

## EDITORIAL

# Low cholesterol and violent death

## The evidence, the gaps, the theory and the practical implications

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### The Problem

The early trials of cholesterol-lowering drugs showed a promising reduction of cardiovascular mortality associated with treatment. Disappointingly, though, overall mortality was frequently not changed, due to an increase in non-cardiovascular deaths. In particular, violent death (suicide, murder and accidents) was increased in those who had received intervention. Some investigators expressed the hope that this was simply an unfortunate coincidence, but by the time Matthew Muldoon (1) reviewed the literature in 1990, the association had occurred in too many trials to be just chance. Furthermore, the effect didn't seem to depend on what drug was used to lower cholesterol; drugs with widely-differing modes of action all seemed to share a common effect. At the time of the publication of the Lipid Research Clinics Trial (2), the Finnish researcher, Matti Virkkunen (3) proposed that the excess of violent deaths in those treated with cholestyramine might be connected to findings he had made linking low cholesterol and low impulse control, though a mechanism by which this happened was far from obvious.

### The Evidence

Concern about a link between low cholesterol and violent death lead investigators to examine data from prospective studies. Juha Pekkanen and his colleagues analysed 25-year follow-up data on the Finnish cohort of the Seven Countries Study, and found no relationship between low serum cholesterol and violent death (4). They suggested, amongst other possible explanations, that the associations found by others between low serum cholesterol and poor impulse control could be due to low serotonin turnover. Low serotonin activity (usually measured as cerebrospinal 5-HIAA) had been linked to suicidal behaviour since 1976, when Asberg and colleagues reported on suicidal behaviour in a group of depressed patients (5). By the time an anonymous editorial in the Lancet reviewed the topic in 1987, low serotonin turnover had been observed in a wide variety

of disorders characterised by low impulse control (6). Pekkanen and his colleagues suggested that low serotonin turnover in the brain could result in enhanced insulin secretion which, in turn, could lower cholesterol levels, though this has yet to be substantiated by research.

One study which found a link between low serum cholesterol on a single measurement and subsequent risk of violent death was a report in Lindberg *et al* (7) who analysed data from over 50,000 men and women who were being followed up by the Värmland study in Sweden. They found that men with a low serum cholesterol <5.3 mmol/L (205 mg%) had an increased risk of violent death in the first six years of the 20-year follow-up period. There was no relationship between low cholesterol and risk subsequently, and the relationship did not emerge in women. Other attempts to link low cholesterol to subsequent violent death in follow-up studies came to negative conclusions, including an analysis of all sixteen cohorts of the Seven Countries Study (8). However, a major review, co-ordinated by the National Heart, Lung and Blood Institute, which pooled data from almost 125,000 people in 19 cohort studies from the United States, Europe, Israel and Japan found that the risk ratio for violent death occurring more than 5 years from baseline cholesterol measurement was 3.0 in men and 1.26 in women whose cholesterol was <4.2 mmol/L (<160 mg%) (9). The reason for their exclusion of deaths occurring in the first five years of follow-up was to exclude those whose cholesterol had been lowered by disease. In a recently-published report on 28-year follow-up of almost 3,000 Dutch civil servants who had their cholesterol measured in 1953 and 1954, Albertine Schuit and her co-authors reported that, adjusted for age and sex, those in the lowest tertile of cholesterol had a 2.4-fold increased risk of violent death over the 28-year period (10). The effects of adjusting for smoking and alcohol consumption were negligible.

Some surveys of coronary risk factors also measured personality characteristics, and researchers examined these to see if hostility, aggressiveness or other relevant traits were associated with cholesterol. The Whitehall study found no relationship between cholesterol and hostility (11), and an analysis of those with low

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