Authors' objectives
To determine whether cholesterol lowering reduces coronary heart disease (CHD) incidence or total mortality, whether cholesterol lowering in general is harmful, and whether some types of intervention to reduce cholesterol have negative side-effects.

Searching
MEDLINE was searched from 1966 to 1994 for English language publications. A review of bibliographies of other meta-analyses was carried out.

Study selection
Study designs of evaluations included in the review
Unifactorial and multifactorial randomised controlled trials (RCTs) were included.

Specific interventions included in the review
Four major types of intervention were included: diet, fibrates, hormones and an 'other' group which included resins, nicotinic acid, lovastatin, and surgery.

Participants included in the review
No inclusion criteria were given for the participants. Data were included from 35 trials of both primary and secondary prevention of CHD, representing data from 77,079 individuals.

Outcomes assessed in the review
CHD mortality, non-CHD mortality and total (all-cause) mortality were assessed.

How were decisions on the relevance of primary studies made?
The authors do not state how the papers were selected for the review, or how many of the authors performed the selection.

Assessment of study quality
Only RCTs of at least 2 years' duration, which related cholesterol reduction to changes in coronary mortality or morbidity, were included. The authors do not state how the papers were assessed for validity, or how many of the authors performed the validity assessment.

Data extraction
The trials were grouped for analysis by the four types of intervention, i.e. dietary, fibrate, hormonal and 'other'. The association between reduction in risk of CHD mortality and serum cholesterol reduction was also examined by combining data separately for all trials, for unifactorial secondary prevention trials and for all unifactorial trials.

Methods of synthesis
How were the studies combined?
Likelihood-based trend analysis was used to model risks for each clinical outcome. This was performed for all the trials combined and for the three subsets of unifactorial trials, with the model including the slope and the specific interventions. Null hypotheses were tested using likelihood ratio chi-squared tests. Chi-squared tests were also used to test goodness of fit. Conventional pooled odds ratio (OR) analyses were calculated for comparison purposes.
How were differences between studies investigated?
The difference between the results of studies of different size was emphasised by weighting up the larger studies in the graphical display of the log ORs. Differences in trial design were investigated by examining data from unifactorial and multifactorial trials, and primary and secondary prevention trials, separately.

Secondary analyses were also carried out to examine the effect of cholesterol reduction on total mortality when hormone findings were excluded. More generally, the heterogeneity in cholesterol lowering, which was introduced by including a range of interventions, was controlled by including the degree of reduction in the statistical analyses.

**Results of the review**
Thirty-five studies in total were included: 31 unifactorial trials, 5 unifactorial primary prevention trials and 26 unifactorial secondary prevention trials. These represented 11 dietary trials, 9 fibrate trials, 4 hormonal trials and 11 ‘other’ trials.

CHD mortality: a reduced risk of CHD was significantly associated with reduction in serum cholesterol in all trials combined (p<0.002), all unifactorial trials (p<0.003) and unifactorial secondary prevention trials (p<0.009), with an estimated 13 to 14% reduction in CHD mortality for every 10% reduction in serum cholesterol. For any given reduction in serum cholesterol, CHD mortality risk was 27% higher with hormonal interventions.

Non-CHD mortality: risk was not related to cholesterol reduction in any of the analyses. Fibrate usage resulted in a 30% increase in risk (p=0.01) for all trials, and also with an increase in risk for unifactorial trials (29% increase, p=0.013) and unifactorial primary prevention trials (39% increase, p=0.005). Hormone use was also associated with an increase in risk (55% increase, p<0.05). The conventional pooled OR estimates indicated a trend towards excess risk in all subsets. This trend was statistically significant for unifactorial trials (19% increase, p<0.05) and for unifactorial primary prevention trials (21% increase, p<0.05).

Total mortality: cholesterol reduction was associated with a reduced risk of mortality in all trials, unifactorial trials and unifactorial secondary prevention trials (all p<0.05). For every 10% reduction in serum cholesterol, mortality risk was reduced by 8 to 10%. Fibrate use was associated with increased total mortality for all trials (17% increase, p=0.02), all unifactorial trials (17% increase, p=0.03) and unifactorial primary prevention trials (35% increase, p<0.02). Hormones were not used in the primary prevention trials included in this analysis, but in all other sets of trials it was associated with increased mortality (32 to 33% increase, p=0.01). The conventional pooled OR analyses did not detect a statistically-significant effect of intervention on total mortality.

**Authors’ conclusions**
Cholesterol lowering is beneficial, with the magnitude of the benefit directly related to the degree of cholesterol reduction. However, fibrates and hormones increase the risk of CHD (hormones only), non-CHD mortality and total mortality. There is no association between reduction in cholesterol and non-CHD mortality.

**CRD commentary**
The review provided a useful quantitative measure of the effects of cholesterol reduction, but there was little assessment of the quality of the included trials, other than the examination of unifactorial and multifactorial trials separately. It was also unclear whether the results were applicable to all patient populations, since there was little summary information on the patients included in the individual trials.

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