

Serum cholesterol concentration and death from suicide in men: Paris prospective study I

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Abstract

Objective—To investigate whether low serum cholesterol concentration or changing serum cholesterol concentration is associated with risk of suicide in men.

Design—Cohort study with annual repeat measurements of serum cholesterol concentration (for up to four years).

Setting—Paris, France.

Subjects—6393 working men, aged 43-52 in 1967-72, who had at least three measurements of serum cholesterol concentration.

Main outcome measures—Individual change over time in serum cholesterol concentration (estimated using within person linear regression method); death from suicide during average of 17 years' follow up after last examination.

Results—32 men committed suicide during follow up. After adjustment for age and other factors, relative risk of suicide for men with low average serum cholesterol concentration (<4.78 mmol/l) compared with those with average serum cholesterol concentration of 4.78-6.21 mmol/l was 3.16 (95% confidence interval 1.38 to 7.22, $P = 0.007$). Men whose serum cholesterol concentration decreased by more than 0.13 mmol/l a year had multivariate adjusted relative risk of 2.17 (0.97 to 4.84, $P = 0.056$) compared with those whose cholesterol remained stable (change of ≤ 0.13 mmol/l a year).

Conclusion—Both low serum cholesterol concentration and declining cholesterol concentration were associated with increased risk of death from suicide in men. Although there is some evidence in favour of a concomitant rather than a causal effect for interpreting these associations, long term surveillance of subjects included in trials of lipid lowering treatments seems warranted.

Introduction

Results from several cohort studies suggest that low serum cholesterol concentration is associated with an increased risk of suicide and attempted suicide.^{1,2} However, this association remains controversial since null and even positive associations have also been reported.² One possible explanation for these discordant results is that studies did not identify subjects whose cholesterol concentrations were changing over time. Few studies have longitudinal data on serum cholesterol concentration over a period of several years, with ensuing long term follow up for suicide. The Paris prospective study I provides an opportunity to address this important question.

Methods

SUBJECTS

Between 1967 and 1972, 7746 native born Frenchmen aged 43-52 and employed by the city of Paris were given initial clinical examinations to study

risk factors for coronary disease. For up to four years after the first examination, all subjects were invited to undergo an annual follow up examination at which cholesterol concentration was measured. The number of subjects who had one, two, three, four, or five examinations was 614, 604, 601, 1671, and 4456 respectively.

CHOLESTEROL CONCENTRATIONS

For our study, we included the 6728 men whose serum cholesterol concentration had been measured at least three times. We considered each subject's average serum cholesterol concentration for all the measurements and the change in concentration over the period. We used the within person linear regression method to calculate change in individual serum cholesterol concentration. Serum cholesterol concentrations were regressed onto calendar time to give an average annual change in concentration (regression slope).

FOLLOW UP

The men were followed up for survival until January 1994 by specific inquiries to hospitals, family doctors, and medical services at work. Vital status after an average of 17 years of follow up was available for 6393 of the 6728 subjects. Date and place of death were noted, and cause of death was obtained from death certificates at the National Institute of Health and Medical Research (INSERM). Death from suicide was defined according to ICD-8 and ICD-9 (international classification of diseases, eighth and ninth revisions) as codes E950-959.

STATISTICAL ANALYSIS

We used Student's *t* test and Cox's proportional hazards model for analysis. All analyses were stratified by the number of measurements of serum cholesterol for each subject (three to five).

Results

During follow up 32 of the men committed suicide. Average serum cholesterol concentration was associated with suicide: compared with men with an average serum cholesterol concentration of 4.78-6.21 mmol/l, subjects who had a low average concentration (<4.78 mmol/l) had an age adjusted relative risk of suicide of 3.28 (95% confidence interval 1.44 to 7.49, $P = 0.005$). Further adjustment for smoking habits and mean corpuscular volume (obtained at the first examination) did not greatly modify the results (table 1). Similar results were also obtained when serum cholesterol concentration at the first examination was used instead of average serum cholesterol concentration (data not shown).

CHANGE IN SERUM CHOLESTEROL

The average serum cholesterol concentration for the whole population increased significantly over time (mean change 0.06 (SD 0.25) mmol/l a year, $P < 0.001$). In the men who committed suicide the average cholesterol concentration declined, and the difference

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Table 1—Relative risks (95% confidence interval) of suicide among 6393 men by average serum cholesterol concentration and change in cholesterol concentration

	No of subjects	No of suicides	Adjusted relative risk (95% confidence interval)*	P value
Average serum cholesterol concentration (mmol/l)†				
<4.78	827	10	3.16 (1.38 to 7.22)	0.007
4.78-6.21	3600	13	1.00	
>6.21	1966	9	1.28 (0.55 to 3.01)	0.56
Change in serum cholesterol concentration (mmol/l a year)‡				
Decline >0.13	1143	11	2.17 (0.97 to 4.84)	0.056
Change ≤0.13	2795	13	1.00	
Increase >0.13	2455	8	0.72 (0.30 to 1.72)	0.46

*Relative risks for average cholesterol concentration were adjusted, using Cox's proportional hazards model, for age, smoking habits (never, former, or current), and mean corpuscular volume at first examination. Relative risks for change in cholesterol concentration were adjusted as above and for average serum cholesterol concentration.

†Mean of serum cholesterol concentrations from all examinations.

‡Estimated using within person linear regression method (0.13 mmol/l equivalent to 5 mg/dl).

Table 2—Relative risks (95% confidence intervals) of suicide among 6393 men by change in serum cholesterol concentration stratified by average cholesterol concentration and by length of time to suicide

Change in serum cholesterol concentration (mmol/l a year)	No of subjects	No of suicides	Adjusted relative risk (95% confidence interval)*	P value
Average cholesterol concentration ≤6.21 mmol/l				
Decline >0.13	661	7	2.78(1.13 to 6.82)	0.03
Decline ≤0.13 or increase	3766	16	1.00	
Average cholesterol concentration >6.21 mmol/l				
Decline >0.13	482	4	2.51(0.67 to 9.39)	0.17
Decline ≤0.13 or increase	1484	5	1.00	
Time to suicide ≤10 years				
Decline >0.13	1107	6	2.60(0.95 to 7.13)	0.06
Decline ≤0.13 or increase	5286	12	1.00	
Time to suicide >10 years†				
Decline >0.13	911	5	2.44(0.79 to 7.46)	0.12
Decline ≤0.13 or increase	4661	9	1.00	

*Relative risks were adjusted, using Cox's proportional hazards model, for age, smoking habits, and mean corpuscular volume at first examination and for average serum cholesterol concentration.

†Excluding the 821 subjects who died in first 10 years.

with those who did not commit suicide was of borderline significance (-0.02 (SD 0.28) *v* 0.06 (SD 0.25) mmol/l a year, $P = 0.07$). Men whose cholesterol concentration decreased more than 0.13 mmol/l a year had an age adjusted relative risk of suicide of 2.18 (0.98 to 4.87, $P = 0.052$) compared with those whose cholesterol concentration changed ≤ 0.13 mmol/l a year. Neither adjustment for other variables nor adding average serum cholesterol concentration to the model (as continuous variable or in three categories) altered the results (table 1).

We divided the men according to the direction in which their cholesterol concentration changed: concentration increased in 4098 men, 14 of whom committed suicide, and declined in 2295, 18 of whom committed suicide. The multivariate adjusted relative risk of suicide for the men with decreasing cholesterol concentrations was 2.13 (1.06 to 4.31, $P = 0.03$) compared with those with increasing concentrations.

When we stratified the cohort according to the average serum cholesterol concentration we found similar associations between change in concentration and suicide, although this was significant only in men with an average cholesterol concentration ≤ 6.21 mmol/l (table 2). We also found that the association between change in cholesterol concentration and suicide remained for those subjects who committed suicide earlier in the follow up period and for those who committed suicide later on (table 2).

Discussion

These results suggest that both low serum cholesterol concentration and a declining serum cholesterol concentration were related to subsequent death from suicide. No observational cohort study has previously reported the relation between change over time in serum cholesterol concentration and the risk of suicide. These results should be interpreted cautiously, however, particularly because of the small number of subjects who committed suicide.

SUICIDE AND LIPID LOWERING DRUGS

Trials of primary prevention of coronary heart disease showed that lowering of serum cholesterol concentration, notably from drugs, was followed by an increased risk of suicide and violent deaths,³ though results were inconsistent.⁴ However, we do not think that the association we found between declining serum cholesterol concentration and suicide could be explained by the action of hypolipidaemic drugs: few people would have been treated with such drugs in the early 1970s, and, more importantly, the relation between declining serum cholesterol and suicide was similar both for those subjects with elevated serum cholesterol concentrations (>6.21 mmol/l), who would have been candidates for treatment, and for those with lower levels (≤ 6.21 mmol/l), who would not. Furthermore, two recent large trials of the lipid lowering drugs simvastatin and pravastatin did not show an increased risk of violent death and suicide.^{5,6}

OTHER EXPLANATIONS

Low or decreasing cholesterol concentration might be a consequence of depression⁷ or of decreased appetite and weight loss in depressed subjects. Effective treatment of depression has been shown to increase serum cholesterol concentration.⁸ An alternative suggestion is that low or declining serum cholesterol concentrations might alter the metabolism of serotonin,^{9,10} leading to depression and thus increasing the risk of suicide.

Another alternative is that the associations we found could have been due to confounding factors. Although we took account of smoking habits and mean corpuscular volume (as a proxy of alcohol consumption), residual effects of these factors and the effects of other factors could not be ruled out. Unfortunately, we had no information about individual reasons for declining serum cholesterol concentrations. As in the general French population,¹¹ the number of deaths from suicide in this cohort might have been underestimated. However, our findings should not be notably modified unless underestimation was related to serum cholesterol concentration, which is unlikely.

Key messages

- The association between low serum cholesterol concentration and suicide is still debated
- In this cohort study of 6393 men with repeated measurements of serum cholesterol concentration, both low serum concentrations and declining concentrations was associated with increased risk of subsequent death from suicide
- Our results, together with those of recent trials of lipid lowering drugs, suggest that these associations might not be causal
- However, long term surveillance of subjects included in trials of lipid lowering treatments seems warranted

CONCLUSION

We found that low or declining serum cholesterol concentrations were associated with death from suicide. Mechanisms that might link cholesterol concentrations to suicide should be thoroughly studied.

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Commentary: Having too much evidence (depression, suicide, and low serum cholesterol)

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Another observational study on low serum cholesterol concentration and suicide appears in this week's *BMJ*,¹ complementing other *BMJ* publications in the past two years.²⁻⁴ These papers all take as their premise that the controversy on low serum cholesterol, depression, and accidents and suicide remains unresolved. They conclude that it remains unresolved.

The past two years have also seen the publication of two large randomised controlled trials of cholesterol reduction using hydroxymethyl glutaryl coenzyme A reductase inhibitors ("statins").⁵⁻⁶ These drugs produce large reductions in serum cholesterol concentration (20-30%) and hence are particularly informative on safety. If smaller trials are taken into account as well, published randomised trials of statins have now accumulated 38 700 person years of observation on active treatment and 33 800 person years on placebo. With a total of 11 deaths from accidents and suicide in treated patients and 14 in controls in these trials, there is no indication of hazard. Most important, however, since one can never prove a negative, is the upper limit of the 95% confidence interval of the combined risk estimate from the numbers in these trials. The greatest likely hazard, if there were any, would be small—one death in about 5000 person years of treatment. Few such potent treatments have so much evidence of safety from randomised trials.

The older trials of cholesterol lowering (average reduction about 10%) are also reassuring. Concern relating to two trials that recorded more deaths from accidents and suicide in treated patients than controls (though neither difference was statistically significant) was resolved by the demonstration that the extra deaths occurred among men who had not taken their allocated tablets (active or placebo).⁷ There had been a chance allocation of more patients with psychiatric illness on entry to active treatment than to placebo.⁷⁻⁸ The rest of the older trials show no excess⁸; table 1 summarises the results.

The issue of low serum cholesterol and depression was directly examined in three randomised, placebo controlled trials of statins in which indices of depression were measured in all the participants—a total of 7400 people taking active treatment and 2400 taking placebo.⁹⁻¹¹ Depression was no more common among those taking active treatment.

With these trial results, why is there continued publication of observational studies that foster the view that the uncertainty persists? The observational and

Table 1—Deaths from accidents and suicide in randomised controlled trials of reduction of serum cholesterol concentration

	Active treatment	Control
Trials of statin drugs (n = 13)	11	14
Trials of older drugs, diet, and ileal bypass surgery:		
The two trials that raised concern:	20	9
Patients who took allocated tablets	9	7
Patients who did not take allocated tablets	11	2
All other trials (n = 25)	78	77
Total:	109	100
Excluding patients who did not take tablets in the two trials	98	98

trial data have tended to be seen in isolation from each other. Some cross sectional studies show an association between low serum cholesterol concentration and depression,¹² and, given this, there is also an association between low serum cholesterol and suicide.⁸ But the associations may arise because low serum cholesterol causes depression or because it is a consequence of depression (simply because depressed people eat less). Cross sectional studies cannot determine which is the cause and which the consequence. Other observational evidence indicates that the low cholesterol concentration is a consequence of the depression since (a) there was no excess mortality with low serum cholesterol in prospective studies of working men (less likely to have serious psychiatric illness on entry to the studies by virtue of being in work),⁸ (b) the excess mortality in the prospective studies was short term with no significant excess after six years,⁸ and (c) treating depression has been shown to increase serum cholesterol concentration.¹³ The recent observational studies have merely introduced variations on the same theme: low serotonin concentrations (which accompany and may cause depression) are, not surprisingly, also associated with low cholesterol,^{2, 14} people who attempt suicide have low serum cholesterol concentrations,³ and, in this week's issue, men with declining serum cholesterol concentrations are particularly likely to commit suicide.¹ If these were the only studies one could not distinguish cause from consequence. The randomised trials resolve the matter, providing compelling evidence that low

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