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Prevalence of Mild Cognitive Impairment and Its Subtypes in the Heinz Nixdorf Recall Study Cohort

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Key Words

Mild cognitive impairment · Prevalence · Subjective cognitive complaints · Alzheimer's disease · Epidemiology · Vascular · Coronary heart disease

Abstract

Aims: We investigated the prevalence of mild cognitive impairment (MCI) and its subtypes according to the original (MCI-original) and modified (MCI-modified; neglecting cognitive complaints) Petersen criteria. ***Methods:*** 4,145 subjects (aged 50–80 years) from a German population-based study completed a cognitive screening test and were poststratified into 2 groups with sample sizes of 1,125 for impaired and 3,020 for age-appropriate performance. Random samples of 445 impaired participants and 211 age-appropriate participants received a detailed neuropsychological evaluation. The prevalence of MCI was estimated by a bias correction estimator based on stratum weights. The association between MCI and age, gender and education was analyzed in a logistic regression model. ***Results:*** The estimated MCI prevalence was 7.8% (95% CI: 5.7–9.9%) for the original, and 12.1% (95% CI: 9.8–14.4%) for the modified criteria. In the MCI-original group, amnestic MCI subtypes were slightly less common than non-amnestic MCI subtypes (3.5 vs. 4.3%). MCI-original was associated with lower education and older age. In the MCI-modified group, the amnestic subtypes were more common than the non-amnestic MCI subtypes (7.8 vs. 4.3%), and MCI was associated with age, gender and education. ***Conclusions:*** Prevalence rates of MCI are high in the general population and vary considerably according to the criteria applied.

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Introduction

The identification of persons at risk for dementia is of great importance for potential treatment options that may delay or prevent cognitive decline. Mild cognitive impairment (MCI) is one of several terms describing the stage between cognitive changes in normal aging and early dementia [1, 2]. Persons with MCI have an increased risk of developing dementia with an estimated progression rate of 10–15% per year, compared to 1–2% in the cognitively normal, elderly population [3]. The progression, prevalence and incidence rates of MCI vary as a result of different diagnostic criteria as well as different sampling and assessment procedures [4]. Estimated prevalence rates range widely from 3 to 29% in population-based studies [5]. The current lack of agreement on the terminology and specific diagnostic criteria poses problems for the identification of a high-risk population. Furthermore, this renders it difficult to determine the public health burden of MCI in different settings and societies.

We therefore examined the concept of MCI by Petersen and the International Working Group on MCI [2, 3] (MCI-original) in a large German population-based study. This concept distinguishes 4 clinical subtypes: amnestic MCI – single and multiple domain, and non-amnestic MCI – single and multiple domain. These 4 clinical MCI subtypes presumably differ in etiology and outcome. Amnestic MCI seems to have a higher likelihood of progressing to Alzheimer's disease (AD), whereas the non-amnestic subtypes have a higher likelihood of progressing to a non-AD dementia [e.g. vascular dementia, frontotemporal dementia (FTD) or dementia with Lewy bodies (DLB)] [3, 5]. The following criteria should be met for the diagnosis of MCI-original: (1) cognitive decline (defined as self- and/or informant-reported cognitive complaints) and impairment of objective cognitive task performance; (2) intact ability to perform activities of daily living, and (3) absence of dementia. The role of subjective cognitive complaints in the progression of MCI to dementia is still controversially debated [6–9]. On the one hand, many cross-sectional studies have shown that subjective cognitive complaints are rather associated with depression or anxiety than with objective test performance [10]. Furthermore, many people do not complain about their memory, especially more highly educated persons [11]. On the other hand, several longitudinal studies have identified subjective cognitive (or memory) complaints as a predictor of future cognitive decline [9]. Moreover, subjective complaints may be the only indication of incipient cognitive decline. Whether they should be a prerequisite for a diagnosis of MCI still remains questionable. Regarding the prevalence calculations and future outcome of our study participants, the present study also investigated a modified MCI definition, which was based on the same criteria as the MCI-original concept [2, 3], except that subjective cognitive complaints were not a diagnostic criterion (MCI-modified).

The aims of the present study therefore were (1) to assess the prevalence of MCI and its subtypes in the population-based Heinz Nixdorf Recall study as an estimate of the prevalence in the general German population, (2) to evaluate the prevalence of MCI according to different diagnostic criteria (MCI-original vs. MCI-modified), and (3) to investigate the association between MCI and sociodemographic characteristics (age, gender, education).

Subjects and Methods

Subjects

This was a substudy of the Heinz Nixdorf Recall (Risk Factors, Evaluation of Coronary Calcium and Lifestyle) study. The major aim of the Heinz Nixdorf Recall study is to evaluate the predictive value of coronary artery calcification using electron beam computed tomography for myocardial infarction and cardiac death in comparison to common risk factors [12]. During the baseline examination between December 2000 and August 2003, a total of 4,814 subjects were recruited (response rate of 55.8%). A detailed analysis of the nonresponders has previously been published [13]. Briefly, there was no age difference between the participants and the nonparticipants of the study, but elderly women were less likely to participate. Furthermore, a school degree at a university entrance qualification level was more often reported among participants than nonparticipants. Participants were contacted on the basis of a random sample of men and women aged between 45 and 74 years and registered in mandatory citizen registries in the German cities of Bochum, Essen and Mülheim/Ruhr. The participants were followed over a 5-year period, after which a second examination was conducted (follow-up examination). The 5-year follow-up visit (response rate: 90.5%; n = 4,359) included a screening test of amnestic and cognitive functioning, which was accomplished in 4,145 study participants (95.1%). A random sample of participants (aged 50–80 years) with impaired screening results (n = 701) and age-appropriate screening results (n = 316) were invited to a detailed neuropsychological (see below) and neurological examination to assess the prevalence of MCI and its subtypes in the study population. A total of 656 participants (65%) accomplished the detailed neuropsychological assessment. The Heinz Nixdorf Recall study as well as this substudy were approved by the ethics committee of the medical faculty, University Hospital Essen, and followed established guidelines on good epidemiological practice. All participants gave their informed written consent.

Assessments

Screening Test

Numerous screening tests have been studied for their efficacy in detecting cognitive impairment. At this time, there is no test that is clearly better than other tests [14]. Thus, our screening test was conceptualized as a multidimensional test with 5 subtests, using established measures of immediate and delayed verbal memory (8-word list [15]), speed of processing/problem solving (labyrinth test [15]), verbal fluency (animals [16]) and visuospatial ability (clock drawing test [17]). To add sensitivity to the screening test along the continuum from normal to MCI (covering the amnestic and non-amnestic MCI subtypes), we decided to define a screening result as 'impaired' if the participant scored 1 SD below the age mean in at least 2 screening subtest (n = 1,125). The screening result was rated as 'age appropriate' if the performance in at least 4 of the 5 administered subtests was above the lower SD boundary (n = 3,020). Other studies have shown that combining subtests for several cognitive domains as in our screening test improved the discriminant validity of the screening and provided an optimum predictive probability of developing dementia [18, 19].

Assessing Subjective Cognitive Complaints

Regarding the MCI-original diagnosis, the role of cognitive complaints may be crucial, especially if there is no information available about cognitive decline over time in objective cognitive tasks [2, 3]. However, there is no agreement on how subjective cognitive complaints should be operationalized [20]. Thus, we assessed subjective cognitive complaints in all study participants by asking whether they experienced memory or other cognitive problems (possible answers: 'yes' or 'no'). The participants were also asked if their cognitive performance had declined over time (possible answers: 'yes' or 'no'). Subjective cognitive complaints were defined as present if a participant answered 'yes' to the first question and 'yes' to the second question to capture the notion of change in cognitive performance. The complaint is meant to represent a change in function for the person [3]. Note that this response was not a spontaneous complaint and was based only on subjective reports. We made no difference between subjective memory complaints or subjective cognitive complaints as both are indicators of cognitive decline as required by the International Working Group on MCI [2].

Neuropsychological and Neurological Assessment

A standardized neuropsychological examination was conducted by a neuropsychologist using the following test assessments: the Alzheimer's Disease Assessment Scale (ADAS); the number connection test of the Nürnberg Gerontopsychological Inventory [15]; the verbal fluency test [16] [2 subtests with a formal lexical category ('S' and 'G-R') and 2 subtests with a semantic category ('food' and 'clothes-flowers')], and the Instrumental Activities of Daily Living [15] scale to assess disability. The subtests of the cognitive test battery covered the following cognitive domains: (1) memory (ADAS subtests 'word recall' and 'word recognition'); (2) orientation/praxis (ADAS subtests 'orientation', 'ideational praxis', 'constructional praxis', 'commands' and 'naming'); (3) information processing speed (number connection test); (4) executive functions (verbal fluency tests), and (5) verbal abilities (ADAS subtests 'spoken language abilities', 'word-finding difficulty' and 'comprehension'). For each cognitive domain, the age-specific test norms were administered. A cognitive domain was rated as impaired if the performance was more than –1 SD below the age-adjusted mean. A cutoff of 1 SD was chosen for the screening test as well as for the detailed neuropsychological assessment because it was found to be associated with a higher relative prognostic power in predicting the development of dementia compared with a cutoff of 1.5 SD [21]. Furthermore, it provides a higher sensitivity, which was particularly important for the screening test in order to detect participants in need of further neuropsychological assessment [21]. Depression was assessed using the depression subscale of the ADAS [22]. A detailed physical examination with particular focus on the neurological examination was conducted by a neurologist. We also gathered information on the medical history related to cognitive functioning, the duration of such symptoms, the history of other medical illnesses and current treatment.

Diagnostic Classifications

A diagnosis of dementia was made according to the criteria of the DSM-IV (Diagnostic and Statistical Manual of Mental Disorders, fourth edition) [23]. Two diagnostic concepts for MCI were established. First, MCI was diagnosed according to the current Petersen/International Working Group on MCI criteria (MCI-original) [2, 3]. The following criteria were obligatory for the diagnosis: (1) the subject or the informant had to express some concern about the person's cognitive function (cognitive complaint); (2) there had to be evidence for a decline in cognitive function on the objective cognitive tasks administered which was not normal for the subject's age; (3) the participant had to show no impairment of functional activities of daily living, and (4) the subject did not fulfill the DSM-IV dementia diagnosis. We distinguished 4 subtypes of MCI, based solely on differences in the number and type of impaired cognitive domains [2, 3]. Participants having an objective impairment of memory but not of any other domain of cognitive functioning received a diagnosis of 'amnestic MCI single domain'. 'Amnestic MCI multiple domain' was diagnosed if memory and at least 1 other cognitive domain were impaired. If a single domain other than memory was impaired, participants received a diagnosis of 'non-amnestic MCI single domain'. 'Non-amnestic MCI multiple domain' was diagnosed if at least 2 cognitive domains other than memory showed an objective impairment. If a participant showed no impairment of any cognitive domain, the cognitive abilities were rated as 'unimpaired'. Second, MCI was diagnosed according to the modified Petersen MCI criteria (MCI-modified; a cognitive complaint was not required for diagnosis). Participants with dementia, severe depression (ADAS depression subscale score >4), Parkinson disease, mental retardation, severe alcohol consumption (for women: >20 g/day; for men: >40 g/day), known brain cancer, severe problems with the German language (foreign persons) and severe sensory impairment leading to invalid cognitive testing were excluded from the MCI prevalence calculations. In all, 41 of the 656 participants (6.3%) with completed neuropsychological assessment met the exclusion criteria.

Statistical Analyses

Summary statistics were calculated to describe and compare the demographic and clinical characteristics of the full sample of 4,145 participants, and of the subsample of 615 participants who accomplished the full neuropsychological assessment and did not meet the exclusion criteria.

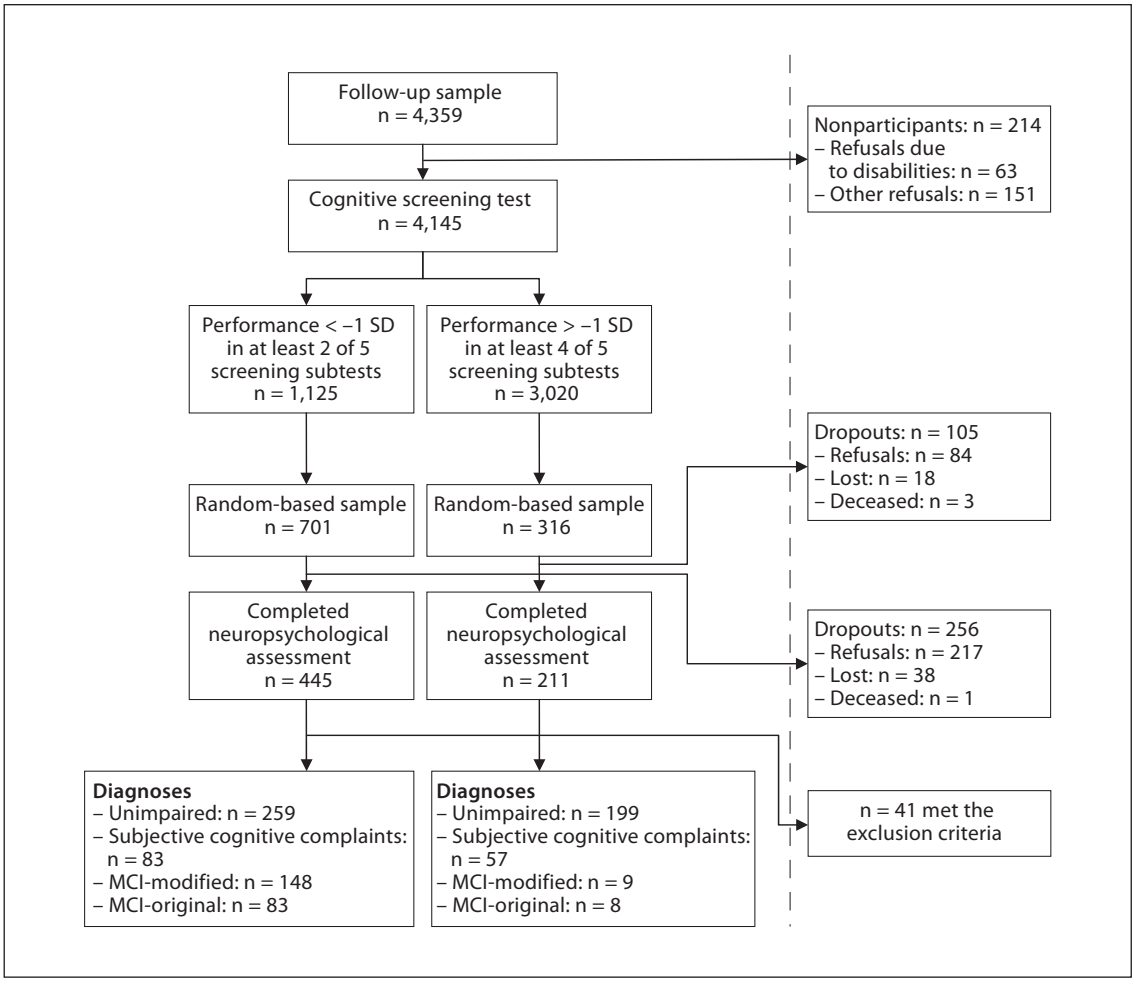

Fig. 1. Flow chart of the Heinz Nixdorf Recall study population (follow-up examination), the diagnostic assessment procedure and the diagnoses.

The prevalence of MCI in the German population was estimated according to Petersen's original and modified criteria for age range (50–65 and 66–80 years old), gender and educational level. Education was classified by the International Standard Classification of Education [24] as total years of formal education, combining school and vocational training. The continuous education variable was grouped into 3 categories, with a highest category of 14 and more years of education and a lowest category of 10 and fewer years.

A stratified subsampling estimator of proportions was used to estimate prevalence [25]. This estimator is given by the following expression: $P_{MCI} = W/N\ p_1 + (1 - W/N)\ p_2$, where N is the total number of participants in the study, W is the total number of participants with positive screening outcome, p_1 is the proportion of positive MCI with positive screening results and p_2 is the proportion of positive MCI with negative screening results. The variance of this estimator is given by $Var(P_{MCI}) = [W/N]^2\ p_1(1 - p_1)/n_1 + [(1 - W/N)]^2\ p_2(1 - p_2)/n_2$, where n_1 and n_2 are the total numbers of participants selected in the strata with positive and negative screening results. Approximated 95% CI were calculated with the classical normal approximation.

The association between MCI (modified and original) and gender, age and education, adjusted by the screening result, was formally analyzed by a logistic regression model [26]. A model selection procedure was established by choosing the model with the minimum Akaike information criterion (AIC) [27, 28]. The model class runs from the model including all covariates to the model with a constant term and a single covariate indicating screening results. In addition, the variable 'age' was categorized by a single optimal threshold value, which was determined in a grid of values between 60 and 80 years. The age value in the grid which corresponded to the minimum AIC was selected to be used in the final model.

The stability of this model selection process was validated by taking 500 bootstrap samples from the 4,145 original participants, and by repeating the full selection process in each sample

Table 1. Demographic characteristics of the population of the full sample of the Heinz Nixdorf Recall study, the random-based sample, the subsample and the dropouts

	Full sample (n = 4,145)	Random-based sample (n = 1,017)	Subsample (n = 656)	Dropouts (n = 361)
Age, years	64.4 ± 7.6	68.6 ± 6.9	68.9 ± 6.6	68.2 ± 7.3
Gender				
Male	2,046 (49.4)	525 (51.6)	348 (53.0)	177 (49.0)
Female	2,099 (50.6)	492 (48.4)	308 (47.0)	184 (51.0)
Education				
≤10 years	419 (10.1)	191 (18.8)	122 (18.6)	69 (19.1)
11–13 years	2,311 (55.8)	627 (61.7)	403 (61.4)	224 (62.0)
≥14 years	1,415 (34.1)	199 (19.5)	131 (20.0)	68 (18.9)

Data are presented as numbers of subjects with percentages in parentheses or means ± SD (for age).
Full sample: All participants of the Heinz Nixdorf Recall study who completed the cognitive screening test.
Random-based sample: 701 participants with screening results 1 SD below age-adjusted norms, and 316 participants with unimpaired screening results.
Subsample: Participants with complete neuropsychological assessment.
Dropouts: Participants of the random-based sample who refused to participate.

[29, 30]. The resulting model is presented with odds ratios (OR) and their 95% CI. An OR of <1 indicates a potentially protective effect of covariates compared to reference values.

Statistical analysis was performed by the R system, version 10.0.0 [31]. R functions were written to calculate the prevalence estimation and its 95% CI, the selection procedure for the threshold point of age and the bootstrap analysis. These functions are available on request.

Results

Descriptive Statistics

A flow chart showing the study population, the diagnostic assessment procedures and the diagnoses is presented in figure 1. Of the 4,814 participants sampled in the baseline recruitment phase, 4,359 individuals (90.5%) participated in the follow-up examination and 4,145 (95.6%) completed the screening test; 1,125 (27.1%) showed a low performance (performance less than –1 SD of the age-adjusted mean) in at least 2 screening subtests, and 3,020 participants (72.9%) showed an age-appropriate performance in at least 4 of the 5 screening tests. To assess the prevalence of MCI according to common criteria, we used random-based samples of 701 participants (62.3%) in the impaired screening group and 316 (10.5%) in the normal screening group, and invited the participants to a further neuropsychological evaluation (random-based total: n = 1,017). In the impaired screening group, 445 subjects (63.5%) participated in the neuropsychological study. In the normal screening group, 211 (66.8%) received a neuropsychological evaluation (subsample total: n = 656). Table 1 summarizes the major sociodemographic characteristics of the study participants. In all, 69% (701 of 1,017) of the participants in the random-based sample were participants with impaired screening results. Compared with the participants in the full sample, the random-based sample participants were significantly older (full sample: 64.4 ± 7.6 years; random-based sample: 68.6 ± 6.9 years; $Z = -20.3$; $p < 0.001$) and had a lower education level (Pearson's $\chi^2 = 192.478$; $p < 0.001$). There was no evidence of any selection bias by gender (Pearson's $\chi^2 = 2.76$; $p = 0.097$). The dropouts (n = 361; 35.5%) of the random-based sample did not significantly differ from the participants of the subsample according to age ($Z = -1.18$; $p = 0.237$), gender (Pearson's $\chi^2 = 1.506$; $p = 0.238$) or education (Pearson's $\chi^2 = 0.200$; $p = 0.905$). We also investigated whether there was a difference between participants and dropouts concerning their cognitive status measured by the screening test. Looking exclusively at the participants (n = 445) and the nonparticipants (n = 256) of the impaired screening subgroup regarding their cognitive performance in the 5 administered screening subtests, there was no significant difference between the groups (all $p > 0.315$; data not present-

Table 2. Estimated overall, and age-, gender- and education-specific prevalence rates of MCI

	MCI-original criteria			MCI-modified criteria		
	MCI cases n	prevalence		MCI cases n	prevalence	
		%	95% CI		%	95% CI
Overall (n = 615)	91	7.8	5.7–9.9	157	12.1	9.8–14.4
Age						
50–65 years (n = 170)	24	7.9	4.1–11.7	34	10.4	6.4–14.4
66–80 years (n = 445)	67	8.5	5.9–11.2	123	14.0	11.1–17.0
Gender						
Male (n = 321)	49	8.5	5.7–11.3	89	14.4	11.3–17.6
Female (n = 294)	42	8.3	4.8–11.9	68	11.7	8.1–15.4
Education						
≤10 years (n = 115)	24	14.2	5.7–22.6	37	18.3	9.7–26.8
11–13 years (n = 382)	57	8.4	5.6–11.2	100	13.4	10.4–16.6
≥14 years (n = 118)	10	4.7	1.6–7.7	20	8.6	5.1–12.2

Prevalence estimated by the stratum-size-weighted estimator P_{MCI}.

ed). Regarding the participants (n = 211) and nonparticipants (n = 105) of the age-appropriate screening group, there was also no difference in cognitive performance (all $p > 0.203$; data not presented). Thus, there is no selection bias concerning the cognitive status of our study participants.

The subsample consisted of 656 participants with the following diagnoses (fig. 1): 458 (69.8%) showed an age-appropriate performance in the neuropsychological assessment, 91 (13.9%) had MCI-original and 157 (23.9%) had MCI-modified, and 41 participants (6.3%) met the exclusion criteria of the study and were excluded from further MCI prevalence calculations (7 of the excluded participants had a dementia diagnosis). Furthermore, 138 of the 656 participants (21.1%) reported a subjective cognitive complaint without any cognitive deficit in the neuropsychological assessment.

Overall Prevalence Rates

Of the 615 responders in the subsample, 91 met the MCI-original criteria [3, 4] and 157 participants met the MCI-modified criteria (cognitive complaints not required). Thus, applying the stratum-size-weighted estimator P_{MCI}, the estimated MCI prevalence was 7.8% (95% CI: 5.7–9.9%) for MCI-original, and 12.1% (95% CI: 9.8–14.4%) for MCI-modified criteria (table 2).

Age-, Gender- and Education-Dependent Prevalence Rates

The age-, gender- and education-dependent prevalence rates for both criteria are summarized in table 2. In the MCI-original group there was only a slight increase in prevalence from 7.9% in participants aged 50–65 years to 8.5% in participants aged 66–80 years. For the MCI-modified criteria there was an age-related increase from 10.4% in participants aged 50–65 years to 14% in participants aged 66–80 years. The prevalence rates only differed for gender in the MCI-modified group (men: 14.4%; women: 11.7%). In the MCI-original group, no difference in gender-dependent prevalence rates was observed (men: 8.5%; women: 8.3%). The highest MCI prevalence according to both diagnostic criteria was found in the lowest education group (MCI-original: 14.2%; MCI-modified: 18.3%). When comparing the prevalence rates in the lower education group with the more highly educated participants, there was a continuous decrease in prevalence according to both diagnostic criteria.

Prevalence of MCI Subtypes

Table 3 shows the criterion-dependent subtype prevalence rates. According to the MCI-original criteria, the non-amnestic MCI single domain subtype is the most frequent subtype (3.7%), followed by the amnestic MCI single domain subtype (2.9%). The lowest prevalence rates were found for the amnestic and non-amnestic MCI

Table 3. Estimated prevalence rates of MCI subtypes

	MCI-original criteria			MCI-modified criteria		
	MCI cases n	prevalence		MCI cases n	prevalence	
		%	95% CI		%	95% CI
Amnestic MCI single domain	34	2.9	1.6–4.3	81	6.1	4.4–7.7
Amnestic MCI multiple domain	10	0.8	0.2–1.4	29	2.0	1.2–2.7
Subtotal amnestic	44	3.5	2.1–4.9	110	7.8	6.1–9.6
Non-amnestic MCI single domain	38	3.7	2.1–5.4	38	3.7	2.1–5.4
Non-amnestic MCI multiple domain	9	0.7	0.1–1.3	9	0.7	0.1–1.3
Subtotal non-amnestic	47	4.3	2.6–6	47	4.3	2.6–6.0

Prevalence estimated by the stratum-size-weighted estimator P_{MCI}.

Table 4. Logistic regression model: relationship between MCI and covariates

Covariates	MCI-original criteria		MCI-modified criteria	
	OR	95% CI	OR	95% CI
Impaired screening results	6.32***	2.98–13.39	13.95***	6.85–28.40
Age (<76.5 years)	0.53*	0.29–0.99	0.28***	0.16–0.50
Female gender	0.61	0.37–1.01	0.46***	0.29–0.72
Education[1]				
11–13 years	0.64	0.36–1.14	0.69	0.41–1.16
≥14 years	0.32*	0.13–0.76	0.35**	0.17–0.72

Impaired screening results: screening results 1 SD below the age-adjusted norms in 2 or more screening subtests. OR shown are adjusted for screening results. * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$.

[1] Reference category: ≤10 years of education.

multiple domain subtypes (0.8 and 0.7%, respectively). The amnestic subtypes were almost as frequent as the non-amnestic subtypes (3.5 vs. 4.3%).

According to the MCI-modified criteria, the amnestic MCI single domain subtype is the most frequent (6.1%), followed by the non-amnestic single domain subtype (3.7%). The multiple domain subtypes were less common (2% for amnestic and 0.7% for non-amnestic). Contrary to the prevalence by MCI-original criteria, the amnestic subtypes were more frequent than the non-amnestic subtypes (7.8 vs. 4.3%). Interestingly, the MCI prevalence rates for the non-amnestic subtypes did not change depending on the MCI criteria (original or modified).

Association between MCI and Age, Gender and Education, Adjusted by Screening Results

The right panel of table 4 presents the resulting logistic regression model for the MCI-modified criteria. This model corresponds to the 4 covariates with age optimally divided into 2 classes by a threshold point of 76.5 years. This model has an AIC of 624.2, which indicates a substantial model fitness compared to the simplest model with screening effects, which had an AIC of 644.4 (the lower the AIC, the better the model fits the data).

This model was validated by taking 500 bootstrap samples from the original 4,145 patients and running the selection process again 500 times. In 65% of the bootstrap samples, the model with a threshold of 76.5 years was se-

lected as the best model. This gives a clear indication of the robustness of this threshold point.

The OR of the screening test (13.95) shows that the screening test was extremely effective for the stratification process. Participants aged 76.5 years or younger are less likely to have an MCI diagnosis (OR = 0.28). The same was found for female participants (OR = 0.46) and for participants with higher education levels (≥14 years of education; OR = 0.35).

The left panel of table 4 describes the results for the MCI-original criteria. In this case, the OR pointed out similar results as the MCI-modified criteria, but the 95% CI were much wider, indicating that there was not enough information to claim a strong relationship between covariates and MCI. Interestingly, education (OR = 0.32) and age (OR = 0.53) remain statistically significant, while female gender (OR = 0.61) only shows a nonsignificant trend.

Discussion

The present results indicate that 7.8% of the German population aged 50–80 years show MCI according to the Petersen [2, 3] criteria, which is within the range of 3–29% of similar population-based studies [32–36]. According to the MCI-modified criteria, a higher prevalence rate was found (12.1%), which also falls within the reported range of 5–42% of other population-based studies [34, 37–39]. This is also consistent with the finding that the modified diagnoses are more common than the original [34], which may be due to the fact that requiring one criterion less increases the sensitivity but reduces the specificity of the MCI concept. As far as we know, there is only one German population-based study (LEILA 75+) [40] which assessed the prevalence of MCI according to different diagnostic criteria. In this study, the prevalence rate for MCI (with a severity level of 1 SD below age- and education-matched norms) was 19.3% according to the original, and 41.5% according to the modified criteria. Although the overall prevalence of MCI in the present study is comparable to other countries, the prevalence compared to the LEILA 75+ study seems rather low. This may be due to the fact that the participants in the LEILA 75+ study were considerably older (75–99 years) and had a lower level of education than our study participants. The most important factor that may contribute to the high discrepancy in prevalence rates might be the use of different psychometric instruments. In the LEILA 75+ study, the impaired domains in persons with MCI were defined using a relatively brief test and not a complete neuropsychological battery as in our study [34]. Thus, the combination of a low severity level (SD = 1) in the brief psychometric tests with the modified criteria might have led to a further reduction in specificity and therefore to an overestimation of the prevalence rate.

There are only few studies which examined all four MCI subtypes [34, 41]. Most studies concentrated on the amnestic subtype [40, 42, 43] or the overall categories of amnestic versus non-amnestic [33]. In concordance with our results for the MCI-original diagnosis, Busse et al. [34] showed that the nonamnestic MCI single domain subtype had the highest prevalence (7.1%), which was slightly higher than ours. The prevalence of the amnestic MCI single domain subtype (2.9%) was as low as reported in several other population-based studies, in which it ranged from 1 to 6% [36, 42, 44]. An opposite and interesting pattern was found for the MCI-modified criteria. In this group, the most frequent subtype was the amnestic MCI single domain subtype (6.1%), followed by the non-amnestic MCI single domain subtype (3.7%), which was the most prevalent one in the MCI-original group. Lee et al. [32] found similar results, with the amnestic subtypes being more frequent than the non-amnestic subtypes. Amnestic MCI in particular may be more specific for identifying the early stage of AD [45]. Individuals at the earliest stage of AD often have no awareness of memory impairments and are generally older [36, 46]. This may explain the significant difference between the amnestic MCI cases depending on diagnostic criteria (44 amnestic MCI-original cases vs. 110 amnestic MCI-modified cases). Interestingly, the non-amnestic subtypes were not affected by the MCI criterion (original vs. modified). All participants with a non-amnestic MCI-modified diagnosis fulfilled the cognitive complaints criterion of the MCI-original diagnosis. Regarding the non-amnestic subtype as a prodromal stage of vascular dementia, DLB or FTD rather than of AD, it can be argued that participants with non-amnestic deficits have greater insight into their cognitive performance. This seems to be plausible for vascular lesions as they are highly associated with fatigue symptoms and neuropsychological cognitive problems such as attention deficits, executive functioning deficits and psychomotor slowing. A vascular lesion pattern therefore might cause a greater cognitive disturbance in the participants and their relatives and thus be more often reported [47]. Looking at the two other likely outcomes of non-amnestic MCI subtypes, it is known that patients with DLB normally do

not suffer from anosognosia and more frequently have symptoms in several neuropsychiatric domains [48, 49]. Thus, they might show greater insight than participants with prodromal AD. This pattern is different for patients with FTD, who often show unawareness of their symptoms. This seems to be inconsistent with our findings. Salmon et al. [50] found out that patients with FTD show a different pattern of unawareness in comparison to AD patients. FTD patients seem to be especially unaware of personality or behavioral changes [50]. Their awareness of cognitive symptoms appears to be as strong as the awareness of patients with AD. The follow-up of all study participants will enable us to determine whether the participants with a nonamnestic MCI subtype more likely progress to a non-AD dementia, and whether subjective cognitive complaints are of additional predictive value. Interestingly, not only the MCI subtypes but also the age- and gender-dependent prevalence rates show quite different patterns depending on the diagnostic criteria. Because the criterion for MCI is corrected for age by using age-specific norms, the prevalence of MCI should normally remain stable across age groups. When applying the MCI-original criteria, there is only a slight age-dependent prevalence increase in the second age group (from 7.9 to 8.5%). In the MCI-modified group there is a significant increase with age from 10.4 to 14.0%. Thus, the effect of age on the prevalence rates might be due to possible differences between our study sample and the normative dataset we used to assess MCI (e.g. for the verbal fluency task, an underrepresentation of participants older than 65 years in the normative dataset). Furthermore, the greater age differences in the MCI-modified group might be due to an observed decrease in subjective cognitive complaints with age [41]. A continuous increase in MCI prevalence with increasing age was found in several studies [32, 36, 46]. For example, Hänninen et al. [39] reported an increase in prevalence from 2.4% (age: 60–64 years) to 8.4% (age: 70–76 years). But there are also studies which did not show any effects of age on prevalence rates [41, 51]. There is no gender difference for the MCI-original criteria, but there is a higher prevalence for men in the MCI-modified group, which is supported by the regression model: female gender was associated with a significant MCI risk reduction of 54%. Only few studies have reported that male gender is associated with a higher MCI risk [42, 52]. Most studies confirm our findings for the original MCI definition with no difference in gender or report a higher prevalence rate for women [38, 39]. A possible explanation could be the limited insight especially of older participants and men into cognitive impairments as part of the MCI-original diagnosis. Concerning the gender differences, it is known that men have a lower frequency of subjective cognitive complaints and therefore less often fulfill the original criteria [53]. This phenomenon was also reported in other studies [34, 41] and fosters the discussion whether cognitive complaints should be a prerequisite for MCI diagnoses. If complaints are included in the diagnosis there is the common problem that some cases of MCI might be missed [6, 54], in particular in those participants which may convert to dementia. However, there are several studies that provide further evidence that dementia reflects a continuum that starts with subjective cognitive impairment and moves to MCI, culminating in dementia [8, 55, 56]. A current study by Reisberg et al. [9] showed that healthy subjects with subjective cognitive impairment who were otherwise cognitively normal were 4.5 times more likely to develop MCI or dementia within about 7 years compared with healthy subjects without subjective cognitive impairment. A follow-up examination of our cohort therefore will enable us to examine the importance and predictive value of subjective cognitive impairment for the progression to dementia. Regarding the education-specific prevalence rate, there is a decrease in MCI (original and modified) in participants with higher education levels, as reported in several studies [32, 35, 38, 39].

To our knowledge, this is the first study in Germany which investigates the prevalence of MCI in a large, unselected population of men and women aged 50–80 years. By combining the screening test results with the detailed neuropsychological evaluation, it was possible to estimate the prevalence of MCI in the total study cohort. Moreover, the detailed examination allowed us to identify participants with subjective complaints without any psychometric deficits (21.1%) as well as the subtypes of MCI with particular implications for the further clinical outcome. Despite these strengths, our study has several limitations. First, the initial sample of the Heinz Nixdorf Recall study with 4,814 participants was more highly educated than the average population. Thus, our study might slightly underestimate the prevalence of MCI. There was also a gender selection bias, with more male participants being selected. Furthermore, we did not have the possibility to perform a detailed neuropsychological examination of all study participants, thus we decided to administer a screening test. The logistic regression showed that the stratification process was extremely effective by dividing the participants into two homogeneous groups. To ensure that we did not miss any MCI cases in the age-appropriate

screening group, we also examined participants with normal screening results, but not to the same extent. A total of 68% of the random-based sample had impaired screening results. However, the participants in and dropouts from the subsamples (impaired screening vs. age-appropriate screening) did not differ in their cognitive performance measured by the screening test, but were older and less educated than the full sample. Hence, the estimated population prevalence rate might be overestimated in our study. To resolve this possible bias, we built stratum weights for the prevalence calculation, which considered the screening test results and the MCI cases in the impaired and age-appropriate screening groups. By this method, the bias should have been minimized. We defined the performance as impaired if it was 1 SD below the age-adjusted mean. Some studies use a stricter threshold with 1.5 SD below the mean [36, 46]. Therefore, compared with these studies, our prevalence rates could be artificially higher. On the other hand, we did not include participants older than 80 years. As MCI and dementia are highly associated with age [36, 46], a higher prevalence rate could be expected in older participants. However, as age is the most important risk factor for AD [57], the age range of our study population provides a better basis for further follow-up examinations, possibly with lower dropout rates as dementia and even MCI seem to be associated with an increased relative risk of disability and mortality [58–60].

The results of this study underline that MCI affects a considerable percentage of the elderly population. The identification of individuals at risk may provide opportunities for future prevention strategies. The longitudinal examination of our participants will enable us to examine the course of cognitive changes in normal and MCI participants in order to assess the rate of progression to dementia, its biological and genetic determinants, the predictive value of subjective cognitive complaints and the association with cardiovascular risk factors.

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