NKR 22: Høfeber og allergisk helårssnue (allergisk rhinoconjunctivitis), PICO 6: Allergen-specifik immunterapi, pollen.

Review information

Authors

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[1][Empty affiliation]

Citation example: S. NKR 22: Høfeber og allergisk helårssnue (allergisk rhinoconjunctivitis), PICO 6: Allergen-specifik immunterapi, pollen.. Cochrane Database of Systematic Reviews [Year], Issue [Issue].

Characteristics of studies

Characteristics of included studies

Blaiss 2011

Methods	**Study design:** Randomized controlled trial **Study grouping:** Parallel group **Open Label:** **Cluster RCT:**
Participants	**Baseline Characteristics** Intervention ● *No. of patients*: 175 ● *Male*: 118 ● *Female*: 57 ● *Age (mean)*: 12.1 Placebo ● *No. of patients*: 169 ● *Male*: 105

	● *Female*: 64 ● *Age (mean)*: 12.6 **Included criteria:** Subjects included in the study were 5 to 17 years of age with a clinicalhistory of physician-diagnosed grass pollen–induced ARC with or withoutasthma. Key inclusion criteria for the observation and treatment periods wereaimed at recruiting subjects with moderate-to-severe ARC and were asfollows: treatment for ARC during the previous GPS; a positive skin prick testresponse to P pratense (standardized timothy grass extract, 100,000 bioequivalentallergen units/mL, 5-mL vial, administered by means of a DuoTip [LincolnDiagnostics, Decatur, Ill] to the inner forearm), with the average of thehorizontal and vertical wheal diameters 5 mm or larger than that elicited bythe saline control (positive control was Histatrol Histamine Positive Control1.0 mg/mL, 5-mL vial [ALK-Abello, Hørsholm, Denmark]), a positive specificIgE level against P pratense of 0.7 kU/L or greater (measured by meansof ImmunoCAP; Phadia AB, Portage, Mich), and an FEV1 of 70% or greater ofpredicted value at screening. **Excluded criteria:** Key exclusion criteria were as follows: clinicalhistory of symptomatic seasonal or perennial ARC, asthma, or both requiringmedication because of an allergen other than grass during or potentially overlappingthe GPS; immunosuppressive treatment in the 3 months before screening;clinical history of persistent severe asthma, chronic urticaria/angioedema,or chronic rhinosinusitis; or current severe atopic dermatitis. For subjects whoparticipated in the observational period, those who did not experience a rhinoconjunctivitissymptom score increase of 4 points or more for at least 2 dayscompared with the preseason score or did not use ARC symptomatic medicationfor at least 2 days during the observational period were also excluded.
Interventions	**Intervention Characteristics** Intervention ● *Treatment*: SLIT 75.000 SQT Placebo ● *Treatment*: placebo tablet
Outcomes	*Continuous*: ● Symptomscore ● Medicinscore ● RQLQ *Adverse Events*: ● Anaphylaxis

Identification	**Sponsorship source:** **Country:** USA **Setting:** **Comments:** **Authors name:** Blaiss M **Institution:** dept. pediatrics and medicine **Email:** **Address:**
Notes	**Identification:** **Participants:** **Study design:** **Baseline characteristics:** *Lone Winther* analysis set include treated patients: 149 intervention and 158 placebo.Grass: 175 started treatment and 142 completed treatment: 33 excluded but of these 7 were included in analysisPlacebo: 169 started treatment and 140 completed: 29 excluded but of these 18 were included in analysis **Intervention characteristics:** **Pretreatment:** **Continuous outcomes:** *Lone Winther* Other studies have used peak seasons as well. This study included. **Dichotomous outcomes:** **Adverse outcomes:** *Lone Winther* 70% vs 25% experienced treatment related AE, in SLIT and placebo, respectively

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Randomization was conducted by an external randomization group using an interactive voice-response system according to a computer-generated sched- ule in appropriately sized blocks and was stratified by study site and the sub- ject's asthma status."
Allocation concealment (selection bias)	Low risk	

Blinding of participants and personnel (performance bias)	Low risk	Quote: "Subjects and investigators were blinded to treatment by using a matching placebo in identical packaging to the grass AIT treatment. Blinding was maintained until the data were locked."
Blinding of outcome assessment (detection bias)	Low risk	Comment: Blinding was maintained until the data were locked.
Incomplete outcome data (attrition bias)	Unclear risk	Comment: Data analysis set included some of the excluded patients.No imputation of missing data. No mention of percentage of daily data completed.
Selective reporting (reporting bias)	Low risk	
Other bias	High risk	

Bufe 2009

Methods	
Participants	
Interventions	
Outcomes	
Identification	
Notes	Estimates and risk of bias assessments are from Radulovic et al (year)

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	
Allocation concealment (selection bias)	Unclear risk	Unclear
Blinding of participants and personnel (performance bias)	Low risk	
Blinding of outcome assessment (detection bias)	Unclear risk	Unclear
Incomplete outcome data (attrition bias)	Low risk	
Selective reporting (reporting bias)	Low risk	

Other bias	Low risk	

Dahl 2006

Methods	
Participants	
Interventions	
Outcomes	
Identification	
Notes	Estimates and risk of bias assessments are from Radulovic et al (year)

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	
Allocation concealment (selection bias)	Low risk	
Blinding of participants and personnel (performance bias)	Low risk	
Blinding of outcome assessment (detection bias)	Unclear risk	Unclear
Incomplete outcome data (attrition bias)	Low risk	
Selective reporting (reporting bias)	Low risk	
Other bias	Low risk	

Durham 2006

Methods	
Participants	
Interventions	
Outcomes	
Identification	
Notes	Estimates and risk of bias assessments are from Radulovic et al (year)

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	
Allocation concealment (selection bias)	Low risk	
Blinding of participants and personnel (performance bias)	Low risk	
Blinding of outcome assessment (detection bias)	Unclear risk	Unclear
Incomplete outcome data (attrition bias)	Low risk	
Selective reporting (reporting bias)	Low risk	
Other bias	Low risk	

Durham 2012

Methods	
Participants	
Interventions	
Outcomes	
Identification	
Notes	Fra opdaterende søgning.

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	
Allocation concealment (selection bias)	Unclear risk	Unclear
Blinding of participants and personnel (performance bias)	Low risk	
Blinding of outcome assessment (detection bias)	Low risk	
Incomplete outcome data (attrition bias)	High risk	
Selective reporting (reporting bias)	Unclear risk	Unclear
Other bias	Low risk	

Frew 2006

Methods	**Study design:** Randomized controlled trial **Study grouping:** Parallel group **Open Label:** **Cluster RCT:**
Participants	**Baseline Characteristics** Intervention ● *No. of patients*: 203 ● *Male*: 110 ● *Female*: 93 ● *Age (mean)*: 38.3 Placebo ● *No. of patients*: 103 ● *Male*: 62 ● *Female*: 41 ● *Age (mean)*: 37.9

	Included criteria: A clinical history of grass pollen–induced SAR that was inadequately controlled in previous years despite using antihistamines, topical steroids, and/or cromoglycate eye drops. Grass pollen allergy was confirmed by means of skin and blood tests (wheal diameter of 3 mm with Soluprick SQ 10 HEP Phleum pretense, ALK-Abello´, Hørsholm, Denmark; grass pollen–specific IgE class 2, Pharmacia CAP, Uppsala, Sweden) **Excluded criteria:** Patients with additional sensitizations were allowed to participate unless they had significant rhinoconjunctivitis, sinusitis, and/or asthma outside the grass pollen season or daily contact with animals causing symptoms. Patients who had received SIT within the past 5 years were also excluded.
Interventions	**Intervention Characteristics** Intervention ● *Treatment*: Alutard 100,000 Placebo ● *Treatment*: Placebo
Outcomes	*Continuous*: ● Symptom score during season ● Medication score during season ● RQLQ *Dichotomous*: ● Anaphylaxis
Identification	**Sponsorship source:** **Country:** England **Setting:** **Comments:** **Authors name:** Frew A. J. **Institution:** allergy and inflammation research subdivision, school of medicine, university of southampton **Email:** **Address:**
Notes	**Identification:** **Participants:** **Study design:**

	Baseline characteristics: **Intervention characteristics:** **Pretreatment:** **Continuous outcomes:** **Dichotomous outcomes:** **Adverse outcomes:**

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "ALK-Abello ´ generated the randomization sequence, which was retained until all assessments and recordings were completed." Comment: Is alka-abello the right ones to generate the sequence?
Allocation concealment (selection bias)	Unclear risk	Quote: "Investigators allocated subjects the next randomization number from the randomized sequence." Comment: is this rodden?
Blinding of participants and personnel (performance bias)	Low risk	Quote: "Study medication was provided as a suspension in vials. Placebo and active medications were identical, except for grass pollen extract."
Blinding of outcome assessment (detection bias)	Low risk	Quote: "Staff administering medication and assessing outcomes were blinded to the treatment."
Incomplete outcome data (attrition bias)	High risk	Comment: They do not use an imputation method for the efficacy results. For the adverse events they dol.
Selective reporting (reporting bias)	Low risk	Comment: Protocol not located. It seems like they have presented all relevant outcomes and adverse events.
Other bias	Unclear risk	unclear

Maloney 2014

Methods	
Participants	
Interventions	
Outcomes	
Identification	
Notes	SE/SDs from Nelson et al 2011 and Durham et al 2006 imputed and used in analyses.

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	A total of 1,501 subjects who continued to qualify for the study were randomized in a 1:1 ratio according to a computer-generated randomization schedule;
Allocation concealment (selection bias)	Low risk	randomization was conducted by an external randomization group using an interactive voice response system and was stratified by asthmatic status and age category
Blinding of participants and personnel (performance bias)	Low risk	The sponsor, subject, and investigational staff (investigator and evaluators) were blinded to treatment. Placebo was indistinguishable from the active tablet in appearance, smell, and taste but contained no pollen extract. Subjects were treated once daily with placebo or MK-7243 for at least 12 weeks before and during the entire 2012 grass pollen season (GPS; eFig 1).
Blinding of outcome assessment (detection bias)	Low risk	The sponsor, subject, and investigational staff (investigator and evaluators) were blinded to treatment. Placebo was indistinguishable from the active tablet in appearance, smell, and taste but contained no pollen extract. Subjects were treated once daily with placebo or MK-7243 for at least 12 weeks before and during the entire 2012 grass pollen season (GPS; eFig 1).
Incomplete outcome data (attrition bias)	Low risk	This was a multicenter, double-blinded, randomized, placebo- controlled, parallel-group study (P08067; clinicaltrials.gov; regis- tration NCT01385371) conducted in the United States and Canada.

Selective reporting (reporting bias)	Low risk	This was a multicenter, double-blinded, randomized, placebo- controlled, parallel-group study (P08067; clinicaltrials.gov; regis- tration NCT01385371) conducted in the United States and Canada.
Other bias	Unclear risk	It is unclear whether funding from pharmaceutical company influenced the study

Murphy 2013

Methods	
Participants	
Interventions	
Outcomes	
Identification	
Notes	Fra opdaterende søgning

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	computer generated (SASS)
Allocation concealment (selection bias)	Low risk	
Blinding of participants and personnel (performance bias)	Low risk	
Blinding of outcome assessment (detection bias)	Unclear risk	unclear
Incomplete outcome data (attrition bias)	Low risk	ITT analysis used
Selective reporting (reporting bias)	Low risk	
Other bias	High risk	high pre season scores. No symptom score flucturation with grass pollen. Mite sensitization high.

Nelson 2011

Methods	**Study design:** Randomized controlled trial **Study grouping:** Parallel group **Open Label:** **Cluster RCT:**
Participants	**Baseline Characteristics** Intervention ● *No. of patients*: 213 ● *Male*: 104 ● *Female*: 109 ● *Age (mean)*: 35.9 Placebo ● *No. of patients*: 225 ● *Male*: 113 ● *Female*: 112 ● *Age (mean)*: 35.9 **Included criteria:** Subjects included in the study (both the observational and treatment years, unless otherwise noted) were 18 to 65 years of age with a physician-diagnosed history of grass pollen–induced ARC with or without asthma and had received treatment for their ARC during the previous GPS. At screening, subjects were required to meet the following criteria: a positive skin prick test response to P pratense defined as a wheal diameter of 5 mm or larger than that elicited by the saline control (standardized timothy grass extract 100,000 BAU/mL, 5 mL [ALK-Abell o, Hørsholm, Denmark] administered to the inner forearm with a DuoTip [Lincoln Diagnostics, Decatur, Ill]; positive control, HistatrolHistamine Positive Control 1.0 mg/mL, 5-mL [ALK-Abello, Hørsholm, Denmark]), a positive P pratense–specific IgE level (_ 0.7 kU/L; measured by using the ImmunoCAP assay, Phadia AB, Portage, Mich), and an FEV 1 of 70% or greater of predicted value. For those subjects who participated in theobservational period, an increase in rhinoconjunctivitis symptom score of 4 or greater (maximum possible score, 18) above the preseasonal average score for at least 2 days or symptomatic medication use for at least 2 days during the ob-servational period was also required to continue into the treatment period of the trial. **Excluded criteria:** Reasons for exclusion from the trial included a history of symptomatic seasonal or perennial ARC, asthma, or both to an allergen other than the northern grasses that required medication during or potentially overlapping the GPS,immunotherapy within the previous 5 years, a history of severe asthma, chronic urticaria/angioedema, chronic

	sinusitis, or current severe atopic dermatitis.
Interventions	**Intervention Characteristics** Intervention ● *Treatment*: Placebo ● *Treatment*:
Outcomes	*Continuous*: ● Symptomscore ● Medicinscore ● RQLQ *Adverse Events*: ● Anaphylaxis
Identification	**Sponsorship source:** **Country:** USA **Setting:** **Comments:** **Authors name:** Nelson **Institution:** Department of medicine, division of allergy and immunology, national jewish health, denver **Email:** **Address:**
Notes	**Identification:** **Participants:** **Study design:** **Baseline characteristics:** **Intervention characteristics:** **Pretreatment:** **Continuous outcomes:** **Dichotomous outcomes:** **Adverse outcomes:**

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Subjects were randomized by using a computer-generated random- ization schedule in blocks of appropriate size."
Allocation concealment (selection bias)	Low risk	Quote: "Randomization was conducted by an external randomization group using an interactive voice-response sys- tem and was stratified by study site and the asthmatic status of the subject."
Blinding of participants and personnel (performance bias)	Low risk	Quote: "Double blinding (subject and investigator) was established by use of a match- ing placebo tablet. Blinding was maintained until the database was locked."
Blinding of outcome assessment (detection bias)	Unclear risk	unclear
Incomplete outcome data (attrition bias)	Low risk	low risk
Selective reporting (reporting bias)	Unclear risk	unclear
Other bias	Unclear risk	Quote: "Supported by Merck & Co." Comment: It is unclear wether this finansial suppor affects the results.

Reich 2011

Methods	
Participants	
Interventions	
Outcomes	
Identification	
Notes	Fra opdaterende søgning.

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	statification was performed by center and randomasation was perfomed in block of 5 by the study sponser using the SAS version 8e
Allocation concealment (selection bias)	Low risk	randomazation code kept strigtly confidential
Blinding of participants and personnel (performance bias)	Low risk	investigators and patients were blinded through out the trial
Blinding of outcome assessment (detection bias)	Unclear risk	not reported
Incomplete outcome data (attrition bias)	Low risk	
Selective reporting (reporting bias)	Low risk	protocol found and likely they have reported what they planned
Other bias	High risk	pharmacutical sponsored throughout all of the study

Varney 1991

Methods	
Participants	
Interventions	
Outcomes	
Identification	
Notes	Fra Dretzkes et al (year)

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Comment: computer generated random numbers
Allocation concealment (selection bias)	Unclear risk	Comment: It is unclear if the sequence was concealed
Blinding of participants and personnel (performance bias)	Unclear risk	Comment: Immune therapists was not blinded. The outcome rapporter of adverse event was not blinded. it is unclear of the patients were blinded despite of a dubbel dummy technique.
Blinding of outcome assessment (detection bias)	Low risk	Comment: the coordinater (blinded) was in charge of testing.
Incomplete outcome data (attrition bias)	High risk	Comment: ITT was not used
Selective reporting (reporting bias)	Unclear risk	Comment: Protocol not located
Other bias	Low risk	

Walker 2001

Methods	**Study design:** Randomized controlled trial **Study grouping:** Parallel group **Open Label:** **Cluster RCT:**
Participants	**Baseline Characteristics** Intervention ● *No. of patients*: 22 ● *Male*: 10 ● *Female*: 12 ● *Age (mean)*: 32 Placebo ● *No. of patients*: 22

	● *Male*: 13 ● *Female*: 9 ● *Age (mean)*: 32 **Included criteria:** Criteria were as follows: (1) a history of severe hayfever uncontrolled by conventional antiallergic drugs, and (2) positiveskin prick test result (wheal > 5 mm) to grass pollen. **Excluded criteria:** Patientswere excluded if they had a history of multiple allergies or hadreceived immunotherapy in the preceding 5 years. Patients with seasonalchest symptoms were actively sought for inclusion providedtheir baseline methacholine PC20 (concentration of inhaled methacholinethat caused a 20% decrease in FEV1) was greater than 2mg/mL (normal range > 16 mg/mL).
Interventions	**Intervention Characteristics** Intervention ● *Treatment*: Alutard. Placebo ● *Treatment*: Placebo 0.01mg/ml histamine acid phosphate.
Outcomes	*Continuous*: ● Symptomscore ● Medicinscore ● RQLQ *Adverse Events*: ● Systemic reactions
Identification	**Sponsorship source:** **Country:** England **Setting:** **Comments:** **Authors name:** Walker **Institution:** Upper respiratory medicine, imperial college school of medicine at the national heart and lung institute, london **Email:** **Address:**

Notes	**Identification:** **Participants:** **Study design:** **Baseline characteristics:** **Intervention characteristics:** **Pretreatment:** **Continuous outcomes:** **Dichotomous outcomes:** **Adverse outcomes:**

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Randomization was performed independently by the supplier of the grass pollen vaccine. The treatment schedule and assessments were performed double-blind,"
Allocation concealment (selection bias)	Low risk	Quote: "The treatment schedule and assessments were performed double-blind, with treatment allocations kept in sealed envelopes by the principal investigator."
Blinding of participants and personnel (performance bias)	Low risk	Quote: "P5. Place- bo injections of identical appearance contained 0.01 mg/mL hista- mine acid phosphate (in PBS) in allergen diluent."
Blinding of outcome assessment (detection bias)	Unclear risk	Comment: Not described
Incomplete outcome data (attrition bias)	Low risk	Quote: "All analyses were performed on an intention-to-treat basis." Comment: ITT was used
Selective reporting (reporting bias)	Unclear risk	Comment: Protocol not located
Other bias	Unclear risk	Comment: funded by ALK Abello

Footnotes

Characteristics of excluded studies

Amar 2009

Reason for exclusion	Wrong intervention

Andre 2003

Reason for exclusion	Wrong patient population

Ariano 2001

Reason for exclusion	Wrong patient population

Balda 1998

Reason for exclusion	Wrong patient population

Bodtger 2002

Reason for exclusion	Wrong intervention

Bousquet 1990

Reason for exclusion	Wrong intervention

Bowen 2004

Reason for exclusion	Wrong patient population

Brewczynski 1999

Reason for exclusion	modificeret allergen

Bufe 2004

Reason for exclusion	Wrong intervention

Casanovas 1994

Reason for exclusion	Wrong patient population

Charpin 2007

Reason for exclusion	Wrong intervention

Corrigan 2005

Reason for exclusion	modificeret allergen

Cortellini 2010

Reason for exclusion	Wrong patient population

Didier 2007

Reason for exclusion	not SQ

DiRienzo 2006

Reason for exclusion	Wrong intervention

Drachenberg 2001

Reason for exclusion	product not in DK

Drachenberg 2001a

Reason for exclusion	Wrong intervention

Durham 2010

Reason for exclusion	Study included in other article

Feliziani 1995

Reason for exclusion	Wrong intervention

Ferrer 2005

Reason for exclusion	Wrong patient population

Hordijk 1998

Reason for exclusion	Wrong intervention

Jutel 2005

Reason for exclusion	Wrong intervention

Kuna 2011

Reason for exclusion	Wrong intervention

LaRosa 1999

Reason for exclusion	Wrong intervention

Lima 2002

Reason for exclusion	Wrong intervention

Ortolani 1984

Reason for exclusion	not SQ

Ortolani 1994

Reason for exclusion	Wrong intervention

Ott 2009

Reason for exclusion	Wrong intervention

Palma Carlos 2006

Reason for exclusion	modificeret allergen

Panzner 2008

Reason for exclusion	Wrong intervention

Passalacqua 1999

Reason for exclusion	Wrong intervention

Pauli 2008

Reason for exclusion	Wrong patient population

Peter 2009

Reason for exclusion	Wrong intervention

Pfaar 2008

Reason for exclusion	Wrong intervention

Pradalier 1999

Reason for exclusion	Wrong intervention

Purello D'Ambrosio 1999

Reason for exclusion	Wrong intervention

Roder 2007

Reason for exclusion	Wrong intervention

Rolinck Werninghaus 2004

Reason for exclusion	Wrong intervention

Skoner 2010

Reason for exclusion	Wrong patient population

Smith 2004

Reason for exclusion	Wrong intervention

Troise 1995

Reason for exclusion	Wrong intervention

Valovirta 2006

Reason for exclusion	Wrong intervention

Vervloet 2007

Reason for exclusion	Wrong intervention

Voltolini 2001

Reason for exclusion	Wrong intervention

Vourdas 1998

Reason for exclusion	Wrong intervention

Wahn 2009

Reason for exclusion	not SQ

Zenner 1997

Reason for exclusion	Wrong intervention

Footnotes

Characteristics of studies awaiting classification

Footnotes

Characteristics of ongoing studies

Footnotes

References to studies

Included studies

Blaiss 2011

Blaiss, M.; Maloney, J.; Nolte, H.; Gawchik, S.; Yao, R.; Skoner, D. P.. Efficacy and safety of timothy grass allergy immunotherapy tablets in North American children and adolescents. Journal of allergy and clinical immunology 2011;127(1):64-71, 71.e1-4. [DOI: http://dx.doi.org/10.1016/j.jaci.2010.11.035]

Bufe 2009

[Empty]

Dahl 2006

[Empty]

Durham 2006

[Empty]

Durham 2012

[Empty]

Frew 2006

Frew,A. J.; Powell,R. J.; Corrigan,C. J.; Durham,S. R.; UK Immunotherapy Study Group. Efficacy and safety of specific immunotherapy with SQ allergen extract in treatment-resistant seasonal allergic rhinoconjunctivitis. The Journal of allergy and clinical immunology 2006;117(2):319-325. [DOI: S0091-6749(05)02533-9 [pii]]

Maloney 2014

Maloney,J.; Bernstein,D. I.; Nelson,H.; Creticos,P.; Hebert,J.; Noonan,M.; Skoner,D.; Zhou,Y.; Kaur,A.; Nolte,H.. Efficacy and safety of grass sublingual immunotherapy tablet, MK-7243: A large randomized controlled trial.. Annals of Allergy, Asthma and Immunology 2014;112(2):146-153.e2. [DOI: http://dx.doi.org/10.1016/j.anai.2013.11.018]

Murphy 2013

[Empty]

Nelson 2011

Nelson,H. S.; Nolte,H.; Creticos,P.; Maloney,J.; Wu,J.; Bernstein,D. I.. Efficacy and safety of timothy grass allergy immunotherapy tablet treatment in North American adults.. Journal of Allergy and Clinical Immunology 2011;127(1):64-71.e4. [DOI: http://dx.doi.org/10.1016/j.jaci.2010.11.034]

Reich 2011

[Empty]

Varney 1991

Varney,V. A.; Gaga,M.; Frew,A. J.; Aber,V. R.; Kay,A. B.; Durham,S. R.. Usefulness of immunotherapy in patients with severe summer hay fever uncontrolled by antiallergic drugs. BMJ (Clinical research ed.) 1991;302(6771):265-269. [DOI:]

Walker 2001

Walker,S. M.; Pajno,G. B.; Lima,M. T.; Wilson,D. R.; Durham,S. R.. Grass pollen immunotherapy for seasonal rhinitis and asthma: a randomized, controlled trial. The Journal of allergy and clinical immunology 2001;107(1):87-93. [DOI: S0091-6749(01)12649-7 [pii]]

Excluded studies

Amar 2009

Amar,S. M.; Harbeck,R. J.; Sills,M.; Silveira,L. J.; O'Brien,H.; Nelson,H. S.. Response to sublingual immunotherapy with grass pollen extract: Monotherapy versus combination in a multiallergen extract.. Journal of Allergy and Clinical Immunology 2009;124(1):150-156.e5. [DOI: http://dx.doi.org/10.1016/j.jaci.2009.04.037]

Andre 2003

Andre,C.; Perrin-Fayolle,M.; Grosclaude,M.; Couturier,P.; Basset,D.; Cornillon,J.; Piperno,D.; Girodet,B.; Sanchez,R.; Vallon,C.; Bellier,P.; Nasr,M.. A double-blind placebo-controlled evaluation of sublingual immunotherapy with a standardized ragweed extract in patients with seasonal rhinitis: Evidence for a dose-response relationship.. International archives of allergy and immunology 2003;131(2):111-118. [DOI: http://dx.doi.org/10.1159/000070926]

Ariano 2001

Ariano,R.; Spadolini,I.; Panzani,R. C.. Efficacy of sublingual specific immunotherapy in Cupressaceae allergy using an extract of Cupressus arizonica. A double blind study. Allergologia et Immunopathologia 2001;29(6):238-244. [DOI: 13024390 [pii]]

Balda 1998

Balda,B. R.; Wolf,H.; Baumgarten,C.; Klimek,L.; Rasp,G.; Kunkel,G.; Muller,S.; Mann,W.; Hauswald,B.; Heppt,W.; Przybilla,B.; Amon,U.; Bischoff,R.; Becher,G.; Hummel,S.; Frosch,P. J.; Rustemeyer,T.; Jager,L.; Brehler,R.; Luger,T.; Schnitker,J.. Tree-pollen allergy is efficiently treated by short-term immunotherapy (STI) with seven preseasonal injections of molecular standardized allergens. Allergy 1998;53(8):740-748. [DOI:]

Bodtger 2002

Bodtger,U.; Poulsen,L. K.; Jacobi,H. H.; Malling,H. J.. The safety and efficacy of subcutaneous birch pollen immunotherapy - a one-year, randomised, double-blind, placebo-controlled study. Allergy 2002;57(4):297-305. [DOI: 1o3532 [pii]]

Bousquet 1990

Bousquet,J.; Hejjaoui,A.; Soussana,M.; Michel,F. B.. Double-blind, placebo-controlled immunotherapy with mixed grass-pollen allergoids. IV. Comparison of the safety and efficacy of two dosages of a high-molecular-weight allergoid. The Journal of allergy and clinical immunology 1990;85(2):490-497. [DOI: 0091-6749(90)90160-6 [pii]]

Bowen 2004

Bowen,T.; Greenbaum,J.; Charbonneau,Y.; Hebert,J.; Filderman,R.; Sussman,G.; Del Carpio,J.; Gold,M.; Keith,P.; Moote,W.; Cecchetto,S.; Cecchetto,O.; Sharp,D.; Broutin,O.; Andre,C.. Canadian trial of sublingual swallow immunotherapy for ragweed rhinoconjunctivitis. Annals of Allergy, Asthma & Immunology : Official Publication of the American College of Allergy, Asthma, & Immunology 2004;93(5):425-430. [DOI: S1081-1206(10)61408-1 [pii]]

Brewczynski 1999

Brewczynski,P. Z.; Kroon,A. M.. Efficacy and safety of immunotherapy with modified grasspollen allergens. Results of a placebo-controlled study.. Allergologie 1999;22(7):411-420. [DOI:]

Bufe 2004

Bufe,A.; Ziegler-Kirbach,E.; Stoeckmann,E.; Heidemann,P.; Gehlhar,K.; Holland-Letz,T.; Braun,W.. Efficacy of sublingual swallow immunotherapy in children with severe grass pollen allergic symptoms: a double-blind placebo-controlled study. Allergy 2004;59(5):498-504. [DOI: 10.1111/j.1398-9995.2004.00457.x [doi]]

Casanovas 1994

Casanovas,M.; Guerra,F.; Moreno,C.; Miguel,R.; Maranon,F.; Daza,J. C.. Double-blind, placebo-controlled clinical trial of preseasonal treatment with allergenic extracts of Olea europaea pollen administered sublingually. Journal of investigational allergology & clinical immunology 1994;4(6):305-314. [DOI:]

Charpin 2007

Charpin,D.; Gouitaa,M.; Dron-Gonzalvez,M.; Fardeau,M. F.; Massabie-Bouchat,Y. P.; Hugues,B.; Fabre,C.; Vivinus,S.; Pegliasco,H.; Andre,C.. Immunotherapy with an aluminum hydroxide-adsorbed Juniperus ashei foreign pollen extract in seasonal indigenous cypress pollen rhinoconjunctivitis: A double-blind, placebo-controlled study.. International archives of allergy and immunology 2007;143(2):83-91. [DOI: http://dx.doi.org/10.1159/000098656]

Corrigan 2005

Corrigan,C. J.; Kettner,J.; Doemer,C.; Cromwell,O.; Narkus,A.; Study,Group. Efficacy and safety of preseasonal-specific immunotherapy with an aluminium-adsorbed six-grass pollen allergoid.. Allergy 2005;60(6):801-807. [DOI: ALL790 [pii]]

Cortellini 2010

Cortellini,G.; Spadolini,I.; Patella,V.; Fabbri,E.; Santucci,A.; Severino,M.; Corvetta,A.; Canonica,G. W.; Passalacqua,G.. Sublingual immunotherapy for Alternaria-induced allergic rhinitis: a randomized placebo-controlled trial.. Annals of Allergy, Asthma, & Immunology 2010;105(5):382-386. [DOI: http://dx.doi.org/10.1016/j.anai.2010.08.007]

Didier 2007

Didier,A.; Malling,H. J.; Worm,M.; Horak,F.; Jager,S.; Montagut,A.; Andre,C.; de Beaumont,O.; Melac,M.. Optimal dose, efficacy, and safety of once-daily sublingual immunotherapy with a 5-grass pollen tablet for seasonal allergic rhinitis. The Journal of allergy and clinical immunology 2007;120(6):1338-1345. [DOI: S0091-6749(07)01447-9 [pii]]

DiRienzo 2006

Di Rienzo,V.; Pucci,S.; D'Alo,S.; Di Cara,G.; Incorvaia,C.; Frati,F.; Romano,A.. Effects of high-dose sublingual immunotherapy on quality of life in patients with cypress-induced rhinitis: A placebo-controlled study.. Clinical and Experimental Allergy Reviews 2006;6(3):67-70. [DOI: http://dx.doi.org/10.1111/j.1365-2222.2005.00102.x]

Drachenberg 2001

Drachenberg,K. J.; Pfeiffer,P.; Urban,E.. Sublingual immunotherapy - Results from a multi-centre, randomised, double-blind, placebo-controlled study with a standardised birch and grass/rye pollen extract.. Allergologie 2001;24(11):525-534. [DOI:]

Drachenberg 2001a

Drachenberg,K. J.; Wheeler,A. W.; Stuebner,P.; Horak,F.. A well-tolerated grass pollen-specific allergy vaccine containing a novel adjuvant, monophosphoryl lipid A, reduces allergic symptoms after only four preseasonal injections. Allergy 2001;56(6):498-505. [DOI: all030 [pii]]

Durham 2010

Durham,S. R.; Emminger,W.; Kapp,A.; Colombo,G.; de Monchy,J. G.; Rak,S.; Scadding,G. K.; Andersen,J. S.; Riis,B.; Dahl,R.. Long-term clinical efficacy in grass pollen-induced rhinoconjunctivitis after treatment with SQ-standardized grass allergy immunotherapy tablet. The Journal of allergy and clinical immunology 2010;125(1):131-8.e1-7. [DOI: 10.1016/j.jaci.2009.10.035 [doi]]

Feliziani 1995

Feliziani,V.; Lattuada,G.; Parmiani,S.; Dall'Aglio,P. P.. Safety and efficacy of sublingual rush immunotherapy with grass allergen extracts. A double blind study. Allergologia et Immunopathologia 1995;23(5):224-230. [DOI:]

Ferrer 2005

Ferrer,M.; Burches,E.; Pelaez,A.; Munoz,A.; Hernandez,D.; Basomba,A.; Enrique,E.; Alonso,R.; Cistero-Bahima,A.; Martin,S.; Rico,P.; Gandarias,B.. Double-blind, placebo-controlled study of immunotherapy with Parietaria judaica: clinical efficacy and tolerance. Journal of investigational allergology & clinical immunology 2005;15(4):283-292. [DOI:]

Hordijk 1998

Hordijk,G. J.; Antvelink,J. B.; Luwema,R. A.. Sublingual immunotherapy with a standardised grass pollen extract; a double-blind placebo-controlled study. Allergologia et Immunopathologia 1998;26(5):234-240. [DOI:]

Jutel 2005

Jutel,M.; Jaeger,L.; Suck,R.; Meyer,H.; Fiebig,H.; Cromwell,O.. Allergen-specific immunotherapy with recombinant grass pollen allergens. The Journal of allergy and clinical immunology 2005;116(3):608-613. [DOI: S0091-6749(05)01486-7 [pii]]

Kuna 2011

Kuna,P.; Kaczmarek,J.; Kupczyk,M.. Efficacy and safety of immunotherapy for allergies to Alternaria alternata in children.. Journal of Allergy & Clinical Immunology 2011;127(2):502-508.e1-6. [DOI: http://dx.doi.org/10.1016/j.jaci.2010.11.036]

LaRosa 1999

La Rosa,M.; Ranno,C.; Andre,C.; Carat,F.; Tosca,M. A.; Canonica,G. W.. Double-blind placebo-controlled evaluation of sublingual-swallow immunotherapy with standardized Parietaria judaica extract in children with allergic rhinoconjunctivitis. The Journal of allergy and clinical immunology 1999;104(2 Pt 1):425-432. [DOI: S0091674999004674 [pii]]

Lima 2002

Lima,M. T.; Wilson,D.; Pitkin,L.; Roberts,A.; Nouri-Aria,K.; Jacobson,M.; Walker,S.; Durham,S.. Grass pollen sublingual immunotherapy for seasonal rhinoconjunctivitis: a randomized controlled trial. Clinical and experimental allergy : journal of the British Society for Allergy and Clinical Immunology 2002;32(4):507-514. [DOI: 1327 [pii]]

Ortolani 1984

Ortolani,C.; Pastorello,E.; Moss,R. B.; Hsu,Y. P.; Restuccia,M.; Joppolo,G.; Miadonna,A.; Cornelli,U.; Halpern,G.; Zanussi,C.. Grass pollen immunotherapy: a single year double-blind, placebo-controlled study in patients with grass pollen-induced asthma and rhinitis. The Journal of allergy and clinical immunology 1984;73(2):283-290. [DOI:]

Ortolani 1994

Ortolani,C.; Pastorello,E. A.; Incorvaia,C.; Ispano,M.; Farioli,L.; Zara,C.; Pravettoni,V.; Zanussi,C.. A double-blind, placebo-controlled study of immunotherapy with an alginate-conjugated extract of Parietaria judaica in patients with Parietaria hay fever. Allergy 1994;49(1):13-21. [DOI:]

Ott 2009

Ott,H.; Sieber,J.; Brehler,R.; Folster-Holst,R.; Kapp,A.; Klimek,L.; Pfaar,O.; Merk,H.. Efficacy of grass pollen sublingual immunotherapy for three consecutive seasons and after cessation of treatment: The ECRIT study.. Allergy: European Journal of Allergy and Clinical Immunology 2009;64(9):1394-1401. [DOI: http://dx.doi.org/10.1111/j.1398-9995.2009.02194.x]

Palma Carlos 2006

Palma-Carlos,A. G.; Santos,A. S.; Branco-Ferreira,M.; Pregal,A. L.; Palma-Carlos,M. L.; Bruno,M. E.; Falagiani,P.; Riva,G.. Clinical efficacy and safety of preseasonal sublingual immunotherapy with grass pollen carbamylated allergoid in rhinitic patients. A double-blind, placebo-controlled study. Allergologia et Immunopathologia 2006;34(5):194-198. [DOI: 13094026 [pii]]

Panzner 2008

Panzner,P.; Petras,M.; Sykora,T.; Lesna,I.. Double-blind, placebo-controlled evaluation of grass pollen specific immunotherapy with oral drops administered sublingually or supralingually.. Respiratory medicine 2008;102(9):1296-1304. [DOI: http://dx.doi.org/10.1016/j.rmed.2008.03.024]

Passalacqua 1999

Passalacqua,G.; Albano,M.; Riccio,A.; Fregonese,L.; Puccinelli,P.; Parmiani,S.; Canonica,G. W.. Clinical and immunologic effects of a rush sublingual immunotherapy to Parietaria species: A double-blind, placebo-controlled trial. The Journal of allergy and clinical immunology 1999;104(5):964-968. [DOI: S0091674999006302 [pii]]

Pauli 2008

Pauli,G.; Larsen,T. H.; Rak,S.; Horak,F.; Pastorello,E.; Valenta,R.; Purohit,A.; Arvidsson,M.; Kavina,A.; Schroeder,J. W.; Mothes,N.; Spitzauer,S.; Montagut,A.; Galvain,S.; Melac,M.; Andre,C.; Poulsen,L. K.; Malling,H. J.. Efficacy of recombinant birch pollen vaccine for the treatment of birch-allergic rhinoconjunctivitis. The Journal of allergy and clinical immunology 2008;122(5):951-960. [DOI: 10.1016/j.jaci.2008.09.017 [doi]]

Peter 2009

Peter,R.; Kleinjans,H.; Hecker,H.. Significant increase in IgG(4) levels after slit grass treatment. A double-blind, placebo-controlled, multi-center study (TWIN grasses study).. Allergy: European Journal of Allergy and Clinical Immunology 2009;64(Journal Article):352-353. [DOI: http://dx.doi.org/10.1111/j.1398-9995.2009.02076.x]

Pfaar 2008

Pfaar,O.; Klimek,L.. Efficacy and safety of specific immunotherapy with a high-dose sublingual grass pollen preparation: a double-blind, placebo-controlled trial. Annals of Allergy, Asthma & Immunology : Official Publication of the American College of Allergy, Asthma, & Immunology 2008;100(3):256-263. [DOI:]

Pradalier 1999

Pradalier,A.; Basset,D.; Claudel,A.; Couturier,P.; Wessel,F.; Galvain,S.; Andre,C.. Sublingual-swallow immunotherapy (SLIT) with a standardized five-grass-pollen extract (drops and sublingual tablets) versus placebo in seasonal rhinitis. Allergy 1999;54(8):819-828. [DOI:]

Purello D'Ambrosio 1999

Purello-D'Ambrosio,F.; Gangemi,S.; Isola,S.; La Motta,N.; Puccinelli,P.; Parmiani,S.; Savi,E.; Ricciardi,L.. Sublingual immunotherapy: a double-blind, placebo-controlled trial with Parietaria judaica extract standardized in mass units in patients with rhinoconjunctivitis, asthma, or both. Allergy 1999;54(9):968-973. [DOI:]

Roder 2007

Roder,E.; Berger,M. Y.; Hop,W. C.; Bernsen,R. M.; de Groot,H.; Gerth van Wijk,R.. Sublingual immunotherapy with grass pollen is not effective in symptomatic youngsters in primary care. The Journal of allergy and clinical immunology 2007;119(4):892-898. [DOI: S0091-6749(07)00003-6 [pii]]

Rolinck Werninghaus 2004

Rolinck-Werninghaus,C.; Wolf,H.; Liebke,C.; Baars,J. C.; Lange,J.; Kopp,M. V.; Hammermann,J.; Leupold,W.; Bartels,P.; Gruebl,A.; Bauer,C. P.; Schnitker,J.; Wahn,U.; Niggemann,B.. A prospective, randomized, double-blind, placebo-controlled multi-centre study on the efficacy and safety of sublingual immunotherapy (SLIT) in children with seasonal allergic rhinoconjunctivitis to grass pollen.. Allergy: European Journal of Allergy and Clinical Immunology 2004;59(12):1285-1293. [DOI: http://dx.doi.org/10.1111/j.1398-9995.2004.00627.x]

Skoner 2010

Skoner,D.; Gentile,D.; Bush,R.; Fasano,M. B.; McLaughlin,A.; Esch,R. E.. Sublingual immunotherapy in patients with allergic rhinoconjunctivitis caused by ragweed pollen.. Journal of Allergy and Clinical Immunology 2010;125(3):660-666.e4. [DOI: http://dx.doi.org/10.1016/j.jaci.2009.12.931]

Smith 2004

Smith,H.; White,P.; Annila,I.; Poole,J.; Andre,C.; Frew,A.. Randomized controlled trial of high-dose sublingual immunotherapy to treat seasonal allergic rhinitis. The Journal of allergy and clinical immunology 2004;114(4):831-837. [DOI: S0091674904022316 [pii]]

Troise 1995

Troise,C.; Voltolini,S.; Canessa,A.; Pecora,S.; Negrini,A. C.. Sublingual immunotherapy in Parietaria pollen-induced rhinitis: a double-blind study. Journal of investigational allergology & clinical immunology 1995;5(1):25-30. [DOI:]

Valovirta 2006

Valovirta,E.; Jacobsen,L.; Ljorring,C.; Koivikko,A.; Savolainen,J.. Clinical efficacy and safety of sublingual immunotherapy with tree pollen extract in children. Allergy 2006;61(10):1177-1183. [DOI: ALL1190 [pii]]

Vervloet 2007

Vervloet D. Birnbaum J. Laurent P. Hugues B. Fardeau M.F. Massabie-Bouchat Y.P. Aferiat-Derome A. Andre C. Safety and efficacy of Juniperus ashei sublingual-swallow ultra-rush pollen immunotherapy in cypress rhinoconjunctivitis: A double-blind, placebo-controlled study. International Archives of Allergy and Immunology 2007;142(3):239-246. [DOI: http://dx.doi.org/10.1159/000097026]

Voltolini 2001

Voltolini,S.; Modena,P.; Minale,P.; Bignardi,D.; Troise,C.; Puccinelli,P.; Parmiani,S.. Sublingual immunotherapy in tree pollen allergy. Double-blind, placebo-controlled study with a biologically standardised extract of three pollens (alder, birch and hazel) administered by a rush schedule. Allergologia et Immunopathologia 2001;29(4):103-110. [DOI: 13020603 [pii]]

Vourdas 1998

Vourdas,D.; Syrigou,E.; Potamianou,P.; Carat,F.; Batard,T.; Andre,C.; Papageorgiou,P. S.. Double-blind, placebo-controlled evaluation of sublingual immunotherapy with standardized olive pollen extract in pediatric patients with allergic rhinoconjunctivitis and mild asthma due to olive pollen sensitization. Allergy 1998;53(7):662-672. [DOI:]

Wahn 2009

Wahn,U.; Tabar,A.; Kuna,P.; Halken,S.; Montagut,A.; de Beaumont,O.; Le Gall,M.; SLIT Study Group. Efficacy and safety of 5-grass-pollen sublingual immunotherapy tablets in pediatric allergic rhinoconjunctivitis. The Journal of allergy and clinical immunology 2009;123(1):160-166.e3. [DOI: 10.1016/j.jaci.2008.10.009 [doi]]

Zenner 1997

Zenner,H. P.; Baumgarten,C.; Rasp,G.; Fuchs,T.; Kunkel,G.; Hauswald,B.; Ring,J.; Effendy,I.; Behrendt,W.; Frosch,P. J.; Przybilla,B.; Brunner,F. X.; Merk,H. F.; Kapp,A.; Schnitker,J.; Wolf,H.. Short-term immunotherapy: a prospective, randomized, double-blind, placebo-controlled multicenter study of molecular standardized grass and rye allergens in patients with grass pollen-induced allergic rhinitis. The Journal of allergy and clinical immunology 1997;100(1):23-29. [DOI: S0091674997001796 [pii]]

Data and analyses

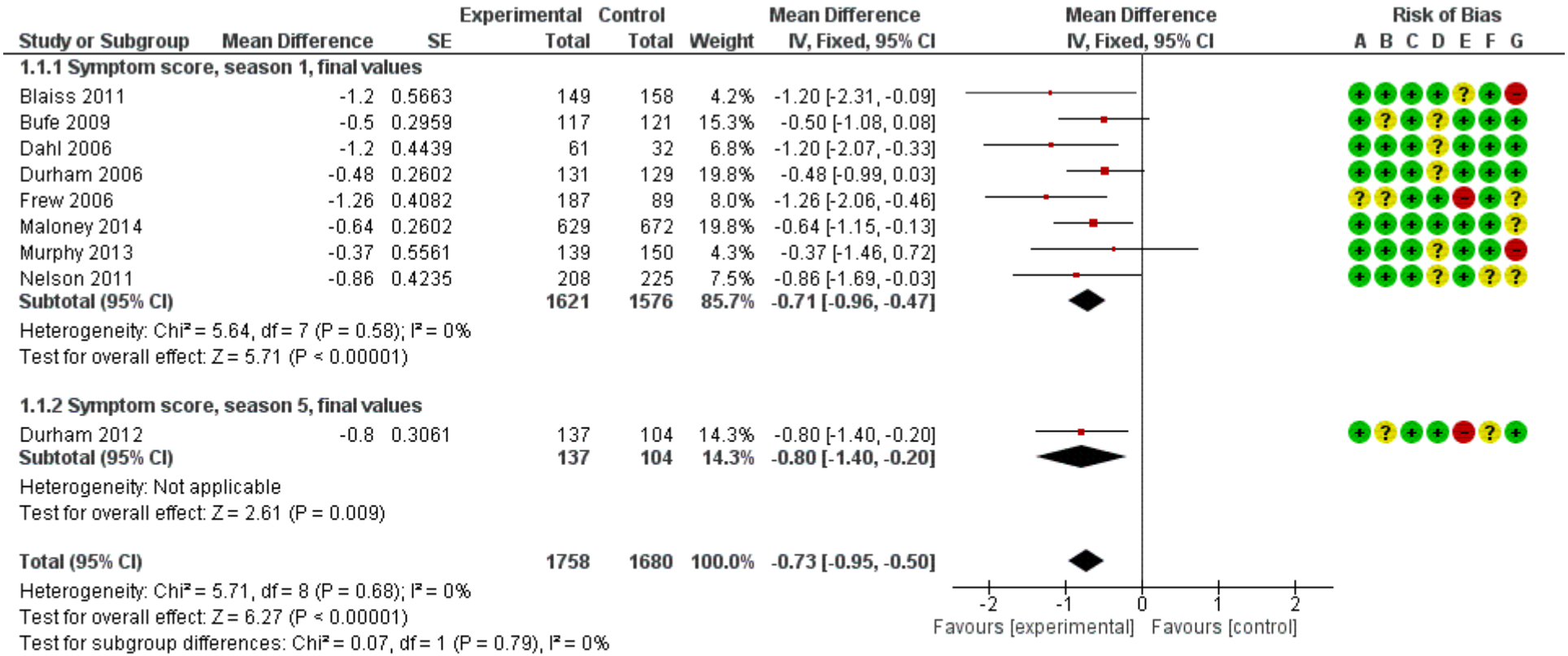
1 Intervention vs Placebo

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
1.1 Symptomscore (Symptom score) (1/2)	9	3438	Mean Difference (IV, Fixed, 95% CI)	-0.73 [-0.95, -0.50]
1.1.1 Symptom score, season 1, final values	8	3197	Mean Difference (IV, Fixed, 95% CI)	-0.71 [-0.96, -0.47]
1.1.2 Symptom score, season 5, final values	1	241	Mean Difference (IV, Fixed, 95% CI)	-0.80 [-1.40, -0.20]
1.2 Symptomscore (Symptom score) (2/2)	1	44	Mean Difference (IV, Fixed, 95% CI)	-109.00 [-1298.45, 1080.45]

1.3 Medicin score, season 1 (medication score)	9	3438	Mean Difference (IV, Fixed, 95% CI)	-0.56 [-0.78, -0.33]
1.3.1 Medicin score, season 1, final value	8	3197	Mean Difference (IV, Fixed, 95% CI)	-0.55 [-0.79, -0.31]
1.3.2 Medicin score, season 5, final value	1	241	Mean Difference (IV, Fixed, 95% CI)	-0.60 [-1.40, 0.20]
1.4 Medicin score, season 2 (medication score)	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.4.1 Medication score, season 2, final values	1	44	Mean Difference (IV, Fixed, 95% CI)	-1494.00 [-2763.86, -224.14]
1.5 Livskvalitet (Quality of life) (RQLQ)	6	2257	Mean Difference (IV, Random, 95% CI)	-0.29 [-0.48, -0.10]
1.5.1 Quality of life, season 2, final values	1	44	Mean Difference (IV, Random, 95% CI)	-0.50 [-1.48, 0.48]
1.5.2 Quality of life, season 1, final values	5	2213	Mean Difference (IV, Random, 95% CI)	-0.28 [-0.49, -0.08]
1.6 Anafylaksi (Anaphylaxia)	12		Risk Ratio (IV, Random, 95% CI)	Subtotals only
1.6.1 Anaphylaxis, within first to third year of treatment, follow up values	12	3857	Risk Ratio (IV, Random, 95% CI)	4.48 [1.15, 17.47]
1.7 Symptomscore- mellemregninger	8	1940	Mean Difference (IV, Random, 95% CI)	-0.74 [-1.01, -0.46]
1.7.1 Symptom score, season 2, follow up values	1	44	Mean Difference (IV, Random, 95% CI)	-109.00 [-1298.45, 1080.45]
1.7.2 Symptom score, season 1, follow up values	7	1896	Mean Difference (IV, Random, 95% CI)	-0.74 [-1.01, -0.46]
1.8 Medicin score - mellemregning	7	1896	Mean Difference (IV, Random, 95% CI)	-0.57 [-0.83, -0.30]
1.8.2 Medication score, season 1, follow up values	7	1896	Mean Difference (IV, Random, 95% CI)	-0.57 [-0.83, -0.30]
1.9 RQLQ - mellemregning	5	1261	Mean Difference (IV, Random, 95% CI)	-0.36 [-0.61, -0.11]
1.9.2 Quality of life, season 2, follow up values	1	44	Mean Difference (IV, Random, 95% CI)	-0.50 [-1.48, 0.48]
1.9.3 Quality of life, season 1, follow up values	4	1217	Mean Difference (IV, Random, 95% CI)	-0.36 [-0.63, -0.08]

Figures

Figure 1 (Analysis 1.1)

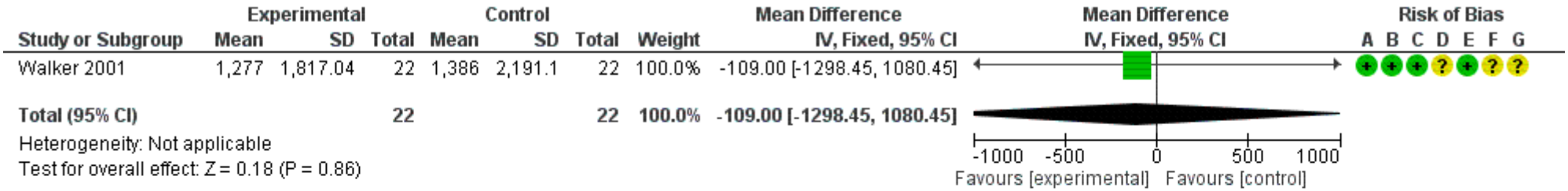


Risk of bias legend

(**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

Forest plot of comparison: 1 Intervention vs Placebo, outcome: 1.1 Symptomscore (Symptom score) (1/2).

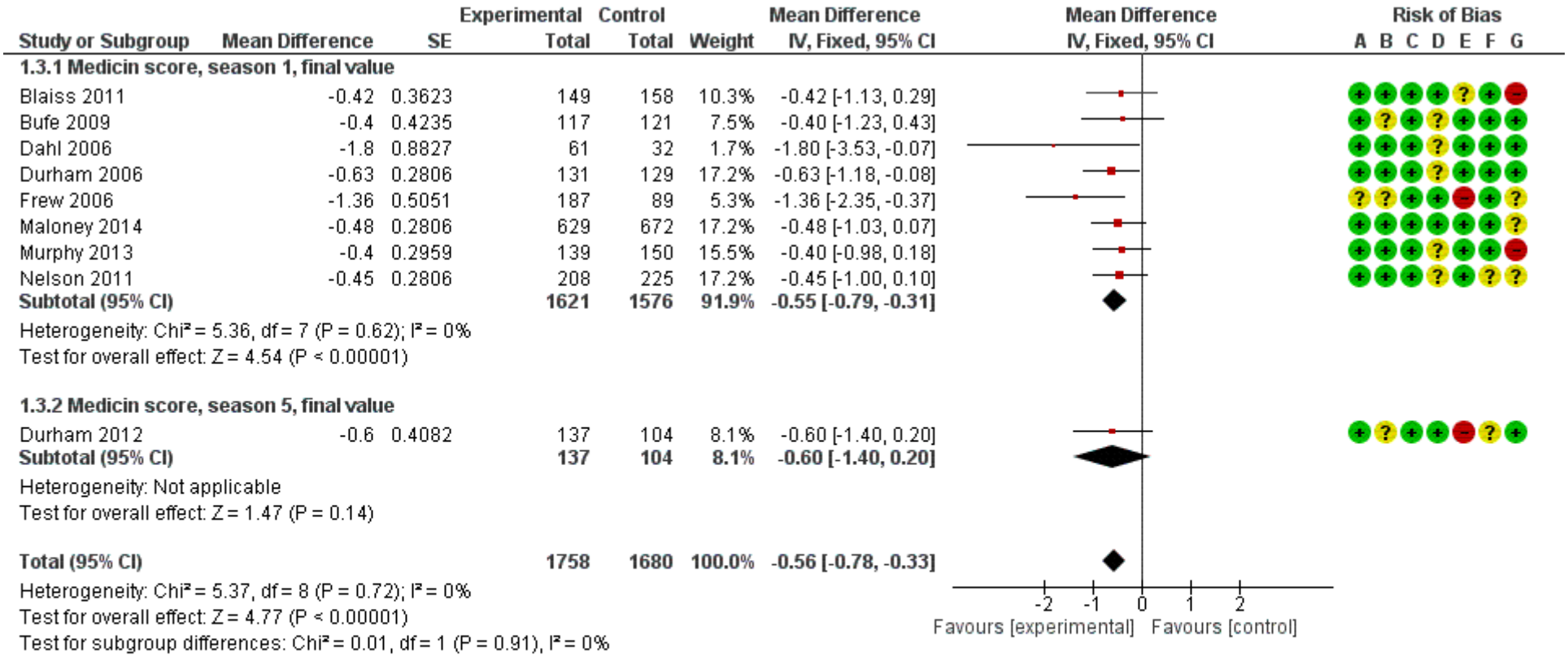
Figure 2 (Analysis 1.2)



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

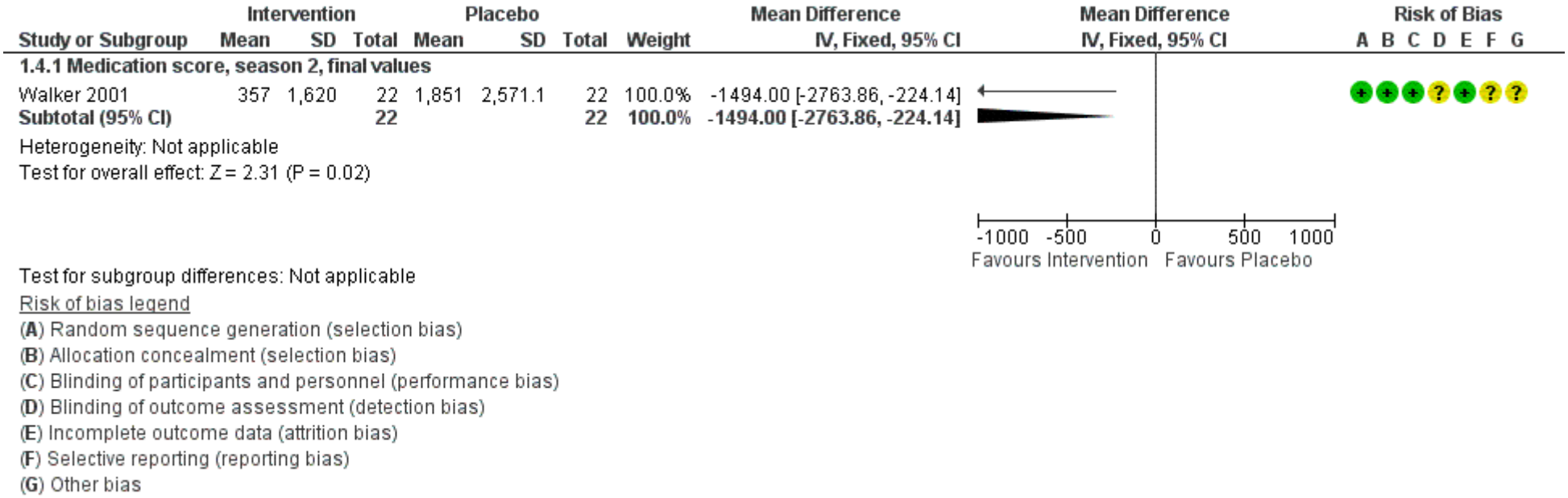
Forest plot of comparison: 1 Intervention vs Placebo, outcome: 1.2 Symptomscore (Symptom score) (2/2).

Figure 3 (Analysis 1.3)



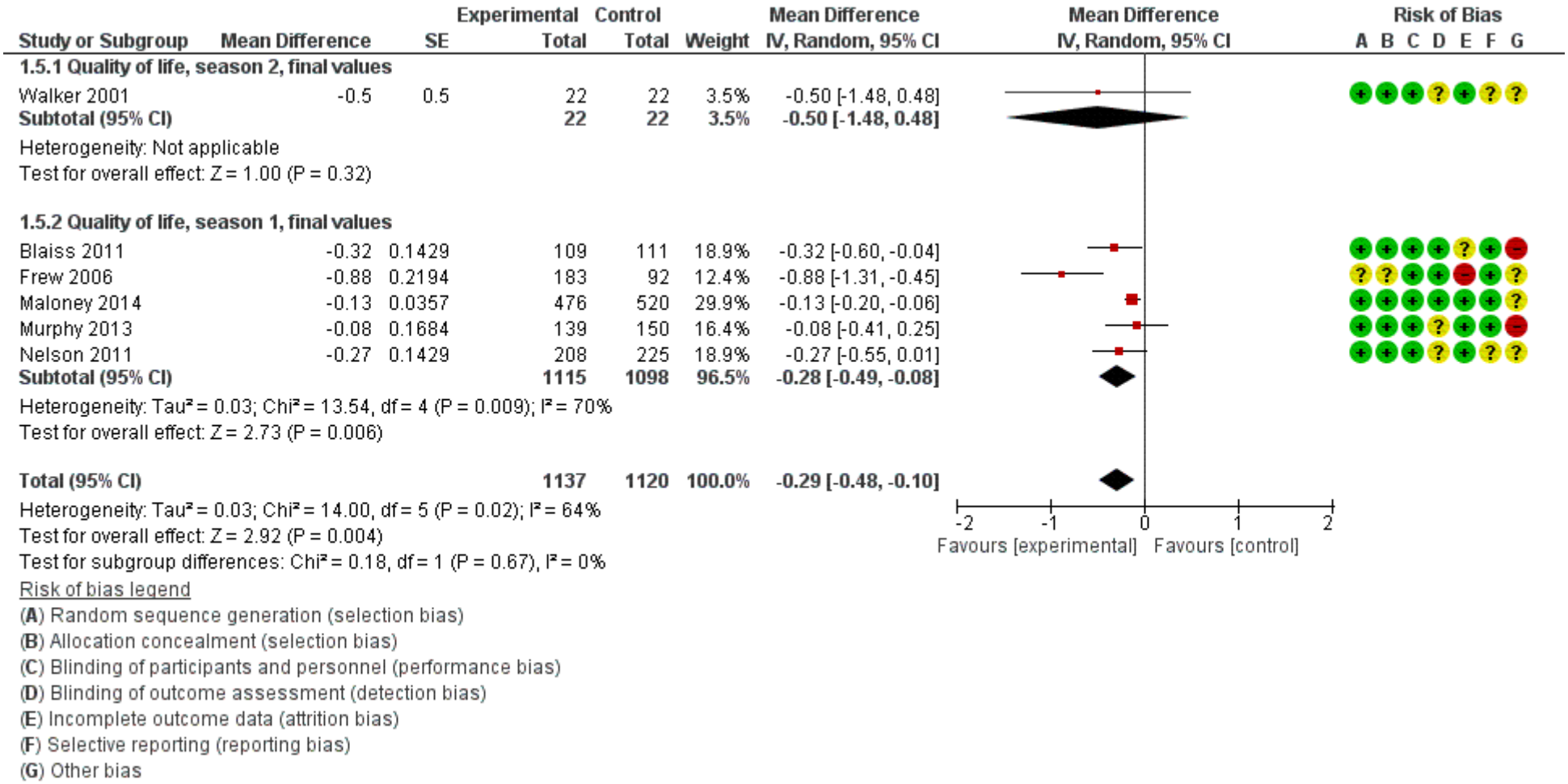
Forest plot of comparison: 1 Intervention vs Placebo, outcome: 1.3 Medicin score, season 1 (medication score).

Figure 4 (Analysis 1.4)



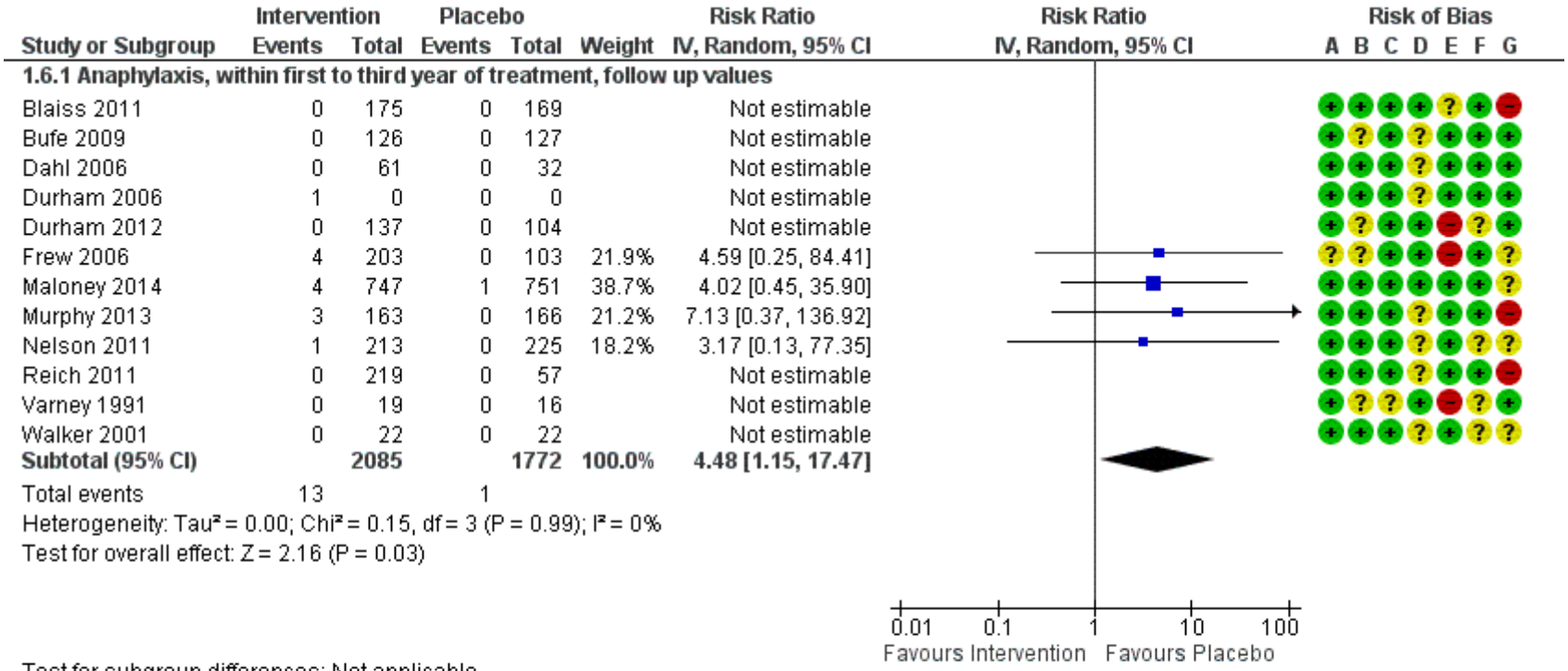
Forest plot of comparison: 1 Intervention vs Placebo, outcome: 1.4 Medicin score, season 2 (medication score).

Figure 5 (Analysis 1.5)



Forest plot of comparison: 1 Intervention vs Placebo, outcome: 1.5 Livskvalitet (Quality of life) (RQLQ).

Figure 6 (Analysis 1.6)



Test for subgroup differences: Not applicable

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

Forest plot of comparison: 1 Intervention vs Placebo, outcome: 1.6 Anafylaksi (Anaphylaxia).