

Effect of mesenchymal stromal (stem) cell (MSC) transplantation in asthmatic animal models: A systematic review and meta-analysis

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ABSTRACT

Background: Over the years, mesenchymal stromal (stem) cells (MSCs) have been pre-clinically applied in the treatment of variety kinds of diseases including asthma and chronic lung diseases. Aim of the current study was to systematically review and to conduct meta-analysis on the published studies of MSC treatment in asthma animal models. **Methods:** Publications on the MSC and asthma treatment was thoroughly searched in the electronic databases. Statistical analysis was then performed using the Comprehensive Meta-Analysis software (Version 3). Effect of MSC therapy on asthma model was assessed by Hedges's g with 95% confidence intervals (95% CIs). Random effect model was used due to the heterogeneity between the studies.

Results: Meta-analysis of the 32 included studies showed that MSC transplantation was significantly in favor of attenuating lung injury and remodeling (Hedges's $g = -9.104 \pm 0.951$ with 95% CI: $-10.969 \sim -7.240$, $P < 0.001$) and airway inflammation (Hedges's $g = -4.146 \pm 0.688$ with 95% CI: $-5.495 \sim -2.797$, $P < 0.001$). The mechanism of MSC therapy in asthma seems to be regulating the balance of Th1 cytokine and Th2 cytokines (IFN- γ : Hedges's $g = 4.779 \pm 1.408$ with 95% CI: $1.099 \sim 2.725$, $P < 0.001$; IL-4: Hedges's $g = -10.781 \pm 1.062$ with 95% CI: $-12.863 \sim -8.699$, $P < 0.001$; IL-5: Hedges's $g = -10.537 \pm 1.269$ with 95% CI: $-13.025 \sim -8.050$, $P < 0.001$; IL-13: Hedges's $g = -6.773 \pm 0.788$ with 95% CI: $-8.318 \sim -5.229$, $P < 0.001$).

Conclusion: Findings of the current systemic review suggested a potential role for MSCs in asthma treatment although it is still challenging in clinical practice. The mechanisms of MSCs in pre-clinical asthma treatment may be associated with attenuating airway inflammation through regulating Th1 and Th2 cytokines.

1. Introduction

Asthma is a chronic respiratory disease that affects millions of people worldwide, and its prevalence varies among countries from 1 to 18% [1]. Asthma is characterized by chronic airway inflammation, which is associated with the accumulation and activation of inflammatory cells including type 2 T-helper (Th2) cells, eosinophils, and mast cells within small airways [2]. Chronic airway inflammation leads to small airway narrowing and remodeling as well as bronchial hyper-reactivity. Over the years, studies have been focused on discovering effective treatments of asthma and preventive approaches for asthma including new strategies to reduce severe asthma attack and to improve the quality of life. In this regard, recently, substantial studies have been interested in using mesenchymal stromal (stem) cells (MSCs) to treat variety kinds of chronic inflammatory diseases and immune disorders including asthma [3–9].

Mesenchymal stromal (stem) cells (MSCs) are multi-potent stem

cells that can be induced to differentiate into variety kinds of cells including chondrocytes, osteoblasts, adipocytes and muscle cells [10,11]. Besides their regenerative properties, many studies have demonstrated that MSCs modulate host immunity and suppression of chronic inflammation. These unique properties of MSCs render the cells being used as a treatment option for variety kinds of diseases including acute myocardial infarction [12], liver cirrhosis [13], crohn's disease [14], and graft-versus-host disease (GVHD) [15] in phase III clinical trials, and type I diabetes [16], arthritis [17] and lung diseases such as COPD [18,19] in phase II clinical trials.

Following hematopoietic stem cell transplant, a variety of adverse events have been reported including allergic reactions to cyclophosphamide, fever, infection, nausea, vomiting and elevations in liver enzymes [20]; macrophage activation syndrome [21,22]; and GVHD following allogeneic transplants [23,24]. Following mesenchymal stromal (stem) cell transplant, however, serious adverse effects have not been reported.

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MSCs can be isolated from various tissues including bone marrow, adipose, or cord blood. The MSCs have been used for allogeneic or autologous cellular therapy due to the lack of immunogenicity of MSCs. In this content, studies have demonstrated that MSCs have anti-inflammatory and immune-modulatory effects in diverse types of tissue injury and allergic inflammation [25,26]. Specifically, MSCs have the capacity to protect lungs from variety kinds of injury including ovalbumin-induced allergic asthma [3,7], cigarette smoke-induced or elastase-induced COPD/emphysema [27–29], bleomycine-induced fibrosis [30,31], bronchopulmonary dysplasia [32,33], ventilator-induced lung injury [34], and bacterial pneumonia [35,36].

While substantial studies of MSC transplantation in asthma animal models have been reported [3–9], clinical trials of MSC administration in the treatment of asthma have not been reported. Therefore, here we conducted systematic review and meta-analysis on studies of MSC administration in the experimental models of asthma and examined the pooled effect of MSCs in protecting lungs from injury and its potential mechanism.

2. Materials and methods

2.1. Data sources

The Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) criteria was applied in this review and meta-analysis [37]. Associated publications were searched in the sites of PubMed, Embase and Web of Science with the following phrases: “mesenchymal stem cell(s)” and “asthma”, or “mesenchymal stem cell(s)” and “asthmatic”. Only English articles were selected, and literature search was performed by LZ and MH.

2.2. Inclusion criteria and data extraction

Followings were inclusion criteria for the current systematic review and meta-analysis study: 1). Studies on the effect of MSCs on the asthmatic models induced by ovalbumin or other antigens. 2). Studies with full text articles in English.

Duplicated publications and non-English or non-Chinese reports

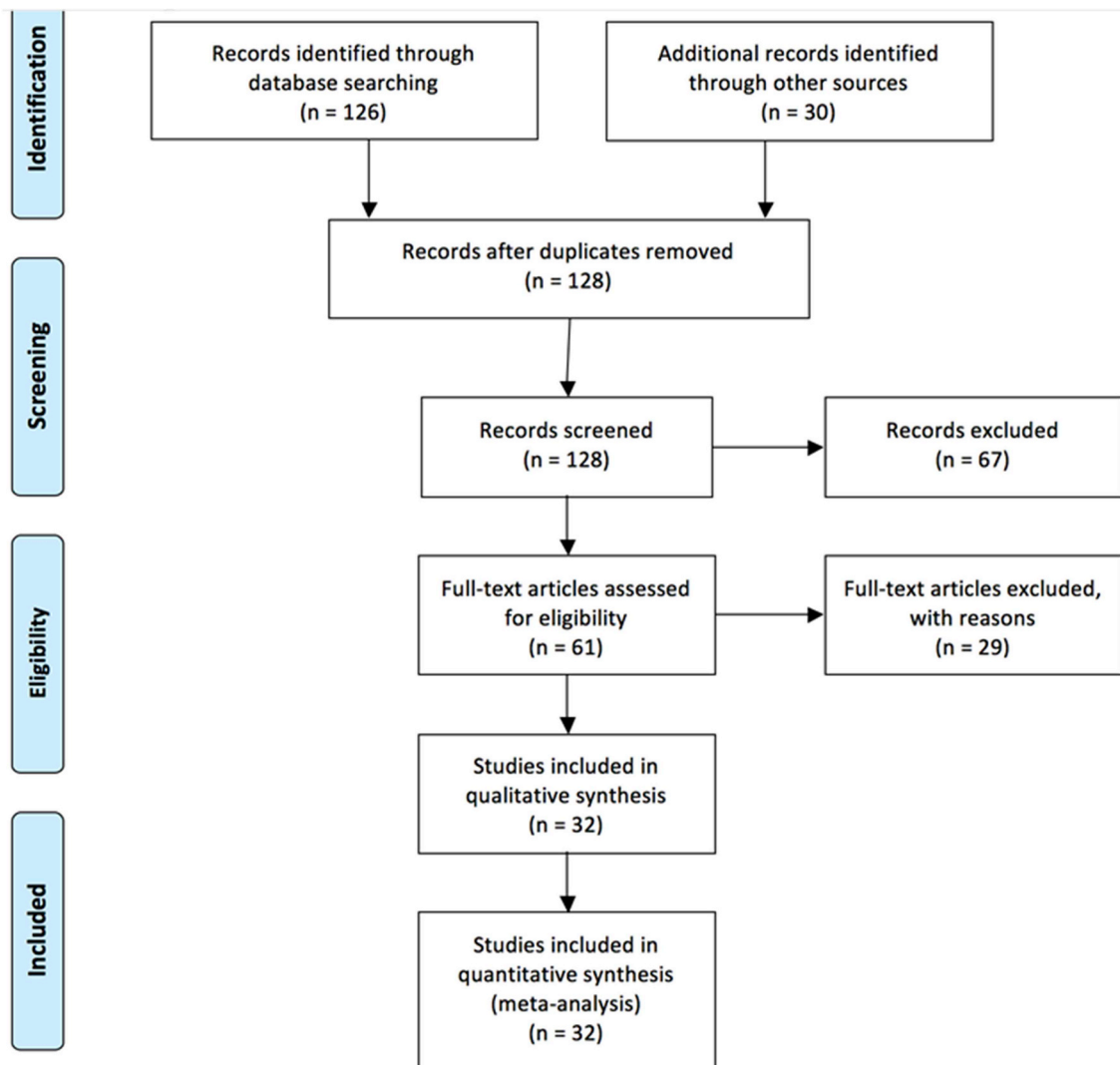


Fig. 1. Flow diagram of literature search and eligible publication selection.

were excluded from this review and meta-analysis.

The following information was extracted from the included literature: the first author's name, year of publication, country of the corresponding author, source and species of MSCs, recipient animal species, total number of cases or replication of the experiment, study design and parameters including lung histology, lung inflammation, total and differential cell numbers in the bronchoalveolar lavage fluid (BALF), serum IgE, IL-4, IL-5, IL-13, IFN- γ , and pro-inflammatory cytokines such as IL-1 β and IL-6.

2.3. Statistical analysis

The following data formats were used to perform meta-analysis: 1). Mean, standard deviation (SD), number of asthma model animals treated with or without MSC administration; 2). Sample size of asthma models treated with or without MSC transplantation, and *P* value of comparison between the two groups. The strength of MSC effect on asthma tissue injury and remodeling (histological alteration), airway inflammation or Th1 and Th2 cytokine synthesis was measured by Hedges's *g*. A random or fixed effect model was applied depending on the significance of data heterogeneity. The heterogeneity between studies was assessed by the *Q*-test and I^2 statistics, and $P < 0.10$ and $I^2 > 50\%$ was considered as heterogeneous between the studies [38]. All meta-analysis was performed using the Comprehensive Meta-analysis software (Version 3, NJ, USA).

3. Results

3.1. General information of the included studies

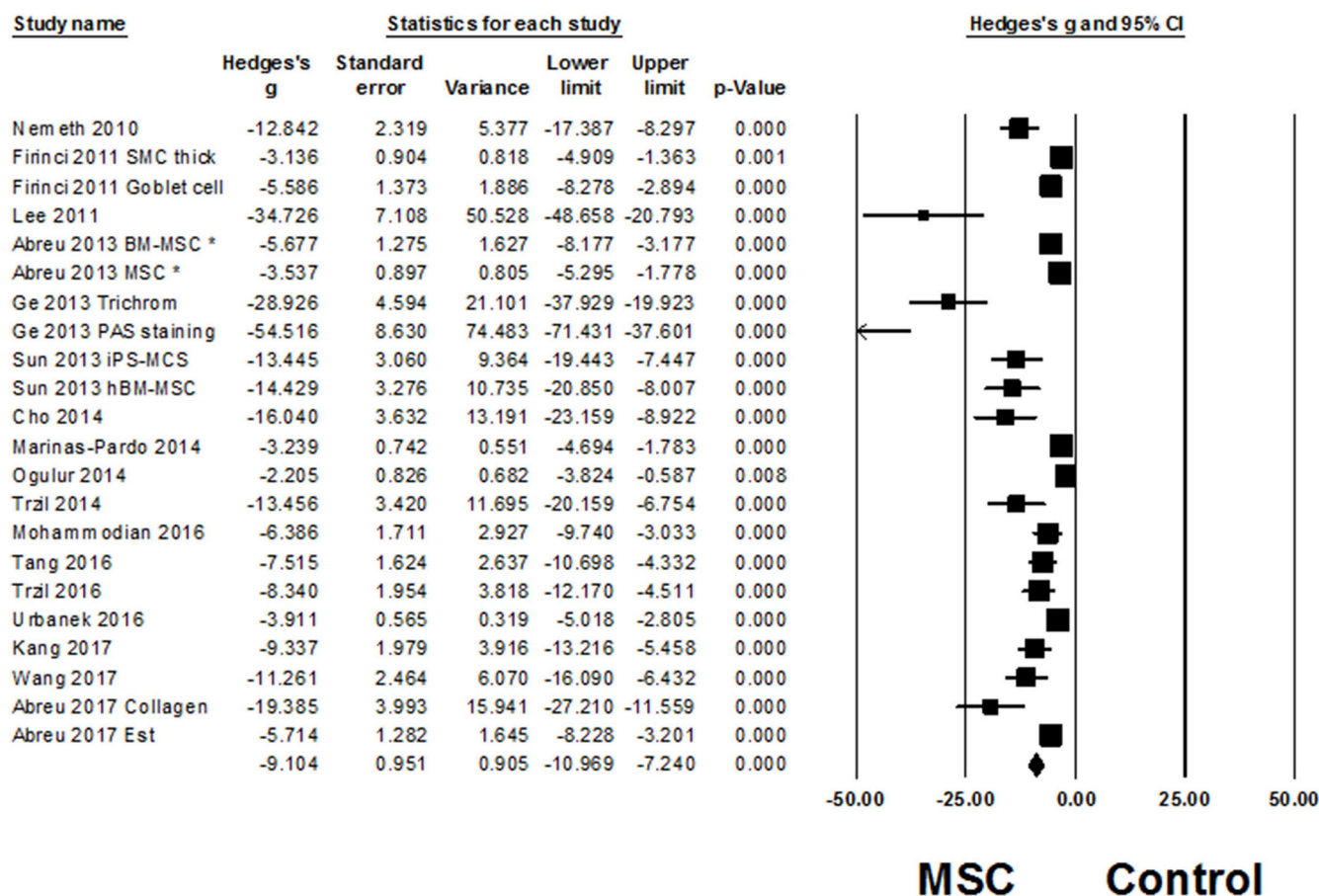
As shown in Fig. 1, total 128 studies were screened and total 61 full-text articles were retrieved after careful reading “abstract” of the publications. The full-text articles were then independently assessed by the authors (LZ and MH). Thirty-two articles were finally included in the current systematic review and meta-analysis. As shown in Table 1, of the 32 studies included in this review, 6 studies tested effect of human bone marrow derived MSCs [7,39–43], 3 studies tested human adipose stromal cells [4,7,44], 4 studies tested human umbilical cord blood cell derived MSCs [7,45–47] and two studies tested effect of human iPSC derived MSCs [40,48], 3 studies tested rat bone marrow derived mesenchymal stem/stromal cells [49–51], 17 studies examined the effect of mice bone marrow or adipose-derived MSCs or lung tissue MSCs [3,5,6,8,9,41,52–62], and one study tested cat adipose-derived MSCs [63]. Among the 32 articles, most of the studies were from USA and China (8 articles from each country) followed by Korea (4 articles), Brazil (2 articles), Iran (2 articles), and Turkey (2 articles). In addition, one article from each of the following countries was also included: Australia, Canada, Spain, Italy, and France.

3.2. Overall systematic review

While 3 clinical trials on the effect of MSC in asthma therapy were

Table 1
Characteristics of included 32 papers.

First author	Country	Year	MSC source	Recipients	MSC dose	Delivery	Infla. Mediators
Bonfield	USA	2010	hBM-MSC	BALB/c mice	106/100 μ L	IV	IL-1 β , IL-5, IL-13
Nemeth	USA	2010	mBM-MSC	C57/Blk mice	0.75 $\times$ 106/300 μ L	IV	IL-4, IL-5, IL-13
Firinci	Turkey	2011	mBM-MSC	BALB/c mice	106/100 μ L	IV	
Goodwin	USA	2011	mBM-MSC	C56/Blk mice	2 $\times$ 106/200 μ L	IV	IL-4, IL-5, IL-6, IL-13
Lee	Korea	2011	rBM-MSC	SD rat	105/100 μ L	IV	
Sun	China	2012	iPS-MSC	BALB/c mice	5 $\times$ 106/200 μ L	IV	IL-4, IL-5, IL-13
			hBM-MSC				
Abreu	Brazil	2013	mBM-MSC	C57/Blk mice	2 $\times$ 106/50 μ L	IT	IL-4, IL-13
Ge	China	2013	mBM-MSC	BALB/c mice	5 $\times$ 105/100 μ L	IT	IL-4, IL-13
Mathias	Australia	2013	hBM-MSC	BALB/c mice	106/200 μ L	IV	IL-4, IL-5, IL-13
			hU-MSC				
			hAD-MSC				
Cho	Korea	2014	mAD-MSC	C57/Blk mice	106/100 μ L	IV	IL-4, IL-5, IL-13
Lathrop	USA	2014	mBM-MSC	C57/Blk mice	106/200 μ L	IV	IL-4, IL-5, IL-6, IL-13
Marinas-Pardo	Canada	2014	mAD-MSC	BALB/c mice	3 $\times$ 105/200 μ L	IV	
Martinez-Gonzalez	Spain	2014	hAD-MSC	BALB/c mice	106/250 μ L	IV	
Ogullur	Turkey	2014	mBM-MSC	BALB/c mice	2.5 $\times$ 105/100 μ L	IV	
Trzil	USA	2014	cat BM-MSC	Cat	1.4 $\times$ 107/200 μ L	IV	
Cruz	USA	2015	hBM-MSC	C57/Blk mice	106/200 μ L	IV	IL-4, IL-5, IL-6, IL-13
			mBM-MSC				
Lin	China	2015	rBM-MSC	SD rat	106/200 μ L	IV	IL-1 β , IL-6
Song	China	2015	hBM-MSC	NOD/SCID mice	106/200 μ L	IV	
Xu	China	2015	mBM-MSC	C57/Blk mice	106/200 μ L	IV	IL-4, IL-13
Zeng	China	2015	mBM-MSC	BALB/c mice	106/200 μ L	IV	IL-4, IL-5, IL-13
Ahmadi	Iran	2016	rBM-MSC	Rat	2 $\times$ 106/200 μ L	IV	
Braza	France	2016	mBM-MSC	BALB/c mice	106/200 μ L	IV	IL-4, IL-5, IL-13
Chan	China	2016	hU-MSC	BALB/c mice	106/200 μ L	IV	IL-4, IL-5, IL-13
Cruz	USA	2016	mBM-MSC	C57/Blk mice	106/200 μ L	IV	IL-4, IL-5, IL-6, IL-13
Mohammadian	Iran	2016	mBM-MSC	BALB/c mice	106/200 μ L	IV	
Tang	China	2016	hBM-MSC	BALB/c mice	5 $\times$ 106/200 μ L	IV	IL-4, IL-5, IL-13
Trzil	USA	2016	cat AD-MSC	cats	2 $\times$ 106-107	IV	
Urbanek	Italy	2016	mBM-MSC	BALB/c mice	5 $\times$ 104/50 μ L	IT	IL-4, IL-5, IL-13
Abreu	Brazil	2017	mBM-MSC	C57/Blk mice	105/50 μ L	IT	IL-4, IL-13
			mAD-MDC				
			m Lung-MSC				
Hong	Korea	2017	hU-MSC	BALB/c mice	3/6 $\times$ 105/200 μ L	IV	IL-13
Kang	Korea	2017	hU-MSC	BALB/c mice	5 $\times$ 105/100 μ L	IV	IL-4, IL-5, IL-13
Wang	China	2017	hiPS-MSC	BALB/c mice	106/200 μ L	IV	IL-4, IL-13



Meta Analysis

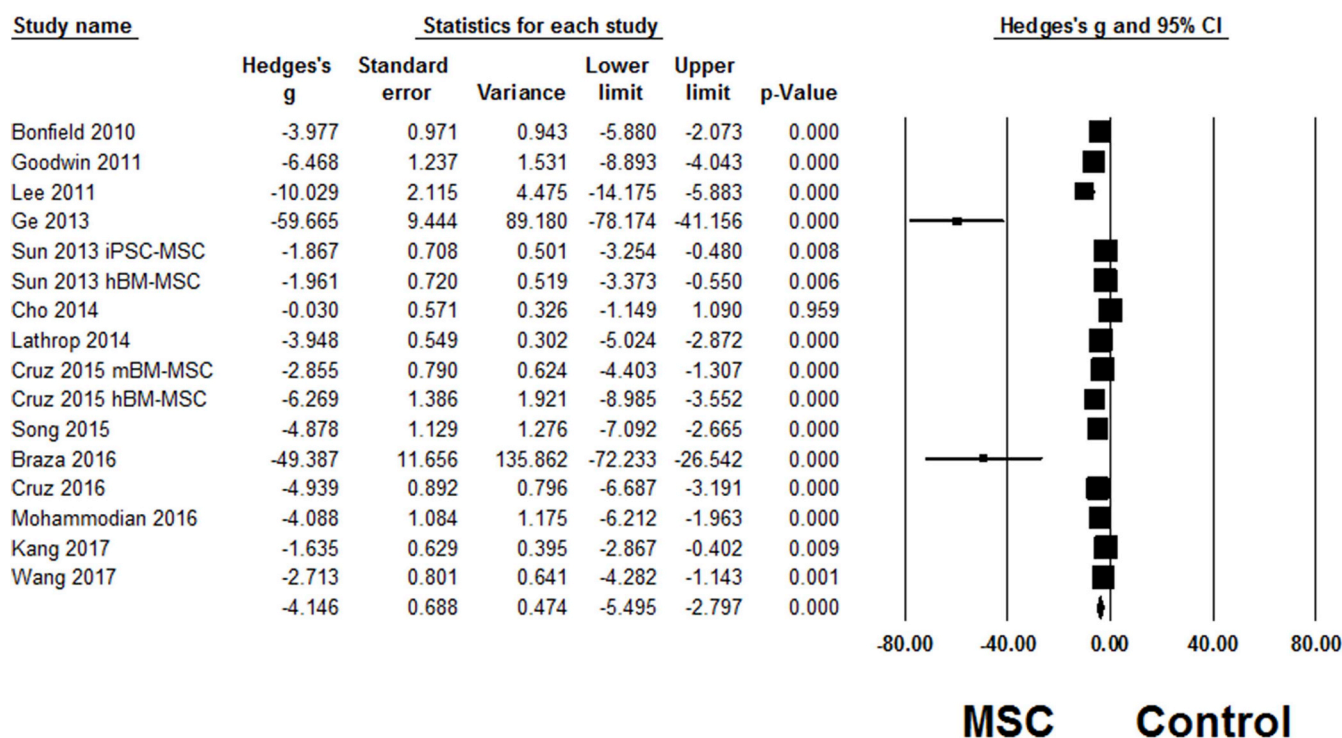
Fig. 2. Forest plot for the MSC effect on histological alteration in asthma model. A random effect model was used due to significant heterogeneity of publications ($I^2 = 88.3$, $P < 0.01$). Effect size was assessed by Hedges's g and 95% CI, and the effect on histological alteration was in favor of MSC treatment (Hedges's $g = -9.104 \pm 0.951$ with 95% CI: $-10.969 \sim -7.240$, $P < 0.001$).

found in the official site (www.clinicaltrials.gov), none of them was completed. Thus, in the current study, only pre-clinical studies on animal models of asthma were included. While Bonfield et al. from USA reported the first study on human bone marrow derived MSC transplantation into mice asthma model in 2010 [39], most studies on MSC transplantation in animal model of asthmatics were published in the last couple of years (2016, $n = 7$; 2015, $n = 5$; 2014, $n = 6$). Most of these studies demonstrated that transplantation of MSCs into asthma models resulted in significant improvement in both structural and functional outcomes, regardless in mice or rats in response to ovalbumin or other allergen challenge. MSCs used in the transplantation were from variety kinds of species including human, mouse, rat or cat as well as organs or tissues including bone marrow, adipose or umbilical cord blood. These MSCs were delivered to the recipient animals through either intravenous (IV, $n = 28$) injection or intra-tracheal (IT, $n = 4$) instillation. One study compared the efficiency of MSCs isolated from human or mice [41], and three studies compared the efficiency of MSCs isolated from different tissues, that is, bone marrow, adipose, iPSC, umbilical cord blood or lung tissue [3,7,40]. It was found that human bone marrow derived MSCs seemed more effective than that from mouse bone marrow [41], and that bone marrow derived MSCs were more effective than that from other sources [3,7,40].

3.3. Effect of MSC transplantation on lung histology and inflammation in asthma models

Effect size of MSC transplantation on airway injury and remodeling was evaluated by histological examinations including trichrom staining, PAS staining and goblet cell hyperplasia etc. Airway inflammation was evaluated by counting inflammatory cells infiltrated into the lung tissues or inflammatory index. Due to the high heterogeneity of the studies ($I^2 = 88.3$ for histological alteration and $I^2 = 87.7$ for inflammation, $P < 0.01$), effect of MSCs on structural restoration and regulation on airway inflammation was assessed by the random effect model. Effect of MSC transplantation on lung histological alteration was statistically significant (Hedges's $g = -9.104 \pm 0.951$ with 95% CI: $-10.969 \sim -7.240$, $P < 0.001$, Fig. 2) with in favor of MSC treatment. Similarly, the effect of MSC transplantation on suppression of airway inflammation was also significant (Hedges's $g = -4.146 \pm 0.688$ with 95% CI: $-5.495 \sim -2.797$, $P < 0.001$, Fig. 3) with in favor of MSC treatment.

Effect of MSC on airway inflammation was further evaluated by the number of total inflammatory cell number and eosinophil number in the bronchoalveolar lavage fluid (BALF). Effect of MSC on the reduction of BALF inflammatory cells was significant (Hedges's $g = -8.218 \pm 0.857$



Meta Analysis

Fig. 3. Forest plot for the inhibitory effect of MSCs on airway inflammation in the asthma models. A random effect model was used due to significant heterogeneity of publications ($I^2 = 87.7$, $P < 0.01$). Effect size was assessed by Hedges's g and 95% CI, and the inhibitory effect on airway inflammation was in favor of MSC treatment (Hedges's $g = -4.146 \pm 0.688$ with 95% CI: $-5.495 \sim -2.797$, $P < 0.001$).

with 95% CI: $-9.897 \sim -6.538$, $P < 0.001$, Fig. 4) with in favor of MSC treatment, and effect of MSC on the reduction of BALF eosinophil was also significant (Hedges's $g = -8.552 \pm 0.866$ with 95% CI: $-10.240 \sim -6.865$, $P < 0.001$, Fig. 5) with in favor of MSC treatment.

Effect size of MSC administration on the production of pro-inflammatory cytokines (IL-1 β and IL-6) was then evaluated. MSC administration resulted in significant inhibition of pro-inflammatory cytokine release in the animal models of asthma, and the effect was statistically significant (Hedges's $g = -6.805 \pm 1.307$ with 95% CI: $-9.366 \sim -4.244$, $P < 0.001$, Fig. 6) with significant heterogeneity ($I^2 = 91.9$, $P < 0.01$). In contrast, MSC administration resulted in up-regulation of anti-inflammatory cytokine (IL-10), which was reported in few studies [3,54] but did not performed meta-analysis due to limited number of studies.

3.4. Effect of MSC transplantation on Th1, Th2 cytokines and IgE production

Next, effect of MSC on asthma model was evaluated by examining the regulatory effect of MSC on the production of Th1, Th2 cytokines and IgE. As shown in Fig. 7, MSC administration resulted in significant up-regulation of Th1 cytokine, IFN- γ , with Hedges's $g = 4.779 \pm 1.408$ with 95% CI: $1.099 \sim 2.725$, $P < 0.001$. In contrast, production of Th2 cytokines (IL-4, IL-5, and IL-13) and IgE was significantly down-regulated in the animals treated with MSCs. IL-4 (Fig. 8): Hedges's $g = -10.781 \pm 1.062$ with 95% CI: $-12.863 \sim -8.699$, $P < 0.001$; IL-5 (Fig. 9): Hedges's $g = -10.537 \pm 1.269$ with 95% CI: $-13.025 \sim -8.050$, $P < 0.001$; IL-13 (Fig. 10): Hedges's $g = -6.773 \pm 0.788$ with 95% CI: $-8.318 \sim -5.229$, $P < 0.001$; IgE (Fig. 11): Hedges's $g = -9.798 \pm 1.645$ with

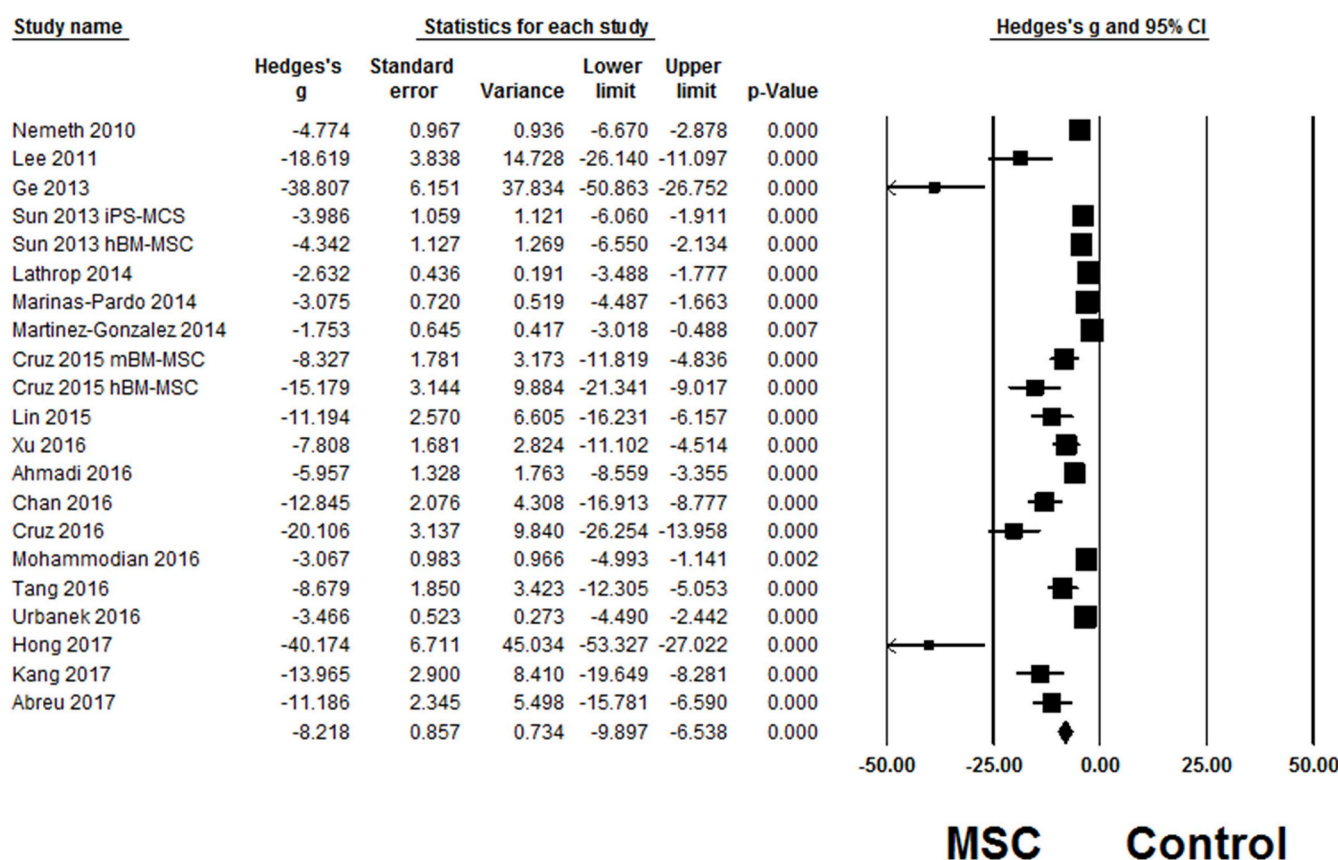
95% CI: $-13.022 \sim -6.573$, $P < 0.001$.

3.5. Publication bias

Publication bias was examined by the funnel plot of standard error versus Hedges's g . As shown in the Supplemental Fig. S1 through S10, distribution of the funnel plot was asymmetric in all of the plots.

4. Discussion

Over the past decade, development to cellular therapies for lung diseases has rapidly progressed. In this regard, studies have reported that MSCs can prevent or have therapeutic effect in asthma animal models. While pre-clinical animal studies demonstrated that MSCs could significantly reduce asthma symptoms and improve lung tissue remodeling, clinical trials of MSC application in asthma has not been reported although three clinical trials had been registered at the official site of www.clinicaltrials.gov. Here, we systematically reviewed 32 publications of MSC administration in the treatment of asthma animal models, and further performed meta-analysis to examine the pooled effect of MSC in asthma therapy. We demonstrated that MSC administration either by intravenous injection or intra-tracheal instillation resulted in significant reduction of airway inflammation and abnormal tissue remodeling in the animal models of asthma, which were induced by ovalbumin or other allergens. MSCs could also significantly attenuate the number of total white blood cells and eosinophils, and significantly suppressed production of Th2 cytokines (IL-4, IL-5, IL-13), pro-inflammatory cytokines (IL-1 β and IL-6) and IgE; and significant up-regulation of Th1 cytokine (IFN- γ). These findings suggested



Meta Analysis

Fig. 4. Forest plot for the inhibitory effect of MSCs on BALF total cell number in the asthma models. A random effect model was used due to significant heterogeneity of publications was observed ($I^2 = 90.5$, $P < 0.01$). Effect size was assessed by Hedges's g and 95% CI, and the inhibitory effect on BALF total cell number was in favor of MSC administration (Hedges's g = -8.218 ± 0.857 with 95% CI: $-9.897 \sim -6.538$, $P < 0.001$).

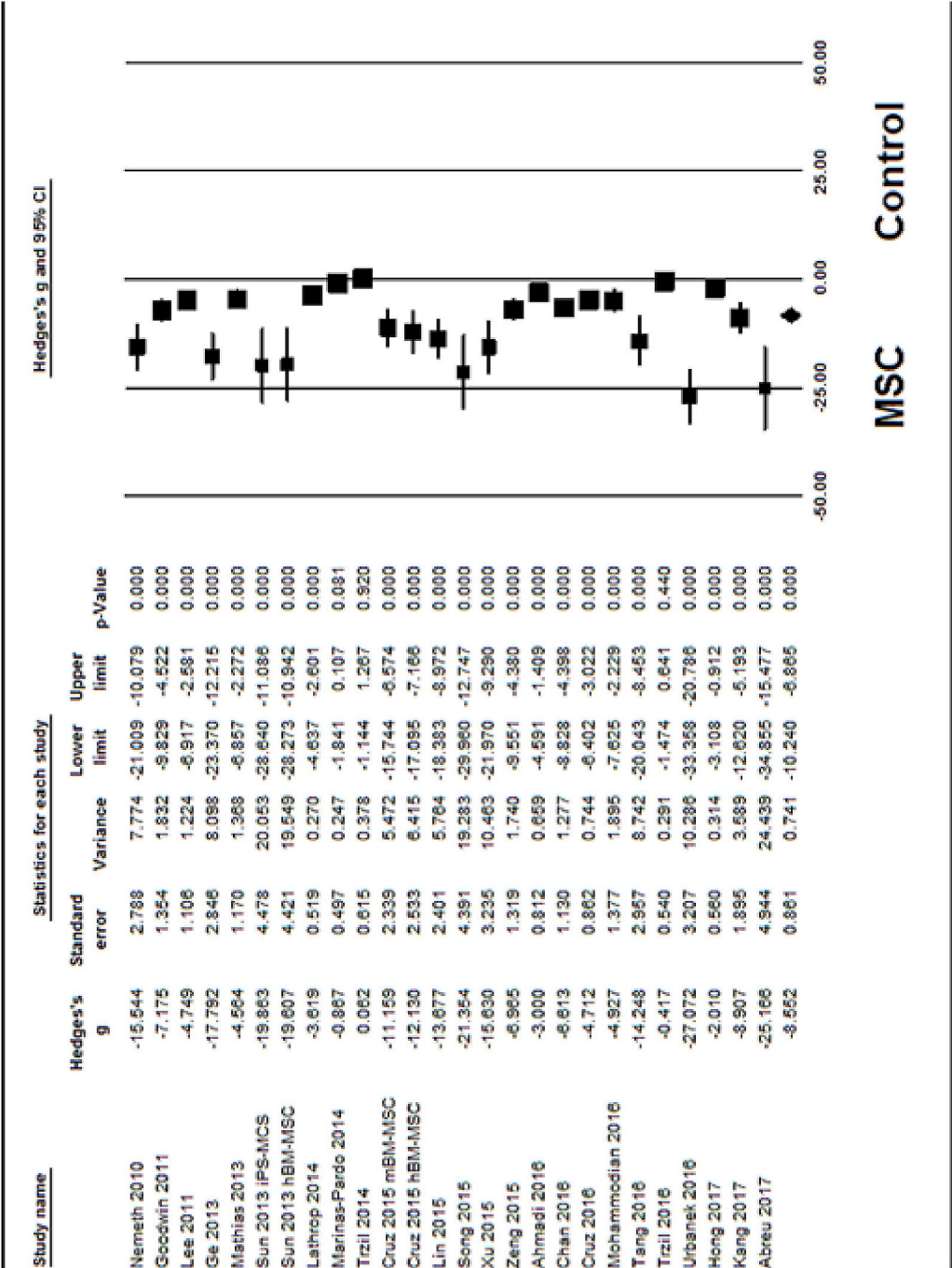
intravenous or intra-tracheal administration of MSCs could be an effective approach to treat asthma.

Recently, focus of MSCs studies have been on the immunomodulatory function and paracrine action of MSCs, which was considered as potent modulators of disease-associated tissue micro-environments [64]. In this regard, effect of MSCs on the damaged and diseased tissues [65] as well as the anti-inflammatory and immunomodulatory properties of MSCs have been extensively studied [25,26,66,67]. Specifically, MSCs have been used to treat variety kinds of diseases associated with immunity including asthma, emphysema, graft-versus-host disease (GVHD), myocardial infarction, liver cirrhosis and crohn's disease [12–15,19]. However, currently, application of MSCs in the treatment of asthma is still on the preclinical stage although three studies had been registered in the official site of clinical trials (www.clinicaltrials.gov). Therefore, the current study was designed to systematically review and analyze recent publications of preclinical studies of MSCs and asthma treatment in animal models, but not clinical trials.

MSCs have been shown to have the therapeutic potential for lung injury [68]. MSCs can be isolated from different tissues including bone marrow, adipose tissue and organs including lung. Studies on animal models of asthma have demonstrated that intravenous injection or intra-tracheal instillation of human bone marrow MSCs (hBM-MSCs), human adipose derived MSCs (hAD-MSCs), mouse bone marrow MSCs (mBM-MSCs) or mouse adipose derived MSCs (mAD-MSCs) were safe

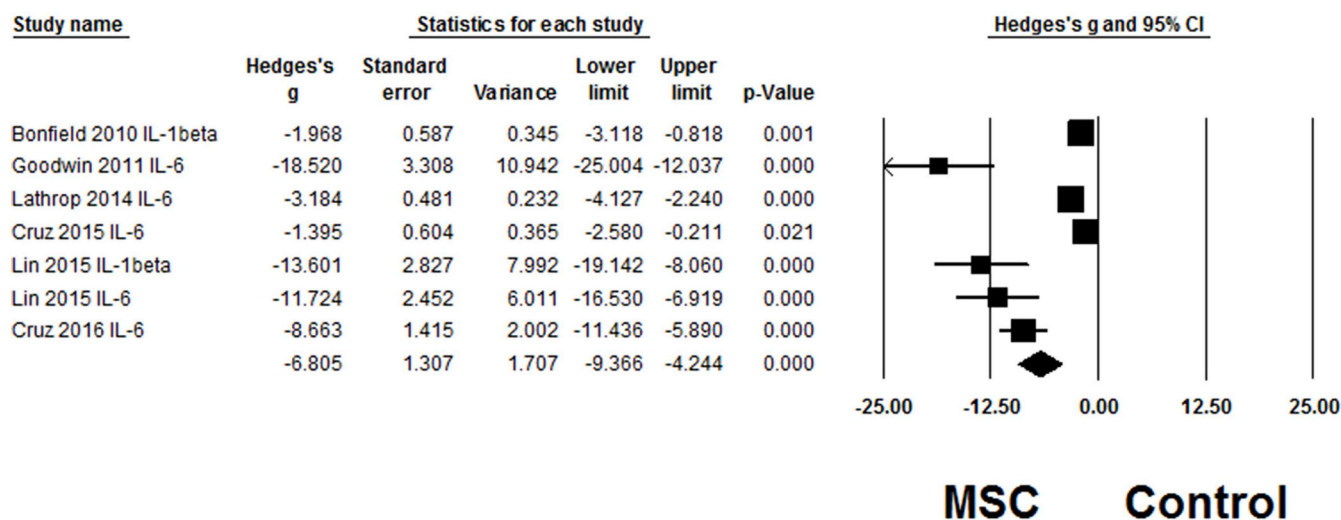
and effective in attenuating airway injuring by ameliorating airway inflammation [3,7,40,41]. In this regard, Mathias et al. reported that administration of MSCs isolated from human bone marrow (hBM-MSCs), umbilical cord blood (hUM-MSCs) or adipose tissue (hAD-MSCs) provoked a pronounced increase in alveolar macrophage, and through which mechanism, MSCs significantly inhibited hallmark features of asthma including airway hyper-responsiveness, eosinophilic accumulation, and Th2 cytokine production [7]. Cruz and colleagues compared the efficacy of hBM-MSCs and mBM-MSCs as well as the extracellular vesicles released by these MSCs [41]. They found that both conditioned medium and extracellular vesicles from hBM-MSCs were generally more potent than those from mBM-MSCs in most of the outcome measures in Aspergillus Hyphal Extract-induced allergic airway inflammation animal models [41]. These preclinical studies provided important evidence of safety, toxicity, therapeutic efficacy and mechanism of MSC action for future clinical use in the asthma therapy.

Comparing to other cells, MSCs are poorly immunogenic, and thus, human BM-MSCs, AD-MSCs, iPSCs, and umbilical cord blood derived MSCs had been tested and evaluated in the experimental models of asthma [7,40–43] 2017, [45,47,48]. Human MSCs were delivered to rodent recipients either by intravenous injection or by intra-tracheal instillation. Administration of these human source MSCs resulted in significant reduction of airway inflammation, number of inflammatory cells and eosinophils, and Th2 cytokines in the animal models of asthma. These findings suggest that the preclinical studies provide



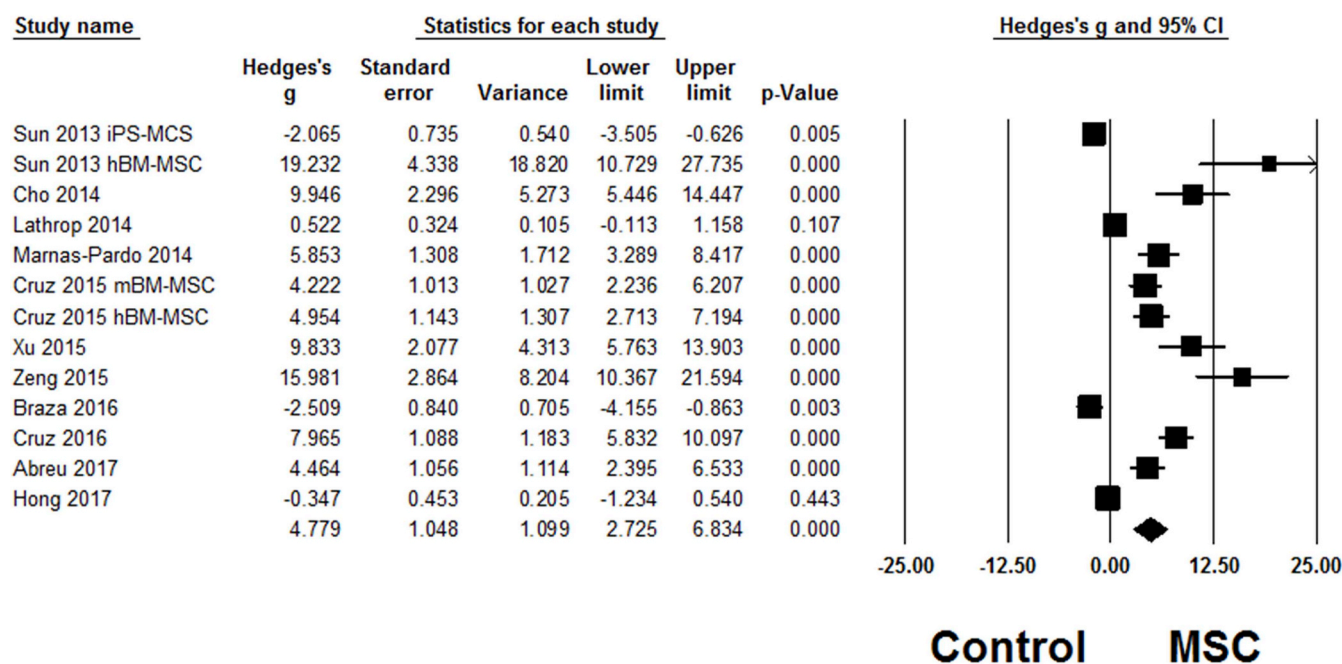
Meta Analysis

Fig. 5. Forest plot for the inhibitory effect of MSCs on BALF eosinophils in the asthma models. A random effect model was used due to significant heterogeneity of publications ($I^2 = 93.0$, $P < 0.01$). Effect size was assessed by Hedges's g and 95% CI, and the inhibitory effect on BALF eosinophils was in favor of MSC administration (Hedges's g = -8.552 ± 0.866 with 95% CI: $-10.240 \sim -6.865$, $P < 0.001$).



Meta Analysis

Fig. 6. Forest plot for the inhibitory effect of MSCs on the release of pro-inflammatory cytokines in lung or blood. A random effect model was used due to significant heterogeneity of publications ($I^2 = 91.9$, $P < 0.01$). Effect size was assessed by Hedges's g and 95% CI, and the inhibitory effect on the release of pro-inflammatory cytokines was in favor of MSC administration (Hedges's g = -6.805 ± 1.307 with 95% CI: $-9.366 \sim -4.244$, $P < 0.001$).



Meta Analysis

Fig. 7. Forest plot for the stimulatory effect of MSCs on IFN- γ synthesis. A random effect model was used due to significant heterogeneity of publications ($I^2 = 94.3$, $P < 0.01$). Effect size was assessed by Hedges's g and 95% CI, and the stimulatory effect on IFN- γ was in favor of MSC administration (Hedges's g = 4.779 ± 1.408 with 95% CI: $1.099 \sim 2.725$, $P < 0.001$).

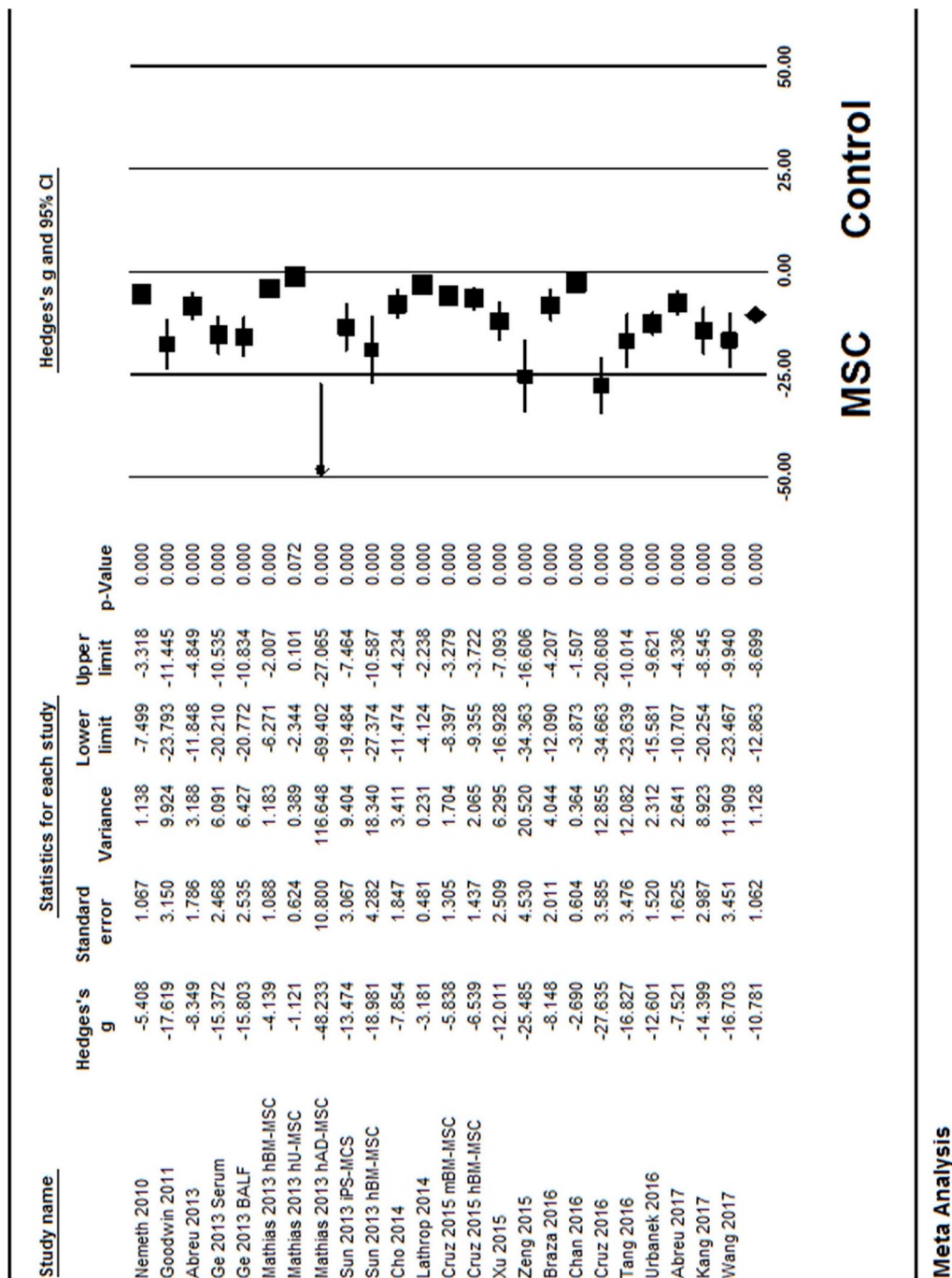
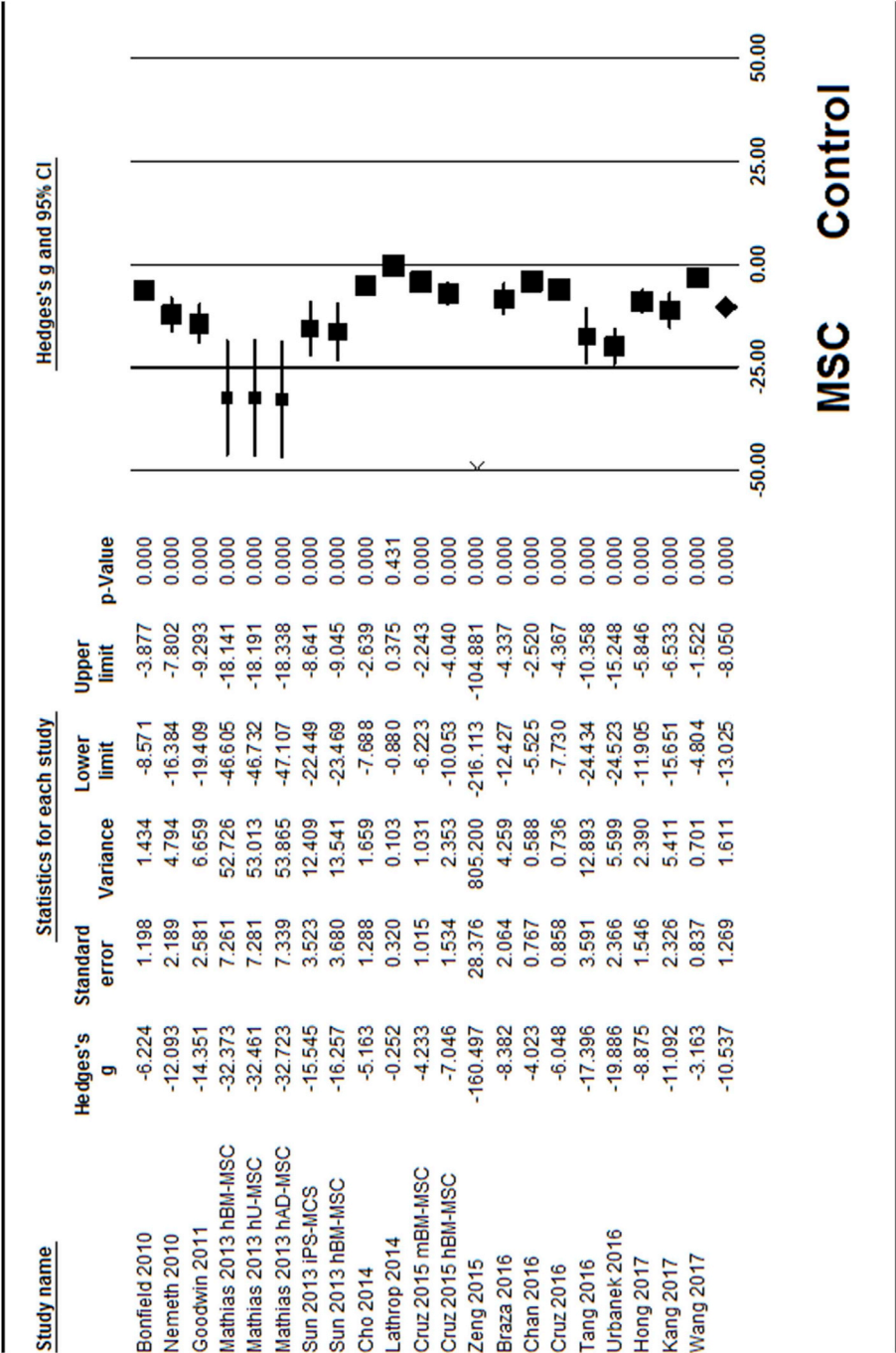
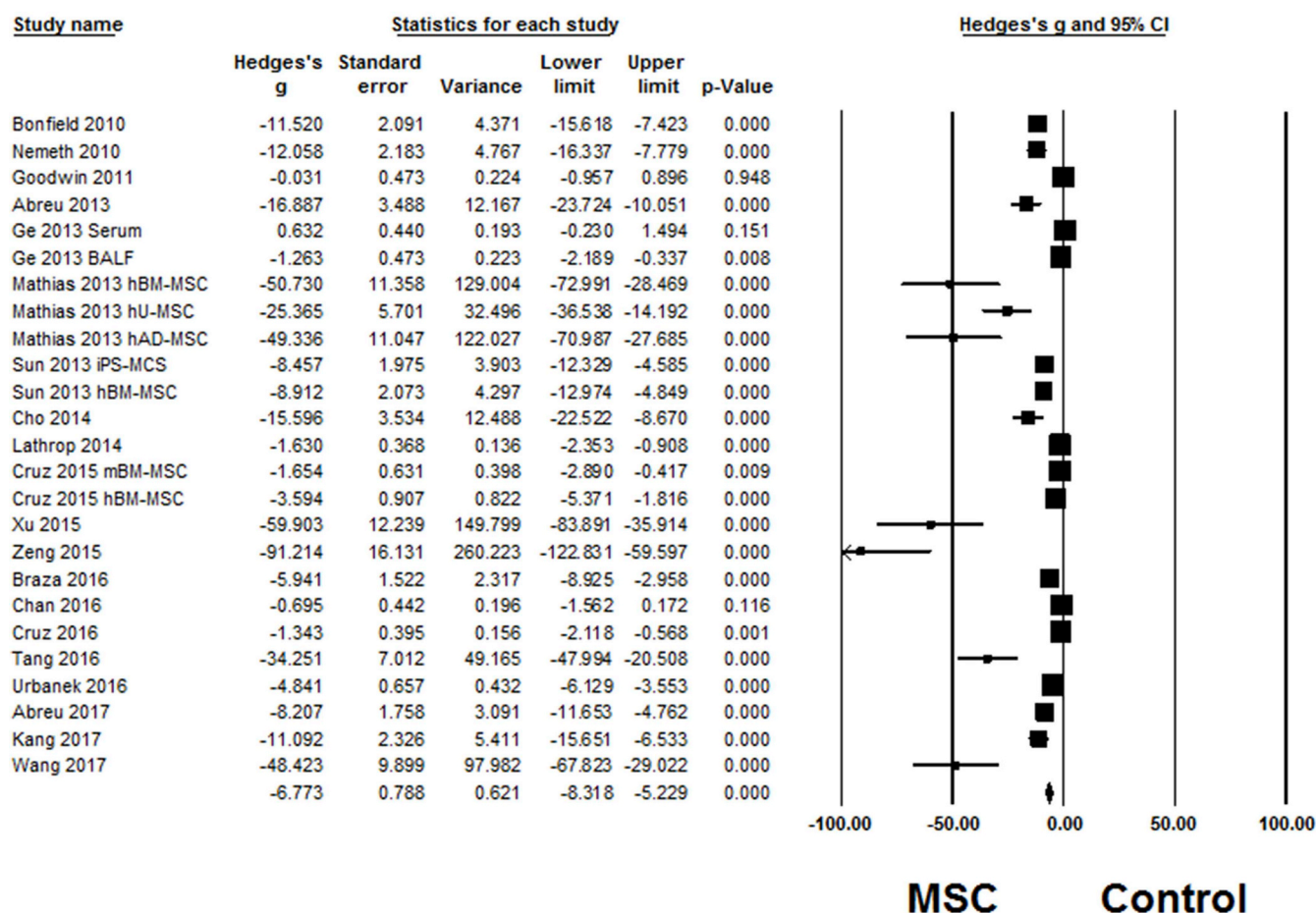


Fig. 8. Forest plot for the inhibitory effect of MSCs on IL-4 synthesis. A random effect model was used due to significant heterogeneity of publications ($I^2 = 92.2$, $P < 0.01$). Effect size was assessed by Hedges's g and 95% CI, and the inhibitory effect on IL-4 was in favor of MSC administration (Hedges's g = -10.781 ± 1.062 with 95% CI: $-12.863 \sim -8.699$, $P < 0.001$).



Meta Analysis

Fig. 9. Forest plot for the inhibitory effect of MSCs on IL-5 synthesis. A random effect model was used due to significant heterogeneity of publications ($I^2 = 94.4$, $P < 0.01$). Effect size was assessed by Hedges's g and 95% CI, and the inhibitory effect on IL-5 was in favor of MSC administration (Hedges's g = -10.537 ± 1.269 with 95% CI: $-13.025 \sim -8.050$, $P < 0.001$).



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Fig. 10. Forest plot for the inhibitory effect of MSCs on IL-13 synthesis. A random effect model was used due to significant heterogeneity of publications ($I^2 = 93.5$, $P < 0.01$). Effect size was assessed by Hedges's g and 95% CI, and the inhibitory effect on IL-13 was in favor of MSC administration (Hedges's g = -6.773 ± 0.788 with 95% CI: $-8.318 \sim -5.229$, $P < 0.001$).

valuable information regarding mechanisms of MSC action, immunogenicity, and safety of therapeutically administered MSCs.

While the mechanisms of immune modulation by MSC remains to be defined, it is believed that MSCs are adapted to their microenvironment through either the release of soluble factors such as PGE₂, kynurenine, IL-10, TNF-stimulated gene 6 protein (TSG-6), nitric oxide (NO), and transforming growth factor (TGF- β 1) [9,69–73], or context-dependent modification of T helper (Th1/Th2) balance or pro-inflammatory Th17 cell differentiation [9,74,75]. Consistent with these concepts, in the experimental models of asthma, MSCs could not only modulate release of inflammation-associated factors including IL-1 β and IL-6 [8,39,50,56], but also regulate the balance of Th1/Th2 cytokines by stimulating INF- γ while inhibiting IL-4, IL-5, and IL-13 [3,5,7–9,39–41,43,46,53–56,58–60,62].

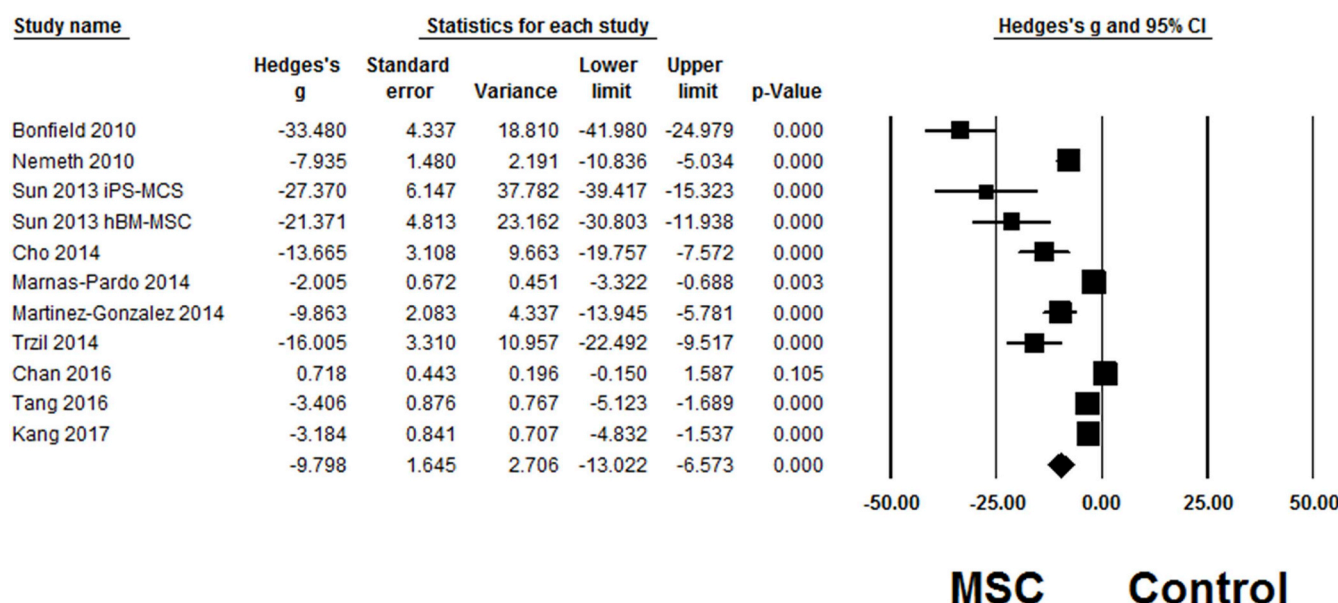
While the current meta-analysis was carried out after careful screening and systematic review that can avoid publication bias, potential publication bias may still exist in the current study [76,77]. In this regard, funnel plots of lung histology, airway inflammation, BALF inflammatory cell accumulation, inflammatory cytokine production, Th1/Th2 cytokine levels were asymmetrically distributed, suggesting publication bias might exist in these analysis.

There are limitations in this review and meta-analysis. First, sub-analysis of stem/stromal cell sources, that is, bone marrow, adipose tissue, lung tissue, and umbilical cord blood, were not performed due to

limited number of cases in each kind of MSCs. Second, various species of rodent animals including mouse, rat, and cat, were used as asthma models in response to variety kinds of allergens including ovalbumin, fungus, ragweed, and toluene diisocyanate. These heterogeneities may cause publication bias in the current review, and thus, a random model of meta-analysis was used to examine the effect size of MSC therapy on asthma models. Third, two different routes of MSC administration, intravenous or intra-tracheal, were used by different investigators, but the efficacy of these two different routes of MSC administration was not compared. Fourth, the animal models of asthma induced by variety kinds of allergens were in acute phase or sub-acute phase, and thus, MSC effect on long-term or chronic asthma may not be included in this review. Fifth, only funnel plot was used to assess the publication bias, which remained to be examined by other methods such as Egger's regression.

5. Conclusion

Recent studies of MSC administration in asthma animal models provided valuable information regarding *in vivo* safety, immunogenicity, pharmacokinetics, and mechanisms of asthma treatment by MSCs. These preclinical studies demonstrated that intravenous injection or intra-tracheal delivery of MSCs (regardless derived from bone marrow, adipose tissue, umbilical cord blood or lung tissue) is safe and



Meta Analysis

Fig. 11. Forest plot for the inhibitory effect of MSCs on IgE release. A random effect model was used due to significant heterogeneity of publications ($I^2 = 94.8$, $P < 0.01$). Effect size was assessed by Hedges's g and 95% CI, and the inhibitory effect on IgE was in favor of MSC administration (Hedges's g = -9.798 ± 1.645 with 95% CI: $-13.022 \sim -6.573$, $P < 0.001$).

effective in the treatment of allergic asthma models. These advances in MSC biology and preclinical studies need to be incorporated in clinical trials of asthma treatment, especially, in the allergic asthmatics. Administration of MSCs may be a safe and feasible clinical approach and may become an effective cell therapy for asthma patients.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.pupt.2018.11.007>.

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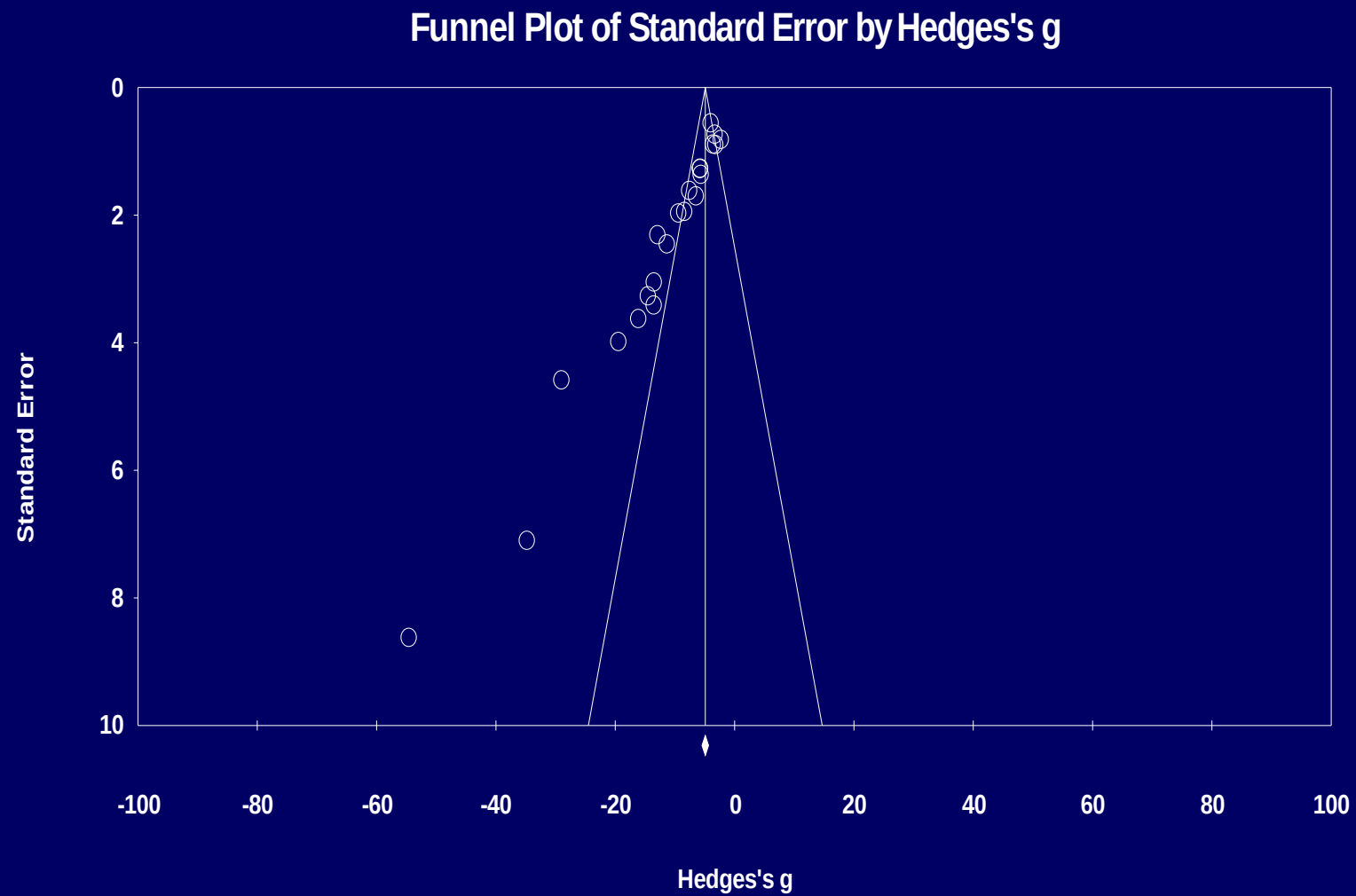


Fig S1. Histology

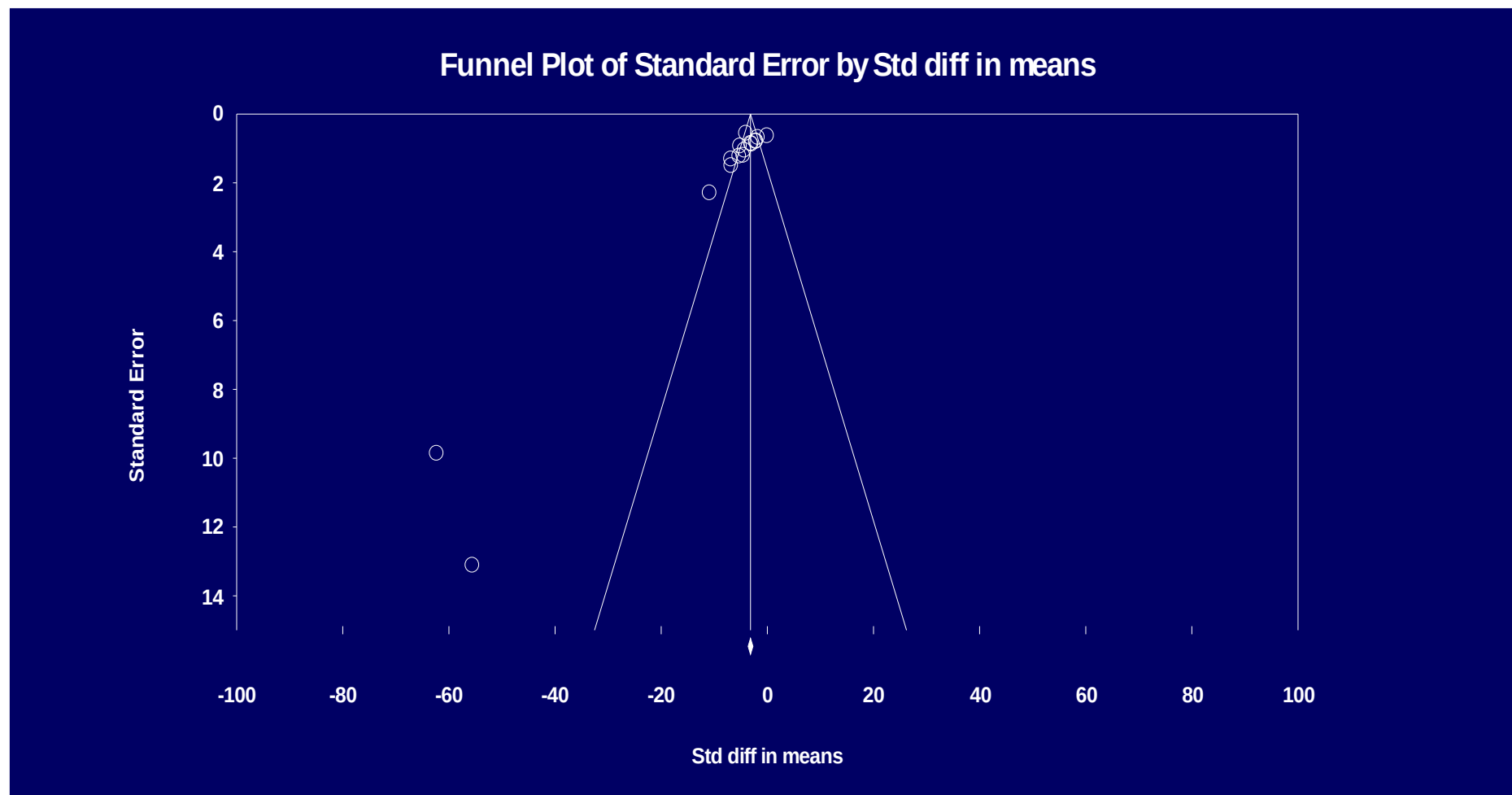


Fig S2. Airway inflammation

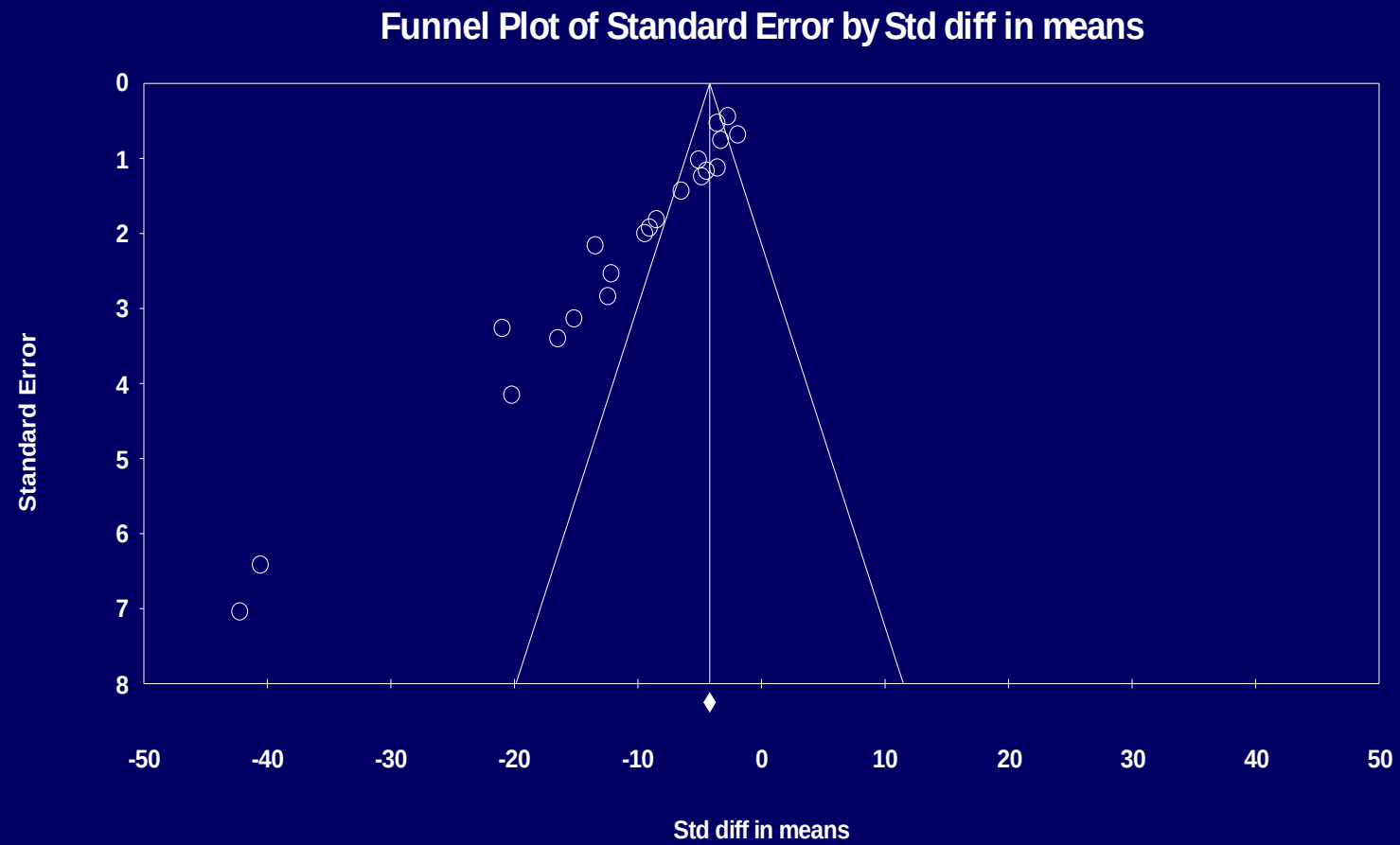


Fig S3. BALF total cell number

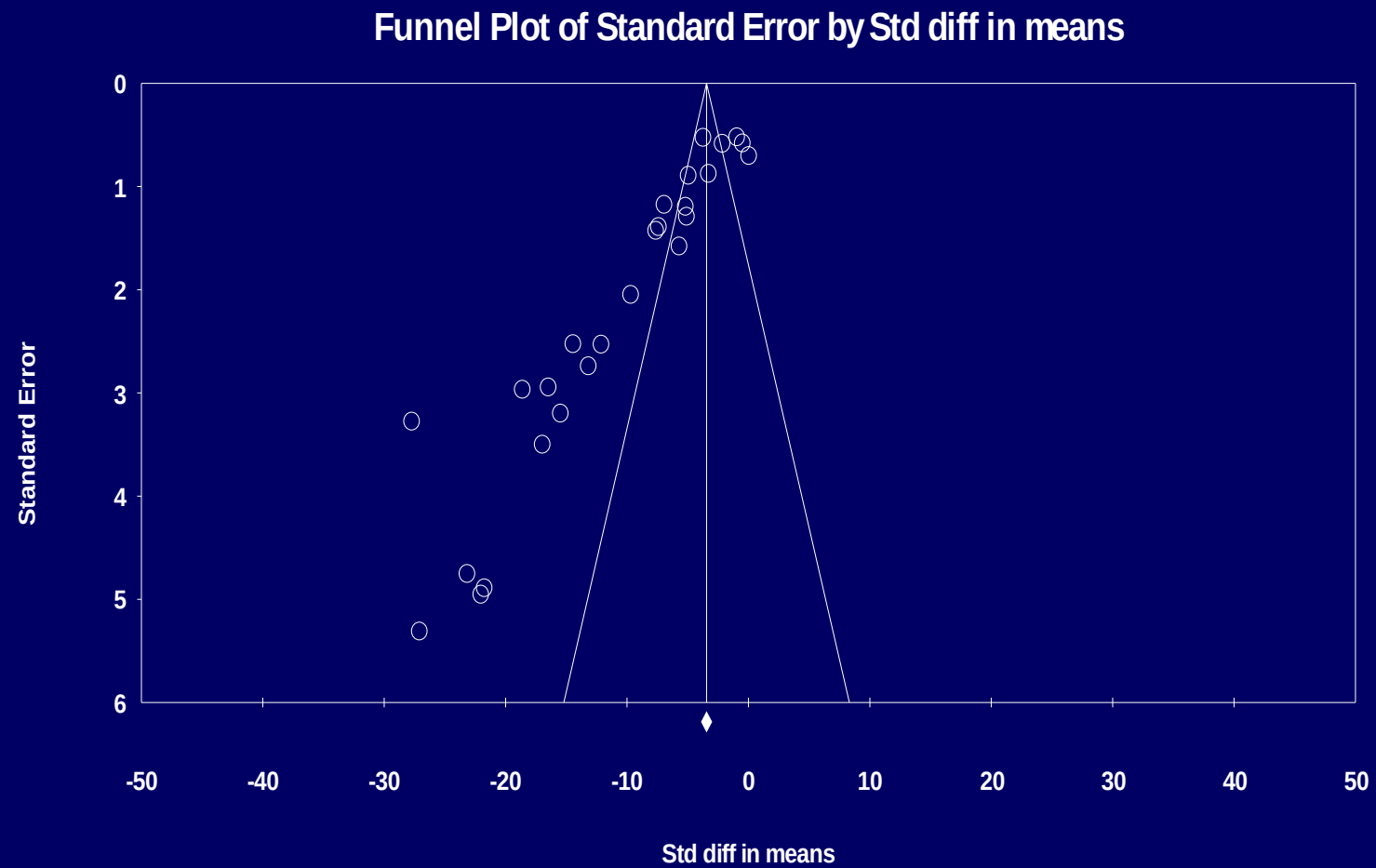


Fig S4. BALF Eosinophil

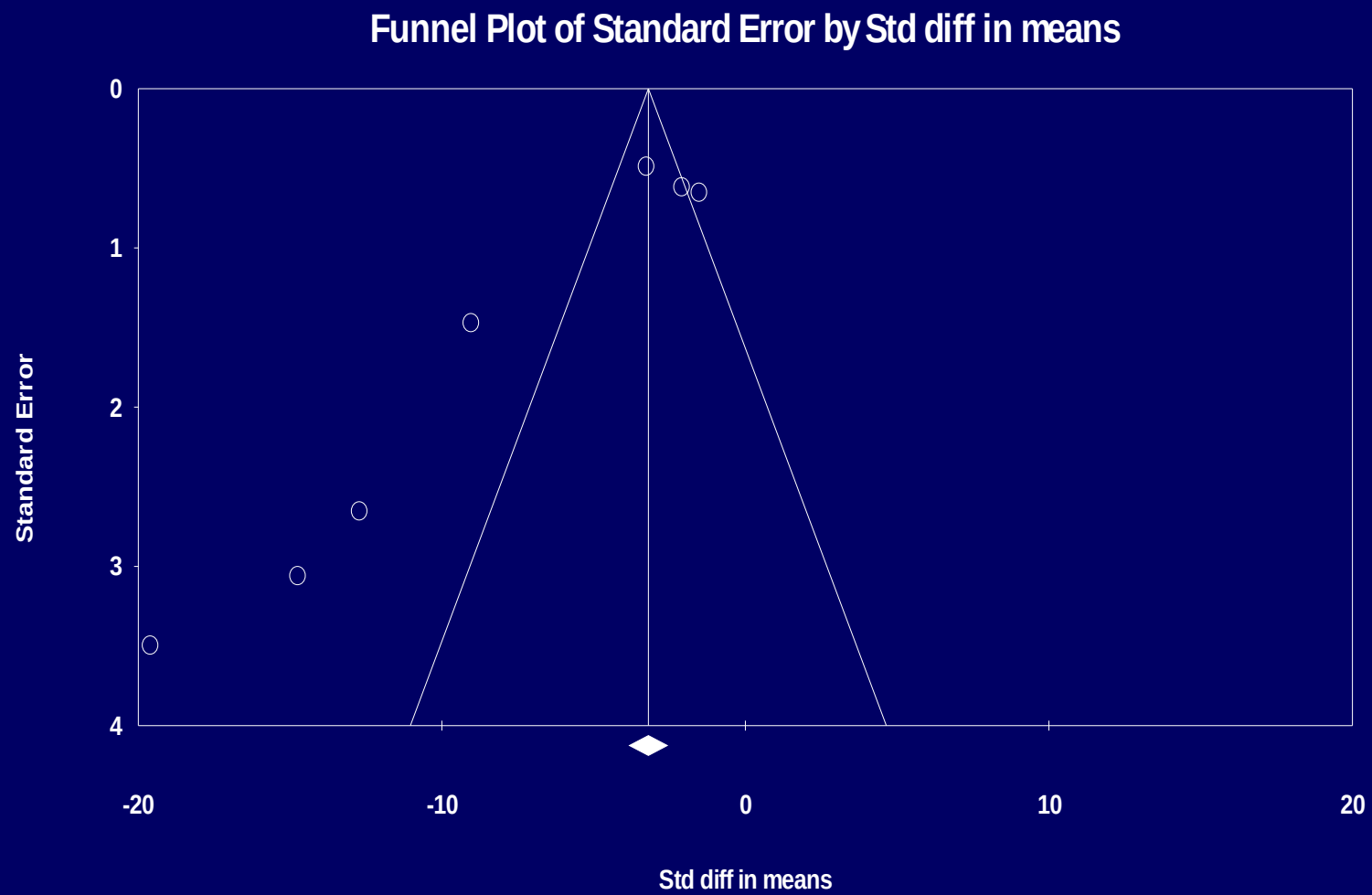


Fig S5. Pro-inflammatory cytokines

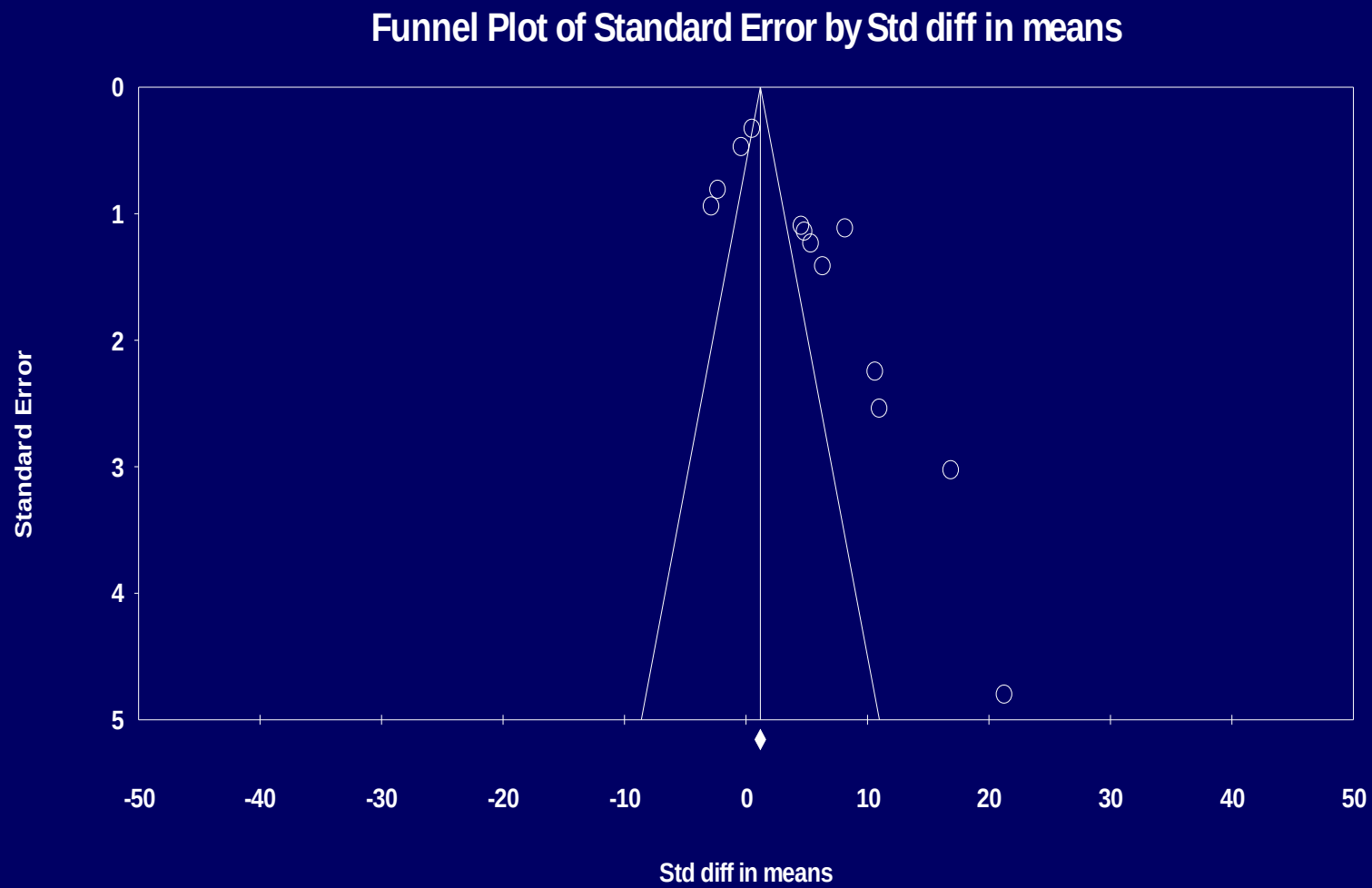


Fig S6. IFN- γ

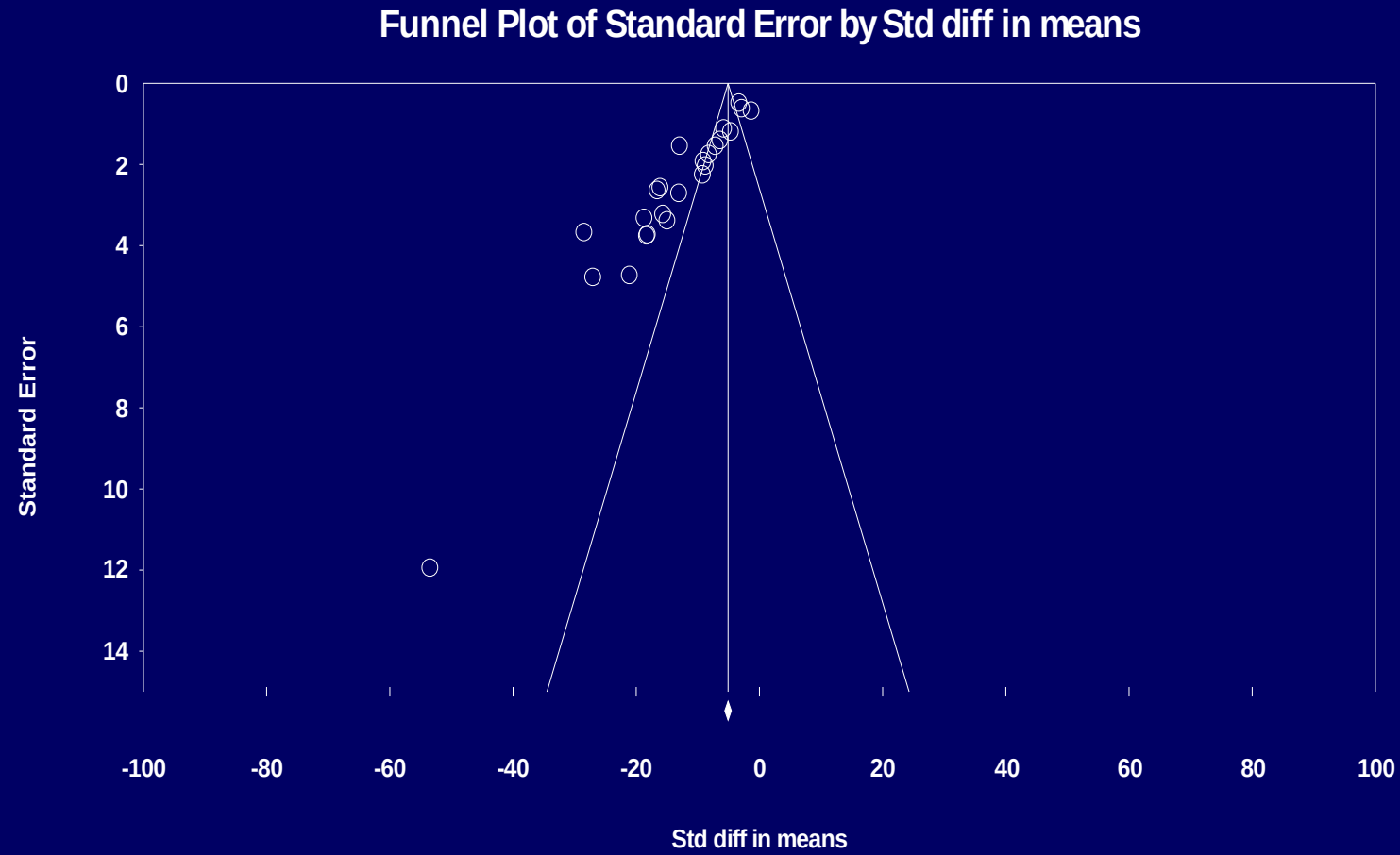


Fig S7. IL-4

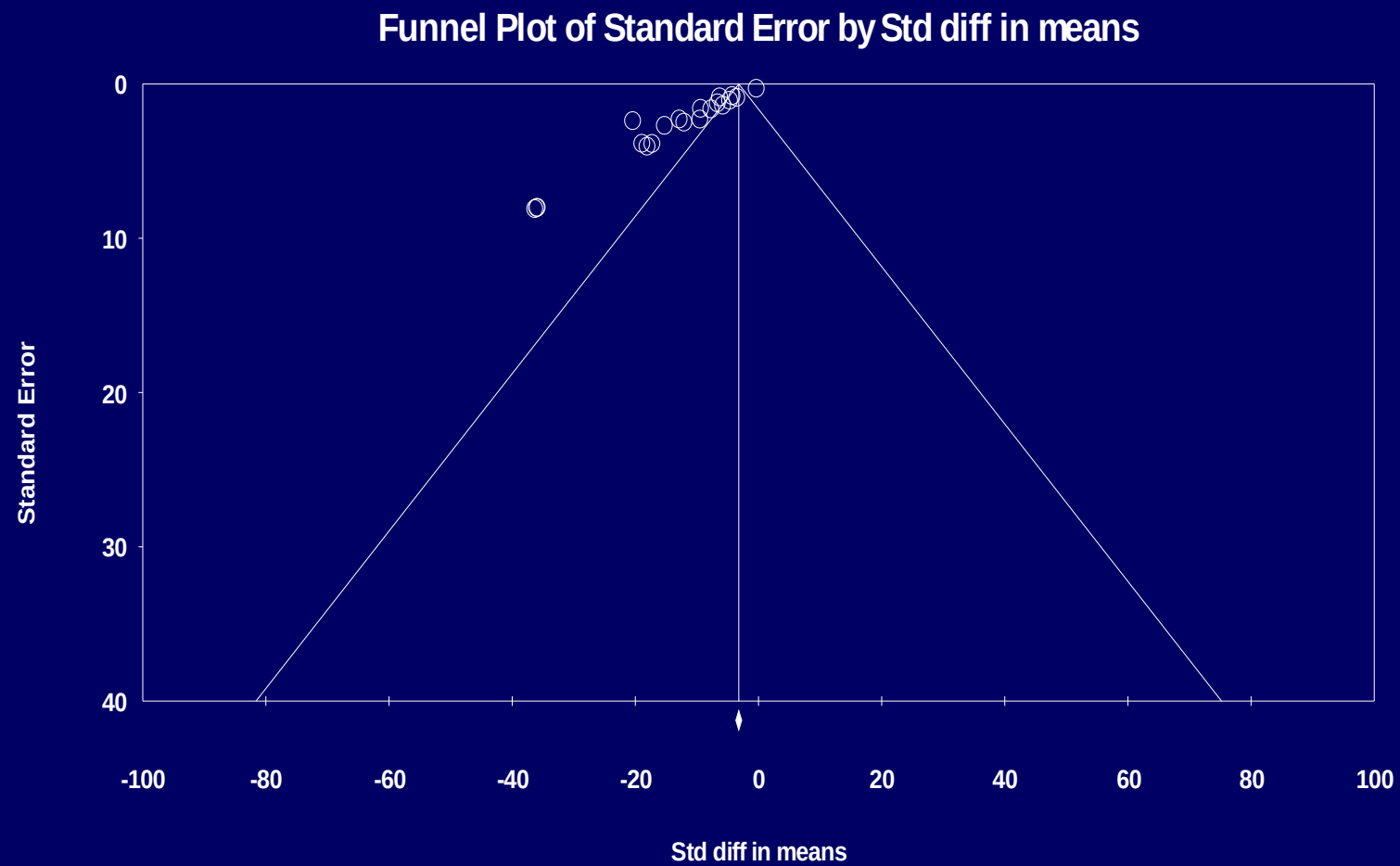


Fig S8. IL-5

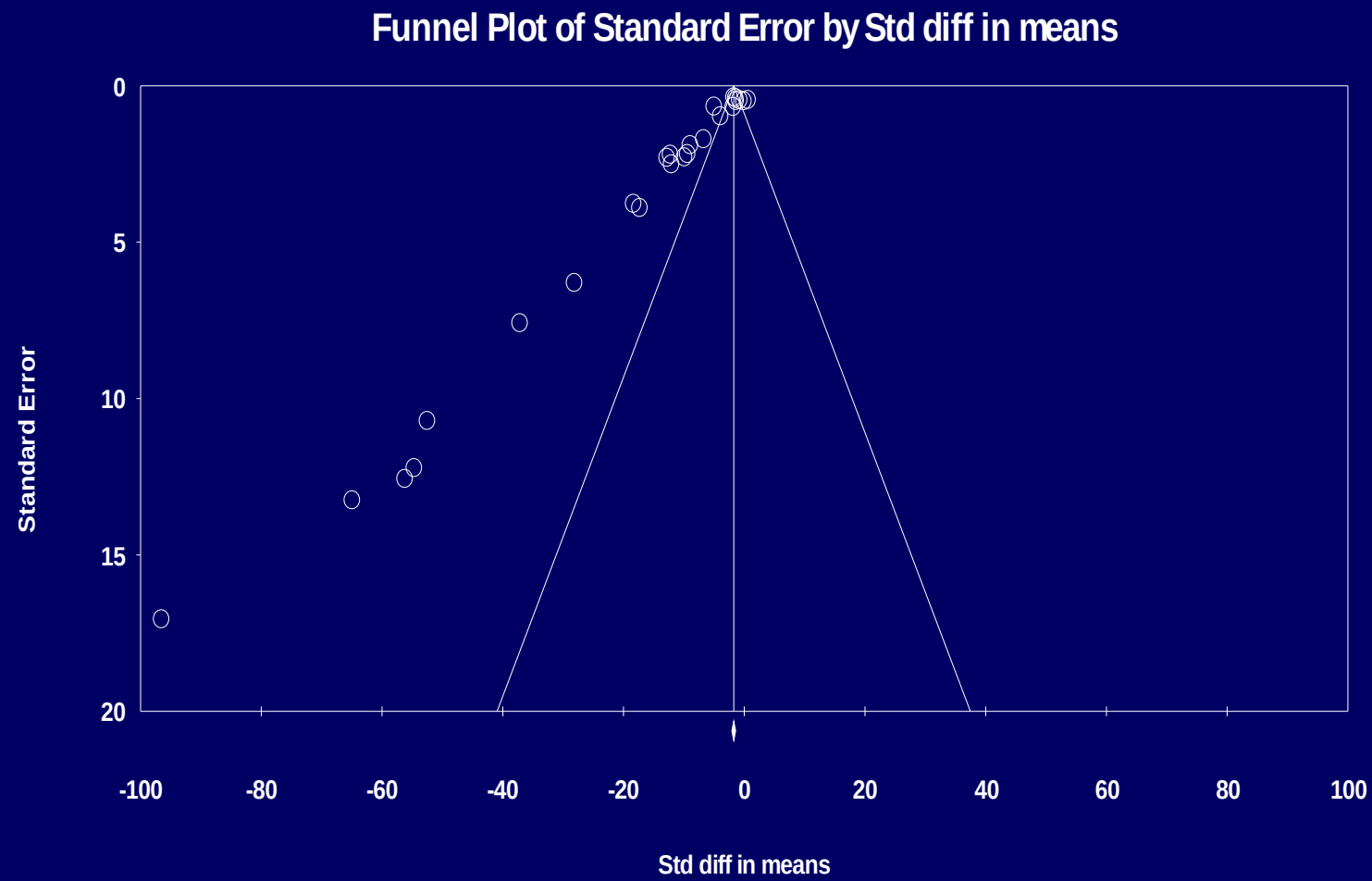


Fig S9. IL-13

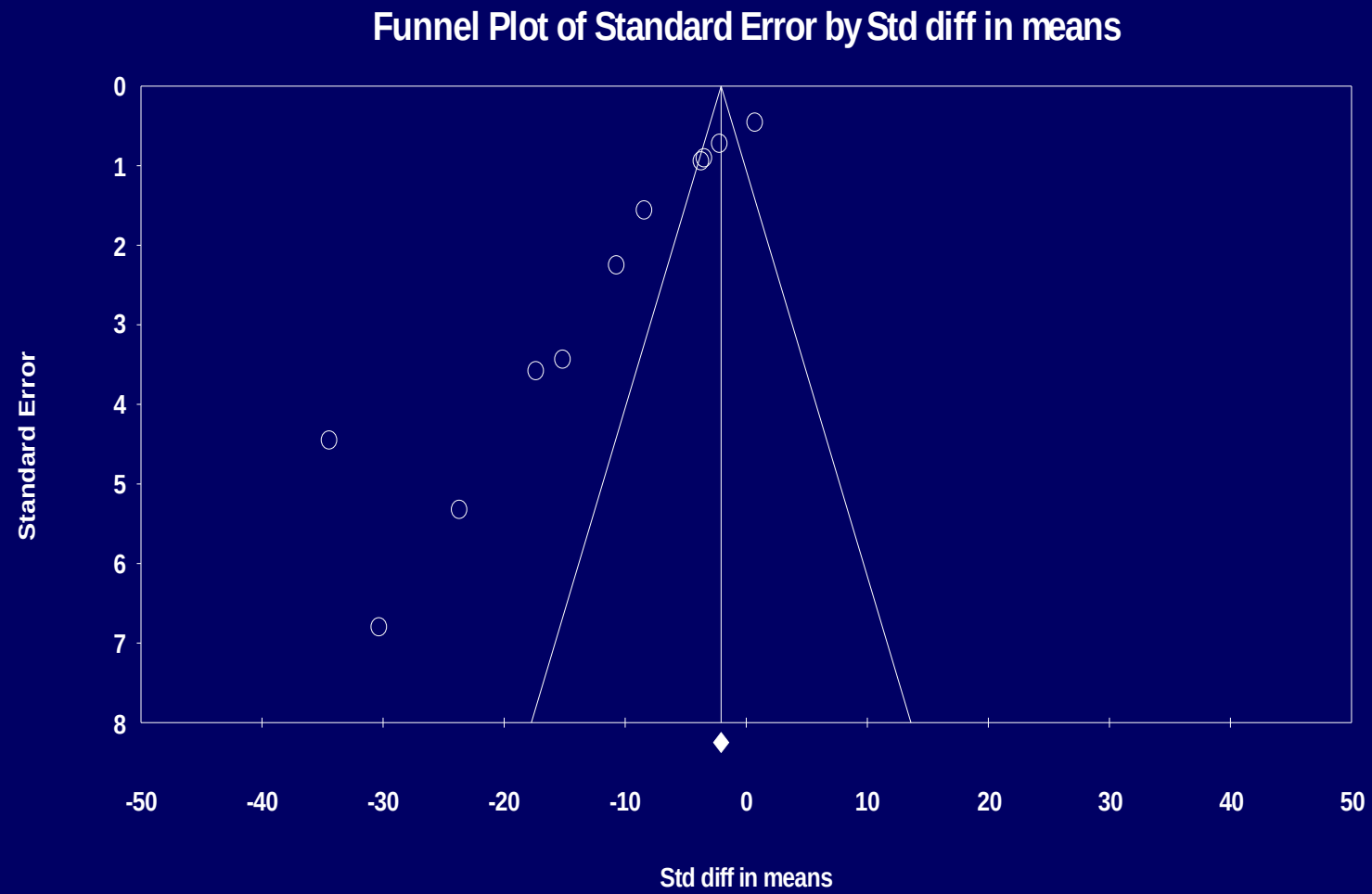


Fig S10. IgE