Depressive symptoms, social support, and lipid profile in healthy middle-aged women

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Depressive Symptoms, Social Support, and Lipid Profile in Healthy Middle-Aged Women

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Objective: Several studies have reported an inverse relationship between cholesterol levels and death from violent causes, including suicide. Because depression and depressive symptoms are associated with suicide and trauma, the relation between cholesterol and depressive symptoms is of interest. The objective of the present study was to examine this relationship in a group of healthy women. The second main objective of the study was to investigate the association between cholesterol and other psychosocial factors (social support, vital exhaustion, and stressful life-events), which are known to be related to depression. *Method:* The study group consisted of 300 healthy women (aged 31 to 65 years) who were representative of women living in the greater Stockholm area. Depressive symptoms were measured by a nine-item questionnaire derived from Pearlin. For the measurement of social support a modified version of the Interview Schedule for Social Interaction was used. Health behaviors were measured by means of standard questionnaires. Lipids were analyzed by enzymatic and immunoturbidometric methods. *Results:* Women with a low serum cholesterol, defined as the lowest tenth of the cholesterol distribution ($\leq$ 4.7 mmol/l), reported significantly more depressive symptoms. In addition, depressive symptoms showed a significant inverse linear association with high-density lipoprotein (HDL). In multivariate models, which adjusted for smoking, alcohol consumption, exercise habits, body-mass index, waist-hip ratio, menopausal status, age, and educational level, these associations remained significant. In addition, when analyzed in relation to other psychosocial factors, low cholesterol was found to be strongly associated with lack of social support. This association was not explained by depressive symptoms. *Conclusions:* Low cholesterol levels in middle-aged healthy Swedish women were associated with a higher prevalence of depressive symptoms and with lack of social support. These findings may constitute a possible mechanism for the association found between low cholesterol and increased mortality, particularly suicide.
Key words: depressive symptoms, social support, serum cholesterol, HDL, women.

BMI = body mass index; LDL = low-density lipoprotein; VLDL = very low-density lipoprotein; HDL = high-density lipoprotein; γ-GT = γ-glutamyltransferase; ECCLS = European committee for clinical laboratory standard; CHD = coronary heart disease; JMP = John's Macintosh program; μkat/1 = 1.67 u/l.

INTRODUCTION

In several clinical trials aimed at reducing cardiovascular disease incidence by lowering lipids, the

paradoxical finding of an increased mortality has been associated with low lipid levels. However, the results from drug and dietary intervention studies with respect to the effect on mortality from nonnatural causes are inconsistent. Some studies report an increase in deaths from unnatural causes in the cholesterol-lowering intervention groups (1, 2) whereas others fail to replicate this finding (3). In addition, two recent studies, the Air Force coronary atherosclerosis prevention study (AFCAPS) and the expanded clinical evaluation of lovastatin (EXCEL) trial, failed to demonstrate that lowering cholesterol affects mood (4). Moreover, potentially adverse drug reactions rather than cholesterol lowering per se are implicated (5, 6). However, as Steegmans (6) emphasized, it may be important to distinguish between naturally occurring low cholesterol levels and lowered cholesterol levels. The first reflects the lower end of the cholesterol distribution whereas the lowered cholesterol levels of patients with hypercholesterolemia are still in the upper part of the distribution. Moreover, the exposure to low cholesterol levels is longer in persons with naturally occurring low cholesterol levels, compared with those with

lowered cholesterol concentrations (6). Several non-experimental studies have reported an association between naturally occurring low cholesterol levels and consequent risk of violent death (7–9). Although conflicting results have also been reported (10, 11) the general picture seems to be more consistent. In the present study the focus is on naturally occurring low cholesterol levels. Because depression and depressive symptoms are closely related to suicide and trauma (12–14), the relation between cholesterol and depression has been an area of interest in this respect. Associations between low serum cholesterol concentrations and depressive symptoms have been found in elderly men (15). Others, however, have reported that this relation disappears after having controlled for general health status (16).

In addition, positive associations between cholesterol and social support have been reported (17). Given the relations between depressive symptoms and poor emotional and social support (18, 19) it could be speculated that there are pathways linking social support, depressive symptoms, and serum cholesterol. In the present study the relations between depressive symptoms, social support, and lipid profiles of healthy middle-aged women are examined.

METHODS

Subjects

The study group consisted of 300 healthy women aged between 30 and 65 years. The subjects were obtained from the census register of the greater Stockholm area. All subjects were free of symptoms of heart disease and without hospitalization for any illness during the past 5 years. None of the women were on lipid-lowering drugs. All women were examined for clinical signs or symptoms of chronic diseases and found to be healthy. They were compared on health-related factors to a random sample of 2500 women of the same age from the general population of Stockholm. No differences in educational level or health behaviors (smoking, exercise, and dietary habits) were found (20). The study group can thus be regarded as representative of healthy women aged 30 to 65 years in the normal population. They were contacted by a letter explaining the objectives and the focus of the study and inviting them to participate. Those who did not call the clinic spontaneously were contacted by phone from the research clinic. When a subject refused to participate a new subject was selected to obtain a final number of 300 healthy women. The nonresponse rate was 17%.

Procedure

Subjects arrived at the clinic between 8:00 and 10:00 AM. They were fasting from midnight. Anthropometric measures were obtained, after which subjects were resting for 30 minutes. Blood pressure was measured and blood samples for lipid and enzyme analyses were drawn, after which the subjects were served a standard breakfast. Questionnaires on psychosocial and life-style factors including depressive symptoms (21), social support (22), vital exhaustion (23), recent stressful life events (24), and alcohol consumption (25) were sent to the subjects 1 week before their visit to the research clinic. Subjects completed the questionnaires at home and brought them to the clinic. The interviewer reviewed the questionnaires with the subjects and completed missing answers. Internal nonresponse was less than 10%.

Depressive Symptoms

Depressive symptoms were measured by means of a 10-item questionnaire derived from Pearlin et al. (21). One question, about sexual activity, was excluded in an effort to avoid potentially threatening items. The present version thus included nine questions with yes and no alternatives. The yes answers were summed, with a low score indicating a low degree of depressive feelings. The scale includes questions on mood, sleeping-problems, appetite, energy, interest in normal activities, crying, and feelings about the future. Some examples of questions are: Do you feel bored or do you have little interest in doing things? Do you feel downhearted or blue? Do you feel hopeless about the future? The questionnaire has been used in previous Swedish studies (26, 27). It was translated to Swedish and back translated into English to check the validity of the translation, which resulted in no real differences. The scale had an adequate internal consistency (Cronbach's $\alpha = 0.85$) and was significantly correlated ($r = .71$) with the Beck Depression Inventory (28) in a subsample of the study-population ($N = 30$).

Social Support

For the measurement of social support, a condensed version of the Interview Schedule for Social Interaction was used (19, 22). This qualitative measure of social support has been modified for use in population studies, and tested for predictive validity both in relation to coronary heart disease (29) and in relation to depression (30). The instrument yields two scales, one describing deep emotional relationships or "attachment" and the other describing the more peripheral contacts of social networks or "social integration." Both consist of six-item continuous scales with ranges in scores from 0 to 6 and 6 to 36, respectively.

Lipid and Enzyme Variables

Blood samples for analyses of lipids and liver enzymes were drawn, while in supine position, from the right arm into serum separate tubes, which were centrifuged for 10 minutes at 3000g (revolutions per minute). Four milliliters of plasma were obtained and stored at −70°C. Samples were stored up to a month and sent in batches to the processing laboratory (CALAB) once a month. The liver enzyme S-γ-glutamyltransferase (γ-GT) was determined by means of an enzyme colorimetric method standardized according to ECCLS (European Committee for Clinical Laboratory Standard). The reagents for the γ-GT assay were from Randox Laboratories Ltd (Crumlin, UK) and the assay automated on a Technicon Dax-96 Multichannel Analyzer. This liver enzyme was measured to validate the measurement of alcohol consumption by questionnaire.

Total cholesterol was determined with CHOD-PAP and s-triglycerides with GDB-PAP enzymatic methods. High-density lipoproteins were determined based on the isolation of LDL and VLDL from serum by precipitation. The cholesterol content of the supernatant, ie, HDL cholesterol, was measured enzymatically. All measurements were performed in the same laboratory (CALAB), using automated Multichannel Analyser (31).

Demographic and Life Style Factors

Age, educational level, smoking behavior, physical exercise, menopausal status, and alcohol consumption were assessed by means of questionnaires and interview procedures. Educational level was classified as follows: I = elementary only, II = high school graduate, and III = college/university. Smoking was operationalized as a dichotomized variable with 0 = never smoked or previous smoker (more than 1 year before examination) and 1 = current smokers. Furthermore, within the current smoker group the number of daily cigarettes smoked was classified as follows: I = 1–4/day, II = 5–10/day, III = 11–20/day, and IV = more than 20/day. Physical activity was assessed according to the World Health Organization criteria and graded into I = reading, watching TV or other sedentary leisure activities, II = walking, cycling or other forms of physical activity, III = exercises to keep fit, heavy gardening, etc., for at least 4 hours a week, and IV = hard training or participation in competitive sports, several times a week. In the analyses, physical activity in leisure time was dichotomized into sedentary (I) and nonsedentary (II-IV). Alcohol consumption was measured in the context of dietary habits by means of the Willett food frequency questionnaire (25). The amount of alcohol ingested was calculated according to Myrhed (32); one bottle of beer (33 centiliter [cl]) was assumed to contain 12 g of absolute alcohol, one bottle of wine (75 cl) 60 g, and one bottle of spirits (75 cl) 250 g (one drink = 5 cl = 17 g absolute alcohol). High alcohol consumption was defined as ≥ 22 mg/day (33). Alcohol consumption was also validated using fasting serum levels of the alcohol specific enzyme γ-GT. Menopausal status was operationalized into the following categories: I = premenopausal, II = postmenopausal without use of hormone-replacement, and III = postmenopausal with use of hormone replacement. Weight, height, and waist/hip ratio were measured by the research nurse during examination. All measurements of circumference were taken to the nearest 0.5 cm. Waist and hip were measured as the most narrow part around the waist line (waist) and widest part between the umbilicus and thighs (hip). Body mass index (BMI) was calculated as weight (kg)/height (m^2) and waist-hip ratio as circumference of waist (cm)/hip (cm).

Statistical Analyses

We used John's Macintosh Program (JMP) Statistics for the Apple Macintosh Version 3.1 for all analyses (34). For all variables, distributions, mean, and SD were calculated. Tests of normality were used. The variables triglycerides and depressive symptoms were skewed and therefore log transformed in the regression analyses. Lipids and psychosocial factors were treated as continuous variables with an exception of cholesterol. Cholesterol was also investigated as a dichotomized variable, applying a cutoff as close as possible to the lowest tenth of the distribution (4.7 mmol/l or below). Regression analyses and analyses of variance (Wilcoxon's test) were used to examine the univariate associations between depressive symptoms, psychosocial factors, and lipids.

Multivariate linear regression was used to control for possible confounders. All statistical tests were two-tailed.

RESULTS

Table 1 shows the sample characteristics. Mean cholesterol concentrations in different age groups were: 5.21 for the group aged 31 to 44 years ($N = 19$); 5.70 for the group aged 45 to 54 years ($N = 97$); and 6.37 for the group aged 55 to 65 years ($N = 184$). In Table 2 the univariate associations between lipids and depressive symptoms are shown. The negative linear association between cholesterol and depressive symptoms was not significant. A test of nonlinear trend showed the quadratic and cubic trends to be nonsignificant ($F = 2.92$; $p = .09$; $F = 2.57$; $p = .11$, respectively). The association between depressive symptoms and cholesterol is displayed in Figure 1. In accordance with previous studies (6, 15, 16) the association was subsequently investigated with cholesterol treated as a dichotomized variable, comparing women in the lowest decile of the cholesterol distribution with the remaining women. Women with serum cholesterol concentrations of 4.7 mmol/l or below had nearly twice as many depressive symptoms as women with higher cholesterol levels (Table 3). In addition, HDL, treated as a continuous variable, was significantly and negatively associated with depressive symptoms. Triglyceride levels were not associated with depressive symptoms.

The aim of the multivariate analyses was to adjust for potential confounders of the associations between lipids and depressive symptoms. Depressive symptoms were not significantly related to educational level, waist/hip ratio, or smoking (p values all above .40). In addition, there was no significant association between menopausal status and depressive symptoms ($p = .29$). These variables therefore were not included in the initial multivariate model. The results of the multivariate linear regressions are shown in Table 4. In the multivariate regression analyses adjustments were made for all covariates that had (borderline) significant univariate associations with depressive symptoms ($p<.20$). These were sedentary lifestyle ($F = 2.74$; $p = .09$), alcohol consumption ($F = 4.09$; $p = .04$), BMI ($F = 1.67$; $p = .19$), and age ($F = 3.95$; $p = .05$). Alcohol consumption and age were both inversely related to depressive symptoms. Sedentary life style and BMI were positively associated with depressive symptoms. After adjusting for these factors, the associations between depressive symptoms and both HDL and low cholesterol were still significant (Table 4). The anal-

TABLE 1.   Sample Characteristics (N = 300)

Variable	N (%)	Mean (SD)	Range (min, max)
Current smokers	98 (33%)		
Smoking frequency (cigarettes/day)			
1–4	15 (15%)		
5–10	23 (24%)		
11–20	51 (52%)		
>20	9 (9%)		
Sedentary lifestyle	55 (18%)		
Menopausal status			
Premenopausal	89 (30%)		
Postmenopausal without hormone replacement	153 (51%)		
Postmenopausal with hormone replacement	58 (19%)		
Educational level			
Elementary	159 (53%)		
High school graduate	60 (20%)		
College/university	81 (27%)		
Low cholesterol (≤4.7 mmol/l)	26 (9%)		
Depressive symptoms (N)		2.02 (2.23)	0, 9
Social support		21.92 (5.29)	6, 36
Alcohol consumption (g/day)		7.83 (8.16)	0.03, 44.76
γ-GT (μkat/l)		0.49 (0.71)	0.13, 10.09
Age (yr)		56.4 (7.1)	31, 65
Body mass index (kilo/m²)		25.6 (4.8)	17.6, 48.6
Waist-hip ratio (cm)		0.80 (0.09)	0.53, 1.44
Total cholesterol (mmol/l)		6.06 (1.07)	3.0, 10.60
Triglycerides (mmol/l)		1.06 (0.55)	0.30, 4.20
High-density lipoprotein (mmol/l)		1.76 (0.45)	0.83, 3.34

TABLE 2.   Results of Univariate Regression Analyses of Depressive Symptoms on Each Lipid Variable (N = 300)

Variable (mmol/l)	β-Coefficient	SE	p Value
Cholesterol	−0.06	0.04	0.16
Triglycerides	0.07	0.09	0.43
High-density lipoprotein	−0.31	0.09	0.01

yses were repeated while adjusting for all covariates (including educational level, current smoking, menopausal status, and waist/hip ratio) without any effect on the results.

To investigate the validity of the measurement of alcohol consumption, the relationship with the alcohol specific liver enzyme γ-GT was examined. High alcohol consumers (N = 20) consuming ≥ 22 mg/ day, corresponding to almost two bottles of beer, had a mean γ-GT concentration of 1.04 μkat/l compared with 0.42 μkat/L in the group consuming less than 22 g of alcohol per day (p = .0002). A γ-GT concentration above 0.80 μkat/l is considered to be slightly deviating (reference and cutoff limits in use at CALAB Medical Laboratories).

The univariate association between γ-GT concentrations and depressive symptoms was nonsignificant (χ^2=3.63, p = .16) but in the same direction as the association with alcohol consumption. The mul-

tivariate regression analyses in which alcohol consumption was a covariate were repeated with the γ-GT concentrations as a proxy measure for alcohol. Results in terms of significances and directions of the associations remained the same.

Of the other psychosocial variables, vital exhaustion and low social support were also significantly associated with low serum cholesterol level (χ^2 = 3.93, p = .04; χ^2 = 6.54, p = .01, respectively). Stressful life events were borderline significantly associated with depressive symptoms (χ^2 = 3.18, p = .07). To investigate the psychosocial factor that was most strongly related to low serum cholesterol, logistic regression analyses were performed yielding lack of social support as the strongest predictor of low cholesterol. Thirteen per cent of the variance was explained by the previously used confounders together. An additional 10% of the variance was explained when lack of social support was brought into the model, compared with 5% of the variance explained by depressive symptoms and only 3% by vital exhaustion (recent stressful life events became nonsignificant in multivariate analyses).

Inasmuch as the correlation between social support and depressive symptoms was only 0.21, these two factors were then entered in a logistic regression model together. They both remained significant pre-
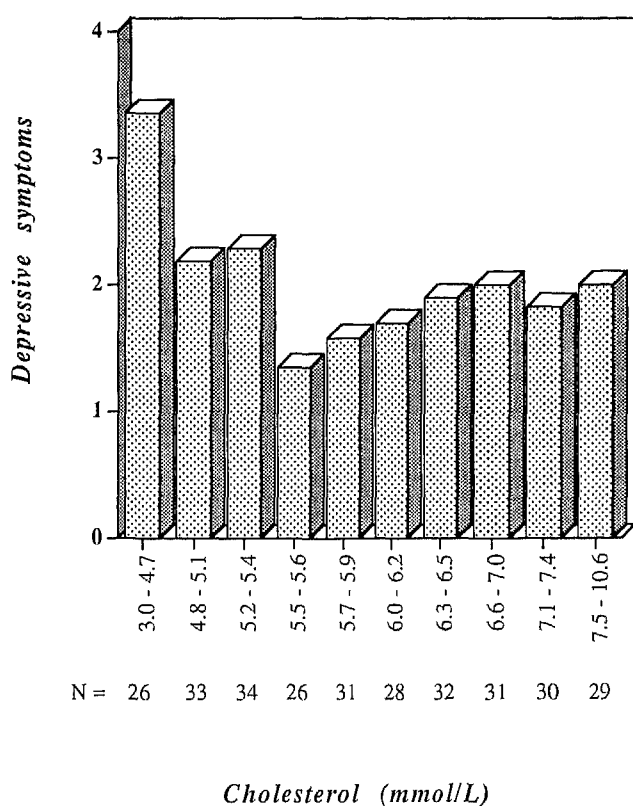
Fig. 1. Mean depressive symptoms in deciles of the cholesterol distribution.

dictors, suggesting that social support and depressive symptoms are independently associated with serum cholesterol. Vital exhaustion and depressive symptoms were not entered in the same regression model because of their high intercorrelation ($r = .61$).

DISCUSSION

As hypothesized, a significant association was found between low serum cholesterol and depressive symptoms. Women with serum cholesterol values in the lowest tenth of the distribution had nearly twice as many depressive symptoms as those with higher concentrations, even after adjustment for age,

alcohol, sedentary lifestyle, BMI, waist/hip ratio, educational level, smoking, and menopausal status. The relation between depressive symptoms and cholesterol has been reported to be age-dependent, and to be mainly present in older age groups ($\geq$70 years) (15, 16). However, in the present study we observed this association in a relatively young group of women (mean age 56.4 years).

The linear association between cholesterol and depressive symptoms not being significant is in accordance with other observations. For instance Rosengren et al. (17) found the associations between serum cholesterol and social support, which is highly related to depressive symptoms (18, 19), to be nonlinear (17). Based on previous studies, cholesterol was subsequently investigated as a dichotomized variable (6, 15, 16). The lowest decile of the cholesterol distribution was selected as the low cholesterol group, a cutoff point that has been used in previous studies (17). In the present study population the mean serum cholesterol was 6.1 mmol/l and the low cholesterol group had cholesterol concentrations of 4.7 mmol/l or less. Although from an international point of view this may not be very low, it represents low cholesterol among Swedish women. Because the association between cholesterol and depressive symptoms is nonlinear, the selection of the cutoff point becomes an important issue. Shifting the cutoff point downward, eg, to 4.5 mmol/l, defining 5% of the population as the low cholesterol group, did not change the results. The same holds for shifting the cutoff point upward to 5.1 mmol/l defining 20% of the population as the low cholesterol group. Consequently, it is unlikely that the selection of the cutoff point for the definition of the low cholesterol group was critical for the results.

Depressive symptoms were also significantly and inversely associated with serum HDL concentrations. However, unlike cholesterol, this association had a significant linear component. Furthermore, it remained significant after adjustment for possible confounders. Triglyceride levels were not related to depressive symptoms. To our knowledge, the only study examining lipid variables, other than total serum cholesterol in relation to depressive symp-

TABLE 3. Comparison of Depressive Symptoms in the Low Cholesterol Group ($\leq$4.7 mmol/l) vs the Group with Cholesterol Concentrations >4.7 mmol/l ($N = 300$)

Variable (mmol/l)	N	Mean	Age Adjusted Mean	SE	p
Cholesterol $\leq$4.7	26	3.36	3.21	0.44	0.01
Cholesterol >4.7	274	1.89	1.90	0.13	

TABLE 4. Multiple Linear Regression Analyses of Depressive Symptoms on Each Lipid Variable Controlling for Age, Alcohol, Exercise, and Body Mass Index ($N = 300$)

Variable (mmol/l)	β-Coefficient	SE	p value
Cholesterol (dichotomized)	−0.44	0.16	0.01
High-density lipoprotein	−0.26	0.11	0.02

toms, was conducted in middle-aged men by Steegmans (6). In this study no association was observed between triglyceride levels and depression, which is in accordance with our results. Other lipid parameters were not reported.

In contrast to most previous work, depressive symptoms were not related to smoking, educational level, nor waist/hip ratio. This could have been a power problem inasmuch as the (nonsignificant) associations found were in the expected direction. The significant inverse relationship between depressive symptoms scores and alcohol consumption is more difficult to explain. Our suggestion would be that alcohol is consumed mainly in connection with social events in this healthy population. Alcohol consumption and social support are positively related ($F = 6.49; p = .01$). Because depressive symptom scores are inversely associated with scores on social integration, it is plausible that Swedish women scoring higher on depressive symptoms consume less alcohol. In addition, high alcohol consumers (7%) had a relatively moderate consumption that is comparable with the findings of the Nurses Health Study (33).

Measuring alcohol consumption with subjective methods is difficult. Underreporting is believed to bias results. To validate the measurement of alcohol consumption, associations with the alcohol-specific liver enzyme γ-GT were examined. Determination of this enzyme is considered to be a valuable and sensitive test of even a moderate alcohol intake (36). The γ-GT level can also be raised as a result of liver and pancreatic disease and use of certain medications. In the present study it is unlikely that the γ-GT levels were influenced by the latter two causes, because all subjects were found to be healthy and without medication. The two measures of alcohol consumption were related in the expected way and gave the same results when used in the multivariate analyses. Therefore, we conclude the validity of the alcohol consumption measurement to be satisfactory.

Previous research has suggested that depression may play a role in the development and progression of coronary heart disease (CHD) (37–39). Although there is a paucity of studies on the role of psychosocial risk factors for CHD in women, there is some evidence that depression may be associated with a greater risk for cardiac events in women (40). Furthermore, low HDL is an important risk factor for coronary heart disease in women (41, 42). In our study a strong negative association between depressive symptoms and HDL was found. It is possible that, at least in women, low HDL levels constitute a

biological mechanism that may explain at least part of the link between depression and CHD.

In the analyses presented above no adjustments were made for self-rated general health. The study-population consisted of healthy women who had not been hospitalized within the last 5 years and were below age 65 years. Studies that included adjustments for self-rated general health were mainly in subjects aged 70 years and older (15, 16). However, as information on self-reported health during the last 5 years was available in the present study, the multivariate analyses were repeated including this variable. This did not affect any of the associations found.

Inasmuch as this is a cross-sectional study, it is difficult to draw any firm conclusions on the direction of the relations. In the regression analyses depressive symptoms were chosen as the dependent variable, suggesting that the low lipid levels cause the depressive symptoms. However, all multivariate regression analyses also were made with the lipid variables as dependent variables and depressive symptoms as predictor, yielding similar significant associations.

The associations between depressive symptoms and lipids may benefit from being considered in a broader psychosocial perspective. The focus of the present study was on depressive symptoms but several additional psychosocial variables were measured, including social support and vital exhaustion (22–24). Social support was the strongest predictor of low serum cholesterol and this finding was independent of depressive symptoms.

These associations may benefit further from being interpreted in a biopsychosocial perspective. A low serum cholesterol level may be seen as an indicator of depletion of energy sources. Cholesterol is used by the body as a substrate for cell growth, in hormone syntheses, and in other crucial biological processes. Lack of ability to mobilize energy from this substrate may be psychologically expressed as vital exhaustion and depressive symptoms, which may be provoked by low social support and stressful life events. A more detailed biological mechanism explaining the reported association between depressive symptoms and low serum cholesterol has been suggested by Engelberg (43) and reformulated by Salter (44). A reduction in dietary cholesterol intake may reflect a reduction in overall fat intake, which results in a decrease in serum fatty acids. Because fatty acids and tryptophan (the precursor of serotonin) compete for a binding site on serum albumin, more tryptophan will be bound. As the enzyme catalyzing the synthesis of serotonin (tryptophan hydroxylase) is

unsaturated with tryptophan, a decrease in free serum tryptophan will lead to a corresponding decrease in brain serotonin synthesis. A decrease in brain serotonin levels could induce depression and vital exhaustion (43, 44). Several parts of the postulated serotonin pathway have been examined by Steegmans (6). Although cross-sectional in nature, their findings support the view that the serotonin hypothesis is involved in the reported association between chronically low cholesterol levels, depression, and violent death (6).

On the other hand there is the alternative hypothesis that depression produces low cholesterol. Law et al. (4) stress in an overview of the literature that the evidence supports the hypothesis that depression lowers cholesterol concentration. To support this the authors mention the observations that anorexia is a common feature of depression (45) and that treating depression leads to an increase in serum cholesterol concentration (46).

In summary, low cholesterol levels in middle-aged healthy Swedish women were predicted by depressive symptoms, but more strongly so by lack of social support. Smoking, alcohol consumption, sedentary life style, obesity, abdominal fat, menopause, and age did not explain the associations. Although caution is needed about the direction of causality, the findings may suggest that cholesterol constitutes a vital source of energy and that low levels have adverse psychosocial correlates such as depression and lack of social support. Additional clarification of the associations between depressive symptoms, social support, and both low serum cholesterol and other lipid parameters is necessary. Longitudinal studies are needed to reveal the mechanism that explains the reported associations.

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