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Original Article

Diabetes mellitus in idiopathic pulmonary fibrosis: a systematic review and meta-analysis

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Abstract: Some contradictory results about the relationship between diabetes mellitus (DM) and idiopathic pulmonary fibrosis (IPF) have been reported. This systematic review aims to estimate the relationship between IPF and DM from the perspective of evidence-based medicine and evaluate the value of DM for the etiology of IPF. Studies published prior to February 2016 in PubMed, Embase, The Cochrane Library and the relevant professional association website were reviewed for relevant studies. Summary odds ratio (OR) and 95% confidence intervals (CI) were performed to evaluate the relationship between DM and the risk of IPF. The sources of heterogeneity and the effect of potential confounding were explored using sensitivity analysis and subgroup analysis. The possible publication bias was evaluated by Begg's test and Egger's test. The search yielded 17 studies for estimating the prevalence of DM in IPF patients, which 9 studies suitable for meta-analysis. The prevalence of DM in IPF patients was 13.9%, 23.67%, 25.23% in Europe, Asia and North America, respectively. DM was significantly associated with IPF and increased the risk of IPF (OR, 1.696; 95% CI, 1.34 to 2.14). Significant publication bias was not found. DM is prevalent in IPF patients. The prevalence of diabetes in IPF patients was higher than the ordinary population. DM constitutes a risk factor for IPF, there was an increase in the odds for developing IPF among diabetics. DM has significant etiologic value for IPF and is expected to be one of the causes of IPF.

Keywords: Idiopathic pulmonary fibrosis, diabetes mellitus, etiology, odds ratio, meta-analysis

Introduction

Studies shown lung is one of the target organs of diabetes mellitus (DM) [1, 2]. van den Borst et al. [3] found diabetes related with restrictive lung function abnormalities. Moreover restrictive lung dysfunction is one of the characteristics of pulmonary fibrosis. Idiopathic pulmonary fibrosis (IPF) is a chronic, progressive, diffuse interstitial lung disease with poor prognosis. The survival time of IPF is only 2.5-3.0 years after initial diagnosis. It kills increasing numbers of individuals each year [4]. But the etiology of IPF remains poorly understood. DM is a very common disease comorbid with IPF. A possible association between IPF and DM has been reported [5]. DM may play a role in the etiology of IPF [6, 7]. It may be one of the etiologies of IPF [8]. In 2011, an official diagnosis and management guidelines for IPF state diabetes is one of the risk factors of IPF, but there is just one reference study related to DM in the guideline [9]. In addition, the reported prevalence of diabetes in IPF patients was highly variable between different studies and the frequency ranges from 9.67% to 56% [7, 10]. Some contradictory results have also been reported. Enomoto et al. [5] found DM may increase risk for IPF, but Miyake et al. [11] found no association with diabetes in IPF patients. To investigate the relationship between DM and IPF further, from the perspective of evidence-based medicine, we performed a systematic analysis on the basis of several related retrospective studies data to evaluate the role of DM for IPF.

Material and methods

Data sources and searches

We followed the guidelines developed by the Meta-analysis of Observational Studies in Epidemiology (MOOSE) group [12]. We conducted a systematic search in PubMed, Embase

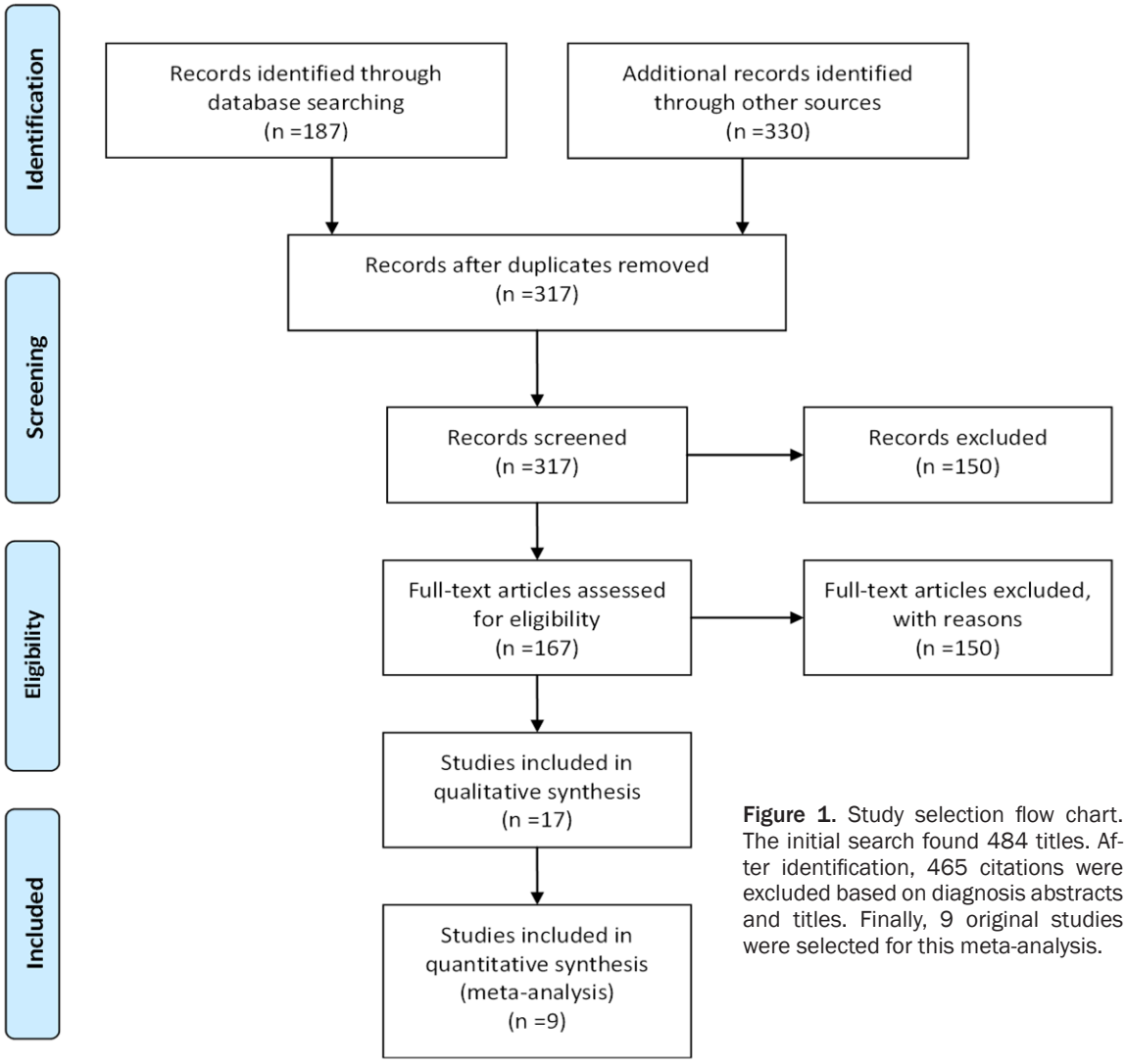

Figure 1. Study selection flow chart. The initial search found 484 titles. After identification, 465 citations were excluded based on diagnosis abstracts and titles. Finally, 9 original studies were selected for this meta-analysis.

and The Cochrane Library, by the latest of literature retrieval in February 2016. We also searched related articles by the relevant professional association website including the American Thoracic Society, American College of Chest Physicians, American Diabetes Association, European Respiratory Society, European Association for the Study of Diabetes and International Diabetes Federation. There was no language restriction. In PubMed, Embase and The Cochrane Library, we using a combination of subject terms (MeSH or Emtree terms) and free text words related to IPF, DM, and observational studies. For other related articles, ([idiopathic pulmonary fibrosis] and [diabetes]) were used or were hand searched. The electronic search was supplemented by hand searching the reference lists of relevant articles.

The search results were independently screened by two reviewers (Jian He, Hailong Zhu). According to inclusion and exclusion criteria, two reviewers separately selected the potentially relevant articles based on the title and abstract of these articles. One of the reviewers was blinded for journal, authors, publication language, and year. Consensus was reached between two reviewers on the selected articles. The selected articles will be further searched for its full text. Finally, the full text of articles was assessed by the two reviewers and reached an agreement. Any different opinions were being resolved by consensus between the reviewers. The following criteria were established for inclusion: (1) case-control study or cohort study, containing two groups, a IPF group as well as a control group; (2) the time period of the study is definite; (3) patients had IPF or DM

Table 1. Baseline characteristics of the studies included in the systematic review

Study/Year	Data setting database/hospital	Period of enrollment	Inclusive definition of IPF	Study design	Characteristics of IPF			Characteristics of Control		
					IPF (n)	Mean age, yr	Male (n)	Control (n)	Mean age, yr	Male (n)
Tatsuji Enomoto et al. [9]/2003	Hospital	1995-2000	ATS/ERS criteria	Retrospective Case-control	52	65.4 (7.8)	41	184	65.6 (8.62)	135
Yoshihiro MIYAKE et al. [11]/2005	Hospital	2001.6.1-2001.11.30	ATS/ERS criteria	Prospective Case-control	104	NR	94	60	NR	55
Jonathan Gribbin et al. [7]/2009	Database	1991-2003	Synonym of IPF to ATS/ERS criteria	Retrospective Case-control	920	71.4	568	3593	71.4	2228
Ma Cecilia et al. [6]/2010	Hospital	2000-2005	ATS/ERS criteria	Retrospective Case-control	97	62.6 (11.0)	71	560	62.3 (12.2)	347
Cecilia Garcı´a-Sancho et al. [27]/2011	Hospital	2007-2009	ATS/ERS criteria	Retrospective Case-control	100	67.8 (9.5)	71	263	67.9 (9.1)	184
Harold R Collard et al. [28]/2012	Database	2001.1.1-2008.9.30	Synonym of IPF to ATS/ERS criteria	Retrospective cohort	9286	74 (9.2)	5072	9286	74 (9.2)	5072
Ning Wu et al. [29]/2013	Database	2006-2011	Synonym of IPF to ATS/ERS criteria	Retrospective cohort	1505	71.0	811	4515	71.0	2434
Won-Young Kim et al. [30]/2015	Hospital and database	2004-2010	ATS/ERS criteria	Retrospective Case-control	460	64.6 (8.0)	364	1925	63.9 (8.0)	1508
William Dalleywater et al. [31]/2015	Database	2000.1-2011.9	Synonym of IPF to ATS/ERS criteria	Retrospective Case-control	3211	75.7 (9.8)	2052	12307	NR	NR

ATS: American Thoracic Society; ERS: European Respiratory Society; IPF: Idiopathic pulmonary fibrosis; NR: Not report; yr: Year.

Table 2. Characteristics of patients with ipf with diabetes mellitus

Study/Year	Continent/ Country	IPF (n)	DM (n)	Diabetes (%)	Control (n)	DM (n)	Diabetes (%)	Included in the meta-analysis
Tatsuji Enomoto et al. [5]/2003	Asia/Nippon	52	17	32.69%	184	21	11.41%	Yes
Yoshihiro MIYAKE et al. [11]/2005	Asia/Nippon	104	13	12.50%	60	7	11.67%	Yes
Jinkyeong Park et al. [32]/2010	Asia/Korea	324	77	23.80%	NR	NR	NR	No
Yu Jin Kim et al. [33]/2012	Asia/Korea	299	53	17.80%	NR	NR	NR	No
Won-Young Kim et al. [30]/2015	Asia/Korea	460	90	19.57%	1925	300	15.58%	Yes
Nahid A Sherbini et al. [10]/2014	Asia/Saudi Arabia	134	75	56.00%	NR	NR	NR	No
Asia		1373	325	23.67%				
Jonathan Gribbin et al. [7]/2009	Europe/UK	920	89	9.67%	3593	275	7.65%	Yes
H Nunes et al. [34]/2009	Europe/French	70	13	18.00%	NR	NR	NR	No
Charlotte Hyldgaard et al. [35]/2014	Europe/Danish	121	21	17.36%	NR	NR	NR	No
Juergen Behr et al. [36]/2015	Europe/Germany	261	54	20.70%	NR	NR	NR	No
Willam Dalleywater et al. [31]/2015	Europe/UK	3211	450	14.01%	12307	1481	12.03%	Yes
Wim Wuyts et al. [37]/2015	European/NR	790	120	15.20%	NR	NR	NR	No
European		5373	747	13.90%				
Ma Cecilia et al. [6]/2010	North America/Mexico	97	11	11.34%	560	16	2.86%	Yes
Cecilia Garcı´a-Sancho et al. [27]/2011	North America/Mexico	100	30	30.00%	263	50	19.01%	Yes
Harold R Collard et al. [28]/2012	North America/US	9286	2329	25.10%	9286	1737	18.71%	Yes
Ning Wu et al. [29]/2013	North America/US	1505	399	26.51%	4515	560	12.40%	Yes
Yanni Yu et al. [38]/2014	North America/US	67	20	30.00%	NR	NR	NR	No
North America		11055	2789	25.23%				
Total		17801	3861	21.70%	32693	4447	13.60%	

DM: Diabetes mellitus; IPF: Idiopathic pulmonary fibrosis; NR: Not report; UK: The United Kingdom; US: The United States.

confirmed by specific diagnostic criteria; (4) the completeness of the data, sufficient information to calculate the prevalence of diabetes of these groups; (5) availability of absolute numbers of IPF with DM, IPF without DM, control with DM, control without DM to allow reconstruction of the 2×2 table. Exclusion criteria: (1) overlapping data; (2) there were a study design flaws, poor quality; (3) data is not complete or cannot be modified to provide or for conversion to OR and 95% CI.

Quality assessment and data extraction

The quality of including studies was evaluated using the Newcastle-Ottawa Scale (NOS) [13]. Studies were examined by selection, comparability, exposure/outcome and graded on a star scoring scale. Higher scores represent higher quality. IPF patients and controls were classified into two groups: those with DM and those without DM. The prevalence of DM means that it is given as a percentage of the normal value as expected for a healthy subject with the same age, sex according to local references. For each study, information was collected on: (1) the use of a valid reference standard in accordance with international IPF guidelines; (2) the design of the study (prospective or retrospective, hospital or database); (3) the country, published year and time interval, for calculate between-study differences in continent and time; (4) the full description of the inclusion and exclusion criteria.

Data synthesis and analysis

Categorical variables from individual studies were presented as a percentage value (n/N), and continuous variables were presented as mean values. For each prevalence of diabetes, pooled estimates were calculated for all studies. The natural log of the odds ratio (OR) and its 95% confidence interval (CI) were used to measure the pooled effect size of all the studies. The amount of heterogeneity across studies was assessed using the Chi-square (χ^2 significant levels at $P \leq 0.05$) and the I^2 test. The criteria for the fixed-effect model was determined by significant heterogeneity with an I^2 statistic value $\leq 50\%$ or $P > 0.05$; Random-effect model was determined by the opposite ($I^2 > 50\%$ or $P \leq 0.05$) [14]. Sources of heterogeneity among different studies were systematically analyzed by sensitivity analysis and subgroup analysis [15]. Assessment of publication bias was performed with the Egger's test and the Begg's funnel plot [16, 17]. *P* values < 0.05

Table 3. Methodological quality of studies included in the final analysis, based on the Newcastle-Ottawa scale for assessing the quality of case-control studies

Case-control	Selection			Comparability		Exposure			
Studies (n = 7)	Adequate definition of cases	Representativeness of cases	Selection of controls	Definition of controls	Control for important factor or additional factor	Ascertainment of exposure	Same method of ascertainment for subjects	Non-response rate	Total (0-9)
Tatsuji Enomoto et al. [5]/2003	★	★	★	★	★★	★	★		8
Yoshihiro MIYAKE et al. [11]/2005	★	★		★	★★	★	★		7
Jonathan Gribbin et al. [7]/2009	★	★		★	★★	★	★		7
Ma Cecilia et al. [6]/2010	★	★		★	★★	★	★		7
Cecilia Garcı´a-Sancho et al. [27]/2011	★	★	★	★	★★	★	★	★	9
Won-Young Kim et al. [30]/2015	★	★	★	★	★★	★	★		8
William Dalleywater et al. [31]/2015		★	★	★	★★		★	★	7

Table 4. Methodological quality of studies included in the final analysis, based on the Newcastle-Ottawa scale for assessing the quality of cohort studies

Cohort study	Selection				Comparability	Outcome			
Studies (n = 2)	Representativeness of the exposed cohort	Selection of the non exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	Comparability of cohorts on the basis of the design or analysis	Assessment of outcome	Was follow-up long enough for outcomes to occur	Adequacy of follow up of cohorts	Total (0-9)
Harold R Collard et al. [28]/2012		★	★	★	★★	★	★	★	8
Ning Wu et al. [29]/2013	★	★	★	★	★		★	★	7

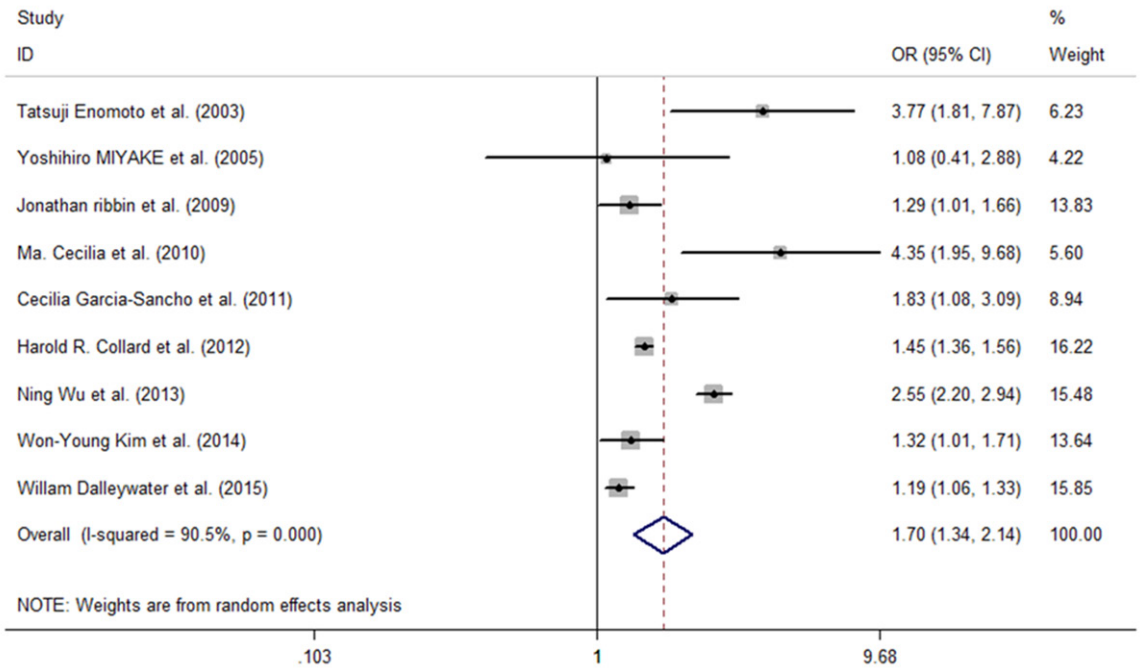

Figure 2. Forest plot of diabetes mellitus and idiopathic pulmonary fibrosis in the meta-analysis. Random-effect model was used to calculate the pooled effect size for OR (chi-squared χ^2 = 84.19, [degree of freedom, df = 8], I^2 = 90.5%, P = 0.000; and Z = 4.44, P = 0.000). The random pooled effect size (OR) for idiopathic pulmonary fibrosis due to diabetes mellitus was 1.696, (95% CI, 1.34 to 2.14).

were considered to be statistically significant. We used Stata version 12 (Stata Corp LP; College Station, TX) for meta-analysis.

Results

Search findings and study characteristics

A flowchart of study selection is presented in **Figure 1**. A total of 517 articles were found after the initial literature search. Briefly, the PubMed, EMBASE and The Cochrane Library yielded 155, 21, 11 hits respectively. Searches in the relevant professional association website added 330 potentially relevant hits. 167 articles were excluded from the meta-analysis because of overlapping data. After identification based on abstracts and titles, 150 citations were excluded because of failure to meet the inclusion criteria. 150 articles were discarded for not provide the prevalence of DM. Finally, 17 original studies were selected for inclusion in the meta-analysis. Among all the included literatures, there were 8 studies only had IPF group, no control group, and 9 studies had IPF and control group. Data from the 17 original studies were sampled across 10 different countries in 3 continents. The characteristics of included studies are presented in **Tables 1** and **2**. Collectively, 15735 patients and 32693 control subjects were extracted from 9 studies which met the inclusion criteria (**Table 1**). 17 studies, including 17801 IPF patients, were used to evaluate the prevalence of DM in IPF patients (**Table 2**). Detailed results of NOS for the 9 studies are available in **Tables 3** and **4**. Scores were from 7 to 9 and match the needs of meta-analysis.

The prevalence of diabetes in patients with IPF

In the 17 studies, the prevalence of DM ranged from 9.67% to 56% for IPF patients. The lowest prevalence was in UK and the highest was in Saudi Arabia. By the retrieved literature, the pooled prevalence of DM was 21.70% for IPF patients and 13.60% for control subjects (**Table 2**). The value of $P = 0.00 < 0.05$. There were statistical differences between the two groups. The prevalence of DM for IPF patients is higher than the control group. IPF patients were divided by the continents, the prevalence of DM for patients with IPF were 13.9%, 23.67%, 25.23% in Europe, Asia, and North America respectively (**Table 2**). The prevalence of DM for patients with IPF was high in Asia and North America

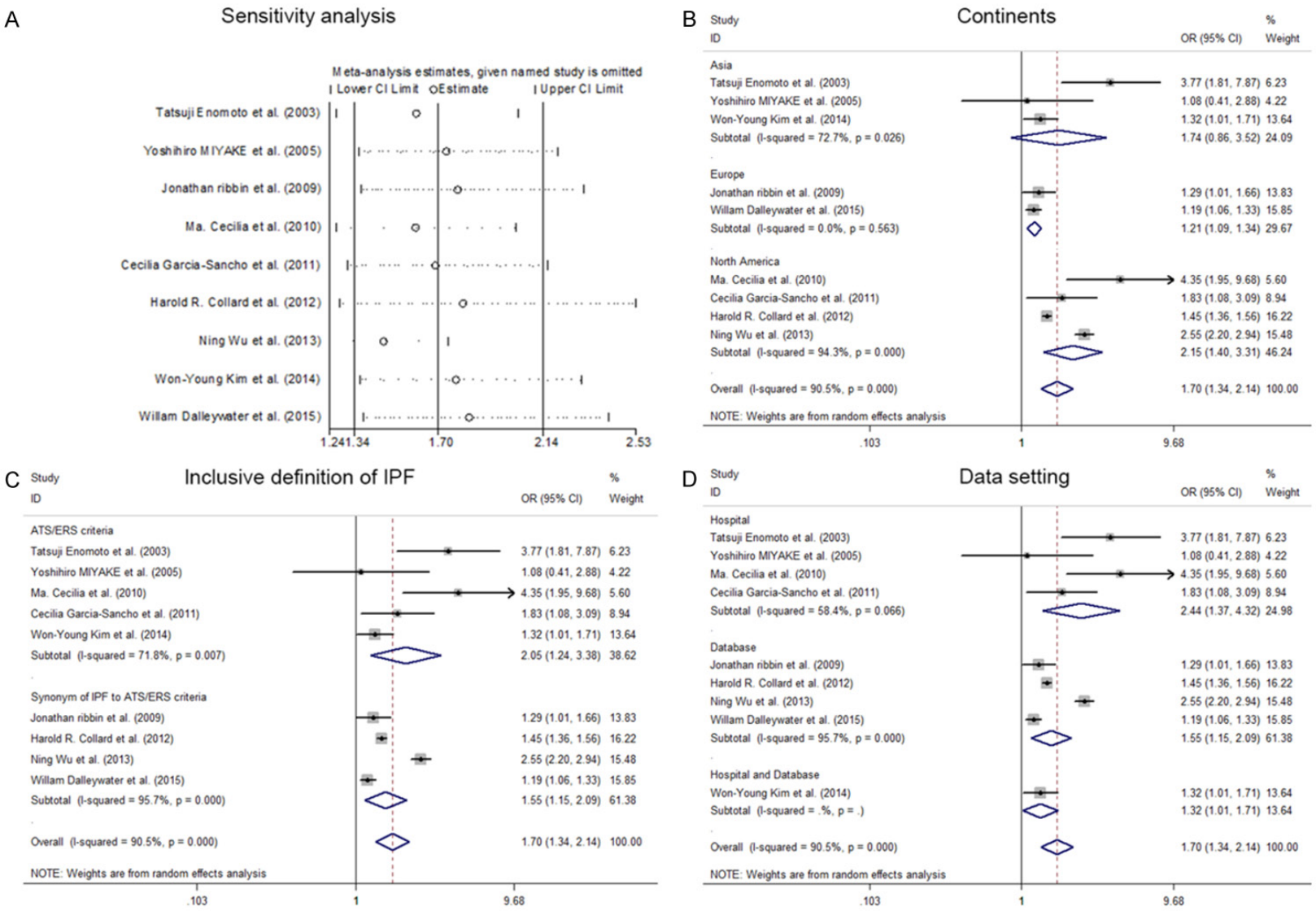

Figure 3. A. Forest plot of sensitivity analysis of the 9 original studies in the meta-analysis. The minimum value of lower CI was 1.24, the maximum value of the upper CI was 2.53. The estimate OR and 95% CI did not change significantly after the individual research is removed. B. Forest plots of subgroup for different continents in the meta-analysis. Random effect models were used to calculate the pooled effect size for Asia, Europe, North America and the OR was 1.740 (95% CI:

0.860-3.524) and 1.208 (95% CI: 1.089-1.340), 2.150 (1.397-3.311), respectively. C. Forest plots of subgroup for the inclusive definition of IPF in the meta-analysis. Random effect models were used to calculate the pooled effect size for both definition of ATS/ERS criteria and synonym of IPF to ATS/ERS criteria, and the OR was 2.050 (95% CI: 1.244-3.379) and 1.550 (95% CI: 1.150-2.089), respectively. D. Forest plots of subgroup for different data setting in the meta-analysis. Random effect models were used to calculate the pooled effect size for data collected from the hospital, and data collected from the database and the OR was 2.435 (95% CI: 1.372-4.321) and 1.550 (95% CI: 1.150-2.089), respectively. Because the degree of freedom is too small, the data collected from the hospital and database not can be calculated.

Table 5. Studies included in the meta-analysis in different groups between diabetes mellitus and idiopathic pulmonary fibrosis

Groups	Reference	Amount	Pooled estimates OR (95% CI)*	Heterogeneity			Test for overall effect	
				χ^2	*p* value	I^2 (%)	Z	*p* value
Continent								
Asia	[4, 7, 18]	3	1.74 (0.86-3.52)	7.33	0.026	72.7	1.54	0.124
European	[2, 15]	2	1.21 (1.09-1.34)	0.33	0.563	0.0	3.58	0.000
North America	[10-13]	4	2.15 (1.40-3.31)	52.75	0.000	94.3	3.48	0.001
Inclusive definition of IPF								
ATS/ERS criteria	[4, 7, 10, 11, 14]	5	2.05 (1.24-3.38)	14.19	0.007	71.8	2.82	0.005
Synonym of IPF to ATS/ERS criteria	[2, 12, 13, 15]	4	1.55 (1.15-2.09)	69.44	0.000	95.7	2.87	0.000
Data setting								
Hospital	[4, 7, 10, 11]	4	2.44 (1.37-4.32)	7.20	0.066	58.4	3.04	0.002
Database	[2, 12, 13, 15]	4	1.55 (1.15-2.09)	69.44	0.000	95.7	2.87	0.004
Hospital and database	[14]	1	1.32 (1.01-1.71)	-	-	-	-	-

*: 95% CI: 95% confidence interval.

than in Europe, P = 0.00 < 0.05. There was significant difference of the pooled prevalence of DM for IPF patients between Asia and North America, P = 0.002 < 0.05. The prevalence was high in North America than Asia.

Diabetes and IPF

The OR of DM for IPF by random-effect model was 1.696, (95% CI, 1.34 to 2.14) (**Figure 2**). Sensitivity analysis results show that the estimate OR and 95% CI did not change significantly after individual research is removed (**Figure 3A**). Countries and continents, inclusive definition of IPF and data setting were evaluated as potential sources of heterogeneity. The effect of these potential confounding was explored using subgroup analysis (**Figure 3B-D**; **Table 5**). The results of the subgroup analysis show that there was no heterogeneity between the 2 studies conducted in Europe (I^2 = 0.0%) and there was still a large heterogeneity in the rest of the subgroups (I^2 > 50%).

Publication bias

The possible publication bias was evaluated with a funnel plot. Scattered points were symmetrical in the funnel plot (**Figure 4A**). The funnel plot did not reveal a significant difference from Begg's test results (Z = 1.67 < 1.96, P > 0.05) (**Figure 4B**). Our data acquired from Egger's test (P = 0.454 > 0.05, 95% CI = -2.65~5.32) also suggested that the publication bias on the relationship between DM and IPF was not detected (**Figure 4C**).

Discussion

The incidence of IPF is increasing in recent years, but the cause of the disease is not yet clear. Diabetes is known to affect various organ systems, such as the cardiovascular system, kidneys, and retina [18]. Tissue fibrosis can be found in diabetic nephropathy and diabetic cardiomyopathy. So we can think about that whether diabetes can cause pulmonary fibrosis. In recent years, a growing number of studies indicate that lung is another important target organ of DM [1-3, 19, 20]. This means that pulmonary fibrosis may be one of the complications of DM, while the correlation between DM and IPF is relatively small. To date, DM has been associated with IPF in a number of case-control studies. The association suggests a potential etiologic role of DM in IPF. However, some contradictory results have also been reported. Since most of these studies were small-scale, case-control study, it has many potential limitations, including selection bias, recall bias and mis-

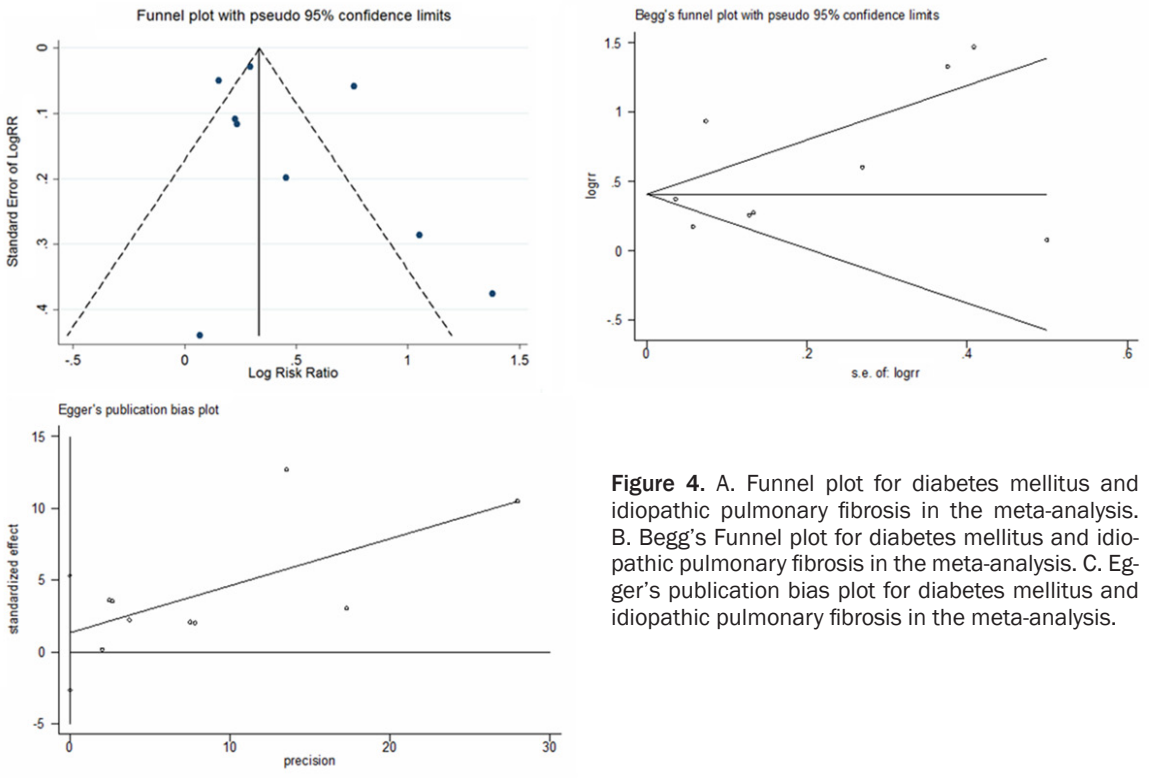

Figure 4. A. Funnel plot for diabetes mellitus and idiopathic pulmonary fibrosis in the meta-analysis. B. Begg's Funnel plot for diabetes mellitus and idiopathic pulmonary fibrosis in the meta-analysis. C. Egger's publication bias plot for diabetes mellitus and idiopathic pulmonary fibrosis in the meta-analysis.

classification of IPF. The statistical power available also would be limited. So, it is important to increase sample size and remove the biases using the meta-analysis method. To our knowledge, this is the only time that a systematic review and meta-analysis have been performed to determine the etiologic value of DM for IPF.

In the results, there was heterogeneity among different studies, which may be caused by some reasons. The heterogeneity may be partially related to the utilization of different control groups and different size samples. Besides, the case number of this meta-analysis was very large and the studies were involved in many countries. The records may have differed in quality of medical record in different countries. In addition, the variation in official definition [21, 22] would be a contributory factor in explaining the heterogeneity and may give rise to a dilution of the estimate of the OR.

It is unclear why DM increases the risk of IPF. The pathogenic mechanisms implicated in this association remain not to be elucidated. Hyperglycemia might influence the severity of bleomycin-induced lung fibrosis in mice. Usuki J and coworkers found that the morphological grade of fibrosis was more severe in streptozotocin-induced diabetic mice than that in mice treated with bleomycin alone [23]. Prolonged incubation of proteins with glucose leads to advanced glycation end products [24]. It is reported that advanced glycation end products-modified proteins accumulated in lung samples from IPF patients, which may be involved in the pathogenesis of IPF [25]. Further studies are needed to confirm the putative pathogenic mechanisms of IPF with DM.

As giant cell interstitial pneumonia has been classified as idiopathic interstitial pneumonia, and after being confirmed as hard metal pneumoconiosis [21]. So, idiopathic pulmonary fibrosis may be an inappropriate use of the name. A number of research results have been made to remove "idiopathic" from the IPF [26]. The main strength of this meta-analysis is the large number of cases. The association between IPF and DM is consistent with the hypothesis that DM is an important risk factor for IPF. Its causal relationship needs to further prove. For example, a prospective cohort study is needed to establish the exposure of diabetes before the occurrence of pulmonary fibrosis and the precise dose-response relationship. Because of the current

understanding of IPF emphasize its "idiopathic". Some potential etiologies were neglected by some scholars. Therefore, except for diabetes, the potential etiology and risk factors of IPF need to be emphasized. It will help to improve the prevention and treatment of IPF.

In the official ATS/ERS/JRS/ALAT statement: idiopathic pulmonary fibrosis: evidence-based guidelines for diagnosis and management, there is little information about the association of IPF and DM [5]. DM increases the risk of IPF. This meta-analysis documents such a relationship from the perspective of evidence-based medicine. This meta-analysis provides a evidence for the diagnosis and management guidelines of IPF. On the basis of meta-analysis and experimental studies, we speculate that DM was a cause of IPF, which is the etiologic value of DM in IPF. The fact that the association between diabetes and IPF had not being widely recognized in clinical practice. The results highlight the importance of DM in IPF. Therefore, in the absence of efficient treatment options for the majority IPF patients, the early diagnosis and treatment of DM and their risk factors may slow the progression and play a role in the effort to improve the prognosis of IPF patients.

Limitations

The data of most studies were collected retrospectively which means that recall may be a source of bias. People with diabetes may receive more medical attention than those without. We cannot exclude this as a source of bias.

Conclusion

In this meta-analysis exposure data were collected and further evidences were provided, the results showed that DM is prevalent in IPF patients. In Europe, Asia and North America, the prevalence of diabetes in patients with IPF increased in turn. The prevalence of diabetes in patients with IPF was higher than the control population. DM was significantly associated with IPF. It constitutes a risk factor for IPF. There was an increase in the odds for developing IPF among diabetics. In summary, DM has significant etiologic value for IPF. Diabetes is likely to be one of the causes of IPF. Because there was still no effective treatment for IPF, looking for the cause of IPF actively will play an important role in the prevention and treatment of IPF. Further prospective studies are needed to determine whether treatments for DM can slow disease progression and fully clarify the impact of DM on prognosis in IPF patients. Additionally, we hope that the results can help the clinicians alert to the possibility of DM in people diagnosed with IPF.

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Disclosure of conflict of interest

None.

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