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Serum cholesterol concentration and mortality from accidents, suicide, and other violent causes

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Abstract

Objective—To study the association of mortality from accidents, suicides, and other violent deaths with serum cholesterol concentration.

Design—Baseline measurements in two randomly chosen independent cohorts were carried out in 1972 and 1977. Mortality was monitored over 10-15 years through the national death registry.

Setting—Eastern Finland.

Subjects—The two cohorts comprised men (n=10898) and women (n=11534) born between 1913 and 1947. There were 193 deaths due to accidents, suicides, and violence among men and 43 among women.

Main outcome measure—Mortality from accidents, suicides, and other violent deaths was used as the end point. Deaths from these causes were pooled together in the analyses.

Results—Serum cholesterol concentration was not associated with mortality from accidents, suicides, and other violent deaths in the univariate analyses or in the proportional hazards regression analyses including smoking, systolic blood pressure, alcohol drinking, and education. In both genders smoking was more prevalent among those who died from accidents, suicides, and other violent causes than from other causes. Frequent use of alcohol increased mortality from these causes.

Conclusion—The risk of accidents, suicides, and other violent deaths was not related to serum cholesterol concentration, whereas such deaths were more prevalent in smokers and alcohol drinkers.

Introduction

Clinical trials have shown that reduction in total serum cholesterol concentration reduces the incidence of coronary heart disease. Lowering serum cholesterol concentration has not affected total mortality. Two reviews of trials to lower cholesterol concentration have suggested that deaths from violence and accidents might have increased in the actively treated groups compared with the control groups. In the first review the risk ratio for mortality not related to illness was 1.75 and was on the same level of randomised dietary and drug trials.¹ In the second, the Finnish mental hospital cross over trial was included in the diet trials and the risk ratio for injury in the diet trial was reduced to 1.2 and was no longer significant.² In the latest review of 28 randomised trials the relative risk of 1.17 between the lowest and highest cholesterol concentrations was not significant.³ Two of the cohort studies have shown that low cholesterol concentration increased the risk for accidental or other violent

deaths,^{4,5} while in three of them no association was seen.⁶⁻⁸ In the review of 10 cohort studies a significant relative risk of 1.29 was found in six studies done in community settings, but no increased risk was observed in four cohorts of employed men.³ These findings have raised concern about the safety of lowering the average serum cholesterol concentration in a population and about the safety and usefulness of lowering serum cholesterol concentration with drug treatment.

We analysed the association between serum total cholesterol concentration and mortality from accidents, suicides, and other violent deaths in two large cohorts of middle aged Finns monitored for 10 and 15 years.

Subjects and methods

Two cross sectional population surveys, in 1972 and 1977, assessed the levels of risk factors for coronary heart disease in the province of North Karelia and Kuopio. For both surveys an independent 6-6% random sample of people born during 1913-47 was drawn from the population register. Details of the survey procedures have been described in earlier reports.⁹ Briefly, the surveys included a self administered questionnaire (mainly questions on socio-economic factors, medical history, health behaviour, and psychosocial factors) and measurements of height, weight, and blood pressure. Venous blood was taken for measurement of serum total cholesterol concentration.

Specially trained nurses took all the measurements. Both surveys used methods as similar as possible. Casual blood pressure was measured in the right arm of the subject, who was seated for five minutes before the measurement. Serum total cholesterol concentration was determined from frozen samples by using the Liebermann-Burchard method.

The frequency of drinking alcohol was assessed from the questionnaire by using an ordinal scale of seven options: daily, once or twice a week, once or twice a month, once in two months, three or four times a year, once or twice a year, and not at all. These categories were used in the univariate analyses. In the multivariate analyses use of alcohol was dichotomised to those who reported use of alcohol at least once or twice a month and to less frequent users. Smoking was assessed from the surveys by using a set of standardised questions in a self administered questionnaire. On the basis of the answers the participants were classified into the categories of never smokers, who had never smoked regularly; former smokers, who had smoked regularly but had stopped smoking more than six months ago; and smokers, who had smoked regularly

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for at least one year and had smoked during the past six months. Smokers were classified on the basis of daily smoking (cigarettes, cigars, and pipes were calculated together) into four groups: those who smoked one or less, two to 14, 15-24, and 25 or more times a day. In the multivariate analyses smoking was dichotomised to smokers and non-smokers.

Information on violent deaths was obtained from the national mortality register and comprised all deaths attributed to causes other than disease (*International Classification of Diseases*, eighth revision, codes 800-999). There were 193 deaths due to accidents, suicides, and other violent causes among the 10 898 men and 43 such deaths among the 11 534 women. The combination of all these causes was used as the outcome variable in the analyses. The present analysis was concerned with subjects aged 25-64 years at the baseline. In the univariate analyses death rates were age standardised by using age distribution of the sample as a standard population. Multivariate analyses were performed by using Cox's proportional hazards regression model.¹⁰ All statistical analyses were done with an SAS program.¹¹ Separate analyses were done for men and women. Age baseline measurement of serum cholesterol concentration, and systolic blood pressure were used as continuous variables in the regression models, and smoking and use of alcohol were dichotomised. The two study cohorts, 1972 and 1977, were first analysed separately. Because the findings were essentially the same in the two cohorts, we have preserved results for the two cohorts combined. A dummy variable for cohort was included in the model. Years of education was used as a measurement of socioeconomic status in the model, but when we repeated the analyses with adjustment for social class instead of education the results were essentially the same.

Results

In men serum cholesterol concentration was not associated with mortality from accidents, suicides, and other violent deaths in univariate analyses (table I) or in

TABLE I—Age standardised mortality from accidents, suicides, and other violent deaths by serum cholesterol concentration in men and in women

Cholesterol concentration (mmol/l)	Men			Women		
	Age standardised mortality (%)	No of deaths	Total	Age standardised mortality (%)	No of deaths	Total
<5.0	1.45	11	854	0.52	2	1 162
5.00-6.49	1.81	76	4 222	0.42	20	4 662
6.50-7.99	1.76	75	4 193	0.36	14	4 040
≥8.00	2.03	33	1 629	0.49	7	1 794
Total	1.79	195	10 898	0.38	44	11 657

TABLE II—Proportional hazards regression model for mortality from accidents, suicides, and other violent deaths*

Variable	Risk ratio (95% confidence interval)	P value
<i>Men</i>		
Age (years)	1.00 (0.98 to 1.02)	0.57
Smoking (no or yes)	2.28 (1.65 to 3.14)	0.0001
Alcohol intake (no use or use)	1.11 (1.03 to 1.19)	0.006
Cholesterol (1 mmol/l)	1.02 (0.91 to 1.15)	0.69
Systolic blood pressure (10 mm Hg)	1.09 (1.01 to 1.16)	0.02
Years of education (0-25)	0.97 (0.92 to 1.02)	0.24
<i>Women</i>		
Age (years)	1.02 (0.97 to 1.06)	0.44
Smoking (no or yes)	2.25 (1.03 to 4.90)	0.04
Alcohol intake (no use or use)	0.97 (0.80 to 1.17)	0.74
Cholesterol (1 mmol/l)	0.93 (0.72 to 1.19)	0.55
Systolic blood pressure (10 mm Hg)	0.90 (0.76 to 1.05)	0.17
Years of education (0-25)	0.94 (0.84 to 1.05)	0.27

*ICD-8 800-999.

TABLE III—Age standardised mortality from accidents, suicides, and other violent deaths by smoking in men

Smoking	Age standardised mortality (%)	No of deaths	Total
Cigarettes/cigars/pipes a day:			
≥25	3.82	39	1 112
15-24	2.54	64	2 516
2-14	2.25	21	918
≤1	1.13	8	526
Former smokers	1.12	29	2 631
Never smokers	1.11	34	3 195
Total	1.79	195	10 898

TABLE IV—Age standardised mortality from accidents, suicides, and other violent deaths by alcohol use in men

Use of alcohol	Age standardised mortality (%)	No of deaths	Total
No use	1.84	27	1 515
Once or twice a year	0.98	13	1 408
Three or four times a year	1.07	17	1 493
Once every other month	1.38	15	1 061
Once or twice a month	2.24	77	3 506
Once or twice a week	2.46	42	1 776
Daily	6.37	4	82
Total	1.80	195	10 841

the Cox's proportional hazards regression analyses including other risk factors (table II). Smoking and alcohol use increased the risk of dying of these causes. The relation with smoking was graded (table III). The risk among never smokers and former smokers was similar. In heavy smokers (those who smoked more than 25 times a day) mortality was 3.9 times higher than among former smokers or never smokers. In the Cox's regression model the risk ratio for smoking was 2.28. Alcohol drinking had a J shaped association with mortality from accidents, suicides, and violent deaths, the rate being lowest among those who used alcohol occasionally, only once or twice a year. The highest risk was found among daily alcohol drinkers (table IV), also in the multivariate analysis the risk ratio of 1.11 was significant ($P=0.006$). In the multivariate analyses socioeconomic status measured as years of education was not associated with mortality from accidents, suicides, and violent deaths. When years of education was added in the model it did not affect the risk ratios of the other variables. Systolic blood pressure had a positive risk ratio of 1.09, which was significant ($P<0.02$). When the cohorts were analysed separately the same association was found only in the 1977 cohort.

In women the mortality from accidents, suicides, and other violent death was 2.3 times higher among smokers than non-smokers. Age, alcohol drinking, serum cholesterol concentration, and blood pressure were not associated with the risk of accidents, suicides, and violent deaths in women.

Discussion

In two earlier cohort studies no association was found between low serum cholesterol concentration and the risk of accidental death. The Finnish cohorts of the seven countries study comprised 1580 men who were first studied in 1959 and followed for 25 years.⁶ During that time 47 men had died from accidents or violence. In the Whitehall study of London civil servants the plasma cholesterol concentration was determined in 17 718 men aged 40-64 years during 1967-9.⁶ During follow up to January 1987, 90 had died from accident or other violence, 36 of whom had committed suicide. In the multinational comparison of the data from the seven countries study no consistent association was found between the initial serum chole-

terol concentration and the 25 year risk of death from suicide, accident, or violence.⁸

In two cohort studies an association was found between low serum cholesterol concentration and accidental or violent deaths, at least during some part of the follow up; in the study of Dutch civil servants and spouses started in 1953-4, a non-significant association for death from violence, accident, or suicide was observed (ratio 3.7) between the lowest and highest third in the 15 year follow up and a significant association (ratio of 2.4) in the 28 year follow up. Twenty one of the 1476 men and 2101 of the 1469 women died from external causes.⁴

In a Swedish study in the Värmland area 26 693 men and 27 692 women were surveyed in 1964-5.⁵ In men the relative risk of violent death in the lowest fourth of the distribution of the serum cholesterol concentration and in the highest fourth was found during the first six years of follow up (ratio 2.8; 95% confidence interval 1.52 to 4.96). During the subsequent seven to 13 year or 14 to 20 year follow up no increase in the risk of violent death was seen. The strongest association was with suicide, with a relative risk of 4.2. When suicides were excluded from the analysis no association was found between serum cholesterol concentration and violent deaths. In women no association was seen during any of the follow up periods.

In their review Law *et al* found that in the cohorts from community settings the relative risk of accidents and suicide was 1.29 in the group with the lowest cholesterol concentrations compared with all others while no increased risk was observed in cohorts of employed men.³ In our cohort, which is a typical community cohort, we did not see any increased risk with a similar type of analysis. The relative risks were 0.84, 0.86, and 0.88 when we used cut off points of 5 mmol/l (about 8% of people), 5.5 mmol/l (17% of people) and 6 mmol/l (30% of people), respectively, for cholesterol concentration.

One possible reason for these unequivocal results among different studies is the heterogeneity of the definition of end point. There are many different reasons for accidents and other violent deaths. In our study we could not separate data on accidents, suicides, and other violent deaths.

The province of North Karelia in eastern Finland has had a community based programme for prevention of cardiovascular disease since 1972.⁹ Serum cholesterol concentration has decreased by about 1 mmol/l (15%) during the past 20 years. Cardiovascular mortality has decreased by 43%, cancer mortality by 29%, mortality from accidents and violence by 12%, and total mortality by 34%. These findings do not support the hypothesis that lowering serum cholesterol concentration in the population would increase accidents or violence.

Smoking was strongly associated with mortality from accidents, suicide, and other violent deaths, and the association was graded. A similar observation was also made in the multiple risk factor intervention trial.¹² It is unlikely that smoking causes accidental or other violent deaths. It could be explained by some other factors—for example, risk taking behaviour. Alcohol intake was also related to accidental and other violent deaths but not as strongly as smoking. Both smoking and alcohol were significant in the multiple logistic regression model, which probably means that alcohol intake cannot explain the association between smoking and violent deaths. The associations were

Clinical implications

- Low total serum cholesterol concentration was not associated with increased mortality from accidents, suicides, or violence
- Mortality from those causes was higher among smokers and increased gradually with the amount of daily smoking
- Mortality was similar among those who had never smoked regularly and former smokers
- Lowering serum cholesterol concentration in a population does not seem to increase accidents or violence

also unchanged after adjustment for education. We repeated the analyses adjusting for social class instead of education. The results were essentially unchanged: smokers had higher risk of deaths due to injury among both upper and lower class white collar workers, among both skilled and unskilled blue collar workers, and among farmers. The small positive association between systolic blood pressure and accidental or other violent deaths is probably by chance. Association was not systematic across all measures of blood pressure, and it was not similar in two cohorts. During the relatively long follow up period there have been changes in the general level of risk factors in Finland, and people may have changed from one category of risk to another. This weakens the association between the risk factors and mortality.

In summary, the observed increase in accidental and other violent deaths seen in some trials that aimed to lower serum cholesterol concentration is not supported by findings from cohort studies. Neither cross population comparisons nor community based programmes indicate that lowering serum cholesterol concentration in the general population will increase the risk of such deaths. Results from clinical trials and unexpected side effects of pharmaceutical agents must be evaluated carefully. Such an evaluation should not confuse the disease prevention programmes continuing in several countries.

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