Journal of Psychiatric Research 43 (2009) 848–854

Contents lists available at ScienceDirect

Journal of Psychiatric Research

journal homepage: www.elsevier.com/locate/jpsychires

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

Joseph A. Boscarino [a,b,*], Porat M. Erlich [a], Stuart N. Hoffman [a,c]

[a] Center for Health Research, Geisinger Clinic, 100 N. Academy Avenue, MC 44-00, Danville, PA 17822, United States
[b] Department of Medicine and General Pediatrics, Mount Sinai School of Medicine, NY, NY, United States
[c] Department of Neurology, Geisinger Clinic, Danville, PA, United States

ARTICLE INFO

Article history:
Received 16 July 2008
Received in revised form 9 November 2008
Accepted 18 November 2008

Keywords:
Cholesterol
Lipoproteins
External-cause mortality
Suicide
Depression
Mental health status

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 $\sim$16-year period.
Results: Multivariate Cox regressions predicting external-cause mortality suggested that three predictor variables were significant: low total cholesterol, morbid depression, and anti-social personality disorder, with hazard ratios (HRs) of 1.97 ($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 $\times$ morbid depression ($p < 0.005$), whereby those with both at baseline were $\sim$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.

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

* Corresponding author. Address: Center for Health Research, Geisinger Clinic, 100 N. Academy Avenue, MC 44-00, Danville, PA 17822, United States. Tel.: +1 570 214 9622; fax: +1 570 214 9451.
E-mail address: jaboscarino@geisinger.edu (J.A. Boscarino).

0022-3956/$ - see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.jpsychires.2008.11.007

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

Disease Control, 1989d,e). For analytical purposes, the low reference range for our study was set at ~10th percentile, which was equivalent to a total cholesterol level ⩽165 mg/dl. For low LDL cholesterol, the 10th percentile was <100 mg/dl; for low HDL cholesterol, the 10th percentile was <32 mg/dl. These cut-points were optimal, given the relatively few external mortality cases in our study ($n = 55$), limiting proportional hazard regression modeling at lower cut-points, such as the fifth percentile (Hosmer and Lemeshow, 1999). It is noted that lab values at the ~10th percentile range are often used in clinical studies as a reference, and this value is consistent with those used in previous cholesterol-suicide studies (Neaton et al., 1992).

2.4. Mental health and psychological status measures

In our study we included measures related to mental health status that could be associated with external mortality. These measures included baseline history of anti-social personality disorder, depression, alcohol abuse/dependence, schizophrenia, posttraumatic stress disorder (PTSD), and impulse-control disorder, as indexed by history of pathological gambling. These measures were based on having met the lifetime diagnostic criteria for these disorders and based on the Diagnostic Interview Schedule (DIS) (Robins et al., 1981, 1987). The DIS was developed from the diagnostic criteria included in the Diagnostic and Statistical Manual of Mental Disorder, Third Edition (American Psychiatric Association, 1980). Reports related to the validity and reliability of the DIS have been reported elsewhere (Robins et al., 1981, 1987). The DIS instrument was administered during the physical examination (Centers for Disease Control, 1989b). We also assessed two additional measures of mental health status, including psychological hostility and morbid depression at baseline, based on the MMPI instrument (Dahlstrom et al., 1972, 1975). Hostility assessment was based on the Wiggins Hostility Scale (WHS) developed from MMPI Scale items (Wiggins et al., 1971). Since its development, the WHS has been widely used in mental health studies over several decades (Dahlstrom et al., 1972, 1975). Morbid depression was based on the results of the D Scale (Scale 2) of the MMPI, one of the main clinical scales of the MMPI instrument (Dahlstrom et al., 1972). This scale was specifically developed to measure clinical symptoms of depression and, in the MMPI, this is characterized by indications of pessimism, feelings of hopelessness or despair, and preoccupation with death and suicide (Dahlstrom et al., 1972). The MMPI-D Scale has been widely used in clinical research (Dahlstrom et al., 1972, 1975). The MMPI was also administered during the physical examination phase of the study (Centers for Disease Control, 1989b).

2.5. Other study variables

Other study measures included age, race, theater status, intelligence, body mass index (BMI), and level of social support. Age was based on the veteran's age at the interview. Race was based on reported race (white 82%; black 11%; hispanic 5%; other 2%) and coded as an indicator variable (white vs. nonwhite), given the numbers for hispanics and other races and previous research (Centers for Disease Control, 1989c; Boscarino, 2004). Intelligence was taken from the military record and based on the General Technical (GT) examination at Army induction (Centers for Disease Control, 1989b). This measure has been reported to be a reliable and valid indictor of general adult intelligence (Centers for Disease Control, 1989b; Boscarino, 1997). Body mass index was based on the subject's weight in kilograms divided by the subject's height in meters squared (weight (kg)/[height (m)]^2), with a score of 30+ used to define obesity for categorical analyses. Our study also included a measure of social support at baseline. This scale, which measures the current level of individual social support available and was included in the DIS instrument, has been described elsewhere (Boscarino, 1995). For categorical analyses, those scoring at the lowest quintile on this scale were categorized as having low social support, as is common in epidemiologic investigations. Finally, as noted below, since we combined the TVs and EVs in our analyses, we also included a binary measure to control for theater status in our multivariate models. Altogether, ~56% of our study population had Vietnam service.

2.6. Statistical methods

For our analyses, we described the bivariate differences found for both low cholesterol and external mortality in terms of our study predictor variables. Next, we used Cox proportional hazard regressions to calculate multivariate hazard ratios [HRs] predicting external mortality by low cholesterol status, assessing the effects for both demographic and risk factor status variables. In the analyses, we analyzed the results for theater and era veterans combined, since no effect modification was confirmed by veteran status for the models examined, and because we had a limited number of deaths that occurred during follow-up. Since all study risk factors were only measured at baseline, they were assumed to be constant in the current study and, thus, no time-dependent variables were assumed. Limitations related to this assumption are discussed in our limitations section. Also, in order to avoid over-adjustment due to the degrees of freedom available and the limited number of events that occurred during the study period (Hosmer and Lemeshow, 1999; Harrell, 2001), predictor variables were eliminated from multivariate models if their p-values were >0.15 in regression models predicting external mortality with low cholesterol and our binary measure for theater status. As suggested, the latter was included to account for any residual differences between the veteran groups in our combined models. In all, in addition to theater status and low total cholesterol, five predictors were retained in the final multivariate analyses (MVA) using our selection criteria. These included alcohol abuse/dependence, anti-social personality disorder, pathological gambling, BMI, and morbid depression. For secondary analyses, we also assessed our model results based on low LDL and low HDL, respectively, and discussed these results.

It is noted that since the focus of our study was on the impact of "low" cholesterol, cholesterol was parameterized as a categorical variable. However, it is noted that we also we ran our multivariate analyses with cholesterol used as a continuous variable. This variable was not significant. We also note that age, intelligence, BMI, hostility, morbid depression, and social support were included as continuous variables in our multivariate analyses. Only morbid depression was significant at $p < 0.05$ when this was used as a continuous measure. Nevertheless, we included morbid depression as a categorical variable in our final analyses, since the MMPI cut-point used for this scale (e.g., T-score > 70), has clinical significance (Dahlstrom et al., 1972, 1975), and is consistent with our other diagnostic-level measures used.

All p-values presented were based on 2-tail tests. It is noted that because several data sources were used in this study and the veterans were on site for several days, very few variables used had missing data. The one exception was for intelligence, whereby 48 cases (~1%) were missing and coded at the median for this variable. For these analyses, we evaluated the main proportional hazard assumptions (Hosmer and Lemeshow, 1999), controlled for potential confounding, and tested for effect modification by race and veteran status. To assess Cox proportional hazard assumptions, we used Schoenfeld residuals and the "stphtest" procedure in Stata to assess fit for our models. This test is equivalent to testing that the log hazards ratio function is constant over time (Cleves et al.,

2002). We also assessed 2 × 2 interactions for low cholesterol by the final predictor variables selected, which included anti-social personality disorder, morbid depression, alcohol abuse/dependence, and pathological gambling (Hosmer and Lemeshow, 1999; Harrell, 2001). Statistical analyses were performed using Stata, version 9.2 (Stata, 2007).

3. Results

For the current study, preliminary descriptive findings indicated that low baseline cholesterol was associated with external mortality at follow-up (odds ratio [OR] = 2.00, $p < 0.05$) as well as low social support (OR = 1.27, $p < 0.05$) (Table 1). In addition, external mortality was associated with history of alcohol abuse/dependence (OR = 2.37, $p < 0.01$), anti-social personality disorder (OR = 2.76, $p < 0.001$), and morbid depression at baseline, as measured by the MMPI-D Scale (OR = 2.08, $p < 0.01$) (Table 2). It should be noted that when age, intelligence, BMI, hostility, morbid depression, and social support were analyzed as continuous variables (not shown in Tables 1 and 2), the following results were found. Younger age was associated with low cholesterol ($p < 0.05$), lower BMI was associated with low cholesterol ($p < 0.001$), higher hostility was associated with external mortality ($p < 0.05$), and higher morbid depression was associated with external mortality ($p < 0.01$).

As discussed, Cox proportional hazard regressions were next conducted, only retaining predictive variables that were significant at $p \leqslant 0.15$ for the minimum model containing the indicator variable for low cholesterol and theater status and each predictor variable, respectively (Table 3). Altogether, in addition to low cholesterol, five significant predictor variables were retained using this selection method, including BMI, alcohol abuse/dependence, anti-social personality, pathological gambling, and morbid depression. These results are presented in three models, representing a cholesterol model without other predictors included (model 1), a cholesterol model with other predictors, but excluding morbid depression (model 2), and a cholesterol model with the other predictors and morbid depression included (model 3) (Table 3). Noteworthy, is that low cholesterol remained significant in all the models assessed, including alone and in both MV models (i.e., models 2 and 3). As can be seen, anti-social personality was the best predictor of mortality, with a hazard ratio (HR) of 2.29 ($p = 0.005$) and 2.22 ($p = 0.006$), respectively, in models 2 and 3. Both low cholesterol (HR = 1.97, $p = 0.046$) and morbid depression (HR = 1.76, $p = 0.043$) remained significant in model 3, containing both these predictor variables. Finally, we tested for separate 2 × 2 interaction effects for low cholesterol by alcohol abuse/dependence, anti-social personality, and morbid depression, respectively. However, only low cholesterol × morbid depression was found significant ($p = 0.005$), as shown in Table 3. Categorical regression analyses isolating the combined effects of the low cholesterol with morbid depression in model 3 revealed a HR of 6.5 (95% CI = 3.07–13.76), in contrast to those without low cholesterol and morbid depression at baseline (Table 3, model 3).

As noted, we also ran our models based on low LDL and low HDL, respectively. For LDL, these results were similar as shown for total cholesterol (Table 3). For HDL cholesterol these results were not. In particular, no interaction effect was detected for low HDL × morbid depression and BMI appeared to be protective for external mortality. However, similar to total low cholesterol, these disparities could not be further explored, due to the relatively few external mortality cases that occurred in the current study ($N = 55$) and being restricted to the 10th percentile for our cholesterol risk factor of interest.

Finally, to assess Cox proportional hazards assumptions, we used Schoenfeld residuals and the "stphtest" procedure in Stata to assess fit for our models. The results of the procedure indicated that the final models used were adequate ($p = 0.993$). We also plotted the multivariate survival functional curves for the final models for cholesterol and these plots indicated adequate model fit as well.

4. Discussion

Earlier investigations have suggested that low blood cholesterol levels were associated with an increase in external mortality, including deaths from suicide, homicide, accidents, and injuries of unknown cause (Lindberg et al., 1992; Muldoon et al., 1990). A causal biological mechanism to explain this association had focused on the reduction in serotonin levels (Schuit et al., 1997), although subsequent studies have suggested that the biology was likely more complex (Lalovic et al., 2007a), since cholesterol is

Table 1
Low total cholesterol at baseline by external mortality and study predictor variables.

Variable	% Total (*N*)	% Normal baseline cholesterol	% Low baseline cholesterol[a]	Crude odds ratio	95% CI
Theater veteran	55.8 (2490)	56.2 (2231)	52.5 (259)	0.86	0.72–1.04
External mortality at follow-up	1.2 (55)	1.1 (44)	2.2 (11)	2.00	1.04–3.97*
Age 40+ at interview (mean age = 37.83, SD = 2.53)	19.8 (883)	20.1 (797)	17.4 (86)	0.84	0.66–1.08
Non-white race	18.1 (808)	17.8 (705)	20.9 (103)	1.22	0.97–1.54
Intelligence – lowest quintile (mean intelligence score = 105.95, SD = 20.18)	18.7 (836)	18.9 (752)	17.0 (84)	0.88	0.69–1.23
Body mass index > 30 (mean BMI = 26.86, SD = 4.47)	16.8 (750)	17.1 (679)	14.4 (71)	0.82	0.63–1.06
History of alcohol abuse/dependence	46.7 (2084)	47.0 (1864)	44.6 (220)	0.91	0.75–1.10
History of depression	10.5 (468)	10.4 (412)	11.4 (56)	1.11	0.82–1.49
History of PTSD	10.0 (446)	10.0 (397)	9.9 (49)	0.99	0.73–1.36
History of schizophrenia	1.0 (46)	1.0 (39)	1.4 (7)	1.45	0.65–3.26
History of anti-social personality disorder	22.1 (988)	21.9(870)	23.9 (118)	1.12	0.90–1.40
History of pathological gambling	1.5 (66)	1.6 (62)	0.8 (4)	0.52	0.19–1.42
Psychological hostility (mean hostility score = 8.89, SD = 4.77)	22.5 (1006)	22.6 (896)	22.3 (110)	0.99	0.79–1.23
Morbid depression (mean depression score = 61.39, SD = 14.14)	24.5 (1092)	24.5 (974)	23.9 (118)	0.97	0.78–1.21
Low social support (mean social support score = 6.47, SD = 1.51)	20.3 (908)	19.9 (790)	23.9 (118)	1.27	1.02–1.58*
(*N*)	(4462)	(3969)	(493)	–	–

Note: Percents based on percents for column variable shown. For example, of those with low cholesterol at baseline, 2.2% experienced external mortality at follow-up. For continuous variables, mean (SD) also shown.
CI, confidence interval.
* $p < 0.05$.
[a] Defined as ~10th percentile, which was equal to a cholesterol level ⩽165 mg/dl. Mean total cholesterol = 212.74, SD = 41.64.

Table 2
External mortality by study predictor variables.

Variable	% Total (*N*)	% No external mortality	% External mortality[a]	Crude odds ratio	95% CI
Theater veteran	55.8 (2490)	55.7 (2454)	65.5 (36)	1.51	0.86–2.64
Low total cholesterol[b] (mean cholesterol = 212.74, SD = 41.64)	11.1 (493)	10.9 (482)	20.0 (11)	2.00	1.04–3.97*
Age 40+ at interview (mean age = 37.83, SD = 2.53)	19.8 (883)	19.9 (875)	14.4 (8)	0.69	0.32–1.46
Non-white race	18.1 (808)	18.1 (796)	21.8 (12)	1.27	0.67–2.41
Intelligence – lowest quintile (mean intelligence score = 105.95, SD = 20.18)	18.7 (836)	18.7 (824)	21.8 (12)	1.21	0.64–2.31
Body mass index > 30 (mean BMI = 26.86, SD = 4.47)	16.8 (750)	16.8 (741)	16.4 (9)	0.97	0.47–1.99
History of alcohol abuse/dependence	46.7 (2084)	46.4 (2047)	67.3 (37)	2.37	1.35–4.18**
History of depression	10.5 (468)	10.4 (458)	18.2 (10)	1.92	0.96–3.83
History of PTSD	10.0 (446)	9.9 (438)	14.5 (8)	1.54	0.72–3.28
History of schizophrenia	1.0 (46)	1.0 (45)	1.8 (1)	1.80	0.24–13.26
History of anti-social personality disorder	22.1 (988)	21.9 (964)	43.6 (24)	2.76	1.62–4.73***
History of pathological gambling	1.5 (66)	1.5 (64)	3.6 (2)	2.56	0.61–10.74
Psychological hostility (mean hostility score = 8.89, SD = 4.77)	22.5 (1006)	22.5 (990)	29.1 (16)	1.42	0.79–2.55
Morbid depression (mean depression score = 61.39, SD = 14.14)	24.5 (1092)	24.3 (1070)	40.0 (22)	2.08	1.21–3.58**
Low social support at baseline (mean social support score = 6.47, SD = 1.51)	20.3 (908)	20.4 (898)	18.2 (10)	0.87	0.44–1.73
(*N*)	(4462)	(4407)	(55)	–	–

Note: Percents based on percents for column variable shown. For example, of those with external mortality at follow-up, 20.0% had low cholesterol at baseline.
For continuous variables, mean (SD) also shown.
CI, confidence interval.
* $p < 0.05$.
** $p < 0.01$.
*** $p < 0.001$.
[a] External mortality included: homicide, suicide, drug overdoses, accidental poisoning, unintended injury, and injury of unknown cause.
[b] Defined as ~10th percentile, which was equal to a cholesterol level ⩽165 mg/dl.

Table 3
Cox proportional hazard regressions for external-cause mortality by low total cholesterol and study predictor variables ($N = 4462$).[a]

Baseline risk factors	Total deaths = 55 (67,067 person years at risk)								
	Model 1[b]			Model 2[b]			Model 3[b]		
	HR	95% CI	*p*-Value	HR	95% CI	*p*-Value	HR	95% CI	*p*-Value
Low total cholesterol[c]	2.07	1.07–4.14	0.031	1.97	1.01–3.84	0.046	1.97	1.01–3.84	0.046
Body mass index (BMI)	–	–	–	0.95	0.89–1.02	0.158	0.95	0.89–1.02	0.152
Lifetime alcohol abuse/dependence	–	–	–	1.77	0.97–3.23	0.061	1.68	0.92–3.07	0.092
Anti-social personality disorder	–	–	–	2.29	1.29–4.07	0.005	2.22	1.25–3.95	0.006
Pathological gambling	–	–	–	3.14	0.74–13.33	0.120	3.01	0.71–12.77	0.136
Morbid depression	–	–	–	–	–	–	1.76	1.02–3.05	0.043
Interaction effects for model 3									
Low total cholesterol × morbid depression[d]	–	–	–	–	–	–	11.09	2.10–58.63	0.005
Low total cholesterol × morbid depression interaction effect[e]	–	–	–	–	–	–	6.50	3.07–13.76	<0.001

Note: HR = hazard ratio; and CI = confidence interval.
[a] External mortality included: homicide, suicide, drug overdoses, accidental poisoning, unintended injury, and injury of unknown cause.
[b] Model also adjusted for theater status as a binary variable.
[c] Defined as ~10th percentile, which was equal to a cholesterol level ⩽165 mg/dl.
[d] This represents the interaction effect detected when the total cholesterol × morbid depression term was added to the regression model 3.
[e] This shows the interaction effect for those with low total cholesterol and morbid depression compared to not having either of these risk factors present using categorical parameters to isolate this specific effect (Hosmer and Lemeshow, 1999).

integral to synaptic function, memory formation, and nervous system functionality (Qiu et al., 2006). In addition, it has been reported that higher body mass index (BMI) was protective of suicide risks in men (Mukamal et al., 2007). Furthermore, other suicidal risk factors, such as depression and alcohol abuse have been associated with lower cholesterol (Budzynski et al., 2003; Morgan et al., 1993). Thus, the reported association between suicide and low cholesterol was potentially confounded. However, with one exception (morbid depression), our analyses suggested that the force of morbidity associated with low cholesterol appeared to be independent of concurrent mental conditions, impulse-control disorders, and other key psychological factors. The hazard ratio for low cholesterol alone compared to the full model with all key covariates identified was essentially the same (HR = 2.07, $p = 0.031$ vs. HR = 1.97, $p = 0.046$).

Our study indicated that the significant predictors of external-cause mortality included not only low cholesterol (HR = 1.97, $p = 0.046$), but also anti-social personality disorder (HR = 2.22, $p = 0.006$) and morbid depression (HR = 1.76, $p = 0.043$) at baseline, neither of which appeared correlated with low baseline cholesterol (Table 1). Furthermore, a significant interaction effect was found for low cholesterol by morbid depression ($p = 0.005$), revealing a substantial increased risk for those with both these baseline risk factors, compared to those with neither present (HR = 6.5, 95% CI = 3.07–13.76). Noteworthy is that these effects were uncovered after examination of a number of potentially interrelated risk factors, including intelligence, BMI, alcohol abuse/dependence, PTSD, schizophrenia, psychological hostility, and low social support at baseline. To our knowledge, this was the only study that examined these psychosocial and biometrical risk factors in a single national population study. As suggested, when we ran our MVA models based on a low LDL classification, the results were similar to those for total cholesterol. The MVA results for low HDL were not, however, and warrant further investigation.

This study has strengths and limitations. Use of multiple sources of vital status allowed for more comprehensive mortality assessment and use of a national sample allowed us to generalize our findings. However, cause-of-death as reported on death certificates, is known to over-report circulatory and ill-defined conditions, and to under report suicides (Boehmer et al., 2004; Boscarino, 2006). It also should be noted that the DIS-III Scales used in the current study for depression and PTSD were based on an earlier version of the DSM nomenclature, and may be less accurate than later measures, especially for PTSD (Boscarino, 2006; Kulka et al., 1990). Other limitations were that the study included only male veterans and only those who survived to participate in the baseline survey. Our study also did not assess the impact of other significant mental health conditions. A limitation also was that the outcome of interest was limited in this study, in that only 55 external-cause deaths occurred during the study period. This restricted our data analyses, including the cut-point used to define low cholesterol, which was restricted to the 10th percentile (cholesterol $\leqslant$ 165 mg/dl). A lower clinical value would have been preferable. Findings seem to suggest that a cut-point at the fifth percentile (i.e., $\leqslant$150 mg/dl) tends to produces a stronger mortality association, and this was confirmed with our study. For example, the crude HR at the 10th percentile in our study was 2.07, $p = 0.031$. For the fifth percentile, the crude HR = 2.77, $p = 0.012$. However, given the data limitations discussed above, this lower cut-point tends to produce results that appear to violate the statistical assumptions associated with proportional hazard regression (Hosmer and Lemeshow, 1999). It is also noted that our external mortality outcomes included not only suicides, but also homicides, drug overdoses, accidental poisoning, unintended injuries, and injuries of unknown cause, potentially confounding study results. It is also important to point out that these data could have been confounded by undiagnosed diseases at baseline, such as cancer, which could be associated with reduced cholesterol levels (due to rapid weight loss) and subsequent suicide. Another limitation was that our study risk factors were only assessed at baseline and, thus, were assumed to be constant throughout the study follow-up, which may not have been the case (Hosmer and Lemeshow, 1999). Study strengths included that this research was based on a large community-based sample not persons identified through medical clinics and it included assessment of a key battery of psychosocial and other risk factors. However, a limitation of our sample was that it only included male Army veterans. As can be seen with regard to the high rates of alcohol abuse (47%) and anti-social personality disorder (22%) (Table 1), our respondents likely differed from the typical civilian population. Therefore, it may not be possible to fully generalize these results to non-veteran populations.

5. Conclusion

In summary, this study suggests that there was a link between low total cholesterol and deaths from external-causes. Research among other populations also has suggested an association (Diaz-Sastre et al., 2007; Favaro et al., 2004; Garland et al., 2000; Golier et al., 1995; Kunugi et al., 1997; Lindberg et al., 1992; Muldoon et al., 1990; Schuit et al., 1997). A particular challenge for this research in the past has been assessing the impact of other risk factors and character traits that could be related to impulse-control, but which also might be associated with external-cause mortality. Here we have shown that anti-social personality disorder represented one of these risk factors. Also, the impact of morbid depression combined with low cholesterol appeared to be of great significance. Whether cholesterol modification could have affected these outcomes, especially among those with morbid depression is an interesting hypothesis that should be addressed in future research.

Although research has failed to show a strong link (Muldoon et al., 2001), we think our findings warrant investigation and might have implications for treatment, prevention, and clinical surveillance among those on cholesterol-reducing regimens (Harris, 2008; Huffman and Stern, 2007; LaRosa et al., 2007). Our study suggested that there was a significant risk of external-cause mortality among those with low cholesterol and morbid depression. Given the risk-level found, we think that increased clinical surveillance is warranted. Future research also might benefit from investigating whether higher baseline cholesterol may be neuroprotective, providing a protective reservoir related to neuronal/synaptic dysfunction that may develop later in life due to disease or weight loss (Dupuis et al., 2008). Conversely, future research should also explore whether low cholesterol is a lifelong trait that increases downstream mortality risks related to onset of neuropsychiatric conditions later in life. While this goes beyond the scope of the current study, researchers need to also consider the possibility that cholesterol status could also represent state as well as a trait variable as well.

While this study has limitations, it is noted that we must reject our original hypothesis that the association between low cholesterol and external mortality could be chiefly explained by confounding factors. It appears that low total cholesterol is an independent and robust predictor of future external-cause mortality in our analyses. This association could not be explained by other obvious interrelated risk factors. Again, clinical surveillance is advised, especially among those with low cholesterol and who are suffering concurrently with clinical depression.

Conflict of interest statement

The authors have no conflict of interest related to the current research.

Contributors

Dr. Boscarino secured the funding and data for this study, designed the study, analyzed the data, and wrote drafts of the manuscript. Dr. Erlich participated in data analyses, literature reviews, statistical consultations, and in the writing of the manuscript. Dr. Hoffman participated in clinical consultations, literature reviews, and in the writing of the manuscript. All authors have approved this manuscript.

Role of funding source

Funding for this study was provided in part by the National Institute of Mental Health Training Grant No. MH-19105 for Dr. Boscarino. This funding source had no involvement in the study design or the content of the current manuscript.

Acknowledgements

Support for this study was provided in part by the National Institute of Mental Health Training Grant No. MH-19105 for Dr. Boscarino.

References

American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 3rd ed. Washington, DC: American Psychiatric Association; 1980.

Boehmer TK, Flanders WD, McGeehin MA, Boyle C, Barrett DH. Post-service mortality in Vietnam veterans: 30-year follow-up. Archives of Internal Medicine 2004;164:1908–16.

Boscarino JA. Post-traumatic stress and associated disorders among Vietnam veterans: the significance of combat exposure and social support. Journal of Traumatic Stress 1995;8:317–36.
Boscarino JA. Diseases among men 20 years after exposure to severe stress: implications for clinical research and medical care. Psychosomatic Medicine 1997;59:605–14.
Boscarino JA. Association between posttraumatic stress disorder and physical illness: results and implications from clinical and epidemiologic studies. Annals of the New York Academy of Sciences 2004;1032:141–53.
Boscarino JA. External-cause mortality after psychologic trauma: the effects of stress exposure and predisposition. Comprehensive Psychiatry 2006;47:503–14.
Budzynski J, Klopocka M, Swiatkowski M, Pulkowski G, Ziolkowski M. Lipoprotein(a) in alcohol-dependent male patients during a six-month abstinence period. Alcohol and Alcoholism 2003;38:157–62.
Centers for Disease Control. Health status of Vietnam veterans, vol. II. Telephone interview. Atlanta, GA: Centers for Disease Control; 1989a.
Centers for Disease Control. Health status of Vietnam veterans, vol. III. Medical examination. Atlanta, GA: Centers for Disease Control; 1989b.
Centers for Disease Control. Health status of Vietnam veterans, vol. IV. Psychological and neuropsychological evaluation. Atlanta, GA: Centers for Disease Control; 1989c.
Centers for Disease Control. Health status of Vietnam veterans: supplement A. Laboratory methods and quality control. Atlanta, GA: Centers for Disease Control; 1989d.
Centers for Disease Control. Health status of Vietnam veterans: supplement C. Medical and psychological procedures and forms. Atlanta, GA: Centers for Disease Control; 1989e.
Cleves MA, Gould WW, Gutierrez RG. Introduction to survival analysis using Stata. College Station, TX: Stata Corporation Press; 2002.
Coryell W, Schlesser M. Combined biological tests for suicide prediction. Psychiatry Research 2007;150:187–91.
Dahlstrom WG, Welsh GS, Dahlstrom LE. An MMPI handbook. revised ed., vol. I. Clinical interpretation. Minneapolis, MN: University of Minnesota Press; 1972.
Dahlstrom WG, Welsh GS, Dahlstrom LE. An MMPI handbook. revised ed., vol. II. Research applications. Minneapolis, MN: University of Minnesota Press; 1975.
Deisenhammer EA, Kramer-Reinstadler K, Liensberger D, Kemmler G, Hinterhuber H, Fleischhacker WW. No evidence for an association between serum cholesterol and the course of depression and suicidality. Psychiatry Research 2004;121:253–61.
Diaz-Sastre C, Baca-Garcia E, Perez-Rodriguez MM, Garcia-Resa E, Ceverino A, Saiz-Ruiz J, et al. Low plasma cholesterol levels in suicidal males: a gender- and body mass index-matched case-control study of suicide attempters and nonattempters. Progress in Neuropsychopharmacological and Biological Psychiatry 2007;31:901–5.
Dupuis L, Corcia P, Fergani A, Gonzalez De Aguilar JL, Bonnefont-Rousselot D, Bittar R, et al. Dyslipidemia is a protective factor in amyotrophic lateral sclerosis. Neurology 2008;70:1004–9.
Engelberg H. Low serum cholesterol and suicide. Lancet 1992;339:727–9.
Favaro A, Caregaro L, Di Pascoli L, Brambilla F, Santonastaso P. Total serum cholesterol and suicidality in anorexia nervosa. Psychosomatic Medicine 2004;66:548–52.
Fiedorowicz JG, Coryell WH. Cholesterol and suicide attempts: a prospective study of depressed inpatients. Psychiatry Research 2007;152:11–20.
Garland M, Hickey D, Corvin A, Golden J, Fitzpatrick P, Cunningham S, et al. Total serum cholesterol in relation to psychological correlates in parasuicide. British Journal of Psychiatry 2000;177:77–83.
Goldman D, Oroszi G, Ducci F. The genetics of addictions: uncovering the genes. Nature Reviews. Genetics 2005;6:521–32.
Golier JA, Marzuk PM, Leon AC, Weiner C, Tardiff K. Low serum cholesterol level and attempted suicide. American Journal of Psychiatry 1995;152:419–23.
Gorwood P. Biological markers for suicidal behavior in alcohol dependence. European Psychiatry 2001;16:410–7.
Harrell Jr FE. Regression modeling strategies: with applications to linear models, logistic regression, and survival analysis. New York, NY: Springer; 2001.
Harris G. FDA requires suicide studies in drug trials. The New York Times; 2008 [January 24, p. 1].
Hosmer DW, Lemeshow S. Applied survival analysis. New York: John Wiley & Sons; 1999.
Huffman JC, Stern TA. Neuropsychiatric consequences of cardiovascular medications. Dialogues in Clinical Neuroscience 2007;9:29–45.
Kulka RA, Schlenger WE, Fairbank JA, Hough RL, Jordan BK, Marmar CR, et al. Trauma and the Vietnam generation: report of findings from the national Vietnam veterans readjustment study. Tables of findings and technical appendices. New York, NY: Brunner/Mazel; 1990.
Kunugi H, Takei N, Aoki H, Nanko S. Low serum cholesterol in suicide attempters. Biological Psychiatry 1997;41:196–200.
Lalovic A, Levy E, Luheshi G, Canetti L, Grenier E, Sequeira A, et al. Cholesterol in the brains of suicide completers. International Journal of Neuropsychopharmacology 2007a;10:159–66.
Lalovic A, Levy E, Canetti L, Sequeira A, Montoudis A, Turecki G. Fatty acid composition in postmortem brains of people who completed suicide. Journal of Psychiatry in Neuroscience 2007b;32:363–70.
LaRosa JC, Grundy SM, Kastelein JJ, Kostis JB, Greten H. Treating to new targets (TNT) steering committee and study investigators. Safety and efficacy of atorvastatin-induced very low-density lipoprotein cholesterol levels in patients with coronary heart disease (a post hoc analysis of the treating to new targets [TNT] study). American Journal of Cardiology 2007;100:747–52.
Lindberg G, Rastam L, Gullberg B, Eklund GA. Low serum cholesterol concentrations and short term mortality from injuries in men and women. British Medical Journal 1992;305:277–9.
Marcinko D, Pivac N, Martinac M, Jakovljevic M, Mihaljevic-Peles A, Muck-Seler D. Platelet serotonin and serum cholesterol concentrations in suicidal and non-suicidal male patients with a first episode of psychosis. Psychiatry Research 2007;150:105–8.
Morgan RE, Palinkas LA, Barrett-Connor EL, Wingard DL. Plasma cholesterol and depression symptoms in older men. Lancet 1993;341:75–9.
Mukamal KJ, Kawachi I, Miller M, Rimm EB. Body mass index and risk of suicide among men. Archives of Internal Medicine 2007;167:468–75.
Muldoon MF, Manuck SB, Mathews KM. Lowering cholesterol concentrations and mortality: a quantitative review of primary prevention trials. British Medical Journal 1990;301:309–14.
Muldoon MF, Manuck SB, Mendelsohn AB, Kaplan JR, Belle SH. Cholesterol reduction and non-illness mortality: meta-analysis of randomised clinical trials. British Medical Journal 2001;322:11–5.
Neaton JD, Blackburn H, Jacobs D, Kuller L, Lee DJ, Sherwin R, et al. Serum cholesterol level and mortality findings for men screened in the multiple risk factor intervention trial. Multiple risk factor intervention trial research group. Archives of Internal Medicine 1992;152:1490–500.
Pagana KD, Pagana TJ. Mosby's diagnostic laboratory test reference. 4th ed. St. Louis, MO: Mosby Press; 1999.
Qiu S, Korwek KM, Weeber E. A fresh look at an ancient receptor family: emerging roles for low density lipoprotein receptors in synaptic plasticity and memory formation. Neurobiology of Learning and Memory 2006;85:16–29.
Robins LN, Helzer JE, Croughan J, Ratcliff KS. National institute of mental health diagnostic interview schedule: its history, characteristics, and validity. Archives of General Psychiatry 1981;38:381–9.
Robins LN, Helzer JE, Cottler LB. The diagnostic interview schedule training manual, version III-A. St. Louis, MO: Veterans Administration; 1987.
Schuit AJ, Dekker JM, Schouten EG. Low serum total cholesterol and mortality from accidents and suicide. In: Hillbrand M, Spitz RT, editors. Lipids, health, and behavior. Washington, DC: American Psychological Association; 1997. p. 263–73.
Stata Corporation. Stata version 9.2. College Station, TX; 2007.
Wiggins JS, Goldberg LR, Applebaum M. MMPI content scales: interpretative norms and correlations with other scales. Journal of Consulting and Clinical Psychology 1971:403–10.