By how much and how quickly does reduction in serum cholesterol concentration lower risk of ischaemic heart disease?

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Authors' objectives
To estimate by how much, and how quickly, a given reduction in serum cholesterol concentration will reduce the risk of ischaemic heart disease (IHD).

Searching
The authors do not specify which sources were searched, or provide details of the search strategy.

Study selection
Study designs of evaluations included in the review
1. Cohort studies of serum cholesterol concentration and IHD that were limited to studies with more than 350 IHD events (death and non-fatal infarcts) in men. The studies were used to estimate the long-term effect of a decrease in concentration of low-density lipoprotein cholesterol on the risk of IHD.

2. International prospective community studies in which serum cholesterol concentrations and mortality from IHD were measured.

3. RCTs of reduction in cholesterol concentration (by drugs, diet, or ileal bypass surgery) and IHD events (deaths and non-fatal infarcts). Trials had to record at least 1 death and document a reduction in serum cholesterol concentration of at least 1%.

Specific interventions included in the review
Decreasing of serum cholesterol concentration through use of drugs, diet or ileal bypass.

Participants included in the review
Participants varied according the study design, and included both those with and without previous history of IHD. The populations in the randomised controlled trials (RCTs) were mostly male.

Outcomes assessed in the review
Decrease in incidence of IHD or mortality for a 0.6 mmol/l (about 10%) decrease in serum cholesterol concentration.

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

Assessment of study quality
For RCTs: diagnoses were made without knowledge of treatment allocation; data were analysed on the basis of intention to treat; and follow-up at the end of the trials was 99%. 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 authors do not state how the data were extracted for the review, or how many of the authors performed the data extraction.

Methods of synthesis
How were the studies combined?
1. Cohort studies were combined using a log linear model to investigate the relationship between risk of IHD and serum cholesterol concentration. Age-adjusted rate of IHD was weighted by the number of events.

2. International studies: for each study, incidence of mortality from IHD (in logarithms) was regressed in the constituent communities on the cholesterol concentration associated with the mean risk in each community. The analysis weighted the age-adjusted rate of IHD by the number of events. Smoking, blood-pressure and cholesterol were included as independent variables.

3. RCTs were divided into 3 time periods: less than 2, 2.1 to 5 and 5.1 to 12 years after entry. Unpublished data on mortality were supplied by authors of 8 RCTs, and numbers of events were estimated from survival curves for 2 trials. The average reduction in IHD over each time period was estimated by logistic regression that combined the odds ratios from each trial to obtain a summary relative odds estimate. Each trial was weighted by the mean difference in the total cholesterol concentration between treatment and control groups.

Results were expressed as the decrease in the risk of IHD associated with a decrease in serum cholesterol concentration of 0.6 mmol/l.

How were differences between studies investigated?
Differences in RCTs were investigated for those trials indicating similar diagnostic criteria for death from IHD and nonfatal myocardial infarction. There was no significant heterogeneity between estimates relating to trial duration.

Results of the review

Ten cohort studies, each recording more than 350 IHD events (deaths and, in 3 studies, nonfatal infarcts): 494,804 men and 18,811 events recorded; 54,832 women and 4,097 events recorded.

Three international studies: number of participants not given.

Twenty-eight published RCTs that recruited 46,254 men and recorded 4,241 events.

1. For cohort studies, a decrease in cholesterol concentration of 0.6 mmol/l was associated with a decrease in the risk of IHD by 54% at age 40, 39% at age 50, 27% at age 60, 20% at age 70 and 19% at age 80.

2. With international studies, a difference in cholesterol concentration of 0.6 mmol/l was associated with a difference in mortality from IHD of, on average, 38% (95% confidence interval, CI: 33, 42) in men. The mean age at death ranged from 55 to 64 years in all studies. Differences in serum cholesterol concentration explained over 80% of the international variation in mortality from IHD.

3. RCTs involving men demonstrated a dose-response association, i.e. trials achieving a greater reduction in serum cholesterol concentration generally showed a greater reduction in IHD (P<0.001).

The reductions in IHD increased with increasing duration of reduced cholesterol levels, and were 7% (95% CI: 0.0, 14, P=0.06) in the first 2 years, 22% (95% CI: 15, 28, P<0.001) from 2.1 to 5 years, and 25% (95% CI: 15, 35, P<0.001) from 5.1 to 12 years; all per 0.6 mmol/l reduction in cholesterol concentration.

The international estimates for women were similar to those for men. Three RCTs with separate data for women showed a significant reduction in IHD, similar in size to that observed in men in the same trials, whereas a fourth trial suggested no effects in women. Different patterns of serum cholesterol concentration in women make it difficult to draw firm conclusions from the studies.

Authors' conclusions
The results of the three categories of data show striking consistency. The trials show little reduction in risk of IHD in the first 2 years after lowering cholesterol, but the summary estimate for the reduction in incidence of IHD at least 5 years after reduction of cholesterol concentration (25%) is close to that from the cohort studies (27%), showing that the full reduction in risk of IHD is achieved within 5 years. A man of 35 who reduces his serum cholesterol concentration...
by 0.6 mmol/l would, therefore, halve his risk of IHD by the age of 40. The limited data available for women show similar trends.

The observational data show that in Western societies there is no threshold below which lower serum cholesterol concentration is not associated with a lower risk of IHD.

On a community-basis, a reduction in serum concentrations of total and low-density lipoprotein cholesterol of 0.6 mmol/l, through dietary change, would reduce mortality from ischaemic heart disease by 25 to 30% in people aged 55 to 64.

**CRD commentary**

This is a complex, but relatively brief review. The literature search is not specified. The review gives an indication of the potential benefit of reduced serum cholesterol levels in decreasing IHD, but does not address effects on all-cause morbidity and mortality.

**Implications of the review for practice and research**

Public health implications include a need to identify mechanisms for assisting the general population to decrease serum cholesterol levels.

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