

Supplementary file

e-Table 1 Other baseline characteristics of included studies

Study	RA diagnostic criteria	ILD diagnostic criteria	Treatment received ^a
Alunno 2018 [38]	ACR/EULAR 2010	X-ray and HRCT in symptomatic cases	-
England 2019 [39]	ACR 1987	1)Pulmonologist diagnosis and imaging, 2)non-pulmonologist diagnosis and two of the followings; imaging, pathology or PFT	PSL 63.0% vs. 42.8%, MTX 21.0% vs. 51.2%, Biologics 30.0% vs. 20.1%
Giles 2014 [40]	ACR 1987	Cardiac MDCT	PSL 51% vs. 32%, MTX 58% vs. 68%, TNF- α 56% vs. 40%
Chen 2013 [41]	ACR 1987	HRCT	-
Chen 2015 [42]	ACR 1987	HRCT	PSL 57% vs. 68%, MTX 63% vs. 67%, TNF- α 18% vs. 9%
Doyle 2015 [43]	-	HRCT	PSL 93.5% vs. 83%, MTX 78.5% vs. 76%, TNF- α 73.5% vs. 55%
Abdel-Hamid 2019 [44]	ACR/EULAR 2010	HRCT	-
Akiyama 2016 [45]	ACR/EULAR 2010	HRCT in symptomatic cases or abnormal radiograph	PSL 51.3% vs. 33.1%, MTX 24.4% vs. 61.8%, Biologics 50.0% vs. 43.2%
Alixiou 2008 [46]	-	-	-
Correia 2019 [47]	ACR/EULAR 2010	CT or radiograph and DLCO or pulmonologist	-

		diagnosis	
Fadda 2018 [48]	ACR/EULAR 2010	HRCT	MTX 6.9±4.2 vs. 7.9±4.3 years (duration)
Furukawa 2012 [49]	ACR 1987	Radiograph or CT	-
Kakutani 2019 [50]	ACR 1987 ACR/EULAR 2010	HRCT	PSL 77.8% vs. 58.1%, MTX 44.4% vs. 66.5%, non- TNF-αI Biologics 10.7% vs. 4.8%
Kelly 2014 [51]	ACR/EULAR 2010	HRCT	-
Liu 2019 [52]	ACR 1987	-	-
Matsuo 2018 [53]	-	CT in abnormal radiograph	PSL 65.4% vs. 41.6%, MTX 57.7% vs. 72.7%, Biologics 19.2% vs. 30.4%
Mori 2012 [54]	ACR 1987	HRCT	MTX 12.5% vs. 12.8%, TNF-αI 0% vs. 0.2%
Ortancil 2011 [55]	ACR 1987	-	-
Park 2016 [56]	ACR/EULAR 2010	CT	-
Paulin 2019 [57]	ACR/EULAR 2010	HRCT	MTX 51.9% vs. 74.2%, TNF-αI 11.5% vs. 24.2%
Restrepo 2015 [58]	ACR 1987	Clinical, PFT, imaging and pathology	PSL 63.7% vs. 46.5%, MTX 50.7% vs. 60.7%, TNF-αI 4.3% vs. 2.7%
Rocha-Munoz 2015 [59]	ACR 1987	Symptoms, PFT and HRCT	PSL 94.9% vs. 88.1%, MTX 100.0% vs. 97.6%
Sargin 2018 [60]	ACR/EULAR 2010	Symptoms, PFT, X-ray and HRCT	-
Sulaiman 2019	ACR/EULAR 2010	Radiograph and HRCT in	-

[61]			positive clinical exam	
Tian 2016 [62]	ACR/EULAR 2010		Clinical, PFT, imaging and/or pathology	-
Wang 2015 [63]	ACR 1987		HRCT	PSL 68.0% vs. 81.3%, MTX 64.0% vs. 81.3%
Yang 2019 [64]	ACR 1987		Clinical, PFT, imaging and/or pathology	MTX 39.0% vs. 76.2%, TNF- α I 5.2% vs. 5.2%
Yin 2014 [65]	ACR 1987		HRCT	PSL 81.7% vs. 82.2%, MTX 53.5% vs. 66.4%, Biologics 8.5% vs. 15.0%
Zhang 2018 [66]	-		-	-

a, Comparisons correspond to RA-ILD vs. RA without ILD;

ACR, American College of Rheumatology; DLCO, diffusing capacity of the lung for carbon monoxide; EULAR, European League Against Rheumatism; HRCT, high resolution computed tomography; ILD, interstitial lung disease; MDCT, multi-detector computed tomography; MTX, methotrexate, PFT, pulmonary function test; PSL, prednisolone; RA, rheumatoid arthritis; TNF- α I, tumor necrosis factor- α inhibitor;

e-Table 2 Meta-regression analysis

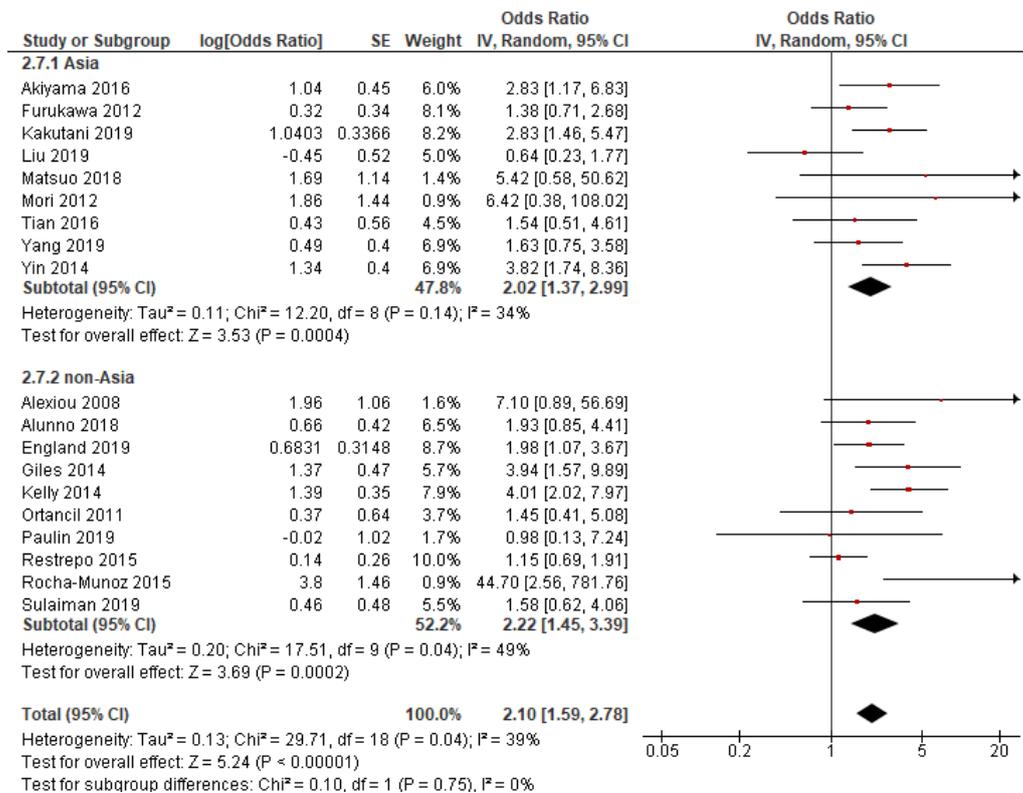
Potential confounder	Positivity of anti-CCP antibody ^a		Titre of anti-CCP antibody ^b	
	Univariate (95%CI)	Multivariate (95%CI) ^c	Univariate (95%CI)	Multivariate (95%CI) ^c
Age (at inclusion) (/year)	0.02 (-0.04-0.07)	0.06 (-0.03-0.16)	-0.01 (-0.08-0.06)	-0.01 (-0.09-0.06)
Gender (male) (/percentage)	0.003 (-0.009-0.02)	0.003 (-0.009-0.02)	-0.02 (-0.04--0.004)	0.004 (-0.04-0.05)
Smoking history (/percentage)	-0.008 (-0.02-0.005)	-0.0005 (-0.03-0.02)	0.001 (-0.01-0.01)	0.0008 (-0.006-0.008)
RA duration (/year)	0.02 (-0.19-0.23)	0.03 (-0.20-0.26)	0.05 (0.01-0.09)	0.06 (-0.03-0.14)
RA diagnostic criteria (ACR/EULAR 2010 vs. ACR 1987)	0.36 (-0.22-0.94)	0.47 (-0.25-1.18)	-0.17 (-0.94-0.59)	0.06 (-1.24-1.36)
ILD diagnostic criteria (CT for all subjects vs. others)	0.02 (-0.60-0.64)	-0.48 (-1.66-0.71)	-0.24 (-1.26-0.78)	0.20 (-0.21-0.61)
Proportion of positivity of anti-CCP antibody in subjects with RA alone (/percentage)	0.009 (-0.01-0.03)	0.02 (-0.02-0.06)	0.01 (-0.01-0.04)	- ^d

Text in bold indicates statistical significance;

a, The positivity of anti-CCP antibody for RA-ILD against RA alone (dependent variable) was regressed against each potential confounder and the value in each cell indicates a change of an OR with one unit increase of each covariate;

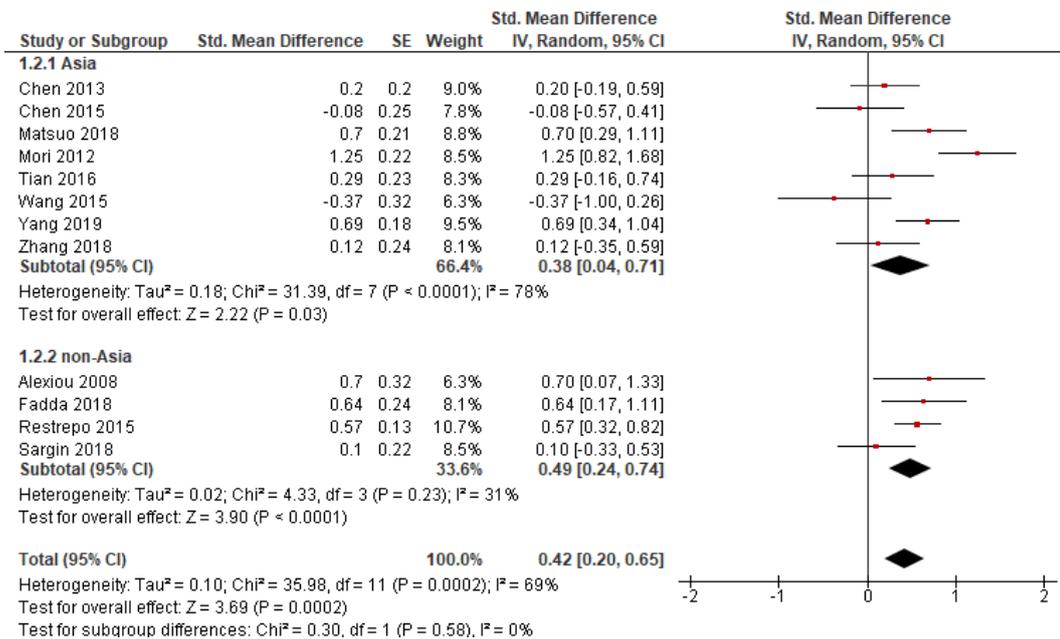
- b, The difference of titres of anti-CCP antibody between RA-ILD and RA alone (dependent variable) was regressed against each potential confounder and the value in each cell indicates a change of an SMD with one unit increase of each covariate;
- c, Each potential confounder was adjusted for RA duration and the effect of RA duration was estimated allowing for gender;
- d, The effect was unable to be estimated due to a small number of studies;

ACR, American College of Rheumatology; CCP, cyclic citrullinated peptide; CI, confidence interval; EULAR, European League Against Rheumatism; ILD, interstitial lung disease; HRCT, high resolution computed tomography; OR, odds ratio; RA, rheumatoid arthritis; SMD, standardized mean difference;



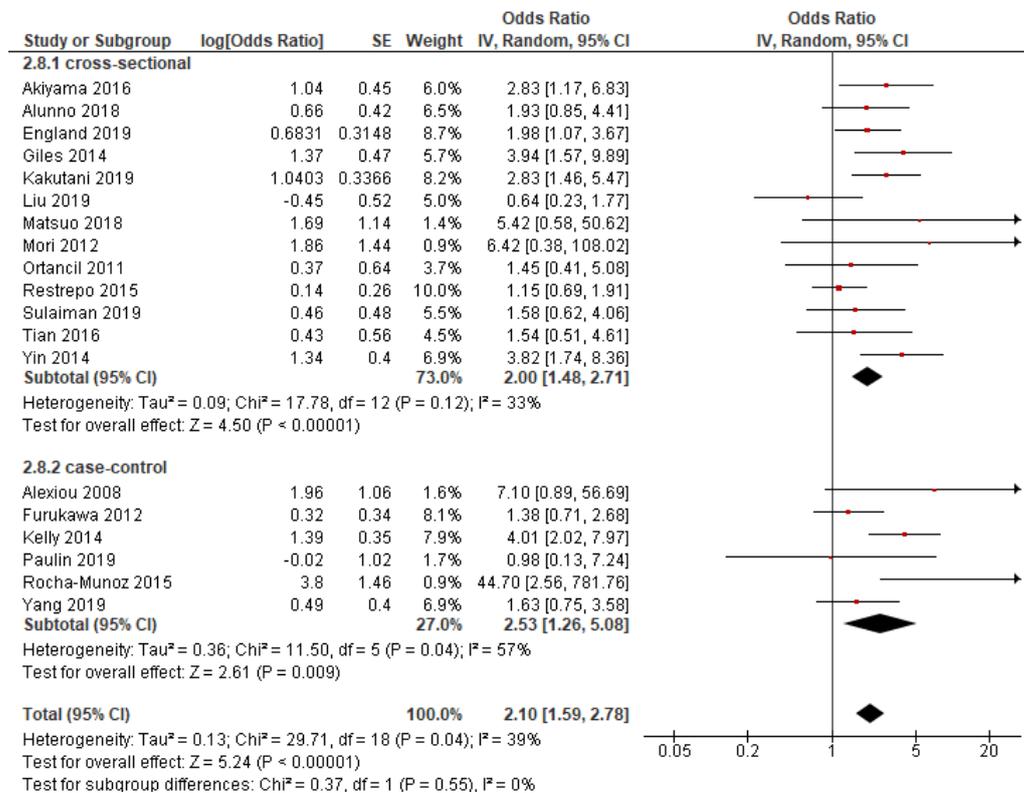
e-Figure 1 Subgroup analysis of the association of the positivity of anti-citrullinated peptide (CCP) antibody with rheumatoid arthritis-associated interstitial lung disease (RA-ILD) based on study location

A pooled analysis of studies in Asia and non-Asia individually demonstrated that the positivity of anti-CCP antibody was significantly associated with RA-ILD with odds ratios (ORs) of 2.02 (95% confidence interval (CI): 1.37-2.99, $p=0.0004$ /95% prediction interval (PI): 0.81-5.05) and 2.22 (95%CI: 1.45-3.39, $p=0.0002$ /95%PI: 0.71-6.98), respectively and there was no significant difference in these results ($p=0.75$). There remained moderate heterogeneity in both Asian and non-Asian studies.



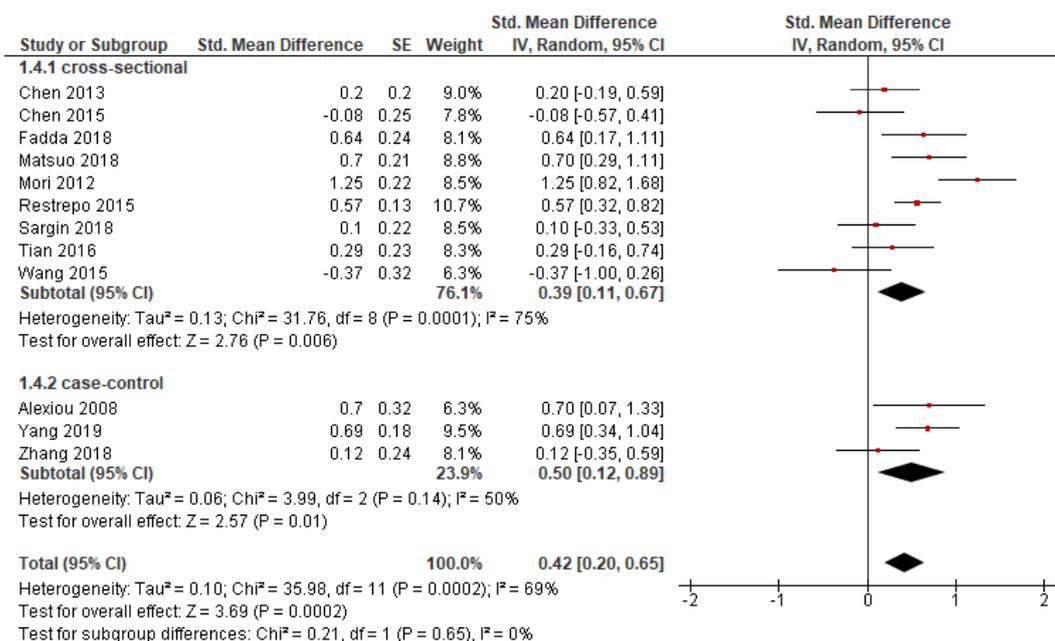
e-Figure 2 Subgroup analysis of the association of the titre of anti-citrullinated peptide (CCP) antibody with rheumatoid arthritis-associated interstitial lung disease (RA-ILD) based on study location

A pooled analysis of studies in Asia and non-Asia individually demonstrated that the titre of anti-CCP antibody was significantly higher for RA-ILD than RA without ILD with standardized mean differences (SMDs) of 0.38 (95% confidence interval (CI): 0.04-0.71, $p=0.03$ /95% prediction interval (PI): -0.74-1.50) and 0.49 (95%CI: 0.24-0.74, $p<0.0001$ /95%PI: -0.33-1.31), respectively and there was no significant difference in these results ($p=0.58$). There remained substantial heterogeneity in Asian studies ($\chi^2=31.4$, $p<0.0001$, $I^2=78\%$).



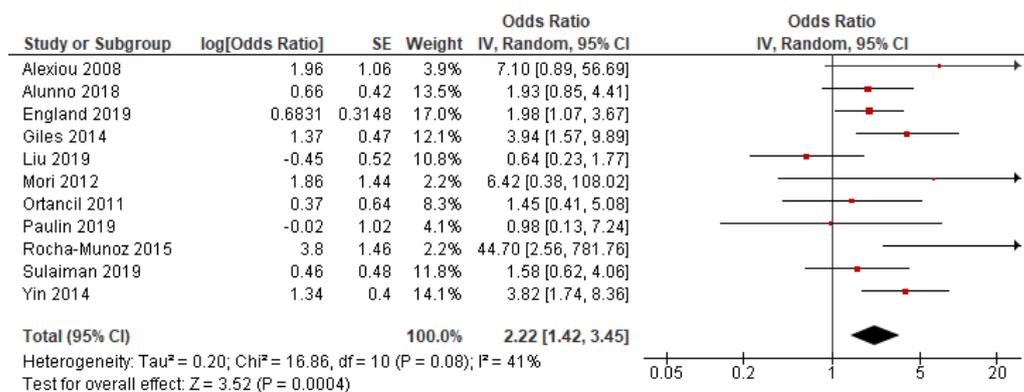
e-Figure 3 Subgroup analysis of the association of the positivity of anti-citrullinated peptide (CCP) antibody with rheumatoid arthritis-associated interstitial lung disease (RA-ILD) based on study design

A pooled analysis of cross-sectional and case-control studies individually demonstrated that the positivity of anti-CCP antibody was significantly associated with RA-ILD with odds ratios (ORs) of 2.00 (95% confidence interval (CI): 1.48-2.71, $p < 0.00001$ /95% prediction interval (PI): 0.95-4.21) and 2.53 (95%CI: 1.26-5.08, $p = 0.009$ /95%PI: 0.36-17.5), respectively and there was no significant difference in these results ($p = 0.55$). There remained considerable heterogeneity in case-control studies ($\chi^2 = 11.5$, $p = 0.04$, $I^2 = 57\%$).



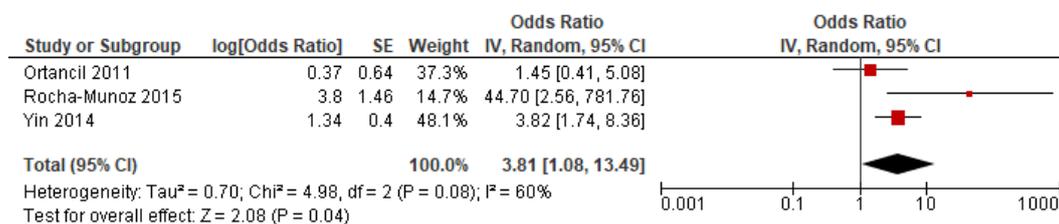
e-Figure 4 Subgroup analysis of the association of the titre of anti-citrullinated peptide (CCP) antibody with rheumatoid arthritis-associated interstitial lung disease (RA-ILD) based on study design

A pooled analysis of cross-sectional and case-control studies individually demonstrated that the titre of anti-CCP antibody was significantly higher for RA-ILD than RA without ILD with standardized mean differences (SMDs) of 0.39 (95% confidence interval (CI): 0.11-0.67, $p=0.006/95\%$ prediction interval (PI): -0.53-1.31) and 0.50 (95%CI: 0.12-0.89, $p=0.01/95\%$ PI: -3.51-4.51), respectively and there was no significant difference in these results ($p=0.65$). There remained substantial heterogeneity in cross-sectional studies ($\chi^2=31.8$, $p=0.0001$, $I^2=75\%$).



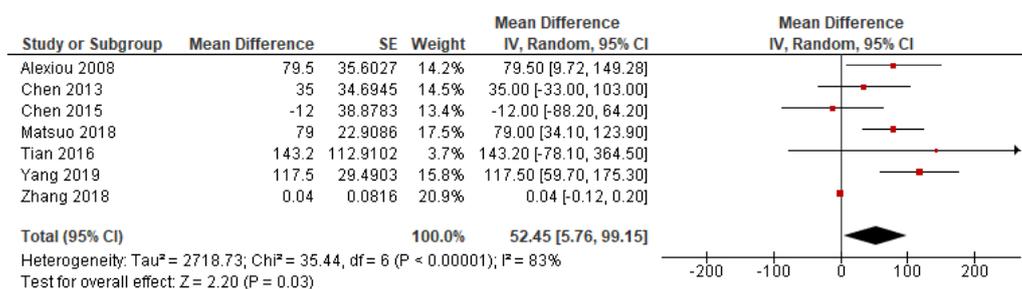
e-Figure 5 Sensitivity analysis of the association of the positivity of anti-citrullinated peptide (CCP) antibody with rheumatoid arthritis-associated interstitial lung disease (RA-ILD) focusing on the same generation of the autoantibody test

The results of univariate analyses in 11 studies that examined the second generation of anti-CCP antibody were pooled for meta-analysis. The positivity of anti-CCP antibody was significantly associated with RA-ILD with an odds ratio (OR) of 2.22 (95% confidence interval: 1.42-3.45, $p=0.00041/95\%$ prediction interval: 0.72-6.89). There remained moderate heterogeneity ($\chi^2=16.9$, $p=0.08$, $I^2=41\%$).



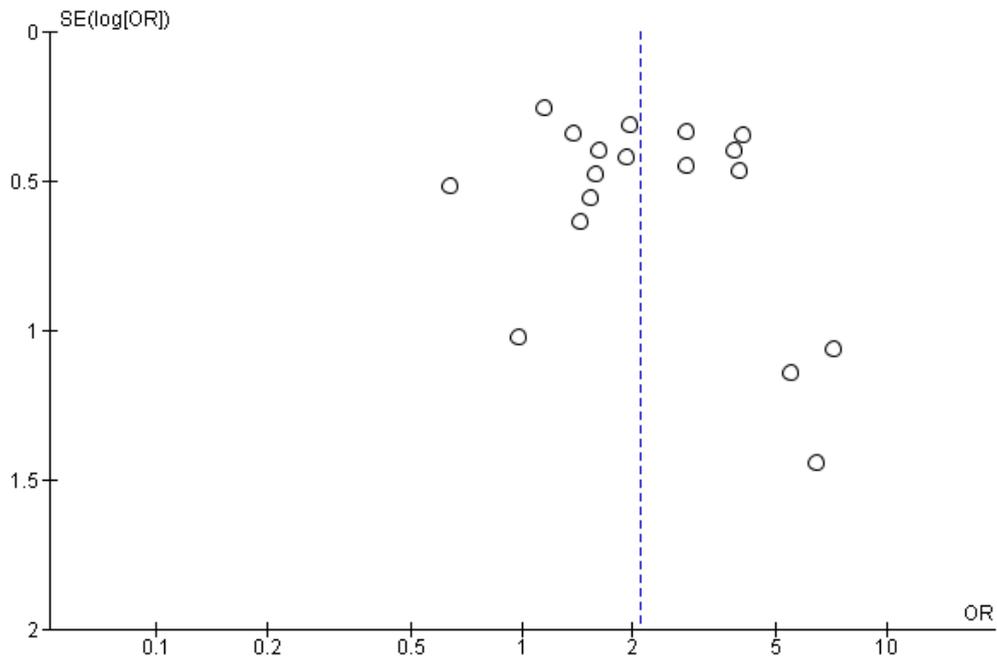
e-Figure 6 Sensitivity analysis of the association of the positivity of anti-citrullinated peptide (CCP) antibody with rheumatoid arthritis-associated interstitial lung disease (RA-ILD) focusing on the same generation of the autoantibody test by the same manufacturer

The results of univariate analyses in three studies that examined the second generation of anti-CCP antibody test by the same manufacturer (Euroimmun, Lübeck, Germany) were pooled for meta-analysis. The positivity of anti-CCP antibody was significantly associated with RA-ILD with an odds ratio (OR) of 3.81 (95% confidence interval: 1.08-13.5, $p=0.04/95\%$ prediction interval: 0.00->100.0). There remained considerable heterogeneity ($\chi^2=4.98$, $p=0.08$, $I^2=60\%$).



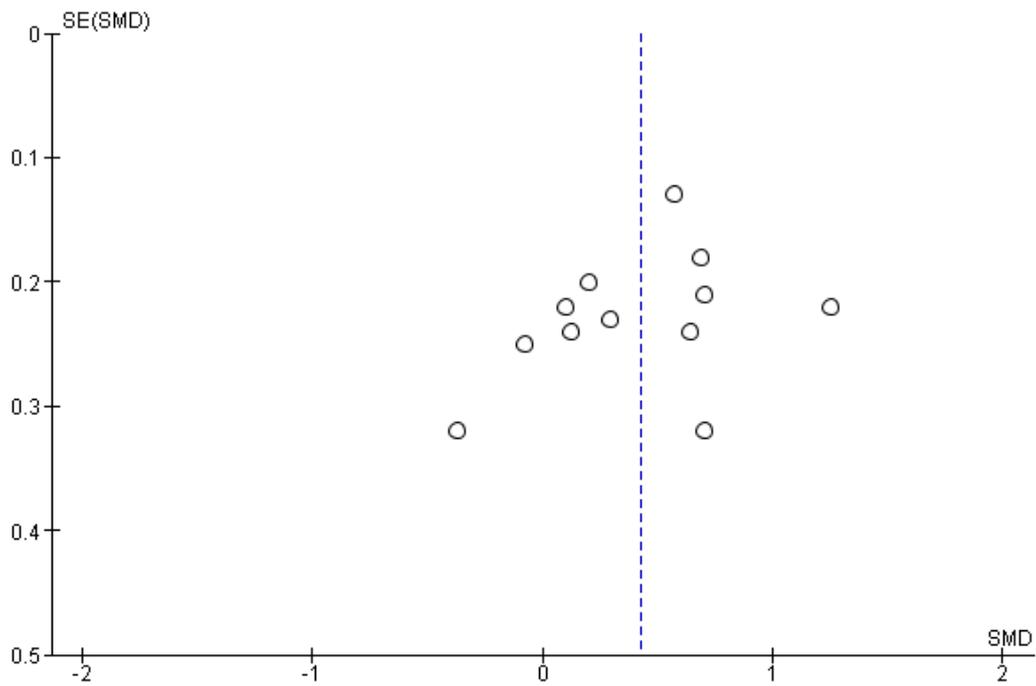
e-Figure 7 Sensitivity analysis of the association of the titre of anti-citrullinated peptide (CCP) antibody with rheumatoid arthritis-associated interstitial lung disease (RA-ILD) focusing on the same summary statistics

A pooled analysis of seven studies where mean differences (MDs) were available without a conversion of summary statistics demonstrated that higher titres of anti-CCP antibody was significantly associated with RA-ILD with an MD of 52.5 (95% confidence interval: 5.76-99.2, $p=0.03/95\%$ prediction interval: -94.9-199.9). There remained substantial heterogeneity ($\chi^2=35.4$, $p<0.00001$, $I^2=83\%$).



e-Figure 8 Funnel plot of the effect of the positivity of anti-citrullinated peptide (CCP) antibody against its standard error

The graphical inspection demonstrated no apparent asymmetry.



e-Figure 9 Funnel plot of the effect of the titre of anti-citrullinated peptide (CCP) antibody against its standard error

The graphical inspection demonstrated no apparent asymmetry.

e-Appendix

Search terms for each electronic database

Medline (Ovid) (1946 through 12 November 2019)

- 1 exp Arthritis, Rheumatoid/ (110375)
- 2 ((rheumatoid or reumatoid or revmatoid or rheumatic or reumatic or revmatic or rheumat\$ or reumat\$ or revmarthrit\$) adj3 (arthrit\$ or artrit\$ or diseas\$ or condition\$ or nodule\$)).mp. (60240)
- 3 exp Lung Diseases, Interstitial/ (57554)
- 4 exp Pulmonary Fibrosis/ (21497)
- 5 (interstitial adj3 lung adj3 disease\$.mp. (14632)
- 6 (interstitial adj3 pneumoni\$.mp. (10671)
- 7 alveolitis.mp. (6068)
- 8 (pulmonary adj3 fibros\$.mp. (29467)
- 9 exp Anti-Citrullinated Protein Antibodies/ (211)
- 10 cyclic citrullinated protein antibod\$.mp. (28)
- 11 cyclic citrullinated peptide antibod\$.mp. (664)
- 12 citrullinated protein antibod\$.mp. (798)
- 13 citrullinated peptide antibod\$.mp. (1001)
- 14 anti-CCP.mp. (1527)
- 15 ACPA.mp. (1369)
- 16 1 or 2 (157282)
- 17 3 or 4 or 5 or 6 or 7 or 8 (88395)

- 18 9 or 10 or 11 or 12 or 13 or 14 or 15 (3452)
- 19 16 and 17 and 18 (64)

EMBASE (Ovid) (1947 through 12 November 2019)

- 1 exp rheumatoid arthritis/ (218675)
- 2 ((rheumatoid or reumatoid or revmatoid or rheumatic or reumatic or revmatic or rheumat\$ or reumat\$ or revmarthrit\$) adj3 (arthrit\$or artrit\$ or diseas\$ or condition\$ or nodule\$)).mp. (106635)
- 3 exp interstitial lung disease/ (82134)
- 4 exp lung fibrosis/ (81580)
- 5 (interstitial adj3 lung adj3 disease\$).mp. (25821)
- 6 (interstitial adj3 pneumoni\$).mp. (22196)
- 7 alveolitis.mp. (29356)
- 8 (pulmonary adj3 fibros\$).mp. (32054)
- 9 exp cyclic citrullinated peptide antibody/ (6135)
- 10 cyclic citrullinated protein antibod\$.mp. (78)
- 11 cyclic citrullinated peptide antibod\$.mp. (6299)
- 12 citrullinated protein antibod\$.mp. (1603)
- 13 citrullinated peptide antibod\$.mp. (6704)
- 14 anti-CCP.mp. (4537)
- 15 ACPA.mp. (4424)
- 16 1 or 2 (285679)
- 17 3 or 4 or 5 or 6 or 7 or 8 (139209)
- 18 9 or 10 or 11 or 12 or 13 or 14 or 15 (11794)
- 19 16 and 17 and 18 (452)

Science Citation Index Expanded (Clarivate Analytics) (1900 through 12 November 2019)

#1 TS=(rheumatoid NEAR/3 arthritis or rheumatoid NEAR/3 disease\$ or rheumatoid NEAR/3 condition\$) (165,017)

#2 TS=("interstitial NEAR/3 lung NEAR/3 disease\$") OR TS=("interstitial NEAR/3 pneumoni*") OR TS=(alveolitis) OR TS=("pulmonary NEAR/3 fibros*") (4,751)

#3 TS=(anti cyclic citrullinated protein antibod* or anti cyclic citrullinated peptide antibod* or anti citrullinated protein antibod* or anti citrullinated peptide antibod* or anti CCP or ACPA) (4,483)

#3 #4 AND #5 AND #6 (2)

Cochrane Central Register of Controlled Trials (Cochrane Library) (accessed on the 12th of November 2019)

#1 MeSH descriptor: [Arthritis, Rheumatoid] explode all trees (5530)

#2 ((rheumatoid or reumatoid or revmatoid or rheumatic or reumatic or revmatic or rheumat* or reumat* or revmarthrit*) near/3(arthrit* or artrit* or diseas* or condition* or nodule*)):ti,ab,kw (17434)

#3 MeSH descriptor: [Lung Diseases, Interstitial] explode all trees (738)

#4 MeSH descriptor: [Pulmonary Fibrosis] explode all trees (429)

#5 interstitial near/3 lung near/3 disease*:ti,ab,kw (1017)

#6 interstitial near/3 pneumoni*:ti,ab,kw (619)

#7 alveolitis:ti,ab,kw (732)

#8 pulmonary near/3 fibros*:ti,ab,kw (1440)

#9 MeSH descriptor: [Anti-Citrullinated Protein Antibodies] explode all trees (6)

#10 (cyclic citrullinated protein antibod*):ti,ab,kw (105)

#11 (cyclic citrullinated peptide antibod*):ti,ab,kw (178)

#12 (citrullinated protein antibod*):ti,ab,kw (199)

#13 (citrullinated peptide antibod*):ti,ab,kw (225)

#14 anti-CCP:ti,ab,kw (335)

#15 ACPA:ti,ab,kw (292)

#16 OR #2 (17673)

#17 #3 OR #4 OR #5 OR #6 OR #7 OR #8 (3148)

#18 #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 (728)

#19 #16 AND #17 AND #18 (9)

Google Scholar (accessed on the 12th of November 2019)

("rheumatoid arthritis" OR "rheumatoid disease") ("interstitial lung disease" OR "interstitial pneumonia" OR "pulmonary fibrosis") ("anti cyclic citrullinated protein antibody" OR "anti cyclic citrullinated peptide antibody" OR "anti citrullinated protein antibody" OR "anti citrullinated peptide antibody")