Cholesterol and Violence: Is There a Connection?

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Purpose: To determine whether the seeming relation between low or lowered cholesterol levels and violence is consistent with causality according to Hill's criteria and whether construct validity is supported by convergence of findings across different types of studies.

Data Sources: Search of the MEDLINE database for English-language articles published between 1965 and 1995 was supplemented by searches of the PsycINFO and Current Contents databases and bibliographies of relevant articles.

Study Selection: Peer-reviewed observational and experimental articles and meta-analyses that presented original research; related cholesterol levels to behaviorally defined violence; and, if experimental, had single-factor (lipid-only) intervention.

Data Extraction: Studies were grouped according to type. Data on the relation of violence to cholesterol levels from each study were recorded.

Data Synthesis: Observational studies (including cohort, case–control, and cross-sectional studies) consistently showed increased violent death and violent behaviors in persons with low cholesterol levels. Some meta-analyses of randomized trials found excess violent deaths in men without heart disease who were randomly assigned to receive cholesterol-lowering therapy. Experimental studies showed increased violent behaviors in monkeys assigned to low-cholesterol diets. Human and animal research indicates that low or lowered cholesterol levels may reduce central serotonin activity, which in turn is causally linked to violent behaviors. Many trials support a significant relation between low or lowered cholesterol levels and violence ($P < 0.001$).

Conclusions: A significant association between low or lowered cholesterol levels and violence is found across many types of studies. Data on this association conform to Hill's criteria for a causal association. Concerns about increased risk for violent outcomes should figure in risk–benefit analyses for cholesterol screening and treatment.

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Violence, which was recently declared a public health emergency (1), is increasingly viewed as the province of the primary care practitioner (1–6). It is a substantial source of morbidity and is the leading cause of death in persons younger than 44 years of age (7) and of years of life lost for persons of all ages (8). Meanwhile, cholesterol screening and treatment remain the subject of vigorous debate (9–11), the outcome of which will influence medical care for millions of persons and annual health expenditures of billions of U.S. dollars. Arguments on both sides of the debate hinge on the costs, risks, and benefits of cholesterol level reduction (12). One possible risk stems from a putative connection between low or lowered cholesterol levels and violent death in men. However, the presence of such a connection remains controversial. In this paper, the medical literature has been systematically evaluated for evidence of this relation, including observational and experimental evidence in humans and nonhuman primates.

Methods

The MEDLINE, PsycINFO, and Current Contents databases were searched for English-language peer-reviewed articles by using the keywords *cholesterol and violence* or *cholesterol and suicide*. Bibliographies from identified articles were also searched. Articles met the inclusion criteria if they presented original research, individual-level data, and single (lipid-only) or no interventions and included persons documented to be violent or used direct measures of violence (as opposed to mood or personality indices). Psychological measures, such as depression and nonbehavioral expressions of hostility, correlate poorly with measures of violent acts (13, 14).

The neurotransmitter serotonin has been implicated in the control of violent behaviors. It is postulated that lowered cholesterol levels may lead to lowered brain serotonin activity; this may, in turn, lead to increased violence. Thus, additional searches were performed to relate brain serotonin to cholesterol and serotonin to violence.

No randomized, controlled trials have been designed to evaluate a causal connection between low or lowered cholesterol levels and violence in humans, but criteria that permit a causal connection to

Table 1. Association of Violent Death and Low Cholesterol Level in Cohort Studies

Study (Reference)	Violent Deaths, n*	Low Cholesterol Level†	High Cholesterol Level†	Covariates	Relative Risk for Violent Death in the Low-Cholesterol Group Compared with the High-Cholesterol Group
Jacobs et al. (16)‡	~3800	<160 mg/dL	160–190 mg/dL	Age, smoking, blood pressure, basal metabolic index, alcohol use	1.5§
Neaton et al. (17)	1277	<160 mg/dL	≥160 mg/dL	Age, smoking, blood pressure, race, socioeconomic status‖, season	1.3¶
Lindberg et al. (18)	376	<204 mg/dL	>294 mg/dL	Age	2.8**
Vartiainen et al. (19)	193	1 mmol/L change		Age, smoking, blood pressure, alcohol use	1.0
Iribarren et al. (20)	75	1 SD change		Age, blood pressure, intake of dietary cholesterol, blood glucose level, alcohol use	1.1
Pekkanen et al. (21)	47	<234 mg/dL	≥234 mg/dL	Age, smoking, blood pressure, socioeconomic status‖, basal metabolic index	1.2
Farchi et al. (22)	35	1 mg/dL change		Age, smoking, blood pressure, FEV_1, arm circumference	~1.0††
Zureik et al. (23)‡‡	32	<184 mg/dL	184–239 mg/dL	Age, mean corpuscular volume§§, smoking	3.2§
Chen et al. (24)	17	≤136 mg/dL	≥179 mg/dL	Age, sex, blood pressure, smoking, alcohol use	6.7¶

* Data shown are for men, except for the study by Chen and colleagues (24), which did not segregate data by sex.
† To convert mg/dL to mmol/L, multiply by 0.02586.
‡ Pooled analysis with data on 18 studies; 12 of 18 studies adjusted for alcohol.
§ $P < 0.01$.
‖ Income or occupation.
¶ $P < 0.05$.
** $P < 0.001$.
†† Exponential of Cox regression coefficient for cholesterol.
‡‡ Evaluated suicide outcomes only; no data on all violent death.
§§ Proxy for alcohol use.

be evaluated in the absence of direct experimental evidence have been developed. The following seven criteria, set forth by Hill (15), are used to guide presentation of the results: strength of association, consistency of association, temporality (cause precedes effect), biological gradient, biological plausibility, coherence with preexisting knowledge, and specific association.

Results

One hundred sixty-three articles that linked cholesterol and violence were identified. Of these, 32 met the inclusion criteria: 9 community cohort analyses (1 of which summarized 18 studies), 6 studies in criminal populations, 6 studies of suicide in psychiatric populations, 8 meta-analyses of randomized trials, 1 mixed-design study, and 2 controlled trials in nonhuman primates. The results of individual randomized trials reporting violent outcomes have in no case been statistically significant, and these results are not presented individually. In community cohorts and meta-analyses of randomized trials, violence was defined as death by homicide, suicide, or accident; in other types of study, violence was defined as noted in the text. Studies relating cholesterol to serotonin and serotonin to violence are briefly reviewed.

Table 2. Difference in Mean Cholesterol Level between Suicidal or Violent Group and Control Group

Study (Reference)	Patients	Sex	Study Group/Control Group	Difference in Average Cholesterol Level in Suicidal or Violent Group Compared with Control Group*
	n			mg/dL
Gallerani et al. (27)	662	Male and female	Patients admitted for parasuicide/controls	−18†
Modai et al. (28)	427	Male and female	Consecutive admissions who had attempted suicide/psychiatric and medical controls	−17‡
Virkkunen (29)	274	Male	Patients with violent antisocial personality disorder/persons with other personality disorders	−37†
Hillbrand and Foster (30)	50	Male	High-severity violent criminals/low-severity violent criminals§	−31‖
Virkkunen et al. (31)	47	Male	Patients with aggressive conduct disorder/patients with attention-deficit disorder	−44†
Gray et al. (32)	40	Male	Criminals/staff	−13

* Negative numbers signify that the average cholesterol level was lower in the suicide or violent group. To convert mg/dL to mmol/L, multiply by 0.02586.
† $P < 0.001$.
‡ $P < 0.01$.
§ According to authors' previously devised severity-of-violence scale.
‖ $P < 0.05$.

Table 3. Suicide Attempts and Violence in Patients with Low Cholesterol Levels Compared with Patients with High Cholesterol Levels

Study (Reference)	Patients, *n*	Sex	Cholesterol Level		Type of Patient	Suicide or Violence Measure	Relative Risk for Parasuicide or Violence
			Low	High			
Golier et al. (34)	343	Female	Low quartile	Rest	Psychiatric inpatients	Medically serious suicide attempt*	NS†
Golier et al. (34)	307	Male	Low quartile	Rest	Psychiatric inpatients	Medically serious suicide attempt*	2.22‡
Sullivan et al. (35)	90	Male and female	Low quartile	High quartile	Outpatients with depression	Suicide ideation or attempt	5.14§
Spitz et al. (36) and Hillbrand et al. (37)	106	Male	<200 mg/dL‖	≥200 mg/dL‖	Violent criminals	Number of aggressive incidents in 2 years	3.3¶

* According to the Medical Lethality Rating Scale.
† Not significant (relative risk not given).
‡ $P < 0.01$.
§ $P < 0.001$.
‖ To convert mg/dL to mmol/L, multiply by 0.02586.
¶ $P < 0.05$.

Hill's Criteria for a Causal Connection

Strength and Consistency of Association

The evidence for an association between cholesterol and violence in humans derives from community cohort studies, observational studies in violent populations, and meta-analyses of randomized trials of cholesterol-lowering therapy.

A meta-analysis of 18 community cohort studies by Jacobs and colleagues (16) (**Table 1**) found 50% more violent deaths in men with cholesterol levels less than 160 mg/dL (4.14 mmol/L) than in the group with the highest cholesterol levels. Results of 8 additional studies are also shown (17–24); 1 of these studies examined only death by suicide (23). Although the number of violent deaths in all of these studies totaled only half of that in the meta-analysis by Jacobs and colleagues (16), 4 of the 8 studies (including the 2 largest studies) independently showed a statistically significant association between low cholesterol levels and violent death. Findings presented are for men, except in the study (24) where data were not segregated by sex. Few studies reported results for women separately, and although the largest of these studies showed a trend toward increased violent death with low cholesterol levels in women (18), the increased risk was less than that in men. In no study was the association of low cholesterol levels with violence significant for women when they were studied separately. Although this may be the result of inadequate power to test the association in this group, women are at substantially lower risk for violence and violent death; therefore, even a similar relative risk would confer comparatively modest absolute risk and clinical importance.

In large community cohort analyses in which suicide was investigated separately, the relative risk for suicide with low cholesterol levels was greater than that for violence overall (17, 18), although one moderate-sized study found a significant positive association between suicide and cholesterol level (20). One meta-analysis found significantly increased violent death with low cholesterol levels only in community cohorts and not in cohorts confined to employed persons (25). However, a recent French cohort study of 6393 employed men with repeated cholesterol level measurements found that a low average cholesterol level was linked to subsequent death by suicide (relative risk, 3.16; $P = 0.007$), and the connection between a decrease in cholesterol level of more than 5 mg/dL per year and subsequent suicide was marginal (relative risk, 2.17; $P = 0.056$) (23). One study of nonhuman primates (26) noted a relation between low baseline cholesterol level and agonistic behaviors. However, multiple measures of association were examined, and the significant relation to aggression could have arisen by chance.

Because violence is rare, studies targeting populations with high rates of violence may show an association between cholesterol level and violence more efficiently. Several cross-sectional, retrospective, cohort, case-control, and mixed-design observational studies have investigated the relation between cholesterol levels and suicide attempts in psychiatric populations or between cholesterol levels and violence in criminally violent persons and controls. Substantially lower cholesterol levels were seen in the parasuicide group (suicide attempts or ideation) in 2 studies (27, 28) and in the violent group in 3 of 4 studies (29–32) (**Table 2**). Another study found that among children with psychiatric diagnoses, patients who had the diagnosis with which the most suicide attempts were associated also had the lowest average cholesterol levels (33). Two of 3 analyses reported significantly more suicide attempts among persons with low cholesterol levels (34, 35) (**Table 3**); the third analysis (34) showed a nonsignificant relation in women. One study reported a higher frequency of violence (36, 37). These psychiatric and criminal data support

criteria of strong association and, in conjunction with community cohort data, show consistency of effect.

An apparent increase in violent deaths was noted in several randomized, primary prevention trials of cholesterol lowering, including the well-designed Lipid Research Clinics and Helsinki Heart trials (38–40). This increase was statistically significant in one trial that included both a cholesterol and a blood pressure intervention (41), but the number of violent deaths in most studies is small, and the excess of violent deaths has not reached statistical significance in any unifactorial intervention trial. To overcome the problem of small numbers of violent deaths, several meta-analyses have been performed.

Table 4 presents results from meta-analyses of unifactorial studies, isolating primary prevention measures and men for cases in which data were separately available (25, 42–46). Overlap exists in the trials that were included; therefore, analyses are not independent. Substantially more violent deaths were found among groups randomly allocated to receive cholesterol-lowering treatment in several meta-analyses; no study found significantly fewer violent deaths. Indeed, for all meta-analyses and for all subject categories (including additional subanalyses [43, 45]), any trend was toward an increased number of violent deaths with reduction of cholesterol level, whether for men or women, primary prevention or secondary prevention, or long trials or all trials. The absolute increase in violent death was similar to the absolute reduction in cardiac death and was statistically more significant than the latter in one meta-analysis that examined both (45) for all but secondary prevention trials. For secondary prevention trials, the trend toward increase in violent death was minimal and the benefit from reduction of cardiac deaths was substantial.

More recent trials of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors have also failed to show a marked increase in violent deaths associated with treatment in populations that received secondary prevention measures. The Cholesterol and Recurrent Events trial (47) and the Scandinavian Simvastatin Survival Study (48), which together contain most of the events (49), show 14 violent deaths in treated persons and 11 in controls. The West of Scotland Coronary Prevention Study (50) contains most of the events among the primary prevention trials that used HMG-CoA reductase inhibitors (49). The reported parity between benefit from reduction of cardiac deaths and harm from violent death in primary prevention (45) was not reflected in this study; moreover, violent deaths in the treatment group ($n = 5$) did not exceed those in the control group ($n = 6$), despite large reductions in cholesterol levels with treatment (50).

Temporality

Temporality requires evidence that cause precedes effect: in this case, that low or lowered cholesterol levels precede violence. Meta-analyses that find a statistically significant increase in violent death with reduction of cholesterol levels support this criterion because an increase in violent death followed random allocation to cholesterol-lowering therapy.

The studies included in meta-analyses were not designed to investigate violent outcomes; moreover, meta-analyses can be challenged on the basis of the studies they include. One blinded study performed in order to examine violent outcomes (violent behaviors rather than death) in nonhuman primates assigned to low- or high-cholesterol diets (51) (**Table 5**) showed a significant effect of cholesterol intervention on violence that indicated increased violence in the low-cholesterol diet group. A retrospectively analyzed study of nonhuman primates showed a similar effect (52). Here, data on lowered cholesterol levels provide temporal evidence for the relation of cholesterol levels to violence; however, the relation of lowered cholesterol levels to violence

Table 4. Meta-Analyses of Randomized Trials in Humans: Violent Death in Persons Who Received Cholesterol-Lowering Treatment Compared with Controls

Study (Reference)	Intervention	Sex	Violent Deaths, *n*	Odds Ratio
Muldoon et al. (42)	Primary prevention	Male	105	1.76*
Cummings and Psaty (43)	Primary prevention	Male	115	1.42
Davey Smith and Pekkanen (44)†	Primary prevention	Male	64	1.75‡
Davey Smith and Pekkanen (44)§	Primary prevention	Male	70	1.20
Muldoon et al. (45)	Primary and secondary prevention	Male	150	1.55*
Ravnskov (46)	Primary and secondary prevention	Male and female	Not stated	1.55‡
Cummings and Psaty (43)	Primary and secondary prevention	Male and female	179	1.24
Law et al. (25)	Primary and secondary prevention	Male and female	184	1.17

* $P < 0.01$.
† Group that received drug therapy.
‡ $P < 0.05$.
§ Group that received diet therapy.

Table 5. Aggression in Monkeys Assigned to Low-Cholesterol Compared with High-Cholesterol Diets

Study (Reference)	Sex	Age	Monkeys, *n*	Type of Aggression	Relative Risk for Aggression
Kaplan et al. (51)	Male and female	Juvenile	17	All aggression*	1.5†
Kaplan et al. (52)	Male	Adult	30	Contact aggression‡	2.0§

* Defined by authors to include contact aggression, threats, and displacement of other animal.
† $P < 0.01$.
‡ Defined by authors to include hitting, grabbing, pushing, grappling, and biting.
§ $P < 0.05$.

may have origins and implications that are distinct from those for low cholesterol levels and violence.

Biological Gradient

If a causal connection is present, risk for violent death might be expected to change monotonically across cholesterol quartiles, tertiles, or other groupings used in community cohort studies (although nonmonotonic relations, such as the U-shaped relation seen with cholesterol and death in men, are also possible). Data on the presence of a dose–response relation are available for community cohort analyses that show a significant link between violent death and the group with the lowest cholesterol levels. In **Table 6**, the group with the highest cholesterol levels serves as the reference and is defined as having a relative risk of 1.0. As one progresses from the group with the highest cholesterol levels through intermediate groups to the group with the lowest cholesterol levels, the risk (where it does change) increases monotonically, an effect that is consistent with a biological gradient.

Biological Plausibility

The connection between cholesterol and violence has perhaps most often been criticized on the grounds that it is biologically implausible. However, cholesterol and fats have many roles and may influence brain function and behavior through modification of membranes; myelin; enzyme function; absorption and transport of fat-soluble vitamins and toxins; and steroid hormones and through effects on production, reuptake, or metabolism of neurotransmitters.

Table 6. Risk for Violent Death by Cholesterol Group in Community Cohort Studies

Study (Reference)	Relative Risk for Violent Death			
	High Cholesterol Level	High Intermediate Cholesterol Level	Low Intermediate Cholesterol Level	Low Cholesterol Level
Jacobs et al. (16)*	1.0	1.08	1.11	1.54
Neaton et al. (17)*	1.0	1.0	1.01	1.28
Lindberg et al. (18)†	1.0	1.79	2.06	2.76‡
Chen et al. (24)§	1.0	3.70	6.26	6.74‖

* Cholesterol groups were as follows: >240 mg/dL, 200 to 239 mg/dL, 160 to 199 mg/dL, and <160 mg/dL.
† Cholesterol quartiles by 5-year age strata.
‡ $P < 0.001$.
§ Cholesterol groups were as follows: ≥179 mg/dL, 159 to 178 mg/dL, 137 to 158 mg/dL, and ≤136 mg/dL.
‖ $P < 0.05$.

Several studies in humans and nonhuman primates (51, 53–57) suggest a specific connection between low or lowered fats or cholesterol levels and low or lowered serotonin activity (**Table 7**). A positive relation between cholesterol and peripheral serotonin was of borderline statistical significance in one psychiatric sample (54) and was statistically significant in a nonpsychiatric analysis that included two measures of cholesterol level (55). More convincing evidence derives from studies in nonhuman primates: Monkeys assigned to diets low in fat or cholesterol showed significantly lower brain serotonin activity (as determined by hormonal measures or cerebrospinal fluid serotonin metabolites) (51, 57). The trend or effect in each study relates low or lowered fat or cholesterol levels to low or lowered serotonin measures.

Meanwhile, much of the literature supports a causal link between low or lowered brain serotonin activity and violence (58–60). Nonhuman primates and other animals with naturally low or experimentally lowered serotonin measures are more aggressive, whether serotonin is reduced by depleting the precursor tryptophan (61, 62), competitively inhibiting tryptophan hydroxylase (the rate-limiting enzyme in serotonin production) (63, 64), lesioning serotonin-producing areas (65, 66), poisoning serotonergic neurons (64, 67), or genetically engineering animals deprived of serotonin 1b receptors (68). Increasing low serotonin or restoring lowered serotonin to higher values returns violent animals to a less aggressive disposition (69–71). Similarly, in humans, low brain serotonin is linked to increased impulsive violence, including homicide, arson, and suicide (an effect that cuts across psychiatric diagnoses) and to violent and repeated suicide attempts (58, 59, 72). Administration of serotonergic drugs has reduced violent behaviors in violent persons who are institutionalized (73–78). Thus, a connection between low cholesterol levels and increased impulsive violence mediated by low serotonin activity is biologically plausible and has some experimental support.

Coherence and Specificity

Coherence refers to the fit of a finding with preexisting knowledge. Because a relation of cholesterol to violence dovetails with experimental evidence for a relation of serotonin to violence, the requirement for coherence is supported. Specificity of association is imperfectly satisfied by the relation of cholesterol to violence because low or lowered cholesterol levels have been linked not only to death from violence but to death from other causes, possibly including digestive disease and cancer. However, specificity should not be unduly emphasized (15) because it is routinely violated in causal relations. For example, smoking is causally related not only to lung cancer but also to emphysema and heart disease.

Convergent Validity

Meta-analysis cannot be used to pool data from studies with dissimilar methods or outcome measures. However, it is precisely the convergence of evidence in and across outcome measures and study types that supports construct validity (the ability of a measure to assess the concept of interest [79]) in the relation between low or lowered cholesterol levels and violence. Convergent validity, a form of construct validity, refers to the degree to which measures or items come together to represent the concept (79). Persons with low or lowered cholesterol levels, measured or lowered in any of several ways, score higher on average on each of several measures of violence (although the same persons are not tested in each case). These findings provide converging evidence that supports the relation between cholesterol and violence and the construct of low cholesterol–associated violence.

Convergence can be quantitatively shown by testing the null hypothesis that there is no systematic relation between low or lowered cholesterol levels and violence across studies. According to this null hypothesis, studies of all types should show statistically significant results equally in the positive and inverse directions. For this purpose, aggregation of studies across study types has advantages. Whereas bias from assorted sources may affect individual studies and some sources of bias may be preserved across studies of the same class, biases are less likely to be preserved when different study types and distinct populations and outcome measures are used. Although publication bias may disproportionately restrict the number of nonsignificant results published (80), no current evidence suggests that this type of bias will selectively affect publication of significant positive findings compared with significant inverse findings.

Because the meta-analyses considered here are not independent, all significant meta-analyses are counted as one. Five community cohort analyses examining cholesterol and all violent deaths or suicides, 10 criminal and psychiatric studies, 1 meta-analysis, and 2 experimental studies of nonhuman primates met the inclusion criteria. Across all study types, all 18 studies had statistically significant results that favored a relation between low or lowered cholesterol levels and violence (ratio, 18:0; binomial $P < 0.001$). A less unfavorable ratio (18:2; $P < 0.001$) can be achieved by including a cohort study that showed a significant association between high cholesterol level and suicide (although the association was statistically nonsignificant for violent death overall and, in fact, showed an association between low cholesterol levels and violent death for one examined subset) (20), by excluding studies of nonhuman primates, and by including published find-

Table 7. Effect of Low or Lowered Cholesterol Levels on Serotonin Measures

Study (Reference)	Design	Cohort	Method of Cholesterol Grouping	Effect of Low or Lowered Cholesterol Levels on Serotonin Measures
Ringo et al. (53)*	Observational	Sample of psychiatric patients	Serum cholesterol level	Decreased cerebrospinal fluid serotonin metabolite 5-hydroxyindolacetic acid (19% reduction)
Delva et al. (54)*	Observational	Hypercholesterolemic patients (treatment group) and controls	Serum cholesterol level	Decreased platelet serotonin†
Steegmans et al. (55)*	Observational	Community cohort	Replicated serum cholesterol level	Decreased peripheral serotonin (21% reduction)‡
Kaplan et al. (51)§	Experimental	Juvenile monkeys	High-cholesterol diet compared with low-cholesterol diet	Decreased cerebrospinal fluid serotonin metabolite 5-hydroxyindolacetic acid (43% reduction)‖
Anderson et al. (56)§	Quasi-experimental	Human dieters	Low-fat diet	Decreased tryptophan‖; altered hormonal measure of central serotonin
Muldoon et al. (57)§	Quasi-experimental	Adult monkeys	High-fat diet compared with low-fat diet	Decreased hormonal measure of central serotonin activity (24% reduction)‡

* Studies of low cholesterol levels.
† Relative risk, 0.3; $P = 0.06$.
‡ $P < 0.05$.
§ Studies of lowered cholesterol levels.
‖ $P < 0.001$.

ings that were not peer-reviewed (81–83). These results quantitatively and strongly support construct validity for the association between low or lowered cholesterol levels and violence.

Discussion

Data relating low or lowered cholesterol levels to behavioral violence from different types of studies in humans and nonhuman primates have been systematically presented and evaluated for consistency by using Hill's criteria for a causal connection. The evidence in the literature is consistent with a causal connection between low or lowered cholesterol levels and violence, and agreement across study types is striking. In humans, the relation is more convincing for men. Men differ from women in the neurobiology of violence and the biological effects of fat and cholesterol; these facts support the possibility of distinct effects in the two sexes. In addition, lipid metabolism differs in persons with and without heart disease (84, 85), a characteristic that dictates the need for separate analyses.

The relation between low or lowered cholesterol levels and violence is unlikely to result exclusively from a deleterious side effect of specific medications for several reasons. First, similar odds ratios for diet and drug treatment were reported in one study (45) but not another (44), although diet therapy in practice is often ineffective at achieving substantial reductions in cholesterol levels. Second, nonhuman primates assigned to dietary cholesterol reduction show a statistically significant excess of aggressive behaviors. Third, low cholesterol levels are linked to violence in populations that are not receiving cholesterol-lowering medications. Finally, reduced brain serotonin activity has been shown with dietary intervention in nonhuman primates (51, 57). Although the relation between cholesterol level and violence cannot be ascribed to toxic drug effects, it remains possible that specific drugs may differ in their propensities to produce this effect or that cholesterol is merely a marker for some other biochemical alteration that accompanies many but not all treatments to lower cholesterol levels.

The evidence for a relation between low or lowered cholesterol levels and violence has several limitations. First, a common cause or a noncausal correlation could produce both low cholesterol levels and violence, promoting a spurious connection in observational studies. Alcohol use and low socioeconomic status have been suggested, but both are unlikely: Alcohol, which increases levels of triglycerides and high-density lipoprotein cholesterol, does not lower cholesterol levels except in advanced liver disease (86–88), and low socioeconomic status is related to high rather than low cholesterol levels in industrialized societies. Young age is an important common cause, but most analyses control for age. Serious illness may lower cholesterol and induce some suicides, but such illness has not been reported in cross-sectional and case–control studies. Moreover, common cause cannot explain the statistically significant relation between the assignment to cholesterol reduction therapy and the subsequent increased violence seen in experimental studies in monkeys and in some meta-analyses of randomized trials in humans. Common cause also cannot explain the prospective demonstration of a relation between assignment to cholesterol reduction therapy and subsequent low serotonin activity in monkeys.

Many observational studies are small or have weak designs. Even large prospective observational studies that controlled for important covariates do not provide persuasive evidence of causality. Experimental studies are relatively few and are imperfect, and no randomized trial in humans has been designed to evaluate the relation of cholesterol levels to violence. Meta-analyses of existing randomized trials designed to evaluate cardiac and total mortality outcomes can be criticized on the basis of the studies that they included, and not all meta-analyses have shown a statistically significant excess of violent death in persons randomly allocated to cholesterol reduction therapy (although none have shown the reverse relation). Meta-analyses have also not included the recent large trials of HMG-CoA reductase inhibitors (statins), although these would at most attenuate the size of the effect and not reverse its direction. These trials have not shown pronounced increases in violent death despite large reductions in cholesterol levels. This may be because the apparent effect of lowered cholesterol levels on violence in previous trials was spurious or was spuriously pronounced; because cholesterol is a marker for violence-related biochemical changes that are not found with statins; because statins exert a protective effect against violence independent of reduction in cholesterol levels, as they seem to do for heart disease (89); or because of study participant selection. Persons with a history of alcohol or drug use were excluded, and only highly compliant participants were randomly assigned (48, 50, 90); the latter criterion may exclude persons at risk for behavioral instability. Direct experimental studies examining behavioral outcomes have been done only in nonhuman primates, and sample sizes have been small by clinical trial standards (although the small sizes are partially offset by large demonstrated effect sizes). Furthermore, a mechanism linking cholesterol levels to violence has not been established with certainty; however, a link has been shown to be biologically plausible.

To put the effect of reduction of cholesterol levels on violence or cardiovascular disease into context, the overall (not just cause-specific) risks and benefits of cholesterol level reduction must be considered. No study has systematically addressed overall morbidity, only cardiovascular events. Overall mortality is reduced with cholesterol level reduction by HMG-CoA reductase inhibitors in high-risk men with existing cardiovascular disease (48). However, some studies have found increased overall mortality with cholesterol level reduction in the primary prevention population (91, 92), whereas no study has found a statistically significant reduction in mortality (one came close [50]). Meta-analysis of overall mortality as a function of baseline risk (defined by the rate of cardiac death in the control group) showed statistically significantly increased mortality in low-risk populations assigned to cholesterol reduction therapy (relative risk, 1.22 [95% CI, 1.06 to 1.42]), no effect or a trend toward benefit in moderate-risk populations (relative risk, 0.96 [CI, 0.84 to 1.09]), and statistically significantly reduced mortality in high-risk populations (relative risk, 0.74 [CI, 0.60 to 0.92]) (92). Because reduction of cholesterol level with nonstatin agents has not been shown to yield overall benefit in persons who do not have cardiovascular disease—that is, most candidates for treatment—any evidence of harm should be regarded seriously. However, statins exert benefits distinct from cholesterol reduction (89, 93–96), and the risk–benefit profile seems to be more favorable with these agents.

A recent meta-analysis of randomized trials involving HMG-CoA reductase inhibitors (49) found a reduction in cardiovascular and total mortality even for the so-called primary prevention analysis (with a combined sample of 7961 persons based largely on the West of Scotland Coronary Prevention Study [50]). This analysis failed to show an increase in noncardiovascular deaths with cholesterol reduction; indeed, a trend toward a reduction in noncardiovascular deaths was seen (49). Violent outcomes were not separately evaluated. Additional research is needed to clarify the overall mortality effect in lower-risk primary prevention populations and the effect (if any) on violence in persons with a history of or risk factors for psychiatric illness or violence.

Many vital questions remain about the relation between low or lowered cholesterol levels and violence, offering important avenues for future investigation. These include whether or the manner in which specific lipoprotein subfractions relate to violence, whether demographic, behavioral, or biochemical factors influence susceptibility to low or lowered cholesterol–associated violence and guide evaluation of risk factors (such as age, sex, alcohol use, psychiatric history, or neurochemical or personality measures), and whether serotonergic drugs attenuate an increased risk for violence in at-risk persons who are candidates for cholesterol-lowering treatment.

By showing convergence of evidence for a relation between cholesterol levels and violence and plausible causality in that relation, this analysis supports a connection between low or lowered cholesterol levels and adverse violent outcomes in certain populations and supplements existing data that show a lack of mortality benefit with reduction of cholesterol levels in persons at low or moderate risk (92). Current evidence suggests a more favorable risk–benefit profile with HMG-CoA reductase inhibitors; nonetheless, additional research is needed to clarify the effect of these agents on violence and on overall mortality in less highly selected hyperlipidemic primary prevention populations. Together, these results favor a conservative approach to cholesterol management in hypercholesterolemic persons who are at low and perhaps moderate risk for death from heart disease. Future research should focus on evaluating the association of cholesterol level reduction with illness from all causes, not just heart disease, and on establishing strategies for quantitative assessment of risks and benefits associated with treatment of hyperlipidemia on the basis of characteristics of individual patients.

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And my body which took for food only a single berry became extremely thin and weak. O monks, like the knots of the asitaki plant or the knots of the kalika plant were my limbs and their joints. Like the sides of the crab, so also were my sides. My rib cage was like an old stable with its sides caved in, so that light shines through—so likewise, you could see light shine through my body. The vertebrae of my spine were like the uneven contours of a braid of hair—high and low, uneven. So were the vertebrae of my spine. Like a gourd cut too young which has withered and finally dried up completely, my head withered until it looked old and wrinkled and dry. Like the reflections of the stars in a well during the last month of summer when the water is so low the reflections are difficult to see, so also my eyeballs sank in, becoming difficult to see. Like the foot of the goat or the hoof of the camel were my shoulders, my stomach, my chest, and the rest.

And, monks, when I thought I was touching my stomach with my hands, it was my spine that I was feeling. When I tried to get up, I was so bent over that I fell backwards. When with difficulty I again got up, and rubbed my limbs with dust, all the hairs came away from my body. Through the rough self-abasement I was undertaking, my former beautiful and delicate complexion disappeared. And the people who dwelt in the neighboring village thought: "Ah, truly, he is black, the Sramana Gautama! Ah, truly, he is dark blue, the Sramana Gautama! Ah, truly, the Sramana Gautama is the color of the madgura fish! His former beautiful and clear complexion has disappeared!"

The Lalitavistara Sutra
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Submissions from readers are welcomed. If the quotation is published, the sender's name will be acknowledged. Please include a complete citation, as done for any reference.—*The Editor*