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(Accepted 1 June 1992)

Low serum cholesterol concentration and short term mortality from injuries in men and women

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Abstract

Objective—To determine whether total serum cholesterol concentration predicts mortality from injuries including suicide.

Design—Cohort study of men and women who had their serum cholesterol concentration measured as part of a general health survey in Värmland, Sweden in 1964 or 1965 and were followed up for an average of 20.5 years.

Subjects—Adults participating in health screening in 1964-5 (26 693 men and 27 692 women). The study sample was restricted to subjects aged 45-74 years during any of the 20.5 years of follow up.

Main outcome measures—Serum cholesterol concentration. Deaths from all injuries and suicides during three periods of follow up (0-6 years, 7-13 years, and 14-21 years) according to the Swedish mortality register in subjects aged 45-74. Adjustment was made for prevalent cancer (identified from the Swedish cancer register) at the time of a suicide.

Results—A strong negative relation between cholesterol concentration and mortality from injuries was found in men during the first seven years of follow up. The relative risk in the lowest 25% of the cholesterol distribution was 2.8 (95% confidence interval 1.52 to 4.96) compared with the top 25%. Most of the excess risk was caused by suicide with a corresponding relative risk of 4.2 (p for trend=0.001). Correction for prevalent cancer did not change the results. Events occurring during the latter two thirds of the 20.5 years of follow up were not predicted. In women no relation between cholesterol concentration and mortality from injuries was found.

Conclusions—Together with observations from intervention trials the findings support the existence of a relation between serum cholesterol concentration and suicide. The causality of such a relation is, however, not resolved.

Introduction

"A moratorium on the use of cholesterol lowering drugs,"¹ has recently been suggested based partly on the observation in clinical trials that the intervention groups suffer an excess mortality from injuries.^{2,3} A meta-analysis including six such primary prevention trials showed an increased mortality in men from "causes not related to illness." This excess risk was found in drug trials as well as in diet trials.⁴ Prospective observational studies covering the relation between serum cholesterol concentration and deaths from injuries are, however, inconclusive.^{5,6}

Observational studies might be biased by confounding. There is a relation between low serum cholesterol concentration and the incidence of cancer.⁷ Suicides constitute an important fraction of all deaths from injuries. Hypothetically, if seriously ill subjects suffer a higher risk of suicide, coexistent cancer might confound a negative correlation between serum cholesterol concentration and suicide. Other hypotheses about possible links between mortality from injuries and cholesterol concentration have been reviewed by Muldoon⁴ and Pekkanen.⁵

One reason for the inconsistent findings in previous cohort studies may be that the numbers of events were too small. In this study data from a large cohort of men and women followed up for two decades were used to investigate the association between total serum cholesterol concentration and mortality from injuries. A special attempt was made to investigate the impact of cancer incidence on such a relation.

Subjects and methods

The study sample from the subcohort of the Värmland survey that was included in this study has been previously described.⁸ In summary, data on several chemical analyses, including serum cholesterol concentration, were collected from 26 693 men and 27 692 women who participated in a general health survey conducted in Värmland, Sweden, in 1964-5. The participation rate was 78.1% in men aged 25-74 years and 81.3% in women of the same age. Serum total cholesterol was analysed on one occasion in non-fasting subjects. A modified Liebermann-Burchard method described by Zak *et al* was used.⁹

The Swedish mortality register, which is regarded as reliable,¹⁰ was used to identify fatal events in the cohort from 1964 to 1985. In the register the underlying cause of death is coded according to the *International Classification of Diseases*. The seventh revision¹¹ was used for deaths occurring from 1964-8 and the eighth revision¹² for deaths occurring from 1969 onwards. In both editions injuries are defined by the codes E 800 to E 999 (see table I). In the seventh edition suicide is defined by the codes E 970 to E 979 and in the eighth edition by the codes E 950 to E 959. Only deaths occurring between the ages of 45 and 74 in subjects who were 25-74 years old at the health examination were considered. Consequently, the study sample was restricted to those who were aged 45-74 years during any of the 20.5 years of follow up. This design has been used in previous studies of this cohort.⁸

The Swedish cancer register was used to identify

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BMJ 1992;305:277-9

cases of cancer in the cohort. Of all cancers diagnosed in Sweden about 96% are reported to the register at the time of diagnosis.¹³

Quartiles for total cholesterol concentration were determined for each five year age stratum at screening (25-29, 30-34 . . . 70-74). These age adjusted quartiles formed the basis for further analysis. Statistical testing of relative risk estimates was performed with a multiplicative generalised linear model (GLIM).¹⁴ Three age groups (45-54, 55-64, and 65-74 years) and three periods of follow up (0-6, 7-13, and 14-20 years) were used in the multivariate calculation of the adjusted relative risks. A Poisson model with the logarithm of person years as offset was used. Differences were considered significant when $p<0.05$. All tests were two tailed.

Results

Of those 26 693 men and 27 692 women aged 25-74 years who were included for follow up, 163 men and 100 women died before the age of 45 and did not contribute person years to this study.⁸ During the 20.5 years of follow up 376 men and 139 women aged 45 to 74 years died from injuries. Of these, 146 men and 44 women committed suicide, and, except for seven cases of homicide, the remainder were classified as accidents (table I).

Table II summarises numbers of deaths from injuries and death rates by cholesterol quartile and gender. There was a non-significant trend of descending rate with increasing cholesterol concentration in men ($p=0.10$). Multivariate analysis, however, uncovered a highly significant interaction between cholesterol quartile and follow up time in men ($p=0.006$). This finding prompted us to handle each follow up period separately. In women, no such interaction was seen ($p=0.94$). There was no significant interaction with age.

During the first period of follow up, 0-6 years after estimation of cholesterol concentration, a strong negative association between cholesterol concentration and mortality from injuries was present in men ($p<0.001$) but not in women (table III). In the lowest

TABLE I—Causes of death in men and women aged 45 to 74 years during follow up who died from injuries

Cause of death	ICD 7 codes	ICD 8 codes	No of men	No of women
Railway and motor vehicle accidents	801-830	800-825	99	48
Water transport accidents	850	832	8	0
Accidental poisoning	870-894	860	11	5
Accidental falls	900-904	880-887	34	21
Other accidents	910-936	840-842, 890-896, 910-946	74	18
Suicide	971-977	950-958	146	44
Homicide	981	960-968	4	3

TABLE II—Numbers and rates of deaths from injuries by quarter of cholesterol distribution and gender

Cholesterol* distribution (quarter)	Mean cholesterol* concentration (mmol/l)	No	Rate per 1000 person years
Men			
First	5.3	107	1.30
Second	6.1	94	1.13
Third	6.7	93	1.12
Fourth	7.6	82	1.01
p For trend			0.10
Women			
First	5.4	37	0.41
Second	6.3	35	0.39
Third	6.9	31	0.35
Fourth	7.9	36	0.40
p For trend			0.73

*At initial examination, age-adjusted.

TABLE III—Relative risks for deaths (RR) and numbers of deaths from injuries by quarter of cholesterol distribution and duration of follow up in men and women

Cholesterol distribution (quarter)	Follow up interval (years)					
	0-6		7-13		14-20	
	No	RR	No	RR	No	RR
Men						
First	41	2.75*	36	1.10	30	0.83
Second	31	2.06*	36	1.10	27	0.74
Third	27	1.79	36	1.11	30	0.82
Fourth	15	1.00	32	1.00	35	1.00
p For trend		0.0005		0.69		0.37
Women						
First	12	0.94	10	1.14	15	1.07
Second	9	0.70	18	2.02	8	0.57
Third	8	0.62	15	1.66	8	0.57
Fourth	13	1.00	9	1.00	14	1.00
p For trend		0.93		0.65		0.84

* $p<0.05$.

p Value for interaction between follow up period and cholesterol quarter=0.006.

TABLE IV—Relative risks in men for deaths (RR) and numbers of deaths from suicide by quarter of cholesterol distribution and duration of follow up

Cholesterol distribution (quarter)	Follow up interval (years)					
	0-6		7-13		14-20	
	No	RR	No	RR	No	RR
Men on cancer register included						
First	21	4.22*	15	1.65	11	0.66
Second	12	2.39	12	1.30	11	0.66
Third	10	1.99	11	1.20	13	0.78
Fourth	5	1.00	9	1.00	16	1.00
p For trend		0.001		0.22		0.24
Men on cancer register excluded†						
First	20	4.10*	14	1.55	11	0.75
Second	11	2.21	9	0.97	11	0.75
Third	10	2.01	9	0.98	12	0.83
Fourth	5	1.00	9	1.00	14	1.00
p For trend		0.002		0.30		0.45

* $p<0.05$.

†p Value for interaction between follow up period and cholesterol quarter=0.02.

quarter (the lowest 25% of the age adjusted cholesterol distribution) the relative risk was 2.75 (95% confidence interval 1.52 to 4.96) compared with the highest quarter. During the following two thirds of follow up, 7-20 years after estimation of cholesterol concentration, no significant association was seen in men or women. The 95% confidence interval for the relative risk associated with the lowest quarter in women (0.94) was 0.43 to 2.07.

When suicide and deaths from other injuries during the first follow up period were analysed separately no significant impact of cholesterol concentration was seen for non-suicide injuries (p for trend during the first seven years=0.074) in men. It was thus obvious that the main part of the negative trend for all injuries during that period was explained by a strong significant negative relation between cholesterol concentration and suicide (p for trend=0.001; table IV). This result did not change significantly after exclusion from analysis of the 2758 men who had a registered cancer (table IV). With this case selection the relative risk for suicide associated with the lowest cholesterol quarter compared with the highest quarter was 4.1 (1.54 to 10.90). This risk corresponds to a relative risk of 1.8 per 1 mmol/l decrease in serum cholesterol concentration. As no overall trends were found in women the latter analyses were not performed for women.

Discussion

Observations from intervention trials to lower cholesterol have raised the question of a possible causal relation between low serum cholesterol concentration

and deaths from injuries. Our study showed a strong relation between low serum cholesterol concentration at screening and deaths from injuries during the first seven years of a total of 20.5 years' follow up. During the last two thirds of the period no relation was found. The predictive power was especially strong for suicide and persisted after removing data on subjects who developed cancer before taking their life.

The present study design was originally used in this cohort for estimating risk of death from cardiovascular disease.⁸ The original restriction to deaths occurring in subjects aged 45-74 years during follow up was kept to permit comparison with the previous studies that addressed the hypothesis^{5,6} and also to conform with clinical trials where increasing risk of violent deaths with cholesterol lowering has been suggested.^{2,3}

A study of two male Finnish cohorts from the seven countries study (the east and the west cohorts) for the relation between cholesterol concentration and mortality from injuries was inconclusive.⁵ In the east cohort only 19 deaths from accidents and violence occurred during 25 years of follow up, and a non-significant negative association was observed. In the west cohort, with 28 deaths during 25 years, a significant positive association was observed. Furthermore, in the Whitehall study of London civil servants, with 90 deaths from violent causes during 20 years of follow up, no significant relation was found between serum cholesterol concentration and all violent deaths or death by suicide.⁶ A recently published study of a Chinese population with low cholesterol concentrations showed a significant trend in the expected direction, but this trend disappeared after adjustment for confounders.¹⁵ The present cohort study is consequently the first of its kind to support the observations made in clinical trials.⁴ It is also the largest, as a total of 376 deaths from injuries were observed in men and 139 in women.

Contrary to observations on the impact of serum cholesterol concentration on mortality from coronary heart disease in this cohort,¹⁶ the impact on death from injuries and suicide became weaker and disappeared totally with increasing length of follow up. The increased risk may therefore be associated with a concentration of cholesterol below a subject's habitual value. This interpretation is consistent with the hypothesis of an increased risk in subjects lowering their cholesterol concentration by diet or drugs.

As the relation between cholesterol concentration and suicide was present only during the early years after estimation of cholesterol concentration a longer observation time results in a weaker relation. Therefore it may be necessary to include a greater number of events in each year to detect the risk. In our study an average of 7.4 suicides a year occurred during the first period of follow up. This compares with 1.8 suicides a year in the Whitehall study,⁶ and 0.8 and 1.1 deaths a year from injuries in the two Finnish cohorts.⁵ This difference in rates is one possible explanation of the diverging results of these studies.

No earlier studies have tested the current hypothesis in women. In the Värmland cohort, the incidence of suicide among women was considerably lower than that among men, and there was no relation between suicide in women and cholesterol concentration. The lack of relation may be due to low power as an average of only 2.1 women committed suicide in each year of follow up. There is no other obvious explanation for the sex differences, but a corresponding dissimilarity between men and women is present in the relation between serum cholesterol concentration and mortality from coronary heart disease (L Råstam *et al*, 31st annual conference on cardiovascular disease epidemiology, Orlando, Florida, 1991).

The biological foundations for our findings are

unknown. The relation might, of course, be explained by some confounder correlating with serum cholesterol concentration and at the same time causing mortality from injuries. It was, however, not confounded by cancer as the risk was virtually the same when subjects entered in the cancer register were excluded from the cohort. Alcohol abuse is also a potential confounder, but the correlation between serum total cholesterol concentration and amount of alcohol consumed is low.^{17,18} Some cases of suicide may have been misclassified as another class of deaths from injuries, but this could not be confirmed in this cohort. It seems unlikely, however, that such misclassification could have had any substantial influence on the relative risks reported here as that would require an interaction with cholesterol concentration. Lower serum cholesterol concentrations have been reported in criminals,¹⁹ people with violent or aggressive conduct disorders,^{20,21} and people with low self control.²² No data are available, however, on serum cholesterol concentration and personality. A recent study showed changing behaviour in monkeys who were fed with a diet low in saturated fat and cholesterol.²³

In summary, our study, together with observations from intervention trials, supports the existence of a relation between serum cholesterol concentration and risk of suicide. The direction of such a relation is, however, not resolved.

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(Accepted 1 June 1992)