data by baseline SISCO scores, which are lowest in the group with highest risk for dementia in AD (subjects with SMI at baseline and with amnestic MCI at follow-up 1). However, none of the subjects fulfilled criteria for MCI at baseline.

The sensitivity and specificity for conversion to dementia in AD among subjects with SMI at baseline and with amnestic MCI at follow-up were 66.7% and 98.3%, respectively. This may qualify SMI with later MCI as an individual predictor of dementia in AD. The value of this longitudinally defined syndrome is its high specificity, distinct from cross-sectional MCI definitions that are sensitive for future dementia but which lack high specificity.[37,38]

Biologic markers such as brain imaging of amyloid or brain volume measurement are also limited with regard to specificity for dementia because older subjects may show evidence of AD (eg, amyloid deposition) without cognitive impairment.[39] It is unresolved whether these subjects will eventually develop cognitive impairment and dementia. However, the combination of MCI and biologic indicators of AD increase specificity for future dementia.[3,40]

The present data contribute to the current efforts toward a predementia diagnosis of AD. We suggest that biomarker studies (such as magnetic resonance imaging, positron emission tomography, and cerebrospinal fluid investigations) should address not only MCI but also earlier SMI, as performed in some studies.[14,15] We also suggest enhancing the specificity of clinical syndromes for future dementia by successive testing, with incorporated SMI assessment. Eventually, future studies will need to evaluate the usefulness of SMI in combination with less invasive and less expensive biologic markers (such as plasma amyloid) for screening purposes.

The age of our study subjects was advanced. Other investigations on SMI and the risk for dementia have included younger subjects. However, because of methodologic differences, direct comparison of studies is limited. One study[41] assessed the risk for dementia by SMI among different age groups and found greater risk among younger subjects (65-75 years) than among older subjects. This age gradient of risk requires further investigation in population-based and clinical samples.

This study has limitations. Because of the a priori definition of different courses of SMI and MCI and the distinction between dementia in AD and vascular dementia, there are few incident cases in some analyses. However, the ORs and the lower limits of the CIs are high in the respective conditions, suggesting clear effects.

The neuropsychological assessment in this study was performed using the SISCO score, which is designed to identify impairment in different cognitive domains. The strength of the SISCO score is the availability of normative data in this age cohort. However, it is not an instrument for in-depth testing, and subtle deficits in specific domains of cognition may be missed. Despite this limitation, the risk for dementia associated with impairment defined by the SISCO score is plausible and suggests sufficient sensitivity to detect relevant cognitive deficits.

Etiologic case definition was based on the interview and neuropsychological test results and included some subjects with dementia diagnosis based only on an informant and the judgment of a GP. The validity of case definition is supported by the temporal sequence model of the manifestation of AD from SMI via MCI to dementia in this study. No significant associations were observed for vascular dementia, which further supports the validity of the diagnostic categorizations. In exploratory analyses after exclusion of those cases defined by an informant and the judgment of a GP only, all associations remained or became stronger. However, the reduced number of subjects increased the size of the CI.

In this study, SMI was not assessed extensively. Future evaluation of SMI in conversion to dementia may identify specific profiles of SMI that are particularly predictive. These investigations should include nonmemory domains to test whether a particular association of SMI is more predictive than the proposed concept of subjective cognitive impairment.[30]

As a subjective condition, experience and judgment of memory decline in SMI may be affected by factors such as education and depressive symptoms. Not all subjects with subsequent dementia will experience or report SMI at the pre-MCI stage. This explains the limited sensitivity of SMI with regard to the prediction of dementia. However, if SMI is present in a subject without cognitive impairment as evidenced by neuropsychological test results, it may inform about the risk for dementia and may contribute to individual decisions about diagnostic procedures and interventions to lower the risk factors for AD based on current knowledge.

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Announcement

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Archives of General Psychiatry is introducing a new feature, Readers Reply, which will publish online readers' discussions of articles published in the *Archives*. We hope that this opportunity will stimulate interactions not only between readers and the authors but also among the readers. Letters can be submitted electronically via the Readers Reply link that appears on the right side of the article's full-text page. Letters that are submitted directly to the *Archives* for consideration for print and online (archival) publication but are not accepted (as space constraints limit our ability to publish most letter submissions) will be returned to the authors for their submission to Readers Reply.

We are pleased to announce the appointment of Peter Siekmeier, MD, MS, who will serve as the editor of Readers Reply. Dr Siekmeier received his BSE from Princeton University, an MS from Massachusetts Institute of Technology, and an MD from Yale University and completed his residency training in psychiatry at the Massachusetts General Hospital–McLean Program.

We hope that this new feature further increases the scientific impact of the *Archives*.