REVIEW ARTICLE

Mild Cognitive Impairment and Dementia

The Importance of Modifiable Risk Factors

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SUMMARY

Background: Mild cognitive impairment (MCI), a common condition among the elderly, is defined as a deterioration of memory, attention, and cognitive function that exceeds what would be expected for the individual's age and level of education, yet does not interfere significantly with the activities of daily living. MCI may be a precursor of dementia; the rate of transition from MCI to dementia is 10% to 20% per year. The role of somatic diseases and modifiable risk factors in MCI and dementia needs further study.

Methods: We analyzed pertinent original articles and reviews published 1990 up to December 2010 that were retrieved by a selective search in PubMed and the Cochrane Library.

Results: MCI and dementia are associated with many somatic disorders and modifiable risk factors. MCI has biologically plausible associations with hypertension, diabetes mellitus, and hyperlipidemia, although the interventional trials performed to date have yielded negative results. Recently, chronic renal failure has also been recognized as a risk factor. Insufficient evidence supports a putative benefit on MCI from the substitution of vitamin B12, vitamin D, or testosterone (when these substances are deficient), the treatment of hyperhomocysteinemia or subclinical thyroid dysfunction, or hormone replacement therapy after menopause. Epidemiological data suggest that a Mediterranean diet, physical activity, and moderate alcohol consumption protect against MCI, while cigarette smoking promotes it and should be stopped.

Conclusion: Modifiable risk factors for MCI should be sought (at the very latest) in persons who already have MCI, as their optimal treatment may improve these patients' cognitive performance or keep the existing deficits from progressing.

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The number of persons affected by dementia is increasing. Therefore, the early detection of possible precursors of dementia and the diagnosis and treatment of modifiable risk factors are assuming increasing importance (1). A central part is played by the concept of mild cognitive impairment (MCI) *(Box 1)*, because in many cases MCI, particularly the amnestic form (affecting memory), represents an early stage of Alzheimer-type dementia. In ca. 10% to 20% of patients with MCI, the mild impairments progress to manifest dementia in the space of 12 months (2). Despite its current pronounced heterogeneity, the concept of MCI permits timely identification of patients at high risk of developing dementia, thus opening a potentially larger therapeutic window and increasing the significance of modifiable risk factors *(Figure 1)*. The importance of this becomes clear when one considers that, to date, all trials of antidementive drugs have had negative results (e1, e2). The data on MCI are sparse compared with dementia, and some studies have drawn no clear line between MCI and dementia or have used other terms (e.g., cognitive decline). The present study is therefore intended to provide an up-to-date overview of the common risk factors for MCI and dementia and of the (ideally prospective) interventional trials carried out to date.

To this end, we conducted a selective literature search of PubMed and the Cochrane Library using the terms "dementia", "mild cognitive impairment", and "cognitive decline" and analyzed pertinent original articles and reviews published between 1990 and December 2010.

"Classic" cardiovascular risk factors

Hypertension

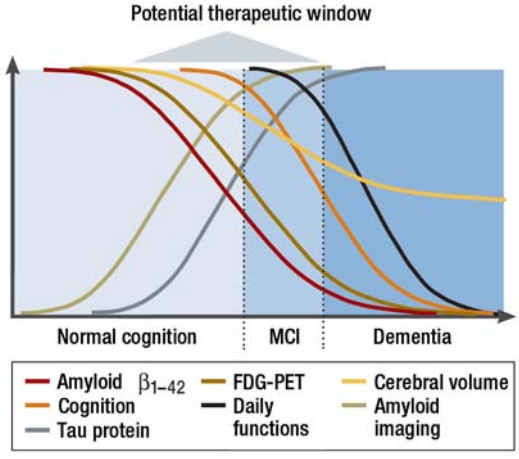
Hypertension can lead to vascular-related cognitive impairment through any one of a number of mechanisms (arteriosclerosis, hypoperfusion, leukoaraiosis, cerebral infarction). Numerous cross-sectional analyses of the association between high blood pressure and cognitive impairment have yielded divergent results, while the majority of longitudinal studies have demonstrated an association (3). Seven large randomized, placebo-controlled interventional trials have been performed to date, with conflicting results *(Table 1)*. Five studies revealed no protective action (e3–e7), while two showed a protective effect (e8, e9). The interpretation of these studies was severely restricted by methodological

BOX 1

Definition of mild cognitive impairment (2, e2)

- Absence of dementia
- Signs of cognitive decline (medical history provided by doctor or patient)
- Demonstration of cognitive disturbance
- Ability to perform regular daily functions preserved; no more than minimal impairment of complex activities

FIGURE 1



Changes in various parameters during development of dementia (modified from e91). This greatly simplified depiction of the development over time of biomarkers (decreasing levels of amyloid ß1–42 in cerebrospinal fluid, increase in level of tau protein in cerebrospinal fluid as indicator of neurofibrillary degeneration), the findings of nuclear medicine (PET amyloid imaging with increasing cerebral deposition of amyloid ß1–42, FDG-PET with changes in cerebral metabolism) and structural imaging (increasing atrophy on CT or MRI), and clinical symptoms (impairment of cognition and daily function) in patients with dementia clearly shows the importance of early diagnosis and treatment. MCI, mild cognitive impairment

problems, and it is possible—as proposed in a recent Cochrane Review—that more precise results can be yielded only by a meta-analysis on the basis of individual patient data (4). The specific pharmacological mechanisms of action of the different antihypertensive agents could also play an important role.

Diabetes mellitus

The existence of a causal link between diabetes mellitus and cognitive impairments is supported by numerous biochemical (e10, e11), imaging-related (e12, e13), and histopathological (e14) findings. A systematic review of 14 longitudinal studies reported an increased incidence of dementias, although it should be noted that there was often no adjustment for relevant confounding variables (e.g., hypertension or stroke) (5). Recent prospective studies that have taken account of these potential sources of error underline the possible importance of diabetes mellitus as an independent risk factor for cognitive decline (e15–e17). Longer duration of diabetes, lack of antidiabetic medication, and a higher number of hypoglycemic episodes were also associated with an increased risk of cognitive decline (e18–e20). A Cochrane Review in 2002 found no randomized studies investigating the link between the type of treatment for diabetes and the development of MCI or dementia (6). The only randomized study of antidiabetic medications published in the intervening period showed no influence on cognitive performance in mild dementia (e21).

Hyperlipidemia

As early as 2003, autopsy studies described an association between cerebral amyloid deposits and hypercholesterolemia (e22). Large population-based studies then revealed that hyperlipidemia and particularly hypercholesterolemia in middle age are associated with the risk of subsequent occurrence of MCI (e23–e25). In contrast, studies of older subjects (>65 years) showed no association between hypercholesterolemia and cognitive decline (e26–e28). The findings of the majority of prospective observational studies suggested a protective connection between statin intake and cognitive impairment (e25, e29, e30). The Rotterdam Study, for example, with 6992 participants and a mean observation period of 9 years, found that the risk of developing Alzheimer-type dementia was reduced by almost half in those taking statins (hazard ratio [HR] 0.57; 95% confidence interval [CI] 0.37–0.90). This effect was independent of the type of statin but specific to statins, in that other cholesterol-lowering drugs (fibrate, nicotinic acid) showed no such influence (e31). However, two large placebo-controlled trials of persons at high risk of vascular disease did not demonstrate a similar association. Neither the Heart Protection Study (HPS; simvastatin, >20 000 participants, age 40–80 years, observation period 5 years) nor the Pravastatin in Elderly Individuals at Risk of Vascular Disease (PROSPER) trial (pravastatin, almost 6000 participants, age 70–82 years, observation period 3 years) showed a protective effect

TABLE 1

Summarized results of the major placebo-controlled studies on the effect of antihypertensive agents on cognitive impairments (modified from [e87])

Study	Number of participants	Age (years)	Inclusion criteria (systolic and diastolic blood pressure in mmHg)	Cognitive test	Observation time (years)	Antihypertensive treatment	Result/ effect on cognitive decline
MRC trial of hypertension (e3)	4396	70.3	Hypertension (syst. 160–209; diast. < 115)	Paired-Associate Learning Test, Trail-Making Test Part A	4.5	Hydrochlorothiazide + amiloride or atenolol	Not significant
Syst-Eur Trial (e8, e88)	2418	69.9	Isolated systolic hypertension (syst. 160–219; diast. < 95)	MMSE	3.9	Nitrendipine ± enalapril ± hydrochlorothiazide	HR 0,38 (95% CI 0.23–0.64) ARR 0.41%
SCOPE (e5)	4964	76.4	Hypertension (syst. 160–179; diast. 90□99)	MMSE	3.7	Candesartan ± hydrochlorothiazide	Not significant
SHEP (e4)	4736	71.6	Isolated systolic hypertension (syst. 160–219; diast. < 90)	Short Care	4.5	Chlorthalidone ± atenolol or reserpine	Not significant
PROGRESS (e9)	6105	64	Stroke/TIA	MMSE	3.9	Perindopril ± indapamide	RRR 19% (95% CI 4–32%) ARR 0.95%
HYVET-COG (e6)	3336	83.5	Hypertension (syst. 160–200; diast. < 110)	MMSE	2.2	Indapamide ± perindopril	HR 0,86 (95% CI 0.67–1.09) ARR 0.5%
ONTARGET-TRANSCEND (e7)	31546	66.5	Atherosclerotic disease	MMSE	3.7	Telmisartan or ramipril or telmisartan + ramipril	Not significant

MMSE, Mini Mental Status Examination; HR, hazard ratio; CI, Confidence interval; ARR, absolute risk reduction; RRR, relative risk reduction; TIA, transient ischemic attack; MRC, Medical Research Council; Syst-Eur, Systolic Hypertension in Europe; SCOPE, Study on Cognition and Prognosis in the Elderly; SHEP, Systolic Hypertension in the Elderly Program; PROGRESS, Perindopril Protection Against Recurrent Stroke Study; HYVET-COG, Hypertension in the Very Elderly Trial Cognitive Function Assessment; ONTARGET, ONgoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial; TRANSCEND, Telmisartan Randomized AssessmeNt Study in ACE iNtolerant subjects with cardiovascular Disease

of statins with regard to cognitive decline. This finding was confirmed by the Cochrane Review based on HPS and PROSPER (7–9). These negative results may possibly be explained by the fact that neither trial was designed primarily to record cognitive impairments, so there was no baseline assessment of cognitive performance. Any effect of statin intake was therefore not measurable (e32). Furthermore, the age range in the HPS was so wide, encompassing middle-aged as well as elderly persons, that the age-dependent influence of cholesterol may have been neutralized. Moreover, recent findings point to differences in the individual fractions of cholesterol. In analogy to coronary heart disease, a high proportion of HDL cholesterol may have a protective function (e33), and future statin studies should take this into account.

Metabolic factors

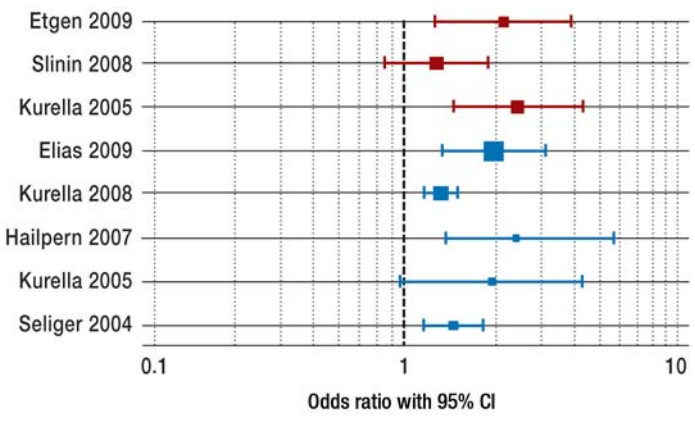
Chronic renal failure

Chronic renal failure represents a new independent risk factor for cognitive decline. Apart from the usual risk factors, other disorders arising in the context of renal failure (e.g., hyperhomocysteinemia, coagulation disorders, inflammation, anemia) may play a part (10). Almost all cross-sectional studies *(Figure 2)* have demonstrated an increased risk for development of a cognitive impairment, in some cases dependent on the severity of the chronic renal failure (e34–e38). Most longitudinal studies *(Figure 2)* have confirmed the association between chronic renal failure and cognitive decline, which has been found even in patients with only mild or moderate restriction of renal function (e39–e42). Unfortunately no specific treatment options have yet been identified. For example, high doses of folic acid, vitamin B6 and vitamin B12 for reduction of the elevated homocysteine concentration in patients with chronic renal failure (see below, "Hyperhomocysteinemia") had no effect on cognition (11).

Vitamin B12 deficiency

The prevalence of vitamin B12 deficiency increases with age (up to 20% in those over 75 years) (e43), and this could play a significant part in cognitive impairments (e44). Although both cross-sectional and longitudinal studies have shown an association between vitamin B12 deficiency and the development of MCI (e45, e46), none of the randomized double-blind placebo-controlled trials conducted to date have demonstrated a positive effect of vitamin B12 substitution on cognitive status (12–14).

FIGURE 2



The association between chronic renal failure and cognitive impairment: findings of large (> 900 participants) cross-sectional (blue) and longitudinal (red) studies. CI, Confidence interval

Vitamin D deficiency

The prevalence of vitamin D deficiency increases to as much as 50% with age, due to reduced sun exposure, reduced vitamin D generation and lower oral intake (e47). Vitamin D plays a part in the synthesis of neurotrophic factors and neurotransmitters (e48) and in receptor regulation in memory-relevant regions of the brain (e49). The results of large cross-sectional studies are inconsistent. No association between low levels of vitamin D and cognitive function was revealed by the 4809 elderly participants in the National Health and Nutrition Examination Survey (NHANES III) (e50). In contrast, three other large studies found that the risk of cognitive impairment was approximately doubled in persons with low vitamin D concentrations (e51–e53). The only large prospective cohort study conducted to date demonstrated no association between vitamin D level and cognitive impairment (15); the study was limited to men, however, and at 20 ng/mL the threshold value for vitamin D deficiency was unusually high.

Hyperhomocysteinemia

Although the level of homocysteine rises with age and with decreasing renal function, it is determined mainly by the nutritional intake or serum concentrations of vitamin B6, vitamin B12, and folic acid. Most of the small cross-sectional studies have demonstrated an association between increased homocysteine concentration and cognitive impairment, but longitudinal studies show inconsistent results (10). The double-blind, randomized, placebo-controlled trials conducted to date have found no clear-cut improvement in cognitive performance despite effective reduction of homocysteine by administration of vitamin B12 and folic acid (16). Another study, however, showed delayed cerebral atrophy in persons with MCI (e54). The problems with these studies include a short study period (≤12 weeks), different homocysteine threshold values, and inhomogeneous study populations (with or without dementia). Sub-study analyses indicate a possible effect in healthy elderly persons with very high levels of homocysteine (16).

Endocrine factors

Testosterone deficiency

Cross-sectional studies on the connection between testosterone deficiency and MCI have had inconsistent results (17). Small studies of patients with testosterone deficiency caused by drug treatment or surgery have found such an association, and in some cases the effect was reversible (e55, e56). The results of the randomized placebo-controlled trials conducted to date on the effect of testosterone substitution are contradictory. However, comparison is hampered by methodological factors (e.g., low numbers of participants [<50 men], variation in type and duration of testosterone administration, and differences in cognitive testing) (17, 18) *(Box 2)*. Testosterone substitution for prevention of cognitive decline is therefore not generally recommended but can be considered after exclusion of other causes and regular urological follow-up in patients with acquired hypogonadism (usually with serum concentration <8–12 nmol/L) and cognitive impairment (e57, e58).

Subclinical thyroid dysfunction

Manifest dysfunction of the thyroid gland (hypo- or hyperthyroidism) is one of the potentially reversible causes of dementia, so subclinical thyroid dysfunction could play a part in MCI. The prevalence of subclinical hypothyroidism (elevated TSH in the presence of normal thyroxine [T4] and triiodothyronine [T3]) rises with increasing age (>25% in persons over 60) (e59). Early small studies reported an association between cognitive impairment and subclinical hypothyroidism, and in some cases cognitive performance improved after substitution (e60, e61). Subsequent larger or prospective studies have not confirmed this association to date (e62–e64). The prevalence of subclinical hyperthyroidism (low TSH with normal T3 and T4) also increases with age (reaching 7–8% in regions of iodine deficiency) (e63, e65). Two investigations showed that the risk of cognitive impairment was 2 to 3 times higher than normal in the presence of subclinical hyperthyroidism (e66, e67), while another study that took numerous parameters into account found no association (e63).

Estrogens

In animal experiments and cell cultures, estrogens exert a neuroprotective effect by favoring neuronal sprouting, by reducing cerebral amyloid, and by virtue of their anti-inflammatory properties (e68, e69). The results of early cross-sectional analyses were encouraging, but prospective studies showed no positive

TABLE 2

Modifiable risk factors for mild cognitive impairment and dementia, and recommendation classes for treatment (e89)

Somatic factor	Change in risk (OR or HR)	Likelihood of relevance	Treatment	Recommendation class*[1]
Hypertension	1.24–1.59 (HR)	Probable	Blood pressure reduction	U
Diabetes mellitus	1.34–1.63 (OR)	Certain	Normoglycemia	U
Hyperlipidemia	1.42–1.90 (HR)	Possible	Early treatment	U
Chronic renal failure	1.32–2.43 (OR)	Certain	Optimization	U
Vitamin B12 deficiency	1.50–2.17 (OR)	Unlikely	No substitution	B
Vitamin D deficiency	NS-2.3 (OR)	Questionable	No substitution	B
Hyperhomocysteinemia	Inconsistent	Unlikely	No substitution	A
Testosterone deficiency	Inconsistent	Possible	Substitution in individual cases	C
Subclinical thyroid gland dysfunction	Inconsistent	Questionable	No substitution	B
Hormone replacement therapy	1.05–2.05 (HR)	Unlikely	No substitution	A
Mediterranean diet	0.72–1.04 (HR)	Probable	Recommended	B
Physical activity	0.62–0.65 (HR)	Probable	Recommended	B
Nicotine consumption	1.27–1.79 (HR)	Probable	Stop	B
Alcohol consumption	0.28–0.82 (OR)	Possible	Slight to moderate consumption tolerated	B

The change in risk (as reported in the most important studies) is described in terms of the odds ratio (OR) or hazard ratio (HR). A value > 1.0 shows an increase in risk; a value < 1.0, a reduction in risk. NS, non-significant results;
*[1] classification of recommendation classes: A, high recommendation based on strong evidence, or on weak evidence with particularly high relevance to patient care; B, moderate recommendation based on moderate evidence, or on weak evidence with high relevance to patient care; C, restricted recommendation based on weak evidence, or on strong evidence with limited relevance to patient care; U, inadequate data, treatment not yet evidence-based

influence of estrogen administration on cognitive performance. Large randomized placebo-controlled trials demonstrated that postmenopausal hormone replacement therapy increases the risk of developing dementia and does not hinder the development of MCI; purely estrogen-based hormone replacement therapy (without progesterone) actually raises the risk of developing MCI (19, e70, e71). Many different variables may affect the results, e.g., varying age groups, type of menopause (natural or postoperative), mode of substitution (transdermal, oral, or intramuscular), and timing of substitution (time elapsed since menopause, duration) (19, e72, e73). A possible beneficial effect of purely estrogen-based hormone replacement therapy on verbal retentiveness in women under 65 has been discussed (e74), but otherwise hormone replacement therapy should not be administered with the aim of preserving cognitive skills.

Lifestyle factors

Diet

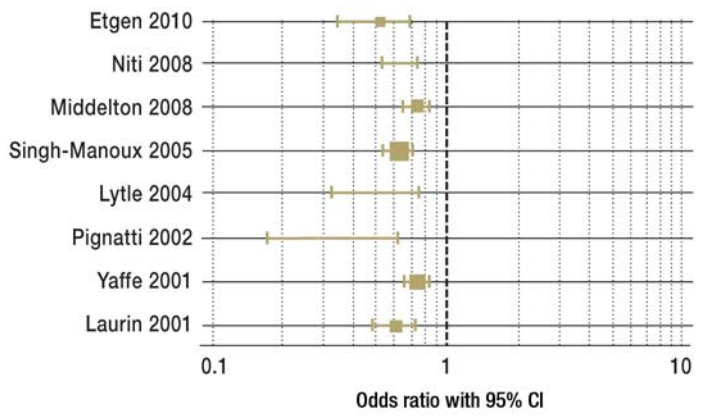
A Mediterranean diet (a high proportion of fish, fruit, vegetables, cereals, and unsaturated fatty acids and a low proportion of dairy products, meat, and saturated fatty acids) could potentially exert a protective effect with regard to cognitive decline via improved carbohydrate metabolism coupled with antioxidative and anti-inflammatory mechanisms (e75).

The only two prospective cohort studies carried out to date differed in some aspects of study design (observation period, composition of diet, etc.), but agreed in suggesting a dose-dependent protective effect of a Mediterranean diet (e76). An American study of 1393 persons with initially normal cognitive function found a 28% reduction in the risk of MCI after 4.5 years among those with a high proportion of Mediterranean-style diet (20). A Cochrane Review of the value of omega-3 fatty acids in the prevention of dementia published in 2006 found insufficient evidence because of the lack of randomized trials at that time.

Physical activity

Various mechanisms (reduction of cardiovascular diseases, improved cerebral perfusion, induction of cortical angiogenesis, etc.) have been discussed for the postulated neuroprotective effect of physical activity. Recent cohort studies *(Figure 3)* have revealed an association between regular exercise and a considerable reduction in the risk of developing MCI (e77–e84). A new meta-analysis of 15 prospective cohort studies

FIGURE 3



The association between exercise and cognitive impairment: findings of large studies (> 1000 participants). CI, Confidence interval

BOX 2

Frequent methodological problems

- Different procedures for testing cognition
- Varying inclusion criteria
- High proportion of actively treated persons in placebo arm of study
- High discontinuation rates
- Short observation period
- Varying clinical endpoints
- Inadequate consideration of covariates (e.g., education level, social support)

embracing a total of 33 816 persons without dementia shows that both intense and moderate exercise reduce the risk of the occurrence of MCI by at least 35% (22). Various interventional trials in recent years have confirmed this effect; however, the numbers of participants were low (<150) and the observation times short (≤1 year) (23). Larger interventional trials are now under way, so more precise recommendations can be expected. It is already clear, however, that not all types of physical activity are suitable; boxing, for example, increases the risk of cognitive impairment (e85).

Alcohol consumption

The neurotoxic action of alcohol, exerted via accelerated cerebral atrophy and reduced acetylcholine synthesis, has been clearly confirmed (24). After numerous cohort studies had shown no unambiguous relationship between alcohol consumption and cognitive impairment, the majority of prospective trials revealed a dose-dependent (J- or U-shaped) effect (24). Most investigators report that low (often defined as <12 g of alcohol/day, 0.1 L wine or one glass of beer) to moderate alcohol consumption has a protective influence on cognitive performance. In contrast, a detrimental effect is described for high consumption of alcohol (e75). However, the available data do not permit definitive conclusions with regard to a causal connection. Furthermore, important details (type of alcoholic drink, amount and duration of consumption) have been insufficiently reported.

Smoking

Nicotine, a cholinergic agonist, could counteract the cholinergic dysfunction in cognitive impairment (e86). In contrast, however, cohort studies have indicated a pronounced increase in risk (24). A meta-analysis of 19 prospective studies with a total of 26 374 participants reported that the risk of developing dementia was up to 70% higher in current smokers than in non-smokers (e87). This increase in risk has also been described in recent studies with MCI as endpoint (25). Interpretation of the results is limited by the fact that some studies display deficiencies in the definition and classification of nicotine consumption (amount consumed, duration of consumption/abstinence, passive smoking).

Conclusion

The results of recent studies confirm that the symptoms and course of MCI and dementia can be influenced by somatic illnesses and other modifiable risk factors *(Table 2)*, although the current data originate largely from not entirely conclusive cross-sectional or longitudinal studies. Despite the current lack of positive interventional trials, we are of the opinion that an association with the classic cardiovascular risk factors—hypertension, diabetes mellitus, and hyperlipidemia—is biologically plausible. Measures to ameliorate these factors would simultaneously represent effective prevention of other vascular diseases (myocardial infarction, stroke). In recent years renal failure has also been

KEY MESSAGES

- Mild cognitive impairment and dementia can be influenced by modifiable factors (e.g., Mediterranean diet and physical activity).
- Despite the negative results of interventional trials, there is a biologically plausible association with the classic cardiovascular risk factors of hypertension, diabetes mellitus, and hyperlipidemia, so we favor early treatment and optimization.
- Chronic renal failure is a newly discovered somatic risk factor, for which no treatment with specific regard to cognitive decline has yet been evaluated.
- With regard to mild cognitive impairment, substitution therapy cannot be generally recommended for vitamin B12, vitamin D, or testosterone deficiency, hyperhomocysteinemia, or subclinical thyroid dysfunction; similarly, postmenopausal hormone replacement therapy should generally not be prescribed.
- Mediterranean diet and physical activity seem to protect against cognitive decline and should be recommended. Low to moderate alcohol consumption can be tolerated, but smoking should be stopped.

identified as a somatic risk factor, though no evidence-based treatment strategies have yet emerged. With regard to MCI, the current data do not support the general recommendation of substitution therapy in the case of vitamin B12, vitamin D, or testosterone deficiency, hyperhomocysteinemia, or subclinical thyroid dysfunction. Purely estrogen-based hormone replacement therapy can be contemplated for improvement of verbal retentiveness in women under 65 after careful consideration of potential contraindications, but no other postmenopausal hormone replacement therapy should be given. Epidemiological data indicate a protective action of Mediterranean diet, physical activity, and moderate alcohol consumption, so these can be encouraged or—in the case of alcohol consumption—tolerated. Smoking increases the risk of developing MCI and should be stopped.

Conflict of interest statement
Prof. Förstl has received funding from Eisai, General Electric Lundbeck, Pfizer, Merz Janssen, Novartis, AstraZeneca, BMS, GSK, Lilly, Nutricia, Sanofi-Aventis, Schwabe, Servier, and other companies.
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The remaining authors declare that no conflicts of interest exist.

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REVIEW ARTICLE

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