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Review

Cholesterol in coronary heart disease and psychiatric disorders: Same or opposite effects on morbidity risk?

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ABSTRACT

The goal of this article is to review the studies that have linked low cholesterol levels with psychiatric symptoms or behavioral disorders in order to clarify which cholesterol fractions may influence psychological well being and mental health. The distinction between "bad" (i.e., pro-atherogenic) and "good" (i.e., anti-atherogenic) cholesterol is crucial to decide if the clinical benefits of low cholesterol levels for cardiovascular health might turn into a risk factor for psychiatric morbidity. Although the data from studies linking low cholesterol to aggression, suicide and self-harm, impulsivity, negative mood, postnatal depression, and cognitive dysfunction are far from unequivocal, the balance of evidence from new randomized controlled trials is reassuring. However, there are some subgroups of vulnerable individuals who, unlike the majority of persons in the general population, are susceptible to the psychological and behavioral adverse outcomes associated with low cholesterol levels. Because in some cases pro-atherogenic lipid and lipoprotein fractions are involved in this vulnerability, reaching the double goal of promoting both cardiovascular and mental health may be problematic for some individuals. A major task of future research is to identify these vulnerable individuals.

Contents

1. Introduction

Coronary heart disease (CHD) is a leading cause of morbidity and mortality, and high-blood cholesterol is a major risk factor for CHD (American Heart Association, 2001). The role of cholesterol in the development and progression of atherosclerosis is well established in experimental studies, and blood cholesterol levels have been associated with CHD risk consistently in multiple clinical investigations. Furthermore, large randomized controlled clinical trials have established the clinical benefits of lowering cholesterol levels in different clinical settings (Grundy et al., 2004). Recent revisions of lipid-lowering guidelines recommend tighter control of cholesterol levels, which may extend treatment to those with "favorable" lipid profiles (Kendall and Nuttall, 2002). However, whether naturally low or therapeutically lowered cholesterol may cause adverse psychological and behavioral effects remains unclear.

The possibility of an unexpected relation between cholesterol and mental health was initially highlighted by the meta-analysis by Muldoon et al. (1990) of drug and diet cholesterol-lowering

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trials, which indicated that lowering cholesterol was associated with reduced morbidity and mortality for CHD but increased deaths from accidents, suicide or violence (“non-illness” mortality). Subsequent analyses of intervention trials and cohort studies, however, only partly confirmed the existence of these adverse effects of low serum cholesterol. In a more recent meta-analysis, Muldoon et al. (2001) found that deaths from suicides, accident, and violence were not significantly increased among participants randomized to a cholesterol-lowering intervention compared with those in the control groups. However, non-illness mortality is not the only outcome variable relevant to an assessment of the potential impact of cholesterol levels on mental health. In fact, “The absence of a significant effect of treatment on non-illness mortality alone does not exclude the possibility of cholesterol reduction having any adverse effects on psychological well being or quality of life.” (Muldoon et al., 2001, p. 14).

The publication of the original meta-analysis by Muldoon et al. (1990) stimulated much interest and, since then, many studies focusing on outcome variables other than non-illness mortality have reported associations between psychiatric symptoms or behavioral disorders and low serum cholesterol concentrations. These findings are disturbing if interpreted as evidence that a negative impact on mental health is the inevitable downside of cholesterol-lowering interventions for reducing CHD risk. Accordingly, the studies linking low-cholesterol levels with psychiatric morbidity have stimulated a harsh debate and their validity has been questioned on the basis of various methodological considerations (Law, 1996).

Another aspect much less discussed in the literature is which cholesterol fractions may influence psychological well being. In cardiovascular research, as a result of extensive studies on the pathogenesis of CHD, putative risk factors have been extended far beyond the conventionally measured total cholesterol (TC). At the present time, guideline groups use multiple cholesterol-related indices to define the overall lipid-related risk of CHD, including low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), apolipoprotein B (apoB), and apolipoprotein A1 (apoA1). Recent studies have shown that the TC/HDL-C ratio (Natarajan et al., 2003) and the apoB/apoA1 ratio (Walldius and Jungner, 2004) are the most useful predictors of CHD. Higher concentrations of TC, LDL-C, and apoB are pro-atherogenic and increase the risk of CHD, but higher concentrations of HDL-C and apoA1 are anti-atherogenic and decrease the risk of CHD. The distinction between “bad” (i.e., pro-atherogenic) and “good” (i.e., anti-atherogenic) cholesterol is crucial to decide if the clinical benefits of low cholesterol levels for cardiovascular health might turn into a risk factor for psychiatric morbidity.

The goal of this article is to review the studies that have linked low cholesterol levels with psychiatric symptoms or behavioral disorders in order to clarify which cholesterol fractions may influence psychological well being and mental health. The present review is selective and does not consider the results of those studies that yielded negative findings. Thus, the article does not address the general question “What is the evidence for and against an association between low cholesterol levels and psychiatric morbidity?” Rather, it focuses on a more specific question “In studies that found an association between low cholesterol levels and psychiatric morbidity, which was the cholesterol fraction implicated? The pro-atherogenic or the anti-atherogenic?”

The article is organized as follows. First, I will briefly summarize the biological hypotheses that have been advanced to explain how serum cholesterol levels may impact on mental health. Then, I will review the data linking low cholesterol to aggression, suicide and self-harm, impulsivity, negative mood, postnatal depression, and cognitive dysfunction in clinical populations and healthy subjects. In reporting data, priority will be given to studies that measured other lipid indices in addition to TC. When TC data will be reported, they will be discussed as reflecting pro-atherogenic activity because TC is strongly correlated with LDL-C but not with HDL-C (Ridker et al., 2005). Finally, I will address the question whether low cholesterol levels are good for both cardiovascular and mental health and suggest research strategies useful for identifying individuals with increased psychiatric vulnerability to low cholesterol levels.

2. Neural mechanisms

The association between cholesterol and mental health has been explained tentatively on the basis of hypothesized neural mechanisms linking serum cholesterol to brain function. This is understandable considering that the central nervous system, which accounts for only 2% of the body mass, contains 25% of free cholesterol present in the whole body (Dietschy and Turley, 2001). Cholesterol forms an integral part of cell membranes and is a major component of myelin. Furthermore, cholesterol also plays a vital role in the development, function and stability of synapses (Chattopadhyay and Paila, 2007).

Most of the hypotheses incorporate serotonin, essentially proposing that low cholesterol is related to reduced serotonergic function, which in turn, is linked to a variety of mood and behavioral disorders. In one often-cited hypothesis, Engelberg (1992) proposed that low serum cholesterol may directly influence brain lipids and the fluidity of the cell membrane, with secondary effects on serotonergic neurotransmission. In this model, reduced cholesterol in brain cell membranes would lead to lower lipid microviscosity, which could affect serotonin receptor exposure resulting in decreased serotonin binding and uptake. Diebold et al. (1998) proposed an alternative model in which a decrease in serum TC or LDL-C would induce a relative increase in brain cell membrane fluidity with increased presynaptic serotonin reuptake and decreased postsynaptic serotonin function.

Whatever the precise physiological underpinnings of the putative cholesterol–serotonin relation, the connection itself appears to be well established. Experimentally decreasing the cholesterol content of cell membranes has been shown to reduce the binding affinity of a serotonin 5-HT1A receptor agonist, alter G-protein coupling of the receptor, and decrease activity of the serotonin transporter (Pucadyil and Chattopadhyay, 2007; Scanlon et al., 2001). Kaplan et al. (1994) found that when monkeys (of the same weight and receiving the same caloric intake) were fed a low-cholesterol diet, they had lower levels of the serotonin metabolite, 5-hydroxyindoleacetic acid (5-HIAA), in their CSF than did monkeys on a high-cholesterol diet. Human studies have confirmed that serum cholesterol levels do have effects on the serotonergic system. Buydens-Branchey et al. (2000) found that the lipid fraction associated with neuroendocrine indices of reduced serotonin function was low HDL-C, not TC or LDL-C. Although other studies have suggested that serum cholesterol may be a marker for central serotonergic activity (Steegmans et al., 1996; Terao et al., 2000; Vevera et al., 2005), it is worth noting that Hibbeln et al. (1998) found a strong correlation between brain serotonin metabolites and omega-3 fatty acids, a finding suggesting that, in previous studies, cholesterol was acting as a “surrogate marker” for omega-3 fatty acids (Hibbeln et al., 2000).

Kaplan et al. (1997) proposed a plausible evolutionary rationale for the cholesterol–serotonin hypothesis. They argue that, rather than being an accidental relation, natural selection may have shaped the behavioral and physiological responses induced by a reduction in serum cholesterol to provide an adaptive advantage. “Specifically,” they write, “during periods of caloric abundance

individuals would be physiologically prompted, perhaps via high central serotonergic activity, to exhibit behavioral complacency, etc. In contrast, scarcity, particularly in calories derived from animal sources, would reduce plasma cholesterol and, perhaps via low central serotonergic activity, trigger impulsive, risk-taking behavior such as hunting or competitive foraging." (p. 74). In conditions of decreased food intake, the cholesterol–serotonin hypothesis implies that, as cholesterol levels decrease, serotonin levels will also drop causing the emergence of adaptive behavioral responses, including an increase in aggression and food competition.

The common assumption underlying each of the proposed hypotheses explaining the association between cholesterol, mood and behavior is that low levels of serum cholesterol reflect low cholesterol content in the brain. However, the exact relation between cholesterol in the blood and cholesterol in the brain remains unclear. Brain cholesterol is synthesized in situ with no available evidence for the transfer of cholesterol from blood plasma to brain (Dietschy and Turley, 2001). Thus, it is unclear how cholesterol in the peripheral system is related to cholesterol in the central nervous system.

Although it remains to be discovered whether and how serum cholesterol concentrations affect cholesterol content in the brain, there is evidence that some psychiatric disorders are associated with changes in brain cholesterol levels. Analyzing samples of visual association cortex obtained postmortem from subjects with bipolar disorder, major depressive disorder, and schizophrenia and from controls, Beasley et al. (2005) found that cholesterol levels were significantly lower in individuals with major depressive disorder or bipolar disorder compared with controls. These authors concluded that lower brain cholesterol levels causing reduced synaptic density or function may be a pathophysiological feature of mood disorders. Lalovic et al. (2007) measured cholesterol content in cortical and subcortical tissue of brains from 41 male suicide completers and 21 male controls that died of sudden causes with no direct influence on brain tissue. No significant differences in cholesterol content were found between suicides and controls in the frontal cortex, amygdala or hippocampus. However, when the suicide completers were stratified into violent or non-violent groups based on the method of death, violent suicides were found to have lower grey-matter cholesterol content overall compared to non-violent suicides, specifically in the frontal cortex.

In the future, molecular genetics could radically change our view of the relation between serum cholesterol levels and central serotonergic function. In a large epidemiological study, Fischer et al. (2006) have unexpectedly found that the short allele of the serotonin transporter polymorphism (5-HTTLPR) strongly influences LDL-C levels. Mean fasting LDL-C levels were higher in individuals with the long allele than in individuals with the short allele. These preliminary findings suggest that the same genetic factor (i.e., the serotonin transporter polymorphism) contributes in opposite ways to cardiovascular and psychiatric vulnerability. In fact, whereas many studies have shown that the short allele is a risk factor for a variety of psychiatric disorders (reviewed in Serretti et al., 2006), two studies found significantly greater risk for myocardial infarction in individuals with the long/long 5-HTTLPR genotype (Coto et al., 2003; Fumeron et al., 2002). Another important implication of the study by Fischer et al. (2006) is that serum cholesterol levels and central serotonergic function can covary without being in fact causally linked because their association may be caused by a third variable.

3. Aggression

Many observational studies (including cohort, case–control and cross-sectional studies) and meta-analyses support a significant relation between low-serum cholesterol, or lowering cholesterol by diet or medication, and violence and severe irritability (reviewed in Golomb, 1998; Hillbrand and Spitz, 1999). In addition, experimental studies have shown an increase in aggressive behavior in monkeys assigned to low-cholesterol diets (Kaplan et al., 1994). These data are apparently difficult to reconcile with the well-established positive association between CHD and type A behavior pattern (of which hostility and anger are important components). For example, in a sample of 98 healthy men, Richards et al. (2000) found that disposition to experience and express anger when frustrated, criticized, or treated unfairly was positively correlated with serum levels of TC and LDL-C.

The recent studies reported below suggest that these conflicting findings could be explained in part by two potential confounding variables: the measures employed to assess aggression and the criteria used to select participants. Chakrabarti and Sinha (2006) compared the serum lipid profile and serum apolipoproteins A1 and B of 30 men with a violent criminal record (including homicide, rape, arson, and grievous injury) and 30 men with no criminal history. The group with a criminal record showed significantly lower TC, lower LDL-C, higher apoA1 and lower apoB1, compared with the comparison group. The HDL-C levels did not differ in the two groups. The results of this study seem to indicate that, among male subjects, an increased propensity to engage in physical violence was associated with lower concentrations of pro-atherogenic lipid and lipoprotein fractions. If so, men with a higher risk of violence would have a lower risk of CHD and vice versa. A different picture emerged from the study by Troisi and D'Argenio (2006). The use of the Aggression Questionnaire allowed the authors to assess different subtypes of aggressive behavior (physical aggression, verbal aggression, anger, and hostility) in two groups of young men with a different propensity toward violence. Like in the study by Chakrabarti and Sinha (2006), serum concentrations of TC, HDL-C, LDL-C, apoA1 and apoB were measured. Among the 40 control subjects with a low propensity toward aggressive behavior, higher levels of physical aggression and anger were correlated with lower levels of LDL-C. However, among the 20 subjects who had been secluded in a forensic unit because they had recently committed a violent offence, ratings of physical aggression were positively correlated with LDL-C levels, and ratings of verbal aggression, anger and hostility were negatively correlated with HDL-C levels. The importance of the psychiatric and/or aggressive status of the subjects in modulating the relation between specific subtypes of aggressive behavior and different lipid and lipoprotein fractions was confirmed by the results of the analysis based on the use of integrated ratio measures of lipoprotein profile (HDL-C/TC, HDL-C/LDL-C, and apoA1/apoB ratios). The distinction between impulsive and premeditated aggression is also important, as shown by Conklin and Stanford (2008). In a small sample of 18 adult males undergoing treatment for substance dependence, these authors found positive correlations between pro-atherogenic cholesterol fractions (i.e., TC and LDL-C, although the latter did not reach statistical significance) and premeditated aggression but not impulsive aggression, as measured by the impulsive/premeditated aggression scales (IPAS).

Taken together, these findings highlight the importance of measuring separately the different subtypes of aggressive behavior (e.g., psychological vs. physical aggression, and impulsive vs. premeditated aggression) and of defining the diagnostic characteristics of the participants when assessing the relative risks for violence and CHD among young men.

The role of genetic factors linking violence with serum cholesterol levels remains largely unexplored but preliminary findings attest their probable importance. Familial hypobetalipo-

proteinemia (FHBL) is a codominant disorder of lipoprotein metabolism characterized by low levels (<5th percentile for age and sex) of LDL-C and apoB. Heterozygous FHBL has been estimated to affect 1 in 3000 individuals. FHBL heterozygotes are usually asymptomatic, but have concentrations of LDL-C and apoB less than half those in normal subjects, and this has been suggested to provide FHBL subjects with resistance to atherosclerosis and thus lower rates of CHD-related mortality. However, the price to pay for such a protection from CHD may be an increased risk of violence. In a family with FHBL, Edgar et al. (2007) found a significant association between hypocholesterolemia and violent behavior. The odds ratio for the association was 16.9 (95% confidence interval 1.1–239.3). Five paternal male relatives of the index patient (a male aged 26 years with persecutory delusions) committed violent suicide using firearms. One paternal uncle also perpetrated a double homicide, using a firearm, before committing suicide.

4. Suicide and self-harm

The relation between suicide and serum cholesterol has been the subject of much debate since the publication of several reports in the early 1990s suggesting the possible relevance of serum cholesterol to suicides. For example, in a 12-year follow-up of 351,000 initially healthy men, it was found that deaths as a result of suicide rose with lower cholesterol concentrations (Neaton et al., 1992). Similarly, in a survey of 52,000 Swedish adults, an inverse relationship was found between baseline total serum cholesterol and risk of death from suicide (Lindberg et al., 1992). Recently, Lester (2002) published a meta-analysis of studies exploring the link between low levels of serum cholesterol and increased risk of suicide. Follow-up studies found that those with lower cholesterol levels do have a tiny but statistically significant increased risk of completing suicide. Individuals who have attempted suicide in the past have lower cholesterol levels, especially if they used violent methods for suicide. Cholesterol lowering studies, however, did not lead to a significant increase in completed suicide. The existence of a relation between suicide and cholesterol levels is further confirmed by the findings that the brains of violent suicide completers had a lower grey-matter cholesterol content (Lalovic et al., 2007) and that family history of suicidal behavior was more frequent among carriers of Smith–Lemli–Opitz syndrome, an autosomal recessive syndrome characterized by abnormally low cholesterol levels (Lalovic et al., 2004).

The distinction between violent and non-violent methods for suicide is likely to be a critical aspect in this area of research. There is substantial evidence that the relation with serum cholesterol levels is much stronger for those suicidal behaviors that are characterized by violence and impulsivity (Vevera et al., 2003). Impulsivity is also a common feature of repeated self-harm (e.g., cutting, burning, etc.), another clinical phenotype related to increased risk of suicide and associated with low cholesterol levels. In addition to distinguishing between different modalities of suicide and self-harm, some studies have also made a distinction between pro-atherogenic and anti-atherogenic cholesterol fractions, which allows to use their findings to address the question inspiring the present review.

Using the data from the third National Health and Nutrition Examination Survey (NHANES III), Zhang et al. (2005) analyzed the relation between cholesterol levels and suicidality in 3237 adults aged 17–39 years. The authors made considerable efforts to avoid the methodological weaknesses of previous studies. They measured serum concentrations of TC, LDL-C, and HDL-C; assessed separately suicide ideation and attempts; and controlled for the confounding effects of socio-demographic variables, health and nutrition status, and medical and psychiatric history. Serum cholesterol was unrelated with either suicide ideation or suicide attempts among young men. In contrast, among young women, low HDL-C was significantly associated with increased prevalence of lifetime suicide attempts but not with suicide ideation.

Although the article by Zhang et al. (2005) reported a negative correlation between HDL-C levels and suicide attempts among young women, most studies point to LDL-C as the cholesterol fraction related to suicidality and self-harm. Measuring serum lipid profiles for 60 patients who had recently experienced failed attempts at suicide and equal numbers of non-suicidal psychiatric patients and normal controls, Lee and Kim (2003) found TC and LDL-C levels to be significantly lower in the parasuicidal group. Agargun et al. (2004) found that, compared with healthy controls ($N = 16$), patients ($N = 16$) with dissociative disorders and self-injurious behavior had lower serum levels of LDL-C but not of HDL-C. Garland et al. (2007) compared the serum concentrations of TC, LDL-C, HDL-C and omega-3 fatty acids of 40 patients who presented acutely with self-harm and 40 matched controls. Compared with controls, patients with self-harm had significantly lower levels of TC, LDL-C, and omega-3 fatty acids. Each of these findings was significant after adjustment for alcohol consumption, smoking, social class and other demographics. There was no significant difference in the HDL-C concentrations between the two groups. Since in a multivariate analysis, self-harm was significantly correlated with levels of omega-3 fatty acids but not cholesterol levels, the authors concluded that cholesterol was acting as a marker or "bystander" for levels of omega-3 fatty acids and was not the primary underlying cause of self-harm among patients. Marčinko et al. (2008) measured serum concentrations of TC, LDL-C, and HDL-C in 40 men with schizoaffective disorder and 20 matched controls. Based on the presence of suicide attempts, the clinical group was divided into two subgroups each including 20 participants. Suicidal patients had significant lower levels of TC and LDL-C, while HDL-C levels were lower but failed to reach statistical significance in relation to non-suicidal patients with schizoaffective disorder.

A large epidemiological study (Stoupel et al., 2000) addressed the question whether there was an inverse correlation between deaths from CHD ($N = 149{,}294$) and suicide ($N = 10{,}792$) recorded over a period of 84 months in Lituania. The results showed that the monthly number of deaths from CHD was significantly and negatively correlated to the monthly number of deaths from suicide. The authors interpreted their findings as at least partly attributable to the role of depression-related cholesterol–serotonin interactions in the development, clinical course and prognosis of both CHD and suicidal behavior.

5. Impulsivity

The data reviewed in the two previous sections indirectly suggest that the relation between aggression (directed toward either self or others) and cholesterol levels is largely attributable to a deficit in impulse control. Such a hypothesis has been directly tested by studies that have correlated serum cholesterol levels with measures of impulsivity such as the Barratt Impulsivity Scale (BIS), the impulse control scale of the Big Five Questionnaire (BFQ-IC), and the Eysenck Impulsiveness Questionnaire (EIQ). Unfortunately, few among these studies have distinguished between pro-atherogenic and anti-atherogenic cholesterol fractions and, moreover, the results are disappointingly discordant.

Buydens-Branchey et al. (2000) found a moderate negative correlation between HDL-C levels and BIS scores in 38 personality disordered cocaine addicts. In contrast, in a small sample of 18 adult males undergoing treatment for substance dependence,

Conklin and Stanford (2008) found that TC levels varied inversely with BIS scores as did LDL-C, indicating that low concentrations of TC and LDL-C (but not HDL-C) were associated with increased impulsivity. In a sample of 40 patients presenting with self-harm and 40 matched controls, Garland et al. (2007) employed multiple regression analysis and found that neither TC nor LDL-C were associated with variation in the BIS score. Yet, the regression model showed that low levels of omega-3 and omega-6 fatty acids were significantly associated with greater impulsivity scores. Different results emerged from another study also using multivariate analysis but based on a much larger sample ($N = 2051$) of young healthy men (Pozzi et al., 2003). These authors found that the subjects with low serum cholesterol, defined as the lowest tenth of the TC distribution (<150 mg/dl) showed greater impulsivity, as indicated by their significantly lower scores on the BFQ-IC scale. In addition, in a multiple regression model, both lower levels of TC and higher levels of HDL-C emerged as significant predictors of impulsivity. However, since the regression model accounted for a 0.6% only of the variance in the score on the BFQ-IC scale, the authors concluded that, in healthy young men, a relationship between cholesterol and impulsivity emerges only when the statistical analysis focuses on subjects with very low levels of cholesterol.

These observations from cross-sectional studies have been reinforced by findings from a double blind pilot trial conducted on 12 subjects (Ormiston et al., 2003), which demonstrated a modest increase in impulsivity after a short course of cholesterol-lowering therapy that dissipated over a longer course of therapy.

6. Negative mood

Among the mental health variables that have been linked to serum lipid profile, negative mood is probably the most studied and, at the same time, the most controversial because of the large number of studies that did not find any significant relation with serum cholesterol levels. Among studies that yielded positive findings, some have been questioned on the basis that their findings could be attributable to poor or declining health (which is frequently associated with both negative mood and low cholesterol levels). Studies with these methodological limitations are not reviewed here.

The results of some studies suggest that the most important lipid fraction is HDL-C. In 300 healthy women, Horsten et al. (1997) found a negative linear association between depressive symptoms and HDL-C but not between depressive symptoms and TC. Maes et al. (1997) found significantly lower serum HDL-C levels in depressed patients ($N = 36$) compared with control subjects ($N = 28$). They also observed that TC was lower in the patients but that the difference between patients and controls was less significant. These data led the authors to speculate that the most important change in serum lipid composition in depressed subjects could occur in HDL-C rather than in TC levels. In a study exploring serum HDL-C levels in a population-based sample with long-lasting depressive symptoms, Lehto et al. (2008) found that, compared with the healthy controls ($N = 61$), patients with long-term depressive symptoms ($N = 63$) had lower HDL-C values and higher pro-atherogenic indices (i.e., LDL-C/HDL-C and TC/HDL-C).

The possibility that there may be a sex difference in the relation between HDL-C and depression is suggested by the finding that, in a nonhuman primate model of stress-induced depression, depressed macaque females had significantly lower levels of HDL-C (Shively et al., 2005). In line with primate data, in a large sample of attendees of general health clinics ($N = 4444$), Chen et al. (2001) found that, after controlling for possible confounding factors, there were significant differences between the high-level and low-level HDL-C groups in depression scores and various other symptoms of psychological distress. Subjects with lower serum levels of HDL-C scored higher for depression, phobic anxiety, and somatization. However, significant differences were only seen in women, not in men.

In contrast with the findings reported above, other studies have shown that TC or the LDL-C fraction are the lipid parameters more strongly correlated with negative mood. In a sample of 644 white-collar workers, Lindberg et al. (1994) found that TC and LDL-C values were lower in those men who had experienced low mood during the past month compared with those who had not. In 121 healthy young adult women, Suarez (1999) found that depression was inversely associated with TC and the ratio of TC to HDL-C. Similarly, anxiety was inversely associated with TC, LDL-C, and the ratio of TC to HDL-C. These associations were significant after adjustment for age, body mass index, physical activity, oral contraceptive use, and hostility. Neither depression nor anxiety was associated with HDL-C levels. In 504 residents (195 men and 309 women) aged 65 years and over in a rural community, Shibata et al. (1999) found that there was no relation between serum cholesterol levels and depressive status in either sex, adjusted for age and educational attainment in cross-sectional analysis. However, lower TC levels at baseline significantly predicted a 4-year longitudinal progression of depressive status in men alone, adjusted for age, education, and the depressive score at baseline. LDL-C levels related in the same fashion as TC, whereas HDL-C did not significantly relate to the progression of depressive status. Rabe-Jabłońska and Poprawska (2000) studied 102 patients with recurrent major depression across different stages of the disorder and found low levels of TC and LDL-C in patients with acute depressive symptoms. During the remission of depressive symptoms, TC and LDL-C levels increased significantly. Recently, in a small sample of 18 adult males undergoing treatment for substance dependence, Conklin and Stanford (2008) found that TC levels varied inversely with Beck Anxiety Inventory scores as did LDL-C, indicating that low concentrations of TC and LDL-C (but not HDL-C) were associated with increased anxiety.

There is some evidence that, in women, the association between low cholesterol and negative mood might be age-dependent. In 73 obese women aged 16–76 years, Troisi et al. (2001) found no significant association between serum cholesterol levels and depression, anger and alexithymia (a cognitive-affective disturbance characterized by difficulty in identifying and describing one's own feelings) in the younger age group (<50 years). In contrast, in the subgroup of older women, TC levels were negatively and significantly correlated with mood ratings. Restricting analysis to the women in the highest quartile of the age distribution (>60 years) yielded stronger correlations between low cholesterol and negative mood. In a sample of 70 post-menopausal women, Brown et al. (2004) found increased depressive symptoms among participants with naturally occurring lower levels of TC and LDL-C but not HDL-C. This relation was only apparent among women not taking hormone replacement therapy.

7. Postnatal depression

In a normal pregnancy, serum cholesterol concentration rises 25–40%, reaching in the third trimester values up to 350 mg/dl (Hachey, 1994). These values undergo a rapid fall after delivery and normalize by the 20th week postpartum. Mild depressive symptoms ("postpartum blues") are a common complication of the puerperium and affect 30–85% of the women in the early postpartum period. Based on these observations, it has been suggested that the sudden fall in cholesterol levels after delivery

could serve as a "natural model" to test the suggested association between cholesterol and mood.

The few studies that have analyzed the relation between cholesterol and mood in the postpartum period have yielded conflicting results (Grussu et al., 2007; Nasta et al., 2002; Ploeckinger et al., 1996; Troisi et al., 2002; van Dam et al., 1999). This is not surprising considering the methodological differences in the characteristics of the participants (e.g., parity, psychiatric history, social support, etc.), time of assessment (ranging from a few days after delivery to the first trimester postpartum) and outcome variables (dimensional measures of mood symptoms vs. categorical diagnosis of psychiatric disorder). Regardless of the inconsistency of the results, with one exception, all these studies limited the measurement of serum lipids to TC.

The only study that distinguished between pro-atherogenic and anti-atherogenic cholesterol fractions is that by Troisi et al. (2002) who interviewed 47 healthy primiparous women with a structured clinical interview on two occasions: during late pregnancy (median: day 20 before the expected delivery) and during early postpartum period (median: day 32 after delivery). On both occasions, serum concentrations of TC and HDL-C were measured and mood symptoms (i.e., anxiety, anger/hostility, and depression) were assessed. There were no significant correlations between cholesterol levels and mood symptoms during late pregnancy. In contrast, lower postpartum levels of TC were significantly and negatively correlated with symptoms of anxiety, anger/hostility, and depression, and lower postpartum levels of HDL-C were correlated with symptoms of anxiety. The authors concluded that TC was a stronger correlate of postpartum mood symptoms than HDL-C among the primiparous mothers of their study.

8. Cognitive dysfunction

All the studies reviewed in the previous sections concern psychological and behavioral disorders that are related to emotional functioning. However, there is evidence that serum cholesterol levels may impact on cognitive function as well. In a naturalistic cross-sectional study of 177 healthy adults aged 25–60 years of both sexes, Muldoon et al. (1997) observed an association between poor performance on the Block Design Test and low serum TC. Similarly, Benton (1995) reported a relation between low TC and slow mental speed from the results of a choice reaction time test in 279 college students. These observations from cross-sectional studies were reinforced by findings from a clinical trial (Muldoon et al., 2000), which found decreased cognitive performance on tests for attention and psychomotor speed in 209 hypercholesterolemic (LDL-C $>$ 160 mg/dl) persons after treatment with lovastatin (a cholesterol-lowering drug), and by findings from a twin study ($N = 88$), which found that low serum TC concentrations predicted a decline in symbol-digit substitution performance (Swan et al., 1992). In a sample of 176 adults with elevated serum cholesterol levels (>198 mg/dl) randomly assigned to either a low-fat diet, a Mediterranean diet, or a waiting-list control, Wardle et al. (2000) found that dietary interventions that successfully lowered serum cholesterol levels had no adverse effect on mood. However, there was some evidence of an adverse effect on cognitive function. Both intervention groups showed impairment compared with controls on the task with the greatest processing load, and impairment was greatest among those who had the largest decrease in TC levels.

As yet, the most robust findings on the association between serum cholesterol levels and cognitive function come from a study conducted on 4110 adults aged 20–59 years. Using the data from the third National Health and Nutrition Examination Survey (NHANES III), Zhang et al. (2004) examined the relation between serum cholesterol concentrations and performance in immediate memory, visuomotor speed, and coding speed tests. They found that low serum TC and low serum non-HDL cholesterol (TC minus HDL-C) concentrations were significantly associated with slow visuomotor speed in men. All of these associations were independent of socio-demographic factors, daily dietary energy intake, leisure time physical activity, and serum trace elements, vitamins, and macronutrients. Among women, there was no association between serum cholesterol and the performance on neurobehavioral tests. The authors concluded that their findings might be helpful in explaining the high incidence of deaths from accidents in persons with low serum cholesterol concentrations. Also a study conducted on 326 women aged 52–63 years suggests that LDL-C is probably the critical lipid variable influencing cognitive performance in middle age adults (Henderson et al., 2003). Among these women, higher serum concentrations of LDL-C, and relatively recent increases in TC and LDL-C concentrations, were associated with better memory performance, whereas there was no association for HDL-C levels.

When evaluating the general validity of the data reported above, one should consider that the relation between pro-atherogenic cholesterol fractions and cognitive performance in younger or middle age adults may differ from that in the elderly, where the prevalence of atherosclerosis and vascular dementia is higher.

9. Conclusions

The research reviewed here shows that the data are far from unequivocal. On the one hand, taking into account recent results from new randomized controlled trials, the balance of evidence on the psychological and behavioral consequences of low cholesterol and cholesterol lowering is reassuring (Gould et al., 2007; Muldoon et al., 2001; Wardle et al., 2000). On the other hand, we cannot ignore the mass of data showing a negative impact of low cholesterol in some clinical populations or healthy subjects. Clearly, there are some subgroups of vulnerable individuals who, unlike the majority of persons in the general population, are susceptible to the psychological and behavioral adverse outcomes associated with low cholesterol levels. Because in some cases pro-atherogenic lipid and lipoprotein fractions are involved in this vulnerability, reaching the double goal of promoting both cardiovascular and mental health may be problematic for some individuals.

A major task of future research is to identify vulnerable individuals (Table 1). The findings reviewed here suggest that age, sex, and psychiatric status are important risk factors for some adverse outcomes but not for others. For example, low cholesterol may be associated with physical aggression and impulsivity in young men with antisocial personality but with cognitive impairment in middle age women with no history of psychiatric disorders. Thus, the possibility to obtain positive findings may largely depend on the right matching between characteristics of

Table 1
Research strategies to detect psychiatric vulnerability to low cholesterol levels

Stratify the sample by age, gender, psychiatric history, and current psychiatric status
Measure serum levels of both pro-atherogenic and anti-atherogenic cholesterol fractions
Measure serum levels of omega-3 fatty acids
Focus on psychological dimensions and behavioral traits rather than on categorical diagnoses of psychiatric disorders
Focus on subgroups with naturally low cholesterol levels
Search for genetic polymorphisms associated with both low cholesterol levels and psychiatric symptoms or behavioral disorders

the sample and choice of the outcome variable. A related problem is how to measure the outcome variable. Some studies have selected categorical psychiatric diagnoses (e.g., major depressive disorder, borderline personality disorder) but dimensional assessment of symptoms that cut across syndromes (e.g., depression, impulsivity, physical aggression) is more likely to yield positive findings.

A further important argument is that adverse psychological changes associated with some cholesterol-lowering dietary and drug treatments might be due to effects on intakes and tissue concentrations of omega-3 fatty acids, and not to a reduction of cholesterol levels. The omega-3 fatty acid docosahexaenoic acid (DHA), which humans mostly attain from dietary fish, can affect synaptic function and cognitive abilities by providing plasma membrane fluidity at synaptic regions. DHA constitutes more than 30% of the total phospholipid composition of plasma membranes in the brain, and thus it is crucial for maintaining membrane integrity and, consequently, neuronal excitability and synaptic function. Dietary DHA is indispensable for maintaining membrane ionic permeability and the function of transmembrane receptors that support synaptic transmission and cognitive abilities. Omega-3 fatty acids also activate energy-generating metabolic pathways that subsequently affect molecules such as brain-derived neurotrophic factor (BDNF) and insulin-like growth factor 1 (IGF1) (Gómez-Pinilla, 2008).

The omega-3 hypothesis is in accord with an evolutionary analysis of the substantial differences between current Western diets and the nutritional patterns of contemporary hunter-gatherers, which largely reflect original or natural human diet. Anthropological research has consistently demonstrated that, despite a fat intake (including cholesterol) that exceeds recommended guidelines and is not dissimilar from current Western intakes, hunter-gatherers have low serum cholesterol levels and are virtually free of CHD. One of the factors explaining such a paradox is that the absolute amount of dietary fat is less important in lowering blood lipid levels and reducing the risk for CHD than is the relative concentrations of specific dietary fatty acids (Cordain et al., 2002). Given an appropriate high intake of omega-3 fatty acids (which is typical of hunter-gatherers), it is entirely possible to consume relatively high-fat diets that do not necessarily produce a plasma lipid profile that promotes CHD. These findings are extremely relevant to the question addressed in this review because there is a considerable body of evidence showing the protective effects of higher intakes of omega-3 fatty acids on both cardiovascular (Harris et al., 2008) and mental (Peet and Stokes, 2005) health. In particular, dietary deficiency of omega-3 fatty acids has been associated with increased risk of several mental disorders, including attention-deficit disorder, dyslexia, dementia, depression, bipolar disorder and schizophrenia (Gómez-Pinilla, 2008).

Finally, we should not overlook the role of genetic factors, which are still largely unexplored. The finding that psychiatric symptoms and behavioral disorders are associated more with naturally low cholesterol (Lester, 2002; Pozzi et al., 2003; Zhang et al., 2005) than with therapeutically lowered cholesterol (Gould et al., 2007; Muldoon et al., 2001; Wardle et al., 2000) points to this direction. Causing naturally low levels of cholesterol, polymorphisms of genes involved in the cholesterol biosynthesis or transport could contribute in opposite ways to cardiovascular and psychiatric vulnerability. These genetic profiles could be much more common in the general population than the extreme but rare conditions described in the previous sections (i.e., familial hypobetalipoproteinemia and Smith–Lemli–Opitz syndrome). If so, the cholesterol story would not be heartening news for everyone's brain.

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