Statin use and exacerbations in individuals with chronic obstructive pulmonary disease

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ABSTRACT

Background We tested the hypothesis that statin use in individuals with COPD is associated with a reduced risk of exacerbations.

Methods We identified 5794 individuals with COPD and a measurement of C reactive protein (CRP) in the Copenhagen General Population Study (2003–2008). During 3 years of follow-up we recorded exacerbations with hospital admissions or oral corticosteroid treatment. In a nested case-control design, matching on age, gender, smoking, COPD severity and comorbidity, we estimated the association between statin use and exacerbations. In addition, we examined the association between statin use and high CRP (>3 mg/L), and the association between high CRP and exacerbations during follow-up.

Results Statin use was associated with reduced odds of exacerbations in crude analysis, OR=0.68 (95% CI 0.51 to 0.91, p=0.01), as well as in multivariable conditional logistic regression analysis, OR=0.67 (0.48 to 0.92, p=0.01). However, in the subgroup with the most severe COPD and without cardiovascular comorbidity, we observed a null association between statin use and exacerbations, OR=1.1 (0.5 to 2.1, p=0.83). Furthermore, statin use was associated with reduced odds of a high CRP, OR=0.69 (0.56 to 0.85, p<0.001), and a high CRP was associated with an increased risk of exacerbations, HR=1.62 (1.35 to 1.94, p<0.001). We estimated the percentage of excess risk of the association of statin use with exacerbations possibly mediated through a reduction of CRP to be 14% (4–51%).

Conclusions Statin use was associated with reduced odds of exacerbations in individuals with COPD from the general population, although this was not apparent in those with the most severe COPD without cardiovascular comorbidity. Statins may thus only associate with reduced risk of exacerbations in patients with COPD with coexisting cardiovascular disease.

INTRODUCTION

COPD is one of the most important global health problems.1 2 COPD is characterised by exacerbations, and these exacerbations constitute key events in COPD progression, prognosis and treatment.3 4 In recent years there has been a growing body of evidence suggesting systemic inflammation as a key element in the pathogenesis of COPD.5 6 As a result, there is an increasing focus on whether use of medications that reduce markers of systemic inflammation may also reduce the risk of exacerbations in COPD.7

Statin use was associated with a reduction in exacerbations in unselected individuals with COPD, but like in a recent randomised controlled trial we observed a null association in those with the most severe COPD and without cardiovascular comorbidity suggesting that statins may only associate with reduced risk of exacerbations in patients with COPD with coexisting cardiovascular disease.

Key messages

What is the key question?

Do statins have beneficial effects on exacerbations in unselected individuals with COPD, and if so, what might be part of the explanation?

What is the bottom line?

Several population based studies have indicated that statin use may reduce the risk of exacerbations in unselected individuals with COPD, but studies have lacked clinical characteristics such as severity of COPD, comorbidities and markers of systemic inflammation.

Why read on?

In unselected individuals from the general population our study indicates that statin use is associated with a reduction in exacerbations in COPD, but like in a recent randomised controlled trial we observed a null association in those with the most severe COPD and without cardiovascular comorbidity suggesting that statins may only associate with reduced risk of exacerbations in patients with COPD with coexisting cardiovascular disease.

Statin use was associated with reduced odds of exacerbations in individuals with COPD associated with a reduced risk of exacerbations. This hypothesis was tested among individuals with different severity of COPD and cardiovascular comorbidity, as well as in the subgroup with the most severe COPD and without cardiovascular comorbidity.
METHODS
Population
We used data from the Copenhagen General Population Study (2003–2008) comprising 55,731 participants. For this study, we identified 5812 individuals with COPD, defined by presence of airflow limitation (FEV₁ divided by FVC, FEV₁/FVC<0.7), no self-reported asthma and age above 40 years. Of these, 5794 (99.7%) individuals had measurement of CRP at the examination.

Linkage to national all-inclusive registers
From the all-inclusive Danish National Patient Registry we retrieved data on hospital admissions with a discharge diagnosis of COPD (ICD-10: J41-J44) to define severe exacerbations of COPD. In addition, we identified previous hospital admissions with a discharge diagnosis of ischaemic heart disease, and/or diabetes mellitus as part of the comorbidity definition; see online supplementary e-table 1 for further details.

From the Danish National Prescription Registry, we retrieved data on treatment with oral corticosteroids alone or in combination with antibiotics to define moderate exacerbations of COPD. Furthermore, we included data on previous use and dose of maintenance pulmonary medications (long-acting bronchodilators and fixed-dose combinations with inhaled corticosteroids) in either the 3 months before an exacerbation, or in the 3 months before measurement of CRP at the examination. In addition, we assessed the use and dose of statins during either the 3 months before an exacerbation, or the 3 months before measurement of CRP. We had access to dispensed medication data from 1995 until 31 December 2009, thus ensuring at least 1 year of complete follow-up for all individuals. See online supplementary e-table 2 for all study anatomical therapeutic chemical codes used to identify dispensed medications.

Study approval
The study was approved by an institutional review board and the regional ethics committee (H-KF01-144/01), and was conducted according to the Declaration of Helsinki. Written informed consent was obtained from all participants.

Study design
Figure 1 shows the study design.

Statin use and exacerbations
To examine the association between statin use and odds of exacerbations, we applied a nested case-control design; see flow diagram in online supplementary e-figure 1. Cases were individuals with a first exacerbation within a maximum of 3 years of follow-up. Exacerbations were defined as a composite of medically treated exacerbations and hospital admissions with COPD. Statin use was defined as at least one dispense of statins in the 3 months prior to the exacerbation date for cases. The exacerbation date for cases defined an index date. Controls were assigned the same index date as their corresponding case, and statin use was calculated in the 3 months prior to this index date. Controls were selected from the COPD cohort by use of risk-set sampling technique. Individuals eligible to become controls were those who matched the index case with respect to age, gender, smoking, COPD severity (Global Initiative for Chronic Obstructive Lung Disease, GOLD grade) and cardiovascular comorbidity, and who did not have an exacerbation prior to the index date (see online supplementary e-table 1 for further details). Two controls were selected for each case. The reason for choosing a nested case-control design was that these case-control studies are computationally more effective than cohort studies, while producing the same estimates as a cohort study with little loss in precision.

In addition, we selected a subgroup of individuals with COPD who were 40–80 years of age, had FEV₁<80%, previous exacerbations (within 10 years), and without cardiovascular comorbidity. This was done to mimic the patients enrolled in a recent randomised controlled trial (RCT). Among these individuals, we identified 89 cases with exacerbations, and selected

Figure 1 Study design. ‘Figure 2’: Conditional logistic regression analysis in case-control study of statin use and associated odds of exacerbations. ‘Figure 3’: Logistic regression analysis of statin use and associated odds of having a high C reactive protein (CRP) level (>3 mg/l). ‘Figure 4’: Cox regression analysis of high CRP and associated risk of exacerbations. ‘Figure 5’: Estimated percentage of excess risk of the association of statin use with exacerbations possibly mediated through CRP, percentage of excess risk mediated (PERM) (CRP).
168 controls as described above, except that the subgroup selection criteria only allowed matching on age, gender and smoking.

Statin use and CRP
We assessed the association between statin use and CRP (see figure 1) by examining the relationship between statin use in the 3 months before the measurement of CRP at the examination, and as main outcome a categorised CRP (low ≤3 mg/L <high).\(^{18}\)

CRP and exacerbations
We analysed the association between a high CRP at the examination and the risk of exacerbations within 3 years of follow-up (see figure 1), by analysing the time to first exacerbation.

Percentage of excess risk mediated
We also estimated the percentage of excess risk of the association of statin use with exacerbations in COPD possibly mediated through CRP, percentage of excess risk mediated (PERM) (CRP).\(^{26}\)

Statistical analyses
Demographics
The statistical software package R (V3.0.1) was used.\(^{27}\) Characteristics of individuals with COPD who were statin users versus those who did not use statins were evaluated using \(\chi^2\) tests or ANOVA for categorical or continuous variables as appropriate.\(^{28}\)

Statin use and exacerbations
We performed a conditional logistic regression analysis (R-package="survival"), to assess the association between statin use in the 3 months before an exacerbation and odds of exacerbations, in the case-control design.\(^{12}\) To assess a possible dose-response relationship, we also included dose of statins (low dose ≤50% of defined daily dosages <high dose).\(^{12} \ 20\) We then adjusted the conditional logistic regression analysis for the level of CRP (high/low).\(^{18}\) Furthermore, we applied a multivariable conditional logistic regression analyses where we included as confounders the use of all maintenance pulmonary medications, health behaviour (regular use of vitamin pills and regular visits to the general practitioner), dose of all maintenance pulmonary medications (high/low) and CRP level (high/low). See online supplementary e-table 1 for a detailed description of all variables.

In sensitivity analyses, we also adjusted our estimates for FEV\(_1\). This was done to see if inclusion of exact pulmonary function, in addition to matching on the rather broad GOLD grades, would affect the size of our estimates. Furthermore, we tested if socioeconomic status assessed by education or household income,\(^{29}\) alcohol consumption categories (daily/weekly or monthly/none)\(^{30}\) and frailty assessed by reporting the feeling of not having accomplished very much recently or reporting a feeling of giving up, were associated with exacerbations or affected our estimates.\(^{31}\)

Individuals with missing values on confounders in multivariable models were not included in the analysis, explaining why the numbers reported in the multivariable models differ slightly. We had complete register follow-up data on all individuals. The average time until first exacerbation was 452 days.

In the subgroup analysis among those with the most severe COPD and without cardiovascular comorbidity, we performed the same analyses as described in our main analysis above.

Statin use and CRP
The association between statin use during the 3 months prior to measurement of CRP at the examination, and high or low CRP was analysed in a logistic regression analysis.\(^{18}\) We adjusted our analyses for the matching variables included in the case-control design described above: age, gender, GOLD grade, smoking and comorbidity. We then included the confounders of use of all maintenance pulmonary medications, health behaviour and doses of all maintenance pulmonary medications (see online supplementary e-table 1 for details). In a sensitivity analysis, we included FEV\(_1\) as a possible confounder.

Using the multivariable logistic regression model,\(^{28}\) we calculated the average predicted probability of having a high CRP in the group using statins and in the group not using statins.

CRP and exacerbations
We analysed time to first exacerbation using Cox regression analysis. Censoring was death, emigration or end of follow-up. First, we adjusted our analyses for age, gender, GOLD grade, smoking and comorbidity. In a sensitivity analysis, we included an additional CRP cut point of 1 mg/L in the analysis (see online supplementary e-table 1 for details). Then we included the confounders of use of all maintenance pulmonary medications, health behaviour, dose of all maintenance pulmonary medications, and in a sensitivity analysis FEV\(_1\).

Using the multivariable Cox regression model,\(^{28}\) we calculated the average predicted probability of exacerbations in the group with high CRP and in the group with low CRP. Furthermore, in a sensitivity analysis to see if high CRP is a stable predictor of exacerbations over time, we also started follow-up from 6 months after the measurement of CRP, and followed our participants for a maximum of 3 years.

Percentage of excess risk mediated
We estimated the percentage of excess risk of the association of statin use with exacerbations in COPD possibly mediated by CRP, PERM(CRP),\(^{26}\) as,

\[
\text{PERM(CRP)} = \frac{\text{RR(adjusted)} - \text{RR (confounder and CRP adjusted)}}{\text{RR(confounder adjusted)} - 1}
\]

CIs were estimated by bootstrap resampling (10 000 samples).\(^{32}\) As a sensitivity analysis we estimated PERM(CRP) by including CRP as a continuous variable instead of a categorical variable (high/low).

RESULTS
Demographics
Among 5794 individuals with COPD, we identified 700 (12.1%) individuals who were statin users in the 3 months before the examination date in the Copenhagen General Population Study. Statin users were older than non-users (71 vs 66 years, \(p<0.001\)), were more likely to be male (53% vs 47%, \(p<0.001\)) and they were less likely to be current smokers (31% vs 40%, \(p<0.001\)). As expected, statin users were more likely to have cardiovascular comorbidities than non-users (63% vs 18%, \(p<0.001\)) and they were more likely to have visited their general practitioner regularly (more than three times in the previous year, 55% vs 29%, \(p<0.001\)). Statin users did not differ from non-users with respect to FEV\(_1\) or use of maintenance pulmonary medications; further details are shown in the left part of online supplementary e-table 3.
During the 3 year follow-up we identified 530 cases with exacerbations, and selected 1016 corresponding controls. There were no statistically significant differences between cases and controls for any of the matching variables (all p values >0.10, χ² tests). Among 1546 individuals with COPD in the case-control study, we identified 320 (20.7%) who were statin users during the 3 months before the index date. The right part of online supplementary e-table 3 shows characteristics of those individuals with statin use versus those not using statins in the case-control study.

Statin use and exacerbations
Statin use in the 3 months before the index date was associated with reduced odds of exacerbations in crude conditional logistic regression analysis, OR=0.68 (95% CI 0.51 to 0.91, p=0.01), as well as in multivariable conditional logistic regression analysis, OR=0.67 (0.48 to 0.92, p=0.01) compared with no use of statins. Estimates were generally robust towards possible confounder adjustments, as shown in the left part of figure 2.

In sensitivity analyses, only FEV₁ and education contributed significantly. When including FEV₁ in the multivariable model the association of statin use with exacerbations remained similar, as shown in figure 2, and this also applied when including education (OR=0.68 (0.5 to 1.0), p=0.049, for the association between statin use and exacerbations).

The online supplementary e-figure 2 shows a forest plot of possible confounding variables included in multivariable conditional logistic regression analysis and their corresponding odds of exacerbations.

CRP and exacerbations
Multivariable Cox regression analysis showed that having a high CRP in COPD was associated with an increased risk of exacerbations during follow-up, HR=1.62 (1.35 to 1.94, p<0.001), as shown in figure 4. The average predicted probability of having exacerbations during follow-up was 13% in the group with high CRP compared with 8% in the group with low CRP (figure 4).

Figure 2  Statin use and exacerbations. Results of the crude and multivariable conditional logistic regression analyses. Left part: Main analysis. Case-control study among 1546 individuals with COPD from the general population. From left to right: number of individuals in study (‘No. of Observations’), number of individuals with exacerbations (‘No. of Exacerbations’), OR of exacerbation with 95% CIs, and a corresponding forest plot. Significance codes: ** for p<0.01; * for p<0.05. Ninety-nine individuals did not have data on health behaviour, and an additional three individuals did not have data on C reactive protein (CRP), explaining why the number of observations differ between the multivariable models. CRUDE ANALYSIS: matched on age, gender, smoking, COPD severity (Global Initiative for Chronic Obstructive Lung Disease, GOLD grade), and cardiovascular comorbidity. Right part: Most severe COPD without cardiovascular comorbidity. Subgroup analysis among 257 individuals with the most severe COPD and without cardiovascular comorbidity. From left to right: number of individuals in study (‘No. of Observations’), number of individuals with exacerbations (‘No. of Exacerbations’), OR of exacerbation with 95% CIs, and a corresponding forest plot. Fifteen individuals did not have data on health behaviour explaining why the number of observations differ between the multivariable models. CRUDE ANALYSIS for this subgroup: matched on age, gender and smoking.

Statin use and CRP
As shown in figure 3, statin use in the 3 months before measurement of CRP at the examination reduced the odds of having a high CRP (>3 mg/L), OR=0.69 (0.56 to 0.85, p<0.001), in multivariable logistic regression analysis. The average predicted probability of having a high CRP in the group using statins was 23% compared with 30% in the group not using statins (figure 3). The online supplementary e-figure 3 shows a forest plot of possible confounding variables included in multivariable logistic regression analysis and the corresponding odds of having a high CRP.

Figure 3  Statin use and CRP. Multivariable logistic regression analysis showed that having a high CRP in COPD was associated with an increased risk of exacerbations during follow-up, HR=1.62 (1.35 to 1.94, p<0.001), as shown in figure 4. The average predicted probability of having exacerbations during follow-up was 13% in the group with high CRP compared with 8% in the group with low CRP (figure 4).

Figure 4  CRP and exacerbations. Multivariable Cox regression analysis showed that having a high CRP in COPD was associated with an increased risk of exacerbations during follow-up, HR=1.62 (1.35 to 1.94, p<0.001), as shown in figure 4. The average predicted probability of having exacerbations during follow-up was 13% in the group with high CRP compared with 8% in the group with low CRP (figure 4).
In a sensitivity analysis, we assessed the impact of exacerba-
tions starting follow-up from 6 months after CRP measurement. In
this analysis, a high CRP remained associated with exacerba-
tions, HR=1.67 (1.41 to 2.02, p<0.001) (data not shown).

Percentage of excess risk mediated
We estimated from bootstrapped resampled PERM (CRP)’s that
approximately 14% (4–51%) of the association of statin use
with exacerbations in COPD may be mediated through a reduc-
tion of CRP; importantly, causal inference cannot be drawn
from this analysis. This is shown in figure 5, which also shows a
summary of our results.

DISCUSSION
Statin use was associated with reduced odds of exacerbations in
individuals with COPD from the general population, although
this was not apparent in those with the most severe COPD and
without cardiovascular comorbidity. Statins may thus only asso-
ciate with reduced risk of exacerbations in patients with COPD
with coexisting cardiovascular disease. Importantly, causal infer-
ence cannot be drawn from our observational analyses.

Mechanistically, studies have shown that statins have several
effects besides a lowering of plasma cholesterol, including anti-
flammatory effects. Furthermore, there is evidence of sys-
temic inflammation in a proportion of individuals with COPD. Our
study indicates that, if present, part of a potential beneficial effect of statin use on exacerbations may be
explained by reduction of systemic inflammation, marked as
reduction of CRP in individuals with COPD and cardiovascular
comorbidity.

Studies using pharmaceutical databases have previously indi-
cated that statin use is associated with reduced odds of exacerba-
tions in COPD. The most recent and well-quoted study showed
that a current statin use could be associated with 40%
reduced odds of exacerbations. Our study finds similar asso-
ciations in a setting where we were able to include several pos-
sible confounders such as the level of CRP. As expected, we
observed that statin use in individuals with COPD is strongly
associated with lower values of CRP, as shown previously in
individuals without COPD. The question is then, how the results of our study should be
interpreted in light of the recent large well-conducted and
convincingly negative RCT of simvastatin on risk of COPD
exacerbations. In contrast to our study, the randomised study
excluded all patients with cardiovascular comorbidity. There is
substantial evidence of the burden of cardiovascular comorbid-
ity in COPD, and studies have also shown that cardiovascular
comorbidity is associated with increased systemic inflamma-
tion in COPD. In our study, cardiovascular comorbidity was
present in a large proportion of individuals with COPD. Inflammation caused by presence of cardiovascular comorbidity
in COPD could act synergistically with pulmonary inflamma-
tion, and thereby explain our findings. Indeed, our subgroup
analysis in individuals without cardiovascular comorbidity as
well as the findings from the recent RCT suggest that statins
have no effect on COPD exacerbations in patients with the most
severe COPD and without cardiovascular comorbidity, which
we believe supports our hypothesis.

If a potential beneficial effect of statins on exacerbations
would only apply among individuals with cardiovascular

Figure 3 Statin use and C reactive protein (CRP). Results of the multivariable logistic regression analysis. From left to right: number of individuals in study (‘No. of Observations’), number of individuals with high CRP (‘No. with high CRP’), OR of high CRP with 95% CIs, a corresponding forest
plot, and a bar plot showing the average predicted probability of having a high CRP. Significance codes: *** for p<0.001. Individuals with missing
values on confounders in multivariable models were not included in the analyses, explaining why the numbers reported in the multivariable models
differ slightly.
comorbidity, this would question the suggestion for giving statins to any patients with COPD. It could namely be argued that most individuals with cardiovascular disease should already be treated with statins, and therefore automatically would receive such treatment. However, this is not always the case and our study suggests that in patients with COPD with cardiovascular comorbidity focus on statin treatment possibly is important, despite the recent negative randomised trial in patients with COPD without cardiovascular comorbidity.14 Furthermore, our observations could also relate to a possible phenotypical variability such as 'systemic COPD',18 and questions whether statins could be preventing dyspnoea in primary pulmonary events, or dyspnoea in cardiac events in those with cardiovascular comorbidity.15

Clinicians are increasingly faced with the task of weighing up evidence from RCTs against findings from pharmacoepidemiology. RCTs are the most prominent way to assess treatment effects, but the results of a single study should be interpreted cautiously.39 Fortunately, RCTs and observational studies mostly come to the same conclusions, and observational studies can be used synergistically to test the external validity and formulate hypotheses.40 However, when the results of a single RCT and observational studies do not concur, it is important to consider possible reasons for the discrepancy.40

Observational studies may be limited by selection bias caused by unmeasured confounders (see figure 1 and see online supplementary e-figure 4) that could cause unmeasured differences between two treatment groups. On the other hand, observational data can be very important for estimating effects in patients who are frequently excluded from clinical trials, such as those with comorbidities. When observational studies restricted to a subgroup with the same set of exclusion and/or inclusion criteria as a RCT show similar results, the results from all individuals in the observational study could still be important. A rationale for performing observational analyses is the ability to provide estimates of drug effectiveness in patients more like those observed in clinical practice than those enrolled in clinical trials, since this can allow suggestions of precisely which patients may benefit from treatment.40

A possible limitation to our study is that severity of COPD was defined by prebronchodilator spirometry. Therefore, although we excluded all individuals with self-reported asthma, we cannot exclude the possibility that some individuals with asthma may have been included in the analyses. A possible bias in our study is a health behaviour bias; that is, that a person who regularly uses any kind of medication, or is regularly provided with healthcare, has certain lifestyle characteristics that may reduce the risk of exacerbations. To minimise such potential bias, multivariable analyses where adjusted for health behaviour and these adjustments did not change our estimates. However, individuals with, for example, previous exacerbations could be more likely to be started on statins, thereby leading to confounding by indication, which an adjustment for a healthy user effect might not have captured fully. Nevertheless, the subgroup analysis among individuals with the most severe COPD with previous exacerbations showed a null association between statin use and exacerbations, and therefore we believe that confounding by indication is unlikely to explain our main findings. Although we had complete data on follow-up for all individuals, another

### Table: CRP Exposure and Exacerbations

<table>
<thead>
<tr>
<th>CRP Exposure</th>
<th>No. of Observations</th>
<th>No. of Exacerbations</th>
<th>Risk of Exacerbation HR (95% CI)</th>
<th>Forest Plot</th>
<th>Probability of Exacerbation</th>
</tr>
</thead>
<tbody>
<tr>
<td>MULTIVARIABLE MODEL: adjusted for statin use, age, gender, GOLD stage, smoking, and comorbidity</td>
<td>Low CRP (reference) 3888</td>
<td>279</td>
<td>1.00</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>High CRP            1603</td>
<td>250</td>
<td>1.68 (1.41-2.00)**</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Very low CRP (reference) 792</td>
<td>48</td>
<td>1.00</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Intermediate CRP    3196</td>
<td>231</td>
<td>1.24 (0.91-1.69)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>High CRP            1603</td>
<td>250</td>
<td>2.00 (1.46-2.74)**</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MULTIVARIABLE MODEL: adjusted for statin use, age, gender, GOLD stage, smoking, comorbidity, and use of all maintenance pulmonary medications</td>
<td>Low CRP (reference) 3888</td>
<td>279</td>
<td>1.00</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>High CRP            1603</td>
<td>250</td>
<td>1.71 (1.44-2.04)**</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MULTIVARIABLE MODEL: adjusted for statin use, age, gender, GOLD stage, smoking, comorbidity, use of all maintenance pulmonary medications, and health behaviour</td>
<td>Low CRP (reference) 3784</td>
<td>266</td>
<td>1.00</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>High CRP            1513</td>
<td>236</td>
<td>1.64 (1.37-1.97)**</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MULTIVARIABLE MODEL: adjusted for statin use, age, gender, GOLD stage, smoking, comorbidity, dose of all maintenance pulmonary medications, and health behaviour</td>
<td>Low CRP (reference) 3784</td>
<td>266</td>
<td>1.00</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>High CRP            1513</td>
<td>236</td>
<td>1.62 (1.35-1.94)**</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MULTIVARIABLE MODEL: adjusted for statin use, age, gender, smoking, comorbidity, use of all maintenance pulmonary medications, health behaviour, and FEV1</td>
<td>Low CRP (reference) 3784</td>
<td>266</td>
<td>1.00</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>High CRP            1513</td>
<td>236</td>
<td>1.63 (1.36-1.95)**</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Figure 4 C reactive protein (CRP) and exacerbations. Results of the multivariable Cox regression analysis. From left to right: number of individuals in study (‘No. of Observations’), number of individuals with exacerbations (‘No. of Exacerbations’), risk of exacerbations (HR) with 95% CIs, a corresponding forest plot, and a bar plot showing the average predicted probability of exacerbations during follow-up. Significance codes: ‘***’ for <0.001. Individuals with missing values on confounders in multivariable models were not included in the analyses, explaining why the numbers reported in the multivariable models differ slightly.

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possible bias is missing baseline data, that could lead to selection bias. However, the percentages of missing values were low, and we consider selection bias as a result of this unlikely. Furthermore, as another possible limitation, even though we had information on all dispensing, that is, all physically retrieved medication at the pharmacy, this does not guarantee that the individuals actually took all of the medication.

Among the strengths of our study is the data collection at one site only with detailed information on all individuals, including pulmonary function tests, and complete follow-up with regard to exacerbations in all-inclusive nationwide registers. Furthermore, in our analysis, we were also able to adjust for use and dose of all maintenance pulmonary medications, that are expected to affect the risk of exacerbations, and our results where robust towards these adjustments. Further strengths of this study include the nested case-control design with a fixed lookback period, avoiding immortal time bias which can cause strong overestimation of treatment efficacy.

In conclusion, statin use was associated with reduced odds of exacerbations in individuals with COPD from the general population, although this was not apparent in those with the most severe COPD and without cardiovascular comorbidity. Statins may thus only associate with reduced risk of exacerbations in patients with COPD with coexisting cardiovascular disease. Importantly, causal inference cannot be drawn from these observational data.

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Contributors Study concept and design: TSI, JV, BGN and JLM. Acquisition of data: PL and BGN. Analysis and interpretation of data: TSI, JLM, JV, BGN and JH. Critical revision of the manuscript: all authors. Statistical analysis: JLM, TSI, JV and BGN. Obtained funding: PL, JV and BGN. Study supervision: JV, BGN, JH, PL, TSI and ILM. All authors had full access to all the data in the study, and take responsibility for the integrity of the data and the accuracy of the data analysis, and for the submission

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Competing interests JV has received honoraria from GlaxoSmithKline, Almirall, AstraZeneca, Boehringer-Ingelheim, Novartis and Takeda for consulting and for presenting at meetings and symposia. PL has received honoraria from GlaxoSmithKline and other pharmaceutical companies for consulting, teaching and for presenting at meetings and symposia. JH has participated in research projects funded by Novartis, Pfizer, MSD, Nycomed and Alkabello with grants paid to the institution where he was employed, and has received fees for teaching or consulting from Nycomed, Pfizer, Novartis, AstraZeneca and other pharmaceutical companies.

Ethics approval The study was approved by an institutional review board and the regional ethics committee (H-KF01-144/01), and was conducted according to the Declaration of Helsinki.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES
Chronic obstructive pulmonary disease