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# On cholesterol levels and statins in cognitive decline and Alzheimer's disease; progress and setbacks

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### Keywords

cholesterol levels; statins; Alzheimer's; cognitive decline

## Introduction

In this issue of ADAD, Carlsson et al. report findings that there support interactions between cholesterol levels and statin use, and cognitive degeneration[1]. They and many others have investigated the link between cholesterol and AD risk as well as statin consumption and AD. These interactions have been investigated from different perspectives including epidemiological studies, animal studies, and clinical trials. The sum total of these observations is that the interactions are neither spurious nor incidental but are related mechanistically making cholesterol reduction a theoretical target for AD treatment or prevention.

## On cholesterol levels and AD

Within recent years, investigators have been increasingly interested in the interactions between the effects of Alzheimer's disease and cholesterol levels. Consequently, many studies have sparked debate on whether statin use could be considered as a possible alternative prevention or even a treatment for AD. Although many are speculating the alternative positive uses of statins in patients who are at risk for AD, there is still uncertainty about whether high cholesterol levels actually increase the risk of AD in patients. Additionally, there are still questionable opinions on whether "cognitive decline" outcomes ultimately correlate with the progression of AD.

The association between high fat/cholesterol diet and increased risk of AD have been investigated extensively [2–7]. Elevated cholesterol levels appears to significantly increase the risk of AD [8–14]. Dufouil et al. have published the results of the Three-city study in France based on 9294 individuals where the authors identified a significant increase in the risk of dementia with hyperlipidemia (OR 1.43)[7].

Not only is hypercholesterolemia a risk factor for AD but AD patients appear to have elevated serum cholesterol levels[2, 15–20]. Carlsson et al find, after adjusting for several variables, that the quartile group that exhibits high levels of non-HDL also happens to be more than two times as likely to be afflicted by cognitive impairment. Regardless, the data at hand provides less clarity in the way of cognitive impairment being synonymous with AD[1].

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Despite the strength of these collective observations, there still lacks total consensus regarding the link between elevated cholesterol and AD. The Framingham study has suggested that any risk of AD is not a result of higher levels of cholesterol[21]. Others report notes that while language performance decreased dramatically in individuals with higher cholesterol levels, the difference was not significant[22].

## On statin therapy and risk of AD

As more clinical data is released, many are suggesting that statin treatment is a possible alternative that could attempt to reduce the risk of AD in patients. There are plausible biological reasons why it is appropriate to test lipid-lowering drugs including statins as treatments for Alzheimer's disease. Statins have been shown to have some influence on the pathogenesis of Alzheimer's disease. They have also been shown to have anti-inflammatory, anti-oxidant, and neuro-protective properties[16]. Studies have also suggested that high levels of cholesterol perhaps contributing to pathology that closely resembles AD. Since statin use may reverse the effects of cholesterol, it may be possible to use statin treatments to prevent or treat AD. Recent neuropathologic studies have investigated whether that antecedent statin therapy was associated with reduced AD pathology. Li et al found that the number of neurofibrillary tangles as a charcteristic lesion of AD[24] was reduced in users of statins. However, investigators from the Religious Orders study found that subjects with prior statin use were less likely to have amyloid plaques without an effect on tangles[25].

Out of 20 studies since the investigation into statin use and reduction of AD risk first began, only two studies reported that there was no benefit from cholesterol-lowering therapy. Early epidemiologic studies showed benefit associated with the use of lovastatin and pravastatin, but not simvastatin or non-statin therapy[26], but others showed benefit associated with cholesterol-lowering therapy, not specifically with statin use[27]. Since that time multiple studies have shown that chronic statin use was associated with reduced risk of AD or dementia in large cohorts or gender specific populations[28–32]. More recently, a population based cohort study of Mexican Americans followed for 5 years showed that those who took statins were significantly less likely to develop incident combined dementia and CIND (cognitive impairment non-demented) [33]. Carlsson et al in the present issue, report that statins significantly reduce risk of cognitive decline in a large elderly cohort[1]. Unlike other studies, they find that the protective effects of statins are most robust in BBB permeable statins.

Statins have been reported to have positive benefits on cognition as well. More recently, a prospective study of atorvastatin versus placebo in younger subjects included baseline and follow-up assessments of cognitive function, and identified significantly superior performance on the MMSE, attention, psychomotor speed, mental flexibility, working memory and memory retrieval in the statin treated population compared to placebo[34].

Risk reductions reported with statin use have ranged from 39–60%[7, 32]. Meta-analysis of the first seven retrospective studies suggested a significant reduction in the risk of later cognitive impairment with statin use (0.43), but not with any other lipid-loweringagent[35]. Results of a nested case-control study of newly diagnosed AD (N= 309) and non-AD controls (N=3088) assessing odds ratios between AD and statin use identified a 39% reduced risk of AD in statin users compared to non-statin users (OR 0.61, 95% 0.42–0.87)[36]. Horsdal et al in the current edition, add to the evidence of protection by looking at prescription data of statin use in Denmark. They found that statin users with dementia were less likely to be hospitalized than non statin users[37]. Their data suggests that long term statin use might reduce morbidity in persons with dementia but there was no mention of a dose response.

In contrast, other studies have shown that statin use did not alter the risk of developing AD. Li et al. suggested that there was no association between statin use and a reduced incidence of

probable AD using a time-dependent proportional hazards model, but if analyzed as a case-controlled study a significant reduction in the odds ratio (OR) risk was identified[38]. These authors proposed that previous studies showing a positive effect of statins employed inappropriate statistical methods. In light if this, it is curious that their studies were not analyzed using hazard ratios. Rea et al also report statins are not protective but some of the data appears to be conflicting[39]. They indicated that prior statin use did not decrease the risk of dementia. However, when they included individuals obtaining treatment in the previous year there was a nearly significant reduction in the hazard ratio for all cause dementia and AD. When including individuals currently using a statin, it was found that there was a significant reduction in the hazard ratio for risk of AD[39].

Other prospective studies have indicated that statins demonstrate no protective effect on cognition in studies assessing statins effects on cardiovascular risk[23, 40]. The Prospective Study of Pravastatin in the Elderly (PROSPER) included administration of the MMSE at the final study visit. The investigators found that the mean performance score did not differ between the placebo and statin groups. This led the investigators to conclude, without any evidence of baseline performance for the two groups, that statins produced no positive effect on cognitive performance[23]. The MRC Heart Protection study (using simvastatin) incorporated the telephone interview of cognitive status (TICS) at the end of the investigation, and concluded that there was no positive effect of statin use on cognitive performance despite the absence of baseline data. Because of the sheer number of subjects involved many researchers place great weight on these two studies, but neither was designed to assess cognitive function.

Collectively these observations provide the impetus to pursue randomized clinical trials of atorvastatin and other statins as treatments for Alzheimer's disease. However, despite early promising findings from pilot studies[41, 42] demonstrating positive cognitive benefit of statins as treatments for AD; large multi-center studies of atorvastatin and simvastatin failed to reach significance[43, 44].

Lingering disparities between clinical trial data and epidemiological evidence will need to be reconciled given the wealth of data suggesting protective effects of statins. One might speculate that the lack of robustness of a positive effect from clinical trial findings reflects inaccuracies of the observations from epidemiological and animal studies. Alternatively, it might reflect the imprecision of clinical trial methodology including incorrect selection of cases (e.g. on the basis of genotype or cholesterol levels or dementia severity) or use of cognitive measures that might not change significantly over time in mild AD. A third alternative is the consideration of the growing disconnect between treatment approaches and prevention approaches.

Since epidemiological data supports risk reduction for AD in statin users, then the appropriate therapeutic approach to be considered moving forward would be a primary prevention or MCI trials rather than another statin based treatment trial. There is neither the impetus nor justification to conduct further AD treatment trials with statins given the negative results of recent trials. . Now is the time to bridge the pools of data by pursuing a primary prevention trial using statins.

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