

# TNF- $\alpha$ inhibitors can increase the risk of respiratory infection when used in rheumatism: a meta-analysis and systematic review

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## Research article

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# Abstract

**Background** The risk of tumor necrosis factor- $\alpha$ (TNF- $\alpha$ ) inhibitors (infliximab, etanercept, adalimumab) for the treatment of rheumatic diseases leading to infection events has not yet been established. This meta-analysis aims to assess the risk of developing serious infections of three TNF- $\alpha$  inhibitors for rheumatic diseases.

**Methods** A systematic literature search of Pubmed, Embase and Cochrane Library was conducted through December 2018. Selecting the RCTs which subjects were diagnosed as rheumatoid diseases according to ACR criteria or other authoritative diagnostic criteria and over 18-year-old. Finally, RCTs with Jadad score greater than or equal to 4 were included in this meta-analysis. The Odds Ratio (OR), Confidence Interval (CI) and p value were calculated to assess the risk of serious infections.

**Results** 34 RCTs involving 14166 subjects were included, including 11 RCTs for infliximab, 7 RCTs for etanercept, and 16 for adalimumab. Meta-analysis demonstrated that, with the pooled OR of 1.29 (95%CI 1.04 to 1.60), the TNF- $\alpha$  inhibitors group had a higher risk of serious infection than control group. In the subgroup analysis, infliximab and adalimumab had a higher risk of serious infection than control group, and the pooled ORs were 1.48 (p=0.03) and 1.47 (p=0.03), respectively. For other infections including pneumonia, upper respiratory infection, and nasopharyngitis, the risks of these adverse events were higher in experimental group than control group, while the risk of tuberculosis were not, with the pooled OR of 2.31 (p=0.08).

**Conclusions** TNF- $\alpha$  inhibitors, especially infliximab and adalimumab, can increase the risk of infections. Among the infections, pneumonia, upper respiratory infection and nasopharyngitis have higher risks in TNF- $\alpha$  inhibitors group than control group. As a result, we summarized that TNF- $\alpha$  inhibitors can increase the risks of respiratory infection when used in rheumatic disease. It is suggested that clinicians should pay attention to the prevention of respiratory infections when using TNF- $\alpha$  inhibitors, so as to achieve a better prognosis for patients with rheumatism.

## Background

TNF- $\alpha$  is a cytokine with many physiological activities. Normal level of TNF- $\alpha$  can regulate the immunity, fight against bacterial, viral and parasitic infections, promote tissue repair, and mediate the apoptosis of tumor cells. However, overexpression of TNF- $\alpha$  will lead to a disorder of immunity, participate in inflammatory reactions, tissue damages, shock and other pathological processes. Abnormal TNF- $\alpha$  concentration and TNF receptor signaling have been shown to contribute to many diseases, including rheumatoid arthritis, Crohn's disease, atherosclerosis, psoriasis, sepsis, diabetes, obesity, et al<sup>[1]</sup>.

Since TNF- $\alpha$  inhibitors can specifically bind to overexpressed TNF- $\alpha$  in vivo and reduce its level, it has a widely application in various rheumatic diseases such as rheumatoid arthritis (RA), ankylosing spondylitis (AS), inflammatory bowel disease (IBD), and psoriasis. However, excessive usage of TNF- $\alpha$

inhibitors will form a low level of TNF- $\alpha$ , affect its normal physiological functions, and lead to infections, even tumors.

The most frequently reported infections are respiratory tract infections<sup>[2,3]</sup>(including sinusitis, pharyngitis, bronchitis) and urinary tract infections<sup>[4]</sup>. Serious infections include pneumonia<sup>[5]</sup>, cellulitis<sup>[5]</sup>, skin ulcers<sup>[5]</sup>, sepsis<sup>[5]</sup>, abscess<sup>[6]</sup>, tuberculosis<sup>[7]</sup>, et al. In the meantime, opportunistic bacterial infections have also been reported, including invasive fungal infections such as aspergillosis<sup>[5]</sup>, parasitic infections such as pneumocystis pneumoniae<sup>[4,8]</sup>, and atypical mycobacterium infections. Meanwhile, TNF- $\alpha$  inhibitors have often been reported to cause transaminase elevation and rare reactivation of hepatitis B and C viruses<sup>[2,9]</sup>. In addition, some randomized clinical trials(RCTs) have found that TNF- $\alpha$  inhibitors can lead to malignancies<sup>[5,8]</sup>.

This meta-analysis searched the published RCTs involving infections, and analyzed OR values of tuberculosis, pneumonia, bronchitis, upper respiratory infection, nasopharyngitis, sinusitis, gastroenteritis, urinary tract infection, cellulitis, sepsis and abscess. Compared with other meta analyses in the past five years<sup>[10-16]</sup>, the innovation points were as follows: (1) This meta-analysis focused on specific types of infection. (2) Studies included in this meta-analysis all were RCTs, which avoided the deficiency of observational studies. (3) The number of included RCTs was much more than other two meta analyses<sup>[12,13]</sup>, so the evaluation of infections was more objective and comprehensive. (4) One meta-analysis had 71 studies<sup>[14]</sup>, but the funnel plot, Begg's test ( $p = 0.06$ ) and the Egger's test ( $p = 0.09$ ) suggested a publication bias, which might overestimate the risk of infections. So far, Bongartz T and leombruno JP published two meta-analysis that systematically and objectively described the risk of infections caused by TNF- $\alpha$  inhibitors in the treatment of rheumatic diseases<sup>[15,16]</sup>. However, these two papers were published before 2009, and the RCTs after 2009 should be added. Few consensus on the risk of infections caused by TNF- $\alpha$  inhibitors have been reached. This meta-analysis systematically retrieved studies and assessed the risk of infections caused by three TNF- $\alpha$  inhibitors, and extended into specific types of infections innovatively.

## **Materials And Methods**

### **Inclusive Criteria**

### **Types of Studies**

RCTs about infliximab, etanercept, and adalimumab in the treatment of rheumatic diseases were included.

### **Types of Subjects**

Subjects, whose age was greater than or equal to 18 years old, had been diagnosed RA, AS, IBD or psoriasis according to American College of Rheumatology criteria or other authoritative and recognized diagnostic criteria. Disease progression, race, nationality and complications are not limited.

## **Types of Interventions**

The experimental group was treated with TNF- $\alpha$  inhibitors, with or without disease-modifying antirheumatic drugs(DMARDs). The control group was treated with placebo, with or without DMARDs, or with DMARDs alone.

## **Exclusive Criteria**

RCTs that accord with any of the following criteria will be excluded: (1) studies with no detailed records of infections and no mention of infections, where severe infection is defined as an infection requiring intravenous antibiotic treatment or requiring hospitalization or life-threatening infection; (2) if both the studies are the same patients in different periods, only the study with the longest follow-up time and the most comprehensive record is selected; (3) studies with improper control group, for instance, the study that allocate TNF- $\alpha$  inhibitor monotherapy in experimental group and DMARDs monotherapy in control group;(4) studies with Jadad score less than or equal to 3 points; (5) studies not published in english; (6) studies with the full text not available.

## **Data Sources and Search Strategy**

We searched MEDLINE, EMBASE and the Cochrane Library with the terms infliximab; etanercept; adalimumab; rheumatoid, arthritis; ankylosing, spondylitis; Crohn' disease; ulcerative, colitis; psoriasis. In a pattern of drug-disease retrieval, using a limitation of clinical trial, we form the retrieval expressions that adapt to different databases. The deadline for retrieval is December 2018.

Two investigators performed the literature screening according to the inclusion and exclusion criteria independently. The repeated studies were excluded firstly. Afterwards, excluding unrelated studies by reading the titles and abstracts and obtaining the full text of all the RCTs that might meet the inclusion criteria. The literatures that met the inclusion and exclusion criteria were further screened by reading the full text. Disagreements were resolved by consensus.

## **Data Extraction**

The extraction data includes the following aspects: (1) Basic information: title, author, contact information, year of publication, research location and funding source. (2) Research methods: research design (randomisation, allocation concealment, blinding method) and statistical analysis methods. (3) Subjects characteristics: sample size, gender and age distribution of experimental group and control

group. (4) Interventions: detailed administration plan of experimental group and control group, including dose, frequency and follow-up period. (5) Outcome indexes: types, cases and incidence rate of infections. (6) Subjects dropped out and drop-out reasons.

## Assessment of risk of bias

Two review authors independently assessed each study. The results were classified as low risk, unclear risk, and high risk. Disagreements were resolved by consensus. The assessments included: (1) Random sequence generation (selection bias). (2) Allocation concealment (selection bias). (3) Blinding of participants and personnel (performance bias). (4) Blinding of outcome assessment (detection bias). (5) Incomplete outcome data (attrition bias). (6) Selective reporting (reporting bias). (7) Other bias.

## Statistical analysis

Revman5.3 software was used for data processing. Odds ratios (ORs) and 95% confidence intervals (95% CIs) were used. Heterogeneity analysis used  $\chi^2$  test and considered its size in combination with p value.  $P < 0.05$  indicates large heterogeneity. Random effects model is adopted and subgroup analysis and sensitivity analysis are performed. Reversely,  $p > 0.05$  indicates low heterogeneity, and fixed effects model is adopted.

## Results

### Search Results

After a preliminary screening through browsing the abstracts, 157 articles were obtained. Of 157 potentially relevant articles, 118 were excluded, including 56 articles with improper control group, 18 non-RCTs articles, 13 articles with a lack of infection information, 14 articles with short follow-up time, 12 repeated studies, 3 articles with subjects under 18, 1 article with unknown classifications of infections. A total of 34 RCTs (39 articles) were eligible for inclusion. Flow diagram of including RCTs is as Figure 1 (Page 27).

### Summary of characteristics of included RCTs

Of the 34 RCTs, 11 infliximab trails<sup>[2-9,17-20]</sup>, 7 etanercept trails<sup>[21-29]</sup> and 16 adalimumab trails<sup>[30-46]</sup> were included, with a total of 14,166 subjects. Among subjects, 8,758 in the experimental group and 5,408 in the control group were followed up between 14 weeks–104 weeks. The basic characteristics are shown in Table 1 [Page 30], the incidence of severe infections and the detailed infections is shown in Appendix 1 [see Additional file 1].

## Risk of bias

Risk of bias graph is as Appendix2 [see Additional file 1], showing no high risk of bias in any of the bias item. Risk of bias summary is shown in Appendix3 [see Additional file 1].

## Statistical analysis results

### Serious Infections

The funnel plot of the included studies is shown in Appendix4 [see Additional file 1], showing no obvious asymmetry and indicating no obvious publication bias.

The forest plot about the risk of serious infections of the 34 included studies is shown in Figure2[Page28]. The value of inconsistency between trials was 0% ( $p = 0.59$ ), indicating that studies were not statistically heterogeneous; we can use the fixed effect model to combine the effect size OR. Results showed that subjects using TNF- $\alpha$  inhibitors had a higher risk of serious infections than the control group, with a serious infection rate of 3.4% and 2.5%, respectively. The results were statistically significant with the pooled OR of 1.29 (95%CI 1.04–1.60,  $p = 0.02$ ).

Comparing the incidence rate of serious infections in infliximab group (4.7%) or adalimumab group(2.7%) to control group(3.2% or 1.8%), the differences were statistically significant with the pooled OR of 1.48(95%CI 1.05–2.08,  $p = 0.03$ ) and 1.47 (95%CI 1.04–2.07,  $p = 0.03$ ), respectively. The incidence rate of serious infections in etanercept group(2.2%) was compared with that in the control group (3.0%), and the results were not statistically significant with the pooled OR of 0.77 (95%CI 0.48–1.23,  $p = 0.28$ ).

### Detailed Infections

#### Tuberculosis

A total of 18 tuberculosis events were reported in 10 of the 34 included studies (Figure3) [Page28]. Subjects in these studies had been initially screened for a history of tuberculosis through the PPD skin test or chest X-ray. Only one of the 18 subjects with tuberculosis was in control group, and the remaining 17 subjects were all subjects of the experimental group. The consistency test showed a low heterogeneity, but the difference was not statistically significant with a pooled OR of 2.31 (95%CI 0.90–5.94,  $p = 0.08$ ).

#### Pneumonia

Of the 34 included studies, 20 reported pneumonia with a pooled OR of 1.72 (95%CI 1.04–2.83,  $p = 0.03$ ) (Figure4) [Page29]. Subgroup analysis showed that only infliximab subgroup had statistically significant.

In the 42 cases of pneumonia, only 1 case was from the control group, and the combined OR was 4.48(95%CI 1.66–12.09,  $p = 0.003$ ), which meant that infliximab increased the risk of pneumonia by 4.48 times. The combined OR of Etanercept and adalimumab groups was 1.52( $p = 0.43$ ) and 0.65( $p = 0.30$ ), respectively.

## Upper Respiratory Infection

There were 11 RCTs reporting upper respiratory infection (Figure5) [Page29]. The incidence rate of it between experimental group and control group were 14.3% and 9.1%, respectively. TNF- $\alpha$  inhibitors were shown to mildly increase the risk of upper respiratory infection with a combined OR of 1.38(95%CI 1.10–1.73,  $p = 0.006$ ).

## Nasopharyngitis

A total of 16 studies reported nasopharyngitis (Figure6) [Page30]. Forest plot showed that TNF- $\alpha$  inhibitors mildly increased the infection rate of nasopharyngitis, with pooled OR of 1.33(95%CI 1.11–1.60,  $p = 0.002$ ). According to the subgroup analysis, etanercept showed no statistical significance (OR1.23,  $p = 0.49$ ), and the Odds ratio of adalimumab was at a critical value (OR1.26,  $p = 0.05$ ). Conservative results of adalimumab subgroup were obtained using the random effect model (OR1.25,  $p = 0.09$ ). Finally, only infliximab subgroup showed statistical significance with the pooled OR of 1.58(95%CI 1.08–2.31,  $p = 0.02$ ). What should be noted is that the results of two adalimumab RCTs<sup>[2,32]</sup> were statistically significant, with OR of 4.04( $p = 0.01$ ) and 1.77( $p = 0.04$ ), respectively.

## Bronchitis

A total of 11 studies reported bronchitis(Appendix5) [see Additional file 1], and the incidence rate of bronchitis in experimental group(1.1%) was compared with that in the control group(0.7%), but the results were not statistically significant with a combined OR of 1.39(95%CI 0.76–2.56,  $p = 0.29$ ).

## Sinusitis

5 RCTs reported sinusitis (Appendix6) [see Additional file 1]. Due to the high heterogeneity ( $I^2 = 61\%$ ), a random effect model was used and the pooled OR was 1.05(95%CI 0.41–2.65,  $p = 0.93$ ). It is important to noted that one RCT<sup>[5,18,19]</sup> showed statistical significance with the OR of 3.41 ( $p = 0.01$ ).

## Gastroenteritis

A total of 7 studies reported gastroenteritis (Appendix7) [see Additional file 1], but the results were not statistically significant with a combined OR of 1.65(95%CI 0.56–4.83,  $p = 0.36$ ). Meanwhile, none of the

included RCTs was statistically significant.

## Urinary Tract Infection

Of the 34 included studies, 6 studies reported urinary tract infection (Appendix 8) [see Additional file 1]. The incidence rates were 1.3% and 0.6% among experimental and control groups, with a pooled OR of 1.81 (95% CI 0.87–3.74,  $p = 0.11$ ).

## Cellulitis

5 studies reported cellulitis (Appendix 9) [see Additional file 1]. The results were not statistically significant with the pooled OR of 2.62 (95% CI 0.65–10.50,  $p = 0.17$ ). However, since all the 11 reported cellulitis cases were from TNF- $\alpha$  inhibitor group, it could not be ignored that TNF- $\alpha$  may increase the risk of cellulitis.

## Sepsis

A total of 4 studies reported sepsis (Appendix 10) [see Additional file 1], but the results were not statistically significant with a pooled OR of 1.19 (95% CI 0.38–3.70,  $p = 0.76$ ).

## Abscess

A total of 4 studies reported abscess (Appendix 11) [see Additional file 1], but the results were not statistically significant with a pooled OR of 0.77 (95% CI 0.35–1.66,  $p = 0.50$ ).

## Summary

The information of infections reported in 34 studies was extracted for meta-analysis. Results showed that the application of TNF- $\alpha$  inhibitors led to increased risk of pneumonia, upper respiratory infection and nasopharyngitis. Odds ratios and confidence intervals were shown in Table 2.

## Discussion

In this meta-analysis, a total of 34 RCTs with JADAD score greater than or equal to 4 were included, which were considered as RCTs closely correlated to the research content through full-text browsing. The significance level  $\alpha$  was 0.05.

## Serious Infections

Results of 34 RCTs suggested that, when used in rheumatic diseases, TNF- $\alpha$  inhibitors such as infliximab, etanercept, and adalimumab, can elevated the risk of serious infections. The risk of serious infections in the intervention group was 1.29 times higher than that in the control group ( $p = 0.02$ ). This result was consistent with some previous meta-analysis<sup>[15]</sup>. Furthermore, there was a meta-analysis suggesting the recommended dose of TNF- $\alpha$  inhibitor did not upgrade the risk of serious infections<sup>[16]</sup>. According to the results of subgroup analysis, the risk of serious infections in infliximab and adalimumab treatment group was significantly higher than that in the control group ( $p = 0.03$ ). However, when it comes to etanercept, no similar result can be reached( $p = 0.28$ ). This result is identical with a real-world study for reasons that are not yet clear<sup>[47]</sup>. A meta-analysis tried to explain it<sup>[48]</sup>, and put forward a view that infliximab and adalimumab were TNF- $\alpha$  monoclonal antibodies, while etanercept was TNF- $\alpha$  soluble receptor. This may determine their risk of infections. It can be concluded that etanercept is more secure than infliximab and adalimumab in the risk of serious infections, which is valuable for clinicians making clinical decisions.

## Detailed Infections

### Tuberculosis

TNF- $\alpha$  did not increase the risk of tuberculosis ( $p = 0.08$ ). However, of the 10 RCTs reporting tuberculosis, 17 out of 18 cases were in the intervention group, suggesting that the use of TNF- $\alpha$  inhibitors may increase the risk of tuberculosis, although the difference could not be measured due to the low incidence rate or the scarce cases. A meta-analysis reported that the risk of tuberculosis using TNF- $\alpha$  inhibitors was 1.94 times as high as that of the control group ( $p = 0.02$ ). Subgroup analysis revealed that the risk of tuberculosis in the intervention group of RA patients was 2.29 times higher than control group ( $p = 0.03$ ). However, the evidence quality assessed by GRADE was “Low”<sup>[49]</sup>. Other real-world studies have shown that the risk of tuberculosis with infliximab and etanercept is 3 to 4 times higher than that with adalimumab, and some patients developed tuberculosis after several years of drug withdrawal<sup>[50]</sup>. Thus, TNF- $\alpha$  inhibitors are associated with a long-term risk of tuberculosis. Before treatment with TNF- $\alpha$  inhibitors, patients must be screened for tuberculosis. For patients with latent tuberculosis infection, preventive anti-tuberculosis treatment should be carried out. Through screening and preventive treatment, lowering the risk of tuberculosis and improving the prognosis of patients with rheumatism.

Besides the infections mentioned above, we selected pneumonia, upper respiratory infection, nasopharyngitis, bronchitis, sinusitis, gastroenteritis, urinary tract infection, cellulitis, sepsis, abscess for statistical analysis.

### Pneumonia

TNF- $\alpha$  inhibitors mildly increased the risk of pneumonia over time, and only infliximab significantly increased the risk of pneumonia after stratified analysis. Infliximab was 4.48 times more likely to cause

pneumonia. Frust DE suggested in his review that the most common sites of infection treated with biologics were respiratory tract (including pneumonia), but the risk was not quantitatively calculated<sup>[51]</sup>. This meta-analysis further proved that infliximab could increase the risk of pneumonia, providing a basis for clinicians to make decisions and strengthen pharmacovigilance.

## Upper Respiratory Infection And Nasopharyngitis

TNF- $\alpha$  inhibitors could mildly increase the risk of upper respiratory infection and nasopharyngitis with the OR of 1.38( $p = 0.006$ ) and 1.33( $p = 0.002$ ), respectively. In the subgroup analysis of nasopharyngitis, only infliximab was found to increase the risk of nasopharyngitis (OR1.58,  $p = 0.02$ ). Similarly, without quantitative analysis, Frust DE in his review concluded that respiratory tract infections were common<sup>[51]</sup>. In this meta-analysis, quantitative analysis was performed. It is confirmed that TNF- $\alpha$  inhibitors, infliximab in particular, can increase the risk of upper respiratory infection and nasopharyngitis.

Only pneumonia, upper respiratory infection and nasopharyngitis showed statistical significance, with pooled OR of 1.72 ( $p = 0.03$ ), 1.38 ( $p = 0.006$ ) and 1.33 ( $p = 0.002$ ), respectively. It is indicated that TNF- $\alpha$  inhibitors can moderately increase the risk of pneumonia, upper respiratory infection and nasopharyngitis. Regrettably, there is a lack of evidence on bronchitis, sinusitis, gastroenteritis, urinary tract infection, cellulitis, sepsis and abscess; other larger RCTs are needed.

The dose of TNF- $\alpha$  inhibitor also affects the occurrence of infections. A meta-analysis found that there was no significant difference among the medium- and low-dose group with the control group, but the high-dose group had a significant higher risk( $p = 0.04$ )<sup>[48]</sup>. Another meta-analysis showed that the risk of infections was 1.4 times higher in low-dose group than control group<sup>[15]</sup>. A systematic review of observational studies had also shown that only when TNF- $\alpha$  inhibitors were used in excess of normal doses will the risk of infection increase<sup>[52]</sup>. The dose-effect relationship suggests that TNF- $\alpha$  inhibitors are indeed associated with infections.

Limitations exist in this meta-analysis. Firstly, some studies may be missed due to manual retrieve. Moreover, how to balance the follow-up time and reported adverse events is another issue. Long-term adverse events may not be observed in studies with short follow-up time, resulting in the omission of serious infections. However, due to the gradual increase of the missing rate and the subjects transferring into the open-label extension period, the results of some subjects will inevitably be invalid. What's more, results about the risk of tuberculosis only apply to developed regions. China has a high incidence rate of tuberculosis, but is lacking an authoritative clinical evidence to prove our conclusion. Despite limitations, results of this meta-analysis are still of certain clinical guiding value, providing a reference for clinicians to better avoid the risk of infections when using TNF- $\alpha$  inhibitors.

## Conclusions

TNF- $\alpha$  inhibitors, especially infliximab and adalimumab, can increase the risk of infections. Among the infections, pneumonia, upper respiratory infection and nasopharyngitis have higher risks in TNF- $\alpha$  inhibitors group than control group. As a result, we summarized that TNF- $\alpha$  inhibitors can increase the risks of respiratory infection when used in rheumatic disease. It is suggested that clinicians should pay attention to the prevention of respiratory infections when using TNF- $\alpha$  inhibitors, so as to achieve a better prognosis for patients with rheumatism.

## **Declarations**

## **Abbreviations**

TNF- $\alpha$ : Tumor necrosis factor- $\alpha$ ; IFX: Infliximab; ETN: Etanercept; ADA: Adalimumab; RA: Rheumatoid Arthritis; AS: Ankylosing Spondylitis; IBD: Inflammatory Bowel Disease; RCT: Randomized Clinical Trial; DMARDs: Disease-Modifying Antirheumatic Drugs; NPX: Naproxen; AZP: Azathioprine; MTX: Methotrexate; HCQ: Hydroxychloroquine; SASP: Salicylazosulfapyridine; PBO: Placebo; eow: every other week; PPD: Purified Protein Derivative; UPI: Upper Respiratory Infection; UTI: Urinary Tract Infection.

## **Ethics approval and consent to participate**

Not applicable.

## **Consent for publication**

Not applicable.

## **Availability of data and materials**

All data generated or analysed during this study are included in this published article [and its supplementary information files]. The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

## **Competing interests**

The authors declare that they have no competing interests.

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Not applicable.

## Authors' contributions

Conceived and designed the meta-analysis: LW, PW. Designed search strategy, screened articles, abstracted data, assessed risk of bias: LW, ZJ, LY, CX. Analysed the data: LW, ZQ. Wrote the first draft of the manuscript: LW. Contributed to the writing of the manuscript: LW, ZJ, LY, CX, ZQ, PW. Agree with manuscript results and conclusions: LW, PW. Jointly developed the structure and arguments for the paper: LW, PW. Made critical revisions and approved final version: LW, ZJ, LY, CX, PW. All authors reviewed and approved of the final manuscript.

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## Tables

Due to technical limitations, Tables 1 & 2 are only available for download from the Supplementary Files section.

## Figures

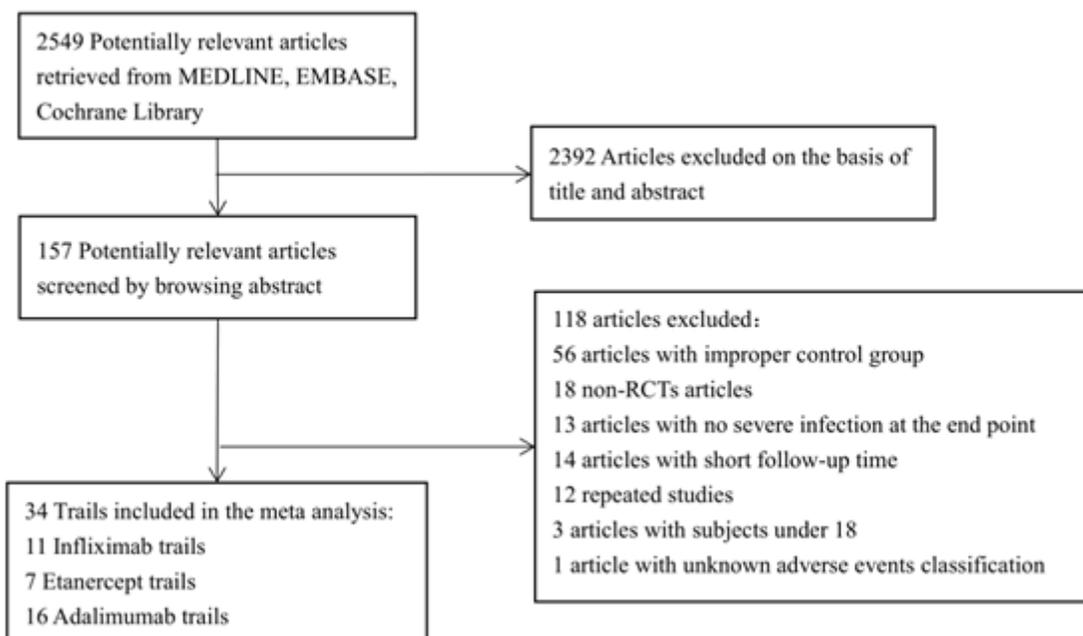


Figure 1

Flow Diagram of Including RCTs

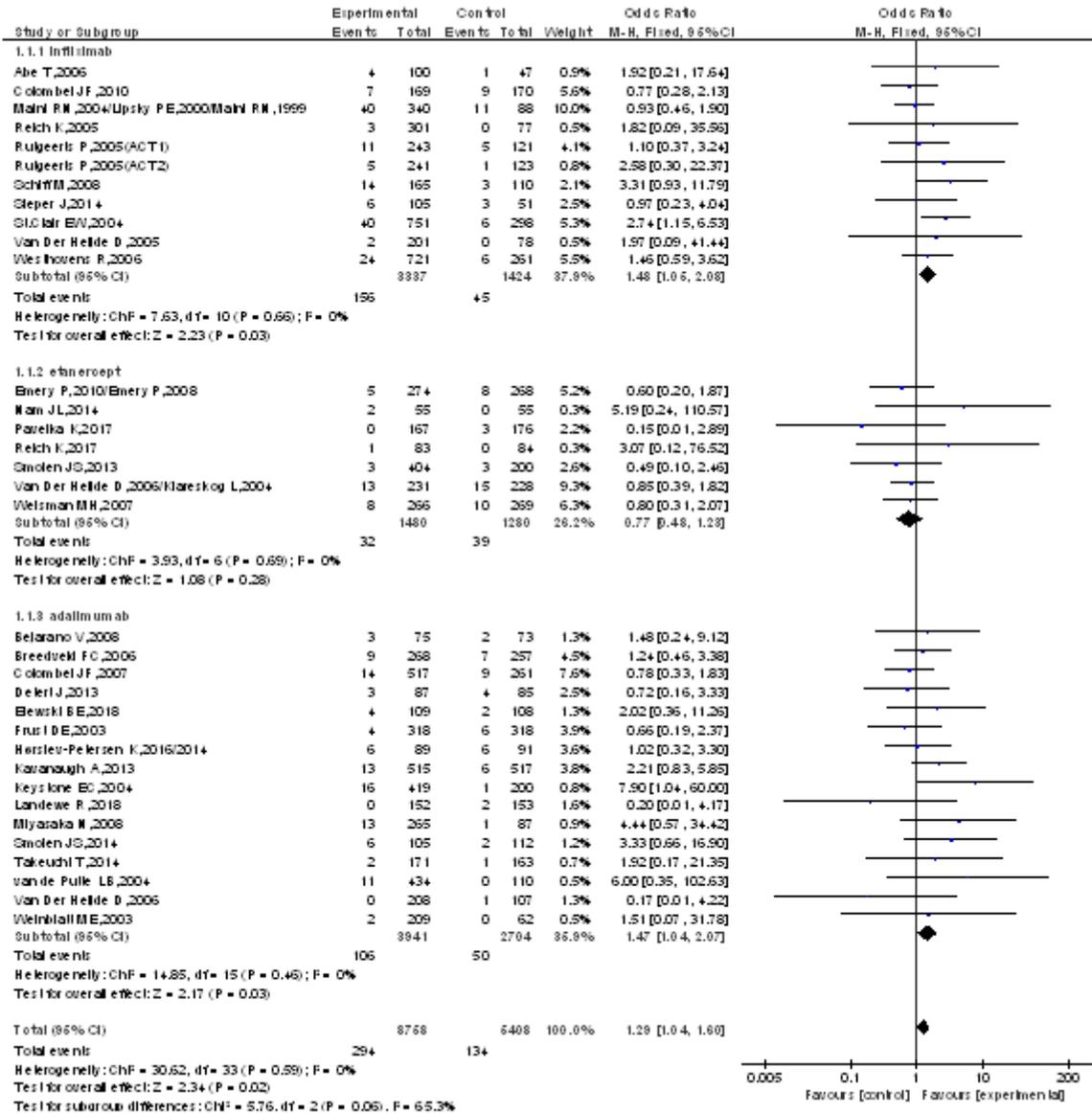


Figure 2

Forest Plot of Risk of Serious Infections Induced by Three TNF- $\alpha$  Inhibitors Versus Control Group

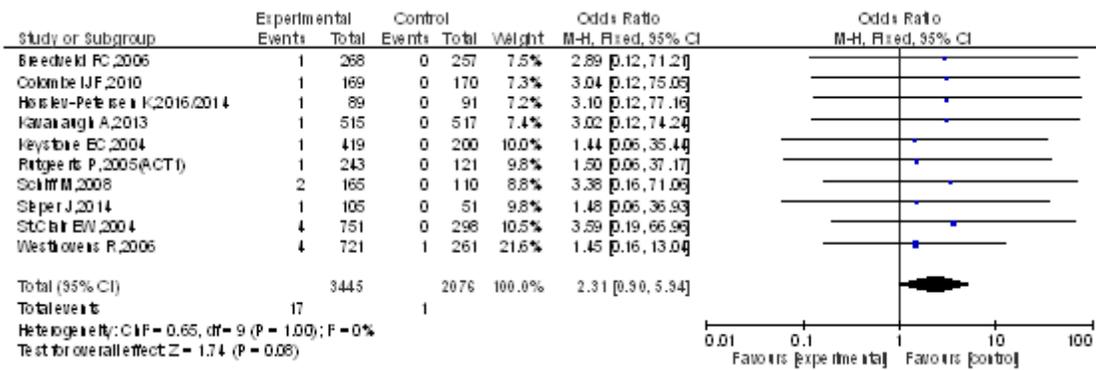


Figure 3

Forest Plot of Risk of Tuberculosis Induced by Three TNF- $\alpha$  Inhibitors Versus Control Group

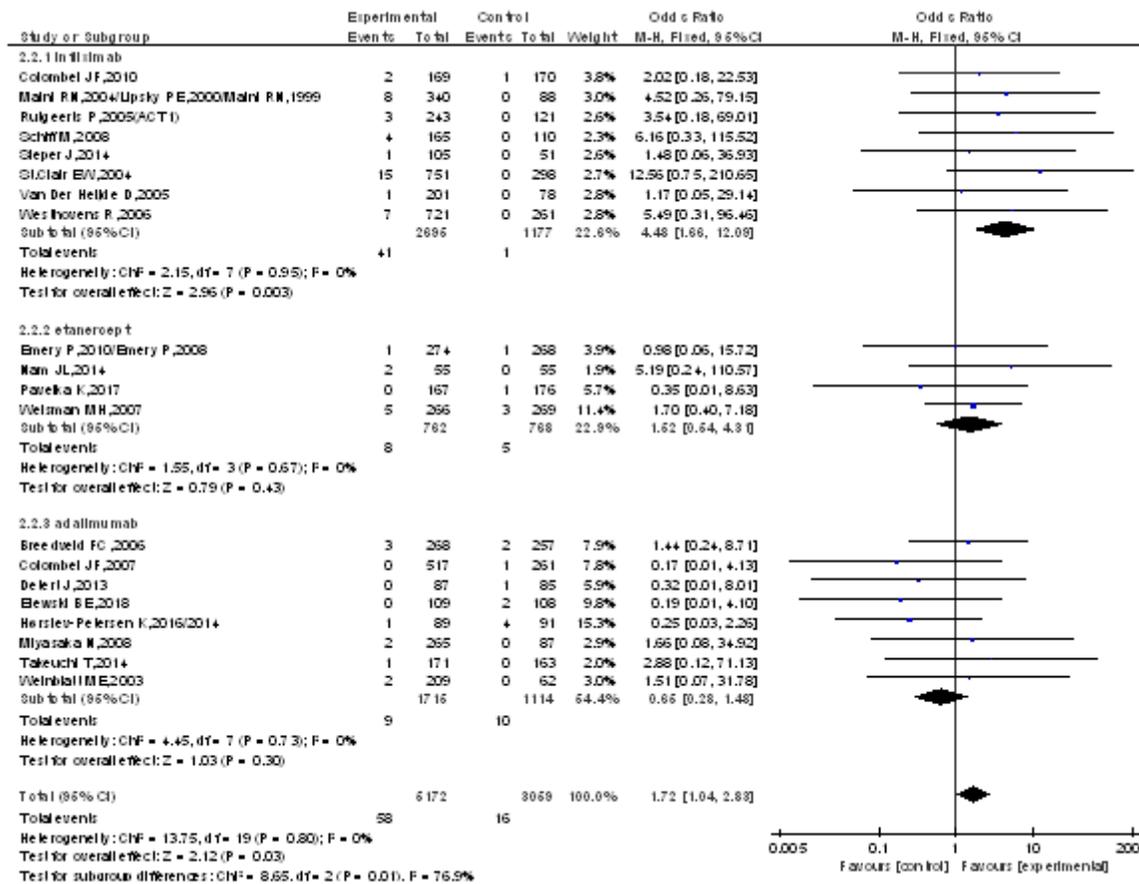
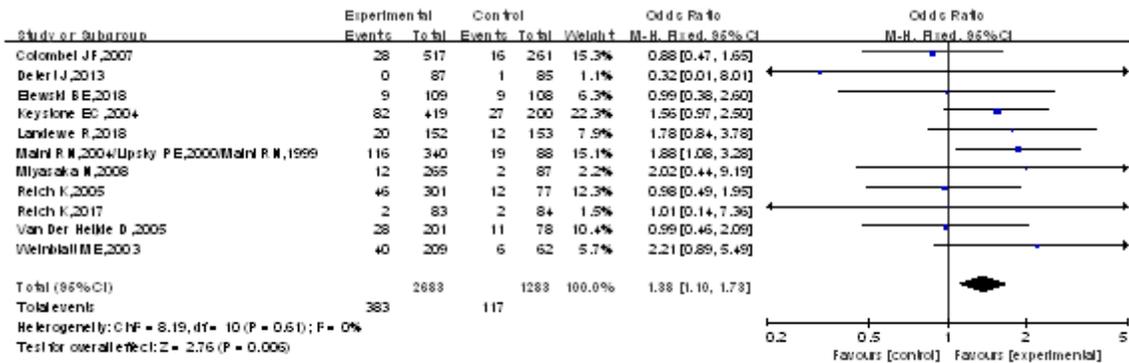


Figure 4

Forest Plot of Risk of Pneumonia Induced by Three TNF- $\alpha$  Inhibitors Versus Control Group



Abbreviations: UPI, Upper Respiratory Infection.

Figure 5

Forest Plot of Risk of UPI Induced by Three TNF- $\alpha$  Inhibitors Versus Control Group

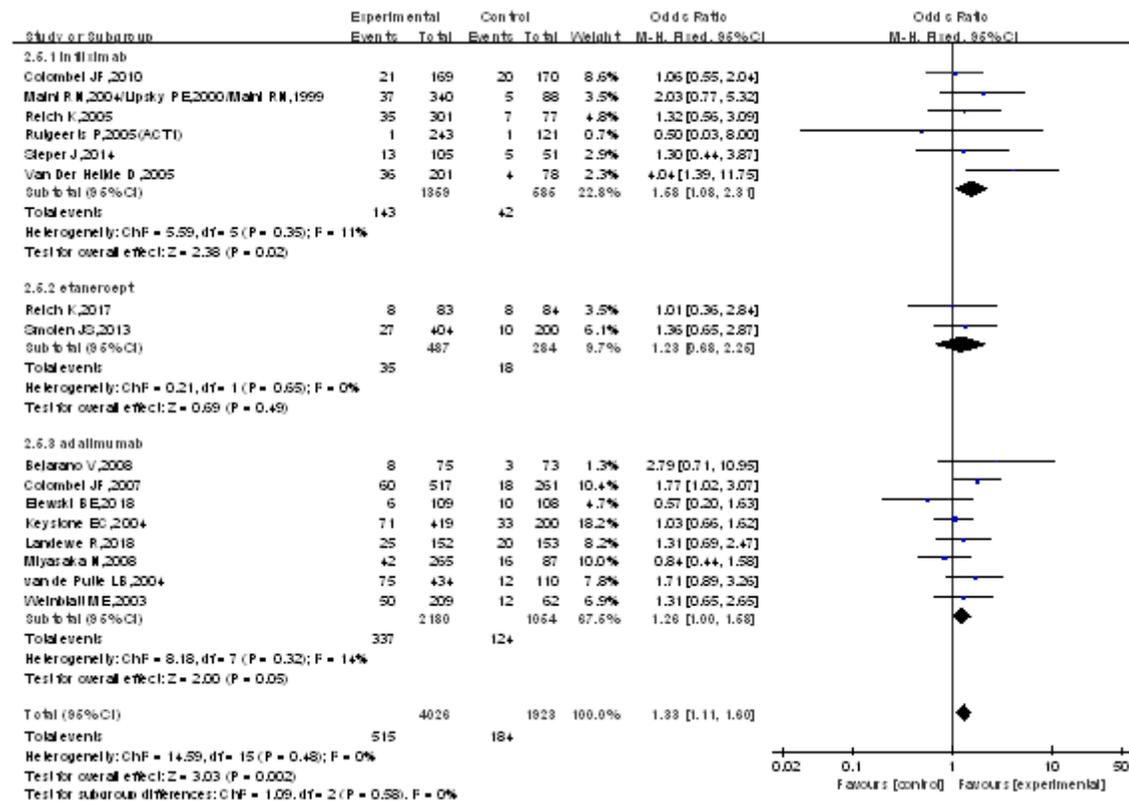


Figure 6

Forest Plot of Risk of Nasopharyngitis Induced by Three TNF- $\alpha$  Inhibitors Versus Control Group

## Supplementary Files

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