



# The LDL Paradox: Higher LDL-Cholesterol is Associated with Greater Longevity

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## Abstract

**Objective:** In a previous review of 19 follow-up studies, we found that elderly people with high Low-Density-Lipoprotein Cholesterol (LDL-C) live just as long as or longer than people with low LDL-C. Since then, many similar follow-up studies including both patients and healthy people of all ages have been published. We have therefore provided here an update to our prior review.

**Methods:** We searched PubMed for cohort studies about this issue published after the publication of our study and where LDL-C has been investigated as a risk factor for all-cause and/or Cardiovascular (CVD) mortality in people and patients of all ages. We included studies of individuals without statin treatment and studies where the authors have adjusted for such treatment.

**Results:** We identified 19 follow-up studies including 20 cohorts of more than six million patients or healthy people. Total mortality was recorded in 18 of the cohorts. In eight of them, those with the highest LDL-C lived as long as those with normal LDL-C; in nine of them, they lived longer, whether they were on statin treatment or not. CVD mortality was measured in nine cohorts. In two of them, it was inversely associated with LDL-C; in five of them, it was not

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associated. In the study without information about total mortality, CVD mortality was not associated with LDL-C. In two cohorts, low LDL-C was significantly associated with total mortality. In two other cohorts, the association between LDL-C and total mortality was U-shaped. However, in the largest of them ( $n > 5$  million people below the age of 40), the mortality difference between those with the highest LDL-C and those with normal LDL-C was only 0.04%.

**Conclusions:** Our updated review of studies published since 2016 confirms that, overall, high levels of LDL-C are not associated with reduced lifespan. These findings are inconsistent with the consensus that high lifetime LDL levels promotes premature mortality. The widespread promotion of LDL-C reduction is not only unjustified, it may even worsen the health of the elderly because LDL-C contributes to immune functioning, including the elimination of harmful pathogens.

## Introduction

### Strengths and limitations of this study

- This is a systematic review of cohort studies where LDL-C has been analyzed as a risk factor for all-cause and/or cardiovascular mortality.
- Studies may not have been included here in which there was an evaluation of LDL-C as a risk factor for mortality but it was not mentioned in the title or in the abstract.
- Studies may not have been included here because we have only searched PubMed and only included papers in English.

### Objective

In a previous review of 19 studies, where the authors had followed 30 cohorts including more than 68,000 elderly people after having measured their LDL-C, we found that in the studies representing more than 90% of the participants, those with the highest LDL-C lived the longest; none of the studies found the opposite [1]. In nine of the cohorts, the authors had recorded cardiovascular (CVD) mortality as well and found that in two of the studies, mortality was the highest in the lowest LDL-C quartile, a result that was statistically significant. In seven cohorts, no association was found.

After the publication of our review, many similar studies have been published. As our findings contradict the general consensus about the impact of LDL-C on cardiovascular and overall health, we felt it was important to review these additional studies in detail.

## Methods

We have performed two systematic searches on PubMed after papers published between May 2016 and July 2020 where the authors have followed patients or healthy people for some years after having measured their LDL-C. In one of our searches we used the following keywords: “follow-up AND LDL-cholesterol AND mortality NOT trial”; in the other one we used: “LDL-cholesterol AND mortality AND (statin OR lipid-lowering) NOT trial.” We also retrieved the references in the relevant publications.

We restricted our analysis to studies where the authors had excluded individuals on lipid-lowering treatment, or where they had adjusted the results for such treatment. The studies required an initial assessment of LDL-C, the age of the participants, the length of the observation time, and information about all-cause and/or cardiovascular mortality at the end of follow-up.

## Results

We identified 394 studies by using PubMed and four studies from the reference lists of some of the studies. Based on the abstracts we excluded 202 irrelevant studies. Among the 192 full papers, we excluded 175 studies that did not satisfy our methods. Thus, we identified a total of 19 relevant studies including 20 cohorts with 6,357,729 patients or healthy individuals (Figure 1 and Table).

The association between LDL-C and CVD mortality was recorded in nine studies (ten cohorts). In one of the studies [6] CVD mortality was associated with LDL-C among those with diabetes ( $n = 1210$ ) but not among those without diabetes ( $n = 915$ ). In the study that included two cohorts [13], the association was mirror J-shaped in one of them which only included young people ( $n = 347,971$ ); in the other one, which included all ages, the association was inverse ( $n = 182,943$ ). No association or an inverse association was found in the other studies ( $n = 36,129$ ) [2,6-8,12,14]. With one exception [7], all of the mentioned studies included young and/or middle-aged individual. The association between LDL-C and total mortality was recorded in 19 of the 20 cohorts (Table 1). In the study without information about total mortality, the association between LDL-C and non-CVD mortality was inverse with no association between LDL-C and CVD mortality ( $n = 5,518$ ) [3]. In a Korean study which only included people below the age of 39 years, the association was weakly U-shaped ( $n = 5,688,055$ ) [18]. In a study of American Indians, the association was U-shaped among those with diabetes ( $n = 1210$ ) and inversely associated among those without diabetes ( $n = 915$ ) [6]. In a Korean study of non-statin users [14], which included two cohorts, the association was mirror J-shaped in one of them, which included only young people ( $n = 347,971$ ). In the other cohort, where the mean age was 53 years ( $n = 182,943$ ) the association was inverse. In one study [20] the association was U-shaped ( $n = 4,485$ ). No association or an inverse association was found in the other studies ( $n = 319,578$ ), eight of which included young and/or middle-aged people [2,4-12,14-17,19].

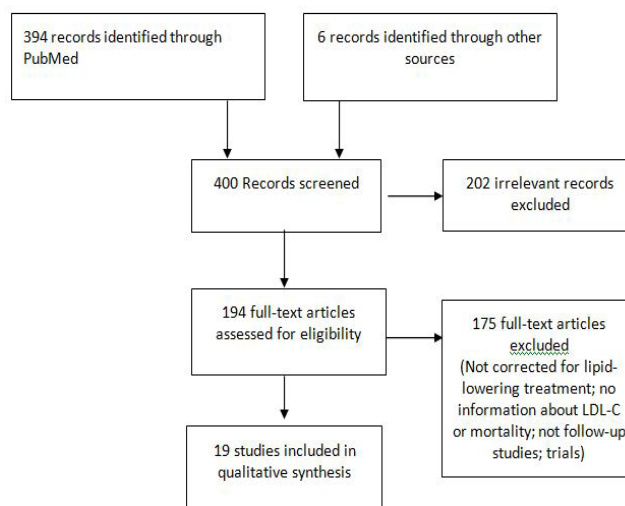
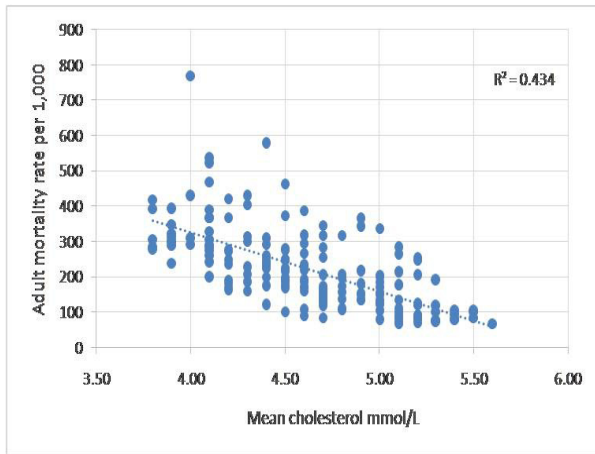
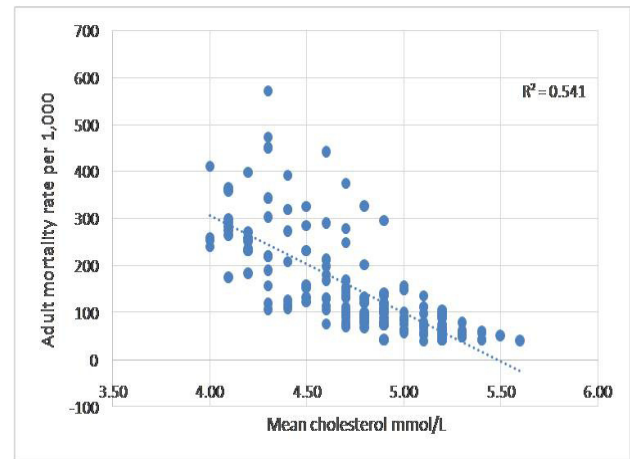


Figure 1: Flow chart.



**Figure 2:** The association between TC measured in 2009 and total mortality per 1,000 during 2010 for men age 15-60 years in 181 countries according to WHO’s Global Health Observatory data repository.



**Figure 3:** The association between TC measured in 2009 and total mortality per 1,000 during 2010 for women age 15-60 years in 181 countries according to WHO’s Global Health Observatory data repository.

**Table 1:** The association between LDL-C and total and/or CVD mortality in 19 follow-up studies (20 cohorts) of 6,357,729 patients and healthy people.

Authors	Participants and country	n	Age	Follow-up	Result	
			(years)	(years)	Total mortality	CVD mortality
Park et al., [2]	Patients on peritoneal dialysis. Korea	749	Mean 59.6	10	Inverse	Inverse
Ghasemzadeh et al., [3]	Community-dwelling people. Iran	5,518	Mean 54	11.9	NI <sup>a</sup>	NS
Bendzala et al., [4]	Patients with hypertension. Slovakia	473	>60	10	NS	NI
Orozco-Beltran et al., [5]	High-risk community-dwelling people. Spain	51,462	>30	3.2	Inverse	NI
Tanamas et al., [6]	Indians. USA	2,125	>40	10.1	Inverse <sup>b</sup>	NS <sup>c</sup>
Zuliani et al., [7]	Community-dwelling people. Italy	1,044	>64	9	Inverse	NS
Harari et al., [8]	Male workers. Israel	4,832	42.1	22	NS	NS
Charach et al., [9]	Patients with heart failure. Israel	305	70.3	20	Inverse	NI
Montesanto et al., [10]	Community-dwelling people. Italy	255	>90	5.3-8.6	NS	NI
Penson et al., [11]	High-risk individuals. USA	6,136	>45	10-13	NS	NI
Berton et al., [12]	Patients with acute CVD. Italy	589	58-74	20	Inverse	NS
Sung et al., [13]	Non-statin users. Korea					
	Cohort 1 (KSHS)	347,971	Mean 39.6	5.6	Significantly higher in the lowest LDL-C quintile than in the 3rd quintile	
	Cohort 2 (KGES)	182,943	Mean 53	8.6		
Yousufuddin et al., [14]	Hospitalized patients with MI or heart failure. USA	23,397	>18	<20	Inverse	Inverse
Dégano et al., [15]	CVD patients. Spain	27,400	Mean 74.8	3	Inverse	NI
Maihofer et al., [16]	Community-dwelling people without statin treatment. USA	3,567	68-91	5	NS	NI
Sittiwet et al., [17]	Community-dwelling men. Finland	398	≥75	3	NS	NI
Lee et al., [18]	Community-dwelling people. Korea	5,688,055	20-39	7.1	Weakly U-shaped <sup>d</sup>	NI
Zhou et al., [19]	Community-dwelling people, China	10,510	≥45	4	NS <sup>e</sup>	NI
Kobayashi et al., [20]	Dyslipidemic patients without CVD. Korea	4,485	Mean 58.4	5.3	U-shaped	NI
		6,357,729				

NI: No information. NS: Not significant. MI: Myocardial infarction. a: No information about total mortality, but the association between LDL-C and non-CVD mortality was inverse. b: U-shaped among those with diabetes mellitus. c: Associated among those with diabetes mellitus. d: 0.27% died in quartile 2 and 3; 0.3% and 0.31% died in quartile 1 and 4. e: Highest mortality in the first LDL-C quintile of men.

## Discussion

### The role of infections

If high LDL-C is the main cause of CVD, people with low and normal levels should live longer than people with high levels because CVD is the most common cause of death in most countries. However, as we have shown, many follow-up studies from around the world have shown that people with high LDL-C live just as long as or longer than other people. This strongly suggests that the cholesterol hypothesis is invalid; a fact that has been demonstrated in many other ways [21]. For example, the WHO's Global Health Observatory data repository from 2010 has shown that people in countries with the highest cholesterol live the longest (Figure 2 and 3).

We would therefore suggest that lowering LDL-C may not be necessary. A proposal that is further strengthened by the fact that independent researchers have documented that statin treatment has many significant adverse effects [21,22]. Of further importance is the fact that many studies have shown that low cholesterol is associated with increased mortality from infections [23], probably because LDL-C partakes in the immune system by adhering to and inactivating many microorganisms and their toxic product [24]. This fact is not widely recognised, but it has been documented by more than a dozen research groups [25].

### Why high cholesterol may appear as a risk factor

A relevant question is why many previous studies have shown that high TC or high LDL-C are associated with CVD. A possible explanation is that stress can considerably increase both TC and LDL-C considerably [26] and stress can increase the risk of CVD by other ways than by raising cholesterol [27,28]. Most of the early follow-up studies only included young and middle-aged people, and this group is likely to be more stressed than those who have reached retirement age. In support of this hypothesis, two of the four cohorts in our review where there was a positive association between mortality and LDL-C included only young and middle-aged individuals [13,18]. In all of the cohorts that were restricted to an older population, those with high LDL-C lived just as long or, in most cohorts, longer than those with low LDL-C. This observation is in accord with sixteen studies published before our review in BMJ Open [1] which have shown that elderly people with high TC live the longest [29-43]. Furthermore, in a prospective cohort study by the UK Biobank including more than half a million healthy British people age 49-69 years, TC was not associated with CVD mortality (risk ratio 0.98; 0.89 to 1.08) [44].

### The role of familial hypercholesterolemia

In the study by Sung et al., [13] CVD mortality among those with the highest LDL-C was higher than among those with normal LDL-C, but the difference was not statistically significant. CVD mortality was in fact highest among those with the lowest LDL-C and with statistical significance. Furthermore, the number who died among those with high LDL-C included less than 0.1% of the participants. In the large study of Lee et al., [18] where the association between LDL-C and total mortality was J-shaped, the difference between the mortality among those with normal LDL-C and those with the highest values was only 0.04%. Most likely, some of those with the highest LDL-C in these studies may have had Familial Hypercholesterolemia (FH), and there is much evidence that the cause of CVD in FH is not high LDL-C but elevated coagulation factors, which a few

of them inherit as well [45]. This observation could explain why LDL-C in FH people with and without CVD is almost the same, and people with FH live on average just as long as other people [46,47]. Furthermore, FH people with the lowest LDL-C become just as atherosclerotic as those with the highest values [48-53]; an observation that is valid for non-FH people as well [54]. A strong argument is also a study of ten young patients (age 3-32 years) with homozygous FH [55]. Six of them had signs and symptoms of coronary heart disease, but all of them were free from ischemic brain lesions and had a normal cerebral blood flow. FH may even protect against infections because in the 19<sup>th</sup> century where infectious diseases was the commonest cause of death, those with FH lived longer than the general population [56].

### The role of diabetes

In one of the studies mentioned in table 1 there was a U-shaped or a linear association between TC and/or LDL-C and total and CVD mortality among those with diabetes, but no associations between those without diabetes [6]. This study included only American Indians and the finding may therefore have a genetic explanation, because several studies have shown that LDL-C is not associated with mortality among diabetics [57-62]. Furthermore, in a systematic review of high quality, double-blind cholesterol-lowering trials, the authors found that such treatment is unable to reduce mortality and cardiovascular complications in type-2 diabetics [63].

### The role of low LDL-C

Reverse causality has been suggested as an explanation of the higher mortality associated with low cholesterol meaning that various diseases, for instance cancer and infections may lower the content of cholesterol in the blood. It is true that low cholesterol is associated with cancer, but the explanation is most likely that low cholesterol predisposes to cancer, because several follow-up studies of healthy youths have shown that the risk of cancer 10-40 years later in life is significantly greater among those with low TC [64]. Also, in three statins trials there was an increased risk of cancer in the treatment arm [64]. Additionally, in several case-control studies the risk of cancer was significantly increased among those who were or had been treated with statins [64].

An apparent contradiction is that in several cohort studies, statin-treated patients suffered less often from cancer, but in these studies, the authors have compared the statin-treated patients with non-treated people from the general population. As untreated people are likely to have lower cholesterol than statin-treated patients, and as a majority of statin-treated patients stop the treatment [65], **these findings are seriously biased, because the authors did not investigate whether the patients had continued with their statin-treatment. It is therefore impossible to know whether the benefit was due to statin treatment or to their high LDL-C.**

### The role of the drug industry

Although dozens of books and medical reviews written by independent scientists have documented a lack of evidence for the cholesterol campaign [21], the main reason for the persistence of the cholesterol hypothesis may be industry influence. Even those who write the guidelines are supported by the drug industry. For instance, in the new European guidelines for chronic coronary syndromes [66], dyslipidaemia [67] and diabetes, [68] the 150 pages long lists of the many authors and re-

viewers' financial conflicts show that almost all of them have been supported by the drug industry; some of them by more than a dozen drug companies. Furthermore, these guidelines have more than 500 references, but none of the contradictory studies mentioned above are mentioned.

As suggested by Moynihan et al., [69] all medical journals, advocacy groups and medical associations should *“move away from financial relationships with companies selling healthcare products and reforms to bind professional accreditation to education free of industry support”*.

### Conclusion

The hypothesis that high LDL-C is the major cause of CVD, the most common cause of death in most countries, is unlikely because follow-up studies of more than half a million of patients and healthy people have shown that those with the highest LDL-C live just as long or longer than those with low LDL-C.

**Contributors:** UR performed the paper search and wrote the first draft of the manuscript. All authors have read the reviewed papers and made improvements of the content and the wording of the manuscript. The figures are constructed by Zoe Harcombe and are based on data from WHO.

**Competing interests:** TH has received speaker fees from Nissui Pharmaceutical and Nippon Suisan Kaisha. KSM has a US patent for a homocysteine-lowering protocol. RH, HO, RS and UR have written books with criticism of the cholesterol hypothesis.

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