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Plasma cholesterol and depressive symptoms in older men

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In several clinical trials of interventions designed to lower plasma cholesterol, reductions in coronary heart disease mortality have been offset by an unexplained rise in suicides and other violent deaths. We have tried to find out whether depressive illness is related to low plasma cholesterol concentrations in men of 50 years and older.

In 1985–87, Beck depression inventories were obtained from 1020 white men, aged 50–89 years, in the Rancho Bernardo, California, cohort. Disease history and behaviours were assessed by standard questionnaires. Plasma cholesterol and weight were measured at this time, as they had been in 1972–74. Among men aged 70 years and older, categorically defined depression was three times more common in the group with low plasma cholesterol (<4·14 mmol/L) than in those with higher concentrations (5/31 [16%] *vs* 22/363 [6%]; p=0·033). Depressive symptom scores correlated significantly and inversely with plasma cholesterol concentrations, even after adjustment for age, health status, number of chronic illnesses, number of medications, and exercise, as well as measured weight loss and change in plasma cholesterol in the previous 13 years.

Our finding that low plasma cholesterol is associated with depressive symptoms in elderly men is compatible with observations that a very low total cholesterol may be related to suicide and violent death. Since cholesterol lowering in the general population is widely recommended, this observation warrants further investigation.

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Introduction

Although the association between high serum cholesterol and coronary heart disease is well documented, the overall health benefit of low serum cholesterol is less clear. Studies of populations with widely differing cholesterol concentrations show that the concentrations parallel mortality rates for coronary heart disease, but are not significantly correlated with all causes of mortality.[1] In a study of Chinese men with low serum cholesterol concentrations (3·8–4·7 mmol/L), there was a marginally

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significant inverse association between cholesterol and deaths attributed to non-medical causes, most of which were violent.[2] Furthermore, prevention trials designed to lower cholesterol in men with high cholesterol concentrations result in significant reduction in the incidence of coronary heart disease, but the improvement in heart disease mortality is often offset by increases in mortality from other causes.[3] Among the most prominent and consistent of these causes are suicide, homicide, and accidents—all possible consequences of overt or covert self-destructiveness.[4] Low serum cholesterol concentrations have also been associated with increased risk of death by suicide and alcohol-related diseases.[5]

Depression is a risk factor for suicides and fatal accidents[6] and there are biologically plausible mechanisms linking low cholesterol with depression. We have carried out a population-based study of depression and cholesterol concentrations in men aged 50 years and over.

Subjects and methods

Between 1972 and 1974, 82% of all adult residents of Rancho Bernardo, California, took part in a survey of risk factors for heart disease as part of a Lipid Research Clinic prevalence study.[7] Since that time (visit I), all original study participants have been contacted annually. In 1984, all surviving participants who had been 40 years or older at visit I were invited to take part in a follow-up study designed primarily to screen for diabetes and other chronic diseases. More than 79% of the men made clinic visits between January, 1984, and June, 1987 (visit III).

Depressed mood was assessed at visit III on the basis of responses to eighteen items of the Beck depression inventory (BDI).[8,9] Three of the original twenty-one items (guilt, expectation of punishment, and self-hate) were excluded from the questionnaire in an effort to reduce both its length and the number of potentially threatening items. The validity of the modified scale is supported by studies showing that as many as three-quarters of the items from highly reliable measures can be dropped with little loss of sensitivity or specificity.[10] For this analysis, total scores were proportionally adjusted to correspond to scores and cut-off points established for the full scale (twenty-one items). Specific questions in the inventory about recent appetite and weight loss, which might have lowered cholesterol, were also considered individually.

36 of the 1056 subjects were excluded because of incomplete or missing answers. Scale reliability (Cronbach's alpha) for the remainder was 0·75, which is similar to coefficients based on samples of elderly community volunteers (alpha = 0·76) and depressed outpatients (alpha = 0·74).[11] A cut-off point of 13 was used to define cases of depression (mild to severe) among study subjects. Neilsen and Williams found that a score of 12–13 had 0·79 sensitivity and 0·77 specificity in an outpatient medical population.[12] Scores of 21–30 indicate moderate depression, and 31 and over severe depression.[10]

At both visits I and III, blood samples were taken in the morning after the subject had fasted overnight; total plasma cholesterol was measured on fresh plasma in a Centers for Disease Control standardised Lipid Research Clinic laboratory. Cholesterol concentrations were classified as low (< 4·14 mmol/L), normal (4·14–5·16 mmol/L), borderline (5·17–6·20 mmol/L), and high (≥ 6·21 mmol/L). Standard questionnaires were used to find out about medical history, current medications, level of physical activity, alcohol use, and cigarette smoking.

Each subject was asked whether he had ever been diagnosed as having or treated for, high blood pressure, emphysema, chronic bronchitis, hepatitis, bladder or urinary infection, kidney disease or infection, arthritis, gallstones, thyroid disorders, stomach or duodenal ulcers, diverticulitis, chronic constipation, cancer, or stroke. We assessed self-reported health status by asking the subject about his health in relation to that in others of his age, and physical functioning by asking about current physical function compared with that 10 years earlier. Height and weight were measured at both visits, and percentage weight change between the visits was used as an indicator of weight loss and nutritional status. Medication use was validated by prescriptions and pills brought to the clinic. Reported activity and alcohol and tobacco use were validated indirectly by looking for correlations with other factors, including pulse rate, liver enzymes, and body fat distribution.

Mean BDI scores, prevalence of categorical depression, mean cholesterol concentrations, cholesterol category distributions, and percentage change in cholesterol and body weight between visits I and III were calculated for men in 10-year age groups. These variables were either logarithmically transformed to allow standard parametric analysis or analysed with non-parametric methods (Mann Whitney U test). Comparisons of measures of depressive symptoms, cholesterol, and weight and appetite change across the four age groups were based on one-way analysis of variance for continuous variables and the chi-square test for trend for categorical variables. Age-specific depressive symptom scores of men with low cholesterol (< 4·14 mmol/L) were compared with scores for men in the other three cholesterol categories combined (> 4·14 mmol/L) by the Mann-Whitney U test. Comparisons of age-specific prevalence rates for categorical depression (BDI scores ≥13) in the low-cholesterol group and in the other cholesterol groups combined were based on chi-square tests for proportion with Yates' correction for continuity. Pearson product-moment correlation coefficients were used to assess associations among the various demographic and health status measures. Each of the independent variables

TABLE I—AGE-SPECIFIC DEPRESSION, CHOLESTEROL CONCENTRATIONS, AND WEIGHT AND APPETITE CHANGES

	Age group				
	50–59 (n = 168)	60–69 (n = 256)	70–79 (n = 394)	80–89 (n = 202)	Statistics*
Depressive symptoms					
Mean (SD) BDI score	3·66 (3·63)	4·76 (3·94)	5·91 (4·46)	6 80 (4·46)	$F = 13·3$ $p < 0·0001$
No of subjects depressed (BDI > 13)	4 *(2·4%)*	6 *(2·3%)*	27 *(6·9%)*	11 *(5·4%)*	$\chi^2 = 5·4$ $p < 0·002$
Cholesterol					
Mean (SD) concentration (mmol/L)	5·60 (0·93)	5·63 (1·01)	5·38 (1·02)	5·12 (0·98)	$F = 11·7$ $p < 0·0001$
No of subjects with low cholesterol	11 *(6·5%)*	17 *(6·6%)*	31 *(7·9%)*	24 *(11·9%)*	$\chi^2 = 3·9$ $p < 0·05$
Mean (SD) % change in cholesterol (mmol/L) between visits	7·5 (13·7)	2·2 (13·7)	−1·1 (14·7)	−4·7 (14·8)	$F = 5·6$ $p < 0·001$
Weight and appetite					
Mean (SD) % change in weight (kg) between visits	4·23 (10·53)	1·28 (7·82)	−2·27 (8·15)	−4·97 (7·65)	$F = 3·2$ $p < 0·02$
Mean (SD) loss of appetite†	0·06 (0·24)	0·05 (0·22)	0·15 (0·37)	0·20 (0·43)	$F = 10·8$ $p < 0·0001$
Mean (SD) weight loss†	0·23 (0·67)	0·27 (0·71)	0·26 (0·69)	0·35 (0·82)	$F = 1·0$ $p = 0·38$

*F statistics reported for BDI score, % change in weight, and % change in cholesterol are from tests on log-transformed values
†Self-reported BDI items.

TABLE II—AGE-SPECIFIC PREVALENCE OF DEPRESSION BY CHOLESTEROL CONCENTRATION

Cholesterol	No depressed*/total *(%)* in age groups			
	50–59	60–69	70–79	80–89
Low	0/11	0/17	5/31 *(16)*	4/24 *(17)*
Normal	0/38	2/66 *(3)*	9/145 *(6)*	2/81 *(3)*
Borderline	3/79 *(4)*	2/97 *(2)*	9/154 *(6)*	2/67 *(3)*
High	1/40 *(3)*	2/76 *(3)*	4/64 *(6)*	2/29 *(7)*
χ^2†	0·3, p = 0·592	0·4, p = 0·509	4·5, p = 0·033	7·9, p = 0·005

*BDI ≥13
†For low cholesterol *vs* all other cholesterol groups

TABLE III—AGE-SPECIFIC MEAN BDI SCORE BY CHOLESTEROL CONCENTRATION

Cholesterol	50–59		60–69		70–79		80–89	
	n	BDI*	n	BDI*	n	BDI*	n	BDI*
Low	11	3·39 (3·89)	17	5·08 (3·30)	31	7·30 (5·76)	24	9·33 (5 08)
Normal	38	3·59 (3·04)	66	5·06 (3·85)	145	6·01 (4·18)	81	6·02 (4·61)
Borderline	79	3·57 (3·85)	97	4·68 (3·43)	154	5·65 (4·19)	67	6·60 (3·56)
High	40	3·97 (3·74)	76	4·54 (4·74)	64	5·65 (4·22)	29	6·92 (4·16)
Z†	−0·40, p=0·687		−0·77, p=0·439		−1·10, p=0·271		−2·69, p=0·007	

*Mean (SD)
†For low cholesterol *vs* all other cholesterol groups, based on Mann-Whitney U test

found to be significantly correlated with depressive symptoms ($p \leq 0{\cdot}01$, two-tailed) was then entered into a stepwise multiple regression model.

Results

The mean depressive symptom score for the whole study population was 5·43 (SD 4·28), and the prevalence of categorically defined depression (depressive symptom scores of 13 and above) was 4·6%. Both mean and categorical measures of depressive symptoms increased significantly with age (table I). Age was also associated with a significant decline in mean plasma cholesterol concentration; the proportion of men with cholesterol concentrations in the low category (<4·14 mmol/L) increased from 6·5% at 50–59 to 11·9% at 80–89. Changes in cholesterol and weight after visit I also varied significantly with age. Mean cholesterol concentrations in men of 50–59 years at visit III were an average of 7·5% higher than those at visit I, whereas in men of 80–89 years mean cholesterol decreased by an average of 4·7% from visit I to visit III. Older groups reported significantly greater recent loss of appetite (BDI item R) than younger groups, but there was no corresponding trend in recent weight loss (BDI item S).

A cholesterol concentration below 4·14 mmol/L was associated with a 16% prevalence of categorical depression in men 70 years and older (table II). In the oldest men, low cholesterol represented a 14·2% attributable risk and an almost seven-fold (6·7) relative risk of categorical depression in comparison with men in the normal cholesterol group (4·14–5·16 mmol/L). Analysis with Fisher's exact test gave the same results as those in table III. Low cholesterol was associated with higher depressive symptom scores in men 70 years and older; this difference was statistically significant (p=0·007) in men 80 years and older (table III).

BDI score was inversely associated with plasma cholesterol and weight, and directly associated with age,

TABLE V—REGRESSION ANALYSIS OF BDI SCORE AND INDICES OF DEMOGRAPHIC AND HEALTH STATUS*

	B (SE B)	Beta	p
Age	0·0155 (0·0025)	0·2005	<0·0001
Health status	0·2213 (0·0461)	0·1595	<0·0001
Level of physical functioning	0·0843 (0·0232)	0·1212	0·0003
Low cholesterol	−0·1745 (0·0852)	−0·0654	0·0408
Constant	0·3677 (0·2655)	..	0·1664

*Current weight, number of chronic diseases, and number of medications were not entered into the model because the *F* value of their beta coefficients was not significant at p<0 05
B=unstandardised regression coefficient, beta=standardised regression coefficient

number of coexisting chronic disorders, number of medications, perceived level of physical functioning, and perceived health status (table IV). Objective measures of weight change and cholesterol change were not significantly associated with BDI. Individual BDI items reflecting loss of appetite (BDI item R) and loss of weight (BDI item S) were predictably highly correlated with total BDI score; the correlations with low cholesterol were similar to that between total BDI score and low cholesterol. These variables were not considered in further analysis.

To find out whether the association between depression and low cholesterol was secondary to increasing age or decline in health status (reported level of physical function, number of chronic conditions, number of medications, weight, and perceived health relative to others the same age), we entered these variables into a stepwise multiple regression model. Although it contributed less than age, health, and level of physical functioning, low cholesterol (<4·14 *vs* ⩾4·14 mmol/L) remained a significant independent predictor of depression (table V). Together, these variables accounted for 10% of the variance in depressive symptoms ($F=30{\cdot}54$, $p<0{\cdot}0001$).

Discussion

In this study, higher depressive symptom scores and the prevalence of categorically defined depression were associated with cholesterol values below 4·14 mmol/L in men 70 years and older. The association seemed to be age-dependent, and is compatible with previous studies, which found no positive association between depression and low cholesterol in young men.[13] The low prevalence of depression in the younger age groups may explain why we found no association between cholesterol and depression in younger men. Alternatively, lowering cholesterol acutely in clinical trials might have a similar but more profound biological effect than baseline low cholesterol, causing changes to be apparent in younger men.

TABLE IV—CORRELATIONS BETWEEN BDI SCORE AND HEALTH STATUS MEASURES

—	1	2	3	4	5	6	7	8	9	10	11	12
1. Log BDI score	1·00											
2. Total cholesterol	−0·10*	1·00										
3. % change in cholesterol	−0·07	<0·01	1·00									
4. Current weight	−0·10*	0·03	0 13*	1·00								
5. % change in weight	−0·04	−0·08	0·21†	0·17†	1·00							
6. Age	0 21†	−0·07	−0·12*	−0·36†	−0·16†	1 00						
7. Exercise ⩾3 times/wk	−0·04	0 02	−0·05	−0·08	−0·06	<0·01	1·00					
8. Number of diseases	0·09*	−0·05	0·03	−0·08	−0·01	0·24†	0 01	1·00				
9. Number of medications	0 14†	−0 10†	−0·02	−0·04	<0·01	0·27†	0·06	0 28†	1·00			
10. Physical functioning	0·20†	<0·01	−0·01	−0 03	−0·07	0·18†	−0·08	0·14†	0·17†	1·00		
11. Health	0 17†	−0·05	0·01	0·08	0·06	−0·10*	−0·04	0·06	0·11†	0·25†	1·00	
12. Appetite loss (BDI)	0·36†	−0 11†	−0·08	−0·16†	−0·07	0·18†	−0·05	0·09*	0·12†	0·09*	0 12†	1·00
13. Weight loss (BDI)	0·30†	−0·10*	−0·07	−0·06	0·05	0·06	−0·02	0·03	0·12†	0·12†	0 02	0·24†

*p<0 01, †p<0 001 (two-tailed)

The homogeneity of this cohort (90% were managers, administrators, or professionals) removes the confounding effect of socioeconomic status on depression. The low prevalence of categorical depression probably is a reflection of their high socioeconomic status. It is possible that depressed individuals were less likely to take part in the follow-up study or more likely to be excluded from this analysis because of incomplete depression inventory data. Such bias seems unlikely to explain the observed association between low cholesterol and depression, however, since there is no reason to suspect that depressed men with low cholesterol would be more likely to take part fully than depressed men with high cholesterol. Alcohol consumption and tobacco use were both not significantly associated with either depression score[8] or low-density-lipoprotein cholesterol[14] in this population, and were therefore not considered in this study.

Although it is difficult to determine causality in a cross-sectional study, several lines of evidence suggest that low cholesterol precedes depression. In primary prevention trials of cholesterol reduction there was an increase in violent deaths in treatment groups but not in controls.[3] Since these trials assessed several different pharmacological and dietary interventions, the higher mortality cannot readily be explained by drug toxicity or malnutrition. An effect of low cholesterol on mood is supported by studies of increased aggressive behaviour in non-human primates when serum cholesterol is decreased by a low-fat diet.[15] Depression cannot easily be measured in these animals, but it is closely linked with aggression in man and both types of behaviour are associated with low serotonin concentrations.

Engelberg[16] has suggested that low serum cholesterol in primary prevention trials led to a rise in suicides and violent deaths because brain serotonin decreased. In mice low membrane cholesterol decreases the number of serotonin receptors, whereas a rise in brain synaptosomal membrane cholesterol seems to increase the number of serotonin receptors. Because membrane cholesterol is in equilibrium with plasma cholesterol, low plasma cholesterol could contribute to low levels of serotonin, which in turn are associated with poor suppression of harmful behavioural impulses.[18]

There is an inverse association between plasma cholesterol concentrations and platelet serotonin uptake velocity,[19] which is a model of serotonin nerve terminal uptake.[20] Low cholesterol could increase serotonin reuptake velocity in the brain,[21] and thereby contribute to depression. In theory, older men would be especially susceptible to such an effect on serotonergic reuptake velocity because of the reductions in biogenic amine neurotransmitters associated with the ageing process.[22]

Depression can cause loss of appetite resulting in weight loss;[23] reduced calorie intake and weight loss tend to lower plasma cholesterol concentrations.[24] Depression may place older men at especial risk for malnutrition[25] because of social and economic factors[26] as well as appetite loss. This possibility is supported by the significant correlations between depressive symptom scores (including the items measuring reported weight and appetite loss), cholesterol concentrations, and percentage weight change between visits I and III. However, the association between cholesterol concentration and depressive symptoms was independent of reported or measured change in weight, which suggests that low cholesterol is not entirely the consequence of depression-related malnutrition.

It is possible that both depression and low cholesterol are indicators of poor health status. Severe hypocholesterolaemia is associated with a poor prognosis in hospital inpatients and has been considered a risk indicator rather than a risk factor.[27] However, neither perceived health status nor number of coexisting chronic illnesses or medications explained the significant independent association between low cholesterol and depressive symptoms in our study.

It is possible that improved measurement of the variables included in our analysis or inclusion of other relevant variables could remove the independent effect of low cholesterol on depressive symptoms. However, we think it is biologically plausible that depression contributed to the violent deaths reported after plasma cholesterol reduction[3] or in subjects with low baseline cholesterol concentrations.[5] Our findings suggest that measures of depressive illness should be included as outcome variables in future clinical trials of lipid-lowering medications or diet. Further clarification of the association between low cholesterol concentrations and depressive symptoms is essential, especially in the elderly, who may have higher "ideal" cholesterol concentrations than younger people.[28] If very low cholesterol concentrations increase depression, the recommendation that cholesterol lowering should be restricted to individuals at high risk of coronary heart disease would be strengthened.[29]

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Induction of lipid peroxidation of pulmonary surfactant by plasma of preterm babies

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Respiratory distress syndrome of the preterm baby is believed to be caused by a deficiency of pulmonary surfactant and leakage of plasma into the alveolar spaces. Since the two pathogenetic factors seem to be inter-related, we postulated that peroxidation of surfactant by plasma iron could be the linking mechanism.

We obtained cord blood samples from 22 preterm babies (mean gestational age 32·2 [SD 2·7] weeks) and 24 term babies (40·1 [1·6] weeks), and venous blood samples from 18 healthy adults. No adult had detectable non-protein-bound iron in the plasma, but 10/21 (48%) preterm babies and 6/24 (25%) term babies had detectable concentrations (rate difference 23% [95% CI −5 to 51%], $p=0·20$). Transferrin and haptoglobin concentrations were higher and free haemoglobin concentrations lower in adults than in babies ($p<0·005$). Only transferrin differed significantly between term and preterm babies. Plasma from all 18 adults and from 23 (96%) term babies inhibited iron-catalysed lipid peroxidation of pulmonary surfactant liposomes. By contrast, plasma from 11 (50%) preterm babies stimulated such peroxidation (difference in stimulation rate 46% [20–71%], $p<0·005$ for preterm *vs* term babies); the ability to stimulate peroxidation was related to the presence of non-protein-bound iron ($p<0·001$). Peroxidation decreased in the babies when apotransferrin was added to plasma and in all subjects when α-tocopherol was incorporated into the surfactant liposomes.

Lipid peroxidation of surfactant may contribute to the pathogenesis of respiratory distress syndrome. Possible therapeutic approaches are increasing babies' iron-binding capacity by plasma transfusions and increasing the antioxidant capacity of commercial surfactant.

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Introduction

Respiratory distress syndrome is an important cause of mortality and morbidity in preterm babies.[1] This disease of the immature lung is believed to be caused by surfactant deficiency and leakage of plasma across the alveolar wall.[2,3] The two processes seem to be linked; surfactant is inactivated by pulmonary oedema fluid. The underlying mechanism is not understood, but in-vitro and animal experiments point to interactions between plasma proteins and surfactant.[4-7] The findings that inorganic iron[4] and iron-loaded transferrin from rabbit lung lavage[8] can peroxidise and inactivate surfactant may be especially important for babies; their plasma transferrin is highly loaded with iron and non-protein-bound iron is often present in plasma.[9,10] Leakage of this plasma into the alveolar spaces could induce peroxidation of surfactant and contribute to the pathogenesis of respiratory distress syndrome. We therefore compared the ability of plasma from preterm and term babies and adults to inhibit or stimulate iron-catalysed peroxidation of surfactant in vitro. We also tested the effects of raising plasma concentrations of the preventive antioxidants apotransferrin (iron-binding protein) and haptoglobin (haemoglobin-binding protein) and incorporating the chain-breaking antioxidant α-tocopherol into surfactant.

Patients and methods

This study was approved by the scientific committee of the Department of Paediatrics and the ethics committee of the University Hospital of Leiden. Cord blood samples were obtained from 22 preterm babies (mean gestational age 32·2 [SD 2·7] weeks) and from 24 term babies (40·1 [1·6] weeks). Samples were taken by gentle venepuncture from the placenta within 15 min of its delivery. We excluded babies who were small or large for gestational age (birthweight <10th or >90th percentile) or who had clinical or haematological evidence of haemolytic disease. The Apgar score was normal (≥8 at 5 min) in all term babies and in 13

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