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AD dementia risk in late MCI, in early MCI, and in subjective memory impairment

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Abstract

Objective: To compare the risk of developing Alzheimer's disease (AD) dementia in late mild cognitive impairment (LMCI), early MCI (EMCI), and subjective memory impairment (SMI) with normal test performance.

Methods: The baseline sample (n = 2892) of the prospective cohort study in nondemented individuals (German Study on Aging, Cognition and Dementia in Primary Care Patients) was divided into LMCI, EMCI, SMI, and control subjects by delayed recall performance. These groups were subdivided by the presence of self-reported concerns associated with experienced memory impairment. AD dementia risk was assessed over 6 years.

Results: Across all groups, risk of AD dementia was greatest in LMCI. In those with self-reported concerns regarding their memory impairment, SMI and EMCI were associated with a similarly increased risk of AD dementia. In those subgroups without concerns, SMI was not associated with increased risk of AD dementia, but EMCI remained an at-risk condition.

Conclusions: SMI and EMCI with self-reported concerns were associated with the same risk of AD dementia, suggesting that pre-LMCI risk conditions should be extended to SMI with concerns.

Keywords: Mild cognitive impairment; Subjective memory impairment; Alzheimer's disease dementia; Prospective cohort study; Risk

1. Introduction

Defining at-risk stages of dementia resulting from Alzheimer's disease (AD) is crucial for biomarker-based predementia AD detection, which in turn is the requirement for future predementia AD treatment [1,2]. The Alzheimer's Disease Neuroimaging Initiative (ADNI) and other large-scale multicenter studies have demonstrated that individuals with mild cognitive impairment (MCI) are at increased risk of developing AD dementia, particularly if they display biomarker evidence of AD [3–5]. MCI in these studies is defined as amnestic MCI by reported memory concerns, memory impairment on standard tests, absence of significant impairment in activities of daily living, and the absence of dementia

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[6]. Impairment on cognitive testing is usually defined as performance below 1.5 standard deviations (SD) of the age-, sex- and education-adjusted normative mean in a standardized test. In the attempt to define an even earlier point in time for disease detection, the recent extensions of ADNI (ADNI go, ADNI 2) have introduced the distinction of MCI into early and late MCI. Late MCI (LMCI) refers to the original definition (performance of 1.5 SD below the normative mean), whereas in early MCI (EMCI), impairment is defined as performance between 1.0 SD and 1.5 SD below the normative mean on a standard test [7].

Epidemiologic studies further propose that the pure report of memory impairment with normal cognitive performance (subjective memory impairment [SMI]) is an at-risk condition of developing AD [8–10]. It has been shown that SMI with self-reported concerns (worries) is associated with a two-fold risk of AD dementia in comparison with SMI without concerns [9].

In the study presented here, we investigate the risk of AD dementia over 6 years for the three categories LMCI, EMCI, and SMI. In addition, we tested the risk of AD dementia in these groups after subdivision based on the presence of self-reported concerns associated with experienced memory impairment. The investigation was performed within the German study on Aging, Cognition and Dementia in primary care patients (AgeCoDe).

2. Methods

2.1. Participants

The AgeCoDe study is a general practice (GP) registry-based longitudinal study in elderly individuals designed to identify predictors of cognitive decline and dementia [11,12]. The study recruitment was undertaken in six German cities (Bonn, Dusseldorf, Hamburg, Leipzig, Mannheim, and Munich) with a total of 138 GPs connected to the study sites. The inclusion criteria for this study were an age of 75 years and older, absence of dementia according to GP judgment, and at least one contact with the GP within the past 12 months. Exclusion criteria were GP consultations by home visits only, living in a nursing home, severe illness with an anticipated fatal outcome within 3 months, language barrier, deafness or blindness, and lack of ability to provide informed consent. Baseline recruitment was performed in 2002 and 2003.

The study was approved by the local ethical committees of the Universities of Bonn, Hamburg, Dusseldorf, Heidelberg/Mannheim, and Leipzig, and the Technical University of Munich.

A total of 3327 subjects provided informed consent for participation after being provided with a complete description of the study protocol. The study assessments were performed by trained interviewers at the subjects' home. Seventy individuals were excluded after baseline interview because of the presence of dementia according to standard assessment, and 40 subjects were excluded for age less than 75 years. For the current analysis, 16 subjects were excluded as a result of a lack of follow-up information on conversion to dementia, and 171 subjects were excluded as a result of conversion to non-AD dementia because the focus of the current analysis was on AD dementia only. In addition, 24 subjects were excluded because of incomplete neuropsychological test data for classification into subgroups of SMI and EMCI and LMCI. Because we also included the apolipoprotein E genotype (*APOE*) in the analyses, another 114 subjects without information on *APOE* status were excluded. After exclusion of these subjects, 2892 individuals remained in the database for analysis.

Four follow-up visits with 18-month intervals were the basis for the analyses. The personal interview rates and the rates of informant-only information (described later), respectively, at follow-up were 2503 and 389 at follow-up 1 (100% total), 2215 and 286 at follow-up 2 (86.5% total), 1797 and 409 at follow-up 3 (76.3% total), and 1509 and 225 (60.0% total) at follow-up 4. The main reasons for lack of follow-up and informant-only information were incident dementia and death. Also, those subjects with only informant-based information at one follow-up were excluded from further follow-ups.

2.2. Assessment procedures

SMI was assessed by the question: Do you feel like your memory is becoming worse? Possible answers were no; yes, but this does not worry me; and yes, this worries me. The expression of worries was rated as self-reported concerns to stay in accordance with the nomenclature of the current MCI definition.

Neuropsychological assessment included the Structured Interview for Diagnosis of Dementia of Alzheimer type, Multi-infarct Dementia and Dementia of other Aetiology according to the *Diagnostic and Statistical Manual of Mental Disorders,* version IV (DSM-IV) and the International Classification of Diseases, version 10 (ICD-10) (SIDAM) [13]. The SIDAM is specifically designed to diagnose dementia according to the named criteria. It contains a 55-item neuropsychological test battery, a 14-item scale for the assessment of activities of daily living (ADL; SIDAM-ADL scale), and the Hachinski Rosen Scale. The neuropsychological battery includes the Mini-Mental State Examination.

The verbal memory test of the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) neuropsychological battery (10-item word list, three presentations, delayed recall after 10 minutes) [14] was administered during all assessments. Subjects also performed the semantic verbal fluency task of the CERAD battery. Depressive symptoms were assessed with the 15-item version of the Geriatric Depression Scale [15].

Level of education was classified by the Comparative Analysis of Social Mobility in Industrial Nations classification system into low, middle, and high [16].

For those subjects, who could not be interviewed in person at follow-up, the Global Deterioration Scale [17] and the Blessed Dementia Rating Scale [18] were completed by the interviewer with an informant and with the GP.

2.3. Definition of LMCI, EMCI, and SMI at baseline

The CERAD verbal memory delayed recall performance was used to define the level of impairment at baseline. Independent age-, sex-, and education-adjusted German normative data for this test are available (www.memoryclinic.ch). The groups were classified as follows: LMCI, reported memory impairment (memory has become worse) and performance on the CERAD delayed recall task of more than 1.5 SD below the normative mean; EMCI, between 1.5 SD and 1.0 SD below the normative mean; or SMI, less than 1.0 SD below the normative mean. In addition, all groups were subdivided by the association of self-reported concerns (worries) with regard to the reported memory impairment. Individuals without the report of memory impairment and with a performance of less than 1.0 SD below the normative mean on the CERAD delayed verbal recall task served as the reference group (control subjects [CO] group). Subjects without the report of memory impairment but with a performance below 1.0 SD of the normative mean on the CERAD delayed verbal recall task (n = 359) were not considered for the primary analyses because they neither met the criteria of MCI or SMI nor of the CO. They were only included in a secondary exploratory analysis (discussed later).

Applying these classification rules, 358 subjects were classified as having LMCI; 251 subjects, EMCI; 1061 subjects, SMI; and 863, CO (total, 2533).

Subgroup classification was performed post hoc during data analysis and was not fed back to interviewers. Interviewers thus were unaware of group membership, ruling out surveillance bias in the detection of incident dementia across the groups.

2.4. Definition of dementia at follow-up

Dementia was diagnosed in a consensus conference with the interviewer and an experienced geriatrician or geriatric psychiatrist according to the criteria set of DSM-IV, which is implemented as a diagnostic algorithm in the SIDAM. The etiological diagnosis of dementia in AD was established according to the National Institute of Neurological and Communicative Diseases and Stroke/Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria for probable AD [19]. Mixed dementia was diagnosed in cases of cerebrovascular events without temporal relationship to cognitive decline. For all analyses, mixed dementia and dementia in AD were combined. Dementia diagnosis in subjects who were not interviewed personally was based on the Global Deterioration Scale (score $\geq$4 points). In these cases, an etiological diagnosis was established if the information provided was sufficient to judge etiology according to the criteria just described.

2.5. Statistical analyses

Multivariate Cox proportional hazard regression analyses were performed to evaluate the influence of selected predictors on the time to onset of AD dementia. The predictors were group membership (LMCI, EMCI, SMI, or CO), age, sex, education (low, medium, high), depressive symptoms (Geriatric Depression Scale scores $<$6 points or $\geq$6 points), and *APOE* ε4-status.

We performed three separate analyses. The first analysis was performed with the total sample (n = 2533). During the second analysis, we restricted the sample to the LMCI, EMCI, and SMI groups with self-reported concerns plus the CO group (n = 1327). The third analysis was performed in the LMCI, EMCI, and SMI groups without concerns plus the CO group (n = 2069).

For the exploratory assessment of the difference in risk between the SMI group and the other two groups of interest (LMCI, EMCI) all analyses were also performed with the SMI group as the reference instead of the CO group.

To describe further the relevance of the subjective report, an exploratory analysis was performed in which subjects without report of impairment, but below normal performance on verbal delayed recall (EMCI–noSMI, between 1.0 SD and 1.5 SD below the normative mean; LMCI–noSMI, below 1.5 SD of the normative mean) were integrated in the model of the second analysis (subjects with self-reported concerns). We chose the model of the second analysis to include both "ends" of subjective report (ie, no report on impairment and reported impairment with concerns).

3. Results

The number of subjects excluded at follow-up 1, follow-up 2, follow-up 3, and follow-up 4, respectively, were in 0, 125, 82, and 143 (n = 350) in the CO group; 0, 111, 99, and 160 (n = 370) in the SMI group; 0, 33, 27, and 40 (n = 100) in the EMCI group; 0, 57, 43, and 69 (n = 169) in the LMCI group; 0, 34, 17, and 19 (n = 70) in the EMCI–noSMI group; and 0, 31, 27, and 41 (n = 99) in the LMCI–noSMI group. The number of conversions to AD dementia at follow-up 1, follow-up 2, follow-up 3, and follow-up 4, respectively, were in 0, 6, 15, and 11 (n = 32; rate of conversion, 3.7%) in the CO group; 4, 17, 22, and 23 (n = 66; rate of conversion, 6.2%) in the SMI group, 2, 7, 11, and 7 (n = 27; rate of conversion, 10.8%) in the EMCI group; 26, 24, 24, and 15 (n = 89; rate of conversion, 24.9%) in the LMCI group; 0, 2, 1, and 1 (n = 4; rate of conversion, 2.5%) in the EMCI–noSMI group; and 7, 4, 5, and 8 (n = 24; rate of conversion, 12.1%) in the LMCI–noSMI group.

The descriptive data of the analyses are listed in Table 1. The number of incident AD cases with respective hazard

Table 1
Sample description for all groups—CO, SMI, EMCI, LMCI—with and without concerns

Sample	Characteristics	CO	SMI	EMCI	LMCI	All	Group differences
Total sample	n	863	1061	251	358	2533	
	Age, years (mean, SD)	79.7 (3.47)	79.8 (3.48)	79.4 (3.79)	79.9 (3.93)	79.7 (3.58)	
	Female, n (%)	584 (67.7)	618 (58.3)	162 (64.5)	277 (77.4)	1641 (64.8)	* † ‡ § * ‖
	Level of education						
	Low, n (%)	530 (61.4)	604 (56.9)	167 (66.5)	229 (64)	1530 (60.4)	
	Middle, n (%)	249 (28.9)	308 (29)	60 (23.9)	96 (26.8)	713 (28.1)	
	High, n (%)	84 (9.7)	149 (14)	24 (9.6)	33 (9.2)	290 (11.4)	
	Depressive symptoms,¶ n (%)	41 (4.8)	98 (9.2)	24 (9.6)	58 (16.2)	221 (8.7)	* † ‡ § **
	APOE ε4+, n (%)	163 (18.9)	210 (19.8)	44 (17.5)	100 (27.9)	517 (20.4)	† ‡ §
Subjects with concerns only	n	863	261	70	133	1327	
	Age, years (mean, SD)	79.7 (3.47)	79.6 (3.42)	78.7 (3.05)	79.7 (4.22)	79.6 (3.52)	
	Female, n (%)	584 (67.7)	180 (69.0)	46 (65.7)	110 (82.7)	920 (69.3)	‡ §
	Level of education						* †
	Low, n (%)	530 (61.4)	162 (62.1)	50 (71.4)	86 (64.7)	828 (62.4)	
	Middle, n (%)	249 (28.9)	61 (23.4)	15 (21.4)	33 (24.8)	358 (27.0)	
	High, n (%)	84 (9.7)	38 (14.6)	5 (7.1)	14 (10.5)	141 (10.6)	
	Depressive symptoms,¶ n (%)	41 (4.8)	49 (18.8)	13 (18.6)	30 (22.6)	133 (10.0)	* † **
	APOE ε4+, n (%)	163 (18.9)	54 (20.7)	10 (14.3)	40 (30.1)	267 (20.1)	† ‡ §
Subjects without concerns only	n	863	800	181	225	2069	
	Age, years (mean, SD)	79.7 (3.47)	79.8 (3.5)	79.7 (4.02)	80.0 (3.76)	79.8 (3.56)	
	Female, n (%)	584 (67.7)	438 (54.8)	116 (64.1)	167 (74.2)	1305 (63.1)	* ‡ § ‖ * ‡
	Level of education						
	Low, n (%)	530 (61.4)	442 (55.3)	117 (64.6)	143 (63.6)	1232 (59.5)	
	Middle, n (%)	249 (28.9)	247 (30.9)	45 (24.9)	63 (28.0)	604 (29.2)	
	High, n (%)	84 (9.7)	111 (13.9)	19 (10.5)	19 (8.4)	233 (11.3)	
	Depressive symptoms,¶ n (%)	41 (4.8)	49 (6.1)	11 (6.1)	28 (12.4)	129 (6.2)	† ‡ §
	APOE ε4+, n (%)	163 (18.9)	156 (19.5)	34 (18.8)	60 (26.7)	413 (20.0)	† ‡

Abbreviations: CO, control group; SMI, subjective memory impairment; EMCI, early mild cognitive impairment; LMCI, late mild cognitive impairment; SD, standard deviation; *APOE* ε4, apolipoprotein E4.

*Group differences ($P < .05$, adjusted for multiple comparisons): CO vs SMI.

†Group differences ($P < .05$, adjusted for multiple comparisons): CO vs LMCI.

‡Group differences ($P < .05$, adjusted for multiple comparisons): SMI vs LMCI.

§Group differences ($P < .05$, adjusted for multiple comparisons): EMCI vs LMCI.

‖Group differences ($P < .05$, adjusted for multiple comparisons): SMI vs EMCI.

¶Depressive symptoms were defined as a score of ≥6 points on the Geriatric Depression Scale.

**Group differences ($P < .05$, adjusted for multiple comparisons): CO vs EMCI.

ratio (HR) for each group throughout the course of the study are listed in Table 2. For the entire sample, the AD dementia risk in subjects with LMCI was increased (HR, 7.27; $P < .001$). The risk was increased also in subjects with EMCI (HR, 3.10; $P < .001$) and with SMI (HR, 1.55; $P = .04$) in comparison with the control subjects. Figure 1A shows the survival curves. In addition, age (HR, 1.13; $P < .001$) and positive *APOE* ε4 carrier status (HR, 1.88; $P < .001$) were associated with an increased risk of AD dementia. With the SMI group as the reference group, both LMCI (HR, 4.69; $P < .001$) and EMCI (HR, 2.0; $P = .003$) were associated with a significantly greater risk of AD dementia.

In the second analysis, all three categories were restricted to those participants reporting concerns regarding their memory impairment. In this analysis, the risk of AD dementia was increased in the LMCI group (HR, 11.13; $P < .001$). The EMCI group (HR, 2.46; $P = .06$) and the SMI group (HR, 2.44; $P = .001$) showed a very similar increase in risk. The increase in risk in the EMCI group did not reach significance, most likely because of the limited size of the group (Fig. 1B). In this analysis there was also an increased risk of AD dementia associated with greater age (HR, 1.15; $P < .001$) and with positive *APOE* ε4 carrier status (HR, 2.2; $P < .001$). Compared with the SMI group, there was a difference in risk of incident AD dementia in the LMCI group (HR, 4.56; $P < .001$), but not in the EMCI group (HR, 1.01; $P = .99$).

In the third analysis, all three categories were restricted to subjects who reported no concerns regarding their memory impairment. Here, the risk of incident AD was increased in LMCI (HR, 5.64; $P < .001$) and EMCI (HR, 3.35; $P < .001$), but not significantly in the SMI group (HR, 1.25; $P = .343$) (Fig. 1C). Age (HR, 1.14; $P < .001$) and positive *APOE* ε4 carrier status (HR, 1.72; $P = .004$) were also associated with a greater risk of incident AD dementia. In addition, depressive symptoms (HR, 1.81; $P = .025$) were associated with increased risk of incident AD dementia in this analysis. When the SMI group was treated as the reference group, both LMCI (HR, 4.51; $P < .001$) and EMCI (HR, 2.67; $P \< .001$) were associated with a greater risk of incident AD dementia.

Table 2
Conversion to Alzheimer's disease for different risk groups

Sample	Incident AD dementia	CO	SMI	EMCI	LMCI	All
Total sample (first analysis)	Cases in each group, n	863	1061	251	358	2533
	Conversion to AD dementia, n (%)	32 (3.7)	66 (6.2)	27 (10.8)	89 (24.9)	214 (8.4)
	Risk,* hazard ratio (CI)	1.0	1.55 (1.02–2.37)	3.1 (1.86–5.18)	7.27 (4.82–10.97)	—
Subjects with concerns only (second analysis)	Cases in each group, n	863	261	70	133	1327
	Conversion to AD dementia, n (%)	32 (3.7)	25 (9.6)	5 (7.1)	45 (33.8)	107 (8.1)
	Risk, * hazard ratio (CI)	1.0	2.44 (1.44–4.14)	2.46 (0.95–6.36)	11.13 (6.92–17.89)	—
Subjects without concerns only (third analysis)	Cases in each group, n	863	800	181	225	2069
	Conversion to AD dementia, n (%)	32 (3.7)	41 (5.1)	22 (12.2)	44 (19.6)	139 (6.7)
	Risk,* hazard ratio (CI)	1.0	1.25 (0.79–2.0)	3.35 (1.94–5.77)	5.64 (3.55–8.97)	—

Abbreviations: CO, control subjects group; SMI, subjective memory impairment; EMCI, early mild cognitive impairment; LMCI, late mild cognitive impairment; AD, Alzheimer's disease; CI, confidence interval.

*Risk in comparison with CO. Covariates: age, sex, education (low, medium, high), depressive symptoms (Geriatric Depression Scale scores <6 points or ≥ 6 points), and apolipoprotein E4 status.

In an exploratory analysis, we included the groups of EMCI-noSMI and LMCI-noSMI in the second model (individuals with concerns). Four subjects (2.5%) in the EMCI-noSMI group and 24 subjects (12.1%) in the LMCI-noSMI group converted to AD dementia. In comparison with the CO group, the risk of AD dementia for EMCI-noSMI was not increased (HR, 0.85; $P = .765$), whereas the risk for LMCI-noSMI was increased (HR, 3.87; $P < .001$).

4. Discussion

We tested the risk of AD dementia in a large sample of dementia-free elderly subjects who were categorized into three groups according to their baseline report on subjectively experienced memory performance and their performance in a verbal memory task. These categories were (*i*) LMCI defined by the report on memory impairment and performance on delayed verbal recall below 1.5 SD of the norm, (*ii*) EMCI defined by the report on memory impairment and performance on delayed verbal recall between 1.0 SD and 1.5 SD below the norm, and (*iii*) SMI defined by the report on memory impairment with performance on delayed verbal recall within the norm (better than 1.0 SD below the normative mean). The distinction of LMCI and EMCI was made specifically because these two stages of MCI have recently been proposed, and EMCI is now used as an inclusion criterion in early AD recognition studies (eg, ADNI [7]. The rationale for this approach is to move the biomarker-based identification of AD in individuals to an even earlier point in time before the originally used definition of MCI, which is now termed LMCI. The reference in our analysis was individuals who reported no memory impairment and who performed within the unimpaired range (better than 1.0 SD below the normative mean) on delayed verbal recall.

Across all individuals, we observed increasing risk of AD dementia in an ordered fashion, with highest risk in LMCI followed by EMCI and SMI. This result substantiates the concept of MCI as a risk factor of AD and shows that risk increases with increasing levels of impairment [20].

In a second analysis, we restricted the groups to those who reported memory impairment and were associated with self-reported concerns. This approach was chosen because LMCI and EMCI are defined by the presence of impairment on tests and by reported concerns regarding memory impairment (http://adni.loni.ucla.edu/) [6]. The second reason for restricting the analysis to subjects with self-reported concerns relates to the finding of a doubling in risk of AD dementia in SMI with self-reported concerns (worries) compared with SMI without concerns [9]. In this analysis, subjects with LMCI had a very high risk of incident AD dementia. Subjects with SMI and normal performance, however, had the same risk of incident AD dementia as subjects with EMCI. Thus, if both the SMI and EMCI groups report memory impairment with concerns, the fact that the subjects with EMCI performed between 1.0 SD and 1.5 SD below the norm on verbal delayed recall had no additional effect on the risk of AD dementia in our data. This suggests that a categorical definition of minimal impairment (EMCI) is of limited sensitivity and specificity to detect individuals at the earliest disease stages. The lack of sensitivity is most likely associated with misclassification of high-performing subjects as normal. The lack of specificity is caused by false classification of actually unimpaired subjects as impaired, who perform poorly in a particular testing situation. To the contrary, the subjective report on impairment, which is present in both SMI and EMCI, reflects the overall longitudinal development of cognitive performance within the recent time and may be a more robust indicator of minor changes than a single time point measurement.

In the third analysis, which was restricted to individuals who report memory impairment but not associated concerns, the effect was different. Here, individuals with SMI were only at a mild, nonsignificant increased risk of AD dementia compared with the CO group. In contrast, individuals with LMCI and EMCI were still at increased risk of AD dementia. It needs to be pointed out that, in this case, LMCI and EMCI definitions differed from the currently proposed MCI definitions (http://adni.loni.ucla.edu/) [6] because those require concerns associated with experienced memory impairment.

The second and third analyses show that SMI becomes predictive only if the self-evaluation of the experienced impairment causes concerns. If the experienced impairment was evaluated by the individuals as being of no concern, there was no prediction of dementia. This suggests that SMI without concerns may actually correspond to normal age-associated decline [21] rather than to the first manifestation of AD. The concept of concerns regarding the experienced impairment is most likely different from an increased intensity of perceived impairment. One study found that subjective impairment was associated with cognitive decline; the increasing intensity of the experienced impairment assessed through a self-report questionnaire, however, did not contribute further to the prediction of decline [22]. The presence of concerns was not assessed explicitly in this study.

The results of our study suggest that explicitly assessed self-reported concerns have predictive value. This suggests that if SMI corresponds to initial disease manifestation, the specific characteristic of experienced memory impairment might be different from normal aging and therefore cause such concerns. If this assumption was true, it might explain the discrepant findings in SMI in the prediction of cognitive decline and dementia across studies (prediction or no prediction) [23] because most studies do not address the specific self-evaluation of SMI (eg, association with concerns), but address SMI in general [24].

We found a higher rate of depressive symptoms in all groups with concerns associated with SMI compared with those with no concerns associated with SMI or without SMI at all. We accounted for this statically in the analyses and it did not change the effects of SMI on prediction of AD dementia. However, the slightly increased level of depressive symptoms may also represent a very early sign of AD [25].

Conceptually, our data strengthen the importance of the subjective experience of memory impairment in dementia prediction. As pointed out earlier, the subjective experience and evaluation of memory impairment (concerns) may actually be an indicator of early disease-related impairment. As an indicator of longitudinal change, it adds information to the cross-sectional measures of performance obtained by tests. Accordingly, it has been shown that SMI and objective measures of cognitive performance both contribute independently to dementia prediction, and that the prediction is improved by the combination of both rather than either one alone [26]. This is of particular importance for prediction models because not all individuals with cognitive impairment report SMI [27]. It can be speculated that the predictive power of the subjective report of AD dementia increases, and the predictive power of objective cognitive test performance decreases, as prediction moves to the earliest disease stages. This assumption is supported by the lack of risk increase of AD dementia in individuals with very mild performance impairment (1.0–1.5 SD below the norm), but without the report on memory impairment (EMCI-noSMI) in opposition to the risk increase in subjects with SMI and concerns but normal performance on testing. The greater relevance of subjective report rather than of test measures at the earliest symptomatic stage of AD may be related to effects of compensation. At this early disease stage, increased compensatory neuronal effort may facilitate still normal performance on tests, but may be experienced subjectively and interpreted as evidence for impairment [28].

Obviously, SMI with concerns alone or in combination with cognitive testing is not sufficient for individual prediction of AD dementia. It has, however, great heuristic value for identification of subjects, which may undergo biomarker-based predementia AD detection [29].

On a practical level, our data suggest that current biomarker-based early disease recognition research (such as ADNI) should consider expansion from EMCI to SMI with concerns because these subjects carry a similar risk of AD dementia as subjects with EMCI. By keeping the requirement for minor cross-sectional impairment on tests (EMCI), those subjects who are classified falsely as not impaired will be missed (eg, those with high premorbid performance levels or with very effective compensatory mechanisms). For these individuals, however, early disease recognition may be of the highest value because they are still at a largely normal level of function.

Our exploratory analysis also showed that individuals with slight memory impairment without subjective report (EMCI-noSMI) had no increased risk of future AD dementia, but those with more severe impairment and no subjective report (LMCI-noSMI) were at increased risk. The LMCI-noSMI individuals may represent a group with cognitive decline resulting from AD pathology, but lack of awareness. One recent fluorodeoxyglucose–positron emission tomography study found evidence that LMCI patients who were unaware of their memory deficits exhibited a more severe and AD-typical hypometabolic pattern than LMCI individuals who were aware of their deficits [30].

This study has limitations. The design of this study is not identical to biomarker-based studies that focus on MCI (eg, ADNI). The participants in our study are not seen in specialist centers, but rather resemble a population-based sample. In addition, the neuropsychological and clinical assessments were not extensive. It has been demonstrated in other studies that the stage of pre-MCI may also be associated with very mild impairment in executive function and increased apathy scores [31], which were not addressed specifically in this study.

One potential confound may be related to the inclusion criterion of at least one visit in the GP office within the past 12 months. This may exclude very healthy subjects or those who do not go to a GP office. In Germany, however, the vast majority of persons older than 75 years of age visit the GP regularly. Thus, we consider the data externally valid. The high age at entry in the study (average, 80 years) does not allow generalization to younger subjects with SMI, in whom other factors such as psychosocial distress may be of great relevance for the presence of SMI [32]. Because we did not use biomarkers, we applied the NINCDS-ADRDA [19] and

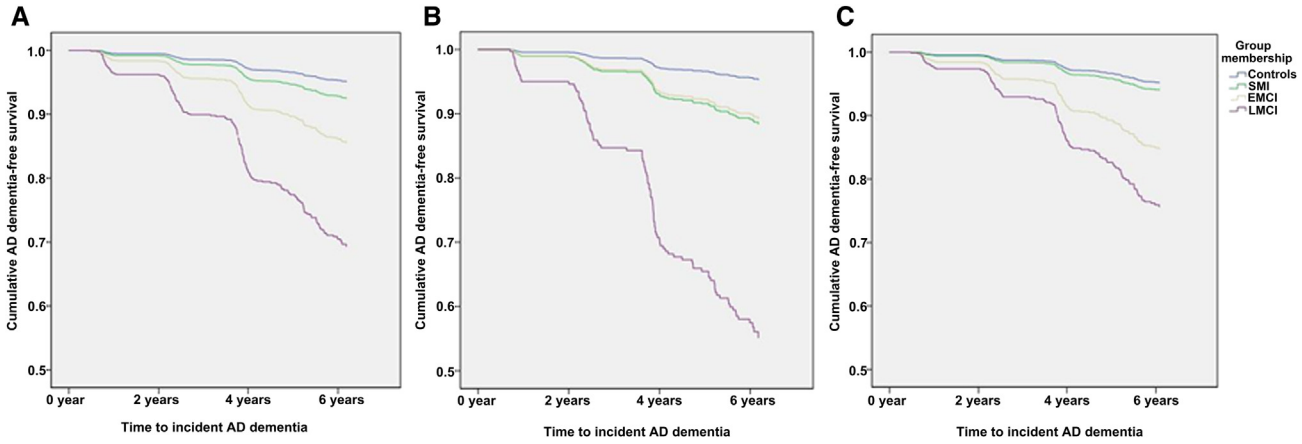

Fig. 1. (A–C) Survival curve across all subjects (A), across all subjects with concerns regarding their experienced memory impairment (B), and across all subjects without concerns regarding their experienced memory impairment (C). AD, Alzheimer's disease; SMI, subjective memory impairment; EMCI, early mild cognitive impairment; LMCI, late mild cognitive impairment.

DSM-IV criteria for AD dementia rather than recently proposed criteria that involve biomarkers [33]. Also, our definition of MCI was restricted to amnestic MCI. It is uncertain how subjective report and performance impairment in other cognitive domains are related to dementia prediction. In a number of cases, only informant-based information could be obtained, mostly because of death or morbidity-related reasons. In an exploratory analysis, we recalculated the models after exclusion of those with informant-based information only. The prediction results were similar across the entire sample (data not shown). Thus, we think that the results are not biased by this approach.

Residual confounding of the data is unlikely because we used well-defined categories for level of education and *APOE* ε4 status. Depressive symptoms were dichotomized according to an established cutoff [34]. In addition, we have also repeated our analyses with the Geriatric Depression Scale as a continuous predictor with similar results (data not shown). Last, the subjective report was based on interview with the participants only. Reports from informants were not considered for classification of SMI.

Overall, our data provide evidence that stages of very mild impairment may not be well captured by standard neuropsychological testing and also highlight the relevance of subjective reports as an indicator of individual change over time and predictor of AD dementia.

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RESEARCH IN CONTEXT

1. Systematic review: We reviewed the literature on prediction of Alzheimer's dementia (AD) by early and late mild cognitive impairment (MCI) and subjective memory impairment (SMI). We included population-based studies and studies on AD biomarkers in clinical samples.
2. Interpretation: Our study shows that SMI without impairment on a standard cognitive test (SMI) but associated with self-reported concerns is as predictive of AD dementia as early MCI defined by SMI plus impairment on a cognitive task of 1.0 to 1.5 standard deviations below the normal range. We conclude that the requirement of very mild impairment on tests is insensitive and that the definition of very early at-risk populations of AD dementia should be extended to SMI.
3. Future directions: The role of SMI as an indicator of early AD and a predictor of AD dementia needs to be evaluated by biomarker studies with long follow-up as it is currently done in early MCI.

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