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**National Centre for Suicide Research and Prevention of Mental Ill-Health**

# **LITERATURE REVIEW: RELATIONSHIP BETWEEN CHOLESTEROL AND SUICIDE**

**Possible explanations and directions for future research**

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Literature Review: relationship  
between cholesterol and suicide

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## SUMMARY

### *Purpose:*

To review literature on the relationship between cholesterol levels and suicide and find possible explanations for this relationship.

### *Data Sources:*

Search of the Cochrane Database of Abstracts of Reviews of Effectiveness and The Cochrane Controlled Trials Register, supplemented by searches of the MEDLINE database, EMBASE, Science Citation Index, PsycInfo and Current Contents databases on relevant articles. Bibliographies of identified articles were also searched.

### *Study selection:*

Observational (including cohort, case-control and cross-sectional studies) and experimental articles, randomized controlled trials, meta-analyses. Representative articles were selected which had not been reviewed in detail elsewhere, namely diet and cholesterol, suicidality and serum lipids and finally depression, diet and cholesterol.

### *Data presentation:*

Studies are grouped according to type and graded according to criteria potentially meeting the CRD quality criteria.

### *Background:*

Several studies suggest that the reduction of total cholesterol in blood by lipid-lowering agents is accompanied by a decrease in the incidence of coronary heart disease, but not in total mortality. Likewise, epidemiological studies show that low total cholesterol concentrations appear to be associated with an increased risk of death from suicide and injuries. Furthermore, the risk of suicidality in psychiatric inpatients increases with low plasma cholesterol. Several studies also document a low cholesterol concentration after attempted suicide (parasuicide) rising the question of low cholesterol concentration as a potential biological marker of suicide risk. However, there is some evidence in favor of a concomitant rather than a causal effect for interpreting the mentioned associations. A number of conflicting results have also been reported. Controversy arises because several trials and observational studies have failed to replicate a link between low or reduced cholesterol levels and increased suicidality.

### *Hypotheses:*

It is speculated that a connection between low cholesterol level and lower activity of central serotonergic structures responsible for the inhibition of impulsive behavior may exist. Other authors argued that interleukins might be mediators in depression and suicide and be capable to decrease

cholesterol. Furthermore, epidemiological studies suggest that decreased n-3 fatty acid consumption correlates with increasing rates of depression. Increased suicide and death due to injuries reported in some cholesterol-lowering trials may also be related to altered concentrations of polyunsaturated fatty acids rather than cholesterol. Lowered cholesterol levels were also suggested to be a consequence of depression related malnutrition.

*Conclusion:*

Following a presentation of epidemiological data, the review intends to assess data originating from experimental trials complemented by a description of hypotheses. The review is targeted to present a comprehensive overview of the current scientific literature on the relationship between cholesterol and suicide. Further studies assessing the validity of the hypotheses are indicated to determine the nature of the observed relationship.

## INTRODUCTION

Several studies suggest that the reduction of total cholesterol in blood by lipid-lowering agents is accompanied by a decrease in the incidence of coronary heart disease, but not in total mortality. Likewise, epidemiological studies show that low total cholesterol concentrations appear to be associated with an increased risk of death from suicide and injuries. Furthermore, the risk of suicidality in psychiatric inpatients increases with low plasma cholesterol. Several studies also document a low cholesterol concentration after attempted suicide (parasuicide) rising the question of low cholesterol concentration as a potential biological marker of suicide risk. However, there is some evidence in favour of a concomitant rather than a causal effect for interpreting the mentioned associations. A number of conflicting results have also been reported. Controversy arises because several trials and observational studies have failed to replicate a link between low or reduced cholesterol levels and increased suicidality. In this study the medical literature on the relationship between cholesterol and suicide has been systematically reviewed and evaluated.

## METHODS

The Cochrane Database of Abstracts of Reviews of Effectiveness and The Cochrane Controlled Trials Register have been searched supplemented by searches of the MEDLINE, EMBASE, Science Citation Index, Psych Info and Current Contents databases for articles. Bibliographies from identified articles were also searched. Representative articles dealing with different explanations for the observed relationship, which had not been reviewed in detail elsewhere, have been added. Articles met the inclusion criteria if they presented original research. Studies are evaluated and graded according to criteria potentially meeting the CRD quality criteria.



## RESULTS

### **Meta-analysis of randomized clinical trials**

Meta-analysis of randomized clinical trials reported conflicting results, sometimes demonstrating an increased non-illness mortality (suicide, accidents) in cholesterol lowering trials and other studies not replicating these findings (Table 1).

A meta-analysis of six randomized clinical trials of cholesterol lowering interventions showed that although mortality from coronary heart disease was reduced, mortality due to suicide and violence increased (Muldoon, et al., 1990). This association was significant only when these data were analyzed collectively and not when the studies were considered separately. Smith and Pekkanen (1992) divided primary prevention studies into those that used diet alone and those that used medication. They concluded that the relative risk for death from injury among men was increased by drug therapy but not by diet. Cummings and Psaty (1994) reported a summary relative risk (RR) for death from injury among treated men compared with controls to be 1.42 in primary prevention trials. In primary and secondary prevention trials in men and women the RR reduced to 1.24. Muldoon, et al. (1993) reported an increase in non-illness mortality with cholesterol lowering treatments for primary and secondary prevention combined, however not in trials of exclusive secondary prevention. Law, et al. (1994) found no significant excess of the mortality from accidents and suicide in cholesterol lowering trials in primary and secondary prevention, whereas Ravnskov found an excess, with an odds ratio of 1.55.

The clinical trials assessing the risk of suicide and other non-illness related mortality have been criticized from a number of perspectives (Shaper & Cook, 1990; Law, et al., 1994). There has been much debate due to variations in samples studied and the analysis of mortality cases and statistical methods used. Furthermore, relevant detailed psychopathology data has not been described (Wysowski & Gross, 1990; Davey Smith & Phillips, 1992; Cummings & Psaty, 1994; Lewis & Tikkanen, 1994). The studies also recorded few deaths from non-illness mortality causes, which may not be sensitive enough to any cause specific hazard.

Table 1. Meta-analyses of randomized trials: deaths from non-illness mortality in persons receiving cholesterol-lowering treatment compared with controls.

Reference	Intervention	N of trials	Sex	Deaths from non-illness Mortality (n)	Odds Ratio (non-illness mortality)
Muldon et al. 1990	Primary prevention	6	M	105	1.76 §
Davey Smith and Pekkanen 1992	Primary prevention, dietary trials	3	M	70	1.20
	Primary prevention, drug trials	5	M	64	1.75*
Cummings and Psaty 1994	Primary prevention	6	M	115	1.42
	Secondary prevention	8	M/F	38	1.06
	Primary and secondary prevention	14	M/F	179	1.24
Muldon et al. 1993	Primary and secondary prevention	8	M	150	1.55§
	Secondary prevention	2	M	31	1.07
Law et al. 1994	Primary and secondary prevention	28	M/F	184	1.17
Ravnskov 1992	Primary and secondary prevention	12	M/F	...	1.55*

... no data  
\* p < 0.05  
§ p < 0.01

The duration of the trials was short and deaths occurred on average only two or three years from the start of treatment. Furthermore it has been suggested that the result of increased mortality from non cardio-vascular-causes might not be associated with cholesterol reduction but result from the effects of the drugs used for cholesterol lowering. The odds ratio (OR) for the dietary intervention was 1.2 compared to 1.75 for drug intervention (Smith & Pekkanen, 1992). Moreover, this relationship could result from a disease causing low cholesterol levels or from some common antecedent causing both low cholesterol levels and the disease itself (Harris, et al., 1992).

Wysowski et al. (1990) mainly raised the issues of compliance and the analysis of mortality cases. They reported that the study subjects with non-illness mortality often had a history of alcohol abuse or emotional problems or had been so non-compliant with the study medication that they achieved little to no cholesterol lowering. Therefore, the authors concluded that little evidence remained to support the hypothesis that cholesterol level-lowering drugs were causally related to these deaths when dropouts, alcohol intoxication and psychiatric conditions were excluded. No statistically significant excess mortality can be demonstrated when one of the categories (suicides, accidents and

homicides) is removed from the sum of "traumatic" deaths (La Rosa, 1995). Furthermore, no dose-response relationship was found between cholesterol lowering and excess mortality in primary prevention trials.

Since these first reports of an unexplained rise in suicides and other violent deaths observed in the mentioned clinical trials, a number of cohort studies have been conducted to investigate a potential association between low cholesterol and heightened rates of death from suicide.

### **Cohort studies**

Epidemiological/ Observational cohort studies have been inconsistent in reporting an association between low baseline cholesterol levels and increased risk of death due to suicide in the general population (Table 2). There have been five positive observational cohort studies and one meta-analysis of 19 epidemiological studies reporting that the relative risk of suicide in subjects, mainly men, with low cholesterol levels was greater than for those with higher cholesterol levels (Lindberg, et al., 1992; Neaton, et al., 1992; Zureik, et al., 1996; Schuit, 1993; Partonen, et al., 1999; Jacobs, et al., 1992).

In a study in Värmland, Sweden, the relative risk of suicide was 4.2 for men in the lowest cholesterol quartile compared to those in the highest quartile during the first 7 years of follow-up. The relative risk decreased, however, in the second 7 years of follow up and was not significant any more. No difference in risk was found in women (Lindberg, et al., 1992). It has to be born in mind that the mean of the cholesterol levels in the lowest quartile was 208 mg/dl in men, generally in the range of physiologically normal levels. Therefore, the observed relationship is unlikely to be due to absolute levels.

Among men screened for the Multiple Risk Factor Intervention Trial, those with cholesterol levels less than 160 mg/dl had a greater risk of suicide than men with levels of 160 mg/dl or higher during the 12 years of follow-up (Neaton, et al., 1992). Among the categories of violent death (accidents, suicides and homicides) only death by suicide was significantly associated with cholesterol levels. Neaton reported a J-shaped relationship between serum cholesterol and all-cause mortality, with the inflection point of the J at 140 mg/dl, below which crude death rates rose with decreasing serum cholesterol values and above which crude death rates rose with increasing serum cholesterol values. Muldoon, et al. (1993) reported a U-shaped relationship.

The Paris prospective study found an association between suicide and declining, as well as low serum cholesterol concentrations in men (Zureik, et al., 1996). The studied population had at least 3 measurements of serum cholesterol levels and an average of 17 years follow-up after the

last examination. Partonen et al. (1999) reported that serum total cholesterol was associated with low mood and subsequently a heightened risk of hospital treatment due to major depressive disorder and of death from suicide in male subjects. An inverse association in men and women between serum cholesterol and death from injuries and suicide was also reported by a not peer-reviewed study by Schuit et al. (1993). The association persisted over 28 years, but seemed stronger in the first 15 years. A meta-analysis that pooled the results of 19 prospective epidemiologic studies (N almost 650,000) further revealed a higher risk of trauma death in both women and men with low cholesterol (Jacobs, et al., 1992).

There have also been negative observational cohort studies (Pekkanen, et al., 1989; Iribarren, et al., 1995 and 1995a; Chen, et al., 1991; Smith, et al., 1992; Vartiainen, et al., 1994; Tanskanen, et al., 2000) that could not replicate these findings. The Honolulu Heart Program observed a positive association between serum cholesterol level and risk of suicide (Iribarren, et al., 1995). The relative risk (RR) of suicide associated with an increment of 38 mg/dl in serum cholesterol was 1.46. In a cohort of 5941 Japanese American men, nonillness mortality (deaths caused by trauma and suicide) could not be related to either total cholesterol change within a six year period between two exams nor with the average of total cholesterol levels at exam 1 or 2 (Iribarren, et al., 1995a).

**Table 2. Cohort studies: association of suicide and cholesterol levels.**

Reference	Suicides n	Sample size	Sex	Low cholesterol mg/dl+	High cholesterol mg/dl+	Covariates	Follow -up (years)	RR
Lindberg et al. 1992	146	26,693	M	Lowest quartile (mean: 208)	Highest quartile (mean: 305)	Age, prevalent cancer, time of suicide	0-7 7-14	* 4.2 * ns
Lindberg et al. 1992	44	27,692	F	Lowest quartile (mean: 205)	Highest quartile (mean: 293)	Age, prevalent cancer, time of suicide	0-7	* ns
Neaton et al. 1992	540	350,977	M	< 160	> 160	Age, smoking, blood pressure, race, season, socioeconomic status	12	* 1.6 †
Zureik et al. 1996	32	6,396	M	< 184	184-239	Age, mean corporeal volume <sup>¶</sup> , smoking	17 17	* 3.2 § * 2.2 †°
Partonen et al. 1999	111	29,133	M	< 195	> 273	Age, BMI, intake of carbohydrate, alcohol, education, marriage, smoking, self reported depression/ anxiety	...	* 2.3 †

**Table 2. Continuation.**

Reference	Suicides n	Sample size	Sex	Low cholesterol mg/dl+	High cholesterol mg/dl+	Covariates	Follow -up (years)	RR
Iribarren et al. 1995	24	7,309	M	Increment of Cholesterol: 38		Age, alcohol, blood pressure blood glucose level	23	** 1.5†
Tanskanen et al. 2000	130 <sup>oo</sup>	37,635	M/F	< 193	> 309	Sex, age, marital status, education, smoking, alcohol, coffee, physical activity, BMI, minor psychiatric symptoms, CHD, psychotropic medication general health	15 1	**2.4 † z

... no data

ns... not significant

\* Relative Risk of Suicide in the Low-Cholesterol Group compared with the High-Cholesterol Group

S P < 0.01

† P < 0.05

‡ P < 0.001

+ Relative Risk of Suicide in the High-Cholesterol Group compared with the Low-Cholesterol Group

† To convert mg/dl to mmol/l, multiply with 0.02586

¶ Proxy for alcohol use

oo RR of Suicide in the group with >5 mg/dl annual cholesterol decrease compared to group with <5 mg/dl

o violent suicides

z risk for violent suicide

Pekkanen, et al. (1989) followed up 1,580 men drawn from two geographically defined areas in rural Finland over 25-years; there was a significant association between higher initial cholesterol levels and 25-year mortality from accidents or violence in one cohort and no significant association in the other cohort. Tanskanen, et al. (2000) reported that serum total cholesterol was positively related to the risk of violent suicide in a sample of 37,635 adults taking part in five independent population surveys. Among subjects whose serum total cholesterol concentration was in the highest category, the adjusted relative risk was more than twofold compared with the lowest category. No association between serum total cholesterol concentration and the risk of non-violent suicide was found.

Chen, et al. (1991) reported the 8.3 years follow-up of 9,021 urban Chinese men and women. The authors noted a marginally significant inverse association between serum cholesterol concentration and "non-medical" causes of death (including accidents, suicide, external injury and other causes). However, this association disappeared after adjustment for confounding variables. Smith, et al. (1990) reported no association between low cholesterol and mortality from violent death or suicide over 20 years of follow-up in 17,718 London civil servants. Vartiainen, et al. (1994) found no association between mortality from accidents, suicides and other violent deaths and low cholesterol levels in men and women.

Cohort/observational studies are likely to be biased by confounding factors and it is possible that a confounding covariate of low serum cholesterol is actually responsible for the epidemiologic association between cholesterol and suicide. Low or decreased cholesterol concentrations might be a consequence of depression or of depression-related anorexia or due to another psychiatric condition like personality/conduct disorders (Muldoon, et al., 1993). Furthermore, they might be due to the incidence of cancer or other underlying illnesses, pharmacologic treatment for psychiatric conditions and alcohol or substance abuse (Muldoon, et al., 1993). Other potential confounding factors may be low occupational status and low social support. Most of the epidemiological studies have been criticized for not having controlled for these confounding effects.

Another reason for the inconsistency of the observational studies might be that the number of suicides was too small. It has to be born in mind that completed suicide is a crude marker for suicidal intention. Severely suicidal subjects are not detected when the study involves only deaths from suicide.

### **Suicidality in psychiatric inpatients**

As opposed to investigate the association of cholesterol and completed suicide in the general population, studies of suicidality in psychiatric inpatients offer another approach. They involve subjects with attempted suicide, suicidal ideation and thoughts and in addition select a sample of higher risk of suicide. A link between cholesterol and suicidal behavior would arise the possibility of developing a biological marker that would facilitate assessment of suicide risk. Several studies of adult psychiatric inpatients have been finding an association between low cholesterol levels and suicidality (Table 3 and 4). Studies in adolescent psychiatric inpatients (Apter, et al., 1999) and children (Glueck, et al., 1994), some studies in adults (Ryan & Murray, 1995; Seneviratne, et al., 1999; Maes, et al., 1997) and one retrospective analysis (Fritze, et al., 1992) could not replicate these findings (Table 3 and 4).

Patients who had attempted suicide had significantly lower serum cholesterol than nonsuicidal patients (Modai, et al., 1994). Serum cholesterol levels were evaluated routinely 24 to 48 hours after admission. When analysis was carried out within different diagnostic categories, this association was shown in unipolar and bipolar depressed patients who attempted suicide compared to the non-suicidal patients. However, there was no significant difference in the schizophrenic patients. The relationship of low cholesterol levels and increased risk of suicidality existed even if the cholesterol levels of suicidal patients (202 mg/dl) were in the normal range.

Serum cholesterol levels were also shown to be significantly lower in patients with mood disorders and patients with personality or neurotic disorders (Kunugi, et al., 1997). Cholesterol concentrations in suicide attempters were found to be significantly lower compared with both psychiatric and normal controls, when sex, age, psychiatric diagnosis and physical conditions were adjusted for. By controlling for physical conditions like serum total protein and red blood cell count, the study was able to exclude that blood loss due to injuries and loss of appetite were major contributing factors to lower cholesterol. Total cholesterol levels showed highly significant linear correlation with age in all subjects and were significantly lower in men than in women. Serum total cholesterol concentration was measured within 24 hours after admission.



**Table 3. Trials in psychiatric inpatients: comparison of mean cholesterol level in suicidal and control group.**

Reference	N	Study Group	Control group	Mean cholesterol, Study group, mg/dl	Mean cholesterol, Control group, mg/dl+ +
Modai et al. 1994	584	Patients hospitalized for attempted suicide	Non-suicidal psychiatric and medical controls	202	217 §
Kunugi et al. 1997	212	Patients hospitalized for attempted suicide	Nonsuicidal psychiatric inpatients	155	184 ‡
		Patients hospitalized for attempted suicide	Patients with accidental injuries	145	166 †
Gallerani et al. 1995	662	Patients hospitalized for parasuicide	Non-suicidal controls	191	209 ‡
Alvarez et al. 1999	34	Patients hospitalized for attempted violent suicide	Healthy controls	147	226 ‡
Takei et al 1994	193	Patients hospitalized for attempted suicide inpatients	Nonsuicidal psychiatric	161	178 §
Ryan et al, 1995	502	Patients with parasuicide	Healthy volunteers	220	208 ‡

+ + To convert mg/dl to mmol/l, multiply with 0.02586,

† P< 0.05

§ P< 0.01

‡ P< 0.001

Gallerani, et al. (1995) included a further cholesterol measurement besides the one collected within 24 hours after admission. Each attempted suicide (parasuicide) subject was matched with a control for age, sex, diabetes, arterial hypertension, heterozygote  $\beta$  thalassaemia, abuse of drugs and alcoholism. Cholesterol levels in the attempted suicide (parasuicide) subjects were significantly lower than those in the control subjects (Table 3). Furthermore, the levels of attempted suicide (parasuicide) subjects at admission for attempted suicide (parasuicide) were also significantly lower compared to the second cholesterol determination (taken at admission for another illness). When split up in diagnostic groups, a significant difference between attempted suicide (parasuicide) subjects and controls was found only for patients with neurotic disorder. The lower cholesterol concentrations were not found to be confounded due to haemodilution secondary to severe trauma or injury, due to the acute stress or due to dietary differences.

One study found that serum cholesterol and platelet 5-HT (serotonin) levels in violent suicide attempters were significantly lower than in the controls (Alvarez, et al., 1999) (Table 3). However, there was no significant correlation between these two variables. Interference from antidepressant drugs were excluded and other sources of variation like age-related decline, gender differences, diurnal and seasonal variations are very unlikely to have biased the results. Another study also found no significant correlation between cholesterol levels and 5-hydroxyindoleacetic acid (5-HIAA), the serotonin metabolite, in suicide attempters (Engström, et al., 1995). The study could find cholesterol levels in the patients with suicide attempts in the lower range, however, could not compare these results due to a absence of a matched healthy control group.

Takei, et al. (1994) also found significant lower cholesterol levels in 105 psychiatric patients admitted to hospital due to an attempted suicide, compared to 88 psychiatric controls (Takei, et al., 1994). This study was not peer-reviewed. 84 of the psychiatric inpatients with attempted suicide had significantly lower cholesterol levels compared to 53 patients admitted to the emergency unit. Cholesterol levels were adjusted for diagnosis, sex, age, illness, red blood cell counts, total protein and triglyceride levels. Thus, account was taken of the effects of treatment and nutritional status.

In a study of adolescent inpatients cholesterol measurements and psychiatric examinations were carried out between days 10 and 14 of inpatient stay (Apter, et al., 1999). This study reported significant higher cholesterol levels in the suicidal group compared to the control group, however cholesterol levels in the suicidal group were inversely correlated with the level of suicidal behavior. Timing of the measurement differs in this study compared to the other psychiatric hospital studies (Modai, et al., 1994; Golier, et al., 1995). Stress and anxiety, the lack of substance abuse and the predominantly female sample might have contributed to the observed elevated cholesterol levels in patients with suicidal tendencies. The authors suggested that longitudinal studies measuring cholesterol at different times in the same subjects and studies assessing perceived stress together with intervening neurologic measures would provide direction for future studies.

A study by Ryan and Murray (1995), not peer-reviewed, also found significantly higher cholesterol levels in patients who had attempted suicide (parasuicide) than in healthy controls. A recently published study from a developing country did not show an association between low serum cholesterol concentrations and attempted suicide (parasuicide) either (Seneviratne, et al., 1999). All subjects admitted to the hospital after attempted suicide (parasuicide) were matched for age, sex, presence

of diabetes and arterial hypertension, substance abuse, body mass index and socioeconomic status with controls. Within 24 hours of admission for attempted suicide (parasuicide) venous blood samples from parasuicides for cholesterol estimation were collected.

The relative risk of acute suicidality has been found to decrease in accordance with increasing total cholesterol levels irrespective of age, gender and nutritional status (i.g. body mass index) (Papassotiropoulos, et al., 1999) (Table 4). Subjects with cholesterol levels above 225 mg/dl had a significantly reduced risk of suicidality compared to those with cholesterol levels below 166 mg/dl. Despite the slightly higher BMI, suicidal patients with affective disorder had significantly lower cholesterol levels than age-and sex-matched nonsuicidal patients with affective disorder. Total cholesterol concentrations in patients with a history of violent suicide attempts were lower than in patients with nonviolent suicide attempts or in those with no history of previous suicide attempt. The study comprised subjects without medication which could interfere with the serotonergic system and alcohol/drug abuse.

Low cholesterol levels have also been shown to be associated with increasing degrees of suicidality ranging from ideation to attempts in depressed patients (Sullivan, et al., 1994) (Table 4). This association, however, did not quite remain statistically significant, when the effects of potential confounders were taken into account. The degree of suicidality was not significantly related to gender, depression severity, body mass index, triglyceride level, significant appetite or weight loss and alcohol abstinence in the prior week. Age was clearly the major potential confounder.

Similarly, low cholesterol has been shown to be associated with medically serious suicide attempts in male psychiatric inpatients (Golier, et al., 1995) (Table 4). However, they were not significantly more likely to have made a suicide attempt of any seriousness. The association of serious suicide attempts and low cholesterol was independent of depression and alcohol use though the study group certainly suffered from substantial psychopathology. There was no association between cholesterol level and attempted suicide or medically serious suicide attempts in women. This study did not control for medical illness or medication which could affect cholesterol levels. Furthermore, the results are limited on one single measurement of serum cholesterol made at admission to a psychiatric hospital.

In a study of children hospitalized for psychiatric disorders, both low cholesterol levels and highest suicidal tendencies (including suicidal ideation and attempts) were found in those with adjustment and depressive disorders compared to other diagnoses and control subjects

(Glueck, et al., 1994). However, no difference in cholesterol levels was noted between suicidal and nonsuicidal patients. Maes, et al. (1997) failed to show an association of suicidal attempts with low cholesterol. However mean high density lipoprotein (HDL)-cholesterol levels were significantly lower in men, not in women, with major depression who had at some time made a serious suicidal attempt than those who had no history of suicide attempts. In a retrospective analysis of 1,088 patients suffering from affective psychoses no relation between serum cholesterol and suicidal behavior could be found (Fritze, et al., 1992).

In most of the studies (except Apter, et al., 1999; Gallerani, et al., 1995), cholesterol was measured only once on admission or within 48 hours. Measurement on admission might confound the results as psychotropic medications which could be given to psychiatric patients or medications taken in suicide attempts or the medical treatment could all effect lipid profile. Furthermore, most studies in psychiatric samples have suffered at least one or more deficiencies. These include the absence of optimal control for one or more confounding variables (Golier, et al., 1995; Modai et al., 1994) and optimal definition of the respective groups with measurements of relevant psychopathologic variables. In addition some studies had small samples sizes, particularly within distinct diagnostic groups (Sullivan, et al., 1998; Golier, et al., 1995; Maes, et al., 1997). No data on the intervals between the attempt and the evaluation was presented in these studies, which might be important due to the potential effect of physical damage on cholesterol levels.

#### **Animal experiments**

Even though a close description of animal experiments is beyond the scope of this paper the main results should be summarized. Kaplan, et al. (1991 and 1994) and Muldoon, et al. (1992) studied the effects of dietary fat and serum cholesterol in cynomolgus monkeys. These studies showed significantly more severe aggression among animals consuming a low-fat diet, and the prolactin response after stimulation of fenfluramine was reduced in low-fat consuming monkeys. This indicates a reduced serotonin activity in the central nervous system. These studies have been reviewed in detail elsewhere (Kaplan, et al., 1997) and the reader is directed to this paper for its comprehensive overview.

**Table 4. Relative risk for suicide attempts in patients in relation to their cholesterol levels.**

Study (Reference)	N	Sex	Age (years)	Cholesterol level mg/dl		Type of patient	Suicide measure	RR for attempted suicide
				Low	High			
Papassotiropoulos, 1999	45	M/F	18-74	< 166	> 225	Acutely suicidal psychiatric inpatients	Acute suicidality or attempt	** 0.15 #
Sullivan, et al. 1994	90	M/F	> 18	<160	>240	Outpatients with depression	Suicide ideation or attempt	* 5.14 ‡
Golier, et al. 1995	307	M	18-59	Low quartile	Rest	Psychiatric inpatients	Medially serious suicide attempt $\alpha$	* 2.22 §
Golier, et al. 1995	343	F	18-59	Low quartile	Rest	Psychiatric inpatients	Medially serious suicide attempt $\alpha$	* NS

\* Relative Risk of Suicide Attempt in the Low-Cholesterol Group compared with the High-Cholesterol Group

\*\* Relative Risk of Suicide Attempt in the High-Cholesterol Group compared with the Low-Cholesterol Group

# RR for acute suicidality

$\alpha$  defined as rated 3 or greater in the 5 - point Medical Lethality Rating Scale

NS...not significant

§ P < 0.01

‡ P < 0.001

### **Serum lipid levels, depression and suicidality**

Several studies suggest that depression and suicidality might be accompanied by a certain serum lipid profile. Besides the lowered cholesterol levels, the triglyceride levels seem to be elevated, while HDL-cholesterol appears to be decreased.

#### *Triglyceride levels, depression and suicidality*

High triglyceride levels have been observed in psychiatric inpatient children with suicide attempts (Glueck, et al., 1994), however, obesity, alcohol and substance abuse and cigarette smoking may have contributed to the hypertriglyceridemia. High triglyceride values may be a determinant of symptoms of depression as the reduction of triglyceride value was positively correlated with the reduction in the Beck Depression Index (Glueck, et al., 1993).

Improvement in the symptoms of depression accompanying treatment of severe hypertriglyceridemia has been reported by Glueck, et al. (1993). Treatment of high triglyceride levels has also been reported to improve scores on dementia screening tests in elderly patients with cerebrovascular disease (Rogers, 1989).

It has been shown that baseline high triglycerid values were significantly associated with depression in women but not in men (Standberg, et al., 1993).

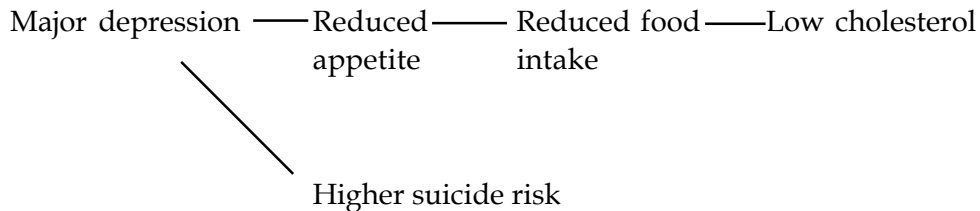
In cross-sectional analyses of 4240 black and white subjects between 23 and 35 years Markovitz, et al. (1997) found among white men only, that increases in hostility during a 5-year follow-up were related to increases in triglycerides. Changes in hostility, however, were unrelated to changes in cholesterol levels. The authors did not find any relationships between hostility, anger suppression, depression and anxiety and low plasma lipid levels.

#### *High density lipoprotein (HDL)-cholesterol, depression and suicidality*

Conflicting results have been reported on HDL-cholesterol levels and suicidality. Mean HDL-C levels were significantly lower in men with major depression who had at some time made a serious suicide attempt than those who had no history of suicide attempts (Maes, et al., 1997). Tanskanen, et al. (2000) reported an increased risk of violent suicide with low HDL-cholesterol levels. There was no significant difference in women. Furthermore, low baseline HDL-cholesterol levels were significantly correlated with depression in women (Strandberg, et al., 1993). However, in an epidemiological study mortality from accidents and suicides, combined, increased steadily with increasing HDL-cholesterol levels in men and women taken part in a cardiovascular disease study in three counties in Norway (Stenvold, 1992).

# HYPOTHESES – INCLUDING BIOLOGICAL AND GENETIC EXPLANATIONS

## 1. Hypothesis: depression, diet and cholesterol



### *Diet and cholesterol*

Several studies suggest that low cholesterol concentration could result from depression-related anorexia and that depression would consequently enhance the risk of parasuicide (Muldoon, 1990; Lindberg, 1992; Neaton, et al., 1992; Morgan, et al., 1993; Weissenburger, et al., 1986; Verddery, et al., 1991). Therefore, those who were most suicidal might have had the poorest nutrition and increased cholesterol levels might be found at a later determination than within 24 hours after admission to the hospital (Greenberg, 1995). The relationship of dietary factors with suicide mortality or attempted suicide remains largely unexamined, and is complicated by the existence of other extradietary differences between individuals consuming low- and high-fat diets.

The effect of poor nutrition on cholesterol is complex. Fasting has been found to increase total serum cholesterol and LDL cholesterol (Savendahl, et al., 1999), but lower HDL-levels. Those suffering from anorexia nervosa sometimes have increased serum cholesterol (Nestel, 1974). Keys, et al. (1950) conclude that although acute starvation might tend to elevate serum cholesterol, a period of semistarvation results in a modest decrease in serum cholesterol. Furthermore, low cholesterol levels occur in malnutrition, especially in elderly patients.

Serum cholesterol is not only affected by caloric intake but also by the amount of cholesterol and types and amounts of fatty acids in the diet (Keys, et al., 1957; Grande, et al., 1965). Intake of saturated fatty acids appears to be the most important dietary determinant of total cholesterol and low density lipoprotein cholesterol (Hegsted, et al., 1965; McNamara, et al., 1987; Keys, et al., 1957; La Rosa, et al., 1990; Katan, et al., 1994) with a wide range of individual responses (Cox, et al., 1995; Grundy, et al., 1988). The influence of dietary cholesterol itself is variable and is enhanced when cholesterol is consumed with saturated fatty acids. Replacement of saturated fat with carbohydrate reduces total and low

density lipoprotein (LDL) cholesterol with only a minor effect on HDL cholesterol and triglycerides and leads to a decrease in body weight (Turley, et al., 1998). Reduction in cholesterol and increase in high polyunsaturated fat has been found to cause significant decreases in plasma cholesterol, LDL and HDL cholesterol (Schaefer, et al., 1981). Men appear to have larger responses of total and low-density lipoprotein cholesterol to saturated fat than women do (Weggemans, et al., 1999).

Alcohol increases triglyceride levels and also raises HDL levels, but it has little effect on LDL metabolism. However, total cholesterol levels have been found to be low in patients with alcohol dependence syndrome.

#### *Depression and diet and nutritional status*

According to a recently published epidemiological study in 40,086 African American and White participants, the primary predictor for clinical depression, suicide ideation and suicidal attempts diagnosed according to the DSM-IV was relative body weight (Carpenter, et al., 2000). Among women, increased BMI was associated with both major depression and suicide ideation. Among men, lower BMI was associated with major depression, suicide attempts, and suicide ideation. A retrospective analysis of a sample of 1,088 patients suffering from affective psychoses also revealed an association between death from suicide and lower body weight (Fritze, et al., 1992). Maes, et al. (1991) could not detect nutritional disorders indicating protein loss (e.g. muscle mass) due to malnutrition in major depression. Fleck (1989) suggested that the reduction in albumin and thus total serum protein, which can be found in major depression, may not be assumed to reflect primary malnutrition when there is evidence for an acute phase response in depression.

According to 3-day food records 22 females experiencing moderate to severe depression consumed a diet that provided 100 % of the Recommended Dietary Allowances (RDA) (Christensen, et al., 1994). The diet of the 7 males, however, was deficient in energy and 4 of 16 nutrients examined. The variation in the dietary intake appeared to be due to a decrease in food intake rather than a deficient diet. Partonen, et al. (1999), however, found no difference in dietary intakes of energy, fat and carbohydrates in those men reporting depression who had lower mean serum total cholesterol.

A significant increase in the desire for "sweets" (carbohydrate - fat-rich foods) was observed during a depressive episode, compared to periods when patients recalled feeling well (retrospective data) (Fernström, et al., 1987). Carbohydrate intake (both sweet and starch) in the second half of the day was elevated during winter depression (Krauchi, et al., 1990).



Depressed subjects seem to consume more carbohydrates and less protein than nondepressed (Christensen, et al., 1996).

#### *Dietary and nutritional assessment*

It is necessary to include dietary variables in this kind of research in which mild-to-moderate malnutrition may affect serum cholesterol levels. Several studies already controlled for nutritional status as a contributing factor to lower cholesterol including parameters like serum total protein, BMI, triglyceride levels and significant weight and appetite loss (Kunugi, 1997; Takei, et al., 1994; Papassotiropoulos, et al., 1999; Sullivan, et al., 1994). However, these parameters might not be sufficient to measure pre-admission malnutrition. A validated dietary frequency questionnaire combined with a 24-hour dietary recall would give more detailed information about the actually consumed amount of fat and energy. Furthermore, the Keys score, an indirect estimate of plasma cholesterol levels based on dietary fat intake, could be derived from dietary data (Anderson, et al., 1979; Markovitz, et al., 1997; Keys, et al., 1965; Clarke, et al., 1997; Hegsted, 1986).

#### *Depression and cholesterol*

The association between low serum cholesterol concentration and suicide may be due to a common link with depression. Depression and depressive symptoms are closely related to suicide and trauma (Angst, et al., 1999; Åsgård, 1990; Liu, et al., 1996). Decreased appetite and weight loss or illness causing weight loss in depressed subjects may underlie the relationship between low cholesterol and depressive symptoms. In a cross sectional study of male and female employees in Sweden, total cholesterol and LDL cholesterol values were inversely correlated with the frequency of low mood in men expressed in a questionnaire (Lindberg, et al., 1994). Serum triglyceride concentrations did not differ. In women, however, the serum triglyceride value, but not the total cholesterol or LDL cholesterol, was lower in those who reported low mood, depression and anxiety during the past six months.

In a study in middle-aged women in Sweden those with low serum cholesterol, defined as the lowest tenth of the cholesterol distribution, reported significantly more depressive symptoms (Horsten, et al., 1997). Furthermore, depressive symptoms showed a significant inverse linear association with high-density lipoprotein. Serum cholesterol levels have also been found to be higher in patients with panic disorder compared to patients with depression (Bajwa, et al., 1992). In healthy young adult women, low lipid and lipoprotein concentrations were inversely associated with trait measures of depression and anxiety (Suarez, 1999). According to Neuroticism, Extraversion, Openness-Personality Inventory (NEO-PI) depression was inversely associated with total cholesterol, triglycerides, and the ratio of total cholesterol to high-density lipoprotein

cholesterol but not with high-density lipoprotein cholesterol. Univariate analyses indicated that women with low total cholesterol concentrations (<160 mg/dl), relative to those with moderate to high cholesterol levels, were more likely to have higher scores on the NEO depression subscale and STPI anxiety subscale. These findings are independent of age, body mass index, physical activity, and other factors known to influence lipid concentrations.

When paired with 1,595 self-referred supermarket screenees by age and sex, 203 patients with affective disorders (depression, bipolar disorder, and schizoaffective disorder) had much lower plasma total cholesterol, low-density lipoprotein cholesterol, and high-density lipoprotein cholesterol, and higher triglyceride concentrations (Glueck, et al., 1994a). A study in 13 702 human dock visitors also revealed that the lowest cholesterol group (< 158 mg/dl) was more likely to be in a depressive state than the other groups except for the middle (196-206 mg/dl) and the highest (<238 mg/dl) (Terao, et al., 2000).

Morgan, et al. (1993) found that depression was three times more common in male Californians aged 70-89 years with a low plasma cholesterol concentration (< 160 mg/dl) compared to those with higher cholesterol concentration. The association between cholesterol concentration and depressive symptoms was independent of reported or measured change in weight. Depressive symptoms were, however, significantly more common in both men and women who had a cholesterol concentration in the lowest quintile compared with all others. For both male and female French volunteers aged 60-69 years those in the low quintile had more than twice the risk of depressive symptomatology of those in other quintiles (Dealberto, et al., 1993).

In 100 patients with major depressive disorder total cholesterol levels were significantly lower than the levels in 100 healthy controls (Olusi & Fido, 1996). In a Finnish study, Strandberg, et al. (1993) however, failed to show such a relationship in either women or men aged 75-85 years. Brown, et al. (1994) could also not relate low cholesterol levels to severe depressive symptoms in 3939 elderly people. Cholesterol levels were not significantly associated with major depression or hostility in a study of 3,490 men aged 31-45 years (Freedman, et al., 1995). Furthermore, a double-blind randomized trial of pharmacological cholesterol reduction did not find alteration in mood (Wardle, et al., 1996).

## 2. Hypothesis: polyunsaturated fatty acids (PFUA), depression and suicidality

Low n:3 PUFAs ——— Low serotonin ——— higher suicide risk

Dietary long-chain polyunsaturated fatty acids (PUFAs), critical to both nervous system and cardiovascular function, may be an important confounding factor in the observations that lowering serum cholesterol may increase the risk of depression, suicide or violence (Hibbeln and Salem, 1995; Hibbeln, et al., 1997). The authors hypothesise that inadequate n-3 PUFAs (especially 22:6n-3) in the nervous system may increase vulnerability to depression. Virkunen, et al. (1987) noted an increase in long-chain n-6 polyunsaturates and a decrease of long-chain n-3 polyunsaturates in the serum of violent impulsive offenders, when comparing with diet-matched control subjects.

In major depression, there seems to be a deficiency of n-3 PUFAs and a compensatory increase in monounsaturated fatty acids (MUFAs) and C22:5n-6 in phospholipids (Maes, et al., 1999). The alterations of the fatty acids in depression appear to be related to the inflammatory response in that illness. A significantly higher C20:4n6/C20:5n3 ratio in both serum cholesteryl esters and phospholipids, and an increased total n6:n3 ratio in cholesteryl esters of patients with major depression compared to normal controls has been reported (Maes, et al., 1996). It has been suggested that these observations may be related to increased production of pro-inflammatory cytokines and eicosanoids (Maes, et al., 1996; Smith, 1991). According to these hypotheses, major depression is accompanied by a certain pattern of serum lipids including the mentioned increased total n6:n3 ratio in cholesteryl esters, but also high triglyceride levels and low HDL-C levels. These TG and HDL pattern in depressed patients have also been reported by Maes, et al. (1997) and Glueck, et al. (1994) (see hypothesis 5).

Furthermore, polyunsaturated fatty acids have been found to predict cerebrospinal fluid (CSF) 5-hydroxyindolacetic acid (5-HIAA) and CSF homovanillic acid (HVA), the serotonin and the dopamine metabolite respectively. Cholesterol, however, was unrelated to either neurotransmitter metabolite in healthy subjects and early and late-onset alcoholics (Hibbeln, et al., 1998, 1998a). On the basis that n-3 polyunsaturates have been inversely related with impulsive behavior and depression in observational and intervention studies, the authors suggest to conduct dietary studies to determine if essential fatty acid supplementation can influence serotonin and dopamine metabolism in the central nervous system and modify impulsive behaviors related to these neurotransmitters.

### 3. Hypothesis: Cholesterol and serotonin

Low cholesterol — reduced serotonin uptake — depression — Higher  
in brain cells suicide  
risk

Brain serotonin has been suggested as a possible factor in the association of serum cholesterol with non-illness mortality, because both suicidal behavior and impulsive aggression are related to low levels of serotonergic activity (Muldoon, et al., 1993). One explanation of the relationship of cholesterol and suicide was proposed by Engelberg (1992). The author suggested that lower cholesterol levels decrease membrane lipid viscosity of the brain cells resulting in a reduced number of serotonin receptors and therefore lowering uptake into the cells. Several studies found an association between decreased levels of the serotonin metabolite 5-hydroxyindoleacetic acid (5-HIAA) in cerebrospinal fluid and violent suicide attempters (Träskman, et al., 1981; Åsberg, et al., 1976; Träskman-Bendz, et al., 1992), more medically damaging suicide attempts and planned suicide attempts (Mann, et al., 1996).

Furthermore, researchers showed that men with naturally occurring low total cholesterol levels (< 175 mg/dl) exhibit lower plasma serotonin concentration (Steegmans, et al., 1996). Terao, et al. (1997) found that serum cholesterol levels positively correlated with serotonergic receptor function in healthy subjects. Changes of dietary cholesterol have been found to alter the fluidity of cellular membranes, affecting the activity of ion channels and neurotransmitter receptor (Preston-Mason, et al., 1991). Delva, et al. (1996), however, did not reveal that cholesterol-lowering drugs reduced brain serotonergic activity in patients with hypercholesterolemia.

Another explanation was proposed by Barradas, et al., (1992) who suggested that a decrease in serum cholesterol causes an increase in platelet 5-HT content and a simultaneous decrease in plasma serotonin. A further hypothesis, suggested by Salter, is that a reduction in dietary cholesterol is likely to go hand in hand with a reduction in overall dietary fat intake, resulting in a decrease in serum fatty acids (Salter, 1992). Fatty acids compete with tryptophan on serum albumin binding sites. Thus, a reduction in fatty acids leads to a decrease in free tryptophan and a respective decrease in 5-HT synthesis. All three of these hypotheses associate cholesterol with the 5-HT system.

Kaplan et al. (1994) has speculated that an inverse association between antagonistic, impulsive behavior and cholesterol may represent a negative feedback mechanism. The threat of dietary deprivation would result in appropriate changes in behavior (Kaplan, et al., 1994). Scarcity in calories

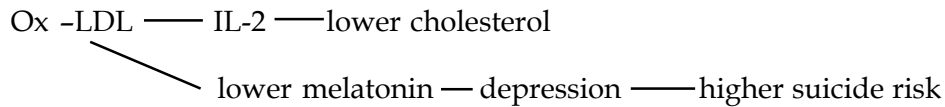
derived from animal sources, would reduce plasma cholesterol and (perhaps by way of low central serotonergic activity) trigger impulsive, risk-taking behavior such as hunting or competitive behavior.

Engelberg's theory is based on findings in the mouse brain, in which an increased membrane lipid viscosity is followed by an increased specific binding of serotonin (Heron, et al., 1980). Several animal studies are in favor of the relationship of cholesterol and serotonin. However, Fernström et al. (1996) could not replicate these findings. Despite the enormous range of cholesterol levels in Mongolian gerbils fed different diets, tryptophan hydroxylation rate and serotonin and 5-hydroxyindoleacetic acid concentrations in the cerebral cortex, hypothalamus and brainstem did not differ significantly among the diet groups.

One association found in genetic research should be mentioned briefly in this context. A polymorphism of the serotonin transporter gene (17q11.1-17q12) has been described, a deletion/insertion polymorphism (5-HTTLPR) in the promoter region of the gene (two alleles: "l" and "s"). Evidence suggests that the 5-HTTLPR polymorphism is associated with bipolar depression (Bellivier, et al., 1998). Collier, et al. (1996) reported an association between the "s" allele and both unipolar and bipolar depression, whereas Kunugi, et al. (1997a) found no association for either unipolar or bipolar depression. The association could also not be replicated by Frisch, et al. (1999) and Ohara (1998). Interestingly, in a group of elderly athletes an unexpected association between serum cholesterol levels and the HTTLPR insertion/deletion polymorphism of the promoter region of the serotonin transporter gene was observed (Comings, et al., 1999).

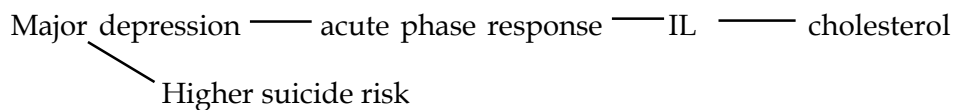
The hypotheses of an association between cholesterol and serotonin have been criticized, because endogenous synthesis appears to be the main source of cholesterol in the brain and uptake of LDL by the brain from the plasma is low in laboratory animals (Dietschy, 1984; Spady, et al., 1983). Severs claimed that since all serum cholesterol levels were around normal range, and since regulatory mechanisms of cellular cholesterol balance membrane cholesterol, the simple explanation of a cholesterol-5-HT relationship is most probably insufficient (Severs, 1992). Furthermore, Alvarez, et al. (1999) and Engström, et al. (1995) did not succeed to demonstrate a relationship between cholesterol and serotonin (5-HT) in suicidal subjects. Hibbeln, et al. (2000) could also not relate CSF 5-HIAA to cholesterol levels in alcoholics, violent groups and healthy subjects.

#### 4a. Hypothesis: Interleukin – 2 and suicide



Another hypothesis proposed by Penttinen is based on the idea of Interleukin-2 (IL-2) being a common mediator for the development of depression and suicide and also for cardio-vascular diseases (Penttinen, 1995). Oxidized LDL is supposed to activate a T-cell mediated immune reaction resulting in the production of IL-2. IL-2 causes a decrease of serum cholesterol, especially HDL and an increase in triglycerids. Frostegard, et al. (1992) found that oxidized LDL may activate T-cells in atherosclerotic lesions. Furthermore, IL-2 leads to depression and suicidal tendencies by suppressing melatonin, the hormone secreted by the pineal gland. On the other hand, interleukin-2 enhances the atherosclerotic process. Thus, the author suggests that suicide and myocardial infarction are competing causes of death.

#### 4b. Hypothesis: Major depression, acute phase response, cholesterol and suicide



Hypothesis 4b presents a slight variation of hypothesis 4a and does not anticipate that all relations are causal, but probably more concomitant. The relation between low cholesterol levels and depression/suicide attempt in depressed subjects may be due to the immune/inflammatory response in major depression. The systematic immune activation involves an increased concentration of plasma soluble interleukin-2 receptor. Cytokines, like IL 2, have been found to lower plasma levels of cholesterol.

Several studies suggest an immune-inflammatory response in major depression, which is accompanied by significant changes in cell mediated and humoral immunity (Table 5). This acute phase response in major depression appears to be further characterized by increased plasma levels of positive and decreased levels of negative acute phase proteins and increased prostaglandin secretion (Sluzewska, et al., 1996). Furthermore, decreased availability of plasma tryptophan and lower serum Zn and Fe have been reported in major depression (Song, et al., 1998; Maes, et al., 1997a) (Table 5).

Increased concentration of plasma soluble interleukin-2 receptor, reflecting an activation of T-lymphocytes, has been observed in major

depression (Maes, et al., 1995) and in psychiatric patients after a suicide attempt (Nassberger, et al., 1993). However, Haack, et al. (1999) could not replicate these findings after taking all confounding factors into account like treatment with clozapine, lithium or benzodiazepines, age, body mass index, gender, smoking habits, ongoing or recent infectious diseases.

IL-2, used in cancer treatment, has resulted in a decrease of LDL, cholesterol and HDL and an increase in TG (Wilson, et al., 1989; Rosenzweig, et al., 1990; Lissoni, et al., 1991; Swaminathan, et al., 1993). Elevated plasma levels of cytokines have been demonstrated in inflammatory, malignant, infectious diseases, traumatic injury and even minor illness (Beisel, et al., 1981; Alvarez, et al., 1986; Lees, et al., 1972; Kateloot, et al., 1992). These disease states are often associated with abnormal lipid metabolism like hypertriglyceridaemia and reductions in plasma cholesterol levels. Khosla, et al. (1991) observed a severe hypertriglyceridaemia, decrease in HDL-cholesterol levels and increase in LDL-cholesterol levels in patients with enteric fever at the peak of fever. Plasma triglycerides were reported to be increased in AIDS, while plasma cholesterol, high density lipoprotein (HDL) cholesterol and low density lipoprotein (LDL) cholesterol were decreased (Grunfeld, et al., 1992). Lower levels of plasma total cholesterol and HDL-cholesterol have been observed during severe infection, but also during minor illness (ill with cold, flu, fever, or vomiting) (Jacobs, et al., 1997).

Cytokines may affect plasma levels of cholesterol and lipoproteins by modulating lipolytic enzyme activities (Jonasson, et al., 1990; Torti, et al., 1985; Feingold, et al., 1989) and gene expression of apoproteins (Sammalkorpi, et al., 1988; Schectman, et al., 1992). Stopeck, et al. (1993) suggest that cytokine-induced hypocholesterolemia may be related to TNF and/or IL-1 stimulation of hepatic LDL receptor gene expression and function.

**Table 5. Serum parameters suggesting an inflammatory response in major depression.**

Serum parameter increased	Serum parameter decreased	Reference
Interleukin (IL) 1b	Total serum protein	Maes M et al. 1995
IL 6	Albumin	Maes et al 1995 a
IL 8	Transferrin	Maes M et al. 1997 a
Soluble IL 6	Gamma globulin	Maes M et al. 1997 b
Soluble IL 6 receptor (R)	Zn	Sluzewska A et al. 1996
Soluble IL 2 R	Fe	Song C et al. 1998
IL 1 R antagonist	Tryptophan	Maes M et al. 1997
Leukocytes, neutrophiles	Tryptophan/CAA ratio	Herbert TB et al. 1993
Transferrin receptor	HDL-C	
Alpha 1 globulin	Total cholesterol	
Alpha 2 globulin	HDL-C/cholesterol ratio	
Cortisol		
Leukocytes		
CD4+/CD8+ T-cell ratio		
C-reactive protein		
Alpha 1-acid glycoprotein		
Prostaglandin E2		



## CONCLUSION

Data relating low or lowered cholesterol levels to suicide and suicidality from different types of studies in humans have been systematically presented and evaluated. Meta-analysis of randomized clinical trials have been found to report conflicting results, sometimes demonstrating an increased non-illness mortality (suicide, accidents) in cholesterol lowering trials and other studies not replicating these findings. Epidemiological/Observational cohort studies have also been inconsistent in reporting an association between low baseline cholesterol levels and increased risk of death due to suicide in the general population. Studies of adult psychiatric inpatients have been rather consistently finding an association between low cholesterol levels and suicide attempts. In adolescent psychiatric inpatients (Apter, et al., 1999) and in children (Glueck, et al., 1994) these findings could not be replicated.

Several studies suggest that depression and suicidality might be accompanied by a certain serum lipid profile. Besides the lowered cholesterol levels, the triglyceride (TG) levels seem to be elevated, while high density lipoprotein (HDL) cholesterol appears to be decreased. In the aim to identify a peripheral marker that may be helpful in the early detection of suicidal behavior and elucidate the relation of cholesterol and other lipids and suicidality, further studies on the relation of blood lipid levels (involving TG, HDL and LDL besides total cholesterol) with neuroendocrines substances (serotonin, melatonin and cortisol) will be advisable.

In most of the studies, cholesterol was measured only once on admission or within 48 hours. Measurement on admission might confound the results and increased cholesterol levels might be found at a later determination. Involving at least one more cholesterol determination besides the one within 48 hours after admission to the hospital would be necessary.

It is important to include dietary variables in this kind of research in which mild-to-moderate malnutrition may affect serum cholesterol levels. A recently published epidemiological study revealed that increased BMI was associated with both major depression and suicide ideation among women, while among men major depression, suicide attempts, and suicide ideation were associated with lower BMI. Therefore, experimental studies investigating this relationship are important. Several studies already controlled for nutritional status as a contributing factor to lower cholesterol including parameters like serum total protein, BMI, triglyceride levels and significant weight and appetite loss. However, these parameters might not be sufficient to measure pre-admission malnutrition. A validated dietary frequency questionnaire combined with a

24-hour dietary recall would give more detailed information about the actually consumed amount of fat and energy.

In major depression, there seems to be a deficiency of omega 3 polyunsaturated fatty acids (PUFAs) and a compensatory increase in monounsaturated fatty acids (MUFAs). Reduced levels of omega 3 PUFAs are suggested to affect serotonin and thereby increase suicide risk. Inclusion of a determination of polyunsaturated fatty acids in studies investigating the relation of cholesterol and suicide would help to test this hypothesis.

The relation between low cholesterol levels and depression/suicide attempt in depressed subjects may be due to an immune/inflammatory response in depression. Increased concentration of plasma soluble interleukin-2 receptor, reflecting an activation of T-lymphocytes, has been observed in major depression and in psychiatric patients after a suicide attempt. Increased monocytic production of interleukins in severe depression may constitute key phenomena underlying the various aspects of the immune and "acute" phase response.

Cytokines like IL 2 have been found to lower plasma levels of cholesterol, HDL-cholesterol and increase plasma triglycerides. Elevated plasma levels of cytokines have been demonstrated in inflammatory, malignant, infectious diseases, traumatic injury and even minor illness. These disease states are often associated with abnormal lipid metabolism like hypertriglyceridaemia and reductions in plasma cholesterol, a similar lipid pattern as the one found in major depression and in patients after a suicide attempt. Cytokines may affect plasma levels of cholesterol and lipoproteins by modulating lipolytic enzyme activities and gene expression of apoproteins. This hypothesis that the acute phase response in major depression and resulting elevated cytokine levels could have an effect on cholesterol levels, has not been tested so far. Therefore, involving determination of cytokines, especially TNF and IL-1 and 2, in studies measuring cholesterol in suicidal patients, would be advisable.

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## Published reports

### **Att satsa på psykisk hälsa - förebygga självmord och självmordsförsök/To focus on mental health - preventing suicide and suicide attempts**

- 1/95 Självmord i Stockholm 1986-90. Kartläggning av självmorden i Stockholms läns sjukvårdsområden och psykiatriska sektorer
- 1/97 Självmordspatient på psykiatrisk klinik
- 2/97 Självmordstankar bland sjuksköterskor i Sverige
- 1/98 Suicidriskbedömning
- 1/99 Den första nationella nätverkskonferensen i självmordsprevention
- 2/99 Future risk after an attempted suicide
- 1/00 "Kärleken är den bästa kicken"
- 2/00 Den andra nationella nätverkskonferensen om självmordsprevention
- 3/00 Att påskynda livets slut. Historik, forskning och aktuell svensk och internationell debatt om eutanasi

### **Röda serien/The red series**

- Hastening the end of life. History, research and current Swedish and international debate on the issue of euthanasia
- Literature review: relationship between cholesterol and suicide
- Guidelines for suicide prevention in schools

### **Gröna serien/The green series**

- Kristeamkris - ett mini-projekt. Debriefing och retrospektiva genomgångar på psykiatrisk öppenvårdsmottagning: Erfarenheter vid implementering



## National Centre for Suicide Research and Prevention of Mental Ill-Health

The Swedish state's and Sockholm County Council's central expert unit in suicide research and suicide prevention.

The Centre has national and regional responsibility for accumulating and disseminating knowledge, and for initiating and conducting research and development projects that promote suicide-prevention measures. The Centre's national responsibility dates from a parliamentary resolution of 1993.

The Centre is a WHO collaborating Centre on Suicide Prevention.

Its activities fall into four main categories:

- \* research and development
- \* analysis and monitoring of epidemiological data
- \* information and publicity
- \* teaching



Stockholm Center of Public Health



Institutet for Psykosocial Medicin



Karolinska Institutet



WHO's Collaborating Centre for Suicide Prevention