INPLASY PROTOCOL

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None declared.

Dysbiosis as a prognostic factor for clinical worsening in chronic respiratory disease: A systematic review and metanalysis

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Review question / Objective: **Is dysbiosis a prognostic factor for clinical worsening in patients with chronic respiratory diseases?.**
Condition being studied: **Dysbiosis, defined as changes in the quantitative and qualitative composition of the microbiota.**
Eligibility criteria: **Over 18 years old adult patients with chronic respiratory diseases clinical diagnosis (cystic fibrosis, chronic obstructive pulmonary disease, asthma, idiopathic pulmonary fibrosis, interstitial lung disease, sarcoidosis, bronchiectasis, non-CF bronchiectasis, pulmonary hypertension) according to the International Statistical Classification of Diseases and Related Health Problems (ICD) from OMS) and international guidelines of each disease.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 15 April 2022 and was last updated on 15 April 2022 (registration number INPLASY202240089).

INTRODUCTION

Review question / Objective: **Is dysbiosis a prognostic factor for clinical worsening in patients with chronic respiratory diseases?.**

Rationale: **The increase in chronic respiratory diseases associated with the morbidity of obesity and metabolic disorders, associated with the latest available preclinical evidence, makes it necessary to search more closely for relationships between these variables.**

Condition being studied: Dysbiosis, defined as changes in the quantitative and qualitative composition of the microbiota.

METHODS

Search strategy: (((gut microbiome) OR (microbiota) OR (Dysbiosis)) AND ((COPD) OR (chronic obstructive pulmonary disease) OR (cystic fibrosis) OR (idiopathic pulmonary fibrosis) OR (interstitial lung disease) OR (asthma) OR (pulmonary hypertension) OR (pulmonary arterial hypertension) OR (sarcoidosis) OR (bronchiectasis)) AND ((mortality) OR (survival) OR (clinical worsening) OR (exacerbation) OR (lung function) OR (pulmonary function test) OR (exercise capacity))).

Participant or population: Over 18 years old adult patients with chronic respiratory diseases clinical diagnosis (cystic fibrosis, chronic obstructive pulmonary disease, asthma, idiopathic pulmonary fibrosis, interstitial lung disease, sarcoidosis, bronchiectasis, non-CF bronchiectasis, pulmonary hypertension) according to the International Statistical Classification of Diseases and Related Health Problems (ICD) from OMS) and international guidelines of each disease.

Intervention: Not applicable.

Comparator: Patients without dysbiosis.

Study designs to be included: We will include randomised clinical trials (RCTs), quasi-randomised clinical trials, and observational studies (retrospective, prospective, cross-sectional, longitudinal, case-control, and cohort). All editorials, letters, review articles, systematic review, and meta-analysis, in vivo and in vitro studies will be excluded.

Eligibility criteria: Over 18 years old adult patients with chronic respiratory diseases clinical diagnosis (cystic fibrosis, chronic obstructive pulmonary disease, asthma, idiopathic pulmonary fibrosis, interstitial lung disease, sarcoidosis, bronchiectasis, non-CF bronchiectasis, pulmonary hypertension) according to the International Statistical Classification of Diseases and Related Health Problems (ICD) from OMS) and international guidelines of each disease.

Information sources: We will conduct a systematic review of the literature to identify those researchs that investigate the microbiota in patients with chronic respiratory diseases. We will search in the Embase, Cochrane Library (CENTRAL), CINAHL, Web of Science, SCOPUS, and PubMed/MEDLINE databases.

Main outcome(s): a. Clinical worsering, defined as hospitalization, referral to transplant, or death. b. Mortality. c. Lung function.

Additional outcome(s): a. Alpha diversity (Shannon Index and Simpson Index). b. Beta diversity index (Bray-Curlis method). c. Number of bacterial taxa and their distribution 16S rRNA sequencing.

Data management: Studies will be selected for inclusion using the predefined and explicit eligibility criteria. The total of articles from the searching results will be screened independently by two reviewers (MBP-RTC) in order to identify all citations that meet the inclusion criteria. Also, the full manuscripts of the selected citations will be retrieved and assessed by two reviewers (MBP- RTC) against the inclusion criteria. Any disagreements about theinclusion of any study will be resolved by consensus or, if necessary, by arbitration by a third reviewer (MH). Study characteristics (design, country), baseline patient characteristics (age, demographic and anthropometric characteristics, disease characteristics, comorbidities), outcomes then will be extracted from the studies selected for inclusion by two reviewers (MBP-AN) using a pre-designed and piloted data extraction form to avoid any errors. Any disagreements between the reviewers will be resolved by consensus or, if necessary, through arbitration by a third reviewer (CF). Authors may be contacted to request the provision of missing data on a case-by-case basis, considering the

importance and relevance of the data which is missing.

Quality assessment / Risk of bias analysis: The risk of bias of the included studies will be assessed with the Quality in Prognosis Studies (QUIPS) risk-of-bias tool. To minimise the bias, the studies will be graded independently by 2 reviewers (MBP-MH). The scoring will be compared and discrepancies will be sorted by a third reviewer (CF).

Strategy of data synthesis: We will provide a narrative synthesis of the findings from the included studies. We will report summaries of association between the risk factor and the outcomes for each study in terms of mean differences or standardised mean differences. If a meta-analysis is appropriate, we will estimate pooled measures of association using a random-effect meta-analysis and calculate 95% confidence intervals for each outcome. A forest plot will be created to display results in order to asses the direction and magnitude of the effects and the overlap between confidence intervals could be analysed. Statistical heterogeneity will be assessed by using Cochran's Q value and the I^2 statistic from the standard χ^2 test. If $I^2 > 50\%$ this will be considered to reflect significant statistical heterogeneity. When $I^2 > 50\%$ the random-effects model using the inverse variance heterogeneity method will be used. To identify the origin of the heterogeneity, sensitivity analysis excluding one study at a time will also be undertaken. Funnel plots will be constructed.

Subgroup analysis: By disease.

Sensitivity analysis: We will perform sensitivity analysis based on sample size, heterogeneity, methodological quality, and statistical model. We will exclude studies with low quality, and ensure the stability of analysis results.

Language: English.

Country(ies) involved: Chile and Spain.

Keywords: Dysbiosis; chronic respiratory disease.

Dissemination plans: National congress of physiology ERS international congress publication in high impact journal.

Contributions of each author:

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