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High Cholesterol Tied to Lower Cognitive Decline Risk in Oldest Old

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Elevated cholesterol levels in individuals older than 85 years has been linked to a reduced risk for marked cognitive decline, compared with persons 10 years younger whose cholesterol levels were similarly elevated, new research shows.

Investigators found that cognitively intact people between the ages of 85 and 94 whose total cholesterol had increased from midlife had a 32% reduced risk for marked cognitive decline during the next decade, compared with individuals aged 75 to 84, who had a 50% increased risk.

"These findings do not imply that the cholesterol itself had a protective effect or that increasing cholesterol consumption will confer a benefit on people of this age," lead author Jeremy Silverman, PhD, professor of psychiatry, Icahn School of Medicine at Mount Sinai, New York City, told *Medscape Medical News*.

Instead, "cholesterol may be a marker for some other protective factor present in these people who are making it to age 85 and maintaining their good cognition at that age," he said.

The study was published online March 5 in *Alzheimer's and Dementia.*

Successful Cognitive Aging

Elevated cholesterol levels in midlife have been associated with cognitive decline, dementia, and Alzheimer's disease (AD), but in most studies, the mean outcome age at the time of cognitive assessment in follow-up is the mid-70s, the authors note.

Longitudinal studies of adults with older outcome ages have yielded "inconsistent" findings, they write.

Additionally, studies of associations between cholesterol and negative cognitive outcomes have focused primarily on differences with respect to midlife vs late-life cholesterol measurement, rather than outcome age.

To investigate the relationship between cholesterol levels and cognitive function in people of very advanced age, the researchers used data from the Framingham Heart Study, which "provides extensive cholesterol measure and cognition information, enabling survival analyses that include changes in association by outcome age," the authors note.

Although an earlier study of the original Framingham cohort found no significant association between cholesterol and AD, the aim of the current study "was to determine whether specific cholesterol measures had different associations with marked cognitive decline at different outcome ages."

The current study also differed from the earlier study in participant eligibility, cognitive outcome, cholesterol predictors, and the survival analysis model, which defines "survival" as "successful cognitive aging — having intact cognition, while living to oldest-old age, 85 years, and above."

To investigate the question, the researchers used datasets of biannual longitudinal examinations from 1948-1953 and 2012-2014, drawn from the original Framingham cohort.

"Intact cognition" was defined as a Mini–Mental State Examination (MMSE) score of ≥25.

The "threshold age" was defined as the age at last intact cognition, and "marked cognitive decline" was defined as "deterioration from intact cognition at the threshold age to the first dementia diagnosis, or having MMSE ≤20."

Inclusion requirements were having intact cognition at some examination, reported years of education, and at least three cholesterol measurements through the threshold age.

The researchers used two subsets of cholesterol predictors.

The first subset consisted of first cholesterol observation (obtained at midlife) and the late-life last observation through the threshold age (called "last cholesterol").

Each subset was dichotomized between "normal" (<200 mg/dL) and at least "borderline high cholesterol" (≥200 mg/dL, which investigators referred to as "high").

The second subset consisted of three predictors using all cholesterol measurements through the threshold age — mean, linear slope (ie, the angle of the fitted line for cholesterol measurements), and the quadratic components of the cholesterol

trajectory.

Covariates included outcome age, sex, and education, with survival analyses using outcome age as the "time" variable, rather than a separate covariate.

Additional covariates were first cholesterol measurement age (called "entry age") on or near the age of Framingham study entry, and whether the individuals had ever used statin drugs.

The five cholesterol predictors (ie, high first cholesterol, high last cholesterol, mean cholesterol, rising linear slope, and quadratic slope) were also used as time-dependent coefficients.

Framingham Cohort

Of the 5079 participants for whom any data from the original Framingham cohort were available, only 1897 met all the inclusion criteria. These patients composed the full sample for the primary survival analysis (mean age ± SD = 40.2 ± 6.8 years; 747 men, 1150 women).

Of these, 316 eventually experienced marked cognitive decline (114 with diagnosed dementia, 202 with MMSE ≤20).

In the sample, there were 1041 participants aged 75 to 84 years (denoted as "{75,85}"), and 391 participants aged 85 to 94 years (denoted as "{85,94}").

The researchers found that in all analyses, "every significant time-dependent coefficient reduced the association of a significant predictor for a marked cognitive decline as the outcome age increased."

For the {75,84} age interval, the 36.7% of the sample with a rising slope had significantly increased risk for marked cognitive decline (χ^2 = 4.196, df = 1, *P* = 0.041; hazard ratio = 1.497, 95% confidence interval [CI], 1.016 - 2.206), compared with individuals who had a falling slope.

In contrast, for the {85,94} age interval, the 23.3% of the sample with a rising slope had a significantly lower risk (χ^2 = 4.228 df = 1, *P* = 0.040; HR = 0.676, 95% CI, 0.457 - 0.999) of cognitive decline, compared with those who had a falling slope.

A significant association was found in the full sample between a rising linear slope in cholesterol measures from midlife, while cognitively intact, and a subsequent marked cognitive decline.

However, the time-dependent coefficient was significant and demonstrated diminishing strength of this association of risk for cognitive decline with rising linear slope as the outcome age increased.

Protected Survival Model

In contrast to previous studies with earlier outcome ages, high first cholesterol was significantly associated with reduced risk in the {85,94} sample, with average outcome age of 90.9 years.

Moreover, fewer years of education, not using statins, and earlier entry age (all of which are significantly associated with marked cognitive decline) were significantly weakened as outcome age increased. The crossover ages — all in the 90s — indicate when this weakening would reverse the direction of the association.

The crossover age for cholesterol linear slope in the full sample was 98 years. However, the {85,94} age interval sample showed an earlier reversed relationship.

These findings illustrate a concept called the "protected survival model" that "posits a minority subpopulation with protection against mortality and cognitive decline associated with cognitive risk factors," the authors state.

"The take-home message for me as an investigator is that the study suggests that there is a phenotype out there that we can use and take advantage of, people who you think should be demented or dead because of risk factors and yet are still doing well," said Silverman.

"Those are the people most likely to be carrying some type of protective factor, so if we can identify that group, we might be in a better position to identify genetic factors protective against cognitive decline as well as mortality," he added.

"Ironic" Findings

Commenting on the findings for *Medscape Medical News*, Bernard G. Schreurs, PhD, professor, Department of Physiology, Pharmacology, and Neuroscience, West Virginia University, Morgantown, who was not involved in the study, called the findings "consistent with what is known in the field — that total cholesterol declines in old age and low cholesterol in old age is associated with poor health, multimorbidity, and deteriorating cognition."

He noted that this is "supported by evidence that there is a lower level of synthesis and absorption of cholesterol as a person ages."

He called the finding "ironic" because, "during middle age, the opposite is true — elevated cholesterol levels are associated with poor cognition that becomes more evident in old age."

Silverman added that he is interested in further exploring "both genetic and environmental factors that may be protective in this population."

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