Memory Concerns, Memory Performance and Risk of Dementia in Patients with Mild Cognitive Impairment

Steffen Wolfsgruber1,2, Michael Wagner1,2, Klaus Schmidtke3, Lutz Frölich4, Alexander Kurz5, Stefanie Schulz6,7, Harald Hampel8, Isabella Heuser9, Oliver Peters9, Friedel M. Reischies9, Holger Jahn10, Christian Luckhaus11, Michael Hüll12, Hermann-Josef Gertz13, Johannes Schröder14, Johannes Pantel15, Otto Rienhoff16, Eckart Rüther7, Fritz Herr17, Jens Wiltfang18, Wolfgang Maier1,2, Johannes Kornhuber19, Christian Luckhaus11, Michael Hüll12, Hermann-Josef Gertz13, Johannes Schröder14, Johannes Pantel15, Otto Rienhoff16, Eckart Rüther7, Fritz Herr17, Jens Wiltfang18, Wolfgang Maier1,2, Johannes Kornhuber19, Frank Jessen1,2

Department of Psychiatry, University of Bonn, Bonn, Germany, 2 German Center for Neurodegenerative Diseases, Bonn, Germany, 3 Center for Geriatric Medicine, Ortenau Klinikum, Offenburg-Gengenbach, Germany, 4 Department of Gerontopsychiatry, Central Institute of Mental Health, Mannheim, Germany, 5 Department of Psychiatry, Technical University of Munich, Munich, Germany, 6 Department of Neurology, University of Aachen, Aachen, Germany, 7 Department of Psychiatry, University of Göttingen, Göttingen, Germany, 8 Department of Psychiatry, Ludwig Maximilian University, Munich, Germany, 9 Department of Psychiatry, Charité Berlin, Campus Benjamin Franklin, Berlin, Germany, 10 Department of Psychiatry, University of Hamburg, Hamburg, Germany, 11 Department of Psychiatry and Psychotherapy, Medical Faculty, Heinrich-Heine-University, Duesseldorf, Germany, 12 Center for Geriatric Medicine and Gerontology, University of Freiburg, Freiburg, Germany, 13 Department of Psychiatry, University of Leipzig, Leipzig, Germany, 14 Department of Psychiatry, University of Heidelberg, Heidelberg, Germany, 15 Institute of General Practice, University of Frankfurt, Frankfurt am Main, Germany, 16 Department of Medical Informatics, University of Göttingen, Göttingen, Germany, 17 Brookhaven National Laboratory, Upton, New York, United States of America, 18 Department of Psychiatry University of Essen, Essen, Germany, 19 Department of Psychiatry, Friedrich-Alexander-University Erlangen, Erlangen, Germany

Abstract

Background: Concerns about worsening memory ("memory concerns"; MC) and impairment in memory performance are both predictors of Alzheimer’s dementia (AD). The relationship of both in dementia prediction at the pre-dementia disease stage, however, is not well explored. Refined understanding of the contribution of both MC and memory performance in dementia prediction is crucial for defining at-risk populations. We examined the risk of incident AD by MC and memory performance in patients with mild cognitive impairment (MCI).

Methods: We analyzed data of 417 MCI patients from a longitudinal multicenter observational study. Patients were classified based on presence (n = 305) vs. absence (n = 112) of MC. Risk of incident AD was estimated with Cox Proportional-Hazards regression models.

Results: Risk of incident AD was increased by MC (HR = 2.55, 95%CI: 1.33–4.89), lower memory performance (HR = 0.63, 95%CI: 0.56–0.71) and ApoE4-genotype (HR = 1.89, 95%CI: 1.18–3.02). An interaction effect between MC and memory performance was observed. The predictive power of MC was greatest for patients with very mild memory impairment and decreased with increasing memory impairment.

Conclusions: Our data suggest that the power of MC as a predictor of future dementia at the MCI stage varies with the patients’ level of cognitive impairment. While MC are predictive at early stage MCI, their predictive value at more advanced stages of MCI is reduced. This suggests that loss of insight related to AD may occur at the late stage of MCI.

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Introduction

The syndrome of mild cognitive impairment [1] (MCI) has been established as a risk state for Alzheimer’s Dementia (AD). Patients with MCI show cognitive impairment objectified by neuropsychological testing while their functional activities are largely intact. In addition, current criteria for MCI [1–3] require report on cognitive decline, provided either by the patient and/or by an informant or clinician who knows the patient well.

Compared to the current knowledge and standards of neuropsychological testing, the criterion of subjective report about cognitive decline in the definition of MCI is less elaborated. It is unknown whether more precise operationalization (either quantitatively or qualitatively) of this criterion may increase the predictive accuracy for AD in MCI patients. In fact, in everyday clinical practice, the criterion of experienced or observed cognitive decline might often be considered fulfilled by the fact that a patient consults the medical system for diagnostic workup of cognitive impairment. Studies that investigated the role of individual and informant reports for the prediction of AD in MCI are rare. One early study [4] found informant reports but not the individual’s memory complaints associated with future AD in memory impaired patients. A recent study [5] in a non-demented elderly community sample found both self and informant reports to be predictive, while in a combined predictive model only informant reports together with neuropsychological tests remained a significant predictor.

Other studies, based on pre-MCI samples, showed elevated risk of future AD [6–8] as well as associations with biomarkers of Alzheimer’s disease in individuals who report self-experienced cognitive decline [9–15]. However, there are also studies that did not find associations of self-reported cognitive decline with either incident AD [16] or biomarkers of Alzheimer’s disease [17,18] in pre-MCI samples. Importantly, comparability of results across studies is limited due to heterogeneity of samples and assessment of self-experienced cognitive decline. Further, it was recently reported that, in individuals with normal cognitive test performance (non-MCI), those who are particularly concerned about their experienced memory decline have a higher risk of developing AD, as compared to those who report a self-experienced memory decline without concerns [19,20]. Thus, the appraisal of the experienced decline as worrying may be of specific predictive value when assessing an individual’s report.

Based on the existing data, the significance of self-reported concerns about worsening memory (hereafter: “memory concerns” [MC]) in MCI is yet unclear and it is largely unknown which factors might influence the report or denial of MC in MCI patients [21,22]. Reduced self-awareness is one factor that might influence the report of MC in this patient group [22]. Self-awareness often becomes impaired during the progression of Alzheimer’s disease. Hence, unawareness (also termed anosognosia) concerning the memory impairment is frequently observed in AD [23]. Reduced self-awareness and anosognosia are also observed in MCI patients [23–25]. However, levels of awareness are heterogeneous among these patients [22]. This might contribute to the fact that MC are not consistently present in patients with MCI [23,24,26].

The heterogeneity in self-awareness may originate from the fact that anosognosia as a core symptom of AD manifests at the stage of MCI and that the likelihood of its occurrence rises with increasing cognitive impairment. Evidence for this assumption comes from studies that investigated self-awareness in patients with AD and patients with amnestic MCI (i.e. with clinical impairment in the memory domain, evidenced by neuropsychological testing [1,2]). Patients with advanced amnestic MCI, scoring lower than two standard deviations (SD) below age-corrected norms on a memory test [24], showed symptoms of anosognosia similarly severe compared to the AD group. In a study on amnestic MCI patients, Nobili and colleagues found that low awareness of memory deficits was associated with more progressed Alzheimer’s disease pathology [27]. Moreover, results from a recent study showed that cognitive complaints decreased with decreasing cognitive performance in MCI patients, while the relationship was opposite (i.e. reported complaints increased with decreasing memory performance) in individuals with only subjective memory impairment but no MCI [18]. These results suggest that, within the stage of MCI, those patients with more severe cognitive impairment tend to have reduced insight into their cognitive deficits.

Based on the empirical evidence a hypothetical model of AD prediction in MCI can be formulated: At the earliest stage of impairment (early MCI) self-awareness of the patient is mostly unaffected. Here, MC should reflect the true self-perceived, longitudinal intra-individual decline and should contribute to AD prediction in addition to cross-sectional impairment on tests. At later stages of MCI, self-awareness is waning and the predictive value of MC is declining. MC as defined in this model comprises two important aspects, i.e. the specific notion of (1) a decline in memory performance and (2) the appraisal of this self-perceived decline as worrying. The appraisal as worrying extends beyond the subjective report about cognitive decline as part of the general MCI criteria and has been found to be of higher predictive value than the notion of a worsening memory without worries [19,20]. This clearly separates the definition of memory concerns in our study from subjective memory decline in general.

In the present study, we tested the proposed model in a sample of MCI patients whose memory impairment ranged from very mild to advanced severity.

Methods

Ethics statement

The protocol of the study was approved by the Institutional Review Board (IRB) of the Medical Faculty, University of...
Participants

Subjects were recruited between 2003 and 2007 at 14 specialized university memory clinics collaborating within the German Dementia Competence Network (DCN). The general procedures for assessment and selection of subjects have been reported in detail previously [28]. Briefly, patients over 50 years of age who were referred to or sought help at one of the participating memory clinics underwent a clinical, neuropsychological and laboratory assessment and brain imaging. Patients with either MCI or mild dementia were asked to participate in this longitudinal observational study.

Clinical and neuropsychological assessment

Patients were assessed annually by experienced physicians and neuropsychologists for up to three years with standardized diagnostic procedures as described in detail previously [28]. This assessment included the neuropsychological test battery of the Consortium to Establish a Registry for Alzheimer’s Disease (CERAD-NP) [29]. The CERAD-NP consists of various subtests, including the Mini Mental State Examination (MMSE) [30], and is specifically designed to assess the cognitive domains most commonly affected in AD. The subtests are (in order of administration) (1) Verbal Fluency, (2) modified Boston Naming Test (15 item version), (3) the MMSE, (4) Word List Learning of a 10-item word list (sum of three learning trials; maximum score of 30), (5) Figure Copying (maximum score of 11), (6) Word List Delayed Recall (maximum score of 10), (7) Word List Recognition (maximum score of 10 or 100%), and (8) Figure Recall (maximum score of 11). We used the Word List Delayed Recall subtest (CERAD-DR) as a measure of objective memory impairment as delayed recall of word lists is considered among the tests that are most sensitive to incipient AD [3]. In addition, high levels of diagnostic accuracy for the CERAD-DR have been reported regarding cross-sectional detection [31] and prediction of AD [32].

Depressive symptoms were rated by the interviewer with the Montgomery Asberg Depression Rating Scale (MADRS) [33]. The MADRS consists of 10 items which are scored from 0 to 6 after a clinical interview. It is well established in psychogeriatric and AD studies [34]. A cut-off score of 13 points is suggested for mild depression. Instrumental activities of daily living were assessed with the Bayer-Activities of Daily Living Scale (BADL), a 25-item, informant-rated questionnaire developed to assess deficits in the performance of everyday activities in patients with MCI or mild-to-moderate dementia [35].

Definition of MCI and incident AD

All diagnoses were established in a consensus conference between physicians and neuropsychologists at each site. The diagnosis of MCI was made according to the consensus criteria proposed in 2004 by the International Working Group on MCI [2]: (1) subjective and/or informant report about cognitive decline, (2) evidence of an impairment on objective cognitive test, (3) no or only minor impairments in instrumental activities of daily living (BADL score <4), and (4) not demented. Criterion (2) was met if patients showed a cognitive deficit of more than 1SD below age- and education-adjusted norms in at least one subtest of the CERAD-NP battery or in the Wechsler-Memory-Scales Logical Memory II subtest. The diagnosis of incident AD was made according to the NINCDS/ADRDA criteria for probable Alzheimer’s disease [36].

Classification of participants into “MCI with memory concerns” vs. “MCI without memory concerns”

Patients were classified as “MCI with memory concerns” (MC+) or “MCI without memory concerns” (MC-) according to their response to the following standardized question [6]: “Do you feel like your memory has become worse?”. Possible answers were: (1) “No”, (2) “Sometimes, but this does not worry me”, (3) “Yes, that worries me”, (4) “Yes, that worries me seriously”. Answers (1) and (2) were combined to the MC- and answers (3) and (4) to the MC+ group, respectively.

The question and response categories were read aloud to patients by the interviewer as part of the initial assessment prior to neuropsychological testing. Duration of MC was not assessed in this study.

The standardized question on memory concerns was not used for the initial diagnosis of MCI but only for division into groups of MC+ and MC- patients respectively. The criterion of subjective report on cognitive decline required for the diagnosis of MCI could be provided either by the subject and/or by an informant according to the criteria of the International Working Group on MCI [2]. Thus the MC+ group constitutes a subgroup of MCI patients who themselves, when questioned in person with a standardized item, report memory decline which they appraise as particularly worrying. MC as operationalized here thus extend beyond the subjective report about cognitive decline as part of the general MCI criteria. Patients in the second response category “sometimes, but this does not worry me” were therefore assigned to the MC- group. We also refrained from keeping the four categories separate as this would have prevented the detailed analysis and straightforward interpretation of moderating effects between categorical (MC+ vs. MC-) and continuous (memory performance) variables, also due to limited number of participants answering “No” to the question on experienced memory decline.

However, we report descriptive statistics of interest (conversion rates and memory performance) for all subgroups.

Statistical analysis

Differences between groups were evaluated using independent sample t-tests for continuous and Chi²-test for categorical variables, respectively. Risk of incident AD was evaluated using stepwise Cox Proportional-Hazards regression analyses (SPSS-Version-20). Hazard Ratios (HR) with corresponding 95% Confidence Intervals (CI) are reported. Continuous predictors were age, years of education and the CERAD-NP delayed recall score (CERAD-DR). These were mean-centred prior to analysis by subtracting the respective sample mean from each observed value. Categorical predictors were gender, ApoE4-status (no E4...
Results

Descriptive statistics of the sample

Of the 417 included patients, 19 patients (4.6%) responded “No” to the question on experienced memory decline, 93 (22.3%) answered “Sometimes, but this does not worry me”, 211 (50.6%) answered “Yes, that worries me” and 94 (22.5%) answered “Yes, that worries me seriously”. Thus, 112 (26.9%) patients were classified as MC- and 305 (73.1%) as MC+. The two groups did not differ in demographical variables, frequency of ApoE4 status, MMSE scores, memory- or overall cognitive impairment on the CERAD-NP and mean follow-up time. MC+ patients showed higher scores on the MADRS scale and slightly higher BADL scores (Table 1).

Risk of AD

Seventy-four patients (17.7%) developed incident AD within a mean follow-up time of 27.6 months. The incidence rate differed significantly between groups (9.8% vs. 20.7% for the MC- and MC+ group respectively). Incidence rates according to the individual response categories of the question on experienced memory decline were 6 out of 19 (31.6%) in the “No” category, 5 out of 93 (5.4%) in the category “Sometimes, but this does not worry me”, 42 out of 211 (19.9%) in the category “Yes, that worries me”, and 21 out of 94 (22.3%) in the category “Yes, that worries me seriously”. With regard to memory performance, the patients answering “No” had the lowest mean CERAD-DR scores (M = 4.37, SD = 2.63) while patients in the other categories displayed better and similar mean CERAD-DR scores (category “Sometimes, but this does not worry me”: M = 5.48, SD = 2.01; category “Yes, that worries me”: M = 5.29, SD = 2.16; category “Yes, that worries me seriously”: M = 5.53, SD = 2.21). Mean CERAD-DR performance in the group of patients answering “No” was significantly lower compared to that of patients in the other three response categories (t = 1.99, df = 415, p = 0.049).

Table 1. Description of the sample.

| Total Sample (n = 417 MCI patients) | MC- group (n = 112 MCI patients) | MC+ group (n = 305 MCI patients) | MC- vs. MC+ group |
|-------------------------------------|---------------------------------|---------------------------------|-------------------|
| **Age (M, SD)**                     | 65.6 (7.93)                     | 66.3 (8.70)                     | 65.4 (7.63)       |
| Years of Education (M, SD)          | 12.6 (2.84)                     | 12.8 (2.81)                     | 12.5 (2.85)       |
| MMSE-Score (M, SD)                  | 27.6 (1.66)                     | 27.6 (1.62)                     | 27.7 (1.67)       |
| CERAD Delayed Recall (M, SD)        | 5.3 (2.21)                      | 5.3 (2.15)                      | 5.4 (2.23)        |
| CERAD Total Score (M, SD)           | 73.3 (10.8)                     | 73.4 (10.9)                     | 73.2 (10.7)       |
| MADRS (M, SD)                       | 7.93 (6.34)                     | 5.13 (5.01)                     | 8.95 (6.47)       |
| BADL-Score (M, SD)                  | 2.16 (1.29)                     | 1.96 (1.37)                     | 2.23 (1.26)       |
| Follow-Up time in months (M, SD)    | 27.6 (9.85)                     | 28.5 (10.5)                     | 27.3 (9.61)       |
| Time to Conversion in months (M, SD)| 19.1 (7.80)                     | 20.8 (7.42)                     | 18.8 (7.87)       |

| **Cohen’s d** | **p-value** |
|----------------|-------------|
| Age            | 0.11        | 0.341       |
| Years of Education | 0.12        | 0.270       |
| MMSE-Score     | 0.06        | 0.617       |
| CERAD Delayed Recall | 0.03        | 0.766       |
| CERAD Total Score | 0.02        | 0.888       |
| MADRS          | <0.001      | <0.001      |
| BADL-Score     | 0.21        | 0.061       |
| Follow-Up time in months | 0.12        | 0.304       |
| Time to Conversion in months | 0.27        | 0.422       |

| **Chi²** | **p-value** |
|----------|-------------|
| Female gender (n, %) | 0.68        | 0.411       |
| Positive ApoE4-status (n, %) | 0.13        | 0.722       |
| Conversion to AD (n, %) | 6.59        | 0.01        |

Note. P-values are derived from independent sample t-tests (2-sided) for comparison of continuous variables, and from Chi²-tests for categorical variables. AD = Alzheimer’s Dementia, BADL = Bayer-Activities of Daily Living Scale, CERAD = Consortium to Establish a Registry for Alzheimer’s Disease, M = Mean, MADRS = Montgomery Asberg Depression Rating Scale, MMSE = Mini-Mental-State-Examination, MCI = Mild Cognitive Impairment, MC- = MCI patients without Memory Concerns, MC+ = MCI patients with Memory Concerns, SD = Standard deviation.

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Table 2. Risk of incident Alzheimer’s Dementia: Results from hierarchically formulated multivariate Cox proportional hazard regression models.

| Model Statistics | Predictor Statistics |
|------------------|----------------------|
|                  | M2LL Chi² | Δ-Chi² (df) | p-value | Nagelkerke R² (%) | B     | SE     | Wald-Chi² | p-value | HR    | 95% CI for HR |
|                  |           |             |         |                 |       |        |           |         |       | Lower  | Upper  |
| Step 1: Model with model variables                      | 723.5     | 107.2 (5)   | 0.000   | 26.2             | 0.03  | 0.02   | 2.33      | 0.127   | 1.03  | 0.99   | 1.06   |
| covariates and   |            |             |         |                 |       |        |           |         |       |        |        |
| Age              |            |             |         |                 |       |        |           |         |       |        |        |
| CERAD-DR as      |            |             |         |                 |       |        |           |         |       |        |        |
| Female gender    |            |             |         |                 |       |        |           |         |       |        |        |
| predictors       |            |             |         |                 |       |        |           |         |       |        |        |
| Education        |            |             |         |                 |       |        |           |         |       |        |        |
| Positive ApoE4 status |          |             |         |                 |       |        |           |         |       |        |        |
| CERAD-DR         |            |             |         |                 |       |        |           |         |       |        |        |
| Step 2: MC added as predictor                          | 713.9     | 9.5 (1)     | 0.002   | 28.3             | 0.03  | 0.02   | 3.34      | 0.068   | 1.03  | 1.00   | 1.07   |
| predictor        |            |             |         |                 |       |        |           |         |       |        |        |
| Age              |            |             |         |                 |       |        |           |         |       |        |        |
| Female gender    |            |             |         |                 |       |        |           |         |       |        |        |
| Education        |            |             |         |                 |       |        |           |         |       |        |        |
| Positive ApoE4 status |          |             |         |                 |       |        |           |         |       |        |        |
| CERAD-DR         |            |             |         |                 |       |        |           |         |       |        |        |
| Presence of MC   |            |             |         |                 |       |        |           |         |       |        |        |
| Step 3: added    |                |             |         |                 |       |        |           |         |       |        |        |
| Model variables  | 709.1     | 4.8 (1)     | 0.028   | 29.3             | 0.03  | 0.02   | 2.97      | 0.085   | 1.03  | 1.00   | 1.07   |
| Interaction       |            |             |         |                 |       |        |           |         |       |        |        |
| between Age      |            |             |         |                 |       |        |           |         |       |        |        |
| CERAD-DR and     |            |             |         |                 |       |        |           |         |       |        |        |
| Female gender    |            |             |         |                 |       |        |           |         |       |        |        |
| MC               |            |             |         |                 |       |        |           |         |       |        |        |
| Education        |            |             |         |                 |       |        |           |         |       |        |        |
| Positive ApoE4 status |          |             |         |                 |       |        |           |         |       |        |        |
| CERAD-DR         |            |             |         |                 |       |        |           |         |       |        |        |
| Presence of MC   |            |             |         |                 |       |        |           |         |       |        |        |
| Linear Interaction: CERAD-DR * MC                      |           |             |         |                 | 0.41  | 0.21   | 4.00      | 0.046   | 1.51  | 1.01   | 2.25   |
| Note. M2LL of the Intercept model = 830.6. Details of the modeling process are given in the methods section. The HR for the CERAD-DR is below one as it represents the HR for a one unit increase in CERAD-DR scores i.e. for better memory performance). Lower CERAD-DR scores are therefore associated with a higher risk of developing incident AD. B = Beta-Coefficient of the predictor, CI = Confidence Interval, CERAD-DR = Delayed Recall of the Consortium to Establish a Registry for Alzheimer’s Disease Neuropsychological Assessment Battery, HR = Hazard Ratio, M2LL = Minus-Two-Log-Likelihood, MC = Memory Concerns, SE = Standard Error for B. doi:10.1371/journal.pone.0100812.t002
The additional analysis with the MADRS score as a predictor added in step 1 of the modelling process revealed that depressive symptoms were not associated with risk of future AD (p = 0.56) and did not alter the results reported above.

**Discussion**

In the present study we found that MC, which extend beyond the subjectively experienced memory decline that is part of the general MCI criteria set, were associated with an increased risk of incident AD. This main effect of MC is of importance as it suggests that reported concerns regarding self-perceived memory decline (rather than just self-report without associated concerns) are predictive for future AD in the MCI stage. We suggest that the magnitude of this main effect (about two-fold increased risk in the MC+ group) is of clinical relevance. Our findings are in line with results from an independent population-based study which found that self-perceived memory decline with reported concerns is associated with a higher risk of incident AD than the mere notion of worsening memory (without concerns) [19,20]. These results also suggest that AD related memory decline might be experienced in a different quality (i.e. as more serious and therefore worrying) compared to memory decline related to other factors such as normal aging. As an alternative hypothesis, proneness to psychological distress, a trait which has been reported as a risk factor for AD [37], might also be associated with a higher proneness to worry about self-perceived memory decline. If true, this could also explain the higher risk of incident AD associated with endorsing worries about worsening memory. We also stress that the main effect of MC does not imply that MCI patients without concerns about worsening memory are of no risk of future AD, but our data suggest that their risk is lower at a group level. Interestingly, in the small patient group who answered “No” to the question on experienced memory decline the conversion rate was highest and the memory performance level was lowest.

We also observed an interaction effect between MC and objective memory performance. The impact of MC on risk of future AD was highest for patients with very mild memory impairment and decreased with increasing memory impairment. Compared to the main effect of MC, this interaction effect was less strong. While this impedes a direct clinical applicability (e.g. for prediction in the individual case), it still highlights that at a group level MC and objective memory impairment interact in the course of AD. We suggest that this interaction between MC and memory performance is meaningful in several ways. Firstly, at the stage of very mild memory impairment, the assessment of self-perceived and worrying intra-individual decline might further contribute to AD prediction in addition to cross-sectional impairment on tests. This is of relevance as it highlights the particular value of self-reported memory decline with associated worries at the stage of very mild impairment [20].

Secondly, the effect of decreasing predictive validity of MC with increasing memory impairment may be caused by the reduction of self-perceived insight into symptoms at later stages of MCI. In this regard, we observed the highest conversion rate (31.6%) in the group answering “No” to the MC question, i.e. in those patients who were neither concerned about worsening memory nor reported any experienced memory decline at all. These patients also had the lowest CERAD-DR performance in the studied sample which is consistent with this potential explanation. Our observation is in line with results from a recent brain 18F-FDG-PET imaging study in a sample of single- and multidomain amnestic MCI patients (memory performance of <1.5 SD below norm), which also included an assessment of awareness [27].
Patients with poor awareness of their memory deficits showed a hypometabolic pattern similar to that of patients with early AD, suggesting that unawareness of memory deficits in MCI is linked to a more progressed pathology. Vogel et al. [24] studied a group of amnestic MCI patients with more severe memory impairment (<1.0 SD below norm). They found similar levels of reduced awareness for this MCI group compared to a group of AD patients and observed lower MMSE scores to be associated with lower levels of awareness. Furthermore, one recent study has shown that, in the group of MCI patients, subjective cognitive complaints decreased with increasing cognitive impairment [18]. Based on these empirical data, we propose that anosognosia, which is a well-known clinical sign of AD, might occur at the stage of late MCI. At the stage of very mild MCI, before this loss of valid self-perception, the presence of MC is predictive of future AD. This is in agreement with several studies showing that subjective memory decline in individuals with normal cognitive function is also predictive for AD [6–8,19,20].

Depressive symptoms did not predict risk of future AD in the present study and inclusion of depressive symptoms as a possible confounding variable did not alter the effects for objective memory impairment and MC. It is important to note, that although the MC+ group scored higher on the MADRS, their mean MADRS score reflected only very mild depressive symptoms and did not correspond to the clinical diagnosis of a major depression. ApoE4 status was associated with a higher risk of incident AD which is in line with recent studies [38,39]. However, frequencies of ApoE4 did not differ between the MC+ and MC- group. Results remained similar when ApoE4 was not accounted for in the models and we did not observe an interaction between MC and ApoE4 with regard to risk of incident AD in additional post-hoc analyses (data not shown). ApoE4 and MC thus independently contributed to risk of AD in the present sample. We also controlled for level of education in our analysis. Regarding the interplay of education and memory concerns, results from a large population based cohort study of non-demented elderly suggest that the clinical relevance of subjective memory complaints might be higher in individuals with higher educational background [40]. We also tested for an interaction between memory concerns and level of education in our analysis but did not find such an effect (data not shown). Differences in samples and design (i.e. community based cohort of non-demented elderly vs. memory clinic MCI sample in our study) might have contributed to these discrepant findings.

Our results are different to those of other studies which did not find a clear association between self-reports of memory decline and incident AD [4,5]. However, besides differences regarding samples and assessment of self-reported memory decline, these studies did also include informant reports in their predictive models. Therefore the comparability of our results to these studies is limited and we acknowledge the lack of informant reports in our study as a limitation.

A strength of the present study is the large number of neuropsychologically well characterized patients who met criteria for MCI [2]. Within these criteria we set the cutoff for cognitive impairment at 1 SD below the normative mean. This procedure is in line with recently established study protocols of large studies, e.g. ADNI-2 where recruitment was extended to early (amnestic) MCI patients with very mild memory impairment (<1.0 SD below the norm) [41]. The present sample therefore enabled us to test the specific contribution of MC for risk of AD at different stages of memory impairment within the MCI spectrum.

This study has limitations. The present sample reflects MCI patients with at least very mild impairment in one cognitive domain. Therefore the present results concerning the prognostic value of MC at different levels of memory impairment only refer to the MCI spectrum and not to cognitively unimpaired individuals. Secondly, we focused on memory concerns only (rather than concerns about other cognitive domains or cognition in general) and on AD as the outcome. It is important to note that other cognitive domains beyond memory can also be affected in MCI due to Alzheimer’s disease [3]. Thirdly, data on duration of MC and on discrepancies between the informant and the patient reporting the regard of MC was not available to us. Finally, our sample reflects a memory clinic population and the transfer to population-based cohort or volunteer samples may not be valid. Dropout analysis also revealed that the patients included in this study were three years younger on average compared to those excluded due to baseline missing data or lack of follow-up. However the two groups differed only slightly regarding baseline cognitive functioning and, more importantly, the groups did not differ in the expression of MC (73.1% MC+ in the study sample vs. 74.8% MC+ in those excluded from the analysis; p = 0.661). Thus, although a small selection bias was observed in our data, we consider the main results of our study not confounded by this bias.

In conclusion, the present study highlights a dynamic of the impact of MCI as a predictor for incident AD in MCI patients. The results may have implications for clinicians working with elderly patients at risk of AD, but also for the design of early intervention trials in Alzheimer’s disease. MC should be taken seriously as a risk indicator for future AD, especially in cases where neuropsychological test results are at the border between normal and impaired.

Author Contributions

Conceived and designed the experiments: SW FJ MW. Analyzed the data: SW FJ MW. Contributed reagents/materials/analysis tools: KS LF AK SS MW FJ MW. Conceived and designed the experiments: SW FJ MW. Contributed reagents/materials/analysis tools: KS LF AK SS MW FJ MW. Analyzed the data: KS LF AK SS HH IH OP FR HJ CL MH HG JS JP OR ER FH JW WM JK. Wrote the paper: SW FJ MW. Acquisition of data: KS LF AK SS HH IH OP FR HJ CL MH HG JS JP OR ER FH JW WM JK. Critical revision of the manuscript for important intellectual content: SW MW FJ KS LF AK SS HH IH OP FR HJ CL MH HG JS JP OR ER FH JW WM JK. Study supervision: MW FJ WM JK JW ER. Obtained funding: WM JW JK.

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