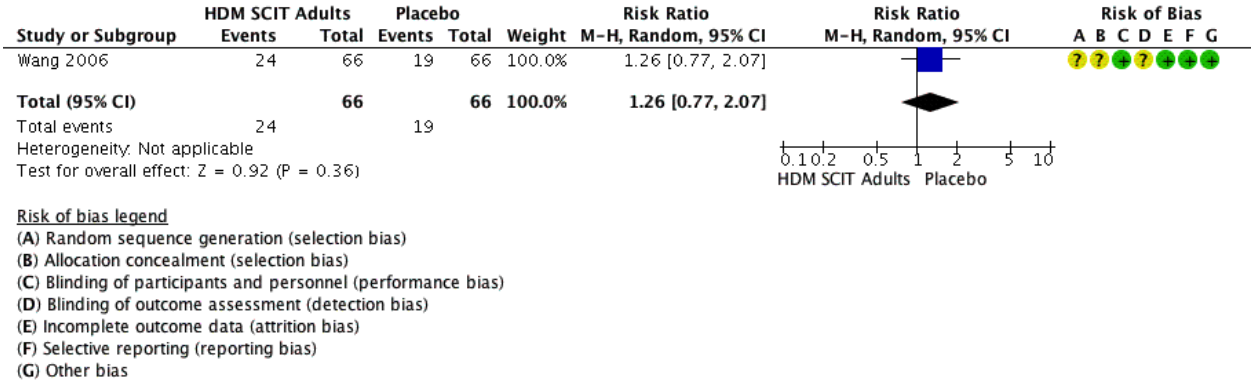
1. Should HDM SCIT versus no HDM SCIT be used for treatment in **adult** patients with asthma?

1.1. FOREST PLOTS

1.1.1. Critical outcomes

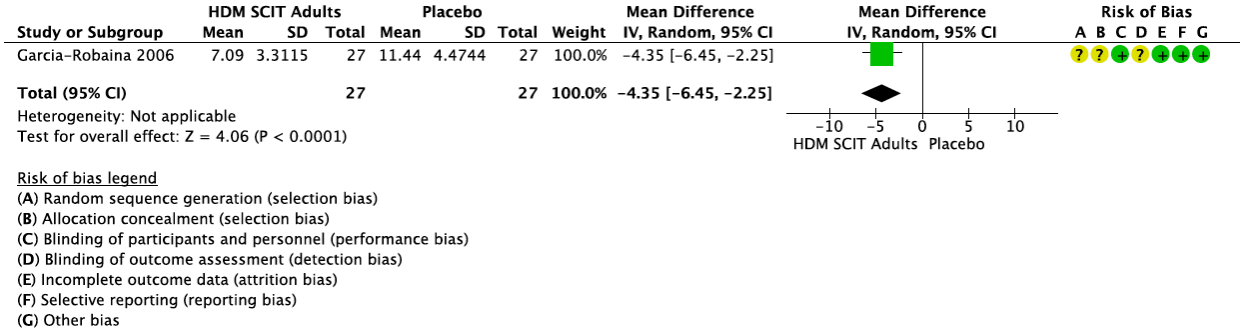
1.1.1.1. Asthma exacerbations – assessed as number of patients required a course oral prednisolone



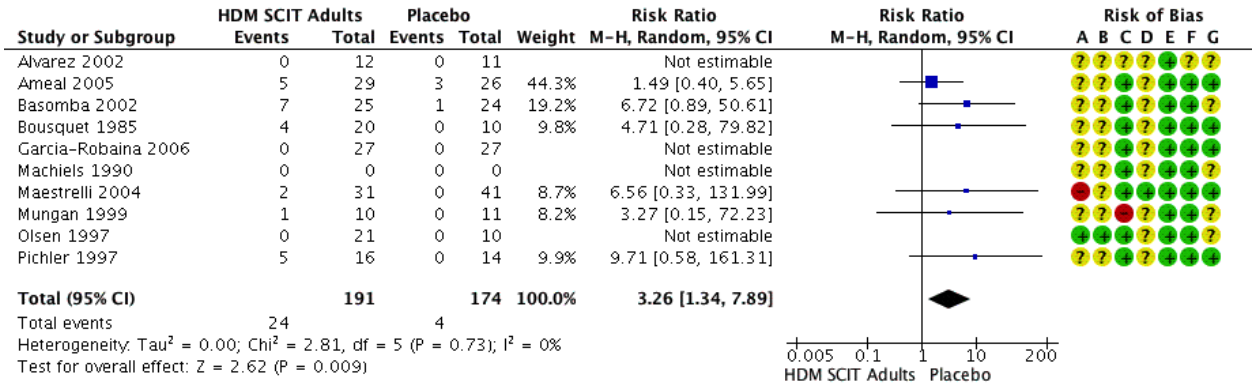
1.1.1.2. Asthma control

We found no evidence

1.1.1.3. Steroid sparing effect (inhaled steroids) assessed as number of weeks without using inhaled steroids



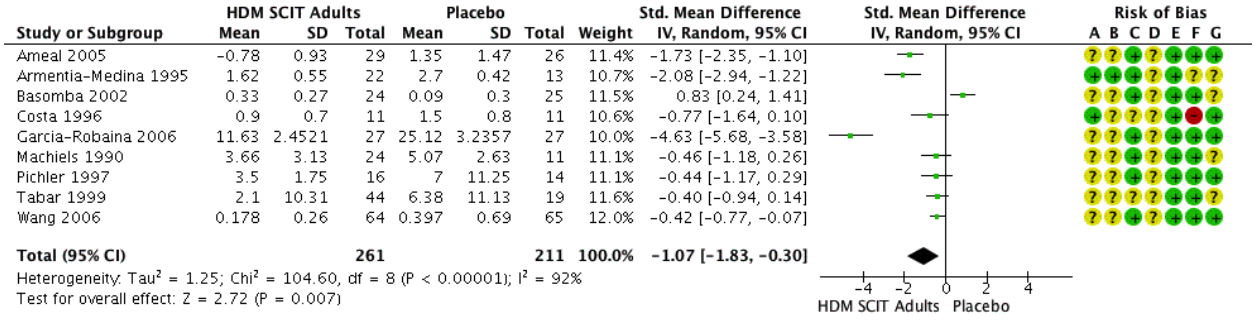
1.1.1.4. Safety (systemic reactions) – assessed as number of patients with at least one reaction



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

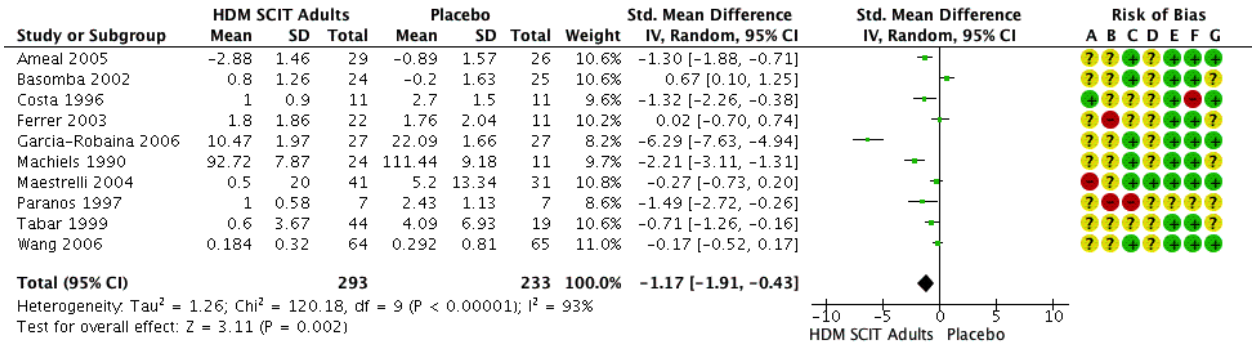
1.1.2. Important but no critical outcomes

1.1.2.1. Symptom score



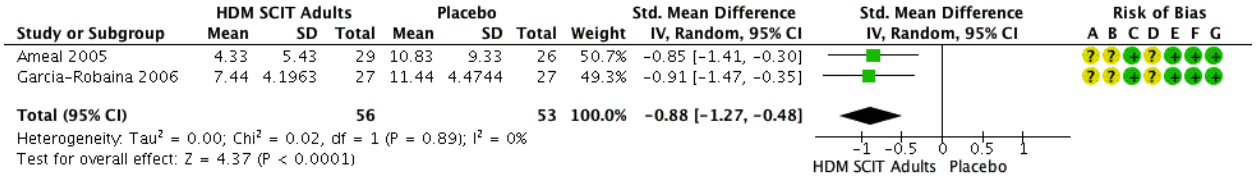
Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

1.1.2.2. Medication score



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

1.1.2.3. Quality of Life

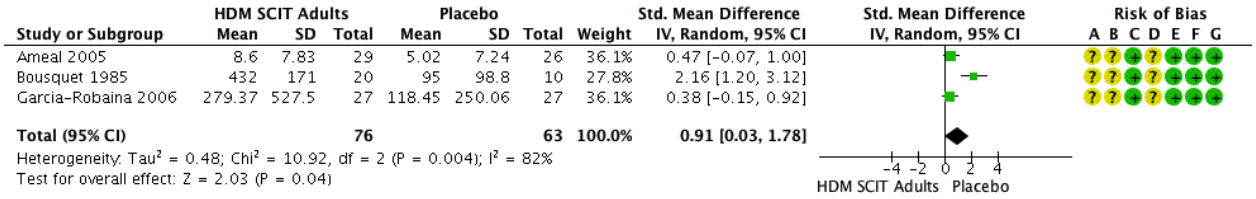


Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

1.1.2.4. Lung function: Small airways assessed as percentage or absolute improvement of MEF 25, MEF 50, MEF 75

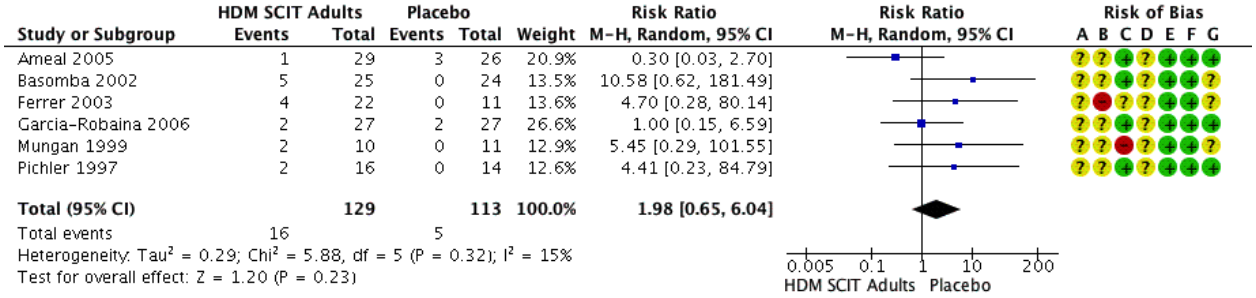
We found no evidence

1.1.2.5. Lung function: Allergen specific bronchial provocation tests (ABPT) assess as PD20 FEV1 to allergen challenge



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

1.1.2.6. Safety (local reactions)



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

1.2. EVIDENCE PROFILE

Author(s): Juan J. Yepes-Nuñez
Date: October 2018
Question: HDM SCIT compared to no HDM SCIT for treatment in adults patients with asthma
Setting: Outpatients

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**HDM SCIT**	**no HDM SCIT**	**Relative (95% CI)**	**Absolute (95% CI)**		
Asthma exacerbations - assessed as number of patients required a course of oral prednisolone (follow up: 1 year)												
1	randomised trials	not serious [a]	not serious	not serious	very serious [b]	none	24/66 (36.4%)	19/66 (28.8%)	**RR 1.26** (0.77 to 2.07)	**75 more per 1,000** (from 66 fewer to 308 more)	⨁⨁◯◯ LOW	CRITICAL
Asthma control - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Corticosteroid use (oral steroids) - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Corticosteroid use (inhaled steroids) - assessed as the number of weeks without using inhaled steroids (follow up: 1 year)												
1	randomised trials	not serious [a]	not serious	serious [c]	serious [d]	none	27	27	-	MD **4.35 lower** (6.45 lower to 2.25 lower)	⨁⨁◯◯ LOW	CRITICAL
Systemic adverse events – assessed as number of patients with at least one reaction (follow up: from 1 year to 3 years)												
10	randomised trials	not serious [e,f]	not serious	not serious [g]	serious [d]	none	24/191 (12.6%)	4/174 (2.3%)	**RR 3.26** (1.34 to 7.89)	**52 more per 1,000** (from 8 more to 158 more)	⨁⨁⨁◯ MODERATE	CRITICAL
Symptom scores (follow up: from 1 year to 2 years)												
9	randomised trials	not serious [h,i]	serious [j]	not serious [g]	serious [d]	none	261	211	-	SMD **1.07 lower** (1.83 lower to 0.3 lower)	⨁⨁◯◯ LOW	IMPORTANT
Medication scores (follow up: from 1 year to 3 years)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	HDM SCIT	no HDM SCIT	Relative (95% CI)	Absolute (95% CI)		
10	randomised trials	not serious [k]	serious [i]	not serious [g]	serious [d]	none	293	233	-	SMD **1.17 lower** (1.91 lower to 0.43 lower)	⨁⨁◯◯ LOW	IMPORTANT
Asthma QoL (follow up: 1 year)												
2	randomised trials	not serious [m]	not serious	not serious [g]	very serious [d]	none	56	53	-	SMD **0.88 lower** (1.27 lower to 0.48 lower)	⨁⨁◯◯ LOW	IMPORTANT
Lung function: Small airways assessed as percentage or absolute improvement of MEF 25, MEF 50, MEF 75 - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	
Lung function: Allergen specific bronchial provocation tests (ABPT) assess as PD20 FEV1 to allergen challenge (follow up: from 1 year)												
3	randomised trials	not serious [m]	serious [n]	not serious [g]	very serious [b]	none	76	63	-	SMD **0.91 higher** (0.03 higher to 1.78 higher)	⨁◯◯◯ VERY LOW	IMPORTANT
Local adverse events (follow up: from 1 year to 1.5 years)												
6	randomised trials	not serious [o]	not serious	not serious [g]	very serious [b]	none	16/129 (12.4%)	5/113 (4.4%)	**RR 1.98** (0.65 to 6.04)	**43 more per 1,000** (from 15 fewer to 223 more)	⨁⨁◯◯ LOW	IMPORTANT

CI: Confidence interval; **RR:** Risk ratio; **SMD:** Standardised mean difference; **MD:** Mean difference

Explanations

a. Allocation concealment and random sequence generation were unclear in the studies included.
b. Very serious imprecision. 95% CI is consistent with the possibility for important benefit and large harm exceeding a minimal important difference, and no optimal information size criterion met.
c. Serious indirectness. The study used a surrogate outcome to assess HDM SCIT efficacy.
d. No optimal information size criterion met.
e. Nine out of ten studies did not provide information about allocation concealment.
f. Two out of ten studies were rated as risk of bias. One study due to lack of random sequence generation, and another one due to lack of blinding of participants.
g. Patients across studies received different HDM SCIT extracts. Allergen extracts are different between each AIT company and batch.
h. Eight out of nine studies did not provide information about allocation concealment.
i. One out of nine studies were rated as risk of bias due to selective reporting.
j. Serious inconsistency. Unexplained inconsistency, with point estimates widely different and confidence intervals not overlapping (P-value chi-square <0.0001; I-square 92%)
k. Four out of ten studies were rated as risk of bias. Two studies due to lack of allocation concealment, one study due to lack of random sequence generation, another one due to lack of blinding of participants, and one study due to selective reporting.

l. Serious inconsistency. Unexplained inconsistency, with point estimates widely different and confidence intervals not overlapping (P-value chi-square <0.0001; I-square 93%)
m. Allocation concealment, random sequence generation, and blinding of outcome assessment were unclear in the studies included.
n. Serious inconsistency. Unexplained inconsistency, with point estimates widely different and confidence intervals not overlapping (P-value chi-square <0.004; I-square 82%)
o. One out of six studies were rated as high risk of bias due to lack of allocation concealment. Another study was also rated as high risk of bias due to lack of blinding.

References

1. Polzehl D, Keck T, Riechelmann H. [Analysis of the efficacy of specific immunotherapy with house-dust mite extracts in adults with allergic rhinitis and/or asthma]. Laryngorhinootologie. 2003;82(4):272-80.
2. Armentia-Medina A, Tapias JA, Martin JF, Ventas P, Fernandez A. Immunotherapy with the storage mite lepidoglyphus destructor. Allergol Immunopathol (Madr). 1995;23(5):211-23.
3. Basomba A, Tabar AI, de Rojas DH, Garcia BE, Alamar R, Olaguibel JM, et al. Allergen vaccination with a liposome-encapsulated extract of Dermatophagoides pteronyssinus: a randomized, double-blind, placebo-controlled trial in asthmatic patients. J Allergy Clin Immunol. 2002;109(6):943-8.
4. Costa JC, Placido JL, Silva JP, Delgado L, Vaz M. Effects of immunotherapy on symptoms, PEFR, spirometry, and airway responsiveness in patients with allergic asthma to house-dust mites (D. pteronyssinus) on inhaled steroid therapy. Allergy. 1996;51(4):238-44.
5. Ferrer A, Garcia-Selles J. Significant improvement in symptoms, skin test, and specific bronchial reactivity after 6 months of treatment with a depigmented, polymerized extract of Dermatophagoides pteronyssinus and D. farinae. J Investig Allergol Clin Immunol. 2003;13(4):244-51.
6. Franco C, Barbadori S, Freshwater LL, Kordash TR. A double-blind, placebo controlled study of Alpare mite D. pteronyssinus immunotherapy in asthmatic patients. Allergol Immunopathol (Madr). 1995;23(2):58-66.
7. Machiels JJ, Somville MA, Lebrun PM, Lebecque SJ, Jacquemin MG, Saint-Remy JM. Allergic bronchial asthma due to Dermatophagoides pteronyssinus hypersensitivity can be efficiently treated by inoculation of allergen-antibody complexes. J Clin Invest. 1990;85(4):1024-35.
8. Maestrelli P, Zanolla L, Pozzan M, Fabbri LM, Regione Veneto Study Group on the "Effect of immunotherapy in allergic a. Effect of specific immunotherapy added to pharmacologic treatment and allergen avoidance in asthmatic patients allergic to house dust mite. J Allergy Clin Immunol. 2004;113(4):643-9.
9. Mungan D, Misirligil Z, Gurbuz L. Comparison of the efficacy of subcutaneous and sublingual immunotherapy in mite-sensitive patients with rhinitis and asthma--a placebo controlled study. Ann Allergy Asthma Immunol. 1999;82(5):485-90.
10. Olsen OT, Larsen KR, Jacobsan L, Svendsen UG. A 1-year, placebo-controlled, double-blind house-dust-mite immunotherapy study in asthmatic adults. Allergy. 1997;52(8):853-9.
11. Paranos S, Petrovic S. Early effects of rush immunotherapy with Dermatophagoides pteronyssinus in asthmatics. J Investig Allergol Clin Immunol. 1997;7(6):588-95.
12. Pichler CE, Marquardsen A, Sparholt S, Lowenstein H, Bircher A, Bischof M, et al. Specific immunotherapy with Dermatophagoides pteronyssinus and D. farinae results in decreased bronchial hyperreactivity. Allergy. 1997;52(3):274-83.
13. Tabar AI, Muro MD, Garcia BE, Alvarez MJ, Acero S, Rico P, et al. Dermatophagoides pteronyssinus cluster immunotherapy. A controlled trial of safety and clinical efficacy. J Investig Allergol Clin Immunol. 1999;9(3):155-64.
14. Wang H, Lin X, Hao C, Zhang C, Sun B, Zheng J, et al. A double-blind, placebo-controlled study of house dust mite immunotherapy in Chinese asthmatic patients. Allergy. 2006;61(2):191-7.
15. Garcia-Robaina JC, Sanchez I, de la Torre F, Fernandez-Caldas E, Casanovas M. Successful management of mite-allergic asthma with modified extracts of Dermatophagoides pteronyssinus and Dermatophagoides farinae in a double-blind, placebo-controlled study. J Allergy Clin Immunol. 2006;118(5):1026-32.
16. Alvarez MJ, Echechipia S, Garcia B, Tabar AI, Martin S, Rico P, et al. Liposome-entrapped D. pteronyssinus vaccination in mild asthma patients: effect of 1-year double-blind, placebo-controlled trial on inflammation, bronchial hyperresponsiveness and immediate and late bronchial responses to the allergen. Clin Exp Allergy. 2002;32(11):1574-82.
17. Ameal A, Vega-Chicote JM, Fernandez S, Miranda A, Carmona MJ, Rondon MC, et al. Double-blind and placebo-controlled study to assess efficacy and safety of a modified allergen extract of Dermatophagoides pteronyssinus in allergic asthma. Allergy. 2005;60(9):1178-83.
18. Bousquet J, Calvayrac P, Guerin B, Hejjaoui A, Dhivert H, Hewitt B, et al. Immunotherapy with a standardized Dermatophagoides pteronyssinus extract. I. In vivo and in vitro parameters after a short course of treatment. J Allergy Clin Immunol. 1985;76(5):734-44.

1.3. SOF TABLE

Summary of findings:

HDM SCIT compared to no HDM SCIT for treatment in adults patients with asthma

Patient or population: adults patients with asthma
Setting: Outpatients
Intervention: HDM SCIT
Comparison: no HDM SCIT

Outcomes	**Anticipated absolute effects*** (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with no HDM SCIT	**Risk with HDM SCIT**				
Asthma exacerbations - assessed as number of patients required a course of oral prednisolone (follow up: 1 year)	288 per 1,000	**363 per 1,000** (222 to 596)	**RR 1.26** (0.77 to 2.07)	132 (1 RCT)	⨁⨁◯◯ LOW [a,b]	
Asthma control - not reported	-	-	-	-	-	
Corticosteroid use (oral steroids) - not reported	-	see_comment	-	-	-	
Corticosteroid use (inhaled steroids) - assessed as the number of weeks without using inhaled steroids (follow up: 1 year)	The mean corticosteroid use (inhaled steroids) - assessed as the number of weeks without using inhaled steroids (follow up: 1 year) was **0**	The mean corticosteroid use (inhaled steroids) - assessed as the number of weeks without using inhaled steroids (follow up: 1 year) in the intervention group was 4.35 lower (6.45 lower to 2.25 lower)	-	54 (1 RCT)	⨁⨁◯◯ LOW [a,c,d]	
Systemic adverse events – assessed as number of patients with at least one reaction (follow up: from 1 year to 3 years)	23 per 1,000	**75 per 1,000** (31 to 181)	**RR 3.26** (1.34 to 7.89)	365 (10 RCTs)	⨁⨁⨁◯ MODERATE [d,e,f,g]	

Summary of findings:

HDM SCIT compared to no HDM SCIT for treatment in adults patients with asthma

Patient or population: adults patients with asthma
Setting: Outpatients
Intervention: HDM SCIT
Comparison: no HDM SCIT

Outcomes	**Anticipated absolute effects*** (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with no HDM SCIT	**Risk with HDM SCIT**				
Symptom scores (follow up: from 1 year to 2 years)	-	-	-	472 (9 RCTs)	⨁⨁◯◯ LOW [d,g,h,i,j]	
Medication scores (follow up: from 1 year to 3 years)	-	-	-	526 (10 RCTs)	⨁⨁◯◯ LOW [d,g,k,l]	
Asthma QoL (follow up: 1 year)	-	-	-	109 (2 RCTs)	⨁⨁◯◯ LOW [d,g,m]	
Lung function: Small airways assessed as percentage or absolute improvement of MEF 25, MEF 50, MEF 75 - not reported - not reported	-	-	-	-	-	
Lung function: Allergen specific bronchial provocation tests (ABPT) assess as PD20 FEV1 to allergen challenge (follow up: from 1 year)	-	-	-	139 (3 RCTs)	⨁◯◯◯ VERY LOW [b,g,m,n]	
Local adverse events (follow up: from 1 year to 1.5 years)	44 per 1,000	**88 per 1,000** (29 to 267)	**RR 1.98** (0.65 to 6.04)	242 (6 RCTs)	⨁⨁◯◯ LOW [b,g,o]	

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio; **SMD:** Standardised mean difference; **MD:** Mean difference

Summary of findings:

HDM SCIT compared to no HDM SCIT for treatment in adults patients with asthma

Patient or population: adults patients with asthma
Setting: Outpatients
Intervention: HDM SCIT
Comparison: no HDM SCIT

Outcomes	**Anticipated absolute effects*** (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with no HDM SCIT	**Risk with HDM SCIT**				

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations

a. Allocation concealment and random sequence generation were unclear in the studies included.
b. Very serious imprecision. 95% CI is consistent with the possibility for important benefit and large harm exceeding a minimal important difference, and no optimal information size criterion met.
c. Serious indirectness. The study used a surrogate outcome to assess HDM SCIT efficacy.
d. No optimal information size criterion met.
e. Nine out of ten studies did not provide information about allocation concealment.
f. Two out of ten studies were rated as risk of bias. One study due to lack of random sequence generation, and another one due to lack of blinding of participants.
g. Patients across studies received different HDM SCIT extracts. Allergen extracts are different between each AIT company and batch.
h. Eight out of nine studies did not provide information about allocation concealment.
i. One out of nine studies was rated as risk of bias due to selective reporting.
j. Serious inconsistency. Unexplained inconsistency, with point estimates widely different and confidence intervals not overlapping (P-value chi-square <0.0001; I-square 92%)
k. Four out of ten studies were rated as risk of bias. Two studies due to lack of allocation concealment, one study due to lack of random sequence generation, another one due to lack of blinding of participants, and one study due to selective reporting.
l. Serious inconsistency. Unexplained inconsistency, with point estimates widely different and confidence intervals not overlapping (P-value chi-square <0.0001; I-square 93%)
m. Allocation concealment, random sequence generation, and blinding of outcome assessment were unclear in the studies included.
n. Serious inconsistency. Unexplained inconsistency, with point estimates widely different and confidence intervals not overlapping (P-value chi-square <0.004; I-square 82%)
o. One out of six studies were rated as high risk of bias due to lack of allocation concealment. Another study was also rated as high risk of bias due to lack of blinding.