

Supplementary Table 1. Search terms for EMBASE, Observational Studies

- 1 rheumatoid arthritis.mp. or exp rheumatoid arthritis/
- 2 (Rituximab or mabthera or rituxan or 174722-31-7).ti,ab,ot,hw,rn.
- 3 (Tocilizumab or roactemra or actemra or 375823-41-9).ti,ab,ot,hw,rn.
- 4 (Etanercept or Enbrel or 185243-69-0).ti,ab,ot,hw,rn.
- 5 or/2-4
- 6 DAS28*.ti,ab,ot,hw,rn.
- 7 HAQ-Di.ti,ab,ot,hw,rn.
- 8 Disease activity score.ti,ab,ot,hw,rn.
- 9 Disease activity score short form.ti,ab,ot,hw,rn.
- 10 Disability index of the Health assessment Questionnaire.ti,ab,ot,hw,rn.
- 11 or/6-10
- 12 exp case-control study/
- 13 Cohort analysis/
- 14 Longitudinal study/
- 15 Prospective study/
- 16 exp Follow-Up Studies/ or follow up.mp.
- 17 Case study/
- 18 cohort\$.ti,ab,ot.
- 19 (case\$ adj5 control\$).tw.
- 20 (case\$ and series).tw.
- 21 (case\$ adj2 report\$).tw.
- 22 (case\$ adj2 stud\$).tw.
- 23 ((observational adj3 (study or studies)) or observational).ti,ab,tw.

- 24 or/12-23
- 25 1 and 5 and 11 and 24
- 26 animal/
- 27 animal experiment/
- 28 (rat or rats or mouse or mice or murine or rodent or rodents or hamster or hamsters or pig or pigs or porcine or rabbit or rabbits or animal or animals or dogs or dog or cat or cats or cow or bovine or sheep or ovine or monkey or monkeys).ti,ab,ot,hw.
- 29 or/26-28
- 30 exp human/
- 31 exp human experiment/ or human experiment.mp.
- 32 or/30-31
- 33 29 not (29 and 32)
- 34 25 not 33
- 35 limit 34 to (adult or aged <65+ years>)
- 36 limit 35 to yr="1990-current"

Study design filter based on:

BMJ Evidence Centre Information Specialists. Study design search filter: Embase cohort, case-control, case series, and case study strategy [Internet]. London: BMJ Publishing Group Limited, 2012 [accessed 04.03.2015]. Available from: <http://clinicalevidence.bmj.com/x/set/static/ebm/learn/665076.html>

Supplementary Table 2. Search terms for Ovid MEDLINE, Observational Studies

- 1 rheumatoid arthritis.mp. or exp rheumatoid arthritis/
- 2 (Rituximab or mabthera or rituxan or 174722-31-7).ti,ab,ot,hw, rn.
- 3 (Tocilizumab or roactemra or actemra or 375823-41-9).ti,ab,ot,hw, rn.
- 4 (Etanercept or Enbrel or 185243-69-0).ti,ab,ot,hw, rn.
- 5 or/2-4
- 6 DAS28*.ti,ab,ot,hw, rn.
- 7 HAQ-Di.ti,ab,ot,hw, rn.
- 8 Disease activity score.ti,ab,ot,hw, rn.
- 9 Disease activity score short form.ti,ab,ot,hw, rn.
- 10 Disability index of the Health assessment Questionnaire.ti,ab,ot,hw, rn.
- 11 or/6-10
- 12 exp case-control studies/
- 13 case reports.pt.
- 14 epidemiologic methods/
- 15 controlled clinical trial.pt.
- 16 exp cohort studies/
- 17 observational.tw.
- 18 clinical practice.tw.
- 19 cohort\$.ti,ab,ot.
- 20 (case\$ and control\$).tw.
- 21 (case\$ and series).tw.
- 22 (case\$ adj2 report\$).tw.
- 23 (case\$ adj2 stud\$).tw.

- 24 (observational adj3 (study or studies)).ti,ab,tw.
- 25 or/12-24 ()
- 26 1 and 5 and 11 and 25
- 27 animal/
- 28 animal experiment/
- 29 (rat or rats or mouse or mice or murine or rodent or rodents or hamster or hamsters or pig or pigs or porcine or rabbit or rabbits or animal or animals or dogs or dog or cat or cats or cow or bovine or sheep or ovine or monkey or monkeys).ti,ab,ot,hw.
- 30 or/27-29
- 31 exp human/
- 32 exp Human Experimentation/ or human experiment.mp.
- 33 or/31-32
- 34 30 not (30 and 33)
- 35 26 not 34
- 36 limit 35 to "all adult (19 plus years)"
- 37 limit 36 to yr="1990-current"

Study design filter based on:

BMJ Evidence Centre Information Specialists. Study design search filter: Medline cohort, case-control, case series and case study strategy [Internet]. London: BMJ Publishing Group Limited, 2012 [accessed 04.03.2015]. Available from: <http://clinicalevidence.bmj.com/x/set/static/ebm/learn/665076.html>

Supplementary Table 3. Search terms for EMBASE, randomized controlled trials

- 1 rheumatoid arthritis.mp. or exp rheumatoid arthritis/
- 2 (Rituximab or mabthera or rituxan or 174722-31-7).ti,ab,ot,hw,rn.
- 3 (Tocilizumab or roactemra or actemra or 375823-41-9).ti,ab,ot,hw,rn.
- 4 (Etanercept or Enbrel or 185243-69-0).ti,ab,ot,hw,rn.
- 5 or/2-4
- 6 DAS28*.ti,ab,ot,hw,rn.
- 7 HAQ*.ti,ab,ot,hw,rn.
- 8 Disease activity score.ti,ab,ot,hw,rn.
- 9 Disease activity score short form.ti,ab,ot,hw,rn.
- 10 Disability index of the Health assessment Questionnaire.ti,ab,ot,hw,rn.
- 11 or/6-10 (13845)
- 12 (random\$ or placebo\$ or single blind\$ or double blind\$ or triple blind\$).ti,ab.
- 13 Retracted Article/
- 14 or/12-13
- 15 animal/
- 16 animal experiment/
- 17 (rat or rats or mouse or mice or murine or rodent or rodents or hamster or hamsters or pig or pigs or porcine or rabbit or rabbits or animal or animals or dogs or dog or cat or cats or cow or bovine or sheep or ovine or monkey or monkeys).ti,ab,ot,hw.
- 18 or/15-17
- 19 exp human/
- 20 exp human experiment/ or human experiment.mp.
- 21 or/19-20

- 22 (book or conference paper or editorial or letter or review).pt. not exp randomized controlled trial/
- 23 (random sampl\$ or random digit\$ or random effect\$ or random survey or random regression).ti,ab.
not exp randomized controlled trial/
- 24 14 not ((18 not 21) or 22 or 23)
- 25 1 and 5 and 11 and 24
- 26 limit 25 to (adult or aged <65+ years>)
- 27 limit 26 to yr="1990-current"

Study design filter based on:

BMJ Evidence Centre Information Specialists. Study design search filter: Embase randomized controlled trial strategy [Internet]. London: BMJ Publishing Group Limited, 2012 [accessed 27.04.2015].

Available from: <http://clinicalevidence.bmj.com/x/set/static/ebm/learn/665076.html>

Supplementary Table 4. Search terms for Ovid MEDLINE, randomized controlled trials

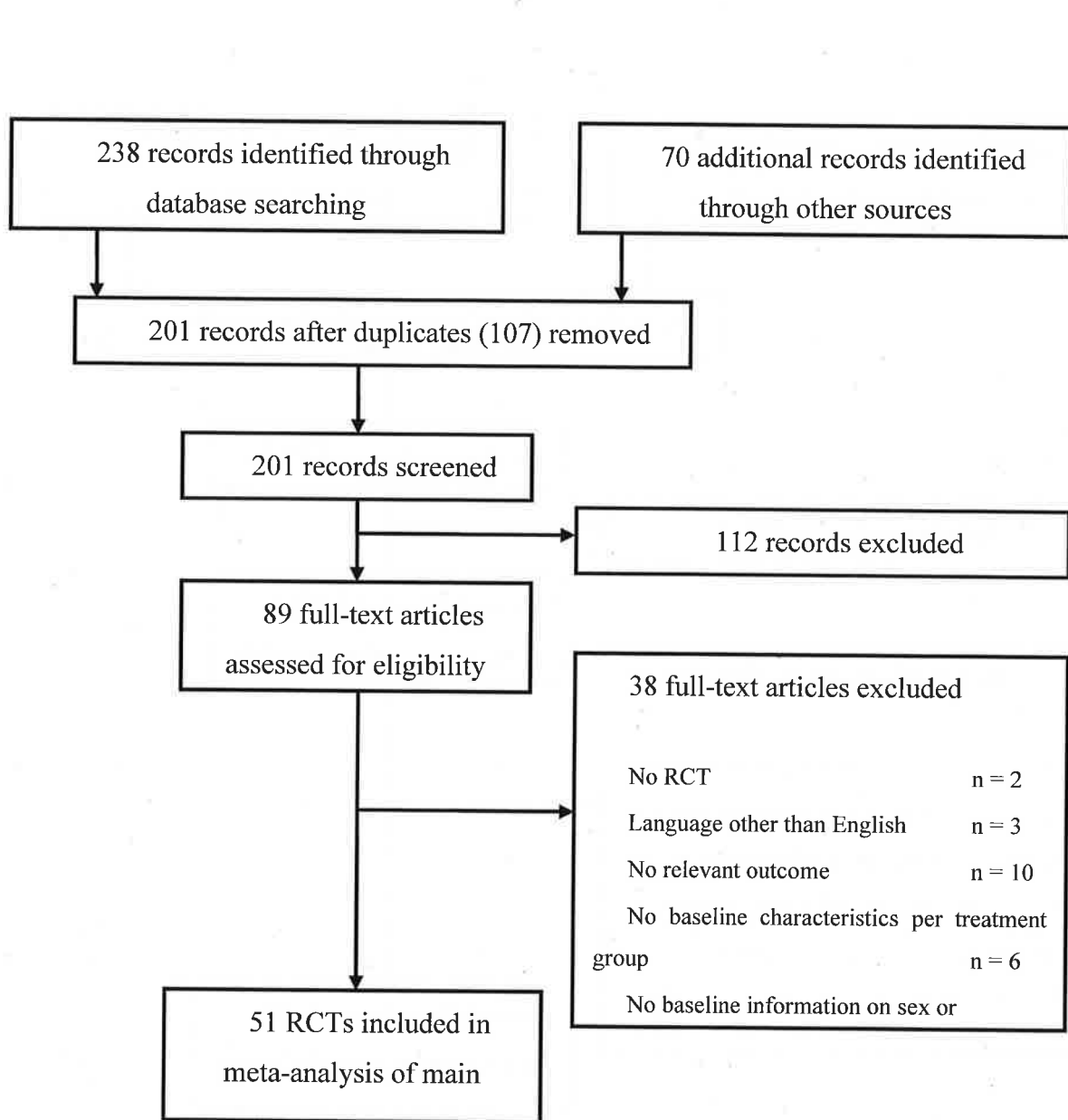
- 1 rheumatoid arthritis.mp. or exp rheumatoid arthritis/
- 2 (Rituximab or mabthera or rituxan or 174722-31-7).ti,ab,ot,hw,rn.
- 3 (Tocilizumab or roactemra or actemra or 375823-41-9).ti,ab,ot,hw,rn.
- 4 (Etanercept or Enbrel or 185243-69-0).ti,ab,ot,hw,rn.
- 5 or/2-4
- 6 DAS28*.ti,ab,ot,hw,rn.
- 7 HAQ*.ti,ab,ot,hw,rn.
- 8 Disease activity score.ti,ab,ot,hw,rn.
- 9 Disease activity score short form.ti,ab,ot,hw,rn.
- 10 Disability index of the Health assessment Questionnaire.ti,ab,ot,hw,rn.
- 11 or/6-10
- 12 "randomized controlled trial".pt.
- 13 (random\$ or placebo\$ or single blind\$ or double blind\$ or triple blind\$).ti,ab.
- 14 (retraction of publication or retracted publication).pt.
- 15 or/12-14
- 16 animal/
- 17 animal experiment/
- 18 (rat or rats or mouse or mice or murine or rodent or rodents or hamster or hamsters or pig or pigs or porcine or rabbit or rabbits or animal or animals or dogs or dog or cat or cats or cow or bovine or sheep or ovine or monkey or monkeys).ti,ab,ot,hw.
- 19 or/16-18
- 20 exp human/

- 21 exp human experiment/ or human experiment.mp.
- 22 or/20-21
- 23 ((comment or editorial or meta-analysis or practice-guideline or review or letter or journal correspondence) not "randomized controlled trial").pt.
- 24 (random sampl\$ or random digit\$ or random effect\$ or random survey or random regression).ti,ab.
not "randomized controlled trial".pt.
- 25 15 not ((19 not 22) or 23 or 24)
- 26 1 and 5 and 11 and 25
- 27 limit 26 to "all adult (19 plus years)"
- 28 limit 27 to yr="1990-current"

Study design filter based on:

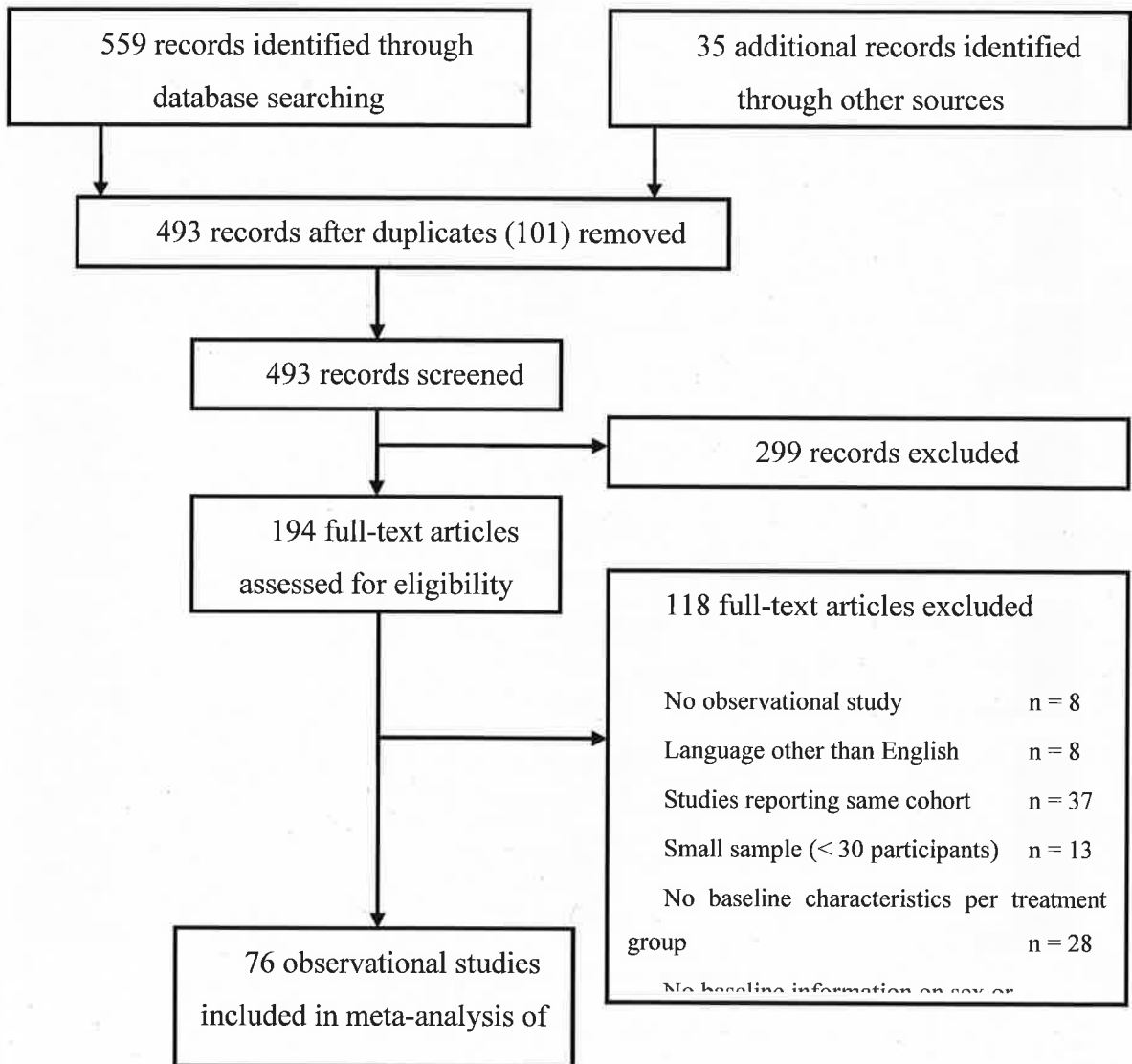
BMJ Evidence Centre Information Specialists. Study design search filter: Medline randomised controlled trial strategy [Internet]. London: BMJ Publishing Group Limited, 2012 [accessed 27.04.2015]. Available from: <http://clinicalevidence.bmj.com/x/set/static/ebm/learn/665076.html>

Supplementary Figure 1: Flow diagram for randomized controlled trials



ESR = erythrocyte sedimentation rate; CRP = C-reactive protein

Supplementary Figure 2: Flow diagram for observational studies

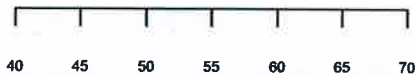
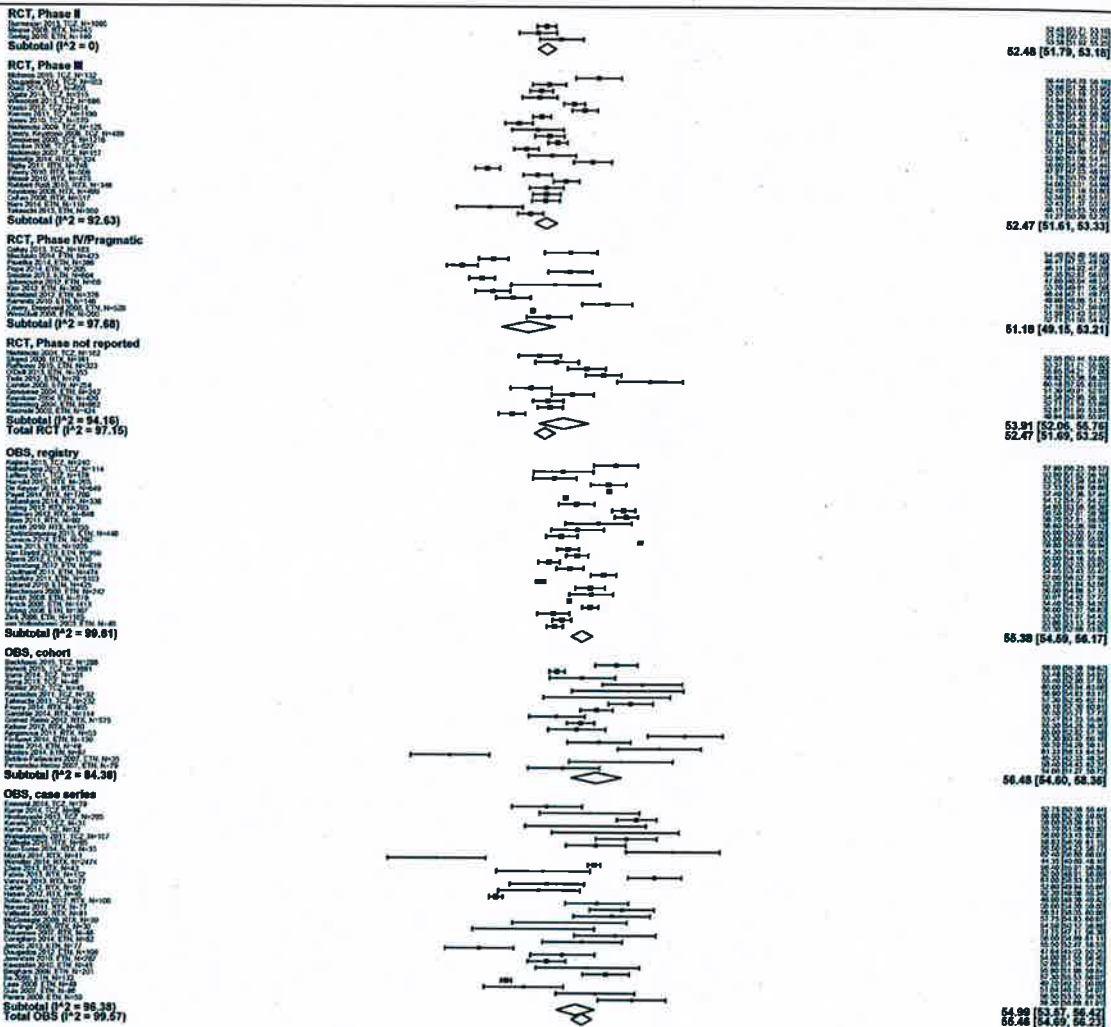


ESR = erythrocyte sedimentation rate; CRP = C-reactive protein

Supplementary Figure 3: Forest plot age

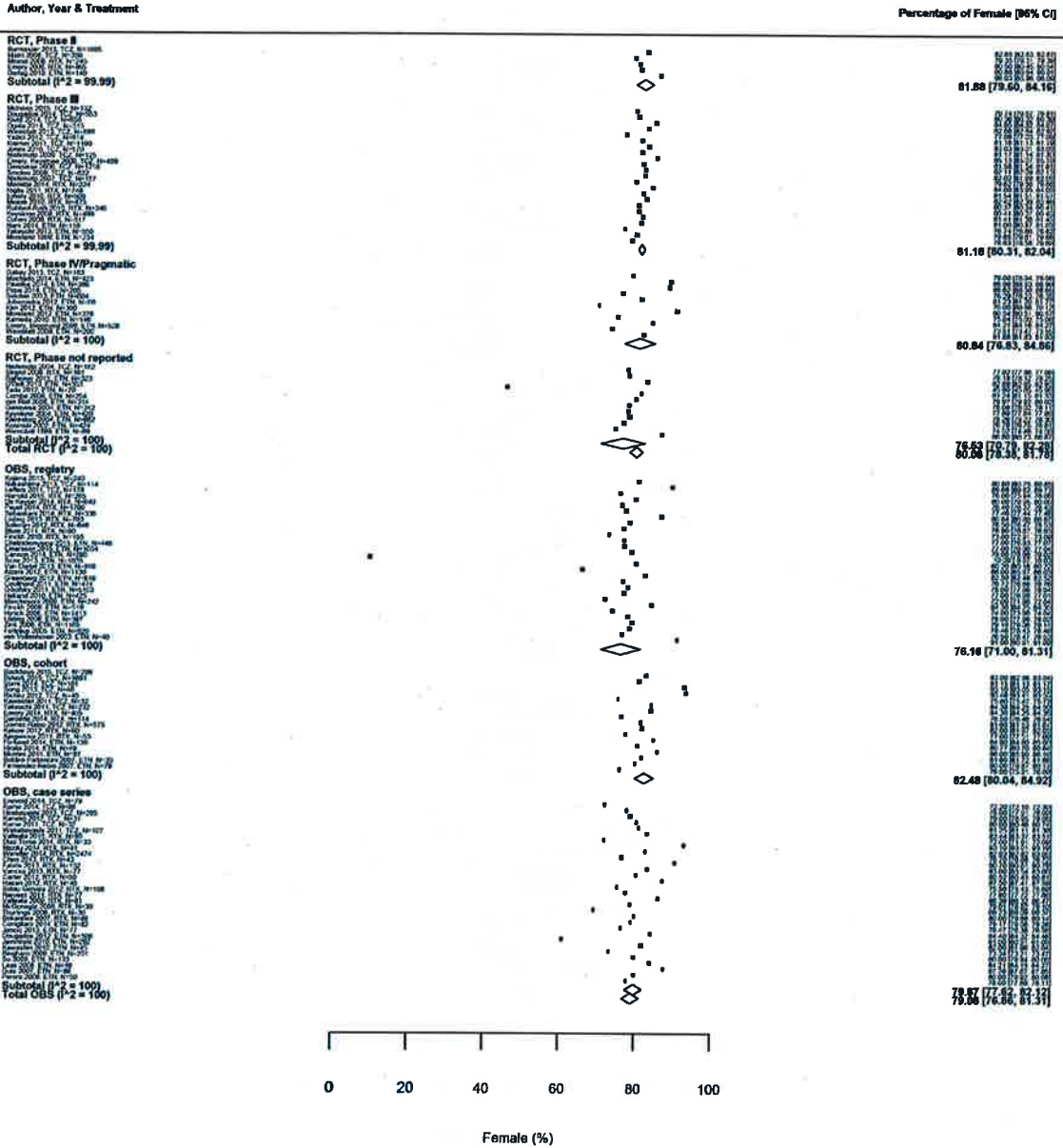
Author, Year & Treatment

Mean Age [95% CI]

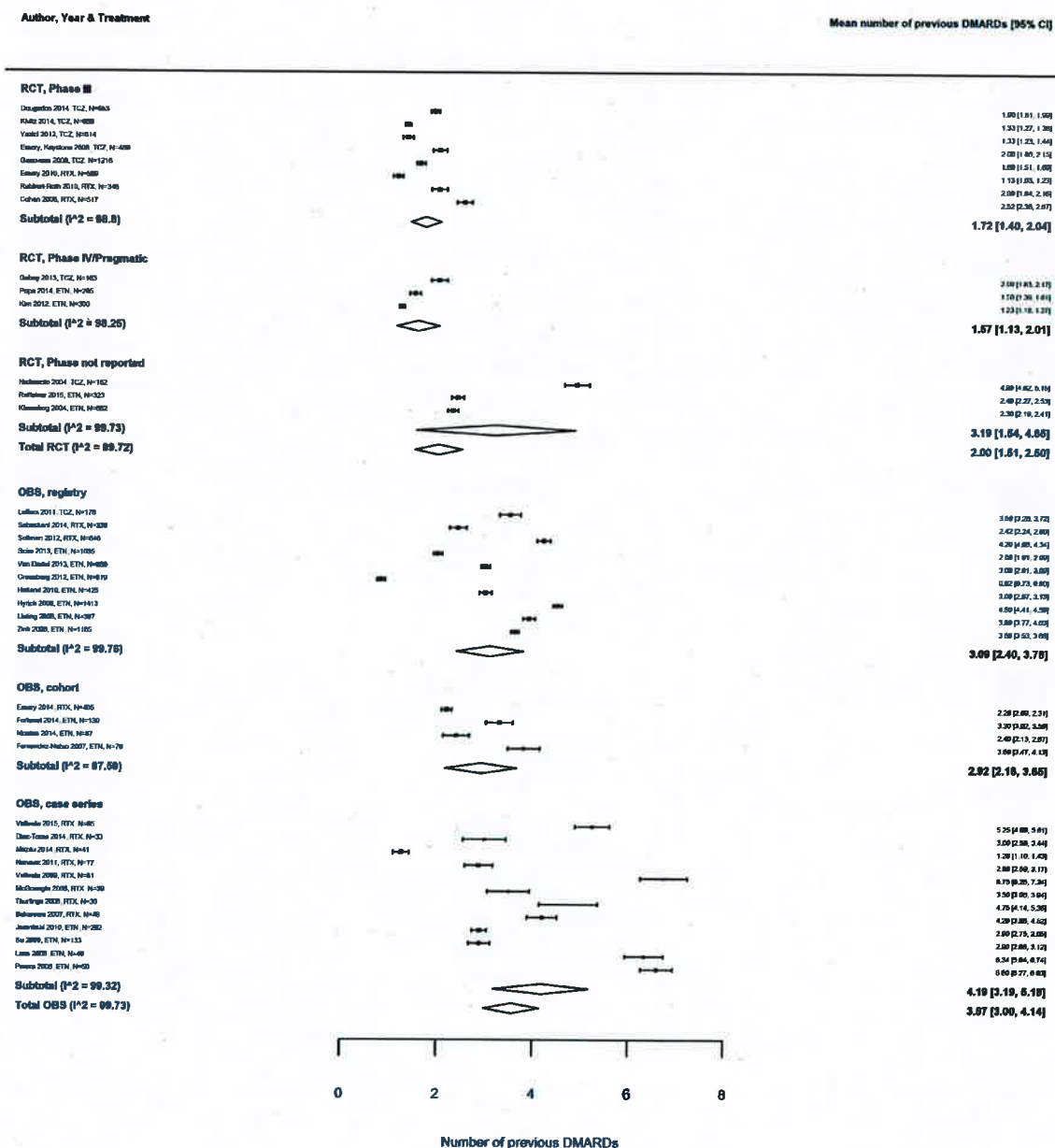


Age (yrs)

Supplementary Figure 4: Forest plot percentage of females



Supplementary Figure 6: Forest plot number of prior DMARDs



Supplementary Figure 8: Forest plot HAQ-DI

Author, Year & Treatment

Mean HAQ-DI at baseline [95% CI]

RCT, Phase II

Burstein 2013, TCZ, N=1000
Mason 2008, RTX, N=543
Gulley 2009, ETR, N=149

Subtotal (I² = 97.72)

1.63 [1.61, 1.66]
1.52 [1.44, 1.58]
1.64 [1.50, 1.77]

RCT, Phase III

Duque 2014, TCZ, N=503
Katz 2014, TCZ, N=494
Ogata 2014, TCZ, N=315
Werner 2011, TCZ, N=1199
Jansen 2016, TCZ, N=102
Foley-Kayakum 2009, TCZ, N=149
Gutierrez 2008, TCZ, N=1248
Sautou 2008, TCZ, N=622
Mason 2014, RTX, N=234
Pope 2011, RTX, N=484
Mason 2010, RTX, N=473
Furukawa 2008, RTX, N=489
Coffee 2008, RTX, N=517
Hart 2014, ETR, N=110
Takeda 2013, ETR, N=629

Subtotal (I² = 99.08)

1.47 [1.42, 1.52]
1.50 [1.45, 1.55]
1.21 [1.14, 1.29]
1.50 [1.47, 1.53]
1.64 [1.40, 1.89]
1.70 [1.65, 1.75]
1.50 [1.47, 1.53]
1.57 [1.52, 1.61]
1.60 [1.72, 1.68]
1.78 [1.74, 1.82]
1.50 [1.45, 1.55]
1.60 [1.52, 1.68]
1.60 [1.65, 1.55]
1.60 [1.62, 1.58]
1.60 [1.62, 1.58]

RCT, Phase IV/Pragmatic

Gulley 2013, TCZ, N=183
Mason 2014, ETR, N=423
Paukku 2014, ETR, N=288
Pace 2014, ETR, N=288
Sautou 2014, ETR, N=604
Kim 2012, ETR, N=300
Mason 2012, ETR, N=378
Kawachi 2010, ETR, N=148
Lewy, Deschamps 2008, ETR, N=138
Woolrich 2008, ETR, N=201

Subtotal (I² = 97.77)

1.60 [1.51, 1.68]
1.60 [1.53, 1.67]
1.11 [1.07, 1.15]
1.44 [1.26, 1.59]
1.60 [1.60, 1.59]
1.40 [1.32, 1.48]
1.50 [1.52, 1.48]
1.54 [1.52, 1.56]
1.60 [1.50, 1.71]
1.51 [1.25, 1.47]

RCT, Phase not reported

Stein 2008, RTX, N=84
O'Dell 2013, ETR, N=353
Tate 2012, ETR, N=79
Lundin 2008, ETR, N=24
Gomova 2009, ETR, N=242

Subtotal (I² = 99.39)

1.62 [1.63, 2.09]
1.65 [1.37, 1.58]
1.60 [1.61, 1.69]
1.64 [1.64, 1.74]
1.51 [1.46, 1.61]

Total RCT (I² = 99.3)

1.50 [1.19, 1.61]
1.49 [1.40, 1.65]

OBS, registry

Goldstein 2014, RTX, N=209
Sullivan 2012, RTX, N=404
Blau 2011, RTX, N=80
Fischl 2010, RTX, N=80
Chakraborty 2015, ETR, N=380
Sims 2013, ETR, N=400
Van Daele 2013, ETR, N=80
Alam 2012, ETR, N=130
Coffman 2011, ETR, N=474
Gulley 2011, ETR, N=503
Hochmann 2009, ETR, N=242
Fisher 2008, ETR, N=616
Hyslop 2008, ETR, N=413
van Vollenhoven 2003, ETR, N=40

Subtotal (I² = 99.78)

1.61 [1.43, 1.88]
2.00 [1.88, 2.05]
1.63 [1.36, 1.89]
1.61 [1.48, 1.65]
1.50 [1.14, 1.78]
1.53 [1.29, 1.78]
1.50 [1.25, 1.52]
1.64 [1.40, 1.89]
2.02 [2.00, 2.05]
1.57 [1.26, 1.59]
1.61 [1.30, 1.69]
1.57 [1.29, 1.78]
2.00 [2.00, 2.13]
1.60 [1.60, 1.69]

1.58 [1.42, 1.74]

OBS, cohort

Byamb 2013, TCZ, N=881
Isard 2014, TCZ, N=193
Yalman 2011, TCZ, N=252
Lewy 2014, RTX, N=80
Keller 2012, RTX, N=80
Alegre 2011, RTX, N=51
Mason 2014, ETR, N=47
Bridson-Peterson 2007, ETR, N=35
Fernandez-Heras 2007, ETR, N=79

Subtotal (I² = 93.6)

1.53 [1.50, 1.59]
1.60 [1.46, 1.70]
1.60 [1.46, 1.89]
1.60 [1.42, 1.66]
1.60 [1.60, 2.00]
1.50 [1.37, 1.63]
1.47 [1.31, 1.62]
1.74 [1.46, 2.02]
1.78 [1.60, 1.80]

1.55 [1.41, 1.65]

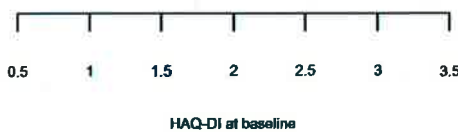
OBS, case series

Kerr 2011, TCZ, N=27
Dini-Yates 2014, RTX, N=23
Wardlaw 2014, RTX, N=274
Hsu 2012, RTX, N=60
Narayan 2011, RTX, N=77
Valente 2009, RTX, N=81
Jansen 2012, ETR, N=77
Rughani 2008, ETR, N=21
Peters 2009, ETR, N=90

Subtotal (I² = 99.03)

Total OBS (I² = 99.68)

1.60 [1.55, 1.77]
1.60 [1.24, 1.72]
1.60 [1.57, 1.63]
2.00 [2.00, 2.18]
1.67 [1.42, 1.71]
1.60 [1.37, 1.89]
1.63 [1.60, 1.71]
1.60 [1.53, 1.67]
1.60 [1.76, 2.04]
1.63 [1.28, 1.98]
1.58 [1.46, 1.71]



Supplementary Figure 9: Forest plot CRP values

Author, Year & Treatment

Mean CRP [95% CI]

RCT, Phase II

Barronick 2013, TCZ, N=1805
 Gavig 2016, ETN, N=140
Subtotal (#2 = 93.66)

21.46 [21.16, 22.81]
24.91 [17.88, 31.95]

RCT, Phase III

Mitchem 2016, TCZ, N=132
 Kikizi 2014, TCZ, N=488
 Ogden 2014, TCZ, N=1011
 Wadland 2013, TCZ, N=888
 Kanner 2011, TCZ, N=1181
 Jones 2010, TCZ, N=570
 Hoshino 2009, TCZ, N=129
 Emery 2009, TCZ, N=1000
 Gombos 2008, TCZ, N=1210
 Gaudin 2008, TCZ, N=522
 Michimoto 2007, TCZ, N=157
 Maimon 2016, RTX, N=224
 Rigby 2011, RTX, N=746
 Akman 2016, RTX, N=475
 Rubinfeld 2015, RTX, N=348
 Kogut 2008, RTX, N=480
 Cohen 2008, RTX, N=577
 Takemai 2013, ETN, N=550
Subtotal (#2 = 98.33)

11.56 [1.33, 13.79]
 19.83 [17.88, 21.88]
 23.44 [19.88, 27.00]
 13.84 [13.54, 14.14]
 24.88 [23.33, 26.43]
 26.46 [27.73, 25.19]
 30.77 [28.83, 32.71]
 31.78 [28.13, 35.43]
 28.88 [24.87, 32.89]
 25.48 [23.38, 27.58]
 47.88 [42.46, 53.34]
 48.42 [47.16, 49.68]
 32.82 [30.97, 34.68]
 32.72 [17.42, 48.02]
 27.78 [25.19, 25.47]
 27.54 [24.18, 30.89]
 27.32 [24.38, 30.26]
 24.88 [19.81, 29.85]
27.27 [23.61, 31.53]

RCT, Phase IV/Pragmatic

Gatway 2013, TCZ, N=183
 Maitland 2014, ETN, N=422
 Paudyal 2014, ETN, N=388
 Pappa 2014, ETN, N=285
 Frenkel 2013, ETN, N=484
 Johnson 2017, ETN, N=450
 Kim 2012, ETN, N=380
 Karande 2016, ETN, N=145
 Emery 2008, ETN, N=328
 Wadland 2008, ETN, N=520
Subtotal (#2 = 98.52)

28.88 [21.24, 36.79]
 20.74 [16.46, 25.02]
 37.58 [18.38, 56.88]
 22.55 [19.48, 25.62]
 17.48 [16.12, 18.82]
 49.23 [11.34, 87.12]
 37.88 [34.18, 41.58]
 28.88 [22.43, 35.33]
 38.72 [33.73, 43.71]
 4.02 [1.13, 10.92]
18.71 [13.21, 24.21]

RCT, Phase not reported

Hoshino 2009, TCZ, N=1002
 Shand 2008, RTX, N=81
 Turk 2012, ETN, N=78
 Gombos 2008, ETN, N=342
 Karim 2004, ETN, N=882
Subtotal (#2 = 98.87)
Total RCT (#2 = 98.88)

47.88 [42.81, 52.95]
 29.24 [24.47, 34.01]
 30.88 [28.18, 33.58]
 20.71 [17.47, 23.95]
 38.58 [38.17, 38.99]
29.33 [18.64, 39.02]
24.89 [21.76, 28.23]

OBS, registry

Kojima 2015, TCZ, N=40
 Nakamura 2013, TCZ, N=114
 Payer 2014, RTX, N=102
 Subram 2012, RTX, N=68
 Blum 2011, RTX, N=60
 Ludwig 2008, ETN, N=287
 Ziv 2008, ETN, N=188
Subtotal (#2 = 99.47)

7.83 [2.46, 13.21]
 32.88 [28.28, 37.48]
 34.28 [31.27, 37.48]
 48.88 [45.28, 52.48]
 22.88 [20.44, 25.32]
 27.88 [25.44, 30.32]
 21.88 [19.44, 24.32]
21.25 [13.49, 29.01]

OBS, cohort

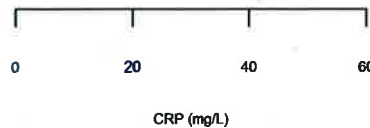
Bachmann 2015, TCZ, N=268
 Rybak 2015, TCZ, N=881
 Izumi 2014, TCZ, N=101
 Kony 2013, TCZ, N=48
 Rodas 2012, TCZ, N=49
 Karamali 2011, TCZ, N=22
 Takemai 2011, TCZ, N=22
 Emery 2014, RTX, N=40
 Gombos 2014, RTX, N=14
 Koller 2012, RTX, N=40
 Aguerre 2011, RTX, N=20
 Fekete 2014, ETN, N=128
 Hoshino 2014, ETN, N=48
 Mikes 2014, ETN, N=87
 Formica 2007, ETN, N=78
Subtotal (#2 = 99.68)

24.88 [20.18, 29.58]
 48.88 [47.88, 49.88]
 19.88 [14.71, 25.05]
 32.78 [30.88, 34.68]
 28.28 [18.12, 38.44]
 3.81 [1.73, 6.47]
 28.18 [22.67, 33.69]
 17.88 [15.47, 19.88]
 57.88 [55.24, 60.52]
 33.88 [34.18, 33.58]
 7.28 [4.56, 10.00]
 10.71 [9.34, 12.38]
 21.18 [19.54, 22.78]
23.26 [16.37, 30.16]

OBS, case series

Eyraud 2014, TCZ, N=78
 Hoshino 2013, TCZ, N=205
 Karim 2011, TCZ, N=2
 Wadland 2011, TCZ, N=107
 Diaz-Tena 2014, RTX, N=33
 Maku 2014, RTX, N=41
 Chen 2013, RTX, N=43
 Hansen 2012, RTX, N=45
 Naveau 2011, RTX, N=77
 Vahouni 2008, RTX, N=81
 Nakagawa 2008, RTX, N=20
 Comellas 2014, ETN, N=82
 Jansen 2013, ETN, N=17
 Dougen 2012, ETN, N=98
 Jansen 2013, ETN, N=292
 Hoshino 2010, ETN, N=67
 Su 2008, ETN, N=13
 Chen 2007, ETN, N=49
 Pappa 2008, ETN, N=50
Subtotal (#2 = 99.79)
Total OBS (#2 = 99.81)

43.28 [39.72, 46.79]
 2.91 [1.27, 4.55]
 10.88 [8.38, 13.38]
 2.91 [1.78, 4.04]
 29.58 [24.14, 35.02]
 22.48 [13.88, 31.08]
 27.88 [20.42, 35.34]
 22.24 [18.11, 26.37]
 18.54 [15.28, 21.80]
 52.88 [49.18, 56.58]
 20.88 [19.88, 21.88]
 30.88 [28.28, 33.48]
 21.18 [14.48, 27.88]
 41.88 [34.44, 49.32]
 21.18 [15.44, 26.92]
 38.28 [30.83, 45.73]
24.87 [17.90, 31.84]
23.26 [18.29, 27.23]



Supplementary Figure 10: Forest plot ESR values

Author, Year & Treatment

Mean ESR [95% CI]

RCT, Phase II

Geisler 2010, ETR, N=142
Subtotal (I² = 0)

56.83 [53.16, 60.56]

RCT, Phase III

Alley 2014, VCZ, N=688
 Ogino 2014, TCZ, N=234
 Yama 2012, TCZ, N=814
 Kawan 2011, VCZ, N=1588
 Jansen 2010, TCZ, N=570
 Makiuchi 2008, VCZ, N=125
 Emery, Regimens 2008, VCZ, N=688
 Cummings 2008, VCZ, N=278
 Suedan 2008, TCZ, N=622
 Makiuchi 2007, VCZ, N=125
 Makiuchi 2004, VCZ, N=224
 Ngaly 2001, VCZ, N=748
 Hwang 2004, VCZ, N=975
 Robinson-Peters 2008, VCZ, N=280
 Koyama 2008, VCZ, N=400
 Cohen 2008, VCZ, N=517
 Takahashi 2003, VCZ, N=500
Subtotal (I² = 95.68)

50.43 [48.51, 52.35]
 48.28 [45.80, 50.87]
 48.47 [46.03, 50.91]
 48.27 [44.98, 47.08]
 49.63 [47.42, 51.85]
 51.60 [47.41, 55.78]
 51.31 [48.71, 53.93]
 48.04 [46.97, 50.09]
 50.88 [47.84, 53.11]
 48.20 [43.44, 75.16]
 46.20 [43.44, 48.48]
 59.21 [57.19, 61.27]
 43.12 [40.77, 45.47]
 49.74 [44.97, 49.49]
 48.85 [45.74, 50.37]
 48.15 [45.07, 50.42]
 42.79 [40.42, 45.19]
49.79 [46.76, 52.82]

RCT, Phase IV/Pragmatic

Geisler 2010, ETR, N=142
 Makiuchi 2004, ETR, N=125
 Pevsner 2014, ETR, N=280
 Papp 2014, ETR, N=280
 Suedan 2013, ETR, N=622
 Kim 2010, ETR, N=280
 Makiuchi 2007, ETR, N=125
 Karamba 2009, ETR, N=280
 Emery, Regimens 2008, ETR, N=688
 Wewers 2014, ETR, N=280
Subtotal (I² = 89.53)

50.50 [48.05, 54.95]
 43.89 [41.48, 46.31]
 22.17 [20.08, 23.34]
 22.38 [19.83, 24.82]
 21.28 [20.37, 22.40]
 39.49 [37.01, 41.97]
 33.43 [31.71, 35.14]
 59.59 [55.15, 64.03]
 48.54 [46.89, 50.39]
 38.48 [27.27, 33.71]
38.73 [29.63, 47.82]

RCT, Phase not reported

Makiuchi 2004, VCZ, N=125
 Suedan 2008, VCZ, N=622
 O'Fallon 2013, ETR, N=280
 Yama 2012, ETR, N=814
 Coombs 2008, ETR, N=280
 Cummings 2008, ETR, N=278
Subtotal (I² = 88.36)
Total RCT (I² = 93.04)

49.18 [46.51, 73.87]
 51.28 [47.29, 55.29]
 28.41 [26.19, 29.72]
 47.43 [45.83, 54.62]
 37.89 [34.43, 40.95]
 47.17 [44.88, 50.67]
48.87 [35.86, 67.94]
46.27 [42.36, 50.17]

OBS, registry

McQuinn 2015, VCZ, N=280
 Makiuchi 2010, VCZ, N=114
 Papp 2014, VCZ, N=280
 Salazar 2012, VCZ, N=688
 Hwang 2014, VCZ, N=975
 Van Dessel 2013, ETR, N=688
 Hwang 2008, ETR, N=142
 Loring 2008, ETR, N=500
 Jahn 2008, ETR, N=142
 van Halbeek 2003, ETR, N=142
Subtotal (I² = 89.5)

63.59 [60.72, 66.07]
 53.07 [51.48, 54.66]
 34.55 [33.38, 35.74]
 44.88 [42.29, 46.01]
 31.69 [29.57, 33.63]
 23.47 [22.40, 24.94]
 24.47 [23.29, 25.65]
 59.09 [48.54, 51.46]
 35.87 [33.18, 38.56]
 33.89 [32.55, 35.39]
 37.49 [36.35, 38.62]
39.23 [31.96, 48.50]

OBS, cohort

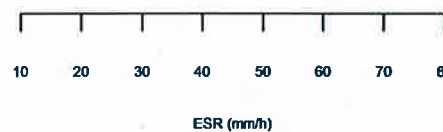
Bloch 2015, VCZ, N=280
 Rivara 2015, VCZ, N=688
 Jahn 2014, VCZ, N=142
 Richman 2012, VCZ, N=688
 Koyama 2011, VCZ, N=400
 Takahashi 2011, VCZ, N=500
 Emery 2014, VCZ, N=688
 Gombay 2014, VCZ, N=142
 Makiuchi 2012, ETR, N=125
 Aghajani 2011, VCZ, N=688
 Fernandez 2014, ETR, N=280
 Makiuchi 2014, ETR, N=125
 Fernandez-Peters 2007, ETR, N=280
Subtotal (I² = 86.74)

38.00 [33.11, 39.89]
 39.89 [37.81, 43.37]
 59.70 [43.85, 57.42]
 38.88 [37.03, 43.37]
 62.20 [50.31, 74.18]
 63.09 [59.27, 66.72]
 38.00 [36.33, 41.53]
 38.87 [38.08, 39.28]
 38.48 [37.18, 40.71]
 43.00 [40.41, 50.88]
 34.20 [30.78, 38.82]
 33.00 [29.51, 36.46]
 33.00 [27.37, 38.00]
40.72 [34.82, 48.82]

OBS, case series

Haskapoulos 2013, VCZ, N=280
 Hwang 2015, VCZ, N=975
 Makiuchi 2011, VCZ, N=125
 Das-Saunier 2014, VCZ, N=142
 Makiuchi 2014, VCZ, N=125
 Vazquez 2013, VCZ, N=125
 Hwang 2012, VCZ, N=975
 Hwang 2011, VCZ, N=975
 Vazquez 2008, VCZ, N=125
 Theodorou 2008, VCZ, N=125
 Campbell 2014, ETR, N=280
 Jansen 2010, ETR, N=570
 Koyama 2008, ETR, N=400
 So 2008, ETR, N=142
 Papp 2014, ETR, N=280
Subtotal (I² = 97.2)
Total OBS (I² = 96.67)

50.80 [48.70, 64.41]
 29.00 [26.37, 31.42]
 48.33 [44.97, 49.69]
 57.40 [47.88, 68.62]
 42.23 [40.88, 43.84]
 39.20 [36.41, 41.89]
 38.50 [33.08, 37.02]
 48.25 [45.48, 54.40]
 49.55 [44.80, 53.79]
 37.00 [35.08, 43.34]
 31.20 [28.42, 33.98]
 25.00 [23.81, 27.58]
 61.70 [41.15, 72.26]
 55.81 [50.47, 60.75]
 66.20 [61.85, 64.55]
43.76 [37.98, 48.54]
41.44 [37.89, 44.99]



Supplementary Figure 11: Forest plot RF positivity

Author, Year & Treatment

Percentage of RF positive [95% CI]

RCT, Phase II

Burvenko 2013, TCZ, N=186
 Meek 2006, TCZ, N=208
Subtotal (I² = 100)

73.98 [73.92, 73.99]
 87.21 [87.17, 87.24]
80.48 [87.88, 83.27]

RCT, Phase III

Demicheli 2014, TCZ, N=393
 Kaku 2014, TCZ, N=85
 Ogata 2014, TCZ, N=151
 Kover 2011, TCZ, N=180
 Doolan 2008, TCZ, N=222
 Madala 2014, RTX, N=224
 Bigly 2011, RTX, N=148
 Fawzy 2018, RTX, N=309
 Mason 2010, RTX, N=175
 R. Albert 2018, RTX, N=348
 Kojouharova 2008, RTX, N=499
 Cohen 2008, RTX, N=517
 Rupp 2018, RTX, N=110
 Talamaci 2013, ETN, N=509
 Moshiri 1988, ETN, N=224
Subtotal (I² = 100)

85.23 [85.19, 85.26]
 81.11 [81.08, 81.14]
 81.82 [81.79, 81.85]
 82.83 [82.81, 82.85]
 78.98 [78.95, 79.02]
 83.00 [82.94, 83.05]
 85.37 [85.34, 85.40]
 74.05 [74.01, 74.08]
 79.38 [79.33, 79.43]
 71.15 [71.10, 71.20]
 79.41 [79.38, 79.44]
 79.08 [79.05, 79.11]
 79.00 [79.00, 79.00]
 78.43 [78.40, 78.47]
 80.05 [80.00, 80.10]
75.38 [71.21, 79.56]

RCT, Phase IV/Pragmatic

Colby 2013, TCZ, N=183
 Michalek 2014, E18, N=423
 Panchan 2013, ETN, N=208
 Page 2014, ETN, N=205
 Smith 2013, ETN, N=484
 Jaramolina 2012, ETN, N=409
 Malmgren 2010, ETN, N=218
 Karamda 2010, ETN, N=148
 Wessman 2006, ETN, N=300
Subtotal (I² = 100)

75.00 [74.93, 75.01]
 85.28 [85.26, 85.42]
 79.84 [79.83, 79.89]
 84.57 [84.51, 84.84]
 77.78 [77.69, 77.75]
 85.00 [84.91, 85.09]
 85.00 [84.91, 85.09]
 83.50 [83.46, 83.54]
78.00 [71.42, 84.57]

RCT, Phase not reported

Ordel 2013, ETN, N=383
 van Riel 2005, ETN, N=14
 Gammone 2004, ETN, N=502
 Fontana 2003, ETN, N=502
 Fawzy 2004, ETN, N=483
 Fawzy 2003, ETN, N=424
 Warden 1998, ETN, N=489
Subtotal (I² = 100)

88.39 [88.25, 88.53]
 76.77 [76.17, 78.37]
 71.06 [70.94, 71.08]
 80.28 [80.22, 80.33]
 80.30 [80.27, 80.33]
 88.18 [88.08, 88.13]
 88.18 [88.08, 88.13]
73.88 [88.22, 81.38]
76.07 [73.00, 78.14]

OBS, registry

Harrod 2015, RTX, N=172
 Page 2014, RTX, N=178
 Subramanian 2014, RTX, N=336
 Lohrey 2013, RTX, N=103
 Salzman 2012, RTX, N=688
 Blum 2011, RTX, N=920
 French 2010, RTX, N=155
 Christodoulopoulos 2010, ETN, N=420
 Casanova 2014, ETN, N=200
 Scola 2013, ETN, N=100
 Van Daele 2013, ETN, N=889
 Azzam 2012, ETN, N=130
 Costantini 2011, ETN, N=474
 Ouedraogo 2011, ETN, N=303
 Moushinski 2009, ETN, N=242
 French 2008, ETN, N=610
 Hirsch 2008, ETN, N=1413
 French 2008, ETN, N=818
 Ziv 2008, ETN, N=138
 van Vollenhoven 2003, ETN, N=40
Subtotal (I² = 100)

70.18 [70.04, 70.31]
 78.84 [78.72, 78.95]
 74.25 [74.11, 74.45]
 80.30 [80.27, 80.33]
 85.00 [84.91, 85.09]
 77.05 [76.91, 77.09]
 80.00 [80.00, 80.00]
 84.58 [84.51, 84.64]
 80.00 [80.00, 80.00]
 88.88 [88.87, 88.88]
 85.00 [84.97, 85.03]
 70.19 [70.20, 70.22]
 82.00 [81.97, 82.03]
 74.00 [73.94, 74.05]
 78.00 [77.98, 78.04]
 72.00 [71.99, 72.02]
 82.18 [82.18, 82.18]
 85.18 [85.17, 85.19]
 82.00 [81.99, 82.01]
76.95 [73.48, 80.43]

OBS, cohort

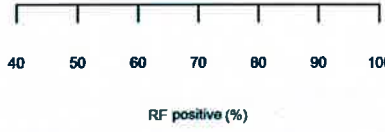
Bachmann 2015, TCZ, N=298
 Izumi 2014, TCZ, N=191
 Hether 2012, TCZ, N=165
 Emery 2014, RTX, N=400
 Desai 2014, RTX, N=114
 Daneshmandi 2012, RTX, N=675
 Koller 2012, RTX, N=40
 Argente 2011, RTX, N=43
 Fehlandt 2014, ETN, N=100
 Hesse 2014, ETN, N=49
 Martin 2014, ETN, N=97
 Fernandez-Noboa 2007, ETN, N=79
Subtotal (I² = 100)

89.00 [89.04, 89.09]
 80.00 [79.92, 80.08]
 77.80 [77.68, 77.83]
 84.18 [84.26, 84.14]
 78.28 [78.12, 78.38]
 84.38 [84.28, 84.34]
 74.48 [74.31, 74.65]
 88.10 [88.09, 88.14]
 71.88 [71.72, 71.88]
 85.00 [84.98, 85.03]
 86.48 [86.33, 86.63]
 77.00 [76.91, 77.09]
77.09 [70.32, 83.86]

OBS, case series

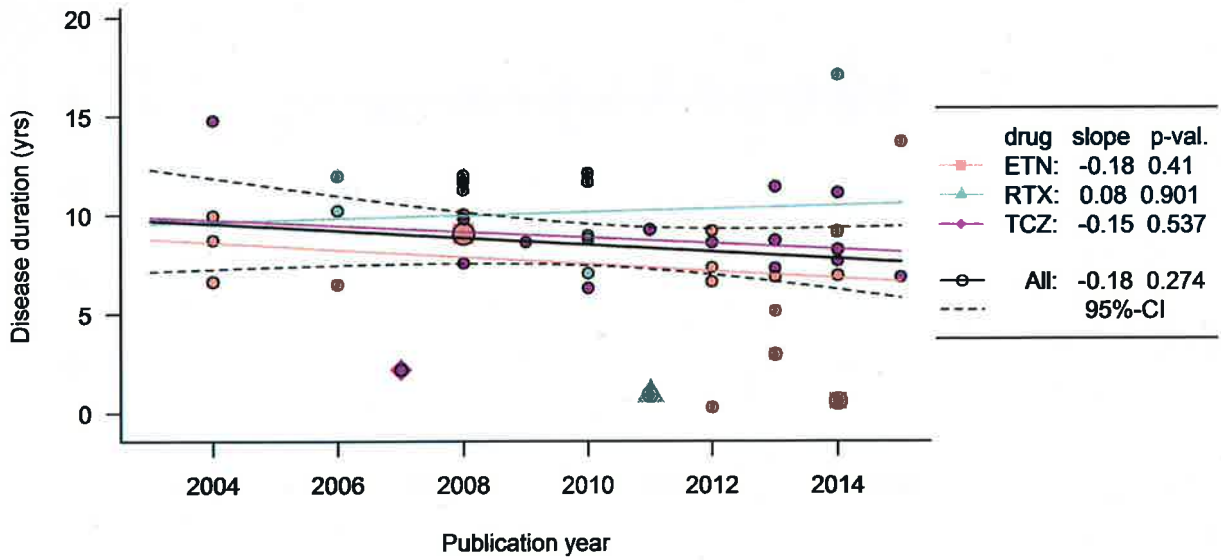
Eravil 2014, TCZ, N=79
 Karim 2014, TCZ, N=88
 Karim 2012, TCZ, N=31
 Karim 2011, TCZ, N=32
 Das-Tanaka 2014, RTX, N=33
 Machi 2014, RTX, N=41
 Wernke 2014, RTX, N=214
 Fawzy 2013, RTX, N=152
 Varca 2013, RTX, N=77
 Carter 2012, RTX, N=50
 Narayan 2011, RTX, N=77
 Valente 2008, RTX, N=61
 McDonough 2008, RTX, N=29
 Dolan 2007, RTX, N=49
 Cavigliani 2014, ETN, N=32
 Jais 2013, ETN, N=87
 Jaramolina 2010, ETN, N=202
 Stegmann 2008, ETN, N=201
 Su 2000, ETN, N=13
 Laine 2000, ETN, N=48
 Cui 2007, ETN, N=48
 French 2005, ETN, N=69
Subtotal (I² = 100)

85.80 [85.70, 85.89]
 83.88 [84.82, 85.05]
 87.78 [88.88, 87.27]
 78.28 [78.28, 78.34]
 83.18 [83.11, 83.38]
 87.18 [87.18, 87.28]
 77.28 [77.28, 77.32]
 83.00 [83.04, 83.08]
 52.00 [51.88, 52.11]
 77.00 [76.88, 77.12]
 88.88 [88.78, 88.97]
 81.10 [81.08, 81.22]
 83.38 [83.23, 83.65]
 83.38 [83.28, 83.48]
 47.88 [47.78, 48.01]
 72.00 [71.93, 72.03]
 86.00 [85.82, 86.01]
 82.88 [82.78, 82.82]
 85.75 [85.58, 85.91]
 82.88 [82.78, 82.91]
 88.00 [87.88, 88.12]
76.29 [70.40, 82.18]
76.72 [73.86, 78.77]

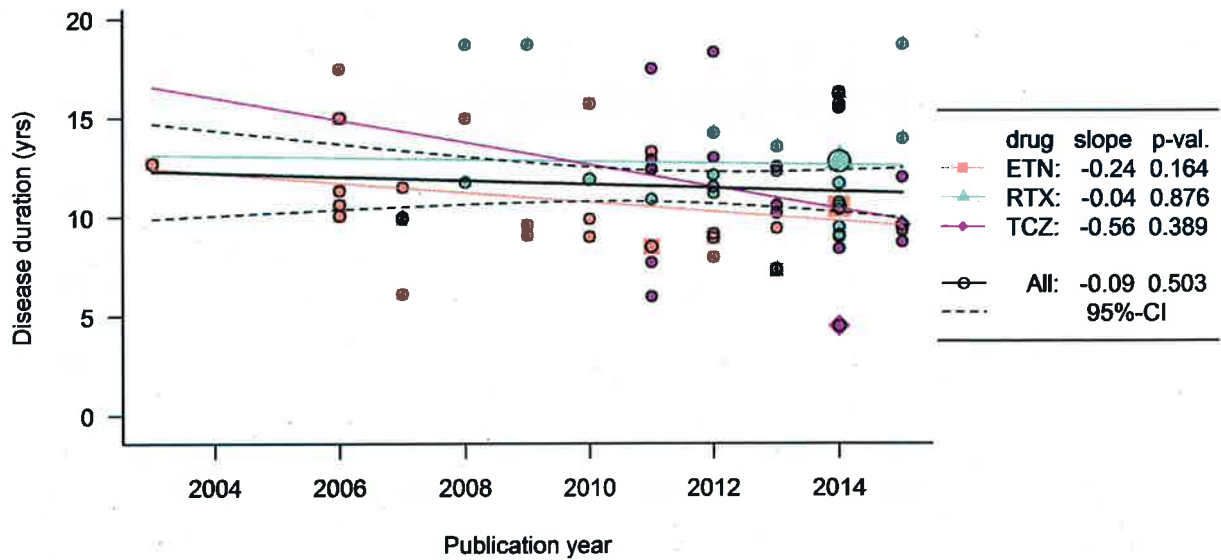


Supplementary Figure 12: Comparison of disease duration between randomized controlled trials and observational studies plotted over time

Randomized controlled trials, all drugs

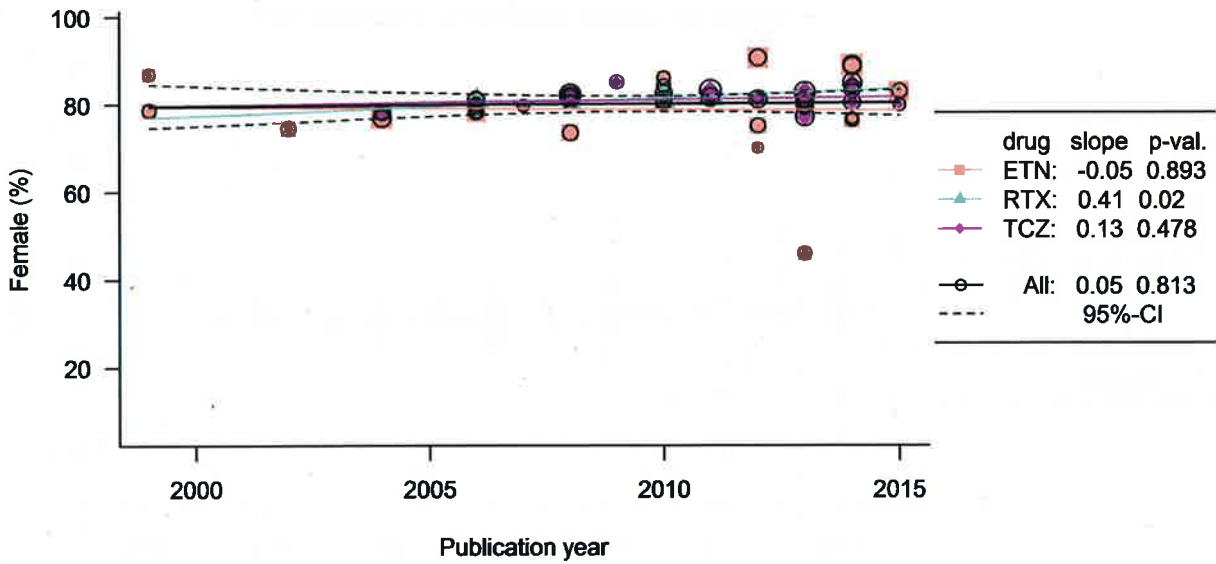


Observational studies, all drugs

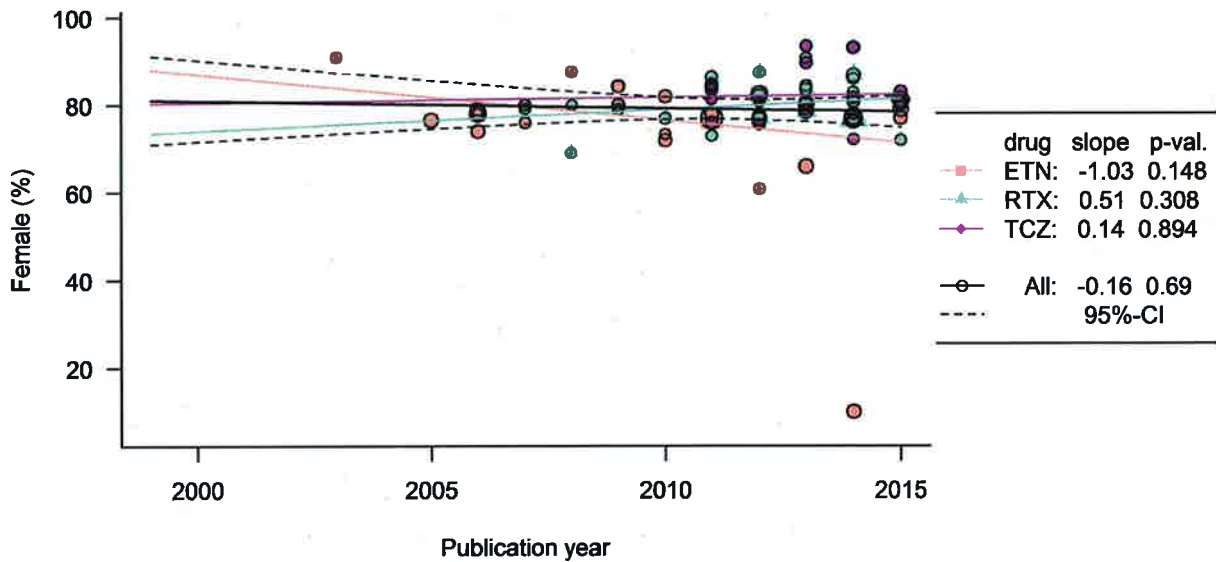


Supplementary Table 13: Comparison of gender between randomized controlled trials and observational studies plotted over time

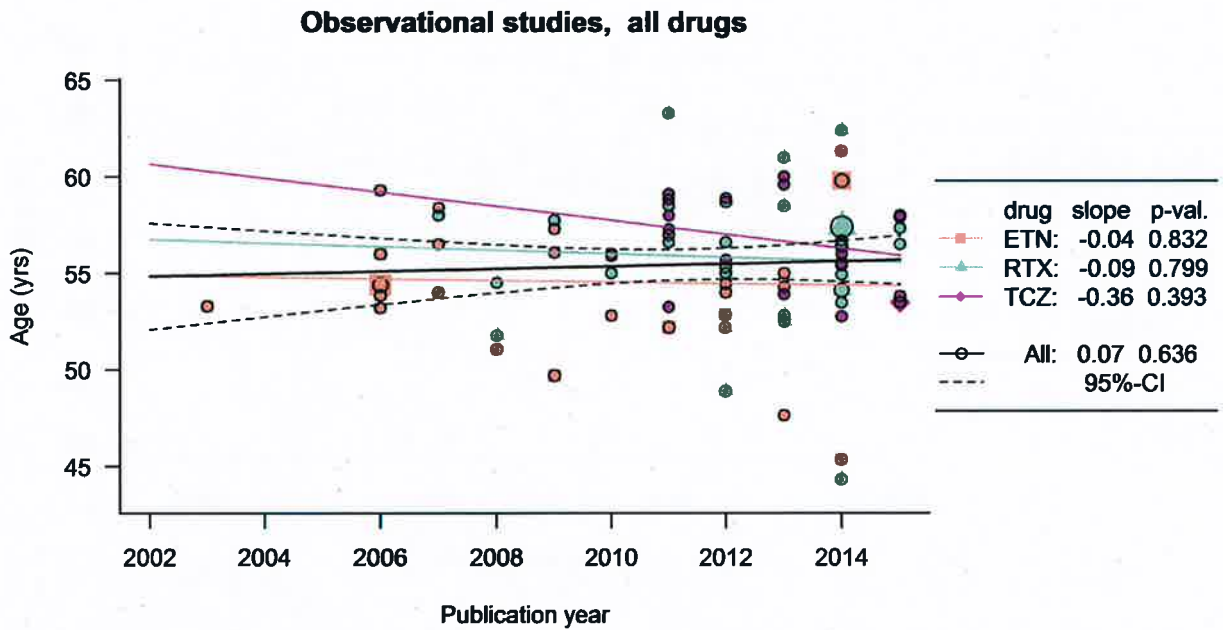
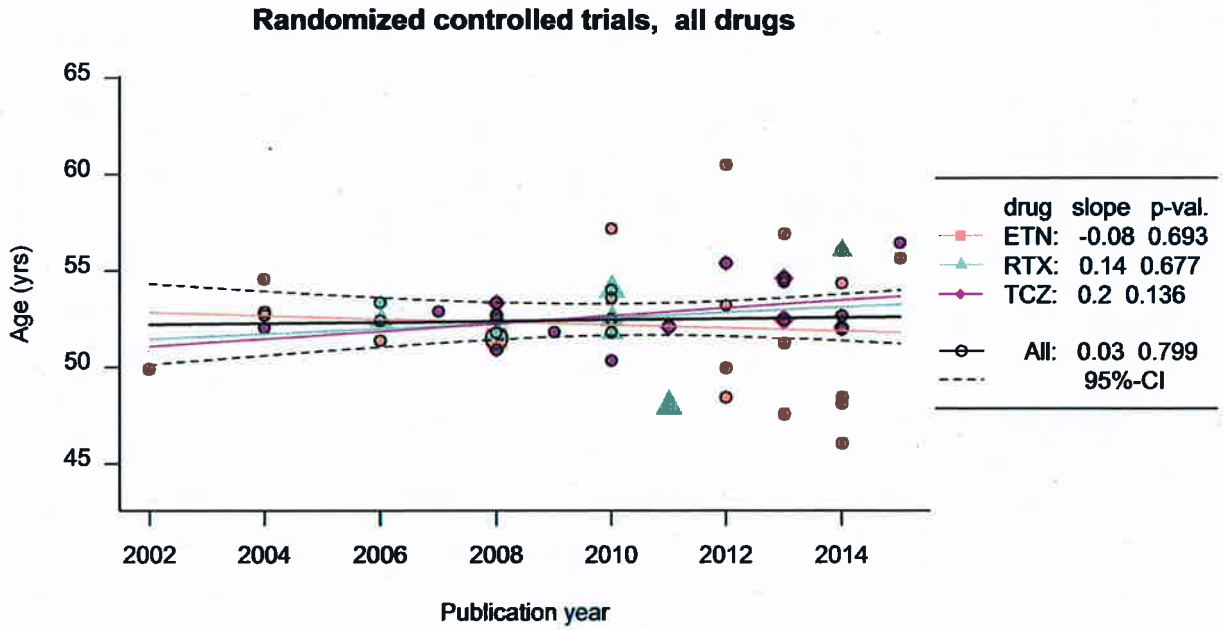
Randomized controlled trials, all drugs



Observational studies, all drugs

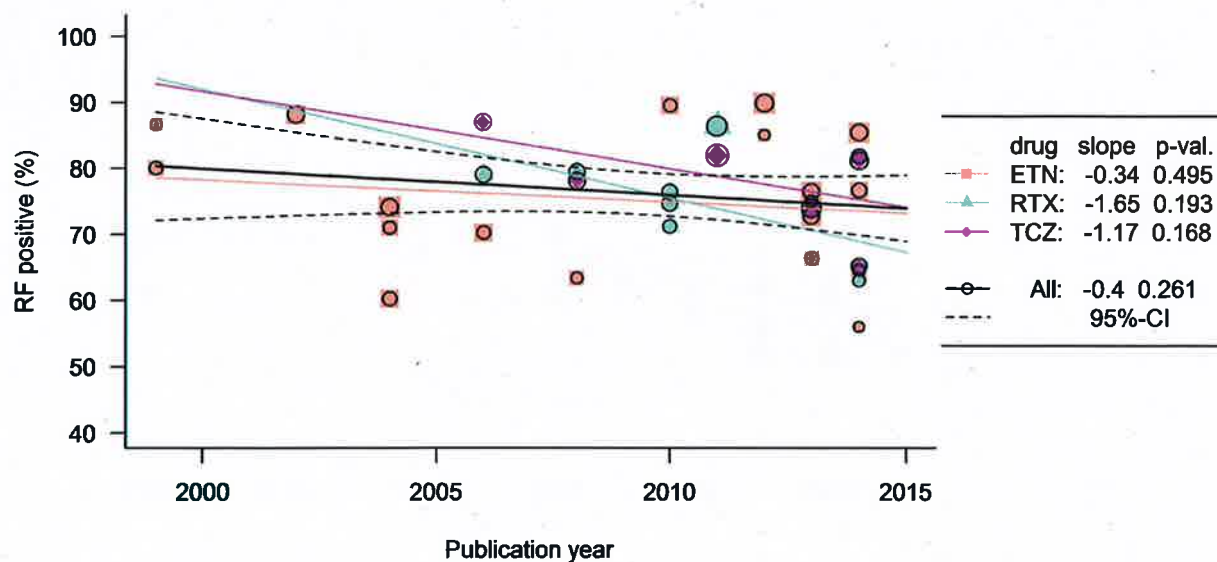


Supplementary Table 14: Comparison of age between randomized controlled trials and observational studies plotted over time

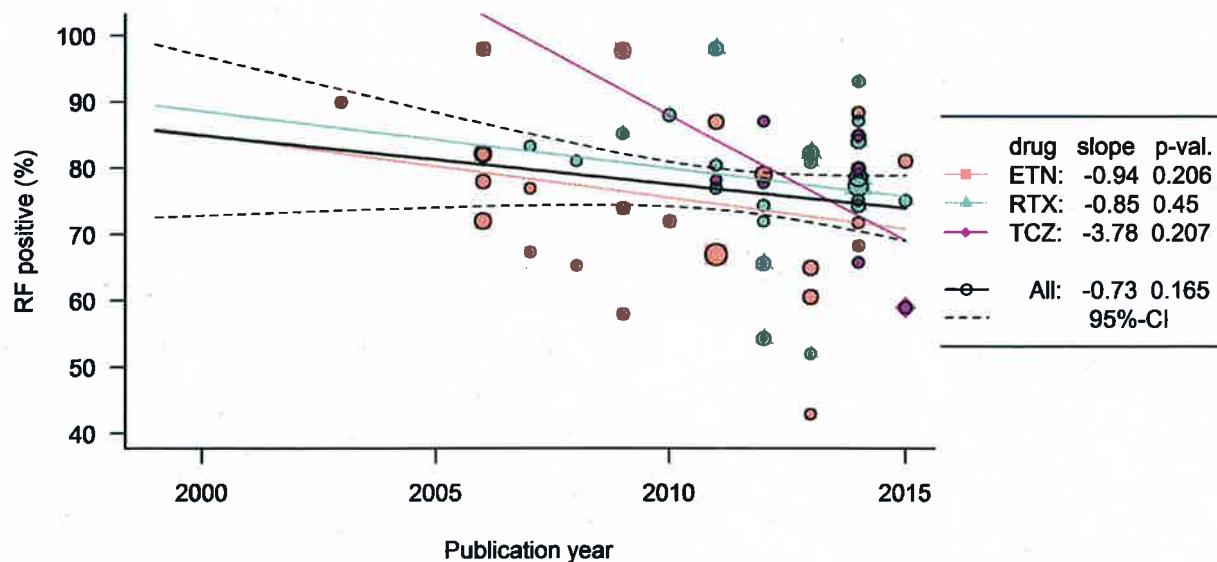


Supplementary Table 15: Comparison of rheumatoid factor positivity between randomized controlled trials and observational studies plotted over time

Randomized controlled trials, all drugs

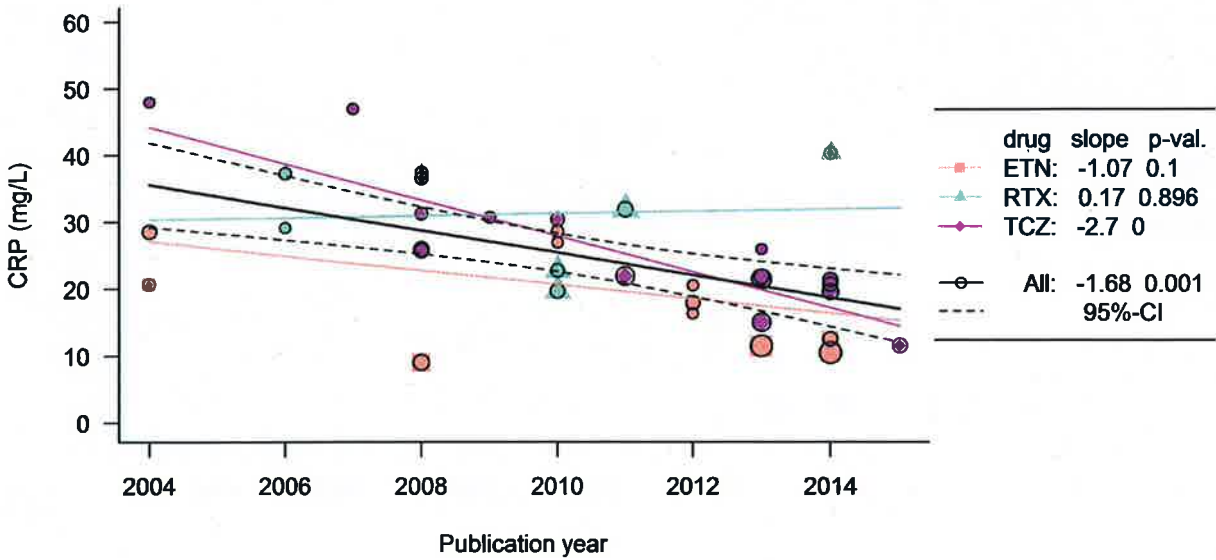


Observational studies, all drugs

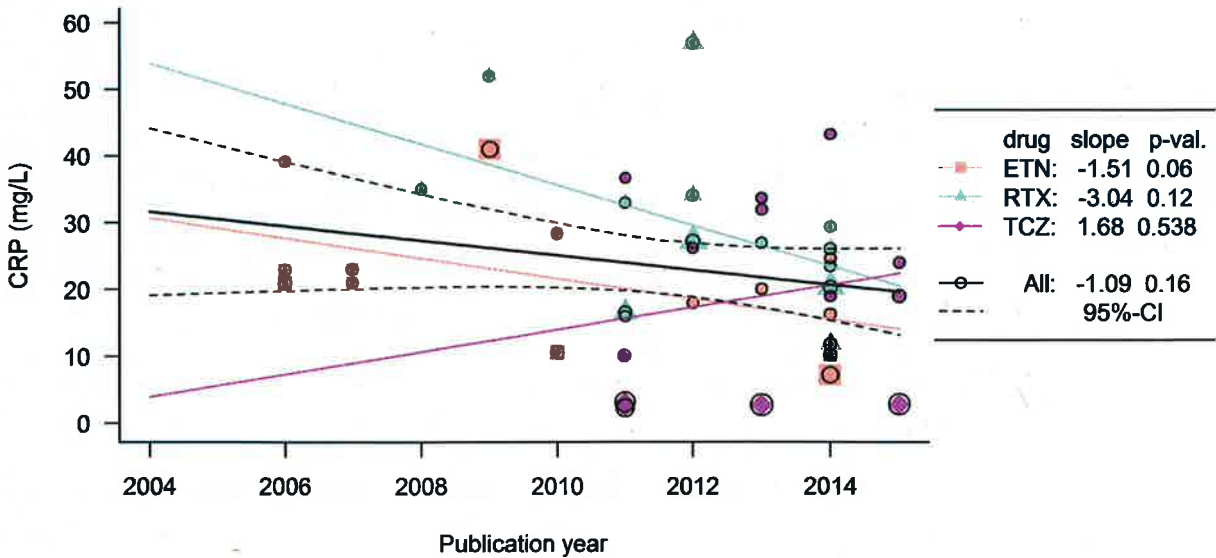


Supplementary Table 16: Comparison of CRP between randomized controlled trials and observational studies plotted over time

Randomized controlled trials, all drugs

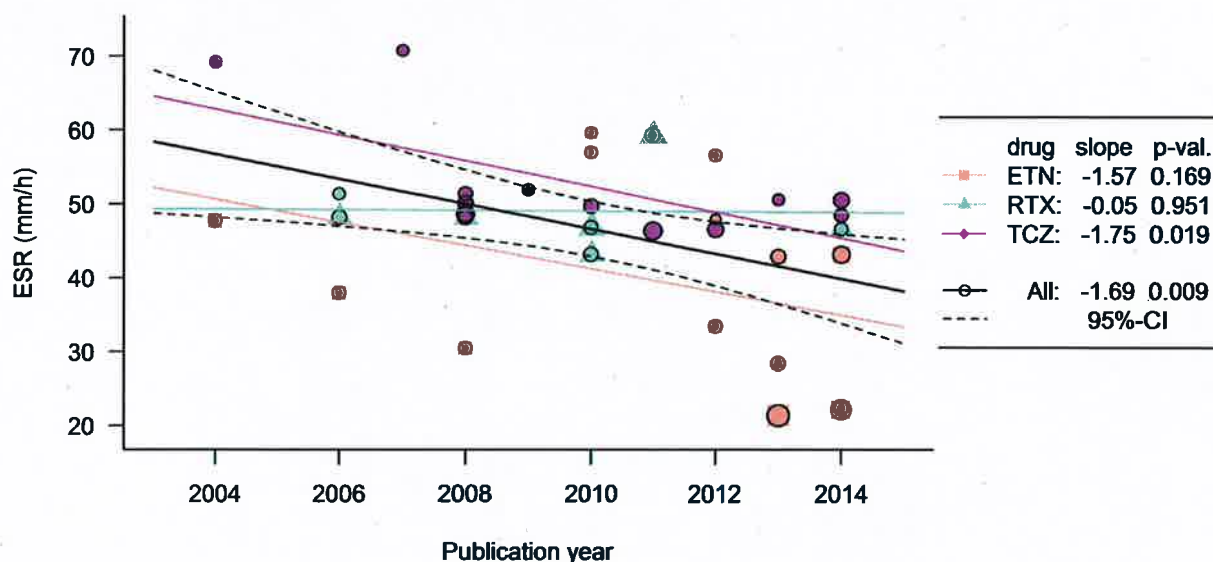


Observational studies, all drugs



Supplementary Table 17: Comparison of ESR between randomized controlled trials and observational studies plotted over time

Randomized controlled trials, all drugs



Observational studies, all drugs

