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Comparison of Noncardiovascular and Cardiovascular Mortality Related to Low Serum Cholesterol Among Males and Females

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Abstract

Background: Contrary to popular belief, no study to date has provided evidence regarding the effect of low cholesterol level on extended overall survival.
Objectives: The aim of the current study was to examine the possible relationship between low serum cholesterol (< 160 mg/dL) and mortality from cardiovascular diseases (CVDs) and non-CVDs in males and females.
Methods: This observational, prospective, cohort study included 19 different large-scale dynamic cohort studies in Italian populations, followed-up for 9 years. The Cox proportional hazard ratio (HR) was measured to analyze the data. The associations were presented as HRs with 95% confidence intervals.
Results: The results showed that 1906 deaths (males, 1439 and females, 467; total non-CVD, 1214 and total CVD, 692) occurred during the 9-year follow-up. Total mortality for non-CVD was almost twice (1.76) higher than that of CVD. There was a significant inverse association between low serum cholesterol and non-CVD mortality in males, unlike females. The association of low cholesterol level with non-CVD mortality was more significant than CVD mortality among males (non-CVD: HR, 2.06; 95% CI, 1.54 - 2.74 vs. CVD: HR, 0.81; 95% CI, 0.54 - 1.22). However, an insignificant association was found between both non-CVD and CVD mortalities and low serum cholesterol among females (non-CVD: HR, 1.52; 95% CI, 0.91 - 2.50 vs. CVD: HR, 1.56; 95% CI, 0.72 - 3.38).
Conclusions: The findings indicated an inverse association between low serum cholesterol and high non-CVD mortality versus CVD mortality. Therefore, non-CVD mortality rate was higher than CVD mortality in males and lower in females at minimum cholesterol level.

Keywords: Mortality, Noncardiovascular Disease, Cardiovascular Disease, Low Serum Cholesterol

1. Background

The relationship of high serum cholesterol with coronary heart disease (CHD) and other cardiovascular diseases (CVD) is well established. On the other hand, a relationship between low serum cholesterol and mortality from non-CHD and non-CVD events has been recently examined in several large studies. Decreased cholesterol level occurs in acute diseases or conditions, such as burns (1), traumas (2), acute infections (3-5), myocardial infarction (6), and chronic diseases.

Low serum cholesterol concentration is also associated with malnutrition (7), cancer (8-15), rheumatoid arthritis (16), and other inflammatory processes (17). Additionally, some researchers have evaluated anthropometric indices, body mass index (BMI), and laboratory parameters to present nutritional status and inflammatory diseases as possible causes of low serum cholesterol level and confounders of risk assessment (18).

Although the mechanisms of low serum cholesterol in acute and chronic diseases have not been established, parenteral administration of lipopolysaccharides or cytokine mediators of inflammation can experimentally reduce cholesterol level (19, 20). The inverse association, although controversial, between cholesterol level and non-CVD mortality has encouraged researchers to conduct further examinations; nevertheless, the literature is still sparse, and conclusions are tentative. Moreover, many early theories have reported controversial results regarding the association between reduced plasma cholesterol level and increased mortality from non-CVDs.

2. Objectives

The current study extensively examined the possible relationship between low serum cholesterol (< 160 mg/dL) and mortality from CVDs and non-CVDs between males and females from populations included in 19 out of 52 cohort studies.

3. Methods

3.1. Study Population

In this pooling epidemiological observational cohort study, data on relative risk for life expectancy in risk factors and life expectancy pooling project (RIFLE) were collected from 19 out of 52 different large-population studies in Italy over 9 years, with a focus on CVDs and other chronic conditions. This study included men and women within the age range of 20 - 69 years.

3.2. Sample Size

In this study, random sampling method was applied. The analysis included 19 out of 52 cohorts, including 30 179 males and 26,005 females. The study was confined to men and women with mortalities during the follow-up (extending to approximately 9 years as the endpoint) (Figure 1).

3.3. Baseline Measurements

The total serum cholesterol was measured in blood samples drawn from the antecubital vein after 12 hours of fasting. Several automated enzymatic methods were employed in different studies. All the involved laboratories were under direct or indirect control of WHO lipid reference center in Prague (21). Blood pressure was measured in a sitting position after a 4-minute rest in the right arm, using a calibrated sphygmomanometer.

The observers were trained and tested, using the WHO manual (22) and cassettes developed by the London school of hygiene (23) and later the laboratory of physiological hygiene, University of Minnesota (24). Systolic blood pressure and diastolic-2 (fifth phase) pressure were determined for the analysis, although diastolic-1 pressure was recorded in most studies (25). Weight was measured in light underwear and rounded off to the nearest kilogram, while height was examined without shoes and expressed in centimeters, based on the WHO manual.

Smoking status was assessed using a questionnaire, which was directly derived from the WHO cardiovascular survey manual (26). Age was measured by the difference between the year of examination and year of birth, with an average error of +6 months. The relative BMI was calculated as percentage of deviation in actual weight from standard weight, based on the mean body weight distribution by height. The weight-to-height ratio was calculated by dividing weight in kilograms by the square of height in meters; it was used as an indicator of obesity and underweight (kg/m^2).

3.4. Ascertainment of Mortality Rates

The mortality rates were calculated for each gender, based on the decile of cholesterol level at equal intervals from < 160 mg/dL (< 4.4 mmol) to > 276 mg/dL (> 7.14 mmol). Gender-specific rates were age-adjusted using direct methods of standardization, considering the age distribution of the total group, which consisted of 30,179 males and 26 005 females. Cause-specific mortality was determined according to the International Classification of Diseases (ICD-10) (25). Moreover, cause-specific mortality from CVD was determined, based on ICD-10 (25): CHD, 410 - 414; cardiovascular accidents (CVAs), 530 - 538; and other CVDs, 390 - 409, 415 - 429, and 440 - 459, respectively.

3.5. Reliability and Validity

To determine reliability and validity, the original data (RIFLE studies) were reviewed in an attempt to ensure that the collected data on the studied variables were as complete as possible. To obtain complete information related to cholesterol level and mortality and to verify the information, all variables, which were documented and related to cholesterol level, were selected for controlling confounding variables or interaction effects.

It was assumed that any significant event, which occurred during the original follow-up studies, was recorded in a data file. Moreover, it was assumed that the laboratory records of test results at Italian laboratories and/or interpretation of the results were precise. Clinical, anthropometric, and sociodemographic information was also assumed to be properly recorded. An attempt was made to ensure that all test results and data were sufficient for obtaining accurate results in the data analysis. However, given the differences in the utilized data and records, in few instances, there might be some data missing or misclassified with possible underestimations.

3.6. Data Analysis

First, the proportional hazard assumption was checked graphically. To determine the association of baseline risk factors with non-CVD and CVD mortalities, univariate and multivariate Cox proportional hazard models were used. With respect to reliability and validity, we made sure that the utilized data were as complete as possible. To obtain complete information on cholesterol level and its association with mortality and to verify the

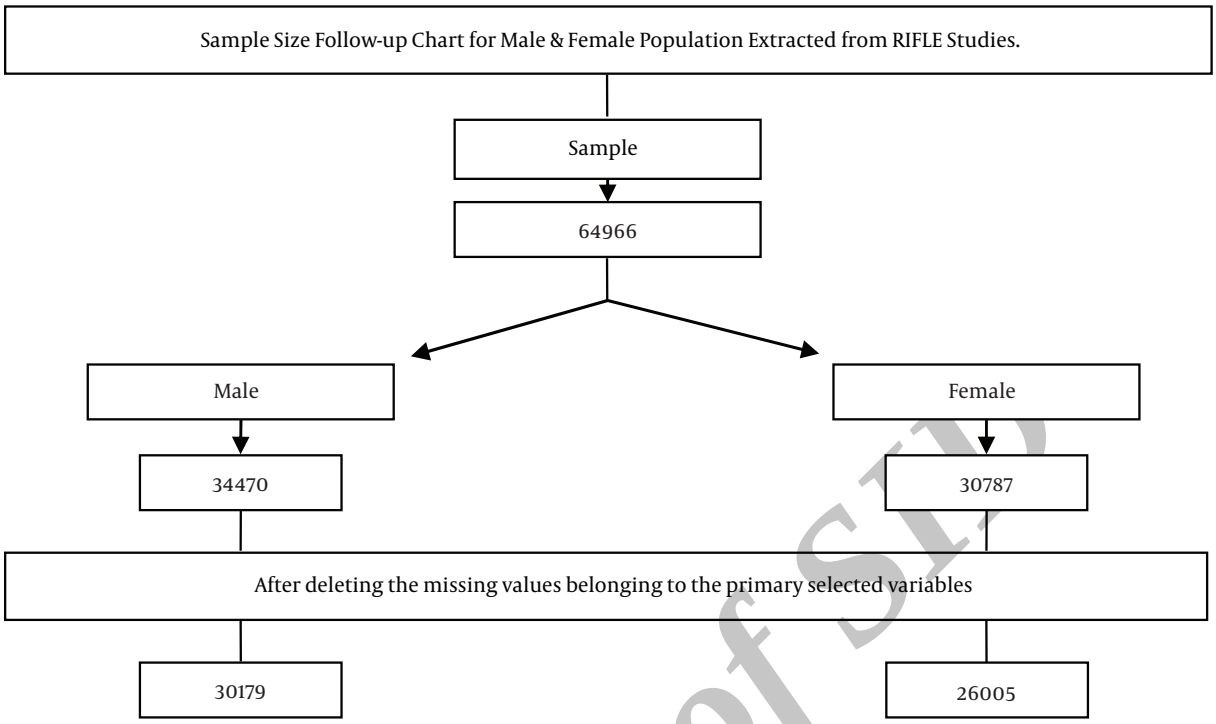

Figure 1. The Follow-Up Chart for Male and Female Populations from RIFLE Studies

information, all variables, including sociodemographic status, anthropometric features, clinical findings, laboratory results, age, smoking status, BMI, and systolic and diastolic blood pressure, were analyzed to control the confounding or interaction effects. Data analysis was performed using SPSS to elaborate the association between mortality and cholesterol level.

4. Results

The groups were selected from the follow-up cohort RIFLE study, conducted on Italian populations over a 9-year period. Of a total of 64,966 men and women, aged 20 - 69 years, 30,179 men and 26,005 women remained in the study after removing the missing values. Table 1 indicates the mean ± SD of BMI, age (years), systolic and diastolic blood pressure (mmHg), total serum cholesterol (mg/dL), smoking status, and follow-up (months) in male compared to female populations, based on the decile of cholesterol levels.

Table 2 indicates the specific cause of mortality in males, compared to the female population, based on the decile of cholesterol level. According to the results, 4.76% (n, 1439) and 1.79% (n, 467) of men and women died in the total male and female populations, respectively. Total mortality from non-CVDs in the male population (n, 1439) was nearly twice higher than that of CVDs (61.0%; n, 882 vs. 39.0%; n, 557). Mortality rates related to CHD (29.6%; n, 424), CVAs (7.2%; n, 102), and other CVDs (2.2%; n, 31) are also indicated in Table 2.

Moreover, in the female population (n, 467), total mortality was 71.0% (n, 332) from non-CVDs and 29.0% (n, 135) from CVDs. CVD-related mortalities included CHD (16.6%; n, 77), CVAs (9.0%; n, 42), and other CVDs (3.4%; n, 16). In total, the findings from male and female populations showed that 63.7% (n, 1214) of mortalities were non-CVD, while 36.3% (n, 692) were CVD-related. These results indicate that the rate of non-CVD mortality is nearly twice higher than CVD mortality.

Table 3 presents the age- and multivariate-adjusted hazard ratios (HRs) of total mortality from non-CVDs and CVDs, according to the total serum cholesterol levels in males and females. There was an inverse association between total serum cholesterol and non-CVD mortality, with age-adjusted and -unadjusted mortality rates for males, but not females. The inverse association for men remained significant at minimum serum cholesterol level (< 160 mg/dL) after adjustments for age, BMI, systolic and diastolic blood pressure, and smoking status (non-CVD: HR, 2.06; 95% CI, 1.54 - 2.74 for multivariate adjustment). Al-

Table 1. The Baseline Characteristics of Male (n, 30 179) Compared to Female (n, 26 005) Populations Based on the Decile of Cholesterol Level

Gender	Cholesterol Level, mg/dL	Mean ± SD				Smoking Status			Follow-Up Status, mo	Total Subpopulation
		BMI	Age, y	Systolic Blood Pressure, mmHg	Diastolic Blood Pressure, mmHg	Never (%)	Ex-Smoker (%)	Current Smoker (%)		
Male										
	160 - 174	25.63 ± 3.66	44.51 ± 12.98	130.62 ± 18.27	82.20 ± 10.91	26.5 (640)	26.9 (647)	46.6 (1122)	86.26 ± 32.58	2409
	175 - 186	25.81 ± 3.51	45.56 ± 12.64	132.13 ± 19.50	83.17 ± 11.28	27.7 (714)	26.8 (691)	45.5 (1171)	85.35 ± 32.78	2576
	187 - 198	26.04 ± 3.56	46.66 ± 11.99	133.32 ± 19.55	83.55 ± 11.27	24.4 (726)	26.9 (802)	48.7 (1450)	85.86 ± 32.43	2978
	199 - 209	26.13 ± 3.47	47.16 ± 11.65	133.74 ± 19.43	84.22 ± 11.00	25.4 (757)	29.3 (876)	45.3 (1351)	84.49 ± 32.82	2984
	210 - 221	26.40 ± 3.51	48.00 ± 11.42	135.37 ± 19.67	85.10 ± 11.13	24.2 (797)	28.7 (943)	47.1 (1547)	84.05 ± 30.87	3287
	222 - 234	26.55 ± 3.40	48.61 ± 10.97	136.36 ± 19.70	85.65 ± 11.46	22.5 (713)	29.6 (939)	47.9 (1518)	85.86 ± 31.03	3170
	235 - 250	26.68 ± 3.41	49.01 ± 10.85	137.38 ± 19.26	86.19 ± 11.07	22.7 (778)	31.1 (1070)	46.2 (1585)	83.14 ± 31.05	3433
	251 - 275	26.83 ± 3.37	49.54 ± 10.66	139.11 ± 19.67	87.07 ± 11.29	21.0 (707)	32.1 (1083)	46.9 (1580)	83.28 ± 30.84	3370
	≥ 276	27.03 ± 3.26	49.72 ± 10.07	142.30 ± 20.31	88.50 ± 11.26	20.3 (641)	33.2 (1095)	46.9 (1466)	82.65 ± 31.41	3152
	Total	26.25 ± 3.52	47.31 ± 11.87	135.21 ± 19.84	84.84 ± 11.41	24.0 (7248)	29.1 (8778)	46.9 (14153)	84.65 ± 31.97	30179
Female										
	< 160	24.34 ± 4.58	37.34 ± 11.05	122.25 ± 18.58	77.52 ± 10.96	62.0 (1732)	8.3 (233)	29.7 (829)	88.74 ± 34.36	2794
	160 - 174	25.06 ± 4.68	39.55 ± 11.10	124.83 ± 19.39	78.92 ± 11.23	63.8 (1632)	8.3 (211)	27.9 (714)	87.69 ± 33.17	2557
	175 - 186	25.59 ± 4.85	41.87 ± 11.39	126.93 ± 19.95	80.35 ± 11.28	66.7 (1744)	7.7 (200)	25.6 (669)	85.67 ± 32.01	2613
	187 - 198	25.97 ± 5.00	43.48 ± 11.99	129.72 ± 20.94	81.45 ± 11.81	69.2 (1802)	6.7 (174)	24.1 (626)	84.98 ± 31.23	2602
	199 - 209	26.38 ± 4.98	45.29 ± 11.58	132.15 ± 22.58	82.24 ± 11.96	68.9 (1729)	7.3 (184)	23.8 (598)	85.16 ± 31.71	2511
	210 - 221	26.48 ± 4.90	46.95 ± 11.42	134.07 ± 22.10	83.53 ± 11.68	70.3 (1887)	7.4 (200)	22.3 (599)	84.42 ± 31.47	2686
	222 - 234	26.85 ± 4.95	48.72 ± 11.23	136.26 ± 23.05	84.38 ± 12.11	72.8 (1833)	7.0 (178)	20.2 (508)	82.92 ± 30.50	2519
	235 - 250	27.33 ± 4.93	50.74 ± 10.84	139.13 ± 22.55	85.50 ± 11.99	74.8 (1903)	6.6 (167)	18.6 (474)	84.68 ± 30.27	2544
	251 - 275	27.33 ± 4.70	52.52 ± 10.11	141.60 ± 22.32	86.04 ± 11.67	73.7 (1925)	6.8 (177)	19.5 (508)	84.67 ± 30.59	2610
	≥ 276	27.23 ± 4.46	54.48 ± 9.73	145.54 ± 22.82	87.72 ± 11.74	73.6 (1890)	7.0 (181)	19.4 (498)	83.37 ± 30.58	2569
	Total	26.2 4 ± 4.90	46.02 ± 12.30	133.16 ± 22.62	82.72 ± 12.05	69.5 (18077)	7.3 (1905)	23.2 (6023)	85.26 ± 31.68	26005

though in the female population, a significant HR was measured for cholesterol levels less than 160 mg/dL, it was insignificant for the total non-CVD mortality (non-CVD: HR, 1.52; 95% CI, 0.91 - 2.50 for multivariate-adjusted HR).

5. Discussion

The primary objective of this study was to determine the association between low serum cholesterol level and mortality due to CVDs and non-CVDs between males and females. The findings indicated that 4.76% of men and 1.79% of women died during 9 years of follow-up, which is approximately 3 times higher among males than females. The observed gender difference is contrary to a previous study by Vigen R. et al. (26) and may be explained by discrepancies in the study populations, age, follow-up duration, sample size, and statistical methods.

Total mortality due to non-CVDs was more than 1.6 times higher than CVD mortality (2.92% vs. 1.84%) among males. In addition, total mortality from non-CVDs (with a smaller sample size) was more than 2.5 times greater than CVD mortality (1.28% vs. 0.51%) among females. According to these findings, in each decile, non-CVD mortality was higher than CVD mortality. The results of this research are consistent with a study by Dennis T. KO et al. (27), in which the dataset by the Cardiovascular Health in Ambulatory Care Research Team (CANHEART) was examined for all-cause mortality due to non-CVDs and CVDs.

The findings of this study showed that in the first decile of serum cholesterol in the male population, non-CVD mortality was approximately 3.5 times higher than CVD-related mortality at minimum cholesterol level. Moreover, the rate of mortality gradually decreased at minimum cholesterol level versus maximum level for non-CVD mortality. However, for CVD, the rate of mortality gradually increased from the first to tenth decile, except for the second and third deciles, compared to total mortality for non-CVDs and CVDs.

On the other hand, in females, unlike males, non-CVD mortality in the highest decile was twice the lowest decile (1.83% vs. 0.93%), except for the second and third deciles where mortality rates increased as cholesterol level increased from the first decile. There was a significant inverse association between total serum cholesterol level and total non-CVD mortality in men, while a higher total non-CVD mortality was observed in the highest decile

Table 2. The Specific Cause of Mortality in the Male Population Compared to Females Based on the Decile of Cholesterol Level

Gender	Cholesterol Level, mg/dL	Non-CVD	CVD			
		Total Non-CVD, % (n)	Total CVD, % (N)	CHD, % (N)	CVA, % (N)	Other CVDs, % (N)
Male						
	< 160	4.11 (116)	1.24 (35)	0.82 (23)	0.35 (10)	0.07 (2)
	160 - 174	3.11 (75)	1.04 (25)	0.70 (17)	0.17 (4)	0.17 (4)
	175 - 186	3.07 (79)	0.93 (24)	0.62 (16)	0.19 (5)	0.12 (3)
	187 - 198	2.72 (81)	1.71 (51)	1.14 (34)	0.47 (14)	0.10 (3)
	199 - 209	2.92 (87)	1.87 (56)	1.40 (42)	0.37 (11)	0.10 (3)
	210 - 221	2.34 (77)	2.04 (67)	1.49 (49)	0.42 (14)	0.13 (4)
	222 - 234	2.49 (79)	1.77 (56)	1.33 (42)	0.41 (13)	0.03 (1)
	235 - 250	2.83 (97)	2.38 (82)	2.04 (70)	0.20 (7)	0.14 (5)
	251 - 275	2.99 (101)	2.53 (85)	2.05 (69)	0.36 (12)	0.12 (4)
	≥ 276	2.85 (90)	2.41 (76)	1.97 (62)	0.38 (12)	0.06 (2)
	Total	2.92 (882)	1.84 (557)	1.40 (424)	0.34(102)	0.10 (31)
Female						
	< 160	0.93 (26)	0.35 (10)	0.25 (7)	0.07 (2)	0.03 (1)
	160 - 174	0.47 (12)	0.35 (9)	0.15 (4)	0.08 (2)	0.12 (3)
	175 - 186	0.88 (23)	0.38 (10)	0.19 (5)	0.04 (1)	0.15 (4)
	187 - 198	1.65 (43)	0.38 (10)	0.15 (4)	0.19 (5)	0.04 (1)
	199 - 209	1.39 (35)	0.76 (19)	0.28 (7)	0.40 (10)	0.08 (2)
	210 - 221	1.30 (35)	0.40 (11)	0.22 (6)	0.11 (3)	0.07 (2)
	222 - 234	1.50 (38)	0.44 (11)	0.24 (6)	0.16 (4)	0.04 (1)
	235 - 250	1.53 (39)	0.63 (16)	0.43 (11)	0.16 (4)	0.04 (1)
	251 - 275	1.30 (34)	0.50 (13)	0.35 (9)	0.15 (4)	0.00 (0)
	≥ 276	1.83 (47)	1.01 (26)	0.70 (18)	0.27 (7)	0.04 (1)
	Total	1.28 (332)	0.51 (135)	0.29 (77)	0.16 (42)	0.06 (16)

among females. The analysis showed no significant association between total serum cholesterol and mortality from CHD for either gender.

In addition, Cox proportional hazard analysis suggested more than a 2-fold increase in the risk of total non-CVD mortality at minimum cholesterol level (95% CI), compared to the maximum cholesterol level in males. However, there was no inverse association with total mortality from non-CVDs and CVDs in females. The findings indicated that total serum cholesterol had an inverse association with total non-CVD mortality, based on age- and multivariate-adjusted HRs. Moreover, total CVD mortality increased as the cholesterol level increased after age adjustments in males, while it slightly changed in both directions for females. Other cohort studies have found an association between high total cholesterol level and CVD mortality (28), whereas others have shown an inconsistent association (29-32).

In this regard, Lewington et al. reported that total cholesterol was positively associated with ischemic heart disease mortality in both genders at middle and old age. In this meta-analysis, including 61 prospective studies on 900,000 adults (age range, 40 - 89 years), an association was found between lower total cholesterol level and nearly a half, a third, and a sixth of lower ischemic heart disease mortality in both genders within the age ranges of 40 - 49, 50 - 69, and 70 - 89 years, respectively (33).

CHD, CVA, and other CVDs fluctuated in both directions for males and females after age adjustments. A low mortality rate was reported for CVAs and other CVDs in both males and females after age adjustment. Total non-CVD and CVD mortality rates, on average, were 2.5 times higher in the

Table 3. Age- and Multivariate-Adjusted HRs for Total Mortality from non-CVDs and CVDs at Different Cholesterol Levels in Males and Females

Gender	Cholesterol level, mg/dL	Non-CVD				CVD			
		N	Age-Adj., HR	Multivariate-Adj[a]		N	Age-Adj, HR	Multivariate-Adj[a]	
				HR	95% Confidence Interval			HR	95% Confidence Interval
Male									
	< 160	116	1.98	2.06	(1.54, 2.74)	35	0.68	0.81	(0.54, 1.22)
	160 - 174	75	1.29	1.36	(0.99, 1.87)	25	0.49	0.59	(0.37, .93)
	175 - 186	79	1.24	1.30	(0.95, 1.78)	24	0.42	0.50	(0.31, .79)
	187 - 198	81	1.07	1.10	(0.81, 1.51)	51	0.71	0.80	(0.56, 1.16)
	199 - 209	87	1.15	1.19	(0.87, 1.61)	56	0.79	0.90	(0.63, 1.29)
	210 - 221	77	0.90	0.92	(0.67, 1.26)	67	0.83	0.94	(0.67, 1.31)
	222 - 234	79	0.93	0.95	(0.69, 1.29)	56	0.67	0.72	(0.51, 1.03)
	235 - 250	97	1.06	1.08	(0.80, 1.44)	82	0.94	1.03	(0.75, 1.42)
	251 - 275	101	1.05	1.07	(0.79, 1.43)	85	0.97	1.04	(0.76, 1.42)
	(RG) ≥ 276	90	1.00	1.00	(-)	76	1.00	1.00	(-)
Female									
	< 160	26	1.46	1.52	(0.91, 2.50)	10	1.40	1.56	(0.72, 3.38)
	160 - 174	12	0.60	0.62	(0.32, 1.21)	9	0.89	1.05	(0.45, 2.45)
	175 - 186	23	1.01	1.04	(0.62, 1.74)	10	0.82	0.89	(0.40, 1.99)
	187 - 198	43	1.72	1.78	(1.16, 2.71)	10	0.84	0.93	(0.45, 1.96)
	199 - 209	35	1.29	1.32	(0.84, 2.06)	19	1.39	1.47	(0.79, 2.73)
	210 - 221	35	1.13	1.16	(0.74, 1.81)	11	0.75	0.80	(0.40, 1.65)
	222 - 234	38	1.06	1.08	(0.69, 1.70)	11	0.72	0.75	(0.37, 1.53)
	235 - 250	39	0.97	0.99	(0.64, 1.54)	16	0.81	0.87	(0.47, 1.64)
	251 - 275	34	0.79	0.81	(0.51, 1.26)	13	0.46	0.48	(0.23, 1.01)
	(RG) ≥ 276	47	1.00	1.00	(-)	26	1.00	1.00	(-)

Abbreviations: Adj., Adjusted; N, Number of Subjects; RG, Reference Group.
[a] Multivariate adjustments for age, BMI, systolic blood pressure, diastolic blood pressure, and smoking status.

male population, compared to the female population in each decile. More specifically, total mortality rate (non-CVD and CVD) was nearly 3 times higher in the male population, compared to the female population (6.92% vs. 2.4%) after age adjustment.

Generally, the analyses showed that increased HR of mortality for patients with low serum cholesterol was modified by gender differences. This finding suggests that the possible biological significance of low cholesterol varies in different groups and genders, particularly among females. As biological factors responsible for cholesterol level have been elucidated, it may be possible to analyze the relations between serum cholesterol, diseases, and mortality by taking these biological factors into account. In addition, the observed gender differences might be due to the lower rate of mortality among females, which could consequently lead to power loss.

Furthermore, an inverse association was found between serum cholesterol level and all-cause mortality (total non-CVD/total mortality) in men; these associations remained significant after controlling for age, cigarette smoking, BMI, and systolic and diastolic blood pressure. The cholesterol-disease association, although insignificant at minimum cholesterol level (< 160 mg/dL), was confirmed for total CVD and CHD mortality after adjustments for age, BMI, systolic and diastolic blood pressure, and smoking status in males. However, this association indicated some risks for females, although it was insignificant at minimum cholesterol level (< 160 mg/dL). Consequently, there was no significant positive association with mortality from either CHD or other CVDs.

Lack of a significant association between serum cholesterol level and CVD is probably due to the smaller number of CVD patients and the inverse association between serum cholesterol and excess non-CVD mortality in the study population. This finding is consistent with the results of a meta-analysis of 19 cohort studies on Caucasian (10, 21, 34, 35) and American-Japanese populations (5, 9, 11, 15, 29, 36), which showed a U-, J-, or L-shaped pattern between total cholesterol and total mortality in men. This pattern included a positive association between blood cholesterol and increased CVD mortality (clearly of clinical and public health significance) and an inverse association between blood cholesterol and excess non-CVD mortality.

Based on the findings of previous studies regarding the effects of age (> 50 years) on the association between low

serum cholesterol and non-CVD mortality, in this study, there was no need to identify age as a separate dominant predictor for non-CVD mortality, even though interaction effects and confounding variables were controlled. Overall, interpretation of the inverse association between cholesterol level and non-CVD mortality is complex. In some studies (32, 37), an inverse association was attenuated or disappeared after excluding early mortality within 1-5 years from the baseline. This finding suggests that the inverse association could be attributed to the preclinical conditions of cancer, which cause lower cholesterol concentrations.

Other studies have shown that the inverse association persists over longer follow-ups, even when the first 5-year (9, 14) or 10-year mortalities are excluded (36, 38). Some of these studies indicated that the persistent inverse association was attenuated when covariates, such as socioeconomic and other laboratory factors, were taken into account. These findings suggest that the inverse associations were due to other factors, which increase the risk of mortality.

The present study showed a persistent inverse association even after adjustments for confounding factors. There is now arguably sufficient biological and epidemiological evidence to warrant a causal relationship between low cholesterol and excess mortality from non-CVD, even though other important confounding and/or unmeasured factors may exist.

5.1. Strengths and Limitations

In the present study, the original data of 19 different large-scale dynamic observational cohort RIFLE studies were coordinated by the same center, and the majority of measurements were made using standardization and quality control. The importance of low-cholesterol risk in excess mortality in this study may not be generalizable to populations other than Italians due to unknown or unmeasured factors, low CVD mortality, and high non-CVD mortality in the study population.

Although this study might have presented an underestimation of some risk factors in the population, biases were considered to be minimal. Despite the biases, the findings demonstrated a strong association between risk factors for significant morbidity and mortality at low cholesterol level and excess mortality. The results could establish an association between cholesterol level and mortality in the study population. The analytical results placed strong emphasis on the medical and pharmacological management of low cholesterol, specifically in non-CVD populations. However, as in any observational cohort study, the findings may be confounded by unmeasured variables, which may cause some limitations in the study.

This research, similar to many other studies, has some limitations. First, information on posttreatment recurrence was insufficient. Second, changes might occur in total serum cholesterol level at some points. Therefore, further prospective research is required to determine the prognostic and therapeutic importance of cholesterol level. The interrelations of different cardiovascular symptoms, mortality, and cholesterol level are complex and likely to be directed towards protective or risk factors. Furthermore, clarification of biological and clinical pathways is needed to examine gender differences of particular interest for further research.

5.2. Conclusion

The findings of this study showed an inverse association between low serum cholesterol level and high non-CVD mortality in each decile, compared to CVD mortality during the follow-up. These associations remained significant after controlling for age, cigarette smoking status, BMI, and systolic and diastolic blood pressure. In addition, analysis of all-cause mortality from non-CVD and CVD indicated a higher HR at minimum cholesterol level for both genders after age and multivariate adjustments at a significance level of 95% CI. These findings have important clinical implications and support public health initiatives directed at the prevention of non-CVD mortality due to major disabilities and morbidities.

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Footnotes

Authors' Contribution: Nader Parsa designed the article, Nader Parsa and Samira Taravatmanesh wrote the manuscript, and Maurizio Trevisan supervised the study.

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