National Institute for Health and Care Excellence

Final

Chronic obstructive pulmonary disease in over 16s: diagnosis and management

[E] Predicting and preventing exacerbations

NICE guideline NG115

Evidence reviews

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Final

These evidence reviews were developed by the NICE Guideline Updates Team

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Predicting exacerbations

Review question

In people with COPD, what factors (for example, viral infection) may cause an exacerbation?

Introduction

An exacerbation is a sustained acute-onset worsening of the person's symptoms from their usual stable state, and goes beyond their normal day-to-day variations. Commonly reported symptoms are worsening breathlessness, cough, increased sputum production and change in sputum colour. Exacerbations have a negative impact on quality of life for people with COPD and they are linked to worse disease prognosis. Exposure to certain factors (such as bacterial infection, pollution and stress) may trigger an exacerbation and as a result, avoidance of these risk factors has the potential to prevent an exacerbation from developing.

This review question aimed to investigate the factors associated with exacerbations in people with an existing diagnosis of COPD. This could allow physicians to better advise people with COPD about triggers for exacerbations and help reduce or avoid them as part of their self-management plan.

In this evidence review, risk factors were restricted to acute triggers that were present before the exacerbation developed. As a result, studies examining the long-term effect of physical activity levels on exacerbation rates were excluded. The guideline already contains a number of strong recommendations for interventions (such as pulmonary rehabilitation) for which exercise is a key component. These were based on randomised controlled trials, agreed to be a higher standard of evidence than that searched for in this question. The effect of physical activity on COPD disease prognosis, including exacerbations, was also considered in the evidence review on diagnosing and predicting outcomes. Other factors considered to be intrinsic features of COPD severity such as a history of previous exacerbations or having worse lung function were not included in this review for the same reason and also formed part of some multidimensional prognostic indices. However, comorbidities were included because acute changes in the severity of comorbidities/uncontrolled comorbidities, such as depression and anxiety, could conceivably trigger an exacerbation.

PICO table

This review identified studies that fulfilled the conditions specified in Table 1. For full details of the review protocol, see appendix A.

Table 1 PICO: factors for COPD exacerbations

Population	People diagnosed with COPD
Predictive factors	Any predictive factors, including: • Individual factors: ○ Smoking ○ Lack of effective self-management (self-efficacy) ○ Multimorbidities including mental health problems ○ Polypharmacy ○ Illegal drug use ○ Viral infection ○ Major life events- stress, anxiety ○ Biomarkers • Environmental factors: ○ Pollution- outdoors, indoors

	○ Flu prevalence ○ Weather and seasonal changes ○ Living environment- air conditioning, perfume, air sprays, damp
Outcome	• Exacerbations
Measures	• Relative risks • Odds ratios • Hazard ratios

Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual. Methods specific to this review question are described in the review protocol in appendix A, and the methods section in appendix B.

Subgroup analyses were not conducted as the majority of trials did not report data for the listed categories in an accessible format.

The search strategies used in this review are detailed in appendix C.

Declarations of interest were recorded according to NICE's 2014 conflicts of interest policy.

Clinical evidence

Included studies

A systematic search was carried out to identify observational studies and systematic reviews of observational studies, which found 5,984 references (see appendix C for the literature search strategy). Evidence identified from the surveillance review and studies referenced in identified systematic reviews were also reviewed (12 references). In total, 5,996 references were identified for screening at title and abstract level. 5,709 were excluded based on their titles and abstracts and 287 references were ordered for screening based on their full texts. Of these, 67 references were included based on their relevance to the review protocol (appendix A). The clinical evidence study selection is presented as a diagram in appendix D. Although priority screening was used for this review, all of the abstracts were screened on title and abstract.

A second set of searches was conducted at the end of the guideline development process for all updated review questions using the original search strategies, to capture papers published whilst the guideline was being developed. These searches, which included articles up to February 2018, returned 3,100 references in total for all the questions included in the update, and these were screened on title and abstract. No additional relevant references were found for this review question.

The process of study identification is summarised in the diagram in appendix D.

For the full evidence tables and full modified GRADE profiles for included studies, please see appendix E and appendix G. The references of individual included studies are given in appendix K.

Excluded studies

Details of the studies excluded at full-text review are given in appendix I.

Summary of clinical studies included in the evidence review

The 67 prospective cohort studies reported on the following risk factors of interest. All risk factors were measured at the beginning of the studies and exacerbations were measured at follow-up. Some of the studies reported on more than one factor.

- Smoking (13 studies)
- Asthma-COPD overlap syndrome (3 studies)
- Other disease related factors (31 studies)
  - Multimorbidity (Charlson index [6 studies], number of comorbidities [2 studies])
  - Cardiovascular conditions (ischaemic heart disease [2 studies], diabetes [2 studies], congestive heart failure [2 studies], history of vascular disease [1 study], hyperlipidaemia [1 study])
  - Respiratory conditions (history of pneumonia [2 studies], emphysema [1 study], history of asthma [2 studies], chronic bronchitis [3 studies])
  - Mental health problems (depression [7 studies], anxiety [4 studies], psychiatric disorders [1 study])
  - Overweight/obesity (1 study)
  - History of reflux or heartburn (1 study), gastroesophageal reflux disease (7 studies)
  - HIV (1 study)
- Biomarkers (21 studies)
- Viral or bacterial infection (4 studies)
- Other medicines (3 studies)
- Pollution (4 studies)
- Weather and seasonal changes (1 study)

See appendix E for full evidence tables.

Some studies were reported by more than one article, with each of these articles reporting different outcomes, factors or follow-up time. As a result, we have added study names to appendix G – GRADE tables to articles reporting on the same study.

Quality assessment of clinical studies included in the evidence review

See appendix G for full GRADE tables.

Economic evidence

Included studies

A single search was conducted to cover all review question topics in this guideline update. This search returned 16,299 records, of which all were excluded on title and abstract for this review question.

Summary of studies included in the economic evidence review

No economic evidence as identified for this review question.

Economic model

Economic modelling was not prioritised for this review question.

Evidence statements

The format of the evidence statements is explained in the methods in appendix B.

Risk factor: smoking

The following factors were independently associated with an increase in COPD exacerbations:

- Current smoker compared to former or non-smoker (9 studies with 28,672 participants, very low to high quality evidence)
- Former smoker exposed to passive smoking compared to former smoker not exposed to passive smoking (1 study with 312 participants, moderate quality evidence)
- Pack years of smoking (1 study with 1,033 participants, high quality evidence)

An association with an increase in COPD exacerbations could not be detected for the following factors:

- Exposed to passive smoking compared to not exposed to passive smoking (1 study with 809 participants, low to moderate quality evidence)
- Former smoker compared to never smoker (2 studies with 1,571 participants, very low to low quality evidence)
- Smoker or former smoker compared to never smoker (1 study with 512 participants, moderate quality evidence)
- Menthol cigarette smokers compared to non-menthol cigarette smokers (1 study with 3,772 participants, very low to low quality evidence)

Risk factor: disease related factors

The following factors were associated with an increase in COPD exacerbations:

- Ischaemic heart disease (2 studies with 2,495 participants, low quality evidence)
- History of reflux or heartburn (1 study with 2,138 participants, moderate to high quality evidence)
- History of pneumonia (2 studies with 1,490 participants, moderate quality evidence)
- Diabetes (2 studies with 637 participants, low to moderate quality evidence)
- Emphysema (1 study with 2,138 participants, moderate quality evidence)
- History of asthma (2 studies with 5,942 participants, moderate quality evidence)
- Overweight/obesity (1 study with 512 participants, low to moderate quality evidence)

An association with an increase in COPD exacerbations could not be detected for the following factors:

- Comorbidities – Charlson index score (6 studies with 2,463 participants, very low to high quality evidence)
- Comorbidities- number of comorbidities from a list (2 studies with 352 participants, very low to high quality evidence)
- Congestive heart failure (2 studies with 1,024 participants, low to moderate quality evidence)
- History of vascular disease (1 study with 1,033 participants, moderate quality evidence)
- Hyperlipidaemia (1 study with 570 participants, low quality evidence)
- Gastroesophageal reflux disease (7 studies with 11,815 participants, very low to moderate quality evidence)
- Chronic bronchitis (3 studies with 6,035 participants, very low to high quality evidence)

- Depression and anxiety (8 studies with 4,585 participants, very low to high quality evidence)
- HIV (1 study with 167 participants, low to moderate quality evidence)
- Psychiatric disorders (1 study with 110 participants, moderate to high quality evidence)

Risk factor: viral or bacterial infection

The following factors were associated with an increase in COPD exacerbations:

- Any bacteria (2 studies with 196 participants, low to moderate quality evidence)
- Moraxella catarrhalis (2 studies with 298 participants, moderate quality evidence)
- Streptococcus pneumoniae (1 study with 81 participants, moderate quality evidence)
- Any new strain including haemophilus influenza, moraxella catarrhalis, streptococcus pneumoniae, or pseudomonas aeruginosa (1 study with 81 participants, moderate quality evidence)
- Rhinovirus (1 study with 217 participants, moderate quality evidence)
- Any viruses other than human rhinovirus (1 study with 217 participants, moderate- quality evidence)

The following factor was associated with a decrease in COPD exacerbations:

- Staphylococcus aureus (1 study with 81 participants, moderate quality evidence)

An association with an increase in COPD exacerbations could not be detected for the following factors:

- Any virus (1 study with 115 participants, low quality evidence)
- Influenza (3 studies with 615 participants, very low to moderate quality evidence)
- Pseudomonas aeruginosa (1 study with 81 participants, very low quality evidence)
- Other gram-negative rods (1 study with 81 participants, very low quality evidence)

Risk factor: biomarkers

The following factors were associated with an increase in COPD exacerbations:

- C-reactive protein (7 studies with 11,096 participants, very low to moderate quality evidence)
- Fibrinogen (1 study with 6,619 participants, moderate quality evidence)
- α1-antitrypsin (2 studies with 15,189 participants, low to moderate quality evidence)
- Brain natriuretic peptide (1 study with 60 participants, moderate quality evidence)
- Serum surfactant protein D (1 study with 2,189 participants, moderate quality evidence)
- Eosinophils (2 studies with 7,692 participants, very low to moderate quality evidence)
- High inflammatory biomarkers (1 study with 6,574 participants, very low to low quality evidence)

The following factors were associated with a decrease in COPD exacerbations:

- Pro-forms of collagen type III (1 study with 506 participants, moderate quality evidence)
- Haemoglobin (1 study with 268 participants, moderate quality evidence)

An association with an increase in COPD exacerbations could not be detected for the following factors:

- IgA (1 study with 602 participants, low to moderate quality evidence)
- IgG (1 study with 43 participants, very low to low quality evidence)

- Interleukin including interleukin-6, interleukin-1β, and interleukin-1 receptor antagonist (4 studies with 2,203 participants, very low to moderate quality evidence)
- Soluble tumour necrosis factor receptor 1 (1 study with 403 participants, high quality evidence)
- Vitamin D (2 studies with 549 participants, moderate quality evidence)
- Hepatocyte growth factor (1 study with 602 participants, low to moderate quality evidence)
- Midkine (1 study with 602 participants, low to moderate quality evidence)
- Monocyte chemotactic protein 4 (1 study with 602 participants, low to moderate quality evidence)
- Sex hormone-binding globulin (1 study with 602 participants, low to moderate quality evidence)
- Sortilin (1 study with 602 participants, low to moderate quality evidence)
- Tumour necrosis factor-related apoptosis-inducing ligand receptor 3 (1 study with 602 participants, low to moderate quality evidence)
- Eotaxin-1 (1 study with 602 participants, low to moderate quality evidence)
- Apolipoprotein A-IV (1 study with 1,544 participants, low to moderate quality evidence)
- Osteoprotegerin (1 study with 1,544 participants, low to moderate quality evidence)
- Neutrophils (1 study with 268 participants, low quality evidence)
- Copeptin (1 study with 159 participants, very low quality evidence)

Risk factor: asthma-COPD

The following factor was associated with an increase in mild, moderate, and severe COPD exacerbations:

- Asthma-COPD overlap syndrome compared to COPD (1 study with 194 participants, high quality evidence)

The following factor was associated with an increase in acute hospital admission for COPD and asthma:

- Asthma-COPD overlap syndrome with early or late asthma onset compared to COPD (1 study with 581 participants, moderate quality evidence)

An association with an increase in moderate or severe COPD exacerbations could not be detected for the following factor:

- Asthma-COPD overlap syndrome compared to COPD (2 studies with 1,025 participants, very low to moderate quality evidence)

Risk factor: other medicines

The following factors were associated with an increase in COPD exacerbations in people with stable GOLD II-IV COPD:

- Anti-gastroesophageal reflux disease therapy (1 study with 638 participants, high quality evidence)

An association with an increase in COPD exacerbations could not be detected for the following factors:

- Use of β-blockers (1 study with 3,464 participants, moderate quality evidence)
- Use of calcium channel blockers (1 study with 3,464 participants, moderate quality evidence)
- Use of angiotensin converting enzyme inhibitors / angiotensin receptor blockers (1 study with 3,464 participants, moderate quality evidence)

- Statin use (2 studies with 1,040 participants, moderate quality evidence)

Risk factor: air pollution

An association with an increase in COPD exacerbations could not be detected for the following factors:

- Particulate matter 10 (3 studies with 152 participants, very low to moderate quality evidence)
- Ozone (2 studies with 133 participants, very low to high quality evidence)
- Sulphur dioxide (1 study with 94 participants, very low quality evidence)
- Nitrogen dioxide (3 studies with 217 participants, very low to low quality evidence)
- Particulate matter 2.5 (1 study with 84 participants, very low to moderate quality evidence)
- Black smoke (1 study with 94 participants, very low quality evidence)

Risk factor: weather and seasonal changes

The following factors were associated with an increase in COPD exacerbations:

- Winter and spring compared to summer (1 study with 403 participants, high quality evidence)

An association with an increase in COPD exacerbations could not be detected for the following factor:

- Autumn compared to summer (1 study with 403 participants, high quality evidence)

The committee's discussion of the evidence

Interpreting the evidence

The outcomes that matter most

The aim of this review was to identify risk factors that could be acted upon to try to prevent a future exacerbation. The committee agreed that for a factor to be considered as a risk factor for exacerbations in people with COPD, acute exposure to the factor had to occur before the exacerbation happened. As a results, this review only included cohort studies that would allow follow up from exposure to the risk factor to the exacerbation at a later date. In particular, cross-sectinal studies that measure a factor during an exacerbation were excluded. Since these studies lack a time dimension they cannot separate factors that are present as a result of an exacerbation from those that could have triggered the exacerbation.

The committee decided to only include factors in the recommendation if there was something that people with COPD could do to reduce or avoid exposure and thus reduce their risk of exacerbations. These factors were smoking (current smoking and exposure to passive smoking), viral or bacterial infections, seasonal variation, and air pollution. The committee agreed that the following factors might not be modifiable or might be more relevant for other purposes: disease related factors, biomarkers, and other medicines.

The quality of the evidence

For each factor, the quality of the evidence varied ranging from very low to high. Smoking exposure was reported differently between studies (e.g. current smoking and pack years of smoking), but most of the studies reported that the risk of exacerbations increase in people who were current smokers. The risk of exacerbations in people exposed to passive smoking was only reported by one study, but the committee highlighted the importance of making people aware of the risk of exacerbations from passive smoking.

Evidence showed that seven disease related factors (ischaemic heart disease, reflux/heartburn, pneumonia, diabetes, emphysema, asthma, and overweight/obesity) were associated with an increase in COPD exacerbations, but the committee agreed that the risk of exacerbations is more likely to happen when these factors are not under control. The committee highlighted that it is well-recognised that many patients with COPD also have co-existent asthma but that the use of the term 'asthma-COPD overlap syndrome' is not well established in clinical practice. Therefore, the presence of co-existent asthma was seen as a disease-related factor. The committee agreed that, although the evidence for asthma-COPD overlap was variable with some studies showing an association while others could not detect one, it was likely that people with asthma-COPD overlap were more at risk of exacerbations, particluary if their asthma was poorly controlled.

There was evidence that 5 biomarkers (C-reactive protein, fibrinogen, brain natriuretic peptide, serum surfactant protein D, and eosinophils) as well as α1-antitrypsin increase the risk of exacerbations, but the committee did not expect that they would be particularly useful in practice for the prediction of exacerbations because these biomarkers are not measured routinely. Three studies reported C-reactive protein at discharge and the committee highlighted that this measure might not be accurate as a baseline reading because C-reactive protein is likely to be different between hospitalised and stable people with COPD. The committee noted that biomarkers are not informative risk factors for people with COPD as they are not readily amenable to change.

The committee was unsure about how to interpret the evidence on anti-gastroesophageal reflux disease therapy because the comparison group was not reported. In addition, they noted that the evidence for an association of gastroesophageal reflux with exacerbations was uncertain as a history of reflux (or heartburn) was associated, but an association could not be detected in 7 studies whose participants had COPD with reflux disease.

The evidence on pollution was not consistent between studies and studies with smaller sample sizes showed a stronger association between pollution and increase exacerbations. However, the committee highlighted that pollution is an accepted risk factor for exacerbations and this might be why studies with big sample sizes have not been done. They were aware of other types of evidence (case-crossover and time series studies) which found that air pollution increased the risk of COPD exacerbations (Li 2016).The evidence on weather and seasonal changes was found from one study and the committee agreed that this is also a well-known risk factor for exacerbations.

Benefits and harms

The risk factors included in the recommendation were chosen on the basis of their association with exacerbations and the committee's view that they were important risk factors that people with COPD could take action to avoid or reduce exposure to. The committee agreed that the appropriate time for discussion of these risk factors would be during the development of a self-management plan for the person with COPD.

Based on their clinical experience and the evidence showing that the risk of exacerbations increase in people who were current smokers, the committee recommended that people with COPD should be warned of the association between smoking, or relapsing for ex-smokers, and exacerbations. Although there was less evidence on the importance of passive smoking the committee decided that it was important to make people aware of the possible risk of exacerbations from passive smoking. They noted, that although the evidence only showed an association for passive smoking and exacerbations in people who were former smokers, it was reasonable to extrapolate this evidence to the entire COPD population as the majority of people with COPD are current or former smokers.

Viral factors and bacterial infection were included as were associated with an increase in exacerbations in some studies and could potentially be avoided. The committee included air pollution based on their clinical experience and specifically expanded this term to cover

indoor and outdoor air pollution to make it clear to people with COPD that air pollution was not confined to outdoors. The committee also included seasonal variation in winter and spring as one study with high quality evidence showed an association between these factors and exacerbations.

Since this review focused on acute triggers of exacerbations, studies examining the long-term effect of physical activity levels on exacerbation rates were excluded from the evidence base. However, the committee included lack of physical activity in the list of risk factors, based on their clinical experience and drawing on recommendations in other parts of the guideline concerning the importance of exercise in the management of stable COPD. In particular, they noted that physical activity is an important component of pulmonary rehabilitation, which is recommended for all people who view themselves as functionally disabled by COPD. In addition, the evidence for the beneficial effects of pulmonary rehabilitation came from randomised controlled trials, which the committee agreed is a higher standard of evidence than that searched for in this question. The committee also noted that the recommendations on self-management plans also included exercise components.

The committee did not include gastroesophageal reflux as a risk factor for exacerbations because the evidence was conflicting. There was no evidence of an association in studies looking at gastroesophageal reflux, however, an association was found in studies looking at gastroesophageal reflux therapy. The committee were unclear whether this was evidence that the treatment itself was a risk factor for exacerbations or whether this study had recruited people with more severe gastroesophageal reflux that required treatment and it was the presence of the more severe gastroesophageal reflux that was the risk factor. Without being able to resolve this uncertainty, the committee felt unable to make a recommendation on this point.

The committee discussed the evidence on β-blockers because health professionals were previously cautious about prescribing β-blockers in people with COPD who were at risk of cardiac disease in the past. However, the evidence from this review suggests that β-blockers might be a protective factor rather than a risk factor, supporting the use of β-blockers in people with COPD and cardiac disease.

Cost effectiveness and resource use

The committee noted that no economic evidence on the factors associated with exacerbations was identified in the literature review. The potential cost effectiveness of the recommendations was discussed, and it was determined that advising people with COPD on the risk factors associated with exacerbations is likely to represent good value for money, since it is associated with a very small marginal cost, but may produce both health benefits and cost savings through prevented exacerbations. For this reason, the recommendations are also unlikely to produce a significant resource impact unless they result in more effective treatment for tobacco dependence and hence lead to a reduction in the prevalence of smoking in the population with COPD.

Other factors the committee took into account

The committee agreed that C-reactive protein and other biomarkers are not routinely measured and the results of biomarkers were not considered to be useful for prediction. However, biomarkers may be useful for recruitment in trials and for treatment targeting.

Preventing exacerbations

Review question

What is the clinical and cost effectiveness of prophylactic oral antibiotics for preventing exacerbations in people with stable COPD?

Introduction

People with COPD commonly experience exacerbations, which have a negative impact on their quality of life and are linked to worse disease prognosis. One component of COPD management focuses on interventions to prevent and reduce the severity of exacerbations and treating them appropriately when they occur. There are a number of recognised triggers for exacerbations that include current smoking and exposure to passive smoking, viral and bacterial infections, changes in air quality and pollution. It is unclear whether the increased bacterial load in people with a COPD exacerbation is due to the exacerbation or whether an increased bacterial load can cause or contribute to an exacerbation. However, if bacterial infection can lead to exacerbations in people with COPD then continued treatment with antibiotics (prophylactic antibiotics) could theoretically be used to prevent or inhibit the development of bacterial infection and thus reduce the number of or severity of exacerbations experienced. Reducing the number of or severity of exacerbations would improve quality of life for the person with COPD including potentially reducing the numbers of days off work and bed-days/hospitalisations, which would also have a wider effect on the families of people with COPD, the health system and economy.

This review aims to address the question of whether the prescription and taking of prophylactic antibiotics is a clinically effect method of preventing exacerbations in people with COPD. The economic costs involved and the potential impact of this line of treatment on the emergence of antibiotic resistance were also considered.

The evidence presented in this review was provided by the Cochrane Airways Group as part of a collaboration between the NICE Guideline Updates Team and the Cochrane group. We thank the Cochrane Airways Group for their assistance in providing the literature searches and data for this review question. The full details and results are provided in the published Cochrane review (Herath 2018).

PICO table

This review identified studies that fulfilled the conditions listed in Table 2, as specified in the protocol followed by the Cochrane Airways Group. For full details of the review protocol, see appendix A. The Cochrane group did not publish a review protocol as this work was carried out as an update of an earlier systematic review (Herath et al 2013).

Table 2 PICO: examining the use of oral antibiotics for prophylaxis

Population	People diagnosed with COPD
Interventions	Oral antibiotics for prophylaxis
Comparator	• Placebo
Outcomes	• Exacerbations • Quality of life (e.g. St. George's respiratory questionnaire, SGRQ, total score or Chronic Respiratory Diseases Questionnaire (CRQ)) • Reduction in lung function from baseline (FEV1)

	• Mortality • Adverse events • Exercise capacity • Resource use and costs

Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual, based on the information provided by the Cochrane Airways Group. The evidence presented here is the work of the Cochrane group, with the exception of any alterations made to reflect the methodology used by the Guideline Updates Team, and these are stated in the relevant sections. In particular, results presented as odds ratios (ORs) in the Cochrane review have been converted to risk ratios (RRs) and the choice of fixed effect or random effects models has been altered to reflect the rules in appendix B. Any errors introduced by these changes are the responsibility of the NICE Guideline Updates Team alone.

In this review, exacerbations have not been subdivided by the Cochrane group and thus include all exacerbations, regardless of severity. In addition, the Cochrane group stratified the included studies into pulsed, intermittent and continuous antibiotics treatment groups. This distinction was not requested by the NICE committee, but was not removed by the Guideline Updates Team as it was potentially informative.

The Cochrane group presented data on the rate of exacerbations per person using incidence rate ratios (IRR). The format of the available data did not allow calculation of the absolute risk (AR) directly as there was no information about the numbers of events and person years in the control arm. For illustrative purposes, the number of events in the placebo arm for the other exacerbation outcome was used as a baseline to calculate the AR in the intervention arm using the IRR.

Methods specific to this review question are described in the review protocol in appendix A, and the methods section in appendix B. In particular, the minimally important differences (MIDs) used in this review are summarised in Table 4 in appendix B. These were selected based on the literature with input from the committee.

The search strategies used in this review are detailed in appendix C.

Declarations of interest were recorded according to NICE's 2014 conflicts of interest policy.

Protocol deviation

The protocol in appendix A was developed with the committee prior to the collaboration with the Cochrane Airways Group. The PICO in Table 2 has been updated to reflect the outcomes available from the Cochrane review that were of interest to the committee. The relevant differences between the NICE Guideline Updates Team protocol and that used by the Cochrane group are listed below:

1. Study types, outcomes or comparators listed in the protocol in appendix A that were removed or amended as they were not included in the Cochrane review:
    a. The comparator in the Cochrane review was placebo, whereas the protocol in appendix A also included routine medical therapy (patient continues on whatever COPD treatment is relevant to their stage of disease, but without antibiotics).

b. Study type in the Cochrane review was limited to randomised trials, cluster randomised trials and crossover trials, with systematic reviews being excluded.
c. Hospital bed-days and re-admissions were removed; hospital admissions were examined under the heading of exacerbations requiring hospitalisation.
d. Symptoms including breathlessness (e.g. Borg dyspnoea score, Modified MRC scale for dyspnoea) and orthopnoea were removed.
e. The subgroup analyses were altered to exclude consideration of smoking status, multimorbidities and trials that recruited patients with at least one COPD exacerbation in the 12 months before study entry. However, the following subgroup analysis was included from the Cochrane review: number of people with one or more exacerbations by exacerbation history.

2. Outcomes from the protocol in appendix A that were retained even though they were not included in the Cochrane review:
    a. Resource use and costs were addressed by the economic searches carried out by the NICE Guideline Updates Team economist.

3. Drug resistance as measured by microbial sensitivity was assessed as an outcome by the Cochrane group, but was not included in the analysis in this review as the data was reported in multiple ways and could not be synthesised. Please refer to the Cochrane review directly for details of their analysis and a discussion of their findings.

Clinical evidence

Included studies

The original Cochrane review (Herath 2013) included 8 studies in the evidence base; 7 of which were included in the qualitative analysis and 4 in the quantitative analysis. In the current update the Cochrane group identified 172 records through database searching and included an additional 35 records identified from other sources. Of the new references, 201 were screened at title and abstract stage. One hundred and sixty four records were excluded as they did not match the review protocol and 37 were ordered for full text screening. Sixteen studies, including those from the original review, were included after full text screening.

A second search was conducted at the end of the guideline development process to capture papers published whilst the guideline was being developed. The search for this review question was carried out separately by the Cochrane group, including articles up to February 2018, and returned 19 studies. After title and abstract screening, no additional relevant references were found for this review question.

The PRISMA diagram for this process is presented in the updated Cochrane review. The evidence tables for the included studies are presented in appendix E and the studies referenced in full in appendix K.

Excluded studies

The excluded studies are listed with reasons in the table in appendix I and as full references in appendix K. These lists include all excluded references from the original Cochrane review and the current update. As a result, the numbers exceed those stated in the PRISMA diagram of the updated Cochrane review.

Summary of clinical studies included in the evidence review

The Cochrane review identified 16 studies that matched the review protocol, however 1 of these has not been published in a peer-reviewed journal (Mygind 2010) and 2 refer to clinical trials that were terminated before any participants were treated (NCT00524095 and NCT02628769). These 3 trials were excluded from the evidence presented in this review for these reasons.

In addition, Banerjee 2005 was included in the narrative summary of the Cochrane review, but was excluded from the NICE review as no data were extracted from it. Suzuki 2001 also formed part of the evidence body in the Cochrane review, but was excluded from the meta-analysis due to the lack of blinding. It was not excluded from the NICE review, but as the study was judged to be at high risk of bias (as a result of the lack of blinding), a sensitivity analysis was carried out to address the impact of including this study on the relevant outcomes.

As a result of these exclusions, the review presented here included 12 studies that fall into the following groups:

- 6 studies examined the use of azithromycin
    - 5 studies (Albert 2011, Berkof 2013, Brill 2015, Simpson 2014, Uzun 2014) investigated the use of azithromycin in a wider COPD population
    - 1 study (Wang 20117) investigated azithromycin use in participants with pulmonary hypertension secondary to COPD, who were also treated with simvastatin for the duration of the study.
- 4 studies (He 2010, Seemungal 2008, Suzuki 2001, Tan 2016) examined the use of erythromycin
- 2 studies (Brill 2015, Sethi 2010) examined the use of moxifloxacin
- 2 studies (Brill 2015, Shafuddin 2015) examined the use of doxycycline
- 1 study (Shafuddin 2015) examined the use of roxithromycin

Brill 2015 and Shafuddin 2015 investigated several antibiotics.

The evidence tables for the included studies are presented in appendix E and the studies are referenced in full in appendix K.

Quality assessment of clinical studies included in the evidence review

The quality assessment of the included trials was carried out by the Cochrane Airways Group and is presented in appendix E following the relevant evidence table. The overall summary of risk of bias for each study was completed by NICE, based on the Cochrane group judgements for each individual domain (Table 8). In some cases, for example where there is a lack of assessor blinding, there are different risk of bias ratings per study for different types of outcome (e.g. subjective and objective).

Suzuki 2001 and Tan 2016 and were both at high risk of bias due to the lack of blinding and information about blinding respectively. As a result, a sensitivity analysis was carried out for each outcome they contributed data to. Wang 2017 was also judged to be at high risk of bias due to a lack of blinding, but was presented separately as the study population was a distinct subgroup of people with COPD, who had secondary pulmonary hypertension. No sensitivity analysis was therefore necessary.

The Guideline Updates Team extracted the data from Wang 2017 that is included in the GRADE table. The Cochrane group did not include Wang 2017 in their meta-analyses because the population different substantially to the other studies and there was a lack of clarity about whether the measures of variance reported were SDs or

SEs. This study was not included in the meta-analysis because the participants were people with COPD and pulmonary hypertension and these people were considered to be sufficiently different from people with COPD alone that pooling of the data would be in appropriate.

The resulting summary risks of bias, and assessment of study applicability to the review protocol are presented in appendix E after the Cochrane evidence tables. Forest plots of the analyses included in the GRADE tables are in appendix F, with the GRADE tables in appendix G.

Hazard ratio data for time to first exacerbation in current and ex-smoker subgroups offered azithromycin versus placebo are presented in Table 9.

Economic evidence

Included studies

A single search was conducted to cover all review question topics in this guideline update. This search returned 16,299 records, of which all were excluded on title and abstract for this review question.

Summary of studies included in the economic evidence review

No economic evidence as identified for this review question.

Economic model

Economic modelling was not prioritised for this review question.

Evidence statements

The format of the evidence statements is explained in the methods in appendix B.

Antibiotics versus placebo

- Very low to low quality evidence from up to 9 RCTs with up to 2,825 people found meaningful improvements in exercise capacity, and reductions in the number of people experiencing exacerbations and the rate of exacerbations per patient per year in people with COPD offered antibiotics compared to placebo.
- Moderate to high quality evidence from up to 9 studies with up 2,978 people found no meaningful difference in change in FEV1, the number of people experiencing adverse events or serious adverse events and SGRQ score between people with COPD offered antibiotics compared to placebo.
- Very low quality evidence from up to 5 RCTs with up to 2,723 people could not differentiate all-cause mortality between people with COPD offered antibiotics or placebo.

Sensitivity analyses removing studies at high risk of bias

- Low quality evidence from 8 RCTS with 2,716 people found an improvement in the number of people experiencing exacerbations in people with COPD offered antibiotics compared to placebo, but the point estimate was less than the defined individual minimal clinically important difference.
- Moderate to high quality evidence from up to 8 studies with up to 2,924 people found no meaningful difference in change in FEV1 or the number of people

experiencing serious adverse events between people with COPD offered antibiotics compared to placebo.

- Moderate quality evidence from up 1 RCT with 77 people could not differentiate exercise capacity between people with COPD offered antibiotics or placebo.

Subgroup analysis: number of people with ≥ 1 exacerbation by exacerbation history

- In studies which recruited people with ≥ 1 exacerbation in the previous year there was an improvement in the number of exacerbations, but this was less than the defined individual minimal clinically important difference.
- In studies where there was no specific inclusion criteria for exacerbations, there was an improvement in the number of exacerbations.

Subgroup analysis: rate of exacerbations per patient per year by exacerbation history

There was no evidence for a difference in effect in people who had an exacerbation in the previous year compared to people in studies where exacerbation history was not an inclusion criteria.

Publication bias assessment

There was no evidence that publication bias influenced the results of the analyses examined (people with ≥1 exacerbation and change in FEV1).

Azithromycin versus usual care in people with pulmonary hypertension secondary to COPD.

- Very low quality evidence from 1 study with 86 people found an improvement in FEV1 and exercise capacity in people with pulmonary hypertension secondary to COPD offered azithromycin compared to placebo.

The committee's discussion of the evidence

Interpreting the evidence

The outcomes that matter most

The committee agreed that the risk of having an exacerbation and the rate of exacerbations per year were one of the most important outcomes for people with COPD and that reducing these could improve quality of life. Serious adverse events were also considered to be of particular importance. The committee also agreed it was important to consider the potential for antibiotic resistance as part of its decision making.

The quality of the evidence

The committee agreed with the list of antibiotics that were eligible for inclusion in the Cochrane review, but commented that moxifloxacin was not prescribed as a first-line antibiotic in the UK and roxithromycin was not commonly used in the UK. They agreed that Suzuki 2001 and Tan 2016 were at high risk of bias due to a lack of blinding (or information about blinding) of participants, personnel and outcome assessors and that it was useful to carry out sensitivity analyses to examine the effect of excluding them from the evidence base.

The committee discussed the inclusion criteria for the trials and noted that some of the studies did not specifically recruit people with COPD who had experienced a severe exacerbation within the last year (for example, Berkof 2013 and Brill 2015). This was important because in practice, the committee agreed that the decision to prescribe prophylactic antibiotic treatment would be based on a history of severe exacerbations. However, they decided that it was unlikely that the antibiotics would be less effective in people with more severe COPD and were confident to make recommendations for this population based on the analyses of all of the included studies. In particular, they agreed it was reasonable to assume that the relative reduction in exacerbation rates would be similar across different severities of COPD, and therefore this would convert to a larger absolute reduction in people with a higher baseline risk of exacerbations.

The committee agreed that Wang 2017 was partially directly applicable as it recruited participants with pulmonary hypertension secondary to COPD, who were also treated with simvastatin for the duration of the study. They agreed that it was appropriate to keep this study separate from the remaining trials. They commented that the levels of improvement in FEV1 and the 6MWD seemed implausibly high and, taking into account the issues with applicability and the lack of blinding in the study, they therefore agreed it was not possible to make recommendations based on this single study.

The committee discussed the prevalence of co-existing bronchiectasis in COPD and implications of this in accounting for some of the antibiotic response rates seen. Hence the recommendation of the need for CT chest scan so that bronchiectasis is diagnosed and can be specifically treated before starting azithromycin to reduce exacerbations in COPD.

Benefits and harms

The committee weighed up the balance of benefits and harms to both the person with COPD and society in making their recommendations. They discussed the problem of emerging antibiotic resistance and how this process could be accelerated by the overuse of antibiotics in situations such as the one being examined here. Moreover, the committee noted that adherence could be a particular problem for prophylactic treatment where there were no current symptoms to treat and that that this could raise the risk of antibiotic resistance. They also noted that, although the analyses found no difference or could not differentiate the number of people experiencing adverse events or severe adverse events and mortality, there was an increased risk of hearing impairment associated with the use of prophylactic antibiotics.

Looking at the benefits of this treatment regimen, the committee noted that prophylactic antibiotic use was associated with a reduced risk of exacerbations and a reduced rate of exacerbations per patient per year. Based on the subgroup analysis by inclusion criteria, the group with ≥ 1 exacerbation in the preceding year showed a significant reduction of 14% in the risk of exacerbations, but this was less than the defined MID. The trials that did not use exacerbation history as an inclusion criteria also showed a meaningful reduction in the risk of exacerbations of 39% based on the point estimate. When the trials were pooled, the reduction in the risk of exacerbations remained meaningful at 24%.The committee commented that these results were not unexpected as it would be harder to reduce the risk of having at least 1 exacerbation (i.e. any exacerbations) in the high history of risk group compared to the lower risk group. They did also note that there was overall a 33% reduction in the number of exacerbations across the whole population, and agreed this would be a highly meaningful difference to individuals, particularly those who are experiencing high baseline rates of exacerbations.

Based on this, the committee agreed it was appropriate to recommend the use of prophylactic antibiotics, but only for people with frequent infective exacerbations or infective exacerbations requiring hospitalisation (those people with considerable capacity to benefit and experiencing the type of exacerbation prophylactic antibiotics would be expected to prevent). They noted that the recommendations made were only for prophylaxis, and were not relevant to the treatment of an exacerbation, which is covered in the managing exacerbations of COPD section of the guideline, and is out of scope of this review question.

The committee recommended azithromycin as the first-line treatment because it was the treatment with the most evidence (largest number of studies and participants) for reducing the risk of exacerbations in people with a history of exacerbation, but included a recommendation warning people of possible adverse effects on hearing as mentioned above. Although erythromycin was also effective at reducing the risk of exacerbations this was not recommended as it is no longer commonly used in the UK to treat exacerbations. Because of its side effect profile it has been replaced by clarithromycin to treat exacerbations.

The committee specified the doses of the antibiotics in the recommendations based on the doses used in the trials and their own clinical experience. In particular, the committee thought that for azithromycin a 3 doses a week regimen would be better tolerated for long-term therapy than daily treatment.

The committee laid out a number of conditions that needed to be met before a person with COPD could be prescribed prophylactic antibiotics. These included actions to reduce exacerbations and improve quality of life such as the treatment of tobacco dependence, pulmonary rehabilitation and optimisation of inhaled therapies. Other criteria were included to ensure that it was safe to prescribe the antibiotics and included 2 specific to azithromycin. It was envisaged that the ECG and CT thorax scan reviews would use existing information on file for the person with COPD. If this was not available and more detailed review was felt to be needed then input from a respiratory specialist could be sought.

The committee recommended these strict conditions be applied, in order to ensure antibiotics were restricted to those individuals where they are safe and likely to be effective, and to avoid the risk of widespread overuse that could raise antimicrobial stewardship concerns. In addition, the committee recommended to restrict the use of prophylactic antibiotics to ex-smokers and non-smokers due to the lack of effect in smokers (Table 9, Han 2014, included under Albert 2011 RCT). The committee also noted that there was a small risk of hearing loss and tinnitus in people with COPD taking prophylactic azithromycin and made a recommendation that people should be made aware of this risk.

In order to reduce unnecessary antibiotic use and the potential for side effects, the committee recommended that the prophylactic antibiotic treatment is reviewed regularly. They chose to review the treatment at 3 months initially as this was the time scale used in a substantial number of the trials. The 6 month time scale for subsequent reviews was thought to be appropriate based on the duration of other included trials.

The committee noted that there was no evidence for the long-term effects of prophylactic antibiotics as the longest trials only lasted for 12 months. Based on the lack of evidence for continued effectiveness and for the severity of adverse events over the long-term, the committee recommended that the use of prophylactic antibiotic treatment should only be continued if there was evidence of continued benefit to the person with COPD. They also included a line to make the lack of long-

term studies clear to the healthcare professional. To try to fill this gap in the evidence, the committee wrote a research recommendation to promote investigation of the long-term effects of prophylactic antibiotic treatment in the population of people with COPD included in the above recommendations.

The committee made a recommendation against using macrolides as the antibiotic to keep at home as part of an exacerbation action plan for people with COPD who are taking prophylactic antibiotics because azithromycin is a macrolide antibiotic. They wanted to ensure that if the person with COPD develops an exacerbation despite taking azithromycin, their action plan medication contains another class of antibiotic that is likely to be effective.

Due to the relatively few trials examining each antibiotic and the limited doses used, the committee made several additional research recommendations to try to address outstanding areas of uncertainty, namely on the most effective antibiotics, doses and regimens; which subgroups of people would be most likely to benefit from this treatment; and the effectiveness of seasonal versus continuous use of prophylactic antibiotics. The risk of exacerbations may be linked to the weather (see the review for predicting exacerbations above) and so seasonal use of prophylactic antibiotics may be sufficient to reduce the risk of exacerbations in people with COPD during those parts of the year where there is a higher risk.

Cost effectiveness and resource use

Although no evidence was identified in the literature regarding the cost effectiveness of prophylactic antibiotic treatment, the committee considered the potential balance of costs and benefits of the recommendations, and determined that they are likely to represent a good use of resources. A pack of azithromycin costs £1.19 for four 250mg tablets (Drug Tariff March 2018), meaning that treatment for one year would cost approximately £46.41. Results from the clinical review suggest that the NNT required to prevent one COPD exacerbation is approximately five people over one year, giving a cost per prevented exacerbation of around £232. Given that the cost of a hospitalised and non-hospitalised exacerbation in the de novo economic model developed for this guideline (see evidence review H for details) is £2,111 and £78 respectively, it seems likely that prophylactic antibiotic treatment would produce a net cost saving. Even if this is not the case, exacerbations also substantially affect quality of life, so antibiotic prevention of exacerbations has the capacity to generate considerable health benefits at a low cost.

The committee also gave thought to the list of actions recommended prior to starting antibiotic treatment. It was concluded that all of these actions constitute good practice in COPD care, and are expected to be cost effective regardless of the intention to prescribe antibiotics.

While it is likely that these recommendations will increase the number of people treated with antibiotics, the low cost of treatment means that the recommendations are unlikely to result in a significant resource impact. Using the cost per year of treatment calculated above, over 20,000 additional patients would have to be treated with azithromycin in order to incur a significant resource impact of over £1 million. The recommendation to offer a CT scan prior to commencing prophylactic antitiotics is also unlikely to produce a substantial resource impact, since it is expected that the majority of eligible patients will have already received a CT scan. This is because prophylactic azithromycin is only recommended in patients with abnormally frequent or severe exacerbations, most of whom will have previously undergone extensive diagnostic testing.

Other factors the committee took into account

The committee discussed the equalities issues surrounding smoking status. In particular, they noted the correlation between smoking status and low socioeconomic status and the link between continued smoking and poor disease prognosis. The committee recommended against using prophylactic antibiotics in people who smoke based on the evidence for a lack of effect in this group of people with COPD (Table 9). However, the committee were clear that this did not mean that smokers should be denied other treatments in general, but that in this specific case prophylactic antibiotics would not be beneficial to them. The committee agreed that smokers should be encouraged and supported to quit smoking, at which point they could be eligible for prophylactic antibiotic treatment if they met the criteria listed in the recommendations from this review.

The committee noted that, due to the large number of factors that needed to be considered and addressed before starting antibiotic prophylaxis, specialist respiratory input may be needed at this stage to ensure a correct decision to prescribe for a trial period prior to review of effectiveness and decision regarding continued prescription, and agreed it was appropriate to include this within the recommendations. They also noted that the trials did not require that the prophylactic antiobiotics be stopped if the person was treated for an acute COPD exacerbation. They agreed it was not necessary to stop prophylaxis solely because a person has an exacerbation, and that it was appropriate to include this in the recommendations.

Appendices

Appendix A – Review protocols

Review protocol for assessing risk factors for exacerbations

Field (based on PRISMA-P)	Content
Review question	In people with COPD, what factors (for example, viral infection) may cause an exacerbation?
Type of review question	Association
Objective of the review	To determine what factors may cause an exacerbation in people with COPD
Eligibility criteria – population	People diagnosed with COPD (by any means including Global Strategy for the Diagnosis, Management and Prevention of COPD, GOLD, guideline; American Thoracic Society criteria for COPD; European Respiratory Society criteria)

Eligibility criteria – predictive factors	Any predictive factors, including:
	• Individual factors:
	  ○ Smoking
	  ○ Lack of effective self-management (self-efficacy)
	  ○ Multimorbidities including mental health problems
	  ○ Polypharmacy
	  ○ Illegal drug use
	  ○ Viral infection
	  ○ Major life events- stress, anxiety
	  ○ Biomarkers
	• Environmental factors:
	  ○ Pollution- outdoors, indoors
	  ○ Flu prevalence
	  ○ Weather and seasonal changes
	  ○ Living environment- air conditioning, perfume, air sprays, damp

Eligibility criteria – outcomes	• Exacerbations
Measures	• Relative risks • Odds ratios

	• Hazard ratios
Eligibility criteria – study design	• Prospective cohort studies • Retrospective cohort studies (if < 5 prospective cohort studies found overall)
Other inclusion exclusion criteria	Non-English language publications

Proposed sensitivity/sub-group analysis, or meta-regression	• Exacerbations:
	  ○ Frequency (no exacerbations, 1-2 exacerbations per year, and 3 or more per year)
	  ○ Severity of exacerbation, stratifying by moderate versus severe exacerbations. Moderate exacerbation is defined as worsening of respiratory status that requires treatment with systemic corticosteroids and/or antibiotics; severe exacerbation is defined as rapid deterioration that requires hospitalisation.
	
	Subgroup analyses will only be conducted if the majority of trials report data for the listed categories in an accessible format.

Selection process – duplicate screening/selection/analysis	10% of the abstracts were reviewed by two reviewers, with any disagreements resolved by discussion or, if necessary, a third independent reviewer. If meaningful disagreements were found between the different reviewers, a further 10% of the abstracts were reviewed by two reviewers, with this process continued until agreement is achieved between the two reviewers. From this point, the remaining abstracts will be screened by a single reviewer. This review made use of the priority screening functionality with the EPPI-reviewer systematic reviewing software. See Appendix B for more details.
Data management (software)	See Appendix B

Information sources – databases and dates	See Appendix C Main Searches: • Cochrane Database of Systematic Reviews – CDSR (Wiley) • Cochrane Central Register of Controlled Trials – CENTRAL (Wiley) • Database of Abstracts of Reviews of Effects – DARE (Wiley) • Health Technology Assessment Database – HTA (Wiley) • EMBASE (Ovid) • MEDLINE (Ovid) • MEDLINE In-Process (Ovid) The search will not be date limited as the previous guideline recommendations were not based on a systematic literature search. Economics: • NHS Economic Evaluation Database – NHS EED (Wiley) • Health Economic Evaluations Database – HEED (Wiley) • EconLit (Ovid) • Embase (Ovid) • MEDLINE (Ovid) • MEDLINE In-Process (Ovid) The economics search will cover all questions and will be date limited from the previous search January 2009-May 2017.
Identify if an update	This is a new question for the 2017 COPD guideline update.
Author contacts	Guideline update
Highlight if amendment to previous protocol	For details please see section 4.5 of Developing NICE guidelines: the manual
Search strategy – for one database	For details please see appendix C

Data collection process – forms/duplicate	A standardised evidence table format will be used, and published as appendix E (clinical evidence tables)
Data items – define all variables to be collected	For details please see evidence tables in appendix E (clinical evidence tables)
Methods for assessing bias at outcome/study level	See Appendix B
Criteria for quantitative synthesis	See Appendix B
Methods for quantitative analysis – combining studies and exploring (in)consistency	See Appendix B
Meta-bias assessment – publication bias, selective reporting bias	See Appendix B
Confidence in cumulative evidence	See Appendix B
Rationale/context – what is known	For details please see the introduction to the evidence review in the main file.
Describe contributions of authors and guarantor	A multidisciplinary committee developed the evidence review. The committee was convened by the NICE Guideline Updates Team and chaired by Damien Longson (until September 2017) and Andrew Molyneux (from September 2017) in line with section 3 of Developing NICE guidelines: the manual. Staff from the NICE Guideline Updates Team undertook systematic literature searches, appraised the evidence, conducted meta-analysis and cost-effectiveness analysis where appropriate, and drafted the evidence review in collaboration with the committee. For details please see Developing NICE guidelines: the manual.
Sources of funding/support	The NICE Guideline Updates Team is an internal team within NICE.

Name of sponsor	The NICE Guideline Updates Team is an internal team within NICE.
Roles of sponsor	The NICE Guideline Updates Team is an internal team within NICE.

Review protocol for assessing the use of antibiotics to prevent exacerbations in people with stable COPD

Review carried out in collaboration with Cochrane Airways group as an update on an earlier review (Herath et al 2013).

Field (based on PRISMA-P)	Content
Review question	What is the clinical and cost effectiveness of prophylactic oral antibiotics for preventing exacerbations in people with stable COPD?
Type of review question	Intervention
Objective of the review	To determine the effectiveness of prophylactic oral antibiotics for preventing exacerbations in people with COPD
Eligibility criteria – population	People diagnosed with COPD (by any means including Global Strategy for the Diagnosis, Management and Prevention of COPD, GOLD, guideline; American Thoracic Society criteria for COPD; European Respiratory Society criteria)
Eligibility criteria – interventions	Oral antibiotics for prophylaxis
Eligibility criteria – comparators	• Placebo • Routine medical therapy (patient continues on whatever COPD treatment is relevant to their stage of disease, but without antibiotics)
Outcomes	• Exacerbations • Mortality • Hospital admissions, re-admissions and bed days • Symptoms including breathlessness (e.g. Borg dyspnoea score, Modified MRC scale for dyspnoea) and orthopnoea

	• Adverse events (diarrhoea, cardiovascular events-long QT interval prolongation, thrush) • Change in FEV1, rate of change in FEV1 • Quality of life (e.g. St. George's respiratory questionnaire, SGRQ, overall score) • Resource use and costs
Eligibility criteria – study design	• RCTs • Systematic reviews of RCTs
Other inclusion exclusion criteria	• Trials of less than 12 weeks duration (to ensure trials looking at acute effects (e.g. on exercise) are excluded and confine search to trials looking at longer term effects of interventions). • Non-English language publications
Proposed sensitivity/sub-group analysis, or meta-regression	Subgroups: • Trials that recruited patients with at least one COPD exacerbation in the 12 months before study entry • Smoking status (smokers versus non-smokers or, data permitting, never smoked, ex-smokers and current smokers). • Multimorbidities (including COPD with asthma, bronchopulmonary dysplasia, bronchiectasis, anxiety or depression) Subgroup analyses will only be conducted if the majority of trials report data for the listed categories in an accessible format.
Selection process – duplicate screening/selection/analysis	10% of the abstracts were reviewed by two reviewers, with any disagreements resolved by discussion or, if necessary, a third independent reviewer. If meaningful disagreements were found between the different reviewers, a further 10% of the abstracts were reviewed by two reviewers, with this process continued until agreement is achieved between the two reviewers. From this point, the remaining abstracts will be screened by a single reviewer. This review made use of the priority screening functionality with the EPPI-reviewer systematic

	reviewing software. See Appendix B for more details.
Data management (software)	See Appendix B
Information sources – databases and dates	See Appendix C Cochrane Airways Group Specialised Register (CAGR): The searches will be undertaken by the Cochrane Airways Group using the following databases: • CENTRAL • MEDLINE (Ovid) • EMBASE (Ovid) • CINAHL (EBSCO) • PSYCINFO (Ovid) • AMED (EBSCO) • Clinicaltrial.gov All databases will be searched from their inception to 9th August 2017. NICE economic search: • NHS Economic Evaluation Database – NHS EED (Wiley) • Health Economic Evaluations Database – HEED (Wiley) • EconLit (Ovid) • Embase (Ovid) • MEDLINE (Ovid) • MEDLINE In-Process (Ovid) The economics search will cover all questions and will be date limited from the previous search January 2009-May 2017
Identify if an update	Update of 2004 COPD guideline question: What is the role of antibiotic therapy in patients with stable COPD?
Author contacts	Guideline update
Highlight if amendment to previous protocol	For details please see section 4.5 of Developing NICE guidelines: the manual

Search strategy – for one database	For details please see appendix C
Data collection process – forms/duplicate	A standardised evidence table format will be used, and published as appendix E (clinical evidence tables).
Data items – define all variables to be collected	For details please see evidence tables in appendix E (clinical evidence tables).
Methods for assessing bias at outcome/study level	See Appendix B
Criteria for quantitative synthesis	See Appendix B
Methods for quantitative analysis – combining studies and exploring (in)consistency	See Appendix B
Meta-bias assessment – publication bias, selective reporting bias	See Appendix B
Confidence in cumulative evidence	See Appendix B
Rationale/context – what is known	For details please see the introduction to the evidence review in the main file.
Describe contributions of authors and guarantor	A multidisciplinary committee developed the evidence review. The committee was convened by the NICE Guideline Updates Team and chaired by Damien Longson (until September 2017) and Andrew Molyneux (from September 2017) in with section 3 of Developing NICE guidelines: the manual. Staff from the NICE Guideline Updates Team undertook systematic literature searches, appraised the evidence, conducted meta-analysis and cost-effectiveness analysis where appropriate, and drafted the evidence review in collaboration with the committee. For details please see Developing NICE guidelines: the manual.
Sources of funding/support	The NICE Guideline Updates Team is an internal team within NICE.

Name of sponsor	The NICE Guideline Updates Team is an internal team within NICE.
Roles of sponsor	The NICE Guideline Updates Team is an internal team within NICE.

Appendix B – Methods

Priority screening

The reviews undertaken for this guideline all made use of the priority screening functionality with the EPPI-reviewer systematic reviewing software. This uses a machine learning algorithm (specifically, an SGD classifier) to take information on features (1, 2 and 3 word blocks) in the titles and abstract of papers marked as being 'includes' or 'excludes' during the title and abstract screening process, and re-orders the remaining records from most likely to least likely to be an include, based on that algorithm. This re-ordering of the remaining records occurs every time 25 additional records have been screened.

Research is currently ongoing as to what are the appropriate thresholds where reviewing of abstract can be stopped, assuming a defined threshold for the proportion of relevant papers it is acceptable to miss on primary screening. As a conservative approach until that research has been completed, the following rules were adopted during the production of this guideline:

- In every review, at least 50% of the identified abstract (or 1,000 records, if that is a greater number) were always screened.
- After this point, screening was only terminated if a pre-specified threshold was met for a number of abstracts being screened without a single new include being identified. This threshold was set according to the expected proportion of includes in the review (with reviews with a lower proportion of includes needing a higher number of papers without an identified study to justify termination), and was always a minimum of 250.

As an additional check to ensure this approach did not miss relevant studies, the included studies lists of included systematic reviews were searched to identify any papers not identified through the primary search.

Incorporating published systematic reviews

For all review questions where a literature search was undertaken looking for a particular study design, systematic reviews containing studies of that design were also included. All included studies from those systematic reviews were screened to identify any additional relevant primary studies not found as part of the initial search.

Quality assessment

Individual systematic reviews were quality assessed using the ROBIS tool, with each classified into one of the following three groups:

- High quality – It is unlikely that additional relevant and important data would be identified from primary studies compared to that reported in the review, and unlikely that any relevant and important studies have been missed by the review.
- Moderate quality – It is possible that additional relevant and important data would be identified from primary studies compared to that reported in the review, but unlikely that any relevant and important studies have been missed by the review.
- Low quality – It is possible that relevant and important studies have been missed by the review.

Each individual systematic review was also classified into one of three groups for its applicability as a source of data, based on how closely the review matches the specified review protocol in the guideline. Studies were rated as follows:

- Fully applicable – The identified review fully covers the review protocol in the guideline.
- Partially applicable – The identified review fully covers a discrete subsection of the review protocol in the guideline.
- Not applicable – The identified review, despite including studies relevant to the review question, does not fully cover any discrete subsection of the review protocol in the guideline.

Using systematic reviews as a source of data

If systematic reviews were identified as being sufficiently applicable and high quality, they were used as the primary source of data, rather than extracting information from primary studies. The extent to which this was done depended on the quality and applicability of the review, as defined in Table 3. When systematic reviews were used as a source of primary data, any unpublished or additional data included in the review which is not in the primary studies was also included. Data from these systematic reviews was then quality assessed and presented in GRADE/CERQual tables as described below, in the same way as if data had been extracted from primary studies. In questions where data was extracted from both systematic reviews and primary studies, these were cross-referenced to ensure none of the data had been double counted through this process.

Table 3: Criteria for using systematic reviews as a source of data

Quality	Applicability	Use of systematic review
High	Fully applicable	Data from the published systematic review were used instead of undertaking a new literature search or data analysis. Searches were only done to cover the period of time since the search date of the review.
High	Partially applicable	Data from the published systematic review were used instead of undertaking a new literature search and data analysis for the relevant subsection of the protocol. For this section, searches were only done to cover the period of time since the search date of the review. For other sections not covered by the systematic review, searches were undertaken as normal.
Moderate	Fully applicable	Details of included studies were used instead of undertaking a new literature search. Full-text papers of included studies were still retrieved for the purposes of data analysis. Searches were only done to cover the period of time since the search date of the review.
Moderate	Partially applicable	Details of included studies were used instead of undertaking a new literature search for the relevant subsection of the protocol. For this section, searches were only done to cover the period of time since the search date of the review. For other sections not covered by the systematic review, searches were undertaken as normal.

Evidence synthesis and meta-analyses

Where possible, meta-analyses were conducted to combine the results of studies for each outcome. For mean differences, where change from baseline data were reported in the trials and were accompanied by a measure of spread (for example standard deviation), these were extracted and used in the meta-analysis. Where measures of spread for change from baseline values were not reported, the corresponding values at study end were used and were combined with change from baseline values to produce summary estimates of effect. All studies were assessed to ensure that baseline values were balanced across the treatment groups; if there were significant differences in important confounding variables at baseline these studies were not included in any meta-analysis and were reported separately.

Evidence of effectiveness of interventions

Quality assessment

Individual RCTs and quasi-randomised controlled trials were quality assessed using the Cochrane Risk of Bias Tool. Cohort studies were quality assessed using the CASP cohort study checklist. Each individual study was classified into one of the following three groups:

- Low risk of bias – The true effect size for the study is likely to be close to the estimated effect size.
- Moderate risk of bias – There is a possibility the true effect size for the study is substantially different to the estimated effect size.
- High risk of bias – It is likely the true effect size for the study is substantially different to the estimated effect size.

Each individual study was also classified into one of three groups for directness, based on if there were concerns about the population, intervention, comparator and/or outcomes in the study and how directly these variables could address the specified review question. Studies were rated as follows:

- Direct – No important deviations from the protocol in population, intervention, comparator and/or outcomes.
- Partially indirect – Important deviations from the protocol in one of the population, intervention, comparator and/or outcomes.
- Indirect – Important deviations from the protocol in at least two of the following areas: population, intervention, comparator and/or outcomes.

Methods for combining intervention evidence

Meta-analyses of interventional data were conducted with reference to the Cochrane Handbook for Systematic Reviews of Interventions (Higgins et al. 2011).

Where different studies presented continuous data measuring the same outcome but using different numerical scales (e.g. a 0-10 and a 0-100 visual analogue scale), these outcomes were all converted to the same scale before meta-analysis was conducted on the mean differences. Where outcomes measured the same underlying construct but used different instruments/metrics, data were analysed using standardised mean differences (Hedges' g).

A pooled relative risk was calculated for dichotomous outcomes (using the Mantel–Haenszel method) reporting numbers of people having an event, and a pooled incidence rate ratio was calculated for dichotomous outcomes reporting total numbers of events. Both relative and absolute risks were presented, with absolute risks calculated by applying the relative risk to the pooled risk in the comparator arm of the meta-analysis (all pooled trials).

Fixed- and random-effects models (der Simonian and Laird) were fitted for all syntheses, with the presented analysis dependent on the degree of heterogeneity in the assembled evidence. Fixed-effects models were the preferred choice to report, but in situations where the assumption of a shared mean for fixed-effects model were clearly not met, even after appropriate pre-specified subgroup analyses were conducted, random-effects results are presented. Fixed-effects models were deemed to be inappropriate if one or both of the following conditions was met:

- Significant between study heterogeneity in methodology, population, intervention or comparator was identified by the reviewer in advance of data analysis. This decision was made and recorded before any data analysis was undertaken.
- The presence of significant statistical heterogeneity in the meta-analysis, defined as $I^2 \geq 50\%$.

In any meta-analyses where some (but not all) of the data came from studies at high risk of bias, a sensitivity analysis was conducted, excluding those studies from the analysis. Results from both the full and restricted meta-analyses are reported. Similarly, in any meta-analyses where some (but not all) of the data came from indirect studies, a sensitivity analysis was conducted, excluding those studies from the analysis.

In situations where subgroup analyses were conducted, pooled results and results for the individual subgroups are reported when there was evidence of between group heterogeneity, defined as a statistically significant test for subgroup interactions (at the 95% confidence level). Where no such evidence as identified, only pooled results are presented.

Meta-analyses were performed in Cochrane Review Manager V5.3.

Minimal clinically important differences (MIDs)

The Core Outcome Measures in Effectiveness Trials (COMET) database was searched to identify published minimal clinically important difference thresholds relevant to this guideline. Identified MIDs were assessed to ensure they had been developed and validated in a methodologically rigorous way, and were applicable to the populations, interventions and outcomes specified in this guideline. In addition, the Guideline Committee were asked to prospectively specify any outcomes where they felt a consensus MID could be defined from their experience. In particular, any questions looking to evaluate non-inferiority (that one treatment is not meaningfully worse than another) required an MID to be defined to act as a non-inferiority margin.

MIDs found through this process and used to assess imprecision in the guideline are given in Table 4.

Table 4: Identified MIDs

Outcome	MID	Source
Borg dyspnoea score	2 units (-2, +2)	Ries AL. Minimally clinically important difference for the UCSD shortness of breath questionnaire, Borg Scale, and Visual Analog Scale. J COPD 2005; 2: 105–110.
6 minute walk distance	26m (-26, +26)	Puhan MA, Chandra D, Mosenifar Z, et al. The minimal important difference of exercise tests in severe COPD. Eur Respir J (2011); 37: 784–790.
Change in FEV1	100ml (-100, +100)	Cazzola M, MacNee W, Martinez M et al. Outcomes for COPD pharmacological trials: from lung function to biomarkers. Eur Respir J 2008; 31: 416–468.
Total score in St. George's respiratory questionnaire	4 points (-4,+4)	Schünemann HJ, Griffith L, Jaeschke R, et al. Evaluation of the minimal important difference for the feeling thermometer and the St. George's Respiratory Questionnaire in patients with chronic airflow obstruction. J Clin Epidemiol (2003); 56: 1170–1176.

For standardised mean differences where no other MID was available, an MID of 0.2 was used, corresponding to the threshold for a small effect size initially suggested by Cohen et al. (1988). The committee specified that any difference in mortality would be clinically meaningful, and therefore the line of no effect was used as an MID. For relative risks where no other MID was available, the GRADE default MID interval for dichotomous outcomes of 0.8 to 1.25 was used. For the assessment of imprecision, the values of the MID borders were taken as falling within the MID.

When decisions were made in situations where MIDs were not available, the 'Evidence to Recommendations' section of that review should make explicit the committee's view of the expected clinical importance and relevance of the findings.

GRADE for pairwise meta-analyses of interventional evidence

GRADE was used to assess the quality of evidence for the selected outcomes as specified in 'Developing NICE guidelines: the manual (2014)'. Data from RCTs was initially rated as high quality and the quality of the evidence for each outcome was downgraded or not from this initial point. If non-RCT evidence was included for intervention-type systematic reviews then these were initially rated as either moderate quality (quasi-randomised studies) or low quality (cohort studies) and the quality of the evidence for each outcome was further downgraded or not from this point, based on the criteria given in Table 5.

Table 5: Rationale for downgrading quality of evidence for intervention studies

GRADE criteria	Reasons for downgrading quality
Risk of bias	Not serious: If less than 33.3% of the weight in a meta-analysis came from studies at moderate or high risk of bias, the overall outcome was not downgraded. Serious: If greater than 33.3% of the weight in a meta-analysis came from studies at moderate or high risk of bias, the outcome was downgraded one level. Very serious: If greater than 33.3% of the weight in a meta-analysis came from studies at high risk of bias, the outcome was downgraded two levels.

GRADE criteria	Reasons for downgrading quality
	Outcomes meeting the criteria for downgrading above were not downgraded if there was evidence the effect size was not meaningfully different between studies at high and low risk of bias.
Indirectness	Not serious: If less than 33.3% of the weight in a meta-analysis came from partially indirect or indirect studies, the overall outcome was not downgraded. Serious: If greater than 33.3% of the weight in a meta-analysis came from partially indirect or indirect studies, the outcome was downgraded one level. Very serious: If greater than 33.3% of the weight in a meta-analysis came from indirect studies, the outcome was downgraded two levels. Outcomes meeting the criteria for downgrading above were not downgraded if there was evidence the effect size was not meaningfully different between direct and indirect studies.
Inconsistency	Concerns about inconsistency of effects across studies, occurring when there is unexplained variability in the treatment effect demonstrated across studies (heterogeneity), after appropriate pre-specified subgroup analyses have been conducted. This was assessed using the I^2 statistic. N/A: Inconsistency was marked as not applicable if data on the outcome was only available from one study. Not serious: If the I^2 was less than 33.3%, the outcome was not downgraded. Serious: If the I^2 was between 33.3% and 66.7%, the outcome was downgraded one level. Very serious: If the I^2 was greater than 66.7%, the outcome was downgraded two levels. Outcomes meeting the criteria for downgrading above were not downgraded if there was evidence the effect size was not meaningfully different between studies with the smallest and largest effect sizes.
Imprecision	If MIDs (1 corresponding to meaningful benefit; 1 corresponding to meaningful harm) were defined for the outcome, the outcome was downgraded once if the 95% confidence interval for the effect size crossed 1 MID, and twice if it crossed both the upper and lower MIDs. If the line of no effect was defined as an MID for the outcome, it was downgraded once if the 95% confidence interval for the effect size crossed the line of no effect (i.e. the outcome was not statistically significant), and twice if the sample size of the study was sufficiently small that it is not plausible any realistic effect size could have been detected. Outcomes meeting the criteria for downgrading above were not downgraded if the confidence interval was sufficiently narrow that the upper and lower bounds would correspond to clinically equivalent scenarios.

The quality of evidence for each outcome was upgraded if any of the following five conditions were met:

- Data from non-randomised studies showing an effect size sufficiently large that it cannot be explained by confounding alone.
- Data showing a dose-response gradient.
- Data where all plausible residual confounding is likely to increase our confidence in the effect estimate.

Publication bias

Publication bias was assessed in two ways. First, if evidence of conducted but unpublished studies was identified during the review (e.g. conference abstracts, trial protocols or trial records without accompanying published data), available information on these unpublished studies was reported as part of the review. Secondly, where 10 or more studies were included as part of a single meta-analysis, a funnel plot was produced to graphically assess the potential for publication bias.

Evidence statements

For outcomes with a defined MID, evidence statements were divided into 4 groups as follows:

- Situations where the data are only consistent, at a 95% confidence level, with an effect in one direction (i.e. one that is 'statistically significant'), and the magnitude of that effect is most likely to meet or exceed the MID (i.e. the point estimate is not in the zone of equivalence). In such cases, we state that the evidence showed that there is an effect.
- Situations where the data are only consistent, at a 95% confidence level, with an effect in one direction (i.e. one that is 'statistically significant'), but the magnitude of that effect is most likely to be less than the MID (i.e. the point estimate is in the zone of equivalence). In such cases, we state that the evidence showed there is an effect, but it is less than the defined MID.
- Situations where the confidence limits are smaller than the MIDs in both directions. In such cases, we state that the evidence demonstrates that there is no meaningful difference.
- In all other cases, we state that the evidence could not differentiate between the comparators.

For outcomes without a defined MID or where the MID is set as the line of no effect (for example, in the case of mortality), evidence statements are divided into 2 groups as follows:

- We state that the evidence showed that there is an effect if the 95% CI does not cross the line of no effect.
- The evidence could not differentiate between comparators if the 95% CI crosses the line of no effect.

The number of trials and participants per outcome are detailed in the evidence statements, but in cases where there are several outcomes being summarised in a single evidence statement and the numbers of participants and trials differ between outcomes, then the number of trials and participants stated are taken from the outcome with the largest number of trials. This is denoted using the terminology ‘up to’ in front of the numbers of trials and participants.

The evidence statements also cover the quality of the outcome based on the GRADE table entry. These can be included as single ratings of quality or go from one quality level to another if multiple outcomes with different quality ratings are summarised by a single evidence statement.

Association studies

In this guideline, association studies are defined as those reporting data showing an association of a predictor (either a single variable or a group of variables) and an outcome variable, where the data are not reported in terms of outcome classification (i.e. diagnostic/prognostic accuracy). Data were reported as hazard ratios (if measured over time) or odds ratios (if measured at a specific time-point. Data reported in terms of model fit or predictive accuracy were not assessed using this method.

Quality assessment

Individual cohort and case-control studies were quality assessed using the CASP cohort study and case-control checklists, respectively. Each individual study was classified into one of the following three groups:

- Low risk of bias – The true effect size for the study is likely to be close to the estimated effect size.
- Moderate risk of bias – There is a possibility the true effect size for the study is substantially different to the estimated effect size.
- High risk of bias – It is likely the true effect size for the study is substantially different to the estimated effect size.

Each individual study was also classified into one of three groups for directness, based on if there were concerns about the population, predictors and/or outcomes in the study and how directly these variables could address the specified review question. Studies were rated as follows:

- Direct – No important deviations from the protocol in population, predictors and/or outcomes.
- Partially indirect – Important deviations from the protocol in one of the population, predictors and/or outcomes.
- Indirect – Important deviations from the protocol in at least two of the population, predictors and/or outcomes.

Methods for combining association studies

Where appropriate, hazard ratios were pooled using the inverse-variance method, and odds ratios were pooled using the Mantel-Haenszel method. Adjusted odds ratios from multivariate models were only pooled if the same set of predictor variables were used across multiple studies.

Fixed- and random-effects models (der Simonian and Laird) were fitted for all syntheses, with the presented analysis dependent on the degree of heterogeneity in the assembled evidence. Fixed-effects models were the preferred choice to report, but in situations where the assumption of a shared mean for fixed-effects model were clearly not met, even after appropriate pre-specified subgroup analyses were conducted, random-effects results are presented. Fixed-effects models were deemed to be inappropriate if one or both of the following conditions was met:

- Significant between study heterogeneity in methodology, population, intervention or comparator was identified by the reviewer in advance of data analysis. This decision would need to be made and recorded before any data analysis is undertaken.
- The presence of significant statistical heterogeneity, defined as $I^2 \geq 50\%$.

In any meta-analyses where some (but not all) of the data came from studies at high risk of bias, a sensitivity analysis was conducted, excluding those studies from the analysis. Results from both the full and restricted meta-analyses are reported. Similarly, in any meta-analyses where some (but not all) of the data came from indirect studies, a sensitivity analysis was conducted, excluding those studies from the analysis.

Meta-analyses were performed in Cochrane Review Manager v5.3.

Minimal clinically important differences (MIDs)

The Core Outcome Measures in Effectiveness Trials (COMET) database was searched to identify published minimal clinically important difference thresholds relevant to this guideline. Identified MIDs were assessed to ensure they had been developed and validated in a methodologically rigorous way, and were applicable to the populations, interventions and outcomes specified in this guideline. In addition, the Guideline Committee were asked to prospectively specify any outcomes where they felt a consensus MID could be defined from their experience. In particular, any questions looking to evaluate non-inferiority (that one treatment is not meaningfully worse than another) required an MID to be defined to act as a non-inferiority margin.

MIDs found through this process and used to assess imprecision in the guideline are given in Table 4. For other outcomes where no MID is given below the line of no effect is used. In these cases, a 95% CI boundary of 1.00 for RR, OR and HR is taken as crossing the line of no effect.

Table 4: Identified MIDs

Outcome	MID	Source
Borg dyspnoea score	2 units (-2, +2)	Ries AL. Minimally clinically important difference for the UCSD shortness of breath questionnaire, Borg Scale, and Visual Analog Scale. J COPD 2005; 2: 105–110.
6 minute walk distance	26m (-26, +26)	Puhan MA, Chandra D, Mosenifar Z, et al. The minimal important difference of exercise tests in severe COPD. Eur Respir J (2011); 37: 784–790.
Total score in St. George's respiratory questionnaire	4 points (-4,+4)	Schünemann HJ, Griffith L, Jaeschke R, et al. Evaluation of the minimal important difference for the feeling thermometer and the St. George's Respiratory Questionnaire in patients with chronic airflow obstruction. J Clin Epidemiol (2003); 56: 1170–1176.
Change in FEV1	100ml	Cazzola M, MacNee W, Martinez M et al., Outcomes for COPD pharmacological trials: from lung function to biomarkers. Eur Respir J 2008; 31: 416–468.

When decisions were made in situations where MIDs were not available, the 'Evidence to Recommendations' section of that review should make explicit the committee's view of the expected clinical importance and relevance of the findings.

Modified GRADE for association studies

GRADE has not been developed for use with association studies; therefore a modified approach was applied using the GRADE framework. Data from cohort studies was initially rated as high quality, and data from case-control studies as low quality, with the quality of the evidence for each outcome then downgraded or not from this initial point (see Table 5).

Table 5: Rationale for downgrading quality of evidence for association studies

GRADE criteria	Reasons for downgrading quality
Risk of bias	Not serious: If less than 33.3% of the weight in a meta-analysis came from studies at moderate or high risk of bias, the overall outcome was not downgraded. Serious: If greater than 33.3% of the weight in a meta-analysis came from studies at moderate or high risk of bias, the outcome was downgraded one level. Very serious: If greater than 33.3% of the weight in a meta-analysis came from studies at high risk of bias, the outcome was downgraded two levels. Outcomes meeting the criteria for downgrading above were not downgraded if there was evidence the effect size was not meaningfully different between studies at high and low risk of bias. In addition, unadjusted odds ratio outcomes from univariate analyses were downgraded one level, in addition to any downgrading for risk of bias in individual studies. Adjusted odds ratios from multivariate analyses were not similarly downgraded, provided they included all important confounding variables in the model.
Indirectness	Not serious: If less than 33.3% of the weight in a meta-analysis came from partially indirect or indirect studies, the overall outcome was not downgraded. Serious: If greater than 33.3% of the weight in a meta-analysis came from partially indirect or indirect studies, the outcome was downgraded one level. Very serious: If greater than 33.3% of the weight in a meta-analysis came from indirect studies, the outcome was downgraded two levels. Outcomes meeting the criteria for downgrading above were not downgraded if there was evidence the effect size was not meaningfully different between direct and indirect studies.
Inconsistency	Concerns about inconsistency of effects across studies, occurring when there is unexplained variability in the treatment effect demonstrated across studies (heterogeneity). This was assessed using the I^2 statistic. N/A: Inconsistency was marked as not applicable if data on the outcome was only available from one study. Not serious: If the I^2 was less than 33.3%, the outcome was not downgraded. Serious: If the I^2 was between 33.3% and 66.7%, the outcome was downgraded one level. Very serious: If the I^2 was greater than 66.7%, the outcome was downgraded two levels.

GRADE criteria	Reasons for downgrading quality
	Outcomes meeting the criteria for downgrading above were not downgraded if there was evidence the effect size was not meaningfully different between studies with the smallest and largest effect sizes.
Imprecision	If MIDs (1 corresponding to a meaningful increase; 1 corresponding to a meaningful decrease) were defined for the outcome, the outcome was downgraded once if the 95% confidence interval for the effect size crossed 1 MID, and twice if it crosses both the upper and lower MIDs. If the line of no effect was defined as an MID for the outcome, it was downgraded once if the 95% confidence interval for the effect size crossed the line of no effect (i.e. the outcome was not statistically significant), and twice if the sample size of the study was sufficiently small that it is not plausible any realistic effect size could have been detected. Outcomes meeting the criteria for downgrading above were not downgraded if the confidence interval was sufficiently narrow that the upper and lower bounds would correspond to clinically equivalent scenarios.

The quality of evidence for each outcome was upgraded if either of the following conditions were met:

- Data showing an effect size sufficiently large that it cannot be explained by confounding alone.
- Data where all plausible residual confounding is likely to increase our confidence in the effect estimate.

Publication bias

Publication bias was assessed in two ways. First, if evidence of conducted but unpublished studies was identified during the review (e.g. conference abstracts or protocols without accompanying published data), available information on these unpublished studies was reported as part of the review. Secondly, where 10 or more studies were included as part of a single meta-analysis, a funnel plot was produced to graphically assess the potential for publication bias.

Evidence statements

Based on the amount of variation between studies and conflicting findings between studies, it was decided that the most useful way of summarising the data in evidence statements was to list those studies that showed an association with increased COPD exacerbations for each potential risk factor and those where an association could not be detected. For a study to show an association the 95% CI needed to not cross the line of no effect.

Health economics

Literature reviews seeking to identify published cost–utility analyses of relevance to the issues under consideration were conducted for all questions. In each case, the search undertaken for the clinical review was modified, retaining population and intervention descriptors, but removing any study-design filter and adding a filter designed to identify relevant health economic analyses. In assessing studies for inclusion, population, intervention and comparator, criteria were always identical to those used in the parallel

clinical search; only cost–utility analyses were included. Economic evidence profiles, including critical appraisal according to the Guidelines manual, were completed for included studies.

Economic studies identified through a systematic search of the literature are appraised using a methodology checklist designed for economic evaluations (NICE guidelines manual; 2014). This checklist is not intended to judge the quality of a study per se, but to determine whether an existing economic evaluation is useful to inform the decision-making of the committee for a specific topic within the guideline.

There are 2 parts of the appraisal process. The first step is to assess applicability (that is, the relevance of the study to the specific guideline topic and the NICE reference case); evaluations are categorised according to the criteria in Table 6.

Table 6 Applicability criteria

Level	Explanation
Directly applicable	The study meets all applicability criteria, or fails to meet one or more applicability criteria but this is unlikely to change the conclusions about cost effectiveness
Partially applicable	The study fails to meet one or more applicability criteria, and this could change the conclusions about cost effectiveness
Not applicable	The study fails to meet one or more applicability criteria, and this is likely to change the conclusions about cost effectiveness. These studies are excluded from further consideration

In the second step, only those studies deemed directly or partially applicable are further assessed for limitations (that is, methodological quality); see categorisation criteria in Table 7.

Table 7 Methodological criteria

Level	Explanation
Minor limitations	Meets all quality criteria, or fails to meet one or more quality criteria but this is unlikely to change the conclusions about cost effectiveness
Potentially serious limitations	Fails to meet one or more quality criteria and this could change the conclusions about cost effectiveness
Very serious limitations	Fails to meet one or more quality criteria and this is highly likely to change the conclusions about cost effectiveness. Such studies should usually be excluded from further consideration

Studies were prioritised for inclusion based on their relative applicability to the development of this guideline and the study limitations. For example, if a high quality, directly applicable UK analysis was available, then other less relevant studies may not have been included. Where selective exclusions were made on this basis, this is noted in the relevant section.

Where relevant, a summary of the main findings from the systematic search, review and appraisal of economic evidence is presented in an economic evidence profile alongside the clinical evidence.

Appendix C – Literature search strategies

NICE search methods

Main searches

Sources searched for this review question:

- Cochrane Database of Systematic Reviews – CDSR (Wiley)
- Cochrane Central Register of Controlled Trials – CENTRAL (Wiley)
- Database of Abstracts of Reviews of Effects – DARE (Wiley)
- Health Technology Assessment Database – HTA (Wiley)
- EMBASE (Ovid)
- MEDLINE (Ovid)
- MEDLINE In-Process (Ovid)

Identification of evidence

The population terms have been updated from the original guideline to include potential comorbidities such as asthma, bronchopulmonary dysplasia and bronchiectasis. These were excluded in the original strategy.

In this update, several lines of the strategy have been focused with the use of the term 'chronic' to reduce retrieval of articles focusing on acute signs or symptoms.

Additional acronyms for COPD have been included and on recommendation from the guideline committee, terms around 'breathlessness' have been added.

Searches were re-run in February 2018 and also included searching Medline epub ahead of print.

Review question search strategy

- In people with COPD, what factors (for example, viral infection) may cause an exacerbation?

The MEDLINE search strategy is presented below. This was translated for use in all of the other databases.

Search strategy

Medline Strategy, searched 1st November 2017 **Database: Ovid MEDLINE(R) 1946 to October Week 3 2017** **Search Strategy:**	
1	lung diseases, obstructive/
2	exp pulmonary disease, chronic obstructive/
3	(copd or coad or cobd or aecb).tw.
4	emphysema*.tw.
5	(chronic* adj4 bronch*).tw.

Medline Strategy, searched 1st November 2017 Database: Ovid MEDLINE(R) 1946 to October Week 3 2017 Search Strategy:
6 (chronic* adj3 (airflow* or airway* or bronch* or lung* or respirat* or pulmonary) adj3 obstruct*).tw. 7 (pulmonum adj4 (volumen or pneumatosis)).tw. 8 pneumonectasia.tw. 9 *Dyspnea/ 10 (chronic* adj3 (breath* or respirat*) adj3 (difficult* or labor* or labour* or problem* or short*)).tw. 11 (chronic* adj3 (dyspnea* or dyspnoea* or dyspneic or breathless*)).tw. 12 or/1-11 13 symptom flare up/ 14 (exacerbat* or flare* or flaring).tw. 15 or/13-14 16 12 and 15 17 animals/ not humans/ 18 16 not 17 19 limit 18 to english language 20 limit 19 to (letter or historical article or comment or editorial or news or case reports) 21 19 not 20

Note: An adapted in-house observational filter was appended

Study design filters and limits

An adapted in-house MEDLINE observational filter was appended to the review question above and is presented below. It was translated for use in the MEDLINE In-Process and Embase databases.

Study design filters

The MEDLINE observational filter is presented below.
Observational filter 1. Observational Studies as Topic/ 2. Observational Study/ 3. Epidemiologic Studies/ 4. exp Cohort Studies/ 5. Controlled Before-After Studies/ 6. Interrupted Time Series Analysis/ 7. Comparative Study.pt. 8. case series.tw. 9. (cohort adj (study or studies)).tw. 10. cohort analy$.tw. 11. (follow up adj (study or studies)).tw. 12. (observational adj (study or studies)).tw. 13. longitudinal.tw. 14. prospective.tw. 15. retrospective.tw. 16. or/1-16

The MEDLINE observational filter is presented below.

17. animals/ not humans/
18. 16 not 17

Note: analysts requested terms relating to case-control, historically controlled studies and cross-sectional studies to be removed

An English language limit has been applied. Animal studies and certain publication types (letters, historical articles, comments, editorials, news and case reports) have been excluded. The search will not be date limited as the previous guideline recommendations were not based on a systematic literature search.

Cochrane Airways Group Specialised Register (CAGR): Sources and search methods for prophylactic oral antibiotics

Review question search strategy

- What is the clinical and cost effectiveness of prophylactic oral antibiotics for preventing exacerbations in people with stable COPD?

Electronic searches: core databases

Database	Frequency of search
CENTRAL (the Cochrane Library)	Monthly
MEDLINE (Ovid)	Weekly
Embase (Ovid)	Weekly
PsycINFO (Ovid)	Monthly
CINAHL (EBSCO)	Monthly
AMED (EBSCO)	Monthly
Clinicaltrial.gov	

MEDLINE search strategy used to identify trials for the CAGR

COPD search

1. Lung Diseases, Obstructive/
2. exp Pulmonary Disease, Chronic Obstructive/
3. emphysema$.mp.

4. (chronic$ adj3 bronchiti$).mp.

5. (obstruct$ adj3 (pulmonary or lung$ or airway$ or airflow$ or bronch$ or respirat$)).mp.

6. COPD.mp.

7. COAD.mp.

8. COBD.mp.

9. AECB.mp.

10. or/1-9

Filter to identify RCTs

1. exp "clinical trial [publication type]"/

2. (randomized or randomised).ab,ti.

3. placebo.ab,ti.

4. dt.fs.

5. randomly.ab,ti.

6. trial.ab,ti.

7. groups.ab,ti.

8. or/1-7

9. Animals/

10. Humans/

11. 9 not (9 and 10)

12. 8 not 11

The MEDLINE strategy and RCT filter were adapted to identify trials in other electronic databases

Airways Group Specialised Register search strategy

1	MeSH DESCRIPTOR Pulmonary Disease, Chronic Obstructive Explode All AND INSEGMENT
2	MeSH DESCRIPTOR Bronchitis, Chronic AND INSEGMENT
3	(obstruct*) near3 (pulmonary or lung* or airway* or airflow* or bronch* or respirat*) AND INSEGMENT
4	COPD:MISC1 AND INSEGMENT
5	(COPD OR COAD OR COBD):TI,AB,KW AND INSEGMENT
6	#1 OR #2 OR #3 OR #4 OR #5 AND INSEGMENT

7 MeSH DESCRIPTOR Anti-Bacterial Agents Explode 1 AND INSEGMENT
8 chemoprophylaxis AND INSEGMENT
9 antibiotic* NEAR prophyla* AND INSEGMENT
10 continuous NEAR antibiotic* AND INSEGMENT
11 antibiotic* AND INSEGMENT
12 penicillin AND INSEGMENT
13 phenoxymethylpenicillin AND INSEGMENT
14 phenethicillin AND INSEGMENT
15 amoxicillin AND INSEGMENT
16 amoxycillin AND INSEGMENT
17 clavulanic acid AND INSEGMENT
18 tetracycline AND INSEGMENT
19 oxytetracycline AND INSEGMENT
20 doxycycline AND INSEGMENT
21 quinolone AND INSEGMENT
22 ciprofloxacin AND INSEGMENT
23 moxifloxacin AND INSEGMENT
24 macrolide AND INSEGMENT
25 erythromycin AND INSEGMENT
26 roxithromycin AND INSEGMENT
27 azithromycin AND INSEGMENT
28 sulphonamide AND INSEGMENT
29 co-trimoxazole AND INSEGMENT
30 sulphaphenazole AND INSEGMENT
31 trimethoprim AND INSEGMENT
32 sigmamycin AND INSEGMENT
33 tetracycline AND oleandomycin AND INSEGMENT
34 sulfamethoxazole AND INSEGMENT
35 sulfaphenazole AND INSEGMENT
36 sulfonamide AND INSEGMENT
37 #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32 or #33 or #34 or #35 or #36 AND INSEGMENT
38 #6 and #37 AND INSEGMENT
39 INREGISTER AND 01/08/2013_TO_09/08/2017:CRSCREATED
40 #39 AND #38

Further information on the CAGR can be found: http://airways.cochrane.org/sites/airways.cochrane.org/files/public/uploads/Search%20strategies%20document_2013_0.pdf

Health economics search strategy

Economic evaluations and quality of life data

Sources searched:

- NHS Economic Evaluation Database – NHS EED (Wiley) (legacy database)
- Health Technology Assessment (HTA Database)
- EconLit (Ovid)
- Embase (Ovid)
- MEDLINE (Ovid)
- MEDLINE In-Process (Ovid)

Search filters to retrieve economic evaluations and quality of life papers were appended to population search terms in MEDLINE, MEDLINE In-Process and EMBASE to identify relevant evidence and can be seen below. Searches were carried out on 5th May 2017 with a date limit from the previous search of January 2009 – May 2017. Searches were re-run in February 2018.

An English language limit has been applied. Animal studies and certain publication types (letters, historical articles, comments, editorials, news and case reports) have been excluded.

Health economics filters

The MEDLINE economic evaluations and quality of life search filters are presented below. They were translated for use in the MEDLINE In-Process and Embase databases.	
Economic evaluations	
1	Economics/
2	exp "Costs and Cost Analysis"/
3	Economics, Dental/
4	exp Economics, Hospital/
5	exp Economics, Medical/
6	Economics, Nursing/
7	Economics, Pharmaceutical/
8	Budgets/
9	exp Models, Economic/
10	Markov Chains/
11	Monte Carlo Method/
12	Decision Trees/
13	econom$.tw.
14	cba.tw.
15	cea.tw.
16	cua.tw.
17	markov$.tw.
18	(monte adj carlo).tw.
19	(decision adj3 (tree$ or analys$)).tw.
20	(cost or costs or costing$ or costly or costed).tw.
21	(price$ or pricing$).tw.

The MEDLINE economic evaluations and quality of life search filters are presented below. They were translated for use in the MEDLINE In-Process and Embase databases.
Economic evaluations
22 budget$.tw.
23 expenditure$.tw.
24 (value adj3 (money or monetary)).tw.
25 (pharmacoeconomic$ or (pharmaco adj economic$)).tw.
26 or/1-25
Quality of life
1 "Quality of Life"/
2 quality of life.tw.
3 "Value of Life"/
4 Quality-Adjusted Life Years/
5 quality adjusted life.tw.
6 (qaly$ or qald$ or qale$ or qtime$).tw.
7 disability adjusted life.tw.
8 daly$.tw.
9 Health Status Indicators/
10 (sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).tw.
11 (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).tw.
12 (sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).tw.
13 (sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).tw.
14 (sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).tw.
15 (euroqol or euro qol or eq5d or eq 5d).tw.
16 (qol or hql or hqol or hrqol).tw.
17 (hye or hyes).tw.
18 health$ year$ equivalent$.tw.
19 utilit$.tw.
20 (hui or hui1 or hui2 or hui3).tw.
21 disutili$.tw.
22 rosser.tw.
23 quality of wellbeing.tw.
24 quality of well-being.tw.
25 qwb.tw.
26 willingness to pay.tw.
27 standard gamble$.tw.
28 time trade off.tw.
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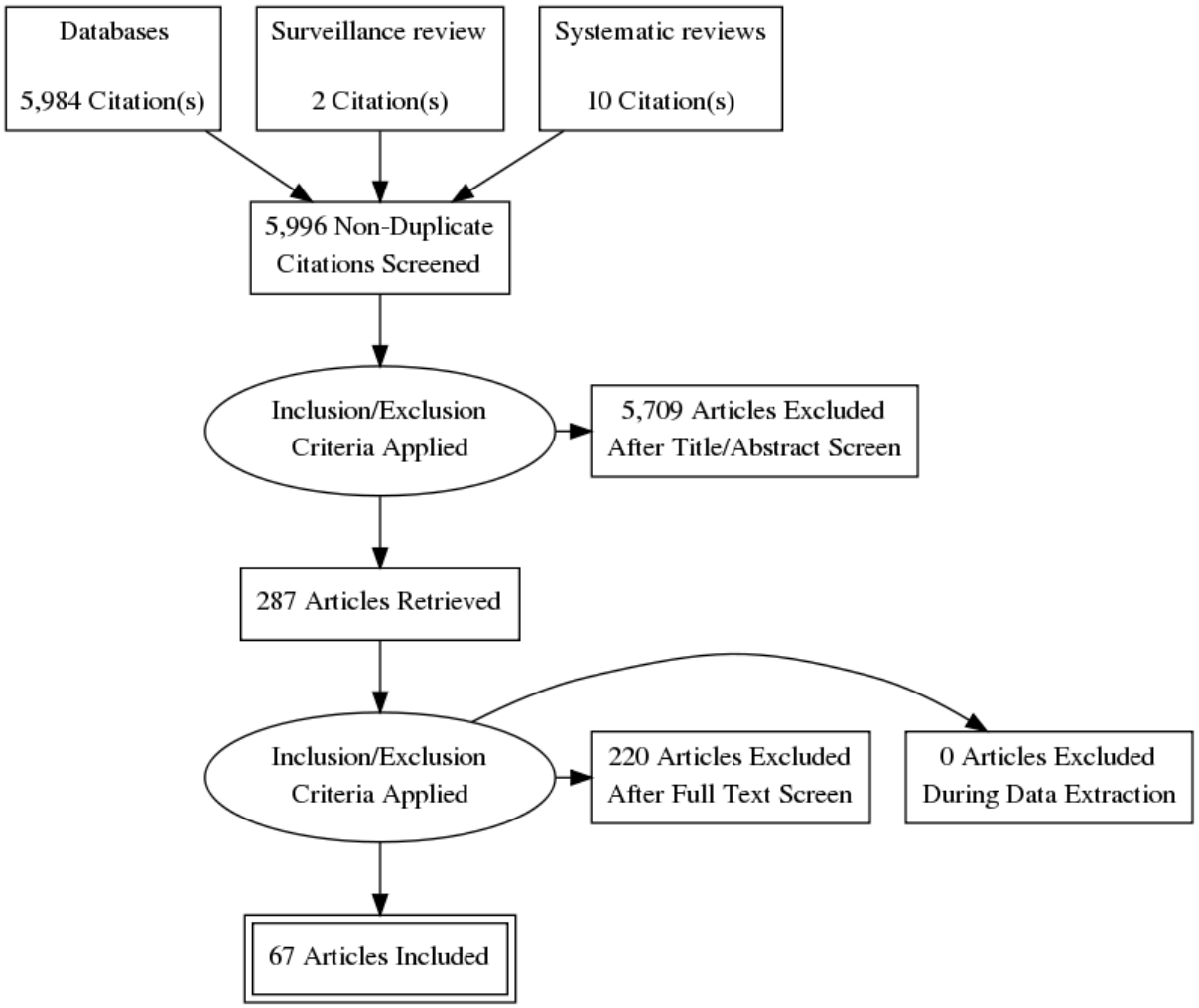
31 or/1-30

Appendix D – Clinical evidence study selection

Predicting exacerbations



Preventing exacerbations

Please refer directly to the Cochrane review for the PRISMA diagram.

Appendix E – Clinical evidence tables

Predicting exacerbations

Author (year)	Title	Study details	Quality assessment
Al (2016)	Hospitalisation of multi-ethnic older patients with AECOPD: Exploration of the occurrence of anxiety, depression and factors associated with short-term hospital readmission	Study type • Prospective cohort study Duration of follow-up • 3 months Study details • Study location Malaysia • Study setting Hospitals • Study dates 2012 to 2013 • Loss to follow-up None • Sources of funding The study did not receive funding Inclusion criteria • Age ≤60 years • Hospitalised for AECOPD Exclusion criteria • Tuberculosis Coexisting active pulmonary tuberculosis	Did the study address a clearly focused issue? • Yes Was the cohort recruited in an acceptable way? • Yes Was the exposure accurately measured to minimise bias? • Unclear The study only reported that clinical characteristics were extracted during the index hospital admission but it was unclear how ischemic heart disease was defined Was the outcome accurately measured to minimise bias? • Yes Have the authors identified all important confounding factors? • Unclear Multivariate analysis was done but

Author (year)	Title	Study details	Quality assessment
		• Cognitive deficit Those unable to respond to the researchers and answer the questions related to the study due to cognitive impairment • Those who died during hospitalisation • Transferred from and to other hospitals • Refuse to participate in the study • Those who did not complete the questionnaires Sample characteristics • Sample size 81 • %female 2.47% • Mean age (SD) Median age (interquartile range): 72 years (66.4 to 78.0) • Smoking status Smoker: 23.45% Ex-smoker: 76.54% Cumulative smoking, pack-years median (interquartile range): 40 (20 to 60) • Previous exacerbations Previous COPD hospitalisation in the previous year: 59.25% • FEV1, % predicted (mean, SD) Not reported Predictive factor (s) - Individual factors • Multimorbidities including mental health problems Ischemic heart disease	confounders were not reported Have they taken account of the confounding factors in the design and/or analysis? • Unclear Multivariate analysis was done but confounders were not reported Was the follow up of subjects complete enough? • Yes Was the follow up of subjects long enough? • Yes Overall risk of bias • High The study only reported that clinical characteristics were extracted during the index hospital admission but it was unclear how ischemic heart disease was defined. Multivariate analysis was done but confounders were not reported Directness • Directly applicable

Author (year)	Title	Study details	Quality assessment
		Outcome(s) • Exacerbations Exacerbations of COPD was defined based on GOLD (the Global Initiative for Chronic Obstructive Lung Disease) guidelines as 'an acute event in the natural course of the disease characterised by a change in the patient's respiratory symptoms that is beyond normal day to day variations leading to a change in regular medication' Measure(s) • Odds ratios Adjusted Covariates for adjustment • Exacerbations in the previous year History of ≥2 AECOPD admission • FEV1 <50% • Medical Research Council Dyspnoea score ≥4 (severe breathlessness)	
Al-ani (2013)	Predictors of exacerbations of asthma and COPD during one year in primary care	Study type • Prospective cohort study Duration of follow-up • 12 months Study details • Study location Norway	Did the study address a clearly focused issue? • Yes Was the cohort recruited in an acceptable way? • Yes

Author (year)	Title	Study details	Quality assessment
		• Study setting General practice • Study dates 2009 to 2011 • Loss to follow-up 40 out of 380 • Sources of funding Grant from the Norwegian Research Council Inclusion criteria • Age 40 years or more • Diagnosis of asthma and/or COPD Registered within the 5 years previous to the start of the study with this diagnosis Exclusion criteria • None reported Sample characteristics • Sample size 340 • %female 62.9% • Mean age (SD) 42.1% were age 65 years or more • Smoking status Never smoker: 25.6% Current smoker: 27.6% Ex-smoker: 46.8% • Previous exacerbations Within the year before baseline: 25.9% • FEV1, % predicted (mean, SD)	Was the exposure accurately measured to minimise bias? • Yes Was the outcome accurately measured to minimise bias? • Yes Have the authors identified all important confounding factors? • Unclear Confounding was not reported Have they taken account of the confounding factors in the design and/or analysis? • Unclear Confounding was not reported Was the follow up of subjects complete enough? • Yes Only 10% were lost to follow-up Was the follow up of subjects long enough? • Yes Overall risk of bias • Moderate

Author (year)	Title	Study details	Quality assessment
		Not reported Predictive factor (s) - Individual factors • Biomarkers C-reactive protein (CRP) Outcome(s) • Exacerbations A COPD exacerbation is defined as an increase in breathlessness, coughing or sputum amount that is acute in onset for at least 1 day, which necessitates a dosage adjustment of medication. Asthma exacerbations are defined as episodes of a progressive increase in shortness of breath, cough, wheezing, chest tightness or a combination of these symptoms. The patients were asked to consult their GP within 2 to 3 days when they experience such an increase in symptoms. Measure(s) • Odds ratios Adjusted Covariates for adjustment • Age 65 years and older • Chest findings Prolonged expiration • Clinical COPD Questionnaire (CCQ) - scores Common cold concern - Few times to almost all the time Depressed because of the breathing - Few times	Confounding factors were not mentioned Directness • Partially applicable Exacerbations included asthma or COPD exacerbations

Author (year)	Title	Study details	Quality assessment
		to almost all the time Coughing - Several times to almost all the time Phlegm - Several times to almost all the time Limitation in moderate activities - Moderately to totally limited Limitation in daily activities - Slightly to totally limited Limitation in social activities - Slightly to totally limited CCQ total score ≥ 2 • Exacerbations in the previous year Subgroup analyses • Frequency of exacerbations 1 or more exacerbations; 2 or more exacerbations	
Au (2009)	The effects of smoking cessation on the risk of chronic obstructive pulmonary disease exacerbations	Study type • Prospective cohort study Duration of follow-up • More than 12 months Median follow-up time 3.87 years (interquartile range: 2.72 to 4.29 years) Study details • Study location US • Study setting General internal medicine clinics • Study dates 1996 to 1999 • Loss to follow-up Not reported • Sources of funding	Did the study address a clearly focused issue? • Yes Was the cohort recruited in an acceptable way? • Yes Was the exposure accurately measured to minimise bias? • Yes Was the outcome accurately measured to minimise bias? • Yes Have the authors identified all important confounding factors?

Author (year)	Title	Study details	Quality assessment
		This study was funded by the Department of Veterans Affairs and by a VA Career Development Award Inclusion criteria • At least one visit to a participant clinic In the previous 12 months • Having an assigned primary care provider • Having a scheduled follow-up visit • Having a valid mailing address Exclusion criteria • None reported Sample characteristics • Sample size Total: 23,971 Current smoker: 8,067 Quit <1 year ago: 1,301 Quit 1 to 5 years ago: 2,321 Quit 6 to 10 years ago: 2,119 Quit >10 years ago: 10,163 • %female Sex breakdown only given for sub-groups, range 2.0% to 4.0% • Mean age (SD) Mean age breakdown only given for sub-groups, range 56.5 years (11.6) to 67.5 years (9.9) • Smoking status Current smoker: 33.6%; Quit <1 year ago: 5.4%; Quit 1 to 5 years ago: 9.7%; Quit 6 to 10 years ago: 8.8%; Quit >10 years ago: 42.4% • Previous exacerbations Previous exacerbations breakdown only given for sub-groups, range 3.4% to 7.9% • FEV1, % predicted (mean, SD)	• Yes Have they taken account of the confounding factors in the design and/or analysis? • Yes Was the follow up of subjects complete enough? • Unclear Loss to follow-up was not reported Was the follow up of subjects long enough? • Yes Overall risk of bias • Low Loss to follow-up was not reported but this was not considered to be important because the sample size was big Directness • Directly applicable

Author (year)	Title	Study details	Quality assessment
		Not reported Predictive factor (s) - Individual factors • Smoking Current, former or never smokers Outcome(s) • Exacerbations Exacerbations were defined as either an inpatient primary ICD-9 discharge diagnosis of COPD (491.x, 492.x, 493.2 and 496.x) or an outpatient diagnosis of COPD accompanied by a prescription dispensed for either prednisone or an antibiotic used to treat outpatient respiratory infections within 2 days of the clinic visit Measure(s) • Hazard ratios Adjusted Covariates for adjustment • Age • Smoking intensity • Markers of COPD and COPD severity Previous COPD exacerbations in the 12 month prior to the index date, the number of canisters filled for bronchodilators, including albuterol and ipratropium bromide, and/or the having filled a prescription for a nebulized bronchodilator • Seattle Index of Comorbidity (SIC score)	

Author (year)	Title	Study details	Quality assessment
		• Sociodemographic characteristics	
Bafadhel (2011)	Acute exacerbations of chronic obstructive pulmonary disease: identification of biologic clusters and their biomarkers	Study type • Prospective cohort study Duration of follow-up • 12 months Study details • Study location UK • Study setting Hospital • Study dates Not reported • Loss to follow-up 41 out of 156 • Sources of funding Supported by the Medical Research Council (UK) and AstraZeneca jointly as a “Biomarker Call Project” Inclusion criteria • Age More than 40 years old • GOLD stage Stages I to IV • Previous exacerbations One or more exacerbations in the preceding 12 months defined as the requirement of emergency health care	Did the study address a clearly focused issue? • Yes Was the cohort recruited in an acceptable way? • Yes Was the exposure accurately measured to minimise bias? • Yes Was the outcome accurately measured to minimise bias? • Yes Have the authors identified all important confounding factors? • Unclear Confounding was not reported Have they taken account of the confounding factors in the design and/or analysis? • Unclear Confounding was not reported Was the follow up of subjects complete enough?

Author (year)	Title	Study details	Quality assessment
		Exclusion criteria • Documented inability to produce sputum after the induced sputum procedure • Asthma Current or previous history of asthma • Tuberculosis Currently active pulmonary tuberculosis • Lung disease Any other clinically relevant lung disease other than COPD Sample characteristics • Sample size 115 • %female 30% • Mean age (SD) 69 years (range: 43 to 88) • Smoking status Current smokers: 29%; Ex-smokers: 69%; Pack-year history: mean 49 (range: 10 to 153) • Previous exacerbations Exacerbation rate in previous 12 months: mean 3 (SEM 0.2) • FEV1, % predicted (mean, SD) 52 (SEM 2) Predictive factor (s) - Individual factors • Viral/bacterial infection Bacteria-associated exacerbations were defined as a positive bacterial pathogen on routine culture (Haemophilus influenzae, Moraxella catarrhalis,	• No 26.3% were lost to follow-up Was the follow up of subjects long enough? • Yes Overall risk of bias • High Confounding was not reported. Loss to follow-up was 26% Directness • Directly applicable

Author (year)	Title	Study details	Quality assessment
		Streptococcus pneumoniae, Staphylococcus aureus, or Pseudomonas aeruginosa) or a total aerobic CFU count greater than or equal to 10 7 cells (12, 15). A virus-associated exacerbation was defined as one that had a positive sputum viral polymerase chain reaction (PCR), whether in isolation or in combination with a positive bacterial pathogen on routine culture. A sputum eosinophil–associated exacerbation was defined as the presence of more than 3% non-squamous cells Outcome(s) • Exacerbations Exacerbations were defined according to Anthonisen criteria and health care use Measure(s) • Odds ratios Adjustment was not reported	
Bartziokas (2011)	Statins and outcome after hospitalization for COPD exacerbation: a prospective study	Study type • Prospective cohort study Duration of follow-up • 12 months Study details • Study location Greece • Study setting Hospitals	Did the study address a clearly focused issue? • Yes Was the cohort recruited in an acceptable way? • Yes Was the exposure accurately measured to minimise bias?

Author (year)	Title	Study details	Quality assessment
		• Study dates 2006 to 2008 • Loss to follow-up 28 participants died within 30-days of baseline and 16 died within 1 year • Sources of funding Not reported Inclusion criteria • Diagnosis of COPD Established by spirometry according to GOLD guidelines Exclusion criteria • Asthma • Respiratory conditions Acute respiratory condition (for example, pneumonia, pneumothorax, pulmonary embolism, etc.) • Inability or unwillingness to cooperate with the investigators • Without available spirometry data • Bronchiectasis • Pulmonary fibrosis • Statins were interrupted >30 days during follow-up • Participants not receiving statins initially but received them during follow-up Sample characteristics • Sample size 245 • %female 9%	• Yes Was the outcome accurately measured to minimise bias? • Yes Have the authors identified all important confounding factors? • Yes Have they taken account of the confounding factors in the design and/or analysis? • Yes Was the follow up of subjects complete enough? • Yes Was the follow up of subjects long enough? • Yes Overall risk of bias • Low Directness • Partially applicable All participants were enrolled during hospitalisation for exacerbation of COPD

Author (year)	Title	Study details	Quality assessment
		• Mean age (SD) 71.2 years (9.6) • Smoking status Current smokers: 38%; pack-years median (IQR): 60 (50 to 90) • Previous exacerbations Not reported • FEV1, % predicted (mean, SD) Median (IQR): 36.5 (26.0 to 50.7) Predictive factor (s) - Individual factors • Other medications Use of statins was recorded on admission at baseline and it was re-evaluated at 2, 6 and 12 months after discharge. During these evaluations, use of statins was checked in participants' personal patient records Outcome(s) • Exacerbations Number of exacerbations of COPD defined as the need for use of antibiotics and/or systemic corticosteroids; number of severe exacerbations of COPD defined as the need for systemic corticosteroids and hospitalisation Measure(s) • Hazard ratios Adjusted Covariates for adjustment • Age	

Author (year)	Title	Study details	Quality assessment
		• Body mass index (BMI) • Sex • Charlson score • GOLD stage • Smoking status Subgroup analyses • Severity of exacerbations Exacerbations of COPD; severe exacerbations of COPD	
Baumeler (2016)	Therapy with proton-pump inhibitors for gastroesophageal reflux disease does not reduce the risk for severe exacerbations in COPD	Study type • Prospective cohort study Duration of follow-up • More than 12 months Median follow-up was 24 months Study details • Study location International multicentre study (Belgium, Germany, Greece, Italy, Netherlands, Serbia, Spain, Switzerland) • Study setting Hospitals • Study dates 2008 to 2012 • Loss to follow-up Not reported • Sources of funding This work was supported by the Pulmonary Medicine	Did the study address a clearly focused issue? • Yes Was the cohort recruited in an acceptable way? • Yes Was the exposure accurately measured to minimise bias? • Yes Was the outcome accurately measured to minimise bias? • Yes Have the authors identified all important confounding factors? • Yes

Author (year)	Title	Study details	Quality assessment
		Clinic, University Hospital Basel, Basel, Switzerland, and by the Swiss National Foundation Inclusion criteria • Age ≥40 years old • Diagnosis of COPD Moderate to severe COPD, clinical stable and at least 4weeks after an exacerbation • Smoking Current or ex-smokers with a smoking history of ≥10 pack-years Exclusion criteria • Respiratory conditions Pulmonary condition other than COPD • Chronic comorbidities Muscle-skeletal or neuromuscular process preventing ambulation • Life expectancy Less than 6 months • Immunosuppression Including organ transplantation or chronic steroid use (>20mg prednisolone equivalent per day) Sample characteristics • Sample size 638 • %female 29.8% • Mean age (SD) Median 67 (IQR 60 to 74)	Have they taken account of the confounding factors in the design and/or analysis? • Yes Was the follow up of subjects complete enough? • Unclear Loss to follow-up was not reported Was the follow up of subjects long enough? • Yes Overall risk of bias • Low Loss to follow-up was not reported but it seems that there was data for all participants at follow-up Directness • Directly applicable

Author (year)	Title	Study details	Quality assessment
		• Smoking status Current smoker: 33.4%; Pack-years: mean 50.2 (SD 29.9) • Previous exacerbations Not reported • FEV1, % predicted (mean, SD) Post-bronchodilated 77.0 (24) Predictive factor (s) - Individual factors • Multimorbidities including mental health problems Congestive heart failure Age-adjusted Charlson score • Other medications Anti-gastroesophageal reflux disease therapy Outcome(s) • Exacerbations Exacerbations were defined as an acute event characterized by a worsening of respiratory symptoms leading to a change in medication. Episodes requiring hospitalization were defined as severe exacerbations Measure(s) • Hazard ratios Adjusted Covariates for adjustment • Anti-GERD therapy • Body mass, airflow obstruction, dyspnoea and exercise capacity (BODE) index • Supervised rehabilitation • Lung volume reduction procedure	

Author (year)	Title	Study details	Quality assessment
		• Congestive heart failure • Adjusted Charlson score • FEV1, % predicted • Medication for comorbidities Aspirin Statins Diuretics ACE-inhibitors/AT-II antagonists Ca-antagonists β-blockers Antidepressives Oral antidiabetics Insulin	
Bertens (2013)	Development and validation of a model to predict the risk of exacerbations in chronic obstructive pulmonary disease	Study type • Prospective cohort study Duration of follow-up • More than 12 months 24 months Study details • Study location Netherlands • Study setting Primary care • Study dates 2001 to 2003 • Loss to follow-up 3 out of 243 • Sources of funding Financially supported by a grant from the Netherlands Organisation for Scientific Research Inclusion criteria • Age Derivation cohort: 65 years and older Validation	Did the study address a clearly focused issue? • Yes Was the cohort recruited in an acceptable way? • Yes Was the exposure accurately measured to minimise bias? • Yes Was the outcome accurately measured to minimise bias? • Yes Have the authors identified all important confounding factors? • Yes Have they taken account of the confounding factors in the design and/or analysis?

Author (year)	Title	Study details	Quality assessment
		cohort: 50 years and older • Diagnosis of COPD Derivation cohort: with a general practitioner's diagnosis of COPD Validation cohort: with a diagnosis of COPD based on available spirometric data (post-bronchodilator FEV1/FVC <70%) Exclusion criteria • None reported Sample characteristics • Sample size Bertens (2013) reports on 2 cohorts (derivation and validation) but ORs are only reported for the validation cohort. Therefore, we only report data on the derivation cohort analysing 240 participants • %female Sex breakdown only given for sub-groups, range 27.1% to 33.5% • Mean age (SD) Mean age breakdown only given for sub-groups, range 73.3 years (5.0) to 73.6 years (5.2) • Smoking status Smoking status breakdown only given for sub-groups, range: Current smokers: 20.0% to 34.3%; Never smokers: 7.1% to 18.2%; Pack years median (IQR): 23.3 (4.1 to 51.8) to 32.8 (18.4 to 54.0) • Previous exacerbations Previous exacerbations breakdown only given for sub-groups, range 13.5% to 47.1% • FEV1, % predicted (mean, SD) FEV1, % predicted breakdown only given for sub-	• Yes Was the follow up of subjects complete enough? • Yes Was the follow up of subjects long enough? • Yes Overall risk of bias • Low Directness • Directly applicable

Author (year)	Title	Study details	Quality assessment
		groups, range 64.2 (20.5) to 74.0 (20.0) Predictive factor (s) - Individual factors • Smoking Pack years of smoking • Multimorbidities including mental health problems History of vascular disease Outcome(s) • Exacerbations Operational definition for exacerbation of COPD was symptomatic deterioration requiring pulsed oral steroid use or hospitalisation Measure(s) • Odds ratios Adjusted Covariates for adjustment • Not reported	
Bhatt (2016)	beta-Blockers are associated with a reduction in COPD exacerbations	Study type • Prospective cohort study Duration of follow-up • More than 12 months Median 2.1 years follow-up Study details • Study location US	Did the study address a clearly focused issue? • Yes Was the cohort recruited in an acceptable way? • Yes Was the exposure accurately measured to minimise bias?

Author (year)	Title	Study details	Quality assessment
		• Study setting Not reported • Study dates Not reported • Loss to follow-up Not reported • Sources of funding NIH Grant Inclusion criteria • Age 45 to 80 years old • Smoking Current and former smokers Exclusion criteria • Asthma • Lung disease Known lung disease other than COPD Sample characteristics • Sample size 3,464 • %female Sex breakdown only given for sub-groups, range 39.9% to 45.1% • Mean age (SD) Mean age breakdown only given for sub-groups, range 62.8 years (8.5) to 66.8 years (7.7) • Smoking status Pack-years of smoking mean (SD) breakdown only given for sub-groups, range 52.6 (27.0) to 56.8 (30.0)	• Yes Was the outcome accurately measured to minimise bias? • Yes Have the authors identified all important confounding factors? • Yes Have they taken account of the confounding factors in the design and/or analysis? • Yes Was the follow up of subjects complete enough? • Unclear Loss to follow-up was not reported Was the follow up of subjects long enough? • Yes Overall risk of bias • Low Loss to follow-up was not reported but it seems that there was data for all participants at follow-up

Author (year)	Title	Study details	Quality assessment
		• Previous exacerbations Severe exacerbation in prior year breakdown only given for sub-groups, range 19.4% to 22.9% • FEV1, % predicted (mean, SD) FEV1, % predicted breakdown only given for sub-groups, range 49.8 (18.2) to 53.2 (15.4) Predictive factor (s) - Individual factors • Other medications β-blockers Calcium channel blockers (CCBs) Angiotensin converting enzyme inhibitors (ACEIs)/angiotensin receptor blockers (ARBs) Outcome(s) • Exacerbations Exacerbations were defined as worsening of respiratory symptoms requiring use of either antibiotics or systemic steroids, and those requiring hospitalization were termed severe exacerbations Measure(s) • Hazard ratios Adjusted Covariates for adjustment • Age • Congestive heart failure • Race • FEV1 • Percentage of emphysema on CT • Respiratory medications	Directness • Directly applicable

Author (year)	Title	Study details	Quality assessment
		• Log coronary artery calcification (CAC) • Propensity to prescribe β-blockers	
Boeck (2014)	Adenovirus-specific IgG maturation as a surrogate marker in acute exacerbations of COPD	Study type • Prospective cohort study Duration of follow-up • 6 months Study details • Study location Switzerland • Study setting Hospital • Study dates 2003 to 2005 • Loss to follow-up Not reported • Sources of funding Swiss National Foundation; Liechtenstein Foundation; Freiwillige Akademische Gesellschaft Basel; Clinic of Pulmonary Medicine, University Hospital Basel Inclusion criteria • Age >40 years old • Diagnosis of COPD Meeting spirometric COPD criteria • AECOPD Meeting the definition of AECOPD	Did the study address a clearly focused issue? • Yes Was the cohort recruited in an acceptable way? • Yes Was the exposure accurately measured to minimise bias? • Yes Was the outcome accurately measured to minimise bias? • Yes Have the authors identified all important confounding factors? • No Adjusted odds ratios were reported for a composite outcome including hospitalisation or death. Risk ratios were calculated for this evidence review using raw data from Boeck 2014 Have they taken account of the confounding factors in the design and/or analysis?

Author (year)	Title	Study details	Quality assessment
		Exclusion criteria • Asthma • Immunosuppression • Cystic fibrosis • Infiltrates As seen on chest radiographs Sample characteristics • Sample size 43 • %female Sex breakdown only given for sub-groups, range 50% to 59% • Mean age (SD) Median (IQR) age breakdown only given for sub-groups, range 65 years (58 to 72) to 71 years (63 to 77) • Smoking status Smoking status breakdown only given for sub-groups, range Current smoker: 46% to 53%; Pack-year smoked median (IQR): 50 (30 to 60) to 50 (34 to 55) • Previous exacerbations Not reported • FEV1, % predicted (mean, SD) FEV1, % predicted breakdown only given for sub-groups, range 42.2 (18.6) to 42.8 (14.8) Predictive factor (s) - Individual factors • Biomarkers Adenovirus-specific immunoglobulin (IgG): Fast IgG maturation (high-avidity adenovirus-specific IgG) Delayed IgG maturation (low-avidity adenovirus-	• No Adjusted odds ratios were reported for a composite outcome including hospitalisation or death. Risk ratios were calculated for this evidence review using raw data from Boeck 2014 Was the follow up of subjects complete enough? • Unclear Loss to follow-up was not reported but it seems that there was data for all participants at follow-up Was the follow up of subjects long enough? • Yes Overall risk of bias • High Adjusted odds ratios were reported for a composite outcome including hospitalisation or death. Risk ratios were calculated for this evidence review using raw data from Boeck 2014 Directness • Directly applicable

Author (year)	Title	Study details	Quality assessment
		specific IgG) Outcome(s) • Exacerbations AECOPD was defined as an acute, sustained worsening of the patient's condition beyond normal day-to-day variation Measure(s) • Relative risks Relative risks were calculated using raw data Subgroup analyses • Severity of exacerbations AECOPD within 6 months; Hospitalisation for AECOPD within 6 months	
Bowler (2014)	Prediction of acute respiratory disease in current and former smokers with and without COPD	Study type • Prospective cohort study Duration of follow-up • More than 12 months Average of 3 years Study details • Study location US • Study setting Not reported • Study dates 2008 to 2011	Did the study address a clearly focused issue? • Yes Was the cohort recruited in an acceptable way? • Yes Was the exposure accurately measured to minimise bias? • Yes Was the outcome accurately measured to minimise bias?

Author (year)	Title	Study details	Quality assessment
		• Loss to follow-up 2,054 out of 10,300 • Sources of funding National Heart, Lung and Blood Institute; National Centre for Research Resources/National Institutes of Health; and National Institute of Nursing Research Inclusion criteria • Age 45 to 80 years old • Smoking History of smoking for at least 10 pack-years Exclusion criteria • Exacerbation An acute respiratory exacerbation for at least 30 days prior to enrolment Sample characteristics • Sample size COPD 3,804 • %female 48% • Mean age (SD) 64 years (8) • Smoking status Current smoker: 39%; Smoking history, pack-years mean (SD): 52 (27) • Previous exacerbations Not reported • FEV1, % predicted (mean, SD)	• Yes Have the authors identified all important confounding factors? • Yes Have they taken account of the confounding factors in the design and/or analysis? • Yes Was the follow up of subjects complete enough? • No 20% were lost to follow-up Was the follow up of subjects long enough? • Yes Overall risk of bias • Moderate 20% were lost to follow-up Directness • Directly applicable

Author (year)	Title	Study details	Quality assessment
		Post-bronchodilator 57 (23) Predictive factor (s) - Individual factors • Multimorbidities including mental health problems Gastroesophageal reflux disease Chronic bronchitis Previous diagnosis of asthma Outcome(s) • Exacerbations Acute episodes of respiratory disease were defined as an episode of increased cough and phlegm or shortness of breath for which antibiotics or corticosteroids were prescribed. A severe episode was a report of hospitalisation for an acute episode of respiratory disease Measure(s) • Hazard ratios Adjusted Covariates for adjustment • Age • Exacerbations in the previous year • Body mass index (BMI) • Current smoking status Current versus former smoker Pack years • Congestive heart failure • FEV1, % predicted • Race • Gender • Height	

Author (year)	Title	Study details	Quality assessment
		• History of gastro-oesophageal reflux • Smoke exposure at work Years of exposure • History of working at a dusty job • History of COPD in a parent • Use of oxygen • History of blood clots • Chronic bronchitis • 6-minute walk test Limited by breathlessness • FEV1/FVC ratio post bronchodilator • Bronchodilator reversibility • Resting oxygen saturation • 6-minute walk distance • St. George's Respiratory Questionnaire (SGRQ) • Modified Medical Research Council (MMRC) dyspnoea score • Emphysema • Gas trapping • Pulmonary artery • Aorta • Pulmonary artery to aorta ratio Subgroup analyses • Severity of exacerbations Moderate to severe exacerbations; Hospitalised exacerbations	
Chang (2014)	Utility of the combination of serum highly-sensitive C-reactive protein level at discharge and a risk index in	Study type • Prospective cohort study	Did the study address a clearly focused issue? • Yes

Author (year)	Title	Study details	Quality assessment
	predicting readmission for acute exacerbation of COPD	Duration of follow-up • 9 months Median of 284 days Study details • Study location China • Study setting Hospital • Study dates 2010 to 2011 • Loss to follow-up 56 out of 191 • Sources of funding Chinese Medical Association Special Fund for Research on Chronic Respiratory Diseases Inclusion criteria • Diagnosis of COPD By post-bronchodilator spirometry, in accordance with the GOLD guidelines Exclusion criteria • Asthma • Tuberculosis • Lung disease Interstitial lung disease • Sleep apnoea syndrome • Bronchiectasis • Pneumonia • Hospitalised for reasons other than AECOPD	Was the cohort recruited in an acceptable way? • Yes Was the exposure accurately measured to minimise bias? • Yes Was the outcome accurately measured to minimise bias? • Yes Have the authors identified all important confounding factors? • Unclear Multivariate analysis is mentioned but confounding factors are not reported Have they taken account of the confounding factors in the design and/or analysis? • Unclear Multivariate analysis is mentioned but confounding factors are not reported Was the follow up of subjects complete enough? • No 29% were lost to follow-up

Author (year)	Title	Study details	Quality assessment
		• Not surviving the hospitalisation period Sample characteristics • Sample size 135 • %female 11.9% • Mean age (SD) Median 66 years (range: 60 to 74) • Smoking status Current smoker: 32.6%; Pack years: median 15 (range: 11 to 27) • Previous exacerbations In the last year: median 2 (range: 1 to 3) • FEV1, % predicted (mean, SD) Median 47 (range: 43 to 55) Predictive factor (s) - Individual factors • Biomarkers Serum level of high-sensitivity CRP (hs-CRP) was measured at discharge Outcome(s) • Exacerbations Acute exacerbation of COPD was defined as acute, sustained worsening of the condition of a patient from a stable state to a level of severity that exceeded the normal day-to-day variation, thus necessitating a change in medication	Was the follow up of subjects long enough? • Yes Overall risk of bias • High Multivariate analysis is mentioned but confounding factors are not reported. 29% were lost to follow-up Directness • Directly applicable

Author (year)	Title	Study details	Quality assessment
		Measure(s) • Hazard ratios Adjusted Covariates for adjustment • Not reported	
Chi (2017)	Exposure to indoor particulate matter worsens the symptoms and acute exacerbations in chronic obstructive pulmonary disease patients of southwestern Taiwan: A pilot study	Study type • Prospective cohort study Duration of follow-up • 12 months Study details • Study location Taiwan • Study setting Outpatient clinics • Study dates 2014 to 2016 • Loss to follow-up 7 out of 26 • Sources of funding Chang Gung Medical Foundation of Taiwan Inclusion criteria • Age ≥40 years • Diagnosis of COPD By physicians and hospital admission of acute exacerbation ≥1 time within the previous 3 months	Did the study address a clearly focused issue? • Yes Was the cohort recruited in an acceptable way? • Yes Was the exposure accurately measured to minimise bias? • Yes Was the outcome accurately measured to minimise bias? • Yes Have the authors identified all important confounding factors? • Yes Have they taken account of the confounding factors in the design and/or analysis?

Author (year)	Title	Study details	Quality assessment
		• GOLD stage Moderate to very severe COPD (FEV1 predicted <80%) • Language Ability to understand and communicate in Chinese or Taiwanese Exclusion criteria • Asthma • Tuberculosis • Heart disease • Cancer Sample characteristics • Sample size 19 • %female There were no females • Mean age (SD) 72.6 (6.8) • Smoking status Quit: 73.7%; Current smoker: 26.3% • Previous exacerbations Not reported • FEV1, % predicted (mean, SD) 42.4 (15.0) Predictive factor (s) - Environmental factors • Pollution- outdoors, indoors Air quality including particulate matter (PM) 2.5 and PM 10 levels	• Yes Was the follow up of subjects complete enough? • No 27% were lost to follow-up Was the follow up of subjects long enough? • Yes Overall risk of bias • Moderate 27% were lost to follow-up Directness • Directly applicable

Author (year)	Title	Study details	Quality assessment
		Outcome(s) • Exacerbations Acute Exacerbation was defined as the number of emergency room visits or COPD-related hospitalisations Measure(s) • Odds ratios Adjusted Covariates for adjustment • Age At baseline • Current smoking status • FEV1, % predicted At each visit (every 2 months for 1 year) Subgroup analyses • Severity of exacerbations Emergency room visit due to acute exacerbation; Hospital admission due to acute exacerbation	
Citgez (2016)	Statins and morbidity and mortality in COPD in the COMIC study: a prospective COPD cohort study	Study type • Prospective cohort study Duration of follow-up • More than 12 months 3 years Study details • Study location	Did the study address a clearly focused issue? • Yes Was the cohort recruited in an acceptable way? • Yes

Author (year)	Title	Study details	Quality assessment
		Netherlands • Study setting Hospital • Study dates 2005 to 2010 • Loss to follow-up Not reported • Sources of funding GlaxoSmithKline Inclusion criteria • Age ≥40 years • Diagnosis of COPD According to the GOLD guidelines • Smoking Current or former smoker • Language Ability to speak Dutch Exclusion criteria • Lung disease Other active lung disease (for example, sarcoidosis) • Medical condition compromising survival Within the follow-up period • Serious psychiatric morbidity • Antibiotics Maintenance therapy with antibiotics Sample characteristics • Sample size 795	Was the exposure accurately measured to minimise bias? • Yes Was the outcome accurately measured to minimise bias? • Yes Have the authors identified all important confounding factors? • Yes Have they taken account of the confounding factors in the design and/or analysis? • Yes Was the follow up of subjects complete enough? • Yes Was the follow up of subjects long enough? • Yes Overall risk of bias • Low Directness • Directly applicable

Author (year)	Title	Study details	Quality assessment
		• %female Sex breakdown only given for sub-groups, range 33.2% to 41.5% • Mean age (SD) Mean age breakdown only given for sub-groups, range 68.2 years (8.4) to 67.6 years (10.5) • Smoking status Smoking status breakdown only given for sub-groups, range Current smoker: 23.3% to 28.2%; Pack-year median: 35.0 to 35.4 • Previous exacerbations Not reported • FEV1, % predicted (mean, SD) FEV1, % predicted breakdown only given for sub-groups, range 50.9 (19.6) to 54.6 (18.7) Predictive factor (s) - Individual factors • Other medications Statin use was recorded from patients' pharmacy records. Statin use was defined as having a statin for at least 90 consecutive days after inclusion in the cohort Outcome(s) • Exacerbations AECOPD was defined as an acute negative change from baseline, reported by the patient, in breathlessness and/or sputum volume and/or colour of sputum (yellowish or greenish sputum) and/or cough, which may warrant additional treatment of prednisolone with or without antibiotics by a physician	

Author (year)	Title	Study details	Quality assessment
		in a patient with underlying COPD Measure(s) • Hazard ratios Adjusted Covariates for adjustment • Body mass index (BMI) • Sex • GOLD stage • Lung function parameters • Comorbidity	
Cosio (2016)	Defining the Asthma-COPD Overlap Syndrome in a COPD Cohort	Study type • Prospective cohort study Duration of follow-up • 12 months Study details • Study location Spain • Study setting 36 Spanish University hospitals • Study dates 2010 to 2013 • Loss to follow-up 337 out of 831 • Sources of funding The study received monetary fees from various	Did the study address a clearly focused issue? • Yes Was the cohort recruited in an acceptable way? • Yes Was the exposure accurately measured to minimise bias? • Yes Was the outcome accurately measured to minimise bias? • Yes Have the authors identified all important confounding factors?

Author (year)	Title	Study details	Quality assessment
		pharmaceutical companies Inclusion criteria • Diagnosis of COPD All patients had COPD diagnosis • Diagnosis of asthma and/or COPD 15.0% of participants met criteria for asthma-COPD overlap syndrome. Exclusion criteria • None reported Sample characteristics • Sample size 831 participants (125 with asthma-COPD overlap syndrome; 706 with only COPD) • %female Sex breakdown only given for sub-groups, range 16.7% to 18.4% • Mean age (SD) Mean age breakdown only given for sub-groups, range 66.5 years (8.7) to 67.8 years (8.9) • Smoking status Smoking status breakdown only given for sub-groups, range 27.8% to 35.2% • Previous exacerbations Moderate to severe exacerbations in the previous year breakdown only given for sub-groups, range 17.6% to 20.6% • FEV1, % predicted (mean, SD) FEV1, % predicted breakdown only given for sub-	• Unclear Unclear as to whether authors identified confounding variables in relation to exacerbations Have they taken account of the confounding factors in the design and/or analysis? • Unclear Unclear as to whether authors adjusted for all confounding variables in relation to exacerbations Was the follow up of subjects complete enough? • No Very high attrition rate (40.6% were lost to follow-up) Was the follow up of subjects long enough? • Yes Overall risk of bias • High Very high attrition rate (40.6% were lost to follow-up) and lack of clarity regarding confounding variable adjustment Directness • Partially applicable

Author (year)	Title	Study details	Quality assessment
		groups, range 59.3 (20.87) to 61.2 (18.1) Predictive factor (s) - Individual factors • Asthma-COPD Asthma-COPD overlap syndrome (ACOS): all COPD patients fulfilled 3 or more of the usual features of COPD, as suggested by the GINA/GOLD joint project, namely: age >40 years, post-bronchodilator FEV1/FVC <0.7, and exposure to cigarette smoke. Among those patients with COPD, several features of asthma were identified. To set the diagnosis of ACOS, at least one major or two minor criteria were required: major criteria (previous history of asthma, bronchodilator response to albuterol higher than 15% and 400 mL), minor criteria (IgE >100 IU, history of atopy, a percentage of blood eosinophils >5%, 2 separated bronchodilator responses to albuterol higher than 12% and 200 mL) Outcome(s) • Exacerbations Exacerbations were defined by use of antibiotics, steroids, or both captured from a diary of exacerbations (handled between the patient, the primary care physician, and the chest physician) or admission to hospital related to worsening of respiratory symptoms with no evidence of alternative diagnosis Measure(s) • Relative risks	Limited data on exacerbations

Author (year)	Title	Study details	Quality assessment
		Relative risks were calculated using raw data	
Coventry (2011)	Psychosocial risk factors for hospital readmission in COPD patients on early discharge services: a cohort study	Study type • Prospective cohort study Duration of follow-up • 12 months Follow-up in first week, at 90 days and at 365 days Study details • Study location UK • Study setting 3 hospitals in Greater Manchester • Study dates 2007 to 2009 • Loss to follow-up 1 participants excluded due to lung cancer diagnosis following enrolment; 17 participants died during follow-up • Sources of funding Author received funding from a UK Medical Research Council Special Training Fellowship in Health Services Research. Inclusion criteria • Diagnosis of COPD Evidenced by diagnosis code and/or clinical history • FEV1:FVC ratio <0.7 • FEV1, predicted	Did the study address a clearly focused issue? • Yes Was the cohort recruited in an acceptable way? • Yes Was the exposure accurately measured to minimise bias? • Yes Was the outcome accurately measured to minimise bias? • Yes Have the authors identified all important confounding factors? • Yes Have they taken account of the confounding factors in the design and/or analysis? • Yes Was the follow up of subjects complete enough? • No Over 10% lost to follow-up. However,

Author (year)	Title	Study details	Quality assessment
		<80% • Other mini mental state >7; systolic BP > 100 mmHg; white cell count (×109/l) 4-20; potassium between 3.5 and 5 mmol/l; arterial blood pH > 7.35; Po2 > 8 Kpa; PCo2 < 6.7 Kpa; registered with a Manchester general practitioner and adequate social support. Exclusion criteria • Respiratory conditions pneumothorax, pneumonia • Cancer • Serious psychiatric morbidity • Other uncontrolled atrial fibrillation; acute ECG changes; required full time nursing; needed intravenous therapy; cardiac chest pain; insulin dependent diabetes; chest X-ray changes; pulmonary embolism; history of falls or non-English speaking Sample characteristics • Sample size 80 participants • %female 44% • Mean age (SD) 65.3 years (9.9) • Smoking status Current smoker: 47%; ex-smoker: 53% • Previous exacerbations Previous COPD admission: 83% • FEV1, % predicted (mean, SD)	these were almost exclusively deaths Was the follow up of subjects long enough? • Yes Overall risk of bias • Low Directness • Directly applicable

Author (year)	Title	Study details	Quality assessment
		42.2 (18.4) Predictive factor (s) - Individual factors • Smoking Smoking status: current, ex/never • Multimorbidities including mental health problems Depression was measured at baseline and follow-up using the Hospital Anxiety and Depression Scale (HADS). The HADS is a 14-item self-reported questionnaire comprising two scales scored 0-21 to detect the presence and severity of anxiety and depression Outcome(s) • Exacerbations Readmission to hospital for AECOPD within 365 days of index admission either initial, isolated or recurrent exacerbations. All exacerbations were discrete events separated by ≥7 days during which no additional symptoms were recorded Measure(s) • Odds ratios Adjusted Covariates for adjustment • Age • Sex • FEV1, % predicted	

Author (year)	Title	Study details	Quality assessment
Crisafulli (2015)	C-Reactive Protein at Discharge, Diabetes Mellitus and >= 1 Hospitalization During Previous Year Predict Early Readmission in Patients with Acute Exacerbation of Chronic Obstructive Pulmonary Disease	Study type • Prospective cohort study Duration of follow-up • 1 month Study details • Study location Spain • Study setting Hospitals • Study dates 2004 to 2006 • Loss to follow-up 30 out of 155 • Sources of funding Centro de Investigacion Biomedica en Red-Enfermedades Respiratorias (CibeRes) and by La Marato TV3 Inclusion criteria • None reported Exclusion criteria • Asthma History as a concomitant chronic respiratory condition • Bronchiectasis History as a concomitant chronic respiratory condition • Pneumonia Community-acquired pneumonia identified clinically and by means of chest x-ray	Did the study address a clearly focused issue? • Yes Was the cohort recruited in an acceptable way? • Yes Was the exposure accurately measured to minimise bias? • Yes Was the outcome accurately measured to minimise bias? • Yes Have the authors identified all important confounding factors? • No Have they taken account of the confounding factors in the design and/or analysis? • No Was the follow up of subjects complete enough? • No 19.4% were lost to follow-up

Author (year)	Title	Study details	Quality assessment
		• Acute heart failure Identified clinically and by means of chest x-ray Sample characteristics • Sample size 125 • %female 6.4% • Mean age (SD) 69.2 years (9.8) • Smoking status Current: 28%; Former: 72% • Previous exacerbations Exacerbations in the preceding year: Patients with ≥2 events: 29.7%; Patients with ≥4 events: 10.4%; Rate (events/patients): Requiring antibiotics: 1.36; Requiring hospitalisations: 1.08 • FEV1, % predicted (mean, SD) Median (25th to 75th percentiles): 45.9 (34.8 to 55.2) Predictive factor (s) - Individual factors • Multimorbidities including mental health problems Comorbidities (chronic heart and renal failure, neurologic and non-cirrhotic liver disease, diabetes and non-active cancer) • Biomarkers C-reactive protein at discharge; Interleukin (IL-6) at discharge Outcome(s) • Exacerbations Anthonisen's criteria, based on an acute increase in	Was the follow up of subjects long enough? • Unclear 30 days Overall risk of bias • High Confounding factors were not identified. Therefore, no confounding factors were taken into account in the design and/or analysis. Loss to follow-up was 19.4%. Follow-up time was 30 days Directness • Directly applicable

Author (year)	Title	Study details	Quality assessment
		breathlessness, sputum volume and sputum purulence, was used to define AECOPD; patients were then classified as type I if they presented all three symptoms, type II with any two of the three symptoms and type III if any one of these symptoms was present. Early readmission to hospital was defined as a second hospitalisation within 30 days of discharge from the index hospitalisation with a new occurrence of symptoms and signs of exacerbation, defined with the same criteria Measure(s) • Odds ratios Adjusted Covariates for adjustment • Exacerbations in the previous year Hospitalisation for AECOPD ≥1 event • Comorbidity Number of comorbidities • Medications Duration of antibiotics treatment • Diabetes • Ratio of partial arterial oxygen pressure to the fraction of inspired oxygen (PaO2/FiO2) • Biomarker CRP at discharge, ≥7.6 mg/L IL-6 at discharge, ≥19.5 pg/mL Cut-offs obtained by receiver operating characteristic (ROC) analysis	

Author (year)	Title	Study details	Quality assessment
Desqueyroux (2002)	Effects of air pollution on adults with chronic obstructive pulmonary disease	Study type • Prospective cohort study Duration of follow-up • More than 12 months 14 months Study details • Study location France • Study setting Not reported • Study dates 1995 to 1996 • Loss to follow-up None reported • Sources of funding Not reported Inclusion criteria • Diagnosis of COPD Moderate to severe, physician diagnosed • FEV1:FVC ratio <0.8 • FEV1, predicted <80% • Other Oxygen pressure < 65 mm Hg or right cardiac insufficiency with systolic pulmonary artery pressure higher than 45 mm Hg, and "dwelling in Paris	Did the study address a clearly focused issue? • Yes Was the cohort recruited in an acceptable way? • Yes Was the exposure accurately measured to minimise bias? • Yes Was the outcome accurately measured to minimise bias? • Yes Have the authors identified all important confounding factors? • Yes Have they taken account of the confounding factors in the design and/or analysis? • Yes Was the follow up of subjects complete enough? • Yes Was the follow up of subjects long enough?

Author (year)	Title	Study details	Quality assessment
		suburbs" Exclusion criteria • None reported Sample characteristics • Sample size 39 • %female 25.6% • Mean age (SD) 67 years (9.0) • Smoking status Never smoker: 18%; current smokers: 23%; former smoker: 59% • Previous exacerbations Not reported • FEV1, % predicted (mean, SD) 34 (11) Predictive factor (s) - Environmental factors • Pollution- outdoors, indoors Air pollution data recorded included values for SO2, PM10, NO2, and O3 from daily measurements by urban background stations. Daily values were given by 28 stations for SO2, 7 stations for PM10, 15 stations for NO2, and 6 stations for O3. SO2 was measured by ultraviolet (UV) fluorescence, O3 by UV photometry, PM10 by β-radiometry, and NO2 by chemiluminescence. Ambient concentrations of air pollutants were obtained from the station closest to each participant's home, and 24-hr average levels	• Yes Overall risk of bias • Low Directness • Directly applicable

Author (year)	Title	Study details	Quality assessment
		were calculated from midnight to midnight every day for SO2, PM10, and NO2. Eight-hr average levels (10am to 6pm) were used for O3. The 1-hr maximum value was also recorded for NO2 and O3 Outcome(s) • Exacerbations The physician defined 'exacerbation of the patient's state' by considering both clinical and functional variations from baseline status. Acute exacerbation of the disease was confirmed by 1 or more of the following: a) decrease in 'vesicular' breath sound; b) bronchial obstruction; c) tachycardia or arrhythmia; and d) cyanosis Measure(s) • Odds ratios Adjusted Covariates for adjustment • Current smoking status • FEV1 • Breathlessness Sadoul's dyspnoea • Oxygen treatment oxygen treatment or ventilation • Carbon dioxide pressure	
Eisner (2009)	The impact of SHS exposure on health status and exacerbations among patients with COPD	Study type • Prospective cohort study	Did the study address a clearly focused issue?

Author (year)	Title	Study details	Quality assessment
		Duration of follow-up • More than 12 months Median 2.1 years Study details • Study location US • Study setting Kaiser Permanente Medical Care Program • Loss to follow-up 14 participants were excluded following invitation to complete study due to not meeting GOLD criteria for COPD after interviews and spirometry were performed, or could not perform spirometry due to previous tracheostomy placement. • Sources of funding funded by National Heart, Lung, and Blood Institute/National Institutes of Health R01HL077618 and UCSF Bland Lane FAMRI Centre of Excellence on Second-hand Smoke CoE2007 Inclusion criteria • Age 40 to 65 years • Diagnosis of COPD Physician diagnosed, evidenced by diagnostic code • Other Two or more prescriptions for COPD-related medication during a 12 month window beginning six months after index date (inhaled anticholinergic medications, inhaled beta agonists, inhaled corticosteroids, or theophylline). Persons must be	• Yes Was the cohort recruited in an acceptable way? • No Identified using diagnostic codes Was the exposure accurately measured to minimise bias? • Yes Was the outcome accurately measured to minimise bias? • No Used diagnostic codes to identify exacerbations Have the authors identified all important confounding factors? • Yes Have they taken account of the confounding factors in the design and/or analysis? • Yes Was the follow up of subjects complete enough? • Yes

Author (year)	Title	Study details	Quality assessment
		living within a 30 mile geographic radius of the research clinic Exclusion criteria • Inability or unwillingness to cooperate with the investigators severe communication difficulties attributable to advanced dementia or aphasia were excluded. Sample characteristics • Sample size 1,216 participants; 809 analysed (current non-smokers only) • %female Sex breakdown only given for sub-groups, range 52% to 61% • Mean age (SD) Mean age breakdown only given for sub-groups, range 58 years (6.3) to 59 years (6.1) • Smoking status Smoking status breakdown only given for sub-groups, range Never smoked: 17% to 23%; ex-smokers: 78% to 83% • Previous exacerbations Not reported • FEV1, % predicted (mean, SD) FEV1, % predicted breakdown only given for sub-groups, range 62 (23) to 65 (22) Predictive factor (s) - Individual factors • Smoking Second-hand smoke was measured with an	Was the follow up of subjects long enough? • Yes Overall risk of bias • Moderate Use of diagnostic codes in outcome measurement and participant selection Directness • Directly applicable

Author (year)	Title	Study details	Quality assessment
		instrument ascertaining exposure during the past seven days in seven microenvironments: the respondent's home, another person's home, traveling in a car or another vehicle, workplace (including dedicated smoking areas), bars and nightclubs, outdoor locations, and other locations. In each area, the instrument queries the total duration (in hours) of exposure during the past seven days. Based on the distribution of responses, three ordinal categories of exposure were defined: no exposure, lower level exposure (up to 1 hour/week), and higher level (≥1 hour/week) Outcome(s) • Exacerbations Emergency department (ED) visits and hospitalisation for COPD were proxy measures of severe disease exacerbation. COPD-related hospitalization was defined as those with a principal ICD-9 discharge diagnosis code for COPD (491, 492, or 496). COPD-related ED visits were identified as those with an ICD-9 code for COPD. In contrast to hospital discharge diagnoses, ED visits do not distinguish primary or secondary diagnoses within the Kaiser system. A composite outcome for hospital-based care was defined as either an ED visit or hospitalisation for COPD Measure(s) • Hazard ratios Adjusted	

Author (year)	Title	Study details	Quality assessment
		Covariates for adjustment • Age • Smoking intensity Smoking history • Sociodemographic characteristics Educational attainment • Sex • GOLD stage • Race • BODE score Subgroup analyses • Severity of exacerbations Emergency department visit for COPD; Hospitalisation for COPD; Any hospital-based care for COPD (combined endpoint of either hospitalisation or emergency department visit for COPD)	
Eisner (2010)	Influence of anxiety on health outcomes in COPD	Study type • Prospective cohort study Duration of follow-up • More than 12 months Median 2.1 years. Unclear follow-up protocol Study details • Study location US • Study setting Members of Kaiser Permanente Medical Care Program	Did the study address a clearly focused issue? • Yes Was the cohort recruited in an acceptable way? • No Recruitment using diagnostic codes Was the exposure accurately measured to minimise bias? • Yes

Author (year)	Title	Study details	Quality assessment
		• Study dates Unclear • Loss to follow-up Not reported • Sources of funding Not reported Inclusion criteria • Diagnosis of COPD Exclusion criteria • None reported Sample characteristics • Sample size 1,504 • %female Sex breakdown only given for sub-groups, range 55% to 71% • Mean age (SD) Mean age breakdown only given for sub-groups, range 55 years (6.6) to 59 years (6) • Smoking status Current smokers breakdown only given for sub-groups, range 30% to 45% • Previous exacerbations Not reported • FEV1, % predicted (mean, SD) Not reported	Was the outcome accurately measured to minimise bias? • No Exacerbations determined by occurrence of hospital visits in follow-up period and evidenced by COPD-related hospitalisation diagnostic code Have the authors identified all important confounding factors? • Yes Have they taken account of the confounding factors in the design and/or analysis? • Unclear Adjusted for anxiety-affecting confounding variables but no mention of adjusting for COPD exacerbation confounding variables Was the follow up of subjects complete enough? • Unclear Unclear attrition Was the follow up of subjects long enough? • Unclear Unclear follow-up protocol

Author (year)	Title	Study details	Quality assessment
		Predictive factor (s) - Individual factors • Multimorbidities including mental health problems Anxiety was measured using the 7-item anxiety subscale of the Hospital Anxiety and Depression Scale (HADS). The anxiety scale score ranges from 0 to 21, with higher scores reflecting more severe anxiety. The optimal cutting point of 8/9 points was used to identify subjects with significant anxiety Outcome(s) • Exacerbations Emergency department (ED) visits and hospitalisation for COPD were used as proxy measures of severe disease exacerbation. ED visits and hospitalisations were ascertained from Kaiser Permanente computerised health care databases that capture complete health care utilisation at its facilities Measure(s) • Hazard ratios Adjusted Covariates for adjustment • Age • Smoking intensity • Sociodemographic characteristics Income and educational attainment • Sex • Comorbidity comorbid cardiovascular conditions including coronary artery disease, hypertension, congestive heart failure	Overall risk of bias • High Unclear follow-up procedure and attrition information, and used diagnostic codes in participant selection and to measure exacerbations Directness • Directly applicable

Author (year)	Title	Study details	Quality assessment
		and hypertension	
Fu (2015)	Airway IL-1beta and Systemic Inflammation as Predictors of Future Exacerbation Risk in Asthma and COPD	Study type • Prospective cohort study Duration of follow-up • 12 months Study details • Study location New England • Study setting Participants recruited from research registers • Study dates Not stated • Loss to follow-up 14 out of 152 • Sources of funding Not stated Inclusion criteria • Diagnosis of asthma and/or COPD Physician diagnosis Exclusion criteria • None reported Sample characteristics • Sample size 152 • %female	Did the study address a clearly focused issue? • Yes Was the cohort recruited in an acceptable way? • No Sample recruited from research registers, which may not give a fully representative population Was the exposure accurately measured to minimise bias? • Yes Was the outcome accurately measured to minimise bias? • Yes Have the authors identified all important confounding factors? • Unclear Only a limited number of variables adjusted for Have they taken account of the confounding factors in the design and/or analysis?

Author (year)	Title	Study details	Quality assessment
		Sex breakdown only given for sub-groups, range 54.3% to 60% • Mean age (SD) Mean age breakdown only given for sub-groups, range 67.2 years (8.7) to 71.3 years (9.0) • Smoking status Smoking status breakdown only given for sub-groups, range; Never smoker: 17 to 22%; Ex-smoker: 24 to 49%; Current smoker: 2 to 4%; Smoking pack-y median (quartile 1-3): 26.5 (10.8-47.0) to 28.2 (15.3-44.0) • Previous exacerbations Previous exacerbations breakdown only given for sub-groups, range; Number of exacerbations in the year prior to baseline visit median (quartile 1-3): 3 (1-4) to 0.5 (0-1); ≥2 exacerbations in the prior year: 23.9% to 65.7% • FEV1, % predicted (mean, SD) FEV1, % predicted breakdown only given for sub-groups, range 50.9 (20.6) to 62.9 (14.7) Predictive factor (s) - Individual factors • Biomarkers Sputum IL-1β protein level, ng/mL Outcome(s) • Exacerbations An exacerbation of COPD was defined as a COPD-related episode that led to (1) hospitalisation, (2) an emergency department visit, or (3) the need for oral corticosteroids, antibiotics, or both for ≥3 days. A "frequent exacerbator" was defined as a participant	• Yes Was the follow up of subjects complete enough? • Yes Was the follow up of subjects long enough? • Yes Overall risk of bias • Moderate Sample recruited from research registers, which may not give a fully representative population. Only a limited number of variables adjusted for Directness • Directly applicable

Author (year)	Title	Study details	Quality assessment
		who had 2 or more exacerbations during the 12 months of follow-up Measure(s) • Odds ratios Adjusted Covariates for adjustment • Age • Exacerbations in the previous year • Sex • VAS symptom score	
Garcia-Aymerich (2003)	Risk factors of readmission to hospital for a COPD exacerbation: a prospective study	Study type • Prospective cohort study Duration of follow-up • More than 12 months Mean 410 days (SD 181) Study details • Study location Spain • Study setting Barcelona tertiary hospitals • Study dates Recruitment took place 1997 to 1999 • Loss to follow-up None. However, 6 died before discharge and 28 further participants died during follow-up without having a re-admission (both therefore excluded from	Did the study address a clearly focused issue? • Yes Was the cohort recruited in an acceptable way? • Yes Was the exposure accurately measured to minimise bias? • Yes Was the outcome accurately measured to minimise bias? • No Exacerbations measured using diagnostic codes

Author (year)	Title	Study details	Quality assessment
		analysis) • Sources of funding None reported Inclusion criteria • Diagnosis of COPD established by the ward pulmonologist based on medical history, current symptoms, and available pulmonary function tests, following the ERS guidelines Exclusion criteria • None reported Sample characteristics • Sample size 346 participants; 340 analysed • %female 8% • Mean age (SD) 69 years (9) • Smoking status Not reported • Previous exacerbations Readmissions in previous year mean (SD): 1.5 (2.0) • FEV1, % predicted (mean, SD) 36 (16) Predictive factor (s) - Individual factors • Smoking	Have the authors identified all important confounding factors? • Yes Have they taken account of the confounding factors in the design and/or analysis? • Yes Was the follow up of subjects complete enough? • Yes Was the follow up of subjects long enough? • Yes Overall risk of bias • Moderate Used diagnostic codes to measure outcome Directness • Directly applicable

Author (year)	Title	Study details	Quality assessment
		Outcome(s) • Exacerbations Time to readmission for a COPD exacerbation was obtained from the Minimum Basic Dataset (CMBD), a national administrative database that is monitored to high quality standards. All admissions with a main and/or secondary diagnosis fulfilling any of the following code combinations (according to the International Classification of Diseases, 9th revision) were recorded as a COPD exacerbation: (1) 490–496 (COPD group), 480–486 (pneumonia), 487 (influenza), or 518.81 (respiratory failure) as the main diagnosis; (2) 428 (cardiac failure) as the main diagnosis if 518.81 (respiratory failure) or 491.21 (acute exacerbation of chronic bronchitis) were the secondary diagnosis; and (3) any other respiratory problems (011 (tuberculosis), 466 (acute bronchitis), 500–505 (pneumoconiosis), 277.6 (deficit a1-antitrypsin)) as the main diagnosis if 518.81 or 491.21 was the secondary diagnosis. Criteria of the expert consensus of the American Thoracic Society were used to define such combinations Measure(s) • Hazard ratios Adjusted Covariates for adjustment • Age • Exacerbations in the previous year 3 or more COPD admissions in year prior to recruitment (yes vs. no); 3 or more emergency room	

Author (year)	Title	Study details	Quality assessment
		visits without admission in the year prior to recruitment (yes vs. no) • Sex • Current smoking status Ex-smoker not exposed to passive smoking; Ex-smoker exposed to passive smoking; Current smoker; Never smoker • FEV1, % predicted • Factors related to medical care Team based primary care (yes vs. no) Controlled by GP (yes vs. no) or pulmonologist (yes vs. no) Site of recruitment (hospital 1, 2 ,3 or 4) • Medications Anticholinergics Oral corticosteroids Influenza vaccination Respiratory rehabilitation Long term oxygen therapy • Compliance Correctly performed essential MDI manoeuvres • Quality of life Physical scale HR-QoL	
Gudmundsson (2005)	Risk factors for rehospitalisation in COPD: role of health status, anxiety and depression.	Study type • Prospective cohort study Duration of follow-up • 12 months Study details • Study location Sweden, Norway, Finland, Iceland, Denmark • Study setting	Did the study address a clearly focused issue? • Yes Was the cohort recruited in an acceptable way? • No ICD-10 codes were used in recruitment

Author (year)	Title	Study details	Quality assessment
		5 hospitals • Study dates Exact study dates not reported • Loss to follow-up 16 out of 406 • Sources of funding Not reported Inclusion criteria • Diagnosis of COPD Only included those patients admitted to hospital for over 24 hours • GOLD stage Stage 1 or higher Exclusion criteria • Asthma Sample characteristics • Sample size 406 • %female 51.2% • Mean age (SD) 69.2 years (10.5) • Smoking status Smokers: 36% • Previous exacerbations COPD hospitalisations in last 12 months median (IQR): 1 (0 to 3) • FEV1, % predicted (mean, SD)	Was the exposure accurately measured to minimise bias? • Yes Was the outcome accurately measured to minimise bias? • Yes Have the authors identified all important confounding factors? • Yes Have they taken account of the confounding factors in the design and/or analysis? • Yes Was the follow up of subjects complete enough? • Yes Was the follow up of subjects long enough? • Yes Overall risk of bias • Low Directness • Partially applicable Diagnostic codes used in participant

Author (year)	Title	Study details	Quality assessment
		38.4 (18.2) Predictive factor (s) - Individual factors • Smoking Current smoker • Multimorbidities including mental health problems Anxiety and depression were evaluated using the Hospital Anxiety and Depression scale (HAD). It is comprised of 2 parts, the first with 7 questions related to anxiety and the second with 7 questions related to depression. A score of 8 or more on either part was used as the cut-off point for diagnosing anxiety and depression, respectively Outcome(s) • Exacerbations An acute exacerbation was defined as a change in condition in a COPD patient from baseline of such a magnitude that it needed an acute hospital admission Measure(s) • Hazard ratios Adjusted Covariates for adjustment • Age • Current smoking status • FEV1, % predicted • St. George's Respiratory Questionnaire (SGRQ) • Anxiety Anxiety diagnosis and anxiety arm of hospital anxiety	identification and only included those participants admitted for over 24 hours

Author (year)	Title	Study details	Quality assessment
		and depression scale (HAD), entered separately. • Depression Depression diagnosis and depression arm of hospital anxiety and depression scale (HAD), entered separately.	
Han (2017)	Frequency of exacerbations in patients with chronic obstructive pulmonary disease: an analysis of the SPIROMICS cohort	Study type • Prospective cohort study Duration of follow-up • More than 12 months 3 years Study details • Study location US • Study setting Clinical centres • Study dates 2010 to 2015 • Loss to follow-up 738 out of 1873 • Sources of funding National Heart, Lung, and Blood Institute Inclusion criteria • None reported Exclusion criteria • None reported	Did the study address a clearly focused issue? • Yes Was the cohort recruited in an acceptable way? • Yes Was the exposure accurately measured to minimise bias? • Yes Was the outcome accurately measured to minimise bias? • Yes Have the authors identified all important confounding factors? • Yes Have they taken account of the confounding factors in the design and/or analysis? • Yes

Author (year)	Title	Study details	Quality assessment
		Sample characteristics • Sample size 1,105 • %female 43% • Mean age (SD) 66.0 years (7.6) • Smoking status Current smokers: 29% • Previous exacerbations Acute exacerbation rate in year before enrolment mean (SD): 0.40 (0.87); One or more acute exacerbations in preceding year: 24%; Two or more acute exacerbations in preceding year: 10% • FEV1, % predicted (mean, SD) 63.27 (22.72) Predictive factor (s) - Individual factors • Smoking Current and former smokers • Biomarkers Interleukin Outcome(s) • Exacerbations Acute exacerbations were defined as events that required health care (that is, office visit, hospital admission, or emergency department visit for a respiratory flare-up) involving the use of antibiotics or systematic corticosteroids, or both. Severe acute exacerbations were defined as those requiring a	Was the follow up of subjects complete enough? • No Only 394 out of 1,105 were included in the logistic regression analysis Was the follow up of subjects long enough? • Yes Overall risk of bias • High Only 394 out of 1,105 were included in the logistic regression analysis Directness • Directly applicable

Author (year)	Title	Study details	Quality assessment
		hospital admission or emergency department visit Measure(s) • Odds ratios Adjusted Covariates for adjustment • Age • Sex • Current smoking status Current smoking • FEV1, % predicted • Race	
Hansel (2013)	In-home air pollution is linked to respiratory morbidity in former smokers with chronic obstructive pulmonary disease	Study type • Prospective cohort study Duration of follow-up • 6 months Clinic visits at 3 and 6 months Study details • Study location US • Study setting Former smokers in Baltimore area • Study dates Not reported • Loss to follow-up None reported • Sources of funding	Did the study address a clearly focused issue? • Yes Was the cohort recruited in an acceptable way? • Yes Was the exposure accurately measured to minimise bias? • Yes Was the outcome accurately measured to minimise bias? • No Several exacerbation related outcomes

Author (year)	Title	Study details	Quality assessment
		Supported by NIEHS funding Inclusion criteria • Age At least 40 years • Smoking More than 10 pack-years but having quit more than 1 year prior to enrolment and having exhaled carbon monoxide level less than or equal to 6 ppm • FEV1:FVC ratio <0.7 • FEV1, predicted <80% Exclusion criteria • Alpha-1-antitrypsin Deficiency • Oral corticosteroids Within the last 3 months • Those with exhaled carbon monoxide (eCO) levels >6 ppm • Planning to move or live away from home during the study period • Other pulmonary diseases Sample characteristics • Sample size 84 • %female 42% • Mean age (SD) 68.9 years (7.4)	relied on self-report measures Have the authors identified all important confounding factors? • Yes Have they taken account of the confounding factors in the design and/or analysis? • Yes Was the follow up of subjects complete enough? • Yes Was the follow up of subjects long enough? • Yes Overall risk of bias • Moderate Use of self-report in measuring outcomes Directness • Directly applicable

Author (year)	Title	Study details	Quality assessment
		• Smoking status All former smokers • Previous exacerbations Severe exacerbations previous year: 19% • FEV1, % predicted (mean, SD) Pre-bronchodilator: 48.6 (15.9); Post-bronchodilator: 52.8 (16.7) Predictive factor (s) - Environmental factors • Pollution- outdoors, indoors In-home air pollution: s home inspection was conducted in the participant's bedroom and the main living area, identified as an additional room where the participant reported spending the most time. Indoor air sampling for PM2.5 (PM with aerodynamic size <2.5 mm) and NO2 was conducted. The limit of detection for PM2.5 was 0.64 mg/m3 and the limit of detection for NO2 was 0.52 ppb Outcome(s) • Exacerbations Any exacerbation was defined as worsening respiratory symptoms requiring antibiotics, oral steroids, or an acute care visit. Severe exacerbations were defined as worsening respiratory symptoms leading to an emergency department visit or hospitalisation Measure(s) • Odds ratios Adjusted	

Author (year)	Title	Study details	Quality assessment
		Covariates for adjustment • Age • Sociodemographic characteristics Education level • Sex • FEV1, % predicted At baseline • St. George's Respiratory Questionnaire (SGRQ) • Modified Medical Research Council (MMRC) dyspnoea score • Season Subgroup analyses • Severity of exacerbations Any exacerbations Severe exacerbations	
Hurst (2010)	Susceptibility to exacerbation in chronic obstructive pulmonary disease	Study type • Prospective cohort study Duration of follow-up • 12 months Study details • Study location 12 countries in ECLIPSE trial, unclear how many of these supplied data for current analysis • Study setting 46 centres in ECLIPSE trial, unclear how many of these provided data for current analysis • Study dates Ongoing with recruitment beginning in 2005	Did the study address a clearly focused issue? • Yes Was the cohort recruited in an acceptable way? • Yes Was the exposure accurately measured to minimise bias? • Yes Was the outcome accurately measured to minimise bias?

Author (year)	Title	Study details	Quality assessment
		• Loss to follow-up Not reported • Sources of funding Supported by grants from GlaxoSmithKline Inclusion criteria • Age 40-75 years • GOLD stage Graded according to GOLD severity criteria • Smoking Smoking history at least 10 pack-years • FEV1:FVC ratio less than or equal to 0.7 • FEV1, predicted <80% Exclusion criteria • Respiratory conditions Excluded if participant has respiratory disorder(s) other than COPD or had previous lung surgery • Exacerbation COPD exacerbation within 3 weeks of enrolment • Cancer Recent cancer diagnosis • Other severe α1-antitrypsin deficiency, history of significant inflammatory disease other than COPD, blood transfusion in 4 weeks prior to study start, inability to walk, partaking in blinded drug study or radiation exposure study, or taking long-term oral corticosteroid	• Yes Have the authors identified all important confounding factors? • Yes Have they taken account of the confounding factors in the design and/or analysis? • Yes Was the follow up of subjects complete enough? • Unclear Unclear attrition rate Was the follow up of subjects long enough? • Yes Overall risk of bias • Low Directness • Directly applicable

Author (year)	Title	Study details	Quality assessment
		therapy. Sample characteristics • Sample size 2,138 • %female 35% • Mean age (SD) 63 years (7) • Smoking status Current smoker: 36% • Previous exacerbations At least one exacerbation in year preceding study: 47%; at least two exacerbations in year 1 of the study: 29% • FEV1, % predicted (mean, SD) 48 (16) Predictive factor (s) - Individual factors • Multimorbidities including mental health problems History of reflux or heartburn Outcome(s) • Exacerbations Exacerbations were defined based on the decision by a patient's primary clinician or by study personnel to prescribe antibiotics or systemic corticosteroids, alone or in combination Covariates for adjustment • Exacerbations in the previous year	

Author (year)	Title	Study details	Quality assessment
		any vs. none • FEV1 per 100-ml decrease • St. George's Respiratory Questionnaire (SGRQ) per increase of 4 points • History of reflux or heartburn Yes vs. no • White cell count per increase of 1×10(3) /mm(3) Subgroup analyses • Frequency of exacerbations Frequency of exacerbations during year 1 were classified as none, 1, or ≥2	
Husebo (2014)	Predictors of exacerbations in chronic obstructive pulmonary disease--results from the Bergen COPD cohort study	Study type • Prospective cohort study Duration of follow-up • More than 12 months 3 years Study details • Study location Norway • Study setting Participants of the Bergen COPD Cohort Study (BCCS) • Study dates Recruitment began in 2006 and ended in 2008 • Loss to follow-up	Did the study address a clearly focused issue? • Yes Was the cohort recruited in an acceptable way? • Yes Was the exposure accurately measured to minimise bias? • Yes Was the outcome accurately measured to minimise bias? • Yes

Author (year)	Title	Study details	Quality assessment
		30 lost to follow-up after baseline visit (8 died, 2 received lung cancer diagnosis, 9 were excluded for oral steroid use and 11 withdrew consent) • Sources of funding none reported Inclusion criteria • Age 44-76 years • Diagnosis of COPD • GOLD stage Stage II-IV • Smoking History of more than 10 pack-years • FEV1:FVC ratio <0.7 at least 15 mins after bronchodilation • FEV1, predicted <80% Exclusion criteria • Lung disease Lung diseases other than COPD • Immunosuppression Any additional active inflammatory disease, such as autoimmune disorders • Exacerbation Having had exacerbation within 4 weeks prior to inclusion Sample characteristics • Sample size 433 patients	Have the authors identified all important confounding factors? • Yes Have they taken account of the confounding factors in the design and/or analysis? • Yes Was the follow up of subjects complete enough? • Yes Was the follow up of subjects long enough? • Yes Overall risk of bias • Low Directness • Directly applicable

Author (year)	Title	Study details	Quality assessment
		• %female Sex breakdown only given for sub-groups, range 38.1% to 41.9% • Mean age (SD) Mean age breakdown only given for sub-groups, range 62.6 years (6.8) to 64.3 years (6.8) • Smoking status Smoking status breakdown only given for sub-groups, range; Current smoking: 38.4% to 47.2%; ex-smoking: 52.8% to 61.6% • Previous exacerbations Previous exacerbations breakdown only given for sub-groups, range; 0 to 1 exacerbations in year prior to inclusion: 70.4% to 93.5%; 2 or more exacerbations in year prior to inclusion: 6.5% to 29.7% • FEV1, % predicted (mean, SD) Not reported Predictive factor (s) - Individual factors • Smoking Current smoking Ex-smoking • Multimorbidities including mental health problems Charlson comorbidity score: 1, 2, 3, 4+ • Biomarkers Soluble tumour necrosis factor receptor 1 (sTNF-R1) 100 µg/ml Predictive factor (s) - Environmental factors • Weather and seasonal changes Season: summer, autumn, winter, spring	

Author (year)	Title	Study details	Quality assessment
		Outcome(s) • Exacerbations Exacerbation was defined as a worsening of respiratory symptoms for two consecutive days or more. Exacerbation duration was patient reported, based entirely on symptomatic recovery. The cut off for late recovery was set at three weeks based on clinical experience Measure(s) • Odds ratios Adjusted Covariates for adjustment • Age • Exacerbations in the previous year 0-1 vs. 2 plus • Sex • Current smoking status Current compared to Ex • Charlson score 1 vs. 2 vs. 3 vs. 4+ • GOLD stage 2007 classification: FEV1 50-80% vs. FEV1 30-50% vs. FEV1<30% • Body composition Normal, Cachectic or obese • Hypoxemia PaO2>8 kPa vs. PaO2<8 kPa • Chronic cough Yes vs. no • Use of inhaled steroids	

Author (year)	Title	Study details	Quality assessment
		yes vs. no • Inflammatory markers Added individually: Leucocyte count (WBC); C-reactive protein (CRP); Neutrophil gelatinase lipocalin; Soluble TNF receptor-1; Osteoprotegrin (OPG)	
Hwang (2015)	History of pneumonia is a strong risk factor for chronic obstructive pulmonary disease (COPD) exacerbation in South Korea: the Epidemiologic review and Prospective Observation of COPD and Health in Korea (EPOCH) study	Study type • Prospective cohort study Duration of follow-up • 12 months Study details • Study location South Korea • Study setting 46 institutions • Study dates Not reported • Loss to follow-up 194 out of 1,114 (including due to death, hospital transfer, general follow up loss and withdrawal of consent) • Sources of funding Sponsored by Takeda Pharmaceuticals Inclusion criteria • Age Over 40 years • Diagnosis of COPD As defined by GOLD criteria, with diagnosis at least 1	Did the study address a clearly focused issue? • Yes Was the cohort recruited in an acceptable way? • Yes Was the exposure accurately measured to minimise bias? • Yes Was the outcome accurately measured to minimise bias? • Yes Have the authors identified all important confounding factors? • Unclear Unclear whether all important confounding variables were considered Have they taken account of the confounding factors in the design and/or analysis?

Author (year)	Title	Study details	Quality assessment
		year prior to enrolment with assessment at investigational site for at least 1 year Exclusion criteria • Cancer If diagnosed with cancer • Other If involved in other investigational study Sample characteristics • Sample size 1,114 • %female 8.9% • Mean age (SD) Mean not given, 86.6% of participants were 60 years or older • Smoking status Current smokers: 21.3%; ex-smokers: 69.2%; never-smokers: 9.5% • Previous exacerbations Not reported • FEV1, % predicted (mean, SD) 59.4 (20.1) Predictive factor (s) - Individual factors • Multimorbidities including mental health problems History of pneumonia Outcome(s) • Exacerbations	• Unclear Unclear whether all important confounding variables were accounted for Was the follow up of subjects complete enough? • No Over 10% lost to follow-up Was the follow up of subjects long enough? • Yes Overall risk of bias • Moderate Relatively high attrition rate (over 10% lost to follow-up) and unclear adjustment for confounding variables Directness • Directly applicable

Author (year)	Title	Study details	Quality assessment
		'Moderate exacerbation' was defined as an event requiring treatment with a systemic corticosteroid and/or antibiotics, 'severe exacerbation' was an event requiring hospitalisation, and 'other exacerbation' included visits to primary-care physicians or a change in the use of regular medication Measure(s) • Odds ratios Adjusted Covariates for adjustment • Exacerbations in the previous year Two or more exacerbations in last year vs. less than two • FEV1, % predicted • CAT score	
Ingebrigtsen (2015a)	Fibrinogen and alpha1-antitrypsin in COPD exacerbations	Study type • Prospective cohort study Duration of follow-up • More than 12 months 10 years Study details • Study location Denmark • Study setting Copenhagen suburban patients examined with pulmonary function and blood tests	Did the study address a clearly focused issue? • Yes Was the cohort recruited in an acceptable way? • Yes Was the exposure accurately measured to minimise bias? • Yes

Author (year)	Title	Study details	Quality assessment
		• Study dates 2003 to 2013 • Loss to follow-up 1189 died, 16 emigrated • Sources of funding Supported by the Capital Region of Copenhagen, the Danish Heart Foundation, the Danish Lung Foundation, the Velux Foundation and Herlev Hospital. Inclusion criteria • Age Aged over 40 • Diagnosis of COPD • FEV1:FVC ratio <0.7 Exclusion criteria • Asthma Sample characteristics • Sample size 13,591 • %female 52% • Mean age (SD) 66.3 years (11.3) • Smoking status Current smokers: 30.1% • Previous exacerbations Not reported • FEV1, % predicted (mean, SD)	Was the outcome accurately measured to minimise bias? • No Relied on discharge codes and/or dispensed antibiotics Have the authors identified all important confounding factors? • Yes Have they taken account of the confounding factors in the design and/or analysis? • Yes Was the follow up of subjects complete enough? • Yes Was the follow up of subjects long enough? • Yes Overall risk of bias • Moderate Use of diagnostic codes/prescriptions dispensed to measure outcome Directness • Directly applicable

Author (year)	Title	Study details	Quality assessment
		84.2 (19.2) Predictive factor (s) - Individual factors • Biomarkers Fibrinogen, high sensitive C-reactive protein, and α1-antitrypsin Outcome(s) • Exacerbations Exacerbations in COPD were defined by a composite of hospital admissions with a discharge diagnosis of COPD in the national Danish Patient Registry and/or dispensed treatments with systemic corticosteroids alone or in combination with antibiotics in the national Danish Medicinal Product Registry Measure(s) • Hazard ratios Adjusted Covariates for adjustment • FEV1, % predicted	
Ingebrigtsen (2015b)	Gastro-esophageal reflux disease and exacerbations in chronic obstructive pulmonary disease	Study type • Prospective cohort study Duration of follow-up • More than 12 months 5 years	Did the study address a clearly focused issue? • Yes Was the cohort recruited in an acceptable way? • Yes

Author (year)	Title	Study details	Quality assessment
		Study details • Study location Denmark • Study setting Patients from Copenhagen City Heart Study • Study dates 1995 to 2002 • Loss to follow-up 148 (11.8%) died • Sources of funding Supported by Capital region of Copenhagen, Danish Heart Foundation, Danish Lung Foundation, Velux Foundation and Herlev Hospital Inclusion criteria • Age over 40 years • Diagnosis of COPD Defined as FEV1:FVC ratio • FEV1:FVC ratio <0.7 Exclusion criteria • Asthma Sample characteristics • Sample size 1,259 • %female Sex breakdown only given for sub-groups, range 35.1% to 52.3% • Mean age (SD)	Was the exposure accurately measured to minimise bias? • Unclear Unclear whether measure of gastro-oesophageal reflux disease used is acceptable Was the outcome accurately measured to minimise bias? • No Relied solely on prescription data for oral corticosteroids Have the authors identified all important confounding factors? • Yes Have they taken account of the confounding factors in the design and/or analysis? • Yes Was the follow up of subjects complete enough? • No Over 10% lost to follow-up Was the follow up of subjects long enough? • Yes

Author (year)	Title	Study details	Quality assessment
		Mean age breakdown only given for sub-groups, range 66.9 years (9.7) to 67.8 years (10.5) • Smoking status Current smokers breakdown only given for sub-groups, range 55.4% to 69.2% • Previous exacerbations Not reported • FEV1, % predicted (mean, SD) Not reported Predictive factor (s) - Individual factors • Smoking Current smoking Former smoking • Multimorbidities including mental health problems Gastro-oesophageal reflux disease defined as reporting coexisting night-time and daytime gastro-oesophageal reflux disease, with or without a regular use of acid inhibitory treatment. The regular use of acid inhibitory treatment was defined by reporting a daily or almost daily use of acid inhibitory treatment Outcome(s) • Exacerbations Medically treated exacerbations of COPD were defined as clusters of oral corticosteroids, with or without antibiotics, dispensed less than 4 weeks apart. All prescriptions of oral corticosteroids and antibiotics were identified using complete record linkage to the national Danish Registry of Medicinal Products Statistics	Overall risk of bias • High Relied solely on prescription data for oral corticosteroids in measuring outcome, use of questionnaire in determining gastro-oesophageal reflux disease and over 10% lost to follow-up due to death Directness • Directly applicable

Author (year)	Title	Study details	Quality assessment
		Measure(s) • Hazard ratios Adjusted Covariates for adjustment • Gastro-oesophageal reflux disease Entered individually: Coexisting night-time and daytime gastro-oesophageal reflux disease and no regular use of acid inhibitory treatment: Yes or no; Coexisting night-time and daytime gastro-oesophageal reflux disease and regular use of acid inhibitory treatment: Yes or no; Either night-time or daytime gastro-oesophageal reflux disease but not coexisting, and no regular use of acid inhibitory treatment: Yes or no; Either night-time or daytime gastro-oesophageal reflux disease but not coexisting, and regular use of acid inhibitory treatment: Yes or no; No gastro-oesophageal reflux disease but regular use of acid inhibitory treatment: Yes or no Subgroup analyses • GOLD grade Breakdown given for all COPD vs. GOLD II-IV only	
Inoue (2009)	High plasma brain natriuretic peptide levels in stable COPD without pulmonary hypertension or cor pulmonale	Study type • Prospective cohort study Duration of follow-up • More than 12 months 3 years	Did the study address a clearly focused issue? • Yes Was the cohort recruited in an acceptable way?

Author (year)	Title	Study details	Quality assessment
		Study details • Study location Japan • Study setting Single hospital • Study dates Not provided • Loss to follow-up None however 2 died during follow-up • Sources of funding None reported Inclusion criteria • Age 40 years or older • Diagnosis of COPD • Smoking 10 or greater pack-years smoking history Exclusion criteria • Respiratory conditions other chronic respiratory diseases such as interstitial pneumonia, old pulmonary tuberculosis, bronchiectasis, and pneumoconiosis • Cancer Active malignancies • Cardiovascular conditions definitive cardiac diseases, congestive heart failure, pulmonary hypertension and cor pulmonale • Other symptoms or a history of oedema, ascites, and dilatation of the jugular vein, or signs of hepato-	• Yes Was the exposure accurately measured to minimise bias? • Yes Was the outcome accurately measured to minimise bias? • Unclear Unclear assessment of exacerbation Have the authors identified all important confounding factors? • Unclear Unclear which confounding factors were input into model Have they taken account of the confounding factors in the design and/or analysis? • Unclear Unclear which confounding factors were input into model Was the follow up of subjects complete enough? • Yes Was the follow up of subjects long enough?

Author (year)	Title	Study details	Quality assessment
		splenomegaly Sample characteristics • Sample size 60 • %female Sex breakdown only given for sub-groups, range 0% to 25% • Mean age (SD) Mean age breakdown only given for sub-groups, range 64.6 years (3.3) to 73.7 years (1.2) • Smoking status Smoking status breakdown only given for sub-groups, range; non-smoker: 0%; current smoker: 9.1% to 58.3%; ex-smoker: 41.6% to 90.9% • Previous exacerbations Not reported • FEV1, % predicted (mean, SD) FEV1, % predicted breakdown only given for sub-groups, range 31.1 (4.1) in GOLD stage IV to 89.8 (2.8) in GOLD stage I Predictive factor (s) - Individual factors • Biomarkers Plasma brain natriuretic peptide levels Outcome(s) • Exacerbations The severity of exacerbation was classified as described by Rodriguez-Roisin (2000)	• Yes Overall risk of bias • Moderate Unclear which confounding factors were input into model, unclear assessment of exacerbation Directness • Directly applicable

Author (year)	Title	Study details	Quality assessment
		Measure(s) • Hazard ratios Adjusted Covariates for adjustment • Not reported	
Ito (2012)	Depression, but not sleep disorder, is an independent factor affecting exacerbations and hospitalization in patients with chronic obstructive pulmonary disease	Study type • Prospective cohort study Duration of follow-up • 12 months Study details • Study location Japan • Study setting Hospital • Study dates 2009 to 2011 • Loss to follow-up 9 out of 85 • Sources of funding Ministry of Health, Labour and Welfare of Japan and by a Grant-in-Aid for Scientific Research from the Ministry of Education, Science, Sports, and Culture of Japan Inclusion criteria • Diagnosis of COPD Stable COPD for at least 4 weeks prior baseline	Did the study address a clearly focused issue? • Yes Was the cohort recruited in an acceptable way? • Yes Was the exposure accurately measured to minimise bias? • Unclear The Centre for Epidemiologic Studies Depression index was used to detect patients with early-phase depression but it was not reported who did this evaluation Was the outcome accurately measured to minimise bias? • Yes Have the authors identified all important confounding factors? • Unclear Multivariate logistic regression was used

Author (year)	Title	Study details	Quality assessment
		assessments Exclusion criteria • Asthma • Tuberculosis • Respiratory conditions Respiratory tract infection • Sleep apnoea syndrome • Heart disease Chronic heart disease • Cancer Active malignancies of any organ • Pneumoconiosis • Renal or liver failure • Central nervous system disorders Including cerebrovascular disease • Psychological diseases Such as major depression, bipolar disorder, schizophrenia or anxiety • Lung volume reduction surgery • Lung transplantation • Pneumonectomy Sample characteristics • Sample size 85 • %female 9.4% • Mean age (SD) 70.0 years (7.9) • Smoking status Non-smoking: 0; Ex-smoking: 71.8%; Current	but confounders were not reported Have they taken account of the confounding factors in the design and/or analysis? • Unclear Multivariate logistic regression was used but confounders were not reported Was the follow up of subjects complete enough? • Yes Was the follow up of subjects long enough? • Yes Overall risk of bias • Moderate The Centre for Epidemiologic Studies Depression index was used to detect patients with early-phase depression but it was not reported who did this evaluation. Multivariate logistic regression was used but confounders were not reported Directness • Directly applicable

Author (year)	Title	Study details	Quality assessment
		smoking: 28.2%; Smoking index, pack-years mean (SD): 57.2 (31.0) • Previous exacerbations Not reported • FEV1, % predicted (mean, SD) 47.1 (13.9) Predictive factor (s) - Individual factors • Multimorbidities including mental health problems Depression was assessed using the validated Japanese Centre for Epidemiologic Studies Depression scale. Score ≥16 indicates pre- or early-phase depression Outcome(s) • Exacerbations The severity of exacerbations was graded as mild (controlled by inhalation of short-acting β2-agonists or by education), moderate (controlled by treatment with antibiotics or systemic corticosteroids) or severe (requiring hospitalisation, increased use of supplemental oxygen, change in non-invasive positive pressure ventilation mode or resulting in death) Measure(s) • Relative risks Adjusted Covariates for adjustment • Body mass index (BMI) • GOLD stage	

Author (year)	Title	Study details	Quality assessment
		• Non-invasive positive pressure ventilation • Use of inhaled steroids • Long-term oxygen therapy Subgroup analyses • Severity of exacerbations Exacerbations Hospitalisations for exacerbations	
Jing (2016)	Systemic Inflammatory Marker CRP Was Better Predictor of Readmission for AECOPD Than Sputum Inflammatory Markers	Study type • Prospective cohort study Duration of follow-up • 12 months Study details • Study location China • Study setting Respiratory department of a tertiary hospital in Peking • Study dates 2009 to 2011 • Loss to follow-up 33 died before any readmission • Sources of funding Chinese Medical Association Special Fund for Research on Chronic Respiratory Diseases Inclusion criteria • Diagnosis of COPD • AECOPD Exacerbation according to Global Initiative of COLD	Did the study address a clearly focused issue? • Yes Was the cohort recruited in an acceptable way? • Yes Was the exposure accurately measured to minimise bias? • Yes Was the outcome accurately measured to minimise bias? • No Relied on self-report to determine exacerbation Have the authors identified all important confounding factors? • Yes

Author (year)	Title	Study details	Quality assessment
		definition Exclusion criteria • Asthma • Sleep apnoea syndrome • Bronchiectasis • Pneumonia • Cancer • Other Hospitalisation for reasons other than COPD exacerbation including acute coronary syndrome; congestive heart failure; need for intubation; length of stay (LOS) longer than 30 days; long-term oral corticosteroid (CS) therapy (more than 3 months treatment with 7.5 mg per day of prednisone or equivalent); patients who had received systemic CS for their exacerbation for more than 48 h before presentation; relapse within 14 days of initial presentation15; patients who died without being readmitted for an AECOPD during the follow-up period Sample characteristics • Sample size 173 included; 54 excluded after applying exclusion criteria; 33 died during follow-up; 86 participants analysed • %female Sex breakdown only given for sub-groups, range 6.4% to 10.3% • Mean age (SD) Median age (IQR) breakdown only given for sub-	Have they taken account of the confounding factors in the design and/or analysis? • Yes Was the follow up of subjects complete enough? • Yes Over 10% attrition however this was due to death before readmission, as this study had a long follow-up period this was not considered to be risk of bias Was the follow up of subjects long enough? • Yes Overall risk of bias • Moderate Use of self-report in measuring exacerbation Directness • Directly applicable

Author (year)	Title	Study details	Quality assessment
		groups, range 64 years (58 to 70) to 68 years (62 to 80) • Smoking status Smoking status breakdown only given for sub-groups, range; current smokers: 21.3% to 25.6%; pack-years median (IQR): 23 (22 to 33) to 26 (17 to 35) • Previous exacerbations 2 or more exacerbations in previous year breakdown only given for sub-groups, range 33.3% to 59.6% • FEV1, % predicted (mean, SD) FEV1, % predicted median (IQR) breakdown only given for sub-groups, range 46.7 (42 to 54) to 52.5 (43 to 55) Predictive factor (s) - Individual factors • Biomarkers High sensitive C-reactive protein Outcome(s) • Exacerbations On the day of admission, AECOPD Anthonisen type was determined according to the symptoms presented before starting treatment Measure(s) • Odds ratios Adjusted Covariates for adjustment • Age	

Author (year)	Title	Study details	Quality assessment
		• CAT score	
Jo (2017)	Different prevalence and clinical characteristics of asthma-chronic obstructive pulmonary disease overlap syndrome according to accepted criteria	Study type • Prospective cohort study Duration of follow-up • 12 months Study details • Study location Republic of Korea • Study setting Outpatients • Study dates 2013 to 2016 • Loss to follow-up 37 out of 338 • Sources of funding Not reported Inclusion criteria • Age 40 years and older • Diagnosis of COPD Exclusion criteria • Inability or unwillingness to cooperate with the investigators Patients who did not agree to the cohort study • Without available spirometry data	Did the study address a clearly focused issue? • Yes Was the cohort recruited in an acceptable way? • Yes Was the exposure accurately measured to minimise bias? • Yes Was the outcome accurately measured to minimise bias? • Yes Have the authors identified all important confounding factors? • Yes Have they taken account of the confounding factors in the design and/or analysis? • Yes Was the follow up of subjects complete enough? • Yes

Author (year)	Title	Study details	Quality assessment
		Post-bronchodilator spirometry Sample characteristics • Sample size 301 • %female 8.3% • Mean age (SD) 70.9 years (8.7) • Smoking status Pack-year mean (SD): 44.5 (25.4) • Previous exacerbations History of exacerbations during past year: 28.9% • FEV1, % predicted (mean, SD) 66.7 (20.4) Predictive factor (s) - Individual factors • Asthma-COPD ACOS by modified Spanish criteria included 6 diagnostic criteria: major criteria included a previous history of asthma and very positive bronchodilator response (BDR) (>400 mL and >15% in FEV1); minor criteria included an elevated immunoglobulin E (IgE) level (>100 IU/mL) or a history of atopy, positive BDR (>12% and 200mL) on at least 2 occasions, and blood eosinophilia (eosinophil count >5%). Patients had to meet at least 1 major or 2 minor criteria to be diagnosed with ACOS. ACOS by ATS roundtable criteria included 6 diagnostic criteria: major criteria included fixed airflow limitation (post-bronchodilator FEV1/FVC ratio <0.70) in patients older than 40 years, with a smoking amount of more than 10 pack-	Was the follow up of subjects long enough? • Yes Overall risk of bias • Low Directness • Directly applicable

Author (year)	Title	Study details	Quality assessment
		years or equivalent indoor or outdoor air pollution exposure, and a history of asthma diagnosis before 40 years or BDR greater than 400 mL in FEV1; minor criteria included a history of atopy, allergic rhinitis, positive BDR (>12% and 200 mL) on at least 2 occasions, and blood eosinophilia (eosinophil count ≥300 cells/μ). ACOS by PLATINO criteria defined ACOS when patients met both criteria for COPD (post-bronchodilator FEV1/FVC ratio <0.70) and for asthma (subjective wheezing in the last 12 months plus post-bronchodilator increase in FEV1 or FVC of 200 mL and 12%; a history of diagnosed asthma could be an alternative) simultaneously. ACOS by GINA/GOLD criteria suggest tick-box approach to ACOS diagnosis and included clinical characteristics (for example, diagnosis of asthma by a physician) and spirometric feature (for example, a significant BDR); ACOS was diagnosed in patients who satisfied at least 3 items in both the asthma and COPD categories simultaneously. ACOS by the European Respiratory Journal were not defined by Jo (2017) Outcome(s) • Exacerbations Exacerbations were assessed on the basis of self-reported aggravation of respiratory symptoms that required the modification of current treatment during the regular follow-up. Total exacerbations included mild, moderate, and severe exacerbations. Mild exacerbation was defined as and exacerbation event spontaneously resolved without medication; moderate exacerbation was defined as an exacerbation that	

Author (year)	Title	Study details	Quality assessment
		required a visit to an outpatient clinic and treatment with short-term systemic corticosteroids or antibiotics; and severe exacerbation was defined as an exacerbation event that required a visit to the emergency department or hospitalisation Measure(s) • Hazard ratios Adjusted Covariates for adjustment • Age • Exacerbations in the previous year Frequency of total exacerbations in the past year before enrolment • Body mass index (BMI) • Sex • FEV1 Initial FEV1 • Use of inhaled steroids or long-acting β2-agonist Subgroup analyses • Severity of exacerbations Moderate to severe exacerbation; Total exacerbation (mild, moderate, and severe exacerbations)	
Jung (2015)	Relationship of vitamin D status with lung function and exercise capacity in COPD	Study type • Prospective cohort study	Did the study address a clearly focused issue? • Yes

Author (year)	Title	Study details	Quality assessment
		Duration of follow-up • More than 12 months At least 3 years in 70% of patients Study details • Study location South Korea • Study setting Participants from the Korean Obstructive Lung Disease cohort covering 17 hospitals across South Korea • Study dates 2005 to 2011 • Loss to follow-up None reported • Sources of funding Supported by a grant of the Korea Healthcare technology R&D Project, Ministry of Health and Welfare (HI10C2020 and A102065) and Handok, Inc. (4-2013-0645). Inclusion criteria • Age Over 40 years of age • Diagnosis of COPD • Smoking 10 or greater pack years smoking history • FEV1:FVC ratio <0.7 • Abnormal chest radiography No or minimal abnormality	Was the cohort recruited in an acceptable way? • Yes Was the exposure accurately measured to minimise bias? • Yes Was the outcome accurately measured to minimise bias? • Yes Have the authors identified all important confounding factors? • Yes Have they taken account of the confounding factors in the design and/or analysis? • Yes Was the follow up of subjects complete enough? • Yes Was the follow up of subjects long enough? • Yes

Author (year)	Title	Study details	Quality assessment
		Exclusion criteria • None reported Sample characteristics • Sample size 193 • %female Not reported • Mean age (SD) Mean age breakdown only given for sub-groups, range 66.1 years (7.3) to 66.9 years (5.6) • Smoking status Smoking status breakdown only given for sub-groups, range; ever smoker: 40.0% to 60.0%; never smoker: 27.5% to 72.5%; pack-years mean (SD): 47.9 (25.4) to 51.7 (31.5) • Previous exacerbations Not reported • FEV1, % predicted (mean, SD) FEV1, % predicted breakdown only given for sub-groups, range 57.9 (18.1) to 64.4 (19.3) Predictive factor (s) - Individual factors • Biomarkers Plasma 25-hydroxy vitamin D3 (25-OH-VitD3): normal (≥30 ng/mL), insufficiency (20 to <30 ng/mL) or deficiency (<20 ng/mL). The non-deficiency group included the normal and insufficiency groups Outcome(s) • Exacerbations Exacerbation was defined as a ≥2-day aggravation of	Overall risk of bias • Low Directness • Directly applicable

Author (year)	Title	Study details	Quality assessment
		one of three symptoms (cough, sputum and breathlessness) requiring an unscheduled hospital visit or hospitalisation for additional treatment. Frequent exacerbation was defined as having two or more exacerbations per year Measure(s) • Odds ratios Adjusted Covariates for adjustment • Age • Smoking intensity Pack years • Body mass index (BMI) • Sex • FEV1, % predicted Subgroup analyses • Frequency of exacerbations 1 exacerbation per year; ≥2 exacerbations per year	
Keene (2017)	Biomarkers Predictive of Exacerbations in the SPIROMICS and COPDGene Cohorts	Study type • Prospective cohort study Duration of follow-up • More than 12 months Mean 4.04 years in COPDGene cohort; mean 2.28 years in SPIROMICS cohort	Did the study address a clearly focused issue? • Yes Was the cohort recruited in an acceptable way? • Yes Pool from two separate studies, each with differing follow-up protocols however

Author (year)	Title	Study details	Quality assessment
		Study details • Study location US • Study setting Participants from the COPDGene and SPIROMICS studies taking place in various institutions across the US • Study dates 2011 to 2015 • Loss to follow-up Not reported • Sources of funding Supported by NHLBI and National Centre for Research Resources/National Institutes of Health Inclusion criteria • Age 45-80 years • Previous exacerbations No acute respiratory exacerbation for at least 30 days • Smoking at least 10 pack years smoking history Sample characteristics • Sample size 2,146 • %female COPDGene cohort 49%; SPIROMICS cohort 45% • Mean age (SD) COPDGene cohort 63.6 years (8.6); SPIROMICS cohort 64.5 years (8.8) • Smoking status	these were entered separately into analysis Was the exposure accurately measured to minimise bias? • Yes Was the outcome accurately measured to minimise bias? • No Relied on self-reported worsening of symptoms and/or medication increases Have the authors identified all important confounding factors? • Yes Have they taken account of the confounding factors in the design and/or analysis? • Yes Was the follow up of subjects complete enough? • Unclear Unclear dropout rate Was the follow up of subjects long enough? • Yes

Author (year)	Title	Study details	Quality assessment
		COPDGene cohort 25% current smoker; SPIROMICS cohort 38% current smoker • Previous exacerbations COPDGene cohort 30% experienced one or more exacerbations in last year; SPIROMICS cohort 24% experienced one or more exacerbations in last year • FEV1, % predicted (mean, SD) COPDGene cohort 68 (30); SPIROMICS cohort 73 (26) Predictive factor (s) - Individual factors • Biomarkers A1AT: α1-Antitrypsin APOA4: apolipoprotein A-IV CCL11: eotaxin-1 CCL13: monocyte chemotactic protein 4 HGF: hepatocyte growth factor IgA: immunoglobulin A IL1RN: interleukin-1 receptor antagonist MDK: midkine SHBG: sex hormone-binding globulin SORT1: sortilin TNFRSF10C: TNF-related apoptosis-inducing ligand receptor 3 Outcome(s) • Exacerbations An exacerbation was recorded when a patient reported a worsening of their respiratory status and were treated with antibiotics and/or systemic steroids for the episode irrespective of their treatment location. The total number of exacerbations was the total number of these events reported. A severe exacerbation was a report of visiting an emergency room and/or hospitalisation for an acute episode of respiratory disease	Overall risk of bias • Moderate Unclear loss to follow-up and use of self-report in measuring outcome Directness • Directly applicable

Author (year)	Title	Study details	Quality assessment
		Measure(s) • Odds ratios Adjusted Covariates for adjustment • Age • Exacerbations in the previous year History of prior exacerbation • Sex • Current smoking status • FEV1, % predicted • History of gastro-oesophageal reflux Self-reported gastro-oesophageal reflux • St. George's Respiratory Questionnaire (SGRQ) • Exposure time Subgroup analyses • Frequency of exacerbations Number of exacerbations: 0, 1, or ≥2	
Kim (2016)	Factors associated with exacerbation in mild-to-moderate COPD patients	Study type • Prospective cohort study Duration of follow-up • More than 12 months Mean 22.3 months Study details • Study location Korea • Study setting	Did the study address a clearly focused issue? • Yes Was the cohort recruited in an acceptable way? • Yes Was the exposure accurately measured to minimise bias?

Author (year)	Title	Study details	Quality assessment
		37 Korean tertiary referral hospitals • Study dates Not reported • Loss to follow-up Not reported • Sources of funding None reported Inclusion criteria • Age over 40 years • Diagnosis of COPD • GOLD stage I-II • FEV1:FVC ratio <0.7 • Other Presence of respiratory symptoms such as cough, sputum, and breathlessness Exclusion criteria • Asthma • Tuberculosis Tuberculosis-destroyed lungs • Other Receiving medication for any respiratory disease mimicking COPD (E.g. bronchiectasis) Sample characteristics • Sample size 570 • %female	• Yes Was the outcome accurately measured to minimise bias? • Yes Have the authors identified all important confounding factors? • Yes Have they taken account of the confounding factors in the design and/or analysis? • Unclear Unclear whether any comorbidities, age and sex were controlled for in analysis Was the follow up of subjects complete enough? • Yes Was the follow up of subjects long enough? • Unclear Unclear follow-up procedure with only the mean follow-up length given Overall risk of bias • Moderate Unclear follow-up procedure and lack of

Author (year)	Title	Study details	Quality assessment
		9.6% • Mean age (SD) 69.8 years (7.8) • Smoking status Smoking amount in pack years mean (SD): 43.8 (24.3) • Previous exacerbations 20% experienced acute exacerbation a year prior • FEV1, % predicted (mean, SD) Post-bronchodilator 66.0 (11.6) Predictive factor (s) - Individual factors • Multimorbidities including mental health problems History of pneumonia Hyperlipidaemia Outcome(s) • Exacerbations Exacerbation was defined as worsening of one of the respiratory symptoms, such as an increase in sputum volume, purulence, or breathlessness, necessitating treatment with systemic corticosteroids, antibiotics, or both. Moderate exacerbation was defined as requiring a visit to the emergency room. Severe exacerbation was defined as requiring hospitalisation Measure(s) • Odds ratios Adjusted Covariates for adjustment • Exacerbations in the previous year	clarity regarding confounding factors Directness • Directly applicable

Author (year)	Title	Study details	Quality assessment
		Previous exacerbation history • St. George's Respiratory Questionnaire (SGRQ) • Modified Medical Research Council (MMRC) dyspnoea score • CAT score • History of pneumonia • Allergic rhinitis • Hyperlipidaemia	
Koul (2015)	Contribution of influenza to acute exacerbations of chronic obstructive pulmonary disease in Kashmir, India, 2010-2012	Study type • Prospective cohort study Duration of follow-up • 1 month Study details • Study location India • Study setting Single tertiary hospital • Study dates 2010 to 2012 • Loss to follow-up 30-day readmission data not available for 181 participants • Sources of funding No funding Inclusion criteria • Age At least 40 years old	Did the study address a clearly focused issue? • Yes Was the cohort recruited in an acceptable way? • Yes Was the exposure accurately measured to minimise bias? • No Influenza was checked for at point of hospitalisation Was the outcome accurately measured to minimise bias? • Yes Have the authors identified all important confounding factors? • Yes

Author (year)	Title	Study details	Quality assessment
		• Diagnosis of COPD • AECOPD 2 or more major symptoms (increased breathlessness, sputum purulence, or sputum amount) or; or 1 or more major AND one or more minor symptom(s) (nasal discharge/congestion, wheezing, sore throat, or cough), for 2 or more consecutive days Exclusion criteria • None reported Sample characteristics • Sample size 498 • %female 38% • Mean age (SD) Mean not given; 81% were 60 years and older • Smoking status Current smoker: 13% • Previous exacerbations Not reported • FEV1, % predicted (mean, SD) Not reported Predictive factor (s) - Individual factors • Viral/bacterial infection Influenza	Have they taken account of the confounding factors in the design and/or analysis? • Yes Was the follow up of subjects complete enough? • Unclear 30-day readmission rates unavailable for high number of participants; unclear drop-out rate for rest of study Was the follow up of subjects long enough? • Yes Overall risk of bias • High High attrition rate and exposure checked for on admission rather than following patients with influenza prospectively Directness • Directly applicable

Author (year)	Title	Study details	Quality assessment
		Outcome(s) • Exacerbations AECOPD was defined as ≥2 major symptoms (increased breathlessness, sputum purulence, or sputum amount) or ≥1 major and ≥1 minor symptom (nasal discharge/congestion, wheezing, sore throat, or cough) for ≥2 consecutive days in a patient with COPD Measure(s) • Odds ratios Adjusted Covariates for adjustment • Age • Comorbidity Comorbid conditions	
Lahousse (2017)	Epidemiology and impact of chronic bronchitis in chronic obstructive pulmonary disease	Study type • Prospective cohort study Duration of follow-up • More than 12 months Median 6.5 years Study details • Study location The Netherlands • Study setting Embedded within the Rotterdam population-based cohort study	Did the study address a clearly focused issue? • Yes Was the cohort recruited in an acceptable way? • Yes Was the exposure accurately measured to minimise bias? • Yes

Author (year)	Title	Study details	Quality assessment
		• Study dates 1989 to 2013 • Loss to follow-up None reported • Sources of funding The Rotterdam Study is supported by several institutions. These sources had no involvement in the collection, analysis, writing, interpretation, or in the decision to submit the paper for publication Inclusion criteria • Diagnosis of COPD Based on FEV1:FVC ratio or failing this, based on physician or GP diagnosis using clinical history, physical examination and spirometry • FEV1:FVC ratio <0.7 • Other Completed questionnaire on chronic bronchitis between 2001 and 2008 Exclusion criteria • None reported Sample characteristics • Sample size 972 • %female Sex breakdown only given for sub-groups; range 44.2% to 49.5% • Mean age (SD) Mean age breakdown only given for sub-groups;	Was the outcome accurately measured to minimise bias? • Yes Have the authors identified all important confounding factors? • Yes Have they taken account of the confounding factors in the design and/or analysis? • Yes Was the follow up of subjects complete enough? • Yes Was the follow up of subjects long enough? • Yes Overall risk of bias • Low Directness • Directly applicable

Author (year)	Title	Study details	Quality assessment
		range 70.5 years (15.2) and 74.1 years (13.6) • Smoking status Smoking status breakdown only given for sub-groups; range; never-smokers: 9.9% to 17.8%; former smokers: 51.7% to 54.1%; current smokers: 28.1% to 38.4% • Previous exacerbations Not reported • FEV1, % predicted (mean, SD) FEV1, % predicted breakdown only given for sub-groups; range 70.5 (27.8) to 82.0 (26.7) Predictive factor (s) - Individual factors • Multimorbidities including mental health problems Chronic bronchitis was assessed by questionnaire and defined as having a productive cough for ≥3 months a year during the past 2 years. All subjects were questioned [1] Did you cough nearly daily for three consecutive months during the last 2 years? and [2] Did you cough up phlegm nearly daily for three consecutive months during the last 2 years? Subjects answering negatively to the second question were defined as having no chronic phlegm production (CB−). Subjects answering positively to the second question were considered to have chronic phlegm production, but were only defined as having chronic bronchitis when they answered both questions positively (CB+) Outcome(s) • Exacerbations Moderate COPD exacerbations were defined as acute	

Author (year)	Title	Study details	Quality assessment
		episodes of worsening symptoms needing a course of steroids and/or antibiotics. Complete information on all filled prescriptions on a day-to-day basis was obtained in automated format from pharmacies and further validated. Severe COPD exacerbations were defined as exacerbations requiring a hospitalisation due to COPD. All hospital admissions were continuously registered in the Dutch medical registry and further validated. COPD subjects with frequent exacerbations were determined as subjects who had at least two (rounded) moderate or severe exacerbations on average per year during follow-up Measure(s) • Odds ratios Adjusted Covariates for adjustment • Sex • Chronic bronchitis Yes vs. no	
Lambert (2015)	HIV Infection Is Associated With Increased Risk for Acute Exacerbation of COPD	Study type • Prospective cohort study Duration of follow-up • More than 12 months Mean 1.5 years Study details • Study location	Did the study address a clearly focused issue? • Yes Was the cohort recruited in an acceptable way? • No Identified via study of current or former injection drug users at-risk or with HIV

Author (year)	Title	Study details	Quality assessment
		US • Study setting Community based: Baltimore, US • Study dates Ongoing since 1988 • Loss to follow-up None reported • Sources of funding Not reported Inclusion criteria • Diagnosis of COPD Defined as FEV1:FVC ratio • FEV1:FVC ratio <0.7 Exclusion criteria • None reported Sample characteristics • Sample size 167 • %female 30% • Mean age (SD) 52.4 years (8.1) • Smoking status Current smokers: 90%; former smokers: 8%; never smoker: 2% • Previous exacerbations Not reported • FEV1, % predicted (mean, SD)	infection and therefore excludes other HIV patients or those at-risk Was the exposure accurately measured to minimise bias? • Yes Was the outcome accurately measured to minimise bias? • Yes Have the authors identified all important confounding factors? • Yes Have they taken account of the confounding factors in the design and/or analysis? • Yes Was the follow up of subjects complete enough? • Yes Was the follow up of subjects long enough? • Unclear Variable follow-up length

Author (year)	Title	Study details	Quality assessment
		74.0 (21) Predictive factor (s) - Individual factors • Multimorbidities including mental health problems Human immunodeficiency virus (HIV) infection was classified as: HIV-Infected Serostatus HIV-Infected RNA HIV-Infected CD4 count Outcome(s) • Exacerbations AECOPD was defined as answering 'yes' to the question 'In the last 6 months, have you had a worsening of your breathing status requiring treatment with antibiotics or steroids?' Measure(s) • Odds ratios Adjusted Covariates for adjustment • Age per 10 year increase • Exacerbations in the previous year Prior acute exacerbation in 6 months • Smoking intensity Smoking pack-years • Sex • FEV1, % predicted Mild (>or=80%) vs. moderate (50-79%) vs. severe (<50%) • Comorbidity	Overall risk of bias • Low Directness • Partially applicable Participants identified via study of current or former injection drug users at-risk or with HIV infection and therefore excludes other HIV patients or those at-risk

Author (year)	Title	Study details	Quality assessment
		'Yes' compared to 'No' any of following comorbidities in last 6 months (diabetes, hypertension, hyperlipidaemia, heart disease, renal disease, seizures disorder, stroke or cancer) Subgroup analyses • HIV breakdown HIV serostatus, HIV RNA and CD4 count	
Lange (2016)	Long-term prognosis of asthma, chronic obstructive pulmonary disease, and asthma-chronic obstructive pulmonary disease overlap in the Copenhagen City Heart study: a prospective population-based analysis	Study type • Prospective cohort study Duration of follow-up • More than 12 months 22 years Study details • Study location Denmark • Study setting Participants in the Copenhagen City Heart Study • Study dates 1991 to 2014 • Loss to follow-up 9 out of 590 • Sources of funding Capital Region of Copenhagen; Danish Heart Foundation; Danish Lung Foundation; Velux Foundation; AstraZeneca	Did the study address a clearly focused issue? • Yes Was the cohort recruited in an acceptable way? • Yes Was the exposure accurately measured to minimise bias? • Yes Was the outcome accurately measured to minimise bias? • No Acute hospital admissions for COPD and asthma were taken from the national Danish Patient Registry Have the authors identified all important confounding factors? • Unclear

Author (year)	Title	Study details	Quality assessment
		Sample characteristics • Sample size 590 • %female Sex breakdown only given for subgroups; range 34 to 54% • Mean age (SD) Mean age breakdown only given for subgroups; range 57 years (14) to 68 years (8) • Smoking status Smoking status breakdown only given for subgroups; range; Never: 0 to 18% Former: 16 to 35% Current: 62 to 84% Smoking history pack-years mean (SD): 23 (23) to 45 (22) • Previous exacerbations Not reported • FEV1, % predicted (mean, SD) FEV1, % predicted breakdown only given for subgroups; range 51 (19) to 69 (18) Predictive factor (s) - Individual factors • Asthma-COPD COPD • post-bronchodilatatory FEV1 to FVC ratio <0.70 • >10 pack-years of tobacco smoking • no self-reported asthma • improvement of <200 mL in FEV1 after inhalation of 1 mg terbutaline from a Turbuhaler Asthma • current self-reported asthma • ≤10 pack-years of tobacco smoking • pre-bronchodilatatory FEV1 to FVC ratio of at least 0.70 Asthma-COPD overlap with early-onset asthma • current self-reported asthma with onset before 40 years of age • post-bronchodilatatory FEV1 to FVC ratio <0.70 Asthma-	Covariates were included in analyses but confounding factors were not mentioned Have they taken account of the confounding factors in the design and/or analysis? • Unclear Covariates were included in analyses but confounding factors were not mentioned Was the follow up of subjects complete enough? • Yes Only 1.5% were lost to follow-up Was the follow up of subjects long enough? • Yes Overall risk of bias • Moderate Acute hospital admissions for COPD and asthma were taken from the national Danish Patient Registry. Covariates were included in analyses but confounding factors were not mentioned Directness • Directly applicable

Author (year)	Title	Study details	Quality assessment
		COPD overlap with late-onset asthma • current self-reported asthma with onset after 40 years of age • post-bronchodilatatory FEV1 to FVC ratio <0.70 Outcome(s) • Exacerbations Severe exacerbations of obstructive lung disease were defined as acute hospital admissions (ICD-8 codes 491-493 and ICD-10 codes J41-46) taken from the national Danish Patient Registry Measure(s) • Hazard ratios Adjusted Covariates for adjustment • Age • Body mass index (BMI) • Sex • Pack-years	
Laurin (2009)	Chronic obstructive pulmonary disease patients with psychiatric disorders are at greater risk of exacerbations	Study type • Prospective cohort study Duration of follow-up • More than 12 months 2 years Study details • Study location Canada	Did the study address a clearly focused issue? • Yes Was the cohort recruited in an acceptable way? • Yes Was the exposure accurately measured to minimise bias?

Author (year)	Title	Study details	Quality assessment
		• Study setting Outpatient clinics • Study dates 2003 to 2005 • Loss to follow-up 6 out of 116 • Sources of funding les Fonds de la recherche en Santé du Québec and the Fondation de l'Hôpital du Sacré-Cœur de Montréal Inclusion criteria • Age <85 years • Diagnosis of COPD Confirmed by spirometry • Previous exacerbations Hospitalisation for an exacerbation within the last 24 months • Smoking History smoking ≥10 pack-years • Clinical stable at baseline >4 weeks post-exacerbation Exclusion criteria • Confounding medical condition Considered to be more severe than COPD (for example, symptomatic cancer) • Cognitive deficit • Living accommodations in a long-term healthcare facility	• Yes Was the outcome accurately measured to minimise bias? • Yes Have the authors identified all important confounding factors? • Yes Have they taken account of the confounding factors in the design and/or analysis? • Yes Was the follow up of subjects complete enough? • Yes Was the follow up of subjects long enough? • Yes Overall risk of bias • Low Directness • Directly applicable

Author (year)	Title	Study details	Quality assessment
		Sample characteristics • Sample size 110 • %female Sex breakdown only given for subgroups; range 39% to 63% • Mean age (SD) Mean age breakdown only given for subgroups; range 68 years (8) to 65 years (8) • Smoking status Smoking status breakdown only given for subgroups; range; active smoker: 27 to 30%; pack-years mean (SD): 52 (30) to 60 (36) • Previous exacerbations Not reported • FEV1, % predicted (mean, SD) Not reported Predictive factor (s) - Individual factors • Multimorbidities including mental health problems Patients underwent a structured psychiatric interview using the Anxiety Disorders Interview Schedule (ADIS-IV) to assess anxiety (panic disorder, phobias, generalised anxiety disorder, obsessive compulsive disorder, social phobia, and post-traumatic stress disorder), and mood disorders (for example, major depression, minor depression, dysthymia, bipolar disorder). ADIS-IV criteria for at least 1 current anxiety and/or mood disorder were classified in the psychiatric group, irrespective of whether or not they were currently undergoing psychological treatment. All psychiatric diagnoses were confirmed independently	

Author (year)	Title	Study details	Quality assessment
		by a psychologist blinded to the patient's medical status Outcome(s) • Exacerbations Exacerbation was defined as a significant deterioration in a patient's condition from the stable state and beyond normal day-to-day variations as evidenced by worsening of respiratory symptoms that required changes in usual treatment. 'Outpatient exacerbations' referred to those occurring and treated in the patient's own environment that did not require a hospital visit but required administration of antibiotics and/or oral corticosteroids. 'Inpatient exacerbations' were defined as those COPD events treated in the hospital setting (that is, either an emergency department visit or hospital ward admission). These events needed a physician diagnosis of an exacerbation related to COPD to be included in the study Measure(s) • Relative risks Adjusted Covariates for adjustment • Age • Sex • Current smoking status Pack-years • Comorbidity • COPD duration	

Author (year)	Title	Study details	Quality assessment
		• Disease severity • Recruitment site • Follow-up intervals • Time interval Between past hospitalisation and baseline interview Subgroup analyses • Severity of exacerbations Any first exacerbation First outpatient exacerbation First inpatient exacerbation	
Liang (2013)	Association of gastroesophageal reflux disease risk with exacerbations of chronic obstructive pulmonary disease	Study type • Prospective cohort study Duration of follow-up • 12 months Study details • Study location China • Study setting Pulmonary clinic • Study dates 2010 to 2011 • Loss to follow-up 42 out of 428 • Sources of funding Not reported Inclusion criteria • Age	Did the study address a clearly focused issue? • Yes Was the cohort recruited in an acceptable way? • Yes Was the exposure accurately measured to minimise bias? • Yes Was the outcome accurately measured to minimise bias? • No Exacerbations of COPD were measured with the CAT questionnaire Have the authors identified all important confounding factors?

Author (year)	Title	Study details	Quality assessment
		40 years or older • Diagnosis of COPD • Able to provide written informed consent Exclusion criteria • Asthma • Respiratory conditions Chronic respiratory disorders other than COPD • Unstable respiratory status In the preceding 4 weeks • Alcohol abuse Recent history • Oesophageal disease Including cancer, achalasia and peptic ulcer disease • Comorbidity Any clinically significant concurrent disease Sample characteristics • Sample size 386 • %female Sex breakdown only given for subgroups; range 17.1% to 20.0% • Mean age (SD) Mean age breakdown only given for subgroups; range 64.6 years (7.2) to 65.8 years (8.0) • Smoking status Smoking status: breakdown only given for subgroups; range; Never-smoker: from 11.8 to 14.2%; Ex-smoker: from 26.3 to 29.7%; Current smoker: from 56.1 to 61.8% • Previous exacerbations	• Yes Have they taken account of the confounding factors in the design and/or analysis? • Yes Was the follow up of subjects complete enough? • Yes Was the follow up of subjects long enough? • Yes Overall risk of bias • Moderate Exacerbations of COPD were measured with the CAT questionnaire Directness • Directly applicable

Author (year)	Title	Study details	Quality assessment
		Not reported • FEV1, % predicted (mean, SD) FEV1, % predicted breakdown only given for subgroups; range 52.8 (6.1) to 64.2 (7.0) Predictive factor (s) - Individual factors • Multimorbidities including mental health problems Gastro-oesophageal reflux disease: the Reflux Diagnostic Questionnaire (RDQ) was used to evaluate the risk of gastro-oesophageal reflux disease. The RDQ contains 4 items including heartburn, sub-sternal pain, sour reflux and food regurgitation, and the frequency and severity of symptoms were graded on a 5-point scale giving total score range from 0 to 40. To define high gastro-oesophageal reflux disease risk, RDQ cut-off score of ≥12 was used. Congestive heart failure Outcome(s) • Exacerbations The COPD Assessment Test (CAT) was used to assess COPD exacerbations. The CAT questionnaire has 8 items assessing cough, phlegm, chest tightness, breathlessness going up hills/stairs, activity limitations at home, confidence leaving home, sleep and energy. Each item is scored from 0 to 5, giving a total score range from 0 to 40, corresponding to the best and worst health status in patients with COPD, respectively. Compared with the CAT scores in the stable states, patients with increased scores of 5 points were considered having exacerbations of	

Author (year)	Title	Study details	Quality assessment
		COPD Measure(s) • Odds ratios Adjusted Covariates for adjustment • Body mass index (BMI) • Congestive heart failure • FEV1, % predicted • Respiratory infection	
Lomas (2009)	Serum surfactant protein D is steroid sensitive and associated with exacerbations of COPD	Study type • Prospective cohort study Duration of follow-up • 12 months Study details • Study location Worldwide • Study setting Multiple centres in US, Europe and New Zealand • Study dates 2005 to 2010 • Loss to follow-up Lost to follow-up for COPD cohort alone was not given • Sources of funding Original study conducted by GlaxoSmithKline	Did the study address a clearly focused issue? • Yes Was the cohort recruited in an acceptable way? • Yes Was the exposure accurately measured to minimise bias? • Yes Was the outcome accurately measured to minimise bias? • No Relied on self-report to measure exacerbations

Author (year)	Title	Study details	Quality assessment
		Inclusion criteria • Age 40-75 years • Smoking 10 or greater pack-years smoking history • FEV1:FVC ratio <0.7 Sample characteristics • Sample size 1888 COPD participants • %female 35% • Mean age (SD) 63.4 years (7.2) • Smoking status Current smokers: 40% • Previous exacerbations Not reported • FEV1, % predicted (mean, SD) 48.7 (15.5) Predictive factor (s) - Individual factors • Biomarkers Serum surfactant protein D Outcome(s) • Exacerbations COPD subjects were asked about exacerbations whether they had been unwell, whether they had seen a doctor or been to hospital and whether they had taken any medication for exacerbations (oral	Have the authors identified all important confounding factors? • Yes Have they taken account of the confounding factors in the design and/or analysis? • Yes Was the follow up of subjects complete enough? • Unclear Unclear loss to follow-up Was the follow up of subjects long enough? • Yes Overall risk of bias • Moderate Unclear loss to follow-up and use of self-report in measuring outcome Directness • Directly applicable

Author (year)	Title	Study details	Quality assessment
		corticosteroids or antibiotics) Measure(s) • Odds ratios Adjusted Covariates for adjustment • Sex • FEV1, % predicted • Inhaled corticosteroid Subgroup analyses • Severity of exacerbations At least 1 exacerbation; Exacerbations requiring antibiotics	
Marin (2010)	Outcomes in patients with chronic obstructive pulmonary disease and obstructive sleep apnea: the overlap syndrome	Study type • Prospective cohort study Duration of follow-up • More than 12 months Median 9.4 years Study details • Study location Spain • Study setting Sleep clinic • Study dates 1996 to 2001 • Loss to follow-up	Did the study address a clearly focused issue? • Yes Was the cohort recruited in an acceptable way? • No Based on referrals to sleep clinic therefore all patients had suspected sleep-disordered breathing Was the exposure accurately measured to minimise bias? • Yes

Author (year)	Title	Study details	Quality assessment
		Not reported • Sources of funding Not reported Inclusion criteria • Diagnosis of COPD Exclusion criteria • Cardiovascular conditions History of heart failure, myocardial infarction or stroke Sample characteristics • Sample size 651 • %female Sex breakdown given only for sub-groups; range 6% to 10% • Mean age (SD) Mean age breakdown given only for sub-groups; range 57 years (8) to 58 years (7) • Smoking status Smoking status breakdown given only for sub-groups; range; current smokers: 40% to 42% • Previous exacerbations Previous exacerbations breakdown given only for sub-groups; range 8% to 15% of patients had one or more exacerbations requiring emergency room visit or hospitalisation in 12 months prior to entry to study • FEV1, % predicted (mean, SD) FEV1, % predicted breakdown given only for sub-groups; range 56 (17) to 57 (16)	Was the outcome accurately measured to minimise bias? • No Exacerbation determined by discharge codes suggesting admission with exacerbations Have the authors identified all important confounding factors? • Yes Have they taken account of the confounding factors in the design and/or analysis? • Yes Was the follow up of subjects complete enough? • Yes Was the follow up of subjects long enough? • Yes Overall risk of bias • Moderate Use of diagnostic codes to determine outcome and recruitment via referral to clinic only

Author (year)	Title	Study details	Quality assessment
		Predictive factor (s) - Individual factors • Multimorbidities including mental health problems The degree of comorbidity was quantified using the Charlson index Outcome(s) • Exacerbations Time to a first severe COPD exacerbation, defined as a change in the respiratory condition that required hospital admission. Hospitalisation events were tracked from the Regional Health Resources Utilisation Register. To accurately capture patients who were admitted with exacerbations, only those with discharge codes ICD-9-CM of 491, 492, 493, and 496 were ultimately included for analysis Measure(s) • Relative risks Adjusted Covariates for adjustment • Age • Exacerbations in the previous year • Body mass index (BMI) • Current smoking status • Charlson score • GOLD stage • Alcohol use Yes vs. No	Directness • Partially applicable Only contained those COPD patients with suspected sleep-disordered breathing

Author (year)	Title	Study details	Quality assessment
Martinez (2014)	Impact of self-reported gastroesophageal reflux disease in subjects from COPDGene cohort	Study type • Prospective cohort study Duration of follow-up • More than 12 months Mean 2 years Study details • Study location US • Study setting 21 clinical study centres across US • Study dates Enrolment 2008 to 2011 • Loss to follow-up Not reported • Sources of funding Funded by NHLBI Inclusion criteria • Age 45-80 years • Diagnosis of COPD • GOLD stage stage I or greater • Smoking 10 pack-years cigarette smoking history • FEV1:FVC ratio <0.7 • Other self-defined non-Hispanic white or African-American	Did the study address a clearly focused issue? • Yes Was the cohort recruited in an acceptable way? • Yes Was the exposure accurately measured to minimise bias? • Yes Was the outcome accurately measured to minimise bias? • No Relied on self-report Have the authors identified all important confounding factors? • Yes Have they taken account of the confounding factors in the design and/or analysis? • Yes Was the follow up of subjects complete enough? • Unclear Unclear attrition rate

Author (year)	Title	Study details	Quality assessment
		ancestry and willingness to undergo study-related tests Exclusion criteria • None reported Sample characteristics • Sample size 4,483 • %female 44.1% • Mean age (SD) 63.1 years (8.6) • Smoking status Current smoking: 43.3%; pack-years mean (SD): 51.6 (27.2) • Previous exacerbations Not reported • FEV1, % predicted (mean, SD) 57.4 (22.8) Predictive factor (s) - Individual factors • Multimorbidities including mental health problems Gastro-oesophageal reflux disease was based on self-report. The patient was asked: 'Have you ever been told by a physician that you have...' and a list of different diseases, including GERD Outcome(s) • Exacerbations Symptoms and self-reported acute exacerbation	Was the follow up of subjects long enough? • Unclear Unclear whether there was variance in follow-up length Overall risk of bias • Moderate Use of self-report in outcome measurement and unclear follow-up Directness • Directly applicable

Author (year)	Title	Study details	Quality assessment
		frequency were quantified using a modified version of the ATS Chronic Respiratory Disease Questionnaire (ATS-DLD-78) with the question: 'Have you had a flare-up of your chest trouble in the last 12 months?' If the answer was 'No', zero exacerbations were recorded, and when the answer was 'Yes', additional questions on the presence, severity, management and number of exacerbations followed. Exacerbations were dichotomised on 'frequent or infrequent', based on the definition of ≥2 exacerbation per year Measure(s) • Odds ratios Adjusted Covariates for adjustment • Age • Body mass index (BMI) • Sex • Current smoking status • FEV1, % predicted	
Miravitlles (2001)	Factors associated with relapse after ambulatory treatment of acute exacerbations of chronic bronchitis. DAFNE Study Group	Study type • Prospective cohort study Duration of follow-up • 1 month Study details • Study location Spain	Did the study address a clearly focused issue? • Yes Was the cohort recruited in an acceptable way? • Yes

Author (year)	Title	Study details	Quality assessment
		• Study setting 268 practices • Study dates 1996 to 1997 • Loss to follow-up Not reported • Sources of funding None reported Inclusion criteria • Bronchitis Acute exacerbated chronic bronchitis Exclusion criteria • Asthma • Cystic fibrosis • Bronchiectasis If severe Sample characteristics • Sample size 2,414 • %female 25.8% • Mean age (SD) 67.1 years (10.3) • Smoking status Active smokers: 20.1% • Previous exacerbations Exacerbations previous year mean (SD): 3.0 (2.2) • FEV1, % predicted (mean, SD)	Was the exposure accurately measured to minimise bias? • Yes Was the outcome accurately measured to minimise bias? • Yes Have the authors identified all important confounding factors? • Yes Have they taken account of the confounding factors in the design and/or analysis? • Yes Was the follow up of subjects complete enough? • Yes Was the follow up of subjects long enough? • No Short (1 month) follow up Overall risk of bias • Moderate Short follow-up (1 month)

Author (year)	Title	Study details	Quality assessment
		Not reported Predictive factor (s) - Individual factors • Multimorbidities including mental health problems Ischemic heart disease Outcome(s) • Exacerbations Diagnosis of acute exacerbation was based on the presence of any combination of the following symptoms: increased breathlessness, increased production and purulence of sputum which led to a change or increase in treatment. Severity of the exacerbation was classified using Anthonisen criteria: exacerbations presenting with any one of the previously mentioned symptoms were classified as type 3, those with two symptoms as type 2, and those with all three symptoms as type 1 Measure(s) • Odds ratios Adjusted Covariates for adjustment • Exacerbations in the previous year Visits to GP in last year • Chronic bronchitis Degree of breathlessness • Ischaemic heart disease	Directness • Partially applicable Specifically acute exacerbated chronic bronchitis

Author (year)	Title	Study details	Quality assessment
Montserrat-Capdevila (2016)	Risk factors for exacerbation in chronic obstructive pulmonary disease: a prospective study	Study type • Prospective cohort study • Additional comments Same study population as Montserrat-Capdevila (2017) but different factors; outcome was reported differently as well Duration of follow-up • More than 12 months 2 years Study details • Study location Spain • Study setting Primary care • Study dates 2013 to 2014 • Loss to follow-up None reported • Sources of funding Not reported Inclusion criteria • Age over 40 years • Diagnosis of COPD According to 2014 GOLD guidelines • FEV1:FVC ratio <0.7	Did the study address a clearly focused issue? • Yes Was the cohort recruited in an acceptable way? • Yes Was the exposure accurately measured to minimise bias? • Yes Was the outcome accurately measured to minimise bias? • Yes Have the authors identified all important confounding factors? • Yes Have they taken account of the confounding factors in the design and/or analysis? • Yes Was the follow up of subjects complete enough? • Yes Was the follow up of subjects long enough?

Author (year)	Title	Study details	Quality assessment
		Exclusion criteria • Without available spirometry data • Spirometry Spirometric criteria were not fulfilled Sample characteristics • Sample size 512 • %female 26.8% • Mean age (SD) 69.5 years (12.2) • Smoking status Non-smokers: 33.2%; ex-smokers: 47.5%; smokers: 19.3% • Previous exacerbations Not reported • FEV1, % predicted (mean, SD) 65.2 (18.4) Predictive factor (s) - Individual factors • Smoking Smoker or ex-smoker • Multimorbidities including mental health problems Comorbidity evaluated using the Charlson Comorbidity Index, where absence of comorbidity: 0 to 1, low comorbidity: 2 and high comorbidity: ≥3. Depression as defined by the 2010 Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) Outcome(s) • Exacerbations	• Yes Overall risk of bias • Low Directness • Directly applicable

Author (year)	Title	Study details	Quality assessment
		Exacerbation included exacerbations that needed hospital admission and exacerbations that needed treatment with antibiotics and/or steroids. If two treatments with antibiotics and/or steroids were separated in time by at least 1 month, they were considered two different exacerbation episodes. The number of exacerbations was calculated for each patient for each year, and patients were then classified into three groups: 1) very frequent exacerbators, if the number of exacerbations was ≥3; 2) patients with 1 or 2 exacerbation episodes; and 3) patients who did not present any exacerbation episodes. Exacerbations were then classified as moderate (treatment with antibiotics and/or corticosteroids) or serious (hospitalisation) exacerbation Measure(s) • Odds ratios Adjusted Covariates for adjustment • Sex • Current smoking status • Charlson score • Depression • Previous hospital admission for COPD exacerbation • Breathlessness Medical Research Council dyspnoea scale (mMRC) scores of 1 or 2 or 3 to 4 • FVC	

Author (year)	Title	Study details	Quality assessment
		Subgroup analyses • Frequency of exacerbations 1 to 2 exacerbations; ≥3 exacerbations	
Montserrat-Capdevila (2017)	Overview of the Impact of Depression and Anxiety in Chronic Obstructive Pulmonary Disease	Study type • Prospective cohort study • Additional comments Same study population as Montserrat-Capdevila (2016) but different factors; outcome was reported differently as well Duration of follow-up • More than 12 months 2 years Study details • Study location Spain • Study setting Primary care • Study dates 2013 to 2014 • Loss to follow-up None • Sources of funding Not reported Inclusion criteria • Age ≥40 years • Diagnosis of COPD	Did the study address a clearly focused issue? • Yes Was the cohort recruited in an acceptable way? • Yes Was the exposure accurately measured to minimise bias? • No Anxiety and depression were measured using a questionnaire Was the outcome accurately measured to minimise bias? • Yes Have the authors identified all important confounding factors? • Unclear Adjustment was done but confounding factors were not mentioned Have they taken account of the confounding factors in the design and/or analysis?

Author (year)	Title	Study details	Quality assessment
		According to 2014 GOLD guidelines • FEV1:FVC ratio <0.7 Exclusion criteria • Without available spirometry data • Spirometry Spirometric criteria were not fulfilled Sample characteristics • Sample size 512 • %female 26.8% • Mean age (SD) 69.5 years (12.2) • Smoking status Non-smokers: 33.2% Smoking cessation: 47.5% Smoker: 19.3% • Previous exacerbations At least 1 exacerbation the previous year: 5.7% • FEV1, % predicted (mean, SD) 65.2 (18.4) Predictive factor (s) - Individual factors • Multimorbidities including mental health problems The Hospital Anxiety and Depression scale (HAD) was used to categorise all patients into 2 cohorts depending on the results (positive/negative for anxiety/depression). The cut-off point of 10 was used to differentiate between presence or absence of	• Unclear Adjustment was done but confounding factors were not mentioned Was the follow up of subjects complete enough? • Yes Was the follow up of subjects long enough? • Yes Overall risk of bias • Moderate Anxiety and depression were measured using a questionnaire. Adjustment was done but confounding factors were not mentioned Directness • Directly applicable

Author (year)	Title	Study details	Quality assessment
		anxiety and depression. Comorbidity evaluated using the Charlson Comorbidity Index, where absence of comorbidity: 0 to 1, low comorbidity: 2 and high comorbidity: ≥3. Obese: body mass index (BMI) ≥30 kg/m2 Overweight: BMI 25 to 30 kg/m2 Normal: BMI <25 kg/m2 Diabetes Outcome(s) • Exacerbations Exacerbation included exacerbations that needed hospital admission and exacerbations that needed treatment with antibiotics and/or steroids. If two treatments with antibiotics and/or steroids were separated in time by at least 1 month, they were considered two different exacerbation episodes. The number of exacerbations was calculated for each patient for each year, and patients were then classified into three groups: 1) very frequent exacerbators, if the number of exacerbations was ≥2; 2) patients with 1 exacerbation episode; and 3) patients who did not present any exacerbation episodes. Exacerbations were then classified as moderate (treatment with antibiotics and/or corticosteroids) or serious (hospitalisation) exacerbation Measure(s) • Odds ratios Adjusted Covariates for adjustment • Body mass index (BMI)	

Author (year)	Title	Study details	Quality assessment
		Obesity Overweight • Body mass, airflow obstruction, dyspnoea and exercise capacity (BODE) index • Comorbidity Charlson index • Diabetes Subgroup analyses • Frequency of exacerbations 1 exacerbation ≥2 exacerbations	
Mullerova (2015)	Hospitalized exacerbations of COPD: risk factors and outcomes in the ECLIPSE cohort	Study type • Prospective cohort study Duration of follow-up • More than 12 months 3 years Study details • Study location Bulgaria, Canada, Czech Republic, Denmark, Netherlands, New Zealand, Norway, Slovenia, Spain, Ukraine, UK, US • Study setting Not reported • Study dates 2005 to 2010 • Loss to follow-up 173 out of 2138 • Sources of funding	Did the study address a clearly focused issue? • Yes Was the cohort recruited in an acceptable way? • Yes Was the exposure accurately measured to minimise bias? • Unclear Emphysema was identified by CT scan but history of asthma was identified by self-report Was the outcome accurately measured to minimise bias? • Yes

Author (year)	Title	Study details	Quality assessment
		GlaxoSmithKline Inclusion criteria • Age 40 to 75 years old • GOLD stage • Smoking History of ≥10 pack-years of smoking • FEV1:FVC ratio ≤0.7 • FEV1, predicted <80% Exclusion criteria • None reported Sample characteristics • Sample size 2138 • %female 35% • Mean age (SD) 63 years (7) • Smoking status Current smoker: 36% • Previous exacerbations Any exacerbation, 12 months prior to baseline visit: 47% Hospitalised exacerbation, 12 months prior to baseline visit: 15% • FEV1, % predicted (mean, SD) 48 (16)	Have the authors identified all important confounding factors? • Yes Have they taken account of the confounding factors in the design and/or analysis? • Yes Was the follow up of subjects complete enough? • Yes Was the follow up of subjects long enough? • Yes Overall risk of bias • Moderate History of asthma was identified by self-report Directness • Directly applicable

Author (year)	Title	Study details	Quality assessment
		Predictive factor (s) - Individual factors • Multimorbidities including mental health problems Emphysema by CT scan: 0= no emphysema, 1= trivial (<5%), 2= mild (5% to 25%), 3= moderate (26% to 50%), 4= severe (51% to 75%), 5= very severe (≥75% involvement of both lungs). History of asthma was self-reported Outcome(s) • Exacerbations Hospitalised exacerbations were defined as those exacerbation episodes that required hospital admission. This information was based on subjects' recall of exacerbation events or available medical records for exacerbation events, supplemented by monthly phone calls Measure(s) • Hazard ratios Adjusted Covariates for adjustment • Exacerbations in the previous year History of hospitalised exacerbations • Sex • Current smoking status	
Papaioannou (2013)	The impact of depressive symptoms on recovery and outcome of hospitalised COPD exacerbations	Study type • Prospective cohort study	Did the study address a clearly focused issue? • Yes

Author (year)	Title	Study details	Quality assessment
		Duration of follow-up • 12 months Study details • Study location Greece • Study setting Two tertiary hospitals • Study dates 2009 to 2011 • Loss to follow-up 44 out of 274 • Sources of funding None reported Inclusion criteria • Diagnosis of COPD • Smoking Smoking history of at least 20 pack-years • AECOPD According to GOLD definition Exclusion criteria • Respiratory conditions Any alternative diagnosis of another acute respiratory condition; or history of respiratory disorders other than COPD • Inability or unwillingness to cooperate with the investigators • Without available spirometry data • Other	Was the cohort recruited in an acceptable way? • Yes Was the exposure accurately measured to minimise bias? • Yes Was the outcome accurately measured to minimise bias? • Yes Have the authors identified all important confounding factors? • Yes Have they taken account of the confounding factors in the design and/or analysis? • Yes Was the follow up of subjects complete enough? • No Over 10% lost to follow up Was the follow up of subjects long enough? • Yes

Author (year)	Title	Study details	Quality assessment
		History of depression treated with antidepressants Sample characteristics • Sample size 274 participants; 230 analysed • %female 11.7% • Mean age (SD) 71.2 years (8.8) • Smoking status Current smokers: 32.6% • Previous exacerbations AECOPD per patient year prior mean (SD): 2.6 (2.2); hospitalisations per patient year prior mean (SD): 1.02 (1.14) • FEV1, % predicted (mean, SD) 52.8 (20.1) Predictive factor (s) - Individual factors • Multimorbidities including mental health problems The presence of depressive symptoms was assessed with the original Beck's depression inventory (BDI). This is a 21-item self-administered rating inventory measuring attitudes and symptoms of depression. The optimal cut-off score was ≥19, which distinguished patients with minimal or mild depressive symptoms from patients with moderate or severe depressive symptoms Outcome(s) • Exacerbations AECOPD was defined as the need for use of	Overall risk of bias • Moderate Over 10% lost to follow up Directness • Directly applicable

Author (year)	Title	Study details	Quality assessment
		antibiotics and/or systemic corticosteroids on an outpatient basis, whereas the recorded hospitalisations were the ones related to AECOPD Measure(s) • Relative risks Relative risks were calculated using raw data Covariates for adjustment • Age • Body mass index (BMI) • Sex • Current smoking status • Charlson score • GOLD stage • Modified Medical Research Council (MMRC) dyspnoea score • Depression Depressive symptoms Subgroup analyses • Severity of exacerbations AECOPD; Hospitalised AECOPD	
Park (2015)	Menthol cigarette smoking in the COPDGene cohort: relationship with COPD, comorbidities and CT metrics	Study type • Prospective cohort study Duration of follow-up • More than 12 months Mean 1.49 years	Did the study address a clearly focused issue? • Yes Was the cohort recruited in an acceptable way?

Author (year)	Title	Study details	Quality assessment
		Study details • Study location US • Study setting Current smokers taking part in the COPDGene study • Study dates Not reported • Loss to follow-up Not reported • Sources of funding Chonbuk National University and Biomedical Research Institute, Chonbuk National University Hospital Inclusion criteria • Age 45-80 years • Diagnosis of COPD • GOLD stage stage I or higher • Smoking 10 or greater pack-year smoking history • FEV1:FVC ratio <0.7 Exclusion criteria • None reported Sample characteristics • Sample size 3,772 participating in the longitudinal follow-up • %female	• No Was the exposure accurately measured to minimise bias? • Yes Was the outcome accurately measured to minimise bias? • No Relied on self-report Have the authors identified all important confounding factors? • Yes Have they taken account of the confounding factors in the design and/or analysis? • Yes Was the follow up of subjects complete enough? • Yes Was the follow up of subjects long enough? • Yes Wide range of follow-up length however this follow-up length was controlled for in negative binomial regression model

Author (year)	Title	Study details	Quality assessment
		Sex breakdown only given for subgroups; range 43.8% to 45.3% • Mean age (SD) Mean age breakdown only given for subgroups; range 54.4 years (6.9) to 58.2 years (8.0) • Smoking status Pack-years mean (SD) breakdown only given for subgroups; range 41.1 (22.3) to 46.5 (24.7) • Previous exacerbations Not reported • FEV1, % predicted (mean, SD) FEV1, % predicted breakdown only given for subgroups; range 77.1 (23.4) to 82.5 (21.8) Predictive factor (s) - Individual factors • Smoking Subjects were asked whether they currently smoked. If the subject answered yes, they were asked 'Do you now smoke or did you smoke menthol cigarettes?' Subjects were placed in the group of menthol cigarette smokers if they answered yes and in the group of non-menthol cigarette smokers if they answered no Outcome(s) • Exacerbations Total exacerbations of COPD were self-reported and quantified by the sum of episodes of emergency room visits, hospitalisations, and treatment with antibiotics or systemic glucocorticoids for lung problems. Additionally, the frequency of severe exacerbations was calculated using the number of emergency room	Overall risk of bias • High Use of self-report in determining exposure and outcome that allows high risk of bias Directness • Directly applicable

Author (year)	Title	Study details	Quality assessment
		visits or hospitalisations Measure(s) • Odds ratios Adjusted Covariates for adjustment • Age • Smoking intensity Pack-years • Body mass index (BMI) • Sex • FEV1, % predicted • Race Subgroup analyses • Severity of exacerbations Exacerbations of COPD; Severe exacerbations of COPD	
Peacock (2011)	Outdoor air pollution and respiratory health in patients with COPD	Study type • Prospective cohort study Duration of follow-up • 12 months Study details • Study location UK • Study setting Patients of London Chest Hospital	Did the study address a clearly focused issue? • Yes Was the cohort recruited in an acceptable way? • Yes Was the exposure accurately measured to minimise bias?

Author (year)	Title	Study details	Quality assessment
		• Study dates 1995 to 1997 • Loss to follow-up 27 out of 125 • Sources of funding None reported Inclusion criteria • Diagnosis of COPD Moderate to severe • Previous exacerbations No exacerbations in 4 weeks prior to study • FEV1, predicted <70% predicted for age and height • Other b2-agonist reversibility <15% or 200ml Exclusion criteria • Asthma • Respiratory conditions bronchiectasis, carcinoma of the bronchus • Inability or unwillingness to cooperate with the investigators Sample characteristics • Sample size 125 patients, 94 analysed • %female 28% • Mean age (SD) 67.5 years (8.2) • Smoking status	• Yes Was the outcome accurately measured to minimise bias? • Yes Have the authors identified all important confounding factors? • Unclear Unclear whether author considered non-pollutant related confounding variables Have they taken account of the confounding factors in the design and/or analysis? • Unclear Unclear whether non-pollutant variables were controlled for Was the follow up of subjects complete enough? • No Over 10% lost to follow up Was the follow up of subjects long enough? • Yes Overall risk of bias • High Over 10% attrition rate and lack of limit

Author (year)	Title	Study details	Quality assessment
		Not reported • Previous exacerbations Not reported • FEV1, % predicted (mean, SD) Not reported Predictive factor (s) - Environmental factors • Pollution- outdoors, indoors NO2, O3, SO2 and PM10 were obtained from the national air quality monitoring network station. The following pollutant measures were derived: maximum hourly NO2, maximum 8 h moving average O3, 24 h mean SO2 and PM10. For black smoke there was a network of monitors (unlike for other pollutants) and 24 h average black smoke data was used from the monitor nearest each patient's home Outcome(s) • Exacerbations Exacerbations were identified by symptoms recorded on the diary cards or from the history when patients presented to the physician, according to the criteria modified from Anthonisen of any two major symptoms or one major and two minor symptoms on two consecutive days Measure(s) • Odds ratios Adjusted	adjustment for confounding variables Directness • Directly applicable

Author (year)	Title	Study details	Quality assessment
		Covariates for adjustment • Not reported	
Puhan (2014)	No association of 25-hydroxyvitamin D with exacerbations in primary care patients with COPD	Study type • Prospective cohort study Duration of follow-up • More than 12 months 2 years Study details • Study location The Netherlands and Switzerland • Study setting Primary care settings in Switzerland and the Netherlands • Study dates Recruitment 2008 to 2009 • Loss to follow-up 34 patients (9.6%) died during follow-up Additional 53 participants excluded from final analysis due to taking vitamin D3 supplements • Sources of funding Supported by the Swiss National Science Foundation [Grant 3233B0/115216/1], Dutch Asthma Foundation [Grant 3.4.07.045], and Zurich Lung League Inclusion criteria • Age 40 years or older • Diagnosis of COPD	Did the study address a clearly focused issue? • Yes Was the cohort recruited in an acceptable way? • Yes Was the exposure accurately measured to minimise bias? • Yes Was the outcome accurately measured to minimise bias? • Yes Have the authors identified all important confounding factors? • Yes Have they taken account of the confounding factors in the design and/or analysis? • Yes Was the follow up of subjects complete enough?

Author (year)	Title	Study details	Quality assessment
		• Previous exacerbations Exacerbation free for at least 4 weeks • FEV1:FVC ratio <0.7 • FEV1, predicted <80% Exclusion criteria • Life expectancy < 12 months • Other Dementia or psychotic morbidity Sample characteristics • Sample size 409 • %female 51.6% • Mean age (SD) 67.2 years (10.0) • Smoking status Smoking pack-years: 0 to 20 (18.8%), 21 to 40 (30.9%), 41 to 60 (26.7%), >60 (23.6%) • Previous exacerbations Number of exacerbations in the year before enrolment: 0 (68.3%), 1 (23.6%), ≥2 (8.2%) • FEV1, % predicted (mean, SD) 56.0 (15.9) Predictive factor (s) - Individual factors • Biomarkers 25-hydroxyvitamin D concentrations: four categories	• Yes Was the follow up of subjects long enough? • Yes Overall risk of bias • Low Directness • Directly applicable

Author (year)	Title	Study details	Quality assessment
		of 25-hydroxyvitamin D representing patients with severe vitamin D deficiency (<10 ng/dL), deficiency (10 to <20 ng/dL), insufficiency (20 to <30 ng/dL), and desirable levels (≥30 ng/dL) Outcome(s) • Exacerbations An event-based definition for exacerbations with two criteria that had to be fulfilled: (1) unscheduled physician contact in a hospital, in private practice, or by telephone for worsening of breathlessness, cough, increased sputum production, or change in sputum colour and (2) electronic or handwritten documentation of a new prescription or a dosage increase of systemic steroids or a new prescription for an antibiotic Measure(s) • Hazard ratios Adjusted Covariates for adjustment • Age • Sex • Current smoking status • FEV1 • Season • Country	

Author (year)	Title	Study details	Quality assessment
Sethi (2002)	New strains of bacteria and exacerbations of chronic obstructive pulmonary disease	Study type • Prospective cohort study Duration of follow-up • More than 12 months 56 months Study details • Study location US • Study setting Single institution • Study dates 1994 to 1998 • Loss to follow-up None reported • Sources of funding Supported by a Merit Review grant from the Department of Veterans Affairs. Inclusion criteria • Bronchitis Chronic bronchitis Exclusion criteria • Asthma • Inability or unwillingness to cooperate with the investigators • Immunosuppression • Bronchiectasis	Did the study address a clearly focused issue? • Yes Was the cohort recruited in an acceptable way? • Yes Was the exposure accurately measured to minimise bias? • Yes Was the outcome accurately measured to minimise bias? • Yes Have the authors identified all important confounding factors? • Unclear Lack of clarity regarding which confounding factors were considered Have they taken account of the confounding factors in the design and/or analysis? • Unclear Lack of clarity regarding whether any confounding factors were controlled for Was the follow up of subjects complete enough?

Author (year)	Title	Study details	Quality assessment
		• Medical condition compromising survival Sample characteristics • Sample size 81 • %female 2.5% • Mean age (SD) 66.5 years (9.4) • Smoking status Current smoker: 35.8%; former smoker: 64.2% • Previous exacerbations Not reported • FEV1, % predicted (mean, SD) 47.3 (19.5) Predictive factor (s) - Individual factors • Viral/bacterial infection Bacterial pathogen: Haemophilus influenza Moraxella catarrhalis Streptococcus pneumoniae Pseudomonas aeruginosa Staphylococcus aureus Other gram-negative rods Outcome(s) • Exacerbations The patients were questioned about the status of their chronic respiratory symptoms (breathlessness, cough, sputum production, viscosity, and purulence), and the responses were graded as 1 (at the usual level), 2 (somewhat worse than usual), or 3 (much worse than usual). A minor worsening of two or more symptoms or a major worsening of one or more symptoms	• Unclear Unclear attrition rate Was the follow up of subjects long enough? • Yes Overall risk of bias • Moderate Lack of clarity regarding confounding variables and unclear whether there were drop outs Directness • Directly applicable

Author (year)	Title	Study details	Quality assessment
		prompted a clinical assessment of the cause. If the patient had fever (a temperature that exceeded 38.3°C), appeared ill, or had signs of consolidation on examination of the lungs, a chest film was obtained to rule out pneumonia. If other causes of the worsening of symptoms, such as pneumonia, upper respiratory infection, and congestive heart failure, were ruled out, the patient was considered to be having an exacerbation of chronic obstructive pulmonary disease Measure(s) • Relative risks Adjusted Covariates for adjustment • Not reported	
Song (2017)	Clinical implications of blood eosinophil count in patients with non-asthma-COPD overlap syndrome COPD	Study type • Prospective cohort study Duration of follow-up • 12 months Study details • Study location Korea • Study setting Patients from Korean COPD subtype study including 28 participating hospitals • Study dates	Did the study address a clearly focused issue? • Yes Was the cohort recruited in an acceptable way? • Yes Was the exposure accurately measured to minimise bias? • Yes

Author (year)	Title	Study details	Quality assessment
		Not reported • Loss to follow-up None reported following application of exclusion criteria • Sources of funding None reported Inclusion criteria • Age > 40 years • Diagnosis of COPD • Smoking Smoking history 10 or greater pack years • FEV1:FVC ratio <0.7 Exclusion criteria • Asthma Asthma-COPD overlap syndrome • Other Unavailable information on the eosinophil count in initial cohort Sample characteristics • Sample size 575 participants selected without ACOS, 467 had sufficient eosinophil data for final analysis • %female 4.1% • Mean age (SD) 69.5 years (7.4) • Smoking status	Was the outcome accurately measured to minimise bias? • Yes Have the authors identified all important confounding factors? • Yes Have they taken account of the confounding factors in the design and/or analysis? • Yes Was the follow up of subjects complete enough? • Yes Was the follow up of subjects long enough? • Yes Overall risk of bias • Low Directness • Directly applicable

Author (year)	Title	Study details	Quality assessment
		Pack-year mean (SD): 47.5 (25.1) • Previous exacerbations Proportion of moderate-to-severe exacerbations over the previous year 31.9% • FEV1, % predicted (mean, SD) 55.5 (18.0) Predictive factor (s) - Individual factors • Biomarkers Eosinophil count Outcome(s) • Exacerbations Moderate-to-severe AECOPD was defined as COPD requiring antibiotics in outpatient clinics, emergency room admission or admission due to an increased quantity of sputum, purulent changes in sputum, or aggravation of breathlessness Measure(s) • Odds ratios Adjusted Covariates for adjustment • Age • Smoking intensity pack-years • Body mass index (BMI) • Sex • FEV1, % predicted • Inhaled corticosteroid	

Author (year)	Title	Study details	Quality assessment
		• Long-acting best 2 agonist	
Stolz (2017)	Systemic Biomarkers of Collagen and Elastin Turnover Are Associated With Clinically Relevant Outcomes in COPD	Study type • Prospective cohort study Duration of follow-up • More than 12 months 2 years Study details • Study location Belgium, Germany, Greece, Italy, Netherlands, Serbia, Spain, Switzerland • Study setting Hospitals • Study dates 2008 to 2012 • Loss to follow-up 132 out of 638 • Sources of funding University Hospital Basel (Switzerland) Inclusion criteria • Age Above 40 years • GOLD stage Moderate to very severe COPD (GOLD II to IV) • Smoking History greater than or equal to 10 pack-years • Clinical stable at baseline At least 4 weeks after resolution of the last	Did the study address a clearly focused issue? • Yes Was the cohort recruited in an acceptable way? • Yes Was the exposure accurately measured to minimise bias? • Yes Was the outcome accurately measured to minimise bias? • Yes Have the authors identified all important confounding factors? • Unclear Covariates were listed for adjustment but confounders were not mentioned Have they taken account of the confounding factors in the design and/or analysis? • Unclear Covariates were listed for adjustment but confounders were not mentioned

Author (year)	Title	Study details	Quality assessment
		exacerbation • Willingness to participate Willingness to participate in a longitudinal, cohort study Willingness of the family physician to have the patient included in a cohort study Written informed consent Exclusion criteria • Respiratory conditions Pulmonary condition other than COPD as the main respiratory disease, for example, bronchiectasis, asthma or pulmonary fibrosis • Inability or unwillingness to cooperate with the investigators Patients unable and unwilling to give written informed consent • Immunosuppression Including human immunodeficiency virus (HIV), organ transplantation or chronic steroid use (more than 10 mg prednisolone-equivalent per day) • Rapid fatal disease • Musculoskeletal Process preventing ambulation Sample characteristics • Sample size 506 • %female 28.1% • Mean age (SD) 66.8 years (10.5) • Smoking status	Was the follow up of subjects complete enough? • No 20% were lost to follow-up Was the follow up of subjects long enough? • Yes Overall risk of bias • Moderate Covariates were listed for adjustment but confounders were not mentioned. 20% were lost to follow-up Directness • Directly applicable

Author (year)	Title	Study details	Quality assessment
		Current smoker: 29.6%; Pack-years mean (SD): 51.5 (30.9) • Previous exacerbations Number of exacerbations in the previous year median (interquartile range): 1 (0 to 1); Number of severe exacerbations in the previous year median (interquartile range): 0 (0 to 1) • FEV1, % predicted (mean, SD) 48.6 (18.2) Predictive factor (s) - Individual factors • Biomarkers Serum levels of pro-forms of collagen type III levels Outcome(s) • Exacerbations Recurrent moderate AECOPD (requiring treatment with systemic corticosteroids, antibiotics, or both) and severe AECOPD (requiring hospitalisation or a visit to the emergency department) Measure(s) • Hazard ratios Adjusted Covariates for adjustment • Body mass index (BMI) • Sex • Adjusted Charlson score Age-adjusted • FEV1, % predicted	

Author (year)	Title	Study details	Quality assessment
		• Modified Medical Research Council (MMRC) dyspnoea score	
Suzuki (2014)	Clinical features and determinants of COPD exacerbation in the Hokkaido COPD cohort study	Study type • Prospective cohort study Duration of follow-up • More than 12 months 5 years Study details • Study location Japan • Study setting 10 hospitals • Study dates Recruited 2003 to 2005 • Loss to follow-up 95 out of 279 • Sources of funding none reported Inclusion criteria • Age 40 years or older • Diagnosis of COPD • Smoking history of 10 pack-years or more	Did the study address a clearly focused issue? • Yes Was the cohort recruited in an acceptable way? • Yes Was the exposure accurately measured to minimise bias? • Yes Was the outcome accurately measured to minimise bias? • Yes Relied on self-report however medical records and physicians were also asked to clarify potential exacerbations Have the authors identified all important confounding factors? • Yes Have they taken account of the confounding factors in the design and/or analysis? • Yes

Author (year)	Title	Study details	Quality assessment
		Exclusion criteria • Asthma Sample characteristics • Sample size 279 participants; 268 analysed • %female 6% • Mean age (SD) 70 years (8) • Smoking status Current smoker at entry: 28%; Smoking index at entry pack-years: 62 (30) • Previous exacerbations Not reported • FEV1, % predicted (mean, SD) 65 (22) Predictive factor (s) - Individual factors • Smoking Current smoking • Biomarkers Neutrophils cells/mm3 Haemoglobin g/dl C-reactive protein mg/dl Outcome(s) • Exacerbations Exacerbation of COPD was defined in the following ways: 1) patient's subjective complaint by prepaid reply postcard (any clinical symptoms that did not meet symptom definition criteria); 2) worsening or new onset of either two major symptoms (increased	Was the follow up of subjects complete enough? • No Over 30% attrition Was the follow up of subjects long enough? • Yes Overall risk of bias • Moderate High attrition (over 30%) Directness • Directly applicable

Author (year)	Title	Study details	Quality assessment
		breathlessness, change in sputum purulence or increased sputum volume) or any one major symptom plus any minor symptoms (fever, increased cough or wheezing) compared with baseline (symptom definition); 3) symptom criteria plus requiring prescription change (prescription definition); 4) symptom criteria plus antibiotic treatment (antibiotic definition); and 5) symptom criteria plus hospital admission (admission definition) Measure(s) • Relative risks Adjusted • Hazard ratios Adjusted Covariates for adjustment • Age 10-year increase • Body mass index (BMI) • FEV1, % predicted • St. George's Respiratory Questionnaire (SGRQ) • Haemoglobin level 1 g/dL-1 increase Subgroup analyses • Severity of exacerbations Prescription definition: symptom criteria plus requiring prescription change; Admission definition: symptom criteria plus hospital admission	

Author (year)	Title	Study details	Quality assessment
Takada (2011)	Prospective evaluation of the relationship between acute exacerbations of COPD and gastroesophageal reflux disease diagnosed by questionnaire	Study type • Prospective cohort study Duration of follow-up • 12 months Study details • Study location Japan • Study setting Single hospital • Study dates 2009 to 2010 • Loss to follow-up Not reported • Sources of funding Not reported Inclusion criteria • Diagnosis of COPD Without exacerbation in month prior • FEV1:FVC ratio <0.7 Exclusion criteria • Acid suppression medication Sample characteristics • Sample size 221 • %female	Did the study address a clearly focused issue? • Yes Was the cohort recruited in an acceptable way? • Yes Was the exposure accurately measured to minimise bias? • No Relied on self-report in measuring gastro-oesophageal reflux disease Was the outcome accurately measured to minimise bias? • Yes Have the authors identified all important confounding factors? • Unclear Unclear which factors were considered in original univariate model however several significant confounders were controlled for Have they taken account of the confounding factors in the design and/or analysis? • Unclear Unclear which factors were inserted into

Author (year)	Title	Study details	Quality assessment
		5% • Mean age (SD) 71.5 years (7.6) • Smoking status Current smoker: 17.3%; ex-smoker: 81.8%; non-smoker: 1.3% • Previous exacerbations AECOPD events in previous year mean (SD) 0.34 (0.73) • FEV1, % predicted (mean, SD) 67.7 (27.3) Predictive factor (s) - Individual factors • Multimorbidities including mental health problems Patients were asked to complete the Frequency Scale for Symptoms of GERD (FSSG) by themselves. The results were assessed as the total FSSG score, acid reflux score and gastric dysmotility score, and the total score required for diagnosis of gastroesophageal reflux disease was ≥8 points Outcome(s) • Exacerbations AECOPD was defined based on symptoms of Anthonisen type 1 or 2 and prescription of additional systemic corticosteroids or antibiotics Measure(s) • Odds ratios Adjusted	original univariate model, however several significant confounders were controlled for Was the follow up of subjects complete enough? • Yes Was the follow up of subjects long enough? • Yes Overall risk of bias • Moderate Use of self-report in measure of gastro-oesophageal reflux disease and lack of clarity regarding potential confounders Directness • Directly applicable

Author (year)	Title	Study details	Quality assessment
		Covariates for adjustment • Exacerbations in the previous year Number of AECOPD events in previous year • Body mass index (BMI) • GOLD stage	
Terada (2008)	Impact of gastro-oesophageal reflux disease symptoms on COPD exacerbation	Study type • Prospective cohort study Duration of follow-up • 6 months Study details • Study location Japan • Study setting Single outpatient clinic • Study dates 2006 • Loss to follow-up Not reported • Sources of funding Supported in part by the Japan Society for the Promotion of Science Grant B 16390234 Inclusion criteria • Smoking >20 pack-years Exclusion criteria • Respiratory conditions	Did the study address a clearly focused issue? • Yes Was the cohort recruited in an acceptable way? • Yes Was the exposure accurately measured to minimise bias? • No Measured using self-report questionnaire Was the outcome accurately measured to minimise bias? • Yes Have the authors identified all important confounding factors? • Yes Have they taken account of the confounding factors in the design and/or analysis? • No

Author (year)	Title	Study details	Quality assessment
		Any comorbid respiratory disorder • Other History of malignant disease within 5 years; active gastrointestinal diseases other than gastro-oesophageal reflux disease; initiations and withdrawal of COPD or gastro-oesophageal reflux disease medication during follow-up, daily use of systemic corticosteroids and current use of long-term oxygen therapy Sample characteristics • Sample size 82 • %female 6.1% • Mean age (SD) 73.0 years (8.0) • Smoking status Current smoker: 12.2%; former smoker: 87.8%; pack-year mean (SD): 65.3 (37.8) • Previous exacerbations Not reported • FEV1, % predicted (mean, SD) 56.9 (20.4) Predictive factor (s) - Individual factors • Multimorbidities including mental health problems Gastroesophageal reflux disease symptoms were evaluated with a self-reported FSSG questionnaire consisting of 12 items. The frequency of each item was quantified on a scale ranging from 0 to 4 points as follows: 0=none (not in the past year); 1=rarely (a	Confounding factors not adjusted for in analysis Was the follow up of subjects complete enough? • Yes Was the follow up of subjects long enough? • Yes Overall risk of bias • High No adjustment for confounders and use of self-report measurement of gastro-oesophageal reflux disease Directness • Directly applicable

Author (year)	Title	Study details	Quality assessment
		few times in the past year); 2=sometimes (a few times in the past month); 3=often (a few times in the past week); 4=always (everyday). The cut-off score for gastroesophageal reflux disease symptoms was set at 8 points Outcome(s) • Exacerbations Exacerbations were defined according to the modified Anthonisen's criteria as the occurrence of two or more of three major symptoms (this is, increase in breathlessness, sputum purulence and increased sputum volume), or any one major symptom with any one minor symptom (i.e., increase in nasal discharge, wheezing, sore throat, cough or fever) for at least 2 consecutive days Measure(s) • Relative risks Adjusted Covariates for adjustment • Age • Body mass index (BMI) • Sex • Current smoking status • FEV1, % predicted • Use of inhaled steroids Inhaled corticosteroids • Partial pressure of oxygen in arterial blood (PACO2)	

Author (year)	Title	Study details	Quality assessment
Thomsen (2013)	Inflammatory biomarkers and exacerbations in chronic obstructive pulmonary disease	Study type • Prospective cohort study Duration of follow-up • More than 12 months 4 years Study details • Study location Denmark • Study setting Random selection of people living in Denmark • Study dates 2001 to 2008 • Loss to follow-up None • Sources of funding Herlev Hospital, Copenhagen University Hospital, the Danish Heart Foundation, the Copenhagen County Foundation, and the University of Copenhagen Inclusion criteria • None reported Exclusion criteria • None reported Sample characteristics • Sample size 6,574 • %female	Did the study address a clearly focused issue? • Yes Was the cohort recruited in an acceptable way? • Yes Was the exposure accurately measured to minimise bias? • Yes Was the outcome accurately measured to minimise bias? • No COPD exacerbation was collected linking the study database to 2 national registries Have the authors identified all important confounding factors? • Unclear Multivariate models were adjusted using covariates but confounding factors were not mentioned Have they taken account of the confounding factors in the design and/or analysis? • Unclear Multivariate models were adjusted using covariates but confounding factors were

Author (year)	Title	Study details	Quality assessment
		53% • Mean age (SD) Median (interquartile range): 67 years (58 to 75) • Smoking status Current smokers: 39%; Former smokers: 39% • Previous exacerbations History of exacerbations: 2% • FEV1, % predicted (mean, SD) Median (interquartile range): 80 (67 to 92) Predictive factor (s) - Individual factors • Biomarkers Inflammatory biomarkers included high sensitive C-reactive protein (cut point 3 mg/L), fibrinogen (cut point 14 µmol/L), and leukocyte count (cut point 9X10 9/L) Outcome(s) • Exacerbations An exacerbation of COPD was defined as a short-course treatment with oral corticosteroids alone or in combination with an antibiotic or a hospital admission due to COPD Measure(s) • Odds ratios Adjusted • Hazard ratios Adjusted	not mentioned Was the follow up of subjects complete enough? • Yes Was the follow up of subjects long enough? • Yes Overall risk of bias • High COPD exacerbation was collected linking the study database to 2 national registries. Multivariate models were adjusted using covariates but confounding factors were not mentioned Directness • Directly applicable

Author (year)	Title	Study details	Quality assessment
		Covariates for adjustment • Age • Body mass index (BMI) • Sex • Current smoking status • FEV1, % predicted • Inhaled medication Use of any inhaled medication • Exacerbation History of frequent exacerbations and time since most recent prior exacerbation Subgroup analyses • Frequency of exacerbations At least 1 exacerbation; Frequent exacerbations (≥2)	
Vedel-Krogh (2016)	Blood Eosinophils and Exacerbations in Chronic Obstructive Pulmonary Disease. The Copenhagen General Population Study	Study type • Prospective cohort study Duration of follow-up • More than 12 months 3 years Study details • Study location Denmark • Study setting Copenhagen general population; Participants selected using Danish Civil Registration system • Study dates 2003 to 2011	Did the study address a clearly focused issue? • Yes Was the cohort recruited in an acceptable way? • No Participants were selected using a population registry Was the exposure accurately measured to minimise bias? • No Only took one measure of blood

Author (year)	Title	Study details	Quality assessment
		• Loss to follow-up No one lost to follow-up • Sources of funding None reported Inclusion criteria • FEV1:FVC ratio Ratio under lower limit of normal - the fifth percentile of a frequency distribution. Exclusion criteria • Asthma Excluded if asthma is self-reported • FEV1:FVC ratio Excluded if equal to or greater than 70% Sample characteristics • Sample size 7,225 • %female 50% • Mean age (SD) Median age (IQR) 64 years (54 to 72) • Smoking status Current smokers: 37%; pack-years of smoking median (IQR): 30 (15 to 45) • Previous exacerbations Not reported • FEV1, % predicted (mean, SD) Median (IQR) 78 (64 to 90)	eosinophils. Was the outcome accurately measured to minimise bias? • Yes Have the authors identified all important confounding factors? • Yes Have they taken account of the confounding factors in the design and/or analysis? • No Author identified diet and medication as potentially confounding that were not included in the study Was the follow up of subjects complete enough? • Yes Was the follow up of subjects long enough? • Yes Overall risk of bias • High Use of registry in participant selection, several potentially confounding variables (medication, diet and comorbidities) were

Author (year)	Title	Study details	Quality assessment
		Predictive factor (s) - Individual factors • Biomarkers Blood eosinophils count Outcome(s) • Exacerbations A severe exacerbation was defined as a hospitalisation due to COPD, and a moderate exacerbation was defined as a short-course treatment of systemic corticosteroids alone or in combination with antibiotics. Information on hospitalisation and medication was obtained by linking the Copenhagen General Population Study to the Danish National Patient Registry, which records all hospital contacts in Denmark, and to the Danish Registry of Medicinal Product Statistics, which records information on all prescriptions dispensed in Danish pharmacies Measure(s) • Relative risks Relative risks were calculated using raw data Subgroup analyses • Severity of exacerbations Moderate and severe exacerbations	identified but not measured/adjusted for in study design, and only took one measure of blood eosinophils Directness • Directly applicable
Wilkinson (2017)	A prospective, observational cohort study of the seasonal dynamics of airway pathogens in the aetiology of exacerbations in COPD	Study type • Prospective cohort study Prospective, observational study	Did the study address a clearly focused issue? • Yes

Author (year)	Title	Study details	Quality assessment
		Duration of follow-up • 12 months Study details • Study location UK • Study setting University Hospital Southampton • Study dates Recruited 2011 to 2012 • Loss to follow-up 22 out of 127 • Sources of funding Funded by GlaxoSmithKline Inclusion criteria • Age Aged 40 - 85 years • Diagnosis of COPD Confirmed diagnosis of moderate, severe or very severe COPD. Exclusion criteria • Lung disease Defined as lung malignancy • Inability or unwillingness to cooperate with the investigators • Contraindicated comorbidity • Severe pain • Withdrew consent	Was the cohort recruited in an acceptable way? • Yes Was the exposure accurately measured to minimise bias? • Yes Was the outcome accurately measured to minimise bias? • Yes Have the authors identified all important confounding factors? • Yes Have they taken account of the confounding factors in the design and/or analysis? • Yes Was the follow up of subjects complete enough? • No 22.3% lost to follow-up Was the follow up of subjects long enough? • Yes

Author (year)	Title	Study details	Quality assessment
		Sample characteristics • Sample size 152 screened, 127 included in analysis • %female 46.5% • Mean age (SD) 66.8 years (8.6) • Smoking status Smoking history pack-years median (IQR): 47.0 (33.7 to 60.0) • Previous exacerbations Exacerbations in previous year: 1 exacerbation 22.0%; 2 exacerbations 29.1%; 3 exacerbations: 19.7%; 4 exacerbation 29.1% • FEV1, % predicted (mean, SD) 46.4 (15.2) Predictive factor (s) - Individual factors • Viral/bacterial infection Non-typeable haemophilus influenzae Moraxella catarrhalis Human rhinovirus Other viruses Seasons were divided into two: high season (October–March) and low season (April–September) Outcome(s) • Exacerbations AECOPD was defined as worsening of at least two major symptoms (breathlessness, sputum volume, and sputum purulence) or worsening of at least one major symptom and one minor symptom (wheeze, sore throat, cold symptoms, cough, and fever without other cause). An exacerbation was considered mild if	Overall risk of bias • Moderate High rate of attrition (22.3% lost to follow-up) Directness • Directly applicable

Author (year)	Title	Study details	Quality assessment
		self-managed by the patient using inhaled therapy, moderate if it required treatment with oral corticosteroids or antibiotics, and severe if the patient required hospitalisation or a home care intervention Measure(s) • Odds ratios Adjusted Covariates for adjustment • Age • GOLD stage • Gender	
Xu (2008)	Independent effect of depression and anxiety on chronic obstructive pulmonary disease exacerbations and hospitalizations	Study type • Prospective cohort study Duration of follow-up • 12 months Study details • Study location China • Study setting Respiratory departments of 10 hospitals in Beijing, China • Study dates 2004 to 2006 • Loss to follow-up 40 out of 491 • Sources of funding	Did the study address a clearly focused issue? • Yes Was the cohort recruited in an acceptable way? • Yes Was the exposure accurately measured to minimise bias? • Yes Was the outcome accurately measured to minimise bias? • Yes

Author (year)	Title	Study details	Quality assessment
		Not reported Inclusion criteria • Age 30 years or older • Diagnosis of COPD defined as physician diagnosed • Diagnosis of asthma and/or COPD No primary diagnosis of asthma • FEV1:FVC ratio ratio of <0.7 • FEV1, predicted <80% of predicted value • Other participants must have (at baseline) no fever, no worsening of respiratory symptoms, no medication change within 4 weeks prior to recruitment, no previous lung volume reduction surgery, no previous lung transplantation, no pneumonectomy and must have an expected survival of at least 6 months Exclusion criteria • None reported Sample characteristics • Sample size 491 • %female Sex breakdown only given for sub-groups, range 30.9% to 34.1% • Mean age (SD) Mean age breakdown only given for sub-groups,	Have the authors identified all important confounding factors? • Yes Have they taken account of the confounding factors in the design and/or analysis? • Yes Was the follow up of subjects complete enough? • Yes Was the follow up of subjects long enough? • Yes Overall risk of bias • Low Directness • Directly applicable

Author (year)	Title	Study details	Quality assessment
		range 65.2 years (10.7) to 67.0 years (10.7) • Smoking status Cumulative smoking, pack-years mean (SD) breakdown only given for sub-groups, range 26.2 (28.9) to 28.9 (31.1) • Previous exacerbations Rate of experiencing past-year exacerbations breakdown only given for sub-groups, range 81.2% to 88.3% • FEV1, % predicted (mean, SD) FEV1, % predicted breakdown only given for sub-groups, range 45.7 (16.4) to 48.2 (15.8) Predictive factor (s) - Individual factors • Multimorbidities including mental health problems Depression and anxiety were assessed at baseline using the Hospital Anxiety and Depression Scale (HADS) The HADS consists of seven items for depression (HAD-D) and seven items for anxiety (HAD-A). The scores range from 0 to 21 for each subscale, with a score of 0–7 denoting a non-case, 8–10 a possible case, and 11 or higher a probable case Outcome(s) • Exacerbations A symptom-based exacerbation was confirmed if, for at least 48 hours, patients experienced a worsening of at least one of three key symptoms (increased sputum amount, changed sputum colour or purulence, and increased breathlessness). An event-based exacerbation was confirmed if patients experienced at least one key symptom worsening plus a change in at	

Author (year)	Title	Study details	Quality assessment
		least one of three medications (antibiotics, corticosteroid, and bronchodilator) Measure(s) • Relative risks Adjusted Covariates for adjustment • Not reported Subgroup analyses • Severity of exacerbations COPD exacerbation; Hospitalisation for COPD exacerbation	
Yang (2014)	Predictors of exacerbation frequency in chronic obstructive pulmonary disease	Study type • Prospective cohort study Duration of follow-up • More than 12 months Mean 5 years Study details • Study location China • Study setting Outpatient department of respiration, Shougang hospital of Beijing University • Study dates 2000 to 2011 • Loss to follow-up	Did the study address a clearly focused issue? • Yes Was the cohort recruited in an acceptable way? • Yes Was the exposure accurately measured to minimise bias? • Yes Was the outcome accurately measured to minimise bias? • Yes

Author (year)	Title	Study details	Quality assessment
		2 out of 227 • Sources of funding Supported by Beijing High-grade Talents Health Technology Fund Inclusion criteria • Age Aged between 45 and 85 years • Diagnosis of COPD Defined as FEV1 <80% of predicted value after bronchodilator use and post-bronchodilator FEV1:FVC ratio of <70% • Previous exacerbations Stable condition with no COPD exacerbations in month prior to enrolment as evidenced by medical records for past year Exclusion criteria • Inability or unwillingness to cooperate with the investigators Excluded if did not consent to long-term follow-up • Medical condition compromising survival If diagnosed with another life-compromising condition Sample characteristics • Sample size 227 • %female 30% • Mean age (SD) 71.65 years (6.80) • Smoking status	Have the authors identified all important confounding factors? • Unclear Have they taken account of the confounding factors in the design and/or analysis? • Unclear Was the follow up of subjects complete enough? • Yes Was the follow up of subjects long enough? • Yes Overall risk of bias • Low Directness • Directly applicable

Author (year)	Title	Study details	Quality assessment
		Current smoker: 58.6% • Previous exacerbations Numbers of preceding year exacerbation median (IQR): 0 (0 to 1.0) • FEV1, % predicted (mean, SD) 37.55 (16.07) Predictive factor (s) - Individual factors • Multimorbidities including mental health problems Comorbidities. The Charlson Index assigns a score to each underlying condition proportional to its corresponding disease-related risk of death. The arithmetical sum of scores for individual comorbidities was used as an index for each patient Outcome(s) • Exacerbations An exacerbation was defined as sustained worsening of respiratory symptoms, such as breathlessness or increased sputum volume or purulence beyond the basal variability and that required treatment with oral corticosteroids or antibiotics. In this study, only exacerbations resulting in hospitalisation were recorded, and exacerbations separated by ≥ 14 days were considered distinct events. Patients were grouped by the median annual exacerbation frequency into those experiencing infrequent exacerbations (Group 1: less than one exacerbation annually) and frequent exacerbations (Group 2: one or more exacerbation annually). Patients experiencing frequent exacerbations were further divided into those experiencing moderately frequent exacerbations	

Author (year)	Title	Study details	Quality assessment
		(Group 2A: fewer than two exacerbations per year) and severely frequent exacerbations (Group 2B: two or more exacerbations per year) Measure(s) • Relative risks Adjusted Covariates for adjustment • Exacerbations in the previous year • FEV1 • Comorbidity • Non-invasive positive pressure ventilation Subgroup analyses • Frequency of exacerbations Frequent exacerbations: <2 exacerbations per year; Severely frequent exacerbations: ≥2 exacerbations per year	
Yohannes (2017)	The Association of Depressive Symptoms With Rates of Acute Exacerbations in Patients With COPD: Results From a 3-year Longitudinal Follow-up of the ECLIPSE Cohort	Study type • Prospective cohort study Duration of follow-up • More than 12 months 3 years Study details • Study location Bulgaria, Canada, Czech Republic, Denmark, Netherlands, New Zealand, Norway, Slovenia, Spain,	Did the study address a clearly focused issue? • Yes Was the cohort recruited in an acceptable way? • Yes Was the exposure accurately measured to minimise bias? • No

Author (year)	Title	Study details	Quality assessment
		Ukraine, UK, US • Study setting Not reported • Study dates 2005 to 2010 • Loss to follow-up 479 out of 2059 • Sources of funding GlaxoSmithKline Inclusion criteria • Age 40 to 75 years • Diagnosis of COPD • Smoking Current or ex-smokers with a smoking history of at least 10 pack-years • FEV1:FVC ratio 70% • FEV1, predicted <80% • Written informed consent A signed and dated written informed consent is obtained prior to participation • Protocol Able to comply with the requirements of the protocol and be available for study visits over 3 years Exclusion criteria • Tuberculosis • Lung disease Lung fibrosis	Depression was measured with a questionnaire Was the outcome accurately measured to minimise bias? • Yes Have the authors identified all important confounding factors? • Unclear Multivariate regression model was used but confounding factors were not mentioned Have they taken account of the confounding factors in the design and/or analysis? • Unclear Multivariate regression model was used but confounding factors were not mentioned Was the follow up of subjects complete enough? • No 23% were lost to follow-up Was the follow up of subjects long enough? • Yes

Author (year)	Title	Study details	Quality assessment
		• Respiratory conditions Known respiratory disorders, or disorders identified at screening/visit 1, other than COPD (for example, sarcoidosis) • Cystic fibrosis • Exacerbation Moderate or severe exacerbation (requiring oral corticosteroid, antibiotics or hospitalisation) within the last 4 weeks • Cancer Lung cancer, any cancer, or have had cancer in the 5 years prior to study entry • Lung volume reduction surgery • Lung transplantation • Alcohol abuse • Comorbidity Serious, uncontrolled disease (including serious psychological disorders) likely to interfere with the study or impact on subject safety • Inflammatory disease Known history of significant inflammatory disease, other than COPD (for example, rheumatoid arthritis and Lupus) • Alpha-1-antitrypsin Known to be severely alpha-1-antitrypsin deficient • Lung surgery • Enrol in another study Enrolled in a long term blinded drug study or a study where there is significant radiation exposure (for example, CT scans) • Drug abuse • Solvent abuse	Overall risk of bias • High Depression was measured with a questionnaire. Multivariate regression model was used but confounding factors were not mentioned. 23% were lost to follow-up Directness • Directly applicable

Author (year)	Title	Study details	Quality assessment
		• Blood transfusion in the 4 weeks prior to study start • Oral corticosteroids Long term oral corticosteroids (long term is considered use for more than 3 consecutive months) • Unable to walk Sample characteristics • Sample size 2,059 • %female 34.7% • Mean age (SD) 63.4 years (7.1) • Smoking status Pack-years mean (SD): 48.7 (27.3); Current smoker: 36.2% • Previous exacerbations Not reported • FEV1, % predicted (mean, SD) 48.0 (15.6) Predictive factor (s) - Individual factors • Smoking Current smoker • Multimorbidities including mental health problems History of gastroesophageal reflux. Depressive symptoms were measured using the CES-D, which assesses the presence of current depressive symptoms experienced in the past 2 weeks. Participants rated the 20 items on a 4-point scale (0 to 3). The CES-D scores ≥16 at baseline study visit,	

Author (year)	Title	Study details	Quality assessment
		which reflect high depressive symptom load, were regarded as a 'case definition' for depression Outcome(s) • Exacerbations Assessment of AECOPD was based on health care utilisation definition, reporting frequency of moderate or severe events consisting of either management of oral corticosteroids and/or antibiotics (moderate) or a hospital admission for COPD exacerbation (severe). AECOPD was based on Hurst definition criteria and by local investigators' clinical opinion and guidelines Measure(s) • Odds ratios Adjusted Covariates for adjustment • Exacerbations in the previous year • Sex Women • Current smoking status Current smoker • Body mass, airflow obstruction, dyspnoea and exercise capacity (BODE) index Increase by 1 point • FEV1 L, per 100 mL decrease • Depression At baseline, CES-D <16 versus ≤16 • White cell count 10 9/L	

Author (year)	Title	Study details	Quality assessment
		• Gastro-oesophageal reflux disease Subgroup analyses • Severity of exacerbations Moderate/severe AECOPD; Hospitalised AECOPD	
Yoo (2011)	Comparison of clinico-physiologic and CT imaging risk factors for COPD exacerbation	Study type • Prospective cohort study Duration of follow-up • 12 months Study details • Study location Korea • Study setting 11 hospitals • Study dates 2005 to 2009 • Loss to follow-up Not reported • Sources of funding Not reported Inclusion criteria • Previous exacerbations No exacerbations for at least 2 months at time of enrolment • Smoking >10 pack-years of smoking history • FEV1:FVC ratio	Did the study address a clearly focused issue? • Yes Was the cohort recruited in an acceptable way? • Yes Was the exposure accurately measured to minimise bias? • Yes Was the outcome accurately measured to minimise bias? • Yes Have the authors identified all important confounding factors? • Yes Have they taken account of the confounding factors in the design and/or analysis? • No Previous exacerbations and use of COPD

Author (year)	Title	Study details	Quality assessment
		<0.7 after administration of 400 µg of inhaled albuterol • Abnormal chest radiography No or minimal abnormality on chest radiography Exclusion criteria • None reported Sample characteristics • Sample size 260 • %female 3.1% • Mean age (SD) 66.2 years (7.2) • Smoking status Current smokers: 35.4% • Previous exacerbations Hospitalisation due to exacerbation in the past year 9.2% • FEV1, % predicted (mean, SD) 53.1 (16.3) Predictive factor (s) - Individual factors • Multimorbidities including mental health problems Comorbidities were assessed using the Charlson index Outcome(s) • Exacerbations Acute exacerbations were defined as worsening symptoms (breathlessness, cough, or sputum)	medication not considered in analysis Was the follow up of subjects complete enough? • Yes Was the follow up of subjects long enough? • Yes Overall risk of bias • Moderate Previous exacerbations and use of COPD medication not considered in analysis Directness • Directly applicable

Author (year)	Title	Study details	Quality assessment
		requiring treatment with systemic steroids or antibiotics, a visit to the emergency room, and/or admission to a hospital, as decided by attending physicians Measure(s) • Odds ratios Adjusted Covariates for adjustment • Age • Exacerbations in the previous year • Charlson score • FEV1, % predicted	
Zhao (2014)	The value of assessment tests in patients with acute exacerbation of chronic obstructive pulmonary disease	Study type • Prospective cohort study Duration of follow-up • 6 months Study details • Study location China • Study setting Hospital • Study dates 2010 to 2011 • Loss to follow-up 73 out of 232 • Sources of funding	Did the study address a clearly focused issue? • Yes Was the cohort recruited in an acceptable way? • Yes Was the exposure accurately measured to minimise bias? • Yes Was the outcome accurately measured to minimise bias? • Yes

Author (year)	Title	Study details	Quality assessment
		Not reported Inclusion criteria • Diagnosis of COPD Exclusion criteria • Asthma • Cystic fibrosis • Cardiovascular conditions Heart failure or myocardial infarction • Spirometry Inability to perform the spirometry or being uncooperative • Age Younger than 40 years • Being unable to understand the questionnaire • Pulmonary resection Sample characteristics • Sample size 159 • %female 22.5% • Mean age (SD) 71 years (11) • Smoking status Pack-years median (IQR): 46 (30 to 70) • Previous exacerbations AECOPD hospitalisation in previous year median (interquartile range): 3 (1 to 6) • FEV1, % predicted (mean, SD)	Have the authors identified all important confounding factors? • Unclear Multivariable analysis was done but confounding factors were not mentioned Have they taken account of the confounding factors in the design and/or analysis? • Unclear Multivariable analysis was done but confounding factors were not mentioned Was the follow up of subjects complete enough? • No 31% were lost to follow-up Was the follow up of subjects long enough? • Yes Overall risk of bias • High Multivariable analysis was done but confounding factors were not mentioned. 31% were lost to follow-up Directness • Directly applicable

Author (year)	Title	Study details	Quality assessment
		49.11 (18.99) Predictive factor (s) - Individual factors • Biomarkers Copeptin; C-reactive protein Outcome(s) • Exacerbations AECOPD was defined as worsening of COPD symptoms or requiring treatment with systemic steroids and/or antibiotics Measure(s) • Odds ratios Adjusted Covariates for adjustment • Exacerbations in the previous year AECOPD hospitalisations • FEV1, % predicted • COPD Assessment Test (CAT)	

AECOPD: acute exacerbations of chronic obstructive pulmonary disease; BP: blood pressure; ECG: electrocardiography; FEV1: forced expiratory volume in 1 second; FVC: forced vital capacity; GOLD: Global Initiative for Chronic Obstructive Lung Disease; GP; general practitioner; IQR: interquartile range; Po2: partial pressure of oxygen; PCo2: partial pressure of carbon dioxide; SD: standard deviation; SEM: standard error of mean

Preventing exacerbations

The following tables were taken from the updated Cochrane review and are based on the work of the Cochrane Airways Group. These tables do not cover studies included by the Cochrane review that were excluded by the NICE review. Please refer to the summary of included studies for details of the studies excluded by NICE.

Albert 2011		
Methods	Prospective, randomised, double-blind, placebo controlled clinical trial with 12 month treatment duration Intention-to-treat analysis	
Participants	N=1142. Aged 40 or over. Mean age 65 years (azithromycin) and 66 (placebo) 41% female Severity of COPD moderate or worse as defined by GOLD criteria Mean FEV 1.10±0.50 (azithromycin) and 1.12±0.52 (placebo) 1 Presence of either a) using continuous supplemental oxygen or b) received systemic glucocorticoids within the previous year /had gone to an emergency room/ hospitalisation for an acute exacerbation No acute exacerbation of COPD for at least 4 weeks Exclusions: asthma, resting heart rate>100/min, Prolonged QT interval > 450 ms, using medications that prolong QTc, hearing impairment documented by audiometry	
Interventions	Prophylaxis: Azithromycin 250 mg daily Placebo	
Outcomes	Primary: 1. Time to the first acute exacerbation of COPD Secondary: Quality of life Nasopharyngeal colonisation of selected respiratory pathogens Compliance to the treatment Adverse events	
Notes	Funding: Grants listed from National Institutes of Health	
Risk of bias table		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The stratified random sequence generation was well described in the journal article under "protocol"
Allocation concealment (selection bias)	Low risk	Well explained. Central allocation was pharmacy controlled
Blinding of participants and personnel (performance bias)	Low risk	Active drug and placebo will be identical in appearance. Both patients and treating medical staff were blinded
Blinding of outcome assessment (detection bias)	Low risk	Trial staff were unaware of the randomisation
Incomplete outcome data (attrition bias)	Unclear risk	All outcome data accounted for in a consort diagram for the entire study

Albert 2011		
		However data on the secondary outcome: HRQOL had reported loss to follow-up of 20% in the prophylactic antibiotic arm and 18% on the placebo arm. The reasons for the missing data pertaining to HRQOL were not given
Selective reporting (reporting bias)	Low risk	All pre-specified outcomes have been reported
Other bias	Low risk	No other bias identified

Berkhof 2013	
Methods	Prospective, randomised, double-blind, placebo controlled clinical trial. Treatment duration of 12 weeks; 6 week post-treatment follow up Intention-to-treat analysis
Participants	N=84. Aged 40 or over. Mean age 67 years (azithromycin) and 68 years (placebo) Female 26% (azithromycin) and 24% (placebo) Mean FEV1 % predicted (SD) 49.8 (16.4) (azithromycin) and 47.4 (12.9) (placebo) Clinical diagnosis of COPD GOLD stage ≥ 2 (defined as a post bronchodilator of forced expiratory volume in 1 second (FEV1) <80% and a ratio of FEV1 to forced vital capacity of <70%), and were suffering from chronic productive cough, defined as cough for at least the last 12 weeks, in two subsequent years Exclusions: prior history of asthma; use of intravenous or oral corticosteroids and/or antibiotics for an exacerbation three weeks before inclusion; other relevant lung or liver diseases at the discretion of the treating physician; pregnancy or lactation; use of macrolides in the last six weeks prior to inclusion; allergy or intolerance to macrolides; or use of other investigational medication started two months prior to inclusion.
Interventions	Prophylaxis: Azithromycin 250 mg 3 times a week Placebo
Outcomes	Primary: 1. mean LCQ total and domain scores Secondary: St. George‚s Respiratory Questionnaire (SGRQ) total score Short Form 36 (SF-36) score Post-bronchodilator spirometry Blood values Microbiology Time to first exacerbation of COPD Exacerbations Hospitalizations for COPD Adverse events
Notes	Funding: "We want to thank Stichting Astma Bestrijding (SAB) for financial support."
Risk of bias table	

Berkhof 2013		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Randomisation codes were generated using a computer allocation program, with a 1:1 ratio and a permutated block size of 4."
Allocation concealment (selection bias)	Unclear risk	Not specifically described, but probably done.
Blinding of participants and personnel (performance bias)	Low risk	Investigators, research nurses, and participants were masked to treatment allocation until final analyses of the data were performed.
Blinding of outcome assessment (detection bias)	Low risk	Investigators, research nurses, and participants were masked to treatment allocation until final analyses of the data were performed.
Incomplete outcome data (attrition bias)	Low risk	Drop out low and balanced. All participants accounted for in flow diagram.
Selective reporting (reporting bias)	High risk	FEV1 measured but not reported in way allowing inclusion in meta-analysis (authors to be contacted). Other planned outcomes according to trial registration relevant to this review reported.
Other bias	Low risk	No other bias identified.

Brill 2015	
Methods	Prospective, randomised, single-blind, placebo controlled clinical trial. Treatment duration of 13 weeks Intention-to-treat analysis
Participants	N=99. Aged 45 to 80 years. Mean age 70.0 (moxifloxacin), 70.4 (doxycycline), 67.9 (azithromycin) and 68.7 (placebo) years Female 32% (moxifloxacin), 28% (doxycycline), 36% (azithromycin) and 25% (placebo) Mean FEV1 % predicted (SD): 52 (13) (moxifloxacin), 53 (14) (doxycycline), 44 (17), (azithromycin) and 53 (13) (placebo) Stable patients with chronic bronchitis (self-reported sputum expectoration on most days when clinically stable) and spirometrically confirmed COPD (defined by FEV1<80% predicted, FEV1 to FVC ratio <0.7 and a history of smoking) Exclusions: Patients who reported either treatment for an exacerbation or an episode of symptom worsening in the 4 weeks prior to screening, or were unable to enrol for safety reasons (significant hepatic/renal impairment, QT prolongation, pre-existing long-term antibiotic use and hypersensitivity to the treatments under investigation).
Interventions	Prophylaxis: Moxifloxacin 400 mg daily for 5 days every 4 weeks Doxycycline 100 mg daily Azithromycin 250 mg 3 times a week Placebo
Outcomes	Primary:

Brill 2015		
	Change in sputum bacterial load, as assessed by quantitative culture. Secondary: Changes in resistance to the three tested antibiotics Changes in FEV1 Adherence to therapy Health status as measured by total SGRQ scores Adverse events Exploratory: Changes in sputum bacterial load as assessed by 16S rRNA gene targeted qPCR Changes in sputum inflammation.	
Notes	Funding: funded by the National Institute for Health Research (NIHR) under the Programme Grants for Applied Research programme (RP-PG-0109-10056) and the NIHR Royal Brompton Respiratory Biomedical Research Unit. The moxifloxacin for the study was provided by Bayer Pharma AG, Berlin, Germany and the study Sponsor was University College London, UK. Neither Bayer, the funder, nor the Sponsor had any influence in the study design, collection, analysis and interpretation of the data, the writing of the report or the decision to submit for publication.	
Risk of bias table		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Internet randomisation into groups of 1:1:1:1 was performed using a computer-generated permuted block system of variable sizes (Sealed Envelope, UK).
Allocation concealment (selection bias)	Low risk	Internet randomisation into groups of 1:1:1:1 was performed using a computer-generated permuted block system of variable sizes (Sealed Envelope, UK). "Patients remained blinded to treatment allocation".
Blinding of participants and personnel (performance bias)	Unclear risk	Patients remained blinded to treatment allocation. However, not clear if study personnel were blinded. Described as single-blind study.
Blinding of outcome assessment (detection bias)	High risk	No description of outcome assessor blinding, although blinded participants assessed outcomes such as quality of life.
Incomplete outcome data (attrition bias)	Low risk	Drop out low and balanced. All participants accounted for in flow diagram
Selective reporting (reporting bias)	Low risk	Planned outcomes according to trial registration relevant to this review reported
Other bias	Low risk	No other bias identified

He 2010			
Methods	Prospective, randomised, double-blind, placebo controlled clinical trial. Treatment duration was 6 months. Intention-to-treat analysis		
Participants	N=36. Patients were 40 years or older. Mean age 68.8y (erythromycin) versus 69.3 (placebo) Females 17% (erythromycin) versus 10% (placebo) FEV between 30-70% predicted. Mean FEV 1.12 (erythromycin) versus 1.02 (placebo) At least 10 pack/year smoking history No acute exacerbations during the previous 1 month Exclusions: Patients with significant other respiratory disorders other than COPD; history of unstable cardiovascular disease; hypersensitivity to macrolides		
Interventions	Prophylaxis: Erythromycin 250 mg 3 times a day Placebo		
Outcomes	Primary: 1. Number of acute COPD exacerbations 2. Neutrophil count in sputum Secondary: Quality of life Spirometry		
Notes	Funding: Not stated		
Risk of bias table			
Bias		Authors' judgement	Support for judgement
Random sequence generation (selection bias)		Unclear risk	Randomisation done but not clearly explained
Allocation concealment (selection bias)		Unclear risk	Allocation concealment not well explained
Blinding of participants and personnel (performance bias)		Low risk	Double-blind trial
Blinding of outcome assessment (detection bias)		Unclear risk	Unknown
Incomplete outcome data (attrition bias)		Low risk	All outcome data described using a CONSORT diagram
Selective reporting (reporting bias)		Low risk	All pre-specified outcomes were reported
Other bias		Low risk	No other bias identified

Seemungal 2008	
Methods	Prospective, randomised, double-blind, placebo controlled clinical trial with 12 month follow-up
Participants	N=109. Patients recruited from outpatient chest clinic from a single centre Mean age 66 (treatment arm) versus 68 in placebo arm

Seemungal 2008			
	Females 38% (treatment arm) versus 36% in placebo arm Severity of COPD was moderate to severe. (FEV between 30-70%). Mean FEV 1.27 (treatment arm) versus 1.36 (placebo arm) Exclusions: History of asthma, bronchiectasis, neoplasia, unstable cardiac status (including prolonged QTc and arrhythmias), macrolide allergy or history of abnormal liver functions		
Interventions	Prophylaxis: Erythromycin 250 mg twice daily Placebo		
Outcomes	Primary: Exacerbation frequency Airway inflammation		
Notes	Calculated sample size was 115 for 90% power and P value 0.05. However only 109 patients were recruited Funding: British Lung Foundation		
Risk of bias table			
Bias		Authors' judgement	Support for judgement
Random sequence generation (selection bias)		Low risk	Computer generated permuted block random sequence generation carried out
Allocation concealment (selection bias)		Low risk	Randomisation numbers were stored in sealed envelopes
Blinding of participants and personnel (performance bias)		Low risk	Placebo and erythromycin were concealed in identical capsules
Blinding of outcome assessment (detection bias)		Low risk	Unblinding occurred only after data entry
Incomplete outcome data (attrition bias)		Low risk	All outcomes/dropouts explained in a CONSORT diagram
Selective reporting (reporting bias)		Low risk	All pre-specified outcomes were reported
Other bias		Low risk	No other bias identified

Sethi 2010	
Methods	Prospective double-blind randomised placebo controlled clinical trial. Total treatment period was 48 weeks Analysis was done using intention-to-treat and per protocol. For this review only the results of the intention-to-treat analysis were taken Exacerbation of COPD was defined by two definitions. A primary definition (any confirmed acute exacerbation of COPD, unconfirmed pneumonia or any other lower respiratory tract infections) and a secondary definition (only confirmed exacerbations of COPD, excluding confirmed/unconfirmed pneumonia and any other lower respiratory tract infection)

Sethi 2010		
	For this review only the primary definition was used as it was an extended definition and hence was the more conservative definition	
Participants	N=1157. Aged 45 or over. Severity of COPD was GOLD stage 2 or worse. Had at least 2 exacerbations requiring treatment with antibiotics and/or oral steroids in the 12 months prior to enrolment Total follow-up period was 72 weeks. Total treatment period was 48 weeks	
Interventions	Pulsed prophylaxis: Moxifloxacin 400 mg/daily for 5 days. Treatment repeated every 8 weeks for a total of 6 courses Placebo daily for 5 days. Treatment repeated every 8 weeks for a total of 6 courses	
Outcomes	Primary: 1. Frequency of exacerbations Secondary: Health-related quality of life (assessed using SGRQ) Hospitalisations Mortality Changes in lung function Adverse events	
Notes	Funding: Received grant support from Bayer HealthCare AG	
Risk of bias table		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation was done but sequence generation not well explained
Allocation concealment (selection bias)	Unclear risk	Not explained
Blinding of participants and personnel (performance bias)	Low risk	Double-blind study
Blinding of outcome assessment (detection bias)	Low risk	Not explained
Incomplete outcome data (attrition bias)	Unclear risk	All outcome data were described using a CONSORT diagram for the entire study However data on the secondary outcome: HRQOL had reported loss to follow-up of 12% in the prophylactic antibiotic arm and 10% in the placebo arm. The reasons for the missing data pertaining to HRQOL outcome were not given
Selective reporting (reporting bias)	Low risk	All pre-specified outcomes were well described
Other bias	Low risk	Data was analysed as intention-to-treat as well as per protocol analysis. Both analysis were published

Shafuddin 2015	
Methods	Prospective, randomised, double blind, placebo controlled trial. Duration of treatment 13 weeks with 48 week post-treatment follow up Intention-to-treat analysis Originally designed to investigate the role antibiotics in eradicating C. pneumoniae in patients with COPD
Participants	N=292. Aged 45 years and above. Mean age 68.5 (roxithromycin/doxycycline), 67.6 (roxithromycin) and 66.7 (placebo) years Female: 36.6% (roxithromycin/doxycycline), 14.4% (doxycycline), 28.7% (placebo) Mean FEV1 % predicted, mean (SD): 32.53 (13.55) (roxithromycin/doxycycline), 33.93 (15.3) (doxycycline), 35.8 (15.2) (placebo) Meeting spirometric criteria for COPD (FEV1 ≤ 70 % predicted, ratio of FEV1 over FVC (FEV1/FVC) ≤60 %, reversibility of ≤ 10 % of predicted FEV1 or ≤ 200 ml if predicted FEV1 ≤2 L); smoking history ≥ 20 pack years; and at least three confirmed moderate or severe COPD exacerbations in the past two years (i.e. requiring treatment with antibiotics and/or oral corticosteroids and/or hospitalisation), positive serology for C. pneumoniae (IgG antibody titre ≥ 1:64). Exclusions: pulmonary disease other than COPD; treatment with antibiotics, exacerbation or an investigational drug in the four weeks before randomisation; pregnancy (serum pregnancy test) or breast feeding; history of hypersensitivity to macrolides, tetracyclines, beta-lactams or sulfamethoxazole: trimethoprim; serious cardiovascular, hepatic, renal or other systemic diseases; known long QT syndrome or corrected QT interval (QTc) >450 ms, sick sinus syndrome, bradycardia (<50 beats per minute) or severe hypokalaemia; epilepsy; treatment with medicine known to have important interaction with macrolides or tetracyclines; impaired hepatic function (aspartate aminotransferase or alanine aminotransferase > 2 times of the upper limit of normal (ULN), alkaline phosphatase ≥1.25 times the ULN, bilirubin >2 times the ULN and albumin <30 g/L); or unlikely to comply.
Interventions	Prophylaxis: Roxithromycin 300mg daily plus doxycycline 100 mg daily Roxithromycin 100 mg daily Placebo
Outcomes	Primary: COPD exacerbations over 48-week post-treatment period Secondary COPD exacerbations over the 12-week treatment period and the first and last 24-week post-treatment periods FEV1 and Forced Vital Capacity (FVC) over 60-week period Chronic Respiratory Disease Questionnaire (CRQ) scores over 60-week period Adverse events

Shafuddin 2015		
Notes	Funding: supported by Sanofi-Aventis Australia Pty Ltd (formally Hoechst Marion Roussel Pty Ltd). Sanofi-Aventis had no role in the preparation of this manuscript for publication.	
Risk of bias table		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Each eligible patient was assigned a sequential subject number followed by randomisation number provided by Hoechst Marion Roussel, Australia. Subjects were supplied with one of the three treatments according to their randomisation number". Clinical trials registry clarifies: computer sequence generation used for randomisation of subjects into treatment arms with 1:1:1 ratio.
Allocation concealment (selection bias)	Low risk	Each eligible patient was assigned a sequential subject number followed by randomisation number provided by Hoechst Marion Roussel, Australia. Subjects were supplied with one of the three treatments according to their randomisation number.
Blinding of participants and personnel (performance bias)	Low risk	Study medication was packed by Hoechst Marion Roussel in bottles labelled with the randomisation and batch numbers. The investigators, pharmacists and subjects were blinded to the study medication in these bottles.
Blinding of outcome assessment (detection bias)	Low risk	Triallists confirm that all participants, personnel and outcome assessors remained blinded until data had been analysed.
Incomplete outcome data (attrition bias)	Unclear risk	More patients dropped out of combined antibiotics treatment arm (21 vs 13 in single antibiotic arm and 10 in placebo arm), although according to triallists reasons were not related to study medication. All patients included in ITT analysis.
Selective reporting (reporting bias)	Low risk	Planned outcomes according to trial registration relevant to this review reported.
Other bias	Low risk	No other bias identified

Simpson 2014	
Methods	Prospective, randomised, double blind, placebo controlled trial. Duration of treatment 12 weeks with 12 week post-treatment follow up Intention-to-treat analysis
Participants	N=30. Aged 55 years and above. Mean age 71.7 (azithromycin) and 69.9 (placebo) years Female: 40% (azithromycin) and 33.3% (placebo) FEV1% predicted, mean (SD): 56.5 (13.7) (azithromycin) and 51.1 (13.7) (placebo) Adults (males and non-pregnant females) with a doctor's diagnosis of symptomatic COPD, post bronchodilator FEV1/FVC <70% and FEV1

Simpson 2014	
	<80% and persistent neutrophilic bronchitis defined as sputum neutrophil proportion of more 4 than 61% or more than 162x10 /mL sputum neutrophils demonstrated on two occasions Exclusions: no reported exacerbations or alterations in respiratory medications in the previous 4 weeks, inability to produce an adequate sputum sample, a FEV1
	<0.5 L, current smoking or having ceased smoking in the past 6 months, a known hypersensitivity to macrolides, an ECG assessment showing a prolonged QTc interval or an impairment of liver function
Interventions	Prophylaxis: Azithromycin 250 mg daily Placebo
Outcomes	Primary: 1. Reduction in sputum CXCL8 Secondary: Change in sputum neutrophil proportion Total bacterial load in sputum Health care utilisation Quality of life (SGRQ) Severe exacerbations Pulmonary function tests Chest computed tomography to measure airway thickness Adverse events
Notes	Funding: funded by the National Health and Medical Research Council of Australia through a project grant, ID 455508 2007_2009. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Concealed random allocation was undertaken by a blinded staff member who took no further part in the study. A random numbers table was computer generated (www.randomization.com) for treatment allocation using permuted blocks of six and participants were stratified according to smoking history (never or previous smokers).
Allocation concealment (selection bias)	Low risk	Concealed random allocation was undertaken by a blinded staff member who took no further part in the study. The active medication and placebo were prepared and packaged identically by a compounding chemist and dispensed by the John Hunter Hospital pharmacy according to the random number table.
Blinding of participants and personnel (performance bias)	Low risk	Both participants and study staff were blinded to the assignment of intervention.

Simpson 2014		
Blinding of outcome assessment (detection bias)	Low risk	The people assessing the outcomes are described as blinded in the trial registration.
Incomplete outcome data (attrition bias)	Low risk	Low and balanced drop out. Reasons for discontinuation unrelated to study medication.
Selective reporting (reporting bias)	Low risk	Planned outcomes according to trial registration relevant to this review reported.
Other bias	Low risk	No other bias identified

Suzuki 2001		
Methods	Prospective, randomised, placebo controlled clinical trial. Non-blinded	
Participants	N=109 Mean age 69y in erythromycin group and 72 in placebo group Mean FEV 1.47 in erythromycin group versus1.30 in placebo group 1 Females 13% in erythromycin group versus 18% in placebo group All study participants were treated with sustained release theophylline and inhaled anticholinergic agents Exclusions: Patients diagnosed with bronchiectasis or diffuse pan bronchiolitis	
Interventions	Prophylaxis: Erythromycin 200 mg to 400 mg/daily Placebo	
Outcomes	Acute exacerbations of COPD Adverse events	
Notes	Funding: not stated	
Risk of bias table		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation performed by random-number table
Allocation concealment (selection bias)	Low risk	The randomisation list was held independently from the investigators
Blinding of participants and personnel (performance bias)	High risk	This study was not blinded
Blinding of outcome assessment (detection bias)	High risk	As the study was not blinded the assessment of outcome would be biased
Incomplete outcome data (attrition bias)	Low risk	One patient excluded due to adverse events of erythromycin, all patients clearly accounted for
Selective reporting (reporting bias)	Low risk	All pre-specified outcomes were reported
Other bias	Low risk	No other bias identified

Tan 2016		
Methods	Prospective, randomised controlled trial. Blinding not stated in main trial report. Treatment duration 52 weeks	
Participants	N=54. Age range 49 to 70 years. Mean age 68.8 (erythromycin 12 months), 67.3 (erythromycin 6 months) and 69.3 (control) years Female 16.7% (erythromycin 12 months), 5.6% (erythromycin 6 months) and 11.1% (control) Mean FEV1 % predicted, mean (SD) 44.8 (13.9) (erythromycin 12 months), 46.5	
	(8.9) (erythromycin 6 months) and 42.1 (18.6) (control) Stable COPD outpatients (GOLD stages II_IV of 2006 guidelines: FEV 1 < 80% predicted and FEV1/forced vital capacity (FVC) < 70% after bronchial relaxation); no acute exacerbation; no change in therapeutic schedule; and no treatment with any antibiotics or glucocorticoids in the previous 4 weeks. Exclusions: patients with bronchial asthma, primary bronchiectasis, diffuse panbronchiolitis (DPB), active tuberculosis, lung cancer, pneumoconiosis, or other lung diseases with restrictive ventilatory impairment; patients with other serious systemic illnesses such as cardiovascular, nervous, or endocrine system illnesses, blood, hepatic, or kidney diseases, and malignant tumours; patients who were not cooperative or were completely unable to communicate; and patients who experienced serious adverse reactions to erythromycin	
Interventions	Prophylaxis: Erythromycin 125 mg 3 times a day for 12 months Erythromycin 125 mg 3 times a day for 6 months Control group (no antibiotic treatment)	
Outcomes	Concentrations of IL-17 and IL-23 in peripheral blood and induced sputum Six-Minute Walk Distance (Primary and secondary outcomes not specified)	
Notes	Funding: funded by the National Nature Science Foundation of China (81460009) and the Guangxi Natural Science Foundation (2015GXNSFAA139189, Z2012077, and Z2012081).	
Risk of bias table		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"randomly divided" - no other details
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias)	High risk	No blinding of participants or personnel described. Assume open-label (although abstract states double blind). Authors contacted - awaiting clarification response.

Tan 2016		
Blinding of outcome assessment (detection bias)	High risk	No blinding of outcome assessors described. Assume open-label (although abstract states double blind). Authors contacted - awaiting clarification response.
Incomplete outcome data (attrition bias)	Unclear risk	Low and balanced drop out but details not given of how many people were analysed at each time point.
Selective reporting (reporting bias)	Unclear risk	No prospective trial registration or protocol identified so not clear if outcomes of interest for this review may have been collected but not reported (e.g. serious adverse events, exacerbations, quality of life).
Other bias	Low risk	No additional bias identified

Uzun 2014	
Methods	Prospective, randomised double blind placebo controlled trial. Treatment duration 52 weeks Intention-to-treat analysis
Participants	N=92. Aged 18 years and above. Mean age 64.7 (azithromycin) and 64.9 (placebo) years Female 53% (azithromycin) and 60% (placebo) FEV1 % predicted, mean (SD) 44.2 (19.3) (azithromycin) and 45.0 (19.5) (placebo) Diagnosis of COPD according to the GOLD guidelines, had received treatment for three or more exacerbations of COPD in the previous year for which they received steroids or antibiotic treatment, clinically stable and could not have had a COPD exacerbation or respiratory-tract infection in the month before involvement in the study. Exclusions: history of other clinically significant respiratory diseases (e.g. asthma, cystic fibrosis); presence of bronchiectasis, as assessed by CT scan; maintenance antibiotic treatment; use of more than 10 mg prednisolone a day; allergy to macrolides; pregnancy or lactation in women; liver disease (alanine transaminase or aspartate transaminase concentrations that were two or more times the upper limit of normal); malignant disease of any kind for which the patient received treatment or was being monitored as part of follow-up after treatment; heart failure; and the use of drugs that could adversely interact with macrolides and for which therapeutic monitoring could not be undertaken.
Interventions	Prophylaxis: Azithromycin 500 mg 3 times a week Placebo
Outcomes	Primary: 1. Rate of exacerbations of COPD Secondary: Time to first exacerbation Hospital admission for acute exacerbations

Uzun 2014	
	Change in proportion of exacerbations needing admission to hospital versus treatment in an outpatient department compared with the previous year Treatment for an acute exacerbation of COPD (FEV1) after bronchodilation FVC bronchodilation Six-minute walk test Quality of life, as assessed by the SF-12 and the St George‚s Respiratory Questionnaire Acquisition of macrolide resistant microorganisms in sputum Adverse events
Notes	Funding: SoLong Trust. The sponsor of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report

Risk of bias table		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	An independent pharmacy randomly assigned patients (1:1), via a computer-generated randomisation sequence with permuted blocks of ten.
Allocation concealment (selection bias)	Low risk	Patients were automatically given the next allocated treatment by clinical trials staff at the hospital pharmacy. Participants and investigators were masked to treatment allocation throughout the study.
Blinding of participants and personnel (performance bias)	Low risk	Participants and investigators were masked to treatment allocation throughout the study.
Blinding of outcome assessment (detection bias)	Low risk	After data collection and data cleaning were completed, and after final database lock, investigators were unmasked and could assess outcomes and complete the data analysis.
Incomplete outcome data (attrition bias)	Low risk	Higher drop out in placebo arm, but results from the unadjusted and adjusted per-protocol analyses were almost identical to those from the intention-to-treat analysis and all participants included in safety analysis.
Selective reporting (reporting bias)	Low risk	Planned outcomes according to trial registration relevant to this review reported.
Other bias	Low risk	No additional bias identified.

Wang 2017	
Methods	Prospective, parallel, randomised controlled trial. Blinding not reported. Duration of treatment 26 weeks
Participants	N=86. Age range 61 to 83 years. Mean age 70.5 (azithromycin) and 72.4 (control) Female 44.2% (azithromycin) and 37.2 (placebo)

Wang 2017		
	10 cases of cardiac functional grade II, 27 cases of grade III and 6 cases of grade IV (azithromycin) and 11 cases of cardiac functional grade II, 23 cases of grade III and 9 cases of grade IV (placebo) Patients with pulmonary hypertension secondary to COPD. Patients whose mean arterial pressure was detected as not less than 25 mmHg by right cardiac catheterization in a quiescent condition or as no less than 30 mm Hg in a motion state and patients who had not suffered from acute attack of COPD or acute lung infection. Exclusions: severe cardiac, hepatic and liver function abnormality, pulmonary thromboembolism, allergic rhinitis, asthma or primary pulmonary hypertension or were allergic to the drugs used in the study	
Interventions	Prophylaxis: Azithromycin 250 mg daily Control group (no antibiotic treatment)	
Outcomes	Arterial oxygen pressure (PaO2) Arterial partial pressure of carbon dioxide (PaCO2) Blood pH FEV1	
	FVC Six minutes walking distance Pulmonary arterial pressure	
Notes	Funding: "Grant Support & Financial Disclosures: None"	
Risk of bias table		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"randomly divided into an observation group and a control group using random number table, 43 in each group"
Allocation concealment (selection bias)	Unclear risk	Not described.
Blinding of participants and personnel (performance bias)	High risk	No blinding of participants or personnel described. Assume open-label.
Blinding of outcome assessment (detection bias)	High risk	No blinding of outcome assessors described. Assume open-label.
Incomplete outcome data (attrition bias)	Unclear risk	Not described.
Selective reporting (reporting bias)	High risk	No prospective trial registration or protocol identified. Dyspnea grade reported as measured in the abstract and not reported. Not clear currently if FEV1 and FVC variance are SDs or SEs.
Other bias	Low risk	No additional bias identified.

Overall study risk of bias and directness

This table was compiled by reviewers at NICE.

Table 8 Overall risk of bias and directness

Study name	Risk of bias	Directness
Albert 2011	Low	Directly applicable
Berkof 2013	Moderate[1]	Directly applicable
Brill 2015	Low/Moderate[2]	Directly applicable
He 2010	Moderate[3]	Directly applicable
Seemungal 2008	Low	Directly applicable
Sethi 2010	Moderate[4]	Directly applicable
Shafuddin 2015	Low	Directly applicable
Suzuki 2001	High[5]	Directly applicable
Simpson 2014	Low	Directly applicable
Tan 2016	High[6]	Directly applicable
Uzun 2014	Low	Directly applicable
Wang 2017	High[7]	Partially directly applicable[8]

1. Moderate risk of bias due to poor reporting of the FEV1 outcome.
2. Low risk for SGRQ outcome assessed by the blinded participants; moderate risk of bias for outcomes measured by the non-blinded assessors.
3. Due to the lack of information regarding the methods of randomisation, allocation concealment and blinding of outcome assessors.
4. Due to the lack of information on the details of randomisation and allocation concealment and the unexplained loss to follow up.
5. Due to the lack of blinding of participants, personnel and outcome assessors.
6. Due to the lack of information regarding randomisation and allocation concealment and the lack of blinding of participants, personnel and outcome assessors.
7. Due to the lack of blinding of participants, personnel and outcome assessors and the lack of a data for the breathlessness outcome.
8. Wang 2017 recruited participants with pulmonary hypertension secondary to COPD.

Table 9 Subgroup data for smokers from Han 2014* (included in under Albert 2011). Hazard ratio (Azithromycin versus placebo) for time to first exacerbation.

Subgroup (n)	HR (95% CI)	P value
All (1,113)	0.71 (0.61, 0.83)	<0.0001
Ex-smoker (867)	0.65 (0.55, 0.77)	<0.0001
Smoker (246)	0.99 (0.71, 1.38)	0.95

1. Data extracted from Han 2014, Table 2.

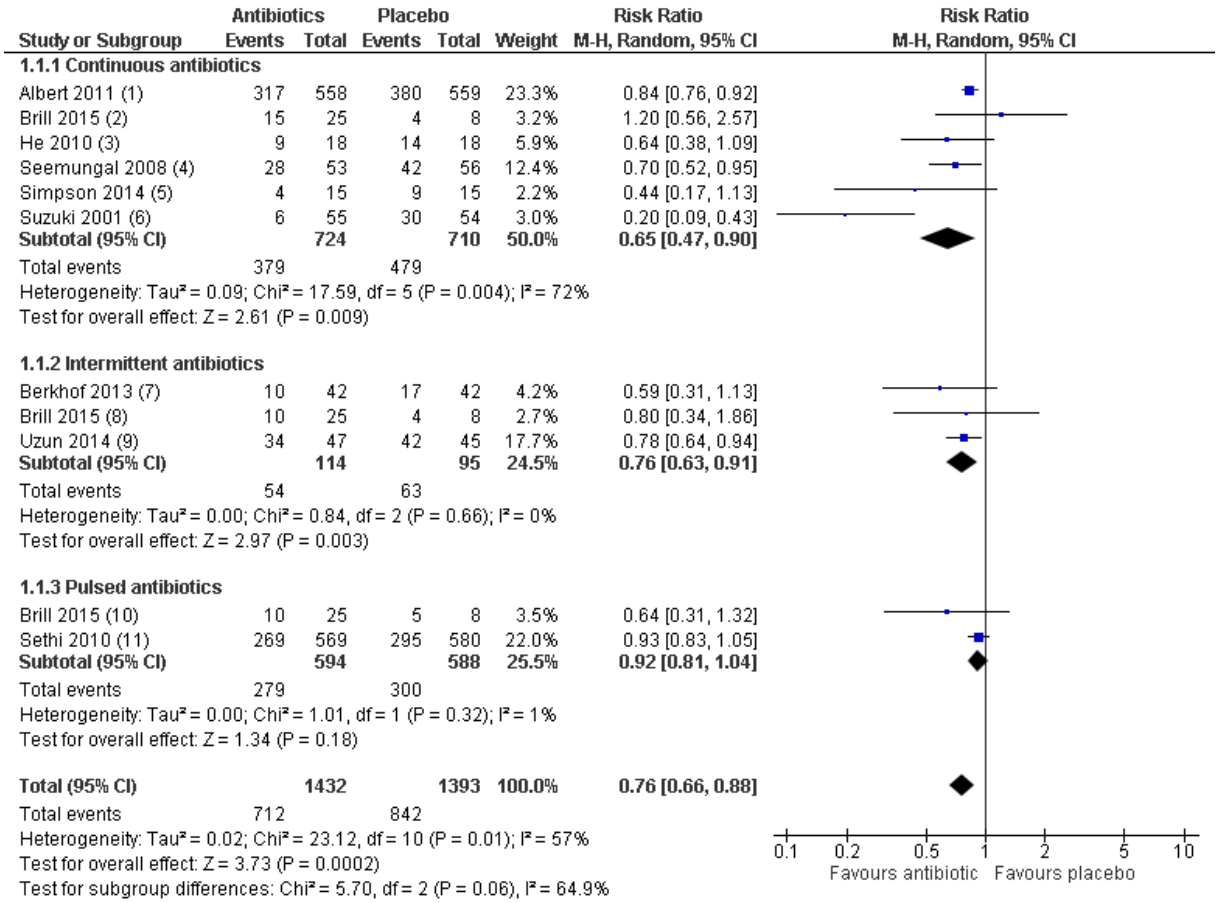
Appendix F - Forest plots

Preventing exacerbations

The following plots were based on data from the Cochrane review with the addition of data from Suzuki 2001. However, the dichotomous data plots have been altered to show RR, not OR, and the choice of fixed effect or random effects model is made according to the methods in appendix B. The sensitivity analyses were carried out by NICE Guideline Updates Team using data from the Cochrane review.

Antibiotics versus placebo

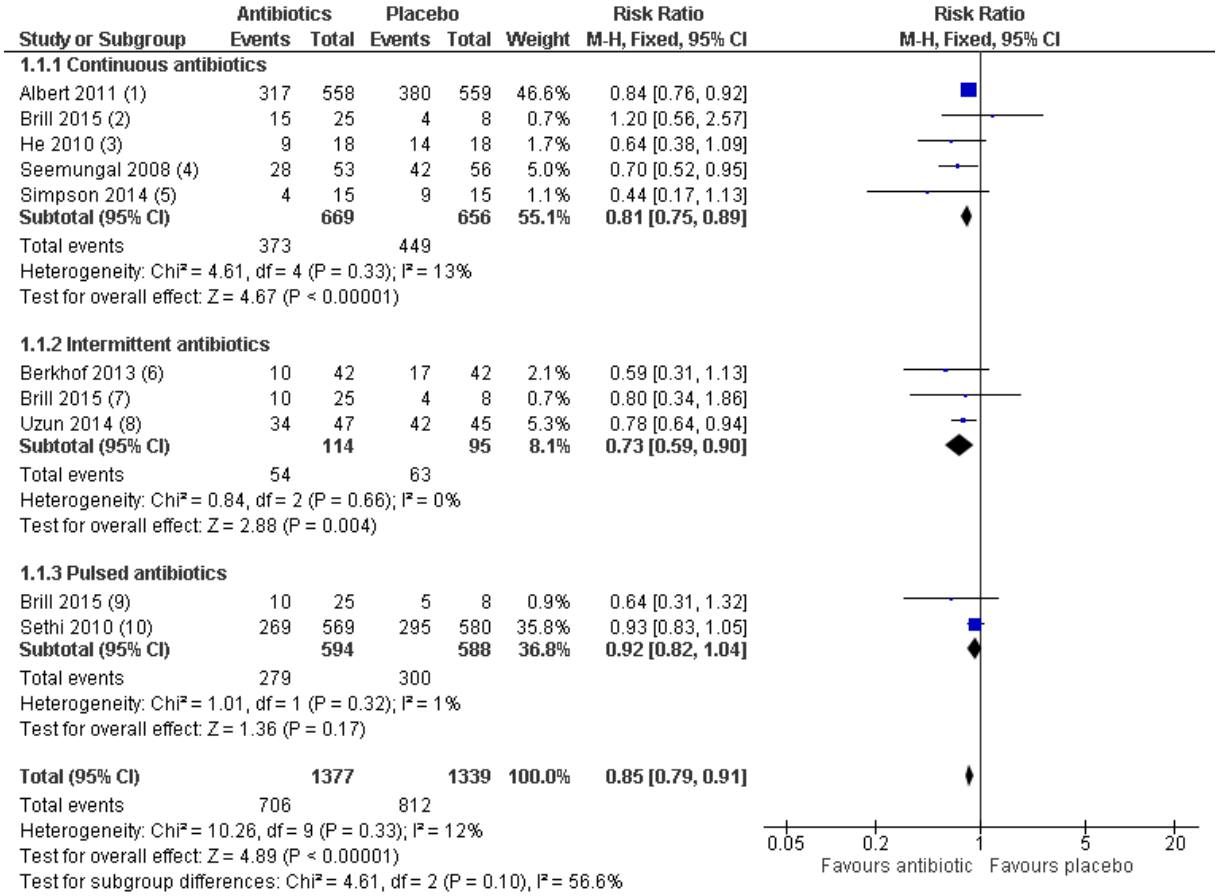
Number of people with ≥ 1 exacerbation



Footnotes

(1) Azithromycin 250mg daily for 12 months.
(2) Doxycycline 100mg daily for 13 weeks. Control group split three ways.
(3) Erythromycin 125mg three times/day for six months.
(4) Erythromycin 250mg twice/day for 12 months.
(5) Azithromycin 250mg daily for 12 weeks. Outcome reported at 26 weeks.
(6) Study lacked blinding
(7) Azithromycin 250mg three times/week for 12 weeks.
(8) Azithromycin 250mg three times/week for 13 weeks. Control group split three ways.
(9) Azithromycin 500mg three times/week for 12 months.
(10) Pulsed moxifloxacin 400mg daily for five days every four weeks for 13 weeks. Control group split three ways.
(11) Moxifloxacin 400mg daily for for five days every eight weeks for 48 weeks.

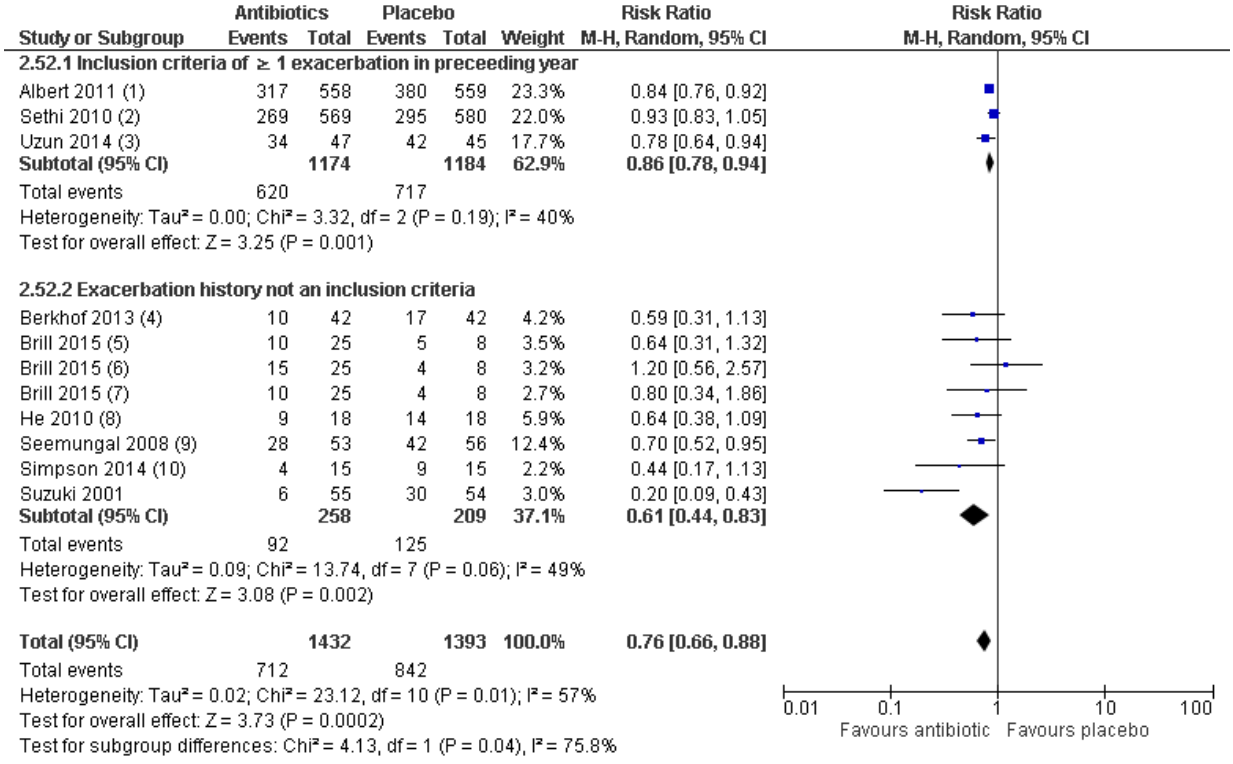
Sensitivity analysis removing studies at high risk of bias: number of people with ≥ 1 exacerbation



Footnotes

(1) Azithromycin 250mg daily for 12 months.
(2) Doxycycline 100mg daily for 13 weeks. Control group split three ways.
(3) Erythromycin 125mg three times/day for six months.
(4) Erythromycin 250mg twice/day for 12 months.
(5) Azithromycin 250mg daily for 12 weeks. Outcome reported at 26 weeks.
(6) Azithromycin 250mg three times/week for 12 weeks.
(7) Azithromycin 250mg three times/week for 13 weeks. Control group split three ways.
(8) Azithromycin 500mg three times/week for 12 months.
(9) Pulsed moxifloxacin 400mg daily for five days every four weeks for 13 weeks. Control group split three ways.
(10) Moxifloxacin 400mg daily for for five days every eight weeks for 48 weeks.

Subgroup analysis: number of people with ≥ 1 exacerbation by exacerbation history

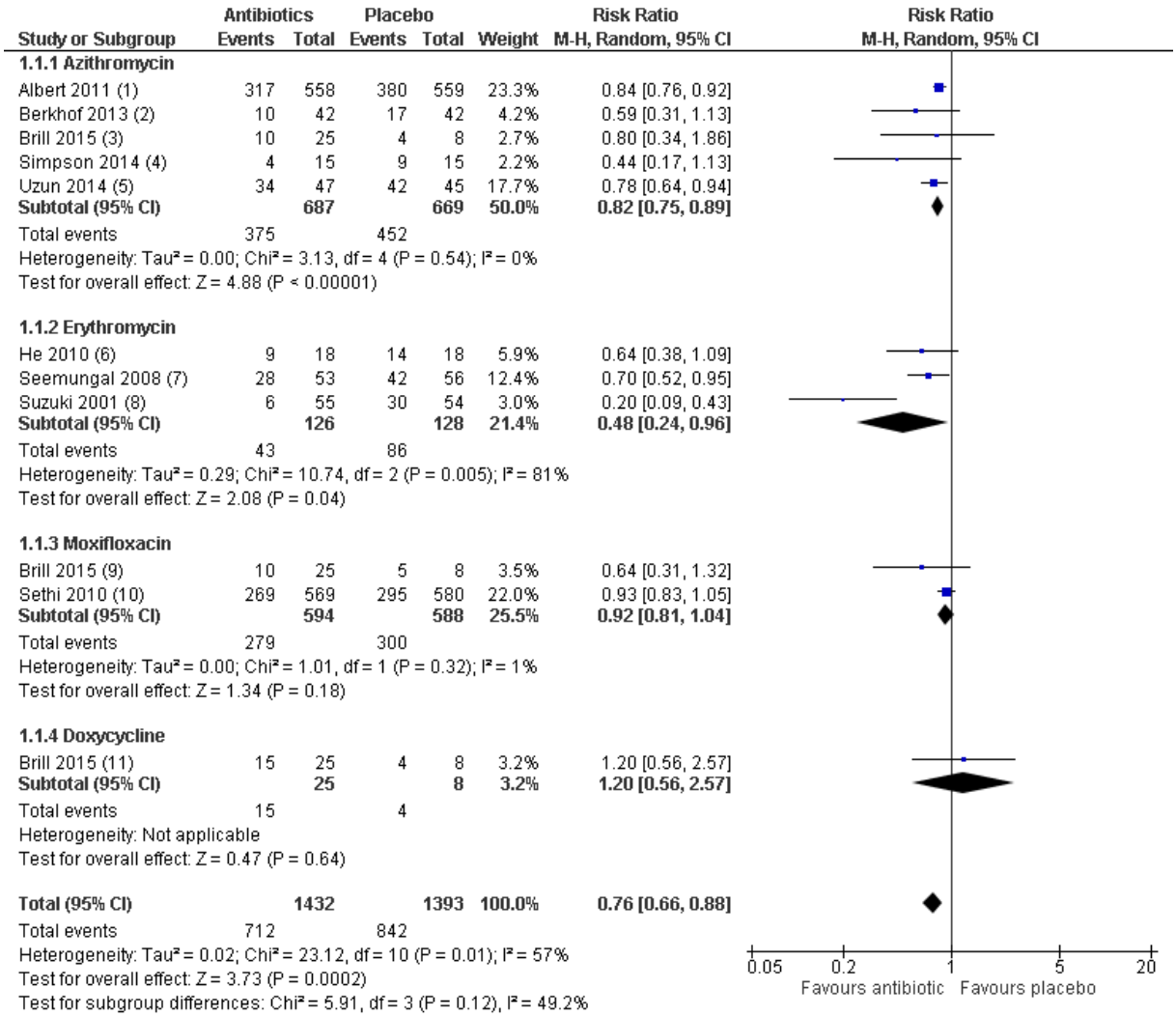


Study or Subgroup	Antibiotics Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
2.52.1 Inclusion criteria of ≥ 1 exacerbation in preceeding year						
Albert 2011 (1)	317	558	380	559	23.3%	0.84 [0.76, 0.92]
Sethi 2010 (2)	269	569	295	580	22.0%	0.93 [0.83, 1.05]
Uzun 2014 (3)	34	47	42	45	17.7%	0.78 [0.64, 0.94]
Subtotal (95% CI)		**1174**		**1184**	**62.9%**	**0.86 [0.78, 0.94]**
Total events	620		717			
Heterogeneity: Tau² = 0.00; Chi² = 3.32, df = 2 (P = 0.19); I² = 40%						
Test for overall effect: Z = 3.25 (P = 0.001)						
2.52.2 Exacerbation history not an inclusion criteria						
Berkhof 2013 (4)	10	42	17	42	4.2%	0.59 [0.31, 1.13]
Brill 2015 (5)	10	25	5	8	3.5%	0.64 [0.31, 1.32]
Brill 2015 (6)	15	25	4	8	3.2%	1.20 [0.56, 2.57]
Brill 2015 (7)	10	25	4	8	2.7%	0.80 [0.34, 1.86]
He 2010 (8)	9	18	14	18	5.9%	0.64 [0.38, 1.09]
Seemungal 2008 (9)	28	53	42	56	12.4%	0.70 [0.52, 0.95]
Simpson 2014 (10)	4	15	9	15	2.2%	0.44 [0.17, 1.13]
Suzuki 2001	6	55	30	54	3.0%	0.20 [0.09, 0.43]
Subtotal (95% CI)		**258**		**209**	**37.1%**	**0.61 [0.44, 0.83]**
Total events	92		125			
Heterogeneity: Tau² = 0.09; Chi² = 13.74, df = 7 (P = 0.06); I² = 49%						
Test for overall effect: Z = 3.08 (P = 0.002)						
Total (95% CI)		**1432**		**1393**	**100.0%**	**0.76 [0.66, 0.88]**
Total events	712		842			
Heterogeneity: Tau² = 0.02; Chi² = 23.12, df = 10 (P = 0.01); I² = 57%						
Test for overall effect: Z = 3.73 (P = 0.0002)						
Test for subgroup differences: Chi² = 4.13, df = 1 (P = 0.04), I² = 75.8%						

Footnotes

(1) Azithromycin 250mg daily for 12 months.
(2) Moxifloxacin 400mg daily for for five days every eight weeks for 48 weeks.
(3) Azithromycin 500mg three times/week for 12 months.
(4) Azithromycin 250mg three times/week for 12 weeks.
(5) Moxifloxacin 400mg daily for five days every four weeks for 13 weeks. Control group split three ways.
(6) Doxycycline 100mg daily for 13 weeks. Control group split three ways.
(7) Azithromycin 250mg three times/week for 13 weeks. Control group split three ways.
(8) Erythromycin 125mg three times/day for six months.
(9) Erythromycin 250mg twice/day for 12 months.
(10) Azithromycin 250mg daily for 12 weeks. Severe exacerbations (requiring unscheduled visit, antibiotics and/or steroids). Outcome...

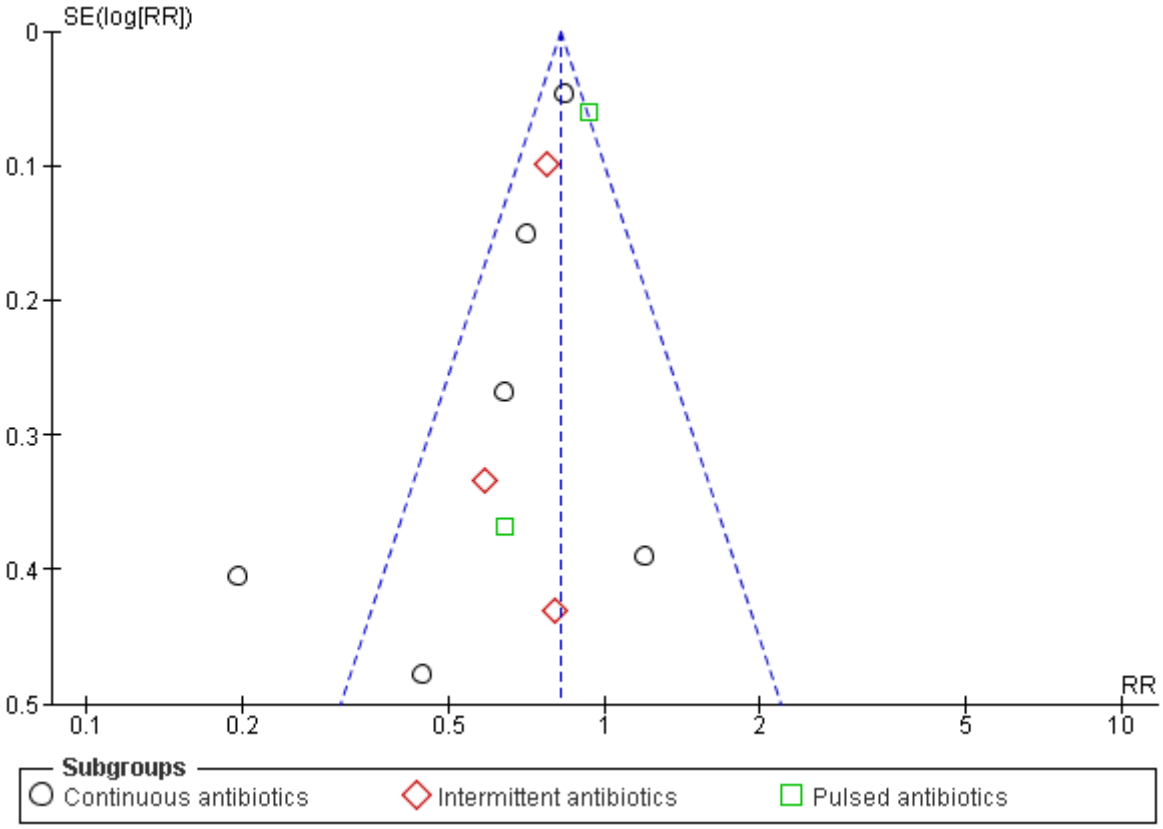
Subgroup analysis: number of people with ≥ 1 exacerbation by drug



Footnotes

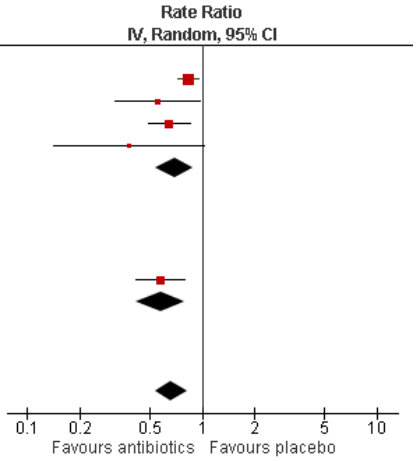
(1) Azithromycin 250mg daily for 12 months.
(2) Azithromycin 250mg three times/week for 12 weeks.
(3) Azithromycin 250mg three times/week for 13 weeks. Control group split three ways.
(4) Azithromycin 250mg daily for 12 weeks. Outcome reported at 26 weeks.
(5) Azithromycin 500mg three times/week for 12 months.
(6) Erythromycin 125mg three times/day for six months.
(7) Erythromycin 250mg twice/day for 12 months.
(8) Study lacked blinding.
(9) Pulsed moxifloxacin 400mg daily for five days every four weeks for 13 weeks. Control group split three ways.
(10) Moxifloxacin 400mg daily for for five days every eight weeks for 48 weeks.
(11) Doxycycline 100mg daily for 13 weeks. Control group split three ways.

Publication bias assessment: funnel plot for number of people with ≥ 1 exacerbation



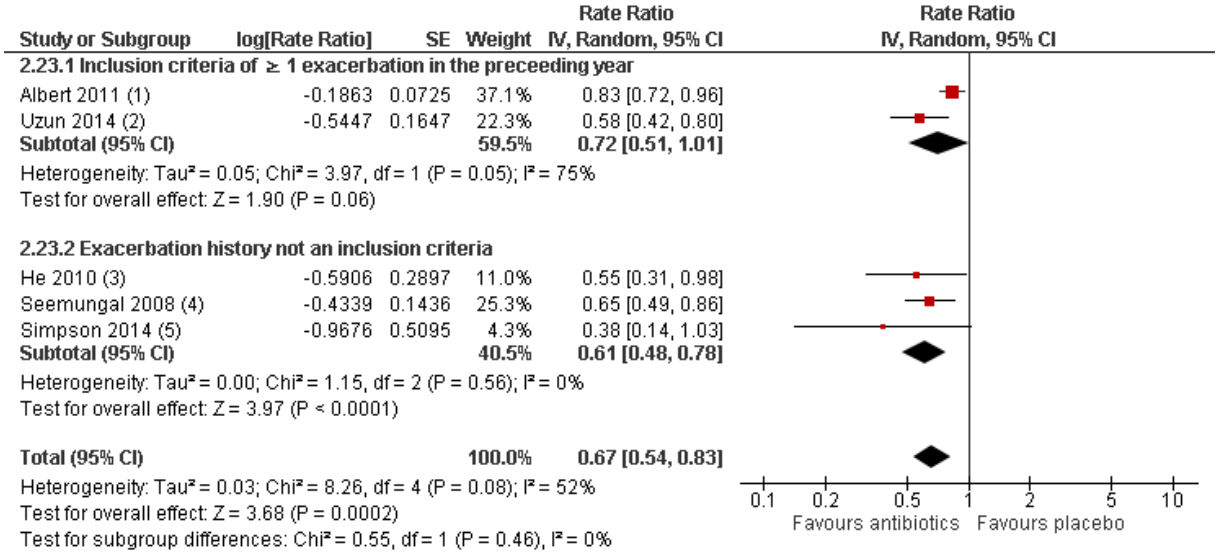
Rate of exacerbations per patient per year

Study or Subgroup	log[Rate Ratio]	SE	Antibiotics Total	Placebo Total	Weight	Rate Ratio IV, Random, 95% CI
1.23.1 Continuous antibiotics						
Albert 2011 (1)	-0.1863	0.0725	558	559	37.1%	0.83 [0.72, 0.96]
He 2010 (2)	-0.5906	0.2897	18	18	11.0%	0.55 [0.31, 0.98]
Seemungal 2008 (3)	-0.4339	0.1436	53	56	25.3%	0.65 [0.49, 0.86]
Simpson 2014 (4)	-0.9676	0.5095	15	15	4.3%	0.38 [0.14, 1.03]
Subtotal (95% CI)			**644**	**648**	**77.7%**	**0.69 [0.54, 0.89]**
Heterogeneity: Tau² = 0.03; Chi² = 5.73, df = 3 (P = 0.13); I² = 48%						
Test for overall effect: Z = 2.94 (P = 0.003)						
1.23.2 Intermittent antibiotics						
Uzun 2014 (5)	-0.5447	0.1647	47	45	22.3%	0.58 [0.42, 0.80]
Subtotal (95% CI)			**47**	**45**	**22.3%**	**0.58 [0.42, 0.80]**
Heterogeneity: Not applicable						
Test for overall effect: Z = 3.31 (P = 0.0009)						
Total (95% CI)			**691**	**693**	**100.0%**	**0.67 [0.54, 0.83]**
Heterogeneity: Tau² = 0.03; Chi² = 8.26, df = 4 (P = 0.08); I² = 52%						
Test for overall effect: Z = 3.68 (P = 0.0002)						
Test for subgroup differences: Chi² = 0.76, df = 1 (P = 0.38), I² = 0%						



Footnotes
(1) Azithromycin 250 mg daily for 12 months.
(2) Erythromycin 125mg three times/day for six months.
(3) Erythromycin 250mg twice a day for 12 months.
(4) Azithromycin 250 mg daily for 12 weeks. Outcome reported at 26 weeks.
(5) Azithromycin 500mg three times/week for 12 months.

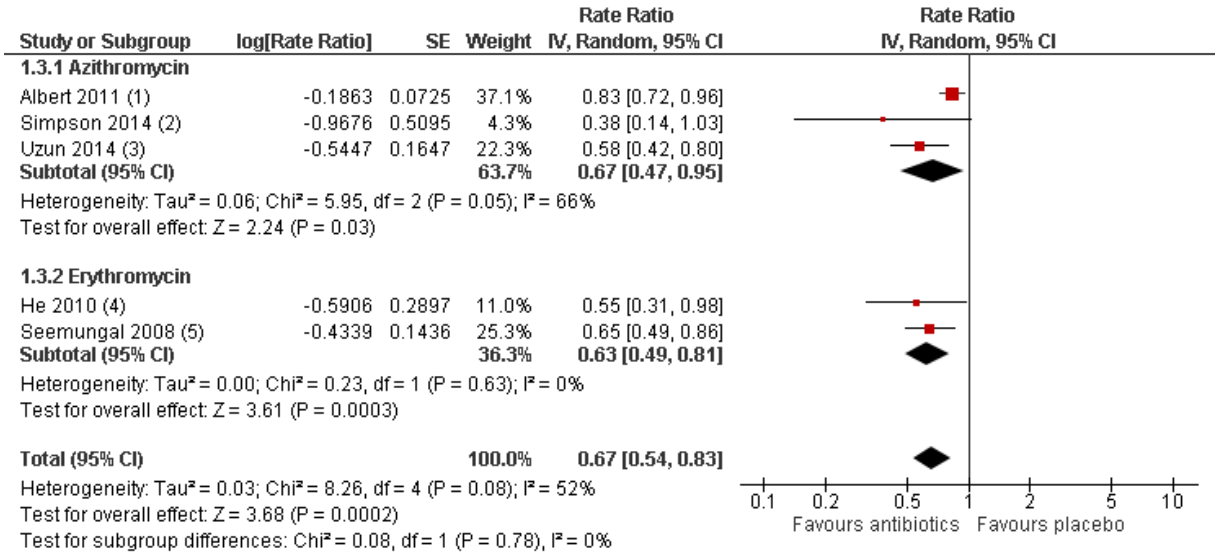
Subgroup analysis: rate of exacerbations per patient per year by exacerbation history



Footnotes

(1) Azithromycin 250 mg daily for 12 months.
(2) Azithromycin 500mg three times/week for 12 months.
(3) Erythromycin 125mg three times/day for six months.
(4) Erythromycin 250mg twice a day for 12 months.
(5) Azithromycin 250 mg daily for 12 weeks. Outcome reported at 26 weeks.

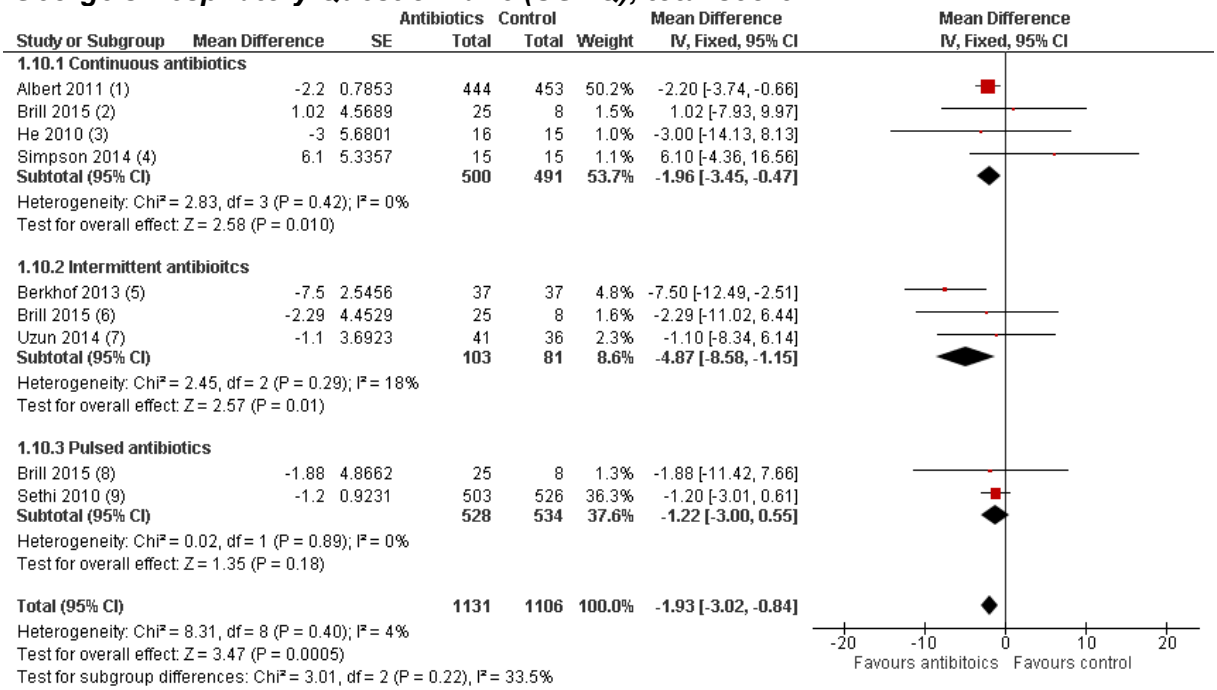
Subgroup analysis: rate of exacerbations per patient per year by drug



Footnotes

(1) Azithromycin 250 mg daily for 12 months.
(2) Azithromycin 250 mg daily for 12 weeks. Outcome reported at 26 weeks.
(3) Azithromycin 500mg three times/week for 12 months.
(4) Erythromycin 125mg three times/day for six months.
(5) Erythromycin 250mg twice a day for 12 months.

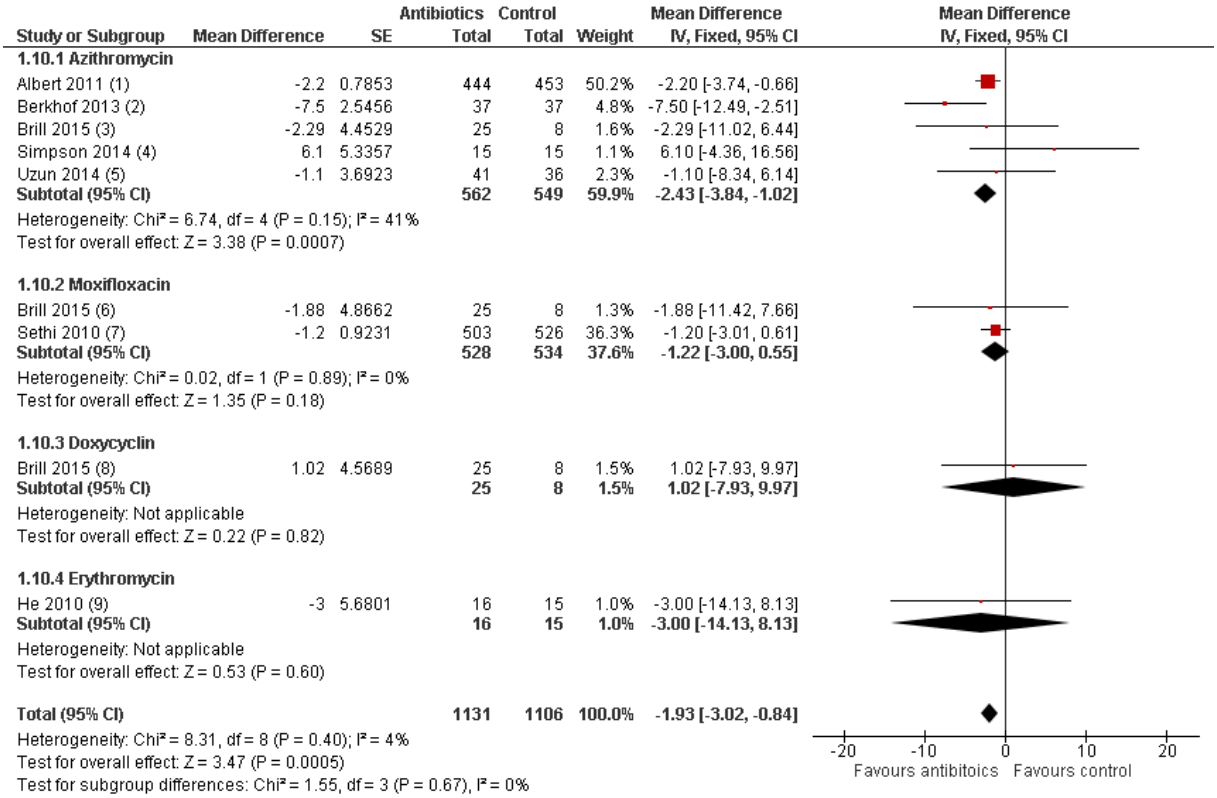
St. George's Respiratory Questionnaire (SGRQ), total score



Footnotes

(1) Azithromycin 250mg daily for 12 months.
(2) Doxycycline 100mg daily for 13 weeks. Control group split three ways.
(3) Erythromycin 125mg three times/day for six months.
(4) Azithromycin 250mg daily for 12 weeks. Outcome reported at 26 weeks.
(5) Azithromycin 250mg three times/week for 12 weeks.
(6) Azithromycin 250mg three times/week for 13 weeks. Control group split three ways.
(7) Azithromycin 500mg three times/week for 12 months.
(8) Pulsed moxifloxacin 400mg daily for 5 days every 4 weeks for 13 weeks. Control group split three ways.
(9) Moxifloxacin 400mg daily for for 5 days every 8 weeks for 48 weeks.

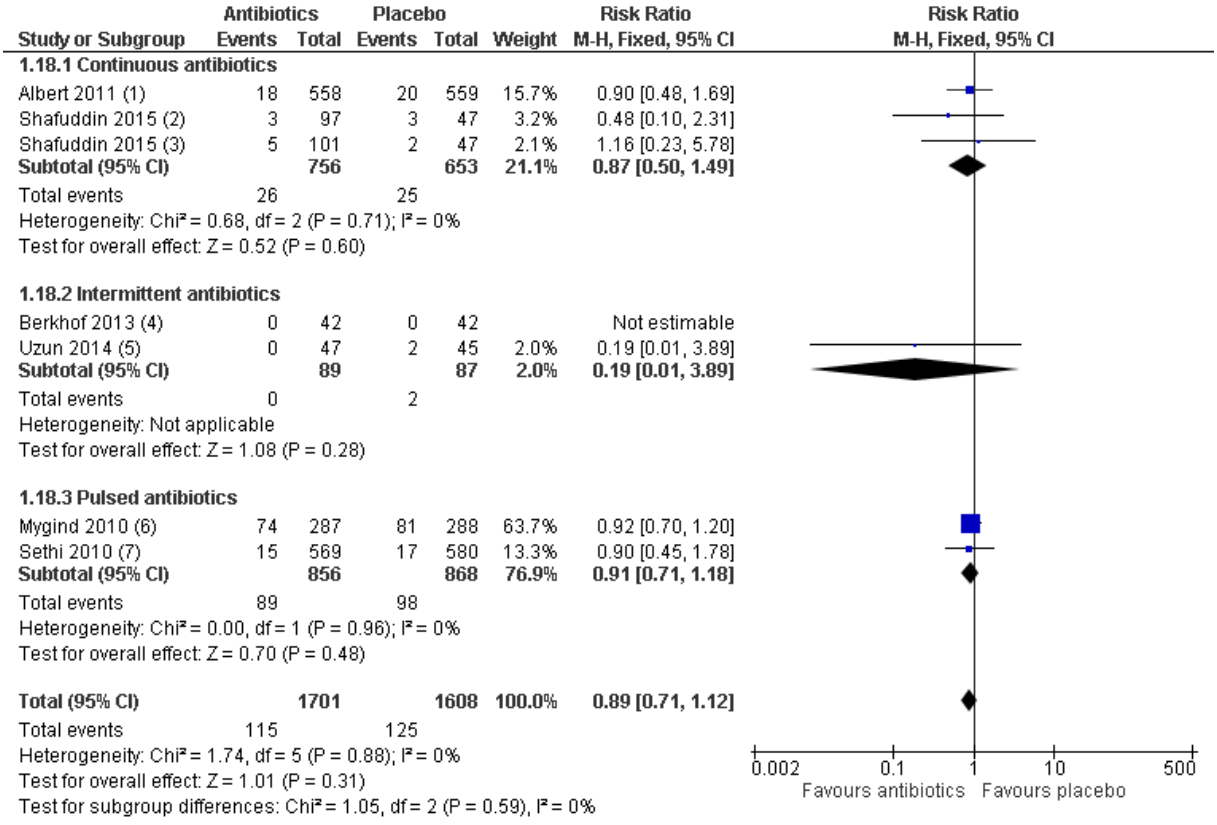
Subgroup analysis: SGRQ total score by drug



Footnotes

(1) Azithromycin 250mg daily for 12 months.
(2) Azithromycin 250mg three times/week for 12 weeks.
(3) Azithromycin 250mg three times/week for 13 weeks. Control group split three ways.
(4) Azithromycin 250mg daily for 12 weeks. Outcome reported at 26 weeks.
(5) Azithromycin 500mg three times/week for 12 months.
(6) Pulsed moxifloxacin 400mg daily for 5 days every 4 weeks for 13 weeks. Control group split three ways.
(7) Moxifloxacin 400mg daily for for 5 days every 8 weeks for 48 weeks.
(8) Doxycycline 100mg daily for 13 weeks. Control group split three ways.
(9) Erythromycin 125mg three times/day for six months.

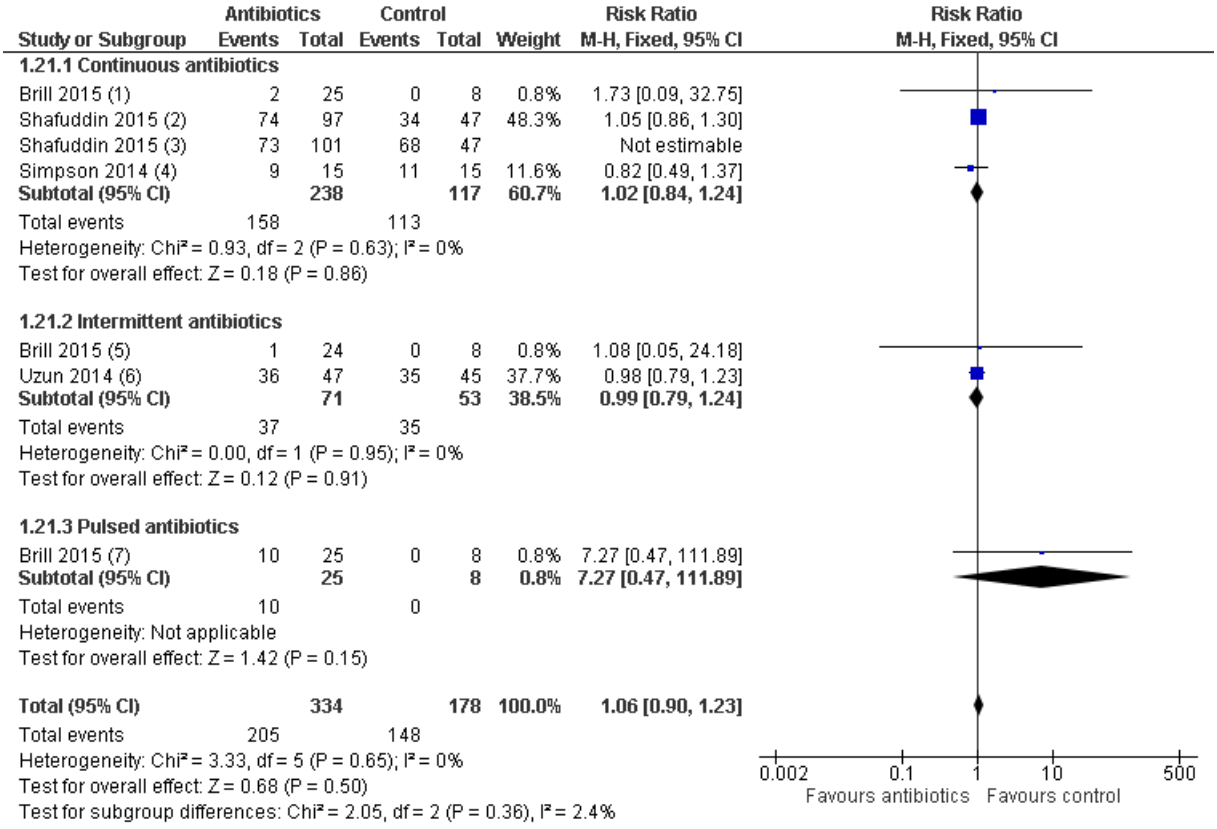
Mortality



Footnotes

(1) Azithromycin 250mg daily for 12 months.
(2) Roxithromycin 300mg daily for 12 weeks. Outcome reported at 60 weeks. Control group (5 deaths total) halved.
(3) Roxithromycin 300mg daily + doxycyline 100mg for 12 weeks. Outcome reported at 60 weeks. Control group (5 deaths total) halved.
(4) Azithromycin 250mg three times/week for 12 weeks.
(5) Azithromycin 500mg three times/week for 12 months.
(6) Azithromycin 500mg daily for 3 days every month for 36 months.
(7) Moxifloxacin 400mg daily for five days every eight weeks for 48 weeks.

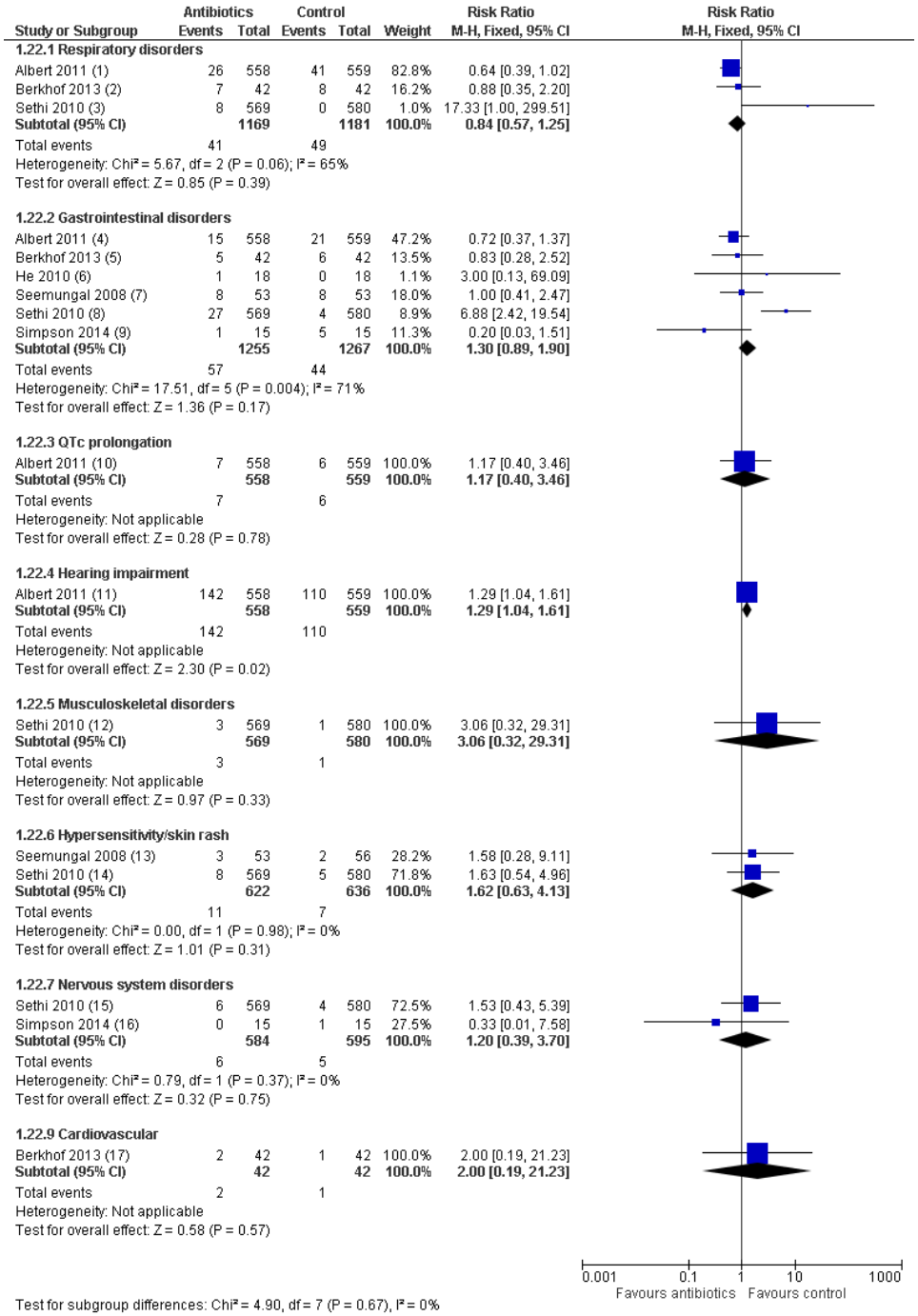
Number of people with ≥ 1 adverse event



Footnotes

(1) Doxycycline 100mg daily for 13 weeks. Treatment related AEs. Control group split three ways.
(2) Roxithromycin 300mg daily for 12 weeks. Outcome reported at 60 weeks. Control group halved.
(3) Roxithromycin 300mg daily + doxycyline 100mg daily. Outcome reported at 60 weeks. Control group halved.
(4) Azithromycin 250mg daily for 12 weeks. "Other" adverse event. Outcome reported at 26 weeks.
(5) Azithromycin 250mg three times/week for 13 weeks. Treatment related AEs. Control group split three ways
(6) Azithromycin 500mg three times/week for 12 months.
(7) Pulsed moxifloxacin 400mg daily for five days every four weeks for 13 weeks. Treatment related AEs. Control group split three ways.

Adverse events by type

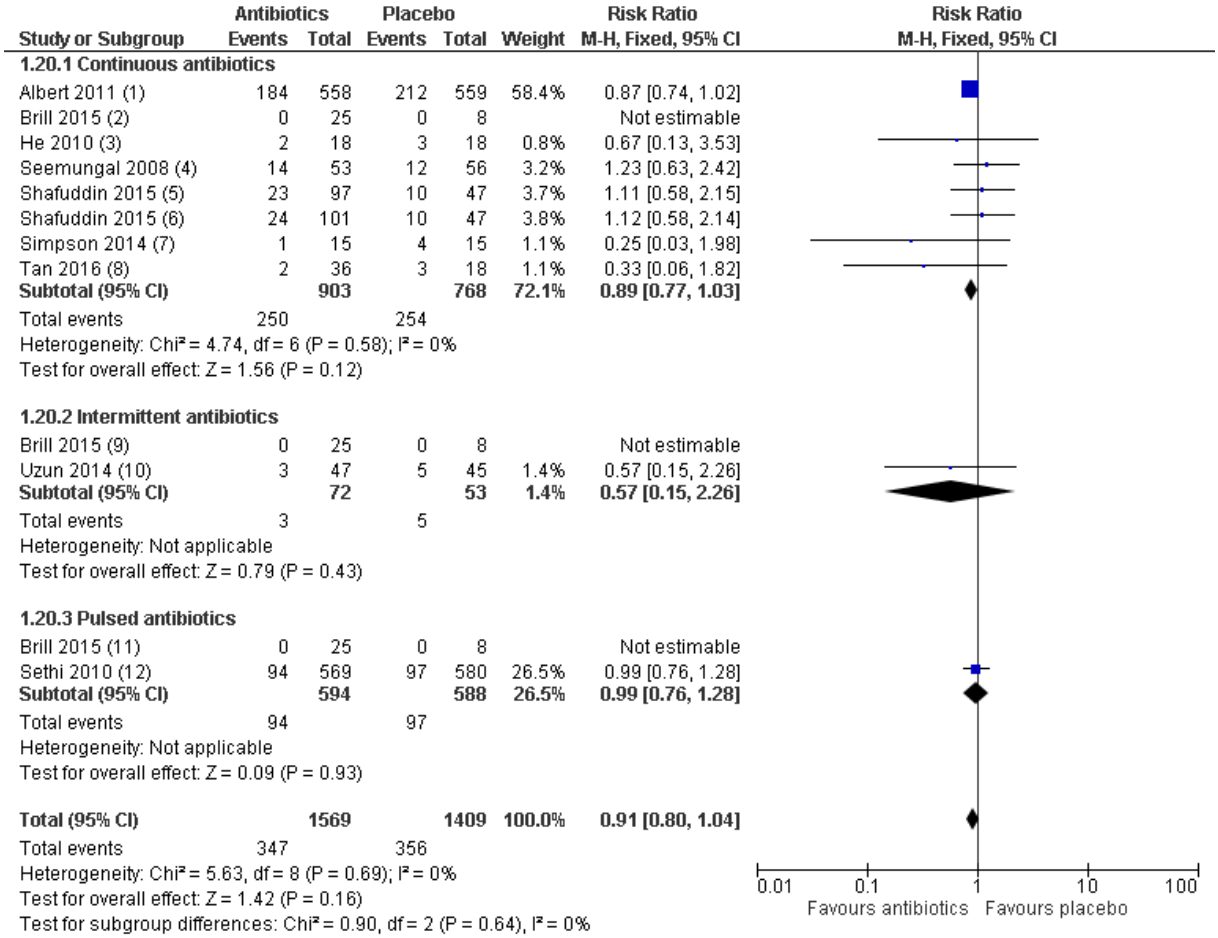


Test for subgroup differences: Chi² = 4.90, df = 7 (P = 0.67), I² = 0%

Footnotes

(1) Azithromycin 250mg daily for 12 months.
(2) Azithromycin 250mg three times/week for 12 weeks.
(3) Moxifloxacin 400mg daily for for five days every eight weeks for 48 weeks (pulsed).
(4) Azithromycin 250mg daily for 12 months.
(5) Azithromycin 250mg three times/week for 12 weeks.
(6) Erythromycin 125mg three times/day for six months.
(7) Erythromycin 250mg twice/day for 12 months.
(8) Moxifloxacin 400mg daily for for five days every eight weeks for 48 weeks (pulsed).
(9) Azithromycin 250mg daily for 12 weeks. "Diarrhoea". Outcome reported at 26 weeks.
(10) Azithromycin 250mg daily for 12 months.
(11) Azithromycin 250mg daily for 12 months.
(12) Moxifloxacin 400mg daily for for five days every eight weeks for 48 weeks (pulsed).
(13) Erythromycin 250mg twice/day for 12 months.
(14) Moxifloxacin 400mg daily for for five days every eight weeks for 48 weeks (pulsed).
(15) Moxifloxacin 400mg daily for for five days every eight weeks for 48 weeks (pulsed).
(16) Azithromycin 250mg daily for 12 weeks. "Headache". Outcome reported at 26 weeks.
(17) Azithromycin 250mg three times/week for 12 weeks.

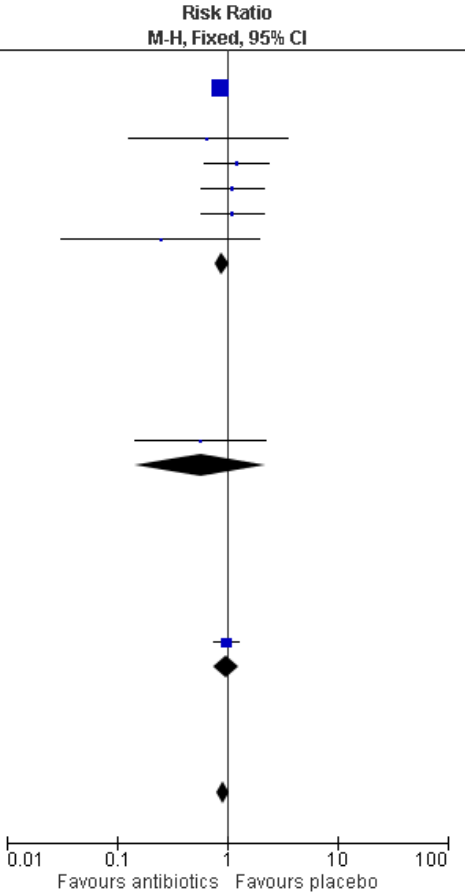
Number of people with ≥ 1 serious adverse event (SAE)



Footnotes

(1) Azithromycin 250mg daily for 12 months.
(2) Doxycycline 100mg daily. Control group split (No events reported)
(3) Erythromycin 125mg three times/day for six months.
(4) Erythromycin 250mg twice a day for 12 months.
(5) Roxithromycin 300mg daily for 12 weeks. Outcome reported at 60 weeks. Control group halved.
(6) Roxithromycin 300mg daily + doxycyline 100mg daily. Outcome reported at 60 weeks. Control group halved.
(7) Azithromycin 250mg daily for 12 weeks. Outcome reported at 26 weeks.
(8) Adverse event leading to discontinuation. Two erythromycin arms combined (erythromycin 125mg three times/day for 6 months and 12...
(9) Azithromycin 250mg three times/week. Control group split (No events reported)
(10) Azithromycin 500mg three times/week for 12 months.
(11) Pulsed moxifloxacin 400mg daily for five days every four weeks for 13 weeks. Control group split (No events reported).
(12) Moxifloxacin 400mg daily for for five days every eight weeks for 48 weeks.

Sensitivity analyses removing studies at high risk of bias: number of people with ≥ 1 serious adverse event (SAE)

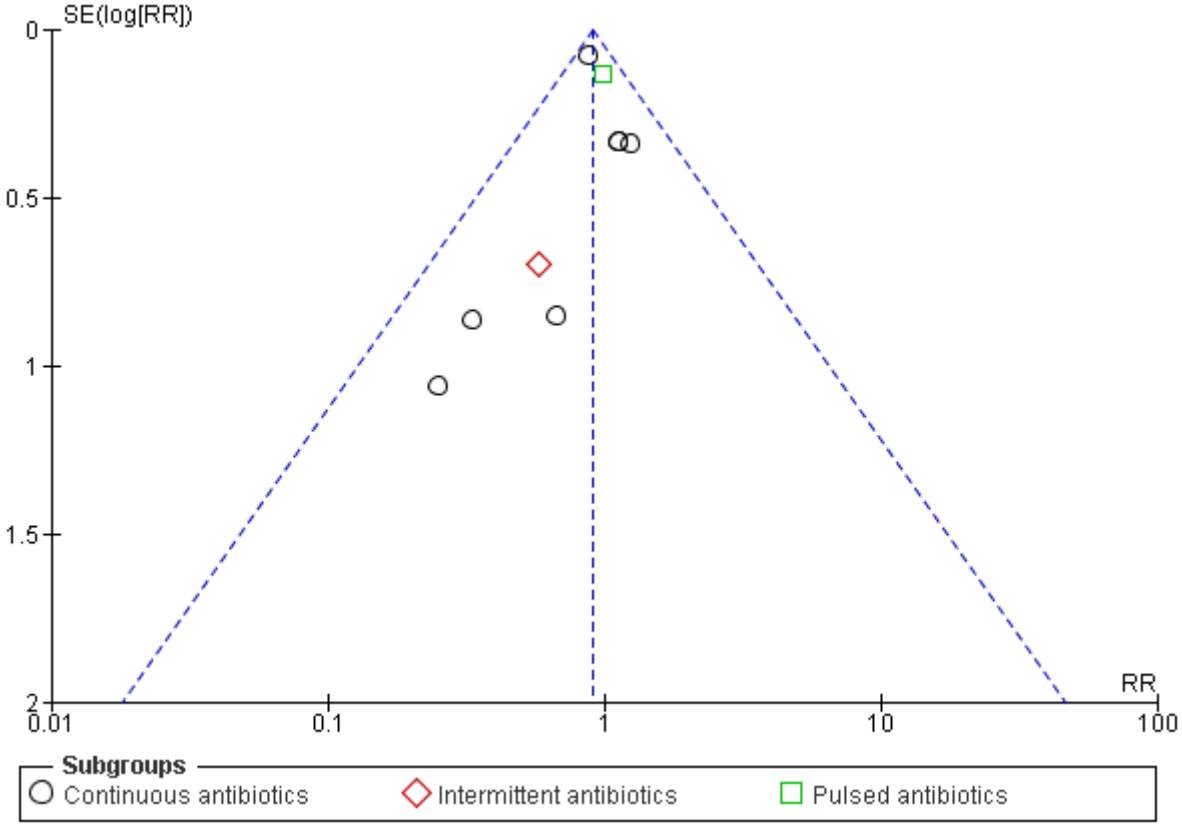


Study or Subgroup	Antibiotics Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
4.20.1 Continuous antibiotics						
Albert 2011 (1)	184	558	212	559	59.0%	0.87 [0.74, 1.02]
Brill 2015 (2)	0	25	0	8		Not estimable
He 2010 (3)	2	18	3	18	0.8%	0.67 [0.13, 3.53]
Seemungal 2008 (4)	14	53	12	56	3.3%	1.23 [0.63, 2.42]
Shafuddin 2015 (5)	24	101	10	47	3.8%	1.12 [0.58, 2.14]
Shafuddin 2015 (6)	23	97	10	47	3.8%	1.11 [0.58, 2.15]
Simpson 2014 (7)	1	15	4	15	1.1%	0.25 [0.03, 1.98]
Subtotal (95% CI)		**867**		**750**	**71.8%**	**0.90 [0.78, 1.04]**
Total events	248		251			
Heterogeneity: Chi² = 3.44, df = 5 (P = 0.63); I² = 0%						
Test for overall effect: Z = 1.42 (P = 0.16)						
4.20.2 Intermittent antibiotics						
Brill 2015 (8)	0	25	0	8		Not estimable
Uzun 2014 (9)	3	47	5	45	1.4%	0.57 [0.15, 2.26]
Subtotal (95% CI)		**72**		**53**	**1.4%**	**0.57 [0.15, 2.26]**
Total events	3		5			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.79 (P = 0.43)						
4.20.3 Pulsed antibiotics						
Brill 2015 (10)	0	25	0	8		Not estimable
Sethi 2010 (11)	94	569	97	580	26.8%	0.99 [0.76, 1.28]
Subtotal (95% CI)		**594**		**588**	**26.8%**	**0.99 [0.76, 1.28]**
Total events	94		97			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.09 (P = 0.93)						
Total (95% CI)		**1533**		**1391**	**100.0%**	**0.92 [0.81, 1.04]**
Total events	345		353			
Heterogeneity: Chi² = 4.28, df = 7 (P = 0.75); I² = 0%						
Test for overall effect: Z = 1.31 (P = 0.19)						
Test for subgroup differences: Chi² = 0.83, df = 2 (P = 0.66), I² = 0%						

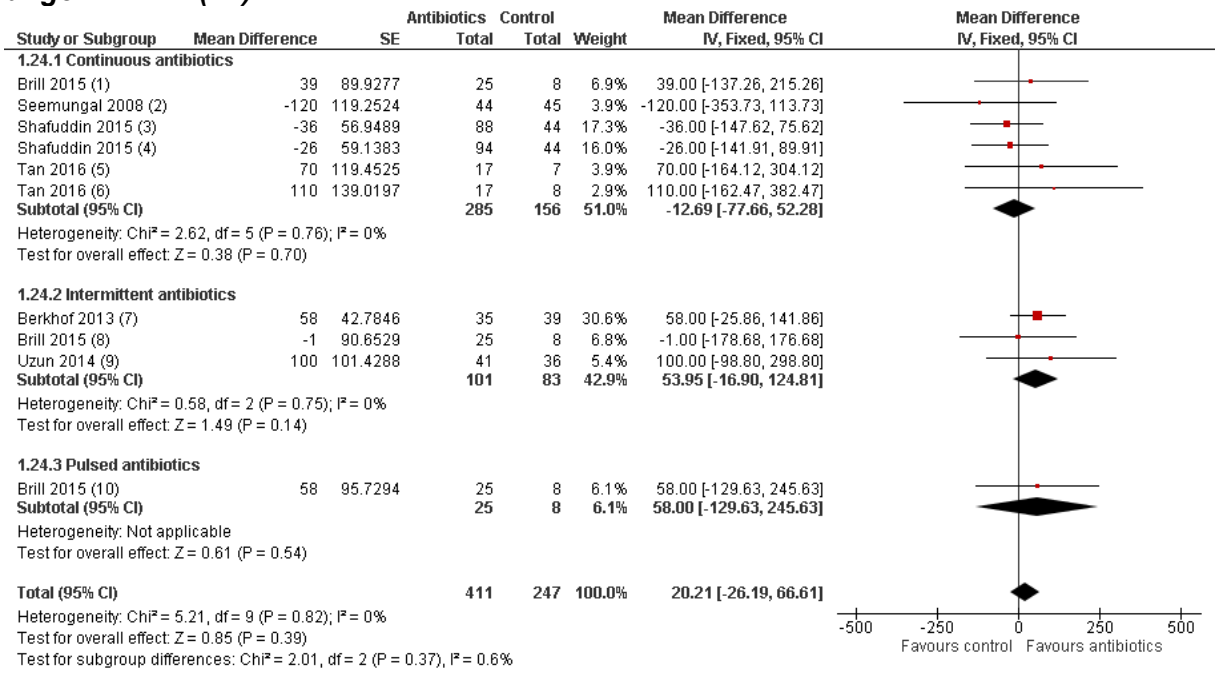
Footnotes

(1) Azithromycin 250mg daily for 12 months.
(2) Doxycycline 100mg daily. Control group split (No events reported)
(3) Erythromycin 125mg three times/day for six months.
(4) Erythromycin 250mg twice a day for 12 months.
(5) Roxithromycin 300mg daily + doxycyline 100mg daily. Outcome reported at 60 weeks. Control group halved.
(6) Roxithromycin 300mg daily for 12 weeks. Outcome reported at 60 weeks. Control group halved.
(7) Azithromycin 250mg daily for 12 weeks. Outcome reported at 26 weeks.
(8) Azithromycin 250mg three times/week. Control group split (No events reported)
(9) Azithromycin 500mg three times/week for 12 months.
(10) Pulsed moxifloxacin 400mg daily for five days every four weeks for 13 weeks. Control group split (No events reported).
(11) Moxifloxacin 400mg daily for for five days every eight weeks for 48 weeks.

Publication bias assessment: funnel plot for number of people with ≥ 1 serious adverse event (SAE)



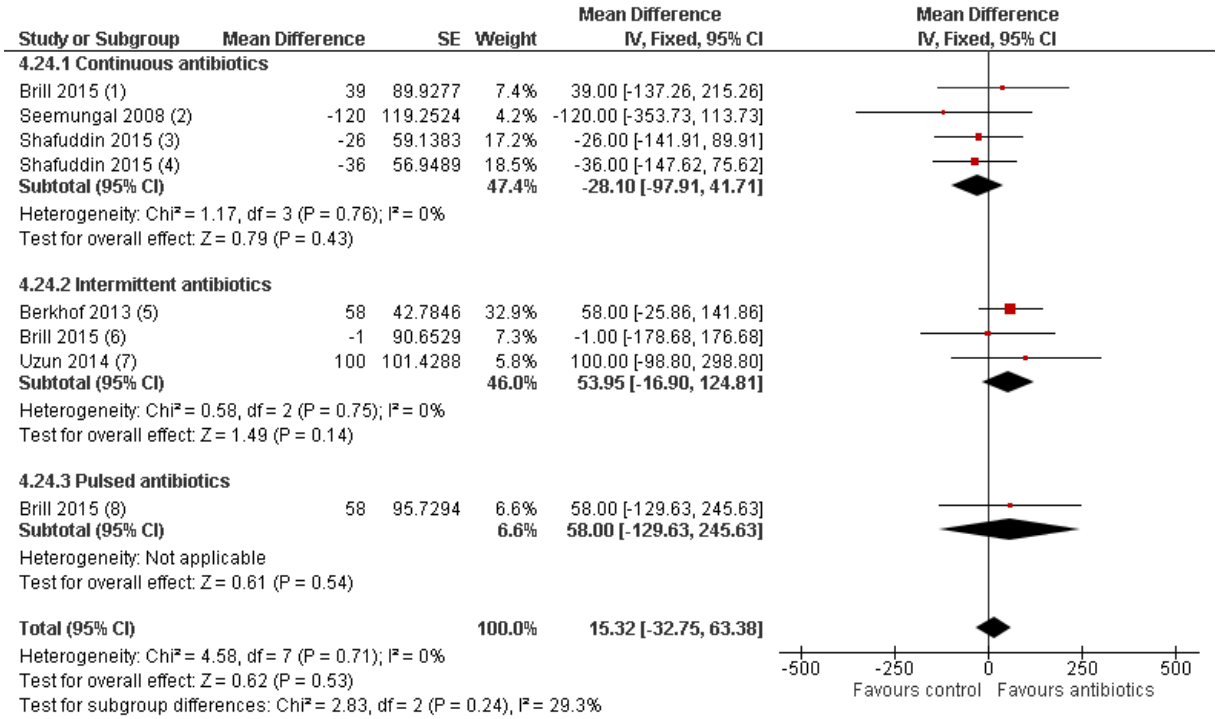
Change in FEV1 (ml)



Footnotes

(1) Doxycycline 100mg daily for 13 weeks. Control group split three ways.
(2) Erythromycin 250mg twice/day for 12 months.
(3) Roxithromycin 300mg daily + doxycyline 100mg for 12 weeks. Outcome reported at 12 weeks. Control group halved.
(4) Roxithromycin 300mg daily for 12 weeks. Outcome reported at 12 weeks. Control group halved.
(5) Erythromycin 125mg three times/day for six months. Control group halved.
(6) Erythromycin 125mg three times/day for 12 months. Control group halved.
(7) Azithromycin 250mg three times/week for 12 weeks. Extracted from database supplied by author.
(8) Azithromycin 250mg three times/week for 13 weeks. Control group split three ways.
(9) Azithromycin 500mg three times/week for 12 months.
(10) Moxifloxacin 400mg daily for five days every four weeks for 13 weeks. Control group split three ways.

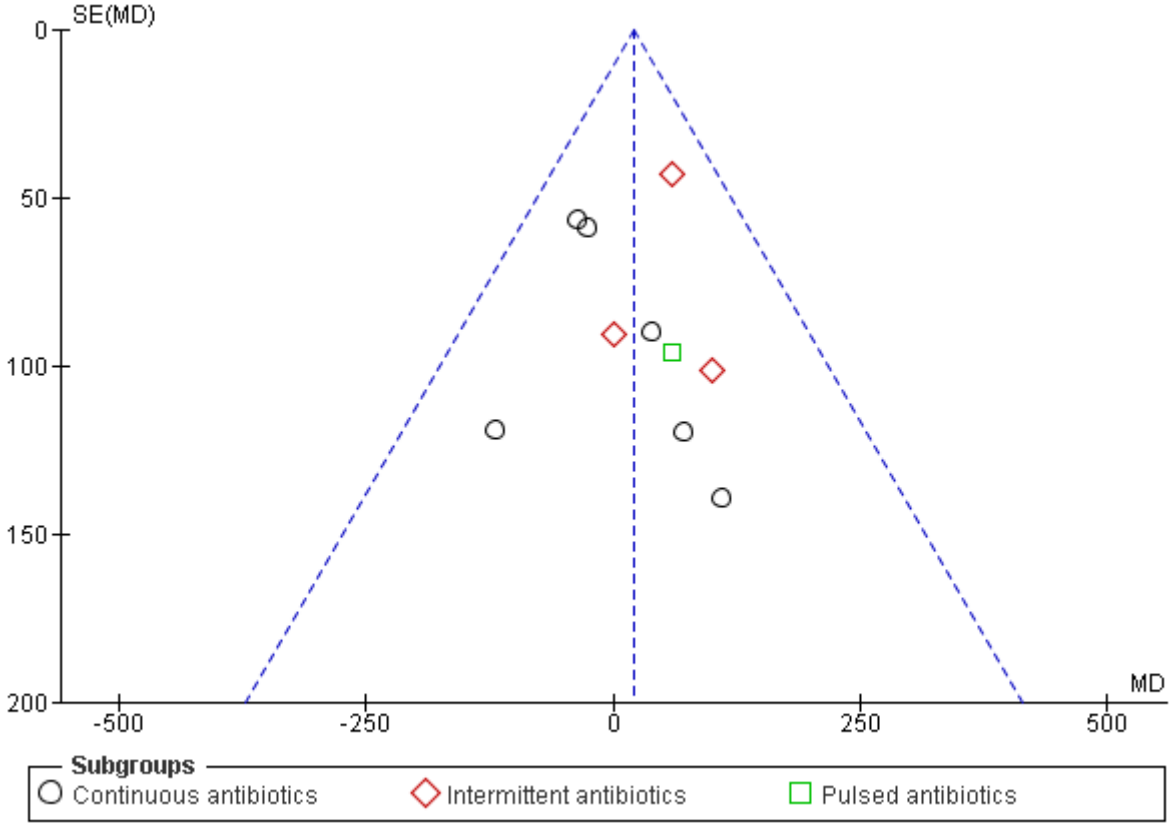
Sensitivity analyses removing studies at high risk of bias: change in FEV1 (ml)



Footnotes

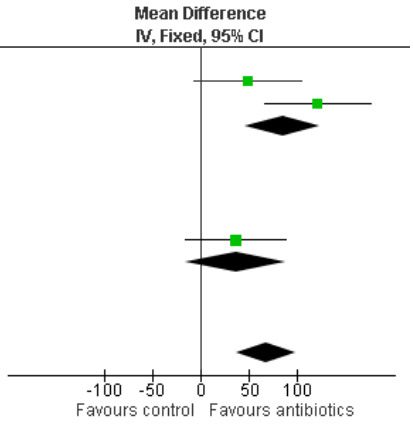
(1) Doxycycline 100mg daily for 13 weeks. Control group split three ways.
(2) Erythromycin 250mg twice/day for 12 months.
(3) Roxithromycin 300mg daily for 12 weeks. Outcome reported at 12 weeks. Control group halved.
(4) Roxithromycin 300mg daily + doxycyline 100mg for 12 weeks. Outcome reported at 12 weeks. Control group halved.
(5) Azithromycin 250mg three times/week for 12 weeks. Extracted from database supplied by author.
(6) Azithromycin 250mg three times/week for 13 weeks. Control group split three ways.
(7) Azithromycin 500mg three times/week for 12 months.
(8) Moxifloxacin 400mg daily for five days every four weeks for 13 weeks. Control group split three ways.

Publication bias assessment: funnel plot for change in FEV1 (ml)



Exercise capacity (6MWD)

Study or Subgroup	Antibiotics Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
1.27.1 Continuous antibiotics								
Tan 2016 (1)	352.8	53.87	17	304.86	70.55	8	31.5%	47.94 [-7.25, 103.13]
Tan 2016 (2)	425.07	32.84	17	304.86	70.55	7	32.3%	120.21 [65.67, 174.75]
Subtotal (95% CI)			**34**			**15**	**63.8%**	**84.50 [45.70, 123.29]**
Heterogeneity: Chi² = 3.33, df = 1 (P = 0.07); I² = 70%								
Test for overall effect: Z = 4.27 (P < 0.0001)								
1.27.2 Intermittent antibiotics								
Uzun 2014 (3)	415	108	41	379	121	36	36.2%	36.00 [-15.53, 87.53]
Subtotal (95% CI)			**41**			**36**	**36.2%**	**36.00 [-15.53, 87.53]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.37 (P = 0.17)								
Total (95% CI)			**75**			**51**	**100.0%**	**66.95 [35.96, 97.95]**
Heterogeneity: Chi² = 5.50, df = 2 (P = 0.06); I² = 64%								
Test for overall effect: Z = 4.23 (P < 0.0001)								
Test for subgroup differences: Chi² = 2.17, df = 1 (P = 0.14), I² = 54.0%								



Footnotes
(1) Erythromycin 125mg three times/day for six months. Control group halved.
(2) Erythromycin 125mg three times/day for 12 months. Control group halved.
(3) Azithromycin 500mg three times/week for 12 months.

Appendix G – GRADE tables

Predicting exacerbations

Risk factor: smoking

No. of studies	Study design	Sample size	Effect size (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
Current smoker (reference category: former smoker) predicting COPD inpatient or outpatient exacerbations – follow-up: median 3.87 years								
1 (Au 2009)	Prospective cohort[1]	23,971	HR 1.28 (1.15, 1.33)	Not serious	Not serious	N/A	Not serious	High
Current smoker (reference category: ex-smoker not exposed to passive smoking) predicting readmission to hospital for a COPD exacerbation – follow-up: 12 months								
1 (Garcia-Aymerich 2003)	Prospective cohort	312	HR 0.97 (0.64, 1.47)	Serious[2]	Not serious	N/A	Serious[3]	Low
Current smoking (reference category: ex-smoking) predicting COPD exacerbation duration more than three weeks – follow-up: 3 years Bergen COPD study								
1 (Husebo 2014)	Prospective cohort	403	OR 1.29 (0.95, 1.76)	Not serious	Not serious	N/A	Serious[3]	Moderate
Smoker (reference category: non-smoker) predicting readmission for AECOPD – follow-up: 12 months								
1 (Coventry 2011)	Prospective cohort	79	OR 0.28 (0.75, 1.07)	Not serious	Not serious	N/A	Very serious[4]	Low
Current smoker (reference category: not reported) predicting readmissions for AECOPD – follow-up: 12 months								
1 (Gudmundsson 2005)	Prospective cohort	406	HR 0.78 (0.55, 1.10)	Not serious	Serious[5]	N/A	Serious[3]	Low
Current smoking (reference category: not reported) predicting AECOPD – follow-up: 3 years SPIROMICS study								

No. of studies	Study design	Sample size	Effect size (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
1 (Han 2017)	Prospective cohort	394	OR 0.62 (0.23, 1.63)	Very serious[6]	Not serious	N/A	Serious[3]	Very low
Current smoking (reference category: not reported) predicting COPD exacerbations– follow-up: 5 years Copenhagen City Heart Study								
1 (Ingebrigtsen 2015b)	Prospective cohort	1,259	HR 1.7 (1.0, 3.1)	Very serious[7]	Not serious	N/A	Not serious	Low
Current smoking (reference category: not current smoking) predicting exacerbation frequency[8] requiring prescription – follow-up: 5 years Hokkaido COPD study								
1 (Suzuki 2014)	Prospective cohort	268	RR 0.87 (0.59, 1.26)	Serious[9]	Not serious	N/A	Serious[3]	Low
Current smoker (reference category: not reported) predicting moderate/severe AECOPD – follow-up: 3 years ECLIPSE study								
1 (Yohannes 2017)	Prospective cohort	1,580	OR 0.87 (0.79, 0.95)	Very serious[10]	Not serious	N/A	Not serious	Low
Ex-smoker exposed to passive smoking (reference category: ex-smoker not exposed to passive smoking) predicting readmission to hospital for a COPD exacerbation – follow-up: 12 months								
1 (Garcia-Aymerich 2003)	Prospective cohort	312	HR 1.63 (1.04, 2.57)	Serious[2]	Not serious	N/A	Not serious	Moderate
Pack years of smoking[11] (reference category: not reported) predicting COPD exacerbations – follow-up: 24 months								
1 (Bertens 2013)	Prospective cohort	1,033	OR 1.16 (1.01, 1.35)	Not serious	Not serious	N/A	Not serious	High
Lower level of second-hand smoke (reference category: no exposure to second-hand smoke) predicting emergency department visit for COPD exacerbation – follow-up: median 2.1 years								
1 (Eisner 2009)	Prospective cohort	809	HR 1.40 (0.96, 2.05)	Serious[12]	Not serious	N/A	Serious[3]	Low
Higher level of second-hand smoke (reference category: no exposure to second-hand smoke) predicting emergency department visit for COPD exacerbation – follow-up: median 2.1 years								

No. of studies	Study design	Sample size	Effect size (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
1 (Eisner 2009)	Prospective cohort	809	HR 1.41 (0.94, 2.13)	Serious[1,2]	Not serious	N/A	Serious[3]	Low
Lower level of second-hand smoke (reference category: no exposure to second-hand smoke) predicting hospitalisation for COPD exacerbation – follow-up: median 2.1 years								
1 (Eisner 2009)	Prospective cohort	809	HR 1.37 (0.72, 2.61)	Serious[1,2]	Not serious	N/A	Serious[3]	Low
Higher level of second-hand smoke (reference category: no exposure to second-hand smoke) predicting hospitalisation for COPD exacerbation – follow-up: median 2.1 years								
1 (Eisner 2009)	Prospective cohort	809	HR 1.15 (0.51, 2.59)	Serious[1,2]	Not serious	N/A	Serious[3]	Low
Lower level of second-hand smoke (reference category: no exposure to second-hand smoke) predicting any hospital-based care for COPD exacerbation (emergency department visit or hospitalisation) – follow-up: median 2.1 years								
1 (Eisner 2009)	Prospective cohort	809	HR 1.52 (1.06, 2.18)	Serious[1,2]	Not serious	N/A	Not serious	Moderate
Higher level of second-hand smoke (reference category: no exposure to second-hand smoke) predicting any hospital-based care for COPD exacerbation (emergency department visit or hospitalisation) – follow-up: median 2.1 years								
1 (Eisner 2009)	Prospective cohort	809	HR 1.40 (0.94, 2.10)	Serious[1,2]	Not serious	N/A	Serious[3]	Low
Ex-smoker not exposed to passive smoking (reference category: never smoker) predicting readmission to hospital for a COPD exacerbation – follow-up: 12 months								
1 (Garcia-Aymerich 2003)	Prospective cohort	312	HR 0.83 (0.43, 1.64)	Serious[2]	Not serious	N/A	Serious[3]	Low
Former smoking (reference category: not reported) predicting COPD exacerbations – follow-up: 5 years Copenhagen City Heart Study								
1 (Ingebrigtsen 2015b)	Prospective cohort	1,259	HR 1.1 (0.6, 2.0)	Very serious[7]	Not serious	N/A	Serious[3]	Very low
Smoker or ex-smoker (reference category: not reported) predicting 1 to 2 exacerbations – follow-up: 2 years								

No. of studies	Study design	Sample size	Effect size (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
1 (Montserrat-Capdevila 2016)	Prospective cohort	512	OR 1.15 (0.70, 1.88)	Not serious	Not serious	N/A	Serious[3]	Moderate
Smoker or ex-smoker (reference category: not reported) predicting ≥3 exacerbations – follow-up: 2 years								
1 (Montserrat-Capdevila 2016)	Prospective cohort	512	OR 2.00 (1.00, 3.99)	Not serious	Not serious	N/A	Serious[3]	Moderate
Menthol cigarette smokers (reference category: non-menthol cigarette smokers) predicting exacerbations of COPD – follow-up: mean 1.49 years								
1 (Park 2015)	Prospective cohort	3,772	OR 1.10 (0.97, 1.25)	Very serious[1][3]	Not serious	N/A	Serious[3]	Very low
Menthol cigarette smokers (reference category: non-menthol cigarette smokers) predicting severe exacerbations of COPD – follow-up: mean 1.49 years								
1 (Park 2015)	Prospective cohort	3,772	OR 1.29 (1.01, 1.54)	Very serious[1][3]	Not serious	N/A	Not serious	Low

1. Data was collected from the Ambulatory Care Quality Improvement Project (ACQUIP), a multi-centre, randomised trial of a quality improvement intervention
2. Moderate risk of bias (used diagnostic codes to measure outcome)
3. Non-significant result
4. Non-significant result and small sample size
5. Diagnostic codes used in participant identification and only included those participants admitted for over 24 hours
6. High risk of bias (only 394 out of 1,105 were included in the logistic regression analysis)
7. High risk of bias (relied solely on prescription data for oral corticosteroids in measuring outcome, use of questionnaire in determining gastro-oesophageal reflux disease and over 10% lost to follow-up due to death)
8. Exacerbation frequency: events per person per year
9. Moderate risk of bias (high attrition: over 30%)
10. High risk of bias (depression was measured with a questionnaire. Multivariate regression model was used but confounding factors were not mentioned. 23% were lost to follow-up)

No. of studies	Study design	Sample size	Effect size (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
11. Log transformed: doubling of the number of log-transformed pack years 12. Moderate risk of bias (use of diagnostic codes in outcome measurement and participant selection) 13. High risk of bias (use of self-report in determining exposure and outcome that allows high risk of bias) N/A: not applicable								

Risk factor: disease related factors

No. of studies	Study design	Sample size	Effect size (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
Ischemic heart disease (reference category: not reported) predicting AECOPD hospital readmission – follow-up: 3 months								
1 (Al Aqqad 2016)	Prospective cohort	81	OR 4.04 (1.11, 14.66)	Very serious[1]	Not serious	N/A	Not serious	Low
Ischemic heart disease (reference category: not reported) predicting relapse of AECOPD – follow-up: 1 month								
1 (Miravitlles 2001)	Prospective cohort	2,414	OR 1.63 (1.07, 2.47)	Serious[2]	Serious[3]	N/A	Not serious	Low
History of reflux or heartburn (reference category: no history of reflux or heartburn) predicting ≥2 versus 0 exacerbations – follow-up: 12 months								
1 (Hurst 2010)	Prospective cohort	2,138	OR 2.07 (1.58, 2.72)	Not serious	Not serious	N/A	Not serious	High
History of reflux or heartburn (reference category: no history of reflux or heartburn) predicting 1 versus 0 exacerbations – follow-up: 12 months								
1 (Hurst 2010)	Prospective cohort	2,138	OR 1.61 (1.23, 2.10)	Not serious	Not serious	N/A	Not serious	High
History of reflux or heartburn (reference category: no history of reflux or heartburn) predicting ≥2 versus 1 exacerbations – follow-up: 12 months								
1 (Hurst 2010)	Prospective cohort	2,138	OR 1.29 (0.97, 1.70)	Not serious	Not serious	N/A	Serious[4]	Moderate

No. of studies	Study design	Sample size	Effect size (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
History of pneumonia (reference category: no history of pneumonia) predicting COPD exacerbation – follow-up: 12 months EPOCH study								
1 (Hwang 2015)	Prospective cohort	920	OR 18.09 (8.86, 36.94)	Serious[5]	Not serious	N/A	Not serious	Moderate
History of pneumonia (reference category: not reported) predicting COPD exacerbations – follow-up: mean 22.3 months								
1 (Kim 2016)	Prospective cohort	570	OR 1.85 (1.06, 3.25)	Serious[6]	Not serious	N/A	Not serious	Moderate
Diabetes (reference category: not reported) predicting 1 exacerbation – follow-up: 2 years								
1 (Montserrat-Capdevila 2017)*	Prospective cohort	512	OR 2.75 (1.45, 5.23)	Serious[7]	Not serious	N/A	Not serious	Moderate
Diabetes (reference category: not reported) predicting 2 or more exacerbations – follow-up: 2 years								
1 (Montserrat-Capdevila 2017)*	Prospective cohort	512	OR 2.56 (1.49, 4.40)	Serious[7]	Not serious	N/A	Not serious	Moderate
Diabetes (reference category: no diabetes) readmission to hospital for COPD exacerbation – follow-up: 30 days								
1 (Crisafulli 2015)	Prospective cohort	125	OR 11.03 (1.77, 68.54)	Very serious[8]	Not serious	N/A	Not serious	Low
Emphysema[9] (reference category: not reported) predicting hospitalised COPD exacerbation – follow-up: 3 years ECLIPSE study								
1 (Mullerova 2015)	Prospective cohort	2,138	HR 1.56 (1.23, 1.97)	Serious[10]	Not serious	N/A	Not serious	Moderate
Emphysema (reference category: not reported) predicting hospitalised COPD exacerbation – follow-up: 3 years ECLIPSE study								
1 (Mullerova 2015)	Prospective cohort	2,138	HR 1.71 (1.28, 2.26)	Serious[10]	Not serious	N/A	Not serious	Moderate
Previous diagnosis of asthma (reference category: not reported) predicting moderate to severe exacerbations follow-up: 6 months COPDGene study								
1 (Bowler 2014)	Prospective cohort	3,804	HR 1.30 (1.15, 1.47)	Serious[11]	Not serious	N/A	Not serious	Moderate
Previous diagnosis of asthma (reference category: not reported) predicting hospitalised exacerbations follow-up: 6 months COPDGene study								

No. of studies	Study design	Sample size	Effect size (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
1 (Bowler 2014)	Prospective cohort	3,804	HR 1.34 (1.13, 1.59)	Serious[11]	Not serious	N/A	Not serious	Moderate
History of asthma (reference category: not reported) predicting hospitalised COPD exacerbation – follow-up: 3 years ECLIPSE study								
1 (Mullerova 2015)	Prospective cohort	2,138	HR 1.45 (1.17, 1.79)	Serious[10]	Not serious	N/A	Not serious	Moderate
Obese (reference category: not reported) predicting 1 exacerbation – follow-up: 2 years								
1 (Montserrat-Capdevila 2017)*	Prospective cohort	512	OR 1.77 (0.87, 3.59)	Serious[7]	Not serious	N/A	Serious[4]	Low
Overweight (reference category: not reported) predicting 1 exacerbation – follow-up: 2 years								
1 (Montserrat-Capdevila 2017)*	Prospective cohort	512	OR 2.25 (1.16, 4.33)	Serious[7]	Not serious	N/A	Not serious	Moderate
Obese (reference category: not reported) predicting 2 or more exacerbations – follow-up: 2 years								
1 (Montserrat-Capdevila 2017)*	Prospective cohort	512	OR 3.02 (1.62, 5.56)	Serious[7]	Not serious	N/A	Not serious	Moderate
Overweight (reference category: not reported) predicting 2 or more exacerbations – follow-up: 2 years								
1 (Montserrat-Capdevila 2017)*	Prospective cohort	512	OR 2.78 (1.54, 5.04)	Serious[7]	Not serious	N/A	Not serious	Moderate
Age-adjusted Charlson score[12] (reference category: not reported) predicting severe exacerbation in participants with GOLD II-IV at stable state – follow-up: 24 months								
1 (Baumeler 2016)	Prospective cohort	638	HR 1.04 (0.96, 1.13)	Not serious	Not serious	N/A	Serious[4]	Moderate
Age-adjusted Charlson score[13] (reference category: not reported) predicting severe exacerbation in participants with GOLD II-IV at stable state – follow-up: 24 months								
1 (Baumeler 2016)	Prospective cohort	638	HR 0.99 (0.90, 1.01)	Not serious	Not serious	N/A	Serious[4]	Moderate
Charlson comorbidity score = 2 (reference category: Charlson comorbidity score = 1) predicting COPD exacerbation duration more than three weeks – follow-up: 3 years Bergen COPD study								

No. of studies	Study design	Sample size	Effect size (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
1 (Husebo 2014)	Prospective cohort	403	OR 0.97 (0.74, 1.27)	Not serious	Not serious	N/A	Serious[4]	Moderate
Charlson comorbidity score = 3 (reference category: Charlson comorbidity score = 1) predicting COPD exacerbation duration more than three weeks – follow-up: 3 years Bergen COPD study								
1 (Husebo 2014)	Prospective cohort	403	OR 0.98 (0.68, 1.42)	Not serious	Not serious	N/A	Serious[4]	Moderate
Charlson comorbidity score 4+ (reference category: Charlson comorbidity score = 1) predicting COPD exacerbation duration more than three weeks – follow-up: 3 years Bergen COPD study								
1 (Husebo 2014)	Prospective cohort	403	OR 0.98 (0.61, 1.57)	Not serious	Not serious	N/A	Serious[4]	Moderate
Charlson index (reference category: not reported) predicting hospitalisation for COPD exacerbation among participants with or without obstructive sleep apnoea who were not treated with continuous positive airway pressure – follow-up: median 9.4 years								
1 (Marin 2010)	Prospective cohort	423	RR 1.06 (0.93, 1.19)	Serious[14]	Serious[15]	N/A	Serious[4]	Very low
Charlson index (reference category: not reported) predicting 1 to 2 exacerbations – follow-up: 12 months								
1 (Montserrat-Capdevila 2016)*	Prospective cohort	512	OR 1.04 (0.93, 1.17)	Not serious	Not serious	N/A	Serious[4]	Moderate
Charlson index (reference category: not reported) predicting ≥3 exacerbations – follow-up: 12 months								
1 (Montserrat-Capdevila 2016)*	Prospective cohort	512	OR 1.19 (1.01, 1.40)	Not serious	Not serious	N/A	Not serious	High
Charlson index (reference category: not reported) predicting 1 exacerbation – follow-up: 2 years								
1 (Montserrat-Capdevila 2017)*	Prospective cohort	512	OR 1.14 (0.97, 1.33)	Serious[7]	Not serious	N/A	Serious[4]	Low
Charlson index (reference category: not reported) predicting 2 or more exacerbations – follow-up: 2 years								
1 (Montserrat-Capdevila 2017)*	Prospective cohort	512	OR 1.13 (0.99, 1.30)	Serious[7]	Not serious	N/A	Serious[4]	Low
Charlson index (reference category: not reported) predicting exacerbation frequency – follow-up: mean 5 years								

No. of studies	Study design	Sample size	Effect size (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
1 (Yang 2014)	Prospective cohort	227	RR 1.22 (1.05, 1.41)	Not serious	Not serious	N/A	Not serious	High
Charlson index score (reference category: not reported) predicting COPD exacerbations – follow-up: 12 months								
1 (Yoo 2011)	Prospective cohort	260	OR 2.07 (1.04, 4.11)	Serious[16]	Not serious	N/A	Not serious	Moderate
Congestive heart failure[17] (reference category: not reported) predicting severe exacerbation in participants with GOLD II-IV at stable state – follow-up: 24 months								
1 (Baumeler 2016)	Prospective cohort	638	HR 1.48 (0.95, 2.30)	Not serious	Not serious	N/A	Serious[4]	Moderate
Congestive heart failure (reference category: not reported) predicting COPD exacerbations – follow-up: 12 months								
1 (Liang 2013)	Prospective cohort	386	OR 1.36 (0.88, 1.54)	Serious[18]	Not serious	N/A	Serious[4]	Low
History of vascular disease (reference category: not reported) predicting COPD exacerbations – follow-up: 24 months								
1 (Bertens 2013)	Prospective cohort	1,033	OR 1.92 (0.89, 4.12)	Not serious	Not serious	N/A	Serious[4]	Moderate
Hyperlipidaemia (reference category: not reported) predicting COPD exacerbations – follow-up: mean 22.3 months								
1 (Kim 2016)	Prospective cohort	570	OR 0.82 (0.52, 1.30)	Serious[6]	Not serious	N/A	Serious[4]	Low
Gastroesophageal reflux disease (reference category: not reported) predicting moderate to severe exacerbations follow-up: 6 months COPDGene study								
1 (Bowler 2014)	Prospective cohort	3,804	HR 1.29 (1.16, 1.45)	Serious[11]	Not serious	N/A	Not serious	Moderate
Gastroesophageal reflux disease (reference category: not reported) predicting hospitalised exacerbations follow-up: 6 months COPDGene study								
1 (Bowler 2014)	Prospective cohort	3,804	HR 1.15 (0.97, 1.35)	Serious[11]	Not serious	N/A	Serious[4]	Low
Coexisting night-time and daytime gastro-oesophageal reflux disease and no regular use of acid inhibitory treatment (reference category: no gastro-oesophageal reflux disease and no regular use of acid inhibitory treatment) predicting COPD exacerbations – follow-up: 5 years Copenhagen City Heart Study								
1 (Ingebrigtsen 2015b)	Prospective cohort	1,259	HR 2.7 (1.3, 5.4)	Very serious[19]	Not serious	N/A	Not serious	Low

No. of studies	Study design	Sample size	Effect size (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
Coexisting night-time and daytime gastro-oesophageal reflux disease and regular use of acid inhibitory treatment (reference category: no gastro-oesophageal reflux disease and no regular use of acid inhibitory treatment) predicting COPD exacerbations – follow-up: 5 years Copenhagen City Heart Study								
1 (Ingebrigtsen 2015b)	Prospective cohort	1,259	HR 1.2 (0.6, 2.7)	Very serious[19]	Not serious	N/A	Serious[4]	Very low
Either night-time or daytime gastro-oesophageal reflux disease but not coexisting, and no regular use of acid inhibitory treatment (reference category: no gastro-oesophageal reflux disease and no regular use of acid inhibitory treatment) predicting COPD exacerbations – follow-up: 5 years Copenhagen City Heart Study								
1 (Ingebrigtsen 2015b)	Prospective cohort	1,259	HR 1.7 (1.0, 3.0)	Very serious[19]	Not serious	N/A	Serious[4]	Very low
Either night-time or daytime gastro-oesophageal reflux disease but not coexisting, and regular use of acid inhibitory treatment (reference category: no gastro-oesophageal reflux disease and no regular use of acid inhibitory treatment) predicting COPD exacerbations – follow-up: 5 years Copenhagen City Heart Study								
1 (Ingebrigtsen 2015b)	Prospective cohort	1,259	HR 0.3 (0.05, 2.4)	Very serious[19]	Not serious	N/A	Serious[4]	Very low
No gastro-oesophageal reflux disease but regular use of acid inhibitory treatment (reference category: no gastro-oesophageal reflux disease and no regular use of acid inhibitory treatment) predicting COPD exacerbations – follow-up: 5 years Copenhagen City Heart Study								
1 (Ingebrigtsen 2015b)	Prospective cohort	1,259	HR 1.8 (0.9, 3.5)	Very serious[19]	Not serious	N/A	Serious[4]	Very low
High gastro-oesophageal reflux disease risk (reference category: not reported) predicting COPD exacerbations – follow-up: 12 months								
1 (Liang 2013)	Prospective cohort	386	OR 2.31 (1.29, 3.87)	Serious[18]	Not serious	N/A	Not serious	Moderate
Gastro-oesophageal reflux disease (reference category: not reported) predicting frequent COPD exacerbations (≥2 exacerbation per year) – follow-up: mean 2 years								
1 (Martinez 2014)	Prospective cohort	4,483	OR 1.40 (1.10, 1.79)	Serious[20]	Not serious	N/A	Not serious	Moderate
Gastroesophageal reflux disease (reference category: not reported) predicting hospitalisation for AECOPD – follow-up: 12 months								
1 (Takada 2011)	Prospective cohort	221	OR 4.09 (1.10, 15.11)	Serious[21]	Not serious	N/A	Not serious	Moderate

No. of studies	Study design	Sample size	Effect size (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
Gastroesophageal reflux disease symptoms (reference category: without gastroesophageal reflux disease symptoms) predicting COPD exacerbations – follow-up: 6 months								
1 (Terada 2008)	Prospective cohort	82	RR 6.55 (1.86, 23.11)	Very serious[22]	Not serious	N/A	Not serious	Low
History of gastroesophageal reflux (reference category: no history of gastroesophageal reflux) predicting moderate/severe AECOPD – follow-up: 3 years ECLIPSE study								
1 (Yohannes 2017)	Prospective cohort	1,580	OR 1.19 (1.09, 1.31)	Very serious[23]	Not serious	N/A	Not serious	Low
History of gastroesophageal reflux (reference category: no history of gastroesophageal reflux) predicting hospitalised AECOPD – follow-up: 3 years ECLIPSE study								
1 (Yohannes 2017)	Prospective cohort	1,580	OR 1.08 (1.04, 1.11)	Very serious[23]	Not serious	N/A	Not serious	Low
Chronic bronchitis (reference category: not reported) predicting moderate to severe exacerbations follow-up: 6 months COPDGene study								
1 (Bowler 2014)	Prospective cohort	3,804	HR 1.14 (1.01, 1.29)	Serious[11]	Not serious	N/A	Not serious	Moderate
Chronic bronchitis (reference category: not reported) predicting COPD exacerbations – follow-up: 5 years Copenhagen City Heart Study								
1 (Ingebrigtsen 2015b)	Prospective cohort	1,259	HR 1.3 (0.9, 1.9)	Very serious[19]	Not serious	N/A	Serious[4]	Very low
Chronic bronchitis (reference category: not reported) predicting frequent COPD exacerbations – follow-up: median 6.5 years								
1 (Lahousse 2017)	Prospective cohort	972	OR 3.96 (2.67, 5.88)	Not serious	Not serious	N/A	Not serious	High
HAD-total 4 units (reference category: not reported) predicting readmissions for AECOPD – follow-up: 12 months								
1 (Gudmundsson 2005)	Prospective cohort	406	HR 1.03 (0.93, 1.13)	Not serious	Serious[24]	N/A	Serious[4]	Low
HAD borderline or pathologic (reference category: not reported) predicting 1 exacerbation – follow-up: 2 years								

No. of studies	Study design	Sample size	Effect size (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
1 (Montserrat-Capdevila 2017)*	Prospective cohort	512	OR 0.61 (0.24, 1.57)	Serious[7]	Not serious	N/A	Serious[4]	Low
HAD borderline or pathologic (reference category: not reported) predicting 2 or more exacerbations – follow-up: 2 years								
1 (Montserrat-Capdevila 2017)*	Prospective cohort	512	OR 1.57 (0.77, 3.22)	Serious[7]	Not serious	N/A	Serious[4]	Low
HADS – depression (reference category: not reported) predicting AECOPD readmission – follow-up: 12 months								
1 (Coventry 2011)	Prospective cohort	79	OR 1.30 (1.06, 1.60)	Not serious	Not serious	N/A	Not serious	High
HAD-depression 4 units (reference category: not reported) predicting readmissions for AECOPD – follow-up: 12 months								
1 (Gudmundsson 2005)	Prospective cohort	406	HR 0.96 (0.80, 1.15)	Not serious	Serious[24]	N/A	Serious[4]	Low
Depression (reference category: not reported) predicting readmissions for AECOPD – follow-up: 12 months								
1 (Gudmundsson 2005)	Prospective cohort	406	HR 1.09 (0.80, 1.51)	Not serious	Serious[24]	N/A	Serious[4]	Low
Depression (reference category: not reported) predicting COPD exacerbations – follow-up: 12 months								
1 (Ito 2012)	Prospective cohort	85	RR 1.85 (0.40, 8.21)	Serious[25]	Not serious	N/A	Very serious[26]	Very low
Depression (reference category: not reported) predicting hospitalisations for exacerbations – follow-up: 12 months								
1 (Ito 2012)	Prospective cohort	85	RR 34.8 (3.66, 10.09)	Serious[25]	Not serious	N/A	Not serious	Moderate
Depression (reference category: not reported) predicting 1 to 2 exacerbations – follow-up: 2 years								
1 (Montserrat-Capdevila 2016)*	Prospective cohort	512	OR 2.72 (1.19, 6.22)	Not serious	Not serious	N/A	Not serious	High
Depression (reference category: not reported) predicting ≥3 exacerbations – follow-up: 2 years								
1 (Montserrat-Capdevila 2016)*	Prospective cohort	512	OR 1.08 (0.35, 3.29)	Not serious	Not serious	N/A	Serious[4]	Moderate

No. of studies	Study design	Sample size	Effect size (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
Depressive symptoms (reference category: not reported) predicting AECOPD – follow-up: 12 months								
1 (Papaioannou 2013)	Prospective cohort	230	RR 1.45 (1.29, 1.62)[27]	Serious[28]	Not serious	N/A	Not serious	Moderate
Depressive symptoms (reference category: not reported) predicting hospitalised AECOPD – follow-up: 12 months								
1 (Papaioannou 2013)	Prospective cohort	230	RR 3.02 (2.28, 3.99)[27]	Serious[28]	Not serious	N/A	Not serious	Moderate
Possible depression ≥8 HADS-D ≤10 (reference category: HADS-D ≤7) predicting COPD exacerbation – follow-up: 12 months								
1 (Xu 2008)	Prospective cohort	491	RR 0.91 (0.56, 1.50)	Not serious	Not serious	N/A	Serious[4]	Moderate
Possible depression HADS-D ≥11 (reference category: HADS-D ≤7) predicting COPD exacerbation – follow-up: 12 months								
1 (Xu 2008)	Prospective cohort	491	RR 1.00 (0.54, 1.84)	Not serious	Not serious	N/A	Serious[4]	Moderate
Possible depression ≥8 HADS-D ≤10 (reference category: HADS-D ≤7) predicting hospitalisation for COPD exacerbation – follow-up: 12 months								
1 (Xu 2008)	Prospective cohort	491	RR 1.29 (0.54, 3.03)	Not serious	Not serious	N/A	Serious[4]	Moderate
Possible depression HADS-D ≥11 (reference category: HADS-D ≤7) predicting hospitalisation for COPD exacerbation – follow-up: 12 months								
1 (Xu 2008)	Prospective cohort	491	RR 2.45 (0.76, 7.87)	Not serious	Not serious	N/A	Serious[4]	Moderate
Depression at baseline CES-D ≥16 (reference category: CES-D <16) predicting moderate/severe AECOPD – follow-up: 3 years ECLIPSE study								
1 (Yohannes 2017)	Prospective cohort	1,580	OR 1.18 (1.07, 1.30)	Very serious[23]	Not serious	N/A	Not serious	Low
Depression at baseline CES-D ≥16 (reference category: CES-D <16) predicting hospitalised AECOPD – follow-up: 3 years ECLIPSE study								
1 (Yohannes 2017)	Prospective cohort	1,580	OR 1.36 (1.09, 1.69)	Very serious[23]	Not serious	N/A	Not serious	Low

No. of studies	Study design	Sample size	Effect size (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
Anxiety (reference category: no anxiety) predicting COPD exacerbation – follow-up: median 2.1 years								
1 (Eisner 2010)	Prospective cohort	1,202	HR 1.39 (1.00, 1.90)	Very serious[29]	Not serious	N/A	Serious[4]	Very low
HAD-anxiety 4 units (reference category: not reported) predicting readmissions for AECOPD – follow-up: 12 months								
1 (Gudmundsson 2005)	Prospective cohort	406	HR 1.10 (0.95, 1.28)	Not serious	Serious[24]	N/A	Serious[4]	Low
Anxiety (reference category: not reported) predicting readmissions for AECOPD – follow-up: 12 months								
1 (Gudmundsson 2005)	Prospective cohort	406	HR 1.06 (0.79, 1.41)	Not serious	Serious[24]	N/A	Serious[4]	Low
Possible anxiety ≥8 HADS-A ≤10 (reference category: HADS-A ≤7) predicting COPD exacerbation – follow-up: 12 months								
1 (Xu 2008)	Prospective cohort	491	RR 1.13 (0.43, 2.96)	Not serious	Not serious	N/A	Serious[4]	Moderate
Possible anxiety ≥8 HADS-A ≤10 (reference category: HADS-A ≤7) predicting COPD exacerbation – follow-up: 12 months								
1 (Xu 2008)	Prospective cohort	491	RR 1.92 (1.04, 3.54)	Not serious	Not serious	N/A	Not serious	High
Possible anxiety ≥8 HADS-A ≤10 (reference category: HADS-A ≤7) predicting hospitalisation for COPD exacerbation – follow-up: 12 months								
1 (Xu 2008)	Prospective cohort	491	RR 1.40 (0.27, 7.39)	Not serious	Not serious	N/A	Serious[4]	Moderate
Possible anxiety ≥8 HADS-A ≤10 (reference category: HADS-A ≤7) predicting hospitalisation for COPD exacerbation – follow-up: 12 months								
1 (Xu 2008)	Prospective cohort	491	RR 1.99 (0.59, 6.72)	Not serious	Not serious	N/A	Serious[4]	Moderate
Number of comorbidities[30] (reference category: not reported) readmission to hospital for COPD exacerbation – follow-up: 30 days								
1 (Crisafulli 2015)	Prospective cohort	125	OR 1.34 (0.84, 2.14)	Very serious[8]	Not serious	N/A	Serious[4]	Very low

No. of studies	Study design	Sample size	Effect size (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
Higher rate of comorbidities[31] (reference category: not reported) predicting 2 or more exacerbations per year – follow-up: mean 5 years								
1 (Yang 2014)	Prospective cohort	227	RR 3.81 (1.24, 11.75)	Not serious	Not serious	N/A	Not serious	High
Total comorbidities (reference category: not reported) predicting exacerbation frequency – follow-up: mean 5 years								
1 (Yang 2014)	Prospective cohort	227	RR 0.74 (0.60, 0.91)	Not serious	Not serious	N/A	Not serious	High
HIV-Infected Serostatus Model (reference category: HIV-uninfected) predicting AECOPD – follow-up: mean 1.5 years ALIVE study								
1 (Lambert 2015)	Prospective cohort	167	OR 1.86 (0.80, 4.30)	Not serious	Serious[32]	N/A	Serious[4]	Low
HIV-Infected RNA Model – undetectable <50 copies/mL (reference category: HIV-uninfected) predicting AECOPD – follow-up: mean 1.5 years ALIVE study								
1 (Lambert 2015)	Prospective cohort	167	OR 2.37 (0.89, 6.34)	Not serious	Serious[32]	N/A	Serious[4]	Low
HIV-Infected RNA Model – detectable ≥50 copies/mL (reference category: HIV-uninfected) predicting AECOPD – follow-up: mean 1.5 years ALIVE study								
1 (Lambert 2015)	Prospective cohort	167	OR 1.19 (0.36, 3.92)	Not serious	Serious[32]	N/A	Serious[4]	Low
HIV-Infected CD4 count Model – count ≥350 cells/mm^3 (reference category: HIV-uninfected) predicting AECOPD – follow-up: mean 1.5 years ALIVE study								
1 (Lambert 2015)	Prospective cohort	167	OR 3.23 (1.29, 8.12)	Not serious	Serious[32]	N/A	Not serious	Moderate
HIV-Infected CD4 count Model – count <350 cells/mm^3 (reference category: HIV-uninfected) predicting AECOPD – follow-up: mean 1.5 years ALIVE study								
1 (Lambert 2015)	Prospective cohort	167	OR 0.63 (0.15, 2.56)	Not serious	Serious[32]	N/A	Serious[4]	Low

No. of studies	Study design	Sample size	Effect size (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
Psychiatric disorders (reference category: not reported) predicting any first COPD exacerbation (out and/or inpatient) – follow-up: mean 2 years								
1 (Laurin 2009)	Prospective cohort	110	RR 1.56 (1.02, 2.37)	Not serious	Not serious	N/A	Not serious	High
Psychiatric disorders (reference category: not reported) predicting any first outpatient COPD exacerbation – follow-up: mean 2 years								
1 (Laurin 2009)	Prospective cohort	110	RR 1.68 (1.08, 2.59)	Not serious	Not serious	N/A	Not serious	High
Psychiatric disorders (reference category: not reported) predicting any first inpatient COPD exacerbation – follow-up: mean 2 years								
1 (Laurin 2009)	Prospective cohort	110	RR 1.36 (0.82, 2.25)	Not serious	Not serious	N/A	Serious[4]	Moderate

1. High risk of bias (the study only reported that clinical characteristics were extracted during the index hospital admission but it was unclear how ischemic heart disease was defined. Multivariate analysis was done but confounders were not reported)
2. Moderate risk of bias (short follow-up: 1 month)
3. Specifically acute exacerbated chronic bronchitis
4. Non-significant result
5. Moderate risk of bias (relatively high attrition rate [over 10% lost to follow-up] and unclear adjustment for confounding variables)
6. Moderate risk of bias (unclear follow-up procedure and lack of clarity regarding confounding factors)
7. Moderate risk of bias (anxiety and depression were measured using a questionnaire; adjustment was done but confounding factors were not mentioned)
8. High risk of bias (confounding factors were not identified; therefore, no confounding factors were taken into account in the design and/or analysis; loss to follow-up was 19.4%; follow-up time was 30 days)
9. COPD hospitalised exacerbations in the prior 12 months before baseline were included in the analysis
10. Moderate risk of bias (history of asthma was identified by self-report)
11. Moderate risk of bias (20% were lost at follow-up)
12. Adjusted by anti-gastroesophageal reflux disease therapy and FEV1 % predicted
13. Adjusted by gastroesophageal reflux disease therapy, FEV1 % predicted, and medication for comorbidities
14. Moderate risk of bias (use of diagnostic codes to determine outcome and recruitment via referral to clinic only)

No. of studies	Study design	Sample size	Effect size (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality

15. Only contained those COPD patients with suspected sleep-disordered breathing
16. Moderate risk of bias (previous exacerbations and use of COPD medication not considered in analysis)
17. Adjusted by anti-gastroesophageal reflux disease therapy, BODE index, supervised rehabilitation, and lung volume reduction procedure
18. Moderate risk of bias (exacerbations of COPD were measured with the CAT questionnaire)
19. High risk of bias (relied solely on prescription data for oral corticosteroids in measuring outcome, use of questionnaire in determining GERD and over 10% lost to follow-up due to death)
20. Moderate risk of bias (use of self-report in outcome measurement and unclear follow-up)
21. Moderate risk of bias (use of self-report in measure of gastroesophageal reflux disease and lack of clarity regarding potential confounders)
22. High risk of bias (no adjustment for confounders and use of self-report measurement of gastroesophageal reflux disease)
23. High risk of bias (depression was measured with a questionnaire; multivariate regression model was used but confounding factors were not mentioned: 23% were lost to follow-up)
24. Diagnostic codes used in participant identification and only included those participants admitted for over 24 hours
25. Moderate risk of bias (the Centre for Epidemiologic Studies Depression index was used to detect patients with early-phase depression but it was not reported who did this evaluation; multivariate logistic regression was used but confounders were not reported)
26. Non-significant result and sample size <100 participants
27. Relative risks were calculated using raw data from Papaioannou 2013
28. Moderate risk of bias (over 10% lost to follow up)
29. High risk of bias (unclear follow-up procedure and attrition information, and used diagnostic codes in participant selection and to measure exacerbations)
30. Comorbidities: chronic heart and renal failure, neurologic and non-cirrhotic liver disease, diabetes and non-active cancer
31. Comorbidities: cardiovascular disease, cerebrovascular disease, diabetes mellitus, and neoplasm
32. Participants identified via study of current or former injection drug users at-risk or with HIV infection and therefore excludes other HIV patients or those at-risk

*Montserrat-Capdevila (2016) and Montserrat-Capdevila (2017) reported on the same population

N/A: not applicable; CES-D: Centre for Epidemiologic Studies Depression Scale; HADS or HAD: Hospital Anxiety and Depression Scale; HADS-D: Scale-Depression; HADS-A: Scale-Anxiety; HIV: Human Immunodeficiency Virus; RNA: ribonucleic acid

Risk factor: viral or bacterial infection

No. of studies	Study design	Sample size	Effect size (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
Bacterial pathogen or sputum eosinophilia at stable stage (reference category: not reported) predicting bacterial pathogen or sputum eosinophil-associated exacerbation – follow-up: 12 months								
1 (Bafadhel 2011)	Prospective cohort	115	OR 4.9 (2.4, 9.9)	Very serious[1]	Not serious	N/A	Not serious	Low
Bacterial pathogen: any pathogen (reference category: no pathogen) predicting exacerbation – follow-up: 56 months								
1 (Sethi 2002)	Prospective cohort	81	RR 1.44 (1.24, 1.68)	Serious[2]	Not serious	N/A	Not serious	Moderate
Bacterial pathogen: moraxella catarrhalis (reference category: no pathogen) predicting exacerbation – follow-up: 56 months								
1 (Sethi 2002)	Prospective cohort	81	RR 1.99 (1.52, 2.62)	Serious[2]	Not serious	N/A	Not serious	Moderate
New strain: moraxella catarrhalis (reference category: no new strain) predicting exacerbation – follow-up: 56 months								
1 (Sethi 2002)	Prospective cohort	81	RR 2.96 (2.39, 3.67)	Serious[2]	Not serious	N/A	Not serious	Moderate
Presence of moraxella catarrhalis irrespective of season (reference category: not reported) predicting AECOPD – follow-up: 12 months AERIS study								
1 (Wilkinson 2017)	Prospective cohort	217	OR 5.09 (2.76, 9.41)	Serious[3]	Not serious	N/A	Not serious	Moderate
New occurrence of moraxella catarrhalis irrespective of season (reference category: not reported) predicting AECOPD – follow-up: 12 months AERIS study								
1 (Wilkinson 2017)	Prospective cohort	217	OR 6.57 (3.40, 12.70)	Serious[3]	Not serious	N/A	Not serious	Moderate
Presence of moraxella catarrhalis irrespective of human rhinovirus (reference category: not reported) predicting AECOPD – follow-up: 12 months AERIS study								
1 (Wilkinson 2017)	Prospective cohort	217	OR 3.52 (2.12, 5.83)	Serious[3]	Not serious	N/A	Not serious	Moderate
New occurrence of moraxella catarrhalis irrespective of human rhinovirus (reference category: not reported) predicting AECOPD – follow-up: 12 months AERIS study								

No. of studies	Study design	Sample size	Effect size (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
1 (Wilkinson 2017)	Prospective cohort	217	OR 4.57 (2.59, 8.05)	Serious[3]	Not serious	N/A	Not serious	Moderate
Bacterial pathogen: streptococcus pneumoniae (reference category: no pathogen) predicting exacerbation – follow-up: 56 months								
1 (Sethi 2002)	Prospective cohort	81	RR 1.40 (1.05, 1.87)	Serious[2]	Not serious	N/A	Not serious	Moderate
New strain: streptococcus pneumoniae (reference category: no new strain) predicting exacerbation – follow-up: 56 months								
1 (Sethi 2002)	Prospective cohort	81	RR 1.77 (1.14, 2.75)	Serious[2]	Not serious	N/A	Not serious	Moderate
Any new strain including haemophilus influenza, moraxella catarrhalis, streptococcus pneumoniae, or pseudomonas aeruginosa (reference category: no new strain) predicting exacerbation – follow-up: 56 months								
1 (Sethi 2002)	Prospective cohort	81	RR 2.15 (1.83, 2.53)	Serious[2]	Not serious	N/A	Not serious	Moderate
Presence of human rhinovirus irrespective of season (reference category: not reported) predicting AECOPD – follow-up: 12 months AERIS study								
1 (Wilkinson 2017)	Prospective cohort	217	OR 10.26 (5.82, 18.10)	Serious[3]	Not serious	N/A	Not serious	Moderate
New occurrence of human rhinovirus irrespective of season (reference category: not reported) predicting AECOPD – follow-up: 12 months AERIS study								
1 (Wilkinson 2017)	Prospective cohort	217	OR 10.15 (5.38, 19.15)	Serious[3]	Not serious	N/A	Not serious	Moderate
Presence of human rhinovirus in absence of non-typeable haemophilus influenzae (reference category: not reported) predicting AECOPD – follow-up: 12 months AERIS study								
1 (Wilkinson 2017)	Prospective cohort	217	OR 5.95 (2.77, 12.79)	Serious[3]	Not serious	N/A	Not serious	Moderate
Presence of human rhinovirus in presence of non-typeable haemophilus influenzae (reference category: not reported) predicting AECOPD – follow-up: 12 months AERIS study								
1 (Wilkinson 2017)	Prospective cohort	217	OR 18.26 (8.31, 40.14)	Serious[3]	Not serious	N/A	Not serious	Moderate
New occurrence of human rhinovirus irrespective of non-typeable haemophilus influenzae (reference category: not reported) predicting AECOPD – follow-up: 12 months AERIS study								

No. of studies	Study design	Sample size	Effect size (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
1 (Wilkinson 2017)	Prospective cohort	217	OR 10.03 (5.31, 18.95)	Serious[3]	Not serious	N/A	Not serious	Moderate
Presence of any viruses other than human rhinovirus irrespective of season (reference category: not reported) predicting AECOPD – follow-up: 12 months AERIS study								
1 (Wilkinson 2017)	Prospective cohort	217	OR 4.97 (3.07, 8.07)	Serious[3]	Not serious	N/A	Not serious	Moderate
New occurrence of any viruses other than human rhinovirus irrespective of season (reference category: not reported) predicting AECOPD – follow-up: 12 months AERIS study								
1 (Wilkinson 2017)	Prospective cohort	217	OR 4.96 (2.94, 8.35)	Serious[3]	Not serious	N/A	Not serious	Moderate
Presence of any viruses other than human rhinovirus irrespective of human rhinovirus (reference category: not reported) predicting AECOPD – follow-up: 12 months AERIS study								
1 (Wilkinson 2017)	Prospective cohort	217	OR 4.40 (2.74, 7.09)	Serious[3]	Not serious	N/A	Not serious	Moderate
New occurrence of any viruses other than human rhinovirus irrespective of human rhinovirus (reference category: not reported) predicting AECOPD – follow-up: 12 months AERIS study								
1 (Wilkinson 2017)	Prospective cohort	217	OR 4.35 (2.59, 7.30)	Serious[3]	Not serious	N/A	Not serious	Moderate
Bacterial pathogen: staphylococcus aureus (reference category: no pathogen) predicting exacerbation – follow-up: 56 months								
1 (Sethi 2002)	Prospective cohort	81	RR 0.15 (0.04, 0.60)	Serious[2]	Not serious	N/A	Not serious	Moderate
Virus at stable stage (reference category: not reported) predicting virus-associated exacerbation – follow-up: 12 months								
1 (Bafadhel 2011)	Prospective cohort	115	OR 0.5 (0.1, 3.9)	Very serious[1]	Not serious	N/A	Serious[4]	Low
Influenza (reference category: without influenza) predicting readmission for AECOPD – follow-up: 30 days								
1 (Koul 2015)	Prospective cohort	317	OR 3.3 (0.9, 12.8)	Very serious[5]	Not serious	N/A	Serious[4]	Very low

No. of studies	Study design	Sample size	Effect size (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
Bacterial pathogen: haemophilus influenza (reference category: no pathogen) predicting exacerbation – follow-up: 56 months								
1 (Sethi 2002)	Prospective cohort	81	RR 1.14 (0.94, 1.38)	Serious[2]	Not serious	N/A	Very serious[6]	Very low
New strain: haemophilus influenza (reference category: no new strain) predicting exacerbation – follow-up: 56 months								
1 (Sethi 2002)	Prospective cohort	81	RR 1.69 (1.37, 2.09)	Serious[2]	Not serious	N/A	Not serious	Moderate
Presence of non-typeable haemophilus influenzae – low season[7] (reference category: not reported) predicting AECOPD – follow-up: 12 months AERIS study								
1 (Wilkinson 2017)	Prospective cohort	217	OR 1.22 (0.68, 2.22)	Serious[3]	Not serious	N/A	Serious[4]	Low
Presence of non-typeable haemophilus influenzae – high season[8] (reference category: not reported) predicting AECOPD – follow-up: 12 months AERIS study								
1 (Wilkinson 2017)	Prospective cohort	217	OR 3.04 (1.80, 5.13)	Serious[3]	Not serious	N/A	Not serious	Moderate
New occurrence of non-typeable haemophilus influenzae irrespective of season (reference category: not reported) predicting AECOPD – follow-up: 12 months AERIS study								
1 (Wilkinson 2017)	Prospective cohort	217	OR 2.35 (1.42, 3.87)	Serious[3]	Not serious	N/A	Not serious	Moderate
Presence of non-typeable haemophilus influenzae in absence of human rhinovirus (reference category: not reported) predicting AECOPD – follow-up: 12 months AERIS study								
1 (Wilkinson 2017)	Prospective cohort	217	OR 1.69 (1.10, 2.59)	Serious[3]	Not serious	N/A	Not serious	Moderate
Presence of non-typeable haemophilus influenzae in presence of human rhinovirus (reference category: not reported) predicting AECOPD – follow-up: 12 months AERIS study								
1 (Wilkinson 2017)	Prospective cohort	217	OR 5.18 (1.92, 13.99)	Serious[3]	Not serious	N/A	Not serious	Moderate
Bacterial pathogen: pseudomonas aeruginosa (reference category: no pathogen) predicting exacerbation – follow-up: 56 months								
1 (Sethi 2002)	Prospective cohort	81	RR 1.09 (0.74, 1.60)	Serious[2]	Not serious	N/A	Very serious[6]	Very low

No. of studies	Study design	Sample size	Effect size (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
New strain: pseudomonas aeruginosa (reference category: no new strain) predicting exacerbation – follow-up: 56 months								
1 (Sethi 2002)	Prospective cohort	81	RR 0.61 (0.21, 1.82)	Serious[2]	Not serious	N/A	Very serious[6]	Very low
Bacterial pathogen: other gram-negative rods (reference category: no pathogen) predicting exacerbation – follow-up: 56 months								
1 (Sethi 2002)	Prospective cohort	81	RR 0.76 (0.49, 1.16)	Serious[2]	Not serious	N/A	Very serious[6]	Very low

1. High risk of bias (confounding was not reported; loss to follow-up was 26%)
2. Moderate risk of bias (lack of clarity regarding confounding variables and unclear whether there were drop outs)
3. Moderate risk of bias (high rate of attrition [22.3% lost to follow-up])
4. Non-significant result
5. High risk of bias (high attrition rate and exposure checked for on admission rather than following patients with influenza prospectively)
6. Non-significant result and sample size <100 participants
7. Low season: April to September
8. High season: October to March

N/A: not applicable

Risk factor: biomarkers

No. of studies	Study design	Sample size	Effect size (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
C-reactive protein (CRP) ≥ 8 mg/l (reference category: negative CRP) predicting 2 or more exacerbations – follow-up: 12 months								
1 (Al-ani 2013)	Prospective cohort	340	OR 2.2 (1.1, 4.8)	Serious[1]	Not serious	N/A	Not serious	Moderate
High sensitive C-reactive protein (hsCRP) level at discharge ≥3 mg/L(reference category: hsCRP <3 mg/L) predicting readmission for AECOPD – follow-up: 9 months								
1 (Chang 2014)	Prospective cohort	135	OR 3.4 (1.9, 6.1)	Very serious[2]	Not serious	N/A	Not serious	Low
C-reactive protein at discharge ≥7.6 mg/L (reference category: median 3.5) readmission to hospital for COPD exacerbation – follow-up: 30 days								

No. of studies	Study design	Sample size	Effect size (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
1 (Crisafulli 2015)	Prospective cohort	125	OR 7.41 (1.34, 40.91)	Very serious[2] [2]	Not serious	N/A	Not serious	Low
High sensitive C-reactive protein per SD increase (reference category: not reported) predicting COPD exacerbations – follow-up: 10 years Copenhagen General Population Study								
1 (Ingebrigtsen 2015a)	Prospective cohort	9,983	HR 1.27 (1.20, 1.35)	Serious[3]	Not serious	N/A	Not serious	Moderate
High sensitive C-reactive protein at discharge (reference category: not reported) predicting readmission for AECOPD – follow-up: 12 months								
1 (Jing 2016)	Prospective cohort	86	OR 1.39 (1.13, 1.71)	Serious[4]	Not serious	N/A	Not serious	Moderate
C-reactive protein 1 mg/dl increase (reference category: mean not reported) predicting exacerbation frequency[5] requiring hospital admission – follow-up: 5 years Hokkaido COPD study								
1 (Suzuki 2014)	Prospective cohort	268	RR 1.23 (0.92, 1.54)	Serious[6]	Not serious	N/A	Serious[7]	Low
C-reactive protein (reference category: median 57) predicting AECOPD – follow-up: 6 months								
1 (Zhao 2014)	Prospective cohort	159	OR 1.00	Very serious[8]	Not serious	N/A	Serious[7]	Very low
Fibrinogen per SD increase (reference category: fibrinogen SD) predicting COPD exacerbations – follow-up: 10 years Copenhagen General Population Study								
1 (Ingebrigtsen 2015a)	Prospective cohort	6,619	HR 1.14 (1.07, 1.22)	Serious[3]	Not serious	N/A	Not serious	Moderate
α_1-antitrypsin per SD increase (reference category: α_1-antitrypsin SD) predicting COPD exacerbations – follow-up: 10 years Copenhagen General Population Study								
1 (Ingebrigtsen 2015a)	Prospective cohort	13,043	HR 1.18 (1.11, 1.25)	Serious[3]	Not serious	N/A	Not serious	Moderate
α_1-antitrypsin (reference category: 0 exacerbations) predicting 1 exacerbation per year – follow-up: COPDGene cohort mean 4.04 years								

No. of studies	Study design	Sample size	Effect size (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
1 (Keene 2017)	Prospective cohort	602	OR 0.64 (0.38, 1.08)	Serious[9]	Not serious	N/A	Serious[7]	Low
α_1-antitrypsin (reference category: 0 exacerbations) predicting ≥2 exacerbation per year – follow-up: COPDGene cohort mean 4.04 years								
1 (Keene 2017)	Prospective cohort	602	OR 1.30 (0.80, 2.10)	Serious[9]	Not serious	N/A	Serious[7]	Low
α_1-antitrypsin (reference category: 1 exacerbations) predicting ≥2 exacerbation per year – follow-up: COPDGene cohort mean 4.04 years								
1 (Keene 2017)	Prospective cohort	602	OR 2.01 (1.06, 3.80)	Serious[9]	Not serious	N/A	Not serious	Moderate
α_1-antitrypsin (reference category: 0 exacerbations) predicting 1 exacerbation per year – follow-up: SPIROMICS cohort mean 2.28 years								
1 (Keene 2017)	Prospective cohort	1,544	OR 1.22 (0.98, 1.50)	Serious[9]	Not serious	N/A	Serious[7]	Low
α_1-antitrypsin (reference category: 0 exacerbations) predicting ≥2 exacerbations per year – follow-up: SPIROMICS cohort mean 2.28 years								
1 (Keene 2017)	Prospective cohort	1,544	OR 0.87 (0.67, 1.14)	Serious[9]	Not serious	N/A	Serious[7]	Low
α_1-antitrypsin (reference category: 1 exacerbations) predicting ≥2 exacerbations per year – follow-up: SPIROMICS cohort mean 2.28 years								
1 (Keene 2017)	Prospective cohort	1,544	OR 0.71 (0.53, 0.97)	Serious[9]	Not serious	N/A	Not serious	Moderate
High brain natriuretic peptide (BNP) levels (>34.2 pg/mL) in participants with very severe COPD defined as GOLD stage IV (reference category: not reported) predicting initial exacerbation – follow-up: 3 years								
1 (Inoue 2009)	Prospective cohort	60	HR 3.78 (1.24, 12.66)	Serious[10]	Not serious	N/A	Not serious	Moderate
Serum surfactant protein D per 100 ng·mL^{-1}(reference category: mean 121.1 ng·mL^{-1}) predicting at least 1 exacerbation during follow-up: 12 months ECLIPSE cohort								
1 (Lomas 2009)	Prospective cohort	2,189	OR 1.22 (1.07, 1.39)	Serious[9]	Not serious	N/A	Not serious	Moderate
Serum surfactant protein D in the upper quartile 174.2 ng·mL^{-1}(reference category: mean 121.1 ng·mL^{-1}) predicting at least 1 exacerbation during follow-up: 12 months ECLIPSE cohort								
1 (Lomas 2009)	Prospective cohort	2,189	OR 1.42 (1.02, 1.97)	Serious[9]	Not serious	N/A	Not serious	Moderate
Serum surfactant protein D above the 99th percentile 382.7 ng·mL^{-1}(reference category: mean 121.1 ng·mL^{-1}) predicting at least 1 exacerbation during follow-up: 12 months ECLIPSE cohort								
1 (Lomas 2009)	Prospective cohort	2,189	OR 1.58 (1.02, 2.44)	Serious[9]	Not serious	N/A	Not serious	Moderate

No. of studies	Study design	Sample size	Effect size (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
Serum surfactant protein D above the 99th percentile 382.7 ng·mL-1(reference category: mean 121.1 ng·mL-1) predicting at least 1 exacerbation during follow-up: 12 months ECLIPSE cohort in participants without exacerbations during the year prior to enrolment								
1 (Lomas 2009)	Prospective cohort	2,189	OR 1.23 (1.02, 1.49)	Serious[9]	Not serious	N/A	Not serious	Moderate
Serum surfactant protein D above the 95th percentile 175.5 ng·mL-1(reference category: mean 121.1 ng·mL-1) predicting at least 1 exacerbation during follow-up: 12 months ECLIPSE cohort								
1 (Lomas 2009)	Prospective cohort	2,189	OR 1.30 (1.03, 1.63)	Serious[9]	Not serious	N/A	Not serious	Moderate
Serum surfactant protein D above the 75th percentile 174.2 ng·mL-1(reference category: mean 121.1 ng·mL-1) predicting at least 1 exacerbation during follow-up: 12 months ECLIPSE cohort								
1 (Lomas 2009)	Prospective cohort	2,189	OR 1.28 (1.02, 1.61)	Serious[9]	Not serious	N/A	Not serious	Moderate
Serum surfactant protein D above the 75th percentile 174.2 ng·mL-1(reference category: mean 121.1 ng·mL-1) predicting exacerbations requiring antibiotics – follow-up: 12 months ECLIPSE cohort								
1 (Lomas 2009)	Prospective cohort	2,189	OR 1.31 (1.05, 1.64)	Serious[9]	Not serious	N/A	Not serious	Moderate
Eosinophil count >600/µL[11] (reference category: median 166.5 cells/µL) predicting moderate to severe AECOPD – follow-up: 12 months KOCOSS study								
1 (Song 2017)	Prospective cohort	467	OR 3.59 (1.00, 12.8)	Not serious	Not serious	N/A	Serious[7]	Moderate
Eosinophil count >600/µL[12] (reference category: median 166.5 cells/µL) predicting moderate to severe AECOPD – follow-up: 12 months KOCOSS study								
1 (Song 2017)	Prospective cohort	467	OR 1.66 (0.43, 6.40)	Not serious	Not serious	N/A	Serious[7]	Moderate
Eosinophil count (/µL)[11] (reference category: median 166.5 cells/µL) predicting moderate to severe AECOPD – follow-up: 12 months KOCOSS study								
1 (Song 2017)	Prospective cohort	467	OR 1.00 (0.99, 1.00)	Not serious	Not serious	N/A	Serious[7]	Moderate
Eosinophil count (/µL)[12] (reference category: median 166.5 cells/µL) predicting moderate to severe AECOPD – follow-up: 12 months KOCOSS study								

No. of studies	Study design	Sample size	Effect size (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
1 (Song 2017)	Prospective cohort	467	OR 1.00 (0.99, 1.00)	Not serious	Not serious	N/A	Serious[7]	Moderate
Blood eosinophils count ≥0.34·10^9 cells/L3 (reference category: <0.34·10^9 cells/L) predicting severe exacerbations – follow-up: 3 years Copenhagen General Population Study cohort								
1 (Vedel-Krogh 2016)	Prospective cohort	7,225	RR 2.06 (1.87, 2.27)[13]	Very serious[14]	Not serious	N/A	Not serious	Low
Blood eosinophils count ≥0.34·10^9 cells/L3 (reference category: <0.34·10^9 cells/L) predicting moderate exacerbations – follow-up: 3 years Copenhagen General Population Study cohort								
1 (Vedel-Krogh 2016)	Prospective cohort	7,225	RR 1.25 (1.17, 1.35)[13]	Very serious[14]	Not serious	N/A	Not serious	Low
Blood eosinophils ≥3.3% (reference category: <3.3%) predicting severe exacerbations – follow-up: 3 years Copenhagen General Population Study cohort								
1 (Vedel-Krogh 2016)	Prospective cohort	7,225	RR 1.42 (1.29, 1.56)[13]	Very serious[14]	Not serious	N/A	Not serious	Low
Blood eosinophils ≥3.3% (reference category: <3.3%) predicting moderate exacerbations – follow-up: 3 years Copenhagen General Population Study cohort								
1 (Vedel-Krogh 2016)	Prospective cohort	7,225	RR 1.02 (0.96, 1.09)[13]	Very serious[14]	Not serious	N/A	Serious[7]	Very low
Blood eosinophils ≥2% (reference category: <2%) predicting severe exacerbations – follow-up: 3 years Copenhagen General Population Study cohort								
1 (Vedel-Krogh 2016)	Prospective cohort	7,225	RR 1.03 (0.94, 1.14)[13]	Very serious[14]	Not serious	N/A	Serious[7]	Very low

No. of studies	Study design	Sample size	Effect size (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
Blood eosinophils ≥2% (reference category: <2%) predicting moderate exacerbations – follow-up: 3 years Copenhagen General Population Study cohort								
1 (Vedel-Krogh 2016)	Prospective cohort	7,225	RR 0.88 (0.84, 0.93)[13]	Very serious[14]	Not serious	N/A	Not serious	Low
One high inflammatory biomarker (reference category: 0 high inflammatory biomarkers)[15] predicting frequent exacerbations (≥2) – follow-up: 12 months Copenhagen City Heart Study and Copenhagen General Population study								
1 (Thomsen 2013)	Prospective cohort	6,574	OR 1.2 (0.7, 2.2)	Very serious[16]	Not serious	N/A	Serious[7]	Very low
Two high inflammatory biomarker (reference category: 0 high inflammatory biomarkers)[15] predicting frequent exacerbations (≥2) – follow-up: 12 months Copenhagen City Heart Study and Copenhagen General Population study								
1 (Thomsen 2013)	Prospective cohort	6,574	OR 1.7 (0.9, 9.2)	Very serious[16]	Not serious	N/A	Serious[7]	Very low
Three high inflammatory biomarker (reference category: 0 high inflammatory biomarkers)[15] predicting frequent exacerbations (≥2) – follow-up: 12 months Copenhagen City Heart Study and Copenhagen General Population study								
1 (Thomsen 2013)	Prospective cohort	6,574	OR 3.7 (1.9, 7.4)	Very serious[16]	Not serious	N/A	Not serious	Low
One high inflammatory biomarker (reference category: 0 high inflammatory biomarkers)[15] predicting at least 1 exacerbation – follow-up: 4 years Copenhagen City Heart Study and Copenhagen General Population study								
1 (Thomsen 2013)	Prospective cohort	6,574	OR 1.2 (1.0, 1.4)	Very serious[16]	Not serious	N/A	Serious[7]	Very low
Two high inflammatory biomarker (reference category: 0 high inflammatory biomarkers)[15] predicting at least 1 exacerbation – follow-up: 4 years Copenhagen City Heart Study and Copenhagen General Population study								

No. of studies	Study design	Sample size	Effect size (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
1 (Thomsen 2013)	Prospective cohort	6,574	OR 1.3 (1.1, 1.6)	Very serious[16]	Not serious	N/A	Not serious	Low
Three high inflammatory biomarker (reference category: 0 high inflammatory biomarkers)[15] predicting at least 1 exacerbation – follow-up: 4 years Copenhagen City Heart Study and Copenhagen General Population study								
1 (Thomsen 2013)	Prospective cohort	6,574	OR 1.8 (1.4, 2.2)	Very serious[16]	Not serious	N/A	Not serious	Low
One high inflammatory biomarker (reference category: 0 high inflammatory biomarkers)[15] predicting frequent exacerbations (≥2) – follow-up: 4 years Copenhagen City Heart Study and Copenhagen General Population study								
1 (Thomsen 2013)	Prospective cohort	6,574	OR 1.4 (1.1, 1.8)	Very serious[16]	Not serious	N/A	Not serious	Low
Two high inflammatory biomarker (reference category: 0 high inflammatory biomarkers)[15] predicting frequent exacerbations (≥2) – follow-up: 4 years Copenhagen City Heart Study and Copenhagen General Population study								
1 (Thomsen 2013)	Prospective cohort	6,574	OR 1.6 (1.3, 2.2)	Very serious[16]	Not serious	N/A	Not serious	Low
Three high inflammatory biomarker (reference category: 0 high inflammatory biomarkers)[15] predicting frequent exacerbations (≥2) – follow-up: 4 years Copenhagen City Heart Study and Copenhagen General Population study								
1 (Thomsen 2013)	Prospective cohort	6,574	OR 2.5 (1.8, 3.4)	Very serious[16]	Not serious	N/A	Not serious	Low
Pro-forms of collagen type III levels (reference category: not reported) predicting shorter time to exacerbation – follow-up: 2 years PROMISE-COPD cohort								
1 (Stolz 2017)	Prospective cohort	506	HR 0.72 (0.59, 0.89)	Serious[17]	Not serious	N/A	Not serious	Moderate

No. of studies	Study design	Sample size	Effect size (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
Haemoglobin 1 g/dl increase (reference category: mean not reported) predicting exacerbation frequency[5] requiring prescription – follow-up: 5 years Hokkaido COPD study								
1 (Suzuki 2014)	Prospective cohort	268	RR 0.84 (0.76, 0.93)	Serious[6]	Not serious	N/A	Not serious	Moderate
Haemoglobin 1 g/dl increase (reference category: mean not reported) predicting recurrent exacerbation[18] requiring prescription – follow-up: 5 years Hokkaido COPD study								
1 (Suzuki 2014)	Prospective cohort	268	RR 0.87 (0.78, 0.97)	Serious[6]	Not serious	N/A	Not serious	Moderate
Immunoglobulin A (IgA) (reference category: 0 exacerbations) predicting 1 exacerbation per year – follow-up: COPDGene cohort mean 4.04 years								
1 (Keene 2017)	Prospective cohort	602	OR 0.82 (0.53, 1.26)	Serious[9]	Not serious	N/A	Serious[7]	Low
IgA (reference category: 0 exacerbations) predicting ≥2 exacerbation per year – follow-up: COPDGene cohort mean 4.04 years								
1 (Keene 2017)	Prospective cohort	602	OR 0.66 (0.45, 0.97)	Serious[9]	Not serious	N/A	Not serious	Moderate
IgA (reference category: 1 exacerbations) predicting ≥2 exacerbation per year – follow-up: COPDGene cohort mean 4.04 years								
1 (Keene 2017)	Prospective cohort	602	OR 0.81 (0.48, 1.35)	Serious[9]	Not serious	N/A	Serious[7]	Low
Fast immunoglobulin G (IgG) maturation (reference category: delayed IgG maturation) predicting AECOPD – follow-up: 6 months								
1 (Boeck 2014)	Prospective cohort	43	RR 0.35 (0.18, 0.70)[19]	Very serious[20]	Not serious	N/A	Not serious	Low
Fast IgG maturation (reference category: delayed IgG maturation) predicting hospitalisation for AECOPD – follow-up 6 months								
1 (Boeck 2014)	Prospective cohort	43	RR 0.33 (0.09, 1.13)[19]	Very serious[20]	Not serious	N/A	Very serious[21]	Very low
Interleukin-6 at discharge ≥19.5 pg/mL (reference category: median 10.5) readmission to hospital for COPD exacerbation – follow-up: 30 days								
1 (Crisafulli 2015)	Prospective cohort	125	OR 4.84 (0.95, 24.51)	Very serious[22]	Not serious	N/A	Serious[7]	Very low

No. of studies	Study design	Sample size	Effect size (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
Interleukin-1β protein level, ng/mL (reference category: not reported) predicting COPD exacerbations – follow-up: 12 months								
1 (Fu 2015)	Prospective cohort	140	OR 1.32 (1.07, 1.62)	Serious[2][3]	Not serious	N/A	Not serious	Moderate
Interleukin 15 ng/mL (reference category: not reported) predicting AECOPD – follow-up: 3 years SPIROMICS study								
1 (Han 2017)	Prospective cohort	394	OR 0.04 (0.001, 0.82)	Very serious[2][4]	Not serious	N/A	Not serious	Low
Interleukin 8 ng/mL (reference category: not reported) predicting AECOPD – follow-up: 3 years SPIROMICS study								
1 (Han 2017)	Prospective cohort	394	OR 1.02 (1.00, 1.04)	Very serious[2][4]	Not serious	N/A	Serious[7]	Very low
Interleukin-1 receptor antagonist (IL1RN) (reference category: 0 exacerbations) predicting 1 exacerbation per year – follow-up: SPIROMICS cohort mean 2.28 years								
1 (Keene 2017)	Prospective cohort	1,544	OR 1.72 (1.09, 2.69)	Serious[9]	Not serious	N/A	Not serious	Moderate
IL1RN (reference category: 0 exacerbations) predicting ≥2 exacerbations per year – follow-up: SPIROMICS cohort mean 2.28 years								
1 (Keene 2017)	Prospective cohort	1,544	OR 1.19 (0.67, 2.12)	Serious[9]	Not serious	N/A	Serious[7]	Low
IL1RN (reference category: 1 exacerbations) predicting ≥2 exacerbations per year – follow-up: SPIROMICS cohort mean 2.28 years								
1 (Keene 2017)	Prospective cohort	1,544	OR 0.69 (0.35, 1.34)	Serious[9]	Not serious	N/A	Serious[7]	Low
Soluble tumour necrosis factor receptor 1 (sTNF-R1) per 1 SD increase of marker value (reference category: median sTNF-R1 6.8) predicting COPD exacerbation duration more than three weeks – follow-up: 3 years Bergen COPD study								
1 (Husebo 2014)	Prospective cohort	403	OR 1.16 (1.00, 1.35)	Not serious	Not serious	N/A	Serious[7]	High
Vitamin D deficiency[25] (reference category: non-deficiency[26]) predicting 1 exacerbation per year – follow-up: 3 years								
1 (Jung 2015)	Prospective cohort	193	OR 0.89 (0.53, 1.49)	Not serious	Not serious	N/A	Serious[7]	Moderate
Vitamin D deficiency[25] (reference category: non-deficiency[26]) predicting ≥2 exacerbations per year – follow-up: 3 years								

No. of studies	Study design	Sample size	Effect size (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
1 (Jung 2015)	Prospective cohort	193	OR 1.24 (0.64, 2.38)	Not serious	Not serious	N/A	Serious[7]	Moderate
25-hydroxyvitamin D deficiency: 10 to <20 ng/dL (reference category: severe deficiency [<10 ng/dL]) predicting exacerbations – follow-up: 2 years								
1 (Puhan 2014)	Prospective cohort	356	HR 1.30 (0.89, 1.89	Not serious	Not serious	N/A	Serious[7]	Moderate
25-hydroxyvitamin D insufficiency: 20 to <30 ng/dL (reference category: severe deficiency [<10 ng/dL]) predicting exacerbations – follow-up: 2 years								
1 (Puhan 2014)	Prospective cohort	356	HR 1.43 (0.88, 2.35)	Not serious	Not serious	N/A	Serious[7]	Moderate
25-hydroxyvitamin D desirable: ≥30 ng/dL (reference category: severe deficiency [<10 ng/dL]) predicting exacerbations – follow-up: 2 years								
1 (Puhan 2014)	Prospective cohort	356	HR 0.77 (0.36, 1.65)	Not serious	Not serious	N/A	Serious[7]	Moderate
Hepatocyte growth factor (HGF) (reference category: 0 exacerbations) predicting 1 exacerbation per year – follow-up: COPDGene cohort mean 4.04 years								
1 (Keene 2017)	Prospective cohort	602	OR 1.78 (1.06, 3.00)	Serious[9]	Not serious	N/A	Not Serious	Moderate
HGF (reference category: 0 exacerbations) predicting ≥2 exacerbation per year – follow-up: COPDGene cohort mean 4.04 years								
1 (Keene 2017)	Prospective cohort	602	OR 0.80 (0.51, 1.24)	Serious[9]	Not serious	N/A	Serious[7]	Low
HGF (reference category: 1 exacerbations) predicting ≥2 exacerbation per year – follow-up: COPDGene cohort mean 4.04 years								
1 (Keene 2017)	Prospective cohort	602	OR 0.44 (0.24, 0.81)	Serious[9]	Not serious	N/A	Not serious	Moderate
Midkine (MDK) (reference category: 0 exacerbations) predicting 1 exacerbation per year – follow-up: COPDGene cohort mean 4.04 years								
1 (Keene 2017)	Prospective cohort	602	OR 1.90 (1.19, 3.04)	Serious[9]	Not serious	N/A	Not serious	Moderate
MDK (reference category: 0 exacerbations) predicting ≥2 exacerbation per year – follow-up: COPDGene cohort mean 4.04 years								
1 (Keene 2017)	Prospective cohort	602	OR 1.34 (0.90, 2.00)	Serious[9]	Not serious	N/A	Serious[7]	Low

No. of studies	Study design	Sample size	Effect size (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
MDK (reference category: 1 exacerbations) predicting ≥2 exacerbation per year – follow-up: COPDGene cohort mean 4.04 years								
1 (Keene 2017)	Prospective cohort	602	OR 0.70 (0.40, 1.23)	Serious[9]	Not serious	N/A	Serious[7]	Low
Monocyte chemotactic protein 4 (CCL13) (reference category: 0 exacerbations) predicting 1 exacerbation per year – follow-up: COPDGene cohort mean 4.04 years								
1 (Keene 2017)	Prospective cohort	602	OR 0.66 (0.41, 1.05)	Serious[9]	Not serious	N/A	Serious[7]	Low
CCL13 (reference category: 0 exacerbations) predicting ≥2 exacerbation per year – follow-up: COPDGene cohort mean 4.04 years								
1 (Keene 2017)	Prospective cohort	602	OR 1.45 (0.95, 2.21)	Serious[9]	Not serious	N/A	Serious[7]	Low
CCL13 (reference category: 1 exacerbations) predicting ≥2 exacerbation per year – follow-up: COPDGene cohort mean 4.04 years								
1 (Keene 2017)	Prospective cohort	602	OR 2.19 (1.26, 3.78)	Serious[9]	Not serious	N/A	Not serious	Moderate
Sex hormone-binding globulin (SHBG) (reference category: 0 exacerbations) predicting 1 exacerbation per year – follow-up: COPDGene cohort mean 4.04 years								
1 (Keene 2017)	Prospective cohort	602	OR 1.63 (1.02, 2.62)	Serious[9]	Not serious	N/A	Not serious	Moderate
SHBG (reference category: 0 exacerbations) predicting ≥2 exacerbation per year – follow-up: COPDGene cohort mean 4.04 years								
1 (Keene 2017)	Prospective cohort	602	OR 0.97 (0.64, 1.46)	Serious[9]	Not serious	N/A	Serious[7]	Low
SHBG (reference category: 1 exacerbations) predicting ≥2 exacerbation per year – follow-up: COPDGene cohort mean 4.04 years								
1 (Keene 2017)	Prospective cohort	602	OR 0.59 (0.33, 1.04)	Serious[9]	Not serious	N/A	Serious[7]	Low
Sortilin (SORT1) (reference category: 0 exacerbations) predicting 1 exacerbation per year – follow-up: COPDGene cohort mean 4.04 years								
1 (Keene 2017)	Prospective cohort	602	OR 1.22 (0.75, 1.98)	Serious[9]	Not serious	N/A	Serious[7]	Low
SORT1 (reference category: 0 exacerbations) predicting ≥2 exacerbation per year – follow-up: COPDGene cohort mean 4.04 years								
1 (Keene 2017)	Prospective cohort	602	OR 1.67 (1.11, 2.52)	Serious[9]	Not serious	N/A	Not serious	Moderate
SORT1 (reference category: 1 exacerbations) predicting ≥2 exacerbation per year – follow-up: COPDGene cohort mean 4.04 years								
1 (Keene 2017)	Prospective cohort	602	OR 1.37 (0.76, 2.44)	Serious[9]	Not serious	N/A	Serious[7]	Low

No. of studies	Study design	Sample size	Effect size (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
Tumour necrosis factor-related apoptosis-inducing ligand receptor 3 (TNFRSF10C) (reference category: 0 exacerbations) predicting 1 exacerbation per year – follow-up: COPDGene cohort mean 4.04 years								
1 (Keene 2017)	Prospective cohort	602	OR 0.99 (0.62, 1.58)	Serious[9]	Not serious	N/A	Serious[7]	Low
TNFRSF10C (reference category: 0 exacerbations) predicting ≥2 exacerbation per year – follow-up: COPDGene cohort mean 4.04 years								
1 (Keene 2017)	Prospective cohort	602	OR 0.61 (0.40, 0.92)	Serious[9]	Not serious	N/A	Not serious	Moderate
TNFRSF10C (reference category: 1 exacerbations) predicting ≥2 exacerbation per year – follow-up: COPDGene cohort mean 4.04 years								
1 (Keene 2017)	Prospective cohort	602	OR 0.61 (0.35, 1.08)	Serious[9]	Not serious	N/A	Serious[7]	Low
Eotaxin-1 (CCL11) (reference category: 0 exacerbations) predicting 1 exacerbation per year – follow-up: COPDGene cohort mean 4.04 years								
1 (Keene 2017)	Prospective cohort	602	OR 2.71 (1.25, 5.87)	Serious[9]	Not serious	N/A	Not serious	Moderate
CCL11 (reference category: 0 exacerbations) predicting ≥2 exacerbation per year – follow-up: COPDGene cohort mean 4.04 years								
1 (Keene 2017)	Prospective cohort	602	OR 2.07 (1.04, 4.10)	Serious[9]	Not serious	N/A	Not serious	Moderate
CCL11 (reference category: 1 exacerbations) predicting ≥2 exacerbation per year – follow-up: COPDGene cohort mean 4.04 years								
1 (Keene 2017)	Prospective cohort	602	OR 0.76 (0.29, 1.94)	Serious[9]	Not serious	N/A	Serious[7]	Low
Apolipoprotein A-IV (APOA4) (reference category: 0 exacerbations) predicting 1 exacerbation per year – follow-up: SPIROMICS cohort mean 2.28 years								
1 (Keene 2017)	Prospective cohort	1,544	OR 0.80 (0.63, 1.02)	Serious[9]	Not serious	N/A	Serious[7]	Low
APOA4 (reference category: 0 exacerbations) predicting ≥2 exacerbations per year – follow-up: SPIROMICS cohort mean 2.28 years								
1 (Keene 2017)	Prospective cohort	1,544	OR 0.70 (0.51, 0.95)	Serious[9]	Not serious	N/A	Not serious	Moderate
APOA4 (reference category: 1 exacerbations) predicting ≥2 exacerbations per year – follow-up: SPIROMICS cohort mean 2.28 years								
1 (Keene 2017)	Prospective cohort	1,544	OR 0.86 (0.60, 1.23)	Serious[9]	Not serious	N/A	Serious[7]	Low
Osteoprotegerin (TNFRSF11B) (reference category: 0 exacerbations) predicting 1 exacerbation per year – follow-up: SPIROMICS cohort mean 2.28 years								

No. of studies	Study design	Sample size	Effect size (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
1 (Keene 2017)	Prospective cohort	1,544	OR 0.88 (0.69, 1.11)	Serious[9]	Not serious	N/A	Serious[7]	Low
TNFRSF11B (reference category: 0 exacerbations) predicting ≥2 exacerbations per year – follow-up: SPIROMICS cohort mean 2.28 years								
1 (Keene 2017)	Prospective cohort	1,544	OR 1.29 (0.94, 1.77)	Serious[9]	Not serious	N/A	Serious[7]	Low
TNFRSF11B (reference category: 1 exacerbations) predicting ≥2 exacerbations per year – follow-up: SPIROMICS cohort mean 2.28 years								
1 (Keene 2017)	Prospective cohort	1,544	OR 1.46 (1.02, 2.08)	Serious[9]	Not serious	N/A	Not serious	Moderate
Neutrophils 1000 cells/mm^3 increase (reference category: mean 3,519 cells/mm^3) predicting exacerbation frequency[5] requiring prescription – follow-up: 5 years Hokkaido COPD study								
1 (Suzuki 2014)	Prospective cohort	268	RR 1.00 (0.83, 1.19)	Serious[6]	Not serious	N/A	Serious[7]	Low
Copeptin (reference category: median 11.89) predicting AECOPD – follow-up: 6 months								
1 (Zhao 2014)	Prospective cohort	159	OR 1.32	Very serious[8]	Not serious	N/A	Serious[27]	Very low

1. Moderate risk of bias (confounding factors were not mentioned)
2. High risk of bias (multivariate analysis is mentioned but confounding factors are not reported; 29% were lost at follow-up)
3. Moderate risk of bias (use of diagnostic codes/prescriptions dispensed to measure outcome)
4. Moderate risk of bias (use of self-report in measuring exacerbation)
5. Exacerbation frequency: events per person per year
6. Moderate risk of bias (high attrition [over 30%])
7. Non-significant result
8. High risk of bias (multivariable analysis was done but confounding factors were not mentioned; 31% were lost to follow-up)
9. Moderate risk of bias (unclear loss to follow-up and use of self-report in measuring outcome)
10. Moderate risk of bias (unclear which confounding factors were input into model; unclear assessment of exacerbation)
11. ORs adjusted with age, sex, pack-year, BMI, and initial FEV1% predicted at enrolment
12. ORs adjusted with age, sex, pack-year, BMI, and inhaled corticosteroid/long-acting beta 2 agonist use at enrolment
13. Relative risks were calculated using raw data from Vedel-Krogh 2016

No. of studies	Study design	Sample size	Effect size (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality

14. High risk of bias (use of registry in participant selection, several potentially confounding variables (medication, diet and comorbidities) were identified but not measured/adjusted for in study design, and only took one measure of blood eosinophils)
15. Thomsen 2013 reported on the following three biomarkers: plasma levels of high sensitivity C-reactive protein (cut point 3 mg/L), plasma levels of fibrinogen (cut point 14 μ), and whole blood leukocyte count (cut point $9X10^9$/L).
16. High risk of bias (COPD exacerbation was collected linking the study database to 2 national registries; multivariate models were adjusted using covariates but confounding factors were not mentioned)
17. Moderate risk of bias (covariates were listed for adjustment but confounders were not mentioned; 20% were lost to follow-up)
18. Recurrent exacerbation: multiple exacerbation events during follow-up
19. Relative risks were calculated using raw data from Boeck 2014
20. High risk of bias (adjusted odds ratios were reported for a composite outcome including hospitalisation or death; relative risks were calculated using raw data from Boeck 2014)
21. Non-significant result and sample size <100 participants
22. High risk of bias (confounding factors were not identified; therefore, no confounding factors were taken into account in the design and/or analysis; loss to follow-up was 19.4%; follow-up time was 30 days)
23. Moderate risk of bias (sample recruited from research registers, which may not give a fully representative population; only a limited number of variables adjusted for)
24. High risk of bias (only 394 out of 1,105 were included in the logistic regression analysis)
25. Vitamin D deficiency was defined as 25-OH vitamin D3 (25-OH-VitD3) plasma levels <20 ng/mL
26. Vitamin D non-deficiency was defined as 25-OH-VitD3 plasma levels ≥20 ng/Ml
27. Confidence intervals were not reported

N/A: not applicable; A1AT: α1-antitrypsin; APOA4: apolipoprotein A-IV; BNP: brain natriuretic peptide; CCL11: eotaxin-1; CCL13: monocyte chemotactic protein 4; HGF: hepatocyte growth factor; IgA: immunoglobulin A; IgG: immunoglobulin G; IL1RN: interleukin-1 receptor antagonist MDK: midkine; SHBG: sex hormone-binding globulin; SORT1: sortilin; TNFRSF10C: TNF-related apoptosis-inducing ligand receptor 3; TNFRSF11B: Osteoprotegerin

Risk factor: asthma-COPD

No. of studies	Study design	Sample size	Effect size (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
ACOS by GINA/GOLD criteria[1] (reference category: COPD) predicting mild, moderate, and severe exacerbations – follow-up: 12 months								
1 (Jo 2017)	Prospective cohort	194	HR 1.90 (1.02, 3.55)	Not serious	Not serious	N/A	Not serious	High
ACO with early asthma onset (reference category: COPD) predicting acute hospital admission for COPD and asthma – follow-up: median 17 years Copenhagen City Heart Study								
1 (Lange 2016)	Prospective cohort	581	HR 1.90 (1.26, 2.87)	Serious[2]	Not serious	N/A	Not serious	Moderate
ACO with late asthma onset (reference category: COPD) predicting acute hospital admission for COPD and asthma – follow-up: median 17 years Copenhagen City Heart Study								
1 (Lange 2016)	Prospective cohort	581	HR 3.52 (2.74, 4.54)	Serious[2]	Not serious	N/A	Not serious	Moderate
ACOS by GINA/GOLD (reference criteria: COPD) predicting moderate or severe exacerbations follow-up: 12 months CHAIN study								
1 (Cosio 2016)	Prospective cohort	831	RR 1.04 (0.58, 1.07)[3]	Very serious[4]	Serious[5]	N/A	Serious[6]	Very low
ACOS by GINA/GOLD criteria[1] (reference category: COPD) predicting moderate to severe exacerbations – follow-up: 12 months								
1 (Jo 2017)	Prospective cohort	194	HR 2.01 (0.97, 4.15)	Not serious	Not serious	N/A	Serious[6]	Moderate

1. Jo 2017 also reported ACOS based on other criteria (modified Spanish criteria, ATS roundtable criteria, PLATINO criteria). However, GINA and GOLD criteria are more widely use to diagnose COPD and asthma
2. Moderate risk of bias (acute hospital admissions for COPD and asthma were taken from the national Danish Patient Registry; covariates were included in analyses but confounding factors were not mentioned)
3. Relative risks were calculated using raw data from Vedel-Krogh 2016
4. High risk of bias (very high attrition rate and lack of clarity regarding confounding variable adjustment)
5. Limited data on exacerbations
6. Non-significant result

No. of studies	Study design	Sample size	Effect size (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
N/A: not applicable; ACOS/ACO: asthma-COPD overlap syndrome; GINA/GOLD: Global Initiative for Asthma/Global Initiative for Chronic Obstructive Lung Disease								

Risk factor: other medications

No. of studies	Study design	Sample size	Effect size (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
Anti-gastroesophageal reflux disease therapy[1] (reference category: not reported) predicting severe exacerbation in participants with GOLD II-IV at stable state – follow-up: 24 months								
1 (Baumeler 2016)	Prospective cohort	638	HR 1.58 (1.01, 2.47)	Not serious	Not serious	N/A	Not serious	High
Anti-gastroesophageal reflux disease therapy[2] (reference category: not reported) predicting severe exacerbation in participants with GOLD II-IV at stable state – follow-up: 24 months								
1 (Baumeler 2016)	Prospective cohort	638	HR 1.91 (1.26, 2.91)	Not serious	Not serious	N/A	Not serious	High
Anti-gastroesophageal reflux disease therapy[3] (reference category: not reported) predicting severe exacerbation in participants with GOLD II-IV at stable state – follow-up: 24 months								
1 (Baumeler 2016)	Prospective cohort	638	HR 1.63 (1.04, 2.53)	Not serious	Not serious	N/A	Not serious	High
Use of β-blockers (reference category: not use of β-blockers) predicting first severe exacerbation – follow-up: median 2.1 years								
1 (Bhatt 2016)	Prospective cohort	3,464	HR 0.69, (0.47, 1.02)	Not serious	Not serious	N/A	Serious[4]	Moderate
Use of β-blockers (reference category: not use of β-blockers) predicting first total exacerbation – follow-up: median 2.1 years								
1 (Bhatt 2016)	Prospective cohort	3,464	HR 0.91 (0.75, 1.11)	Not serious	Not serious	N/A	Serious[4]	Moderate
Use of CCBs (reference category: not use of CCBs) predicting first severe exacerbation – follow-up: median 2.1 years								

No. of studies	Study design	Sample size	Effect size (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
1 (Bhatt 2016)	Prospective cohort	3,464	HR 1.05 (0.75, 1.47)	Not serious	Not serious	N/A	Serious[4]	Moderate
Use of CCBs (reference category: not use of CCBs) predicting first total exacerbation – follow-up: median 2.1 years								
1 (Bhatt 2016)	Prospective cohort	3,464	HR 1.05 (0.83, 1.32)	Not serious	Not serious	N/A	Serious[4]	Moderate
Use of ACEI/ARBs (reference category: not use of ACEI/ARBs) predicting first severe exacerbation – follow-up: median 2.1 years								
1 (Bhatt 2016)	Prospective cohort	3,464	HR 1.07 (0.82, 1.41)	Not serious	Not serious	N/A	Serious[4]	Moderate
Use of ACEI/ARBs (reference category: not use of ACEI/ARBs) predicting first total exacerbation – follow-up: median 2.1 years								
1 (Bhatt 2016)	Prospective cohort	3,464	HR 1.01 (0.84, 1.21)	Not serious	Not serious	N/A	Serious[4]	Moderate
Statin use (reference category: not statin use) predicting first hospitalisation for an AECOPD – follow-up: 3 years								
1 (Citgez 2016)	Prospective cohort	795	HR 0.95 (0.74, 1.22)	Not serious	Not serious	N/A	Serious[4]	Moderate
Statin use (reference category: no statins) predicting exacerbations of COPD – follow-up: 12 months								
1 (Bartziokas 2011)	Prospective cohort	245	HR 0.65 (0.45, 0.94)	Not serious	Serious[5]	N/A	Not serious	Moderate
Statin use (reference category: no statins) predicting severe exacerbations of COPD – follow-up: 12 months								
1 (Bartziokas 2011)	Prospective cohort	245	HR 0.60 (0.38, 0.97)	Not serious	Serious[5]	N/A	Not serious	Moderate

1. Adjusted by BODE index, supervised rehabilitation, lung volume reduction procedure, and congestive heart failure
2. Adjusted by adjusted Charlson score and FEV1 % predicted
3. Adjusted by adjusted Charlson score, FEV1 % predicted, and medication for comorbidities
4. Non-significant result
5. All participants were enrolled during hospitalisation for exacerbation of COPD

N/A: not applicable; ACEIs: angiotensin converting enzyme inhibitors; ARBs: angiotensin receptor blockers; CCBs: calcium channel blockers

Risk factor: pollution – outdoors, indoors

No. of studies	Study design	Sample size	Effect size (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
Outdoor PM_{10} abnormal[1] (reference category: PM_{10} normal[2]) predicting emergency room visit due to AECOPD – follow-up: 12 months								
1 (Chi 2017)	Prospective cohort	19	OR 30.1 (4.9, 184.2)	Serious[3]	Not serious	N/A	Not serious	Moderate
Living room PM_{10} abnormal[1] (reference category: PM_{10} normal[2]) predicting emergency room visit due to AECOPD – follow-up: 12 months								
1 (Chi 2017)	Prospective cohort	19	OR 23.8 (3.0, 191.3)	Serious[3]	Not serious	N/A	Not serious	Moderate
Bedroom PM_{10} abnormal[1] (reference category: PM_{10} normal[2]) predicting emergency room visit due to AECOPD – follow-up: 12 months								
1 (Chi 2017)	Prospective cohort	19	OR 12.1 (2.5, 60.0)	Serious[3]	Not serious	N/A	Not serious	Moderate
Kitchen PM_{10} abnormal[1] (reference category: PM_{10} normal[2]) predicting emergency room visit due to AECOPD – follow-up: 12 months								
1 (Chi 2017)	Prospective cohort	19	OR 38.5 (4.8, 311.8)	Serious[3]	Not serious	N/A	Not serious	Moderate
Outdoor PM_{10} abnormal[1] (reference category: PM_{10} normal[2]) predicting hospital admission due to AECOPD – follow-up: 12 months								
1 (Chi 2017)	Prospective cohort	19	OR 19.5 (4.7, 80.6)	Serious[3]	Not serious	N/A	Not serious	Moderate
Living room PM_{10} abnormal[1] (reference category: PM_{10} normal[2]) predicting hospital admission due to AECOPD – follow-up: 12 months								
1 (Chi 2017)	Prospective cohort	19	OR 16.2 (3.1, 84.9)	Serious[3]	Not serious	N/A	Not serious	Moderate
Bedroom PM_{10} abnormal[1] (reference category: PM_{10} normal) predicting hospital admission due to AECOPD – follow-up: 12 months								
1 (Chi 2017)	Prospective cohort	19	OR 10.5 (2.5, 44.6)	Serious[3]	Not serious	N/A	Not serious	Moderate
Kitchen PM_{10} abnormal[1] (reference category: PM_{10} normal[2]) predicting hospital admission due to AECOPD – follow-up: 12 months								
1 (Chi 2017)	Prospective cohort	19	OR 18.5 (3.7, 91.9)	Serious[3]	Not serious	N/A	Not serious	Moderate
Multipollutant model with O_3 and PM_{10} (reference category: not reported) predicting COPD exacerbations – follow-up: 14 months Mean 24-hr PM_{10} (-1 to -5 d)[4]								
1 (Desqueyroux 2002)	Prospective cohort	39	OR 0.70 (0.37, 1.32)	Not serious	Not serious	N/A	Very serious[5]	Low
PM_{10} ($\mu g/m^3$) 1 unit change in pollutant level (reference category: mean 37.7) predicting COPD exacerbations – follow-up: 2 years East London COPD study								

No. of studies	Study design	Sample size	Effect size (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
1 (Peacock 2011)	Prospective cohort	94	OR 1.00 (0.99, 1.01)	Very serious[6]	Not serious	N/A	Very serious[5]	Very low
Multipollutant model with O_3 and SO_2 (reference category: not reported) predicting COPD exacerbations – follow-up: 14 months Maximum 1-hr O_3 (-1 to -3 d)[7]								
1 (Desqueyroux 2002)	Prospective cohort	39	OR 1.44 (1.13, 1.83)	Not serious	Not serious	N/A	Not serious	High
Multipollutant model with O_3 and PM_{10} (reference category: not reported) predicting COPD exacerbations – follow-up: 14 months Maximum 1-hr O_3 (-1 to -3 d)[4]								
1 (Desqueyroux 2002)	Prospective cohort	39	OR 1.43 (1.14, 1.79)	Not serious	Not serious	N/A	Not serious	High
Multipollutant model with O_3 and NO_2 (reference category: not reported) predicting COPD exacerbations – follow-up: 14 months Maximum 1-hr O_3 (-1 to -3 d)[7]								
1 (Desqueyroux 2002)	Prospective cohort	39	OR 1.42 (1.11, 1.81)	Not serious	Not serious	N/A	Not serious	High
O_3 (ppb) 1 unit change in pollutant level (reference category: mean 15.5) predicting COPD exacerbations – follow-up: 2 years East London COPD study								
1 (Peacock 2011)	Prospective cohort	94	OR 1.00 (0.98, 1.02)	Very serious[6]	Not serious	N/A	Very serious[5]	Very low
Multipollutant model with O_3 and SO_2 (reference category: not reported) predicting COPD exacerbations – follow-up: 14 months Mean 24-hr SO_2 (-1 to -5 d)[4]								
1 (Desqueyroux 2002)	Prospective cohort	39	OR 0.64 (0.19, 2.19)	Not serious	Not serious	N/A	Very serious[5]	Low
SO_2 (ppb) 1 unit change in pollutant level (reference category: mean 7.5) predicting COPD exacerbations – follow-up: 2 years East London COPD study								
1 (Peacock 2011)	Prospective cohort	94	OR 1.00 (0.98, 1.02)	Very serious[6]	Not serious	N/A	Very serious[5]	Very low

No. of studies	Study design	Sample size	Effect size (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
Multipollutant model with O_3 and NO_2 (reference category: not reported) predicting COPD exacerbations – follow-up: 14 months Mean 24-hr NO_2 (-1 to -5 d)[5]								
1 (Desqueyroux 2002)	Prospective cohort	39	OR 0.82 (0.37, 1.85)	Not serious	Not serious	N/A	Very serious[5]	Low
In-home air pollution per 20 ppb increase NO_2 (reference category: NO_2 mean) predicting any exacerbations – follow-up: 6 months								
1 (Hansel 2013)	Prospective cohort	84	OR 1.15 (0.61, 2.17)	Serious[8]	Not serious	N/A	Very serious[5]	Very low
In-home air pollution per 20 ppb increase NO_2 (reference category: NO_2 mean) predicting severe exacerbations – follow-up: 6 months								
1 (Hansel 2013)	Prospective cohort	84	OR 1.86 (0.79, 4.40)	Serious[8]	Not serious	N/A	Very serious[5]	Very low
NO_2 (ppb) 1 unit change in pollutant level (reference category: mean 51.4) predicting COPD exacerbations – follow-up: 2 years East London COPD study								
1 (Peacock 2011)	Prospective cohort	94	OR 1.00 (0.99, 1.00)	Very serious[6]	Not serious	N/A	Very serious[5]	Very low
In-home air pollution per 10 µg/m^3 increase in $PM_{2.5}$ (reference category: $PM_{2.5}$ mean) predicting any exacerbations – follow-up: 6 months								
1 (Hansel 2013)	Prospective cohort	84	OR 1.05 (0.73, 1.50)	Serious[8]	Not serious	N/A	Very serious[5]	Very low
In-home air pollution per 10 µg/m^3 increase in $PM_{2.5}$ (reference category: $PM_{2.5}$ mean) predicting severe exacerbations – follow-up: 6 months								
1 (Hansel 2013)	Prospective cohort	84	OR 1.50 (1.04, 2.18)	Serious[8]	Not serious	N/A	Not serious	Moderate
Black smoke (µg/m^3) 1 unit change in pollutant level (reference category: mean 10.1) predicting COPD exacerbations – follow-up: 2 years East London COPD study								
1 (Peacock 2011)	Prospective cohort	94	OR 1.00 (0.99, 1.01)	Very serious[6]	Not serious	N/A	Very serious[5]	Very low

1. Abnormal PM_{10}: daily mean or 24-h maximum of PM_{10} is above 125 µg/m^3
2. Normal PM_{10}: daily mean or 24-h maximum of PM_{10} is below 125 µg/m^3
3. Moderate risk of bias (27% were lost at follow-up)
4. Average from the 1 to 5 days preceding the COPD exacerbation for SO_2 or PM_{10} or NO_2

No. of studies	Study design	Sample size	Effect size (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality

5. Non-significant result and small sample size
6. High risk of bias (over 10% attrition rate and lack of limit adjustment for confounding variables)
7. Maximum of the hourly maximum from the 1 to 3 days preceding the COPD exacerbation
8. Moderate risk of bias (use of self-report in measuring outcomes and short (6 month) follow-up)

N/A: not applicable; NO_2: nitrogen dioxide; O_3: ozone; PM_{10}: particulate matter 10; $PM_{2.5}$: particulate matter 2.5; SO_2: sulphur dioxide; ppb: parts per billion

Risk factor: weather and seasonal changes

No. of studies	Study design	Sample size	Effect size (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
Winter (reference category: summer) predicting COPD exacerbation duration more than three weeks – follow-up: 3 years								
1 (Husebo 2014)	Prospective cohort	403	OR 1.51 (1.08, 2.12)	Not serious	Not serious	N/A	Not serious	High
Spring (reference category: summer) predicting COPD exacerbation duration more than three weeks – follow-up: 3 years								
1 (Husebo 2014)	Prospective cohort	403	OR 1.45 (1.02, 1.35)	Not serious	Not serious	N/A	Not serious	High
Autumn (reference category: summer) predicting COPD exacerbation duration more than three weeks – follow-up: 3 years								
1 (Husebo 2014)	Prospective cohort	403	OR 1.33 (0.94, 1.89)	Not serious	Not serious	N/A	Serious[1]	Moderate

1. Non-significant result

N/A: not applicable

Preventing exacerbations

The following tables are based on evidence on effect sizes from the Cochrane review. However, the dichotomous data has been altered to show RR, not OR, and the choice of fixed effect or random effects model is made according to the methods in appendix B. The completion of the GRADE tables was carried out by the NICE Guideline Updates Team. The sensitivity analyses were carried out by NICE Guideline Updates Team using data from the Cochrane review.

Antibiotics versus placebo

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control	Absolute risk: intervention (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
People with ≥ 1 exacerbation (lower values favour antibiotics)										
9 studies (11 comparisons)	RCT	2,825	RR 0.76 (0.66, 0.88)	60.45 per 100	45.94 per 100 (39.89, 53.19)	Serious[5]	Serious[2]	Not serious	Serious[3]	Very low
Sensitivity analysis[9]: People with ≥ 1 exacerbation (lower values favour antibiotics)										
8 studies (10 comparisons)	RCT	2,716	RR 0.85 (0.79, 0.91)	60.64 per 100	51.55 per 100 (47.9, 55.18)	Serious[1]	Not serious	Not serious	Serious[3]	Low
Rate of exacerbations per patient per year[8] (lower values favour antibiotics)										
5 studies (5 comparisons)	RCT	1,384	IRR 0.67 (0.54, 0.83)	60.45 per 100	40.50 (32.64, 50.17)	Not serious	Serious[2]	Not serious	Serious[3]	Low
St. George's Respiratory Questionnaire (SGRQ) total score (lower values favour antibiotics)										
7 studies (9 comparisons)	RCT	2,237	MD -1.93 (-3.02,-0.84)	_	_	Not serious	Not serious	Not serious	Not serious	High
All-cause mortality (lower values favour antibiotics)										

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control	Absolute risk: intervention (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
5 studies (6 comparisons)	RCT	2,723	RR 0.89 (0.71,1.12)	3.33 per 100	2.80 per 100 (1.83, 4.27)	Serious[1]	Not serious	Not serious	Serious[4]	Low
People with ≥ 1 adverse event (lower values favour antibiotics)										
4 studies (7 comparisons)	RCT	512	RR 1.06 (0.90, 1.23)	83.15 per 100	88.13 per 100 (74.83, 102.27)	Not serious	Serious[2]	Not serious	Not serious	Moderate
People with ≥ 1 Serious Adverse Event (SAE) (lower values favour antibiotics)										
9 studies (11 comparisons)	RCT	2,978	RR 0.91 (0.80, 1.04)	25.27 per 100	22.99 per 100 (20.21, 26.28)	Not serious	Not serious	Not serious	Not serious	High
Sensitivity analysis[6]: People with ≥ 1 SAE (higher values favour antibiotics)										
8 studies (10 comparisons)	RCT	2,924	RR 0.92 (0.81, 1.04)	25.38 per 100	23.35 per 100 (20.56, 26.39)	Not serious	Not serious	Not serious	Not serious	High
Change in FEV1 (ml) (higher values favour antibiotics)										
6 studies (10 comparisons)	RCT	658	MD 20.21 (-26.19, 66.61)	_	_	Serious[5]	Not serious	Not serious	Not serious	Moderate
Sensitivity analysis[6]: Change in FEV1 (ml) (higher values favour antibiotics)										
5 studies (8 comparisons)	RCT	609	MD 15.32 (-32.75, 63.38)	_	_	Serious[1]	Not serious	Not serious	Not serious	Moderate
Exercise capacity (6MWD) (higher values favour antibiotics)										
2 studies (3 comparisons)	RCT	126	MD 66.95 (35.96, 97.95)	_	_	Very serious[7]	Serious[2]	Not serious	Not serious	Very low
Sensitivity analysis[6]: Exercise capacity (6MWD) (higher values favour antibiotics)										

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control	Absolute risk: intervention (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
1 (Uzun 2014)	RCT	77	MD 36.00 (-15.53,87.53)	_	_	Not serious	N/A	Not serious	Serious[3]	Moderate

1. >33.3% of the studies were at moderate risk of bias.
2. I^2 between 33.3% and 66.7%.
3. 95% confidence interval crosses one end of a defined MID interval.
4. Non-significant result.
5. > 33.3% of studies are at moderate or high risk of bias.
6. Analysis minus Tan 2016, which was at high risk of bias due to a lack of information regarding randomisation and allocation concealment and the lack of blinding of participants, personnel and outcome assessors.
7. >33.33% of studies were at high risk of bias.
8. AR are Illustrative values based on the AR presented for having ≥1 exacerbation in the placebo arm as the real control numbers are not calculable from data in Cochrane review.
9. Analysis minus Suzuki 2001, which was at high risk of bias due to a lack of blinding of participants, personnel and outcome assessors.

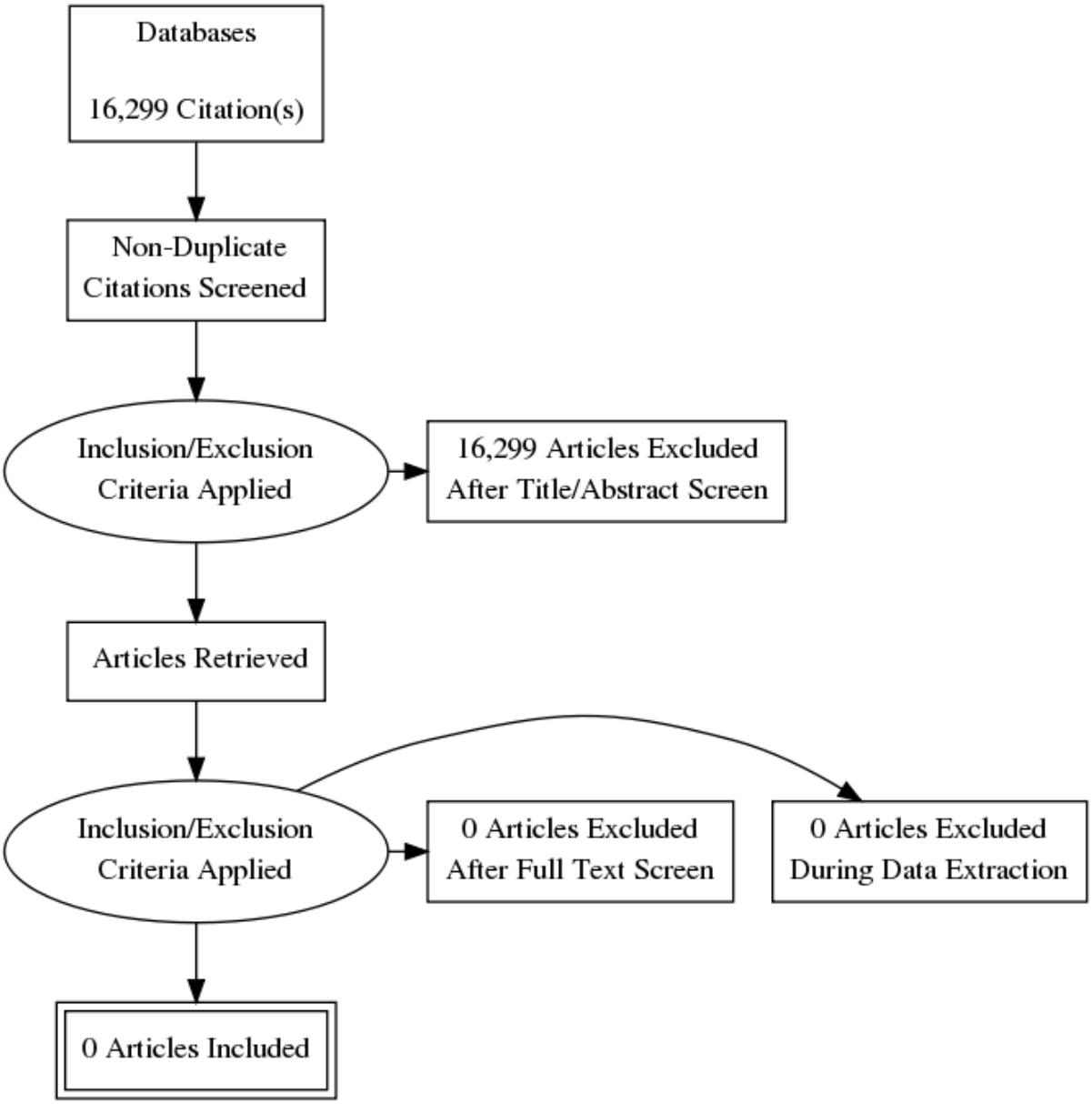
Azithromycin versus placebo in people with pulmonary hypertension secondary to COPD

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control	Absolute risk: intervention (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
Change in FEV1 (ml) (higher values favour azithromycin)										
1 (Wang 2017)	RCT	86	MD 430.00 (363.17, 495.83)	-	-	Very serious[1]	N/A	Serious[2]	Not serious	Very low
Exercise capacity (6MWD) ((higher values favour azithromycin)										
1 (Wang 2017)	RCT	86	MD 83.90 (71.00, 96.80)	-	-	Very serious[1]	N/A	Serious[2]	Not serious	Very low

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control	Absolute risk: intervention (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality

1. Study was at high risk of bias due to the lack of blinding of participants, personnel and outcome assessors and the lack of a data for the breathlessness outcome.
2. Study was partially directly applicable as the participants were in people with pulmonary hypertension secondary to COPD.

Appendix H – Economic evidence study selection



Appendix I – Excluded studies

Predicting exacerbations

Author (year)	Title	Reason for exclusion
Aaron (2001)	Granulocyte inflammatory markers and airway infection during acute exacerbation of chronic obstructive pulmonary disease.	• Data not reported in an extractable format
Abrams (2011)	Acute exacerbations of chronic obstructive pulmonary disease and the effect of existing psychiatric comorbidity on subsequent mortality.	• Retrospective study
Accortt (2017)	Retrospective analysis to describe associations between tumor necrosis factor alpha inhibitors and COPD-related hospitalizations	• Retrospective study
Agusti (2012)	Persistent systemic inflammation is associated with poor clinical outcomes in COPD: a novel phenotype	• Data not reported in an extractable format
Al (2015)	Prognostic factors associated with poor outcomes among multiethnic patients with acute exacerbation of chronic obstructive pulmonary disease	• Retrospective study
Alamoudi (2007)	Bacterial infection and risk factors in outpatients with acute exacerbation of chronic obstructive pulmonary disease: a 2-year prospective study	• Data not reported in an extractable format
Almagro (2006)	Risk factors for hospital readmission in patients with chronic obstructive pulmonary disease	• Data not reported in an extractable format
Almagro (2012)	Comorbidities and short-term prognosis in patients hospitalized for acute exacerbation of COPD: the EPOC en Servicios de medicina interna (ESMI) study	• Data not reported in an extractable format
Alshabanat (2015)	Asthma and COPD Overlap Syndrome (ACOS): A Systematic Review and Meta Analysis	• Systematic review used as a source of individual studies, but not for data extraction
Angeloni (2013)	beta-Blockers improve survival of patients with chronic obstructive pulmonary disease after coronary artery bypass grafting	• Data not reported in an extractable format
Antoniou (2015)	Safety of valproic acid in patients with chronic obstructive pulmonary disease: a population-based cohort study	• Retrospective study
Antus (2013)	Relationship between exhaled nitric oxide and the frequency of severe acute exacerbation of COPD: 3-year follow-up	• Retrospective study

Author (year)	Title	Reason for exclusion
Aoki (2013)	Relevance of hemoglobin A1c and acute exacerbations of chronic obstructive pulmonary disease	• Conference abstract
Atlantis (2013)	Bidirectional associations between clinically relevant depression or anxiety and COPD: a systematic review and meta-analysis	• Systematic review used as a source of individual studies, but not for data extraction
Bahadori (2009)	Risk factors and outcomes associated with chronic obstructive pulmonary disease exacerbations requiring hospitalization	• Retrospective study
Bai (2017)	Asthma-COPD overlap syndrome showed more exacerbations however lower mortality than COPD	• Retrospective study
Baker (2013)	Risk assessment of readmissions following an initial COPD-related hospitalization	• Retrospective study
Baris (2017)	Frequency of Exacerbations and Hospitalizations in COPD Patients Who Continue to Smoke	• Retrospective study
Barker (2015)	Association between pathogens detected using quantitative polymerase chain reaction with airway inflammation in COPD at stable state and exacerbations	• Data not reported in an extractable format
Bartziokas (2011)	Statins and outcome after hospitalization for COPD exacerbation: a prospective study	• Prospective study
Bartziokas (2014)	Serum uric acid as a predictor of mortality and future exacerbations of COPD	• Data not reported in an extractable format
Bathoorn (2009)	Change in inflammation in out-patient COPD patients from stable phase to a subsequent exacerbation	• Not a relevant study design (cross-sectional, case-control, RCT)
Beckham (2005)	Respiratory viral infections in patients with chronic, obstructive pulmonary disease.	• Data not reported in an extractable format
Bhatia (2016)	A search for covert precipitating clinical parameters in frequent exacerbators of chronic obstructive pulmonary disease	• Not a relevant study design (cross-sectional, case-control, RCT)
Bhatt (2008)	Serum magnesium is an independent predictor of frequent readmissions due to acute exacerbation of chronic obstructive pulmonary disease	• Retrospective study
Bhowmik (2000)	Relation of sputum inflammatory markers to symptoms and lung function changes in COPD exacerbations	• Retrospective study

Author (year)	Title	Reason for exclusion
Black-Shinn (2014)	Cardiovascular disease is associated with COPD severity and reduced functional status and quality of life	• Not a relevant study design (cross-sectional, case-control, RCT)
Blamoun (2008)	Statins may reduce episodes of exacerbation and the requirement for intubation in patients with COPD: evidence from a retrospective cohort study	• Retrospective study
Boeck (2015)	Longitudinal Measurement of Serum Vascular Endothelial Growth Factor in Patients with Chronic Obstructive Pulmonary Disease	• Data not reported in an extractable format
Bonten (2017)	Defining asthma-COPD overlap syndrome: A population-based study	• Conference abstract
Bornheimer (2017)	Risk of exacerbation following pneumonia in adults with heart failure or chronic obstructive pulmonary disease	• Retrospective study
Bourbeau (2013)	Making collaborative self-management successful in COPD patients with high disease burden	• Retrospective study
Bowler (2017)	Electronic Cigarette Use in US Adults at Risk for or with COPD: Analysis from Two Observational Cohorts	• Data not reported in an extractable format
Bozinovski (2008)	Serum amyloid a is a biomarker of acute exacerbations of chronic obstructive pulmonary disease	• Data not reported in an extractable format
Brims (2011)	Weekend admission and mortality from acute exacerbations of chronic obstructive pulmonary disease in winter	• Retrospective study
Brzezinska-Pawlowska (2016)	Environmental factors affecting seasonality of ambulance emergency service visits for exacerbations of asthma and COPD	• Retrospective study
Caillaud (2017)	Asthma-COPD overlap syndrome (ACOS) vs 'pure' COPD: a distinct phenotype?	• Retrospective study
Candrilli (2015)	Factors associated with inpatient readmission among managed care enrollees with COPD	• Retrospective study
Cao (2006)	Frequent hospital readmissions for acute exacerbation of COPD and their associated factors	• Retrospective study
Carneiro (2010)	Risk factors for readmission after hospital discharge in chronic obstructive pulmonary disease. The role of quality of life indicators	• Data not reported in an extractable format
Chen (2006)	Factors related to chronic obstructive pulmonary disease readmission in Taiwan.	• Study does not contain any of the outcomes of interest
Chung (2015)	Comparison of acute respiratory events between: Asthma-COPD overlap syndrome and COPD patients	• Retrospective study

Author (year)	Title	Reason for exclusion
Couillard (2017)	Eosinophils in COPD Exacerbations Are Associated With Increased Readmissions	• Retrospective study
Dalal (2011)	Clinical and economic burden of depression/anxiety in chronic obstructive pulmonary disease patients within a managed care population	• Retrospective study
Dalal (2011)	Clinical and economic burden of patients diagnosed with COPD with comorbid cardiovascular disease	• Retrospective study
Davydow (2016)	Serious Mental Illness and Risk for Hospitalizations and Rehospitalizations for Ambulatory Care-sensitive Conditions in Denmark: A Nationwide Population-based Cohort Study	• Retrospective study
de Laurentiis (2008)	Exhaled nitric oxide monitoring in COPD using a portable analyzer	• Data not reported in an extractable format
de Melo (2004)	Rates and patterns of chronic obstructive pulmonary disease exacerbations	• Retrospective study
De Oca (2009)	Frequency of self-reported COPD exacerbation and airflow obstruction in five latin American cities: The Proyecto Latinoamericano de Investigacion en Obstruccion Pulmonar (PLATINO) study	• Retrospective study
Depp (2016)	Risk factors associated with acute exacerbation of chronic obstructive pulmonary disease in HIV-infected and uninfected patients	• Retrospective study
Desalu (2011)	Seasonal variation in hospitalisation for respiratory diseases in the tropical rain forest of South Western Nigeria	• Retrospective study
Dickens (2011)	COPD association and repeatability of blood biomarkers in the ECLIPSE cohort	• Not a relevant study design (cross-sectional, case-control, RCT)
Djamin (2015)	Occurrence of virus-induced COPD exacerbations during four seasons	• Not a relevant study design (cross-sectional, case-control, RCT) Cross-sectional
Dobler (2009)	Associations between statins and COPD: a systematic review	• Systematic review does not contain relevant studies Included studies were 1 RCT, 1 case-control study, 1 ecological study and 5 retrospective studies

Author (year)	Title	Reason for exclusion
Dogan (2014)	Determining the diagnostic value of endogenous carbon monoxide in chronic obstructive pulmonary disease exacerbations	• Not a relevant study design (cross-sectional, case-control, RCT)
Donaldson (2003)	Longitudinal changes in the nature, severity and frequency of COPD exacerbations	• Study does not contain any relevant predictive variables
Donaldson (2005)	Exacerbations and time spent outdoors in chronic obstructive pulmonary disease	• Study does not contain any relevant predictive variables
Donaldson (2012)	Influence of season on exacerbation characteristics in patients with COPD	• Data not reported in an extractable format
Dong (2017)	Evidence of potential bias in a comparison of beta blockers and calcium channel blockers in patients with chronic obstructive pulmonary disease and acute coronary syndrome: results of a multinational study	• Retrospective study
Du (2014)	Beta-blockers reduced the risk of mortality and exacerbation in patients with COPD: a meta-analysis of observational studies	• Systematic review does not contain relevant studies
Duffy (2015)	Effect of beta-blockers on the rate of chronic obstructive lung disease (COPD) exacerbation in the macro placebo arm and STATCOPE cohort	• Conference abstract
Duffy (2017)	Effect of beta-blockers on exacerbation rate and lung function in chronic obstructive pulmonary disease (COPD)	• Retrospective study
Eagan (2010)	Neutrophil gelatinase-associated lipocalin: a biomarker in COPD	• Retrospective study
Eagan (2010)	Systemic inflammatory markers in COPD: results from the Bergen COPD Cohort Study	• Retrospective study
Fan (2007)	Physiologic variables and functional status independently predict COPD hospitalizations and emergency department visits in patients with severe COPD	• Not a relevant study design (cross-sectional, case-control, RCT) RCT
Fan (2007)	Sex, depression, and risk of hospitalization and mortality in chronic obstructive pulmonary disease.	• Study does not contain any of the outcomes of interest
Farland (2013)	beta-Blocker use and incidence of chronic obstructive pulmonary disease exacerbations	• Retrospective study
Feng (2017)	Association of serum galectin-3 with the acute exacerbation of chronic obstructive pulmonary disease	• Not a relevant study design (cross-sectional, case-control, RCT)
Flattet (2017)	Determining prognosis in acute exacerbation of COPD	• Retrospective study

Author (year)	Title	Reason for exclusion
Fleehart (2014)	Prevalence and correlates of suicide ideation in patients with COPD: a mixed methods study	• Not a relevant study design (cross-sectional, case-control, RCT)
Franciosi (2006)	Markers of exacerbation severity in chronic obstructive pulmonary disease	• Systematic review does not contain relevant studies Included studies do not contain relevant predictors
Franciosi (2006)	Markers of disease severity in chronic obstructive pulmonary disease	• Systematic review does not contain relevant studies Exacerbations were not reported
Freeman (2015)	Acute exacerbations of chronic obstructive pulmonary disease are associated with decreased CD4+ & CD8+ T cells and increased growth & differentiation factor-15 (GDF-15) in peripheral blood	• Data not reported in an extractable format
Fu (2014)	Longitudinal changes in clinical outcomes in older patients with asthma, COPD and asthma-COPD overlap syndrome.	• Study does not contain any of the outcomes of interest
Garcia-Rivero (2016)	Risk Factors of Poor Outcomes after Admission for a COPD Exacerbation: multivariate Logistic Predictive Models	• Composite outcome Poor patient outcome, which was defined as the presence of a moderate exacerbation, readmission or death within 3 months after discharge
Garcia-Sanz (2012)	Factors associated with hospital admission in patients reaching the emergency department with COPD exacerbation	• Not a relevant study design (cross-sectional, case-control, RCT)
Genao (2015)	Early and Long-term Outcomes of Older Adults after Acute Care Encounters for Chronic Obstructive Pulmonary Disease Exacerbation	• Retrospective study
George (2014)	Human rhinovirus infection during naturally occurring COPD exacerbations	• Data not reported in an extractable format
Groenewegen (2008)	Increased systemic inflammation is a risk factor for COPD exacerbations	• Not a relevant study design (cross-sectional, case-control, RCT) RCT
Guldaval (2009)	Respiratory viruses and atypical agents in acute exacerbations of chronic obstructive pulmonary diseases in Izmir District, Turkey	• Not a relevant study design (cross-sectional, case-control, RCT)

Author (year)	Title	Reason for exclusion
Gump (1976)	Role of infection in chronic bronchitis	• Does not contain a population of people with COPD
Gumus (2014)	Association of serum magnesium levels with frequency of acute exacerbations in chronic obstructive pulmonary disease: a prospective study	• Data not reported in an extractable format
Hasegawa (2016)	Prevalence of blood eosinophilia in hospitalized patients with acute exacerbation of COPD	• Retrospective study
Herrin (2013)	Combination antihypertensive therapy among patients with COPD	• Retrospective study
Hijjawi (2015)	Chronic obstructive pulmonary disease exacerbation: A single-center perspective on hospital readmissions	• Retrospective study
Ho (2017)	Eosinophilia and clinical outcome of chronic obstructive pulmonary disease: a meta-analysis	• Systematic review used as a source of individual studies, but not for data extraction
Howard (2016)	Statin Effects on Exacerbation Rates, Mortality, and Inflammatory Markers in Patients with Chronic Obstructive Pulmonary Disease: A Review of Prospective Studies	• Review article but not a systematic review
Huang (2011)	Statin use and hospitalization in patients with chronic obstructive pulmonary disease: a nationwide population-based cohort study in Taiwan	• Retrospective study
Huang (2017)	Impact of selective and nonselective beta-blockers on the risk of severe exacerbations in patients with COPD	• Retrospective study
Hunter (2016)	Patient characteristics associated with risk of first hospital admission and readmission for acute exacerbation of chronic obstructive pulmonary disease (COPD) following primary care COPD diagnosis: a cohort study using linked electronic patient records	• Retrospective study
Husebo (2017)	Growth differentiation factor-15 is a predictor of important disease outcomes in patients with COPD	• Data not reported in an extractable format
Ito (2015)	Nasal Mucociliary Clearance in Subjects With COPD After Smoking Cessation	• Retrospective study
Iyer (2016)	Depression Is Associated with Readmission for Acute Exacerbation of Chronic Obstructive Pulmonary Disease	• Retrospective study

Author (year)	Title	Reason for exclusion
Izquierdo-Alonso (2013)	Prevalence and characteristics of three clinical phenotypes of chronic obstructive pulmonary disease (COPD).	• Not a relevant study design (cross-sectional, case-control, RCT)
Janda (2009)	Statins in COPD: a systematic review	• Systematic review does not contain relevant studies Included studies did not have a relevant study design
Jayes (2016)	SmokeHaz: Systematic Reviews and Meta-analyses of the Effects of Smoking on Respiratory Health	• Systematic review does not contain relevant studies Included studies did not contain the outcome of interest
Jedrychowski (1985)	Confronting the effects of smoking and air quality on the development of chronic respiratory diseases	• Study not reported in English Japanese
Jenkins (2012)	Seasonality and determinants of moderate and severe COPD exacerbations in the TORCH study	• Not a relevant study design (cross-sectional, case-control, RCT) RCT
Jennings (2009)	The association between depressive symptoms and acute exacerbations of COPD	• Retrospective study
Jeong (2016)	Comorbidity as a contributor to frequent severe acute exacerbation in COPD patients	• Retrospective study
Johannesdottir (2013)	Hospitalization with acute exacerbation of chronic obstructive pulmonary disease and associated health resource utilization: a population-based Danish cohort study	• Retrospective study
Johansson (2014)	Microfibrillar-associated protein 4: a potential biomarker of chronic obstructive pulmonary disease	• Data not reported in an extractable format
Johnston (2010)	The Christmas season as a risk factor for chronic obstructive pulmonary disease exacerbations	• Data not reported in an extractable format
Kerkhof (2015)	Predicting frequent COPD exacerbations using primary care data	• Retrospective study
Kherad (2010)	Upper-respiratory viral infection, biomarkers, and COPD exacerbations	• Study does not contain any of the outcomes of interest
Khialani (2014)	Emergency department management of acute exacerbations of chronic obstructive pulmonary disease and factors associated with hospitalization	• Retrospective study

Author (year)	Title	Reason for exclusion
Kim (2010)	Risk factors associated with frequent hospital readmissions for exacerbation of COPD	• Retrospective study
Kim (2013)	Association between chronic obstructive pulmonary disease and gastroesophageal reflux disease: a national cross-sectional cohort study	• Retrospective study
Kobayashi (2013)	Impact of a large-scale natural disaster on patients with chronic obstructive pulmonary disease: the aftermath of the 2011 Great East Japan Earthquake	• Retrospective study
Konstantelou (2017)	Serum periostin in patients hospitalized for COPD exacerbations	• Data not reported in an extractable format
Kubota (2015)	Impact of beta-blocker selectivity on long-term outcomes in congestive heart failure patients with chronic obstructive pulmonary disease	• Retrospective study
Kumar (2013)	Satellite-based PM concentrations and their application to COPD in Cleveland, OH	• Data not reported in an extractable format
Kunisaki (2012)	Vitamin D levels and risk of acute exacerbations of chronic obstructive pulmonary disease: a prospective cohort study	• Not a relevant study design (cross-sectional, case-control, RCT) Secondary analysis of an RCT
Kupeli (2010)	Metabolic syndrome is associated with increased risk of acute exacerbation of COPD: a preliminary study	• Not a relevant study design (cross-sectional, case-control, RCT) Case-control study
Lee (2016)	Impacts of coexisting bronchial asthma on severe exacerbations in mild-to-moderate COPD: results from a national database	• Retrospective study
Levy (1977)	Relationship between acute respiratory illness and air pollution levels in an industrial city	• Retrospective study
Li (2016)	Short-term exposure to ambient fine particulate matter increases hospitalizations and mortality in COPD: A systematic review and meta-analysis	• Systematic review does not contain relevant studies Included studies did not have a relevant study design
Li (2017)	Statins reduce all-cause mortality in chronic obstructive pulmonary disease: an updated systematic review and meta-analysis of observational studies	• Systematic review used as a source of individual studies, but not for data extraction
Liang (2017)	Clinical characteristics of patients with chronic obstructive pulmonary disease overlapped with bronchial asthma	• Retrospective study

Author (year)	Title	Reason for exclusion
Liao (2017)	The evaluation of beta-adrenoceptor blocking agents in patients with COPD and congestive heart failure: a nationwide study	• Retrospective study
Lin (2015)	Newly diagnosed gastroesophageal reflux disease increased the risk of acute exacerbation of chronic obstructive pulmonary disease during the first year following diagnosis--a nationwide population-based cohort study	• Retrospective study
Lode (2007)	A prediction model for bacterial etiology in acute exacerbations of COPD	• Not a relevant study design (cross-sectional, case-control, RCT)
Mahan (2016)	COPD Exacerbation and Cholinesterase Therapy in Dementia Patients	• Retrospective study
Malinovschi (2014)	Severe vitamin D deficiency is associated with frequent exacerbations and hospitalization in COPD patients	• Retrospective study
Mandal (2015)	Mannose-binding lectin protein and its association to clinical outcomes in COPD: a longitudinal study	• Study does not contain any of the outcomes of interest
Mantero (2017)	Role of Streptococcus pneumoniae infection in chronic obstructive pulmonary disease patients in Italy	• Data not reported in an extractable format
McGarvey (2015)	Characterisation of the frequent exacerbator phenotype in COPD patients in a large UK primary care population	• Retrospective study
Medrek (2017)	Admission for COPD Exacerbation Is Associated with the Clinical Diagnosis of Pulmonary Hypertension: Results from a Retrospective Longitudinal Study of a Veteran Population	• Retrospective study
Menezes (2014)	Increased risk of exacerbation and hospitalization in subjects with an overlap phenotype: COPD-asthma.	• Retrospective study
Mercer (2005)	MMP-9, TIMP-1 and inflammatory cells in sputum from COPD patients during exacerbation	• Not a relevant study design (cross-sectional, case-control, RCT)
Meszaros (2015)	An observational study of PM10 and hospital admissions for acute exacerbations of chronic respiratory disease in Tasmania, Australia 1992-2002	• Retrospective study
Milanese (2014)	Asthma control in elderly asthmatics. An Italian observational study	• Study does not contain any of the outcomes of interest

Author (year)	Title	Reason for exclusion
Miravitlles (2013)	Characterisation of the overlap COPD-asthma phenotype. Focus on physical activity and health status.	• Not a relevant study design (cross-sectional, case-control, RCT)
Mohan (2010)	Prevalence of viral infection detected by PCR and RT-PCR in patients with acute exacerbation of COPD: a systematic review	• Systematic review does not contain relevant studies Only prevalence is reported
Montserrat-Capdevila (2015)	Predictive Model of Hospital Admission for COPD Exacerbation	• Retrospective study
Montserrat-Capdevila (2015)	Risk of exacerbation in chronic obstructive pulmonary disease: a primary care retrospective cohort study	• Retrospective study
Mortensen (2009)	Impact of statins and ACE inhibitors on mortality after COPD exacerbations	• Retrospective study
Mullerova (2014)	Risk factors for acute exacerbations of COPD in a primary care population: a retrospective observational cohort study	• Retrospective study
Murphy (2005)	Moraxella catarrhalis in chronic obstructive pulmonary disease: burden of disease and immune response	• Data not reported in an extractable format
Murphy (2008)	Pseudomonas aeruginosa in chronic obstructive pulmonary disease	• Data not reported in an extractable format
Nantsupawat (2012)	Factors affecting chronic obstructive pulmonary disease early rehospitalization	• Retrospective study
Ng (2007)	Depressive symptoms and chronic obstructive pulmonary disease: effect on mortality, hospital readmission, symptom burden, functional status, and quality of life	• Study does not contain any of the outcomes of interest
Ni (2015)	Clinical characteristics of patients with chronic obstructive pulmonary disease with comorbid bronchiectasis: a systemic review and meta-analysis	• Systematic review does not contain relevant studies
Nielsen (2015)	Clinical characteristics of the asthma-COPD overlap syndrome--a systematic review	• Systematic review used as a source of individual studies, but not for data extraction
Omachi (2011)	Matrix metalloproteinase-9 predicts pulmonary status declines in alpha1-antitrypsin deficiency	• Data not reported in an extractable format
Ozyilmaz (2013)	Unsuspected risk factors of frequent exacerbations requiring hospital admission in chronic obstructive pulmonary disease.	• Retrospective study
Pande (2002)	Outdoor air pollution and emergency room visits at a hospital in Delhi	• Data not reported in an extractable format

Author (year)	Title	Reason for exclusion
Papi (2006)	Infections and airway inflammation in chronic obstructive pulmonary disease severe exacerbations	• Not a relevant study design (cross-sectional, case-control, RCT) Virus and bacteria were measured at exacerbation and convalescence without further follow-up
Parameswaran (2009)	Moraxella catarrhalis acquisition, airway inflammation and protease-antiprotease balance in chronic obstructive pulmonary disease	• Not a relevant study design (cross-sectional, case-control, RCT)
Parameswaran (2011)	Effects of bacterial infection on airway antimicrobial peptides and proteins in COPD	• Not a relevant study design (cross-sectional, case-control, RCT)
Park (2012)	Prognosis in patients having chronic obstructive pulmonary disease with significant coronary artery lesion angina	• Retrospective study
Park (2014)	Study Design and Outcomes of Korean Obstructive Lung Disease (KOLD) Cohort Study	• Not a relevant study design (cross-sectional, case-control, RCT)
Park (2017)	ReAsthma- COPD overlap shows favorable clinical outcomes compared to pure COPD in a Korean COPD cohort	• Retrospective study
Patel (2012)	The impact of ischemic heart disease on symptoms, health status, and exacerbations in patients with COPD	• Data not reported in an extractable format
Paulin (2015)	Occupational exposures are associated with worse morbidity in patients with chronic obstructive pulmonary disease	• Retrospective study
Pavasini (2017)	Amino terminal pro brain natriuretic peptide predicts all-cause mortality in patients with chronic obstructive pulmonary disease: Systematic review and meta-analysis	• Systematic review does not contain relevant studies Included studies do not contain the outcome of interest
Perotin (2013)	Detection of multiple viral and bacterial infections in acute exacerbation of chronic obstructive pulmonary disease: a pilot prospective study	• Data not reported in an extractable format
Persson (2015)	Vitamin D, vitamin D binding protein, and longitudinal outcomes in COPD	• Data not reported in an extractable format
Persson (2017)	Antimicrobial peptide levels are linked to airway inflammation, bacterial colonisation and exacerbations in chronic obstructive pulmonary disease	• Conference abstract

Author (year)	Title	Reason for exclusion
Pienaar (2015)	A descriptive study of patients admitted with acute exacerbation of chronic obstructive pulmonary disease in three hospitals in Cape Town, South Africa	• Retrospective study
Piras (2012)	Chronic systemic inflammatory syndrome in patients with AECOPD presenting to emergency department	• Not a relevant study design (cross-sectional, case-control, RCT)
Polosa (2016)	Evidence for harm reduction in COPD smokers who switch to electronic cigarettes	• Retrospective study
Ponka (1994)	Chronic bronchitis, emphysema, and low-level air pollution in Helsinki, 1987-1989	• Retrospective study
Pothirat (2016)	Effects of seasonal smog on asthma and COPD exacerbations requiring emergency visits in Chiang Mai, Thailand	• Retrospective study
Poulakou (2012)	First influenza season after the 2009 pandemic influenza: characteristics of intensive care unit admissions in adults and children in Vall d'Hebron Hospital	• Not a relevant study design (cross-sectional, case-control, RCT)
Puente-Maestu (2014)	Multicentric study on the beta-blocker use and relation with exacerbations in COPD	• Retrospective study
Quint (2008)	Relationship between depression and exacerbations in COPD	• Data not reported in an extractable format
Rajesh (2015)	Factors associated with outcome of acute exacerbation of chronic obstructive pulmonary disease - A prospective study	• Data not reported in an extractable format
Rascon-Aguilar (2006)	Role of gastroesophageal reflux symptoms in exacerbations of COPD	• Retrospective study
Rennard (2015)	Identification of five chronic obstructive pulmonary disease subgroups with different prognoses in the ECLIPSE cohort using cluster analysis	• Data not reported in an extractable format
Renom (2010)	Prognosis of COPD patients requiring frequent hospitalization: role of airway infection	• Data not reported in an extractable format
Ringshausen (2009)	Frequency and clinical relevance of human bocavirus infection in acute exacerbations of chronic obstructive pulmonary disease	• Retrospective study
Rinne (2015)	Thiazolidinediones are associated with a reduced risk of COPD exacerbations	• Data not reported in an extractable format
Roberts (2016)	A retrospective analysis to identify predictors of COPD-related rehospitalization	• Retrospective study
Rodriguez (2014)	Lifetime occupational exposure to dusts, gases and fumes is associated with bronchitis symptoms and higher diffusion capacity in COPD patients	• Not a relevant study design (cross-sectional, case-control, RCT)

Author (year)	Title	Reason for exclusion
Rogha (2010)	Association of gastroesophageal reflux disease symptoms with exacerbations of chronic obstructive pulmonary disease	• Retrospective study
Rohde (2005)	Relevance of human metapneumovirus in exacerbations of COPD	• Not a relevant study design (cross-sectional, case-control, RCT)
Rutten (2010)	Beta-blockers may reduce mortality and risk of exacerbations in patients with chronic obstructive pulmonary disease	• Retrospective study
Sakae (2013)	Exacerbations of COPD and symptoms of gastroesophageal reflux: a systematic review and meta-analysis	• Systematic review used as a source of individual studies, but not for data extraction
Salte (2015)	Depression is associated with poor prognosis in patients with chronic obstructive pulmonary disease - a systematic review	• Systematic review used as a source of individual studies, but not for data extraction
Santibanez (2016)	Predictors of Hospitalized Exacerbations and Mortality in Chronic Obstructive Pulmonary Disease	• Retrospective study
Seemungal (2000)	Detection of rhinovirus in induced sputum at exacerbation of chronic obstructive pulmonary disease	• Not a relevant study design (cross-sectional, case-control, RCT)
Seemungal (2001)	Respiratory viruses, symptoms, and inflammatory markers in acute exacerbations and stable chronic obstructive pulmonary disease	• Data not reported in an extractable format
Sethi (2007)	Airway bacterial concentrations and exacerbations of chronic obstructive pulmonary disease	• Data not reported in an extractable format
Sethi (2008)	Inflammatory profile of new bacterial strain exacerbations of chronic obstructive pulmonary disease	• Data not reported in an extractable format
Shawon (2017)	Current evidence on prevalence and clinical outcomes of co-morbid obstructive sleep apnea and chronic obstructive pulmonary disease: A systematic review	• Systematic review used as a source of individual studies, but not for data extraction
Shimizu (2012)	Different gastoroesophageal reflux symptoms of middle-aged to elderly asthma and chronic obstructive pulmonary disease (COPD) patients	• Retrospective study
Short (2011)	Effect of beta blockers in treatment of chronic obstructive pulmonary disease: a retrospective cohort study	• Retrospective study

Author (year)	Title	Reason for exclusion
Singh (2010)	Sputum neutrophils as a biomarker in COPD: findings from the ECLIPSE study	• Data not reported in an extractable format
Singh (2010)	Human rhinovirus proteinase 2A induces TH1 and TH2 immunity in patients with chronic obstructive pulmonary disease	• Data not reported in an extractable format
Stephenson (2012)	Cholinesterase inhibitors and adverse pulmonary events in older people with chronic obstructive pulmonary disease and concomitant dementia: a population-based, cohort study	• Retrospective study
Stolz (2007)	Copeptin, C-reactive protein, and procalcitonin as prognostic biomarkers in acute exacerbation of COPD	• Data not reported in an extractable format
Sunil (2013)	Acute exacerbations of chronic obstructive pulmonary disease requiring in-patient care: Clinical characteristics and outcome	• Conference abstract
Suzuki (2016)	Asthma-like Features and Clinical Course of Chronic Obstructive Pulmonary Disease. An Analysis from the Hokkaido COPD Cohort Study	• Data not reported in an extractable format
Tan (2003)	Epidemiology of respiratory viruses in patients hospitalized with near-fatal asthma, acute exacerbations of asthma, or chronic obstructive pulmonary disease	• Data not reported in an extractable format
Tian (2014)	Ambient carbon monoxide and the risk of hospitalization due to chronic obstructive pulmonary disease	• Data not reported in an extractable format
Tseng (2013)	The effect of cold temperature on increased exacerbation of chronic obstructive pulmonary disease: a nationwide study	• Not a relevant study design (cross-sectional, case-control, RCT)
Ulasli (2012)	Mean platelet volume as an inflammatory marker in acute exacerbation of chronic obstructive pulmonary disease	• Retrospective study
Unni (2015)	Drug utilization pattern in chronic obstructive pulmonary disease inpatients at a tertiary care hospital	• Retrospective study
van Dijk (2016)	Risk of exacerbations in COPD and asthma patients living in the neighbourhood of livestock farms: Observational study using longitudinal data	• Retrospective study
Vozoris (2014)	Benzodiazepine drug use and adverse respiratory outcomes among older adults with COPD	• Retrospective study
Vozoris (2016)	Incident opioid drug use and adverse respiratory outcomes among older adults with COPD	• Retrospective study

Author (year)	Title	Reason for exclusion
Wang (2015)	A GIS-based spatial correlation analysis for ambient air pollution and AECOPD hospitalizations in Jinan, China	• Data not reported in an extractable format
Westerik (2017)	Associations between chronic comorbidity and exacerbation risk in primary care patients with COPD	• Retrospective study
Wilkinson (2006)	Effect of interactions between lower airway bacterial and rhinoviral infection in exacerbations of COPD	• Data not reported in an extractable format
Williams (2014)	Coronary artery calcification is increased in patients with COPD and associated with increased morbidity and mortality	• Study does not contain any of the outcomes of interest
Williams (2017)	Seasonality, risk factors and burden of community-acquired pneumonia in COPD patients: a population database study using linked health care records	• Retrospective study
Wiwatcharagoses (2016)	Factors Associated with Hospitalization of Chronic Obstructive Pulmonary Disease Patients with Acute Exacerbation in the Emergency Department, Rajavithi Hospital	• Retrospective study
Wong (2008)	Acute exacerbation of chronic obstructive pulmonary disease: influence of social factors in determining length of hospital stay and readmission rates	• Retrospective study
Wu (2014)	Prevalence and risk of viral infection in patients with acute exacerbation of chronic obstructive pulmonary disease: a meta-analysis.	• Systematic review used as a source of individual studies, but not for data extraction
Xiong (2017)	Can we predict the prognosis of COPD with a routine blood test?	• Not a relevant study design (cross-sectional, case-control, RCT)
Yadavilli (2014)	Hospital readmissions with exacerbation of obstructive pulmonary disease in illicit drug smokers	• Retrospective study
Yamanda (2013)	The impact of the 2011 Great East Japan Earthquake on hospitalisation for respiratory disease in a rapidly aging society: a retrospective descriptive and cross-sectional study at the disaster base hospital in Ishinomaki	• Retrospective study
Yayan (2015)	No significant detectable anti-infection effects of aspirin and statins in chronic obstructive pulmonary disease	• Retrospective study
Yerkovich (2012)	Reduced rhinovirus-specific antibodies are associated with acute exacerbations of chronic obstructive pulmonary disease requiring hospitalisation	• Data not reported in an extractable format

Author (year)	Title	Reason for exclusion
Yohannes (2016)	Long-term Course of Depression Trajectories in Patients With COPD: A 3-Year Follow-up Analysis of the Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints Cohort	• Study does not contain any of the outcomes of interest
Zhu (2014)	Sputum myeloperoxidase in chronic obstructive pulmonary disease	• Systematic review does not contain relevant studies Only 6 of 24 included studies reported data on exacerbations but did not meet our inclusion criteria
Zhu (2015)	Vitamin D deficiency is associated with the severity of COPD: a systematic review and meta-analysis	• Systematic review does not contain relevant studies Studies reporting on exacerbations were RCTs
Zhu (2016)	The association between vitamin D and COPD risk, severity, and exacerbation: An updated systematic review and meta-analysis	• Systematic review used as a source of individual studies, but not for data extraction
Zwaans (2014)	The relevance of respiratory viral infections in the exacerbations of chronic obstructive pulmonary disease-a systematic review	• Systematic review used as a source of individual studies, but not for data extraction

Preventing exacerbations

The following excluded studies list with reasons for exclusion was taken directly from the updated Cochrane review. This list includes studies excluded at full text screening from the both the original and updated Cochrane reviews. In addition, Banerjee 2005 was excluded from the evidence review by the Guideline Updates Team as, although the paper was relevant to the review question, the data was not presented in a useful format for inclusion in the evidence review.

Banerjee 2004a	
Reason for exclusion	Duplicate of the study by Banerjee et al 2004 published in Respiratory Medicine 2005;99:208-15
Beeh 2016	
Reason for exclusion	Comparison: ELOM-080 versus placebo Problem: Drug under investigation not an conventional antibiotic
Bier 1971	
Reason for exclusion	Comparison: Doxycyclin versus placebo Problem: Spirometric criteria were not used in diagnosing COPD
Blasi 2010	
Reason for exclusion	Comparison: Azithromycin 500 mg three day a week for 6 months versus placebo Problem: Pilot study, uncontrolled Study done on tracheostomy patients
Bruninx 1973	
Reason for exclusion	Comparison: Bactrim versus Ledermycin over 1070 months Problem: 1) Heterogenic patient population including bronchiectasis, anthracosilicosis and bronchitis; 2) No placebo arm
Buchanan 1958	
Reason for exclusion	Comparison: tetracycline 250 mg BD versus placebo for 12 months duration Problems: Single blinded (only patients were blinded); Spirometric criteria were not used to diagnosed COPD
Bussi 1980	
Reason for exclusion	Comparison: Intermittent tetracycline 200 mg /weekly for 3 years versus placebo Problem: Spirometry criteria not used for diagnosis of COPD. Heterogenic group of patients
Calder 1968	
Reason for exclusion	Duplicate of Fletcher et al 1966
Davies 1961	
Reason for exclusion	Comparison: Tetracycline for 2 days each week versus placebo Problem: Spirometric criteria were not used in diagnosing COPD; blinding not known
Douglas 1957	
Reason for exclusion	Not a randomised controlled trial Heterogenic group of patients including large proportion with bronchiectasis Initial treatment with intramuscular penicillin

	Patients who failed penicillin were allocated to either chloramphenicol 0.5g Q6h or oxytetracycline 0.5g Q6h.
Edwards 1958	
Reason for exclusion	Comparison: Oxytetracycline or sulphonamide versus placebo Problems: H. influenzae vaccination co-administered; no suitable outcome measures
Elmes 1957	
Reason for exclusion	Comparison: Oxytetracycline versus placebo Problem: Not truly prophylactic, antibiotic versus placebo at the onset of symptoms
Fletcher 1966	
Reason for exclusion	Comparison: Treatment for 7 months/year over 5 year period. 1) Oxytetracycline 0.5g daily for 7 months over years 1 to 3; 2) Oxytetracycline 0.5g BD over 7 months in year 4; 3) Oxytetracycline 1g BD over 7 months in year 5; versus placebo Problem: Spirometric criteria not used to diagnose COPD
Frances 1964	
Reason for exclusion	Problem: Spirometric criteria were not used to diagnose COPD
Francis 1960	
Reason for exclusion	Comparison: 3 groups: 1) Tetracycline 250 mg BD for 3 months; 2) Penicillin V 312 mg BD for 3 months; 3) Placebo for 3 months Problems: Spirometric criteria were not used in diagnosing COPD
Goslings 1967	
Reason for exclusion	Comparison: 1) Sulfaphenazole 500 mg BD; 2) Tetracycline 500 mg BD; 3) saccharum 500 mg BD (placebo) over 5 month period Problem: Spirometric criteria were not used to diagnose COPD
Grossman 1998	
Reason for exclusion	Comparison: Ciprofloxacin 500 mg BD versus placebo for acute exacerbations of chronic bronchitis, treatment given during acute exacerbations during 12 month period versus usual care during an acute exacerbation Problem: Ciprofloxacin was given during an exacerbation of chronic bronchitis. Not truly prophylaxis
Hahn 1972	
Reason for exclusion	Comparison: Tetracycline or ampicillin versus placebo Problems: Not a true long term prophylaxis. Prophylaxis is defined as antibiotics instituted by the patients at the first sign of a cold and were continued only for 5 days
Haidl 2013	
Reason for exclusion	Comparison: Inhaled tobramycin versus placebo Problem: Antibiotic given via inhalation, not orally
Hallett 1959	
Reason for exclusion	Comparison: Erythromycin 250 mg 4 times a day versus placebo for 12 week duration

	Problem: Not a randomised controlled trial; Patients were matched in pairs (treatment and placebo groups) on the basis of similar clinical characteristics
Helm 1956	
Reason for exclusion	Not a randomised controlled trial
Johnston 1961	
Reason for exclusion	Comparison: Four treatment arms 1.Tetracycline 500 mg BD for 6 months treatment per year for 5 years Placebo for 6 months treatment per year for 5 years Tetracycline for the first 2 winters and placebo for the next three Placebo for 2 winters and tetracycline for the next three Problem: Partial crossover due to re: randomisation after two years Spirometric criteria were not used to diagnose COPD
Johnston 1961	
Reason for exclusion	Comparison: Phenethicillin versus placebo Problems: Spirometric criteria were not used to diagnose COPD
Kilpatrick 1954	
Reason for exclusion	Comparison: Sulphadimidine 0.5 g TDS versus placebo for 3 to 6 months Problem: Spirometric criteria were not used when diagnosing COPD
Legler 1977	
Reason for exclusion	Problem: Not randomised Spirometric criteria were not used for diagnosing COPD
Liippo 1987	
Reason for exclusion	Comparison: Trimethoprim 300 mg day versus placebo. Treatment for 6 months duration Problem: Heterogenic group of patients. Patients with bronchiectasis and asthma included. Spirometry criteria for COPD not used
Reason for exclusion	Review article on 13 previous randomised controlled trials from 1957 to 2010
Matthys 2015	
Reason for exclusion	Wrong intervention: drug being trialled is not an antibiotic
May RJ 1956	
Reason for exclusion	Comparison: Oxytetracycline or tetracycline versus "controlled group" who were observed and antibiotic prophylaxis was not given Problem: Not a true randomised controlled trial. The "controlled group" consisted of 14 patients who were observed without any prophylactic therapy. They were not randomly selected
Miravitlles 2009	
Reason for exclusion	Comparison: Moxifloxacin 400 mg daily versus placebo Problem: Short duration of study with only 5 days of treatment
Moyes 1959	

Reason for exclusion	Comparison: Four groups: 1) Erythromycin 1g daily for 7 days ,then a course of 1g daily for five days taken at the sign of first infection; 2) Erythromycin 1g daily for 7 days, then a regular course of 1g daily for five days every 4 weeks; 3) Tetracycline 1g daily for 7 days , then a course of 1g daily for five days taken at the sign of first infection 4) Tetracycline 1g daily for 7 days , then 750 mg/daily for 4 months Problems: No placebo group
Murdoch 1959	
Reason for exclusion	Comparison: Sigamycin (167 mg of tetracycline and 83 mg of oleandomycin) versus placebo for 3 months Problem: Spirometric criteria not used in diagnosing COPD
Murray 1964	
Reason for exclusion	Comparison: Ampicillin 250 mg 4 times daily versus placebo over 17 months Problem: Spirometric criteria were not used to diagnose COPD. Unclear whether randomisation took place
Nicholson 2016	
Reason for exclusion	Problem: Not an randomised controlled trial
Norman 1962	
Reason for exclusion	Comparison: Tetracycline 1 g daily or placebo for 3 months and crossover the groups with continuation of treatment for further 3 months Problem: Randomised crossover trial. Spirometry criteria not used when diagnosing COPD
Pines 1967	
Reason for exclusion	Comparison: Sulphormethoxine 2 g weekly for 10 weeks versus placebo Problems: Spirometric criteria were not used in diagnosing COPD patients
Pridie 1960	
Reason for exclusion	Comparison: Penicillin-sulphonamide, oxytetracycline versus placebo Problem: Spirometric criteria were not taken into account when diagnosing COPD
Prins 2016	
Reason for exclusion	Duration of intervention too short: 3 weeks of doxycycline
Ras 1984	
Reason for exclusion	Comparison: 1) Erythromycin 1500 mg/day for 2 weeks followed by 100 mg/day for 12 weeks; 2) Amoxycillin 1500 mg/day for 2 weeks followed by 100 mg/day for 12 weeks; 3) Placebo Problem: Randomisation not well explained. Spirometric criteria not used when diagnosing COPD
Segal 2017	
Reason for exclusion	Comparison: Azithromycin versus placebo Problem: Study of effect on microbiome; duration too short (8 weeks)
Siva 2014	
Reason for exclusion	Duration of intervention too short: 7 days of levofloxacin
Stass 2013	
Reason for exclusion	Problem: Trial of one-off dose of inhaled ciprofloxacin to assess lung deposition patterns

Takizawa 1994	
Reason for exclusion	Comparison: Three oral prophylactic antibiotic regimens: 1) Ciprofloxacin 200 mg daily for 6 months (Regimen A); 2) Erythromycin 200 mg daily for 6 months (Regimen B); 3) Ciprofloxacin 200 mg/d and Erythromycin 200 mg/d for 6 months (Regimen C) Problems: No placebo arm. Heterogenic group of patients including large number with bronchiectasis
Torrence 1999	
Reason for exclusion	Duplicate of Grossman 1998
Vandenbergh 1970	
Reason for exclusion	Comparison: sulphonamide 2 g once a week versus placebo for 6 months Problem: None of the primary outcomes were measured (frequency of exacerbations or quality of life) Spirometric criteria were not used in diagnosing COPD
Velzen 2016	
Reason for exclusion	Comparison: Long term effects of antibiotics given for acute exacerbations of COPD Problem: Antibiotics given for acute COPD, not as prophylaxis
Vermeersch 2016	
Reason for exclusion	Comparison: Azithromycin versus placebo for acute exacerbations of COPD Problem: Antibiotics given for acute COPD, not as prophylaxis
Watanabe 1991	
Reason for exclusion	Comparison; 1) Ofloxacin 200 mg daily for 6 months; 2) Ofloxacin 200 mg TDS for 2 weeks followed by 2 weeks without treatment for 6 months Problem: Prophylaxis was given to patients with ANY chronic respiratory tract infection, including bronchiectasis and pulmonary tuberculosis. No placebo arm
Watanabe 1994	
Reason for exclusion	Comparison: ciprofloxacin 200 mg/daily versus erythromycin 200 mg/daily versus combined ciprofloxacin 200 mg/d + erythromycin 200 mg/d Problem: No placebo. Patients with bronchiectasis included
Watanabe 1995	
Reason for exclusion	Duplicate study of Watanabe 1991 with addition of 7 patients
Webster 1971	
Reason for exclusion	Comparison: Trimethoprim-sulphamethoxazole versus sulphamethoxazole Problem: No placebo group. Treatment duration was only 10 days

Appendix J – Research recommendations

Research recommendation 1

Question	What is the long-term clinical and cost effectiveness of prophylactic antibiotics for people with stable COPD who are at high risk of exacerbations?
Population	People diagnosed with stable COPD who are at high risk of exacerbations
Interventions	Long-term oral antibiotics for prophylaxis (greater than 1 year)
Comparator	Placebo
Outcomes	• Exacerbations (numbers and severity) • Respiratory health-related quality of life • Reduction in lung function from baseline (FEV1) • Mortality • Adverse events (including hearing loss) • Serious adverse events • Antibiotic resistance • Exercise capacity
Study design	Randomised controlled trial

Potential criterion	Explanation
Importance to patients, service users or the population	People with COPD commonly experience exacerbations, which have a negative impact on their quality of life and are linked to worse disease prognosis. Certain groups of people with COPD are at higher risk of exacerbations and reducing the numbers they experience should improve quality of life for them and their families. However, the use of long-term antibiotics for prophylaxis also has the potential for a wider effect on society as it may increase the risk of antibiotic resistance. In addition, the long-term use of antibiotics may be associated with adverse events (such as hearing loss) in people with COPD. As a result, it is important that the antibiotics are used carefully and with consideration of the potential side effects for the person with COPD and society at large of long-term use.
Relevance to NICE guidance	Low-priority: it was possible to make recommendations based on the available evidence, but new evidence in this area has the potential to alter the recommendations substantially.
Current evidence base	Although there were a number of studies looking at the use of prophylactic antibiotics to prevent or reduce exacerbations, these studies were confined to a small number of antibiotics and the trials did not last more than 12 months. As a result, the long-term effects of using prophylactic antibiotics remains unclear.
Equality	No specific equality concerns are relevant to this research recommendation.
Feasibility	There is a large enough population of people with COPD who are at high risk of exacerbations that intervention studies in this area should be feasible.

Research recommendation 2

Question	What is the comparative effectiveness of different antibiotics, doses and regimens of prophylactic antibiotics for people with stable COPD who are at high risk of exacerbations?
Population	People diagnosed with stable COPD who are at high risk of exacerbations
Interventions	Oral antibiotics for prophylaxis (different doses and frequency)
Comparator	• Placebo • Each other
Outcomes	• Exacerbations (numbers and severity) • Respiratory health-related quality of life • Reduction in lung function from baseline (FEV1) • Mortality • Adverse events (including hearing loss) • Serious adverse events • Antibiotic resistance • Exercise capacity
Study design	Randomised controlled trial

Potential criterion	Explanation
Importance to patients, service users or the population	People with COPD commonly experience exacerbations, which have a negative impact on their quality of life and are linked to worse disease prognosis. Certain groups of people with COPD are at higher risk of exacerbations and reducing the numbers they experience should improve quality of life for them and their families. However, the use of long-term antibiotics for prophylaxis also has the potential for a wider effect on society as it may increase the risk of antibiotic resistance and there is a risk of adverse events associated with prophylactic treatment for the person with COPD. As a result, it is important that the most effective doses of antibiotics and dosing regimens are identified to ensure the maximum benefit for the person with COPD, whilst minimising antimicrobial resistance.
Relevance to NICE guidance	Low-priority: it was possible to make recommendations based on the available evidence, but they could be improved by additional studies in this area.
Current evidence base	Although there were a number of studies looking at the use of prophylactic antibiotics to prevent or reduce exacerbations, these studies were confined to a small number of antibiotics and there was little variation in dose or frequency of administration of the antibiotic. In addition, the majority of the studies were small and recruited less than 100 people with COPD.
Equality	No specific equality concerns are relevant to this research recommendation.
Feasibility	There is a large enough population of people with COPD who are at high risk of exacerbations that intervention studies in this area should be feasible.

Research recommendation 3

Question	What is the comparative effectiveness of seasonal versus continuous prophylactic antibiotics for people with stable COPD who are at high risk of exacerbations?
Population	People with stable COPD who are at high risk of exacerbations
Interventions	Continuous administration of prophylactic antibiotics
Comparator	Seasonal administration of prophylactic antibiotics
Outcomes	• Exacerbations (numbers and severity) • Respiratory health-related quality of life • Reduction in lung function from baseline (FEV1) • Mortality • Adverse events (including hearing loss) • Serious adverse events • Antibiotic resistance • Exercise capacity
Study design	Randomised controlled trial

Potential criterion	Explanation
Importance to patients, service users or the population	People with COPD commonly experience exacerbations, which have a negative impact on their quality of life and are linked to worse disease prognosis. Certain groups of people with COPD are at higher risk of exacerbations and reducing the numbers they experience should improve quality of life for them and their families. However, the use of long-term antibiotics for prophylaxis also has the potential for a wider effect on society as it may increase the risk of antibiotic resistance. In addition, the long-term use of antibiotics may be associated with adverse events (such as hearing loss) in people with COPD. Risk factors for exacerbations include seasonal variations (e.g. cold weather in winter and allergies in spring). Prescribing prophylactic antibiotics during these periods might be equally effective as prescribing continuous prophylactic antibiotics at reducing or preventing exacerbations. If this was the case, then the prescription of prophylactic antibiotics could be targeted to specific times of the year, based on individual responses to risk factors, reducing the overall prescription of antibiotics and the potential for adverse side effects for the person with COPD and society.
Relevance to NICE guidance	Low-priority: it was possible to make recommendations for the use of prophylactic antibiotics based on the available evidence, but new evidence in this area has the potential to alter the recommendations substantially.
Current evidence base	The existing trials examined pulsed or continuous prophylactic antibiotics administered irrespective of time of year. There was no evidence regarding the effectiveness of targeting prophylactic antibiotics to specific times of the year when environmental risk factors are present.
Equality	No specific equality concerns are relevant to this research recommendation.
Feasibility	There is a large enough population of people with COPD who are at high risk of exacerbations that intervention studies in this area should be feasible.

Research recommendation 4

Question	Which subgroups of people with stable COPD who are at high risk of exacerbations are most likely to benefit from prophylactic antibiotics?
Population	People with stable COPD who are at high risk of exacerbations
Interventions	Prophylactic antibiotics
Comparator	Placebo
Outcomes	• Exacerbations (numbers and severity) • Respiratory health-related quality of life • Reduction in lung function from baseline (FEV1) • Mortality • Adverse events (including hearing loss) • Serious adverse events • Antibiotic resistance • Exercise capacity
Study design	Randomised controlled trials

Potential criterion	Explanation
Importance to patients, service users or the population	People with COPD commonly experience exacerbations, which have a negative impact on their quality of life and are linked to worse disease prognosis. Certain groups of people with COPD are at higher risk of exacerbations and reducing the numbers they experience should improve quality of life for them and their families. However, subgroups of these people may benefit particularly from this treatment. Identifying and targeting these people for prescription of prophylactic antibiotics should help improve their quality of life, whilst reducing the risk of antibiotic resistance developing by reducing the numbers of people taking antibiotics in this manner. Randomised trials that include subgroup analysis of participants based on factors such as biomarkers, clinical features, bacterial patterns and comorbidities could provide useful information on this topic.
Relevance to NICE guidance	High-priority: it was possible to make recommendations for the use of prophylactic antibiotics based on the available evidence, but new evidence in this area has the potential to substantially improve the recommendations.
Current evidence base	Although there were a number of studies looking at the use of prophylactic antibiotics to prevent or reduce exacerbations, the majority of the studies were small and recruited less than 100 people with COPD. As a result, the decision about which subgroups of people with COPD would benefit from the use of prophylactic antibiotics was based on whole trial inclusion criteria and the clinical experience of the committee.
Equality	No specific equality concerns are relevant to this research recommendation.
Feasibility	There is a large enough population of people with COPD who are at high risk of exacerbations that intervention studies in this area should be feasible.

Appendix K – References

Cochrane review used as basis for preventing exacerbations reviews

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Preventing exacerbations

This list was taken from the Cochrane review directly and contains papers that relate to the included RCTs, including conference abstracts. This is in contrast to the usual process employed by the Guideline Updates Team where papers are only included if data has been extracted from them. Without duplicating the data extraction process, it is unclear which papers were used by the Cochrane group as a source of included data and so all of the related papers are included in the list below. However, Banerjee 2005, has been moved to the excluded studies list by the Guideline Update Team as this consists of a single study and no data was extracted. The studies are grouped according to the main reference author and year in bold.

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Preventing exacerbations

This list was taken directly from the Cochrane review. The first name and year is used to reference the study in the excluded studies tables in appendix I. In 2 cases (Vermeersch 2016 and Segal 2017), the reason for exclusion applies to 2 related papers by the same author. These have been grouped under the author name and year below for clarity. Banerjee 2005 was added to the following list as it was excluded by the Guideline Updates Team from the evidence review.

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