Title

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Time to lower cholesterol: the potential effect of cholesterol reduction on the incidence of cardiovascular disease

(see also page 635)

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ABSTRACT Cardiovascular disease imposes a major burden on our community through its high morbidity, mortality and health-care costs. Elevated cholesterol levels have been recognized increasingly as an important and modifiable risk factor for this disease. We assessed the impact of a reduction in cholesterol levels in our community and compared its importance with the reduction of another major risk factor for this disease, namely, smoking. Results from this analysis indicate that a greater proportion of cardiovascular disease can be attributed to elevated cholesterol levels compared with smoking in our population. This difference is due largely to the prevalence of elevated cholesterol levels in the community. Evidence from international studies indicates that a 5% reduction in the cholesterol level of Australians is a realistic health target for the population and that this reduction would lead to a major reduction in the burden of cardiovascular disease and to substantial economic savings. This paper provides further evidence to support the National Heart Foundation of Australia's recommendations for a reduction of cholesterol levels in the Australian population.
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Approximately 120 000 deaths occur in Australia every year and almost half these deaths are of diseases of the circulatory system. Myocardial infarction alone accounted for over 22 000 deaths in 1985.[1]

High blood cholesterol levels have long been shown to be associated with a high incidence of heart disease in the population, and recent evidence shows that persons with moderately-increased levels of cholesterol are at an increased risk of heart disease.[2,3] The Multiple Risk Factor Intervention Trial found:[4]

> The pattern of a continuous, graded, strong relationship between serum cholesterol and six-year age-adjusted CHD [coronary heart disease] death rate prevailed for nonhypertensive nonsmokers, nonhypertensive smokers, hypertensive nonsmokers, and hypertensive smokers [. . .] the relationship [. . .] is *not* a threshold one [. . .] but rather is a continuously graded one.

On the basis of evidence such as this, the National Heart Foundation of Australia issued a policy statement to recommend that the threshold level for cholesterol lowering action be reduced from 6.5 mmol/L to 5.5 mmol/L.[5] This new "cut-off" level has particular significance for Australia. It means that, according to the last National Heart Foundation survey, half our population is "at risk" of heart disease as a result of their blood cholesterol levels alone,[6] and so are eligible for cholesterol-lowering interventions.

In 1987, both the National Heart Foundation and the NSW Department of Health made the reduction of cholesterol levels a major priority. What effect on the incidence of myocardial infarction can be expected from a cholesterol-lowering campaign? How successful are different types of intervention likely to be in lowering community cholesterol levels? What is the maximal amount of money that should be put into the achievement of that success to maintain a positive benefit-to-cost ratio? How does the population-attributable fraction of cholesterol compare with that of smoking when risk factors for heart disease are considered?

With available data from international and Australian studies this paper considers these questions. It also makes a conservative estimate (direct costs only) of the savings that will accrue if the National Heart Foundation and the NSW Department of Health are successful in reducing the mean cholesterol level in the community.

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Methods

The population-attributable fraction is the proportion of all new cases in a given period that are attributable to the risk factor of interest. The population-attributable fraction can be calculated provided that the prevalence of the risk factor in the community is known, as well as its relative risk for the outcome of interest (in this case, coronary heart disease).[7]

If there were only one category of exposure then the equation would be:

$$\text{Population-attributable fraction} = \frac{p(RR-1)}{p(RR-1)+1}$$

where p is the proportion of the population with the risk factor and RR is the relative risk for the disease compared with that of persons who do not have the risk factor.[7]

This calculation can be extended to deal with multiple-category exposures such as different categories of cholesterol or smoking levels. The equation is:

$$\text{Population-attributable fraction} = 1 - \frac{1}{\sum_{i=0}^{k} p(RR_i)}$$

where p is the proportion of the population in the ith risk-factor category ($i = 0, \ldots, k$) and RR_i is the relative risk for the disease in the ith risk-factor category compared with that of persons who do not have the risk factor.[7]

TABLE 1: Proportion of Australian men aged 40–64 years at various cholesterol levels at baseline, and after a cholesterol-reduction campaign

Cholesterol levels (mmol/L)	Proportion of population with baseline cholesterol level[6]	Proportion if cholesterol level decreased by: 5%	10%	20%
Less than 4.68	0.14	0.21	0.31	0.57
4.71–5.22	0.18	0.21	0.24	0.20
5.25–5.69	0.20	0.19	0.17	0.11
5.72–6.31	0.20	0.19	0.15	0.08
Greater than 6.34	0.29	0.20	0.13	0.04

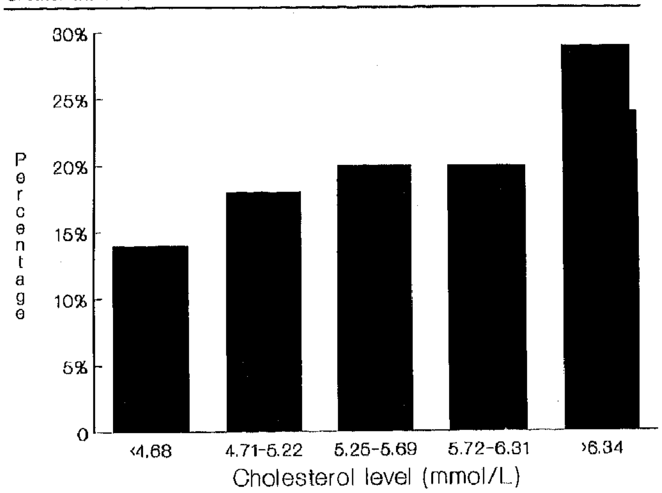

FIGURE: Percentage of Australian men of 40-64 years of age at various cholesterol levels.[6]

Blood cholesterol levels for the Australian male population of between the ages of 40 and 64 years were obtained from the 1983 National Heart Foundation Risk Factor Prevalence Survey[6] and were analysed to attain the population of men in each cholesterol category. The cholesterol categories that were used were the same as those that were used in the Multiple Risk Factor Intervention Trial.[4] The relative risks of suffering a cardiovascular event at each cholesterol category were obtained from the Multiple Risk Factor

Intervention Trial data (study sample, 356 222 subjects). The prevalence of smoking and levels of smoking for men of the same age were obtained from the 1983 "Quit. For Life" evaluation.[8] The relative risks for each level of tobacco consumption were obtained from the Pooling Project data in *The health consequences of smoking*.[9] The proportions of the population and the relative risk of each category of cholesterol and smoking are shown in Table 1, the Figure and the list below.

Smoking habit	*Proportion of male community (aged 40–60 years) smoking*	*Relative risk*[9]
None	0.7359	1.000
Less than one pack/day	0.0667	1.793
One pack/day	0.0880	2.069
Greater than one pack/day	0.1094	3.155

The proportion of Australian men in each cholesterol category was recalculated on the assumption that the intervention reduced all serum cholesterol levels as measured in the National Heart Foundation study by 5%, 10% and 20%, respectively. The population-attributable fraction was estimated for each reduction by means of the multiple-category exposure equation, in order to estimate the percentage reduction in coronary heart disease in Australian men. The estimated reduction is compared with similar estimates from the Lipid Research Clinics study.[10]

To calculate the likely effectiveness of cholesterol-lowering campaigns, it is necessary to know what sort of reduction in cholesterol levels could be achieved in this population. Data from international studies are presented as the basis for these estimates.

The estimation of possible savings is based on direct costs. Direct costs are those that reflect the cost of treatment and are the sum of prehospital treatment, initial hospital care, the treatment of recurrent myocardial infarctions, medical care outside hospital and pharmaceutical costs.[12] Costs are estimated from the results of an incidence-based method for the direct costs of acute myocardial infarctions and sudden deaths for New South Wales.[12] As this costing was undertaken with 1979 data, the average adjusted bed-day cost for 1987 was obtained and then the ratio of 1987 to 1979 costings was applied to the predicted savings. The percentage predicted fall in coronary heart disease events was then applied to the estimated costs for 1987. If indirect costs, or the costs of lost productivity were included, the calculated amount would be increased by a factor of five times.

Results

The Figure shows the prevalence of different levels of cholesterol. Persons with cholesterol levels of less than 4.68 mmol/L have a relative risk of coronary heart disease of one.[4] From this particular study, it would appear that a further lowering of serum cholesterol levels below 4.68 mmol/L did not lead to a further important reduction in coronary heart disease.[4]

The estimate of the impact of smoking and high blood cholesterol levels on heart disease is shown below.

Relative risk	*Population-attributable fraction*	
	Cholesterol level	*Smoking*
As measured	54%	28%
Relative risk reduced by 10%	48%	20%
Relative risk increased by 10%	58%	34%

Although the relative risks for smoking are of the same order as are those for cholesterol levels, the much lower prevalence of smoking in the community means that the population-attributable fraction is much lower than that of cholesterol levels (28% compared with 54%).

The amount of confidence that can be placed in these estimates can be judged by how much they vary if the relative risk were overestimated or underestimated by as much as 10% in a sensitivity analysis. Even with a 10% overestimate in the relative risk of a high serum cholesterol level for coronary heart disease, in 48% of persons who suffer a cardiovascular event, the condition is attributable to a high serum cholesterol level. The population-attributable fraction is almost double that of smoking.

If serum cholesterol levels are reduced by 5%, a 6% reduction in the incidence of heart disease could be expected.

Serum cholesterol level	*Population-attributable fraction*
Not reduced	0.54
Reduced by 5%	0.48
Reduced by 10%	0.41
Reduced by 20%	0.25

This expected reduction is rather less than that which was reported by the Lipid Research Clinics study,[10] which estimated that for every 1% reduction in cholesterol level that is achieved, there will be a 2% reduction in the later onset of heart disease.

How realistic is a target of a 5% reduction in cholesterol levels? A summary of the international evidence on studies which have resulted in the successful reduction of serum cholesterol levels is presented in Table 2. There are two major types of studies: those that are community-based and those which recruit volunteers who are at high risk. The majority of studies — with the exception of the Oslo study, which showed exceptionally good results without the use of medication[15] — indicate that a 3% reduction could be expected in the mean cholesterol levels of the community through the use of mass media, screening and counselling interventions. If doctors treat high-risk cases aggressively (as in the Lipid Research Clinics study[10]), the reduction in community levels would be greater. A conservative estimate would be a 5% reduction in cholesterol levels.

TABLE 2: Cholesterol level reduction in international interventional studies

Study	Intervention type	Study period (years)	Mean cholesterol change
Community study			
Stanford Three Community Study[13]	Screening and mass media campaign	2	3%
	High risk including intensive intervention	2	3%
North Karelia[14]	Community organization	5	3.8%
High risk			
Oslo[15]	Screening and counselling	5	15%
Multiple Risk Factor Intervention Trial[16]			
Control	Screening and refer to general practitioner	1	3%
		6	5%
Intervention	Screening and intensive programme	1	6%
		6	7%
Lipid Research Clinics[10]			
Control	Screen only	7.4	5%
Intervention	Screen and drug treatment	7.4	13.4%
Cholesterol-lowering Atherosclerosis Study[17]	Screen and drug treatment	2	26%

The estimated savings that would have accrued in New South Wales in 1987 should there have been a reduction of 6% in the incidence of heart disease are shown below.

1987 Direct costs of coronary heart disease (extrapolated*)[12]	$92 942 286
Savings in 1987 if incidence of coronary heart disease were reduced by 6%	$5 390 653

*Extrapolation uses the ratio between adjusted bed-day costs in 1979 and 1987, which was 2.874.

A yearly saving of approximately $5.4 million at 1987 costs could have been expected.

Discussion

The contributions of cholesterol levels, smoking and hypertension to heart disease are well established. While hypertension is a major risk factor for heart disease, we have chosen to compare smoking and cholesterol levels in this analysis as modifiable life-style factors. While hypertension remains a major risk factor for heart disease on the basis of all known prospective studies, interventional studies have not established clearly that treating hypertension reduces the incidence of myocardial infarctions. This paper assumes that the relative risks of elevated cholesterol levels and smoking for the development of disease in Australia are similar to those in the United States.

When these relative risks are used with the best estimates of prevalence in the Australian male community, the relative contribution of a high blood cholesterol level to heart disease is calculated to be almost twice that of smoking. Therefore, one-half of men of between the ages of 40 and 64 years who suffer with heart disease will have elevated cholesterol levels under these assumptions. Even when the relative risks and prevalence levels are assumed to have been overestimated by 10% in a sensitivity analysis, the association between elevated cholesterol levels and the later development of heart disease is very high. These figures give strong support to the National Heart Foundation's campaign theme that "it is high time to lower cholesterol".

Given the importance of the reduction of community levels of cholesterol, international data can be used to indicate the sort of effect that is possible from a successful cholesterol-lowering campaign. These studies indicate that should doctors support such a campaign to treat persons with elevated cholesterol levels, then the reduction that is achieved could be in the order of 5%.

Our estimates are that a 6% reduction in the population-attributable fraction would follow a 5% reduction in cholesterol levels. The authors of the Lipid Research Clinics study concluded that a 5% reduction in cholesterol levels gave a 10% reduction in heart disease.[10] Thus, if doctors intervene aggressively to reduce cholesterol levels and to achieve a 5% reduction, a fall in the incidence of heart disease of 6%-10% could be expected. The potential benefit is greater than these estimates might suggest, as reports of the effect of the new cholesterol-lowering drug, lovastatin, suggest that a 20% lowering of cholesterol levels is a conservative estimate of effect.[18]

A 6% reduction in the incidence of heart disease at 1987 cost estimates would result in savings of $5.4 million in direct costs in New South Wales alone. If indirect costs were to be included, this figure would be about five-times higher. The importance of this result is that it can give health administrators a benchmark for expenditure on a campaign (assuming that it has a certain success level), in order for such a campaign to have a positive benefit-to-cost ratio. Even if a cholesterol-lowering campaign achieved only half the estimated possible reduction, a total of $2.7 million could be spent to accomplish this before the "break-even" point were reached.

A number of published studies support the results of the current study.[4,10,19] An exception is a recent publication that questioned the benefits of lowering cholesterol levels. Taylor et al.,[20] who used a multiple logistic model that was based on data from the Framingham study,[3] established the model's credibility by indicating that the results that were obtained are consistent with the Lipid Research Clinics' data.[10] However, their conclusion of a very modest effect is at odds with the large effect that was indicated by more recent studies such as the Lipid Research Clinics Study,[10] the Whitehall Study[19] and the Multiple Risk Factor Intervention Trial.[4]

In view of the high prevalence of elevated cholesterol levels and the high risk of coronary heart disease in Australia, we believe there is a need to support actively programmes that are aimed at lowering cholesterol levels.

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