REVIEW ARTICLE

Relationships of MMP-9 and TIMP-1 proteins with chronic obstructive pulmonary disease risk: A systematic review and meta-analysis

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Background: We performed this meta-analysis in order to collect all the relevant studies to clarify the correlations of matrix metalloproteinase-9 (MMP-9) and tissue inhibitor of metalloproteinase-1 (TIMP-1) with chronic obstructive pulmonary disease (COPD). **Materials and Methods:** After a literature search in electronic databases, pertinent case-control studies investigating the correlations of MMP-9 and TIMP-1 protein expressions within a COPD setting were enrolled based on our strict inclusion and exclusion criteria. We used key words such as "chronic obstructive pulmonary disease," "COPD" or "COAD" or "chronic obstructive airway disease" and "matrix metalloproteinases" or "MMPs" to make a searching strategy in this study. STATA software (version 12.0, Stata Corporation, College Station, TX, USA) was utilized for statistical analysis. **Results:** A total of 20 studies were enrolled into this meta-analysis including 923 COPD patients and 641 healthy controls. The findings of this meta-analysis revealed that serum expression levels of MMP-9 and TIMP-1 protein in COPD patients were higher than those of healthy controls (MMP-9: SMD = 1.44, 95%CI = 0.85 ~ 2.04, $P < 0.001$; TIMP-1: SMD = 3.53, 95% CI = 2.31 ~ 4.75, $P < 0.001$). Subgroup analysis based on ethnicity revealed that both Caucasians and Asian COPD patients exhibited higher MMP-9 and TIMP-1 serum protein levels than healthy controls (MMP-9: SMD = 0.81, 95%CI = 0.15~1.48, $P = 0.016$; TIMP-1: SMD = 4.43, 95%CI = 1.98 ~ 6.87, $P = 0.016$) and in Caucasians (MMP-9: SMD = 2.30, 95%CI = 1.21 ~ 3.38, $P < 0.001$; TIMP-1: SMD = 2.86, 95%CI = 1.47 ~ 4.24, $P < 0.001$). **Conclusion:** The result of this meta-analysis indicates that elevated levels of MMP-9 and TIMP-1 proteins may be correlated with the pathogenesis of COPD, and the two proteins may represent important biological markers for the early diagnosis of COPD.

Key words: Chronic obstructive pulmonary disease, matrix metalloproteinase, matrix metalloproteinase-9, meta-analysis, tissue inhibitor of metalloproteinase, tissue inhibitor of metalloproteinase-1, pathogenesis,

How to cite this article: Li Y, Lu Y, Zhao Z, Wang J, Li J, Wang W, Li S, Song L. Relationships of MMP-9 and TIMP-1 proteins with chronic obstructive pulmonary disease risk: A systematic review and meta-analysis. J Res Med Sci 2016;21:12.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD), a type of obstructive lung disease, is characterized by chronic inflammation throughout the parenchyma, airways and pulmonary vasculature.[1,2] COPD is ranked as the fourth leading cause of death and effects more than 200 million people worldwide.[3] According to the statistics, the number of deaths from COPD between 1990 and 2010 has decreased slightly from 3.1 million to 2.9 million.[4] In the United States, there has been a pronounced increase in the mortality rate in women compared with a modest increase in men.[5] Host factors and environmental exposures are the major risk factors for COPD, and this disease frequently results from an interaction between these factors.[6,7] Host factors, such as a rare hereditary deficiency of alpha 1-antitrypsin, and environmental factors such as tobacco smoke, indoor/outdoor air pollution and heavy exposure to occupational dusts and chemicals contribute to COPD pathogenesis.[8,9] It has been recognized that patients with COPD usually suffer from concurrent comorbidities, such as diabetes, lung cancer, cardiovascular and cerebrovascular diseases.[10] Numerous studies have indicated that

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Received: 31-03-2015; **Revised:** 18-08-2015; **Accepted:** 20-01-2016

COPD can be prevented by cessation of smoking and improving indoor and outdoor air quality.[11-13] COPD patients also have treatment options based on the state of the disease, including vaccinations, rehabilitation, and inhaled bronchodilators and steroids, long-term oxygen therapy as well as lung transplantation.[14-16] Recently, study has shown that matrix metalloproteinase (MMPs) and their inhibitors play a central role in lung remodeling in COPD.[17]

MMPs refer to a family of over twenty conserved and zinc-dependent endopeptidases, which modulates the cell proliferation, differentiation due to their enzymatic activities in turnover and degradation of extracellular matrix (ECM).[18] MMP-9 is one of the most important members of MMPs family, and is variously known as 92kDa type IV collagenase, 92 kDa gelatinase or gelatinase B (GELB).[19,20] It is well established that MMP-9, as an elastolytic endopeptidase produced in large quantities by activated macrophages and inflammatory cells, which may play a role in the development of human pulmonary emphysema.[21] MMP-9 is overexpressed in many solid tumors and it enhances the ability of tumor cell invasion and metastasis.[22] Tissue inhibitor of metalloproteinases consists of a family of 4 secreted proteins (TIMP 1-4), which bind MMPs in a ratio of 1: 1 manner to inhibit their proteolytic activity.[23,24] TIMP-1 is as a natural inhibitor of MMPs and is a glycoprotein expressed in multiple tissues in many organisms.[25] In addition to its inhibitory role, TIMP-1 is able to promote cell proliferation and inhibit apoptosis as well as regulate cell growth in a wide range of cell types.[26] Accumulated evidence suggested that MMP-9 is inhibited by TIMP-1 and an imbalance in the MMP-9/TIMP-1 ratio could be involved in COPD pathogenesis.[27] However, this theory is contradicted by other studies.[28,29] We conducted a meta-analysis based study to investigate the correlations between MMP-9 and TIMP-1 protein expressions with COPD.

MATERIALS AND METHODS

Literature search

Literatures were comprehensively screened for studies that explored the correlations of MMP-9 and TIMP-1 protein expression with COPD by utilizing the following electronic databases: PubMed, EBSCO, Ovid, Medline, Springerlink, Wiley Online Library, Web of Science, Chinese Biomedical Database, the Chinese Journal Full-Text Database, China National Knowledge Infrastructure (CNKI), the WANFANG Database and the Weipu Journal Database (since inception to October 1st, 2014). Additional pertinent literatures were obtained by manual search. Likewise, the combination of key words and free words was applied in the process of collecting literature with a highly efficient and sensitive searching strategy: ("pulmonary disease, chronic obstructive" or "chronic respiratory diseottom" or "COPD" or "chronic obstructive pulmonary disease" or "COAD" or "chronic obstructive airway disease" or "chronic obstructive lung disease" or "airflow obstruction, chronic" or "pulmonary emphysema") and ("matrix metalloproteinases" or "metalloproteinases, matrix" or "MMPs" or "MMP").

Inclusion and exclusion criteria

The following inclusion criteria were applied to published articles for the present studies:

1. Study types should be case-control study concerning the correlation of MMP-9 and TIMP-1 protein expression with COPD;
2. Subjects should include COPD patients and healthy controls;
3. Detection method should be enzyme-linked immunosorbent assay (ELISA);
4. End outcomes should include the expressions of MMP-9 and TIMP-1 protein in serum.

Only the studies with the largest sample sizes or latest study were considered when the extracted studies were published by the same authors, using the same case materials. The corresponding exclusion criteria were:

1. Reviews, letters, non-human research and literature duplications;
2. Studies unrelated to the research theme;
3. Lack of document data integrity;
4. Non-English and non-Chinese studies.

Data extraction and quality assessment

Two investigators independently carried out data extraction on the basis of a predefined form. The main data information including first author, publication time, country, language, ethnicity, disease type, detection method, the number of cases and controls, age, gender, sample source, sample size, expressions of MMP-9 and TIMP-1 protein were displayed in the current meta-analysis. Any disputes appeared in the process of data extraction was resolved through discussion with the multiple researchers. The quality of enrolled studies was assessed by critical appraisal skill program (CASP) criteria by two independent investigators (http://www.casp-uk.net/). The CASP criteria are scored as follows: The study address a clearly focused issue (CASP01); the research problem is appropriate and the research design answers the research problem (CASP02); the cases recruited in an accep way (CASP03); the controls selected in an accep way (CASP04); the measurement for exposure factors is accurate to minimize bias (CASP05); the study controls other important confounding factors (CASP06); the research result is complete (CASP07); the research result is precise (CASP08); the research result is reliable (CASP09); the research result is applicable to the local population (CASP10); the research result fit with other available evidence (CASP11).

Statistical analysis

The STATA statistical software (Version 12.0, Stata Corporation, College Station, TX, USA) was used in the current meta-analysis. The correlations of MMP-9 and TIMP-1 protein expressions with COPD were estimated after the calculation of the summary standard mean difference (SMD) with 95% confidence interval (95%CI). *Z* test was employed to detect the significance of overall effect size.[30] Heterogeneity among studies was evaluated by the Cochran's Q-statistic ($P < 0.05$ was considered significant) and I^2 test (0%, no heterogeneity; 100%, maximal heterogeneity).[31,32] Random effects model was used if there was considerable heterogeneity ($P < 0.05$ or $I^2 > 50\%$), otherwise fixed effects model was employed.[33] Univariate and multivariate meta-regression analysis were utilized to identify potential sources of heterogeneity, and further confirmed by means of Monte Carlo method.[31,34] One-way sensitivity analysis was performed to evaluate whether removal of one single study could influence the overall outcomes. The Contuor-enhanced funnel plot and Egger's linear regression test was adopted to assess publication bias to ensure the reliability of the results. All tests were two-sided, and $P < 0.05$ indicating a significant difference.[35]

RESULTS

Baseline characteristics of included studies

A total of 667 articles, which studied the correlations between MMP-9 protein expression and COPD or between TIMP-1 protein expression and COPD, were initially reviewed. After excluded duplicates ($n = 30$), non-human studies ($n = 203$), letters, reviews, meta-analysis ($n = 8$) and unrelated topic ($n = 355$), 71 full-text articles remained. Twenty studies ultimately satisfied the inclusion criteria after we eliminated studies that were not case-control study ($n = 11$), studies not associated with MMP-9 or TIMP-1 ($n = 23$), studies unrelated to COPD (n = 16), and those that had insufficient information ($n = 1$).[27,36-54] To compare the differences in MMP-9 and TIMP-1 protein expression between COPD patients and the healthy controls, 923 patients with COPD and 641 healthy controls were included as study subjects in this meta-analysis. All included studies were published between 2003 and 2014. Among the 20 case-control studies, 10 were performed in Asians, and another 10 were performed in Caucasians. Based on the country of the published studies, 9 studies were from China, 2 from Poland, 1 each from America, Japan, Germany, England, Mexico, Sweden, Turkey, Finland, and Czech Republic, respectively. All samples data were estimated from serum. Method for detecting MMP-9 and TIMP-1 proteins was enzyme linked immunosorbent assays (ELISA). Baseline characteristics and the quality scores of all included studies were displayed in Table 1 and Figure 1, respectively.

Results of meta-analysis

Heterogeneity test revealed a significant heterogeneity among studies that compared serum MMP-9 and TIMP-1 protein expressions between COPD patients and the healthy

Table 1: Baseline characteristics of all included trails

First author	Year	Country	Ethnicity	Gender (M/F)		Age (years)		Total
				COPD	Control	COPD	Control	
Montano[27]	(2014)	Mexico	Caucasians	0/40	0/40	72±8	65±10	80
Liu[36]	(2014)	China	Asians	24/2	20/4	65±8	66±9	50
Ji[37]	(2014)	Sweden	Caucasians	11/17	15/8	61 (48-73)	55 (41-72)	51
Hao[39]	(2013)	China	Asians	33/13	10/10	68.5±7.4	69.4±5.6	66
Yildirim[38]	(2013)	Turkey	Caucasians	34/2	19/1	68.9±8.8	59.5±9.1	56
D'Armiento[40]	(2013)	USA	Caucasians	58/43	43/29	65.5±7.5	24.2±3.7	173
Liu[41]	(2012)	China	Asians	61/4	22/4	66.6±8.1	66.7±10.0	91
Navratilova[42]	(2012)	Czech Republic	Caucasians	49/25	14/6	67±6.95	39.5±11.35	94
Kwiatkowska[43]	(2012)	Poland	Caucasians	10/7	14/8	68±10	57±11	39
Jiao[45]	(2011)	China	Asians	16/12	20/8	68.1±11.1	64.3±8.2	56
Ilumets[44]	(2011)	Finland	Caucasians	35/9	12/28	61.3±8.5	53.3±8.8	84
Zhou[46]	(2009)	China	Asians	28/14	11/9	65.2±10.3	61.2±10.2	62
Guo[47]	(2009)	China	Asians	26/20	18/10	58.1 (48-79)	56 (49-80)	74
Bolton[48]	(2009)	UK	Caucasians	40/30	19/20	61.6±9.2	65.6±9.4	109
Brajer[49]	(2008)	Poland	Caucasians	17/6	17/6	59.6±9.4	55.2±9.1	46
Wang[51]	(2007)	China	Asians	72/0	66/0	73.2±0.7	61.5±1.5	138
Kong[50]	(2007)	China	Asians	39/19	20/10	67.95±7.95	69.67±5.60	88
Yan [52]	(2006)	China	Asians	18/5	12/8	68.22±9.80	61.26±8.84	43
Higashimoto[53]	(2005)	Japan	Asians	72/0	66/0	73.2±0.7	61.6±1.5	138
Beeh[54]	(2003)	Germany	Caucasians	9/3	8/6	64 (56-73)	31 (20-55)	26

M = Male; F = Female; COPD = Chronic obstructive pulmonary disease

Figure 1: Quality of all enrolled studies by critical appraisal skill program

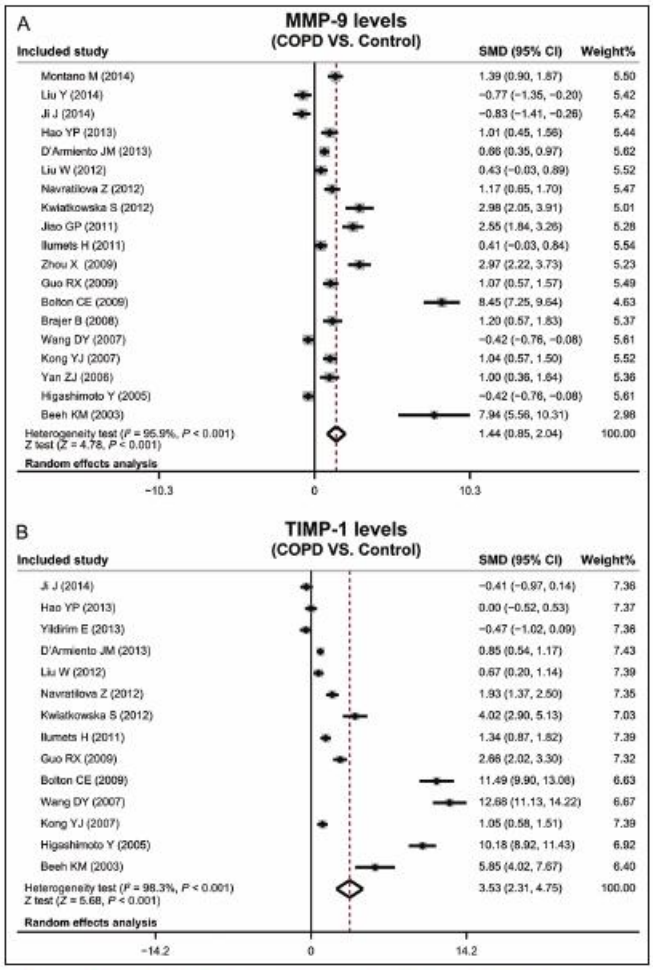

Figure 2: Forest plots of the correlation of MMP-9 with TIMP-1 and chronic obstructive pulmonary disease

controls (MMP-9: $P < 0.001$, $I^2 = 95.9\%$; TIMP-1: $P < 0.001$, $I^2 = 98.3\%$), and therefore a random-effects model was employed. The results of this meta-analysis suggested that the serum MMP-9 and TIMP-1 protein expressions were markedly higher in COPD patients compared with those in the healthy controls (MMP-9: SMD = 1.44, 95%CI = 0.85 ~ 2.04, $P < 0.001$; TIMP-1: SMD = 3.53, 95%CI = 2.31 ~ 4.75, $P < 0.001$) [Figure 2].

Subgroup analysis based on ethnicity revealed that the serum MMP-9 and TIMP-1 protein levels in COPD patients were significantly higher than those in healthy controls in Asians (MMP-9: SMD = 0.81, 95%CI = 0.15 ~ 1.48, $P = 0.016$; TIMP-1: SMD = 4.43, 95%CI = 1.98 ~ 6.87, $P = 0.016$) and in Caucasians (MMP-9: SMD = 2.30, 95%CI = 1.21 ~ 3.38, $P < 0.001$; TIMP-1: SMD = 2.86, 95%CI = 1.47 ~ 4.24, $P < 0.001$). Additionally, as shown in Figure 3, subgroup analysis on the basis of sample size indicated that in both small sample size ($n < 90$) and large sample size ($n > 90$), the serum MMP-9 ($n < 90$: SMD = 1.41, 95%CI = 0.76 ~ 2.07, $P < 0.001$; $n > 90$: SMD = 1.48, 95%CI = 0.32 ~ 2.64, $P = 0.012$) and TIMP-1 ($n < 90$: SMD = 1.57, 95%CI = 0.56 ~ 2.57, $P = 0.002$; $n > 90$; SMD = 6.19, 95%CI = 3.41 ~ 8.97, $P < 0.001$) protein levels were markedly higher in COPD patients than those in healthy controls.

Sensitivity analysis and publication bias

The sensitivity analysis demonstrated that any single study had no significant effect on the pooled SMDs. As shown in Figure 4, most included studies interspersed in the interval range of P less than 0.05. And $P < 0.05$ suggested there was publication bias among studies. The Contour-enhanced funnel plots of comparisons on MMP-9 and TIMP-1 protein expressions in serum between COPD patients and healthy controls indicated that there was publication bias ($P < 0.05$), which was further affirmed by Egger's test ($P < 0.05$) [Figure 4].

Regression analysis

As shown in Figure 5, Tables 2 and 3, both univariate meta-regression and multivariate meta-regression analyses revealed that publication year, sample size, country, language, and ethnicity were not the source of heterogeneity among studies between serum MMP-9 protein levels and COPD.

DISCUSSION

COPD is known as a progressive and incurable lung disease characterized by abnormal tissue repair,

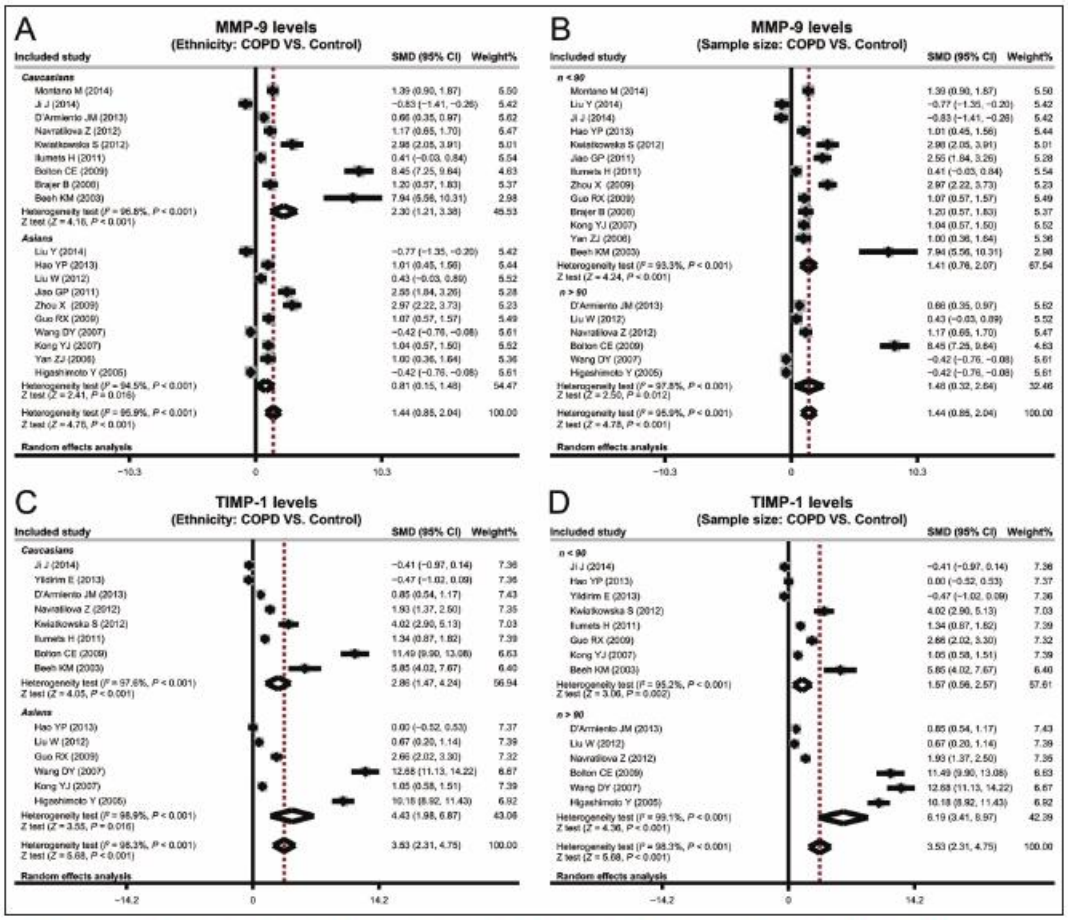

Figure 3: Forest plots for subgroup analysis investigating the correlation of MMP-9 with TIMP-1 and chronic obstructive pulmonary disease

resulting in small airways fibrosis or emphysema.[55] Destruction of the ECM of the lung is a characteristic feature of COPD.[56] The MMP family members, a group of metzincin metalloproteases, function primarily extracellularly and are important in the maintenance and remodeling of tissues mainly through degradation of the ECM.[57] TIMPs, natural MMP inhibitors, control important cellular processes including proliferation, apoptosis and angiogenesis by mechanisms independent of their MMP inhibitory activity.[58] TIMP-1 and TIMP-2 are two main members that lead to pulmonary diseases with changes of alveolar structure in asthma or COPD. This balance plays an important role in optimal function while any over/under production of relevant proteinases can result in tissue damage and undesirable alterations in ECM.[59] MMPs and their inhibitors, play a central role in the lung remodeling in COPD, And their presence in the sputum and bronchoalveolar lavage are regarded as a sign of the local inflammation in COPD patients.[56] Inappropriate expression and excessive activity of several MMPs and TIMP, including MMP-9 and TIMP-1, has been implicated in the tissue destructive processes associated with chronic lung diseases including COPD.[43,60]

Table 2: Meta-regression analyses of potential source of heterogeneity (MMP-9)

Heterogeneity factors	Coefficient	SE	*t*	*P* (Adjusted)	95% CI LL	95% CI UL
Year	−0.044	0.246	−0.18	1.000	−0.576	0.488
Sample size	−0.014	0.013	−1.08	0.711	−0.043	0.014
Country	0.488	0.323	1.51	0.438	−0.210	1.187
Language	−3.510	2.111	−1.66	0.355	−8.071	1.051
Ethnicity	2.771	1.686	1.64	0.365	−0.871	6.413

SE = Standard error; LL = Lower limit; UL = Upper limit

Table 3: Meta-regression analyses of potential source of heterogeneity (TIMP-1)

Heterogeneity factors	Coefficient	SE	*t*	*P* (Adjusted)	95% CI LL	95% CI UL
Year	−0.635	0.540	−1.18	0.622	−1.880	0.611
Sample Size	0.040	0.027	1.45	0.468	−0.024	0.103
Country	0.511	0.833	0.61	0.927	−1.409	2.431
Language	−2.045	6.734	−0.30	0.996	−17.575	13.484
Ethnicity	0.677	4.869	0.14	1.000	−10.551	11.905

SE = Standard error; LL = Lower limit; UL = Upper limit

To evaluate the roles MMP-9 and TIMP-1 in the pathogenesis of COPD, we performed a meta-analysis and uncovered that the serum MMP-9 and TIMP-1 protein levels in COPD patients were significantly higher than

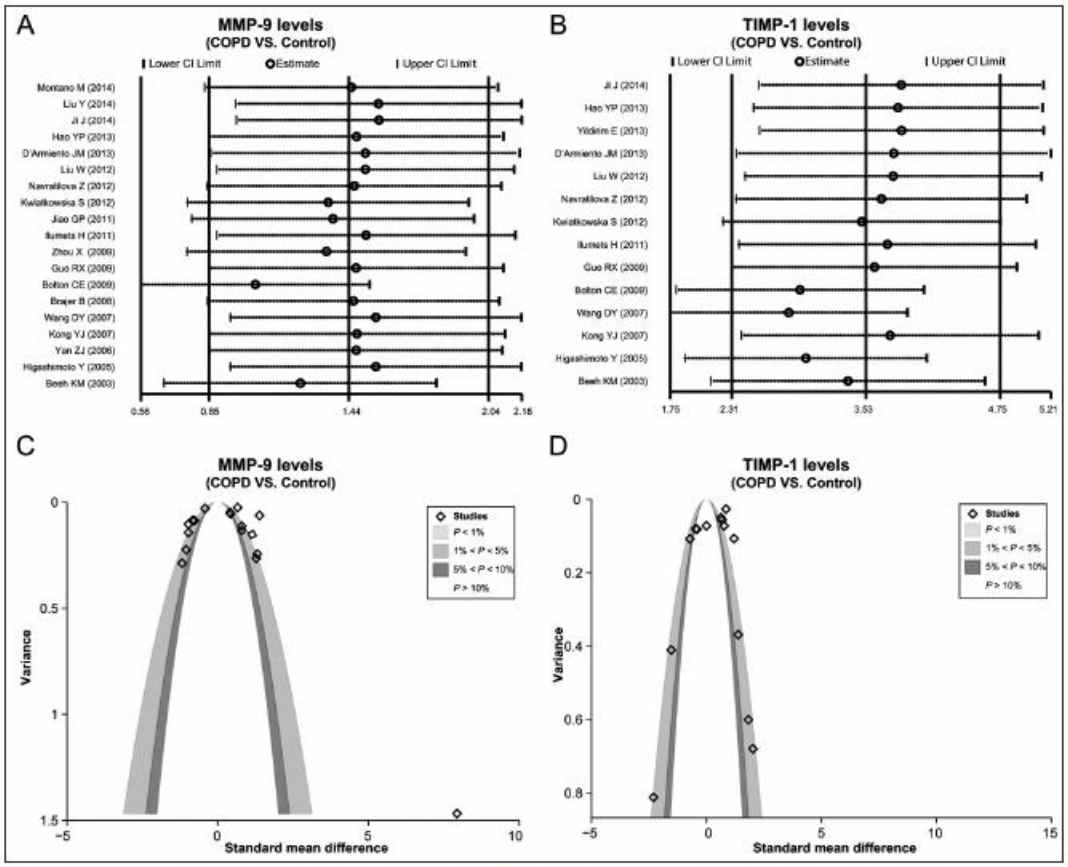

Figure 4: Sensitivity analyses and funnel plots of the correlation of MMP-9 with TIMP-1 and chronic obstructive pulmonary disease

those in the healthy controls, suggesting that MMP-9 and TIMP-1 proteins indeed play a role in the pathogenesis of COPD through degradation of ECM. The ECM is a dynamic structure, and equilibrium between synthesis and degradation of ECM components is required for the maintenance of its homeostasis.[61,62] MMP-9 is responsible for tissue remodeling and repairing by the degradation of basement membrane type IV collagen, it is released by macrophages that are derived from neutrophils and from circulating monocytes.[49] Increased MMP-9 activity can promote the degradation of alveolar wall basement membranes, and therefore plays a significant role in the development of emphysema and airway fibrosis.[63] TIMP-1 has been found as an MMP-9 activity inhibitor through binding to its precursors and active form.[64] Increased expressions of MMP-9 and TIMP-1 and alveolar macrophages trigger larger amounts of MMP-9 with greater enzymatic activity in COPD patients. The imbalances between the levels of MMP-9 and TIMP-1 might result in the aberrant ECM degradation or the accumulation of ECM proteins in pulmonary alveoli and small airway walls, which would lead to COPD.[65,66]

Subgroup analyses on the basis of ethnicity and sample size indicated in Asians and Caucasians, and in small sample size and large sample size, the serum MMP-9 and TIMP-1 protein levels in COPD patients were consistently significantly higher than those in the healthy controls, further confirming the main result of this meta-analysis.

Several limitations of the present meta-analysis should be recognized. First, a potential important weakness about our included studies in meta-analysis is that the control participants are less than case group; second, some studies were excluded due to our failure to obtain original data from the communicating author third, this meta-analysis included data from Asians, Caucasians, Americans, but no studies from Africans and mixed population, consequently, our study is not representative of all ethnicities. In summary, our study revealed that the expression levels of MMP-9 and TIMP-1 protein markedly increased in serum of patients with COPD and an imbalance in the MMP-9/TIMP-1 ratio could be involved in COPD pathogenesis, suggesting MMP-9 and TIMP-1 protein could be an important biological indicator in prognosis of COPD. In the future, prospective studies with larger control participant size, more completely original data and no publication bias are needed to validate our results.

Acknowledgements

We would like to gratitude our instructors for their valuable advice. We also appreciate the reviewers that they give us precious comments on this article.

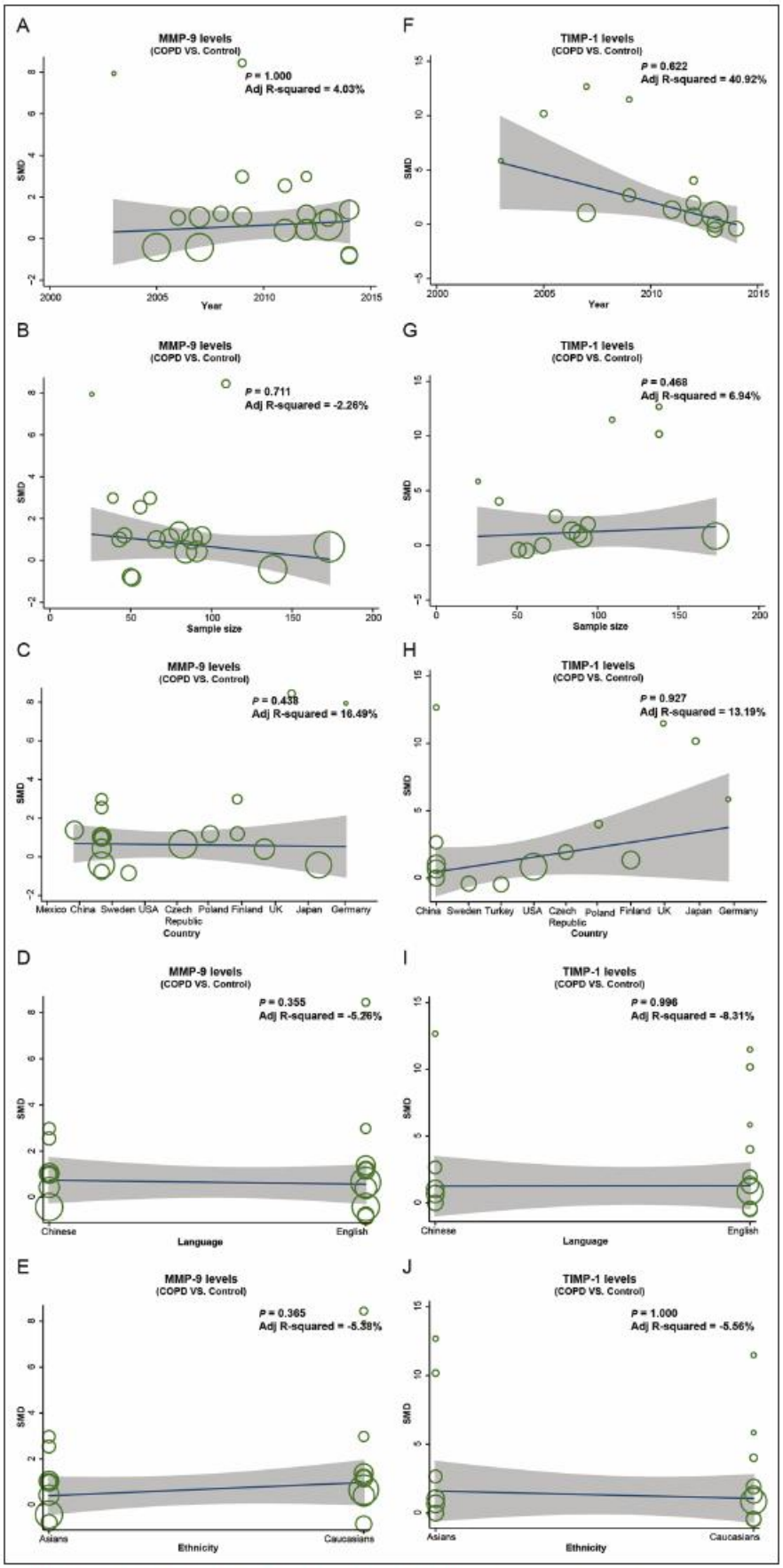

Figure 5: Regression analyses of the correlation of MMP-9 with TIMP-1 and chronic obstructive pulmonary disease

Financial support and sponsorship

This study was supported by National Natural Science Foundation of China (81470024).

Conflicts of interest

There are no conflicts of interest.

AUTHOR'S CONTRIBUTION

YL (Yangxue Li) contributed in the conception of the work, conducting the study, revising the draft, approval of the final version of the manuscript, and agreed for all aspects of the work. YL (Yang Lu), ZZ and JW contributed in conducting the study and agreed for all aspects of the work. JL and WW contributed in revising the draft, approval of the final version of the manuscript, and agreed for all aspects of the work. SL and LS contributed in the conception of the work, approval of the final version of the manuscript, and agreed for all aspects of the work.

REFERENCES

1. Lange P, Marott JL, Vestbo J, Olsen KR, Ingebrigtsen TS, Dahl M, *et al.* Prediction of the clinical course of chronic obstructive pulmonary disease, using the new GOLD classification: A study of the general population. Am J Respir Crit Care Med 2012;186:975-81.
2. Decramer M, Janssens W, Miravitlles M. Chronic obstructive pulmonary disease. Lancet 2012;379:1341-51.
3. Singh S, Loke YK, Enright PL, Furberg CD. Mortality associated with tiotropium mist inhaler in patients with chronic obstructive pulmonary disease: Systematic review and meta-analysis of randomised controlled trials. BMJ 2011;342:d3215.
4. Lozano R, Naghavi M, Foreman K, Lim S, Shibuya K, Aboyans V, *et al.* Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: A systematic analysis for the Global Burden of Disease Study 2010. Lancet 2012;380:2095-128.
5. Alfageme I, Reyes N, Merino M, Reina A, Gallego J, Lima J, *et al.* The effect of airflow limitation on the cause of death in patients with COPD. Chron Respir Dis 2010;7:135-45.
6. Brusselle GG, Joos GF, Bracke KR. New insights into the immunology of chronic obstructive pulmonary disease. Lancet 2011;378:1015-26.
7. Vestbo J, Hurd SS, Agusti AG, Jones PW, Vogelmeier C, Anzueto A, *et al.* Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: GOLD executive summary. Am J Respir Crit Care Med 2013;187:347-65.
8. Foreman MG, Campos M, Celedon JC. Genes and chronic obstructive pulmonary disease. Med Clin North Am 2012;96:699-711.
9. Brode SK, Ling SC, Chapman KR. Alpha-1 antitrypsin deficiency: A commonly overlooked cause of lung disease. CMAJ 2012;184:1365-71.
10. Divo M, Cote C, de Torres JP, Casanova C, Marin JM, Pinto-Plata V, *et al.* Comorbidities and risk of mortality in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2012;186:155-61.
11. Andersen ZJ, Hvidberg M, Jensen SS, Ketzel M, Loft S, Sørensen M, *et al.* Chronic obstructive pulmonary disease and long-term exposure to traffic-related air pollution: A cohort study. Am J Respir Crit Care Med 2011;183:455-61.
12. Gan WQ, FitzGerald JM, Carlsten C, Sadatsafavi M, Brauer M. Associations of ambient air pollution with chronic obstructive pulmonary disease hospitalization and mortality. Am J Respir Crit Care Med 2013;187:721-7.
13. Laumbach RJ, Kipen HM. Respiratory health effects of air pollution: Update on biomass smoke and traffic pollution. J Allergy Clin Immunol 2012;129:3-13.
14. Mackay AJ, Hurst JR. COPD exacerbations: Causes, prevention, and treatment. Med Clin North Am 2012;96:789-809.
15. Carlucci A, Guerrieri A, Nava S. Palliative care in COPD patients: Is it only an end-of-life issue? Eur Respir Rev 2012;21:347-54.
16. Puhan MA, Gimeno-Santos E, Scharplatz M, Troosters T, Walters EH, Steurer J. Pulmonary rehabilitation following exacerbations of chronic obstructive pulmonary disease. Cochrane Database Syst Rev 2011;CD005305.
17. MacNee W. Systemic inflammatory biomarkers and co-morbidities of chronic obstructive pulmonary disease. Ann Med 2013;45:291-300.
18. Miletti-González KE, Murphy K, Kumaran MN, Ravindranath AK, Wernyj RP, Kaur S, *et al.* Identification of function for CD44 intracytoplasmic domain (CD44-ICD): Modulation of matrix metalloproteinase 9 (MMP-9) transcription via novel promoter response element. J Biol Chem 2012;287:18995-9007.
19. Atkinson JJ, Lutey BA, Suzuki Y, Toennies HM, Kelley DG, Kobayashi DK, *et al.* The role of matrix metalloproteinase-9 in cigarette smoke-induced emphysema. Am J Respir Crit Care Med 2011;183:876-84.
20. Jeong S, Ledee DR, Gordon GM, Itakura T, Patel N, Martin A, *et al.* Interaction of clusterin and matrix metalloproteinase-9 and its implication for epithelial homeostasis and inflammation. Am J Pathol 2012;180:2028-39.
21. Sharov AA, Schroeder M, Sharova TY, Mardaryev AN, Peters EM, Tobin DJ, *et al.* Matrix metalloproteinase-9 is involved in the regulation of hair canal formation. J Invest Dermatol 2011;131:257-60.
22. Dziembowska M, Milek J, Janusz A, Rejmak E, Romanowska E, Gorkiewicz T, *et al.* Activity-dependent local translation of matrix metalloproteinase-9. J Neurosci 2012;32:14538-47.
23. Nieuwesteeg MA, Willson JA, Cepeda M, Fox MA, Damjanovski S. Functional characterization of tissue inhibitor of metalloproteinase-1 (TIMP-1) N- and C-terminal domains during Xenopus laevis development. ScientificWorldJournal 2014;2014:467907.
24. Mroczko B, Groblewska M, Okulczyk B, Kedra B, Szmitkowski M. The diagnostic value of matrix metalloproteinase 9 (MMP-9) and tissue inhibitor of matrix metalloproteinases 1 (TIMP-1) determination in the sera of colorectal adenoma and cancer patients. Int J Colorectal Dis 2010;25:1177-84.
25. Fu ZY, Lv JH, Ma CY, Yang DP, Wang T. Tissue inhibitor of metalloproteinase-1 decreased chemosensitivity of MDA-435 breast cancer cells to chemotherapeutic drugs through the PI3K/AKT/NF-κB pathway. Biomed Pharmacother 2011;65:163-7.
26. Muller V, Riethdorf S, Rack B, Janni W, Fasching PA, Solomayer E, *et al.* DETECT Study Group. Prospective evaluation of serum tissue inhibitor of metalloproteinase 1 and carbonic anhydrase IX in correlation to circulating tumor cells in patients with metastatic breast cancer. Breast Cancer Res 2011;13:R71.
27. Montano M, Sansores RH, Becerril C, Cisneros J, Gonzalez-Avila G, Sommer B, *et al.* FEV1 inversely correlates with metalloproteinases 1, 7, 9 and CRP in COPD by biomass smoke exposure. Respir Res 2014;15:74.
28. Pinto-Plata V, Casanova C, Müllerova H, de Torres JP, Corado H, Varo N, *et al.* Inflammatory and repair serum biomarker

pattern: Association to clinical outcomes in COPD. Respir Res 2012;13:71.
29. Yao H, Hwang JW, Sundar IK, Friedman AE, McBurney MW, Guarente L, *et al.* SIRT1 redresses the imbalance of tissue inhibitor of matrix metalloproteinase-1 and matrix metalloproteinase-9 in the development of mouse emphysema and human COPD. Am J Physiol Lung Cell Mol Physiol 2013;305:L615-24.
30. Chen H, Manning AK, Dupuis J. A method of moments estimator for random effect multivariate meta-analysis. Biometrics 2012;68:1278-84.
31. Jackson D, White IR, Riley RD. Quantifying the impact of between-study heterogeneity in multivariate meta-analyses. Stat Med 2012;31:3805-20.
32. Peters JL, Sutton AJ, Jones DR, Abrams KR, Rushton L. Comparison of two methods to detect publication bias in meta-analysis. JAMA 2006;295 676-80.
33. Zintzaras E, Ioannidis JP. Heterogeneity testing in meta-analysis of genome searches. Genet Epidemiol 2005;28:123-37.
34. Huizenga HM, Visser I, Dolan CV. Testing overall and moderator effects in random effects meta-regression. Br J Math Stat Psychol 2011;64:1-19.
35. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ 1997;315:629-34.
36. Liu Y, Liu X, Lin G, Sun L, Li H, Xie C. Decreased CD34+ cell number is correlated with cardiac dysfunction in patients with acute exacerbation of COPD. Heart Lung Circ 2014;23:875-82.
37. Ji J, von Schéele I, Bergström J, Billing B, Dahlén B, Lantz AS, *et al.* Compartment differences of inflammatory activity in chronic obstructive pulmonary disease. Respir Res 2014;15:104.
38. Yıldırım E, Kormi I, Başoğlu ÖK, Gürgün A, Kaval B, Sorsa T, *et al.* Periodontal health and serum, saliva matrix metalloproteinases in patients with mild chronic obstructive pulmonary disease. J Periodontal Res 2013;48:269-75.
39. Yan-ping HA. Study of interaction of MMP-9, TIMP-1 and ICAM-1 in patients with COPD. 2013;18:500-1.
40. D'Armiento JM, Goldklang MP, Hardigan AA, Geraghty P, Roth MD, Connett JE, *et al.* Increased matrix metalloproteinase (MMPs) levels do not predict disease severity or progression in emphysema. PLoS One 2013;8:e56352.
41. Wei LI, Rong-chang C, Yan T. Study on the correlation of serum MMP-9 and TIMP-1 with treatment response of patients with chronic obstructive pulmonary disease. J Clin Res 2012;29:2298-301.
42. Navratilova Z, Zatloukal J, Kriegova E, Kolek V, Petrek M. Simultaneous up-regulation of matrix metalloproteinases 1, 2, 3, 7, 8, 9 and tissue inhibitors of metalloproteinases 1, 4 in serum of patients with chronic obstructive pulmonary disease. Respirology 2012;17:1006-12.
43. Kwiatkowska S, Noweta K, Zieba M, Nowak D, Bialasiewicz P. Enhanced exhalation of matrix metalloproteinase-9 and tissue inhibitor of metalloproteinase-1 in patients with COPD exacerbation: A prospective study. Respiration 2012;84:231-41.
44. Ilumets H, Mazur W, Toljamo T, Louhelainen N, Nieminen P, Kobayashi H, *et al.* Ageing and smoking contribute to plasma surfactant proteins and protease imbalance with correlations to airway obstruction. BMC Pulm Med 2011;11:19.
45. GP J. Patients with chronic obstructive pulmonary disease serum TNF-α, expression and correlation Mmp-9's. Chin J Gerontol 2011;31:1314-5.
46. Xu Z, Fei Z. Levels of serum TNF-α, IL-8 and MMP-9 in COPD patients and its clinical significance. J Clin Res 2009;26:948-50.
47. XIA GR. Value of matrix metalloproteinases and their inhibitors in patients with chronic obstructive pulmonary disease therapy. China Modern Doctor 2009;47:23,9.
48. Bolton CE, Stone MD, Edwards PH, Duckers JM, Evans WD, Shale DJ. Circulating matrix metalloproteinase-9 and osteoporosis in patients with chronic obstructive pulmonary disease. Chron Respir Dis 2009;6:81-7.
49. Brajer B, Batura-Gabryel H, Nowicka A, Kuznar-Kaminska B, Szczepanik A. Concentration of matrix metalloproteinase-9 in serum of patients with chronic obstructive pulmonary disease and a degree of airway obstruction and disease progression. J Physiol Pharmacol 2008;59(Suppl 6):145-52.
50. JUN KY. The expressions of matrix metalloproteinase and their inhibitor, and ICAM-1, VCAM-1 in lung tissue associated with COPD. Chin J Pract Intr Med 2007;27:1294-6.
51. Dongying W. The research on serum concentrations of matrix metalloproteinase-9 and tissue inhibitors of metalloproteinase-1 in COPD patients. J Clin Pulm Med 2007;12:836-7.
52. JUN YZ. Detection serum levels of IL-8 and MMP-9 in patients with chronic obstructive pulmonary disease and their clinical significance. Chin J Clin Med 2006;13:377-8.
53. Higashimoto Y, Yamagata Y, Iwata T, Okada M, Ishiguchi T, Sato H, *et al.* Increased serum concentrations of tissue inhibitor of metalloproteinase-1 in COPD patients. Eur Respir J 2005;25:885-90.
54. Beeh KM, Beier J, Kornmann O, Buhl R. Sputum matrix metalloproteinase-9, tissue inhibitor of metalloprotinease-1, and their molar ratio in patients with chronic obstructive pulmonary disease, idiopathic pulmonary fibrosis and healthy subjects. Respir Med 2003;97:634-9.
55. Brandsma CA, van den Berge M, Postma DS, Jonker MR, Brouwer S, Paré PD, *et al.* A large lung gene expression study identifying fibulin-5 as a novel player in tissue repair in COPD. Thorax 2015;70:21-32.
56. Piesiak P, Brzecka A, Kosacka M, Passowicz-Muszynska E, Dyla T, Jankowska R. Concentrations of matrix metalloproteinase-9 and tissue inhibitor of metalloproteinases-1 in serum of patients with chronic obstructive pulmonary disease. Pol Merkur Lekarski 2011;31:270-3.
57. Gialeli C, Theocharis AD, Karamanos NK. Roles of matrix metalloproteinases in cancer progression and their pharmacological targeting. FEBS J 2011;278:16-27.
58. Murphy G. Tissue inhibitors of metalloproteinases. Genome Biol 2011;12:233.
59. Ghanei M, Ghalejooghi NA, Nourani MR, Harandi AA, Fooladi AA. Effect of TGFß1 and TIMP2 on disease activity in asthma and COPD. Iran J Allergy Asthma Immunol 2010;9:79-86.
60. Esa SA, Rawy AM, EL-Behissy MM, Kamel MH, El-Hwaitty HM. Study of the level of sputum matrix metalloproteinase-9 (MMP-9) and tissue inhibitor metalloproteinase-1 (TIMP-1) in COPD patients. Egypt J Chest Dis Tuberc 2014;63:861-7.
61. J Kolb MR, Gauldie J. Idiopathic pulmonary fibrosis: The matrix is the message. Am J Respir Crit Care Med 2011;184:627-9.
62. Garofalo R, Cesari E, Vinci E, Castagna A. Role of metalloproteinases in rotator cuff tear. Sports Med Arthrosc 2011;19:207-12.
63. Lindberg A, Larsson LG, Muellerova H, Rönmark E, Lundbäck B. Up-to-date on mortality in COPD-report from the OLIN COPD study. BMC Pulm Med 2012;12:1.
64. Zhuang Y, Qian Z, Huang L. Elevated expression levels of matrix metalloproteinase-9 in placental villi and tissue inhibitor of metalloproteinase-2 in decidua are associated with prolonged bleeding after mifepristone-misoprostol medical abortion. Fertil Steril 2014;101:166-71 e2.
65. Tency I, Verstraelen H, Kroes I, Holtappels G, Verhasselt B, Vaneechoutte M, *et al.* Imbalances between matrix metalloproteinases (MMPs) and tissue inhibitor of metalloproteinases (TIMPs) in maternal serum during preterm labor. PLoS One 2012;7:e49042.
66. Lambers C, Qi Y, Eleni P, Costa L, Zhong J, Tamm M, *et al.* Extracellular matrix composition is modified by β_2-agonists through cAMP in COPD. Biochem Pharmacol 2014;91:400-8.