

Low cholesterol and increased dementia risk

Mielke et al. examined the association between cholesterol level and dementia in a population-based 70-year-old birth cohort followed for 18 years. Low, not high, cholesterol in late life was associated with an increased risk of dementia.

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Timing is of the essence

Commentary by Mary Ganguli, MD, MPH

The relationship between lipid metabolism and dementia remains intriguing and unresolved. Mielke et al. have added another twist to the plot. Their findings are at odds with data suggesting that statins lower the probability of dementia (thus far unsupported by clinical trials) and that lowering cholesterol may reduce beta amyloid in the brain.¹ Superficially, their results also appear incongruous with previous reports of high cholesterol in midlife increasing risk of subsequent dementia.² However, the current finding relates to low cholesterol levels in late life, not midlife.

A similar paradox has been observed with both high blood pressure in midlife and decreasing blood pressure in late life being associated with late-life dementia.^{2,3} Likewise, for agents such as nonsteroidal anti-inflammatory

agents or antioxidants to exert their putative protective effects against dementia, it might be necessary for them to be taken during or before midlife; to prescribe them to older adults might be to shut the stable door after the horse has bolted. The timing of the exposure may be critical.

It is noteworthy that only total cholesterol was measured, that the lowest mean cholesterol level reported is 226 mg/dL, that individual declines in cholesterol level over the study period were not associated with dementia onset, and that the association did not hold up in smokers (potentially suggesting a survivor effect).

It seems unlikely that the mechanism here involves the amyloid cascade. Perhaps cholesterol supports other elements of neural integrity. Or perhaps cholesterol is lowered by some aspect of the in-

ipient dementing process, such as decreasing nutrition, years before onset of symptoms: cholesterol lowering might be an effect rather than a cause of dementia.² The fact that relatively lower cholesterol at age 70 precedes the onset of dementia does not mean that lipid-lowering therapies should be withheld from middle-aged individuals. The plot thickens.

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Neurology 2005;64;1671
DOI 10.1212/WNL.64.10.1671

This information is current as of May 23, 2005

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