Low serum cholesterol and external-cause mortality: Potential implications for research and surveillance

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ARTICLE INFO

ABSTRACT

Objective: Previous studies suggested that low total cholesterol was associated with external mortality, including deaths from suicide, homicide, and accidents. However, this reported association was potentially confounded, since cholesterol was also reported to be associated with alcohol abuse, anti-social personality disorder, and other risk factors for external mortality.
Method: We examined external-cause mortality among a national sample of 4462 male, US veterans at baseline in 1985. Using Cox regressions to estimate survival time, we assessed the impact of low baseline total cholesterol $\leqslant 165$ mg/dl, age, race, intelligence, BMI, alcohol abuse, anti-social personality disorder, depression, and other factors at follow-up. Study follow-up continued until December 31, 2000. A total of 55 external mortalities occurred during this ~16-year period.
Results: Multivariate Cox regressions predicting external-cause mortality suggested that three predictor variables were significant: low total cholesterol, morbid depression, and anti-social personality disorder, with hazard ratios (HRs) of 1.97 ($p = 0.046$), 1.76 ($p = 0.043$), and 2.22 ($p = 0.006$), respectively. In addition, a significant interaction was detected for low cholesterol × morbid depression ($p < 0.005$), whereby those with both at baseline were ~7 times more likely to die from external mortality (HR = 6.5, 95% CI = 3.07–13.76).
Conclusion: Among a national random sample of community-based men, lower baseline cholesterol predicted external mortality and revealed an interaction with morbid depression. Patients presenting with low cholesterol and morbid depression in clinical practice may warrant clinical attention and surveillance.

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1. Introduction

In the 1990s, epidemiologic investigations suggested that low cholesterol levels were associated with external mortality, including deaths from suicide, homicide, accidents, and injuries of unknown cause (Lindberg et al., 1992; Muldoon et al., 1990). During the following decade and a half, different investigators have replicated these findings (Diaz-Sastre et al., 2007; Favaro et al., 2004; Garland et al., 2000; Golier et al., 1995; Kunugi et al., 1997; Schuit et al., 1997), although there have been negative findings reported (Deisenhammer et al., 2004). In terms of a causal mechanism to explain this association, it was hypothesized that reductions in cholesterol may cause a decrease in serotonergic

functioning, which in turn may result in poorer suppression of aggressive behaviors (Engelberg 1992; Fiedorowicz and Coryell, 2007; Schuit et al., 1997). More specifically, it has been suggested that low membrane cholesterol decreases serotonin, and since cellular membrane functions are dependent on cholesterol, a lowered plasma cholesterol concentration was thought to result in decreased brain serotonin availability (Engelberg 1992; Schuit et al., 1997). Although the exact reasons for this association are unclear (Lalovic et al., 2007a), a recent postmortem study of suicide completers has found that the frontal cortex of violent suicide completers had lower cholesterol concentrations compared to non-violent suicide cases in the orbital-frontal and the ventral prefrontal cortex (Lalovic et al., 2007b). It has been noted, however, that since cholesterol is integral to neuronal functioning and neurotransmission, additional biological mechanisms are also likely involved (Marcinko et al., 2007).

The consistency of the association between low cholesterol and suicide has been sufficiently replicated as to suggest that this biomarker might be a candidate measure for suicidality (Coryell and

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Schlesser, 2007). This association has also led to clinical concerns related to the risks associated with use of cholesterol-lowering drugs (Huffman and Stern, 2007; LaRosa et al., 2007), which to date have not been confirmed (Muldoon et al., 2001). Nevertheless, recently, the US Food and Drug Administration announced that it would require drug makers to routinely assess the possible psychiatric effects of experimental medicines, including the onset of suicidal thoughts (Harris, 2008). It has also been reported that increased depression symptoms, a risk factor for suicide, were also correlated with lower cholesterol (Morgan et al., 1993), suggesting the potential for confounding in this association. Some have noted that the association between cholesterol and suicidal behavior was more complex than originally hypothesized (Lalovic et al., 2007a). For example, it has been reported that higher body mass index was protective of suicide risks in men (Mukamal et al., 2007). In addition, it has been suggested that a psychological mediator between suicidal behavior and low cholesterol was impulsivity (Garland et al., 2000), a personality trait thought to be associated with genetic and environmental factors (Goldman et al., 2005). In addition, alcohol abuse was reported to be associated with lower total cholesterol (Budzynski et al., 2003), and this substance use disorder was often correlated with both anti-social personality disorder and suicide (Gorwood, 2001).

To better understand the association between low cholesterol and suicide we undertook a prospective 16-year follow-up study of external-cause mortality among men. In this study, we assessed the impact of cholesterol, intelligence, depression, alcohol abuse/dependence, schizophrenia, posttraumatic stress disorder (PTSD), anti-social personality disorder, impulse-control disorder, psychological hostility, body mass index, and social support on external-cause mortality among middle-age men. Our hypothesis was that the association between low cholesterol and external mortality could be chiefly explained by these other factors. To our knowledge, no study has assessed these risk factors in a single national population study.

2. Methods

2.1. Study population

The current study was based on a random sample of men who served in the US Army during the Vietnam War era. The men were identified through the National Personnel Records Center (St. Louis, MO). From these persons, 18,581 met the study criteria, including: entering the military between 1965 and 1971, serving one enlistment, and having a service rank of sergeant or lower. These men were randomly selected (by a computer program) from data tapes that essentially contained all service personnel from this period (Centers for Disease Control, 1989a,b). Participants were classified as TVs (theater veterans) if they served in Vietnam or as EVs (era veterans) if they served elsewhere. Starting in January 1985, attempts were made to complete telephone interviews with these men. From these efforts, 87% of TVs (7924) and 84% of the EVs (7364) were interviewed (overall completion rate = 86%). Among these men, a random sample was selected for personal interviews and examinations. Altogether, 75% of the TVs (*N* = 2490) and 63% of the EVs (*N* = 1972) participated in this phase. A detailed non-response analysis reported no significant differences between participants and non-participants in the baseline study (Centers for Disease Control, 1989a,b). Personal interviews and examinations required several days on site at Lovelace Medical Foundation (LMF), Albuquerque, NM, between June 1985 and September 1986. More detailed reports regarding this study have been published and are available elsewhere (Boehmer et al., 2004; Centers for Disease Control, 1989a,b,c). The CDC's Human Subject Review Committee approved the study protocols (Centers for Disease Control, 1989a,b).

2.2. Ascertainment of external-cause mortality

For the current study, vital status was assessed from the date of completion of the telephone interviews starting in January 1985 until the end of the mortality follow-up in December 31, 2000. Vital status was ascertained using three databases: the Department of Veterans Affairs Beneficiary Identification Record Locator Death File, Social Security Administration Death Master File, and the National Death Index (NDI) Plus file (Boehmer et al., 2004). Status determination was obtained by combining all mortality sources. Veterans with uncertain vital status were assumed to be living on December 31, 2000. Underlying cause-of-death was obtained from the NDI Plus file. Cause-of-death was coded according to the International Classification of Diseases (ICD) revision in place at the time of death (Centers for Disease Control, 1989a; Boehmer et al., 2004). For cases in which cause-of-death codes were not available, investigators obtained copies of official death certificates, which were coded by a nosologist at the National Center for Health Statistics (Boehmer et al., 2004). In the current study, the outcome of interest included mortality due to external-causes, which included homicide, suicide, drug overdoses, accidental poisoning, unintended injury, and injury of unknown cause. It is noted that in our study we use the term "external mortality" to be synonymous with death from unnatural causes (Boscarino, 2006). During the follow-up period, a total of 55 deaths were classified as due to external-causes. Among these, 14 (25%) were classified as suicide, 11 (20%) as homicide, and 2 (4%) classified as intent undetermined. Furthermore, 19 of these deaths (34%) were firearm related and 18 (33%) alcohol or drug related deaths (total 67%). As has been previously reported, suicides are typically underreported on death certificates and often misclassified as accidental poisonings or as other types of accidents (Boscarino, 2006).

2.3. Laboratory methods

The current study included laboratory results for serum cholesterol and triglycerides. For these assessments, morning blood collection at 7AM, via venipuncture method, was preceded by an overnight fast (Centers for Disease Control, 1989d,e). All blood specimens were collected on the second onsite examination day. After collection, all specimens were placed in a cooler or refrigerated and maintained at 2–8° centigrade until processed. Generally all specimens were processed within 24 h or less. For serum cholesterol, an enzymatic method was used that employed an Eastman Kodak cholesterol kit using the Ekachem test method, which included laboratory-prepared reagents (Eastman Kodak, Rochester, NY). High-density lipoprotein (HDL) cholesterol was assessed using Kodak Eltachem analyzers with Kodak clinical chemistry slides. For this analysis, low-density lipoprotein (LDL) was removed using dextran sulfate. Triglycerides were assessed also using Kodak Ektachem test kits based on a totally enzymatic method. For our analyses, LDL was estimated based on the Friedewald formula (i.e., LDL = total cholesterol − (HDL + triglycerides × 0.20)) (Centers for Disease Control, 1989d,e; Pagana and Pagana, 1999). All laboratory determinations were monitored using quality-control procedures and under the supervision of board-certified Clinical Pathologists (Centers for Disease Control, 1989d,e). Laboratory testing was performed at the Clinical and Research Division, Department of Laboratories, Lovelace Medical Foundation. The coefficient of variation (CV) for the laboratory procedures were within acceptable quality-control standards, with the CVs reported for cholesterol and triglycerides equal to about 2%. Additional information on these laboratory procedures has been published elsewhere (Centers for