Incidence of Mild Cognitive Impairment: A Systematic Review

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Key Words

Mild cognitive impairment, incidence • Review, mild cognitive impairment • Risk factor, dementia • Epidemiology

Abstract

Background/Aims: Subjects with mild cognitive impairment (MCI) constitute a risk population of developing dementia and thus a population of clinical interest. This study reviews recent work on the incidence of MCI in the elderly.

Methods: Incidence papers were identified by a systematic literature search. Studies on the incidence of MCI were considered if they identified ‘cognitively mildly impaired’ subjects by application of the MCI criteria, used the ‘person-years-at-risk’ method, and were based on population- or community-based samples. **Results:** Nine studies were identified. The incidence of amnesic MCI subtypes ranged between 9.9 and 40.6 per 1,000 person-years, and the incidence of non-amnesic MCI subtypes was 28 and 36.3 per 1,000 person-years. Regarding any MCI, incidence rates of 51 and 76.8 per 1,000 person-years were found. A higher risk of incident MCI mainly resulted for higher age, lower education and hypertension. **Discussion:** The incidence rates of MCI varied widely, and possible risk factors for incident MCI were analysed only to a limited extent. The findings call for an agreement concerning the criteria used for MCI and the operationalisation of these criteria.

Introduction

Dementia is not only one of the most burdensome diseases for sufferers and their caregivers, it is also one of the biggest challenges for developed countries and their health care systems. Based on 24.3 million dementia sufferers in the year 2001, Ferri et al. [1] estimated a worldwide increase of 4.6 million new dementia cases every year. Without changes in mortality and new effective prevention strategies or curative treatments, the number of affected people will double every 20 years to 81.1 million by 2040. Dementia – particularly of the Alzheimer’s type – is normally preceded by a period of mild cognitive impairments (MCI). Several concepts, like age-associated memory impairment [2], aging-associated cognitive decline [3] or cognitively impaired, not demented [4, 5] have been used in the past in order to define those mild impairments. Today, especially the concept of MCI [6–9] has become increasingly popular in clinical research and practice [10, 11]. Several studies [12–15] have shown that elderly individuals with MCI constitute a high-risk population of developing dementia. MCI – compared to most of the other concepts – has always been defined in order to characterise an abnormal clinical state, prodromal to dementia [10]. The prodromal state of MCI has been demonstrated with regard to neuropathological substrates (e.g. neuritic plaques, neurofibrillary tangles, hippocampal atrophy) in numerous studies [10, 16, 17].

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In order to assess the possible need for secondary prevention and care as well as to explore preventive approaches for MCI leading to dementia, reliable data on the epidemiology are required. Many existing epidemiological studies on MCI are mainly based on prevalent cases [e.g. 13, 18–23]. Studies based on incident MCI cases provide the opportunity to look at cognitively impaired subjects from the onset of their impairment. This allows precise statements concerning the course of the impairment by including a prospective analysis of possible risk factors. To the best of our knowledge, there is no existing systematic review of results on the incidence of MCI in the international literature. Thus, we aimed to systematically review all published population- or community-based studies analysing the incidence of MCI with the following objectives: (i) describing characteristics of the studies (country, sample, observation interval, MCI criteria and their operationalisation, etc.); (ii) comparing findings on MCI incidence rates in consideration of the study characteristics and identified risk factors, and (iii) summarising current research findings and drawing conclusions for future research in this area.

Methods

Definition of MCI

During the last few years, the MCI concept has continuously been further developed, and studies have often additionally modified original criteria. General criteria of the different definitions of the MCI concept [6–9], however, are rather identical and usually comprise: (1) a cognitive complaint (self-reported and/or informant); (2) preserved basic activities of daily living; (3) cognitive impairment (not normal for age and education) or decline in cognition evidenced by performance on objective cognitive tasks; (4) preserved general cognitive functioning (not required in [6, 9]), and (5) absence of dementia.

Discrepancies between the different definitions of the MCI concept mainly consist of the number and type of the impaired cognitive domains. Primarily, the MCI concept only requires impairment in memory with preserved general cognitive functioning at the same time [8]. Today, MCI can be divided into 4 subtypes [6, 9].

- Amnestic MCI single domain: objective impairment in memory but not in another cognitive domain.
- Amnestic MCI multiple domain: objective impairment in memory and in at least 1 other cognitive domain.
- Non-amnestic MCI single domain: objective impairment in a single cognitive domain other than memory.
- Non-amnestic MCI multiple domain: objective impairment in at least 2 cognitive domains other than memory.

Systematic Literature Search

Relevant publications on the incidence of MCI were identified by searching the electronic databases Medline, Web of Science,

Cochrane Library and Psycinfo as well as bibliographies of several articles. ‘Mild cognitive impairment’, ‘MCI’ and ‘incidence’ served as keywords. The following selection criteria were applied: (i) application of the MCI criteria [6–9] in order to identify ‘cognitively mildly impaired’ subjects; (ii) studies considering the incidence of MCI as outcome criteria using the ‘person-years-at-risk’ method¹; (iii) studies with population- or community-based samples, and (iv) studies in English or German. Because the first MCI criteria [8] had already been used in some previous studies [24], the systematic literature search comprised the time period between January 1995 and September 2009.

Results

The results of the systematic literature search are presented in figure 1. Altogether, 9 studies on the incidence of MCI fulfilling the specified selection criteria were found.

Tables 1 and 2 provide an overview of the studies. Six of the 9 studies were conducted in Europe, 2 in the USA and 1 in Brazil. European studies were related to population-based samples and American and Brazilian studies to community-based samples. The population at risk for incident MCI ranged between 245 and 1,800 subjects. In the majority of the studies, the age of the participants at baseline was at least 65 or 75 years. Younger participants (≥ 60 years) were only included in the studies by Tervo et al. [25] and Chaves et al. [26]. The observation intervals for incident MCI ranged between 3 and 9 years and the number of follow-ups between 1 and 3.

Regarding MCI subtypes, information on the incidence of amnestic MCI single domain was given in 2 studies [28, 30] and on the incidence of amnestic MCI multiple domain, non-amnestic MCI single domain and non-amnestic MCI multiple domain in 1 study [28]. Eight studies [21, 22, 25–29, 31] provided information on the incidence of the amnestic MCI subtypes combined (single + multiple domain) and 2 [21, 28] on the incidence of the non-amnestic MCI subtypes combined. Information on the incidence of any MCI (all 4 subtypes combined) was also given in 2 studies [21, 28].

As shown in table 1, 4 of the 9 studies have modified original MCI criteria; 3 reports provide information on incidence of MCI omitting the criterion of cognitive complaint [21, 22, 30] and 1 study omitting the criteria of cognitive complaint and preserved basic activities of daily living [25]. Studies also differ in the operationalisation of

¹ Incidence is calculated as the number of new MCI cases divided by the time at risk of developing MCI (person-years).

Table 1. Studies on incidence of MCI

Study	MCI subtypes/ underlying definition of MCI	MCI criteria			
		cognitive complaint	preserved basic activities of daily living	cognitive impairment	exclusion of dementia
Chaves et al. (2009) [26], Brazil	aMCI-SD/MD- combined ¹ Petersen et al. [24]	Memory complaint; reported by participant, family, physician	No impairment on Katz ADL scale	<i>Memory impairment:</i> test scores >1.5 standard deviations below age- appropriate norms or abnormal memory function for age; tests n.s. Preserved general cognitive functioning; n.s. CDR global score = 0.5	DSM-IV criteria for dementia, NINCDS-ADRDA criteria for AD
Caracciolo et al. (2008) [27], Kungsholmen Project, Sweden	aMCI-SD/MD- combined ¹ Petersen et al. [8]	Memory complaint; reported by participants, close informant or both	No impairment on Katz ADL scale or slight functional impairment (judged by an examining physician to not be attributable to cognitive impairment)	<i>Memory impairment:</i> test performance <1.5 standard deviations below the mean of age- and education-specific norms on a verbal memory task (free recall) <i>Preserved general cognitive functioning:</i> test performance not <1 standard deviation below age- and education- specific means on the MMSE	DSM-III-R criteria
Manly et al. (2008) [28], USA	(1) aMCI-SD (2) aMCI-MD (3) aMCI-SD/MD- combined (4) naMCI-SD 4a: executive 4b: language 4c: visuospatial (5) naMCI-MD (6) naMCI-SD/MD- combined (7) any MCI Petersen [6], Petersen et al. [7]	No indication of memory problems on the DFL and BFA scales	Reported by participants or caregivers; assessed by the DFL scale for IADLs	<i>Cognitive impairment:</i> test performance in at least 1 cognitive domain <1.5 standard deviations below the mean, corrections for age, education, ethnicity, and sex based on previously established norms; assessed by SRT and BVRT for memory; LF, CF and WAIS-Revised Similarities subtest for executive function; BNT and BDAE for language; RDT and BVRT matching for visual- spatial ability <i>Preserved general cognitive functioning:</i> for MCI subtypes with isolated impairment in 1 cognitive domain (aMCI SD, naMCI SD), no impairment (test performance not <1.5 standard deviations below the mean, corrections for age, education, ethnicity and sex based on previously established norms) in other cognitive domains	DSM-III-R criteria for dementia, NINCDS-ADRDA criteria for AD and NINDS-AIREN criteria for VD and consortium on DLB international workshop criteria for DLB; CDR for severity rating
Ravaglia et al. (2008) [21], CSBA, Italy	(1) aMCI-SD/MD- combined (2) naMCI-SD/MD- combined (3) any MCI Winblad et al. [9]	The criterion has been omitted	No need for supervision or external help to perform any ADL (Katz ADL Scale) or IADL (Lawton and Brody IADL Scale; no exclusion of subjects with functional dependency due to physical impairment)	<i>Cognitive impairment:</i> age- and education-adjusted test scores 1.5 standard deviations or fewer below the reference thresholds in at least 1 cognitive domain; assessed by PMT for memory and MDB for memory, language, frontal function, abstract reasoning and visuospatial abilities <i>Preserved general cognitive functioning:</i> not required	DSM-IV criteria for dementia, NINCDS- ADRDA criteria for AD and NINDS- AIREN criteria for VD
Verghese et al. (2006) [29], Bronx Aging Study, USA	aMCI-SD/MD- combined ¹ Petersen et al. [8]	Memory complaint; reported by participants, informant report when available	No impairment on a 10-item ADL/IADL scale	<i>Memory impairment:</i> 3 or more errors on the 5-item Blessed test memory phrase (corresponds to performance at or below 1.5 standard deviations below the mean) <i>Preserved general cognitive functioning:</i> verbal IQ (WAIS) score not <1 standard deviation below the population mean and a score of <8 on the Blessed test	DSM-III-R criteria, NINCDS-ADRDA criteria for AD and ADRCC criteria for VD

Sample	OI (years)/ No. of FUPs	Age at baseline years	Population at risk for incident MCI	Incident MCI cases % (n)	Incidence per 1,000 person-years (95% CI)
community-based	8/n.s.	60+	245 ²	7.3 ³ (18)	13.2 (7.79–20.91)
population-based	9/3	75+	1,070	6.0 ³ (64)	13.7 (10.3–18.2) ⁴
community-based (multiethnic community: Caribbean Hispanic, black and non-Hispanic white people)	mean = 4.7 (SD = 2.8)/ mean = 2.3	65+	1,800	(1) 5.8 ³ (105) (2) 3.6 ³ (65) (3) 9.4 ³ (170) (4a) 1.1 ³ (19) (4b) 3.7 ³ (67) (4c) 4.7 ³ (85) (4) 9.5 ³ (171) (5) 2.1 ³ (38) (6) 11.6 ³ (209) (7) 21.1 ³ (379)	(1) 14 (11–17) (2) 9 (7–11) (3) 23 (19–26) (4a) 3 (1–4) (4b) 9 (7–11) (4c) 11 (9–14) (4) 23 ⁵ (5) 5 (1–7) (6) 28 (24–32) (7) 51 (46–56)
population-based	mean = 3.8 (SD = 0.8)/1	65+	685	(1) 11.5 (79) (2) 11.1 (76) (3) 22.6 (155)	40.6 (33.5–49.2) 36.3 (29.6–44.5) 76.8 (66.8–88.4)
community-based	mean = 5.6 (SD = 4.1)/ FUPs every 12–18 months	75–85	437	13.3 ³ (58)	21.4 ³

Table 1 (continued)

Study	MCI subtypes/ underlying definition of MCI	MCI criteria			
		cognitive complaint	preserved basic activities of daily living	cognitive impairment	exclusion of dementia
Tervo et al. (2004) [25], Finland	aMCI-SD/MD- combined Petersen et al. [8]	The criterion has been omitted	The criterion has been omitted	<i>Memory impairment:</i> test performance <1.5 standard deviations below the average (in relation to a healthy sub- group of the sample) in delayed recall in the LM from the WMS-R or in the VR from the WMS; CDR = 0.5; no exclusion of subjects with deficits in cognitive domains other than memory <i>Preserved general cognitive functioning:</i> MMSE ≥20	DSM-IV criteria for dementia, NINCDS- ADRD criteria for AD
Solfrizzi et al. (2004) [22], ILSA, Italy	aMCI-SD/MD- combined ¹ Petersen et al. [8]	The criterion has been omitted	No impairment on Katz ADL Scale and on Lawton and Brody IADL Scale; no exclusion of subjects (a) with slight ADL impairment but no IADL impairment, (2) with visual, auditory or skeletal muscle disabilities compro- mising ADL, but not cognitive skills, (3) with ADL impaired by comorbid illnesses (2 or more)	<i>Memory impairment:</i> test performance in the lowest 10th percentile of the dis- tribution of age- and education-adjusted scores after exclusion of prevalent dementia at entry; assessed by the total BRST score (immediate plus delayed recall) <i>Preserved general cognitive functioning:</i> performance on the MMSE not <1.5 standard deviations below the mean of age- and education- adjusted scores after exclusion of subjects with prevalent de- mentia	DSM-III-R criteria for dementia syndrome, NINCDS-ADRD criteria for possible and probable AD, ICD-10 criteria for VD and OD
Busse et al. (2003) [30], LEILA, Germany	aMCI-SD with (1) and without (2) criterion of subjective com- plaint Petersen et al. [8]	(1) Memory complaint; reported by participants, informants or both (2) The criterion has been omitted	No impairment on SIDAM ADL Scale, impairment due to physical disease was not sufficient for exclusion	<i>Memory impairment:</i> test performance <1 standard deviation below the mean of age- and education-specific norms; as- sessed by the memory subtest of the SIDAM (impairment on the memory subtest only and not on subtests relating to other cognitive functions) <i>Preserved general cognitive functioning:</i> test performance not <1 standard devia- tion below the mean of age- and educa- tion-specific norms; assessed by the 'in- tellectual abilities' subtest of the SIDAM	DSM-IV criteria
Larrieu et al. (2002) [31], PAQUID, France	aMCI-SD/MD- combined ¹ Petersen et al. [8]	Memory complaint; 2 questions on self- perceived forgetfulness in daily activities or in recent events	No impairment on Katz ADL Scale	<i>Memory impairment:</i> test performance <1.5 standard deviations of the mean of age- and education-defined strata; assessed by the BVRT <i>Preserved general cognitive functioning:</i> performance on the MMSE not <1 stan- dard deviation below the mean of age- and education-defined strata in the cohort after exclusion of prevalent dementia at entry	DSM-III-R criteria

AD = Alzheimer's dementia; ADL = activities of daily living; ADRC = Alzheimer's disease research centers of California; aMCI = amnesic MCI; BDAE = Boston diagnostic aphasia examination; BFA = blessed functional activities; BNT = Boston naming test; BRST = Babcock story recall test; BVRT = Benton's visual retention test; CDR = clinical dementia rating; CF = category fluency; CI = confidence interval; CSBA = Conselice Study of Brain Ageing; DFL = disability and functional limitation; DLB = dementia with Lewy bodies; DSM = Diagnostic and Statistical Manual of Mental Disorders; FUPs = follow-ups; IADL = instrumental activities of daily living; ICD = international statisti-

cal classification of diseases and related health problems; ILSA = Italian longitudinal study on aging; IQ = intelligence quotient; LEILA = Leipzig longitudinal study of the aged; LF = letter fluency; LM = logical memory; MD = multiple domain; MDB = mental deterioration battery; MMSE = mini-mental status examination; naMCI = non-amnesic MCI; NINCDS-ADRD = National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association; NINDS-AIREN = National Institute of Neurological and Communication Disorders and Stroke/Association Internationale pour la Recherche et l'Enseignement en Neurosciences; n.s. = not

Sample	OI (years)/ No. of FUPs	Age at baseline years	Population at risk for incident MCI	Incident MCI cases % (n)	Incidence per 1,000 person-years (95% CI)
population-based	mean = 3.3 (SD = 0.7)/1	60–76	747	8.8 (66)	25.9 (20.1–33.4)
population-based (stratified for age and gender)	3.5/1	65–84	1,524	7.4 ³ (113)	21.5 (17.9–25.8)
population-based	3/2	75+	(1) 900 (2) 882	(1) 1.7 ³ (15) (2) 2.4 ³ (21)	(1) 8.5 (4.8–14.1) (2) 12.2 (7.6–18.7)
population-based (institutionalised subjects not included at baseline)	5/2	65+	1,265	3.2 ³ (40)	9.9 (9.6–10.2)

specified; OD = other dementia; OI = observation interval; PAQUID = person-
nes âgées QUID; PMT = prose memory test; RDT = Rosen drawing test; SD =
single domain; SIDAM = structured interview for diagnosis of dementia of
Alzheimer type, multi-infarct dementia and dementia of other aetiology;
SRT = selective reminding test; VD = vascular dementia; VR = visual reproduc-
tion; WAIS = Wechsler adult intelligence scale; WMS = Wechsler memory scale;
WMS-R = Wechsler memory scale-revised.

¹ Objective impairments in cognitive domains other than memory were not ex-
cluded explicitly and preserved general cognitive functioning also does not ex-

clude the possibility of impairments in specific non-amnestic cognitive do-
mains explicitly. Thus, the type of MCI investigated in the study should not be
Amnestic MCI Single Domain but rather Amnestic MCI subtypes combined
(Single + Multiple Domain).

² At least 1 follow-up completed. ³ Calculated from the study results. ⁴ Cor-
rected for mortality during follow-up. ⁵ Addition of the incidence rates of
naMCI-SD executive, language and visuospatial.

Table 2. Risk factors for incident MCI

Study	MCI subtypes/ underlying definition of MCI	Statistical model	Risk factors	
			significant	not significant
Caracciolo et al. (2008) [27], Kungsholmen Project, Sweden	aMCI-SD/MD-combined Petersen et al. [8]	Poisson regression	higher age	gender
Manly et al. (2008) [28], USA	(1) aMCI-SD/MD-combined (2) naMCI-SD/MD-combined (3) any MCI Petersen [6] Petersen et al. [7]	Cox proportional hazards model	(1) aMCI-SD/MD-combined: – higher age – history of a diagnosis of hypertension – history of heart disease (protective) (2) naMCI-SD/MD-combined: – lower education (<12 years) (3) any MCI: – higher age – ethnicity ¹ (black, Hispanic vs. non-Hispanic white) – history of a diagnosis of hyper- tension	(1) aMCI-SD/MD-combined: – gender – education – ethnicity (black, Hispanic vs. non-Hispanic white) – cohort – diabetes mellitus – stroke – psychiatric illness (2) naMCI-SD/MD-combined: – age – gender – ethnicity (black, Hispanic vs. non-Hispanic white) – cohort – history of heart disease – history of a diagnosis of – hypertension – diabetes mellitus – stroke – psychiatric illness (3) any MCI: – gender – education – cohort – history of heart disease – diabetes mellitus – stroke – psychiatric illness – apoE ε4 allele ¹
Vergheze et al. (2006) [29], Bronx Aging Study, USA	aMCI-SD/MD-combined Petersen et al. [8]	Cox proportional hazards model	– cognitive activity (protective)	– physical activity
Tervo et al. (2004) [25], Finland	aMCI-SD/MD-combined Petersen et al. [8]	Multiple logistic regression analysis	– higher age – higher education (protective) – apoE ε4 allele – medicated hypertension	– gender – cardiovascular diseases (significant risk factor when analysed separately) – cerebrovascular diseases – diabetes mellitus – elevated blood pressure
Solfrizzi et al. (2004) [22], ILSA, Italy	aMCI-SD/MD-combined Petersen et al. [8]	Poisson regression	– higher age – higher education (protective)	– cigarette pack-years – coronary artery disease – hypertension – higher levels of serum total cholesterol (borderline non- significant trend for a protec- tive effect)

aMCI = Amnesic MCI; ILSA = Italian Longitudinal Study on Aging; MD = multiple domain; naMCI = non-amnesic MCI; SD = single domain.

¹ Among a subsample with apoE data (n = 1,472) higher age and hypertension remained risk factors, but ethnicity and apoE ε4 allele failed to be significant risk factors.

Fig. 1. Results of the systematic literature search.

the MCI criteria. For example, objective memory impairment was defined either as test performance <1.0 standard deviations or as test performance <1.5 standard deviations below the mean of a reference group or as test performance in the lowest 10th percentile in relation to a reference group. Moreover, test norms were mostly corrected for age and education but also for ethnicity and sex.

Incidence Rates of MCI

MCI was developed in 1.7–22.6% of the study populations at risk. Altogether, the incidence rates of MCI varied between 8.5 and 76.8 per 1,000 person-years.

With regard to amnesic MCI single domain, incidence rates of 8.5 [30], 12.2 (criterion of cognitive complaint omitted) [30] and 14 [28] per 1,000 person-years were found. Concerning amnesic MCI multiple domain, non-amnesic MCI single domain and non-amnesic MCI multiple domain, Manly et al. [28] reported incidence rates of 9, 23 and 5 per 1,000 person-years. The incidence rates of amnesic MCI subtypes combined (single + multiple domain) ranged between 9.9 and 40.6 per 1,000 person-years [21, 22, 26–29, 31], whereas the highest rates (25.9 and 40.6 per 1,000 person-years) were found in studies omitting the criterion of cognitive complaint [21, 25] and the lowest ones (9.9 and 13.2 per 1,000 person-

years) in trials including the criterion [26, 31]. Regarding non-amnesic MCI subtypes combined, incidence rates of 28 [28] and 36.3 (criterion of cognitive complaint omitted) [21] per 1,000 person-years have been reported.

Information on the incidence of any MCI (all 4 subtypes combined) was given in 2 studies; Manly et al. [28] reported an incidence of MCI of 51 per 1,000 person-years and Ravaglia et al. [21] of 76.8 per 1,000 person-years omitting the criterion of cognitive complaint.

Risk Factors for Incidence of MCI

Possible risk factors for the incidence of MCI were analysed in 5 of the 9 studies using multivariate statistical methods like Poisson regression, multiple logistic regression or Cox proportional hazards models (table 2). All 5 studies referred to amnesic MCI subtypes combined (single + multiple domain). Manly et al. [28] additionally referred to non-amnesic MCI subtypes combined and any MCI.

Regarding amnesic MCI subtypes, a significant impact of age on the incidence was found in all 4 studies that analysed age as a possible risk factor [22, 25, 27, 28]. By contrast, a significant impact of gender on the incidence of amnesic MCI subtypes could not be identified. A higher level of education was found to be a rather protective factor for incident amnesic MCI subtypes in 2 stud-

ies [22, 25] but not in all [28]. Ethnicity failed to have a significant effect. The impact of higher cognitive activity on the incidence of amnesic MCI subtypes was analysed in 1 study and could be identified as a protective factor [29]. The influence of vascular factors and diseases on the incidence of amnesic MCI subtypes was analysed in 3 studies [22, 25, 28]. Hypertension could be identified as a risk factor in 2 of the 3 trials [25, 28]. History of heart disease was analysed in 1 study [28] and was found to be a rather protective factor. Cardiovascular diseases in general (when analysed multivariately [25]), however, failed to be significant risk factors; this was also true for coronary artery disease, serum total cholesterol [22], cerebrovascular diseases [25], stroke [28], diabetes mellitus [25, 28], cigarette pack-years [22] and psychiatric illness [28]. ApoE ϵ 4 allele – analysed in 1 study [25] – was found to be a risk factor for the incidence of the amnesic MCI subtypes.

Regarding incident non-amnesic MCI subtypes, only lower education (<12 years) was found to be a significant risk factor [28]. With respect to the incidence of any MCI – according to the result for amnesic MCI subtypes – higher age and history of a diagnosis of hypertension were found to be significant risk factors. Ethnicity (black, Hispanic vs. non-Hispanic white) was only found to be a risk factor for MCI in an overall sample [28]. No impact on the incidence of any MCI was found for gender, education, history of heart disease, diabetes mellitus, stroke, psychiatric illness and the apoE ϵ 4 allele [28].

Discussion

MCI Incidence Rates in Consideration of Study Characteristics and Identified Risk Factors

Our review shows that findings on the incidence rates of MCI vary widely particularly with regard to the amnesic MCI subtypes. These variations in the incidence rates generally might be affected by differences in the study characteristics like the age of the sample or in the criteria used for MCI and their operationalisation. With regard to the age of the study samples, being older was found to be strongly associated with a higher risk or a higher incidence rate of MCI. Concerning the impact of MCI criteria, 4 of the 9 studies reported incidence rates for MCI concepts omitting the criteria of cognitive complaint. If MCI is diagnosed including an obligate criterion of cognitive complaint, the incidence rates should be lower because a high percentage of objectively cognitively impaired subjects does not complain about their cogni-

tion [20]. Regarding the study by Busse et al. [30], for example, the inclusion of memory complaint lowered the incidence of amnesic MCI single domain from 12.2 to 8.5 per 1,000 person-years (table 1). Whether a subjective cognitive complaint should be mandatory for a diagnosis of MCI, raises a controversial issue [32–34]. For example, objectively cognitively impaired subjects who do not complain about their cognition would not be classified as cognitively mildly impaired according to MCI criteria including a mandatory criterion of subjective cognitive complaint. Thus, they would be excluded a priori from a possible risk population for progression to dementia. Moreover, many cross-sectional studies have shown that subjective memory impairments, for example, are rather associated with factors like depression or anxiety [35, 36] than with objective test performance. A predictive value of subjective cognitive impairments for future cognitive decline, however, was found in many longitudinal studies with larger representative population samples [34, 37]. Additionally, subjective impairments are often the only indication of incipient cognitive deterioration in highly educated persons [38]. The inclusion of subjective cognitive complaints in a definition of MCI can be expedient for an early detection of dementia, yet it requires a standardised and validated set of criteria of these complaints according to the set proposed by Abdulrab and Heun [39] – for subjective memory impairments, for example.

A ‘gold standard’ is not only necessary for the operationalisation of the subjective cognitive complaints, it is also required for the operationalisation of the remaining criteria of MCI. With regard to the criterion of objective cognitive impairment, for example, there are significant differences in the applied cognitive tests and test norms used for operationalisation. As an example, if objective cognitive impairment is defined as a test performance <1.5 standard deviations below the mean of a reference group, the incidence of MCI will – only for statistical reasons – be lower than if the objective cognitive impairment were defined as a test performance <1.0 standard deviations below the mean of a reference group. Moreover, studies that use short cognitive test batteries may miss a significant number of cases due to a lack of sensitivity to detect the less severe MCI syndromes, which would produce an underestimation of MCI incidence.

Possible risk factors for incident MCI were analysed only to a limited extent in most of the included studies. However, a higher risk of incident MCI was particularly found for higher age, lower education and hypertension, but not for gender. An increase in the incidence of MCI with age is not unexpected, as MCI represents a pre-de-

mentia stage in many cases [12–14], and the incidence of dementia itself also increases with age [40, 41]. The findings regarding gender and education are consistent with those from many prevalence studies showing a lack of association between gender and prevalence of MCI and a positive relationship between higher education and lower prevalence of MCI [22, 23, 42–44]. A high level of education was also found to be associated with a decreased risk for incident Alzheimer's disease (AD) yet with a faster cognitive decline in clinically manifest AD [45]. These findings have been explained by the cognitive reserve theory [45–47]: a decreased risk for incident AD can be found in persons with higher education because they have more cognitive reserve than persons with low education, enabling them to cope with progressive AD pathology longer before it is expressed clinically. However, if AD becomes clinically manifest in highly educated persons, the AD pathology should be more advanced than in less educated persons and thus associated with a faster cognitive decline. As shown by Scarmeas et al. [45], findings on an advanced AD pathology in highly educated persons have been supported through some imaging studies.

The apoE ϵ 4 allele represents a proven genetic risk factor for AD [48, 49]. In the study by Tervo et al. [25], the apoE ϵ 4 allele was also identified as a risk factor for incident MCI. The association between apoE ϵ 4 genotype and MCI needs to be seen in a nuanced light, since a significant impact of the apoE ϵ 4 genotype on the incidence of MCI could not be found in all studies [28]. There is evidence that apoE ϵ 4 is generally associated with memory impairment, and not solely in subjects with AD [50]. Conversely, there is also evidence that the effect of apoE ϵ 4 on memory definitely depends on an underlying AD pathology, yet only in higher age [51]. Thus, further studies are required in order to better understand the association between apoE ϵ 4 and developing MCI and AD.

Unlike non-modifiable genetic risk factors such as apoE ϵ 4, vascular risk factors and diseases provide an opportunity for preventive approaches (sport, avoidance of smoking and excessive drinking, etc.) and thus an opportunity to influence the development of MCI and dementia. Regarding the included incident studies, hypertension was particularly found to be a significant risk factor for future MCI. The mechanisms underlying the association between hypertension and future MCI, however, are not completely clarified. Explanations like increased frequency of neurofibrillary tangles, increased brain atrophy, higher risk of white matter hyperintensities and lacunar brain infarcts or dysfunction of the blood-brain

barrier in hypertensive subjects have been outlined by Reitz et al. [52]. Regarding cross-sectional findings, a significant association with MCI was also found for vascular diseases like transient ischaemic attack [38], stroke/MRI-identified infarct/cerebral haemorrhage [38, 43, 53], atrial fibrillation [43] or peripheral arterial obstructive disease [20].

Most of these diseases, however, were not analysed as separate risk factors in the incident studies. Stroke was considered separately but not found to be a significant risk factor for incident MCI [28]. The lack of association with future MCI might be due to the fact that stroke usually causes cognitive deficits immediately. Subjects with stroke and coincidental cognitive deficits (MCI), however, had to be excluded in incident MCI studies at baseline. By contrast, subjects with stroke and without cognitive deficits at the baseline date of an incident study might suffer from less severe strokes. Moreover, the stroke might have appeared earlier in life, meaning cognitive deficits might already have improved by the beginning of the incident study.

Implications for Research

This review on the incidence of MCI may contribute to estimating the need for secondary prevention of incipient cognitive deterioration up to dementia and for the development of new preventive and curative approaches. However, the compiled findings also reveal grey areas where continuative research efforts are required.

Firstly, as mentioned above, possible risk factors for incident MCI were analysed only to a limited extent in most of the included studies. At present, neuroimaging measures and biomarkers (e.g. hippocampal atrophy, reduced hippocampal metabolism, increased tau protein in cerebrospinal fluid) become more and more important with regard to an identification of the subjects (with MCI) who are at high risk of developing dementia [16, 54–56]. Of course, it is not possible to analyse all possible risk factors for MCI in large community- and population-based studies exhaustively. Nevertheless, neuroimaging measures and biomarkers should be taken into account increasingly in future research.

Secondly, the MCI concept in general has to be empirically validated further. As shown by Busse et al. [13], the course of MCI is heterogeneous. A substantial number of subjects with MCI progresses to dementia, but there are also patients who improve to 'normal' after MCI diagnosis, and there are subjects with a stable or unstable course of MCI over several observation points in time. Thus, future studies on the incidence of MCI should in-

clude a substantial number of follow-ups with short time intervals in between to examine the course of MCI more exactly. Furthermore, an agreement concerning the criteria used for MCI and the operationalisation of these criteria is required (e.g. the use of a consistent cut-off in cognitive tests for the definition of objective cognitive impairment) to ensure the comparability of different epidemiological and clinical findings on MCI.

Finally, a diagnosis of MCI is clinically useful for the identification of a high-risk population for the development of dementia. With regard to the substantial number of subjects with MCI who do not progress to dementia, an MCI diagnosis alone cannot, however, be equated with a pre-dementia stage of a neurodegenerative disorder [11] and therefore does not allow the implementation of treatment like medication. In order to define an MCI

concept allowing these treatments, Förstl et al. [54, 55] have supplemented the MCI diagnosis with predictors of a rapid cognitive decline (older age, vascular risk factors, neurological symptoms, apoE ϵ 4 genotype, etc.). Advancement and validation of such an MCI plus [54, 55] concept should be the utmost concern of future research on MCI.

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