

Cognitive decline: the relevance of diabetes, hyperlipidaemia and hypertension

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Abstract

Cognitive decline including mild cognitive impairment describes a heterogeneous condition with cognitive changes between normal ageing and dementia. Cognitive impairment can be promoted or caused by treatable somatic factors. In this review, three important cardiovascular risk factors, diabetes mellitus, hypercholesterolaemia and hypertension, and their association with cognitive decline, are assessed. Though there are many hints of a causal association between diabetes mellitus and the development of cognitive decline, definitive proof of a protective effect of antidiabetic treatment by controlled or randomised placebo-controlled studies is needed. In midlife, elevated cholesterol levels comprise a risk factor for cognitive decline. In elderly subjects, cholesterol levels decline and are not clearly associated with cognitive impairment. The evidence for treatment of hypercholesterolaemia by statins solely for prevention of cognitive decline remains unclear. There is an age-dependent relationship between blood pressure and cognitive impairment. Midlife hypertension is associated with an increased risk of developing cognitive decline and antihypertensive treatment may therefore be beneficial, whereas hypertension later in life does not carry the same risk of cognitive dysfunction. Diagnosis of these somatic factors is essential in cognitive impairment, as diligent treatment may improve cognitive performance and postpone the manifestation of dementia.

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Abbreviations and acronyms

ACE	angiotensin-converting enzyme
ARB	angiotensin receptor blocker
BMI	body mass index
BP	blood pressure
CAIDE	Cardiovascular Risk Factors, Aging and Dementia
CI	confidence interval
HPS	Heart Protection Study
HR	hazard ratio
HYVET-COG	Hypertension Treatment in the Very Elderly Cognitive function assessment
MCI	mild cognitive impairment
MMSE	mini-mental state examination
MRC	Medical Research Council
MRI	magnetic resonance imaging
OR	odds ratio
PROGRESS	Perindopril Protection Against Recurrent Stroke Study
PROSPER	Prospective Study of Pravastatin in the Elderly at Risk
SCOPE	Study on Cognition and Prognosis in the Elderly
SHEP	Systolic Hypertension in the Elderly Program
Syst-Eur	Systolic Hypertension in Europe

Introduction

Cognitive decline includes MCI which is defined as cognitive impairment greater than expected for an individual's age and education level but that does not interfere notably with activities of daily life. In contrast, dementia is characterised by more severe and widespread cognitive deficits that have a substantial effect on daily function.¹ MCI with memory deficits (amnestic MCI) has a high risk of progression to dementia, particularly of the Alzheimer type.¹ Incidence and prevalence of different predementia syndromes including MCI vary as a result of different diagnostic criteria, sampling, and assessment procedures. According to recent epidemiological data, the prevalence of MCI among the population aged > 65 years in industrialised countries is as high as 10–25%.^{2,3} The progression rate from MCI into dementia is estimated at about 5–10% per year.⁴

Recent preventative strategies include the identification of risk factors and predictors among patients with rapid cognitive decline (MCI-plus).⁵ As somatic co-morbidity often contributes

to cognitive decline and somatic risk factors are modifiable, the early detection and treatment of these risk factors offers important opportunities to delay and to avoid the manifestation of dementia.⁶

This review considers the association of important cardiovascular risk factors, i.e. diabetes mellitus, hyperlipidemia and hypertension, with cognitive decline, as most studies did not explicitly focus on MCI. Based on up-to-date references the value of possible therapeutic interventions is discussed. These risk factors contribute importantly to the modern concept of vascular cognitive impairment, which incorporates the complex interactions between vascular risk factors, cerebrovascular aetiologies and cellular changes within the brain and cognition. While cerebrovascular disease is preventable and treatable, it clearly is a major factor in the prevalence of cognitive impairment in the elderly worldwide.⁷

Diabetes mellitus

The association between diabetes mellitus and cognitive decline is supported by evidence from biochemistry, neuroimaging and pathology. The hyperglycaemia-induced mitochondrial superoxide overproduction leads to glucose-mediated microvascular damage.⁸ A dysfunction of the insulin-degrading enzyme may result in both hyperinsulinaemia and accumulation of cerebral amyloid protein β , thus providing an association between diabetes and dementia.⁹ Diabetes often develops in the context of the metabolic syndrome leading to the indirect ischaemic effects of diabetes-associated cerebrovascular disease.¹⁰ MRI studies revealed a higher frequency of brain atrophy and a reduced volume of memory-relevant structures (hippocampus, amygdala) in diabetic patients.^{11,12} A large autopsy study detected more microvascular infarcts and an activation of neuroinflammation in demented patients with diabetes.¹³

Studies

Initial evidence regarding an association between diabetes and cognitive dysfunction was derived from several smaller case-control studies. Though these studies had some methodological problems, they demonstrated poorer performance in diabetic patients in at least one aspect of cognitive function, mostly verbal memory.¹⁴ A systematic review of 14 longitudinal population-based studies assessing the incidence of cognitive decline revealed a higher incidence of dementia in the majority of studies but also criticised the lack of relevant confounders like hypertension, stroke and glycaemic control.¹⁵ Additional prospective studies accounting for these deficits have been published and add further evidence that diabetes is an independent factor in cognitive decline (table 1).

In the Osteoporotic Fractures Research Group which included 9,679 older women, controlled for several confounding factors and showed that diabetes was associated with greater cognitive decline.¹⁶ The Nurses' Health Study followed 16,596 women, aged 70–81 years, for two years and included details about treatment and duration of diabetes. The study showed an

increased risk of poor cognition among women who had had diabetes for > 15 years (OR 1.52; 95% CI 1.15–1.99) and for women not using any medication (OR 1.45; 95% CI 1.04–2.02).¹⁷ Use of oral antidiabetic therapy may reduce risk of cognitive decline as diabetic women treated with these agents performed similarly to women without diabetes (OR 1.06 and 0.99).¹⁷ In a subanalysis of data from a four-year randomised trial of raloxifene among 7,027 osteoporotic postmenopausal women the risk of developing cognitive impairment among diabetic women was almost doubled.¹⁸ The Physicians' Health Study II with 5,907 men and the Women's Health Study with 6,326 women revealed that participants with longer duration of diabetes (> 5 years) had generally a greater cognitive decline.¹⁹ More recent trials like the Washington Heights–Inwood Columbia Aging Project focused on the relationship of diabetes to MCI and found a higher risk of amnesic MCI among diabetic participants.²⁰

Hypoglycaemic episodes are an important barrier to the achievement of optimal glycaemic control. A large cohort study with 16,667 elderly diabetic people showed an association with the number of severe hypoglycaemic episodes and increased risk of dementia.²¹ In contrast, a smaller study found no contribution of hypoglycaemic episodes to cognitive impairment, but reported a higher risk of hypoglycaemia in patients with dementia.²²

Limitations

Limitations of these studies include being restricted to special populations like women,¹⁶ women with osteoporosis¹⁸ or nurses.¹⁷ Another common limitation is the ascertainment of diabetes by self-report^{16,17,20} or even mailed self-report questionnaire.¹⁹ The cognitive assessment was sometimes performed by telephone,^{17,19} which may be less reliable than examinations by qualified or trained assessors. One study introduced two additional cognitive tests during follow-up (Digit Symbol Test and Trails B test) but the only test used at baseline and follow-up (modified MMSE) did not generate statistically significant data.¹⁶ The utilisation of confounders varied among the studies ranging from only a few confounders (age, education, race and depression)¹⁸ to a broad spectrum of covariates (age, education and hormone use in women, baseline score, BMI, hypertension, hypercholesterolaemia, depression, smoking, alcohol and physical activity).¹⁹

Summary

Though there are many hints of a causal association between diabetes and the development of cognitive decline, definitive proof of a protective effect of antidiabetic treatment by controlled or even randomised placebo-controlled studies is still required.

Hyperlipidaemia

Pathological and experimental data suggest that cholesterol may play a role in the pathogenesis of cognitive impairment and

Table 1. Summary of major prospective studies of the association of diabetes mellitus and cognitive performance

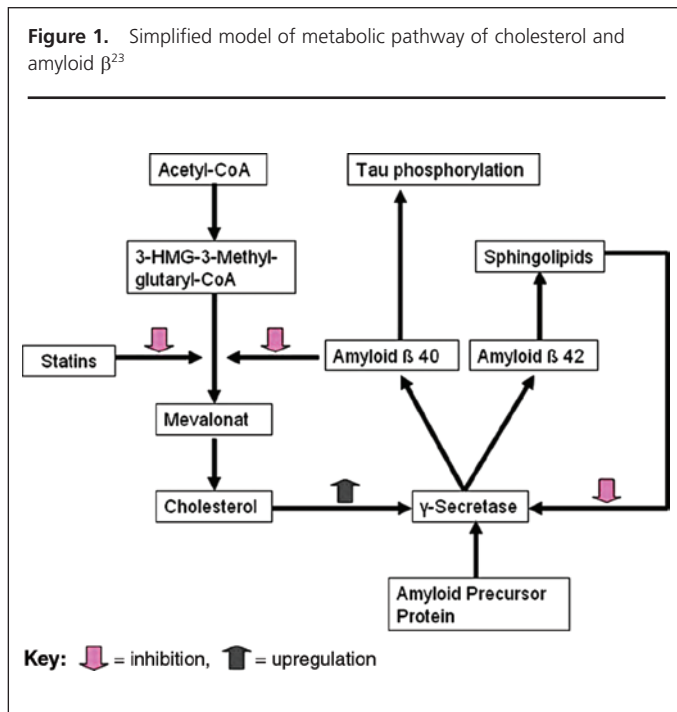
Study	Participants	Mean age (years)	Follow-up (years)	Cognitive test	Assessment of diabetes	Covariates	Result (OR/HR; 95% CI) for cognitive decline in diabetes
Osteoporotic Fractures Research Group¹⁶	9,679 ♀	> 65	3–6	Digit symbol test, Trails B and MMSE at baseline	Self-report	Age, education, depression, stroke, visual impairment, heart disease, hypertension, physical activity, estrogen use and smoking	1.63; 1.20–2.23
Nurses' Health Study¹⁷	16,596 ♀	74.2	2	Telephone interview for cognitive status	Self-report	Age, education, duration and medication of DM	1.34; 1.14–1.57
Multiple Outcomes of Raloxifene Evaluation¹⁸	7,027 ♀	66.3	4	Five cognitive tests at baseline and after four years	Self-report + antidiabetic medication + increased fasting glucose	Age, education, race, depression	1.79; 1.14–2.81
Physicians' Health Study + Women's Health Study¹⁹	5,907 ♂ + 6,326 ♀	♂ 74.1; ♀ 71.9	♂ 2; ♀ 4	Telephone interview for cognitive status	Self-reported questionnaire	Age, education and hormone use (women), baseline score, BMI, hypertension, cholesterol, depression, smoking, alcohol, physical activity	-0.74; -1.05 to -0.43 mean difference of decline in DM
Washington Heights–Inwood Columbia Ageing Project²⁰	918	75.9	6	Complete neuropsychological testing	Self-report or antidiabetic medication	Age, sex, education, ethnic group, apo E, hypertension, LDL, smoking, stroke, heart disease	1.4; 1.1–1.8

Key: apo E = apolipoprotein E; BMI = body mass index; CI = confidence interval; DM = diabetes mellitus; HR = hazard ratio; LDL = low-density lipoprotein; OR = odds ratio; ♂ = men; ♀ = women

dementia (figure 1).²³ A relationship between amyloid deposition and serum hypercholesterolaemia in the human brain was detected in autopsy cases of patients older than 40 years.²⁴ An association between severe circle of Willis atherosclerosis and sporadic dementia was found among 54 autopsy cases.²⁵

Studies on hyperlipidaemia and cognitive decline

The Finnish CAIDE study evaluated the impact of midlife serum cholesterol levels on the subsequent development of mild cognitive impairment among 1,449 participants. After an average follow-up of 21 years, a midlife elevated serum cholesterol level



(≥ 6.5 mmol/L) was a significant risk factor for MCI (OR 1.9; 95% CI 1.2–3.0) after adjustment for age and BMI.²⁶ In a retrospective cohort study of 8,845 participants, aged 40–44 years, high cholesterol was associated with a 40% (HR 1.42; 95% CI 1.22–1.66) increase in risk of dementia after 30 years.²⁷ The French Three-City-Study, a population-based cohort of 9,294 subjects, reported an increased risk for subjects with hyperlipidaemia (OR 1.43; 95% CI 1.03–1.99) independent of all major potential confounders.²⁸

In contrast to these trials, studies with participants of older age could not confirm this result of elevated cholesterol being a risk factor. In the Italian Longitudinal Study on Aging with 2,963 participants (age 65–84 years), serum total cholesterol had a borderline (non-significant) trend for a protective effect.²⁹ A population-based cohort study with 2,356 participants, aged 65 and older, found no association between cholesterol and subsequent risk of dementia after adjustment for several cofounders (age, sex, education, baseline cognition, vascular comorbidities, BMI and lipid-lowering agent use).³⁰ In a cross-sectional and prospective community-based cohort study including 4,316 Medicare recipients, 65 years and older, only a weak relationship between cholesterol levels and the risk of vascular dementia was observed.³¹

Several reasons could explain the paradoxical situation that hypercholesterolaemia is apparently a risk factor in midlife but becomes a more protective factor in older age. Hypercholesterolaemia in the elderly may reflect a good dietary status and overall health, whereas low levels of cholesterol could be the result of poor nutrition caused by cognitive decline or other medical problems.³²

Studies with statins

The majority of observational and prospective studies suggested an association between statin use and cognitive decline, especially Alzheimer's dementia.^{28,33,34} A population-based cohort study comprising 1,674 older Mexican Americans with a five-year follow-up found, after adjustment for several risk factors, that statin users were about half as likely as non-statin users to develop cognitive decline (HR 0.52; 95% CI 0.34–0.80).³⁵ In the prospective population-based Rotterdam Study with 6,992 participants and a mean follow-up of nine years, statin use was associated with a decreased risk of Alzheimer dementia (HR 0.57; 95% CI 0.37–0.90), compared with no use of cholesterol-lowering drugs. There was no difference between lipophilic (simvastatin, atorvastatin, cerivastatin) or hydrophilic statins (pravastatin, fluvastatin, rosuvastatin), but non-statin cholesterol-lowering drug use (fibrates, nicotinic acid, etc.) was not effective.³⁶

On the other hand, two large placebo-controlled trials found no positive association between statin therapy and cognitive decline. The HPS reported no protective effect of simvastatin on cognitive decline after five years among 20,536 high-risk vascular participants aged between 40 and 80 years.³⁷ In the PROSPER trial, which included 5,804 elderly high-risk vascular participants (aged 70–82 years), pravastatin had no significant effect on cognitive function.³⁸ A recent Cochrane review based on these two randomised trials concluded that statins given in late life to individuals at risk of vascular disease have no effect in preventing dementia.³⁹ Detailed analyses of the latter study designs might explain the negative results despite the large number of participants. Both studies were not primarily designed to assess cognitive function. Neither included a baseline measurement of cognitive function, which makes an accurate evaluation of any statin effect difficult.⁴⁰ The final cognitive assessment in the HPS was performed by telephone interview which is less reliable. Lastly, the HPS included midlife and elderly subjects, and thus the above mentioned age-dependent paradoxical influence of cholesterol level could have been neutralised.

Summary

There exists a bi-directional association between hypercholesterolaemia and cognitive function. In midlife, elevated cholesterol levels comprise a risk factor for cognitive decline. In elderly subjects, cholesterol levels decline and are not clearly associated with cognitive impairment. The evidence of treatment of hypercholesterolaemia by statins solely for prevention of cognitive decline remains unclear.

Hypertension

Hypertension accelerates arteriosclerotic changes through atheroma formation in large diameter blood vessels and arteriolar tortuosity of small vessels.⁴¹ These vascular changes lead to hypoperfusion producing discrete cerebral infarctions and diffuse ischaemic changes in the periventricular and deep white matter (leukoaraiosis) causing vascular cognitive impairment. It has been suggested that decreased BP reduces mechanisms contributing

to generalised neurodegenerative changes, which may account for improvements in impairments on memory tasks.⁴² A post-mortem study detected substantially fewer neuropathological changes (neuritic plaques and neurofibrillary tangle) in medicated hypertensive patients compared with non-hypertensive controls suggesting a salutary effect of antihypertensive therapy.⁴³

Studies

The results of 28 cross-sectional studies investigating the relationship between elevated BP and cognition showed conflicting relationships with positive, negative and J- and U-shaped associations.⁴⁴ Cross-sectional studies, however, are limited in determining the direction of an association because both exposure and outcome are assessed simultaneously.

Longitudinal studies have therefore been suggested to be more appropriate in assessing the relationship between hypertension and cognitive function. The majority of 22 longitudinal studies demonstrated elevated BP to be associated with cognitive decline but some studies showed quadratic, J- and U-shaped relationships between BP and cognitive performance in addition to three studies showing elevated BP to be associated with improved cognitive performance.⁴⁴

Observational studies may demonstrate associations but do not determine causality; the latter only being shown by intervention studies. Nine completed randomised placebo-controlled clinical trials investigating the efficiency of antihypertensive treatment on the development of cognitive impairment have been reported. Three of these trials had fewer than 100 participants and a follow-up of less than one year. The remaining six major placebo-controlled studies showed conflicting results (table 2): The MRC trial of hypertension found no significant difference for change in cognitive function among 4,396 subjects who were randomised to receive hydrochlorothiazide plus amiloride, atenolol, or placebo over 54 months.⁴⁵ The Syst-Eur Trial investigated, among 2,418 elderly people, whether treatment with nitrendipine, including the possible addition of enalapril, hydrochlorothiazide or both drugs, could reduce the incidence of dementia. The follow-up was only two years as the trial was terminated early because of significant differences in the incidence of stroke, the primary end point. At this time, active treatment reduced the incidence of dementia by 50% from 7.7 to 3.8 cases per 1,000 patient-years (21 vs. 11 patients, $p=0.05$), compared with placebo.⁴⁶ In the extended phase of this trial the evidence was reinforced that BP-lowering therapy initiated with a long-acting dihydropyridine protects against dementia in older patients with systolic hypertension.⁴⁷

SHEP was conducted over an average of five years' follow-up involving 4,736 elderly persons with isolated elevated systolic BP. Participants on antihypertensive treatment showed a slight positive, but non-significant effect on cognitive function.⁴⁸ The SCOPE trial in 4,964 participants assessed whether candesartan therapy in mildly to moderately hypertensive elderly patients reduced cognitive decline. The result was non-significant as mean MMSE score fell from 28.5 to 28.0 in the candesartan group and from 28.5 to 27.9 in the control group ($p=0.20$).⁴⁹

PROGRESS included 6,105 people with prior stroke or transient ischemic attack who received either perindopril plus indapamide or matching placebo. After nearly four years, cognitive decline occurred more often in the actively treated group, but in the absence of recurrent stroke no clear effect on either dementia or cognitive decline was detected.⁵⁰ HYVET-COG assigned 3,336 elderly patients either indapamide (plus perindopril, if necessary) or placebo. After two years no significant difference between treatment and placebo groups was detected.⁵¹

Altogether, four studies showed no protective effect,^{45,48,49,51} whereas two studies demonstrated some positive effect.^{46,50} The latest Cochrane review included four of these trials with 15,936 hypertensive subjects without any history of cerebrovascular disease, average age of 75.4 years and mean BP at entry of 171/86 mm Hg. The combined result of incidence of dementia indicated no significant difference between treatment and placebo (OR 0.89; 95% CI 0.74–1.07).⁵² On the other hand, a meta-analysis of the combined data of HYVET, Syst-Eur, SHEP and PROGRESS showed a borderline pooled ratio favouring treatment (HR 0.87; 0.76–1.00, $p=0.045$).⁵¹

Limitations

Several limitations, even of these 'gold standard' randomised placebo-controlled studies restrict their interpretation or generalisation. For example, the proportion of placebo patients given active treatment was 27% in Syst-Eur,⁴⁶ 44% in SHEP⁴⁸ and even 84% in SCOPE.⁴⁹ In PROGRESS, only a selected study population (prior cerebrovascular disease) was assessed.⁵⁰ The inclusion criteria, hypertension, varied between isolated systolic hypertension^{46–48} and hypertension with different thresholds.^{45,49,51} The observation period of two years for the assessment of cognitive decline was very short in Syst-Eur and HYVET-COG.^{46,51} Furthermore, differences within the antihypertensive drugs may explain the divergent results.⁵³ Data from animal studies indicate that an ARB (olmesartan) prevents beta-amyloid-induced vascular dysregulation and partially attenuates the impairment of hippocampal synaptic plasticity.⁵⁴ The Cardiovascular Health Study Cognition Substudy revealed that centrally active ACE inhibitors (those that cross the blood–brain barrier, e.g. captopril or ramipril) were associated with a highly significantly reduced cognitive decline compared with other antihypertensive drugs.⁵⁵ In addition, the methods of assessing cognitive function varied among the studies; for example, in the MRC trial cognitive function was tested by the rate of change in paired associate learning test and trail making test scores over time,⁴⁵ whereas Syst-Eur and SCOPE used the MMSE.⁴⁶ Considering the complex relationship between BP and cognitive function, the need for various assessments for evaluating cognitive impairment of differing aetiologies has been suggested⁵⁶ and the diverse results shown in both epidemiological and interventional studies may in part be explained by the use of a variety of cognitive instruments.

Summary

There exists an age-dependent relationship between BP and cognitive impairment. Midlife hypertension is associated with

Table 2. Summary of major placebo-controlled antihypertensive trials assessing protection of cognitive dysfunction

Study	Participants	Mean age (years)	Inclusion criteria of hypertension (SBP and DBP - mmHg)	Cognitive test	Follow-up (years)	Antihypertensive drugs	Result/ Effect on cognitive decline
MRC trial of hypertension ⁴⁵	4,396	70.3	Hypertension (SBP 160–209; DBP < 115)	Paired associate learning test, trail making test part A	4.5	Hydrochlorothiazide + amiloride or atenolol	Not significant
Syst-Eur trial ^{46,47}	2,418	69.9	Isolated systolic hypertension (SBP 160–219; DBP <95)	MMSE	3.9	Nitrendipine ± enalapril ± hydrochlorothiazide	HR 0.38 (95% CI 0.23–0.64)
SCOPE ⁴⁹	4,964	76.4	Hypertension (SBP 160–179; DBP 90–99)	MMSE	3.7	Candesartan ± hydrochlorothiazide	Not significant
SHEP ⁴⁸	4,736	71.6	Isolated systolic hypertension (SBP 160–219; DBP < 90)	Short care	4.5	Chlorthalidone ± atenolol or reserpine	Not significant
PROGRESS ⁵⁰	6,105	64	Stroke/TIA	MMSE	3.9	Perindopril ± indapamide	Relative RR 19% (95% CI 4–32%)
HYVET-COG ⁵¹	3,336	83.5	Hypertension (SBP 160–200; DBP <110)	MMSE	2.2	Indapamide ± perindopril	0.86 (0.67–1.09)

Key: CI = confidence interval; DBP = diastolic blood pressure; HR = hazard ratio; MMSE = mini-mental state examination; HYVET-COG = Hypertension Treatment in the Very Elderly Cognitive function assessment; MRC = Medical Research Council; PROGRESS = Perindopril Protection Against Recurrent Stroke Study; RR = relative risk; SBP = systolic blood pressure; SCOPE = Study on Cognition and Prognosis in the Elderly; SHEP = Systolic Hypertension in the Elderly Program; Syst-Eur = Systolic Hypertension in Europe; TIA = transient ischaemic attack

an increased risk of developing cognitive decline, whereas hypertension later in life does not carry the same risk.⁵⁷ Evidence for a protective effect of antihypertensive treatment on cognitive deterioration remains controversial, although this therapy is in any case mandatory for its well-proven cardiovascular benefit. Further open questions include the extent of antihypertensive treatment as current guidelines recommend a target BP of 140/90 mm Hg. The duration of BP lowering therapy medication is not known but apparently for persons aged ≤ 75 years there exists an increasing benefit per year of treatment.⁵⁸ Finally, the latency of a protective effect remains unclear and may carry potential risks as BP sometimes spontaneously declines in the years before dementia onset.⁵⁹

Conclusion

Though there are many hints for a causal association between diabetes and the development of cognitive decline, a definitive proof for a protective effect of antidiabetic treatment by controlled or even randomised placebo-controlled studies is required.

A bi-directional association exists between hypercholesterolaemia and cognitive function. In midlife, elevated cholesterol levels comprise a risk factor for cognitive decline. In elderly subjects, cholesterol levels decline and are not clearly associated with cognitive impairment. The evidence for treatment of hypercholesterolaemia by statins solely for prevention of cognitive decline remains unclear.



Key messages

- Mild cognitive impairment can be caused by treatable somatic factors
- Diabetes mellitus has a causal relationship in the development of cognitive decline and there are indirect hints for a possible benefit of antidiabetic therapy
- Hypercholesterolaemia in midlife is a risk factor for cognitive decline
- In elderly subjects, cholesterol levels decline and are not clearly associated with cognitive impairment
- The role of statin treatment of hypercholesterolaemia in the prevention of cognitive decline remains unclear
- Midlife hypertension is associated with an increased risk of developing cognitive decline and antihypertensive treatment may be beneficial
- Hypertension later in life does not carry the same risk of cognitive dysfunction

An age-dependent relationship is found between BP and cognitive impairment. Midlife hypertension is associated with an increased risk of developing cognitive decline, whereas hypertension later in life does not carry the same risk. Cardiovascular benefit of antihypertensive treatment is well-proven, while its efficacy regarding cognitive performance remains controversial.

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