Exacerbations of COPD and symptoms of gastroesophageal reflux: a systematic review and meta-analysis*,**

Exacerbações de DPOC e sintomas de refluxo gastroesofágico: revisão sistemática e meta-análise

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Abstract

Objective: To examine the relationship between gastroesophageal reflux (GER) and COPD exacerbations. **Methods:** We conducted a systematic search of various electronic databases for articles published up through December of 2012. Studies considered eligible for inclusion were those dealing with COPD, COPD exacerbations, and GER; comparing at least two groups (COPD vs. controls or GER vs. controls); and describing relative risks (RRs) and prevalence ratios—or ORs and their respective 95% CIs (or presenting enough data to allow further calculations) for the association between GER and COPD—as well as exacerbation rates. Using a standardized form, we extracted data related to the study design; criteria for GER diagnosis; age, gender, and number of participants; randomization method; severity scores; methods of evaluating GER symptoms; criteria for defining exacerbations; exacerbation rates (hospitalizations, ER visits, unscheduled clinic visits, prednisone use, and antibiotic use); GER symptoms in COPD group vs. controls; mean number of COPD exacerbations (with symptoms vs. without symptoms); annual frequency of exacerbations; GER treatment; and severity of airflow obstruction. **Results:** Overall, GER was clearly identified as a risk factor for COPD exacerbations (RR = 7.57; 95% CI: 3.84-14.94), with an increased mean number of exacerbations per year (mean difference: 0.79; 95% CI: 0.22-1.36). The prevalence of GER was significantly higher in patients with COPD than in those without (RR = 13.06; 95% CI: 3.64-46.87; $p < 0.001$). **Conclusions:** GER is a risk factor for COPD exacerbations. The role of GER in COPD management should be studied in greater detail.

Keywords: Pulmonary disease, chronic obstructive; Gastroesophageal reflux; Meta-analysis; Risk factors; Evidence-based medicine.

Resumo

Objetivo: Examinar a relação entre refluxo gastroesofágico (RGE) e exacerbações da DPOC. **Métodos:** Foi realizada uma revisão sistemática de artigos publicados até dezembro de 2012 utilizando várias bases de dados. Os critérios de elegibilidade incluíram estudos sobre DPOC, exacerbações da DPOC e RGE que comparavam ao menos dois grupos (DPOC vs. controle ou RGE vs. controle) e descrevendo riscos relativos (RRs), razões de prevalência ou ORs e respectivos IC95% (ou com dados que permitissem o seu cálculo) para a associação entre RGE e DPOC, assim como taxas de exacerbações. Os dados foram coletados com um formulário padronizado que incluía o tipo de estudo; critérios para diagnóstico de RGE; idade e gênero dos participantes; número de participantes; método de randomização; escores de gravidade; métodos de avaliação dos sintomas de RGE; critérios de definição de exacerbação; taxa de exacerbações (hospitalizações, visitas à emergência, consultas não programadas, uso de prednisona e uso de antibióticos); sintomas de RGE no grupo DPOC vs. controles; média de exacerbações da DPOC (com sintomas vs. sem sintomas); frequência anual de exacerbações; tratamento para RGE; e gravidade da obstrução. **Resultados:** O RGE foi claramente identificado como um fator de risco para exacerbações da DPOC (RR = 7,57; IC95%: 3,84-14,94), com um aumento na média de exacerbações por ano (diferença média: 0,79; IC95%: 0,22-1,36). Houve uma prevalência significativamente maior de RGE em pacientes com DPOC do que naqueles sem DPOC (RR = 13,06; IC95%: 3,64-46,87; $p < 0,001$). **Conclusões:** O RGE é um fator de risco para exacerbações da DPOC. O papel do RGE no manejo da DPOC deve ser mais profundamente investigado.

Descritores: Doença pulmonar obstrutiva crônica; Refluxo gastroesofágico; Metanálise; Fatores de risco; Medicina baseada em evidências.

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Introduction

Exacerbations of COPD are critical events in the natural history and management of the disease because they are related to the worsening of quality of life,[1,2] accelerated decline in lung function,[1,2] hospital admissions,[2-5] increased risk of death,[1,3,5] and high use of health care resources.[1,3,4] Despite the negative impact of exacerbations on the natural course of the disease, little is known about their causes.[2,5]

Recent studies have suggested that the main determinants for COPD exacerbations are a previous history of exacerbations,[2,4] a low level of physical activity,[4] the severity of the disease,[2,4,5] and the presence of comorbidities, such as gastroesophageal reflux (GER), congestive heart failure, coronary artery disease, and chronic renal/liver failure.[4,6-8] However, the role of GER in this setting remains unclear.

Roughly one-half of the adult population in industrialized countries has a personal experience of GER symptoms, and 20-30% suffer from GER disease (GERD).[9] Presumably, GERD is the most common disease of the digestive tract[9,10] and has been shown to worsen asthma control, due to esophagobronchial reflex,[11,12] and to heighten bronchial reactivity.[11,13,14] In addition, GERD is a determinant of microaspiration.[14,15] It has also been reported that GER is accompanied by neutrophilic airway inflammation,[16] and COPD has the same type of inflammation,[17] which in turn could be increased by this association. Moreover, microaspiration of gastric contents or bronchospasm induced by the vagus nerve due to the irritation of the esophagus caused by the gastric acid might contribute to the association between GER and pulmonary disease/symptoms.[4,15,18]

The association between GER and COPD exacerbation remains unclear.[15,19] One explanation is that GER acts as a collaborating factor of COPD exacerbations by increasing airway inflammation. Therefore, the aim of this meta-analysis was to evaluate the impact of GER on COPD exacerbations.

Methods

We conducted a systematic search of the Medline (PubMed, from 1966 to December 2012), EMBASE (from 1974 to December 2012), the Cochrane Controlled Trials Register (1960-2007), and LILACS (from 1982 to December 2012) databases. We created three groups of keywords, using the connectors "OR" and "AND" within each group and between groups, respectively. We used the following keywords in the first group: "COPD", "chronic bronchitis", and "emphysema". For the explanatory variable, the second group comprised the terms "GERD", "GORD", "GOR" "gastroesophageal reflux", "gastro esophageal reflux", "gastroesophageal reflux disease", "gastro esophageal reflux disease", "gastrooesophageal reflux", "gastro oesophageal reflux", "gastrooesophageal reflux disease", "gastro oesophageal reflux disease", "laryngopharyngeal reflux", and "swallowing". The third group of keywords was used in order to restrict the study design: "cohort", "prospective", "retrospective", "clinical trial", "cross sectional", or "case-control". The bibliographic references of all of the selected articles were also searched, even if they had not been identified by the database search.

Eligibility criteria

Eligibility criteria for the selection of articles were as follows: articles published in English, Spanish, or Portuguese; articles involving patients with COPD (defined by the Global Initiative for Chronic Obstructive Lung Disease criteria),[1] emphysema, or chronic bronchitis; articles reporting the rate of COPD exacerbations, defined by the number of hospitalizations, emergency room visits, and unscheduled clinic visits, as well as by the need for prednisone course/antibiotics or the use of the criteria described by Anthonisen et al.[20]; articles comparing at least two groups (COPD vs. control, or GER vs. control); articles describing the relative risk, prevalence ratio, or odds ratios for the association between GER and COPD with the corresponding 95% CIs or with sufficient data to allow further calculations; and articles reporting exacerbations rates with corresponding 95% CIs or enough data to allow further calculations. No limitations were set for age or for the definition of GER.

Two reviewers screened the titles and abstracts of the identified citations independently and independently acquired the full text of any article that either one judged potentially eligible. The reviewers independently applied the eligibility criteria to the methods section of potentially eligible trials. Disagreements were solved by discussions with a third reviewer.

Data abstraction

Data abstraction was performed independently by two reviewers, using a protocol adapted from the study by Vandenbroucke et al.[21]

Data collection and analysis

The data were analyzed with freeware MIX, version 1.7.[22] We pooled the included studies to yield the risk ratio (RR) or odds ratio for COPD exacerbations and mean number of exacerbations per year with their respective 95% CIs or standard errors.

Selection of reviews

Data extraction and management

The data were extracted using a standardized form, including type of study design; criteria for GER diagnosis (pH monitoring or questionnaires); age and gender of participants; number of participants; randomization method; severity score (i.e., COPD classification); evaluation methods of GER symptoms; definition criteria for exacerbations; rate of exacerbations (hospitalizations, ER visits, unscheduled clinic visits, prednisone use, and antibiotics use); GER symptoms in COPD group vs. controls; mean number of COPD exacerbations (with symptoms vs. without symptoms); annual frequency of exacerbations; GER treatment; and severity of airflow obstruction.

Assessment of methodological quality of included reviews

Data synthesis

We presented all point estimates as RR or as mean ± SE. We used forest plots in order to display the results. The selected trials were combined with freeware MIX.[22] For dichotomous variables, we calculated a fixed-effect RR and the respective 95% CIs for individual studies.

We calculated the mean difference (MD) with 95% CI for continuous variables. When standard deviations (SD) were reported, they were used in order to calculate SE using the following formula:

$$SD = SE \times \text{sqrt}(N) \quad (1)$$

If SDs were unavailable for continuous variables, we analyzed them by transforming 95% CIs into SEs according to the following formula:

$$SE = (\text{upper limit of 95\% CI} - \text{lower limit of 95\% CI}) \div (1.96 \times 2) \quad (2)$$

In addition, OR was adapted to the relative risk using the following formula[23]:

$$\text{Relative risk} = \frac{OR}{(1 - Po) + (Po \times OR)} \quad (3)$$

where Po is the observed prevalence.

We quantified inconsistencies among the pooled estimates using the following formula:

$$I^2 = [(Q - df)/Q] \times 100\% \quad (4)$$

where Q is chi-square, and df is its degrees of freedom.

This illustrates the percentage of the variability, which, in effect, reveals estimates resulting from heterogeneity rather than from a sampling error.[24] If heterogeneity was found, we used a random-effects model. We performed sensitivity analyses by comparing random-effects and fixed-effect models. Potential for publication bias was assessed using the Egger test and funnel plots.

Results

The electronic database searches identified a total of 543 articles. We excluded 507 articles upon review of the titles and abstracts. The review of titles yielded 36 articles that were further examined. Among the remaining 36 articles, some were further excluded due to the following causes: missing information on COPD, GER, or exacerbations[25-32]; review articles[6,12,15,33-37]; lack of adequate data for the meta-analysis[18,28,38-42]; and inclusion/exclusion criteria that made the study unrepresentative of the population.[43] After that, a review of the abstracts and the full texts yielded 11 articles that appeared to fulfill the inclusion criteria. Of the 11 articles, 7 met the inclusion criteria and were included in the analysis (Figure 1).[4,19,44-48] The characteristics of the studies included in the meta-analysis are presented in Table 1. No unpublished or ongoing studies were included.

Increased risk of COPD exacerbations in GER patients

An elevated risk of COPD exacerbations in GER patients was researched by calculating the

RR of COPD exacerbations between patients with and without GER. We found that GER patients showed a risk of having an exacerbation seven times higher than did those without GER (RR = 7.57; 95% CI: 3.84-14.94; z = 5.83; $t^2 = 0.0$; p < 0.0001). We used a fixed-effect model, justified by the low heterogeneity (Q = 1.07; $I^2 = 0.0$; p = 0.89) of the studies (Figure 2). The analysis included 341 patients from all studies.

We further examined the increase in the number of COPD exacerbations in GER patients. In that analysis, we used a random-effects model because of the high heterogeneity (Q = 9.95; p < 0.04; $I^2 = 59.8\%$) instead of a fixed-effect model. Patients with GER showed a higher number of exacerbations per year (MD = 0.79; 95% CI: 0.22-1.36; z = 2.69; $t^2 = 0.23$; p < 0.007) than did those without GER (Figure 3). The analysis included 2,418 patients from all studies.

Association between GER and COPD

In order to determine the association between GER and COPD, we used a fixed-effect model (Q = 0.39; p = 0.94). The pooled analysis found a significantly higher prevalence of GER in COPD patients than in those without COPD (RR = 13.06; 95% CI: 3.64-46.87; z = 3.94; $t^2 = 0.0$; p < 0.001; Figure 4). The analysis included 476 patients from all studies.

Discussion

The present systematic review with meta-analysis showed that GER is a risk factor for COPD exacerbations based on the higher risk for exacerbations and the increased number of exacerbations per year in these patients. In addition, our analyses showed a significant association between GER symptoms and COPD diagnosis. This association is corroborated by the increased frequency of exacerbations per year in patients with GER.

This is the first meta-analysis investigating GER as a risk factor for COPD exacerbations. The major issues about the effect of GER in COPD exacerbations are how exacerbations are determined or defined and whether such determinations are carried out prospectively or retrospectively. Recent retrospective studies[47,48] suggested that GER symptoms were associated with exacerbations; however, in those studies, the subjects were asked to report the number of exacerbations that had occurred during the previous year, which was an approach that could result in a recall bias. To solve this type of problem, other studies[19,45] utilized a prospective questionnaire-based data collection system that allowed us to identify exacerbations according to a more reliable definition of COPD exacerbation, such as the modified criteria by Anthonisen et al.[20] The prospective analyses of Terada et al.[19] and Hurst et al.[4] presented the most reliable information about exacerbations and were the most influential studies on the forest plots about the risk of COPD exacerbations associated with GER (Figure 5).

When less rigid criteria for the definition of an exacerbation were used, we found an increase in the frequency of exacerbations among GER patients. We conducted a preliminary analysis including studies with less rigid criteria,[40,41,48] which demonstrated a similar tendency of the risk of exacerbations (RR = 7.68), a similar increase in the frequency of exacerbations (mean increase = 1,02 per year) among GER patients, and a similar increased risk of GER associated with COPD (RR = 2.82) when compared with the results found in our final analysis (data not shown). Although only one study[44] utilized pH monitoring as the gold standard for the diagnosis of GER, the risk of exacerbations and GER in subjects with COPD demonstrated a good homogeneity across the studies.

Exacerbations of COPD are an important outcome in the natural history of the disease,[29,49-52] not only because they pose a considerable economic burden,[53] but, more importantly, because repeated COPD exacerbations can deteriorate health-related quality of life, accelerate the progression of the disease,[50-52] and lead to premature death.[3,50,52]

Over time, COPD exacerbations become more frequent and more severe, and this is associated with increasing functional impairment.[52] Risk factors for repeated exacerbations include low pre-treatment FEV_1,[4,49,51] increased use of bronchodilators or corticosteroids,[4,48] previous exacerbations (more than two in the last two years),[4,49] prior use of antibiotics,[4,51] and presence of comorbid conditions.[4,29]

Studies have reported in-hospital mortality rates of 11-24%[17] and of 35.6%[50] after two years. Patients with frequent exacerbations had the highest mortality rates (p < 0.001), with a risk of death 4.3 times greater than that for patients requiring no hospital management.[51] Thus, the

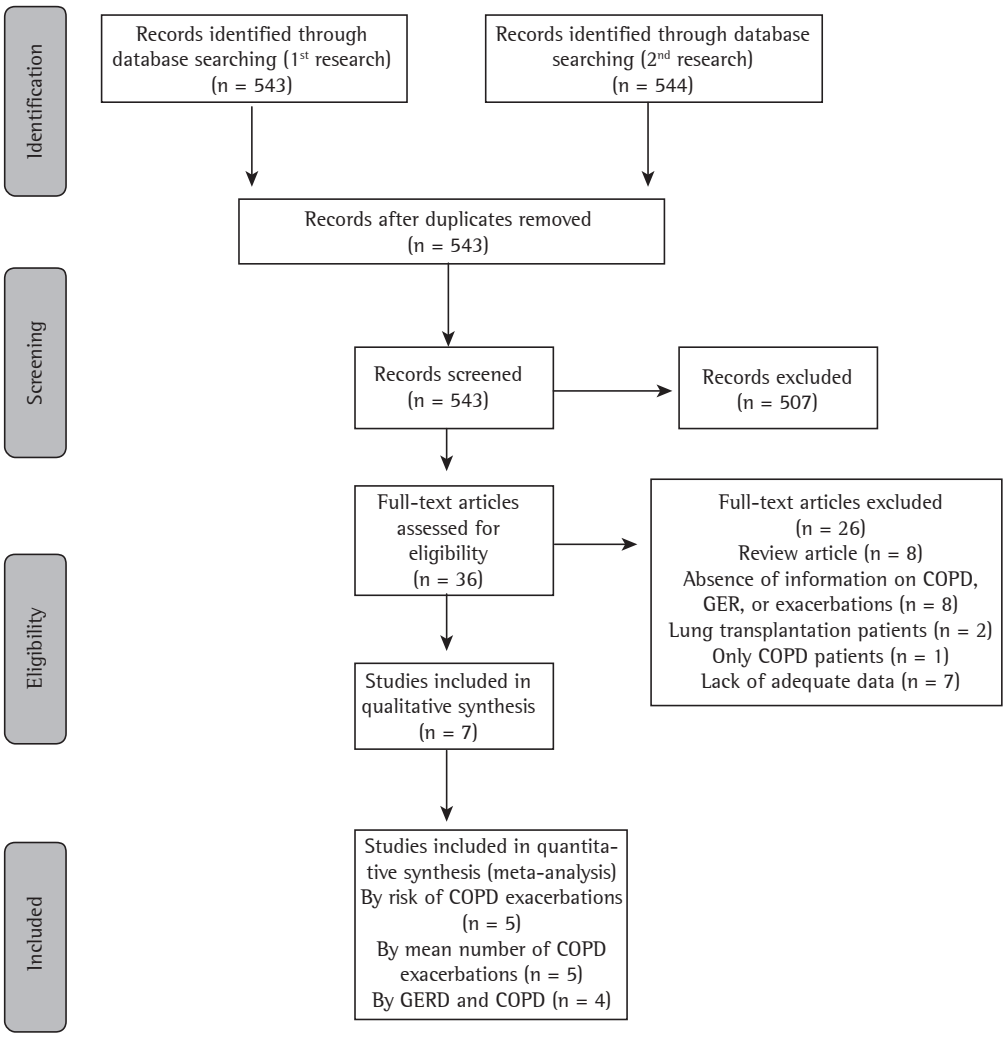

Figure 1 - Flowchart of study selection. GER(D): gastroesophageal reflux (disease).

exacerbation itself might be a significant factor associated with increased mortality in COPD patients; however, the severity of the underlying disease might influence the patient outcome. Some studies[4,19,45,47,48] demonstrated an increase in the number of exacerbations per year related to GER, but its independent association with GER, using adequately controlled multivariate analysis, is yet to be tested.[25]

Another issue is the lack of a gold standard or of objective measurements in order to diagnose GER in the different studies, which makes it difficult to select studies and homogenize the data regarding the diagnosis of GER. The lack of a gold standard can overestimate or underestimate GER in some populations or samples. Respiratory patients frequently experience chest discomfort that can be confused with reflux symptoms, primarily pyrosis, leading to an overestimation of reflux symptoms. According to Sweet et al.,[6] the typical reflux symptoms (heartburn, regurgitation, and dysphagia), have a limited correlation with objectively measured reflux, reaching a sensitivity of 89.5% and a specificity of only 47.1%. These data make studies based on symptom questionnaires inaccurate when compared with those based on more specific tests, such as 24-h pH monitoring and esophageal scintigraphy.[30] In our meta-analysis, 6 of the 7 studies included were based on questionnaires, and, therefore, all of the conclusions should be inferred from GER symptoms as a risk factor, since there was

no diagnostic confirmation of GER. However, the impact of studies based on questionnaires might underestimate this association. The only study[44] included in the present meta-analysis that had objective criteria demonstrated the strongest association between GER symptoms and COPD exacerbations. Prospective studies must be designed in order to identify GER objectively and to demonstrate the impact of GER treatment on COPD exacerbations.

A subanalysis of COPD patients receiving antireflux therapy[47] has shown that the number of COPD exacerbations per year in those patients who had controlled or non-symptomatic GER tended to decrease. In a randomized controlled trial, Sasaki et al.[25] showed that the treatment with lansoprazole

Table 1 - Characteristics of the seven studies included in the present meta-analysis.

Study	Characteristics of the study	Results	Comments
Hurst et al.[4]	Population-based cohort study; 2,138 COPD patients; stages 2 to 4 according to GOLD criteria; females/males: 35%/65%; mean age = 63 years; self-reported symptoms and history of GER or heartburn.	Mean number of COPD exacerbations: GER group = 1.41 per person per year; no GER group = 1.11 per person per year; risk of exacerbations in first year: OR =1.69 (95% CI: 1.38-2.06).	Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints (ECLIPSE) study.
Terada et al.[45]	Population sample; 67 COPD patients and 19 controls; both genders.	Number of exacerbations: COPD group = 2.82 (95% CI: 1.92-3.72) per year; controls = 1.56 (95% CI: 0,92-2.19) per year; GER risk for COPD exacerbations: RR = 6.24 (95% CI: 0.90-43.34); in the multivariate analysis, abnormal swallowing reflex was associated with ≥ 3 exacerbations per year; p = 0,01).	Abnormal swallowing reflex: COPD (22/67), controls (1/19; p = 0.02).
Eryuksel et al.[48]	29 COPD patients (ATS criteria); LPR criteria: reflux symptoms index by Belafsky et al., reflux finding score (Belafsky et al.) and indirect laryngoscope.	13/29 patients with LPR (44%); number of exacerbations in the last year: GER (or LPR) = 1.38 ± 1.5; no GER (or no LPR) = 1.06 ± 1.06.	COPD symptom score: patients were asked about the severity of dyspnea, cough, wheezing, and the frequency of use of short-acting β_2 agonist during the last month. Definition of COPD exacerbation: any worsening of dyspnea, increase in the amount of sputum, or change in the color of sputum during the previous year. The frequency of exacerbations in each subject was retrospectively collected. At baseline, the groups were similar in terms of the incidences of antibiotic use (p = 0.652), steroid use (p = 0.267), ER visits (p = 0.677), outpatient visits (p = 0.620), hospitalizations (p = 0.448), and number of exacerbations (p = 0.52) during the last year.

Table 1 - Continued...

Study	Characteristics of the study	Results	Comments
Terada et al.[19]	Prospective and retrospective study; 82 COPD patients and 40 matched controls; moderate to severe COPD (GOLD criteria); symptoms evaluated by questionnaire (FSSG), surveyed for 6 months; exacerbations defined according to criteria by Anthonisen et al.[20]	Simple analysis: GER symptoms vs COPD exacerbation: RR = 1.93 ($p < 0.01$); mean number of COPD exacerbations (retrospective - previous year): with GER symptoms: 1.73 ± 1.58; without GER symptoms: 0.70 ± 1.20. Additional 6 months surveyed: GER symptoms were also significantly associated with annual frequency; the frequency was 2.6 ± 2.0 in subjects with GER symptoms and 1.5 ± 1.7 in subjects without such symptoms ($p = 0.048$). GERD symptoms were significantly related to frequent (≥ 3 episodes per year) exacerbations (RR = 2.18; 95% CI: 1.10-5.70; $p = 0.046$). GER symptoms vs. COPD: RR = 2.15 (95% CI: 0.88-5.25).	GER symptoms: 22/82 (COPD), 5/40 (controls). Frequency of exacerbations associated with FSSG score ($p = 0.03$; $r = 0.24$). EBC pH was significantly lower in subjects with GER symptoms than in subjects without GER symptoms (6.47 ± 1.22 vs. 7.17 ± 1.05; $p = 0.02$) in COPD patients and in controls (6.34 ± 1.22 vs. 7.22 ± 0.53; $p = 0.03$). Multiple regression: association between GERD symptoms and occurrence of exacerbations (RR = 6.55).
Rascon-Aguillar et al.[47]	GER definition: heartburn and/or acid regurgitation weekly. Patients with COPD: FEV_1/FVC ratio < 70%; 91 patients: 5 lost to follow-up, 1 twice; total: 86 patients (32 GER+, 54 GER–) GER+ = 37% of the sample.	Exacerbations/year (GER+ vs. GER– groups) = 3.2 ± 3.1; SE = 0.548 vs. 1.6 ± 1.6; SE = 0,21 ($p = 0.02$; RR = 2.0; SE = 2.60). Patients who had weekly GER symptoms had significantly more hospitalizations due to COPD than did those without weekly GER symptoms ($p = 0.007$). All types of exacerbations were also significantly increased in the weekly GER group with the exception of prednisone use, which showed only an increased numerical trend.	A subanalysis of the patients receiving antireflux therapy demonstrated that the number of COPD exacerbations in the patients who were receiving PPIs and had controlled or non-symptomatic GER had a mean of 1.6 ± 0.9 exacerbations/year compared with symptomatic GER group receiving PPIs (3.7 ± 3.3 exacerbations/year; $p = 0.09$), indicating a trend toward a higher number of yearly exacerbations.
Phulpoto et al.[46]	Prospective case-control study; 100 COPD patients, 150 controls.	Patients with GER: COPD group, 25%; controls, 9.33%; $p = 0.001$. GER and COPD: RR = 2.68 (95% CI: 1.47-4.90).	GER symptoms vs. reduced FEV_1 (25% vs. 0%; $p = 0.001$).
Casanova et al.[44]	42 COPD male patients, 16 volunteers; 24-h pH monitoring for GERD diagnosis.	GER: 26/42 COPD patients (62%) and 3/16 controls (19%); RR = 3.30 (95% CI: 1.16-9.41).	58% presented with any GER symptoms; decreased saturation coincided with esophageal acidity in 40% in the GER group.

GOLD: Global Initiative for Chronic Obstructive Lung Disease; GER(D): gastroesophageal reflux (disease); LPR: laryngopharyngeal reflux; ATS: American Thoracic Society; FSSG: frequency scale for the symptoms of gastroesophageal reflux disease; EBC: exhaled breath condensate; and PPIs: proton pump inhibitors.

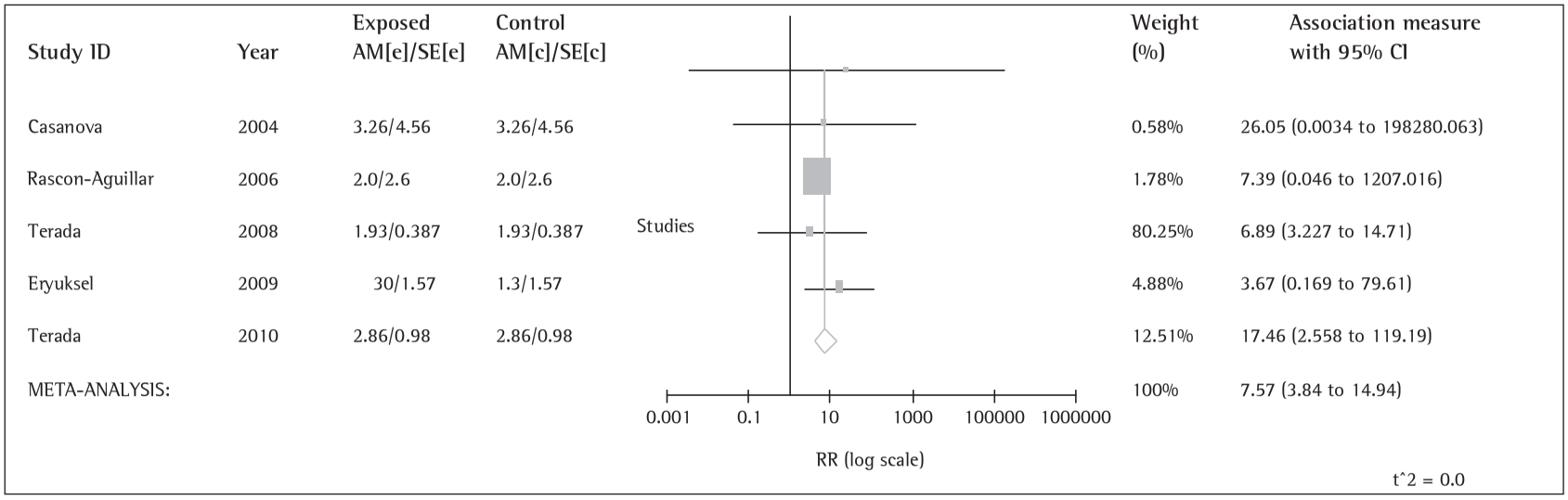

Figure 2 - Risk of COPD exacerbations according to gastroesophageal reflux. RR: relative risk.

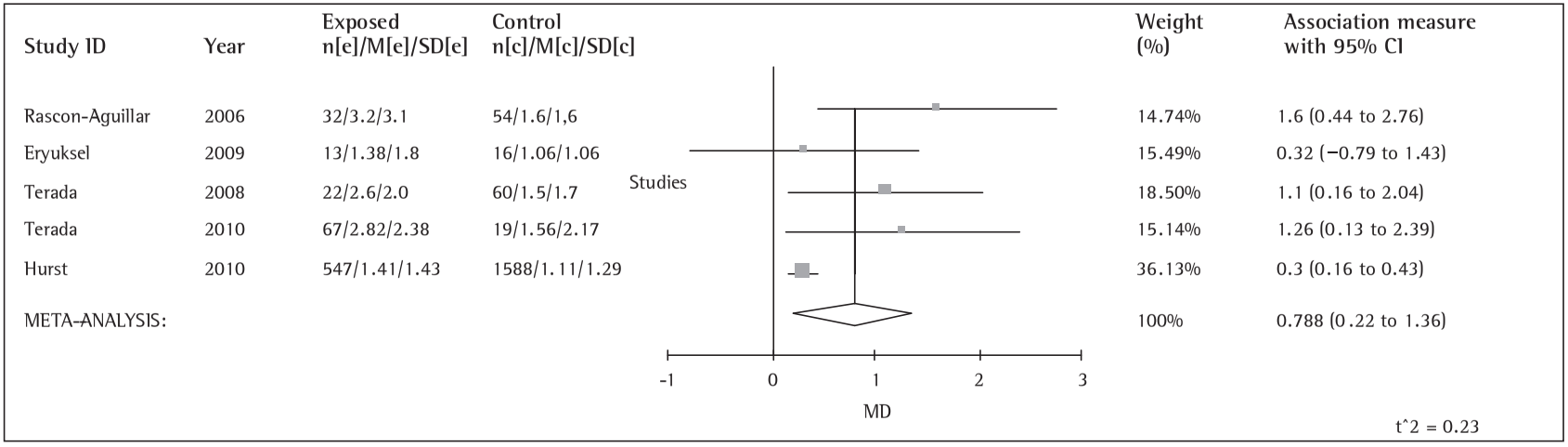

Figure 3 - Mean number of COPD exacerbations associated with gastroesophageal reflux. MD: mean difference.

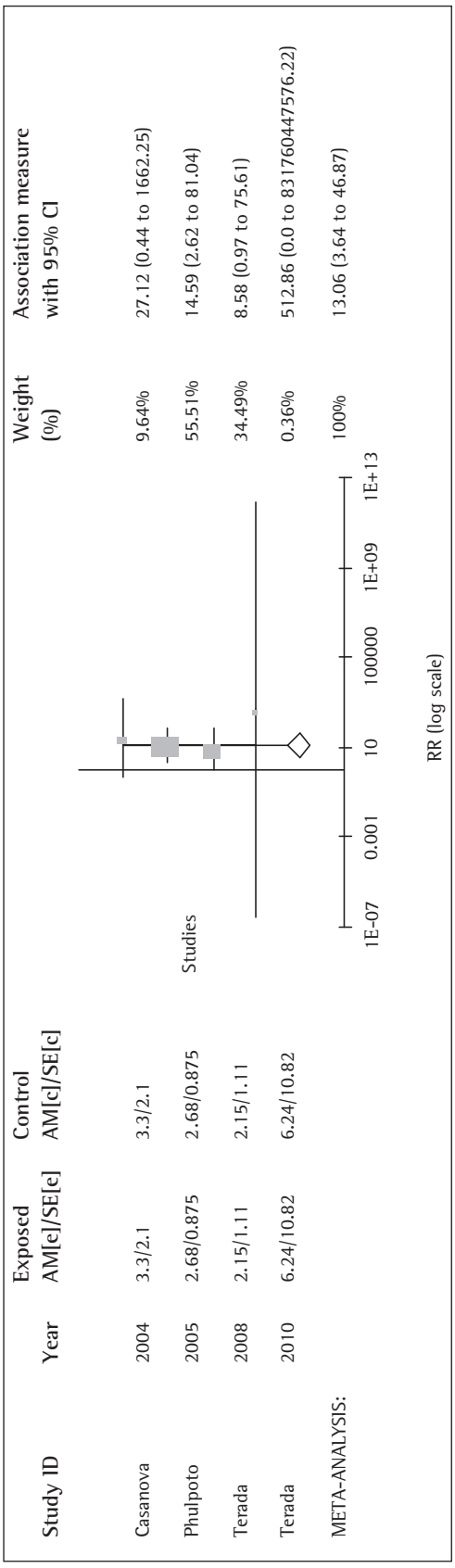

Figure 4 - Risk of gastroesophageal reflux associated with COPD. RR: relative risk.

(15 mg/day) in COPD patients without GER was capable to avoid COPD exacerbations in 77% of the patients (OR = 0.23). Those results must be seen with caution. Some authors[9,10] are skeptical about such data, since the association between asthma and GER is apparently stronger[14,16] than is the association between COPD and GER. In addition, intensive acid suppression in asthma patients, a population more likely to experience acid reflux, with esomeprazole (40 mg bid) did not reduce the number of exacerbations.[11,13] Clinically, silent acid reflux is not a reliable predictor of the success of antireflux treatment in asthma patients.[10]

The reason for such an association is unclear. The most common explanation is that the aspiration of reflux, either acid or not, increases airway inflammation and leads to an increased risk of exacerbations. However, the occurrence of chronic bronchitis clinically increases the risk of COPD exacerbations. A comparative analysis of COPD patients with and without chronic bronchitis, corrected for smoking status, body mass index, medication use, and pulmonary function, would be a much stronger argument for the presence or absence of a role played by GER in COPD exacerbations than would the present analysis. However, the differentiation between chronic bronchitis and emphysema was not performed in the studies included here.[2] We can speculate that there is a higher risk of COPD exacerbations or of GER in COPD patients with a history of chronic bronchitis.

Alternatively, it has been suggested by a number of investigators[26,28,34,47,54,55] that the association between GER and a wide range of respiratory diseases is best explained by the diseases causing or contributing to GER. There are various plausible hypotheses supporting this explanation. First, the high prevalence of hiatus hernia is due to chronic cough associated with different lung diseases.[26,39] Although there is not a perfect correlation between hiatus hernia and reflux, reflux is more likely to occur in the presence of larger hiatus hernia.[10] The diaphragm contributes to reduce the esophageal function, and any alteration between the two will affect its function. Second, bronchodilators also relax gastrointestinal smooth muscles and can facilitate reflux, and some drugs, such as theophylline, increase the production of gastric acid and, consequently, can cause acid reflux.[18,27,38,48]

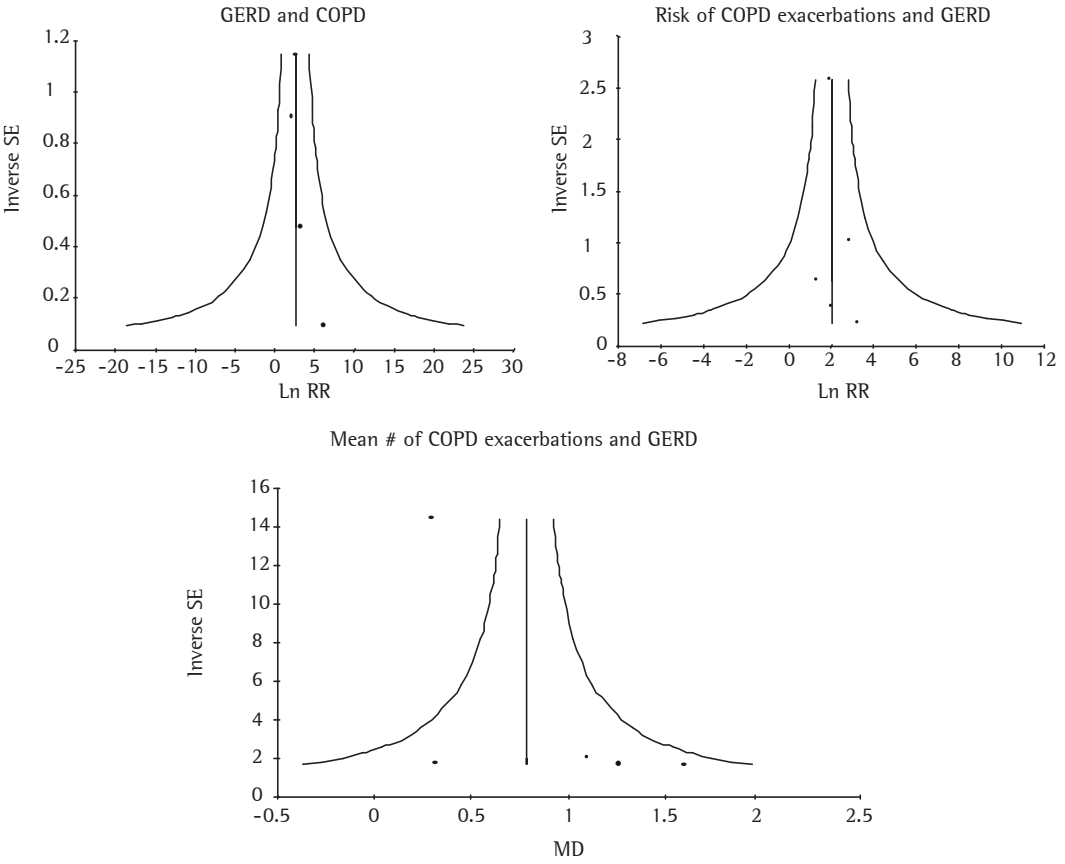

Figure 5 - Funnel plots. GERD: gastroesophageal reflux disease; Ln RR: linear relative risk; and MD: mean difference.

In conclusion, we found that COPD patients with GER symptoms were more likely to experience exacerbations than were those lacking these symptoms. Objectively evaluating the presence of GER in such patients might determine future strategies to reduce or control GER and, subsequently, decrease the number of COPD exacerbations.

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