Low-density lipoprotein cholesterol and risk of COPD: Copenhagen General Population Study

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Low plasma levels of LDL cholesterol are associated with increased risk of COPD, COPD exacerbation and COPD-specific mortality in adults in the general population https://bit.ly/3Ow16BC

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Abstract

Background Randomised controlled trials found that low-density lipoprotein (LDL) cholesterol-lowering statins increase lung function and possibly decrease rate of exacerbations in individuals with COPD. However, it is unknown whether high levels of LDL cholesterol are associated with increased susceptibility to COPD.

Methods We tested the hypothesis that high LDL cholesterol is associated with increased risk of COPD, severe COPD exacerbation and COPD-specific mortality. We examined 107 301 adults from the Copenhagen General Population Study. COPD outcomes were ascertained at baseline and prospectively through nationwide registries.

Results In cross-sectional analysis, low LDL cholesterol was associated with increased risk of COPD (odds ratio for 1st *versus* 4th quartile: 1.07 (95% CI 1.01–1.14)). Prospectively, low LDL cholesterol was associated with increased risk of COPD exacerbations with hazard ratios of 1.43 (1.21–1.70) for 1st *versus* 4th quartile, 1.21 (1.03–1.43) for 2nd *versus* 4th quartile, and 1.01 (0.85–1.20) for 3rd *versus* 4th quartile of LDL cholesterol (p-value for trend=6×10^{-6}). Finally, low LDL cholesterol was likewise associated with increased risk of COPD-specific mortality (log-rank test: p=0.0009). Sensitivity analyses with death as competing risk provided similar results.

Conclusion Low LDL cholesterol was associated with increased risks of severe COPD exacerbation and COPD-specific mortality in the Danish general population. As this is opposite of that observed in randomised controlled trials with statins, our findings might be a result of reverse causation indicating that individuals with severe phenotypes of COPD have lower plasma levels of LDL cholesterol due to wasting.

Introduction

COPD is a heterogeneous lung disease with an estimated prevalence of 10% worldwide [1]. The most frequent comorbidity observed in COPD is atherosclerotic cardiovascular disease reported in about 13% of individuals with COPD *versus* 4% in subjects with normal lung function [2, 3]. The most important causal risk factor for atherosclerotic cardiovascular disease is elevated low-density lipoprotein (LDL) cholesterol [4]. Several observational studies have reported an association between statins (LDL cholesterol-lowering drugs) and lower risk of exacerbations and disease-related hospitalisations in individuals with COPD [5, 6], and a meta-analysis of randomised controlled trials found improvement in exercise capacity and lung function in the individuals with COPD, who used statins [7]. Nevertheless, the two largest double-blinded randomised controlled trials investigating effect of statins on frequency and severity of COPD exacerbations have shown contradicting results [8, 9], although one of the studies found a decreased rate of COPD exacerbations [9]. Despite these results, it is unknown whether high levels of LDL cholesterol are associated with increased susceptibility to COPD.

We tested the hypothesis that high LDL cholesterol in plasma is associated with increased risks of COPD, severe COPD exacerbation and COPD-specific mortality. This is important to know for doctors treating patients with COPD, since atherosclerotic cardiovascular disease is a major cause of morbidity and mortality in these patients. We examined 107 301 adults from the Copenhagen General Population Study and recorded COPD outcomes ascertained at baseline using spirometry and prospectively through nationwide registries during a median of 10.2 years of follow-up.

Material and methods

The Copenhagen General Population Study

The Copenhagen General Population Study is a contemporary population-based cohort study initiated in 2003 with ongoing enrolment [10]. Individuals included in the current study were enrolled from 2003 to 2015 with a median of 10.2 years of follow-up. Participants in the Copenhagen General Population Study are invited to participate by random selection on the basis of the national Danish Civil Registration System to reflect the Danish population aged 20 to 100 years. The Copenhagen General Population Study was approved by Herlev Gentofte Hospital and a Danish Ethical committee (identification no. H-KF-01-144/01). It is conducted in accordance with the Declaration of the Helsinki. Participants gave written informed consent prior to enrolment.

Baseline data

Baseline data were collected from self-reported questionnaires, physical health examinations, pulmonary function tests and blood samples for biochemical analyses [10]. All blood samples were collected non-fasting in accordance with international guidance [11]. LDL cholesterol, high-density lipoprotein (HDL) cholesterol and triglycerides were all measured using standard hospital assays. When plasma triglyceride concentration was $\leqslant 4\ mmol \cdot L^{-1}$, LDL cholesterol was calculated with the Friedewald equation. When plasma triglycerides were $>4\ mmol \cdot L^{-1}$, LDL cholesterol was measured directly. In participants receiving lipid-lowering medication, LDL cholesterol was multiplied by 1.43 to adjust for a 30% average reduction as in the studies of Jones *et al.* [12], Benn *et al.* [13], Beheshti *et al.* [14] and Langsted *et al.* [15]. EasyOne Spirometer (ndd Medical Technologies, Andover, MA, USA) measured prebronchodilator forced expiratory volume in 1 s (FEV_1) and forced vital capacity (FVC) as previously described [16]. Spirometric COPD was defined as FEV_1/FVC ratio <0.7 excluding asthmatic patients [10]. If participants who reported they had asthma were included, the results were similar to those presented. Smoking status was categorised according to number of pack-years smoked into light smokers (<10 pack-years) and heavy smokers (⩾10 pack-years). Body mass index (BMI) was measured as weight in kilograms divided by measured height in metres squared. Underweight was defined as BMI $< 18.5\ kg \cdot m^{-2}$, normal weight as BMI $18.5–24.9\ kg \cdot m^{-2}$ and overweight as BMI $\geqslant 25\ kg \cdot m^{-2}$. Information on use of lipid-lowering medication, physical inactivity and alcohol consumption was self-reported in the questionnaires. Physical inactivity was defined as leisure-time light physical activity for ⩽4 h per week.

Prospective outcomes

Severe COPD exacerbation was defined as a hospital admission with ICD10 J44 as a primary diagnosis, or ICD10 J44 as a secondary diagnosis with respiratory failure (ICD10 J96) or pneumonia (ICD10 J18) as primary diagnosis as recommended by the Danish Register of Chronic Obstructive Pulmonary Disease, who found a positive predictive value of an acute COPD discharge diagnosis of 92% using the current definition [17]. COPD-specific mortality was ICD10 J41–J44 listed as primary cause of death. COPD diagnoses were collected prospectively from the national Danish Patient Registry until December 2018 and the national Danish Cause of Death Registry until December 2019. The national Danish Patient Registry is a database founded in 1977 that includes data on treatment, examinations and diagnoses from all Danish hospitals [18]. Participants were followed from baseline until outcome, death (n=12 193), emigration (n=852) or end of study, whichever came first.

Statistics

Baseline characteristics were analysed according to quartiles of LDL cholesterol using one-way ANOVA or Kruskal–Wallis tests for continuous data and Pearson's Chi-squared test for categorical data. Logistic regression adjusted for age, sex, BMI, alcohol consumption, physical inactivity, smoking status and pack-years calculated odds ratios for spirometric COPD according to quartiles of LDL cholesterol. Cox proportional hazards regression with left truncation and delayed entry at study examination, using age as the underlying time scale and adjusting for age (time scale), sex, BMI, alcohol consumption, physical inactivity, smoking status and pack-years, was used to calculate hazard ratios for the risk of severe COPD exacerbation according to quartiles of LDL cholesterol. Competing risk scores were used to account for death as competing risk in Fine and Gray cumulative incidence function curves for severe COPD exacerbation and

TABLE 1 Baseline characteristics of individuals from the Copenhagen General Population Study according to quartiles of plasma low-density lipoprotein (LDL) cholesterol

	All	1st quartile	2nd quartile	3rd quartile	4th quartile	p-values
Participants n	107 301	28 113	27 658	24 750	26 780	
Age years	58 (48–68)	53 (44–66)	58 (48–68)	60 (50–68)	60 (52–68)	0.0001
Women	59 279 (55)	16 418 (58)	15 204 (55)	13 178 (53)	14 479 (54)	<0.0001
LDL cholesterol mmol·L^{-1}	3.4±1.0	2.3±0.4	3.0±0.2	3.6±0.2	4.6±0.6	<0.0001
Body mass index kg·m^{-2}	26.2±4.2	25.1±4.2	26.0±4.3	26.5±4.2	27.1±4.2	<0.0001
Never-smokers	42 194 (42.0)	11 664 (44.3)	11 161 (43.1)	9549 (41.2)	9820 (39.1)	<0.0001
Light smokers (⩽10 pack-years)	20 980 (20.8)	5931 (22.4)	5547 (21.4)	4701 (20.2)	4801 (19.1)	<0.0001
Heavy smokers (>10 pack-years)	39 192 (38.8)	9230 (34.9)	9635 (37.1)	9389 (40.3)	10 938 (43.4)	<0.0001
Cumulative smoking pack-years	15.5 (6.0–30)	13.8 (5.0–28.5)	15.0 (5.6–30)	16.4 (6.5–30.0)	18.0 (7.5–32.0)	0.0001
Lipid-lowering therapy	12 922 (12.1)	3250 (11.6)	3176 (11.5)	2598 (10.5)	3898 (14.6)	<0.0001
Alcohol g·week^{-1}	96 (48–180)	96 (36–168)	96 (48–180)	96 (48–180)	108 (48–192)	0.0001
Physical inactivity	51 486 (48.4)	12 455 (44.7)	12 977 (47.3)	12 095 (49.3)	13 959 (52.6)	<0.0001
FEV_1 % predicted	96.4±16.1	96.5±16.0	96.8±16.1	96.4±16.1	96.0±16.2	<0.0001
FVC % predicted	101.2±15.7	101.5±15.5	101.6±15.6	101.2±15.7	100.5±15.9	<0.0001
FEV_1/FVC	76.8±7.7	77.0±7.9	76.8±7.7	76.5±7.6	76.8±7.5	<0.0001

Data are presented as n (%) for categorical variables and mean±SD or median (interquartile range) for continuous variables depending on whether data were normally distributed. Cumulative smoking values are only from former and current smokers. FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity.

COPD-specific mortality after adjustment for age, sex, BMI, alcohol consumption, physical inactivity, smoking status and pack-years. Data analyses were performed using STATA/MP version 17.1.

Results

Baseline characteristics

Clinical characteristics of participants according to quartiles of plasma LDL cholesterol are shown in table 1. Individuals who had LDL cholesterol in the 1st *versus* 4th quartile were on average younger, more likely women, had lower BMI, consumed less tobacco and alcohol, used lipid-lowering therapy less often, were less physically inactive and had increased lung function (p-values <0.001).

COPD cross-sectionally

Lower levels of LDL cholesterol were associated with increased risk of spirometric COPD with odds ratios of 1.07 (95% confidence interval (CI) 1.01–1.14) for 1st *versus* 4th quartile of LDL cholesterol, 1.06 (95% CI 1.00–1.13) for 2nd *versus* 4th quartile of LDL cholesterol, and 1.10 (95% CI 1.04–1.17) for 3rd *versus* 4th quartile of LDL cholesterol (figure 1). Lower levels of LDL cholesterol were also associated with lower values of FEV_1/FVC (supplementary figure S1).

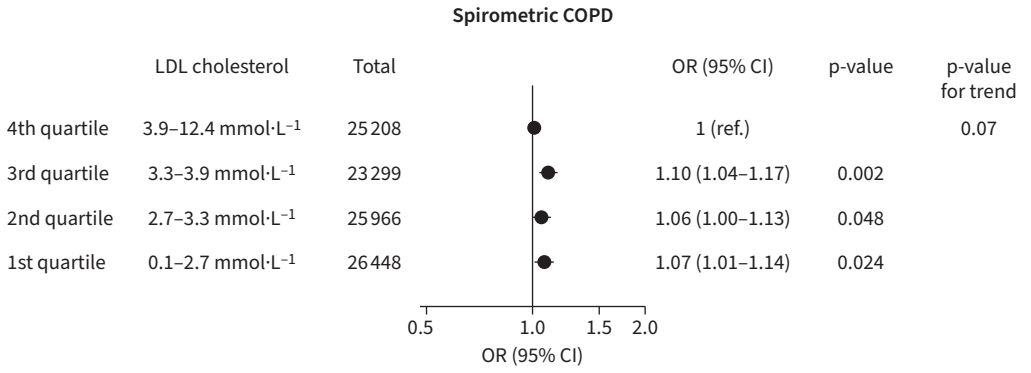

FIGURE 1 Risk of COPD according to quartiles of plasma low-density lipoprotein (LDL) cholesterol. The logistic regression model was adjusted for age, sex, body mass index, alcohol consumption, physical inactivity, smoking status and pack-years. Spirometric COPD = forced expiratory volume in 1 s (FEV_1)/forced vital capacity (FVC) <0.7 excluding asthmatic patients. CI: confidence interval; OR: odds ratio.

COPD outcomes prospectively

Lower levels of LDL cholesterol were associated with increased risk of severe COPD exacerbation during follow-up with hazard ratios of 1.43 (95% CI 1.21–1.70) for 1st *versus* 4th quartile of LDL cholesterol, 1.21 (95% CI 1.03–1.43) for 2nd *versus* 4th quartile of LDL cholesterol, and 1.01 (95% CI 0.85–1.20) for 3rd *versus* 4th quartile of LDL cholesterol (p-value for trend=6×10^{-6}) (figure 2). Similar results were obtained when the analyses were adjusted for death as a competing risk.

Plasma levels of LDL cholesterol were lower in individuals who subsequently had a COPD outcome than in those who did not: adjusted cumulative incidences of severe COPD exacerbation and COPD-specific mortality were increased with lower baseline LDL cholesterol from 3rd/4th quartile to 2nd quartile to 1st quartile of LDL cholesterol (p-values 7×10^{-10} and 0.0009) (figure 3).

High HDL cholesterol was associated with increased risk of severe COPD exacerbation with a hazard ratio of 1.26 (95% CI 1.04–1.52) for 4th *versus* 1st quartile of HDL cholesterol (supplementary figure S2). Low triglycerides were associated with increased risk of severe COPD exacerbation with a hazard ratio of 1.27 (95% CI 1.06–1.52) for 1st *versus* 4th quartile of triglycerides (supplementary figure S2).

Sensitivity analyses on severe COPD exacerbations

When stratifying the analysis on risk of severe COPD exacerbations by quartiles of LDL cholesterol according to sex, smoking status, cardiovascular disease, BMI or use of lipid-lowering medication, results were similar to the overall analysis but with wider confidence intervals in subgroups with low number of events, while the associations appeared attenuated in women, underweight and overweight individuals, and in individuals who used lipid-lowering medication at baseline (compare figure 4 with figure 2). Because of the smaller size of the subgroups analysed, results should be interpreted with care.

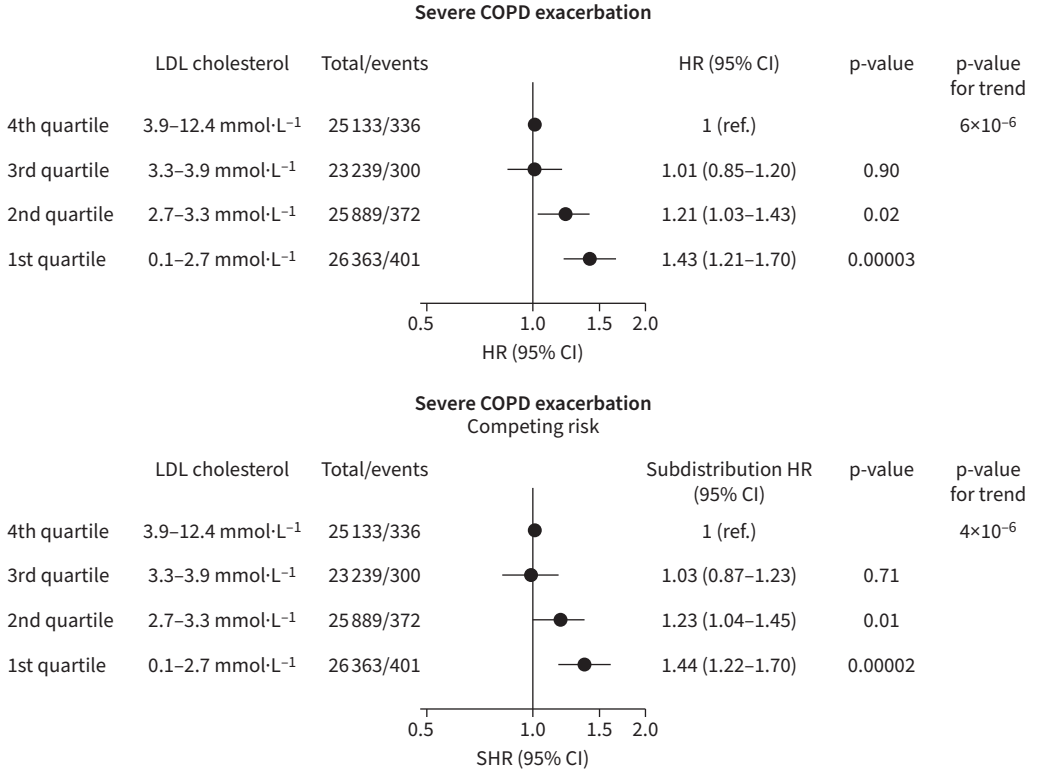

FIGURE 2 Risk of severe COPD exacerbation according to quartiles of plasma low-density lipoprotein (LDL) cholesterol at baseline. The Cox regression model was adjusted for age, sex, body mass index, alcohol consumption, physical inactivity, smoking status and pack-years. In competing risk regression, all-cause death was included as competing risk. Severe COPD exacerbation: primary diagnosis of COPD (ICD10 J44) or a primary diagnosis of respiratory failure (ICD10 J96) or pneumonia (ICD10 J18) together with COPD as a secondary diagnosis; CI: confidence interval; HR: hazard ratio; SHR: subdistribution hazard ratio.

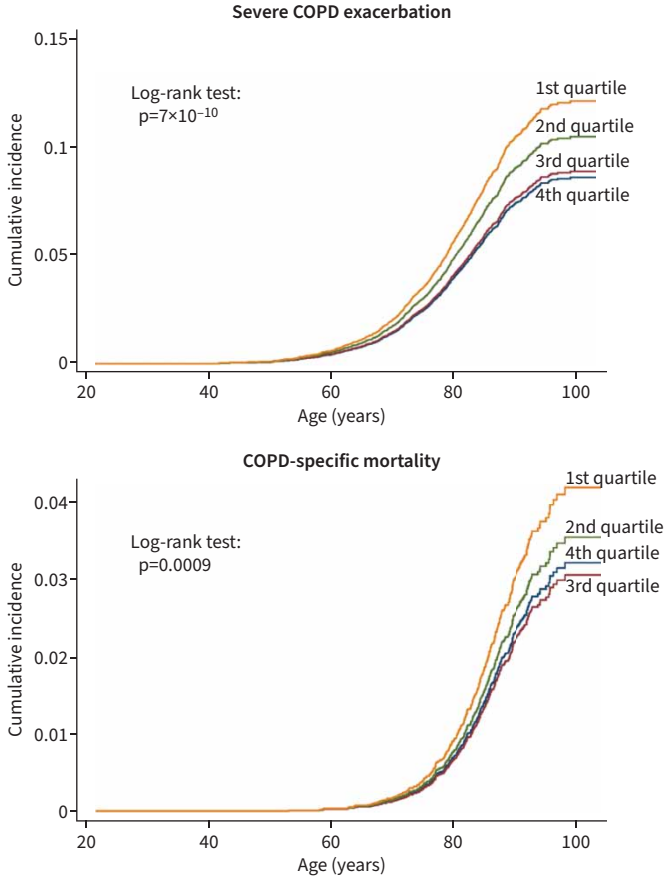

FIGURE 3 Fine and Gray cumulative incidence function curves of severe COPD exacerbation and COPD-specific mortality according to quartiles of plasma low-density lipoprotein (LDL) cholesterol at baseline. The Fine and Gray curves were adjusted for age, sex, body mass index, alcohol consumption, physical inactivity, smoking status and pack-years. Severe COPD exacerbation: primary diagnosis of COPD (ICD10 J44) or a primary diagnosis of respiratory failure (ICD10 J96) or pneumonia (ICD10 J18) together with COPD as a secondary diagnosis; COPD-specific mortality: primary cause of death listed as ICD10 J41-J44.

When analysing those individuals who were ⩾40 years of age only or adjusting the analyses for potential influence from high-sensitivity C-reactive protein (CRP), similar results to those presented were seen (compare supplementary figures S3 and S4 with figure 2). Furthermore, adjusting the analysis for lipid-lowering medication rather than adjusting the level of LDL cholesterol for use of lipid-lowering medication gave similar results to those presented (compare supplementary figure S5 with figure 2). Individuals who used lipid-lowering medication at baseline had an increased risk of severe COPD exacerbation during follow-up compared to individuals who did not use lipid-lowering medication with a hazard ratio of 1.23 (95% CI 1.07–1.42) (supplementary figure S6).

Discussion

This cross-sectional and prospective study of 107 301 adults from the Danish general population revealed that low plasma levels of LDL cholesterol were associated with increased risk of severe COPD exacerbation and COPD-specific mortality. There was a dose–response relationship between lower LDL cholesterol and risk of severe COPD exacerbation, and the findings were independent of influences from age, sex, BMI, smoking and other possible risk factors related to COPD. To our knowledge, no studies have previously investigated the association between LDL cholesterol and risk of COPD, severe COPD exacerbation and COPD-specific mortality in the general population.

Several previous studies have investigated plasma levels of LDL cholesterol in patients with COPD with inconsistent results. An overall meta-analysis reported nominally lower LDL cholesterol in COPD patients compared to controls [19]; however, individual studies have been inconsistent, reporting respectively higher LDL cholesterol [20], lower LDL cholesterol [21, 22] and no significant difference in individuals

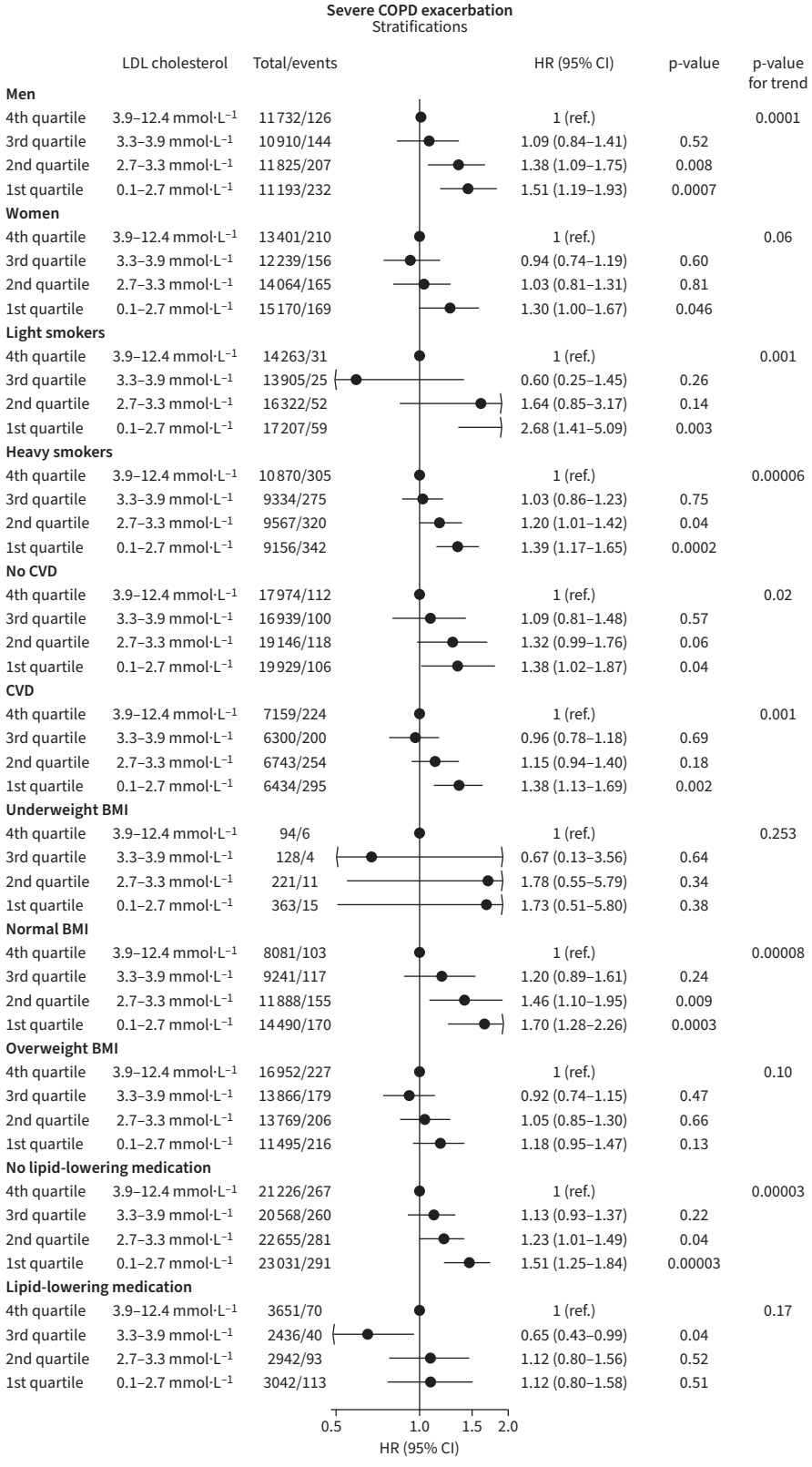

FIGURE 4 Stratifications of sex, smoking status, cardiovascular disease (CVD), body mass index (BMI) and use of lipid-lowering medication on risk of severe COPD exacerbation according to quartiles of plasma low-density lipoprotein (LDL) cholesterol at baseline. The Cox regression models were adjusted for age, sex, BMI, alcohol consumption, physical inactivity, smoking status and pack-years. Severe COPD exacerbation: primary diagnosis

of COPD (ICD10 J44) or a primary diagnosis of respiratory failure (ICD10 J96) or pneumonia (ICD10 J18) together with COPD as a secondary diagnosis. Light and heavy smoker were defined as <10 and ⩾10 pack-years, respectively. Underweight BMI was defined as <18.5 $kg \cdot m^{-2}$, normal BMI as 18.5–24.9 $kg \cdot m^{-2}$ and overweight BMI as ⩾25 $kg \cdot m^{-2}$. Use of lipid-lowering medication was self-reported. CI: confidence interval; HR: hazard ratio.

with COPD compared to controls [23–25]. Chan *et al*. [26] investigated the association between hyperlipidaemia, pneumonia and mortality in 1491 Taiwanese individuals with COPD, finding decreased incidence of pneumonia and mortality in individuals with COPD and hyperlipidaemia, supporting the findings for COPD-specific mortality in the present study. Further, in a second study, hyperlipidaemia was associated with higher FEV_1 in individuals with COPD, which is in accordance with our results for FEV_1/FVC ratio and LDL cholesterol (supplementary figure S1) [27].

A possible explanation for our results is reverse causation, where participants with severe phenotypes of COPD, and higher risk of future exacerbations, may have lower plasma levels of LDL cholesterol due to low calorie intake and increased energy expenditure, that is, wasting. In accordance with this, lower levels of total cholesterol have been proposed to be a marker of frailty in elderly patients [28]. In our study, only participants with normal BMI, not under- nor overweight, had a statistically significant difference in hazard ratio for severe COPD exacerbation between quartiles of LDL cholesterol (figure 4). Underweight individuals showed higher hazard ratio for lower quartiles of LDL cholesterol (1.73 (95% CI 0.51–5.80) for 1st *versus* 4th quartile) with wide confidence intervals crossing the null hypothesis; however, statistical power was quite low for these estimates. These results could indicate that our findings are mainly driven by frail and undernourished individuals with higher risk of future COPD outcomes. Reverse causation has likewise been speculated to be the cause of a U-shaped association between plasma levels of LDL cholesterol and all-cause mortality [29]. In previous studies, LDL cholesterol has been reported as a negative acute phase reactant [30, 31], which could be another possible explanation for our results. However, when further adjusted for high-sensitivity CRP, a strong positive acute phase reactant, the results remained similar to those presented. Lastly, it is possible that low LDL cholesterol matters in reverse cholesterol transport of macrophages adding to inflammatory cell dysfunction and thereby an increased susceptibility to COPD exacerbation.

Though this study found lower levels of LDL cholesterol to be associated with higher risk of exacerbations and lower FEV_1/FVC ratio, these findings should not be used as an argument against the use of lipid-lowering medication in individuals with COPD, as randomised controlled trials have reported increased lung function and decreased rate of exacerbations in individuals with COPD who were given statins [7, 9]. As the mechanisms underlying statins' ameliorating effects on COPD have not been investigated, further studies examining these mechanisms are needed.

It is of importance for clinicians to have insight into how hypercholesterolaemia may influence COPD prognosis. Our results indicate that individuals with higher levels of LDL cholesterol have a less severe phenotype of COPD than those with lower levels; however, as causality cannot be addressed in classical observational studies, future large-scale studies should investigate the LDL cholesterol and COPD correlation using randomised controlled trials or Mendelian randomisation study designs [32].

This study has a number of strengths. Firstly, a large number of participants randomly selected from the general population were included in the study ensuring high statistical power. Further, it was possible to adjust for multiple confounders in the analysis. Thirdly, information on severe COPD exacerbation and COPD-specific mortality was obtained from complete national Danish health registries essentially without loss to follow-up. Limitations of the study include that participants primarily consisted of a Caucasian population, and results therefore cannot necessarily be extrapolated to other populations. However, we are not aware of information that would suggest that the present results should not apply to people of all ethnicities. Secondly, since this study is of an observational nature, causality cannot be addressed. Finally, postbronchodilator spirometry was not available in this study, which might falsely increase the number of individuals classified as having spirometric COPD, while they in fact had asthma. However, as prospective analyses of COPD showed similar results, we do not believe this substantially biased our results.

Conclusion

Low plasma levels of LDL cholesterol were associated with an increased risk of severe COPD exacerbation and COPD-specific mortality in the Danish general population. The prospective results remained when

analyses were further adjusted for death as a competing risk or for other confounders including high-sensitivity CRP. These findings might be a result of reverse causation indicating that individuals with severe phenotypes of COPD have lower plasma levels of LDL cholesterol due to wasting; however, further investigations are needed to assess causality.

Provenance: Submitted article, peer reviewed.

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Conflict of interest: J. Freyberg, E.M. Landt, S. Afzal, B.G. Nordestgaard and M. Dahl have nothing to disclose.

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