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Editorial

Lipid-lowering regimens in Alzheimer's disease dementia: small effects with potential long-term benefit☆

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Alois Alzheimer's initial characterization of the pathological features of the disease that bears his name encompassed three key molecular hallmarks: neurofibrillary tangles, amyloid plaques, and glial adipose saccules (intracellular lipid accumulation) [1]. The latter observation received little attention until approximately three decades ago, when Science posed the question "Bad for the Heart, Bad for the Mind?" and discussed the recently identified potential of statins to lower Aβ, alongside ApoE4, epidemiological observations and emerging clinical trial data [2]. Since then, elevated midlife cholesterol has been established as an important modifiable risk factor for Alzheimer's disease prevention. It is a relevant factor in identifying people at risk and for multimodal FINGER preventive intervention. However, the effectiveness of pharmacologically lowering LDL cholesterol remains uncertain: randomized controlled trials (RCTs) of statins have not provided clear evidence, often due to limitations in trial design, while observational cohort studies suggest no harm and a possible reduction in dementia risk [3]. Although the absence of harm and a potential reduction in risk may be considered sufficient in some settings, statins and lipid-lowering regimens (LLRs) rank among the most commonly prescribed long-term interventions globally and are associated with significant reductions in mortality. This raises the critical question of whether LLRs also provide clinically meaningful slowing of cognitive-functional decline.

Sternberg and colleagues offer important additional insight into this issue [4]. In a prospective study with 10 years of follow-up, they assessed the impact of LLRs on conversion from normal cognition to MCI and subsequent progression to dementia, using the CDR-SB as a quantitative measure of effect size. Despite the large sample size (nearly 50,000 participants) and robust statistical significance, the absolute effects were very small: for conversion to MCI, the difference amounted to approximately a 1/100th CDR-SB point per year compared with non-LLR use, a clinically negligible magnitude. Among individuals older than 50 years with greater impairment (CDR-SB >3), the effect increased to −0.17 points annually. Although still small, such incremental benefits may accumulate over time. This perspective aligns with recent work by Dickson and Hendrix, who translated treatment effects in CDR-SB into time gained in RCTs. For example, CDR-SB differences of −0.36 points over 76 weeks for donanemab and −0.6 points over 24 months for Fortasyn Connect corresponded to delays in disease progression of 5.2 and 10.5 months, respectively [5,6]. By extension, sustained annual reductions of −0.17 points may potentially translate into clinically relevant delays in progression over the disease course.

Several important limitations merit consideration. No significant differences were detected in hippocampal atrophy, CSF tau concentrations, or Braak staging, which may indicate the absence of a clear disease-modifying effect, distinguishing these findings from those reported in the above-mentioned randomized trials. From an AD perspective, observational studies of statins are frequently considered vulnerable to bias, potentially leading to an overestimation of treatment effects on disease progression. In this study, inclusion criteria were deliberately broad to approximate real-world conditions, with prior exposure to a lipid-lowering drug as the principal inclusion criterion. However, exclusion of individuals receiving antidiabetic or antihypertensive therapies, together with the absence of biomarker confirmation of Alzheimer's pathology in both cognitively normal and MCI participants, limits this real-world generalizability. In addition, LLRs comprised a heterogeneous group of therapies, predominantly statins but also other agents; pooling these treatments may obscure differences in efficacy across drug classes.

LLRs offer several advantages for use in Alzheimer's disease prevention. These therapies are affordable, widely indicated in older populations, and supported by extensive cardiovascular evidence. In addition, they are associated with a low incidence of adverse effects,

☆ OpenAI 5.3 in auto setting was used to correct spelling and grammar.

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supporting their suitability for long-term use. Many LLRs are well tolerated in combination with other medications. Given the modest magnitude of observed effects, future clinical trials will need to evaluate LLRs in combination with other available interventions if they are to play a role in Alzheimer's disease prevention. A more detailed understanding of which LLR agents are associated with greater slowing of cognitive-functional decline will be essential.

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Tobias Hartmann: Conceptualization, Writing – original draft, Writing – review & editing.

Declaration of competing interest

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