Determinants of cognitive function in old age

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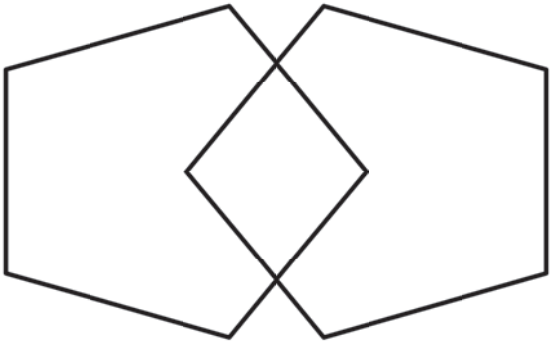
Chapter 2

The influence of age on the association between cholesterol and cognitive function



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Abstract

With the increasing emphasis on vascular disease as a risk factor for dementia and cognitive impairment, lowering cholesterol has received much attention to maintain cognitive function. Observational studies have shown that high total serum cholesterol levels in middle age, but not in old age, associate with cognitive impairment in later life. This can in part be explained as the association between high levels of total serum cholesterol levels and cardiovascular disease becomes weaker with increasing age and is absent in old age. Most studies on HDL-cholesterol levels show a protective association with cardiovascular disease up to old age, whereas data on the protective association with late-life cognitive impairment is absent. In contrast to general belief, randomized controlled trials and most longitudinal observational studies do not show a positive effect of statin treatment on the risk of dementia when prescribed in later life. In conclusion, high total serum cholesterol in middle age is associated with cognitive impairment and statin therapy is likely to have a benefit on cognitive function via a decrease of cardiovascular pathologies. A beneficial effect of cholesterol lowering in old age is uncertain.

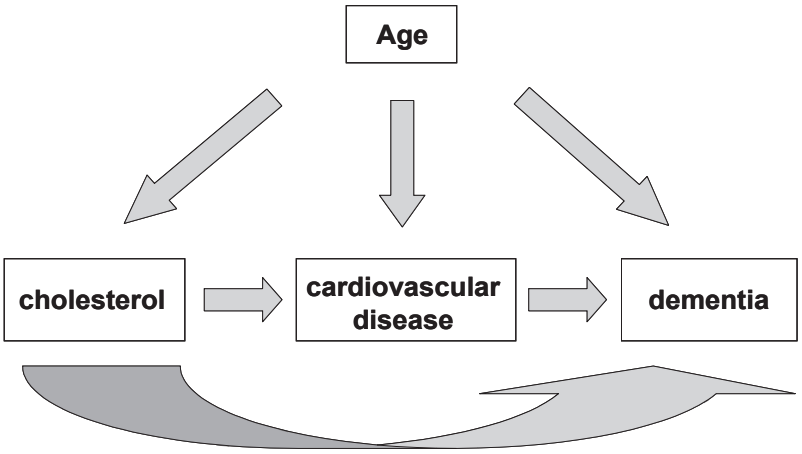
Introduction

Dementia is a common disorder in old age. The prevalence of dementia increases from 1% in people age 65-69 years to 30% in people aged over 90 years, whereas the incidence of dementia increases from 10 cases to 200 cases per 1000 person years [1,2]. Classically the two major forms of dementia are Alzheimer's Disease (AD) and Vascular Dementia (VaD). AD is characterized as a neurodegenerative disease, with the presence of neurofibrillary tangles and neuronal plaques in the brain as the pathological hallmark. VaD on the other hand is characterized as a disorder of vascular origin, with ischemic lesions in cerebro as the hallmark of disease. However, evidence is emerging that vascular pathology is also involved in AD [3,4], and some even propose to classify AD as a vascular disorder [5].

Known risk factors for cardiovascular disease, such as hypertension and hypercholesterolemia, have been shown to increase the risk of dementia. However, the influence of these risk factors on cognitive function is clearly dependent on age. Although hypertension in midlife is a risk factor for late-life cognitive impairment, high diastolic blood pressure in late-life is protective for cognitive function [6]. The role of age in the relation between cholesterol levels and cognitive impairment has far less been studied.

Here, we review the results from human observational studies on the association between cholesterol levels and cognitive function in order to clarify the role of age in the observed associations. Emphasis will be put on a direct etiological pathway and an indirect etiological pathway via atherosclerosis, both depicted in figure 1, through which cholesterol levels may influence cognitive function. Finally, we summarize the findings from both cross-sectional and longitudinal observational studies, and randomized controlled trials, on the effect of lipid-lowering treatment to preserve cognitive function.

Figure 1. **The role of age in the (in)direct association between cholesterol and dementia**



Search strategy and obtained results

Articles included in this review were identified by searching Pubmed from 1980 until March 2008 with the terms “cholesterol level”, “HDL cholesterol”, “dementia”, “cognitive function”, “cardiovascular disease”, “cardiovascular mortality”, “statin treatment”, and “age”. Only papers published in English were reviewed. Supplementary tables 1-6 (available online) show the results from all reviewed articles. For the association between total serum cholesterol levels and cognitive function 22 studies were included and for the association between HDL cholesterol levels and cognitive function 13 studies were included. 18 Studies reported on the relation between total serum cholesterol levels and cardiovascular disease and 9 studies reported on the association between HDL cholesterol levels and cardiovascular disease. The association between cardiovascular disease and cognitive function was reviewed in 20 studies, and 21 studies reported on the effect of statin treatment on cognitive function.

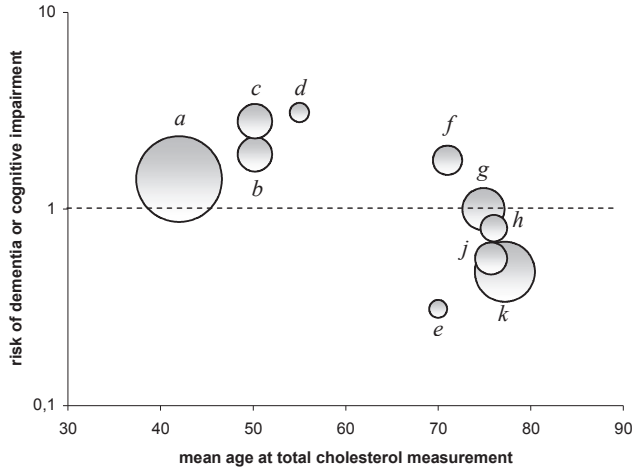
Total serum cholesterol levels and risk of dementia and cognitive decline

Figure 2 shows the results from the studies providing data that allowed for estimating risks of cognitive impairment for categorized levels of total serum cholesterol. [7-19]. When measured in midlife, a high total serum cholesterol level associated with an increased risk of late-life dementia and mild cognitive impairment [7,9-11,14,18,20,21]. In a population based study situated in Finland, participants with midlife (mean age: 50 years) total serum cholesterol levels higher than 6.5 mmol/l had an increased risk of mild cognitive impairment, AD, and all-cause dementia at a mean age of 71 years [9-11]. The same results for comparable age categories were found in the 'Kaiser Permanente Medical Care Program' [18]. On the contrary, when measured in late-life, the relation between total cholesterol and dementia is unclear [8,13,15-17,22-24]. In the 'Framingham Study', the 'Group Health Cooperative Study' and a cohort study amongst Medicare recipients in Manhattan, total serum cholesterol levels in subjects older than 65 years did not associate with the incidence of dementia or a change in cognitive function during follow-up [15,17,24]. An inverse relation between late-life total serum cholesterol levels and the risk of dementia was found in population based studies in Finland, New York and in the '1901 Swedish Birth Cohort Study', both cross-sectionally and longitudinally [8,13,16,19,22]. Three cross-sectional studies performed in selected populations, consisting of two populations of native Africans living in the United States and one population of postmenopausal women showed a positive association between late-life high total serum cholesterol levels and the presence of dementia [12,25,26].When summarized, various studies show that high total serum cholesterol levels measured in midlife are associated with an increased risk of cognitive impairment in late-life. On the contrary, despite few opposing studies, a high total serum cholesterol level in old age seems to associate with a decreased risk of cognitive impairment or have no relation with cognitive impairment.

High density lipoprotein cholesterol levels and risk of dementia and cognitive decline

Risks of dementia and cognitive impairment for categories of high density lipoprotein (HDL) cholesterol levels are shown in figure 3 [13,15,19,27-29]. Most cross-sectional studies, that included subjects aged over 75 years, showed an association between increased HDL cholesterol levels and a decreased prevalence of dementia, better performance on cognitive tests, and less Alzheimer pathology in cerebro [23,27-31]. On the contrary, one cross-sectional study and all follow-up studies, performed in larger populations, showed no association between HDL cholesterol levels and cognitive function [12,13,15,17,19,24,32].

Figure 2. **Influence of age on the relation between total serum cholesterol levels and the risk of dementia and cognitive impairment.**



Size of circles corresponds to study size.

a. Whitmer *et al*. **Kaiser Permanente Medical Care Program.** Hazard ratio for dementia for high compared to low total serum cholesterol level.

b/*c*. Kivipelto *et al*. **Population based study in Eastern Finland.** Odds ratio for Mild Cognitive Impairment (b) or Alzheimer's Disease (c) for high compared to low total serum cholesterol level.

d. Notkola *et al*. **Seven Countries Study.** Odds ratio for Alzheimer's Disease at age 80 years for high compared to low total serum cholesterol level.

e. Mielke *et al*. **1901 Swedish birth cohort study.** Hazard ratio for dementia for highest compared to lowest quartile of total serum cholesterol level.

f. Yaffe *et al*. **Heart and Estrogen / progestin Replacement Study.** Odds ratio for cognitive impairment for highest compared to lowest three quartiles of total serum cholesterol level.

g. Li *et al*. **Group Health Cooperative Study.** Hazard ratio for Alzheimer's Disease for highest compared to lowest quartile of total serum cholesterol level.

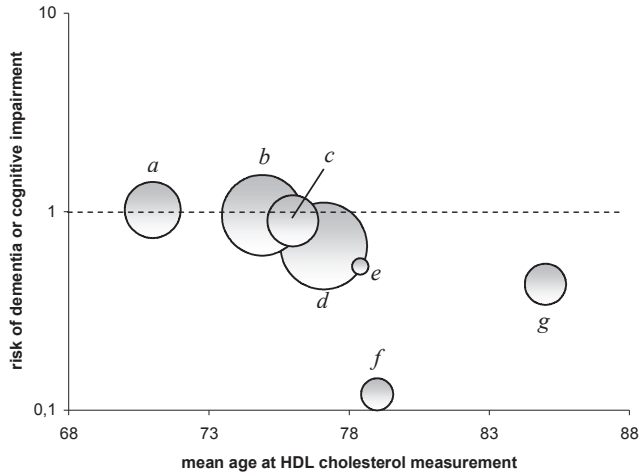
h. Reitz *et al*. **Cohort Study amongst Medicare Recipients in Northern Manhattan.** Hazard ratio for mild cognitive impairment for highest compared to lowest quartile of total serum cholesterol level.

j. Romas *et al*. **Study amongst Medicare beneficiaries in Washington Heights.** Relative risk for Alzheimer's Disease foe highest compared to lowest quartile of total serum cholesterol level.

k. Reitz *et al*. **Cohort study amongst Medicare recipients in Northern Manhattan.** Relative risk for Alzheimer's Disease for highest compared to lowest quartile of total serum cholesterol level.

In both the 'Framingham Study' and the 'Group Health Cooperative Study', HDL cholesterol levels did not associate with the risk of dementia during follow-up, and in the 'Heart and Estrogen / progestin Replacement Study', and a cohort study amongst Medicare recipients in Manhattan, HDL cholesterol levels did not associate with a change in cognitive function during follow-up. All these studies were performed in old age and no studies have been reported on the association between midlife HDL cholesterol and late-life cognitive function. In summary, there is not yet conclusive evidence for a beneficial effect of HDL cholesterol levels and the risk of dementia or cognitive decline in late-life.

Figure 3. **Influence of age on the relation between serum HDL cholesterol levels and the risk of dementia and cognitive impairment.**



Size of circles corresponds to study size.

a. Yaffe *et al*. **Heart and Estrogen / progestin Replacement Study.** Odds ratio for cognitive impairment for highest three quartiles compared to lowest quartile of HDL cholesterol level.

b. Li *et al*. **Group Health Cooperative Study.** Hazard ratio for dementia for highest compared to lowest quartile of HDL cholesterol level.

c. Reitz *et al*. **Cohort study amongst Medicare recipients in Northern Manhattan.** Odds ratio for mild cognitive impairment for highest compared to lowest quartile of HDL cholesterol level.

d. Reitz *et al*. **Cohort study amongst Medicare recipients in Northern Manhattan.** Odds ratio for dementia for highest compared to lowest quartile of HDL cholesterol level.

e. Wolf *et al*. **Cross sectional study.** Relative risk for dementia for highest three quartiles compared to lowest quartile of HDL cholesterol level.

f. Bonarek *et al*. **Personnes Agees Quid Study.** Odds ratio for dementia for high compared to low HDL cholesterol level.

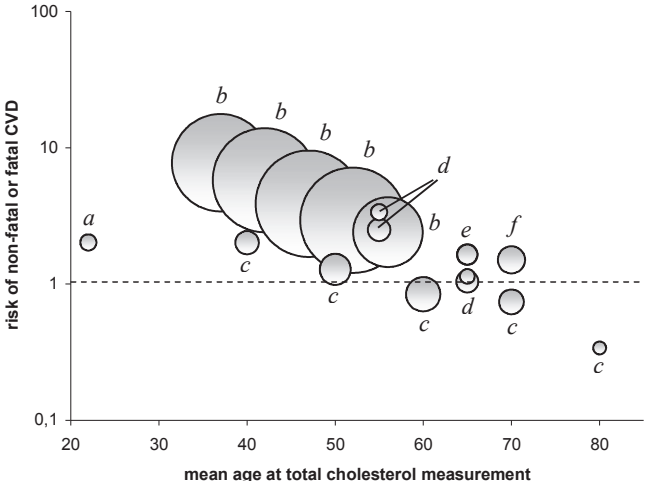
g. Van Exel *et al*. **Leiden 85-plus Study.** Odds ratio for dementia for highest compared to lowest tertile of HDL cholesterol level.

Total serum cholesterol levels and risk of cardiovascular disease and mortality

Figure 4 shows results from studies that investigated the association between categories of total serum cholesterol levels and the risk of cardiovascular disease and mortality. [33-38]. All studies in middle age showed increased total serum cholesterol levels to be associated with coronary heart disease, cardiovascular disease or mortality from coronary heart disease and cardiovascular disease [33-47]. However, with increasing age the relation between high cholesterol levels and cardiovascular disease attenuated [36,38,41] and even disappeared in old age [38,40,42,43,48]. In the 'Framingham Heart Study' an increase in total serum cholesterol level associated with an increased risk of coronary heart disease mortality in subjects who were 40, 50 or 60 years old at baseline, but not in subjects that were 70 years old. Subjects aged 80 years at baseline were even protected for coronary heart disease mortality with increasing total serum cholesterol levels.

The 'Leiden 85-Plus Study' and the 'Established Populations for the Epidemiologic Study of the Elderly Study' confirmed the lack of an association between serum cholesterol levels and cardiovascular disease in old age [49,50]. The 'Framingham Heart Study' and the 'Established Populations for the Epidemiologic Study of the Elderly Study' showed that the waning risk of cardiovascular disease for subjects with a high total serum cholesterol level with increasing age was most outspoken in men [43,45]. In summary, studies show that increased total serum cholesterol levels in midlife associate with an increased risk of cardiovascular disease and mortality. With increasing age the effect of a high total serum cholesterol level on cardiovascular disease and mortality attenuates and is weak or absent in old age.

Figure 4. **Influence of age on the relation between total serum cholesterol levels and the risk of fatal and non-fatal cardiovascular disease.**



Size of circles corresponds to study size.

a. Klag *et al*. **Johns Hopkins Study.** Relative risk for cardiovascular disease mortality for highest compared to lowest quartile of total serum cholesterol level.

b. Stamler *et al*. **Multiple Risk Factor Intervention Trial.** Relative risk for coronary heart disease mortality for highest compared to lowest quintile of total serum cholesterol level.

c. Kronmal *et al*. **Framingham Heart Study.** Relative risk for all-cause mortality for highest compared to lowest quartile of total serum cholesterol level.

d. Mariotti *et al*. **Seven Countries Study.** Odds ratio for coronary heart disease mortality for high compared to low total serum cholesterol level.

e. Benfante *et al*. **Honolulu Heart Program.** Relative risk for coronary heart disease for highest compared to lowest quartile of total serum cholesterol level.

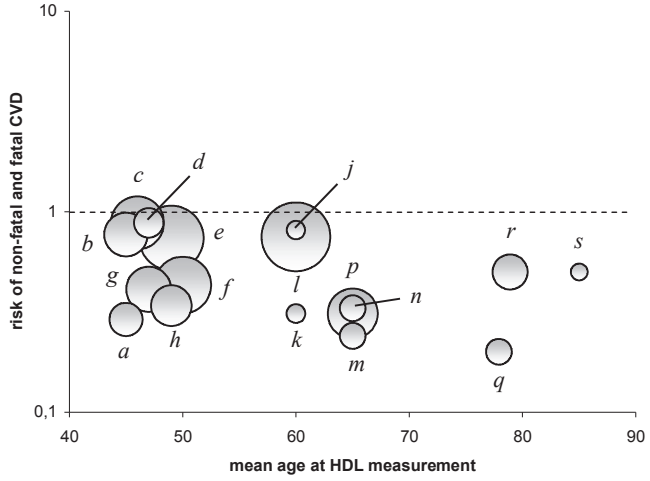
f. Rubin *et al*. **Kaiser Permanente Coronary Heart Disease in the Elderly Study.** Relative risk for coronary heart disease mortality for highest quartile compared to lowest three quartiles of total serum cholesterol level.

High density lipoprotein cholesterol levels and risk of cardiovascular disease and mortality

All studies that reported on the association between HDL cholesterol levels and cardiovascular disease showed that lower HDL cholesterol levels confer an increased risk of cardiovascular disease and mortality during follow-up (figure 5) [39,45,50-56]. This association was found over a wide age range, varying from subjects aged 35-57 years at inclusion in the 'Multiple Risk Factor Intervention Trial' [53] to subjects aged

85 years at inclusion in the 'Leiden 85-Plus Study' [50]. In contrast to total cholesterol, the association between HDL cholesterol and cardiovascular disease did not become weaker with increasing age. In addition, in the 'Framingham Heart Study', the 'Multiple Risk Factor Intervention Trial', the 'Coronary Primary Prevention Trial', and the 'Lipid Research Clinics Prevalence Study', women had a larger decrease in incidence of and mortality from coronary heart disease with increasing HDL cholesterol levels than men [51,53]. In summary, these reports indicate that increasing HDL cholesterol levels are associated with a decreased risk of coronary heart disease and cardiovascular mortality up to (very) old age.

Figure 5. **Influence of age on the relation between serum HDL cholesterol levels and the risk of fatal and non-fatal cardiovascular disease.**



Size of circles corresponds to study size.

a/b. Gordon *et al*. **Lipid Research Clinics Prevalence Study.** Relative risk for cardiovascular disease mortality for highest compared to lowest tertile of HDL cholesterol level in men (a) and women (b).

c Gordon *et al*. **Multiple Risk Factor Intervention Trial.** Relative risk for cardiovascular disease mortality for highest compared to lowest tertile of HDL cholesterol level in men.

d. Gordon *et al*. **Coronary Primary Prevention Trial.** Relative risk for cardiovascular disease mortality for highest compared to lowest tertile of HDL cholesterol level in men.

e. Goldbourt *et al*. **Cohort study amongst Israeli civil servants.** Relative risk for coronary heart disease mortality for normal compared to low HDL cholesterol level in men.

f. Goldbourt *et al*. **Cohort study amongst Israeli civil servants.** Relative risk for coronary heart disease mortality for highest compared to lowest quintile of HDL cholesterol level in men.

g/h. Jacobs *et al*. **Multiple Risk Factor Intervention Trial.** Relative risk for cardiovascular disease mortality for highest compared to lowest quintile of HDL cholesterol level in men (g) and women (h).

j/k. Gordon *et al*. **Framingham Heart Study.** Relative risk for cardiovascular disease mortality for highest compared to lowest tertile of HDL cholesterol level in men (j) and women (k).

l. Barter *et al*. **Treating to New Targets Study.** Hazard ratio for major cardiovascular event for highest compared to lowest quartile of HDL cholesterol level.

m/n. Wilson *et al*. **Framingham Heart Study.** Relative risk for coronary heart disease mortality for highest compared to lowest quintile of HDL cholesterol level in men (l) and women (m).

p. Castelli *et al*. **Framingham Heart Study.** Relative risk for coronary heart disease for highest compared to lowest quartile of HDL cholesterol level.

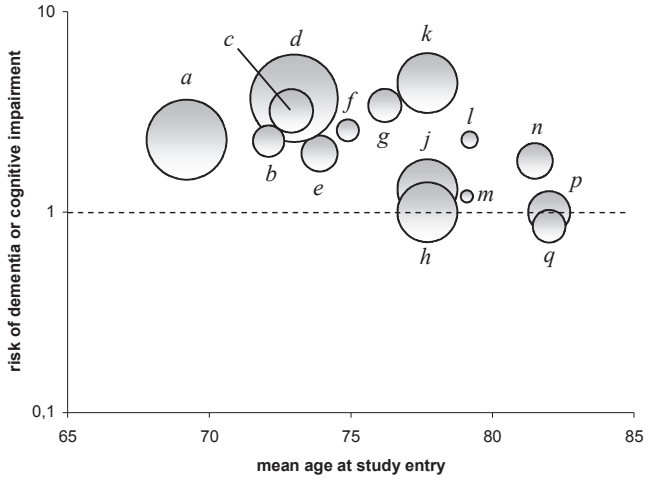
q/r. Corti *et al*. **Established Populations for Epidemiological Studies of the Elderly.** Relative risk for coronary heart disease mortality for highest compared to lowest tertile of HDL cholesterol level in men (p) and women (q).

s. Weverling-Rijnsburger *et al*. **Leiden 85-plus Study.** Relative risk for cardiovascular mortality for highest compared to lowest tertile of HDL cholesterol level.

Cardiovascular disease and risk of dementia and cognitive decline

Figure 6 shows results from studies reporting on the association between cardiovascular disease and the risk of cognitive impairment [57-68]. The majority of studies showed that the presence of cardiovascular disease associated with an increased risk of dementia and worse cognitive function [57-65,67-75]. Several cross-sectional studies, both population-based and case-control designed, showed that the presence of cardiovascular pathologies, such as atherosclerotic disease, congestive heart failure, and a history of stroke, associated with a higher prevalence of dementia or worse cognitive test scores [58-62,68-70,72,73]. In the 'Rotterdam Study' atherosclerotic disease, and in the 'Congestive Heart Failure Italian Study' the presence of congestive heart failure associated with worse scores on the Mini Mental State Examination (MMSE) and an increased atherosclerotic burden with increasing risks of dementia [58,62,69,70]. The 'Brain Donation Program Study' showed that Alzheimer's Disease (AD) patients had a higher number and more severe atherosclerotic lesions in the circle of Willis compared to non-demented controls [73].

Figure 6. **Influence of age on the relation between cardiovascular disease and the risk of dementia and cognitive impairment.**



Size of circles corresponds to study size.

a. Ott *et al*. **Rotterdam Study.** Odds ratio for dementia for subjects with atrial fibrillation compared to subjects without.

b. Vermeer *et al*. **Rotterdam Scan Study.** Hazard ratio for dementia for the presence compared to the absence of silent brain infarcts.

c. Hofman *et al*. **Rotterdam Study.** Odds ratio for dementia for subjects with severe atherosclerosis compared to subjects without atherosclerosis.

d. De Ronchi *et al*. **Faenza Community Aging Study.** Relative risk for dementia for subjects with compared to subjects without a history of stroke.

e. Cacciatore *et al*. **Osservatorio Geriatrico Regione Campania Study.** Odds ratio for cognitive impairment for subjects with compared to subjects without congestive heart failure.

f. Trojano *et al*. **Congestive Heart Failure Italian Study.** Odds ratio for abnormal cognitive performance for subjects with compared to subjects without congestive heart failure.

g. Luchsinger *et al*. **Cohort Study amongst Medicare recipients in Northern Manhattan.** Hazard ratio for Alzheimer's Disease for subjects with 3-4 compared to subjects without cardiovascular risk factors.

h/*j*/*k*. Petrovitch *et al*. **Honolulu Heart Program.** Odds ratio for poor cognitive performance for men with a history of coronary bypass grafting (g), a history of myocardial infarction (h), or a history of stroke (j) compared to men without.

l/*m*. Aronson *et al*. **Bronx Aging Study.** Relative risk for dementia for subjects with compared to subjects without a history of myocardial infarction for men (k) and women (l).

n. Qiu *et al*. **Kungsholmen Project.** Hazard ratio for dementia for subjects with compared to subjects without heart failure.

p/*q*. Bursi *et al*. **Rochester Epidemiology Project.** Odds ratio for dementia for subjects with a history of myocardial infarction (n), or a history of coronary bypass grafting (p) compared to subjects without.

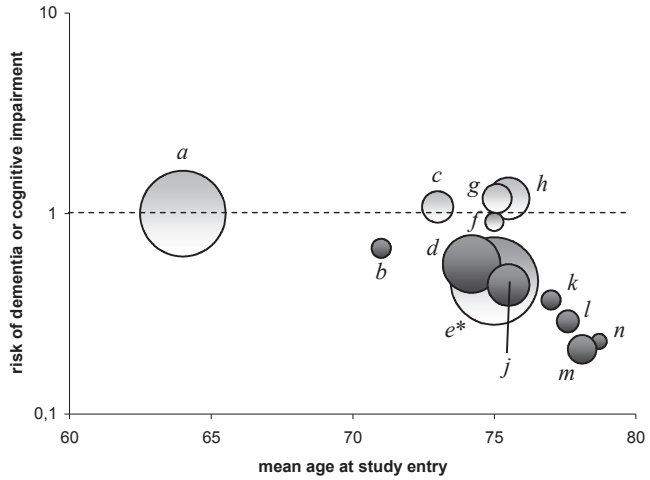
The 'Honolulu Heart Program' showed that men with a history of stroke had a higher prevalence of poor cognitive performance than men without a history of stroke [61]. However, in conjunction with results from the 'Rochester Epidemiology Project', a previous history of myocardial infarction or coronary artery bypass grafting (CABG) did not associate with cognitive performance [66,76]. A series of follow-up studies showed that the presence of cardiovascular disease associated with an increased risk of dementia or an increased decline in cognitive function [57,63-65,67,71,74]. In the 'Cardiovascular Health Study' and the 'Leiden 85-Plus Study' generalized atherosclerosis associated with steeper declines in cognitive test scores [65,71]. The relation between vascular disease and the risk of dementia has also been subject of several MRI-studies. The 'Rotterdam Scan Study' reported on an increased risk of dementia for subjects that suffered from a higher severity of periventricular white matter lesions and for subjects with the presence of silent brain infarcts [63,74]. There was no specific effect of age on the relation between cardiovascular disease and cognitive function in the studies presented here. When summarized, there is strong evidence that the presence of cardiovascular pathologies is associated with an increased risk of cognitive impairment at all ages.

Studies on cholesterol lowering treatment

The abundant evidence for a detrimental effect of high cholesterol led to the investigation of the efficacy of lipid lowering treatment to prevent cardiovascular disease, and to whether it also prevents cognitive decline. Figure 7 shows the results from the studies that investigated the influence of lipid lowering treatment on the risk of cognitive impairment. [12,77-88]. These results show a sharp distinction between the outcomes in the cross-sectional studies, compared to the outcomes in the randomized controlled trials and most observational longitudinal studies.

All cross-sectional studies showed a beneficial effect of lipid lowering treatment on cognitive function [12,77,78,80,83,86,89]. In the 'Canadian Study of Health and Aging', the 'Three City Study', and the 'Heart and Estrogen / progestin Replacement Study', use of lipid lowering agents, almost exclusively statins, associated with a lower prevalence of dementia, AD, and cognitive impairment [12,80,83,86]. Strongest support for a beneficial effect of statin treatment comes from a recently published large numbered observational study with two years of follow-up, which showed that simvastatin users had a lower risk of dementia than non-users [87].

Figure 7. **Influence of age on the association between statin use and the risk of dementia and cognitive impairment.**



Size of circles corresponds to study size.

*e** circle size scaled down by factor 60

Longitudinal studies

Cross-sectional studies

a. Heart Protection Study Collaborative Group. **Heart Protection Study.** Relative risk for incidence of dementia for statin use compared to non-use.

b. Yaffe *et al*. **Heart and Estrogen / progestin Replacement Study.** Odds ratio for prevalence of cognitive impairment for statin use compared to non-use.

c. Rea *et al*. **Cardiovascular Health Study.** Hazard ratio for incidence of dementia for statin use compared to non-use.

d. Dufouil *et al*. **Three City Study.** Odds ratio for prevalence of dementia for statin use compared to non-use.

e. Wolozin *et al*. **US Veterans Affair Database Study.** Hazard ratio for dementia for simvastatin use compared to non-use.

f. Arvanitakis *et al*. **Religious Orders Study.** Hazard ratio for Alzheimer's disease for statin use compared to non-use.

g. Li *et al*. **Adult Changes in Thought Study.** Hazard ratio for incidence of dementia for statin use compared to non-use.

h/j. Zandi *et al*. **Cache County Study.** Hazard ratio for incidence of dementia (f) and odds ratio for prevalence of dementia (g) for statin use compared to non-use.

k. Rockwood *et al*. **Canadian Study of Healthy Aging.** Odds ratio for cognitive impairment, not dementia (CIND) for statin use compared to non-use.

l. Jick *et al*. **UK-based General Practice Research Database.** Relative risk for prevalence of dementia for statin use compared to non-use.

m. Rockwood *et al*. **Canadian Study of Health and Aging.** Odds ratio for prevalence of dementia for statin use compared to non-use.

n. Hajjar *et al*. C**ase-control study.** Odds ratio for prevalence of dementia for statin use compared to non-use.

Opposing these results are two large randomized controlled trials that were designed to investigate the effect of statin use on cardiovascular and cerebrovascular health [79,81]. The 'Heart Protection Study', which was performed in subjects in an age-range from 40-80 years, showed that allocation to statin treatment did not decrease the risk of developing dementia during follow-up [79]. The 'Prospective Study of Pravastatin in the Elderly at Risk', performed in elderly subjects, showed that subjects that were treated with statins had similar changes in cognitive function as placebo-treated subjects [81]. This lack of a beneficial effect of statins on cognitive function was confirmed by several large observational follow-up studies, such as the 'Adult Changes in Thought Study', the 'Cardiovascular Health Study', and the 'Cache County Study' [82,84,85]. Two small sized statin trials in AD patients, one with a pilot proof-of-concept design, and the other with a non-randomized design, with follow-up periods up to one year, showed some beneficial effect of statin use on cognitive test scores [90,91]. To summarize, statin use associates with better cognitive function in cross-sectional and short follow-up studies. Randomized controlled trials and observational studies with a longer follow-up show that statin use does not associate with the risk of cognitive impairment.

Discussion

When measured in midlife, high total serum cholesterol levels associate with an increased risk of late-life cognitive impairment. This can in part be explained by high cholesterol levels causing cardiovascular pathologies that increase the risk of cognitive impairment. In late-life total serum cholesterol levels do not associate with cognitive function, which is consistent with the waning effect of high total serum cholesterol levels on cardiovascular disease with increasing age. High HDL cholesterol levels protect against cardiovascular disease, both in midlife and late-life. However, irrespective of age, HDL cholesterol levels do not associate with cognitive function in longitudinal studies, although there is a lack of information on the effect of midlife HDL cholesterol levels on cognitive function in late-life. Finally, in late-life, the presence of cognitive impairment associates with lower total serum cholesterol levels and, less consistently, with lower HDL cholesterol levels.

Cerebral hypoperfusion is an underlying pathophysiological mechanism that could explain how high cholesterol levels, via cardiovascular pathologies, can lead to cognitive impairment. This explains why congestive heart failure, a severe resultant of coronary heart disease, is a strong risk factor of cognitive impairment

[62,67,70]. Due to an abating heart function sufficient blood flow to the brain may no longer be maintained. Demented patients have been shown to have a lower cerebral blood flow [92], and specific brain regions in AD patients have been shown to have a lower blood flow than those in control patients [93]. Moreover, a low diastolic blood pressure in older adults has been suggested to be a risk factor for dementia and AD [6]. The negative association between cholesterol and cognitive function could also be explained, more strictly, by cerebrovascular disease. Cerebral infarctions and white matter lesions, have been associated with an increased risk of dementia [63,74]. Moreover, a large autopsy study showed that the proportion of subjects with multiple vascular pathology was larger in demented subjects than in non-demented subjects [4]. Atherosclerosis, a major risk factor for both cardiovascular and cerebrovascular disease [94,95], is caused by an unfavorable lipid profile and cognitive function may therefore be influenced by high total serum cholesterol and low HDL cholesterol levels, especially in young and middle age.

Although cardiovascular pathologies can explain for the association, serum cholesterol levels might also influence the risk of cognitive decline through a direct etiological process. A possible explanation for a direct etiological pathway might be the interference of serum cholesterol levels with β-amyloid formation and deposition in the brain. Although brain cholesterol is almost exclusively produced in situ by astrocytes, and there is no evidence for cholesterol transfer from plasma into the brain over the blood brain barrier [96], a study showed that rabbits that were fed a cholesterol rich diet had an increase in the accumulation of β-amyloid in the brain [97]. Even though total serum cholesterol levels do not correlate with cerebrospinal fluid cholesterol levels, HDL cholesterol levels do associate with cerebrospinal fluid cholesterol levels [98] and human studies showed that high total serum cholesterol levels associated with larger amounts of β-amyloid deposition in autopsied brains from AD patients and with lower cerebrospinal fluid levels of β-amyloid [99,100]. The latter finding can be explained by an increased deposition of β-amyloid in the brain, with the resultant decrease in β-amyloid levels in cerebrospinal fluid. Therefore, serum cholesterol levels may influence cognitive function through interplay with β-amyloid formation and deposition, which is one of the hallmarks of AD [101].

In contrast to the detrimental effects of high midlife cholesterol levels on late-life cognitive function, evidence points to an absence of effect or even a reversed effect in late-life. A likely explanation for this could be found in the fact that low total serum cholesterol levels in late-life can be a sign of bad health, amongst which there is emerging dementia [102,103]. Moreover, with increasing age there is a drop in cholesterol levels [104,105]. Although detrimental in midlife, higher total serum cholesterol levels reflect a better health status in late-life and therefore may associate with better

cognitive function in observational studies, and more so in cross-sectional than in longitudinal studies. Indeed, subjects that suffer from AD have shown to be subject to extensive weight loss, which can be accompanied by a decrease in cholesterol levels [106]. For HDL cholesterol levels a reversal of the effect on cardiovascular disease and cognitive function with increasing age is less likely to occur. It is a high HDL cholesterol level that is shown to be protective for cardiovascular disease and possibly cognitive impairment and a better health status in late-life will most likely be reflected by higher HDL cholesterol levels. Secondly, reports on the change in HDL cholesterol levels during the course of aging have shown contradicting results and the change is therefore unclear [104,105].

The ultimate test to study the influence of cholesterol levels on the risk of dementia is to interfere in the cholesterol metabolism by treatment with lipid-lowering agents. All cross-sectional and some longitudinal observational studies with relatively short follow-up periods showed a positive association between statin use and cognitive function. In contrast, randomized controlled trials and several longitudinal studies did not show a beneficial effect. The discordance between the results could well be explained by the way treatment was allocated. Subjects in the trials were allocated to statin treatment based on randomization, whereas subjects in the observational studies were prescribed statins by their physicians. Because statins are mainly prescribed for preventive measures, the health status of study subjects may have interfered in prescription behavior of physicians. In line with the observational studies between cholesterol and cognitive function described above, subjects that received statin treatment might have been in a better condition than subjects that did not receive a statin prescription, because more health benefit from prevention could have been expected in these subjects. Supporting this explanation is the finding that observational studies with longer follow-up periods did not show a beneficial effect. One of the explanations why statins failed to have beneficial effects on cognitive function in the randomized controlled trials might be found in the older age of the populations in which the experiments were performed. Because high total serum cholesterol levels at this age are no risk factor for dementia, it may not be surprising that treatment with statins did not change the risk of dementia and cognitive decline. Another explanation might be found in a possible unwanted side-effect of statin treatment. Statins, when lipophilic, are able to cross the blood brain barrier and exert their effect in cerebro. Statins have been shown to affect cerebral cholesterol metabolism by decreasing cholesterol production [107]. It cannot be excluded that lowering cholesterol levels in cerebro causes a decrease in brain plasticity. With the protective effect of statin treatment on cardiovascular disease, also in late-life [79,81],

and the postulated adverse effect of statin treatment on cholesterol metabolism in cerebro, use of statins may result in the absence of a net effect on cognitive function.

In conclusion, studies that investigate the effect of midlife statin treatment on cognitive function in old age are needed to substantiate the likely beneficial effect. With current knowledge there is no clear indication for statin treatment in old age to prevent cognitive decline.

Supplementary tables 1-6

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