Mild cognitive decline. A position statement of the Cognitive Decline Group of the European Innovation Partnership for Active and Healthy Ageing (EIPAHA).

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HIGHLIGHTS

1) MCI is important because it defines an intermediate step in the progress to dementia.
2) Risk factors are crucial to design effective preventive strategies.
3) Screening at population level is debated.
4) New ICT technologies provide tools for screening at great scale.
5) The role of lifestyle in risk reduction is promising.

ABSTRACT

Introduction

Mild cognitive impairment (MCI) is a term used to describe a level of decline in cognition which is seen as an intermediate stage between normal ageing and dementia, and which many consider to be a prodromal stage of neurodegeneration that may become dementia. That is, it is perceived as a high risk level of cognitive change. The increasing burden of dementia in our society, but also our increasing understanding of its risk factors and potential interventions, require diligent management of MCI in order to find strategies that produce effective prevention of dementia.

Aim

To update knowledge regarding mild cognitive impairment, and to bring together and appraise evidence about the main features of clinical interest: definitions, prevalence and stability, risk factors, screening, and management and intervention.

Methods

Literature review and consensus of expert opinion.

Results and conclusion

MCI describes a level of impairment in which deteriorating cognitive functions still allow for reasonable independent living, including some compensatory strategies. While there is evidence for some early risk factors, there is still a need to more precisely delineate and distinguish early manifestations of frank dementia from cognitive impairment that is less likely to progress to dementia, and furthermore to develop improved prospective evidence for positive response to intervention. An important limitation derives from the scarcity of studies that take MCI as an endpoint. Strategies for effective management suffer from the same limitation, since most

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studies have focused on dementia. Behavioural changes may represent the most cost-

effective approach.

1. Introduction and concept

The term Mild Cognitive Impairment (MCI) was introduced as a clinical entity over twenty years ago. Initially, Reisberg and colleagues [1] used this term to describe patients who were at the intermediate stage between normal ageing and dementia state. Later, a set of diagnostic criteria was defined [2]. These diagnostic criteria included abnormal memory function for the person's age and, in association, memory complaints, as well as normal general cognitive function and normal activities of daily living (ADL). In addition, the absence of dementia was inferred, although it was suggested that MCI can constitute a prodromal form of Alzheimer´s Disease (AD) [3].

More recently, the investigation from clinical, pathological, genetic, imaging and epidemiological perspectives suggests that MCI should be expanded to include other cognitive domains such as executive function or visuospatial skills [4-7]. Simultaneously, memory impairment was no longer considered a necessary diagnostic condition. The criteria related to preservation of independence in functional abilities, and to the absence of dementia, were maintained.

According to this new approach [5], MCI was defined by a decline in cognitive functioning that is greater than would be expected for the patient's age and educational background and that goes beyond normal changes seen in ageing. This decline from a previous level can include a variety of cognitive domains, including learning and memory, complex attention, executive functions, language, perceptual-motor domain and social cognition [8], although it is common that decline manifests in a single domain only. Changes in cognitive functioning should be serious enough to be noticed either by the individuals experiencing them, by other people who know the patient well or by a skilled clinician in an appropriate clinical context [5]. For example, impairment in memory can be evidenced by forgetting of important events

such as appointments or social engagements, trouble remembering the names of people met recently, word-finding difficulties, trouble remembering the flow of a conversation or the thread of books or movies and an increased tendency to misplace things. While these cognitive changes should not be severe enough to interfere with ADL, complex functional tasks, for example, interpretation of instructions, planning subsequent activities or making decisions, may require the engagement of compensatory strategies by the individual [8].

1.1 Amnestic MCI versus non-amnestic MCI

Longitudinal studies have indicated that MCI can evolve into different forms of dementia and that this evolution depends on the nature and extent of cognitive impairments experienced in the transitory stage [4]. In order to define better the determinants for making diagnostic decisions, and provide more targeted interventions, differentiation between MCI with (amnestic MCI, a-MCI) or without (non-amnestic MCI, na-MCI) decline in the memory domain has been proposed. Additionally, it is considered relevant to specify whether the diminishing of functioning involves only one cognitive domain or more [4,9].

1.2 Mild Cognition Impairment in DSM-5 perspective

The clinical criteria for MCI are also considered in The Diagnostic Statistical Manual-5 (DSM-5) [10], although, in this case, a term used for diagnostic purposes is Mild Neurocognitive Disorder (mild NCD). Mild NCD is included together with Major Neurocognitive Disorders (major NCD) in the general category of Neurocognitive Disorders (NCD).

The common feature of NCD is the absence of cognitive impairment at the moment of birth or during early life. Thus, evidence of cognitive decline, necessary to complete

the diagnosis, should be based on the previous level of performance. Importantly, the decline in cognitive domains should not appear in the context of delirium or result from other mental disease. This clarification is pertinent, because NCD may result from aetiologies different to neurocognitive disorders. For example, a person with suspected AD may be classified as having mild NCD due to AD. Other causes may be vascular, traumatic, or others [10].

Conceptual definitions of MCI have changed over time. Despite intense effort to clarify neuropsychological and clinical profile of this condition, there is still lack of consensus about its neuropathological substratum. It is also necessary to harmonize definitions and labels across working groups and disciplines.

2. Prevalence and stability

Reported prevalence of MCI varies, with annual incidence rate ranging from 5.5 to 7.7 per cent of persons aged 60 or over [11], and Plassman et al [12] estimating 22% of people aged over 71 as having cognitive impairment but not dementia. In terms of the concept of MCI as an intermediate phase of AD [6], it has been demonstrated that 15-41% of MCI cases per year progress to AD or other dementias [13-15]. For example, in a four year study, Lonie et al [16] found a mean annual conversion rate of 11% when assessed using the Addenbrooke's Cognitive Examination criteria, although other authors suggest this may be less (5.8%) [17].

Conversely, studies have also shown that up to 44% of patients with MCI return to a non-MCI diagnosis a year later [14,18] suggesting that it can be viewed as unstable. For example, in an eight year longitudinal study, Anstey et al [19] found that 45% of diagnoses were unstable for their group of young-old participants aged 62-64 at

baseline. Thus MCI could be viewed as a transient and high risk phase, and interventions to promote improved health or cognitive functioning could be particularly pertinent for this group. However, these data also indicate that diagnosis or screening of MCI may still be imprecise.

3. Risk factors

Studies on risk factors for MCI suffer from the limitation that the cohorts are almost always contaminated by those cases that are already at an early stage of dementia but do not yet fulfil the necessary criteria for a dementia diagnosis. Of course, this is unavoidable on account of the inherent difficulty in distinguishing between cases of MCI and those individuals who are suffering from mild dementia. It follows then, that there is a high interest in detecting factors that predict membership of the second group, for example, the APOE4 allele, and there is a large literature on risk factors which examines that issue. This "contamination" also raises the philosophical question of whether MCI is in itself a different entity to early-stage dementia, or whether all cases of MCI are in fact preliminary dementias, with diverse aetiologies and varying prognoses depending on the potential for disease progression.

Furthermore, there are also inconsistencies in how different studies define MCI when attempting to determine risk factors. Many studies simply refer to cognitive decline or cognitive impairment, usually operationalised as a decline in objective cognitive functioning over time, or falling below a threshold score at a single point in time. Finally, there is the related issue of the instability of an MCI diagnosis, as many cases considered as such no longer meet the criteria at follow-up assessment. These limitations and inconsistencies undoubtedly hamper cross-study comparisons and

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limit the generalisability of the findings from any single study. This highlights the importance of meta-analysis and related tools in determining risk factors that are robust to these variations until such time as MCI as a diagnostic entity is more consistently defined and characterised.

The process leading to MCI is undoubtedly complex, involving multiple, sometimes interrelated, risk factors. There is an expanding literature on the topic. This section will summarise current knowledge on some of the main factors identified with particular reference to studies focusing on MCI as an outcome. An overview of these risk factors is provided in Table 1.

3.1 Demographic factors

Higher age is the best known demographic risk factor, particularly being over the age of 85 [20]. However, estimating the true extent of the association has been problematic, in part because age-corrected normative data for cognitive tests are frequently used to identify individuals with probable MCI. The influence of gender on the development of MCI is not yet clear. Some studies have demonstrated no gender difference [21], others that males have higher prevalence [22], and others that women have a greater risk of MCI [20].

3.2 Genetic factors

In terms of genetic markers, the only widely accepted risk factor is the presence of the APOE4 allele, which is for Alzheimer's dementia [6]. A recent cross-sectional analysis from the Framingham Heart study found an association between APOE4 and MCI, particularly among participants aged 65 and older [23]. Similarly, a study of 46 Cuban MCI patients and 28 controls found the frequency of the APOE4 allele to be

10 times higher in patients compared to controls, although the absolute frequency in patients was only 20% [24].

3.3 Cardiovascular risk factors

A large amount of clinical, pathologic and epidemiological evidence supports the association between cardio-metabolic risk factors and cognitive impairment, from its mild expression to overt dementia, including both vascular cognitive impairment [25] and AD, independently of the occurrence of stroke.

Diabetes mellitus, but also higher glucose levels and insulin resistance in non-diabetic individuals, have been linked to a higher risk of cognitive impairment [26-28]. Higher baseline blood pressure [29], cholesterol levels [30], weight and body mass index [31] are associated with faster decline in cognitive performance over time, either when studied individually, clustered in metabolic syndrome or summed up in cardiovascular risk scores [32,33]. However, the available evidence on the association between the traditional vascular risk factors and cognitive impairment is not always consistent and might appear controversial if some elements are not considered, for example, age at which the risk factor is detected and the study design are important. Longitudinal studies in cognitively healthy midlife participants have found the strongest associations [34,35]; however, this may be complicated by the presence of a confounding effect of the decrease of cholesterol levels and weight that might accompany an unhealthy ageing process and particularly dementia in older adults [36]. The duration of exposure to vascular risk also likely plays a role [37].

For certain vascular risk factors, the relationship might not be monotonic. For example, a U-shaped relationship between blood pressure and cognitive decline has been suggested by several studies (e.g. [38]). Repeated episodes of cerebral

hypoperfusion associated with orthostatic hypotension are as likely to be deleterious as chronic hypertension [39]. This might be one reason the data on the effect of hypoglycemic therapies, antihypertensive drugs, or statin use on the risk of cognitive impairment are not conclusive [40,41]. Finally, effect of vascular risk factors might be modified by the interaction with other risk factors, or with different cognitive disease subtypes, which the existing limited classification criteria might not ascertain.

Several cross-sectional and longitudinal studies have also shown that patients with atrial fibrillation (chronic or paroxysmal) present with worse cognitive and functional performance, and worse trajectories of cognitive test score over time, compared with those in sinus rhythm, even in absence of clinical stroke [42]. Silent cerebral cardio-embolic infarctions may represent the pathological substrate [43]. Mainly because of methodological difficulties, there is no clear evidence regarding a possible protective effect of anticoagulant agents [44].

Encouragingly, most of the major vascular risk factors are modifiable, offering attractive opportunities for disease prevention. For the above mentioned reasons, the timing of any intervention is likely to be crucial to favour success and avoid any iatrogenic harm.

3.4 Sensory factors

Sensory deficits are common in older adults with approximately one-third of adults aged 65 and over affected by hearing loss [45]. Oxidative stress, inflammation and neurological degeneration have been implicated in the development of hearing loss, retinal, macular and olfactory degeneration – potentially leading to a generalised sensory impairment [46]. This may impact on an individual's independence and ability to interact with their environment, with implications for cognitive function.

Hearing impairment in particular has been related to physical frailty and poorer mental health [47,48]. The mechanisms linking sensory deficits and cognitive function are still unclear.

3.4 Behavioural factors

Over the last decade in particular, there has been considerable interest in physical activity as both a modifiable risk factor and an interventional tool for preventing or ameliorating cognitive impairment. Meta-analyses of prospective studies have shown that physical activity, in particular moderate activity, is associated with a lower risk of cognitive decline [49,50]. Recently, studies have started to examine MCI as a distinct outcome but the relationship between physical activity and incident cognitive impairment rather than dementia remains somewhat equivocal [51,52]. However, it is clear that exercise is beneficial for cognitive health and thus represents a very good modifiable risk factor to target. A limitation of many investigations in this area to date is the reliance on self-report instruments to ascertain level of physical activity, which are susceptible to recall and other biases. It is encouraging, however, that studies using objective measurements of activity and measured improvements in cardiovascular fitness are coming to the fore [53].

Evidence that smoking is a risk factor for dementia is mounting. Much of the evidence supports an increased risk for current smokers when compared with individuals who have never smoked, with the risk attributable to previous smoking less clear [54]. To date, investigations of smoking and incident MCI specifically, rather than dementia, have been lacking. However, studies examining the impact of

current smoking on subsequent change in cognitive performance suggest that current smoking is associated with cognitive decline in individuals without dementia [55,56].

Many studies have investigated the association between alcohol consumption and risk of cognitive impairment. In the main, the body of evidence supports a reduced risk of dementia for light to moderate drinkers compared with abstainers and heavy drinkers [57,58]. Fewer studies have focused on MCI only; among those available, the results have been more mixed, with some studies reporting an U-shaped relationship between alcohol intake and MCI risk [59] and others finding no protective effect of alcohol intake at any level [11]. However, the concentration and type of alcohol consumed as well as the frequency of intake varies between studies, making cross-comparisons somewhat challenging. More research on this is warranted, in particular where MCI as the outcome is concerned.

3.5 Psychosocial factors

Lower education has been associated with higher risk of MCI [60] and, unlike age and gender, there is the potential to modify this risk factor at the population level, so it presents an attractive target for risk reduction. There is evidence that education may alter neurobiological substrates to change the brain, by increasing grey matter volume and through continuous activation of the noradrenergic system [61-63]. There are however, some important points to note when endeavouring to interpret epidemiological data on education and risk of MCI: (i) some assessment measures (e.g. MMSE) are not sensitive enough to detect mild changes in cognition in highly educated people [64]; (ii) according to DSM 5, "norms for neuropsychological testing tend to be available only for broad populations, and thus they may not be easily applicable to individuals with less than high school education or those being evaluated outside their primary language or culture"; (iii) education level may affect

the level of concern, awareness and reporting of cognitive symptoms, and therefore has the potential to influence the likelihood of diagnosis.

A growing body of literature has found that it is not purely formal education that may protect against cognitive decline but mental stimulation in its many forms, including social and cognitive engagement. One of the first studies to show the potentially protective effects of social engagement on cognitive function was that by Bennett et al. who found that older adults with high social networks had higher levels of cognitive function regardless of the level of AD pathology present in their brains at autopsy [65]. This finding has been replicated in other samples (e.g. [66]). However, other studies suggest that high social networks may be concomitant with high cognitive function rather than protective [67]. It is possible that the quality of social engagement is more important than the size of social networks in protecting against cognitive decline [68]. Furthermore, a recent meta-analysis on the association between social relationship and risk of dementia found that social network size and satisfaction with social networks were not associated with cognitive decline but low social participation and less frequent social contact were [69]. Although an encouraging area of investigation, more research into the exact nature of the benefit conferred by social relationships on cognitive health is needed.

Prosocial behaviour may also protect against cognitive impairment by supporting mental health. Among the different types of psychiatric illness, depression has been most consistently associated with MCI and dementia in the literature. However, the causal nature of the relationship has often been called into question. It has been argued that the three may sit along a continuum, as clinical manifestations of the same underlying neurodegenerative process [70]. There is, nonetheless, considerable support for depression as a risk factor for MCI; for example, a recent study by Chung

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and colleagues found an association between lifetime history of major depression and amyloid beta deposition in individuals with MCI, regardless of current depressive symptoms [71].

4. Screening and assessment

Because of the potential malleability, and the opportunity for intervention, the role of screening and assessment for MCI is paramount. It is commonly thought that population based screening for cognitive impairments would be unacceptable to individuals and unfeasible to healthcare systems [72], although studies that explore whether there is evidence for such attitudes are not found in the literature, and would be a useful contribution. However, the increasing understanding of risk factors and opportunities for prevention and treatment in the early stages of cognitive decline offer promising avenues for reducing the frequency of dementia in our populations. Clarifying whether earlier screening can be operationalised and simplified for routine clinical use is therefore vital.

4.1 Relationship between diagnostic criteria and appropriate assessment

Key criteria for diagnosing MCI were defined by Petersen et al., [2] as (i) a memory complaint (ii) normal activities of daily living (ADL) (iii) normal general cognitive function (iv) abnormal memory for age (v) no dementia. These criteria have since been expanded to include the concept of decline in functions other than memory so that an amnestic and non-amnestic category of MCI are used (see 1. Introduction and concept). However, studies have also indicated a differentiation between basic activities of daily living (BADL) and instrumental activities of daily living (IADL) such that while people with MCI do not show any BADL deficits (feeding, bathing or dressing oneself etc), IADL (taking care of one's own finances, medication, shopping,

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etc) can be impaired before the actual onset of dementia [73,74].

In that context, Winblad et al [75], in an international consensus report, suggested that the definition should be amended to "preserved BADL and/or minimal impairment in complex instrumental functions", therefore allowing for discrete IADL deficits in MCI. This turns out to be useful. A review and meta-analysis by Jekel et al [76] indicated that deficits in IADL were very commonly found in people diagnosed with MCI, but with specific emphasis on those IADL that demanded higher cognitive skills. For example, deficits in managing finance were almost universally found. Given that MCI patients with reduced IADL seem to be more likely to convert to dementia [77-80], any screening and assessment needs to include IADL as a central part, not just because of its predictive utility, but also because of its use in enabling the focused planning of support or rehabilitation strategies to enable continued independence. Indeed, Jekel et al [76] recommend the use of IADL measures that are specifically designed for MCI, that include performance measures rather than self-declaration or even informant rating, and, in the reality of a short time scale for assessment in a clinical situation, focus on those IADL known to differentiate, that is, those with higher cognitive demand such as financial management. Increasingly, in terms of independence in today's systems, the ability to use technology such as on-line banking or social benefits applications are recommended to be included in new formulations of IADL assessment where appropriate.

Thus in addition to the standard expected cognitive screening, evidence for factors that predict progressive decline, as well as definitions, imply the use of appropriate IADL screening, screening for depression, and screening/medication treatment review for co-morbidities.

4.2 Assessing cognitive impairment

4.2.1 Mini-Mental State Exam (MMSE)

 Probably the best known brief screening for cognitive impairment internationally is the Mini-Mental State Exam (MMSE [81]). Validated in many countries and languages, this is perhaps the most widely used in both clinical and community settings. It has many weaknesses as the score is affected by level of education and intelligence, inability to monitor change in severe cases, lack of executive functions testing and absence of consideration of cultural differences. Therefore, it is acceptable only as an initial indicator that a person may need further investigation.

The MMSE has been evaluated in a variety of settings, with a meta-analysis by Mitchell [82] suggesting that its sensitivity and specificity varies according to the population, and reported very limited utility of this measure for diagnosing MCI. In a Cochrane review [83] specifically examining the utility of the MMSE for predicting the likelihood of dementia amongst people with MCI, the authors concluded that it was not recommended for this purpose, although with the caveat that decline in the score over repeated testing may prove useful. Use of a "delayed verification" period (usually used in diagnosing dementias, for example, to rule out temporary causes of impairment) would support such validation. Furthermore, given that executive functioning is required to control the allocation of attention and is specifically implicated in compensatory function in situations of mild impairment (e.g. [84]), and it is impaired in a significant proportion of MCI patients [85], measures such as the MMSE which do not include an executive component would be inappropriate for assessment of MCI.

4.2.2 Other screening instruments

In a review of screening in dementia and cognitive impairment, Cullen et al [86] counsel against recommendations for the universal adoption of specific screening measures in different settings and for different purposes, given that a "one size fits all" approach is unlikely to be appropriate. Tools designed for indicating dementia may simply not be appropriate on their own for indicating MCI.

In a review of screening measures, Lonie, Tierney and Ebneier [87] presented analyses of fifteen screening assessments in terms of their use for identifying MCI. Full descriptions of the sensitivities and specificities can be found in that reference, but it was clear that clinically relevant period re-test (6 or 12 months) scores, so important for this population, were absent. Most provided cut-off values to differentiate MCI from normal ageing (the exception was the CERAD, Consortium to Provide a Registry for Alzheimer's Disease) and one provided demographic adjustment equations (the Montreal Cognitive Assessment, MoCA [88]). The Addenbrookes Cognitive Examination- Revised (ACE-R) [89] and the DemTect [90] had been validated with non-AD dementias and MCI, but most had not. Only four of the fifteen measures were found to have adequate sensitivity and specificity values (≥79%) for distinguishing MCI from normal healthy age matched controls: these were the ACE-R, DemTect, MoCA and the Memory Alteration Test (M@T, [91]), although of these, only the ACE-R and the MoCA covered all the recommended categories of cognitive function. Lonie et al [87] reported that adequate sensitivity values, to distinguish a wider range of possible early dementias, were only available for the ACE-R.

However, none of these measures reported specificity values for depression that, as commented above, may be associated with MCI [70,92]. Furthermore, none of the

measures included any assessment of speed of processing or reaction time, or of inter-individual variability, with change in both sets of measures being increasingly recognised as predictors of cognitive decline [93,94].

The advent of tablet versions will make the availability of such assessments much more possible in clinical and community settings. Reliability and predictive validity of the measures did not appear to be available in the studies reviewed, although Lonie et al [87] went on to provide this for the ACE-R.

Table 2 presents these assessment tests and their main features.

4.2.3 The issue of low literacy, education and culture

Finally, many of these assessments are of very limited use in populations with very low education and literacy levels, and despite an awareness that dementias are more common amongst people with low education and that this decreases the chance of detecting the earlier stages of dementia or MCI [95], there are few evidenced strategies to deal with this concern. Reviews (e.g.[96]) recommend using a combination of screening and informant information, with an emphasis on reports from a person who knows the patient well, comparing the person's present and past performance.

Of the screening tools used, the most commonly employed were specific items such as verbal fluency or immediate and delayed recall of verbal material. Most included subjective memory complaint. One study delineated education adjusted cut-offs for the MoCA which may be useful for similar samples [97], whereas others recommended informant/interview based measures such as the Clinical Dementia Rating (CRD) scale or the Alzheimer's disease 8 questionnaire (AD8 [98]).

The assessment of cognitive decline in patients from minority ethnicities where they are being assessed in a language which is not their first language, and maybe where social expectations for older people are low, remains a major barrier for clinical practice [99].

5. Management

5.1 Non-pharmacological interventions

Non-pharmacological strategies constitute an approach that usually acts on modifiable risk factors, social engagement, cognitive training, and lifestyle interventions, including physical activity and diet/nutritional interventions.

Interventions focusing on specific risk factors have some uncertainties that need to be considered in the appraisal of the success of the intervention. One important uncertainty is the still open questions about the real impact of their modification, as described above. Also, risk factors are usually related, therefore interventions may usefully target multiple risk factors at once. For example, involvement in group-based exercise might increase physical activity and social engagement while helping to improve cardiovascular risk factors.

Social interaction has been assayed in intervention studies, which have shown reduced risk of progression from mild to severe cognitive impairment associated with a greater frequency of engagement in social activities while mildly impaired (OR = 0.72, 95% CI: 0.55–0.93, p = 0.01) [100]. In a recent meta-analysis, cognition-based intervention was associated with improved global cognitive function in people with MCI and weak evidence of improvements in the specific domains of executive function and delayed memory [101]. However, these types of intervention rely on the resources to implement and sustain them in practice, and the field has a need to

develop evidence-based training which can be sustained by the individuals. In addition, evidence for the role of supportive environments is important. For example, support for active engagement or more general, long-term environmental support and accessible environments can enable social interaction, or a reduction of the demand of instrumental activities of daily living such as shopping.

Physical activity is, as detailed above, a valuable modifiable risk to target. Despite the limitations of the available information, several meta-analyses of longitudinal studies are consistent in the value of physical activity as a risk reduction strategy for MCI [49,50]. Results, however, have been less clear when analyzing the limited number of randomized controlled trials (RCTs). Recent meta-analyses have concluded that physical activity either improves global cognition with no specific effects on executive function and memory [101] or lacks consistent evidence of significant improvements [102] in people with MCI.

Diet is a key factor to promoting brain health [103]. A meta-analysis of available prospective trials (n=5) found that a higher adherence to a Mediterranean-type diet is associated with a reduced risk of MCI and AD, as well as the progression from MCI to overt dementia [104]. Mediterranean diet could potentially exert neuroprotective effects via different mechanisms, such as reduction of inflammation and oxidative stress.

In sum, non-pharmacological interventions may be associated with small cognitive benefits for people with MCI and currently its role can be considered as promising at best. Overall, the methodology of these studies needs further refinement. Most studies are underpowered, and lack of evidence of efficacy is not evidence of lack of efficacy [105]. In addition, consistency across studies is limited by the existence of several diagnostic criteria for MCI, which is a heterogeneous concept [102]. Results are also

limited by the diversity of interventions and outcomes and short follow-up periods [105]. Further prospective studies with longer follow-up and high-quality RCTs are required to draw definitive conclusions. Future research should also test whether combination of these strategies (multimodal interventions) is associated with more benefits than monotherapy for MCI patients.

5.2 Pharmacological interventions.

There is a variety of interventions focusing on trials of medications, often those prescribed to people diagnosed with dementias, or on management of co-morbidities.

5.2.1 Against MCI

There is no approved treatment for MCI. No drugs have so far shown evidence to reverse cognitive impairment [106]. However, given the heterogeneity of MCI, further studies testing different compounds in all subtypes of MCI are necessary to draw clear conclusions. However, the instability and spontaneous reversion to non-MCI levels of cognition already mentioned (44% within a year) [14,18] adds difficulty to the interpretation of results.

5.2.1.1 Acetylcholinesterase inhibitors

Cholinergic deficits have been identified as a pathophysiological origin of AD, suggesting the use of acetylcholinesterase inhibitors to slow down the progression of MCI. Although one study [107] showed a positive significant effect of donepezil on cognition, this drug, widely used in AD, has not demonstrated to be effective in decreasing the risk of progression from MCI to dementia over 1, 2 and 3 years[108] nor in having significant effect on cognition over the short term [109].

Concerning galantamine, one study did not show a positive effect on cognition at 16 weeks [110] and another [111] did not demonstrate benefits on the progression to

dementia. Finally, a further study with rivastigmine [112] did not improve cognitive performance nor prevent conversion to dementia within 4 years.

In addition, significant side effects may appear with the use of these compounds [108]. Hence, after reviewing all these data, there is no evidence to support the use of cholinesterase inhibitors in MCI [109], although the inclusion of patients on these trials with non AD-related aetiology could have biased or confounded these [113].

Furthermore, concerning acetylcholine related cognitive dysfunction, the loss of nicotinic receptors has been demonstrated in patients with AD, suggesting the possible benefits of nicotinic agonists on cognitive function of patients with MCI. Newhouse et al [114] provided evidence for nicotine-induced cognitive improvement in non smoking patients with amnestic MCI after 6 months of treatment with transdermal nicotine. Nevertheless larger studies are necessary to confirm this hypothesis.

5.2.1.2 Other pharmacological interventions

Oxidative stress has been associated with neuronal death in areas of the medial temporal lobe in patients with MCI or AD. The use of antioxidants can neutralize metabolic products which trigger neuronal injury and death via free radicals. These substances have been tested as possible cognitive enhancers in MCI and AD.

The role of B vitamins has been assayed in several trials, but a recent meta-analysis reported only weak evidence of a beneficial effect on memory and a lack of adequate evidence of an effect on general cognitive function, executive function and attention in people with MCI [115]. One small double-blind study demonstrated that B vitamins appeared to slow cognitive and clinical decline in MCI patients with elevated homocysteine [116].

Ginkgo Biloba, widely used to enhance memory, was studied in a randomized, double-blind, placebo-controlled clinical trial of 3069 community-dwelling older patients, failing to prevent cognitive decline in those with MCI or normal cognition [117], although positive effects have been reported in studies with smaller samples [118].

The use of omega 3 fatty acids such as docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) is promising and studies [119] have shown an improvement in depressive symptoms and general function in patients with MCI, although further research is necessary to confirm these data and clarify their specific influence on cognition.

Testosterone supplementation in men has been studied as a possible memory enhancer but the review of several studies suggests that this effect could only be detected in the short term and was restricted to men with low testosterone levels [120-122].

Other compounds, like anti-inflammatory drugs, platelet aggregation inhibitors, or piracetam, have been investigated but the results have been inconclusive [123].

5.2.2 Against co-morbidities

Advances in the treatment of comorbidities have been considered as an alternative option to improve outcomes.

Antihypertensive drugs have been shown to help reduce the risk of developing dementia [124], and regular use of oxygen therapy for COPD patients decreases risk of cognitive decline (OR 0.14; 95% CI: 0.07–0.27; $p < 0.0001$) [125]. Thus additional healthcare support, medication review and monitoring may subsequently improve cognitive outcomes for these individuals. However, commonly prescribed medications such as statins which showed some benefits for cognitive decline in

observational studies, failed to prove any significant effect in several large RCTs such as The PROSPER Study (PROspective study of pravastatin in the elderly at risk) [126].

Additionally, although patients with MCI and depression are suggested as being at more than twice the risk of developing AD than those without depression, the effect of treating depression has been very poorly investigated. One study found that those with depression at baseline seem to respond poorly to anti-depressant medication [127], while another study found that sertraline, a selective serotonin reuptake inhibitor (SSRI), improved performance on tests of attention, episodic memory, and executive function, but only in treatment responders [128].

This also suggests that behavioural intervention or lifestyle change that can improve psychological health could be particularly effective for this high-risk group.

6. Conclusion

MCI defines a clinical condition that is important because it identifies an intermediate state in the progression to dementia. The original clinical definition has been extended, although there is still doubt over whether it constitutes a clinical entity *per se*, or instead, it is only an early manifestation of an eventual dementia.

Risk factors have been defined, and further research is needed to determine clearer indicators that will enable identification of factors that discriminate cases that will progress to dementia. Further research in the area of risk factors is also needed to identify the earliest predictors of impairment. This is because, encouragingly, many of the known risk factors are potentially modifiable, either through behavioural change, pharmaceutical intervention or promoting social engagement, and have already started to inform management and prevention strategies. How, and the extent to which such

modifications delay progression of MCI is an important area for future clinical trials. Furthermore, emerging research methods, such as next generation genetic sequencing and the 'omics' technologies, have the potential to characterise the biological underpinnings of cognitive decline in much greater detail, facilitating the development of novel therapeutics [129].

The debate on screening, including the potential for population screening, is crucial in the European-wide development of prevention and modification strategies. However, further research with improved screening is needed to determine the extent to which the currently observed instability of a diagnosis of MCI is indeed due to malleability of the condition or simply to imprecise assessment. The concept of providing evidence of change, or decline is central, as is the concomitant assessment of generally preserved independent functioning. The role of co-morbidities and medication should also be considered in a fuller screening, but in brief screenings, it is recommended that at least depression is screened for. Applications for everyday technology such as tablets and smart phones should make it possible for brief screenings to include assessments of processing speed or reaction times, and within task variability, both highlighted as highly predictive of potential decline in the literature, with clear links to neurobiological health.

Conflict of interest:

None of the authors have conflict of interest in what concerns the content of this manuscript.

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Funding

Instituto de Salud Carlos III- Fondo de Investigación Sanitaria is an agency sustained by the Spanish government. The EU 3rd Health Programme has been issued by the DG Santé of the European Commission.

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Tables

Table 1: Overview of potential Mild Cognitive Impairment risk factors

Demographic		
	Age	• Higher age associated with MCI, depending on definition
	Sex	• Evidence equivocal, studies have suggested higher prevalence in men or women or no gender difference
Genetic		
	APOE polymorphism	• APOE-4 allele established risk factor for Alzheimer's disease, associated with MCI
Cardiovascular		
	Diabetes/glucose metabolism	• Diagnosed diabetes associated with cognitive impairment • Higher glucose levels and insulin resistance associated with cognitive impairment in non-diabetics
	Cholesterol levels, BMI	• Hypercholesterolemia and overweight/obesity in midlife associated with faster declines in cognitive performance
	Blood pressure	• Midlife hypertension associated with cognitive decline • Possible U-shaped relationship in older adults with low blood pressure also associated • Repeated bouts of cerebral hypoperfusion associated with orthostatic hypotension, maybe as deleterious as hypertension
	Cardiovascular risk burden	• Cumulative burden of risk factors based on CVD risk scores or presence of metabolic syndrome also associated
	Heart rhythm	• Atrial fibrillation associated with poorer cognitive function
Behavioural		
	Physical Activity	• Moderate exercise associated with lower risk of cognitive decline • Limited studies on MCI as outcome
	Smoking	• Current smoking associated with dementia and with cognitive performance in non-demented individuals
	Alcohol	• Possible U-shaped relationship with moderate drinking associated with lower dementia risk compared to heavy drinking and abstainers • Protective effect of alcohol controversial

Psycho-social		
	Education	• Lower education associated with higher risk of MCI • Assessment tools may not be sensitive to small cognitive changes in highly educated people • Available norms may not be applicable to people with less than secondary level of education
	Social participation	• Some evidence larger social networks associated with better cognitive function • Quality of social networks, frequency of social contact and participation may be more important • Unclear if good social networks and participation is protective or just concomitant with higher cognitive function
	Depression	• Current and life time history of depressive symptoms associated with higher risk of MCI • Causal relationships unclear; may be related clinical manifestations of the same underlying process

MCI = Mild Cognitive Impairment; APOE = Apolipoprotein E

Table 2. Summary of tests described.

Screening assessment	Item coverage									Sensitivity and specificity for distinguishing MCI ≥79%	Cut-off values for MCI?
	Orientation	Memory	Language/naming/command and following	Attention/updating	Fluency	Visuo-spatial	Processing speed/reaction times	Within session variability	Depression	Instrumental Activities of Daily living		
ACE-R	✔	✔	✔	✔	✔	✔	-	-	-	-	✔	✔
MoCA	✔	✔	✔	✔	✔	✔	-	-	-	-	✔	✔
CERAD	✔	✔	✔	✔	✔	✔	-	-	-	-	-	-
MMSE	✔	✔	✔	✔	-	✔	-	-	-	-	-	-
M@T	✔	✔	-	-	-	-	-	-	-	-	✔	✔
DemTect	-	✔	-	✔	✔	-	-	-	-	-	✔	✔
CamCog	✔	✔	-	-	-	-	-	-	-	-	-	✔