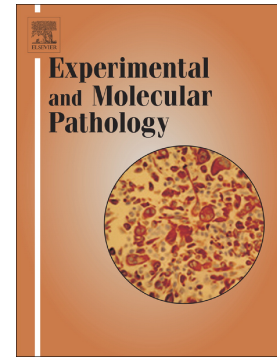


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Associations of tumor necrosis factor- α polymorphisms with the risk of asthma: a meta-analysis

Hao Sun, M.D.¹, Qingsong Li, M.D.², Yingji Jin, M.D.¹ and Hongmei Qiao, M.D.³

1. Department of Paediatrics, Taizhou People's Hospital, Taizhou, China

2. Department of Orthopedics, Taizhou People's Hospital, Taizhou, China

3. Department of Paediatrics, First Hospital of Jilin University, Changchun, China

Correspondence to: Dr. Hongmei Qiao, Department of Paediatrics, First Hospital of Jilin University, No. 71 Xinmin street, Changchun 130021, Jilin, China

E-mail: hongmeiqiao99869@163.com

Abstract

Objective

Recently, potential correlations between tumor necrosis factor- α (*TNF- α*) polymorphisms and asthma were investigated by some pilot studies, but the results of these studies were inconsistent. Therefore, we performed this meta-analysis to better evaluate the relationship between *TNF- α* polymorphisms and the risk of asthma.

Methods

Eligible studies were searched in PubMed, Medline, Embase and CNKI. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated to assess correlations between *TNF- α* polymorphisms and asthma.

Results

A total of 50 studies were included for analyses. Significant associations with the risk of asthma were detected for *TNF- α* -238 G/A, -308 G/A and -857 C/T polymorphisms

in overall analyses. Further subgroup analyses according to ethnicity of participants revealed that *TNF- α* -238 G/A polymorphism was significantly correlated with the risk of asthma in Caucasians, *TNF- α* -308 G/A polymorphism was significantly correlated with the risk of asthma in West Asians, *TNF- α* -857 C/T polymorphism was significantly correlated with the risk of asthma in Caucasians, *TNF- α* -863 C/A polymorphism was significantly correlated with the risk of asthma in East Asians, and *TNF- α* -1031 T/C polymorphism was significantly correlated with the risk of asthma in Caucasians and East Asians.

Conclusions: Our findings indicated that *TNF- α* -238 G/A, -308 G/A, -857 C/T, -863 C/A and -1031 T/C polymorphisms may serve as potential biological markers for asthma in certain ethnicities.

Keywords: Tumor necrosis factor- α (*TNF- α*); Gene polymorphisms; Asthma; Meta-analysis

Introduction

Asthma is featured by chronic airway inflammation, airway hyper-responsiveness, reversible airway obstruction and wheezing (Xie et al., 2017). It is an extremely common lower respiratory tract disorder, with an estimated prevalence of 3%-38% in children, and 2%-12% in adults (Cavkaytar et al., 2014). According to a recent investigation, asthma currently affects nearly 300 million people worldwide, and causes over 250 thousand deaths annually. Furthermore, asthma is often accompanied by co-morbidities like infections, cardiovascular diseases and gastro-esophageal abnormalities, which lead to more complex conditions and worse outcomes

(Pawankar et al., 2012).

To date, the exact cause of asthma is still largely unknown. Nevertheless, it has become evident recently that genetic defects play a vital role in its development. Firstly, family clustering of asthma was observed in over two-thirds of patients, and first-degree relatives of asthma patients were at a higher risk of developing this disease (Zhang et al., 2012). Secondly, multiple genetic variants were found to be correlated with an increased risk of developing asthma by past experimental studies (Wills-Karp and Ewart, 2004; Freeman et al., 2010). However, asthma is a highly complex disorder and genetic determinants underlying this disease are still not fully elucidated.

Tumor necrosis factor- α (TNF- α) plays a crucial part in the regulation of adaptive and innate immune responses. Previous clinical investigations have shown that TNF- α levels were increased in bronchoalveolar lavage fluids of asthmatic patients, and treatment with anti-TNF antibody could induce symptomatic improvements in asthmatic patients (Sharma et al., 2006; Chen et al., 2001). As a consequence, functional *TNF- α* polymorphisms were thought to be ideal candidate genetic markers of asthma. Recently, numerous studies have been conducted to investigate associations between *TNF- α* polymorphisms and the risk of asthma. But the results of these studies were conflicting and the sample size of individual studies was inadequate to draw a definite conclusion (Jiffri et al., 2011; Shin et al., 2004; Ricciardolo et al., 2013). Therefore, we conducted this meta-analysis to better analyze the roles of *TNF- α* polymorphisms in asthma.

Materials and methods

Literature search and inclusion criteria

This meta-analysis adhered to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guideline (Moher et al., 2009). Potentially eligible articles were searched in PubMed, Medline, Embase and CNKI using the combination of following key words: “tumor necrosis factor- α ”, “TNF- α ”, “polymorphism”, “variant”, “mutation”, “genotype”, “allele”, “asthma” and “wheezing”. The initial literature search was conducted in March 2018 and the latest update was performed in August 2018. The reference lists of all retrieved publications were also screened to identify other potentially relevant articles.

Included studies must met all the following criteria: (1) case-control study on correlations between *TNF- α* polymorphisms and the risk of asthma; (2) provide adequate data to calculate odds ratios (ORs) and 95% confidence intervals (CIs); (3) full text in English or Chinese available. Studies were excluded if one of the following criteria was fulfilled: (1) not relevant to *TNF- α* polymorphisms and asthma; (2) family-based association studies; (3) case reports or case series; (4) abstracts, reviews, comments, letters and conference presentations. For duplicate reports, only the study with the largest sample size was included.

Data extraction and quality assessment

The following data were extracted from included studies: (1) name of the first author; (2) year of publication; (3) country and ethnicity of participants; (4) the number of cases and controls; and (5) genotypic distributions of *TNF- α* polymorphisms in cases and controls. Additionally, the probability value (*p* value) of Hardy-Weinberg equilibrium (HWE) test was also calculated according to genotypic frequency of *TNF- α* polymorphisms in the control group.

The Newcastle-Ottawa scale (NOS) was used to assess the quality of eligible studies from three aspects: (1) selection of cases and controls; (2) comparability between cases and controls, and (3) exposure in cases and controls (Stang 2010). The NOS has a score range of zero to nine, and studies with a score of more than seven were thought to be of high quality.

Two reviewers conducted the data extraction and quality assessment independently. When necessary, the reviewers wrote to the corresponding authors for extra information or raw data. Any disagreement between two reviewers was solved by discussion until a consensus was reached.

Statistical analyses

All statistical analyses in the present study were conducted with Review Manager Version 5.3.3 (The Cochrane Collaboration, Software Update, Oxford, United Kingdom). ORs and 95% CIs were used to assess potential associations of *TNF- α* polymorphisms with the risk of asthma in the dominant, recessive, additive and allele models, and a *p* value of 0.05 or less was considered to be statistically significant.

Between-study heterogeneities were evaluated on the basis of Q test and I^2 statistic. If p value of Q test was less than 0.1 or I^2 was greater than 50%, random-effect models (REMs) would be used for analyses due to the existence of significant heterogeneities. Otherwise, fixed-effect models (FEMs) would be applied for analyses. Subgroup analyses by ethnicity of participants were subsequently conducted to obtain more specific results. Sensitivity analyses were carried out to test the stability of the results. Funnel plots were applied to evaluate possible publication bias.

Results

Characteristics of included studies

The literature search identified 710 potentially relevant articles. After exclusion of irrelevant and duplicate articles by reading titles and abstracts, 141 articles were retrieved for further evaluation. Another 91 articles were subsequently excluded after reading the full text. Finally, a total of 50 eligible studies were included in this meta-analysis (see Fig. 1). Characteristics of included studies were summarized in Table 1.

Overall analyses

To investigate potential correlations of *TNF- α* polymorphisms with the risk of asthma, 11 studies about *TNF- α* -238 G/A polymorphism (1854 cases and 2156 controls), 50 studies about *TNF- α* -308 G/A polymorphism (9971 cases and 17894 controls), 5

studies about *TNF- α* -857 C/T polymorphism (1778 cases and 1300 controls), 3 studies about *TNF- α* -863 C/A polymorphism (1377 cases and 898 controls) and 6 studies about *TNF- α* -1031 T/C polymorphism (1781 cases and 1331 controls) were enrolled for analyses. Significant associations with the risk of asthma were detected for *TNF- α* -238 G/A (dominant model: $p = 0.006$, OR = 0.47, 95%CI 0.28-0.80; additive model: $p = 0.03$, OR = 1.87, 95%CI 1.06-3.30; allele model: $p = 0.004$, OR = 0.50, 95%CI 0.31-0.80), -308 G/A (dominant model: $p = 0.001$, OR = 0.76, 95%CI 0.65-0.90; additive model: $p = 0.002$, OR = 1.29, 95%CI 1.10-1.51; allele model: $p = 0.0009$, OR = 0.81, 95%CI 0.71-0.91) and -857 C/T (dominant model: $p = 0.03$, OR = 1.23, 95%CI 1.02-1.48; additive model: $p = 0.04$, OR = 0.81, 95%CI 0.67-0.99; allele model: $p = 0.006$, OR = 1.24, 95%CI 1.06-1.44) polymorphisms in overall analyses. No any other positive results were found for investigated polymorphisms in overall analyses (see Table 2 and Supplementary figure 1).

Subgroup analyses

Further subgroup analyses according to ethnicity of participants revealed that *TNF- α* -238 G/A polymorphism was significantly correlated with the risk of asthma in Caucasians (dominant model: $p < 0.0001$, OR = 0.18, 95%CI 0.11-0.29; additive model: $p < 0.0001$, OR = 6.25, 95%CI 3.80-10.28; allele model: $p < 0.0001$, OR = 0.24, 95%CI 0.16-0.38), *TNF- α* -308 G/A polymorphism was significantly correlated with the risk of asthma in West Asians (dominant model: $p = 0.0001$, OR = 0.54, 95%CI 0.39-0.74; additive model: $p < 0.0001$, OR = 1.93, 95%CI 1.40-2.67; allele

model: $p < 0.0001$, OR = 0.63, 95%CI 0.52-0.76), *TNF- α* -857 C/T polymorphism was significantly correlated with the risk of asthma in Caucasians (allele model: $p = 0.009$, OR = 0.64, 95%CI 0.45-0.89), *TNF- α* -863 C/A polymorphism was significantly correlated with the risk of asthma in East Asians (dominant model: $p = 0.002$, OR = 0.66, 95%CI 0.51-0.86; additive model: $p = 0.007$, OR = 1.45, 95%CI 1.11-1.91; allele model: $p = 0.002$, OR = 0.69, 95%CI 0.55-0.87), and *TNF- α* -1031 T/C polymorphism was significantly correlated with the risk of asthma in Caucasians (dominant model: $p = 0.02$, OR = 1.32, 95%CI 1.04-1.68; recessive model: $p = 0.02$, OR = 0.63, 95%CI 0.44-0.92; allele model: $p = 0.005$, OR = 1.28, 95%CI 1.08-1.53) and East Asians (dominant model: $p = 0.003$, OR = 0.68, 95%CI 0.52-0.88; additive model: $p = 0.03$, OR = 1.35, 95%CI 1.04-1.76; allele model: $p = 0.002$, OR = 0.70, 95%CI 0.57-0.88) (see Table 2 and Supplementary figure 1).

Sensitivity analyses

Sensitivity analyses were carried out to examine the stability of meta-analysis results by eliminating studies that deviated from HWE. No changes of results were observed in any comparisons, which indicated that our findings were statistically reliable.

Publication biases

Potential publication biases in the current study were evaluated with funnel plots. No obvious asymmetry of funnel plots was observed in any comparisons, which suggested that our findings were unlikely to be influenced by severe publication

biases.

Discussion

To the best of our knowledge, this is so far the most comprehensive meta-analysis on correlations between *TNF- α* polymorphisms and asthma. Significant associations with the risk of asthma were detected for *TNF- α* -238 G/A, -308 G/A and -857 C/T polymorphisms in overall analyses. Further subgroup analyses based on ethnicity of participants revealed that *TNF- α* -238 G/A polymorphism was significantly correlated with the risk of asthma in Caucasians, *TNF- α* -308 G/A polymorphism was significantly correlated with the risk of asthma in West Asians, *TNF- α* -857 C/T polymorphism was significantly correlated with the risk of asthma in Caucasians, *TNF- α* -863 C/A polymorphism was significantly correlated with the risk of asthma in East Asians, and *TNF- α* -1031 T/C polymorphism was significantly correlated with the risk of asthma in Caucasians and East Asians. No any other positive results were found for investigated polymorphisms in overall and subgroup analyses. The stability of the synthetic results was subsequently evaluated in sensitivity analyses, and no changes of results were observed in any comparisons, which indicated that our findings were quite stable and reliable. As for the evaluation of heterogeneities, obvious between-study heterogeneities were detected for the -308 G/A polymorphism in certain comparisons (data not shown). But in further stratified analyses, a great reduction of heterogeneity was found in the West Asian subgroup, which suggested

that differences in ethnic background could partially explain observed heterogeneities between studies.

As with all meta-analysis, this study certainly has some limitations. First, our findings were derived from unadjusted analyses due to lack of raw data, and failure to perform adjusted analyses for potential confounding factors such as age, gender and co-morbidity conditions may impact the reliability of our findings (Xie et al., 2017). Second, obvious heterogeneities were detected in certain subgroup comparisons for the -308 G/A polymorphism (East Asians and Caucasians), which indicated that the inconsistent results of included studies could not be fully explained by differences in ethnic background, and other unmeasured characteristics of participants may also partially attribute to between-study heterogeneities (Xie et al., 2017). Third, associations between *TNF- α* polymorphisms and asthma may also be influenced by gene-gene and gene-environmental interactions. However, the majority of studies did not evaluate these potential interactions, which impeded us to perform relevant analyses accordingly (Yang et al., 2014). Taken these limitations into consideration, the results of the current study should be interpreted with caution.

Conclusions

Overall, our meta-analysis suggested that *TNF- α* -238 G/A, -308 G/A, -857 C/T, -863 C/A and -1031 T/C polymorphisms may serve as potential biological markers for asthma in certain ethnicities. However, further well-designed studies with larger

sample sizes are warranted to confirm our findings. Additionally, future investigations are needed to explore potential roles of other *TNF- α* polymorphisms in the development of asthma.

Authors' contributions

Hao Sun and Hongmei Qiao conceived of the study, participated in its design. Hao Sun and Qingsong Li conducted the systematic literature review. Hao Sun, Qingsong Li and Yingji Jin performed data analyses. Hao Sun and Hongmei Qiao drafted the manuscript. All authors have read and approved the final manuscript.

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None.

Conflict of interest

The authors declare that they have no conflict of interest.

Compliance with ethical standards

Ethical approval

This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent

For this type of study formal consent is not required.

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Fig. 1. Flowchart of study selection for the present study.

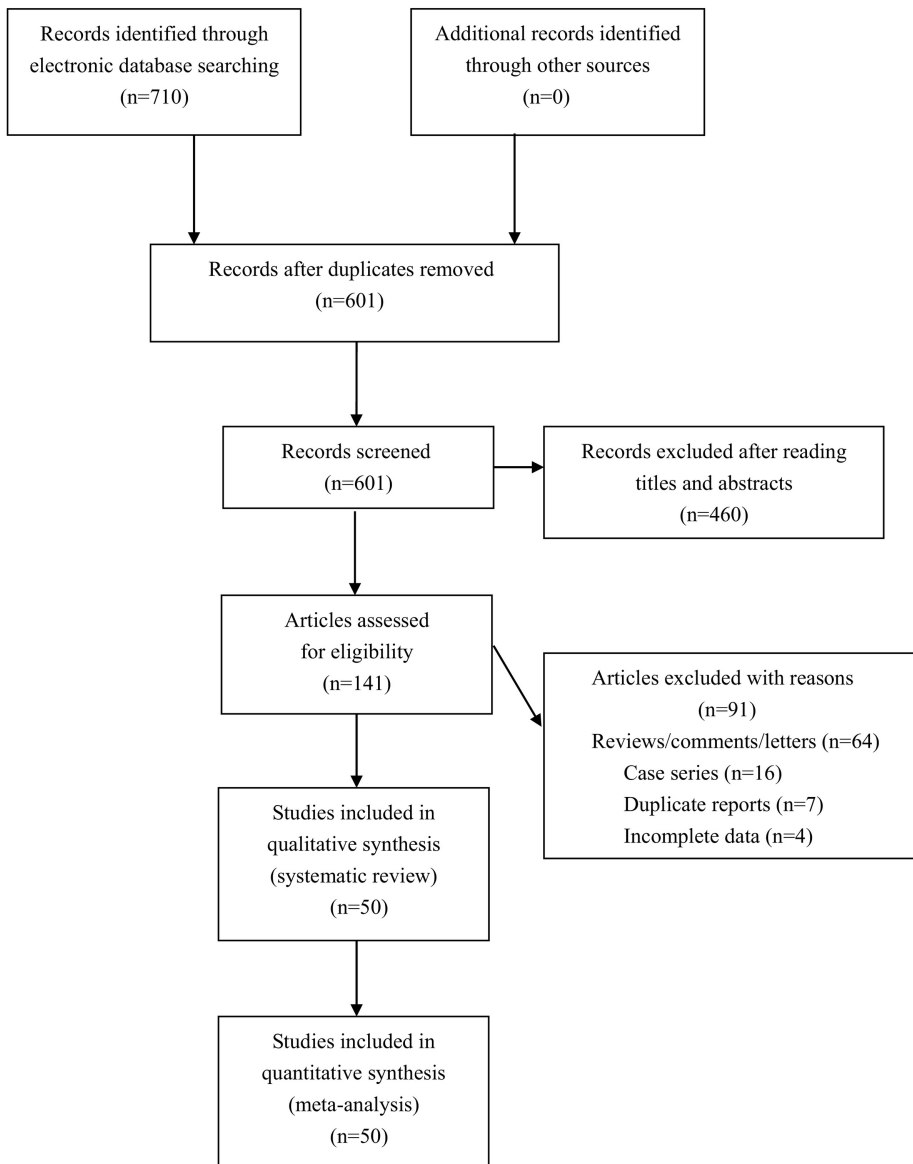
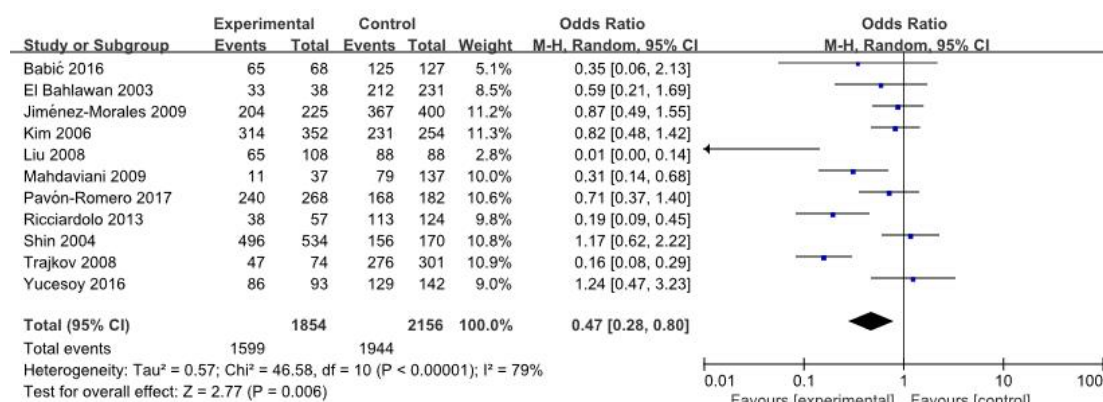
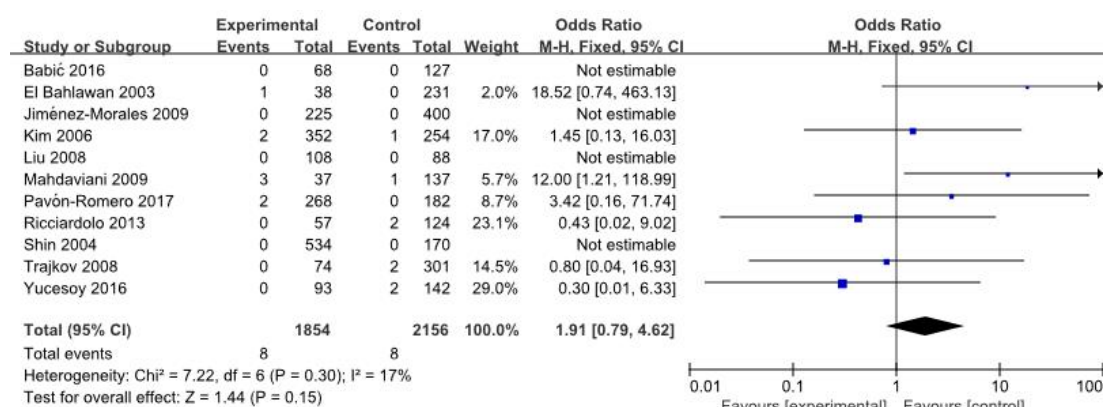


Figure 1

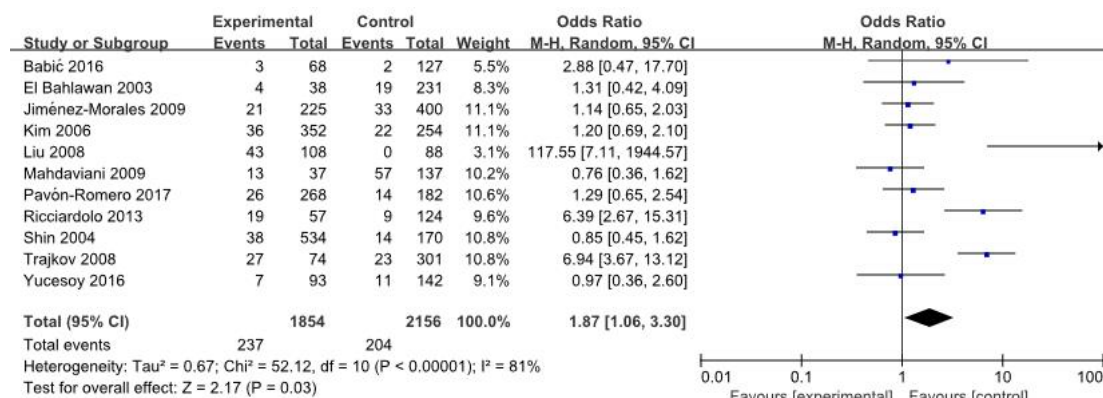
Forest plots of investigated polymorphisms



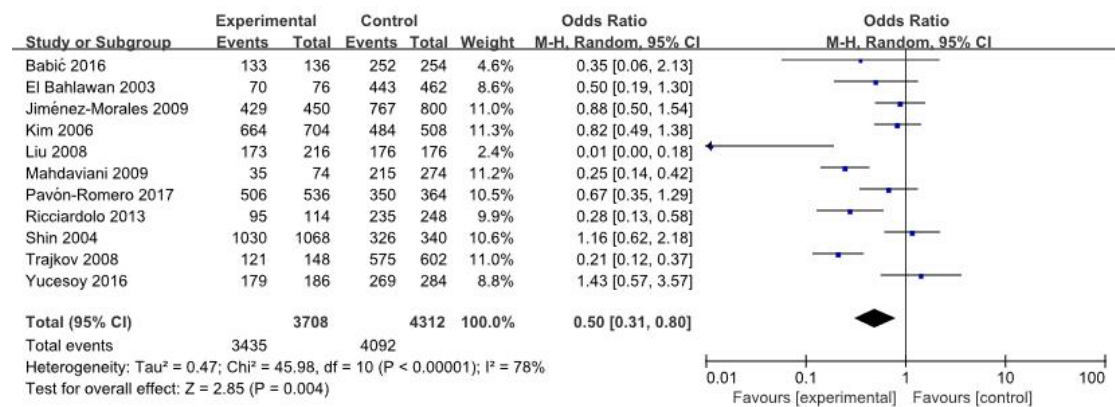
Forest plot of -238 G/A polymorphism and asthma under dominant comparison



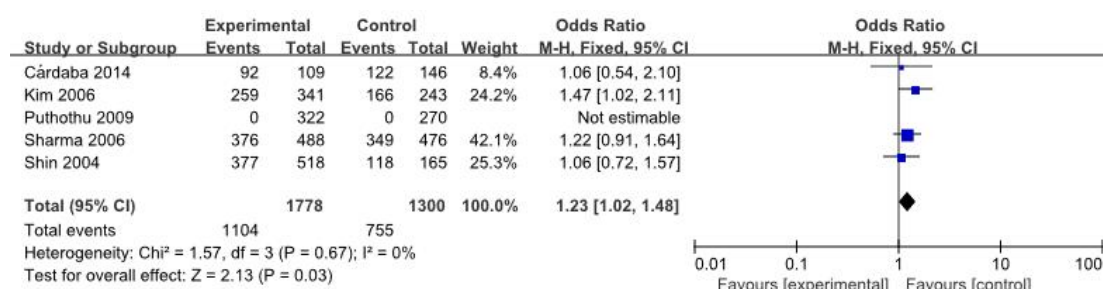
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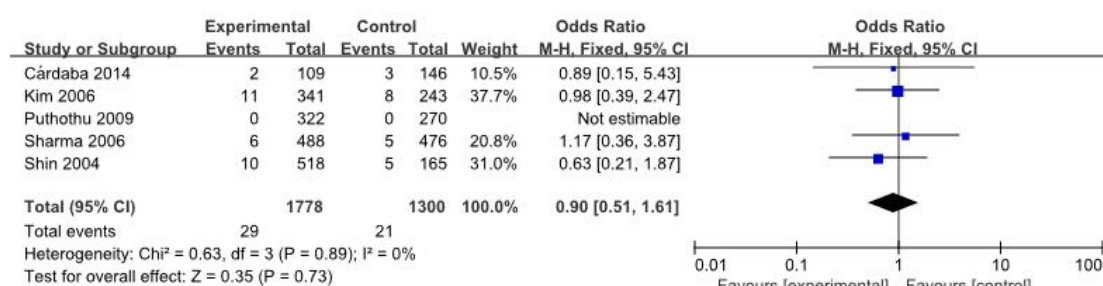
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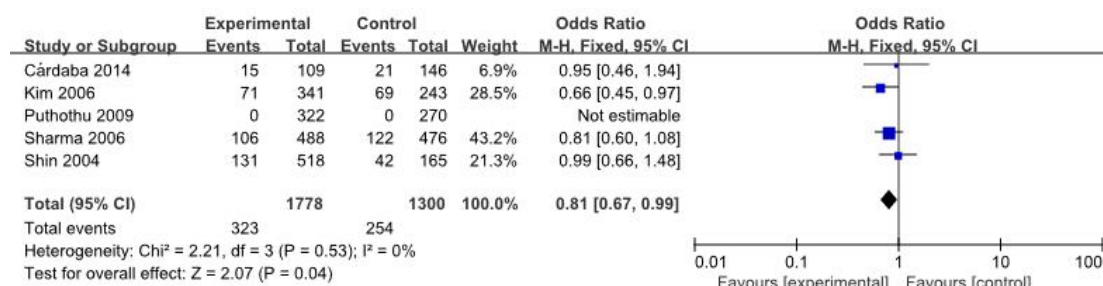
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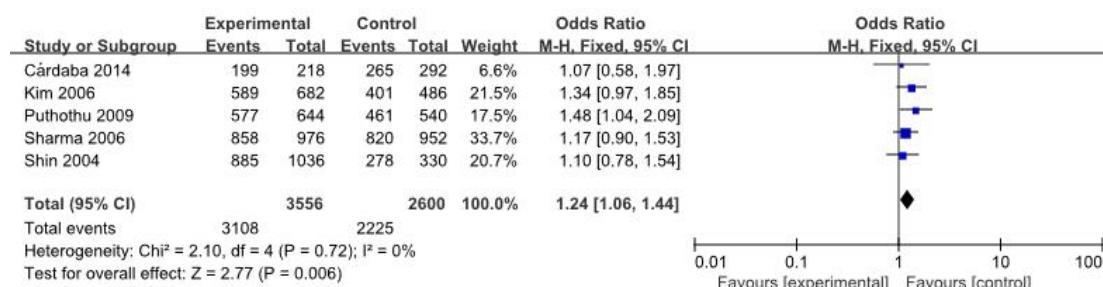
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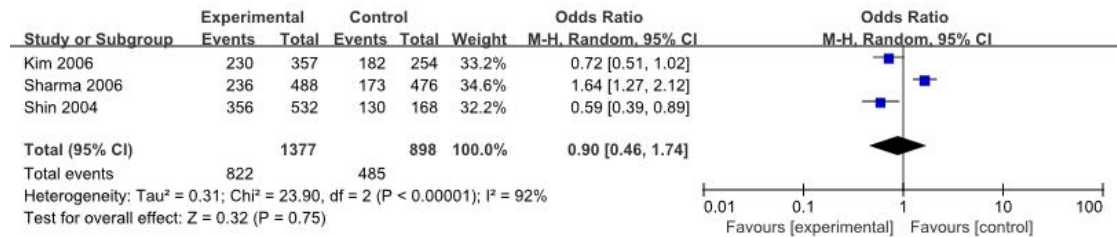
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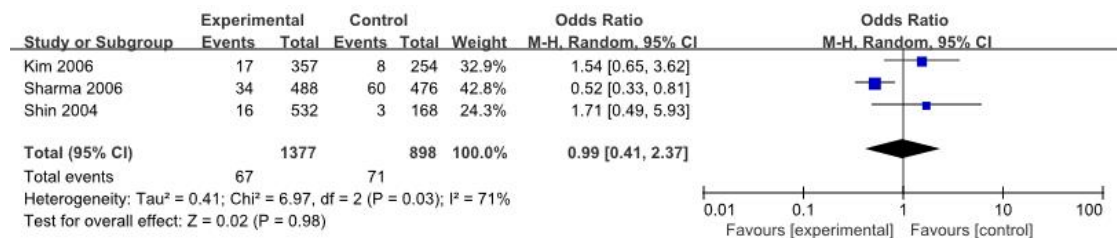
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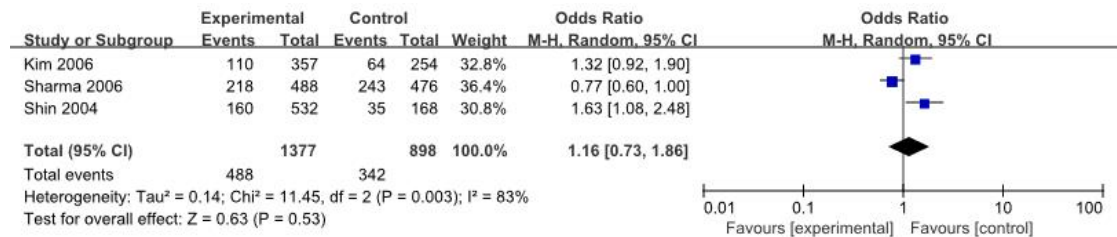
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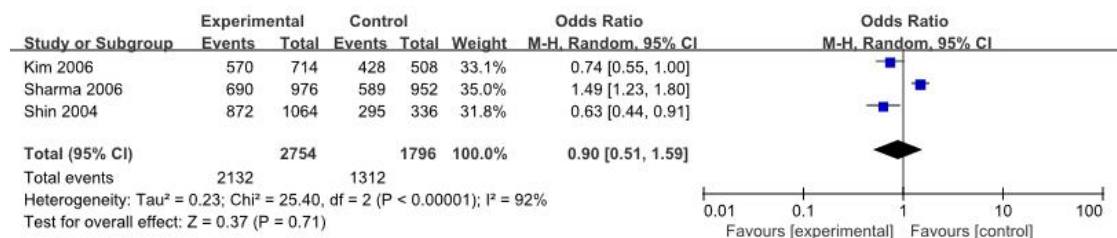
Forest plot of -863 C/A polymorphism and asthma under dominant comparison



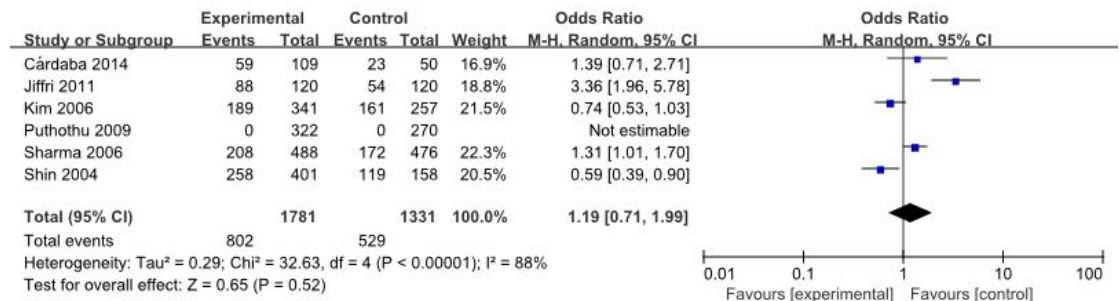
Forest plot of -863 C/A polymorphism and asthma under recessive comparison



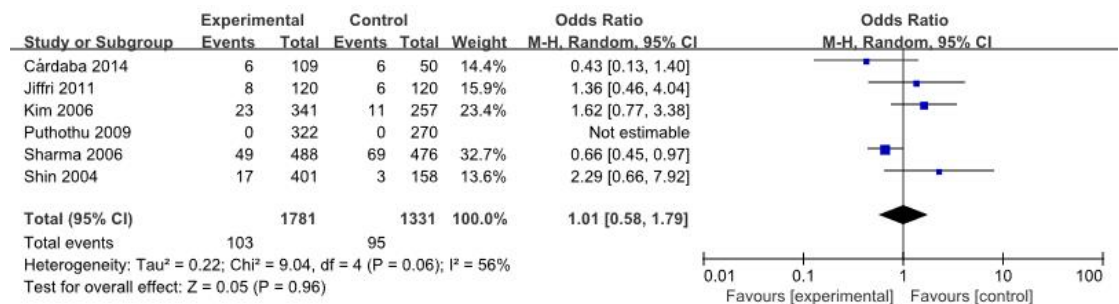
Forest plot of -863 C/A polymorphism and asthma under additive comparison



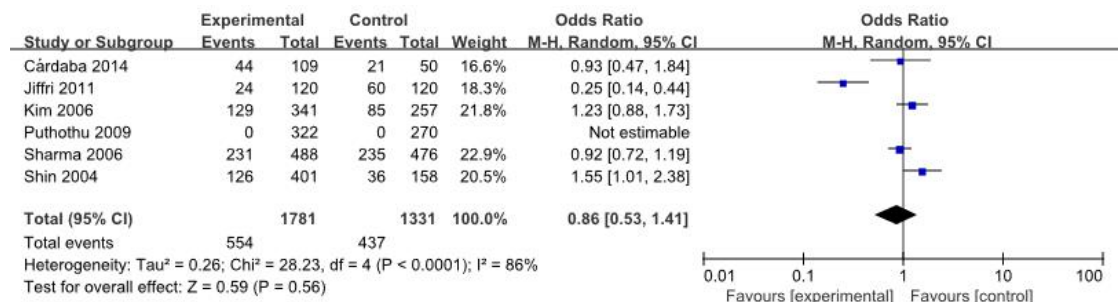
Forest plot of -863 C/A polymorphism and asthma under allele comparison



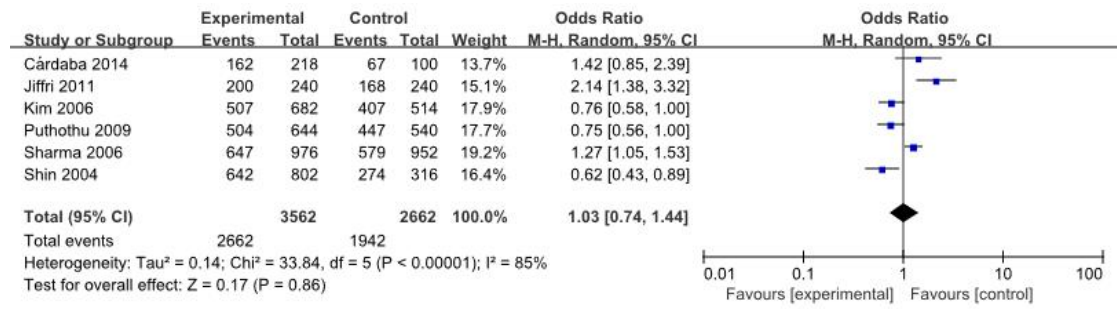
Forest plot of -1031 T/C polymorphism and asthma under dominant comparison



Forest plot of -1031 T/C polymorphism and asthma under recessive comparison



Forest plot of -1031 T/C polymorphism and asthma under additive comparison



Forest plot of **-1031 T/C** polymorphism and asthma under allele comparison