

# Elevated low-density lipoprotein cholesterol: An inverse marker of morbidity and mortality in patients with myocardial infarction

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**Abstract.** Schubert J, Lindahl B, Melhus H, Renlund H, Leosdóttir M, Yari A, et al. Elevated low-density lipoprotein cholesterol: An inverse marker of morbidity and mortality in patients with myocardial infarction. *J Intern Med*. 2023;**294**:616–627.

**Background.** The incidence of atherosclerotic cardiovascular disease increases with levels of low-density lipoprotein cholesterol (LDL-C). Yet, a paradox may exist where lower LDL-C levels at myocardial infarction (MI) are associated with poorer prognoses.

**Objective.** To assess the association between LDL-C levels at MI with risk factor burden and cause-specific outcomes.

**Methods.** Statin-naïve patients hospitalized for a first MI and registered in SWEDEHEART were included. Data were linked to Swedish registers. Primary outcomes were all-cause mortality and nonfatal MI. Associations between LDL-C and outcomes were assessed using adjusted proportional hazards models.

**Results.** Among 63,168 patients (median age, 66 years), the median LDL-C level was 3.0 mmol/L

(interquartile range 2.4–3.6). Patient age and comorbidities increased as LDL-C decreased. During a median follow-up of 4.5 years, 10,236 patients died, and 4973 had nonfatal MI. Patients with the highest LDL-C had a lower risk of mortality (hazard ratio [HR] 0.75; 95% confidence interval [CI] 0.71–0.80). The risk of hospitalization for pneumonia, hip fracture, chronic obstructive pulmonary disease, and new cancer diagnosis was lower with higher LDL-C (HR range, 0.40–0.81). Patients with the highest LDL-C had a greater risk of recurrent MI (HR 1.16; 95% CI 1.07–1.26).

**Conclusions.** Patients with the highest LDL-C levels at MI had the lowest incidence of mortality and morbidity. This seems to reflect lower age at MI, less underlying morbidities, paired with the modifiability of LDL-C. However, supporting the causal association between LDL-C and ischemic heart disease, elevated LDL-C was simultaneously associated with an increased risk of nonfatal MI.

**Keywords:** atherosclerosis, cholesterol, myocardial infarction, lipid lowering, observational, prevention

## Introduction

Elevated low-density lipoprotein cholesterol (LDL-C) promotes the development of atherosclerotic cardiovascular diseases (CVD) and death [1]. Clinical trials and observational studies demonstrate that lowering LDL-C after a myocardial infarction (MI) improves prognosis, regardless of the LDL-C

level at the time of the MI. Further, the larger the decline and the lower LDL-C reached, the better the prognosis [2–4].

Despite this, several observational studies suggest that lower LDL-C in acute coronary syndromes is associated with increased mortality, referred to as the “LDL-C paradox” [5–8]. Many

of these studies report an association between increased age and prevalence of comorbidities with lower LDL-C at MI. Indeed, low LDL-C or total cholesterol has been observed in various disease states [9–13].

Considering the contradicting evidence, this study used the SWEDEHEART registry including nearly all MI hospitalizations in Sweden to investigate the associations between LDL-C at MI with cardiovascular risk factors and long-term prognosis. Additionally, this study explored if low LDL-C was a risk factor of common non-cardiovascular morbidity and mortality.

## Methods

### Study population

This observational study included all patients aged >18 years hospitalized for an MI in Sweden and subsequently included in the SWEDEHEART registry between January 2006 and December 2016. Patients with previous coronary artery disease, coronary artery revascularization (i.e., percutaneous coronary intervention or coronary artery bypass grafting), ischemic stroke, peripheral artery disease, or ongoing statin treatment were excluded (Table S1). For patients with multiple admissions for MI, only the first event was included. Data detailing acute coronary care, coronary interventions, and secondary prevention were obtained from the SWEDEHEART registry [14]. Information from the SWEDEHEART registry was linked to data from the Swedish National Inpatient Register (detailing hospitalizations after discharge), the Total Population Register (all-cause mortality), the Swedish Cause of Death Register (cause-specific mortality), and the Swedish Prescribed Drug Register (filled prescriptions of statins before the index MI and at discharge). The Regional Ethics Committee in Stockholm approved the study in accordance with the Helsinki Declaration (approval numbers 2012/6013/2 and 2018/1957-32).

### Outcomes

The outcomes were all-cause mortality and recurrent nonfatal MI (Table S2). Mortality was further categorized by the most common cardiovascular and non-cardiovascular causes of death in Sweden according to the National Board of Health and Welfare: death from CVD, cancer, chronic lung disease (e.g., chronic obstructive pulmonary disease [COPD] and emphysema), dementia, and influenza

and pneumonia. All other causes of death were categorized as “other” (Table S2).

Four common non-cardiovascular reasons for hospitalization unrelated to LDL-C were chosen as a proxy for overall morbidity and biological ageing: (1) pneumonia; (2) hip fracture; (3) COPD; and (4) new cancer diagnosis (Table S2). Diagnoses were identified in the national inpatient register from the index MI until the end of follow-up.

### Laboratory variables

In a routine lipid panel, drawn in a fasted state within 24 h of hospital admission, LDL-C was estimated using the Martin-Hopkins formula recommended by the United States National Lipid Association: [15] [total cholesterol] – [high-density lipoprotein cholesterol] – [triglycerides/adjustable factor] [16]. The adjustable factor is patient-specific for the ratio of directly measured triglycerides to very-LDL-C. In a few cases, direct analysis was used according to local standardized methods that are subject to regular inspection and accreditation from a government authority. Furthermore, in sensitivity analyses, LDL-C was assessed using the Friedewald formula [17]. NonHDL-C was calculated using the formula: [total cholesterol] – [high-density lipoprotein cholesterol].

### Statistical analyses

Patients were stratified into quartiles according to their (baseline) LDL-C level (Quartile group [Q]1,  $\leq 2.4$  mmol/L; Q2,  $> 2.4 - \leq 3.0$  mmol/L; Q3,  $> 3.0 - \leq 3.6$  mmol/L;  $> 3.6$  mmol/L) at the time of their index MI. Demographics and other baseline characteristics were also compared among these quartiles. Continuous variables are presented as median (interquartile range [IQR]) and were compared between groups using the Kruskal–Wallis test. Categorical variables are presented as frequencies and percentages and were compared between groups using the  $\chi^2$ -test.

The relationship between baseline characteristics and the exposure variable, LDL-C, was explored using multivariable linear and logistic regression. Relationships between baseline LDL-C stratum and the outcomes of interest are presented in cumulative Kaplan–Meier curves, with event rates expressed as the number of events per 1000 patient years of follow-up for the whole population and by below or above the median age. The relationship between LDL-C and each outcome was

analyzed using Cox proportional hazards models (hazard ratio [HR] and 95% confidence interval [CI]) with LDL-C used as both a continuous variable and as a categorical variable (Q1–Q4, detailed above). HR used patients in Q1 as the reference. Any subsequent MI within 28 days of discharge from the index MI was censored. Patients were censored if they had a nonfatal event at the time of a given outcome but could be included in analyses for fatal and other nonfatal outcomes.

Recent guidelines suggest using nonHDL-C when calculating cardiovascular risk [18]. Accordingly, analyses using nonHDL-C instead of LDL-C were also performed.

Analyses were adjusted for age, sex, body mass index, cardiovascular risk factors, statin treatment at discharge, ongoing use of aspirin before the index MI, and the year of inclusion (Table S3). In a secondary analysis, the adjustment for body mass index and diabetes was omitted as each of these variables influences lipoprotein levels, and, thus, LDL-C can be considered a mediator between these variables and CVD [19]. In a sensitivity analysis, the association between LDL-C estimated with Friedewald formula and mortality was assessed.

The assumption of proportional hazards was assessed visually by inspecting unadjusted Kaplan–Meier curves. Secondary analyses were adjusted for age and sex only. An extended adjustment model including data for relevant comorbidities and concomitant medication was also completed in the secondary analyses (Table S4).

The relationships between LDL-C and both all-cause mortality and new nonfatal MI were explored using restricted cubic splines. The median concentration and the clinical cut-off for LDL-C (1.8 mmol/L) were used as the reference HR (i.e., 1.00), and four knots at the 5th, 35th, 65th, and 95th percentiles were used to allow for nonlinearity. This clinical threshold was chosen in the consideration of guideline directed targets for LDL-C that existed throughout the follow-up period, which in very high-risk patients was <1.8 mmol/L. Considering that the target is <1.4 mmol/L in current cardiovascular prevention guidelines [18], this has also been used as a threshold. The *p*-value was based on the Wald test. In patients who died during follow-up, filling of a statin prescription was

assessed during the 6 months prior to the date of death.

To explore outcomes in patients with a low baseline LDL-C, a landmark sensitivity analysis was performed, starting with a cardiac rehabilitation visit 6–10 weeks after discharge that included all patients where a follow-up LDL-C value was available (follow-up routine was restricted to patients <75 years of age). In this subset, event rates were calculated for those with an LDL-C value below the median level at the time of the index MI and were stratified by quartile decrease in LDL-C (LDL-C at baseline vs. LDL-C at the cardiac rehabilitation visit). In that analysis, outcomes were censored until the patient had had their cardiac rehabilitation visit. To ensure that these associations were not driven by a healthy cohort of patients attending cardiac rehabilitation, a sensitivity analysis was performed to compare the risk of patients attending the cardiac rehabilitation visit to that of the entire study population, starting at the median time of this visit.

HRs for outcomes related to biological ageing and overall morbidity according to baseline LDL-C were calculated with Cox proportional hazards models, adjusted for age and sex.

Missing data in covariates were addressed using multiple imputations by chained equations. *p*-Values <0.05 from two-sided tests were considered statistically significant. All analyses were performed at the Uppsala Clinical Research Center, Uppsala University, Uppsala, Sweden, using R Core Team (2022) R Foundation for Statistical Computing, Vienna, Austria.

## Results

### *Patient characteristics*

A total of 63,168 patients (32% [19,915] women) with a median age of 66 years (IQR 58–75) were included (Fig. S1). The median baseline LDL-C was 3.0 mmol/L (IQR 2.4–3.6).

### *Risk factors and comorbidities*

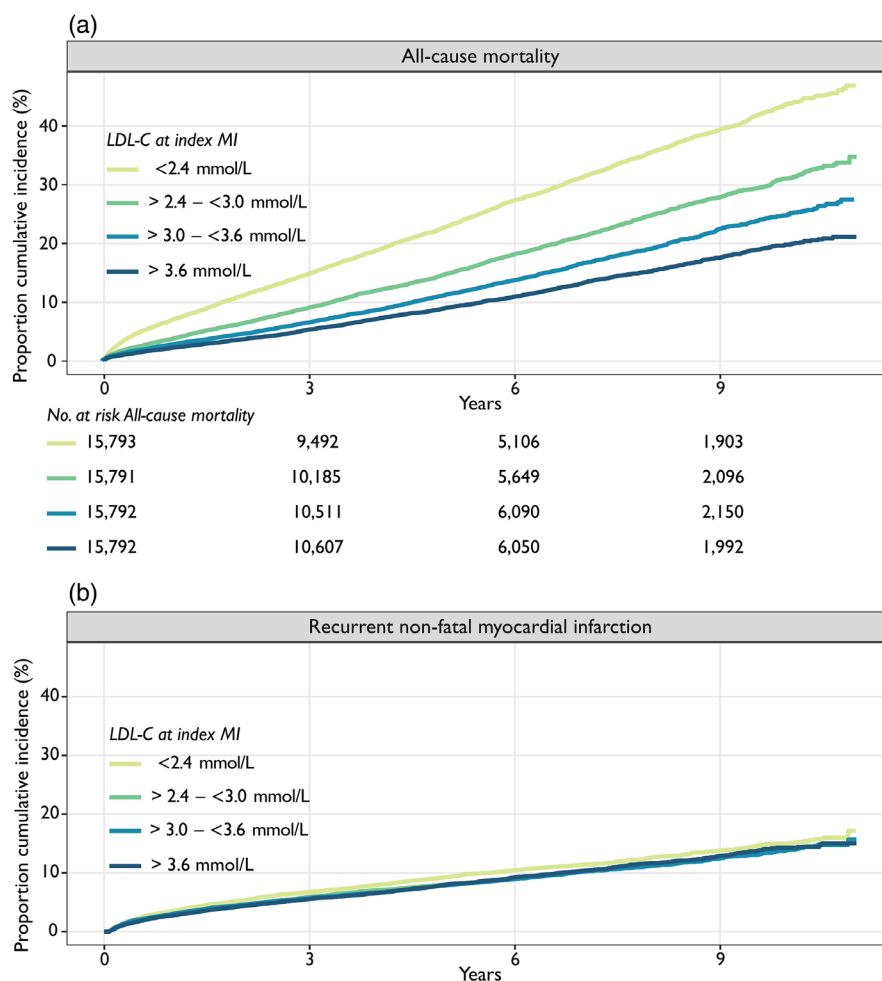
Patient characteristics for the overall cohort and for that population stratified by quartile baseline LDL-C levels are detailed in Table 1. The proportion of patients with diabetes, hypertension, reduced kidney function, and a left ventricular ejection fraction

**Table 1.** Baseline characteristics of the study population.

	Overall	LDL-C at admission for myocardial infarction (mmol/L)			
		≤2.4	>2.4–≤3.0	>3.0–≤3.6	>3.6
Number of patients	63,168	15,793	15,791	15,792	15,792
<b>Demographics</b>					
Age (years)	66 (58–75) [0]	71 (62–79)	68 (59–76)	65 (57–74)	62 (54–71)
Female	19,915 (32%) [0]	5473 (35%)	4829 (31%)	4668 (30%)	4945 (31%)
BMI (kg/m <sup>2</sup> )	26 (24–29) [7045]	25 (23–28)	26 (24–29)	27 (25–30)	27 (25–30)
<b>Risk factors</b>					
Current smoker	17,010 (28%) [2,208]	3579 (24%)	3967 (26%)	4484 (29%)	4980 (32%)
Former smoker	19,030 (31%)	47,874 (32%)	4837 (32%)	4746 (31%)	4663 (30%)
Hypertension	22,736 (36%) [0]	5969 (38%)	5962 (38%)	5612 (36%)	5193 (33%)
Diabetes mellitus	8057 (13%) [63]	2273 (14%)	2035 (13%)	1886 (12%)	1863 (12%)
Moderate or severe reduction in kidney function	880 (1%) [833]	344 (2%)	197 (1%)	163 (1%)	176 (1%)
Moderate or severe reduction in LVEF	2012 (4%) [9077]	818 (6%)	489 (4%)	393 (3%)	312 (2%)
<b>Comorbidities</b>					
Chronic obstructive pulmonary disease	2861 (5%) [0]	1079 (7%)	760 (5%)	549 (4%)	473 (3%)
Dementia	181 (<1%) [0]	59 (<1%)	53 (<1%)	39 (<1%)	30 (<1%)
Cancer	2351 (4%) [0]	780 (5%)	623 (4%)	551 (4%)	397 (3%)
<b>Laboratory variables</b>					
LDL-C (mmol/L)	3.0 (2.4–3.6) [0]	1.9 (1.6–2.2)	2.7 (2.5–2.8)	3.3 (3.1–3.4)	4.1 (3.9–4.6)
eGFR	83 (68–94) [833]	81 (64–92)	83 (68–93)	84 (70–95)	87 (72–97)
Systolic blood pressure (mm Hg)	150 (130–170) [1572]	143 (125–160)	149 (130–168)	150 (131–170)	153 (135–171)
Diastolic blood pressure (mm Hg)	87 (75–99) [3296]	82 (71–95)	85 (75–98)	88 (78–100)	90 (80–100)
<b>Medication at time of admission</b>					
Statin	0 (0%) [0]	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Beta blocking agent	9991 (16%) [211]	2673 (17%)	2537 (16%)	2426 (15%)	2355 (15%)
ACE inhibitor or ARB	12,274 (19%) [374]	3441 (22%)	3207 (20%)	3014 (19%)	2612 (17%)
Acetylsalicylic acid	5733 (9%) [33]	1880 (12%)	1463 (9%)	1320 (8%)	1070 (7%)

Note: Patient characteristics at admission to hospital due to a myocardial infarction; overall and stratified by the baseline low-density lipoprotein cholesterol (LDL-C) quartiles. Values are medians (interquartile ranges) and *n* (%) for categorical variables. [*n*] is numbers of missing values. *p*-Values for comparing characteristics by LDL-C stratum, using the Kruskal–Wallis test for continuous variables and the  $\chi^2$  test for categorical variables, were <0.0001 for all variables except dementia (*p* = 0.0091).

Abbreviations: ACE, angiotensin converting enzyme; ARB, angiotensin receptor blocker; BMI, body mass index; eGFR, estimated glomerular filtration rate estimated by the Chronic Kidney Disease Epidemiology Collaboration equation; LDL-C, low density lipoprotein cholesterol; LVEF, left ventricular ejection fraction.



**Fig. 1** Cumulative incidence by outcome and baseline low-density lipoprotein cholesterol (LDL-C) quartile. Unadjusted Kaplan–Meier event curves for each baseline LDL-C quartile group for (a) all-cause mortality and for (b) recurrent nonfatal myocardial infarction.

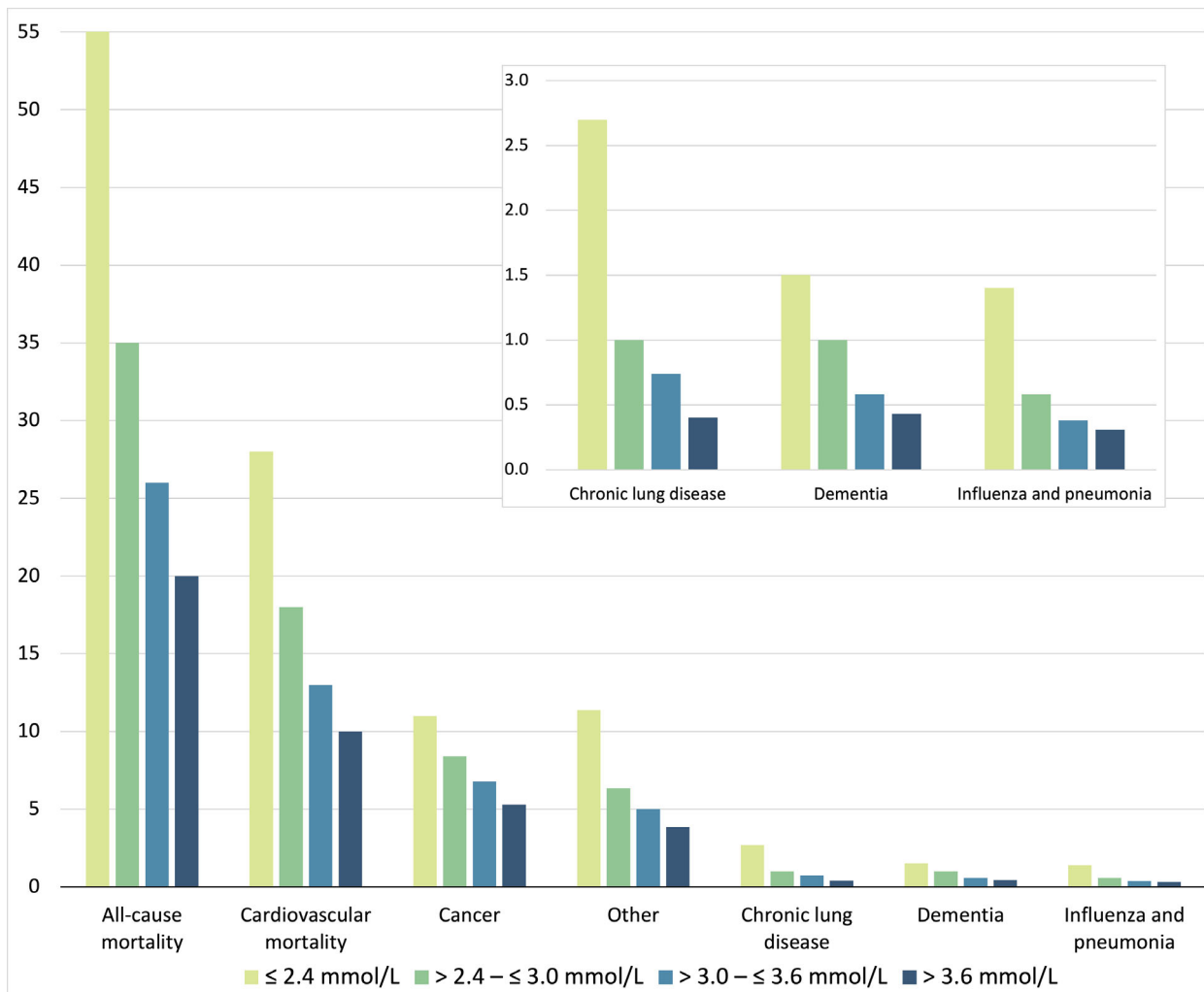
<40% was highest in the quartile with the lowest LDL-C (Table 1 and Fig. S2).

Among patients with the lowest baseline LDL-C levels (Q1), 17% were discharged without statin therapy, and 35% were discharged with high-intensity statin therapy. In those with the highest LDL-C levels (Q4), the corresponding numbers were 4% and 46%, respectively (Table S5). Baseline characteristics of the 5447 (9%) patients discharged without statin therapy are detailed in Table S6.

### Outcomes

Patients were followed for a median of 4.5 years (IQR 2.0–7.4), during which 10,236 died from

any cause and 4973 had a recurrent nonfatal MI. The unadjusted frequency of all-cause mortality was lower in patients with the highest baseline LDL-C (Table S7), and there was a stepwise reduction in the incidence of all-cause mortality with each increasing LDL-C quartile group (Fig. 1(a)). There was no difference in the distribution of recurrent nonfatal MI between the four LDL-C quartiles (Fig. 1(b)). When examining different causes of death, there was a stepwise reduction in the incidence of cause-specific mortality with each increasing LDL-C quartile (Fig. 2 and Table S7). The quartile with the highest LDL-C (Q4) had the lowest incidence of mortality. A stepwise reduction in mortality, regardless of cause, was also observed when stratifying patients



**Fig. 2** Mortality rates by baseline low-density lipoprotein cholesterol (LDL-C) quartile. Unadjusted cause-specific mortality rates by 1000 person-years for each baseline LDL-C quartile group.

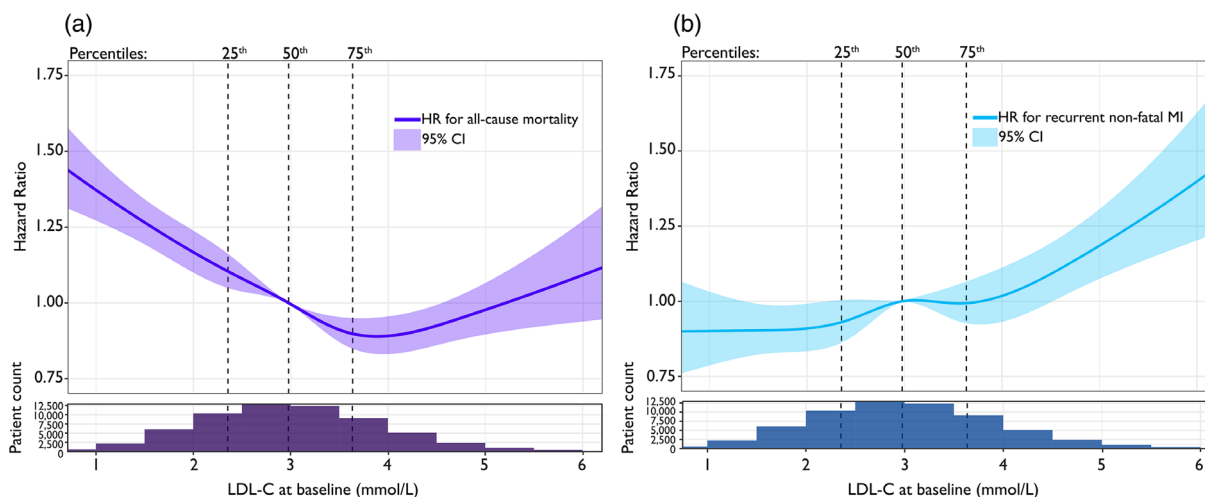
according to above or below the median age (Fig. S3).

In patients discharged without statin therapy, 50% died before end of follow-up. The corresponding proportions in the patients discharged with low/medium intensity and high-intensity statin therapy were 19% and 5%, respectively (Fig. S4). Of all patients who died, 47% had not filled a statin prescription during the 6 months prior to death. Most of the patients who died with a filled prescription had been discharged with low/medium intensity statin (Fig. S4). Half of those who died without filled pre-

scription had been discharged without statin therapy.

In models adjusted according to variables in Table S3, patients with a baseline LDL-C >3.6 mmol/L (Q4) had a lower risk of all-cause mortality (HR 0.75, 95% CI 0.71–0.80) than patients whose LDL-C was ≤2.4 mmol/L (Q1). When modeling continuous baseline LDL-C in spline analyses (Fig. 3(a)), the adjusted HR for all cause death reached a plateau around 4 mmol/L LDL-C. Conversely, the risk of nonfatal MI increased almost linearly with higher LDL-C when Q4 was compared to Q1 in spline models (HR





**Fig. 3** Association between baseline low-density lipoprotein cholesterol (LDL-C) and all-cause mortality and recurrent myocardial infarction (MI). Hazard ratios for (a) all-cause mortality and (b) recurrent nonfatal MI across the continuum of LDL-C levels. Adjusted for age, sex, body mass index, diabetes, history of hypertension, moderately or severely reduced left ventricular ejection fraction, an estimated glomerular filtration rate  $<30$  mL/min/1.73 m<sup>2</sup>, current smoking, ongoing aspirin treatment, statin intensity at discharge, and the year of inclusion. The median concentration of LDL-C (3.0 mmol/L) was used as the reference (hazard ratio = 1.00) in each analysis. The Wald test for LDL-C spline effect: all-cause mortality  $p < 0.0001$  and recurrent MI  $p < 0.0001$ . Solid line: hazard ratio (with 95% confidence interval, shadowed area) in relation to LDL-C using restricted cubic splines with four knots. Vertical dotted lines: percentiles. X-axis presented on a linear scale. Population distribution in relation to LDL-C below spline.

1.16, 95% CI 1.07–1.26; Fig. 3(b)). The results for these models using nonHDL-C were nearly identical (Fig. S5).

In a secondary analysis, where body mass index and diabetes were not adjusted for, results were quantitatively and qualitatively similar (data not shown).

Splines where the clinical LDL-C thresholds 1.8 and 1.4 mmol/L were used as the reference HR, instead of the median value of the cohort, are presented in Fig. S6. When only adjusting for age and sex, the risk of all-cause mortality was lower in patients in the highest LDL-C quartile group compared to those in the lowest (HR 0.62, 95% CI 0.59–0.66; Fig. S7A). In the extended adjustment model including amongst others, prior non-CVD, prior cardiovascular medication, type of infarction, and C-reactive protein, (Table S4), the risk of all-cause mortality was again lower in patients with an LDL-C  $>3.6$  mmol/L than in those with an LDL-C  $\leq 2.4$  mmol/L (HR 0.81, 95% CI 0.76–0.86; Fig. S7B).

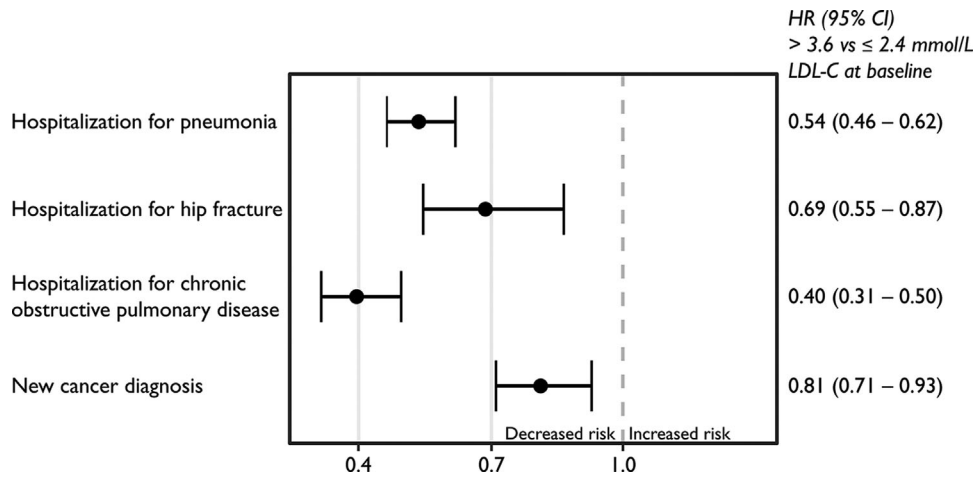
#### Non-cardiovascular morbidity

In analyses relating LDL-C with non-cardiovascular morbidity, there was a 19%–60% lower risk for hospitalization for pneumonia, hip fracture, and COPD, as well as a new cancer diagnosis, at any time during follow-up in patients with the highest baseline LDL-C (Q4), compared to those in Q1 (Fig. 4). The results for these analyses using nonHDL-C were nearly identical (Fig. S8).

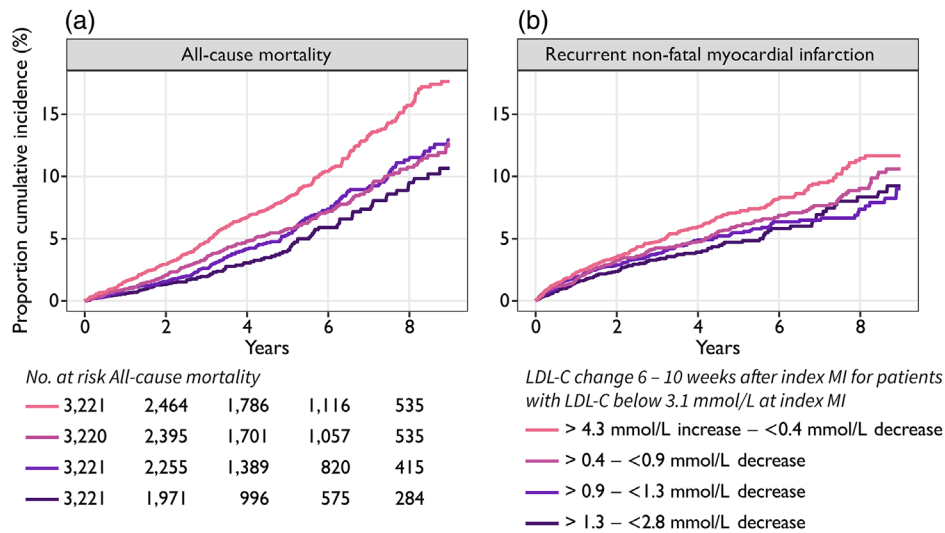
#### Sensitivity analysis

A follow-up LDL-C value was recorded 6–10 weeks after discharge in 25,766 patients (median age was 62 years [IQR 55–68], 25% female; Table S8). During that period, the median LDL-C level decreased by 1.3 mmol/L (IQR 0.7–1.8 mmol/L). During follow-up, 1287 of these patients died from any cause and 1324 had a recurrent nonfatal MI.

In patients with a baseline LDL-C level equal to or below the median (3.1 mmol/L) and a recorded follow-up LDL-C value, there was a significant decrease in both all-cause mortality and recurrent



**Fig. 4** Association between baseline low-density lipoprotein cholesterol (LDL-C) and hospitalization for non-cardiovascular outcomes related to biological ageing and overall morbidity. Cox proportional hazards analysis adjusted for age and sex comparing the highest (>3.6 mmol/L) to the lowest LDL-C quartile group (≤2.4 mmol/L). The hazard ratio (HR) and the corresponding 95% confidence interval (CI) for each outcome are presented.



**Fig. 5** Cumulative incidence rates by outcome and the change in low-density lipoprotein cholesterol (LDL-C) for patients with a baseline LDL-C below the median. Unadjusted Kaplan-Meier curves of the cumulative incidence rates for (a) all-cause mortality and (b) recurrent nonfatal myocardial infarction (MI) for the follow-up population who had a baseline LDL-C below median (≤3.1 mmol/L), stratified by the quartile change in LDL-C at 6–10 weeks after discharge.

nonfatal MI in the quartile of patients with the greatest reduction in LDL-C (Fig. 5). The reduction in mortality was observed regardless of cause (Fig. S8).

The risk of all-cause mortality (HR 0.74, 95% CI 0.69–0.79) and recurrent nonfatal MI (HR 1.17, 95% CI 1.08–1.28) in the whole population with

outcomes censored until the landmarks (at 53 days after the index MI and corresponding to median follow-up time for patients with a follow-up visit) were nearly identical to that of the primary analysis. Further, when assessing LDL-C using the Friedewald equation, the HR for all-cause mortality was almost identical (data not shown).



## Discussion

In this large nationwide study of statin naïve patients without known atherosclerotic CVD prior to the index MI, the risk of mortality was lower in patients with higher LDL-C than those with lower LDL-C at the time of their MI hospitalization. Patients with higher baseline LDL-C were younger and had less comorbidities and CVD risk factors. Additionally, they had a lower risk of non-cardiovascular mortality and morbidity outcomes associated with biological ageing and frailty. Conversely, the risk of recurrent nonfatal MI increased with higher LDL-C. Finally, half of those who died without a filled prescription had been discharged without statin therapy; and of all patients who died, 47% had not filled a statin prescription during the 6 months before death.

Similar findings, suggesting a favorable prognosis for patients with high LDL-C, the “LDL-C paradox”, have been described in large cohort studies focusing on in-hospital mortality after MI and in smaller studies with longer follow-up. However, this study is the first to explore this association in a large cohort with a long follow-up and extensive phenotype data, including both cardiovascular and non-cardiovascular outcomes, and conditions related to biological ageing and morbidity.

In a single center study of patients with non-ST-elevation MI, those with lower LDL-C had more comorbidities and higher all-cause mortality after 3 years follow-up [7]. There was no difference in the incidence of recurrent MI after 6 months follow-up between those with elevated or low LDL-C. In another study that included patients with acute coronary syndrome undergoing percutaneous coronary intervention, lower LDL-C was an independent predictor of all-cause mortality [6].

As our study's population was formed using a registry restricted to patients with MI, the findings may be affected by collider bias (i.e., most individuals with low LDL-C do not develop MI and are not included in the registry) [20]. Therefore, the observation that lower LDL-C is associated with increased risk of mortality may be driven, in part, by patients who had an MI despite low LDL-C. It should be noted, however, that patients with previous MI and ongoing statin treatment were excluded, and that the data were adjusted for baseline comorbidities (i.e., factors that influence both the risk of an MI and the risk of mor-

tality), to minimize the influence of collider bias. In a similar approach, a study including patients who underwent percutaneous coronary intervention after MI indicated that patients were younger and less likely to have comorbidities as LDL-C increased [5]. Additionally, low LDL-C was found to predict mortality at 12 months post-MI, but not when adjusted for >30 variables, including comorbidities, medication, other laboratory values, and MI type. Similarly, in a study of patients with ST-elevation MI, the association between low LDL-C and increased risk of in-hospital mortality was not statistically significant after adjusting for >40 variables, although the U-shaped curve was still present in the spline model [21].

In a large study of the general population, a U-shaped association existed between the risk of both all-cause and cause-specific mortality and LDL-C in individuals not receiving lipid-lowering treatment [22]. Comorbidities were more frequent in individuals with the lowest LDL-C, similarly to our study. The association between low LDL-C and the risk of all-cause mortality was reduced when data were adjusted for baseline comorbidities, but the U-shaped association remained. Findings from these studies might be influenced by collider bias, but it is unlikely that those results are entirely attributable to that bias.

From our study's data, low LDL-C seems to be associated with increased overall morbidity in terms of increased age, higher burden of comorbidities (COPD and cancer) and greater use of primary preventive medications (aspirin, beta-blockers, and ACE-inhibitors). This association was further demonstrated by a higher incidence of non-cardiovascular outcomes such as hospitalization for pneumonia, COPD, hip fracture, and new cancer diagnosis, which are not influenced by LDL-C per se.

Lower total cholesterol and LDL-C have been observed in many inflammatory conditions, such as active rheumatoid arthritis [23]. Although it was proposed that systemic inflammation may lower circulating lipid levels [23], it has been reported that patients with rheumatoid arthritis have an increased risk of CVD, even when cholesterol levels are relatively low [24]. To evaluate the concurrent contribution of inflammation to the findings of this present study, the fully adjusted analysis included adjustment for levels of C-reactive protein.

High levels of proinflammatory markers have been linked to ageing and are considered a risk factor for CVD, cancer, dementia, multimorbidity, sarcopenia, and premature death, among others [25]. In a study comparing community-dwelling adults stratified by their frailty, LDL-C was lower in the frail group, both when including and excluding patients with diabetes or CVD [26]. Recently, low total cholesterol levels have predicted long-term mortality in primary care patients [13], and frailty in heart failure patients [12]. Similarly, low LDL-C was associated with worse prognoses in patients with advanced kidney disease and coronary artery disease [11] and reported to be decreased in patients with COPD [10]. Low total cholesterol was also an independent predictor of mortality [9].

Considering this, it seems that low LDL-C may be promoted by many diseases and is correlated with worse prognoses, regardless of the patient's primary illness. In our study, the risk of all-cause mortality was higher when data were only adjusted for age and sex and slightly attenuated when adjusting for all variables pertaining to the patient's health prior to admission.

LDL-C is a highly modifiable risk factor for CVD. Lipid-lowering treatment, especially statins, is perhaps the most easily administered secondary preventive measure and can often be prescribed at the target dose from the beginning of treatment. Suffering an MI despite low LDL-C suggests that other underlying mechanisms promote atherosclerosis, which may be more difficult to treat or eliminate. In this study, patients with the lowest LDL-C were more likely to have diabetes, hypertension, reduced kidney function, reduced left ventricular ejection fraction, and COPD. Despite the inverse association between LDL-C and mortality and non-CV morbidity, the risk of recurrent nonfatal MI still increased as LDL-C increased, in accordance with the causal relation between LDL-C and atherosclerosis. By lowering LDL-C after an MI, as shown in this study's sensitivity analysis, and by applying other effective secondary prevention measures, recurrent MI can be prevented, even in the presence of comorbidities [18]. This was consistent in patients with the lowest LDL-C levels in our study.

A matched cohort study of 270,000 patients with type 2 diabetes, without previous CVD, found a similarly U-shaped relationship between LDL-C and death from any cause. Interestingly, this U-shaped relationship was also apparent for sys-

tolic blood pressure and glycated hemoglobin [27]. Meanwhile, the relationship between LDL-C and acute MI was monotonical, further highlighting differences in the underlying pathophysiology for mortality and supporting LDL-C as causal in development of atherosclerotic CVD.

Variations in lipid and lipoprotein levels at the time of MI have been suggested [28]. Therefore, in our previous publication using the same cohort, analyses were performed to account for the potential decline in LDL-C after ischemic onset and for the magnitude of myocardial damage [4]. Neither the time between MI and LDL-C sampling, nor the degree of left ventricular ejection fraction as a marker for myocardial damage and the magnitude of infarction, affected the results.

#### *Strengths and limitations*

This study assesses patients without prior atherosclerotic CVD or ongoing statin therapy. The study is strengthened by the inclusion of a large cohort from the universal public healthcare system in Sweden, long follow-up, and comprehensive data with linkage between phenotype and outcome registries. However, there are limitations. Inherent to observational research, there is a risk of important confounders and unknown patient characteristics (e.g., cumulative exposure to LDL-C before MI and compliance to lipid-lowering medications during follow-up) that could not be controlled for. Additionally, baseline characteristics differed greatly between the quartiles, potentially affecting comparisons between groups. This was addressed by adjusting for many of these variables in a fully adjusted model. Despite efforts to control for the reduction in LDL-C associated with MI, it cannot be discounted that older patients with more comorbidities have a greater acute reduction in LDL-C. However, the proportion of unknown major cardiovascular risk factors missed was minimized by the use of detailed phenotype data and linkage to several parallel data sources.

Patients with low LDL-C might still have residual cardiovascular risk mediated by small dense LDL-C particles, which are more atherogenic despite the low absolute level. Patients with diabetes, insulin resistance, and obesity might be particularly subject to this [29]. In this study, the proportion of patients with diabetes decreased with each incremental increase in baseline LDL-C. Neither the

LDL-C particle count nor ApoB was available in the dataset.

### Conclusion

Patients with a first MI despite low LDL-C levels have increased risk of mortality and outcomes associated with ageing, compared with patients with higher LDL-C. Conversely, higher LDL-C was associated with an increased incidence of recurrent nonfatal MI. Further, a greater reduction in LDL-C after MI was associated with reduced mortality, even in those with the lowest LDL-C at the time of MI. These results indicate that there is no real paradox, rather that LDL-C is a marker of overall frailty reflecting morbidity and biological ageing and that patients who suffer an MI, despite low LDL-C, have other strong drivers of atherosclerotic CVD. This emphasizes the importance of continuing lipid-lowering treatment in patients with MI, regardless of the level of LDL-C at the time of that MI. This is of special significance when untreated LDL-C is low at the time of MI, as this might increase the risk of undertreating the patient.

### Author contributions

*Conceptualization; investigation; methodology; project administration; validation; visualization; writing—original draft; writing—review and editing:* Jessica Schubert. *Investigation; supervision; writing—review and editing:* Bertil Lindahl and Håkan Melhus. *Data curation; formal analysis; methodology; software; visualization:* Henrik Renlund. *Investigation; writing—review and editing:* Ali Yari, Peter Ueda and Tomas Jernberg. *Conceptualization; funding acquisition; investigation; methodology; project administration; resources; supervision; validation; visualization; writing—original draft; writing—review and editing:* Emil Hagström.

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### Conflict of interest statement

J.S.: Institutional grant from AMGEN during the conduct of the study. B.L., H.M., H.R., P.U., and T.J.: No conflict of interest to disclose. M.L.: Institutional grants from Pfizer, and honoraria from Astra Zeneca, NovoNordisk, Amgen, and Sanofi

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### Data availability statement

SWEDEHEART does not allow individual data sharing to third parties. Access to aggregated data might be granted following review by the SWEDEHEART steering committee.

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