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Immunotherapy in asthma: an updated systematic review

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Background

Allergen-specific immunotherapy ("hyposensitization" or "desensitization") has long been a controversial treatment for asthma. Although beneficial effects upon clinically relevant outcomes have been demonstrated in randomized controlled trials, there remains a risk of severe and sometimes fatal anaphylaxis. The recommendations of professional bodies have ranged from cautious acceptance (1) to outright dismissal (2). A recent WHO position paper, which has been endorsed by eight other international and national bodies, concluded that allergen immunotherapy was an effective treatment for patients with allergic asthma (3).

We have previously conducted a meta-analysis of 20 randomized controlled trials of allergen immunotherapy for asthma published between 1954 and 1990 (4). We subsequently conducted a systematic review for the Cochrane Collaboration, including a further 34 trials published between 1957 and 1997 (5). Both reviews concluded that subjects randomized to immunotherapy reported significantly fewer asthma symptoms, required significantly less asthma medication, and demonstrated both reduced non-specific and reduced allergen-specific bronchial hyperreactivity (BHR) compared to those randomized to placebo.

During recent years, there has been increasing interest in new allergen vaccines and new methods of delivery including oral, sublingual, and inhaled immunotherapy. Recombinant peptides containing the relevant epitopes, but lacking the ability to cross-link IgE bound to mast cells, have been evaluated in clinical trials. Finally, the Cochrane Collaboration has standardized protocols for systematic

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reviews and improved the statistical software for performing meta-analysis. Thus, it was again opportune to update our systematic review of allergen-specific immunotherapy for asthma.

Objectives

The objectives were as follows:

- 1) to identify as many as possible of the published randomized controlled trials of allergen-specific immunotherapy for allergic asthma
- 2) to assess the methodological quality of these randomized controlled trials
- 3) to estimate the overall efficacy of allergen-specific immunotherapy upon asthma symptoms, medication requirements, lung function, nonspecific BHR, and allergen-specific BHR
- 4) to compare the efficacy in asthma of mite, pollen, and animal dander immunotherapy with extracts of other allergens.

Methods

Selection criteria

This review was restricted to randomized controlled trials (RCTs), which provide the best evidence for the efficacy of any medical treatment (6). Only studies which focused upon asthma were included. Studies of immunotherapy for hay fever were considered only if the results for subjects with asthma were separately identified. For the purposes of this review, allergen-specific immunotherapy included the administration of extracts of house-dust mites, pollens, animal danders, or moulds; chemically modified allergoids; or antigen-antibody complexes. Only the subcutaneous route of administration was considered.

Placebo-controlled trials are methodologically stronger, although studies which have administered house dust or other relatively inactive antigenic preparations to the control group were also considered. Double-blind trials were preferred, but single-blind and open studies were also reviewed for possible inclusion.

At least one of the following clinical outcomes had to be reported:

- asthma symptoms (including symptom scores)
- asthma medication requirements (including medication scores)

- lung function (including peak expiratory flow, FEV₁, and thoracic gas volume)
- nonspecific BHR (to histamine, methacholine, or acetylcholine)
- allergen-specific BHR.

Studies which reported only nonclinical outcomes such as allergen-specific IgE (by RAST or skin prick test) or other *in vitro* results were excluded.

Studies published in languages other than English were considered if the translated abstract indicated that the study was an RCT of allergen immunotherapy for asthma, and a translator was sought (see Acknowledgments).

Search strategy

MEDLINE searches were undertaken for 1966–98 for studies of immunotherapy and asthma. Review articles identified in this process were surveyed for additional and earlier citations. Dissertation abstracts and Current Contents were also searched to identify more recently published and unpublished studies.

A search was performed of the Asthma database maintained by the Cochrane Airways Group at St George's Hospital Medical School, London, UK. This database included all studies with the key words "Asthma" or "Wheeze" from the MEDLINE, EMBASE, and Cinahl databases, together with other studies identified by hand searching. A total of over 900 nonunique citations were identified with the key words "Immunotherap*", "Hyposensiti*", or "Desensiti*" and were examined for possible inclusion.

Inclusion of studies in the review was decided by a simple majority of all three reviewers, who independently read the Methods sections of papers identified by the search strategy and applied the stated criteria. Quality assessment was performed by two reviewers, who independently assessed the concealment of allocation by the guidelines of the Cochrane Collaboration and applied the scoring system of Jadad et al. (7).

Statistical considerations

The planned comparisons were as follows:

- allergen immunotherapy vs placebo
- allergen immunotherapy vs antigenically inactive control
- house-dust extracts vs placebo
- allergen immunotherapy vs untreated control
- allergen immunotherapy vs inhaled steroid.

These comparisons were performed separately for each outcome, namely, asthma symptoms, medication, lung function, nonspecific BHR, and allergen-specific BHR, whenever the results were reported.

Outcome data were extracted and entered into RevMan, version 3.1.1 (Update Software, Oxford, 1998), for statistical analysis (8). Categorical outcomes were analysed as odds ratios (OR) and 95% confidence intervals (95% CI) calculated by Peto's method for individual studies. The odds ratio is simply the ratio between the immunotherapy and control groups for the odds of subjects being the same or worse to subjects being better after treatment. The convention of the Cochrane Collaboration is to consider odds ratios greater than 1.0 as indicating clinically undesirable outcomes (in this review, worse symptoms, increased medication, deteriorating lung function, and increased nonspecific and allergen-specific BHR).

Continuous outcomes (symptom and medication scores, lung-function parameters, and indices of nonspecific and allergen-specific BHR) were also extracted from tables of results. Where the results were presented only in graphs, these were digitized and then converted to numbers with Un-Scan-It v4.0 (Silk Scientific Corporation, Orem UT, 1996). Continuous outcomes were analysed as standardized mean differences (SMD). The SMD is a statistic which expresses the difference in means between immunotherapy and control groups in units of the pooled standard deviation. Although the Cochrane Collaboration currently favours the weighted mean difference, we chose the SMD because many studies measured the same outcomes on different scales.

Fixed effects models were generally used to obtain summary statistics for the overall efficacy of allergen immunotherapy upon both categorical and continuous outcomes, and chi-square tests were performed to assess heterogeneity between studies. In this context, a *P* value of <0.05 indicates significant differences between studies and raises the question of whether the results can be meaningfully combined. When significant heterogeneity was found, the overall efficacy was recalculated by random effects models, which provide more realistic estimates of the confidence intervals under these circumstances (9).

Results

Description of studies

Sixty-two randomized controlled trials published in 67 papers between 1954 and 1998 were identified which satisfied

the inclusion criteria. The methods, participants, allergens administered, and outcomes of the included studies are listed in Table 1. There were 28 studies reporting immunotherapy for mite allergy, generally *Dermatophagoides pteronyssinus* or *D. farinae*, although Armentia Medina et al. (15) used extracts of the storage mite *Lepidoglyphus destructor*. Three early studies (10, 16, 75) used extracts of house dust, which has since generally been considered antigenically inactive. There were 15 studies of immunotherapy for pollen allergy, utilizing extracts of Bermuda grass, orchard grass/cockfoot, timothy grass, velvet grass, sweet vernal grass, perennial ryegrass, or ragweed pollen. Nine studies reported immunotherapy for animal dander allergy, particularly to cats and dogs. Two studies utilized extracts of the mould *Cladosporium*, and five attempted simultaneous immunotherapy for multiple aeroallergens. Four studies from one group of investigators (43–46) used allergen–antibody complexes for immunotherapy.

A further 125 studies were excluded from this review (77–201). The most common but not mutually exclusive reasons for exclusion were as follows: 37 studies were not randomized (84, 86, 91, 93, 97, 98, 103, 105, 108, 114, 116, 120, 122, 123, 126, 130, 132, 133, 135, 140, 145, 146, 149, 151, 157, 159, 163, 164, 166, 176, 177, 180, 185, 189, 193, 194, 198), 25 studies were not controlled (87–89, 99, 101, 107, 115, 121, 128, 131, 134, 137, 140, 148–150, 155, 169, 172, 181, 184, 189, 195, 199, 201), 29 studies solely or predominantly involved subjects who had allergic rhinitis/conjunctivitis rather than asthma (77, 79, 80, 82, 85, 90, 94, 96, 100, 108–113, 117–119, 127, 130, 138, 139, 153, 158, 160, 161, 174, 176, 192), 13 studies did not report clinically relevant outcomes (81, 129, 134, 144, 152, 155, 165, 166, 173, 179, 190, 196, 200), and one study was not analysed by intention to treat (171).

We also identified 14 clinical trials of oral immunotherapy (92, 106, 124, 125, 139, 156, 158, 167, 170, 175, 186–188, 191), seven trials of inhaled or intranasal immunotherapy (79, 80, 95, 142, 143, 147, 183), nine trials of sublingual immunotherapy (78, 90, 102, 110, 154, 158, 162, 182, 197), and one trial of homoeopathic immunotherapy (168) which were beyond the scope of the present review. Finally, six abstracts (83, 104, 119, 136, 141, 178) contained insufficient information for further assessment.

Two studies included in our previous review were excluded after closer examination, as they did not meet all the inclusion criteria. The untreated controls in Murray et al. (149) were not randomly allocated and the “placebo” controls were contaminated by concurrent administration of pollen immunotherapy. The allocation of subjects to

Table 1. Randomized controlled trials of allergen-specific immunotherapy for asthma included in this systematic review: methods, participants, allergen extracts, outcomes, and methodological quality (see text)

Study (Ref.)	Methods	Participants, age	Allergen extracts	Outcomes	Quality
Aas (10)	DB PC RCT	80 asthma, 12–14 years	House dust	Symptoms, AS-BHR	4 A
Adkinson et al. (11)	DB PC RCT	121 asthma, 5–14 years	Multiple	Symptoms, medication, PEF	4 B
Alvarez Cuesta et al. (12)	DB PC RCT	28 asthma and rhinitis, 15–28 years	Cat	Symptoms, Medication, NS-BHR, AS-BHR	3 B
Amaral Marques & Avila (13)	DB PC RCT	28 asthma, 12–55 years	Mite	Symptoms, medication	2 B
Armentia Medina et al. (14)	DB PC RCT	30 pollen-allergic, 12–50 years	Pollen	NS-BHR, AS-BHR	1 B
Armentia Medina et al. (15)	DB RCT	35 mite-allergic, 13–63 years	Mite	Symptoms, medication, NS-BHR	4 B
British Tuberculosis Association (16)	DB PC RCT	96 asthma, mean 24 years	House dust	Symptoms, medication, PEF	4 A
British Thoracic Association (17)	DB PC RCT	70 asthma, 66% >30 years	Mite	Symptoms, medication, FEV ₁	3 B
Baur (18)	SB PC XO RCT	39 asthma, 18–45 years	Multiple	AS-BHR	1 B
Bertelsen et al. (19)	Open UC RCT	27 asthma, 7–15 years	Cat/dog	AS-BHR	2 D
Bousquet et al. (20)	Open PC RCT	48 pollen-allergic, 10–51 years	Pollen	Symptoms, medication	1 D
Bousquet et al. (21)	DB PC RCT	30 asthma, 18–42 years	Mite	AS-BHR	2 A
Bousquet et al. (22)	Open UC RCT	215 asthma, 3–72 years	Mite	Symptoms, medication, FEV ₁	1 D
Bousquet et al. (23)	Mixed PC RCT	60 pollen-allergic, 12–46 years	Pollen	Symptoms, medication	2 A
Bousquet et al. (24)	DB PC RCT	57 pollen-allergic, 11–45 years	Pollen	Symptoms	3 A
Bruce et al. (25)	PC RCT	39 asthma	Pollen	Symptoms, AS-BHR	3 B
Buchanan et al. (26)	DB PC RCT	55 adult asthma	Mite	Symptoms, medication, asthma attacks	2 B
Cantani et al. (27)	DB PC RCT	20 asthma, 4–13 years	Multiple	Symptoms, medication, global evaluation	2 A
Choovaravech (28)	SB HDC RCT	57 asthma, Mean 30.4 years	Mite	Symptoms, medication, PEF	1 B
Creticos et al. (29)	DB PC RCT	77 adult asthma, Mean 35.5 years	Pollen	Symptoms, medication, PEF, AS-BHR	4 A
D'Souza et al. (30)	DB PC RCT	91 asthma, >10 years	Mite	Symptoms, medication	4 B
Dolz et al. (31)	DB PC RCT	28 pollen-allergic, 15–35 years	Pollen	Symptoms, medication, AS-BHR	3 B
Dreborg et al. (32)	DB PC RCT	30 mould-allergic, 5–17 years	Mould	Symptoms, medication, PEF, AS-BHR	2 B
Franco et al. (33)	DB PC RCT	49 asthma, mean age 24.5 years	Mite	Symptoms, medication, PEF, NS-BHR	1 B
Frankland & Augustin (34)	DB PC RCT	200 pollen-allergic, >10 years	Pollen	Symptoms	3 B
Gaddie et al. (35)	DB PC RCT	55 asthma, 13–68 years	Mite	Symptoms, medication, FEV ₁	2 B
Haugaard & Dahl (36)	DB PC RCT	24 animal-allergic asthma, 13–48 years	Cat/dog	Symptoms, NS-BHR, AS-BHR	3 C

Table 1. Continued

Study (Ref.)	Methods	Participants, age	Allergen extracts	Outcomes	Quality
Hill et al. (37)	Open PC RCT	20 asthma, 9–14 years	Pollen	Symptoms, medication	1 D
Johnstone (38)	DB PC RCT	112 pollen-allergic children	Pollen	Symptoms	1 C
Johnstone & Crump (39)	DB PC RCT	173 asthmatic children	Multiple	Symptoms	5 B
Johnstone & Dutton (40)	DB PC RCT	130 asthma, <16 years	Multiple	Symptoms	5 B
Kohno et al. (41)	Open UC RCT	16 asthma, 19–41 years	Mite	Symptoms, PEF, NS-BHR, AS-BHR	2 D
Kuna et al. (42)	DB PC RCT	24 asthma Mean 27.2 years	Pollen	Symptoms, FEV ₁ , NS-BHR	3 A
Machiels et al. (43)	DB PC RCT	39 asthma, 16–57 years	Mite	Symptoms, medication, PEF, NS-BHR, AS-BHR	3 B
Machiels et al. (44)	DB PC RCT	30 pollen-allergic, 14–57 years	Pollen	Symptoms, medication	3 B
Machiels et al. (45)	DB PC RCT	51 pollen-allergic, 12–51 years	Pollen	Symptoms, medication	3 B
Machiels et al. (46)	DB PC RCT	39 asthma, 16–57 years	Mite	Symptoms, medication, FEV ₁ , NS-BHR, AS-BHR	3 B
Malling (47), Malling et al. (48, 49)	DB PC RCT	22 asthma, 16–60 years	Mould	Symptoms, medication, AS-BHR	4 B
Maunsell et al. (50)	DB HDC RCT	34 asthma, 16–56 years	Mite	Symptoms	2 B
Mosbech et al. (51–53)	DB PC RCT	46 asthma, 18–56 years	Mite	Symptoms, medication, PEF, NS-BHR, AS-BHR	2 A
Newton et al. (54)	DB PC RCT	14 asthma, 18–44 years	Mite	Symptoms, medication, PEF, AS-BHR	3 B
Ohman et al. (55)	DB PC RCT	17 asthma, 22–48 years	Cat	Symptoms, PEF, NS-BHR, AS-BHR	3 A
Olsen et al. (56)	DB PC RCT	31 asthma, 18–64 years	Mite	Symptoms, medication, PEF, FEV ₁ , AS-BHR	5 A
Ortolani et al. (57)	DB PC RCT	15 asthma, 15–45 years	Pollen	Symptoms, AS-BHR	2 B
Paranos & Petrovic (58)	SB PC RCT	14 asthma, 20–40 years	Mite	Medication, PEF, FEV ₁	1 B
Pauli et al. (59)	DB PC RCT	18 asthma, 19–40 years	Mite	Symptoms, medication, PEF	4 B
Pichler et al. (60)	DB PC RCT	30 asthma, 20–46 years	Mite	Symptoms, medication, NS-BHR	2 B
Price et al. (61)	DB PC RCT	25 asthma, 5–15 years	Mite	Symptoms, medication, TGV	3 B
Reid et al. (62)	DB PC RCT	18 asthma, 20–39 years	Pollen	Symptoms, medication	4 A
Sabbah et al. (63)	DB PC RCT	52 asthma, mean 28.7 years	Mite	Symptoms, medication	2 B
Shaikh (64)	Open ISC RCT	51 asthma, 22–36 years	Mite	Symptoms, medication, FEV ₁	3 D
Smith (65)	DB PC RCT	22 asthma, 11–48 years	Mite	Symptoms, medication, PEF	3 B
Sundin et al. (66)	DB PC RCT	39 asthma, 8–47 years	Cat/dog	Symptoms, NS-BHR, AS-BHR	3 B
Taylor et al. (67)	DB PC RCT	42 asthma, 6–15 years	Mite	Lung function, height and weight, chest examination	2 B

Table 1. Continued

Study (Ref.)	Methods	Participants, age	Allergen extracts	Outcomes	Quality
Taylor et al. (68)	DB PC RCT	10 asthma, 20–43 years	Cat	NS-BHR, AS-BHR	4 B
Torres Costa et al. (69)	Open ISC RCT	22 asthma, 12–28 years	Mite	Symptoms, medication, PEF, FEV ₁ , NS-BHR	3 D
Valovirta et al. (70, 71)	DB PC RCT	27 asthma, 5–18 years	Dog	Symptoms, AS-BHR	3 A
van Bever & Stevens (72)	DB PC RCT	18 asthma, 7–22 years	Mite	NS-BHR, AS-BHR	3 B
van Metre et al. (73)	DB PC RCT	22 asthma, 21–52 years	Cat	NS-BHR, AS-BHR	3 B
Varney et al. (74)	DB PC RCT	28 asthma, 19–50 years	Cat	Symptoms, AS-BHR	3 B
Vooren (75)	DB PC RCT	12 asthma	House dust	Symptoms, medication, FEV ₁ , AS-BHR	3 B
Warner et al. (76)	DB PC RCT	51 asthma, 5–14 years	Mite	Symptoms, medication, TGV, AS-BHR	4 B

DB PC RCT: Double-blind, placebo-controlled, randomized controlled trial; SB PC XO: Single-blind, placebo-controlled, crossover; Open UC: open untreated controls; SB HDC: Single-blind, house dust extract controlled; open ISC: open inhaled steroid controlled; AS-BHR: allergen-specific bronchial hyperreactivity; PEF: peak expiratory flow rate; NS-BHR: nonspecific bronchial hyperreactivity; TGV: thoracic gas volume; concealment of allocation: A) clearly adequate, B) unclear, C) inadequate, D) not used.

high- or low-dose immunotherapy by Tuchinda & Chai (189) was not randomized. A further 13 studies published before or during 1998 were considered for possible inclusion. Clarification was sought from the authors as to whether they had conducted randomized controlled trials, but no replies were received by the time of submission.

Methodological quality

A key criterion for assessing the quality of randomized controlled trials for which there is evidence of a relationship to the potential for bias in the results is concealment of allocation after randomization to active treatment or control (6). For this review, concealment of allocation was assessed (Table 1) as clearly adequate (category A) in only 13 studies (10, 16, 21, 23, 24, 27, 29, 42, 51, 55, 56, 62, 70). The adequacy or otherwise of 40 studies could not be determined from the details published in the papers (category B) and further information was sought from the authors. Only two studies (36, 45) used a clearly inadequate method for concealment of allocation (category C). A further seven open studies did not use any concealment of allocation (category D).

The quality score developed by Jadad et al. (7) awarded points for randomization, double blinding, whether these methods were well described and appropriate, and whether withdrawals and dropouts were described. Only three studies (39, 40, 56) achieved the maximum possible score of five points. Eleven studies received four points, 24 received three points, 15 received two points, and nine received only one point for methodological quality (Table 1).

There was a high level of agreement between reviewers, and differences were resolved by consensus.

Fifty-three studies were placebo-controlled trials of allergen-specific immunotherapy, two compared immunotherapy with an antigenically inactive control (28, 50), three compared house dust with placebo (10, 16, 75), and three utilized untreated controls (19, 22, 41). Only one study directly compared immunotherapy with inhaled steroids (64), although Torres Costa et al. (69) administered inhaled beclomethasone to both the active treatment and control groups for the first 18 months.

Asthma symptoms

The results of the individual placebo-controlled trials and combined effects for each outcome are presented in Figs. 1–10. Symptom scores were reported by 22 studies, although neither Dreborg et al. (32) nor Olsen et al. (56) published the standard deviations (SDs), thus preventing the calculation of the standardized mean difference (SMD) for these studies. The combined SMD for symptom scores after mite immunotherapy was -0.71 with a 95% confidence interval of -1.37 to -0.05 , which excluded 0, thus indicating a significant reduction in asthma symptoms (Fig. 1). The combined SMD after pollen immunotherapy was -0.72 (95% CI -1.14 to -0.31) also indicating significant symptomatic improvement. However, there was no significant improvement after immunotherapy with cat, dog, or multiple allergen extracts. For all allergens combined, the SMD was -0.73 (95% CI -1.07 to -0.39), but there was significant heterogeneity between studies ($\chi^2=86.2$,

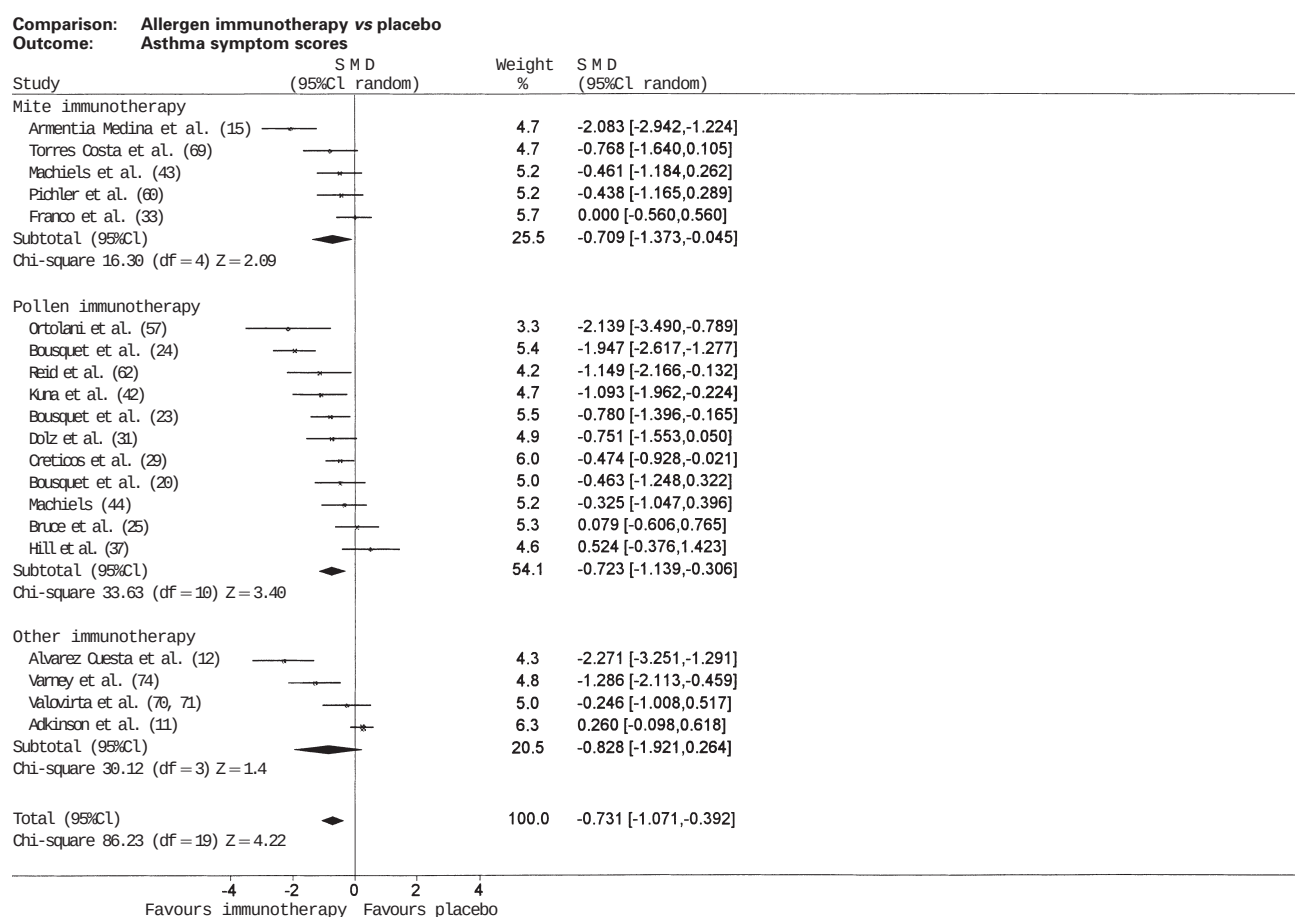


Figure 1. Meta-analysis of asthma symptom scores from placebo-controlled trials of allergen immunotherapy for asthma – standardized mean differences (with 95 % confidence intervals) for each study, studies of mite, pollen, and other immunotherapy and all studies combined.

$P < 0.0005$), with three studies (11, 25, 37) not finding any reduction in symptoms.

Symptoms were simply reported as worse, the same, or improved in another 22 studies. The combined odds ratio (OR) was 0.26, with a 95 % CI from 0.17 to 0.41, which excluded 1, again indicating that patients randomized to immunotherapy were significantly less likely to report a deterioration in asthma symptoms than those randomized to placebo (Fig. 2). There were significant homogeneous improvements after immunotherapy with extracts of pollen (OR 0.13, 95 % CI 0.04–0.42), animal dander (OR 0.20, 95 % CI 0.05–0.87), and other allergens (OR 0.17, 95 % CI 0.09–0.32). Less improvement was seen after mite immunotherapy (OR 0.39, 95 % CI 0.21–0.75), and there was significant heterogeneity between these studies ($\chi^2 = 21.3$, $P < 0.05$). Although the results of studies of children were relatively homogeneous (data not shown), there was significant heterogeneity between the results of adult studies ($\chi^2 = 40$, $P < 0.001$), two studies (17, 26) actually finding symptoms to be more likely in treated patients.

Medication requirements

Asthma medication scores were reported by 13 studies, with Cantani et al. (27), Dreborg et al. (32), and Olsen et al. (56) failing to publish the SDs. The combined SMD was -0.71 (95 % CI -1.09 to -0.32), indicating a significant reduction in medication after immunotherapy (Fig. 3). There was a large reduction after mite immunotherapy, although this was accompanied by significant heterogeneity ($\chi^2 = 16.1$, $P < 0.005$). The reduction after pollen immunotherapy achieved statistical significance in a fixed effects model (SMD $= -0.54$, 95 % CI -0.85 to -0.23). Medication requirements were simply reported as increased, unchanged, or decreased in 16 studies. The combined OR was 0.32 (95 % CI 0.22–0.46), indicating that patients randomized to immunotherapy were significantly less likely to require increased medication than those randomized to placebo (Fig. 4). Although there was significant heterogeneity between the studies reporting medication scores ($\chi^2 = 28.7$, $P < 0.001$), there was substantial homogeneity between the latter 15 studies.

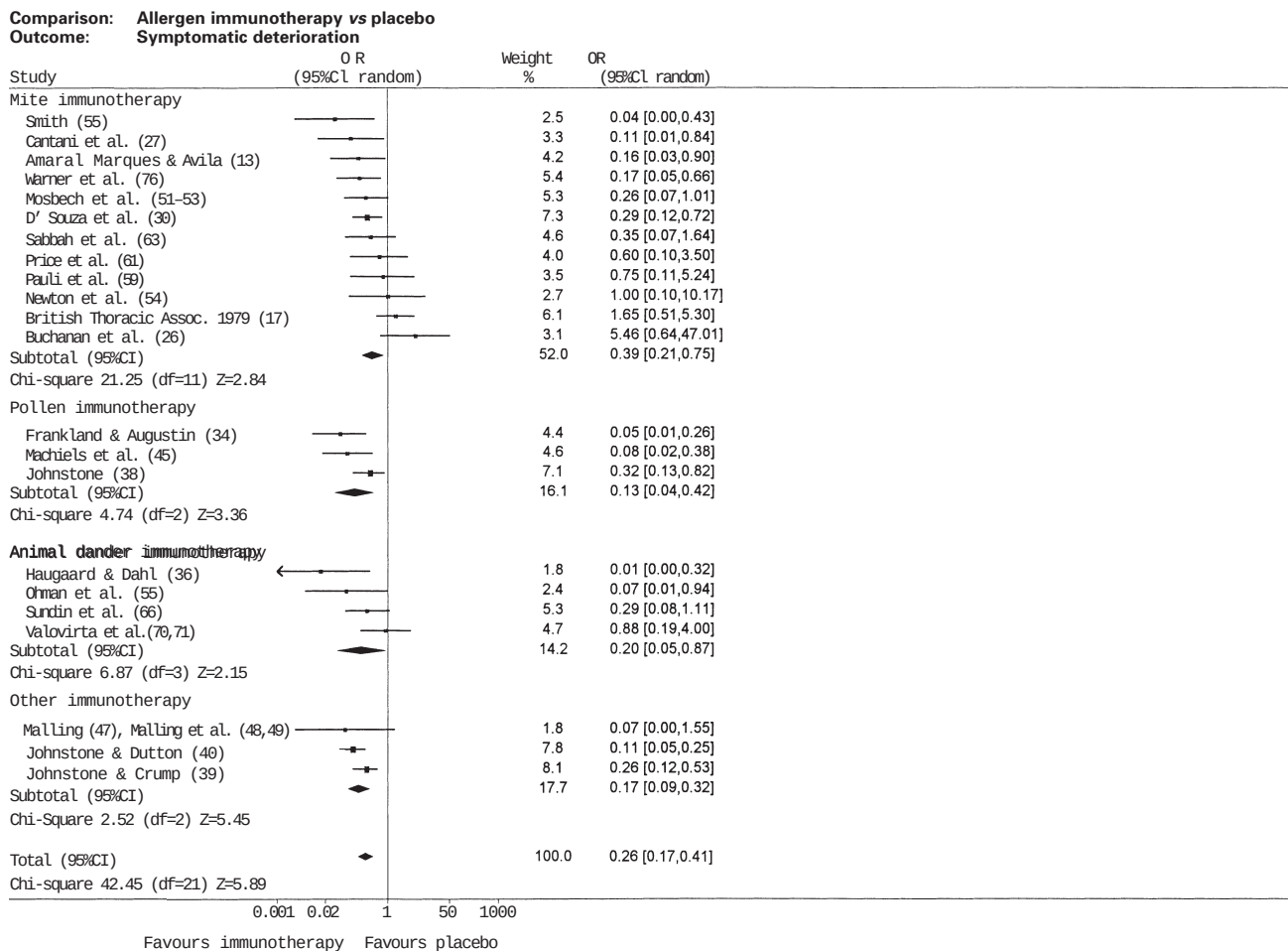


Figure 2. Meta-analysis of symptomatic deterioration from placebo-controlled trials – odds ratios (with 95 % confidence intervals) for each study, studies of mite, pollen, animal dander, and other immunotherapy and all studies combined.

Lung function

Lung-function results were reported by 14 studies, with several studies failing to provide SDs for peak expiratory flow (32), FEV₁ (35, 46), or thoracic gas volume (61, 76). There was no overall improvement in lung-function parameters after immunotherapy (Fig. 5), and there was marked heterogeneity in peak expiratory flow between studies ($\chi^2=27.6$, $P<0.0005$). Indeed, there was even a suggestion that FEV₁ deteriorated after immunotherapy in a small study by Paranos & Petrovic (58), in which the baseline lung function of patients randomized to mite immunotherapy and placebo was poorly matched. Lung function was simply reported as worse, the same, or improved in seven studies. Although there was homogeneity between these studies and an overall trend against a deterioration in lung function after immunotherapy, this did not achieve statistical significance (Fig. 6).

Bronchial hyperreactivity (BHR)

Indices of nonspecific BHR were reported by 12 studies. There were significant improvements in PD₂₀ FEV₁ to methacholine challenge (SMD -0.30 , 95% CI -0.54 to -0.05) and in PC₃₅ sGaw to acetylcholine after immunotherapy with allergen-antibody complexes (43). The improvement in PC₂₀ FEV₁ to histamine challenge failed to achieve statistical significance in a random effects model. Although there was significant heterogeneity between the results of these studies ($\chi^2=22.7$, $P<0.025$), there was an overall reduction in nonspecific BHR after immunotherapy (SMD -0.48 , 95% CI -0.81 to -0.14) (Fig. 7). Nonspecific BHR was simply reported as increased, unchanged, or reduced in five small studies. There was homogeneity between these studies, and the combined OR of 0.22 (95% CI 0.10–0.48) indicated that patients randomized to immunotherapy were significantly

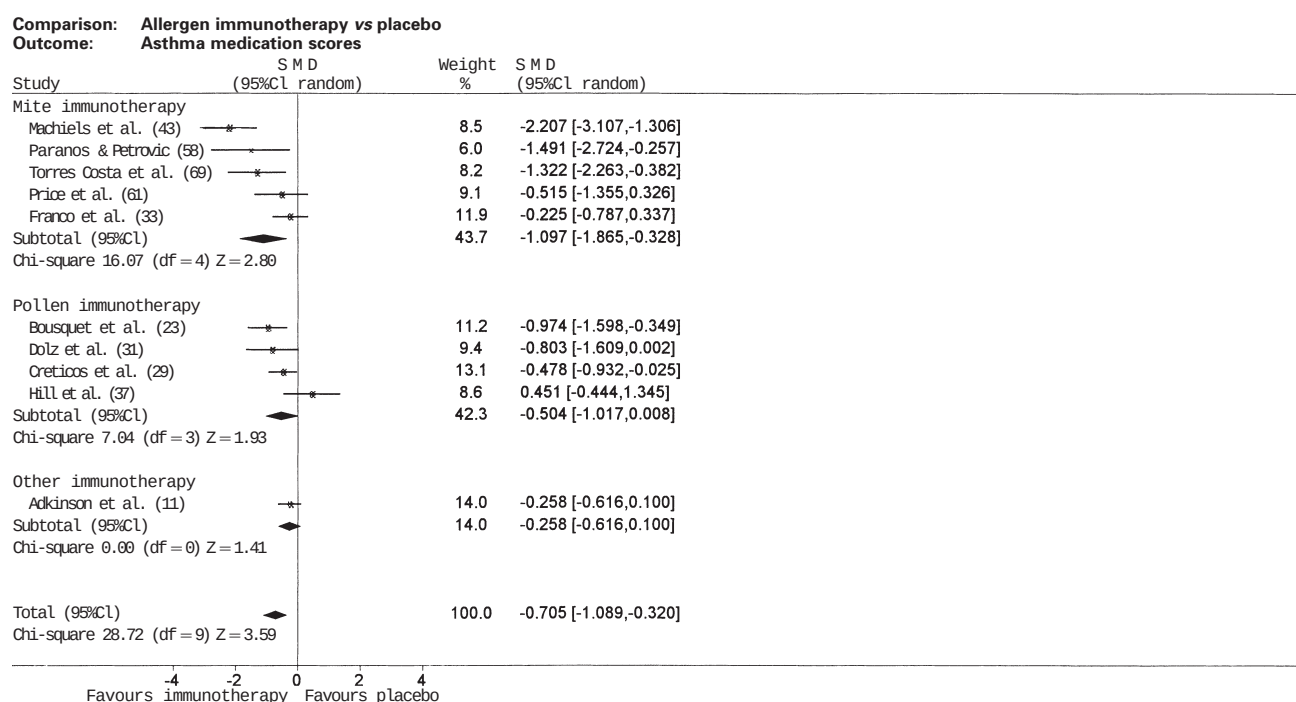


Figure 3. Meta-analysis of asthma medication scores from placebo-controlled trials – standardized mean differences (with 95 % confidence intervals) for each study, studies of mite, pollen, and other immunotherapy and all studies combined.

less likely to develop increased nonspecific BHR than those randomized to placebo (Fig. 8).

Indices of allergen-specific BHR (such as PD₂₀ FEV₁ to allergen challenge) were reported by 14 studies. There was homogeneity between these studies with an overall SMD of -0.70 (95 % CI -0.91 to -0.48), indicating a significant reduction in allergen-specific BHR after immunotherapy (Fig. 9). The effect was most marked for mite immunotherapy (SMD -1.14, 95 % CI -1.62 to -0.65), and similar for pollen (SMD -0.69, 95 % CI -1.09 to -0.30) and animal dander (SMD -0.71, 95 % CI -1.08 to -0.34), but not significant for other

allergens. Allergen-specific BHR was simply reported as increased, unchanged, or reduced by 16 studies. There was homogeneity between studies, and the combined OR of 0.28 (95 % CI 0.19–0.41) indicated that patients randomized to immunotherapy were significantly less likely to develop increased allergen-specific BHR (Fig. 10).

Other comparisons

Because of the small number and disparate outcomes reported by the non-placebo-controlled randomized

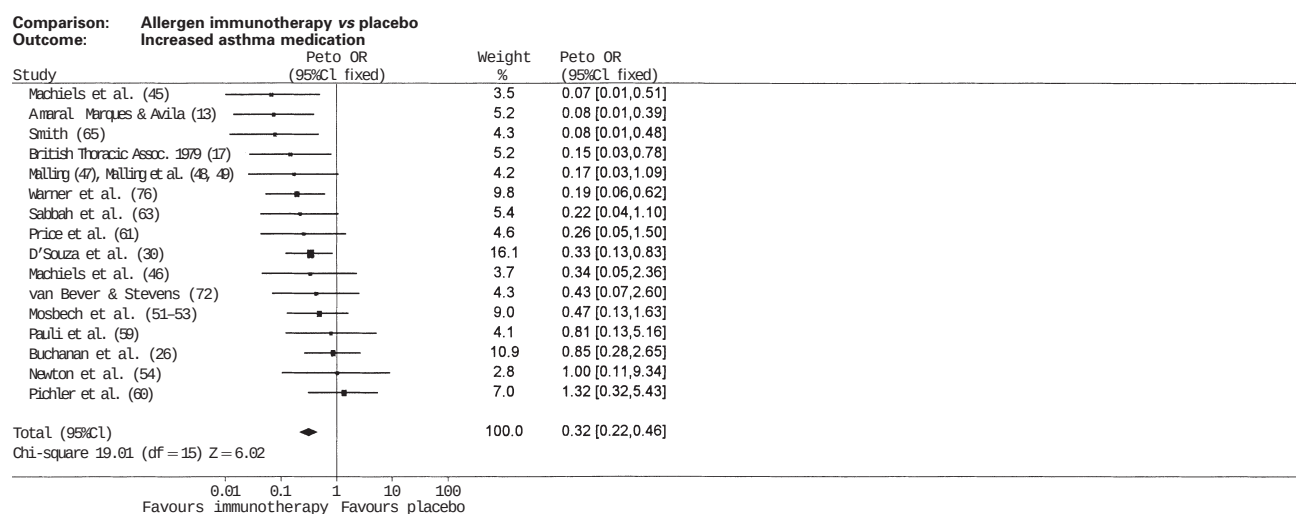


Figure 4. Meta-analysis of increased asthma medication requirements from placebo-controlled trials – odds ratios (with 95 % confidence intervals) for each study and all studies combined.

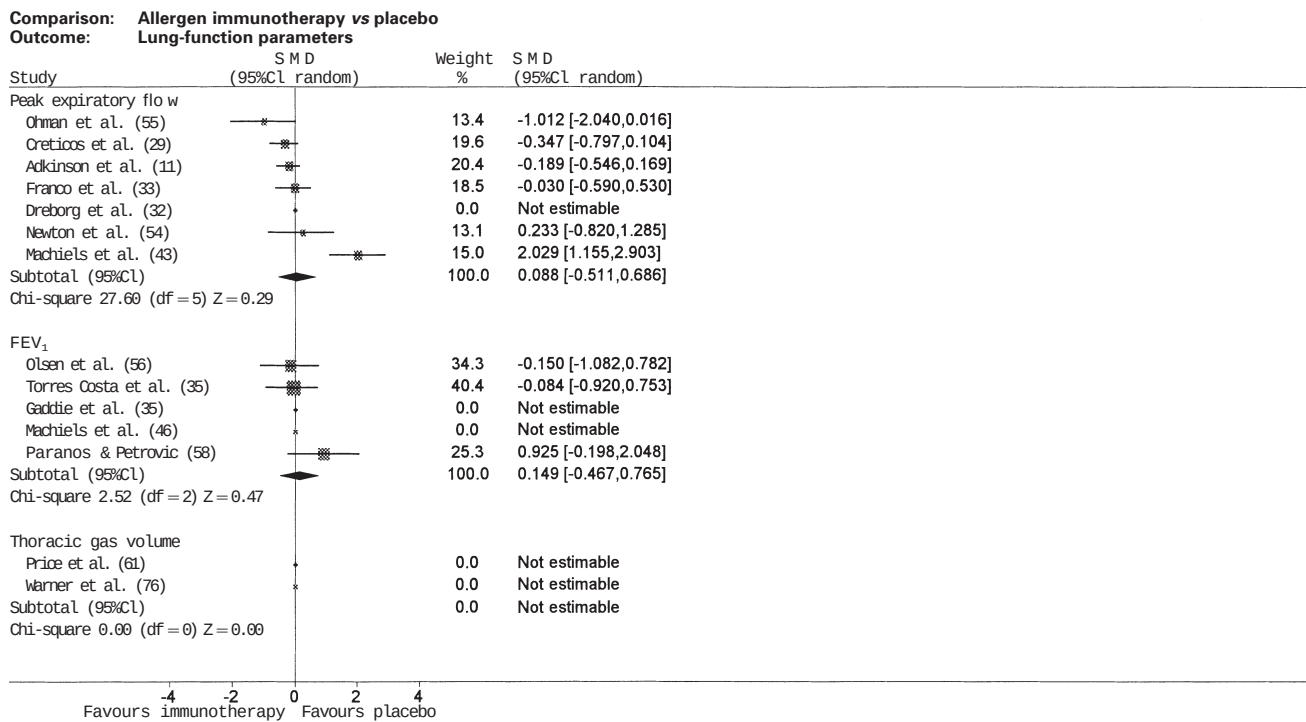


Figure 5. Meta-analysis of lung function parameters from placebo-controlled trials – standardized mean differences (with 95 % confidence intervals) for each study, peak expiratory flow, FEV₁, and thoracic gas volume.

trials, only limited meta-analysis could be performed. Choovoravech (28) did not find a significant reduction in asthma symptoms comparing house-dust-mite (HDM) immunotherapy with house dust (SMD = -0.23, 95 % CI -0.77 to 0.30). However, Maunsell et al. (50) did find that patients randomized to HDM were significantly less likely to report asthma symptoms than those randomized to house dust (OR = 0.2, 95 % CI 0.05–0.8). Choovoravech (28) did not find any significant reduction in asthma medications after immunotherapy (OR = 0.5, 95 % CI 0.15–1.7).

The three studies (10, 16, 75) which compared house-dust extracts with placebo found negative results for most outcomes. Subjects randomized to house dust were less likely to report worse asthma symptoms, but the combined

effect did not achieve statistical significance (OR = 0.45, 95 % CI 0.14–1.4). In the British Tuberculosis Association (16) study, those randomized to house dust had minimal reduction in asthma medication (OR = 0.76, 95 % CI 0.27–2.2) and were marginally less likely to show deterioration in lung function (OR = 0.79, 95 % CI 0.3–2.1). However, Aas (10) found that asthmatic children randomized to house dust had significantly reduced allergen-specific BHR (OR = 0.19, 95 % CI 0.06–0.59).

On the other hand, studies with untreated controls reported strongly positive results of allergen immunotherapy. Both Bousquet et al. (22) and Kohno et al. (41) found that patients randomized to immunotherapy demonstrated a significant reduction in asthma symptoms (combined

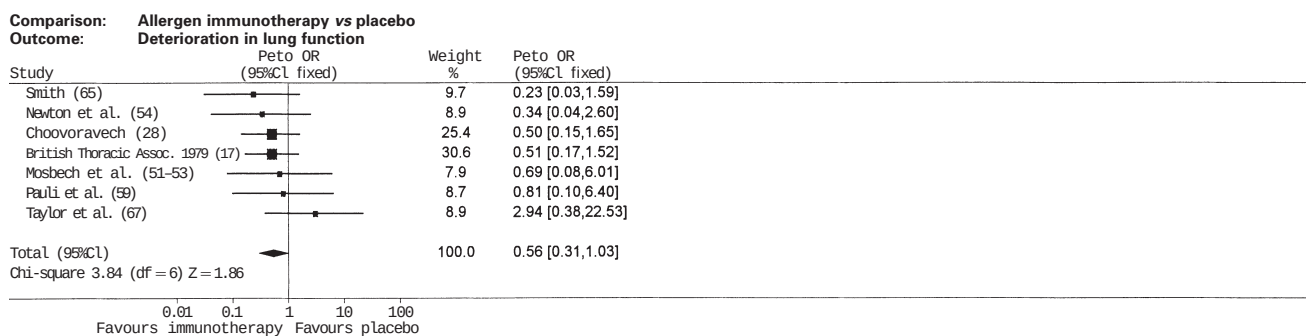


Figure 6. Meta-analysis of deterioration in lung function from placebo-controlled trials – odds ratios (with 95 % confidence intervals) for each study and all studies combined.

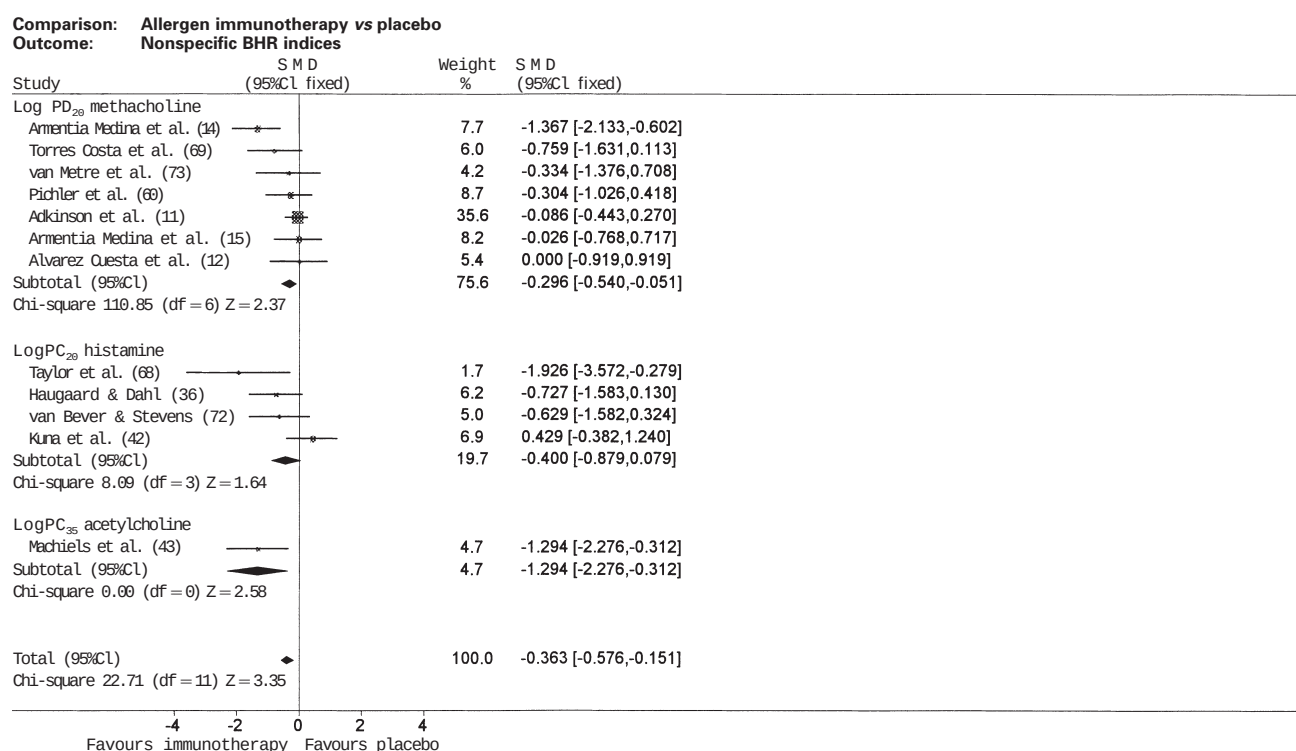


Figure 7. Meta-analysis of indices of nonspecific bronchial hyperreactivity from placebo-controlled trials – standardized mean differences (with 95 % confidence intervals) for each study, logPD₂₀ to methacholine, logPC₂₀ to histamine, logPC₃₅ to acetylcholine, and all studies combined.

SMD = -2.5, 95 % CI -3.0 to -2.0) and a significant improvement in lung function (combined SMD = -0.81, 95 % CI -1.21 to -0.39). Bousquet et al. (22) also reported significantly reduced medication requirements in the immunotherapy group (SMD = -2.6, 95 % CI -3.1 to 2.0). Finally, Bertelsen et al. (19) found that those randomized to immunotherapy were significantly less likely to develop increased allergen-specific BHR (OR = 0.2, 95 % CI 0.05–0.9).

The only trial to compare allergen immunotherapy directly with inhaled steroids (64) found that symptom scores and FEV₁ improved more rapidly in the group randomized to budesonide. However, as no standard deviations were reported, it was not possible to calculate standardized mean differences. In any case, there were no other trials with which these results could be meaningfully combined.

Discussion

This updated systematic review of allergen immunotherapy for asthma has identified an additional 10 randomized controlled trials which were not covered by our previous review of studies published up to 1997 (5). Most of the studies not previously included were published during or after 1997. Two trials which were included in the previous review were excluded on this occasion after closer examination revealed that they did not meet all the inclusion criteria. A total of 125 studies were excluded from the review, mainly because they were not randomized, not controlled, did not report clinically relevant outcomes, or involved only subjects with allergic rhinoconjunctivitis.

Given the well-recognized bias for the publication of positive studies, it is quite possible that some additional

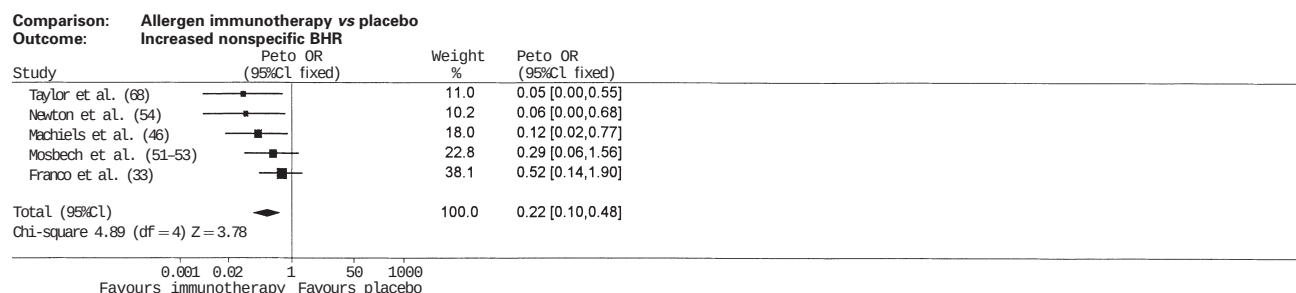


Figure 8. Meta-analysis of increased nonspecific bronchial hyperreactivity from placebo-controlled trials – odds ratios (with 95 % confidence intervals) for each study and all studies combined.

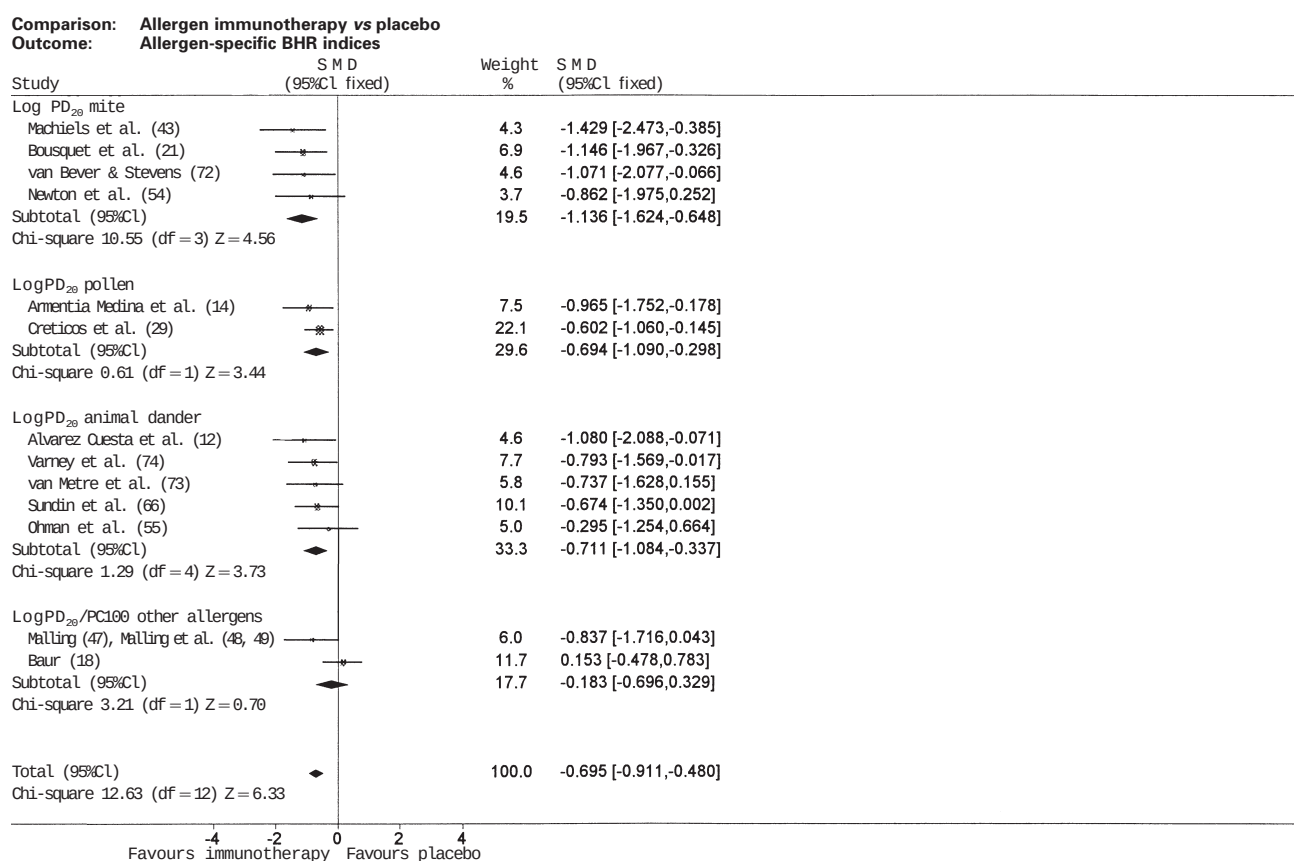


Figure 9. Meta-analysis of indices of allergen-specific bronchial hyperreactivity from placebo-controlled trials – standardized mean differences (with 95% confidence intervals) for each study, studies of mite, pollen, animal dander, and other immunotherapy and all studies combined.

negative studies have been conducted, but that their results have not been published in the medical literature. This problem could be avoided in the future by prospective registration of all clinical trials of allergen immunotherapy, as has been attempted in other clinical disciplines. Unfortunately, the concealment of allocation after randomization could not be clearly determined from the information presented in most of the papers. We would encourage authors of future papers to follow the CONSORT guidelines (202) and fully report such details. However, there was no obvious relationship between concealment or methodological quality and the findings of individual RCTs of immunotherapy.

This meta-analysis has confirmed that allergen-specific immunotherapy can significantly reduce asthma symptoms and medication requirements. The heterogeneity of symptom and medication scores is likely to have arisen from the different scoring schemes used in different studies. The heterogeneity of symptom scores remained significant after stratifying for the allergen administered. All but one study (23) combined both symptomatic and anti-inflammatory medications into a single score. We have previously

criticized this approach (203), as changes in bronchodilator requirements could be obscured by changes in inhaled corticosteroid therapy. Standardization of asthma symptom and medication scores is required for easier interpretation of future studies. However, we do not believe that the heterogeneity of the results means that the studies should not be combined at all or that it invalidates the conclusions.

Medication requirements which were reported as categories, in contrast to the analysis using medication scores, showed significant homogeneity. We believe that this finding can translate into a clinically useful outcome, as one of the principal aims of attempting allergen immunotherapy is to decrease medication requirements. While inhaled corticosteroid therapy remains the mainstay of asthma management, any reduction in this type of treatment while maintaining good asthma control would be welcome.

There was no consistent effect of immunotherapy upon lung function. The marked heterogeneity may have arisen from attempting to combine such diverse measures of lung function as FEV₁, peak expiratory flow, and thoracic gas volume. These parameters presumably reflect different

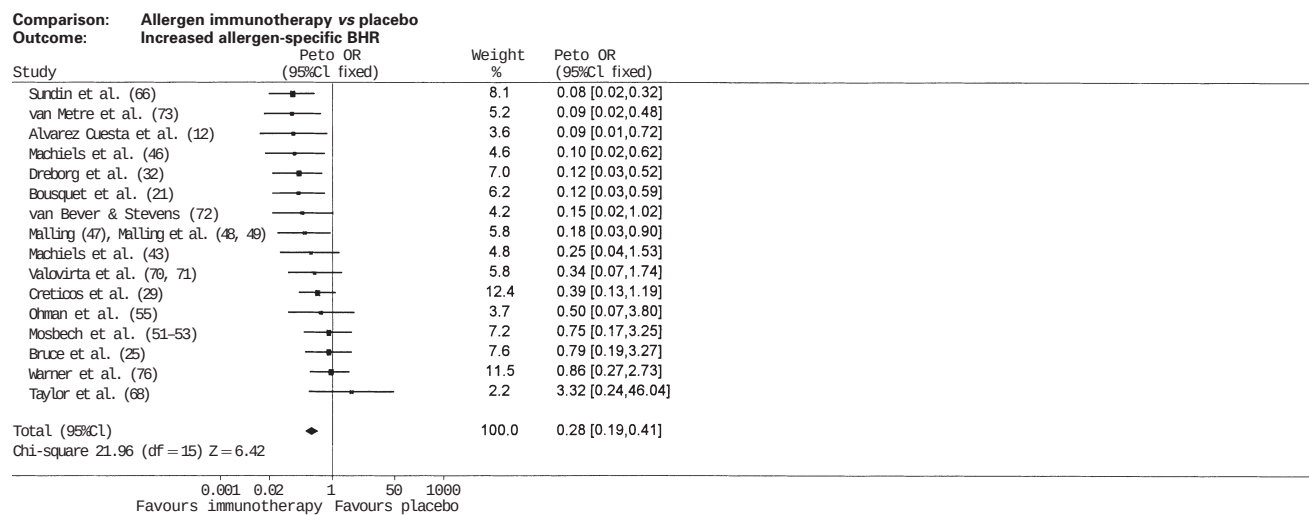


Figure 10. Meta-analysis of increased allergen-specific bronchial hyperreactivity from placebo-controlled trials – odds ratios (with 95 % confidence intervals) for each study and all studies combined.

aspects of the pulmonary pathophysiology of asthma, such as reduced airway calibre, variable airflow limitation, and hyperinflation. However, significant heterogeneity remained after stratifying the analysis for each parameter. In contrast, our first meta-analysis (4) did find a modest improvement in lung function. However, in retrospect, this conclusion resulted substantially from the retrospective exclusion of one negative study (61) in response to a reviewer’s concerns.

Patients randomized to immunotherapy were significantly less likely to develop increased nonspecific BHR, and there were modest improvement indices of nonspecific BHR. Homogeneity was achieved by stratifying the meta-analysis for each index of nonspecific BHR: PD₂₀ FEV₁ to methacholine, PC₂₀ FEV₁ to histamine, and PC₃₅ sGaw to acetylcholine. Since indices of BHR are generally considered to follow a log normal distribution, the means and standard deviations of logPD₂₀ were entered into RevMan to calculate the SMD.

Allergen immunotherapy significantly reduced allergen-specific BHR. Homogeneity was achieved by stratifying the meta-analysis for the allergen administered and expressing the results as logPD₂₀. It would be desirable for future studies to use a standardized protocol for bronchial allergen challenges and to report the results in a more consistent fashion. Not surprisingly, it would appear that allergen immunotherapy has a greater effect upon allergen-specific BHR than upon nonspecific BHR.

The finding that allergen immunotherapy significantly and homogeneously improves allergen-specific bronchial BHR is clinically important. Patients with brittle extrinsic

(allergic) asthma are at risk of sudden deterioration when exposed to increased levels of an aeroallergen to which they are sensitive. Any intervention which reduces the risk of an acute episode of asthma under these circumstances would be clinically useful. Currently, the measurement of allergen-specific BHR is the only accurate method of assessing such a risk.

Less importance should be attached to the results of the relatively small number of non-placebo-controlled trials. There is some evidence that HDM extracts may reduce asthma symptoms and allergen-specific BHR compared to house-dust extracts. One study even suggested that house-dust extracts alone could reduce allergen-specific BHR, challenging the view that such extracts are antigenically inactive. However, taken together, these results are consistent with the greater efficacy of HDM extracts compared with placebo. Studies with untreated controls are particularly susceptible to bias and may overestimate the true benefit of treatment. The effects of immunotherapy upon symptoms, medication, and lung function found in such studies are beyond the upper confidence limits for placebo-controlled studies.

The results of this systematic review are consistent with our previous meta-analyses (4, 5), and, importantly, the positive findings have not been overturned by the inclusion of additional randomized controlled trials. If anything, the combined effects of allergen immunotherapy upon symptom and medication scores are greater than previously estimated. In this review, greater control of heterogeneity was achieved with stratification by allergen and calculation of combined effects by random rather than fixed

effects models. The effects on all other outcomes were unchanged.

None the less, there are still some limitations to the present review. None of the studies included any data relating to asthma exacerbations, emergency room visits, or hospital admissions. Such unstable patients are rarely included in clinical trials, especially those of allergen immunotherapy. The safety of immunotherapy, particularly the occurrence of major systemic reactions, lies beyond the scope of the present review. Rare side-effects are often not adequately assessed in reports of clinical trials (4) and are better captured by schemes reporting adverse reactions. A narrative review by Lockey (204) identified 27 fatal anaphylactic reactions over a 6-year period (1985–91) during which up to 10 million allergen injections were administered annually in the USA. The mean rate of systemic reactions was 1/200 injections.

Conclusions

This report confirms the efficacy of immunotherapy; in particular, we emphasize the clinically useful outcomes of decreased medication requirements and improved allergen-specific BHR. Not only did these two outcomes show statistically significant improvement, but also the results were homogeneous. We believe that a reduction in medication and decreased allergen-specific BHR are clinically important findings and can lead to improved asthma control.

These results give no direct guidance concerning the clinical application of allergen immunotherapy. We have previously stated the well-accepted principles that we follow in using immunotherapy in asthma (4). These issues are discussed more fully in a joint position statement

of the Thoracic Society of Australia and New Zealand and the Australasian Society of Clinical Immunology and Allergy (205) and the WHO position paper (3). We fully endorse these position papers and recommend that interested readers refer to them.

However, certain questions remain to be answered. What are the most important determinants of the clinical relevance of an allergen? Which patient is the ideal recipient of immunotherapy? Is the result better when there is a narrow range of positive skin tests, or is it just as effective in panreactors? Is monocomponent immunotherapy better than the use of multiple allergens to which the patient reacted? What is the optimal length of treatment and the best duration of effect? How does the cost-effectiveness of immunotherapy compare to new pharmacologic treatments for asthma? Some of these questions may be answered in the studies currently available, but others will require new and better designed randomized controlled trials.

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