CHEST

Meta-analysis of Gastroesophageal Reflux Disease and Idiopathic Pulmonary Fibrosis

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BACKGROUND: The relationship between gastroesophageal reflux disease (GERD) and idiopathic pulmonary fibrosis (IPF) is controversial. Current guidelines recommend that clinicians use regular antacid treatment, while two recent meta-analyses of antacid therapy in IPF were inconclusive. The objective of this study was to examine the evidence regarding the association between GERD and IPF through a systematic review and a meta-analysis, with special reference to the methodologic quality of the observational studies.

METHODS: The MEDLINE, EMBASE, Ovid, and Web of Science (1966-May 2018) databases were searched for original articles published in any language, and we then systematically reviewed the bibliographies of the retrieved articles. Observational studies (cohort and case-control studies) were selected if they allowed the calculation of a measure of association relating GERD to IPF.

RESULTS: Eighteen case-control studies including 3,206 patients with IPF and 9,368 control subjects met the inclusion criteria of the meta-analysis. The meta-analysis indicated that GERD is associated with IPF (OR, 2.94 [95% CI, 1.95-4.42]; *P* homogeneity $< .0001$). Overall, the results remained consistent whatever the data source (clinical studies vs databases) or the type of control subject (healthy volunteers, patients with respiratory diseases other than interstitial lung disease, or patients with non-IPF interstitial lung disease). In a meta-regression, after controlling for smoking, GERD and IPF were not related.

CONCLUSIONS: GERD and IPF may be related, but this association is most likely confounded, especially by smoking. Our confidence in the estimate of association is low because it is exclusively from case-control studies.

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ABBREVIATIONS: GERD = gastroesophageal reflux disease; IPF = idiopathic pulmonary fibrosis

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Idiopathic pulmonary fibrosis (IPF) is a progressive form of chronic fibrosing interstitial pneumonia of unknown etiology.[1] Its incidence ranges between three and nine cases per 100,000 people per year in North America and Europe.[2] IPF has a poor prognosis as its median survival is usually 2 to 3 years.[3] The pathogenesis of IPF is complex and not fully understood. An emerging concept is that IPF results from genetic mutations in the epithelial cells of the lung. External stressors (eg, cigarette smoke, air pollution) would then contribute to the development of lung fibrosis in predisposed individuals.[4] Gastroesophageal reflux disease (GERD) with its consequent microaspiration has been identified as one of the potential external factors predisposing to IPF.[5]

The hypothesis of an association between GERD and IPF has stimulated uncontrolled trials of antireflux medical therapy[6] and antireflux surgery,[7] as well the secondary analysis of three randomized trials of different pharmacologic therapies.[8] This pooled analysis suggested that the decline in lung function was slowed in those receiving antacid treatment at baseline and led to the recommendation that clinicians use regular antacid medication (eg, proton pump inhibitors, histamine$_2$-blocker receptor antagonists) for patients with IPF.[9] However, two recent meta-analyses of antacid therapy in IPF were inconclusive, and both underlined the poor quality of the available evidence.[10,11] In addition, a pooled analysis of three large Phase III trials of pirfenidone in IPF found that antacid therapy did not improve outcomes and that it might even be associated with an increased risk of infection in those with advanced disease.[12]

Whether GERD and IPF are truly associated is still controversial, as retrospective studies have yielded conflicting results.[13,14] A systematic review of the literature published in 2011 found an increased prevalence of GERD in IPF but concluded that the causal relationship between GERD and IPF could not been established.[15] No meta-analysis was attempted in this review. Our objective therefore was to examine the evidence regarding the association between GERD and IPF through a systematic review and a meta-analysis, with special reference to the methodologic quality of the observational studies.

Materials and Methods

This study protocol was registered in PROSPERO (http://www.crd.york.ac.uk/PROSPERO), an international prospective register of systematic reviews, in December 2016 (registration no. CRD42016053728). The methods that we used and the writing of this report are in accordance with the recommendations of the Meta-analysis of Observational Studies in Epidemiology Group[16] and the Preferred Reporting Items for Systematic Reviews and Meta-analyses guidelines,[17] respectively.

Literature Search

The MEDLINE, EMBASE, Ovid, and Web of Science (1966–May 2018) databases were searched for original articles published in any language using Medical Subject Heading terms as well as title, abstract, and text words related to IPF and GERD. Our complete search strategy is available in e-Table 1. We also searched for additional articles from the reference list of relevant articles obtained from the electronic search. Our last update is dated May 15, 2018.

Study Selection

Observational studies (cohort and case-control studies) were selected if they reported results allowing the computation of a measure of association (eg, relative risk or OR) between GERD and IPF. Narrative reviews, letters to the editor, clinical commentaries, case series, and case reports were disregarded. IPF was defined as a pulmonary fibrosis without identifiable etiology. The comparison group could include healthy control subjects and/or patients with any other respiratory disorder (including interstitial lung diseases associated with collagen vascular disease). We differentiated between asymptomatic reflux and GERD and considered only GERD. The latter is diagnosed when troublesome symptoms and/or complications are caused by reflux.[18] Its diagnosis could be made either clinically (ie, on the basis of symptoms only), or with any objective diagnostic method such as pH-metry.

Two reviewers (D. B. M. and E. L.) successively applied inclusion and exclusion criteria to the titles and abstracts of all citations obtained. If the title of an article or its abstract suggested any possibility that it might be relevant, the article was retrieved and independently assessed by the same reviewers for a final decision about its inclusion in the meta-analysis. Throughout this process, the reviewers were blinded to authors' names, journal, and year of publication of the articles. Those articles published in languages other than English or French were translated into English. Any disagreement was resolved through consensus or by consulting a third reviewer (Y. L.). When studies were identified that had been reported in multiple articles, we limited our analysis to the most recent report, unless the necessary data had appeared only in an earlier article. Agreement between reviewers was measured by using the quadratic weighted kappa statistic.[19] We kept a log of reasons for rejection of citations identified from the searches.

Data Extraction

Two reviewers (D. B. M. and E. L.) extracted information from all articles selected for inclusion in the meta-analysis. The extracted information included the following: (1) the study design; (2) the data source; (3) the sample size; (4) whether confounders were accounted for; (5) whether the control group consisted of healthy participants or had a particular pulmonary disease; and (6) the diagnostic methods for GERD and IPF. For each study, a 2 × 2 table was constructed considering GERD as the exposure and IPF as the outcome.

Risk of Bias Assessment

Study validity was evaluated by using the Newcastle-Ottawa scale that was specifically developed for assessing the quality of nonrandomized studies in meta-analyses (e-Table 2).[20] This scale systematically considers three important sources of bias in observational studies: (1) selection bias, which stems from the absence of comparability between groups being studies; (2) information bias, which results from incorrect (or differential) determination of exposure or outcome; and (3) confounding bias, which is likely when the results could be accounted for by the presence of a factor associated with both the exposure and the outcome but not directly involved in the causal pathway.[21] We focused on two sources of bias specific to the association between GERD and IPF. First, smoking is a risk factor for both IPF[22] and GERD[23] and may consequently confound the association between the two disorders. Second, the selection of patients with systemic sclerosis as control subjects is problematic because it may blur the correlation between GERD and IPF if it truly exists. The reason is that both pulmonary fibrosis (with pathologic features indistinguishable from IPF) and GERD are common manifestations of systemic sclerosis,[24] and their causal association is still a matter of debate.[25,26] Publication bias was assessed visually from a funnel plot.[27]

Data Synthesis and Meta-analysis

Using the 2 × 2 tables constructed for each study, ORs were calculated that we weighted by the inverse of their variance and combined according to a random effects model.[28] Heterogeneity was assessed from visual inspection of the forest plots, χ^2 tests, and the I^2 statistic.[29] Statistically significant heterogeneity was considered present at P values $< .10$ and $I^2 > 50\%$. The analyses were performed with Review Manager (RevMan Version 5.3; Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014).

The effect of smoking was investigated as a potential confounding factor in several ways.[21] First, we restricted the meta-analysis to those studies in which the proportion of smokers and ex-smokers was well balanced between IPF and control subjects, or to those in which smoking status was accounted for in the analysis. Second, random effects meta-regression analyses were performed to adjust the association between GERD and IPF for the ratio of proportions of smokers and ex-smokers in cases and control subjects.[30] We also investigated through a meta-regression whether the imbalance in the proportion of smokers and ex-smokers in case and control subjects had an effect on the strength of association between GERD and IPF.

We hypothesized a priori that the following study characteristics could modify the association between GERD and IPF: (1) clinical studies vs databases as data sources; (2) type of control subjects (healthy individuals, general population, or those with other respiratory diseases, including interstitial lung disease associated with systemic sclerosis); (3) methods of diagnosis for both GERD and IPF; and (4) higher risk of bias. Subgroup and sensitivity analyses were conducted accordingly.

Results

Study Selection and Characteristics

A total of 1,458 separate publications were retrieved. We reduced these to a list of 157 potentially eligible articles, of which 137 were excluded (Fig 1). Both primary reviewers agreed to include 18 studies reported in 20 articles[13,14,31-46] (weighted kappa, 0.92; 95% CI, 0.85-1.0). Disagreement was always resolved by consensus.

Table 1 summarizes the 18 studies that met the inclusion criteria of the meta-analysis. All were case-control studies. Sample size ranged from 20 to 6,020 patients (median, 85), with the two largest studies conducted from primary care databases.[36,46] With the exception of a single study that included only healthy volunteers as control subjects[34] and two database studies that included control subjects from the general population,[36,46] patients with IPF were compared vs patients with other respiratory disorders at different stages of disease.

Risk of Bias

Details of the risk of bias assessment are provided in e-Figure 1. Our assessment identified two important sources of bias. First, smoking as a confounding factor was not accounted for in any study but one.[35] The proportion of smokers and ex-smokers was higher in the IPF group than in the control group in all but three studies (Table 2), a situation that favors a positive association between GERD and IPF. The proportion of smokers or ex-smokers was similar in both the IPF and the control groups in only one study originating from a database[36] and larger in the control group in two studies.[14,35] Second, the diagnostic methods for both GERD and IPF varied across studies and were not always objective (Table 1). The diagnosis of GERD was based on pH-metry in 11 studies[13,31,32,35,37,38,40-44] and on clinical symptoms in five studies.[14,33,34,39,45] In the two database studies, the diagnosis of GERD was inferred from the diagnostic code entries without further validation. The diagnosis of IPF relied on objective methods in 13 studies[13,14,32-35,37,39-41,43-45]; the American Thoracic Society/European Thoracic Society criteria[1] were explicitly used in eight of them. The number of patients with systemic sclerosis in the control groups was small and unlikely to lead to significant bias. We found no clear indication of publication bias from the visual inspection of the funnel plot (Fig 2).

Meta-Analyses and Meta-Regression

A total of 3,206 participants with IPF and 9,368 control subjects contributed to the primary analysis (Fig 3). The meta-analysis indicated that GERD is associated with IPF (OR, 2.94 [95% CI, 1.95-4.42]). We found significant heterogeneity among study results, however. Subgroup and sensitivity analyses are presented in Table 3 and e-Figure 2. Separate analyses of clinical studies and

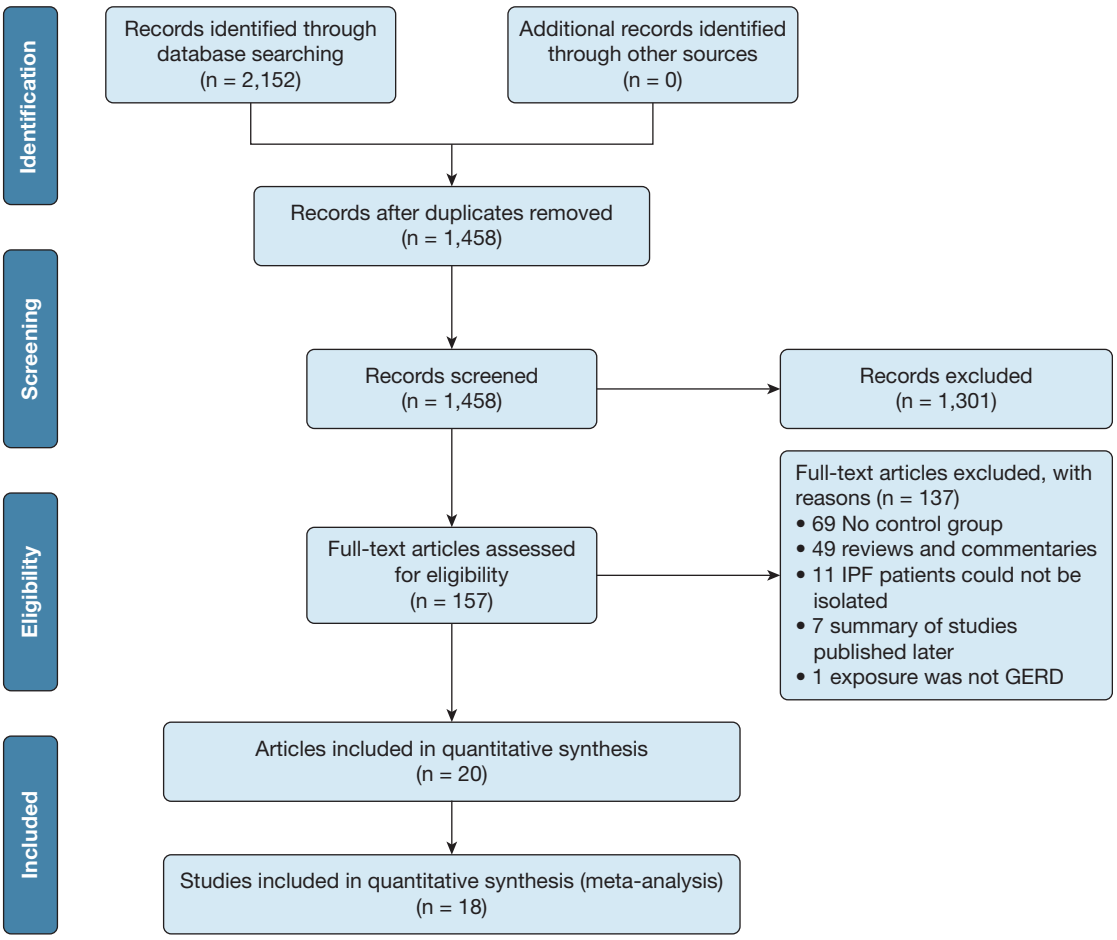

Figure 1 – *Preferred Reporting Items for Systematic Reviews and Meta-analyses flow diagram. GERD = gastroesophageal reflux disease.*

studies from databases led to similar common effects. In the latter analysis, the association did not reach the threshold of statistical significance. The results remained consistent irrespective of the type of control subject (healthy volunteers, patients with respiratory diseases other than interstitial lung disease, and patients with non-IPF interstitial lung disease). Significant heterogeneity persisted in five of these six subgroup analyses reported in Table 3.

In the single study in which the proportion of smokers and ex-smokers was well balanced in case subjects and control subjects (47% and 45%, respectively), GERD slightly increased the risk of IPF (OR, 1.58 [95% CI, 1.25-2.00]).[36] In the single study that accounted for smoking in multivariate regression models (also adjusted for age, BMI, and lung disease severity), increased total reflux episodes and increased reflux exposure time were associated with IPF (ORs of 4.9 [$P = .03$] and 4.0 [$P = .05$]).[35] Finally, in the meta-regression, after adjusting for the ratio of proportions of smokers and ex-smokers in case subjects and control subjects, the association between GERD and IPF was not statistically significant (nine studies; OR, 0.66 [95% CI, 0.34-1.27]), suggesting that smoking is a confounder. Further evidence of the confounding effect of smoking comes from the significant correlation between the ratio of proportions of smokers and ex-smokers in case subjects and control subjects and the strength of the association between GERD and IPF reported in individual studies (Fig 4).

Discussion

The results of our main analysis suggested that GERD and IPF may be associated. However, this association is most likely confounded, especially by smoking. Our confidence in the estimate of association is low because it is exclusively from case-control studies. Although this design is particularly well suited when the outcome of interest is rare or takes time to develop, such as in IPF, case-control studies are particularly susceptible to threats to internal validity through unmeasured

TABLE 1] Primary Studies Included in the Meta-analysis

Study	Country	Design	Case Subjects	Control Subjects	Method of GERD Diagnosis	Method of IPF Diagnosis
D'Ovidio et al (2005)[31]	Canada	Case-control	25 IPF	35 other respiratory diseases (21 COPD, 5 CF, and 9 SSc)	pH-metry: DeMeester score > 15	Not stated
Embarak et al (2015)[32]	Egypt	Case-control	20 IPF	20 ILD other than IPF	MII with pH-metry: total distal esophageal acid exposure ≥ 4.2% over 24 h	Absence of an identifiable etiology of ILD and a histopathologic and/or a radiologic pattern of UIP on surgical lung biopsy and HRCT scan
Fahim et al (2011)[33]	United Kingdom	Case-control	40 IPF	50 control subjects (40 healthy volunteers, 6 COPD, and 4 rheumatoid lung)	Clinical: HARQ score > 13	ATS/ERS criteria
Garcia-Sancho et al (2011)[34]	Mexico	Case-control	100 IPF	263 healthy control subjects matched for age, sex, and place of residence	Clinical: current or past presence of medical conditions, including GERD	ATS/ERS criteria (35% biopsy)
Gavini et al (2015)[35]	United States	Case-control	54 pre-transplant IPF	36 pretransplant COPD	MII with pH-metry: 95th percentile, derived from cohorts of normal volunteers for reflux episodes and % time in reflux	Exclusion of other ILD, presence of UIP pattern on HRCT scan if lung biopsy not done, and specific combinations of HRCT and UIP pattern on biopsy on the basis of ATS/ERS criteria
Gribbin et al (2009)[36]	United Kingdom	Case-control	920 IPF	3,593 control subjects	Read Code (diagnostic terms) in the Health Improvement Network primary care database	Read Code (diagnostic terms) in the Health Improvement Network primary care database
Liang et al (2010)[37]	China	Case-control	24 IPF	23 non-IPF ILD (14 CTD, 2 TB, 2 COP, 4 NSIP, 1 amiodarone, and cyclophosphamide-induced)	MII with pH-metry: DeMeester score ≥ 14.72 and/or total distal esophageal acid exposure ≥ 4.2% over 24 h	ATS/ERS criteria
Lo et al (2015)[38]	United States	Case-control	15 pretransplant IPF	17 pretransplant other respiratory diseases (6 COPD, 6 CF, 2 COP, 1 AAT deficiency, 1 sarcoidosis, 1 other)	MII with pH-metry: increased distal reflux exposure (> 1.4% total reflux exposure over 24 h)	Not stated

(Continued)

TABLE 1] *(Continued)*

Study	Country	Design	Case Subjects	Control Subjects	Method of GERD Diagnosis	Method of IPF Diagnosis
Mays et al (1976)[39]	United States	Case-control	48 IPF	270 control subjects, including 15 with immune-mediated ILD and 23 with ILD of known etiology	Clinical: symptoms compatible with GERD	No serologic evidence of altered immunity (negative ANA, RF, and immunoelectrophoresis)
Oldham et al (2015)[14]	United States	Case-control	196 IPF	196 COPD	Clinical: symptoms compatible with GERD	ATS/ERS criteria
Qi et al (2015)[40]	China	Case-control	25 IPF	23 other DPLD (6 sarcoidosis, 2 COP, 3 Sjögren's syndrome, 4 vasculitis, 7 NSIP, and 1 dermatomyositis)	pH-metry: DeMeester score ≥ 14.72 and/or total distal oesophageal acid exposure ≥ 4.2% of total recording time (24 h)	ATS/ERS criteria
Raghu et al (2006)[41]	United States	Case-control	65 IPF	133 intractable asthma	pH-metry: % time with pH lower than 4 ≥ 4.5% of the total time (distal sensor) over 20-24 h recording	ATS criteria
Salvioli et al (2006)[42]	Italy	Case-control	18 IPF	10 SPF (2 extrinsic allergic alveolitis, 5 CTD, and 3 NSIP)	pH-metry: % time pH lower than 4 > 4.7% over 24 h and/or interdigestive acid exposure > 5% and/or postprandial acid exposure > 10.8% and/or nocturnal acid exposure > 2.2%	Not stated
Savarino et al (2013)[13]	Italia	Case-control	40 IPF	40 ILD other than IPF (10 sarcoidosis, 6 SLE, 14 MCTD, and 10 COP)	MII with pH-metry: total distal esophageal acid exposure ≥ 4.2% of total recording time (24 h)	Absence of an identifiable etiology of ILD and a histopathologic/radiologic pattern of UIP on surgical lung biopsy and HRCT scan
Soares et al (2011)[43]	United States	Case-control	16 IPF	18 CTD; 10 sarcoidosis	pH-metry: DeMeester score > 14.7	ATS/ERS criteria
Tobin et al (1998)[44]	United States	Case-control	17 IPF	8 ILD other than IPF (4 sarcoidosis, 1 SLE, 1 MCTD, 1 COP, and 1 Langerhans cell granulomatosis)	pH-metry: % time with pH lower than 4 ≥ 4.5% of the total time (distal sensor) over 20-24 h recording	Chest radiography with diffuse parenchymal, negative autoimmune panel and histologic features of UIP on surgical lung biopsy

(Continued)

TABLE 1] *(Continued)*

Study	Country	Design	Case Subjects	Control Subjects	Method of GERD Diagnosis	Method of IPF Diagnosis
Tossier et al (2016)[45]	France	Case-control	78 IPF	70 non-IPF ILD (22 CHP, 13 SSc, and 35 non-SSc CTD)	Clinical: presence of GERD symptoms	ATS/ERS criteria
Wu et al (2013)[46]	United States	Case-control	1,505 IPF	4,515 control subjects from a national administrative claims database	Not stated	Data obtained from a national administrative database: ≥ 2 claims with pulmonary fibrosis or idiopathic fibrosing alveolitis as the primary diagnosis, a procedure of lung biopsy, or HRCT scan within ± 90 days of receiving the earliest IPF diagnosis and ≥ 2 confirmatory diagnoses after the procedure

AAT = alpha$_1$-antitrypsin; ANA = antinuclear antibody; ATS = American Thoracic society; CF = cystic fibrosis; CHP = chronic hypersensitivity pneumonitis; COP = cryptogenic organizing pneumonia; CTD = connective tissue disease; DPLD = diffuse parenchymal lung disease; ERS = European Thoracic Society; GERD = gastroesophageal reflux disease; HARQ = Hull Airway Reflux Questionnaire Study; HRCT = high-resolution CT; ILD = interstitial lung disease; IPF = idiopathic pulmonary fibrosis; MCTD = mixed connective tissue disease; MII = multichannel intraluminal impedance; NSIP = nonspecific interstitial pneumonia; RF = rheumatoid factor; SLE = systemic lupus erythematosus; SPF = secondary pulmonary fibrosis; SSc = systemic sclerosis; UIP = usual interstitial pneumonia.

confounders.[47] The interpretation of these results is also limited by the heterogeneity across studies that we could not satisfactorily explain in subgroup and sensitivity analyses.

Our conclusions are similar to those of another systematic review of the literature published in 2011.[15] In this review, the inclusion criteria of the studies were not clearly defined. The review was not limited to IPF; it also considered interstitial lung disease associated with connective tissue disease. Uncontrolled studies were included, as were trials of antireflux therapy and surgery. No meta-analysis was attempted. Eleven of the 18 studies that met the inclusion criteria of our review became available after the publication of this review; five case-control studies were common to both reviews. The authors concluded that "a causal relationship between GERD and IPF cannot be established."

Even if a statistical association between GERD and IPF truly existed, causal association would yet have to be shown. From the nine causality criteria suggested by Hill,[48] only those of biological plausibility and coherence are met, since pathologic changes in lung fibrosis have been reported in an experimental rat model of chronic acid reflux esophagitis.[49] The seven other criteria are not satisfied. As to strength of association, the effect of GERD on IPF would be qualified as weak per current standards.[21] Heterogeneity across studies does not support consistency of association.

In humans, the evidence is not from experiments but only from observations. IPF is not specific to GERD because reflux has been involved in the pathogenesis of other respiratory disorders, including asthma, exacerbations of COPD, organizing pneumonia, and bronchiolitis obliterans.[50-53] The analogy between GERD and other environmental exposures such as pollution, smoke, or dust as "external stressors" and risk factors for IPF has been suggested,[4] although the role of these external exposures in the pathogenesis of IPF is only hypothetical. Whether a dose-response relationship exists (ie, whether increased exposure to gastroesophageal reflux increases the incidence and stimulates the progression of IPF) is unknown. In patients with systemic sclerosis, studies have suggested such a relationship.[25] However, the demonstration of a causal association between GERD and pulmonary fibrosis in systemic sclerosis is particularly difficult because both manifestations may only coexist without being causally related.[54] More importantly, evidence of temporality is also lacking. Whether GERD is the cause

TABLE 2] Potential Sources of Confounding and Selection Bias

Study	Smoking Status (% Current or Ex-Smokers)		SSc Among Control Subjects
	Case Subjects	Control Subjects	
D'Ovidio et al (2005)[31]	Not stated	Not stated	No patient
Embarak et al (2015)[32]	50%	35%	No patient
Fahim et al (2011)[33]	Not stated	Not stated	No patient
Garcia-Sancho et al (2011)[34]	58%	33.5%	No patient
Gavini et al (2015)[35]	54.7%	100%	No patient
Gribbin et al (2009)[36]	47%	45%	Not stated
Liang et al (2010)[37]	75%	30%	No patient
Lo et al (2015)[38]	Not stated	Not stated	No patient
Mays et al (1976)[39]	Not stated	Not stated	3.6% of CTD (n = 11) and 4.9% of immune-mediated pulmonary fibrosis (n = 15)
Oldham et al (2015)[14]	74%	91%	No patient
Qi et al (2015)[40]	88%	35%	No patient
Raghu et al (2006)[41]	Not stated	Not stated	No patient
Salvioli et al (2006)[42]	Not stated	Not stated	Not stated
Savarino et al (2013)[13]	55%	35%	No patient
Soares et al (2011)[43]	Not stated	Not stated	64% of CTD (n = 18)
Tobin et al (1998)[44]	Not stated[a]	Not stated[a]	No patient
Tossier et al (2016)[45]	78%	61%	19% of patients with scleroderma (n = 13) in the control group
Wu et al (2013)[46]	Not stated	Not stated	Not stated

See Table 1 legend for expansion of abbreviations.
[a]No patient in either group had smoked within 6 months of the pH study.

or the effect of IPF is a matter of debate. It has been hypothesized that pulmonary fibrosis results in altered respiratory mechanics that can subsequently induce gastroesophageal reflux.[55] Reduced lung compliance leads to increased negative intrapleural pressures,[56] which can be transmitted to other mediastinal structures, including the lower esophageal sphincter, to induce reflux.[55]

The most obvious limitation of the present systematic review and meta-analysis is that we used only aggregate data, as opposed to individual data. Consequently, subgroup and sensitivity analyses to achieve homogeneity between study groups were limited to the exclusion of studies with specific characteristics.[21] None of these secondary analyses satisfactorily explained the heterogeneity across studies, although in all analyses, GERD increased the risk of IPF. Two meta-regressions provided evidence of the confounding effect of smoking. First, after adjusting for the ratio of proportions of smokers and ex-smokers in case and control subjects, the association between GERD and IPF was not statistically significant. Second, we found a significant correlation between the ratio of proportions of smokers and ex-smokers in case and control subjects and the strength of the association between GERD and IPF reported in the individual studies. This finding emphasizes that the design of case-control studies is susceptible to bias from unmeasured confounders.

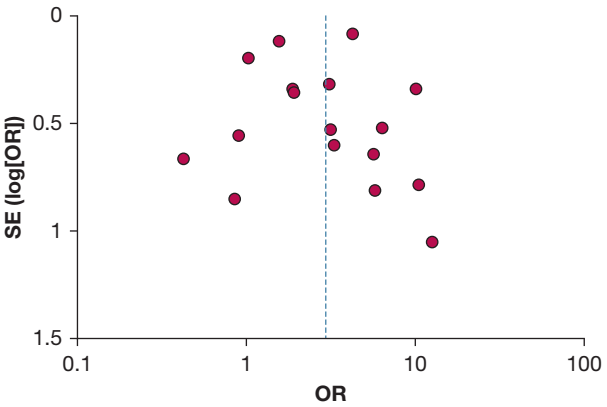

Figure 2 – *Study of publication bias: funnel plot including all 18 case-control studies that met the inclusion criteria of the meta-analysis.*

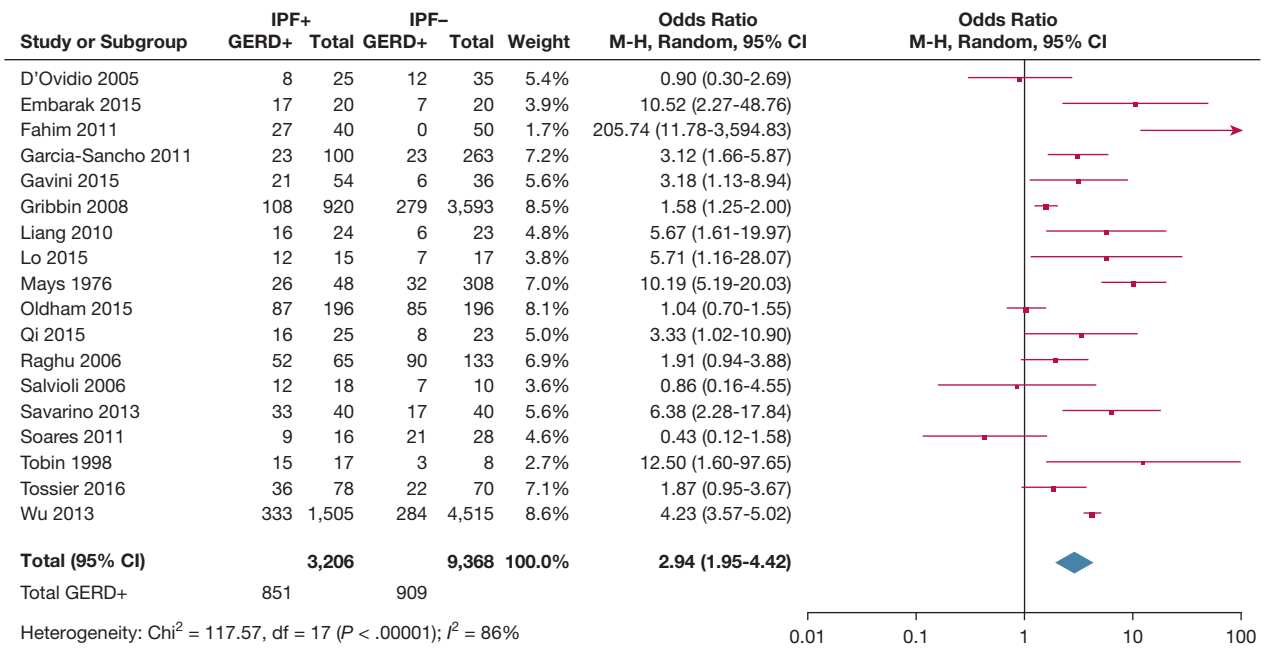

Figure 3 – *Primary meta-analysis: association between GERD and IPF. IPF = idiopathic pulmonary fibrosis. See Figure 1 legend for expansion of other abbreviation.*

We realize that studying the association of GERD and IPF is difficult. Cohort studies are higher in the hierarchy of designs when addressing issues of harm[47] and would therefore provide stronger evidence of an association between GERD and IPF if it truly existed. However, prospective cohort studies specifically addressing the issue of GERD and IPF are unlikely to be conducted in the future. For instance, we computed that a sample size of approximately 30,000 patients would be needed to show that GERD increases the risk of IPF in a 10-year cohort study with the following specifications: relative risk to be detected, 3.0; prevalence of GERD in the population, 25%[57]; incidence of IPF, nine per 100,000 per year[2]; power of study, 90%; and type I error, 0.05.[58] Retrospective cohort studies would need to rely on large databases with validated diagnoses of GERD and IPF. Randomized trials of antireflux therapy could also inform on the contribution of GERD to the

TABLE 3] Sensitivity Analyses

Study Characteristic	Studies	Sample Size		GERD (+)		OR	95% CI	Tests for Heterogeneity
		IPF	Control	IPF	Control			
Clinical studies only (ie, excluding studies from databases)	16	781	1,260	410	346	3.11	1.85-5.25	$P < .00001$ $I^2 = 78\%$
Including only studies from databases	2	2,425	8,108	441	563	2.59	0.99-6.82	$P < .00001$ $I^2 = 98\%$
Healthy control subjects	1	100	263	23	23	3.12	1.66-5.87	…
Control subjects with non-ILD pulmonary disease	5	355	404	180	195	1.61	1.00-2.59	$P = .17$ $I^2 = 37\%$
Control subjects with other ILD	11	326	272	200	105	2.80	1.45-5.40	$P = .002$ $I^2 = 65\%$
Diagnosis of GERD based on pH-metry	11	319	373	211	184	2.80	1.57-5.00	$P = .0007$ $I^2 = 59\%$
Objective method of IPF diagnosis	12	675	890	352	288	3.10	1.78-5.39	$P < .00001$ $I^2 = 76\%$
Equal proportion of smokers and ex-smokers in case and control subjects	1	920	3,593	108	279	1.58	1.25-2.00	…

See Table 1 legend for expansion of abbreviations.

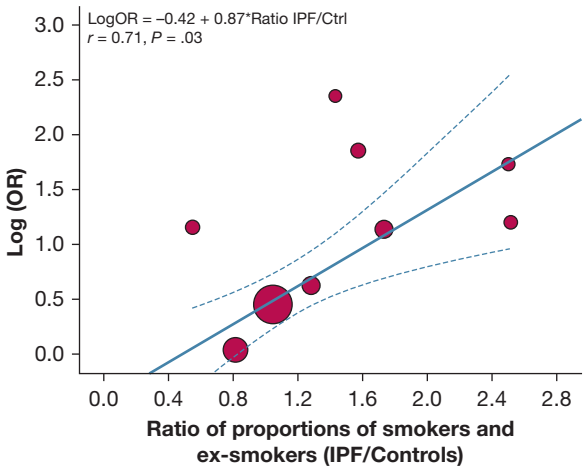

Figure 4 – *Meta-regression showing the relationship between the ratio of proportions of smokers and ex-smokers in case and control subjects and the measure of association between GERD and IPF reported in individual studies. See Figure 1 and 3 legends for expansion of abbreviations.*

pathogenesis of IPF. Now that nintedanib and pirfenidone (the only treatment options that can reduce disease progression)[59] are available, placebo-controlled trials in treatment-naive patients are unlikely to be conducted. However, future trials may investigate the effect of combinations of therapies (eg, pirfenidone + antacid therapy vs pirfenidone + placebo) to isolate the effect of antacid therapy without denying patients an effective treatment.

Conclusions

GERD and IPF may be related, but this association is most likely confounded, especially by smoking. This finding does not necessarily oppose the recommendation of the recent American Thoracic Society /European Thoracic Society /Japanese Respiratory Society/Latin American Thoracic Association clinical practice guideline on the treatment of IPF, which suggests that clinicians use regular antacid treatment for patients with IPF.[9] This recommendation places a high value on possible (and yet unproved) increases in lung function and survival and the low cost of therapy. The finding that antacid therapy might be associated with an increased risk of infection in those with advanced disease is of concern.[12] Further observational and interventional studies targeting GERD in IPF are needed.

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