


# The Mutual Impact of Smoking and Low Cholesterol on All-Cause, Non-Cardiovascular, and Cardiovascular Mortalities in Males

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## Abstract

The aim of the current study was to examine the possible relationship between the mutual effects of smoking and low cholesterol on all-cause, non-cardiovascular, and cardiovascular mortalities in males. This is a prospective cohort study of 30,179 males sampled from the Risk Factors and Life Expectancy (RIFLE) studies in the Italian population. The RIFLE data are from 19 different large-scale studies over a 9.5-year follow-up period. The Cox Proportional Hazard model was applied to analyze the data. The associations are presented as hazard ratios (HRs) with 95% confidence interval (CI). Cholesterol data were reported in categories. There were significant mortality risk mutual associations for never-smokers and those in the low cholesterol category (<160 mg/dl) for all-cause (HR = 3.13, 95% CI [1.69, 5.80]), and non-cardiovascular disease (CVD) (HR = 6.51, 95% CI [2.19, 19.33]) mortality in men with an insignificant risk for CVD mortality (HR = 1.90, 95% CI [0.85, 4.22]).

There were significant mortality risk associations of the mutual effects of ex-smokers and low cholesterol for non-CVD in the first to third cholesterol categories (HR = 2.50, 95% CI [1.40, 4.46]; HR = 2.65, 95% CI [1.50, 4.71]; HR = 2.12, 95% CI [1.17, 3.82], respectively), but no significant findings for all-cause and CVD deaths.

Furthermore, there were significant mortality risk association of mutual effects of current-smokers and low cholesterol for non-CVD (HR = 1.56, 95% CI [1.11, 2.28]) in the first category of cholesterol level, but insignificant risk associations for all-cause deaths (HR = 1.21, 95% CI [0.89, 1.66]). Interestingly, findings indicate a mutual protective association for current-smokers and low cholesterol (<160 mg/dl) for CVD risk in males (HR = 0.42, 95% CI [0.19, 0.91]).

Findings of this study identified significant mortality risk association for mutual effects of never-smokers, ex-smokers, and low cholesterol for non-CVD. However, there is significant protective association for current-smokers and low cholesterol for CVD.

## Keywords

smoking status, low serum cholesterol, mortality, male

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Based upon estimates by the World Health Organization (WHO), tobacco continues to kill nearly 6 million people each year, including more than 600,000 passive smokers through lung cancer, atherosclerosis, and other illnesses (WHO, 2008).

At present, about 1.1 to 1.2 billion people smoke in the world, and this figure is expected to increase to 1.6 billion in 2025. In fact, while smoking is declining in most westernized countries, it is substantially increasing in developing countries due to a growth in adult population and increased tobacco consumption. In Italy, the National Institute of Statistics reported that smoking prevalence is

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decreasing in men, from 35.1% in 1993 to 31.2% in 2001, while remaining stable in women, being 16.4% in 1993 and 16.9% in 2001. However, these prevalence values largely underestimate overall tobacco sale rates in Italy and are much lower than those reported by other surveys, which range between 41% and 43% in men and between 24% and 30% in women (Verlato et al., 2006).

The effect of hypercholesterolemia and cardiovascular disease has been extensively researched. There are ample published data documenting that chronic exposure to tobacco smoke leads to a pathological alteration of endothelial function. Endothelial dysfunction may be caused by metabolic (dyslipidemia), environmental (smoking), and physical (arterial hypertension) factors, or by inflammation that provokes pathological conditions (Endemann & Schiffrin, 2004). The possible synergistic and non-synergistic pathophysiologic mechanisms for cigarette smoking and associations for all-cause death, non-CVD, and CVD mortalities are undeniable (Ambrose & Barua, 2004; Lubin, Couper, Lutsey, & Yatsuya, 2016; McHowat, Kuenzel, Kispert, Marentette, & Kolar, 2016; Messner & Bernhard, 2014; Qin, Chen, Lou, & Yu, 2013; Zhang et al., 2016). This link is strengthened in that smoking is known to contain many oxidants that increase damage to critical biologic substances (Ch, 2013). El-Zaatari, Chami, and Zaatari (2015) conducted a study on the short-term and long-term effects of smoking for total morbidity and mortality from non-cardiovascular disease (CVD). This study reported that smoking has numerous effects on lipoprotein metabolism and composition, which promote thermogenesis. It has been hypothesized that many of the adverse effects of smoking may result from oxidative damage to critical biologic substances (Harats et al., 1989; Morrow et al., 1995; Rao et al., 2013).

Both active and passive cigarette smoke impacts all phases of atherosclerosis from endothelial dysfunction to acute clinical events, the latter being largely thrombotic in smokers (Messner & Bernhard, 2014). Cigarette smoke is divided into two phases: a tar phase and a gas phase. The radicals associated with the tar phase are long-lived, whereas the radicals associated with the gas phase have a shorter life span (Pryor & Stone, 1993; Pryor, Stone, Zang, & Bermúdez, 1998; Smith & Fischer, 2001). Epidemiological studies have conclusively proven the relationship between smoking and CVD. The pathobiologic mechanisms behind this link, however, are not clearly understood.

Originally, the Risk Factors and Life Expectancy (RIFLE) studies were presented for conducting an epidemiological observational project which pooled data from nine Italian field studies covering over 70,000 men and women aged 20–69 years, belonging to 52 population samples distributed in 13 different regions of the country. The entry examinations of the population samples were performed for

lengths of follow-up over 9.5 years with the measurements of risk factors and other personal characteristics mainly related to CVD and other chronic conditions. They include many anthropometric, social, biochemical, biophysical, clinical, nutritional, and behavioral measurements, although only a limited subset are common to all the studies.

The current analysis extensively examined the mutual effects of smoking and low serum cholesterol on mortality in males by using RIFLE study data.

## Material and Methods

### Study Population

This is a prospective cohort study conducted on 34,470 males extracted from the RIFLE studies, confined to mortality, over a 9.5-year follow-up period.

### Sample Size

Sample size after quality control of data was 30,179 males. The inclusion criteria were ages 20–69 years old without any underlying disease and cholesterol levels <160 mg/dl to  $\geq$ 276 mg/dl. Exclusion criteria were ages less than or equal to 19 years or greater than or equal to 70 years old, with underlying disease.

### Baseline Measurement

Initially, total serum cholesterol was measured after a 12-hr fast utilizing automated enzymatic methods standardized from the WHO Lipid Reference Center in Prague. Blood pressure, weight, and smoking status were recorded and used for analysis. Age was measured, using the difference between the year of examination and the year of birth, accepting average error of  $\pm$  6 months. Relative body mass index (BMI) was calculated as a percent deviation of actual weight to standard weight based on mean of body weight distributions by height (The RIFLE Research Group, 1993).

### Ascertainment of Mortality Rates

Mortality rates were calculated for males, based upon category cholesterol levels in intervals from <160 mg/dl (<4.4 mmol) to  $\geq$ 276 mg/dl (>7.14 mmol). Cause-specific all-cause, non-CVD, and CVD mortalities were determined according to the ICD-10 (WHO, 2010).

### Statistical Analysis

The dependent or outcome variable is mortality of all-cause, non-CVD, CVD, and the independent variables are cholesterol categories (<160 mg/dl to  $\geq$  276 mg/dl) corresponding the WHO definition, smoking status, and

followed-up time for at least 9.5 years as the study period. To achieve reliability and validity, an attempt was made to ensure that the utilized data were as complete as possible. To obtain complete information related to cholesterol levels and mortalities, and to verify the information, all relevant variables (e.g., sociodemographic, clinical, laboratory, age, smoking status, BMI, systolic and diastolic pressure) were analyzed for controlling confounding or possible interaction effects.

The baseline characteristics were presented as frequencies, Mean  $\pm$  SD and multivariate Cox proportional hazard models applied for testing association of risk factors with all-cause, non-CVD, and CVD mortalities by using SPSS software. Multivariate Cox proportional hazard models were used to adjust for several covariates simultaneously to estimate the hazard ratios (HRs) of mutual impact of smoking and low cholesterol category on all-cause, non-CVD, and CVD mortalities in males. Among these variables, the focus was on more relevant variables and adjusted for others. Male-specific HR of death and its 95% CI were calculated with the reference group to the risk of persons with cholesterol levels of  $\geq 276$  mg/dl. These estimates were adjusted for age and other potential confounding factors by using the Cox proportional hazard models.

## Results

Sociodemographic and clinical characteristics results have been summarized in Table 1. Twenty-four percent (7,248) fell into the category of "passive or never-smoked," 29.1% (8,778) were ex-smokers, and almost half of the total population, 46.9% (14,153), fell into the category of "current-smokers."

Table 2 indicates age-adjusted and multivariate-adjusted HRs of all-cause, non-CVD, and CVD deaths according to serum total cholesterol level by stratified smoking status such as never-smoker, ex-smoker, and current-smoker. Findings in the never-smoker category that were mutual with the first cholesterol category (<160 mg/dl) identified a significant association with all-cause and non-CVD mortalities (HR = 3.13, 95% CI [1.69, 5.80]; HR = 6.51, 95% CI [2.19, 19.33]). There was some risk for CVD death, though not significant (HR = 1.90, 95% CI [0.85, 4.22]). This mutual association was significant only for the non-CVD (HR = 3.33, 95% CI [1.02, 10.89]; HR = 3.35, 95% CI [1.06, 1.56]; HR = 3.27, 95% CI [1.05, 10.17]), never-smoker category in the cholesterol levels 160–174, 175–186, and 199–209 mg/dl. There were marginally significant risks for all-cause and statistically significant risks for non-CVD deaths associated with the ex-smoker category and cholesterol <160 mg/dl (HR = 1.51, 95% CI [0.99, 2.30]; HR = 2.50, 95% CI [1.40, 4.46]).

The association of <160 mg/dl of cholesterol and CVD deaths in ex-smokers was protective, but not significant (HR = 0.78, 95% CI [0.39, 1.54]). There were mutual significant non-CVD mortality risk associations and ex-smokers in the 160–174 mg/dl and 175–186 mg/dl categories of cholesterol (HR = 2.65, 95% CI [1.50, 4.71]; HR = 2.12, 95% CI [1.17, 3.82], respectively).

The mutual effects of <160 mg/dl cholesterol and current-smoker with non-CVD deaths were significant (HR = 1.56, 95% CI [1.11, 2.28]). The mutual effects of <160 mg/dl cholesterol and current-smoker for all-cause of death were not significant (HR = 1.21, 95% CI [0.89, 1.66]).

There is a significant protective association for CVD mortality, mutually with the <160 mg/dl cholesterol level and current-smoker (HR = 0.42, 95% CI [0.19, 0.91]).

## Discussion

The primary objective of this study was to determine the possible relationship between the mutual effects of smoking and low cholesterol on all-cause, non-CVD, and CVD mortalities in males. The study identified (24%) "never-smokers," (29.1%) "ex-smokers," and (46.9%) "current-smokers." This study findings are attributed to a large population, young age, low BMI, low systolic and diastolic blood pressure, long follow-up period, precise and standard method of data measurement, comprehensive advanced analytic procedures, and smoking status. In this study, smoking status is not consistent with a study conducted by Banks (Banks et al., 2015) due to differences in study subjects' characteristics and mutual impact of smoking and low cholesterol on all-cause death.

Mortality rates were calculated for males, based upon different interval cholesterol level categories and smoking status related to cause-specific all-cause, non-CVD, and CVD mortalities determined according to the ICD-10 (WHO, 2010). Distribution of the subpopulation in the smoking categories "never-smoker," "ex-smokers," and "current smokers" from the lowest level of serum cholesterol to the highest is nearly similar. The study identified smoking status as an independent risk factor for all-cause, non-CVD, and CVD mortality among the study subjects. Findings are consistent with previous studies (Ambrose & Barua, 2004; Lubin et al., 2016; McHowat et al., 2016; Messner & Bernhard, 2014; Qin et al., 2013).

The following analytical results comprehensively elaborated the study outcome of mutual effect of smoking status such as never-smokers, ex-smokers, and current smokers with different serum cholesterol categories related to all-cause, non-CVD, and CVD mortality among the study subjects. This research determined that the never, passive, and nonsmoker study population had more mortality risk than other smoking categories due to

**Table 1.** Sociodemographic and Clinical Characteristics Based Upon Cholesterol Categories.

Gender	Cholesterol level mg/dl	Age (year)	Body-mass index (BMI)	Mean $\pm$ SD			Smoking status			Follow-up status (month)	Total subpopulation
				Systolic blood pressure(SBP) (mm/Hg)	Diastolic blood pressure (DBP) (mm/Hg)	Never-smoker (%)	Ex-smoker (%)	Current-smoker (%)			
Male	<160	42.45 $\pm$ 13.82	24.98 $\pm$ 3.65	128.72 $\pm$ 19.01	80.74 $\pm$ 11.32	27.5 (775)	24.2 (682)	48.3 (1363)	86.58 $\pm$ 34.28	2,820	
	160–174	44.51 $\pm$ 12.98	25.63 $\pm$ 3.66	130.62 $\pm$ 18.27	82.20 $\pm$ 10.91	26.5 (640)	26.9 (647)	46.6 (1122)	86.26 $\pm$ 32.58	2,409	
	175–186	45.56 $\pm$ 12.64	25.81 $\pm$ 3.51	132.13 $\pm$ 19.50	83.17 $\pm$ 11.28	27.7 (714)	26.8 (691)	45.5 (1171)	85.35 $\pm$ 32.78	2,576	
	187–198	46.66 $\pm$ 11.99	26.04 $\pm$ 3.56	133.32 $\pm$ 19.55	83.55 $\pm$ 11.27	24.4 (726)	26.9 (802)	48.7 (1450)	85.86 $\pm$ 32.43	2,978	
	199–209	47.16 $\pm$ 11.65	26.13 $\pm$ 3.47	133.74 $\pm$ 19.43	84.22 $\pm$ 11.00	25.4 (757)	29.3 (876)	45.3 (1351)	84.49 $\pm$ 32.82	2,984	
	210–221	48.00 $\pm$ 11.42	26.40 $\pm$ 3.51	135.37 $\pm$ 19.67	85.10 $\pm$ 11.13	24.2 (797)	28.7 (943)	47.1 (1547)	84.05 $\pm$ 30.87	3,287	
	222–234	48.61 $\pm$ 10.97	26.55 $\pm$ 3.40	136.36 $\pm$ 19.70	85.65 $\pm$ 11.46	22.5 (713)	29.6 (939)	47.9 (1518)	85.86 $\pm$ 31.03	3,170	
	235–250	49.01 $\pm$ 10.85	26.68 $\pm$ 3.41	137.38 $\pm$ 19.26	86.19 $\pm$ 11.07	22.7 (778)	31.1 (1070)	46.2 (1585)	83.14 $\pm$ 31.05	3,433	
	251–275	49.54 $\pm$ 10.66	26.83 $\pm$ 3.37	139.11 $\pm$ 19.67	87.07 $\pm$ 11.29	21.0 (707)	32.1 (1083)	46.9 (1580)	83.28 $\pm$ 30.84	3,370	
	$\geq 276$	49.72 $\pm$ 10.07	27.03 $\pm$ 3.26	142.30 $\pm$ 20.31	88.50 $\pm$ 11.26	20.3 (641)	33.2 (1095)	46.9 (1466)	82.65 $\pm$ 31.41	3,152	
	Total	47.31 $\pm$ 11.87	26.25 $\pm$ 3.52	135.21 $\pm$ 19.84	84.84 $\pm$ 11.41	24.0 (7248)	29.1 (8778)	46.9 (14153)	84.65 $\pm$ 31.97	3,0179	

**Table 2.** Age-Adjusted and Multivariate-Adjusted Hazard Ratio of All-Cause, Non-CVD, and CVD Deaths According to Serum Total Cholesterol Categories, Stratified by Never-Smoker, Ex-Smoker, and Current Smoking Status in Males.

Smoking status	Total serum cholesterol (mg/dl)	All-cause of death				Non-CVD				CVD			
		Age-adj <sup>b</sup>		Multivariate-adj <sup>b</sup>		Age-adj <sup>b</sup>		Multivariate-adj <sup>b</sup>		Age-adj <sup>b</sup>		Multivariate-adj <sup>b</sup>	
		n <sup>a</sup>	hazard ratio	Hazard ratio 95% confidence interval	n <sup>a</sup>	hazard ratio	Hazard ratio 95% confidence interval	n <sup>a</sup>	hazard ratio	Hazard ratio 95% confidence interval	n <sup>a</sup>	hazard ratio	Hazard ratio 95% confidence interval
Never-smoker (7,248)	<160	34	2.91	3.13 [1.69, 5.80]	19	6.07	6.51 [2.19, 19.33]	15	1.76	1.90 [0.85, 4.22]			
	160–174	12	1.08	1.19 [0.55, 2.55]	9	3.06	3.33 [1.02, 10.89]	3	0.36	0.40 [0.11, 1.46]			
	175–186	16	1.14	1.22 [0.59, 2.51]	12	3.16	3.35 [1.06, 1.56]	4	0.41	0.44 [0.14, 1.41]			
	187–198	13	0.76	0.82 [0.37, 1.79]	7	1.83	1.96 [0.57, 6.73]	6	0.37	0.40 [0.13, 1.28]			
	199–209	18	1.09	1.15 [0.60, 2.34]	13	3.08	3.27 [1.05, 10.17]	5	0.36	0.39 [0.12, 1.22]			
	210–221	22	1.38	1.48 [0.77, 2.87]	9	2.13	2.27 [0.69, 7.39]	13	1.10	1.19 [0.53, 2.69]			
	222–234	17	1.09	1.14 [0.57, 2.29]	9	2.18	2.25 [0.69, 7.33]	8	0.69	0.73 [0.29, 1.84]			
	235–250	23	1.36	1.45 [0.75, 2.81]	9	2.08	2.18 [0.67, 7.11]	14	1.09	1.20 [0.53, 2.69]			
	251–275	23	1.31	1.36 [0.70, 2.64]	13	2.84	2.90 [0.93, 9.02]	10	0.76	0.80 [0.33, 1.99]			
	(RG) <sup>c</sup> ≥276	16	1.00	1.00 (-----)	5	1.00	1.00 (-----)	11	1.00	1.00 (-----)			
	Ex-smoker (8,778)	<160	46	1.47	1.51 [0.99, 2.30]	34	2.62	2.50 [1.40, 4.46]	12	0.69	0.78 [0.39, 1.54]		
		160–174	43	1.35	1.40 [0.92, 2.15]	35	2.71	2.65 [1.50, 4.71]	8	0.44	0.49 [0.22, 1.10]		
		175–186	37	1.10	1.16 [0.75, 1.80]	29	2.15	2.12 [1.17, 3.82]	8	0.40	0.46 [0.21, 1.01]		
187–198		40	1.04	1.06 [0.69, 1.63]	25	1.60	1.58 [0.86, 2.84]	15	0.66	0.70 [0.37, 1.31]			
199–209		47	1.17	1.21 [0.81, 1.83]	25	1.56	1.54 [0.84, 2.83]	22	0.91	0.99 [0.56, 1.76]			
210–221		48	1.04	1.07 [0.71, 1.61]	25	1.35	1.34 [0.73, 2.45]	23	0.83	0.89 [0.51, 1.56]			
222–234		48	1.06	1.09 [0.72, 1.63]	25	1.40	1.40 [0.77, 2.55]	23	0.82	0.87 [0.50, 1.59]			
235–250		54	1.06	1.08 [0.73, 1.61]	26	1.24	1.23 [0.68, 2.25]	28	0.93	0.99 [0.58, 1.68]			
251–275		53	1.03	1.02 [0.69, 1.52]	28	1.28	1.29 [0.72, 2.33]	25	0.80	0.84 [0.44, 1.44]			
(RG) <sup>c</sup> ≥276		52	1.00	1.00 (-----)	23	1.00	1.00 (-----)	29	1.00	1.00 (-----)			
Current smoker (14,153)		<160	71	1.05	1.21 [0.89, 1.66]	63	1.44	1.56 [1.11, 2.28]	8	0.32	0.42 [0.19, 0.91]		
		160–174	45	0.69	0.78 [0.55, 1.12]	31	0.76	0.81 [0.52, 1.26]	14	0.58	0.72 [0.39, 1.34]		
		175–186	50	0.70	0.76 [0.54, 1.08]	38	0.84	0.89 [0.59, 1.34]	12	0.45	0.53 [0.28, 1.03]		
	187–198	79	0.85	0.95 [0.70, 1.28]	49	0.85	0.90 [0.62, 1.32]	30	0.85	1.03 [0.63, 1.68]			
	199–209	78	0.87	0.96 [0.72, 1.31]	49	0.88	0.93 [0.64, 1.37]	29	0.84	1.02 [0.62, 1.68]			
	210–221	74	0.69	0.76 [0.57, 1.04]	43	0.66	0.70 [0.47, 1.03]	31	0.75	0.88 [0.54, 1.44]			
	222–234	70	0.63	0.68 [0.50, 0.93]	45	0.68	0.71 [0.48, 1.05]	25	0.54	0.61 [0.36, 1.04]			
	235–250	102	0.90	0.96 [0.73, 1.28]	62	0.90	0.94 [0.66, 1.34]	40	0.90	1.01 [0.64, 1.60]			
	251–275	110	0.96	1.02 [0.78, 1.28]	60	0.84	0.88 [0.61, 1.26]	50	1.16	1.26 [0.82, 1.95]			
	(RG) <sup>c</sup> ≥276	98	1.00	1.00 (-----)	62	1.00	1.00 (-----)	36	1.00	1.00 (-----)			

Note. <sup>a</sup>N = number of study subjects; <sup>b</sup>Age-adj. = age-adjusted, multivariate-adjusted for (age, body mass index, systolic blood pressure, and diastolic blood pressure); <sup>c</sup>RG = reference group.

a higher vulnerability of exposure to carbon monoxide than smokers.

Findings identified a threefold risk of mortality for all-cause, a 6.5-fold risk for non-CVD mortality with a significant association of the mutual effects of never-smoker and lowest cholesterol category (<160 mg/dl); however, insignificant risk association was found for CVD mortality. Also, significant association exists for non-CVD mortalities in 160–174, 175–186, and 199–209 mg/dl cholesterol levels, though, a protective association exists for CVD that was not significant. In the never-smoker, the HR of non-CVD mortality was twofold higher than all-cause death in the lowest cholesterol category (6.51 vs. 3.13). There were distinguishable risks of mortality for almost all the remaining categories of cholesterol levels for all-cause death and non-CVD for never-smokers. The CVD mortalities were noticeable in the lowest level of cholesterol (<160 mg/dl) for never-smokers, after age-adjusted and multivariate-adjusted HR but were not significant.

These results are consistent with findings of the studies by the USA Institute of Medicine of the National Academies and Rietbrock, Kunkel, Worner, and Eyer, which found nonsmokers were more susceptible to carbon dioxide than smokers due to simply being exposed to cigarette smoke which may reduce their maximal oxygen uptake ( $VO_{2max}$ ; Rietbrock, Kunkel, Wörner, & Eyer, 1992; USA Institute of Medicine of the National Academies, 2009, and retrieved 2013). This finding disagrees with a previous study conducted by Thun et al. (2013) due to differences in sociodemographic characteristics, diets, and eating habits, smoking status, and methodological issues.

Moreover, study results are consistent with recent studies of short-term and long-term effects of smoking for total morbidity and mortality from non-CVD such as cancer, lung disease, oral diseases, and osteoporosis (El-Zaatari et al., 2015).

In ex-smokers, findings identified 1.5 times the mortality risk for all-cause in the lowest serum cholesterol. In addition, 2.5 times mortality risk with significant association was found in the lowest cholesterol for non-CVD mortalities in ex-smokers. Also, significant association exists for non-CVD mortalities in 160–174 and 175–186 mg/dl cholesterol levels. However, protective association existed for CVD but it was not significant. Analytical findings indicated insignificant association in the remaining categories of cholesterol levels for all-cause, non-CVD, and CVD mortalities related to ex-smokers. In general, this research revealed an interesting concept in that the mutual effect of being an ex-smoker with various levels of cholesterol identified a mortality risk association for all cause and non-CVD however, there was a protective association for CVD. These

findings are consistent with results of the study by Campbell which found smoking cessation reduced CVD risk (Campbell et al., 2008).

Findings identified some insignificant mortality risk for all-cause, significant risk for non-CVD mortality association in mutual effect of current-smoker and lowest cholesterol category (<160 mg/dl), and significant protective association for CVD mortality. Also, insignificant protective association existed for all-cause and non-CVD mortalities in the remaining categories of cholesterol levels and current-smoker.

The novel and interesting finding is that there was a significant protective association against CVD death in the study population of subjects currently smoking who had low cholesterol level of <160 mg/dl. This demonstrated a mutual association between smoking and low cholesterol that decreased CVD mortality risk. There were insignificant protective associations in the second, third, sixth, and seventh categories of cholesterol with currently smoking subjects for CVD mortality.

In summary, findings indicated the highest mortality rates were related to all-cause and non-CVD at the cholesterol level of <160 mg/dl and the category of passive or never-smokers compared to the other smoking categories in the study population, but no significant protective associations for never-smokers or ex-smokers. In the end, mortality for all-cause, non-CVD, and CVD drastically decreased starting in the categories of never-smoker to ex-smoker to current-smokers after age-adjusted and multivariate-adjusted HR. This trend identified the magnitude of a mutual effect of never-smoker and lowest serum cholesterol mortalities compared with ex-smoker and current-smoker mortalities.

It is notable that the study findings identified the least subpopulation (7,248) with significantly high mortality ratios for the lowest level of cholesterol (<160 mg/dl) in the passive or never-smoker categories compared to the ex-smoker (8,778) and highest numbers (14,153) in the current-smoker subpopulations.

These findings are supported by previous studies (Rietbrock et al., 1992; USA Institute of Medicine of the National Academies 2009, retrieved 2013).

It is noteworthy that these results do not conflict with many previous studies regarding total cholesterol. However, unlike previous research, this study precisely indicated risk of specific cholesterol level related to smoking-status in terms of all-cause, non-CVD, and CVD mortalities.

## Strengths and Limitations

Although this study may have reported an underestimation of risk factors in the study population, reporting biases were thought to be minimal due to continuous

evaluation, quality control and cleaned up missing and unknown data. We measured HRs precisely at each level of cholesterol relative to the reference level to indicate magnitude of low serum cholesterol mortalities. It was expected, according to the hypothesis of this study, that each level has a degree of risk that is independent of its previous and next levels in relation to the reference level, along with the nature of the data. However, the nature of the data has increased or decreased the risk or protection in the present study. Despite study biases, these findings demonstrated a strong association between risk factors as a factor of significant morbidity and mortality in low cholesterol level and excess death rate.

In addition, results of this research were able to associate low cholesterol magnitude with mortalities in study subjects. Analytical results of this study emphasize careful medical and pharmacological management for the low cholesterol population, specifically for all-cause and non-CVD and protection for CVD death in the study.

However, as in any observational cohort studies, the findings may be confounded by unmeasured variables with limited impact on the study. Nevertheless, this study has some limitations in that other risk factors may have been involved although minimal. The impact of other coincidental risk factors may express causes of death as mutual effects of a smoker's status and low cholesterol for the study population. The interrelation of all-cause, non-CVD, and protection against CVD deaths with different cholesterol levels is complex and likely to diverge directions toward risk or factors that are protective. A larger prospective cohort study and longer follow-up is required to determine the prognostic and treatment value of low cholesterol, for clarification of the biological and clinical pathway.

## Conclusion

In conclusion, multivariate-adjusted findings identified significant association of risk for the mutual effects of never-smokers and the lowest cholesterol level for all-cause and non-CVD mortality, with some risk for CVD mortality. For ex-smokers and current-smokers, there is significant risk association with the lowest serum cholesterol level for non-CVD and marginally significant for all-cause of deaths. The findings are novel and interesting, in that there is a significant protective association for CVD and mutual effects of current-smokers and low cholesterol level. This study highlighted important clinical implications and would be supportive of public health initiatives directed to prevention of these deaths. Furthermore, clarification of the biological and clinical pathway is needed to examine the related issues of interests for further research.

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## Contribution

Dr. Nader Parsa designed the article. Dr. Nader Parsa and Samira Taravatmanesh did write the article. Dr. Maurizio Trevisan was supervisor. Dr. Pari Mahlegaha Zaheri edited the article.

## Declaration of Conflicting Interests

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