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Workplace interventions for treatment of occupational asthma (Review)

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[Intervention Review]

Workplace interventions for treatment of occupational asthma

Paul K Henneberger[1], Jenil R Patel[2,3], Gerda J de Groene[4], Jeremy Beach[5], Susan M Tarlo[6], Teake M Pal[4], Stefania Curti[7]

[1]Respiratory Health Division, National Institute for Occupational Safety and Health, Morgantown, West Virginia, USA. [2]Department of Epidemiology, Human Genetics and Environmental Sciences, University of Texas School of Public Health, Houston, Texas, USA. [3]Department of Epidemiology, University of Arkansas for Medical Sciences, Little Rock, Arkansas, USA. [4]Netherlands Center of Occupational Diseases, Coronel Institute of Occupational Health, Academic Medical Center, Amsterdam, Netherlands. [5]Department of Medicine, University of Alberta, Edmonton, Canada. [6]Department of Medicine, and Dalla Lana School of Public Health, University of Toronto, Toronto, Canada. [7]Department of Medical and Surgical Sciences, University of Bologna, Bologna, Italy

Contact address: Paul K Henneberger, Respiratory Health Division, National Institute for Occupational Safety and Health, 1095 Willowdale Road, Morgantown, West Virginia, 26505, USA. pkh0@cdc.gov.

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ABSTRACT

Background

The impact of workplace interventions on the outcome of occupational asthma is not well understood.

Objectives

To evaluate the effectiveness of workplace interventions on occupational asthma.

Search methods

We searched the Cochrane Central Register of Controlled Trials (CENTRAL); MEDLINE (PubMed); EMBASE(Ovid); NIOSHTIC-2; and CISILO (CCOHS) up to July 31, 2019.

Selection criteria

We included all eligible randomized controlled trials, controlled before and after studies and interrupted time-series of workplace interventions for occupational asthma.

Data collection and analysis

Two authors independently assessed study eligibility and risk of bias, and extracted data.

Main results

We included 26 non-randomized controlled before and after studies with 1,695 participants that reported on three comparisons: complete removal from exposure and reduced exposure compared to continued exposure, and complete removal from exposure compared to reduced exposure. Reduction of exposure was achieved by limiting use of the agent, improving ventilation, or using protective equipment in the same job; by changing to another job with intermittent exposure; or by implementing education programs. For continued exposure, 56 per 1000 workers reported absence of symptoms at follow-up, the decrease in forced expiratory volume in one second as a percentage of a reference value (FEV1 %) was 5.4% during follow-up, and the standardized change in non-specific bronchial hyperreactivity (NSBH) was -0.18.

In 18 studies, authors compared removal from exposure to continued exposure. Removal may increase the likelihood of reporting absence of asthma symptoms, with risk ratio (RR) 4.80 (95% confidence interval (CI) 1.67 to 13.86), and it may improve asthma symptoms, with RR 2.47 (95% CI 1.26 to 4.84), compared to continued exposure. Change in FEV1 % may be better with removal from exposure, with a mean difference (MD) of 4.23 % (95% CI 1.14 to 7.31) compared to continued exposure. NSBH may improve with removal from exposure, with standardized mean difference (SMD) 0.43 (95% CI 0.03 to 0.82).

In seven studies, authors compared reduction of exposure to continued exposure. Reduction of exposure may increase the likelihood of reporting absence of symptoms, with RR 2.65 (95% CI 1.24 to 5.68). There may be no considerable difference in FEV1 % between reduction and continued exposure, with MD 2.76 % (95% CI -1.53 to 7.04) . No studies reported or enabled calculation of change in NSBH.

In ten studies, authors compared removal from exposure to reduction of exposure. Following removal from exposure there may be no increase in the likelihood of reporting absence of symptoms, with RR 6.05 (95% CI 0.86 to 42.34), and improvement in symptoms, with RR 1.11 (95% CI 0.84 to 1.47), as well as no considerable change in FEV1 %, with MD 2.58 % (95% CI −3.02 to 8.17). However, with all three outcomes, there may be improved results for removal from exposure in the subset of patients exposed to low molecular weight agents. No studies reported or enabled calculation of change in NSBH.

In two studies, authors reported that the risk of unemployment after removal from exposure may increase compared with reduction of exposure, with RR 14.28 (95% CI 2.06 to 99.16). Four studies reported a decrease in income of 20% to 50% after removal from exposure.

The quality of the evidence is very low for all outcomes.

Authors' conclusions

Both removal from exposure and reduction of exposure may improve asthma symptoms compared with continued exposure. Removal from exposure, but not reduction of exposure, may improve lung function compared to continued exposure. When we compared removal from exposure directly to reduction of exposure, the former may improve symptoms and lung function more among patients exposed to low molecular weight agents. Removal from exposure may also increase the risk of unemployment. Care providers should balance the potential clinical benefits of removal from exposure or reduction of exposure with potential detrimental effects of unemployment. Additional high-quality studies are needed to evaluate the effectiveness of workplace interventions for occupational asthma.

PLAIN LANGUAGE SUMMARY

Workplace interventions to deal with occupational asthma

Clinicians and researchers have proposed several changes in workplaces to improve the status of workers who have occupational asthma, which is asthma whose onset is caused by occupational exposures. These workplace changes are also called interventions, and for occupational asthma include early removal from exposure and reduction of exposure. However, the actual benefits of these interventions are still unclear.

What is the aim of this review?

To determine the effectiveness of workplace interventions for the treatment of occupational asthma.

Key messages

We conducted a systematic review of workplace interventions for treating occupational asthma. Asthma symptoms and lung function may improve when persons with occupational asthma are removed from exposure, usually by ending their job, compared to continued exposure on the same job. Asthma symptoms but not lung function may improve after reducing exposure, for example by training and education, compared to continued exposure. Removal from exposure may improve symptoms and lung function more than exposure reduction among workers exposed to low molecular weight agents, but removal from exposure may also increase the risk of unemployment. All evidence was of very low quality and therefore there is a need for better studies to investigate the effectiveness of workplace interventions for occupational asthma.

What was studied in the review?

The review is based on 26 studies that included 1,695 participants with occupational asthma. Sensitizers caused nearly all cases. We focused on the interventions of removal from exposure and reduction of exposure, which were compared with continued exposure. Outcomes were changes in asthma symptoms, lung function, and non-specific bronchial hyperreactivity between baseline and follow-up.

What are the main results of the review?

Both removal from exposure and reduction of exposure may improve asthma symptoms when compared to continued exposure. Removal from exposure, but not reduction of exposure, may improve lung function when compared to continued exposure. Removal from exposure may improve symptoms and lung function more than reduction of exposure among patients exposed to low molecular weight agents, but

removal may also increase the risk of unemployment. Consequently, the benefit of a better improvement has to be weighed against the potential for a higher risk of job loss.

Further research is needed to determine the effectiveness of interventions at reducing the impact of occupational asthma.

How up-to-date is this review?

We searched for studies that had been published through 31July 2019.

Summary of findings for the main comparison. Removal from exposure compared to continued exposure for treatment of occupational asthma

Removal from exposure compared to continued exposure in workers with occupational asthma

Patient or population: workers with occupational asthma
Setting: various occupations and industries
Intervention: removal from exposure
Comparison: continued exposure

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with continued exposure	Risk with Removal from exposure				
Absence of asthma symptoms; mean follow-up time 4.2 years	56 per 1,000	269 per 1,000 (94 to 776)	RR 4.80 (1.67 to 13.86)	641 (9 observational studies)	⊕⊖⊖⊖ VERY LOW [1 2 3]	
Improvement of asthma symptoms; mean follow-up time 4.8 years	142 per 1,000	351 per 1,000 (179 to 688)	RR 2.47 (1.26 to 4.84)	435 (9 observational studies)	⊕⊖⊖⊖ VERY LOW [1 2 3]	
Change in FEV1 % predicted: follow-up minus baseline values; mean follow-up time 4.3 years	The mean change in FEV1 % predicted: follow-up minus baseline values was -5.4 %	MD 4.23 % points higher (1.14 higher to 7.14 higher)	-	898 (10 observational studies)	⊕⊖⊖⊖ VERY LOW [1 2 3]	
Change in NSBH: follow-up minus baseline values; mean follow-up time 3.5 years	The standardized mean change in NSBH: follow-up minus baseline values was -0.18	SMD 0.43 higher (0.03 higher to 0.82 higher)	-	387 (6 observational studies)	⊕⊖⊖⊖ VERY LOW [1 2]	

*__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; **FEV1:** forced expiratory volume in one second; **MD**: mean difference; **SMD**: standardized mean difference

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

[1] Downgraded one level because of risk of bias due to selection of participants and because baseline differences were not adjusted for in most studies. No upgrading for large effect size.
[2] Downgraded one level because of high heterogeneity as indicated by I^2
[3] Downgraded one level because publication bias expected based on funnel plot

Summary of findings 2. Reduction of exposure compared to continued exposure for treatment of occupational asthma

Reduction of exposure compared to continued exposure in workers with occupational asthma

Patient or population: workers with occupational asthma
Setting: various occupations and industries
Intervention: reduction of exposure
Comparison: continued exposure

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with continued exposure	Risk with Reduction of exposure				
Absence of asthma symptoms; mean follow-up time 1.9 years	36 per 1,000	95 per 1,000 (45 to 205)	RR 2.65 (1.24 to 5.68)	334 (7 observational studies)	⊕⊖⊖⊖ VERY LOW [1 2]	
Improvement of asthma symptoms						Nos studies reported or enabled calculation of improvement of symptoms
Change in FEV1 % predicted: follow-up minus baseline values; mean follow-up time 2.1 years	The mean change in FEV1 % predicted: follow-up minus baseline values was -3.0 %	MD 2.76 % higher (1.53 lower to 7.04 higher)	-	224 (4 observational studies)	⊕⊖⊖⊖ VERY LOW [1 2]	
Change in NSBH: follow-up minus baseline values	-	-	-	-	-	No studies reported or enabled calculation of change in NSBH

***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; **FEV1:** forced expiratory volume in one second; **MD**: mean difference

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

[1] Downgraded one level because of risk of bias due to selection of participants and because baseline differences were not adjusted for in most studies. No upgrading for large effect size.
[2] Downgraded one level because of imprecision (fewer than 300 participants)

Summary of findings 3. Removal from exposure compared to reduction of exposure for treatment of occupational asthma

Removal from exposure compared to reduction of exposure in workers with occupational asthma

Patient or population: workers with occupational asthma
Setting: various occupations and industries
Intervention: removal from exposure
Comparison: reduction of exposure

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with reduction of exposure	Risk with Removal from exposure				
Absence of asthma symptoms; mean follow-up time	127 per 1000	770 per 1000 (109 to 1000)	RR 6.05 (0.86 to 42.34)	359 (6 observational studies)	⊕⊖⊖⊖ VERY LOW[1 2 3]	
Improvement of asthma symptoms; mean follow-up time 2.9 years	839 per 1,000	931 per 1,000 (705 to 1,000)	RR 1.11 (0.84 to 1.47)	140 (5 observational studies)	⊕⊖⊖⊖ VERY LOW[1 2 3]	
Change in FEV1 % predicted: follow-up minus baseline values; mean follow-up time 5.2 years	The mean change in FEV1 % predicted: follow-up minus baseline values was -0.6 %	MD 2.58 % higher (3.02 lower to 8.17 higher)	-	388 (7 observational studies)	⊕⊖⊖⊖ VERY LOW [1 2]	

Change in NSBH: follow-up minus baseline values	-	-	-	-	-	No studies reported or enabled calculation of change in NSBH
Being unemployed; mean follow-up time 3.5 years	36 per 1,000	510 per 1,000 (74 to 1,000)	RR 14.28 (2.06 to 99.16)	64 (2 observational studies)	⊕⊖⊖⊖ VERY LOW [1] [3]	

*__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; **FEV1:** forced expiratory volume in one second; **MD**: mean difference

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

[1] Downgraded one level because of risk of bias due to selection of participants and because baseline differences were not adjusted for in most studies.No upgrading for large effect size.
[2] Downgraded one level because of high heterogeneity as indicated by I^2
[3] Downgraded one level because of imprecision (i.e., fewer than 300 participants)

BACKGROUND

Description of the condition

Work-related asthma includes both occupational asthma that is caused by workplace exposures, and work-exacerbated asthma that is preexisting or concurrent asthma that is worsened by workplace exposures or conditions (Henneberger 2011). While a review of relevant literature concluded that 16.3% of adult-onset asthma cases are attributable to occupation (Toren 2009), this is likely an underestimate of the true frequency. For example, it appears that many physicians take inadequate occupational histories from their asthma patients and do not refer suspected cases to occupational medicine or pulmonary physicians for additional evaluation (Milton 1998; Shofer 2006). Occupational asthma agents include both sensitizers and irritants. Sensitizer-induced asthma is characterized by a distinct immunologic response, and can be the result of exposure to either high molecular weight (HMW) agents (e.g., animal or plant proteins) that typically cause release of specific IgE antibodies, or low molecular weight (LMW) agents (e.g., diisocyanates) that act through mechanisms that are less well understood (Tarlo 2014). Irritant-induced occupational asthma has typically been defined as having onset within 24 hours of a high-level exposure to respiratory irritants (e.g., chlorine gases), consistent with the definition of reactive airways dysfunction syndrome (RADS)(Brooks 1985). Another type of irritant-induced occupational asthma might be caused by chronic low- to moderate-level irritant exposures, but additional research is needed to clarify this etiology (Dumas 2016). Also, some agents have both sensitizing and irritant qualities such as various anhydrides, diisocyanates, glutaraldehyde, and welding fumes (Baur 2013). Occupational asthma agents number in the hundreds, with new ones continually being discovered. For example, a comprehensive review of the literature by Baur 2013 detected 372 different allergic causes and 184 different irritant causes of occupational asthma. The Association of Occupational and Environmental Clinics in the USA maintains an online list of work-related asthma agents that numbered 327 in 2015 (AOEC 2018; Rosenman 2015). A list of occupational asthma agents maintained by the Commission des normes, de l'équité, de la santé et de la sécurité du travail in the Canadian province of Quebec includes over 400 entries (CNESST 2018).

Consensus statements from professional medical organizations have emphasized the importance of considering the possibility of work-related asthma in any working adult with asthma, and using various objective tests to document the association of asthma with workplace exposures (Baur 2012; Moscato 2012;Tarlo 2008). Specific inhalation challenge (SIC) with the suspected workplace agent is considered the reference method for confirming a suspected case of occupational asthma (Vandenplas 2014). However, this test is rarely available worldwide outside of specialized centers in Europe and some provinces in Canada (Suojalehto 2014).

Occupational asthma can adversely affect the quality of life, employment status, and income of the patient. A national study of adults with asthma in the United States reported that cases with work-related asthma had worse health-related quality of life, being more likely to have physical and mental impairments, and activity limitations (Knoeller 2013). Also, follow-up studies of occupational asthma cases reported rates of prolonged unemployment ranging from 14% to 69% and of income loss ranging from 44% to 72% (Vandenplas 2008).

Description of the intervention

The most commonly recommended workplace interventions for managing occupational asthma are removal from exposure or reduction of exposure to the causal agents, in contrast to allowing the patient to work in circumstances with continued exposure. Cessation of exposure can be accomplished by eliminating the agent from the work environment with or without substituting another product. For example, healthcare and laboratory workers using non-latex gloves instead of natural rubber latex gloves has benefited occupational asthma cases sensitized to natural rubber latex (Tarlo 1994). Of course, this is impossible in settings where the responsible agent is essential to the functioning of the operation, as with flour exposure in a bakery. Another option is for the worker to leave the job with the harmful exposure by just quitting or transferring to an unexposed job with the same or a different employer. The follow-up of occupational asthma cases attributable to colophony, an ingredient of soldering fluxes, inks, and adhesives, determined that those who had left employment after diagnosis were less reactive to histamine (Burge 1982).

Reduction of exposure can be achieved by introducing or improving engineering controls like local exhaust ventilation or with respiratory personal protective equipment (PPE). Also, the worker with occupational asthma can potentially move to another job with less exposure, either with the same employer as their old job or with another employer entirely.

How the intervention might work

The purpose of workplace interventions for treating occupational asthma is to prevent or significantly reduce the inhalation of airborne substances that are harmful for people who suffer from asthma. This is achieved in workplaces by either completely removing the symptomatic worker from the workplace where the exposure occurs or by reducing the exposure (i.e., the cause of asthma) by limiting use of the causal agent or improving ventilation and use of protective equipment in the same job, changing to another job with intermittent exposure, and education programs.

During 2005 to 2012, four different professional societies or government agencies organized committees of experts that conducted systematic literature searches, assessed the quality of the evidence, and published recommendations for the diagnosis and management of occupational asthma (Baur 2012; Beach 2005; Newman Taylor 2004; Nicholson 2010; Nicholson 2012; Tarlo 2008). Each report addressed the value of cessation and reduction of exposure for the management of occupational asthma. All four reports recommended that once a case of occupational asthma is diagnosed, removal from exposure to the causal agents is the best option for improvement or prevention of deterioration of disease. The American College of Chest Physicians (ACCP) report noted that removal from exposure is especially important for patients with sensitizer-induced occupational asthma (Tarlo 2008). However, even removal from exposure does not ensure complete recovery (Baur 2012).

Reduction of exposure has received more qualified support than removal from exposure. The 2005 report by the USA Agency for Healthcare Research and Quality (AHRQ) did not reach firm conclusions about the value of reducing exposure because of insufficient evidence (Beach 2005). The ACCP panel advised reducing workplace exposures for irritant-induced asthma cases, and if that is not

successful, then changing to a workplace with fewer asthma triggers (Tarlo 2008). The committee organized by the British Occupational Health Research Foundation (BOHRF) concluded that transfer to a low-exposure work area may result in improvement or even resolution of symptoms, or prevent deterioration in some but not all workers (Newman Taylor 2004; Nicholson 2010). The European Respiratory Society (ERS) task force recommended that reduction of exposure is a second-choice option relative to complete avoidance of exposure and it should be combined with medical monitoring to provide timely identification if the worker's asthma worsens (Baur 2012). PPE as a method to reduce exposures received the least support. The BOHRF document concluded that an air fed helmet respirator might reduce symptoms for some cases who continue to be exposed (Newman Taylor 2004; Nicholson 2010). The ERS task force concluded that respiratory PPE is not a safe approach to limit exposures for occupational asthma cases, particularly not for long periods and for cases with severe asthma (Baur 2012).

Why it is important to do this review

This is an update of a Cochrane review by de Groene 2011. The authors concluded that occupational asthma cases removed from exposure are more likely to experience improvements in symptoms and pulmonary function than cases who continue to be exposed (de Groene 2011). Reduction of exposure was also associated with improved symptoms, but was less effective than complete removal. An important negative aspect of removal from exposure compared to reduction of exposure was an increased risk of unemployment. The authors of de Groene 2011 called for better studies to determine which approaches to exposure reduction yield the best results. Additional reports on workplace interventions for occupational asthma have been published since the 2011 Cochrane review and could potentially strengthen or challenge earlier conclusions.

OBJECTIVES

To evaluate the effectiveness of workplace interventions on occupational asthma.

METHODS

Criteria for considering studies for this review

Types of studies

We included randomized controlled trials (RCTs) that had individual person-directed interventions.

Exposure removal or reduction often occur at the group level, making it difficult to randomize at the individual level. Consequently, we also included controlled clinical trials (defined as inadequately randomized studies), controlled before and after (CBA) studies and interrupted time-series (ITS) (according to the criteria of the Cochrane Effective Practice and Organisation of Care (EPOC) Group) (EPOC).

The CBA studies we accepted included an intervention group and a concurrent comparison (or control) group and measured the outcome before and after the intervention in both groups.

We excluded case studies and case-control studies.

Types of participants

We included studies conducted with participants who were workers of all genders with asthma and a work-related pattern of symptoms, pulmonary function changes, immunological or inflammatory changes, and/or changes in airway hyperreactivity, such that occupational asthma was considered to be the most likely diagnosis by their treating physician. We excluded studies conducted with people who had work-exacerbated asthma. We accepted the following tests for determining a work-related pattern of changes: SIC, history and questionnaires, serial lung function testing, non-specific bronchial provocation testing, immunological testing, measures of airway inflammation and doctor's diagnosis of occupational asthma by a pulmonary physician or an occupational physician (Aasen 2013; Beach 2005; Chan-Yeung 1995; Nicholson 2005; Tarlo 2008).

Types of interventions

We included studies evaluating any type of workplace intervention intended to reduce the symptoms or severity of occupational asthma by eliminating or reducing the patient's exposure at work. We compared actual interventions with no intervention or an alternative intervention. We excluded studies that investigated the effects of medication only or medical surveillance. We categorised the interventions into groups described below.

Removal from exposure

- Complete removal from exposure
- Substitution of causal agents

Reduction of exposure

- Introduction into use of respiratory personal protective equipment (PPE) or more effective respiratory PPE
- Implementation of educational programs designed to prevent or reduce exposure through increased worker awareness and knowledge
- Relocation of the affected worker to another work area with less exposure with the same or a different employer

Types of outcome measures

Primary outcomes

1. Asthma symptoms

We included all eligible studies that had used improvement in asthma symptoms as a primary outcome. We accepted using interviews or questionnaires for obtaining information about asthma symptoms.

2. Lung function

2a. FEV1 % predicted

We also included all eligible studies that had measured forced expiratory volume in the first second (FEV1) as a percentage of a predicted or reference value (FEV1 %) as a measure of airway obstruction. We considered all reference values to be equally valid.

2b. Non-specific bronchial hyperreactivity

Finally, we also included all eligible studies that had measured non-specific bronchial hyperreactivity (NSBH). A positive NSBH test indicates that an individual's airways are extremely sensitive to inhaled stimuli, and is considered an important hallmark of asthma. NSBH

can be measured using different bronchoconstrictors. The results are commonly expressed as either the provocative concentration of the bronchoconstrictor causing a 20% decline in FEV1 (PC20) and expressed in the units of milligrams per millilitre (mg/ml) or the provocative dose of the bronchoconstrictor causing a 20% decline in FEV1 (PD20) and expressed in units of mg. A 2017 ERS technical standard for bronchial challenge recommended that of these two endpoints, the PD20 should be used preferentially because it provides comparable results from different devices and different protocols (Coates 2017). For this review, we considered NSBH testing conducted with different methods and the findings expressed as either PC20 or PD20 as equally valid.

Secondary outcomes

We also included studies that had measured the effectiveness of interventions not only by using one or more of the primary outcomes listed above but also with one or more of our secondary outcomes listed here.

- Disability outcomes comprising the period of sickness absence due to occupational asthma (defined as the average number of days listed as unavailable for work due to the specific illness)
- Changes in employment status and income following diagnosis

Search methods for identification of studies

Electronic searches

The search strategies were dictated by the objective of the review: to evaluate the effectiveness of workplace interventions on the clinical outcome of individuals with occupational asthma. We searched for the disease of asthma directly and also for wheeze, which is a sentinel symptom of asthma. To focus on the subset of asthma related to occupation, we used different terms that included "occupation" (e.g., occupational diseases, occupational exposures, and occupational medicine) and also searched on "work." Other search terms addressed "interventions" and different aspects of interventions, including evaluation, follow-up, and effectiveness.

The systematic search for references as reported in the original de Groene 2011 review searched five databases from inception to February 2011. Since additional references from before February 2011 may have been added to the databases after that date, we conducted an initial update that started with January 2010, and deleted any references that had already been considered for inclusion by de Groene 2011. We conducted three systematic searches for references using the same data bases and search strategies as in de Groene 2011. These searches covered successive time periods: January 2010 through December 2015, December 2015 through April 2018, and May 2018 through July 2019. The five databases are listed below, followed by the appendices that contain the search strategies and the number of references retrieved at each search.

- Cochrane Central (Cochrane Library on Wiley), Appendix 1 (31 July 2019)
- Medline (Pubmed), Appendix 2 (31 July 2019)
- Embase (Ovid), Appendix 3 (31 July 2019)
- NIOSHTIC-2 (Internet), Appendix 4 (30 July 2019)
- CISILO (CCOHS), Appendix 5 (30 July 2019)

Searching other resources

We scrutinized the reference lists of all included study reports for additional relevant citations.

Data collection and analysis

Selection of studies

Two review authors (JP and PH) each assessed the titles and abstracts of half the papers to judge relevance for inclusion. We assigned the articles in equal numbers to the other five authors (GG, TP, JB, ST, SC) to provide a second assessment. We then obtained the full text of all papers considered relevant based on their title and abstract and we evaluated each one against the inclusion criteria described above.

Data extraction and management

Two review authors (JP and PH) performed data extraction independently. These two review authors each extracted data from half of all included studies. The other five review authors (GG, TP, JB, ST, SC) provided second data extractions, with each handling an equal proportion of the papers. We used a consensus method to reconcile differences in extracted information between authors where these occurred. However, if a pair of review authors could not resolve their differences, we asked a third author to re-extract the data. Where relevant information was thought to be missing from an included paper, but it was thought it might have been collected as a part of the study, we contacted the original authors of the paper to ask if they could provide this additional information.

Assessment of risk of bias in included studies

We evaluated study quality using the Downs and Black checklist (Downs 1998), and used the 'Internal Validity' section of this assessment tool to evaluate risk of bias. We did not use question 18 on appropriate statistical tests because we had a specific list of outcomes and non-parametric tests were not relevant given our fixed list of outcomes, and added no value to the task of assessing methodological quality. We interpreted a score less than 50% (i.e., less than six of the 12 questions we used) for any study as indicating a 'high risk of bias'.

Measures of treatment effect

For the included studies, we plotted the results of each trial as risk ratios (RR) for dichotomous outcomes and means and standard deviations (SD) for continuous outcomes. When the results could not be plotted, such as for income loss or compensation costs, we described them in the table of characteristics of included studies, entered the data into 'other data tables', or described them in the text to show the change or effect if a visual or statistical analysis was not possible. For outcomes utilizing continuous measures, preference was given to analysing the results for which a mean difference (MD) between groups could be estimated. The standardized mean difference (SMD) is used to combine results from studies that have used different instruments to measure the same construct. The SMD expresses the effect of the intervention in standard deviations rather than the original units of measurement. The SMD is the difference in mean effects in the experimental and control groups divided by the pooled SD of participants' outcomes. We made the calculations as recommended in the *Cochrane Handbook for Systematic Reviews of Interventions* Chapter 9, section 9.2.3.2 and Chapter 12, section 12.6.4 and 16.4.6.2 (Higgins 2011). We interpreted SMDs according

to the following criteria: < 0.40 = small, 0.40 to 0.70 = moderate and > 0.70 = large.

Unit of analysis issues

Based on the principles of units of analysis, there is an assumption that analysis must take into account the level at which randomization occurred, and the number of observations in the analysis should match the number of units that were randomized. We did not come across these issues in this review because we could not include any randomized trials. None of the included studies had used randomization of individuals or clusters or a randomized cross-over design.

Dealing with missing data

When a study paper missed important statistical information required for analysis or had calculations that needed to be clarified, we attempted to contact the authors to gather the required information. When authors had not calculated relevant statistics but had presented supporting data, we conducted calculations using methods described in the 2011 *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

When data were presented in subgroups, we generated a combined mean and SD using methods in the *Cochrane Handbook for Systematic Reviews of Interventions* Chapter 7.7.3.8 (Higgins 2011).

When we could not directly calculate the SD for the change we estimated it from an assumed correlation coefficient of 0.7 and the formula recommended in the *Cochrane Handbook for Systematic Reviews of Interventions* Chapter 16.1.3.2. (Higgins 2011)

When studies did not report SDs for differences, but did provide information on means, SD or t test values, and population sizes across groups, we calculated SDs for differences by methods recommended in the *Cochrane Handbook for Systematic Reviews of Interventions* Chapter 7.7.3.3 (Higgins 2011).

Some studies reported data as a median and inter-quartile range. When the values in these studies seemed to be relatively normally distributed, we assumed that the median value was equal to the mean and calculated the SD by dividing the interquartile range by 1.35, as recommended in Chapter 7.7.3.5 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

When the standard error of the mean (SEM) but not the SD was provided, we calculated an SD so that the data could be entered into the meta-analysis. We used the method recommended in Chapter 7.7.3.2 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

Assessment of heterogeneity

We defined clinical homogeneity as having similar interventions or exposure to the same kind of agent(s). It was necessary for outcomes to be measured at both baseline and follow-up. We used the I^2 statistic to test statistical heterogeneity in the meta-analyses. We interpreted values of $I^2 > 50\%$ to indicate substantial heterogeneity, as recommended in Chapter 9.5.2 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

Assessment of reporting biases

We used a funnel plot to check for publication bias whenever more than five studies were available for inclusion in the analysis.

We identified three papers with the same first author and suspected that they had employed overlapping groups of participants (Talini 2012; Talini 2013; Talini 2015). We consulted the first author and learned that all participants in Talini 2015 were also included in the earlier two papers. In contrast, the participants in the earlier two papers overlapped very little and each addressed a different objective. As a result, we concluded we were dealing with two studies rather than three, excluded Talini 2015 and included data from the studies reported in Talini 2012 and Talini 2013.

Data synthesis

We pooled studies that we judged to be clinically homogeneous, using RevMan 5.3 software (RevMan 2014). We used a random effects model when a group of studies was statistically heterogeneous as indicated by $I^2 > 50$, and otherwise we used a fixed effects model. We could not combine the two outcomes of 'improvement of symptoms' and 'absence of symptoms' because they yielded such statistically different results. Therefore, we considered these as separate outcomes and classified results for asthma symptoms as either one or the other. For the outcome 'improvement of symptoms' we counted only participants who had improved and not those that had no symptoms at follow-up.

Quality of evidence

We evaluated quality of evidence for each outcome by using the GRADE approach (Balshem 2011). The ratings of quality of evidence were based on five factors: limitations of studies, inconsistency of results, indirectness of evidence, imprecision and publication bias.

These factors are defined as follows.

- Limitations of a study refers to a high risk of bias as assessed using the risk of bias checklist.
- Inconsistency refers to any unexplained heterogeneity of results.
- Indirectness refers to the situation in which there are no direct comparisons between groups but the effect of an intervention is inferred from two different comparisons.
- Imprecision refers to the results of studies that include relatively few patients and few events and consequently have wide confidence intervals around the estimate of the effect.
- Publication bias refers to the systematic underestimation or overestimation of the underlying beneficial or harmful effect due to selective publication of studies.

For non-randomized studies we started quality at low and downgraded further if one of the above limitations were apparent. We upgraded the quality of the evidence for one or more of the following factors:

- Large effect size
- All potential confounders would have reduced the effect size
- The presence of a dose-response

(Appendix 6).

Subgroup analysis and investigation of heterogeneity

We intended to analyze subgroups of studies that were defined by different exposure levels to investigate whether this changed the effect of the intervention. Only two of all the included studies, both identified in de Groene 2011, had information about levels of ex-

posure or information about measurements (Dressel 2007; Soyseth 1995). As a result, we could not meaningfully analyze data for subgroups with different exposure levels.

We investigated whether heterogeneity could be due to variations in participant characteristics, interventions, and measured outcomes.

Sensitivity analysis

We had planned to conduct a sensitivity analysis to determine whether studies with a more stringent diagnosis of occupational asthma had different results than studies that had a lower diagnostic threshold. However, we could not perform a meaningful analysis because most studies used specific SIC or other appropriate methodologies for diagnosis, there were limited differences in diagnostic thresholds, and the causal agents and interventions were too varied.

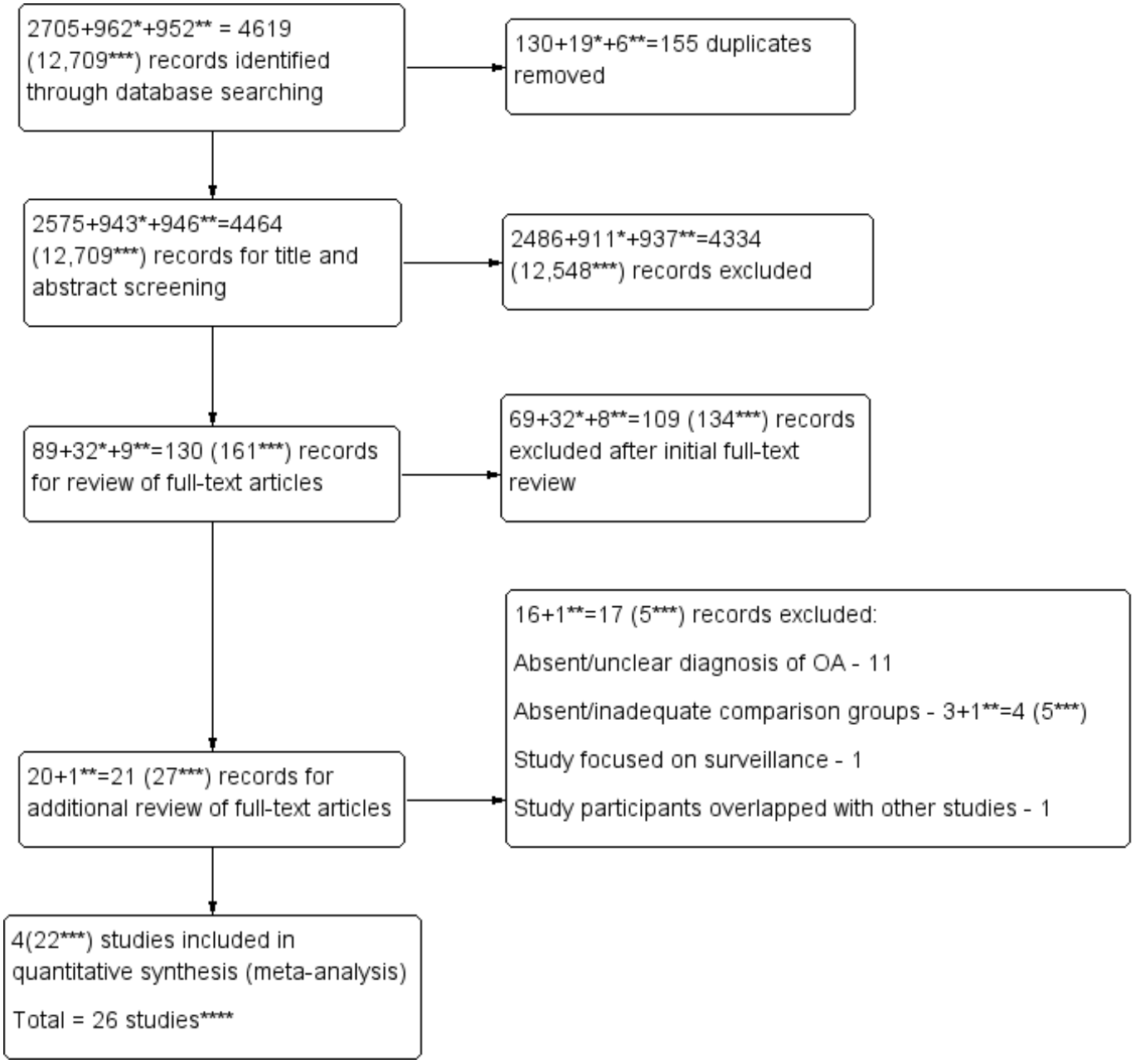
RESULTS

Description of studies

Results of the search

Figure 1 provides a diagram summarizing the number of articles identified and selected for inclusion.

Figure 1. PRISMA diagram for number of studies in review * Studies identified in second phase of update ** Studies identified in third phase of update * Studies included in de Groene 2011 Cochrane Review **** The final 26 studies include Dressel 2009, which was excluded in de Groene 2011 but included in the update.**



The searches covering the period 2011 - 2015 resulted in 2705 references including 130 duplicates, which we eliminated, yielding 2575 unique references.

The screening of titles and then abstracts resulted in the identification of 20 new articles for full-text evaluation. Our initial review of articles identified eight with appropriate methods. However, three of the eight lacked comparison groups (Carlsten 2013; Kim 2013; Lemiere 2010). The remaining five articles fulfilled the inclusion criteria and all described occupational asthma (DiGiampaolo 2012; Munoz 2014; Talini 2012; Talini 2013; Talini 2015). Three of these five references reported studies with different subsets of the same 70 patients treated in an asthma clinic (Talini 2012; Talini 2013; Talini 2015). All participants in the Talini 2015 study were included in either the Talini 2012 or Talini 2013 study, so we included results only from the two earlier articles.

In de Groene 2011, the authors excluded the Dressel 2009 study because of concern that the investigators selectively excluded potential participants who smoked or suffered a respiratory tract infection because of the potential impact on the fraction of exhaled nitric oxide in exhaled breath (FeNO), and none of the other included studies had made a similar exclusion. However, because the study fulfilled the inclusion criteria and smoking status was not part of those criteria, we decided to include it in the current update.

The searches covering the period 2015 - 2018 yielded 962 references . We eliminated 19 duplicates, yielding 943 unique references. The screening of titles and abstracts resulted in the identification of 32 articles for full-text evaluation. Our detailed assessment of these articles determined that none of them fulfilled the inclusion criteria.

We conducted a final update of the literature search to cover the period from May 1, 2018, to July 31, 2019, using the same search strategies and databases as the previous searches. The combined search of the databases yielded 952 references. We eliminated 6 duplicates, yielding 946 unique references. The screening of titles and abstracts yielded 9 articles for full-text evaluation. Our detailed assessment of these articles determined that one of them fulfilled the screening criteria (Ilgaz 2019) but the study lacked a comparison group and was excluded from the review.

From the three search periods, we screened a total of 4464 references. At final count, five articles provided data on five studies that we added to the 21 studies included in de Groene 2011, for a total of 26 studies that were reported in 26 articles. Four of the five additional studies contributed data for one type of comparison: Munoz 2014 for removal from exposure versus continued exposure; Dressel 2009 for reduction of exposure versus continued exposure; and DiGiampaolo 2012 and Talini 2013 for removal from exposure versus reduction of exposure. Talini 2012 was unique in providing three types of comparisons: removal versus reduction of exposure, reduction versus continued exposure, and removal versus reduction of exposure. Consequently, we added seven comparisons to the 29 initial comparisons, for a new total of 36.

Included studies

The current review is based on a total of 26 included studies.

See also the Characteristics of included studies.

Design

We identified neither randomized studies nor ITS. As a result, all comparisons are based on results obtained with a CBA design.

It was apparent in some of the CBA studies that the intervention and control groups did not have the same severity of occupational asthma at baseline. Only three studies were intentionally designed as intervention studies (Dressel 2007; Dressel 2009; Soyseth 1995), two of which had the same first author and were based on the same intervention. All the other 23 studies were prospective or retrospective follow-up studies, and it was unclear in many of the studies how patients were allocated to an intervention or control group. We assume that allocation to different groups was usually made in the context of treating the patient, with the guiding principle of doing what was best for the individual. This approach may have resulted in differences in level of severity between the intervention and control groups. For example, treating clinicians likely assigned more severe cases to removal or reduction of exposure rather than continuation of exposure.

Interventions

The interventions identified in the included studies were as follows.

Removal from exposure

Included studies achieved ‘removal from exposure’ by arrangements where the case was no longer exposed to the causative agent. This was accomplished in different ways, such as transferring to an unexposed job with the same employer, finding an unexposed job at a different workplace, or leaving the workforce entirely. None of the included studies had evaluated the effects of substitution, meaning the replacement of a causal agent with a material that would not cause or aggravate asthma. Overall, 23 studies reported this type of intervention (see Table 1): Bernstein 2003 removal; Burge 1982; Chan-Yeung 1982; Chan-Yeung 1987 removal; DiGiampaolo 2012; Innocenti 1981; Lin 1996; Mapp 1988; Marabini 1993; Marabini 1994; Moscato 1993 removal; Moscato 1999; Munoz 2008; Munoz 2014; Padoan 2003; Paggiaro 1984; Pisati 1994; Rosenberg 1987 removal; Talini 2012; Talini 2013; Valentino 2002; Vandenplas 2002; Visentin 2003.

Reduction of exposure

Included studies accomplished ‘reduction of exposure’ in the following ways: relocation of the worker to another job and work area with less exposure to the causal agent either in the same company or in another company; introduction or enhancement of PPE; or implementation of an educational or training program that was intended to reduce exposure. Thirteen studies reported findings associated with reducing exposures to causal agents by relocating workers to different jobs or work areas: Burge 1982; Chan-Yeung 1987 removal; DiGiampaolo 2012; Marabini 1994; Moscato 1993 reduction; Moscato 1999; Rosenberg 1987 reduction; Soyseth 1995; Talini 2012; Talini 2013; Valentino 2002; Vandenplas 2002; Visentin 2003. Four studies evaluated the effects of the reduction of exposure by changes in PPE: Bernstein 2003 reduction; Rosenberg 1987 reduction; Vandenplas 2002; Talini 2012, three of which also involved exposure reduction by moving workers to a different job or work area with less exposure: Rosenberg 1987 reduction; Talini 2012; Vandenplas 2002. We included only two studies that were based on the same intervention to reduce exposure by implementing an educational or training program (Dressel 2007; Dressel 2009).

Continued exposure

Included studies evaluated the effects of 'Continued exposure' with groups of participants who received no intervention at the workplace, and as such served as comparison or control groups, enabling the evaluation of the impact of removal from exposure or reduction of exposure in comparison to continued exposure.

Comparisons based on the interventions

Using the three interventions, the included studies reported on three types of comparisons:

- Removal from exposure versus continued exposure;
- Reduction of exposure versus continued exposure; and
- Removal from exposure versus reduction of exposure.

Primary outcomes

1. Asthma symptoms

We compared asthma symptoms before and after an intervention in two ways: 1) the number of subjects who reported an absence of symptoms after an intervention; and 2) the number of subjects who reported improvement of symptoms after an intervention. We analyzed these data as a dichotomous outcome and reported the RR

for both absence of symptoms and improvement (but no absence) of symptoms.

Authors of studies obtained information about asthma symptoms using different methods. Eleven studies used interviews, and the authors reported little information about the content of the interviews (Chan-Yeung 1982; Chan-Yeung 1987 reduction; Mapp 1988; Marabini 1993; Moscato 1993 reduction; Moscato 1999; Munoz 2008; Padoan 2003; Paggiaro 1984; Talini 2012; Talini 2013). Other authors used questionnaires, the content of which varied among studies. The format for presenting symptom results varied among the studies. Some authors reported numbers of symptomatic and asymptomatic individuals, or these numbers could be derived using the data presented (Chan-Yeung 1982; Chan-Yeung 1987 reduction; Dressel 2007; Dressel 2009; Innocenti 1981; Lin 1996; Mapp 1988; Marabini 1994; Padoan 2003; Paggiaro 1984; Talini 2012; Talini 2013; Visentin 2003). Others described numbers of workers with improvement (Bernstein 2003 reduction; Burge 1982). Another approach used was to classify the symptoms into groups and to report for each either presence, severity or both (Marabini 1993; Moscato 1999; Munoz 2008; Munoz 2014; Pisati 1994). We considered the information obtained with these various methods as equally valid. For the studies with a classification of symptoms into groups or for each report of an indication of presence, severity or both we calculated the individuals with improvement of symptoms.

2. Lung function

2a. FEV1 % predicted

Many studies conducted spirometry and expressed FEV1 as a percentage of a predicted reference value, or FEV1 % (Burge 1982; Chan-Yeung 1982; Chan-Yeung 1987 reduction; Chan-Yeung 1987 removal; Dressel 2007; Lin 1996; Mapp 1988; Marabini 1993; Moscato 1999; Munoz 2008; Munoz 2014; Paggiaro 1984; Rosenberg 1987 reduction; Rosenberg 1987 removal;Talini 2012; Talini 2013; Valentino 2002; Vandenplas 2002). Authors reported the lung function parameter FEV1 in various ways, but most commonly as a percentage of a predicted or reference value, or FEV1 %. We used this metric for comparisons in the analyses. Following a similar protocol of minimizing the influence of baseline differences, we used the MD in change in FEV1 % between baseline and follow-up for the intervention group and the control group as the main measure of treatment effect. We also reported separate values at baseline and follow-up.

With four studies (Chan-Yeung 1982; Chan-Yeung 1987 removal; Mapp 1988; Marabini 1993) it was necessary to combine FEV1 % data from subgroups for removal from exposure. We accomplished this for means and SDs using methods in the *Cochrane Handbook for Systematic Reviews of Interventions* Chapter 7.7.3.8 (Higgins 2011). It was necessary to do the same for both removal from exposure and reduction of exposure with FEV1 % data from Talini 2013.

With most of the studies that reported FEV1 % (Burge 1982; Chan-Yeung 1982, Chan-Yeung 1987 reduction; Chan-Yeung 1987 removal; Dressel 2007; Lin 1996; Mapp 1988; Marabini 1993; Moscato 1999; Munoz 2008; Munoz 2014; Paggiaro 1984; Talini 2012; Talini 2013; Valentino 2002; Vandenplas 2002), we could not directly calculate the SD for change and estimated it from an assumed correlation coefficient of 0.7 and the formula recommended in the *Cochrane Handbook for Systematic Reviews of Interventions* Chapter 16.1.3.2 (Higgins 2011).

Three studies (Munoz 2014; Talini 2012; Talini 2013) did not report SDs for differences in FEV1 %, but provided information on means, SD or t test values, and population sizes across groups. In these instances, we calculated the SDs for differences by methods recommended in Chapter 7.7.3.3 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011)

Two studies reported FEV1 % data as a median and inter-quartile range (Moscato 1999; Vandenplas 2002). Because the values in these studies seemed to be relatively normally distributed, we assumed that the median value was equal to the mean and calculated the SD by dividing the interquartile range by 1.35, as recommended in Chapter 7.7.3.5 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

In some studies, the authors failed to report whether the value used to describe the distribution of FEV1 % values was an SD or a SEM (Chan-Yeung 1987 reduction; Chan-Yeung 1987 removal; Lin 1996; Paggiaro 1984). We assumed that higher values were SDs and lower values were SEMs. For example, we classified values below five as low and above 20 as high.

The study by DiGiampaolo 2012 reported results for annual FEV1 decline from baseline to follow-up, (normalized by dividing by height cubed), in graphs with no numbers. We asked the authors to provide the relevant numbers, but they were unable to provide them. We estimated numerical results for annual FEV1 decline from the graphs.

2b. Non-specific bronchial hyperreactivity (NSBH)

The researchers measured NSBH as PC20, PC15, PD20, or PD15. We considered all NSBH information obtained with these different methods as equally valid (see Table 2). Most of the included studies measuring this outcome used methacholine or histamine as the bronchoconstrictor when testing for NSBH. The authors presented results most often as PC20 and PC15, or PD20 and PD15. Four studies reported subjects with 'abnormal' values (Burge 1982; Munoz 2008; Paggiaro 1984; Rosenberg 1987 reduction; Rosenberg 1987 removal) and 12 studies reported a continuous outcome in dose or concentration (Chan-Yeung 1982; Chan-Yeung 1987 reduction; Chan-Yeung 1987 removal; Mapp 1988; Marabini 1993; Moscato 1999; Munoz 2014; Paggiaro 1984; Pisati 1994; Talini 2012; Talini 2013; Valentino 2002; Vandenplas 2002). We used the mean difference in change in the outcome measure before and after the intervention in the intervention minus the control group as the effect-size. Given the variation in how studies conducted NSBH testing and reported results, we used SMDs.

With four studies (Chan-Yeung 1982; Chan-Yeung 1987 removal; Mapp 1988; Marabini 1993), it was necessary to combine NSBH data from subgroups for removal from exposure. We accomplished this for means and SD using methods in the *Cochrane Handbook for Systematic Reviews of Interventions* Chapter 7.7.3.8 (Higgins 2011).

With the six studies that contributed NSBH data to the comparison of removal from exposure with continued exposure (Chan-Yeung 1982; Chan-Yeung 1987 removal; Mapp 1988; Marabini 1993; Moscato 1999; Munoz 2014), we could not directly calculate the SD for change and estimated it from an assumed correlation coefficient of 0.7 and the formula recommended in the *Cochrane Handbook for Systematic Reviews of Interventions* Chapter 16.1.3.2 (Higgins 2011).

The study by Munoz 2014 did not report SDs for differences in NSBH, but did provide information on means, t-test values, and population sizes across groups. In these instances, we calculated the SD for differences by methods recommended in Chapter 7.7.3.3 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011)

The study by Moscato 1999 reported NSBH data as a median and inter-quartile range. Because the values seemed to be relatively normally distributed, we assumed that the median value was equal to the mean and calculated the SD by dividing the interquartile range by 1.35, as recommended in Chapter 7.7.3.5 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

Secondary outcome

Seven studies reported information about employment, income, or both at follow-up (see Table 3). Four studies reported information about employment for the intervention group and five studies reported information about income for the intervention group. Three studies provided additional comments about the employment situation in their own countries. None of the included studies reported disability or sickness absence as an outcome.

Agents

The agents reported as the cause of occupational asthma in the included studies were dominated by sensitizers, including isocyanates (eight studies), western red cedar (four studies), natural rubber latex (three studies), several high molecular weight (HMW) and low molecular weight (LMW) agents combined (five studies), cow dander and storage mites (two studies), and persulfates, colophony, cobalt and pot room gases in one study each (see Table 4). Thus, the causal agent was of HMW in five studies, LMW in 15 studies, both HMW and LMW in five studies and pot room gases in one study (see Table 5).

Follow-up time

Twenty-six studies reported mean follow-up time, with a range of five weeks to 12 years, and median 3.2 years. The mean follow-up time among these studies was 4.5 years (mean of study-specific means weighted by number of participants in each study) (see Table 6).

The follow-up times could vary considerably among participants in the same study, for example from 12 to 45 months in Burge 1982 or from 26 to 83 months in Vandenplas 2002. Investigators often described the variability as a SD or SEM.

Duration of exposure prior to symptoms

Ten studies reported the duration of exposure prior to diagnosis. The range was 2.9 to 15.6 years and median 5.6 years (see Table 6). The study-specific mean values were bimodal, with six in the range 2.9 to 5.9 years, and four in the range 11.1 to 15.6 years.

Duration of symptoms prior to diagnosis

Thirteen studies reported the duration of symptoms prior to diagnosis. The study-specific mean values had a range of 1.4 to 8.5 years, median 3.8 years, and mean 3.3 (mean of study-specific means weighted by number of participants in each study) (see Table 6).

Sample size

The included studies had from nine in Pisati 1994 to 232 participants in Chan-Yeung 1987 reduction and Chan-Yeung 1987 removal. The median number of participants was 41 and the mean was 62. The number of participants in the intervention groups varied from four in Bernstein 2003 removal to 136 in Chan-Yeung 1987 reduction and the number of participants in the control groups varied from one in Bernstein 2003 reduction and Pisati 1994 to 92 in Lin 1996 (see Table 6).

Setting

The setting for almost all studies was a university clinic or a hospital department specializing in occupational medicine or pulmonary medicine. Only one study by Soyseth 1995 was undertaken within a business or workplace setting.

Only three studies reported the funding source. Two German statutory accident insurance institutions for agricultural workers supported two studies based on the same intervention (Dressel 2007; Dressel 2009), and the Services Federaux des Affaires Scientifiques et Culturelles in Belgium supported another study (Vandenplas 2002). We felt it unlikely that source of funding introduced a significant conflict of interest in these studies.

Twenty-one studies were conducted in Europe (Italy 13, Belgium one, France one, Germany two, Great Britain one, Norway one, Spain two), four in Canada (British Columbia) and one in the United States (Ohio).

The 26 included studies were reported in 26 articles published between 1984 and 2014, with 14 published prior to 2000.

The included articles were written in English (22) or Italian (four).

Participants

All participants were workers (as specified in the inclusion criteria), had occupational asthma, and had experienced exposure to an agent with the potential to cause asthma. Three studies (Bernstein 2003 reduction; Bernstein 2003 removal; Vandenplas 2002; Visentin 2003) reported results for workers exposed to latex. In two of these studies (Bernstein 2003 reduction; Bernstein 2003 removal; Vandenplas 2002), the authors included some workers with pre-existing asthma but they did not attempt to separate occupational asthma and work-exacerbated asthma in their analyses. One study included a single worker with probable work-exacerbated asthma (Rosenberg 1987 removal).

The diagnosis of occupational asthma was based on SIC with the suspected causative agent in 20 studies (although results were not always available for all subjects), or based on history and questionnaires, lung function and immunological testing in two studies (Bernstein 2003 reduction; Bernstein 2003 removal; Visentin 2003). In three studies the authors did not report the methods of diagnosis (Dressel 2007; Dressel 2009; Soyseth 1995).

Four of every five participants (79.1%) were male in the 23 studies that reported the distribution of participants by sex. The study-specific percentage of male participants ranged from zero to 100% with a median of 71%, and only five studies had samples that were majority female. These five studies addressed particular types of workers and exposures, including hairdressers and cosmetics workers (Munoz 2008), healthcare workers exposed to latex (Vandenplas

2002; Bernstein 2003 reduction; Bernstein 2003 removal; Visentin 2003), and electronics workers exposed to colophony (Burge 1982). The studies that were majority male included those dominated by a single agent, such as western red cedar or diisocyanates, and those with a mix of agents.

Twenty-four studies specified mean age of participants at baseline, with a range from 32 to 50.2 years and a median of 39 years. The mean age of all participants was 41.1 years (mean of study-specific means weighted by number of participants in each study).

Type of asthma reaction

Thirteen studies reported the type of asthma reaction and often only at baseline. Based on baseline data from 12 studies, an immediate reaction was found in 0% to 63% of the participants (median = 23%), a late reaction in 4% to 87.5% of the participants (median = 42%), and a dual reaction in 12.5% to 50% (median = 27%) (see Table 6).

Atopy

Twenty studies reported the atopic status of participants. Between 0% and 89% of participants were atopic in these studies, and the median was 28%. The percentage atopic varied by type of agent, with higher values for the two studies of cases exposed to HMW agents (64% and 89%) compared to the 14 studies with cases exposed to LMW agents (range 0% to 57%, median = 24%) (Table 6).

Smoking

Twenty-two studies reported smoking status in one form or another. Among the 14 studies that reported the distribution of participants at baseline by three categories of smoking status, 4% to 35% (median = 11%) of the participants were current smokers, 12.5% to 49% (median = 28%) were ex-smokers, and 35% to 75% (median = 63%) were non-smokers (Table 6).

Excluded studies

See also the Characteristics of excluded studies.

We excluded 22 studies that were reported in 22 articles. Eleven studies did not have occupational asthma cases clearly identified and studied as a distinct group, some of which focused on the broader categories of work-related asthma or work-related asthma symptoms (Antao 2011; Bailey 2009; Donoghue 2011; Durham 2011; Fishwick 2011; Karvala 2011; Madureira 2014; Schoj 2010; Singh 2010; Stocks 2013; Stocks 2015). Nine studies had no control group or a control group that did not include occupational asthma cases (Carlsten 2013; De Zotti 2000; Ilgaz 2019; Kim 2013; Klusackova 2006; Lemiere 2010; Patovirta 2004; Pohl 2003; Saetta 1992). The intervention in the excluded study by Labrecque 2011 was workplace medical surveillance and education that took place prior to diagnosis of occupational asthma, and the comparison group was occupational asthma cases identified by other means.

Three studies conducted by the same study center (Talini 2012; Talini 2013; Talini 2015) were based on subsets of 70 occupational asthma cases. The 2012 study had 41 participants, the 2013 study had 46 participants, and the two studies shared 17 individuals. We decided to include both Talini 2012 and Talini 2013 because the overlap was less than a majority of cases in either study. The final study was reported in 2015 and had 39 participants that were included in either one or both of the other two studies. We excluded the Talini 2015 study because all its participants were represented in the other two studies.

Risk of bias in included studies

All included studies are nonrandomized controlled before and after studies. We used the internal validity subscales of the Downs and Black checklist (Downs 1998) to assess the included studies' risk of bias. The overall internal validity score for all included studies ranged from zero to 7 out of a maximum score of 12 (median 3, mean 3.3, SD 2.0) (Table 7; Table 8). A majority of the included studies (22 of 26) had an overall score less than 50%, which we considered a high risk of bias. The four studies with an internal validity score of at least 50% were Lin 1996, Moscato 1999, Soyseth 1995,and Talini 2013. None of the studies had blinded the people measuring outcomes. Four studies (Moscato 1993 reduction; Moscato 1993 removal; Moscato 1999; Soyseth 1995; Talini 2013) clarified that results were based on data dredging. Seven studies adjusted for length of follow-up in analysis. Most studies reported accurate outcome measurements (18 of 26), and that the participants were recruited from the same population (18 of 26) and over the same time period (17 of 26). Information was limited regarding why or how participants were allocated to different treatment groups, and for compliance with the interventions. Loss to follow-up was rarely addressed. Seven of the 26 studies conducted adequate adjustment for confounding factors.

Effects of interventions

See: **Summary of findings for the main comparison** Removal from exposure compared to continued exposure for treatment of occupational asthma; **Summary of findings 2** Reduction of exposure compared to continued exposure for treatment of occupational asthma; **Summary of findings 3** Removal from exposure compared to reduction of exposure for treatment of occupational asthma

Comparison 1: Removal from exposure versus continued exposure

Asthma symptoms at follow-up

Seventeen studies reported asthma symptoms, 12 of which reported results for low molecular weight (LMW) agents (Chan-Yeung 1982; Chan-Yeung 1987 removal; Innocenti 1981; Lin 1996; Mapp 1988; Marabini 1993; Marabini 1994; Munoz 2008; Padoan 2003; Paggiaro 1984; Pisati 1994; Rosenberg 1987 removal, one for high molecular weight (HMW) agents (Bernstein 2003 removal) and four for a combination of HMW and LMW agents (Moscato 1993 removal; Moscato 1999; Munoz 2014; Talini 2012).

Nine studies reported the presence or absence of asthma symptoms. In addition, nine studies reported numbers, percentages or symptom scores that made it possible to calculate the numbers of individuals with improvement in symptoms.

Absence of asthma symptoms (mean follow-up 4.2 years)

Asthma symptoms were significantly more often absent at follow-up after complete removal with a pooled risk ratio (RR) of 4.80 (95% confidence interval (CI) 1.67 to 13.86) based on the nine studies included in this comparison. Heterogeneity was substantial with I^2 = 67%. (Analysis 1.1)

In total, six of the nine studies reported on LMW agent studies (Chan-Yeung 1982; Chan-Yeung 1987 removal; Innocenti 1981; Mapp 1988; Marabini 1994; Padoan 2003). For these studies, the pooled risk ratio for absence of symptoms was also significantly greater than one, with a RR of 9.06 (95% CI 2.05 to 40.17).

The very high RRs in these comparisons were mainly due to three older studies carried out in the 1980s that had high risk ratios that were all greater than 20 and larger numbers of participants (Chan-Yeung 1982; Chan-Yeung 1987 removal; Innocenti 1981).

The three studies that had participants with a combination of HMW and LMW exposures had an elevated risk ratio that was not quite statistically significant: RR = 1.85, 95% CI 0.97 to 3.50 (Moscato 1993 removal; Munoz 2014; Talini 2012).

Improvement of asthma symptoms (mean follow-up 4.8 years)

The pooled risk ratio for improvement of asthma symptoms was 2.47 (95% CI 1.26 to 4.84) for all nine studies that we included in this comparison. Heterogeneity was substantial with I^2 = 67% (Analysis 1.2).

For the six LMW agent studies, the pooled risk ratio for improvement was significantly greater than one with a RR of 2.82 (95% CI 1.08 to 7.31)(Lin 1996; Marabini 1993; Munoz 2008; Paggiaro 1984; Pisati 1994; Rosenberg 1987 removal). Heterogeneity was substantial for these LMW studies with I^2 = 78%. The one study with HMW agents (Bernstein 2003 removal) and the two studies with a combination of HMW and LMW agents (Moscato 1993 removal; Moscato 1999) had risk ratios with wide confidence intervals that included one: RR=3.60 (95% CI 0.32 to 40.41) and RR=1.60 (95% CI 0.64, 4.02), respectively.

Change in FEV1 % (follow-up minus baseline values, mean follow-up 4.3 years)

Ten studies compared the FEV1 % between baseline and follow-up . The pooled mean difference (MD) in FEV1 % was 4.23 percentage points (95% CI 1.14 to 7.31), indicating that removal from exposure may result in a higher FEV1 % than continued exposure. Heterogeneity in this comparison was substantial with I^2 = 55% (Analysis 1.3).

Seven studies reported results for LMW agents (Chan-Yeung 1982; Chan-Yeung 1987 removal; Lin 1996; Mapp 1988; Marabini 1993; Munoz 2008; Paggiaro 1984) and three for a combination of HMW and LMW agents (Moscato 1999; Munoz 2014; Talini 2012). For the LMW agent studies, the MD for change in FEV1 % between baseline and follow-up was statistically significant: 5.70 percentage points (95% CI 3.55 to 7.84). The three studies with both HMW and LMW agents had a MD that was close to zero: −1.06 percentage points (95% CI −7.36 to 5.24).

Change in non-specific bronchial hyperreactivity (NSBH) (follow-up minus baseline values, mean follow-up 3.5 years)

The six studies with data for change of NSBH between baseline and follow-up had a pooled SMD of 0.43 (95% CI 0.03 to 0.82) that was statistically significant when comparing complete removal from exposure to continued exposure. A greater SMD indicates a greater improvement for removal from exposure. Heterogeneity was substantial with I^2= 64%.(Analysis 1.4)

The four studies with results for LMW agents (Chan-Yeung 1982; Chan-Yeung 1987 removal; Mapp 1988; Marabini 1993) had an SMD of 0.43 (95% CI −0.01 to 0.84) that was essentially the same as the result for all six studies. For the two studies with a combination of HMW & LMW agents(Moscato 1999; Munoz 2014), the change in NSBH did not differ statistically significantly between the intervention and control groups, with SMD 0.54 (95% CI −0.79 to 1.86).

Income or employment at follow-up

Five studies reported some information about income, employment, or both. Three studies reported that unemployment was common among occupational asthma cases removed from exposure, with values of 44% (Vandenplas 2002), 65% (Burge 1982), and 66% (Marabini 1993). Four studies reported a reduction in income for members of the intervention group, ranging from 20% to 50% (Bernstein 2003 removal; Marabini 1993; Moscato 1999; Vandenplas 2002. (Table 3).

Comparison 2: Reduction of exposure versus continued exposure

Absence of asthma symptoms at follow-up (mean follow-up 1.9 years)

Of the seven studies comparing asthma symptoms between reduction of exposure and continued exposure, two reported results for LMW agents (Chan-Yeung 1987 reduction; Rosenberg 1987 reduction), three for HMW agents (Bernstein 2003 reduction; Dressel 2007; Dressel 2009) and two for a combination of HMW and LMW agents (Moscato 1993 reduction; Talini 2012). All studies reported the absence of symptoms at follow-up rather than improvement of symptoms. Reduction of exposure resulted in an increased number of participants with asthma symptoms absent at follow-up compared to continued exposure, with a pooled RR of 2.65 (95% CI 1.24 to 5.68) and very low heterogeneity of I^2 = 0% (Analysis 2.1). The three studies of cases exposed to HMW agents also had a statistically significant RR of 4.89 (95% CI 1.04 to 22.96).

Change in FEV1 % (follow-up minus baseline values, (mean follow-up 2.1 years)

The analysis of change in FEV1 % between baseline and follow-up yielded a MD = 2.76 percentage points that was not statistically significant (95% CI −1.53 to 7.04) for the three studies (Chan-Yeung 1987 reduction; Dressel 2007; Talini 2012) that contributed observations to this comparison. Heterogeneity was very low with I^2 = 0%. Of these three studies, one reported results for LMW agents, one for HMW agents, and one for both HMW and LMW agents. A fourth study (Rosenberg 1987 reduction) had investigated cases with LMW exposures and provided point estimates for change in FEV1 %, but we did not include those results in the current summary analyses because it was not possible to estimate standard deviations (Analysis 2.2).

Income or employment at follow-up

The two studies by Burge 1982 and Vandenplas 2002 reported some information about income, employment, or both for occupational asthma cases with reduced exposure. These studies reported that 100% of the cases were employed at follow-up (see Table 3).

Comparison 3: Removal from exposure versus reduction of exposure

Asthma symptoms at follow-up

Of the ten studies that reported asthma symptoms, five reported results for LMW agents, three for HMW agents and two for a combination of HMW and LMW agents that we could use in the pooled estimates. Six of these studies reported about absence of asthma symptoms (Chan-Yeung 1987 removal; Moscato 1993 removal; Talini 2012; Talini 2013; Valentino 2002; Visentin 2003), and five reported numbers, percentages or scores that made it possible to calculate the numbers of individuals with improvement (Bernstein 2003 removal; Burge 1982; Moscato 1993 removal; Rosenberg 1987 removal; Vandenplas 2002).

Absence of asthma symptoms (mean follow-up 5.4 years)

The combined results from the six included studies indicated that removal from exposure did not significantly increase the likelihood of a participant reporting the absence of asthma symptoms at follow-up compared to reduction of exposure, with RR = 6.05 (95% CI 0.86 to 42.34). Heterogeneity was substantial with I^2 = 82% (Analysis 3.1). However, statistically significant results were observed for the subset of three studies with LMW agents (Chan-Yeung 1987 removal; Talini 2013; Valentino 2002), with RR = 9.31 (95% CI 1.56 to 55.73).

Improvement of asthma symptoms (mean follow-up 2.9 years)

Based on data from the five studies included in this analysis, improvement of symptoms was not significantly more likely for those removed from exposure compared to those with reduction of exposure. The RR was 1.11 (95% CI 0.84 to 1.47) for all five studies in this comparison and heterogeneity was substantial with I^2 = 61% (Analysis 3.2). In contrast, the RR for improvement of symptoms was statistically significant for the two studies that investigated cases attributed to LMW agents (Burge 1982; Rosenberg 1987 removal), with RR = 1.61 (95% CI 1.02 to 2.53).

Change in FEV1 % (follow-up minus baseline values, mean follow-up 5.2 years)

Six studies had relevant complete data that we included in these analyses (Burge 1982; Chan-Yeung 1987 removal; Talini 2012; Talini 2013; Valentino 2002; Vandenplas 2002). The MD of change in FEV1 % between baseline and follow-up (with a greater MD indicating a greater improvement for removal) was 2.58 percentage points and had a wide confidence interval (95% CI −3.02 to 8.17). Heterogeneity was substantial with I^2 = 70%, which is explained by the fact that the study-specific MD estimates were equally split between less than zero and greater than zero (Analysis 3.3).

The four studies of cases with LMW exposures (Burge 1982; Chan-Yeung 1987 removal; Talini 2013; Valentino 2002) had an MD for change in FEV1 % between baseline and follow-up that was statistically significant: 5.79 % (95% CI 0.02 to 11.56).

Two studies had FEV1 results that we did not include in the summary statistics for change in FEV1. The Rosenberg 1987 removal study had investigated cases with LMW exposures and provided point estimates for change in FEV1 %, but it was not possible to estimate standard deviations for the point estimates. FEV1 % change for the DiGiampaolo 2012 study was reported as normalized annual decline, expressed in units of Liters (L)/ height cubed (ht3)/ year (yr), rather than percentage of predicted as reported in other included studies. The normalized annual decline in FEV1 was less for the 30 participants with removal from exposure (mean −0.007 l/ht3/yr, 95% CI −0.008 to −0.006) than for the 28 participants with reduction of exposure (mean −0.012 l/ht3/yr, 95% CI −0.014 to −0.010), with p < 0.001.

Income or employment at follow-up

Five studies included in this comparison reported at least some information about income, employment, or both (Bernstein 2003 removal; Burge 1982; Chan-Yeung 1987 removal; Moscato 1993 removal; Vandenplas 2002). Three studies reported employment status of the removal from exposure group at follow-up, and the frequency of unemployment ranged from 0/4=0% (Bernstein 2003 removal) to 7/16=44% (Vandenplas 2002) to 13/20=65% (Burge 1982). The reduction in income for the removal from exposure group was a median of 20% in the Vandenplas 2002 study and a mean of 24% in the Bernstein 2003 removal study. The control group in these two studies, which was characterized by reduction of exposure, had no unemployment. In addition, participants in the control group in the Vandenplas 2002 study had a median 0% loss in income. For the two studies that reported sufficient data (Burge 1982; Vandenplas 2002), those that were removed from exposure had an increased risk of unemployment after a mean of 3.5 years of follow-up, with RR = 14.28 (95% CI 2.06 to 99.16). See Analysis 3.4 and Table 3 for details.

Explanation of heterogeneity

For all the comparisons, the heterogeneity in findings among the different studies might be due, in part, to differences in the types of allergens. In general, the interventions may have had better results with OA cases attributed to LMW agents than for cases attributed to HMW agents or the combination of HMW and LMW agents. For example, the benefit of removal from exposure versus continued exposure was more evident for LMW agents than the combination of HMW and LMW agents for absence of symptoms (see Analysis 1.1), improvement in symptoms (see Analysis 1.2), and change in FEV1 % (see Analysis 1.3). Also, for comparisons of removal from exposure versus reduction in exposure, positive results for LMW agents were observed for absence of symptoms (see Analysis 3.1),improvement in symptoms (see Analysis 3.2), and change in FEV1 % (see Analysis 3.3), but not for HMW agents and the combination of HMW and LMW agents. However, positive results were not limited to OA patients exposed to LMW agents. For example, with the comparison of reduction of exposure versus continued exposure and the outcome of absence of symptoms, a positive effect was most evident from the studies of cases exposed to HMW agents, with RR=4.89 (95% CI 1.04 to 22.96) (see Analysis 2.1).

Publication bias

We examined funnel plots for the three types of comparisons for the outcome absence of asthma symptoms (Analysis 1.1; Figure 2; Analysis 2.1; Figure 3; Analysis 3.1; Figure 4). Each plot had a noticeable gap in the bottom left corner, suggesting possible publication bias in which studies with lower precision and negative non-significant results may have never been published.

Figure 2. Funnel plot of comparison: 1 Removal from exposure versus continued exposure, outcome: 1.1 Absense of asthma symptoms.

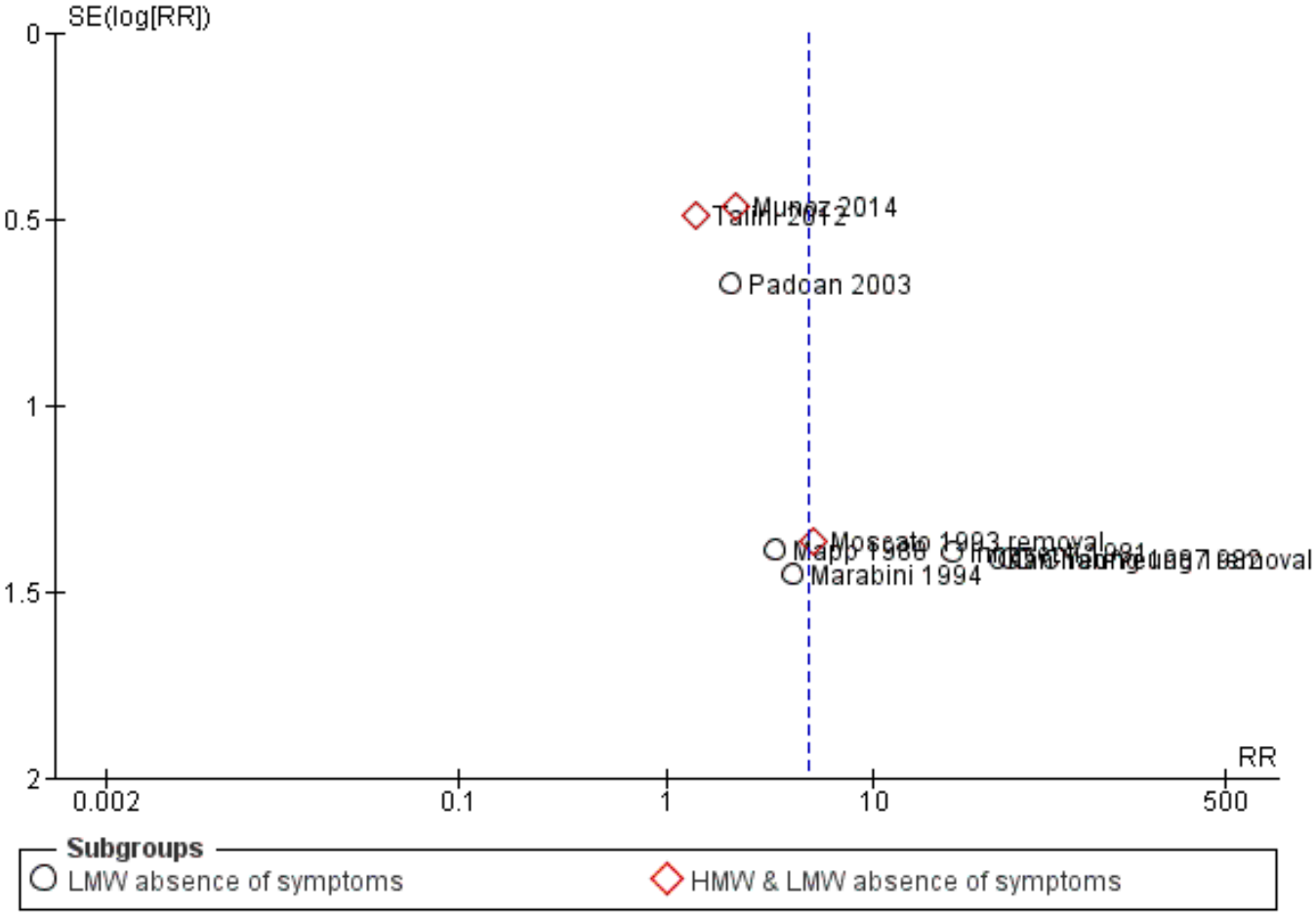


Figure 3. Funnel plot of comparison: 2 Reduction of exposure versus continued exposure, outcome: 2.1 Absence of asthma symptoms.

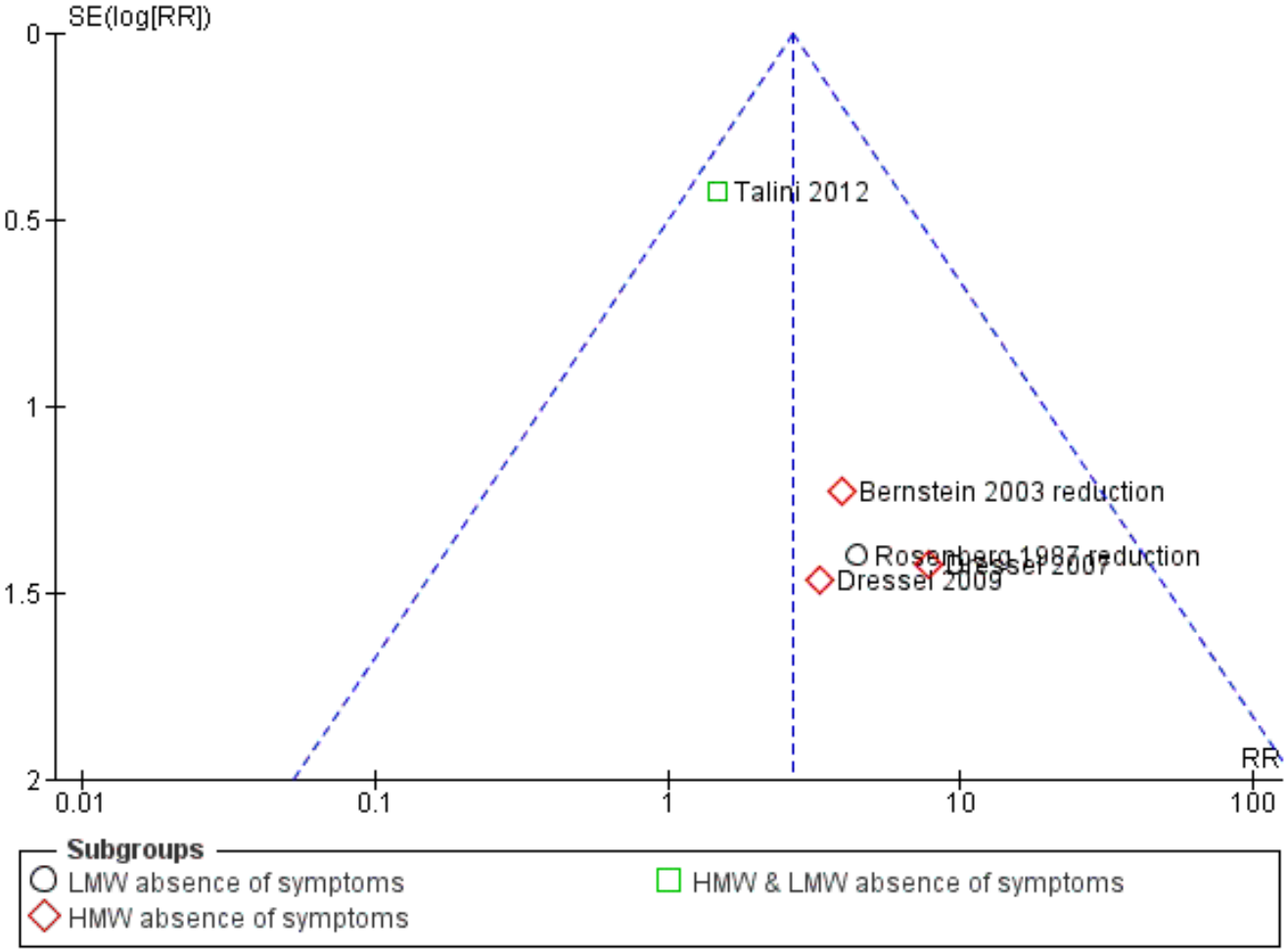
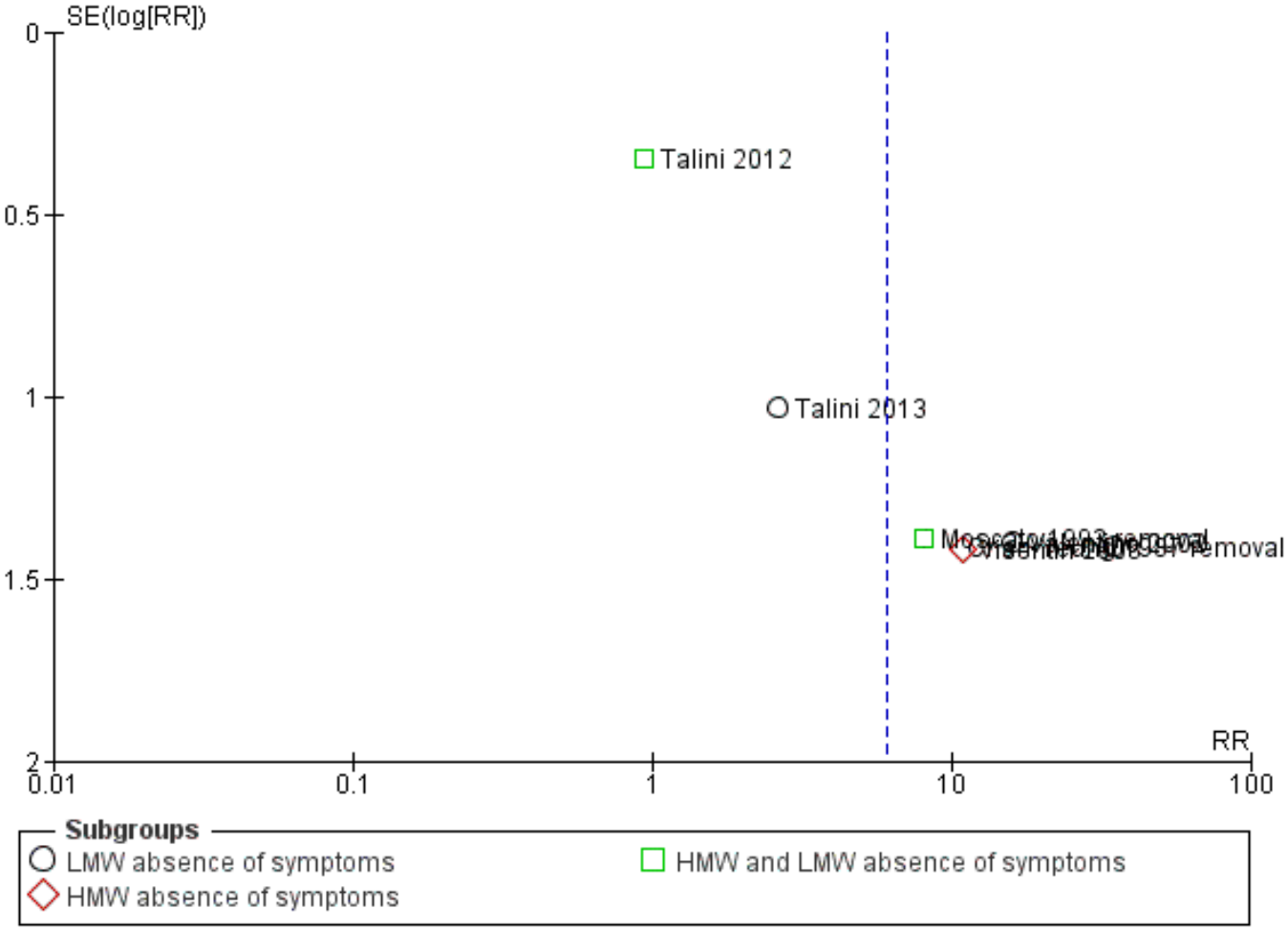


Figure 4. Funnel plot of comparison: 3 Removal from exposure versus reduction of exposure, outcome: 3.1 Absence of asthma symptoms.



A similar gap was also seen for improvement of asthma symptoms and FEV1% after removal from exposure versus continued exposure (Analysis 1.2; Analysis 1.3).

We did not find an indication of publication bias for the comparison removal versus continued exposure.

Quality of the Evidence

We used the five GRADE domains to assess the certainty of the evidence per comparison-outcome combination, and started from 'low quality' because we included only observational studies. We also considered upgrading factors, including a large effect size, confounding limited to reducing the effect size, and evidence of a dose-response effect. We downgraded all the comparisons to 'very low quality'.

In 'Comparison 1: Removal from exposure versus continued exposure,' we downgraded the comparisons for asthma symptoms (both absence and improvement) and change in FEV1 % a total of three levels, one level for each of the following 3 reasons: 1. limitations in the studies because of risk of bias due to selection of participants and failure to adjust for baseline differences in most studies; 2. inconsistency because of high heterogeneity as indicated by I^2 values that we could not explain; and 3. the likelihood of publication bias as indicated by the funnel plots. We downgraded the evidence for change in NSBH two levels for the first two factors noted above. Because of the high risk of bias we did not upgrade for a large effect size in any comparison.

In 'Comparison 2: Reduction of exposure versus continued exposure,' we downgraded all comparisons one level because of limitations in studies such as the risk of bias from participant selection, and because baseline differences were not adjusted for in most studies. We also downgraded the comparison for change in FEV1 % one level because of imprecision (i.e., fewer than 300 participants). We downgraded the comparison for absence of asthma symptoms because of the likelihood of publication bias as indicated by the funnel plot. Because of high risk of bias we did not upgrade because of a large effect size.

In 'Comparison 3: Removal from exposure versus reduction of exposure,' we downgraded all comparisons because of limitations in studies due to the risk of bias from selection of participants, and because baseline differences were not adjusted for in most studies. We downgraded the comparisons for asthma symptoms (both absence and improvement) and change in FEV1 % because of high

heterogeneity as indicated by I^2 values. However, heterogeneity was very low for the outcome of being unemployed. We downgraded the comparisons for improvement of asthma symptoms and being unemployed one level because of imprecision (i.e., fewer than 300 participants). We downgraded the comparison for absence of asthma symptoms because of the likelihood of publication bias as indicated by the funnel plot. Because of high risk of bias we did not upgrade because of a large effect size.

DISCUSSION

Summary of main results

See: 'Summary of findings' tables (Summary of findings for the main comparison; Summary of findings 2; Summary of findings 3. The 26 studies we included in this updated review reported three types of comparisons . We assessed the quality of evidence for all outcomes to be very low, which means that all the findings are very uncertain.

For removal of a worker from exposure compared to continued exposure, there is very low quality evidence that removal may improve asthma symptoms more, which can be measured either as absence or improvement of symptoms. Also FEV1 and NSBH may improve more after complete removal compared to continued exposure.

Reducing exposure compared to continued exposure may reduce asthma symptoms but not FEV1, and NSBH was not measured for this comparison.

Complete removal may improve asthma symptoms and FEV1 more than reduced exposure among the subset of patients with LMW exposures. NSBH was not measured for this comparison. Total removal from exposure may lead to unemployment more often than reduction of exposure.

Overall completeness and applicability of evidence

While many researchers worldwide have addressed occupational asthma, few have published systematic reviews of the effectiveness of workplace interventions for managing occupational asthma. The literature searches for this review relied on a variety of search terms applied in several electronic reference databases such as Cochrane Cental, Medline (Pubmed), Embase (Ovid), and NIOSHTIC-2. The searches were inclusive, netting thousands of articles that when we judged them for acceptability yielded 26 relevant articles. The searches for the initial review yielded 22 studies published over 29 years (1981-2010), while the recent update added four new studies from the eight-year period (2011 to 2019) following the publication of the original review by de Groene 2011. This suggests little change in the pace of production of research devoted to workplace interventions for occupational asthma.

Authors of studies achieved reduction of exposure in different ways. In the majority of studies, patients were transferred to an area of the workplace with reduced exposure to the causal agent. In some studies, the reduction was achieved by a change in PPE (introduction of new equipment, or an improvement in existing equipment) (Bernstein 2003 reduction; Rosenberg 1987 reduction; Talini 2012; Vandenplas 2002). Two studies achieved reduction of exposure with an education and training program (Dressel 2007; Dressel 2009). None of the studies included measurements of exposure levels. Overall, these studies were small, but still yielded statistically significant pooled results for the absence of asthma symptoms.

Generalizability of the results we found is limited to industrialized nations, with the best representation for Canada with four studies (all from the western province of British Columbia) and Western Europe with 21 studies. Canada far exceeded other countries for the number of occupational asthma patients considered in this review, with 45.1% (n = 765 of all 1,695 patients) from four studies. With 13 studies originating from Italy, this country had the best representation of the variety of asthma-related occupational exposures, and accounted for almost one third (n = 526, 31.0%) of all included patients. Another 379 patients included in eight studies, or 22.4% of the 1,695 total, were from other countries in Western Europe. The one study from the United States had only 25 cases (1.5%). Africa, Asia, Eastern Europe, and South America were not represented at all.

All studies addressed patients with sensitizer-induced asthma, with the possible exception of the potroom asthma investigation (Soyseth 1995). When categorized according to types of agents, the 26 included studies included five with findings specific for HMW agents, 15 with LMW agents, five with both HMW and LMW agents, and one with exposure to aluminum potroom agents. Among the 15 studies with LMW agents, four focused on plicatic acid in western red cedar (all from British Columbia in Canada) and nine focused on isocyanates.

Quality of the evidence

None of the included studies was a randomized controlled trial but three studies (Dressel 2007; Dressel 2009; Soyseth 1995) clearly evaluated and at least clearly allocated the intervention to study participants. All included studies are controlled before and after studies and we judged all of them to have a high risk of bias. None of the studies used a blinded outcome assessment. which resulted in a low quality score for all but four studies on the Downs and Black quality rating, defined as a score less than 50% for internal validity (Downs 1998).

Authors of included studies rarely described the methods they used for diagnosing occupational asthma. In the few studies that described their diagnostic methods, there was large variation between studies, and two studies included some cases of work-exacerbated asthma. Time issues were also a challenge, since we could not always determine exactly when individuals began an intervention, and the periods for exposure and follow-up could vary considerably among participants. The values for relevant health indicators such as FEV1 % and NSBH often differed between intervention and control groups at baseline, and we attempted to take these differences into account by examining changes in these values by the time of follow-up.

Not all studies reported the same critical health outcomes or presented them in a way that would have allowed us to include them in meta-analyses. The number of participants across all included studies ranged from 9 to 232. Because of the wide variation in many variables, including types of agents, outcome measurements, and follow-up periods, as well as the relatively small sample sizes, it was not feasible to conduct subgroup analyses.

We also downgraded the evidence because of heterogeneity in study results that we could not explain.

The studies reported in the review had a wide range of average follow-up times (5 weeks to 12 years), which might lead to the speculation of non-comparable results. In particular, improvement in health might be less likely with a short period of follow-up and yield a different effect estimate than with a longer period of follow-up. We assessed this possibility by comparing results between studies with average follow-up periods of up to one year and greater than one year. The five studies with short follow-up periods (and the average length of those periods) were Dressel 2007 (5 weeks), Dressel 2009 (1 year), Innocenti 1981 (<1 year), Mapp 1988 (0.8 years), and Moscato 1999 (1 year). When comparing removal from exposure to continued exposure, effect estimates for studies with short follow-up periods were distributed both below and above the median estimate for all studies. For example, with absence of asthma symptoms (Analysis 1.1), the risk ratios for the two short follow-up studies were ranked fourth (Mapp 1988) and seventh (Innocenti 1981) among all nine studies. For change in FEV1 % (Analysis 1.3), the mean differences for the two short follow-up studies were ranked second (Moscato 1999) and sixth (Mapp 1988) among all ten studies. Similar patterns were observed when comparing reduction of exposure to continued exposure. For absence of asthma symptoms (Analysis 2.1), the risk ratios for the short follow-up studies Dressel 2009 and Dressel 2007 were ranked second and sixth among the six studies. In addition, the mean difference in FEV1 % for Dressel 2007 was between the estimates from the other two studies (Analysis 2.2), close to the lowest of the three estimates.

Our review focuses on findings from occupational health studies that could involve support of a company, clinic, or insurance institution, potentially giving rise to a conflict of interest should they have a preference for a specific result. However, we concluded these conflicts of interest were unlikely or were minor if they did occur.

Potential biases in the review process

We believe our literature searches were comprehensive and unlikely to miss a relevant study reporting high-quality evidence that would have altered the current findings. The literature searches relied on appropriate databases and employed search terms consistent with the objectives of the review. The searches were very sensitive, with 4464 references screened for the current update, in addition to the 12,709 screened in the original Cochrane review by de Groene 2011. We did not intentionally search for abstracts from conference proceedings, a choice motivated by the fact that the content is typically not reviewed with the same rigor as peer-reviewed articles, so we do not consider this omission a weakness. We attempted to avoid omissions or bias by including articles in any language, and translated non-English articles into English using native speakers.

There was a considerable overlap of participants among the three studies led by one author (Talini 2012; Talini 2013; Talini 2015). We contacted the author and based on the information we received (one study did not have new set of participants), we excluded Talini 2015. This strategy helped us in avoiding double counts of the data contributed by the same participants in multiple publications. We contacted the authors of the study DiGiampaolo 2012 and asked for the actual numbers for annual FEV1 decline that were only presented graphically in the article. They were unable to provide these numbers, so we estimated the results for annual FEV1 decline from the graphs..

We also otherwise had to to make assumptions and calculations to obtain data for the meta-analysis. However, we believe that the assumptions were reasonable and the calculations correct.

Agreements and disagreements with other studies or reviews

Findings in the current review were the same as reported in the original Cochrane review by de Groene 2011. In short, removal from exposure may have a more favorable impact than continued exposure regarding absence of asthma symptoms, improvement in asthma symptoms, change in FEV1 %, and change in NSBH. Reduction of exposure may increase the likelihood of absence of asthma symptoms in comparison to continued exposure, but not of a change in FEV1 %. Removal from exposure may increase the likelihood of improvement of symptoms and FEV1 % change more than reduction of exposure among patients with LMW exposures. However, removal may also increase the likelihood of being unemployed.

Other reviews have also identified complete removal or avoidance of exposure as the best workplace intervention for managing occupational asthma. The European Respiratory Society (ERS) Task Force on the Management of Work-related Asthma reviewed the literature to address major issues related to occupational asthma (Baur 2012; Vandenplas 2012). Specific to management options for occupational asthma, the authors search of databases yielded 462 titles, from which they selected 50 for their review. Relevant to the objectives of our review, they concluded that persistence of exposure is likely to lead to worsening of asthma, and complete removal of exposure is associated with the highest probability of improvement. They also reached the conclusion that reduction of exposure has a beneficial effect for asthma status that is less than that of exposure removal, and, consequently, this approach should not be considered a “first choice therapeutic strategy” (Vandenplas 2012). The authors observed that although removal of exposure has the best chance of improving asthma status, it leads to recovery in less than one-third of the cases. In addition, they observed that PPE does not provide complete protection from the harmful effects of exposure, and recommended it should not be considered as a long-term option or for cases with severe asthma.

The Health and Safety Executive Asthma Partnership commissioned BOHRF to develop guidelines for the prevention, identification, and management of occupational asthma. The guidelines were published initially in 2004, followed by a 2010 update that was based on over 300 studies (Newman Taylor 2004; Nicholson 2005; Nicholson 2010). The authors concluded that complete avoidance of exposure was the best option for diagnosed cases of occupational asthma, and that reduction of exposure might lead to improvement but is not always effective (Nicholson 2010; Newman Taylor 2004).

Another systematic review by Rachiotis 2007 evaluated the effects on symptomatic and functional outcomes when occupational asthma cases ceased exposure to the causative agents. The authors did not judge the quality of the studies as part of the selection process, and they excluded studies that addressed reduction of exposure following diagnosis. They identified 39 relevant papers, the majority of which (n = 25) addressed cases associated with LMW agents. The frequency of complete symptomatic recovery ranged from zero to 100%, with a pooled prevalence of 32%. In addition, the re-

view revealed that NSBH at follow-up was common, with a pooled prevalence of 73% among the 39 articles.

The American College of Chest Physicians convened an expert panel and published a consensus document about the diagnosis and management of occupational asthma (Tarlo 2008). This document relied on a prior systematic review by Beach 2005. The expert panel's conclusions about workplace exposures after diagnosis varied by type of causative agent, recommending removal from exposure for sensitizer-induced cases and reduction of exposure for irritant-induced occupational asthma and work-exacerbated asthma.

In summary, these different reviews agree that removal from exposure is the best option for cases of occupational asthma, and reduction of exposure is less effective than removal.

Evidence suggests that PPE can contribute to primary (Heederik 2012) and secondary prevention (Beach 2005; Vandenplas 2012) of work-related asthma for some cases, at least on a temporary basis while more permanent solutions are sought further up the hierarchy of controls. A more recent study (Ilgaz 2019) reported some improvement in serial peak expiratory flow for occupational asthma cases attributed to metal-working fluids following the introduction of air-fed respirators, but the study did not include a comparison group.

AUTHORS' CONCLUSIONS

Implications for practice

Our review indicates that removing individuals with occupational asthma from exposure may be associated with several beneficial health outcomes (i.e., for asthma symptoms, FEV1 %, and NSBH) in comparison to continuing exposure. We are unsure because of the very low quality of the evidence. Reduction of exposure may also be associated with beneficial effects in symptoms relative to continued exposure, but not for FEV1 %. Removal of exposure may be associated with better results for asthma symptoms and FEV1 % in comparison to reduction of exposure for cases attributed to LMW agents. Reduction of exposure may be associated with less unemployment than removal from exposure. Providers should balance the potential clinical benefits of removal from exposure versus reduction of exposure with potential detrimental effects of unemployment.

Implications for research

The low quality of evidence in the current review and the relatively small numbers of studies and participants point to the need for better quality studies with larger numbers of participants. Only five of the 26 studies that provided evidence had more than 100 participants, and all but one of the five were published before the year 2000. Additional data are especially needed for workers exposed to HMW agents and for the study of reduction of exposure. Among the papers that reported results for included studies, only five had data for asthma cases exposed to HMW agents while fifteen had data on cases exposed to LMW agents (see Table 5). The deficit in sample sizes to study the impact of HMW agents is illustrated in Analysis 1.2, in which only one study with five participants addressed improvement of symptoms among cases with HMW exposures when comparing removal from exposure to continued exposure. If the HMW cases had the same RR = 2.47 as observed for all the studies in Analysis 1.2, and assuming alpha = 0.05 and power = 0.80, then there would need to be a total of 132 participants (i.e., 66 for each exposure status) based on standard sample size calculations (Rosner 2006-a, Rosner 2006-b).

Additional studies are also needed to address the effectiveness of workplace interventions for occupational asthma. Improvements in exposure data are needed, as are more information about symptom history prior to diagnosis and between diagnosis and the start of the intervention. We hope that future studies will include more information about asthma symptoms, FEV1, NSBH, FeNO, sputum eosinophilia, and other relevant indicators of asthma status before and during interventions.

The use of PPE is low in the hierarchy of controls for occupational exposure, but is often embraced by both asthma cases and their physicians and employers as a means to reduce exposures and maintain a patient's current job and income. More definitive conclusions about the effectiveness of PPE for occupational asthma depend on the completion of additional research.

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REFERENCES

References to studies included in this review

Bernstein 2003 reduction *{published data only}*

Bernstein DI, Karnani R, Giagini RE, Bernstein CK, Murphy K, Berendts B, et al. Clinical and occupational outcomes in health care workers with natural rubber latex allergy. *Annals of Allergy, Asthma & Immunology* 2003;**90**:209-13.

Bernstein 2003 removal *{published data only}*

Bernstein DI, Karnani R, Giagini RE, Bernstein CK, Murphy K, Berendts B, et al. Clinical and occupational outcomes in health care workers with natural rubber latex allergy. *Annals of Allergy, Asthma & Immunology* 2003;**90**:209-13.

Burge 1982 *{published data only}*

Burge PS. Occupational asthma in electronics workers caused by colophony fumes: follow-up of affected workers. *Thorax* 1982;**37**(5):348-53.

Chan-Yeung 1982 *{published data only}*

Chan-Yeung M, Lam S, Koener S. Clinical features and natural history of occupational asthma due to western red cedar (Thuja plicata). *American Journal of Medicine* 1982;**72**(3):411-5.

Chan-Yeung 1987 reduction *{published data only}*

Chan-Yeung M, MacLean L, Paggiaro PL. Follow-up study of 232 patients with occupational asthma caused by western red cedar (Thuja plicata). *Journal of Allergy and Clinical Immunology* 1987;**79**(5):792-6.

Chan-Yeung 1987 removal *{published data only}*

Chan-Yeung M, MacLean L, Paggiaro PL. Follow-up study of 232 patients with occupational asthma caused by western red cedar (Thuja plicata). *Journal of Allergy and Clinical Immunology* 1987;**79**(5):792-6.

DiGiampaolo 2012 *{published data only}*

Di Giampaolo L, Cavallucci E, Braga M, Renzetti A, Schiavone C, Quecchia C, Petrarca C, Di Gioacchino M. The persistence of allergen exposure favors pulmonary function decline in workers with allergic occupational asthma. *Int Arch Occup Environ Health* 2012;**85**:181–188.

Dressel 2007 *{published data only}*

Dressel H, Gross C, De La Motte D, Sultz J, Jorres RA, Nowak D. Educational intervention decreases exhaled nitric oxide in farmers with occupational asthma. *European Respiratory Journal* 2007;**30**(3):545-8.

Dressel 2009 *{published data only}*

Dressel H, Gross C, de la Motte D, Sultz J, Jorres RA, Nowak D. Educational intervention in farmers with occupational asthma: long-term effect on exhaled nitric oxide. *Journal of Investigational Allergology and Clinical Immunology* 2009;**19**(1):49-53.

Innocenti 1981 *{published data only}*

Innocenti A, Franzinelli A, Sartorelli E. Longitudinal study of workers suffering from polyurethane asthma [Studio longitudinale in lavoratori affetti da asma da resine poliuretaniche]. *La Medicina del Lavoro* 1981;**3**:231-7.

Lin 1996 *{published data only}*

Lin FJ, Dimich-Ward H, Chan-Yeung M. Longitudinal decline in lung function in patients with occupational asthma due to western red cedar. *Occupational and Environmental Medicine* 1996;**53**(11):753-6.

Mapp 1988 *{published data only}*

Mapp CE, Corona PC, De Marzo N, Fabbri L. Persistent asthma due isocyanates. A follow-up study of subjects with occupational asthma due to toluene diisocyanate (TDI). *American Review of Respiratory Disease* 1988;**137**(6):1326-9.

Marabini 1993 *{published data only}*

Marabini A, Dimich-Ward H, Kwan SY, Kennedy SM, Waxler-Morrison N, Chan-Yeung M. Clinical and socioeconomic features of subjects with red cedar asthma. A follow-up study. *Chest* 1993;**104**(3):821-4.

Marabini 1994 *{published data only}*

Marabini A, Brugnami G, Curradi F, Severini C, Siracusa A. Response to bronchoprovocation test and outcome of occupational asthma. A follow up study of subjects with TDI asthma [Risposta al test di prococazione bronchtale specifica ed evoluzione dell'asma professionale. Studio longitudinale in soggetti con asma da toluendiisocianato (TDI)]. *Medicina del Lavoro* 1994;**85**(2):134-41.

Moscato 1993 reduction *{published data only}*

Moscato G, Bertoletti R, Biscaldi G, Dellabianca A, Niniano R, Colli MC. Occupational asthma: fate and management after the diagnosis. *Giornale Italiano di Medicina del Lavoro* 1993;**15**(1-4):27-31.

Moscato 1993 removal *{published data only}*

Moscato G, Bertoletti R, Biscaldi G, Dellabianca A, Niniano R, Colli MC. Occupational asthma: fate and management after the diagnosis. *Giornale Italiano di Medicina del Lavoro* 1993;**15**(1-4):27-31.

Moscato 1999 *{published data only}*

Moscato G, Dellabianca A, Perfetti L, Brame B, Galdi E, Niniano R, et al. Occupational asthma: a longitudinal study on the clinical and socioeconomic outcome after diagnosis. *Chest* 1999;**115**(1):249-56.

Munoz 2008 *{published data only}*

Munoz X, Gomez-Olles S, Cruz MJ, Untoria MD, Orriols R, Morell F. Course of bronchial hyper responsiveness in patients with occupational asthma caused by exposure to persulfate salts [Evolución de la hiperrespuesta bronquialen pacientes con asma ocupacional porexposición a sales de persulfato]. *Archivos de Bronconeumologia* 2008;**44**(3):140-5.

Munoz 2014 *{published data only}*

Munoz X, Viladrich M, Manso L, del Pozo V, Quirce S, Cruz MJ, Carmona F, Sanchez-Pla A, Sastre J. Evolution of occupational

asthma: does cessation of exposure really improve prognosis?. *Respir Med* 2014;**108**(9):1363-70.

Padoan 2003 *{published data only}*

Padoan M, Pozzato V, Simoni M, Zedda L, Milan G, Bononi I, et al. Long-term follow-up of toluene diisocyanate-induced asthma. *European Respiratory Journal* 2003;**21**(4):637-40.

Paggiaro 1984 *{published data only}*

Paggiaro PL, Loi AM, Rossi O, Ferrante B, Pardi F, Roselli MG, et al. Follow-up study of patients with respiratory disease due to toluene diisocyanate (TDI). *Clinical Allergy* 1984;**14**(5):463-9.

Pisati 1994 *{published data only}*

Pisati G, Zedda S. Outcome of occupational asthma due to cobalt hypersensitivity. *Science of the Total Environment* 1994;**150**(1-3):167-71.

Rosenberg 1987 reduction *{published data only}*

Rosenberg N, Garnier R, Rousselin X, Metz TR, Gervais P. Clinical and socio-professional fate of isocyanate-induced asthma. *Clinical Allergy* 1987;**17**(1):55-61.

Rosenberg 1987 removal *{published data only}*

Rosenberg N, Garbnier R, Rousselin X, Metz TR, Gervais P. Clinical and socio-professional fate of isocyanate-induced asthma. *Clinical Allergy* 1987;**17**(1):55-61.

Soyseth 1995 *{published data only}*

Soyseth V, Kongerud J, Aalen OO, Botten G, Boe J. Bronchial responsiveness decreases in relocated aluminium potroom workers compared with workers who continue their potroom exposure. *International Archives of Occupational & Environmental Health* 1995;**67**(1):53-7.

Talini 2012 *{published data only}*

Talini D, Novelli F, Bacci E, Bartoli M, Cianchetti S, Costa F, Dente FL, Di Franco A, Latorre M, Malagrino L, Vagaggini B, Celi A, Paggiaro P. Sputum eosinophilia is a determinant of FEV1 decline in occupational asthma: results of an observational study. *BMJ Open* 2015;**5**(1):e005748.

* Talini D, Novelli F, Melosini L, Bacci E, Bartoli ML, Cianchetti S, Dente FL, Di Franco A, Vagaggini B, Paggiaro PL. May the reduction of exposure to specific sensitizers be an alternative to work cessation in occupational asthma? Results from a follow-up study. *Int Arch Allergy Immunol* 2012;**157**(2):186-193.

Talini 2013 *{published data only}*

Talini D, Novelli F, Bacci E, Bartoli M, Cianchetti S, Costa F, Dente FL, Di Franco A, Latorre M, Malagrino L, Vagaggini B, Celi A, Paggiaro P. Sputum eosinophilia is a determinant of FEV1 decline in occupational asthma: results of an observational study. *BMJ Open* 2015;**5**(1):e005748.

* Talini D, Novelli F, Bacci E, Costa F, Dente FL, Di Franco A, Malagrino L, Vagaggini B, Paggiaro P. Mild improvement in symptoms and pulmonary function in a long-term follow-up of patients with toluene di-isocyanate-induced asthma. *Int Arch Allergy Immunol* 2013;**161**(2):189-94.

Valentino 2002 *{published data only}*

Valentino M, Rapisarda V. Course of isocyanate-induced asthma in relation to exposure cessation: longitudinal study of 50 subjects [Evoluzione dell'asma da isocianati in rapporto alla cessazione dell'esposizione: studio longitudinale su 50 soggetti]. *Giornale Italiano di Medicina del Lavoro Ed Ergonomia* 2002;**24**(1):26-31.

Vandenplas 2002 *{published data only}*

Vandenplas O, Jamart J, Delwiche JP, Evrard G, Larbanois A. Occupational asthma caused by natural rubber latex: outcome according to cessation or reduction of exposure. *Journal of Allergy & Clinical Immunology* 2002;**109**(1):125-30.

Visentin 2003 *{published data only}*

Visentin A, Fedeli U, Zanetti C, Marcer G, Bordin A, Zedda L, et al. Follow up of latex-induced occupational asthma [Follow up dell'asma professionale da latice]. *Giornale Italiano di Medicina del Lavoro Ed Ergonomia* 2003;**25**(Suppl 3):190-1.

References to studies excluded from this review

Antao 2011 *{published data only}*

Antao VC, Pallos LL, Shim YK, Sapp JH 2nd, Brackbill RM, Cone JE, Stellman SD, Farfel MR. Respiratory protective equipment, mask use, and respiratory outcomes among World Trade Center rescue and recovery workers. *Am J Ind Med* 2011;**54**(12):897-905. [PUBMED: 21932428]

Bailey 2009 {*unpublished data only***}**

Bailey R, Park JH, Rena Saito CIH, Kreiss K, Cox-Ganser J. Evaluation of dampness-associated respiratory symptoms with relocation of staff during remediation of an elementary school - North Carolina.. NIOSH Health Hazard Evaluation Report 2009; Vol. HETA-2009-0172-3124:http://www.cdc.gov/niosh/hhe/reports/pdfs/2009-0172-3124.pdf.

Carlsten 2013 *{published data only}*

Carlsten C, Dybuncio A, Pui MM, Chan-Yeung M. Respiratory impairment and systemic inflammation in cedar asthmatics removed from exposure. *PLoS ONE* 2013;**8**(2):e57166.

De Zotti 2000 *{published data only}*

De Zotti R, Myuran A, Negro C. Follow-up of allergic symptoms in a group of health care workers sensitised to latex [Follow-up dei sintomi allergici in un gruppo di operatori sanitari sensibilizzati al lattice]. *La Medicina del Lavoro* 2000;**91**(1):53-60.

Donoghue 2011 *{published data only}*

Donoghue AM, Frisch N, Ison M, Walpole G, Capil R, Curl C, Di Corleto R, Hanna B, Robson R, Viljoen D. Occupational asthma in the aluminum smelters of Australia and New Zealand: 1991-2006.. *Am J Ind Med* 2011;**54**(3):224-231.

Durham 2011 *{published data only}*

Durham AD, Bergier S, Morisod X, Locatelli I, Zellweger JP, Huynh CK, Cornuz J. Improved health of hospitality workers after a Swiss cantonal smoking ban. *Swiss Med Wkly* 2011;**141**:w13317.

Fishwick 2011 *{published data only}*

Fishwick D, Harris-Roberts J, Robinson E, Evans G, Barraclough R, Sen D, Curran AD. Impact of worker education on respiratory symptoms and sensitization in bakeries. *Occup Med (Lond)* 2011;**61**(5):321-327.

Ilgaz 2019 *{published data only}*

Ilgaz A, Moore VC, Robertson AS, Walters GI, Burge PS. Occupational asthma; the limited role of air-fed respiratory protective equipment. *Occup Med (Lond)* 2019;**69**(5):329 335. [DOI: 10.1093/occmed/kqz074]

Karvala 2011 *{published data only}*

Karvala K, Toskala E, Luukkonen R, Uitti J, Lappalainen S, Nordman H. Prolonged exposure to damp and moldy workplaces and new-onset asthma. *Int Arch Occup Environ Health* 2011;**84**(7):713-721.

Kim 2013 *{published data only}*

Kim MH, Jung JW, Kang HR. The usefulness of job relocation and serum eosinophil cationic protein in baker's asthma. *Int Arch Allergy Immunol* 2013;**161**(3):252-257.

Klusackova 2006 *{published data only}*

Klusackova P, Pelclova D, Jindriska Levedova D, Mareckova H, Brabec M. Occupational asthma after withdrawal from the occupational allergen exposure. *Industrial Health* 2006;**44**(4):629-38.

Labrecque 2011 *{published data only}*

Labrecque M, Malo JL, Alaoui KM, Rabhi K. Medical surveillance programme for diisocyanate exposure.. *Occup Environ Med* 2011;**68**(4):302-307.

Lemiere 2010 *{published data only}*

Lemiere C, Chaboillez S, Welman M, Maghni K. Outcome of occupational asthma after removal from exposure: A follow-up study. *Can Respir J* 04/28/2010;**17**(2):61-6.

Madureira 2014 *{published data only}*

Madureira J, Mendes A, Teixeira JP. Evaluation of a smoke-free law on indoor air quality and on workers' health in Portuguese restaurants. *J Occup Environ Hyg* 2014;**11**(4):201-209.

Patovirta 2004 *{published data only}*

Patovirta RL, Husman T, Haverinen U, Vahteristo M, Uitti JA, Tukiainen H, et al. The remediation of mold damaged school - a three-year follow-up study on teachers' health. *Central European Journal of Public Health* 2004;**12**(1):36-42.

Pohl 2003 *{published data only}*

Pohl K, Negro C, D'Agostin F, Giommi E, De Zotti R. Follow up of symptoms, lung function and specific sensitization in a group of workers with latex asthma ans rhinitis [Follow up dei sintomi, dei parametri di funzionalita respiratoria e dei dati di sensibilizzazione specifica in un gruppo di soggetti con asma e rinite da lattice]. *Giornale Italiano di Medicina del Lavoro Ed Ergonomia* 2003;**25**(Suppl):235-6.

Saetta 1992 *{published data only}*

Saetta M, Maestrelli P, Di Stefano A, De Marzo N, Milani GF, Pivirotto F, et al. Effect of cessation of exposure to toluene diisocyanate (TDI) on bronchial mucosa of subjects with TDI-induced asthma. *American Review of Respiratory Disease* 1992;**145**(1):169-74.

Schoj 2010 *{published data only}*

Schoj V, Alderete M, Ruiz E, Hasdeu S, Linetzky B, Ferrante D. The impact of a 100% smoke-free law on the health of hospitality workers from the city of Neuquen, Argentina. *Tob Control* 2010;**19**(2):134-137.

Singh 2010 *{published data only}*

Singh A, Syal M, Grady SC, Korkmaz S. Effects of green buildings on employee health and productivity. *Am J Public Health* 2010;**100**(9):1665-1668.

Stocks 2013 *{published data only}*

Stocks SJ, McNamee R, Turner S, Carder M, Agius RM. Assessing the impact of national level interventions on workplace respiratory disease in the UK: part 2--regulatory activity by the Health and Safety Executive. *Occup Environ Med* 2013;**70**(7):483-490.

Stocks 2015 *{published data only}*

Stocks SJ, Jones K, Piney M, Agius RM. Isocyanate exposure and asthma in the UK vehicle repair industry. *Occup Med (Lond)* 2015;**65**(9):713-718.

Talini 2015 *{published data only}*

Talini D, Novelli F, Bacci E, Bartoli M, Cianchetti S, Costa F, Dente FL, Di Franco A, Latorre M, Malagrino L, Vagaggini B, Celi A, Paggiaro P. Sputum eosinophilia is a determinant of FEV1 decline in occupational asthma: results of an observational study. *BMJ Open* 2015;**5**(1):e005748.

Additional references

Aasen 2013

Aasen TB, Burge PS, Henneberger PK, Schlunssen V, Baur X. Diagnostic approach in cases with suspected work-related asthma. *J Occup Med Toxicol* 2013;**8**(1):17.

AOEC 2018

AOEC. Exposure Code Lookup. http://www.aoecdata.org/ExpCodeLookup.aspx. Accessed November 17, 2018.

Balshem 2011

Balshem H, Helfand M, Schunemann HJ, Oxman AD, Kunz R, Brozek J, et al. GRADE guidelines: 3. Rating the quality of evidence. *Journal of clinical epidemiology* 2011;**64**(4):401-6. [PUBMED: 21208779]

Baur 2012

Baur XT, Sigsgaard T, Aasen B, Burge PS, Heederik D, Henneberger P, Maestrelli P, Rooyackers J, Schlunssen V, Vandenplas O, Wilken D. Guidelines for the management of work-related asthma. *European Respiratory Journal* 2012;**39**(3):529-545.

Baur 2013

Baur X. A compendium of causative agents of occupational asthma. *Journal of Occupational Medicine and Toxicology.* 2013;**8**:15.

Beach 2005

Beach J, Rowe BH, Blitz S, Crumley E, Hooton N, Russell K, et al. Diagnosis and management of work-related asthma. University of Alberta Evidence-based Practice Center; 2005. Evidence Report/Technology Assessment.

Brooks 1985

Brooks SM, Weiss MA, Bernstein IL. Reactive airways dysfunction syndrome (RADS). Persistent asthma syndrome after high level irritant exposures. *Chest* 1985;**88**(3):376-384.

Chan-Yeung 1995

Chan-Yeung MB, Malo JL. Occupational asthma. *New England Journal of Medicine* 1995;**333**(2):107-12.

CNESST 2018

CNESST. Occupational asthma. List of agents causing occupational asthma with references. http://www.csst.qc.ca/en/prevention/reptox/occupational-asthma/Documents/AgentsAnglais.pdf. Accessed November 17, 2018.

Coates 2017

Coates A, Wanger L, Cockcroft J, Culver DW, Carlsen BH, Diamant KH, Gauvreau Z, Hall G, Hallstrand GL, Horvath TS, De Jongh I, Joos FHC, Kaminsky G, Laube DA, Leuppi BL, Sterk JD. ERS technical standard on bronchial challenge testing: General considerations and performance of methacholine challenge tests. *European Respiratory Journal* 2019;**49**(5):1-17.

Downs 1998

Downs SH, Black N. The feasibility of creating a checklist for the assessment of the methodological quality both of randomised and non-randomised studies of health care interventions. *Journal of Epidemiology and Community Health* 1998;**52**:377-84.

Dumas 2016

Dumas O, Le Moual N. Do chronic workplace irritant exposures cause asthma?. *Current Opinion in Allergy and Clinical Immunology* 2016;**16**(2):75-85.

EPOC

Cochrane Effective Practice and Organisation of Care Group. EPOC resources for review authors. http://www.epoc.cochrane.org/en/handsearchers.html (accessed 19 February 2009).

Heederik 2012

Heederik D, Henneberger PK, Redlich CA. Primary prevention: Exposure reduction, skin exposure and respiratory protection. *Europ Resp Rev* 2012;**21**(124):112-124.

Henneberger 2011

Henneberger PK, Redlich CA, Callahan DB, Harber P, Lemiere C, Martin J, Tarlo SM, Vandenplas O, Toren K. An official American Thoracic Society statement: work-exacerbated asthma. *Am J Respir Crit Care Med* 2011;**184**:368-378.

Higgins 2011

Higgins JPT, Green S. Cochrane Handbook for Systematic Reviews of Interventions. Vol. **5.1.0**, The Cochrane Collaboration, 2011.

Knoeller 2013

Knoeller GE, Mazurek JM, Moorman JE. Health-related quality of life among adults with work-related asthma in the United States. *Qual Life Res* 2013;**22**(4):771-780.

Milton 1998

Milton DK, Solomon EM, Rosiello RA, Herrick RF. Risk and incidence of asthma attributable to occupational exposure among HMO members. *American Journal of Industrial Medicine* 1998;**33**(1):1-10.

Moscato 2012

Moscato G, Pala G, Barnig C, De Blay F, Del Giacco SR, Folletti I, et al. EAACI consensus statement for investigation of work-related asthma in non-specialized centres. *Allergy: European Journal of Allergy and Clinical Immunology* 2012;**67**(4):491-501.

Newman Taylor 2004

Newman Taylor AJ, Nicholson PJ, Sullinan P, Boyle C, Burge PS. Guidelines for the prevention, identification & management of occupational asthma: Evidence review & recommendation. London: British Occupational Health Research Foundation, 2004.

Nicholson 2005

Nicholson PJ, Cullinan P, Newman AJ, Burge PS, Boyle C. Evidence based guidelines for the prevention, identification, and management of occupational asthma. *Occupational & Environmental Medicine* 2005;**62**:290-9.

Nicholson 2010

Nicholson PJ, Cullinan P, Burge PS, Boyle C. Occupational asthma: Prevention, identification & management: Systematic review & recommendations. British Occupational Health Research Foundation. London 2010:1-71.

Nicholson 2012

Nicholson PJ, Cullinan P, Burge S. Concise guidance: Diagnosis, management and prevention of occupational asthma. *Clinical Medicine, Journal of the Royal College of Physicians of London* 2012;**12**(2):156-159.

Rachiotis 2007

Rachiotis G, Savani R, Brant A, MacNeill SJ, Newman Taylor A, Cullinan P. Outcome of occupational asthma after cessation of exposure: a systematic review. *Thorax* 2007;**62**:147-52.

RevMan 2014

Cochrane. Review Manager (RevMan), Version 5.3 [Computer Program]. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014.

Rosenman 2015

Rosenman KD, Beckett WS. Web based listing of agents associated with new onset work-related asthma. *Respiratory Medicine* 2015;**109**(5):625-631.

Rosner 2006-a

Rosner, B. Chapter 10 Hypothesis Testing: Categorical Data. Fundamentals of biostatistics. 6th Edition. Belmont, CA: Thomson-Brooks/Cole, 2006:385-463. [ISBN: 0534418201]

Rosner 2006-b

Rosner, B. Chapter 8 Hypothesis Testing: Two-Sample Inference. Fundamentals of biostatistics. 6th Edition. Belmont, CA: Thomson-Brooks/Cole, 2006:296-358. [ISBN: 0534418201]

Shofer 2006

Shofer S, Haus BM, Kuschner WG. Quality of occupational history assessments in working age adults with newly diagnosed asthma. *Chest* 2006;**130**(2):455-462.

Suojalehto 2014

Suojalehto H, Cullinan P. Specific inhalation challenge tests for occupational asthma in Europe: A survey.. *European Respiratory Review* 2014;**23**(132):266-270.

Tarlo 1994

Tarlo SM, Sussman G, Contala A, Swanson MC. Control of airborne latex by use of powder-free latex gloves. *The Journal of Allergy and Clinical Immunology* 1994;**93**(6):985-989.

Tarlo 2008

Tarlo SM, Balmes J, Balkissoon R, Beach J, Beckett W, Bernstein D, et al. Diagnosis and management of work-related asthma: American College of Chest Physicians Consensus Statement. *Chest* 2008;**134**(Suppl 3):1s-41s.

Tarlo 2014

Tarlo SM, Lemiere C. Occupational asthma. *New England Journal of Medicine* 2014;**370**(7):640-649.

Toren 2009

Toren K, Blanc PD. Asthma caused by occupational exposures is common - a systematic analysis of estimates of the population-attributable fraction. *BMC Pulmonary Medicine* 2009;**9**(7):1-10.

Vandenplas 2008

Vandenplas 2008. Socioeconomic impact of work-related asthma. *Expert Review of Pharmacoeconomics and Outcomes Research* 2008;**8**(4):395-400.

Vandenplas 2012

Vandenplas O, Dressel H, Nowak D, Jamart J. What is the optimal management option for occupational asthma?. *Eur Respir Rev* 2012;**21**(124):97-104.

Vandenplas 2014

Vandenplas O, Suojalehto H, Aasen TB, Baur X, Burge PS5, de Blay F. Specific inhalation challenge in the diagnosis of occupational asthma: Consensus statement. *European Respiratory Journal* 2014;**43**(6):1573-1587.

References to other published versions of this review

de Groene 2011

de Groene GJ, Pal TM, Beach J, Tarlo SM, Spreeuwers D, Frings-Dresen MHW, Mattioli S, Verbeek JH. Workplace interventions for treatment of occupational asthma. *Cochrane Database of Systematic Reviews* 2011, Issue 5. [DOI: 10.1002/14651858.CD006308.pub3]

* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Bernstein 2003 reduction

Methods	Controlled before and after study; retrospective
Participants	21 (67) participants with asthma; 3 men, 64 women Age: mean 36.1 years Occupations: healthcare workers Patients were recruited through advertisement Asthma was diagnosed on history and questionnaires and immunological testing: work-related asthma, unclear whether OA or WAA
Interventions	Intervention: reduction of exposure: 20; 19 change to personal use of non-latex gloves at work, 1 area transfer Controls: continued exposure: 1
Outcomes	1. Respiratory symptoms; questionnaire, modified from instrument used by Liss et al; improvement of symptoms in numbers of individuals was reported 2. Income; reported numbers of individuals with reduction in income.

Bernstein 2003 reduction *(Continued)*

Notes	Exposed to: natural rubber latex (NRL) Intervention not planned Follow-up: mean 3.9 years Duration of exposure before onset of symptoms in years: mean 5.2, range: 0 to 32 Duration of symptoms before diagnosis in years: mean 4.5 Unclear whether OA or WAA Place (country, region): USA, Ohio Bernstein 2003 removal and Bernstein 2003 reduction are subdivisions of the same study/article Sources of funding not stated

Bernstein 2003 removal

Methods	Controlled before and after study; retrospective
Participants	25 (67) participants with asthma (work-related asthma, unclear whether OA or WAA); 3 men, 64 women Age: mean 36.1 years Occupations: healthcare workers Patients were recruited through advertisement Asthma was diagnosed on history and questionnaires and immunological testing: work-related asthma, unclear whether OA or WAA
Interventions	Intervention: removal from exposure: 4, due to job change or exit workplace Controls: continued exposure:1
Outcomes	1. Respiratory symptoms; questionnaire, modified from instrument used by Liss et al; improvement of symptoms in numbers of individuals was reported 2. Income; reported numbers of individuals with reduction in income
Notes	Exposed to: natural rubber latex (NRL) Intervention not planned Follow-up: mean 3.9 years Duration of exposure before onset of symptoms in years: mean 5.2, range: 0 to 32 Duration of symptoms before diagnosis in years: mean 4.5 Unclear whether OA or WAA Place (country, region): USA, Ohio Bernstein 2003 removal and Bernstein 2003 reduction are subdivisions of the same study/article Sources of funding not stated

Burge 1982

Methods	Controlled before and after study; retrospective
Participants	28 (39) participants; 2 men, 26 women Age: mean 50 years Occupations: electronic workers Patients diagnosed before with OA were asked for follow-up in the same hospital Occupational asthma diagnosed based on specific inhalation challenge
Interventions	Intervention: removal from exposure; left company: 20 Controls: reduction of exposure; moved to alternative work within the same company: 8
Outcomes	1. Respiratory symptoms; questionnaire based on the 1976 MRC respiratory questionnaire; improvement of and free of symptoms in numbers of individuals was reported 2. Spirometry; lung function expressed as percent predicted 3. NSBP histamine PC20 4. Employment; reported numbers of individuals employed
Notes	Exposed to: colophony Intervention not planned Study analysed 3 groups: workers with OA who left company and who moved to other work and workers with asthma, not OA Follow-up: mean 28 months, range: 12 to 45 Duration of exposure before onset of symptoms: not mentioned Duration of symptoms before (diagnosis) leaving work in months: 30, range: 10 to 108 Place (country, city): United Kingdom, Birmingham Sources of funding not stated

Chan-Yeung 1982

Methods	Controlled before and after study; retrospective
Participants	125 participants: all men ? Age: mean 41.1 years Occupations: red cedar workers They were recalled for examination at the university clinic of Vancouver Occupational asthma diagnosed based on specific inhalation challenge
Interventions	Intervention: removal from exposure: 75 Controls: continued exposure: 50
Outcomes	1. Respiratory symptoms; interview; results presented as asymptomatic and symptomatic numbers of individuals 2. FEV1 % predicted 3. FVC % predicted

Chan-Yeung 1982 *(Continued)*

	4. FEF 25% to 75% 5. NSBP methacholine PC20 6. Type of asthmatic reaction
Notes	Exposed to: western red cedar (WRC) Intervention not planned Follow-up: mean 3.5 years Duration of exposure before onset of symptoms in months: mean 50.5 (SD 75.3) Duration of symptoms before diagnosis in months: mean 28.9 (SD 58.9) Analysed in 3 groups: removal from exposure with and without symptoms and continued exposure Place (country, region): Canada, British Columbia Sources of funding not stated

Chan-Yeung 1987 reduction

Methods	Controlled before and after study; retrospective
Participants	96 participants: 94 men, 2 women Age: mean 40.5 years Occupations: red cedar workers They were recalled for examination at the university clinic of Vancouver Occupational asthma diagnosed based on specific inhalation challenge
Interventions	Intervention: reduction of exposure: 42 Controls: continued exposure: 54
Outcomes	1. Respiratory symptoms; interview; results presented as asymptomatic and symptomatic numbers of individuals 2. FEV1 % predicted 3. FVC % predicted 4. NSBP methacholine PC20 5. Type of asthmatic reaction 6. Employment; text to explain differences was provided
Notes	Exposed to: west red cedar (WRC) Intervention not planned Follow-up: mean 50 months Duration of exposure before onset of symptoms in years: 3.8 versus 3.1 Duration of symptoms before diagnosis in years: 1.7 versus 2.6 Analysed in four groups: removal from exposure with and without symptoms, daily and intermittently exposure Place (country, region): Canada, British Columbia

Chan-Yeung 1987 reduction *(Continued)*

	Chan-Yeung 1987 removal and Chan-Yeung 1987 reduction are subdivisions of the same study/article
	Sources of funding not stated

Chan-Yeung 1987 removal

Methods	Controlled before and after study; retrospective
Participants	190 participants: 186 men, 4 women Age: mean 41.9 years Occupations: red cedar workers They were recalled for examination at the university clinic of Vancouver Occupational asthma diagnosed based on specific inhalation challenge
Interventions	Intervention: removal from exposure: 136 Controls: continued exposure: 54
Outcomes	1. Respiratory symptoms; interview; results presented as asymptomatic and symptomatic numbers of individuals 2. FEV1 % predicted 3. FVC % predicted 4. NSBP methacholine PC20 5. Type of asthmatic reaction
Notes	Exposed to: western red cedar (WRC) Intervention not planned Follow-up: 48 months Duration of exposure before onset of symptoms in years: 4.6 versus 3.1 Duration of symptoms before diagnosis in years: 2.2 versus 2.6 Analysed in 4 groups: stop exposure with and without symptoms, daily and intermittently exposure Place (country, region): Canada, British Columbia Chan-Yeung 1987 removal and Chan-Yeung 1987 reduction are subdivisions of the same study/article Sources of funding not stated

DiGiampaolo 2012

Methods	Controlled Before-After Study, prospective
Participants	Participants: 58 participants Age : mean 37.6 years Sex distribution: not reported All allergic asthmatic workers evaluated during 1995-1997 that had been referred to a center; all with confirmed occupational asthma by American Thoracic Society criteria

DiGiampaolo 2012 *(Continued)*

Interventions	Intervention group changed jobs after diagnosis and were no longer exposed to sensitizing allergens (n=30). Comparison group had not changed jobs but had a reduced level of exposure as a result of preventive measures in the work place (n=28),
Outcomes	1. Loss of lung function as FEV1 normalized to the third power of the subject's height. This outcome was subdivided by smoking status, FEV1 variability at follow-up, and disease duration
Notes	Exposed to: Asthmatic allergens, mix of HMW and LMW agents Intervention not planned Follow-up: 12 years Duration of exposure before onset of symptoms: Not mentioned Duration of symptoms before diagnosis: 6.5 years for group A, 6.8 years for group B Data only listed in graphs, not tables Place (Country, city): Italy, Milan Source of funding: Not stated

Dressel 2007

Methods	Controlled before and after study; prospective
Participants	105 participants: 68 men, 37 women Age: mean 47.1 years Occupations: farmers (cow, swine, pig) Diagnosis based on history, questionnaires and immunological testing ? (not clearly mentioned) Intervention voluntary and organised by 2 German statutory accident insurance institutions for agriculture, Bavaria
Interventions	Intervention: education program: lecture about asthma, technical and organisational means of allergen avoidance and demonstration of use of protective equipment; 81 farmers Controls: no education program; 24 farmers
Outcomes	1. Respiratory symptoms; interview-based questionnaire; reported current symptoms at work in numbers of individuals 2. Exhaled nitric oxide fraction (FeNO) 3. FEV1 % predicted 4. FVC % predicted
Notes	Exposed to: cow dander and storage mite Intervention planned Follow-up: mean 5 weeks Same intervention as examined in Dressel 2009 study, but in this report with a follow-up interval of 5 weeks rather than the 1 year as done in the Dressel 2009 study. Duration of exposure before onset of symptoms: not mentioned Duration of symptoms before diagnosis: not mentioned Place (country, region): Germany, Bavaria Study supported by 2 German statutory accident insurance institutions for agriculture, Bavaria

Dressel 2009

Methods	Controlled before and after study; prospective
Participants	58 participants: 39 men, 19 women Age: mean 45.9 years Occupations: farmers (cow, swine) Diagnosis based on history, questionnaires and immunological testing ? (not clearly described) Intervention voluntary and organised by 2 German statutory accident insurance institutions for agriculture, Bavaria
Interventions	Intervention: education program: lecture about asthma, technical and organisational means of allergen avoidance and demonstration of use of protective equipment; 43 farmers Controls: no education program; 15 farmers
Outcomes	1. Respiratory symptoms; interview-based questionnaire; reported wheeze and shortness of breath 2. Exhaled nitric oxide fraction (FeNO) 3. FEV1, liters 4. FEV1/FVC %
Notes	Exposed to: cow dander and storage mite Intervention planned Follow-up: 1 year Same intervention as examined in Dressel 2007 study, but in this report with a follow-up interval of 1 year rather than the 5 weeks as done in the Dressel 2007 study, and with a smaller subset of the original study participants Duration of exposure before onset of symptoms: not mentioned Duration of symptoms before diagnosis: not mentioned Place (country, region): Germany, Bavaria Study supported by 2 German statutory accident insurance institutions for agriculture, Bavaria

Innocenti 1981

Methods	Controlled before and after study; retrospective
Participants	50 participants: 39 men, 11 women Age: 19 to 67 years 35 furniture factory workers and 15 refrigerator factory workers with occupational asthma Participants were patients from occupational health clinic, University of Siena Diagnosis of OA was based on specific inhalation challenge
Interventions	Intervention: removal from exposure (due to job change): 37 workers Controls: continued exposure (same job): 13 workers

Innocenti 1981 *(Continued)*

Outcomes	1. Respiratory symptoms. Results presented as asymptomatic and symptomatic numbers of individuals. 2. Mean annual decrease FEV1 ml/yr 3. Mean annual decrease FVC ml/yr
Notes	Exposed to: toluene di isocyanate (TDI) Intervention not planned. Follow-up > 12 months; exact timing of follow-up not reported Outcome 2 & 3: restricted to 25 workers Duration of exposure before onset of symptoms: not mentioned Duration of symptoms before diagnosis: not mentioned Place (country, city): Italy, Siena Article written in Italian language Sources of funding not stated

Lin 1996

Methods	Controlled before and after study; retrospective
Participants	201 participants: all men Age: mean 40.9 years Occupations: western red cedar workers in the lumber industry Follow-up examination at the respiratory clinic of the university of British Columbia Diagnosis of OA was based on specific inhalation challenge
Interventions	Intervention: removal from exposure: 122 Controls: continued exposure: 158
Outcomes	1. Respiratory symptoms; items: cough, phlegm, wheeze or shortness of breath; results presented as numbers of individuals with symptoms 2. FEV1 % predicted 3. Use of inhaled corticosteroids
Notes	Exposed to: western red cedar (WRC) Intervention not planned Follow-up: mean 72 months Duration of exposure before onset of symptoms in years: not mentioned Duration of exposure before time of diagnosis: 6.19 versus 6.04 Duration of symptoms before diagnosis in years: 1.83 versus 2.30 Study of subjects with red cedar asthma, divided in exposed and not exposed at follow-up, compared to sawmill workers without occupational asthma Place (country, region): Canada, British Columbia

Lin 1996 *(Continued)*

	Sources of funding not stated

Mapp 1988

Methods	Controlled before and after study; prospective
Participants	35 participants: 25 men, 10 women Age: mean 34.7 years Occupations: all worked in the lumber industry in northern Italy All were diagnosed with occupational asthma in the university clinic in Padova Diagnosis of OA was based on specific inhalation challenge
Interventions	Intervention: Removal from exposure: 30 Controls: Continued exposure: 5
Outcomes	1. Respiratory symptoms; interview; results presented as numbers of individuals with symptoms 2. FEV1 % predicted 3. PD20 methacholine 4. Type of reaction (immediate, late, dual)
Notes	Exposed to: toluene di isocyanate (TDI) Intervention not planned Follow-up: mean 10 months Duration of exposure before onset of symptoms in years: 15 versus 13.2 Duration of symptoms before diagnosis in years: 3.7 versus 3.7 Place (country, city): Italy, Padua Sources of funding not stated

Marabini 1993

Methods	Controlled before and after study; retrospective
Participants	128 participants: all men Age: mean 47.3 years Occupations: red cedar workers in the lumber industry Participants in follow-up assessment Diagnosis of OA was based on specific inhalation challenge
Interventions	Intervention: removal from exposure (53 unemployed; 27 other job): 80 Controls: continued exposure: 48
Outcomes	1. Respiratory symptoms; interview; results presented as numbers of individuals with symptoms. 2. FEV1 % predicted

Marabini 1993 *(Continued)*

	3. FVC % predicted 4. NSBP methacholine PD20 5. Income; information about unemployment and reduction in income in number of individuals was reported 6. Medication score 7. Severity of asthma
Notes	Exposed to: western red cedar Intervention not planned Follow-up: mean 58 months Duration of exposure before onset of symptoms: not mentioned Duration of symptoms before diagnosis: not mentioned Study compared working subjects, still exposed and unexposed, to unemployed. Place (country, region): Canada, British Columbia Sources of funding not stated

Marabini 1994

Methods	Controlled before and after study; retrospective
Participants	40 participants: 34 men, 6 women Age: mean 40 years Occupations: exposed to polyurethane, occupations not specified Participants were patients of the university clinic in Perugia Diagnosis of OA was based on specific inhalation challenge
Interventions	Intervention: removal from exposure: 28 workers Controls: continued exposure: 12 workers
Outcomes	1. Respiratory symptoms; results presented as numbers of individuals without symptoms 2. Mean annual decrease in FEV1 ml/yr 3. Mean annual decrease in FVC ml/yr
Notes	Exposed to: toluene di isocyanate (TDI) Intervention not planned Follow-up: mean 82 months Duration of exposure before onset of symptoms: not mentioned Duration of symptoms before diagnosis: not mentioned Place (country, city): Italy, Perugia Article written in Italian language Sources of funding not stated

Moscato 1993 reduction

Methods	Controlled before and after study; retrospective
Participants	11 (29) participants: 21 men, 8 women Age mean: 36.4 years Occupations: various; not stated Follow-up of patients diagnosed with OA in their university clinic between 1989 and 1992 Diagnosis of OA was based on specific inhalation challenge
Interventions	Intervention: reduction of exposure: 7 Controls: continued exposure: 4
Outcomes	1. Respiratory symptoms; interview; results presented as asymptomatic numbers of individuals 2. Require pharmacologic treatment for asthma 3. FEV1 % analysed according to symptom group (asymptomatic, improved, not improved) 4. Methacholine PC20 analysed according to symptom group (asymptomatic, improved, not improved 5. income; contact with the National Insurance Institute for Occupational Diseases was reported
Notes	Exposed to: isocyanates, chromium salts, styrene, silk, formaldehyde, glutaraldehyde, chloramine T, phthalic anhydride, ammonium persulfate, colophony, proteolytic enzymes. Intervention not planned Follow-up: 14 months Duration of exposure before onset of symptoms: not mentioned Duration of symptoms before diagnosis: not mentioned Place (country, city): Italy, Pavia Moscato 1993 removal and Moscato 1993 reduction are subdivisions of the same study/article Sources of funding not stated

Moscato 1993 removal

Methods	Controlled before and after study; retrospective
Participants	22 (29) participants: 21 men, 8 women Age mean: 36.4 years Occupations: various; not stated Follow-up of patients diagnosed with OA in their university clinic between 1989 and 1992 Diagnosis of OA was based on specific inhalation challenge
Interventions	Intervention: removal from exposure: 18 Controls: continued exposure: 4
Outcomes	1. Respiratory symptoms; interview; results presented as asymptomatic numbers of individuals 2. Require pharmacologic treatment for asthma

Moscato 1993 removal *(Continued)*

	3. FEV1 % analysed according to symptom group (asymptomatic, improved, not improved) 4. Methacholine PC20 analysed according to symptom group (asymptomatic, improved, not improved) 5. Income; contact with the National Insurance Institute for Occupational Diseases was reported
Notes	Exposed to: isocyanates, chromium salts, styrene, silk, formaldehyde, glutaraldehyde, chloramine T, phthalic anhydride, ammonium persulfate, colophony, proteolytic enzymes. Intervention not planned Follow-up: mean 14 months Duration of exposure before onset of symptoms: not mentioned Duration of symptoms before diagnosis: not mentioned Place (country, city): Italy, Pavia Moscato 1993 removal and Moscato 1993 reduction are subdivisions of the same study/article Sources of funding not stated

Moscato 1999

Methods	Controlled before and after study; prospective
Participants	25 participants: 18 men, 7 women Age: mean 34 years Occupations: various Patients of this university clinic diagnosed with OA from 1992 to 1995 were invited to participate in this study Diagnosis of OA was based on specific inhalation challenge
Interventions	Intervention: removal from exposure: 13 Controls: 12; 5 reduction of exposure (other work, same workplace); 7 continued exposure
Outcomes	1. Respiratory symptoms; interview; reported as symptom severity 2. Asthma severity 3. FEV1 % predicted 4. Number with PEFR more than 20% variability 5. Methacholine PD20 6. Treatment 7. Income; work-derived monthly/annual income was reported
Notes	Exposed to: HMW and LMW agents (3 and 22) Agents: LMW: isocyanates, disinfectants (chloramine-T, glutaraldehyde), drugs (piperacillin, cefmetazole), 1-2 benzisothiazolin 3-one, ammonium persulfate, phthalic anhydride, potassium dichromate. HMW: sodium caseinate, alcalase, pig epithelium Intervention planned Controls consisted of workers who continued to have the same exposure and workers who had reduced exposure. The measurements are not reported separately. They were analysed in the group with same exposure.

Moscato 1999 *(Continued)*

	Follow-up: mean 12 months Duration of exposure before onset of symptoms in months: mean 45.5 Duration of symptoms before diagnosis in months: mean 21 Place (country, city): Italy, Pavia Sources of funding not stated

Munoz 2008

Methods	Controlled before and after study; retrospective
Participants	10 participants: 10 women Age: mean 37.6 years Occupations: 3 worked in cosmetics factory and 7 as hairdressers in beauty salons Patients diagnosed with OA in a specialised respiratory clinic in a tertiary-level hospital studied prospectively between 1997 and 2002 were asked to participate Diagnosis of OA was based on specific inhalation challenge
Interventions	Intervention: removal from exposure: 7 Controls: continued exposure: 3
Outcomes	1. Respiratory symptoms; interview; reported as asthma symptom score 2. FEV1 % predicted 3. Methacholine PC20 4. Skin test 5. Total IgE
Notes	Exposed to: persulfates Intervention not planned Follow-up: mean 63 months Duration of exposure before onset of symptoms: not mentioned Duration of symptoms before diagnosis: not mentioned Place (country, region): Spain, Catalonia Sources of funding: partly funded by the Carlos III Institute of Health

Munoz 2014

Methods	Controlled before-after study; retrospective
Participants	OA Patients from two study centers in Spain were identified during 2000-2009 and invited 105 of the 178 patients with positive SIC were excluded due to no contact (n=67) or refused to participate (n=38).

Munoz 2014 *(Continued)*

	Had immunological OA by specific inhalation challenge (SIC), with at least 1 year of follow-up since diagnosis. 42 men, 31 women Age: mean 42 years Occupations: not specified, LMW agents 50 and HMW agents 23 Current smoker 15, ex-smoker 10, never smoker 48 Mean 15 pack years (range 5 - 60)
Interventions	Intervention: removal from exposure: 55 Controls: continued exposure: 18
Outcomes	1. FEV1 % predicted 2. Methacholine PC20 3. Skin test 4. Total IgE 5. GINA level of asthma severity
Notes	- Clinical study based on OA patients, not a randomized study - Authors did not explicitly compare two group at baseline, but post-hoc testing of crude numbers suggests they were similar - The study design is not well explained and not clear that the authors properly evaluated effectiveness of intervention. - Many points not described, including timing of intervention during follow-up. - Authors concluded: Avoiding exposure to the causative agent in patients with OA does not seem to improve prognosis in this disease. However, there is insufficient evidence to recommend a change in current management guideline. Place (country, region): Spain

Padoan 2003

Methods	Controlled before and after study; retrospective
Participants	87 participants: 63 men, 24 women Age: mean 38 years Occupations: furniture factories and carpentry shops workers with occupational asthma Participants were patients of university clinic in Ferrara Diagnosis of OA was based on specific inhalation challenge
Interventions	Intervention: removal from exposure: 74 Controls: continued exposure: 13
Outcomes	1. Respiratory symptoms; interview; reported as percentage of the patients with symptoms 2. Spirometry; analysed with logistic regression

Padoan 2003 *(Continued)*

	3. Methacholine PD20
Notes	Exposed to: toluene di isocyanate (TDI) Intervention not planned Follow-up: 11 to 12 years Duration of exposure before onset of symptoms in years: mean 12 Duration of symptoms before diagnosis in years: mean 3.8 Place (country, city): Italy, Ferrara Sources of funding not stated

Paggiaro 1984

Methods	Controlled before and after study; retrospective
Participants	47 participants; 27 diagnosed with OA: 16 men, 11 women Age: mean 50.2 years All workers of the furniture industry, exposed to polyurethane varnish They were recalled for examination and had after 2 (mean) years a follow-up examination at the university Diagnosis of OA was based on specific inhalation challenge
Interventions	Intervention: removal from exposure: 12 Controls: continued exposure: 15
Outcomes	1. Respiratory symptoms; interview; reported as numbers of individuals having symptoms 2. FEV 1 % predicted 3. FVC % predicted 4. Bethanechol inhalation test
Notes	Exposed to: toluene di isocyanate (TDI) Intervention not planned Follow-up: mean 24 months (14.9 to 39.4 months) Duration of exposure before onset of symptoms in years: mean 15.6 Duration of symptoms before diagnosis: not mentioned Place (country, city): Italy, Pisa Sources of funding not stated

Pisati 1994

Methods	Controlled before and after study; retrospective
Participants	9 participants; sex unknown

Pisati 1994 *(Continued)*

	Age unknown Occupations: cobalt workers Follow-up study of patients of their own hospital clinic Diagnosis of OA was based on specific inhalation challenge
Interventions	Intervention: removal from exposure: 8, left company Controls: continued exposure: 1
Outcomes	1. Respiratory symptoms; questionnaire; the symptom score was reported 2. Medication use 3. FEV1 'normal'= > 80% 4. NSBP methacholine PD15 5. Evolution of asthma
Notes	Exposed to: cobalt Intervention not planned Follow-up: 3 years Duration of exposure before onset of symptoms: not mentioned Duration of symptoms before diagnosis: not mentioned Place (country, city): Italy, Lecco Sources of funding not stated

Rosenberg 1987 reduction

Methods	Controlled before and after study; retrospective
Participants	31 participants; sex not clear: 27 men, 4 women ? Age: mean 35.9 years Occupations: 20 car spray-painters, 4 manufacturers polyurethane foam, 4 workers near isocyanate compounds, 2 cabinet makers Follow-up study of patients of their own hospital clinic Diagnosis of OA was based on specific inhalation challenge (16), work-related symptoms, NSBP and peak flow
Interventions	Intervention: reduction of exposure: 7 (4 alternative job with only unusual contact with isocyanates; 3 same job with improved conditions: respirators, ventilation) Controls: continued exposure: 4
Outcomes	1. Respiratory symptoms; questionnaire; various symptoms in number of individuals were reported 2. Change FEV1 % predicted 3. Change FVC % predicted 4. Bronchial hyperreactivity to acetylcholine
Notes	Exposed to: di isocyanates

Rosenberg 1987 reduction *(Continued)*

	Intervention not planned Follow-up: mean 24 months (6 to 54 months) Duration of exposure before onset of symptoms in months: mean 35.6 Duration of symptoms before diagnosis in months: mean 16.9 Place (country, city): France, Paris Rosenberg 1987 removal and Rosenberg 1987 reduction are subdivisions of the same study/article Sources of funding not stated

Rosenberg 1987 removal

Methods	Controlled before and after study; retrospective
Participants	31 participants; sex not clear: 27 men, 4 women ? Age: mean 35.9 years Occupations: 20 car spray-painters, 4 manufacturers polyurethane foam, 4 workers near isocyanate compounds, 2 cabinet makers Follow-up study of patients of their own hospital clinic Diagnosis of OA was based on specific inhalation challenge (16), work-related symptoms, NSBP and peak flow
Interventions	Intervention: removal from exposure: 20; changed job Controls: continued exposure: 4
Outcomes	1. Respiratory symptoms; questionnaire; various symptoms in number of individuals were reported 2. Change FEV1 % predicted 3. Change FVC % predicted 4. Bronchial hyperreactivity to acetylcholine
Notes	Exposed to: di isocyanates Intervention not planned. Follow-up: 24 months (6 to 54 months) Duration of exposure before onset of symptoms in months: 35.6 Duration of symptoms before diagnosis in months: 16.9 Place (country, city): France, Paris Rosenberg 1987 removal and Rosenberg 1987 reduction are subdivisions of the same study/article Sources of funding not stated

Soyseth 1995

Methods	Controlled before and after study; prospective

Soyseth 1995 *(Continued)*

Participants	38 participants: all men ? not mentioned Age: mean 36.8 years Occupations: pot room workers, aluminium In company organised by occupational physician WASTH diagnosed; doctor's diagnosis by occupational physician
Interventions	Intervention: reduction of exposure: 12; other place in same factory Controls: continued exposure: 26
Outcomes	1. Respiratory symptoms; questionnaire; improvement was reported for the different groups as a whole 2. FEV1 % predicted (only baseline) 3. BR: natural logarithm (dose response slope +0.5)
Notes	Exposed to: pot room gases (fluoride) and particulates Intervention planned Follow-up: 24 months Duration of exposure before onset of symptoms: not mentioned Duration of symptoms before diagnosis: not mentioned Place (country, city): Norway, Ardal Sources of funding not stated; although organised (and paid for ?) by the company

Talini 2012

Methods	Controlled before-after study
Participants	- Consecutive patients: 41 OA cases attributed to different sensitizers treated in asthma clinic, from 1987 to 2005, Pisa, Italy - All 41 had a) diagnosis of OA with positive SIC; b) proven exposure to a known occupational sensitizer; c) showed asthma symptoms that deteriorated at work; d) positive nonspecific bronchial hyperresponsiveness (BH) during a working period; e) observed at least once a year during follow-up period. Also, many subjects showed a relationship between asthma manifestations and exposure at work based on visual analysis of a 3-week monitoring of symptoms and peak expiratory flow (PEF). - 33 male, 8 female - mean age 40 years - Baseline characteristics similar among groups for sex but not age. Cessation was younger, with mean age (SD) for Cessation 35.4 (15.4), for Reduction 40.1 (10.8), and for Persistence 40.8 (11.8)

Talini 2012 *(Continued)*

	- Duration of exposure varied by group, with shorter for cessation. Median (range) in years of 7 (2-40) for cessation, 15 (5-45) for reduction, and 16.0 (3-40) for persistence - Occupations not reported, but exposed to variety of occupational exposures, including diisocyanates, persulfates, latex, hairdressing products, and wood and flour dusts.
Interventions	9 cessation of exposure, 22 reduction of exposure, 10 persistence of exposure
Outcomes	1. Respiratory symptoms; interview; reported as percentage of individuals having symptoms 2. FEV1 % predicted 3. Methacholine PD 20
Notes	- Participants overlap considerably with participants in Talini 2015 - Patients not assigned to groups; classification based on observation of occupational exposure during the 6 months prior to follow-up observations - The study group consisted only of patients that met the inclusion criteria and had been followed. Unclear if number of patients recruited was known, and whether number recruited equalled the number who met the inclusion criteria. - Did not report time from start of symptoms to diagnosis, and the time from OA diagnosis OA to intervention - Unclear if fitting of regression models optimized to control for confounding - Authors concluded: The reduction of occupational exposure was not as effective as work cessation, which remained the best treatment for OA. - Clinical study based on OA patients, not a randomized study - Place (country, city): Italy, Pisa

Talini 2013

Methods	Controlled before-after study
Participants	-46 OA patients identified 1985-2000 from clinic in Pisa, Italy, and followed up -All had toluene diisocyanate (TDI)-induced asthma confirmed by positive specific inhalation challenge (SIC), and took part in follow-up. -Follow-up lasted a mean of 11 years (SD=3.6) -Started with 81 original TDI OA patients, but 35 did not participate in follow-up and not included in analysis, but reasons for not participating not given

Talini 2013 *(Continued)*

	- Age: mean 47 years - Sex: 32 males, 14 females - Occupation: 54 (67%) of the 81 TDI OA cases invited for follow-up worked in furniture factories or carpentry plants. - Smoking: 17.3% current, 37.0% former, 45.7% never; Atopy: 22%
Interventions	- 32 cessation of exposure: removed from exposure by follow-up - 14 persistence of exposure, reduced exposure: still working at follow-up and remained indirectly exposed to TDI because moved to different job in same factory where TDI exposure was occasional
Outcomes	1. Respiratory symptoms; interview; reported as percentage of individuals having symptoms 2. FEV1 % predicted, with results divided by researchers by level of FEV1 at baseline (<82% pred FEV1, >82% pred FEV1) 3. Methacholine PD 2
Notes	- Participants overlap considerably with participants in Talini 2015 - Clinical study based on OA patients, not a randomized study - Place (country, city): Italy, Pisa

Valentino 2002

Methods	Controlled before and after study; retrospective
Participants	50 participants: 35 men, 15 women Age: mean 32.6 years 50 workers in furniture manufacturing and motor vehicle coach workshops with occupational asthma Patients with asthma due to isocyanates diagnosed in university clinic. Diagnosis of OA was based on specific inhalation challenge
Interventions	Intervention: removal from exposure: 37 Controls: reduction of exposure: 13
Outcomes	1. Respiratory symptoms; reported improvement in symptoms for number of individuals 2. Change FEV1 % predicted 3. Change FVC % predicted 4. Change PD20 methacholine in mcg
Notes	Exposed to: toluene di isocyanate (TDI) Intervention not planned Follow-up: mean 101 months Duration of exposure before onset of symptoms: not mentioned Duration of symptoms before diagnosis: not mentioned Place (country, city): Italy, Ancona

Valentino 2002 *(Continued)*

	Article written in Italian language
	Sources of funding not stated

Vandenplas 2002

Methods	Controlled before and after study; prospective?
Participants	36 participants: 4 men, 32 women Age: mean 32 years
	Occupations: 30 healthcare workers and 6 non-healthcare workers
	Patients were referred to this hospital by the workers' compensation board or by their attending physicians
	Diagnosis of OA was based on specific inhalation challenge; 25 OS and 11 work-aggravated asthma
Interventions	Intervention: removal from exposure: 16
	Controls: reduction of exposure: 20
Outcomes	1. Respiratory symptoms; questionnaire; scores were reported 2. FEV1 % predicted 3. NSBP histamine PD20 4. Type of asthma reaction 5. Employment; no employment at follow-up was reported and the consequences for income
Notes	Exposed to: latex
	Intervention not planned
	Follow-up: mean 56 months
	Duration of exposure before onset of symptoms: 68 versus 73
	Duration of symptoms before diagnosis in months: 78 versus 94
	11 subjects had asthma before employment; group consists of OA and WAA
	Place (country): Belgium
	Study is supported by the Services Federaux des Affaires Scientifiques et Culturelles

Visentin 2003

Methods	Controlled before and after study; retrospective
Participants	29 participants: 3 male, 26 female Age: mean 32 years
	29 workers with occupational asthma due to latex, occupations not reported
	Patients presenting with latex sensitisation in university clinic
	Diagnosis of OA was based on history and questionnaires, serial lung function testing and immunological testing

Visentin 2003 *(Continued)*

Interventions	Intervention: removal from exposure: 17 Controls: reduction of exposure: 12
Outcomes	1. Respiratory symptoms; questionnaire; the number of asymptomatic individuals was reported
Notes	Exposed to: latex Intervention not planned. Follow-up: mean 60 months Duration of exposure before onset of symptoms: not mentioned Duration of symptoms before diagnosis: not mentioned Place (country, city): Italy, Padua Article written in Italian language Sources of funding not stated

BR:bronchial provocation
FEF:forced expiratory flow
FeNO: fraction of exhaled nitric oxide in exhaled breath
FEV1: forced expiratory volume in the first second
FVC:forced vital capacities
HMW: high molecular weight
IgE: immunoglobulin E
LMW: low molecular weight
NRL: natural rubber latex
NSBP:non-specific bronchial provocation
OA: occupational asthma
PD20: provocative dose of methacholine causing a 20% drop in FEV1
PEFR: peak expiratory flow rate
SIC: specific inhalation challenge
TDI: toluene di isocyanate
WAA: work-aggravated asthma
WASTH: work-related asthma symptoms
WRC: western red cedar
yr: year

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Antao 2011	It is unclear who/how many persons were diagnosed with OA - Asthma: there is no information about how the asthma is diagnosed Outcome: - It is unclear whether asthma/RADS at W2 (also no information about diagnosis) is new, better or worse compared with the situation before 9/11. Table IV and V - No group is reported with asthma/RADS before 9/11, combined with the use of different masks and the outcome at W2 - Occupational asthma is not mentioned anywhere. The asthma/RADS at W2 can be occupational, but even that is unknown.

Study	Reason for exclusion
	- No group with OA at baseline is described.
Bailey 2009	Of 7 with ever asthma in follow-up (FU) survey, only 1 had onset after building opened in 2005. Asthma cases not addressed separately since baseline and FU cohorts not compared within person. At best, work-related exacerbation of asthma improved.
Carlsten 2013	No comparison group
De Zotti 2000	No comparison group
Donoghue 2011	No clear diagnosis of OA
Durham 2011	No OA cases; surveyed workers with asthma (13 baseline, 10 FU) and improvement seen. At best: less work-related exacerbation of asthma
Fishwick 2011	30 with self-reported asthma history; OA implied but not confirmed: WR symptoms and IgE to workplace allergen. BUT, may have had symptoms without asthma. At best: WR symptoms improved.
Ilgaz 2019	No comparison group
Karvala 2011	The disease outcome was new onset asthma and not diagnosed OA.
Kim 2013	No comparison group
Klusackova 2006	Not a controlled before and after study because the control group was only measured at follow-up. The controls did not have occupational asthma.
Labrecque 2011	Comparisons only between occupational asthma cases who were identified by workplace medical surveillance and education that took place prior to diagnosis and occupational asthma cases identified by other means.
Lemiere 2010	No comparison group
Madureira 2014	Asthmatic workers not included in study. Improvements in symptoms independent of asthma cases.
Patovirta 2004	Controls were not from the same group. Controls did not have occupational asthma.
Pohl 2003	No comparison group
Saetta 1992	Controls did not have occupational asthma
Schoj 2010	5 self-reported asthma cases out of 198 participants, and are not addressed separately. At best: about asthma related symptoms
Singh 2010	26 of 175 participants had SR medical history of asthma. Combine asthma and respiratory allergy cases in one group, so cannot judge asthma cases separately. Do not define respiratory allergies. At best: WR exacerbation of asthma
Stocks 2013	Intervention was government activities. Authors investigate WR asthma from SWORD surveillance that includes both OA and WEA. Unclear if OA or WEA is driving results.
Stocks 2015	Authors investigate WR asthma from SWORD surveillance that includes both OA and WEA. Unclear if OA or WEA is driving results.

Study	Reason for exclusion
Talini 2015	Overlap of data with two other included studies from same author.

DATA AND ANALYSES

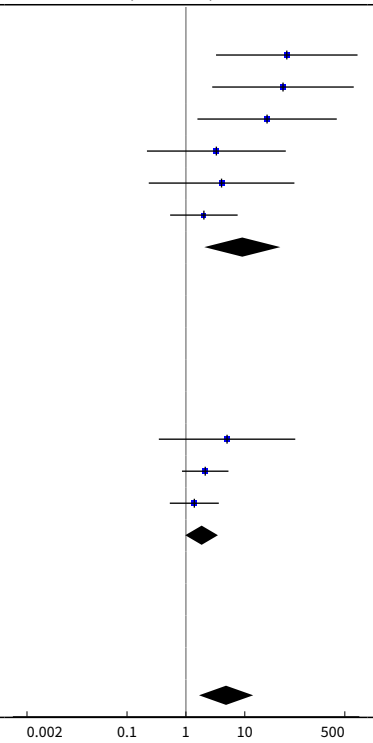
Comparison 1. Removal from exposure versus continued exposure

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Absence of asthma symptoms	9	641	Risk Ratio (M-H, Random, 95% CI)	4.80 [1.67, 13.86]
1.1 LMW absence of symptoms	6	527	Risk Ratio (M-H, Random, 95% CI)	9.06 [2.05, 40.17]
1.2 HMW & LMW absence of symptoms	3	114	Risk Ratio (M-H, Random, 95% CI)	1.85 [0.97, 3.50]
2 Improvement of asthma symptoms	9	435	Risk Ratio (M-H, Random, 95% CI)	2.47 [1.26, 4.84]
2.1 LMW improvement of symptoms	6	383	Risk Ratio (M-H, Random, 95% CI)	2.82 [1.08, 7.31]
2.2 HMW improvement of symptoms	1	5	Risk Ratio (M-H, Random, 95% CI)	3.60 [0.32, 40.41]
2.3 HMW & LMW improvement of symptoms	2	47	Risk Ratio (M-H, Random, 95% CI)	1.60 [0.64, 4.02]
3 Change in FEV1 % predicted: follow-up minus baseline values	10	898	Mean Difference (IV, Random, 95% CI)	4.23 [1.14, 7.31]
3.1 LMW	7	781	Mean Difference (IV, Random, 95% CI)	5.70 [3.55, 7.84]
3.2 HMW & LMW	3	117	Mean Difference (IV, Random, 95% CI)	-1.06 [-7.36, 5.24]
4 Change in NSBH: follow-up minus baseline values	6	387	Std. Mean Difference (IV, Random, 95% CI)	0.43 [0.03, 0.82]
4.1 LMW	4	289	Std. Mean Difference (IV, Random, 95% CI)	0.43 [0.01, 0.84]
4.2 HMW & LMW	2	98	Std. Mean Difference (IV, Random, 95% CI)	0.54 [-0.79, 1.86]
5 FEV1 % predicted: baseline	10	898	Mean Difference (IV, Fixed, 95% CI)	-1.69 [-3.91, 0.54]
5.1 LMW	7	781	Mean Difference (IV, Fixed, 95% CI)	-1.50 [-3.97, 0.97]
5.2 HMW & LMW	3	117	Mean Difference (IV, Fixed, 95% CI)	-2.48 [-7.57, 2.61]
6 FEV1 % predicted: follow up	10	898	Mean Difference (IV, Random, 95% CI)	2.23 [-2.15, 6.61]

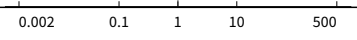
Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
6.1 LMW	7	781	Mean Difference (IV, Random, 95% CI)	4.39 [1.54, 7.24]
6.2 HMW & LMW	3	117	Mean Difference (IV, Random, 95% CI)	-4.22 [-13.64, 5.20]
7 NSBH: baseline	6	387	Std. Mean Difference (IV, Random, 95% CI)	-0.06 [-0.32, 0.20]
7.1 LMW	4	289	Std. Mean Difference (IV, Random, 95% CI)	-0.00 [-0.25, 0.25]
7.2 HMW & LMW	2	98	Std. Mean Difference (IV, Random, 95% CI)	-0.41 [-1.54, 0.72]
8 NSBH: follow up	6	387	Std. Mean Difference (IV, Random, 95% CI)	0.26 [-0.01, 0.52]
8.1 LMW	4	289	Std. Mean Difference (IV, Random, 95% CI)	0.33 [-0.05, 0.72]
8.2 HMW & LMW	2	98	Std. Mean Difference (IV, Random, 95% CI)	0.07 [-0.37, 0.52]

Analysis 1.1. Comparison 1 Removal from exposure versus continued exposure, Outcome 1 Absence of asthma symptoms.

Study or subgroup	Removal n/N	Continued n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.1.1 LMW absence of symptoms					
Chan-Yeung 1982	38/75	0/50		8.4%	51.67[3.25,822.21]
Chan-Yeung 1987 removal	55/136	0/54		8.4%	44.56[2.8,708.76]
Innocenti 1981	32/37	0/13		8.55%	23.95[1.57,365.35]
Mapp 1988	8/30	0/5		8.58%	3.29[0.22,49.69]
Marabini 1994	4/28	0/12		8.13%	4.03[0.23,69.58]
Padoan 2003	23/74	2/13		15.07%	2.02[0.54,7.56]
Subtotal (95% CI)	**380**	**147**		**57.13%**	**9.06[2.05,40.17]**
Total events: 160 (Removal), 2 (Continued)					
Heterogeneity: Tau^2=1.86; Chi^2=11.36, df=5(P=0.04); I^2=55.98%					
Test for overall effect: Z=2.9(P=0)					
1.1.2 HMW & LMW absence of symptoms					
Moscato 1993 removal	9/18	0/4		8.75%	5[0.35,72.04]
Munoz 2014	26/55	4/18		17.18%	2.13[0.86,5.28]
Talini 2012	5/9	4/10		16.94%	1.39[0.53,3.62]
Subtotal (95% CI)	**82**	**32**		**42.87%**	**1.85[0.97,3.5]**
Total events: 40 (Removal), 8 (Continued)					
Heterogeneity: Tau^2=0; Chi^2=1.1, df=2(P=0.58); I^2=0%					
Test for overall effect: Z=1.88(P=0.06)					
Total (95% CI)	**462**	**179**		**100%**	**4.8[1.67,13.86]**



Study or subgroup	Removal n/N	Continued n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Total events: 200 (Removal), 10 (Continued)					
Heterogeneity: Tau²=1.49; Chi²=24.16, df=8(P=0); I²=66.89%					
Test for overall effect: Z=2.9(P=0)					
Test for subgroup differences: Chi²=3.7, df=1 (P=0.05), I²=72.98%					

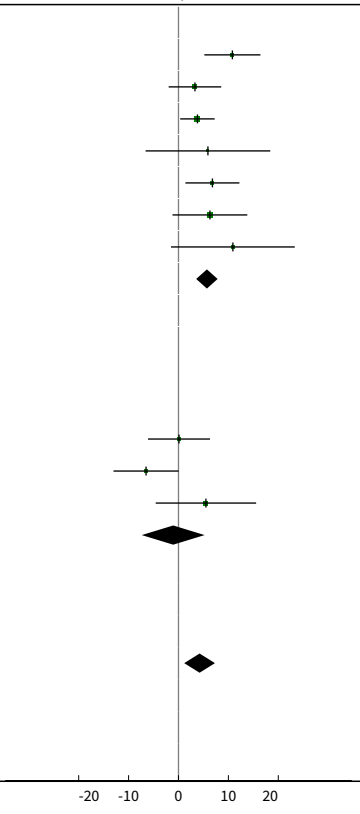


Analysis 1.2. Comparison 1 Removal from exposure versus continued exposure, Outcome 2 Improvement of asthma symptoms.

Study or subgroup	Removal n/N	Continued n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.2.1 LMW improvement of symptoms					
Lin 1996	37/90	13/95		19.37%	3[1.71,5.27]
Marabini 1993	22/80	3/48		13.53%	4.4[1.39,13.92]
Munoz 2008	6/7	3/3		19.95%	0.93[0.56,1.53]
Paggiaro 1984	4/12	1/15		7.26%	5[0.64,39.06]
Pisati 1994	8/8	0/1		5.81%	3.78[0.34,41.88]
Rosenberg 1987 removal	14/20	0/4		5.03%	6.9[0.49,97.25]
Subtotal (95% CI)	**217**	**166**		**70.95%**	**2.82[1.08,7.31]**
Total events: 91 (Removal), 20 (Continued)					
Heterogeneity: Tau²=0.88; Chi²=22.93, df=5(P=0); I²=78.19%					
Test for overall effect: Z=2.13(P=0.03)					
1.2.2 HMW improvement of symptoms					
Bernstein 2003 removal	4/4	0/1		5.77%	3.6[0.32,40.41]
Subtotal (95% CI)	**4**	**1**		**5.77%**	**3.6[0.32,40.41]**
Total events: 4 (Removal), 0 (Continued)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.04(P=0.3)					
1.2.3 HMW & LMW improvement of symptoms					
Moscato 1993 removal	9/18	0/4		4.97%	5[0.35,72.04]
Moscato 1999	9/13	6/12		18.31%	1.38[0.71,2.71]
Subtotal (95% CI)	**31**	**16**		**23.28%**	**1.6[0.64,4.02]**
Total events: 18 (Removal), 6 (Continued)					
Heterogeneity: Tau²=0.13; Chi²=1.13, df=1(P=0.29); I²=11.79%					
Test for overall effect: Z=1(P=0.32)					
Total (95% CI)	**252**	**183**		**100%**	**2.47[1.26,4.84]**
Total events: 113 (Removal), 26 (Continued)					
Heterogeneity: Tau²=0.53; Chi²=24.52, df=8(P=0); I²=67.37%					
Test for overall effect: Z=2.63(P=0.01)					
Test for subgroup differences: Chi²=0.88, df=1 (P=0.64), I²=0%					

Analysis 1.3. Comparison 1 Removal from exposure versus continued exposure, Outcome 3 Change in FEV1 % predicted: follow-up minus baseline values.

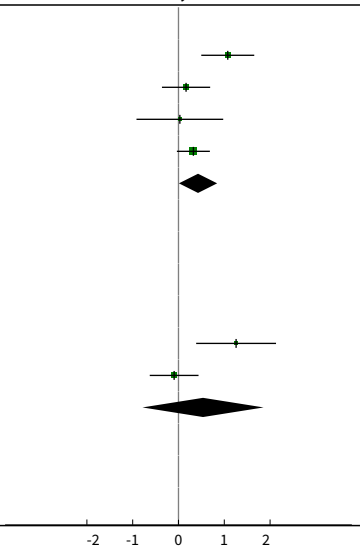
Study or subgroup	Removal N	Removal Mean(SD)	Continued N	Continued Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
1.3.1 LMW							
Chan-Yeung 1982	75	6.3 (16.7)	50	-4.5 (15)		12.08%	10.8[5.18,16.42]
Chan-Yeung 1987 removal	129	-0.5 (15.7)	47	-3.8 (15.8)		12.69%	3.3[-1.97,8.57]
Lin 1996	122	-4.1 (14.7)	158	-7.9 (14.5)		16.1%	3.8[0.35,7.25]
Mapp 1988	30	-1.1 (11.2)	5	-7 (13.5)		4.68%	5.9[-6.59,18.39]
Marabini 1993	80	-2.7 (14.1)	48	-9.5 (15.7)		12.44%	6.8[1.39,12.21]
Munoz 2008	7	-2.7 (9.3)	3	-9 (2.6)		9.2%	6.3[-1.19,13.79]
Paggiaro 1984	12	3 (17.4)	15	-7.9 (14.9)		4.73%	10.9[-1.5,23.3]
Subtotal ***	**455**		**326**			**71.92%**	**5.7[3.55,7.84]**
Heterogeneity: Tau²=0; Chi²=5.99, df=6(P=0.42); I²=0%							
Test for overall effect: Z=5.19(P<0.0001)							
1.3.2 HMW & LMW							
Moscato 1999	13	-1 (9.5)	12	-1.1 (6.1)		11.09%	0.1[-6.11,6.31]
Munoz 2014	55	-3 (6.7)	18	3.5 (13.6)		10.59%	-6.5[-13.03,0.03]
Talini 2012	9	-1.7 (11.5)	10	-7.2 (10.8)		6.4%	5.5[-4.56,15.56]
Subtotal ***	**77**		**40**			**28.08%**	**-1.06[-7.36,5.24]**
Heterogeneity: Tau²=16.64; Chi²=4.36, df=2(P=0.11); I²=54.18%							
Test for overall effect: Z=0.33(P=0.74)							
Total ***	**532**		**366**			**100%**	**4.23[1.14,7.31]**
Heterogeneity: Tau²=12.26; Chi²=19.9, df=9(P=0.02); I²=54.77%							
Test for overall effect: Z=2.69(P=0.01)							
Test for subgroup differences: Chi²=3.96, df=1 (P=0.05), I²=74.73%							



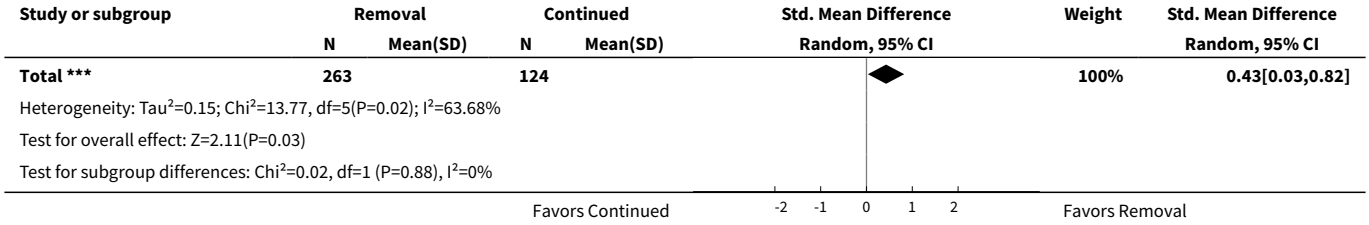
Favors Continued — Favors Removal

Analysis 1.4. Comparison 1 Removal from exposure versus continued exposure, Outcome 4 Change in NSBH: follow-up minus baseline values.

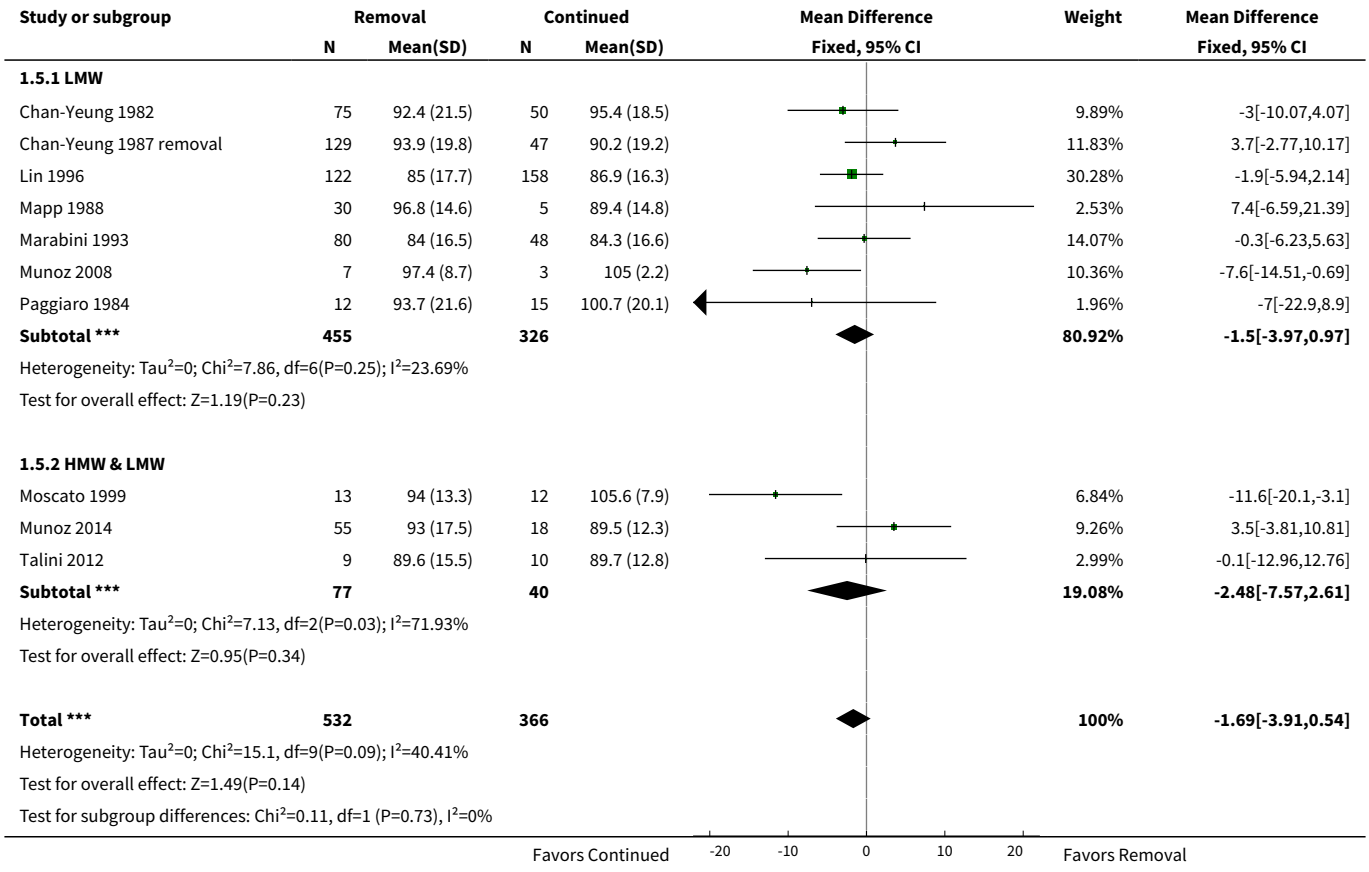
Study or subgroup	Removal N	Removal Mean(SD)	Continued N	Continued Mean(SD)	Std. Mean Difference Random, 95% CI	Weight	Std. Mean Difference Random, 95% CI
1.4.1 LMW							
Chan-Yeung 1982	33	6 (8)	22	-0.8 (1.7)		17.49%	1.08[0.5,1.65]
Chan-Yeung 1987 removal	52	0.9 (6.8)	19	-0.2 (7.3)		18.69%	0.17[-0.36,0.69]
Mapp 1988	30	0.2 (5.5)	5	0 (3)		10.77%	0.03[-0.92,0.98]
Marabini 1993	80	2.7 (12.4)	48	-0.7 (5.9)		22.64%	0.33[-0.03,0.69]
Subtotal ***	**195**		**94**			**69.58%**	**0.43[0.01,0.84]**
Heterogeneity: Tau²=0.1; Chi²=6.75, df=3(P=0.08); I²=55.58%							
Test for overall effect: Z=2(P=0.05)							
1.4.2 HMW & LMW							
Moscato 1999	13	1.1 (1.3)	12	-0.8 (1.5)		11.88%	1.26[0.39,2.13]
Munoz 2014	55	-0.4 (5.8)	18	0.1 (2.5)		18.54%	-0.09[-0.63,0.44]
Subtotal ***	**68**		**30**			**30.42%**	**0.54[-0.79,1.86]**
Heterogeneity: Tau²=0.78; Chi²=6.74, df=1(P=0.01); I²=85.16%							
Test for overall effect: Z=0.79(P=0.43)							



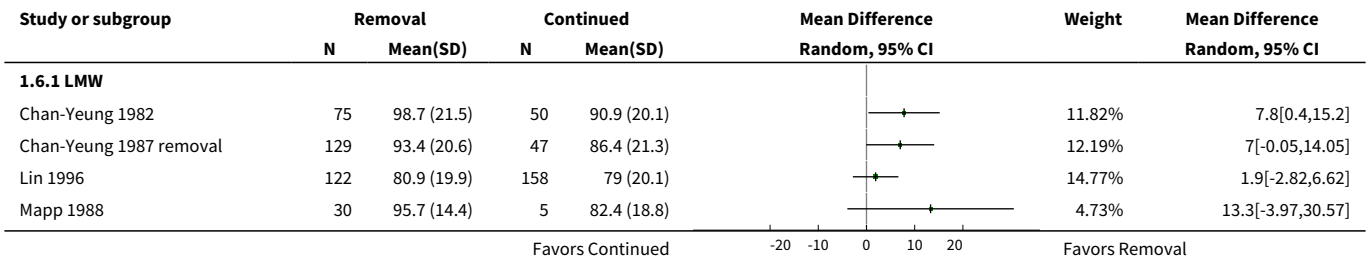
Favors Continued — Favors Removal

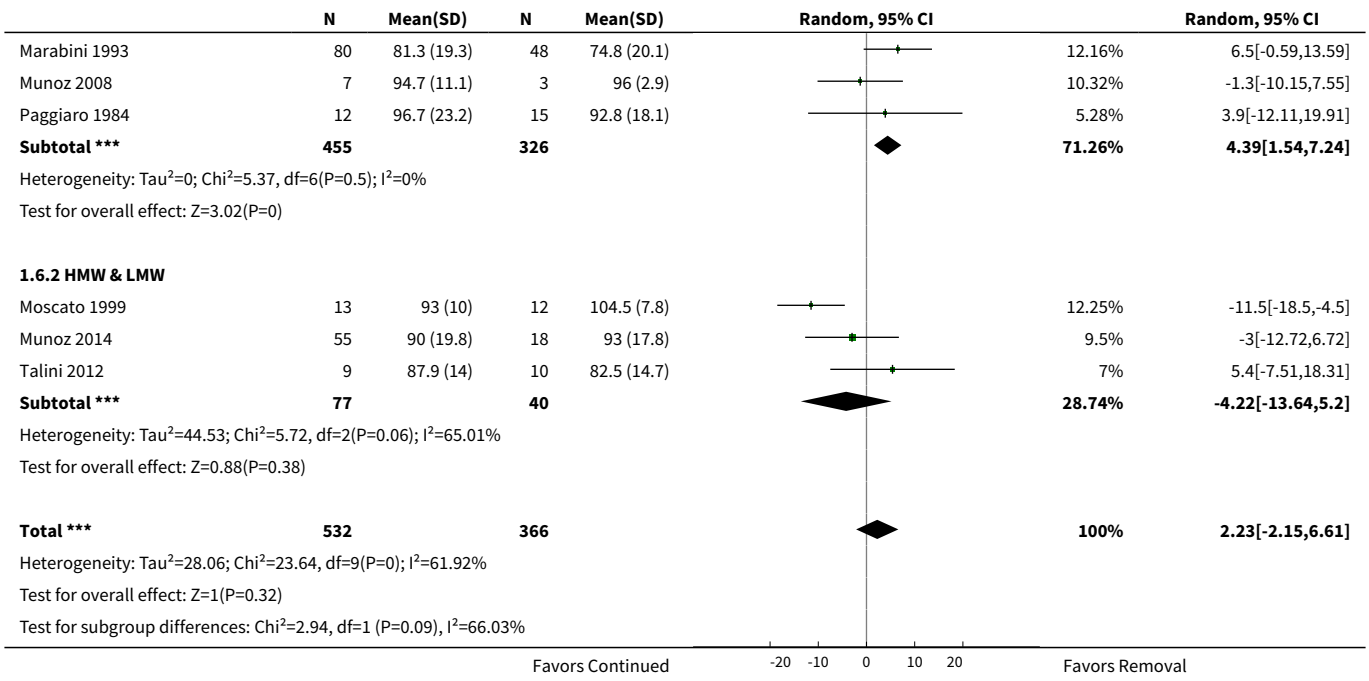


Analysis 1.5. Comparison 1 Removal from exposure versus continued exposure, Outcome 5 FEV1 % predicted: baseline.

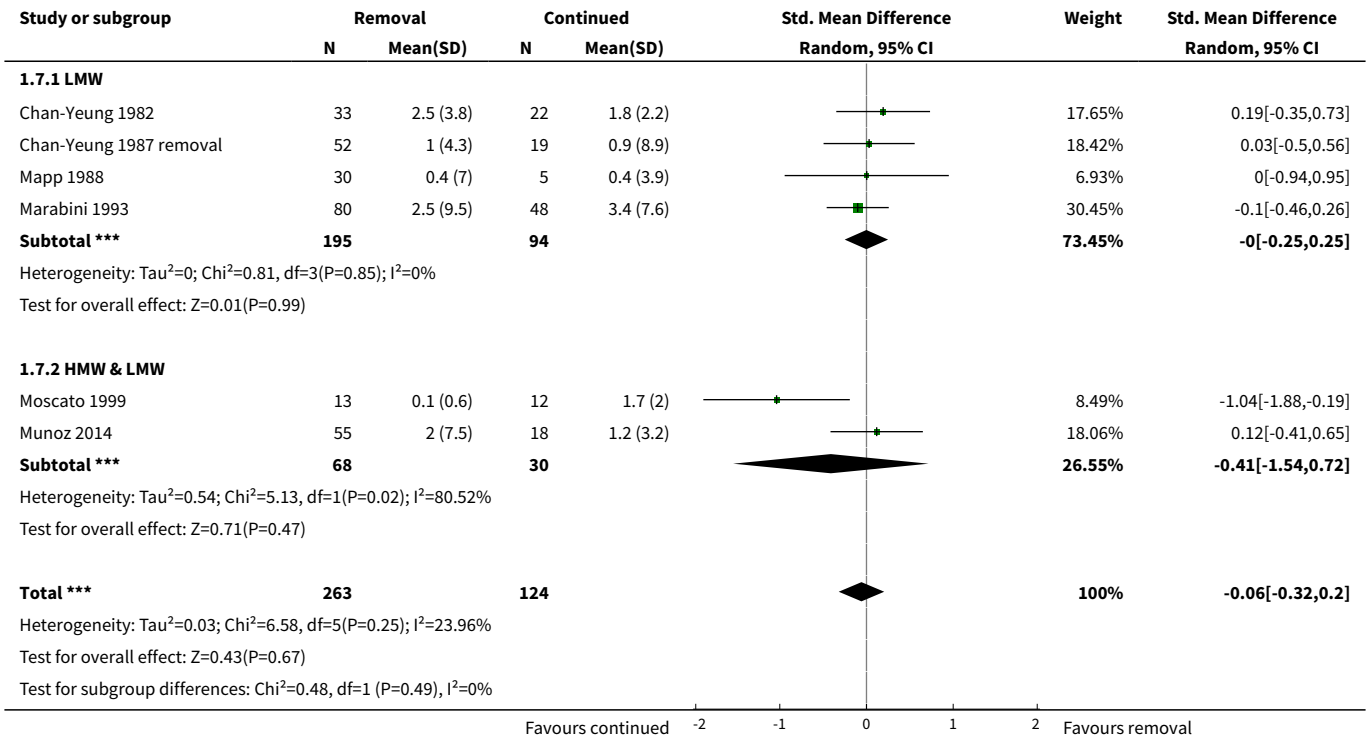


Analysis 1.6. Comparison 1 Removal from exposure versus continued exposure, Outcome 6 FEV1 % predicted: follow up.

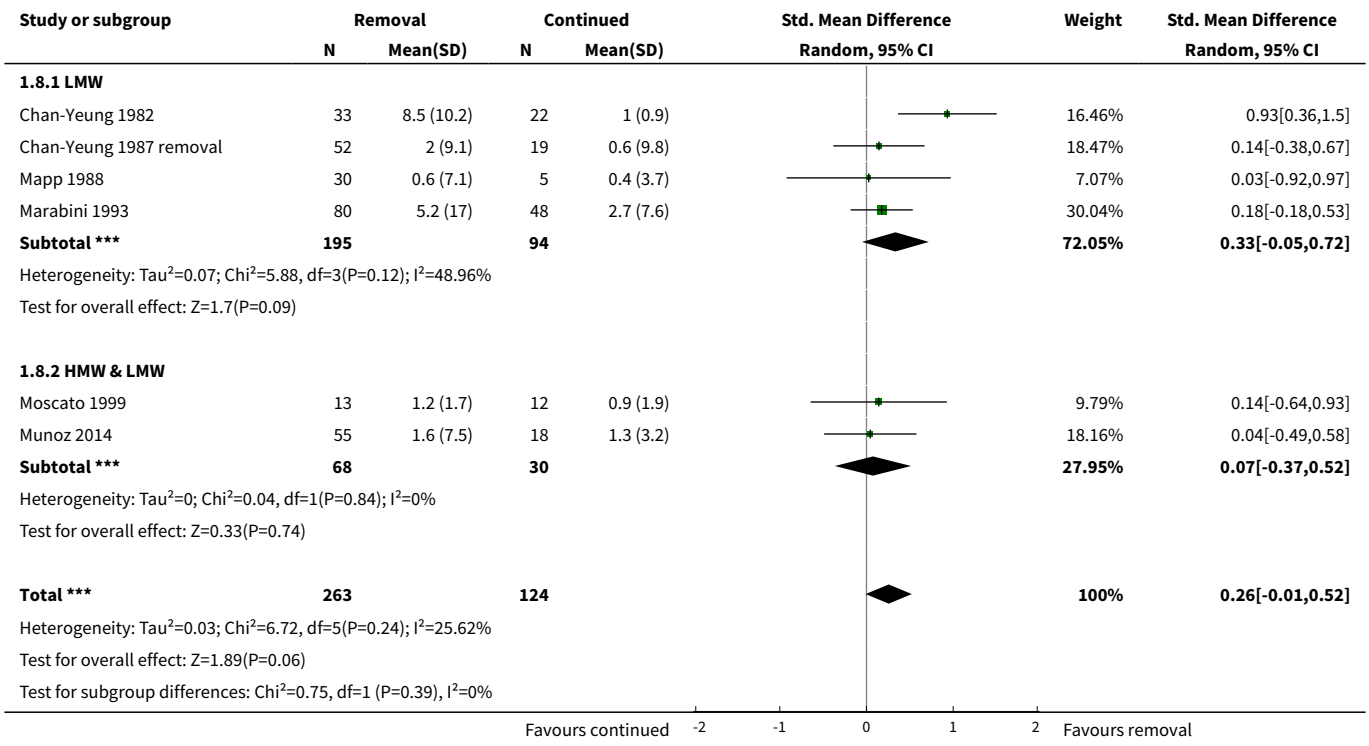




Analysis 1.7. Comparison 1 Removal from exposure versus continued exposure, Outcome 7 NSBH: baseline.



Analysis 1.8. Comparison 1 Removal from exposure versus continued exposure, Outcome 8 NSBH: follow up.



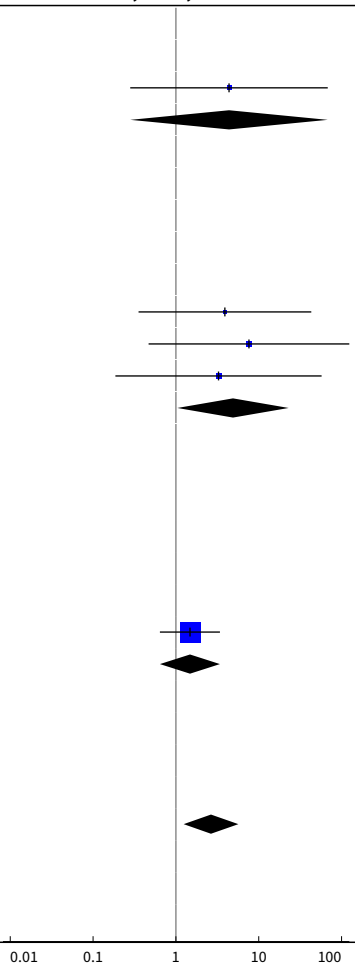
Comparison 2. Reduction of exposure versus continued exposure

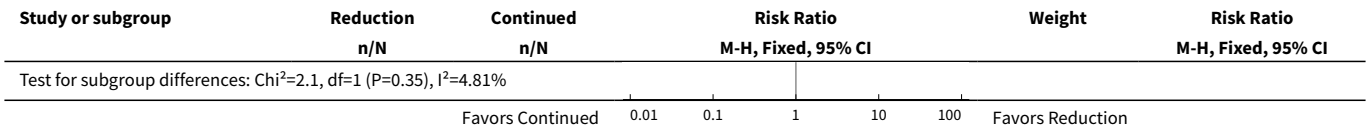
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Absence of asthma symptoms	7	334	Risk Ratio (M-H, Fixed, 95% CI)	2.65 [1.24, 5.68]
1.1 LMW absence of symptoms	2	107	Risk Ratio (M-H, Fixed, 95% CI)	4.38 [0.28, 68.06]
1.2 HMW absence of symptoms	3	184	Risk Ratio (M-H, Fixed, 95% CI)	4.89 [1.04, 22.96]
1.3 HMW & LMW absence of symptoms	2	43	Risk Ratio (M-H, Fixed, 95% CI)	1.48 [0.64, 3.40]
2 Change in FEV1 % predicted: follow-up minus baseline values	4	224	Mean Difference (IV, Random, 95% CI)	2.76 [-1.53, 7.04]
2.1 LMW	2	99	Mean Difference (IV, Random, 95% CI)	1.10 [-5.50, 7.70]
2.2 HMW	1	93	Mean Difference (IV, Random, 95% CI)	1.3 [-6.56, 9.16]
2.3 HWM and LWM change in % predicted FEV1	1	32	Mean Difference (IV, Random, 95% CI)	6.8 [-1.30, 14.90]
3 FEV1 % predicted: baseline	4	224	Mean Difference (IV, Fixed, 95% CI)	5.17 [-0.21, 10.55]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.1 LMW	2	99	Mean Difference (IV, Fixed, 95% CI)	10.30 [2.26, 18.34]
3.2 HMW	1	93	Mean Difference (IV, Fixed, 95% CI)	0.40 [-9.93, 10.73]
3.3 HMW and LMW	1	32	Mean Difference (IV, Fixed, 95% CI)	1.60 [-8.54, 11.74]
4 FEV1 % predicted: follow up	4	224	Mean Difference (IV, Fixed, 95% CI)	7.47 [1.89, 13.05]
4.1 LMW	2	99	Mean Difference (IV, Fixed, 95% CI)	11.40 [2.52, 20.28]
4.2 HMW	1	93	Mean Difference (IV, Fixed, 95% CI)	1.70 [-8.23, 11.63]
4.3 HMW and LMW	1	32	Mean Difference (IV, Fixed, 95% CI)	8.40 [-1.96, 18.76]

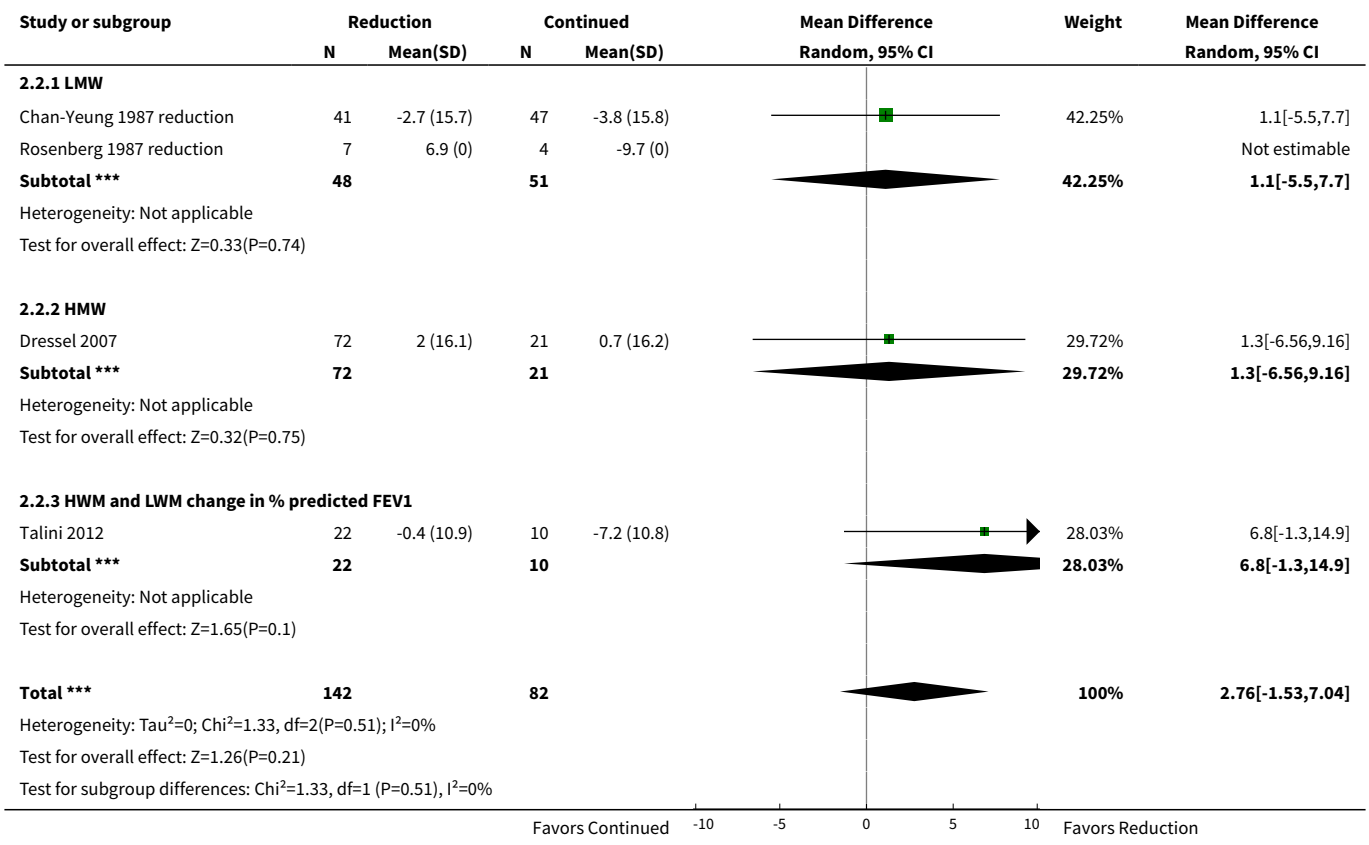
Analysis 2.1. Comparison 2 Reduction of exposure versus continued exposure, Outcome 1 Absence of asthma symptoms.

Study or subgroup	Reduction n/N	Continued n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
2.1.1 LMW absence of symptoms					
Chan-Yeung 1987 reduction	0/42	0/54			Not estimable
Rosenberg 1987 reduction	3/7	0/4		7.22%	4.38[0.28,68.06]
Subtotal (95% CI)	**49**	**58**		**7.22%**	**4.38[0.28,68.06]**
Total events: 3 (Reduction), 0 (Continued)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.05(P=0.29)					
2.1.2 HMW absence of symptoms					
Bernstein 2003 reduction	20/20	0/1		10.71%	3.9[0.35,43.1]
Dressel 2007	12/81	0/24		8.99%	7.62[0.47,124.22]
Dressel 2009	4/43	0/15		8.6%	3.27[0.19,57.44]
Subtotal (95% CI)	**144**	**40**		**28.29%**	**4.89[1.04,22.96]**
Total events: 36 (Reduction), 0 (Continued)					
Heterogeneity: Tau^2=0; Chi^2=0.21, df=2(P=0.9); I^2=0%					
Test for overall effect: Z=2.01(P=0.04)					
2.1.3 HMW & LMW absence of symptoms					
Moscato 1993 reduction	0/7	0/4			Not estimable
Talini 2012	13/22	4/10		64.49%	1.48[0.64,3.4]
Subtotal (95% CI)	**29**	**14**		**64.49%**	**1.48[0.64,3.4]**
Total events: 13 (Reduction), 4 (Continued)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.92(P=0.36)					
Total (95% CI)	**222**	**112**		**100%**	**2.65[1.24,5.68]**
Total events: 52 (Reduction), 4 (Continued)					
Heterogeneity: Tau^2=0; Chi^2=2.69, df=4(P=0.61); I^2=0%					
Test for overall effect: Z=2.51(P=0.01)					

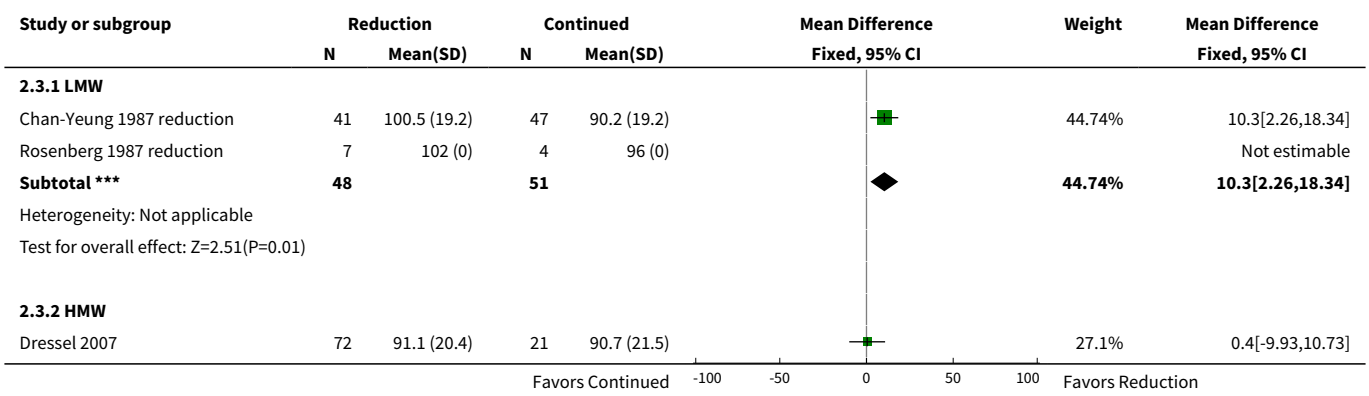


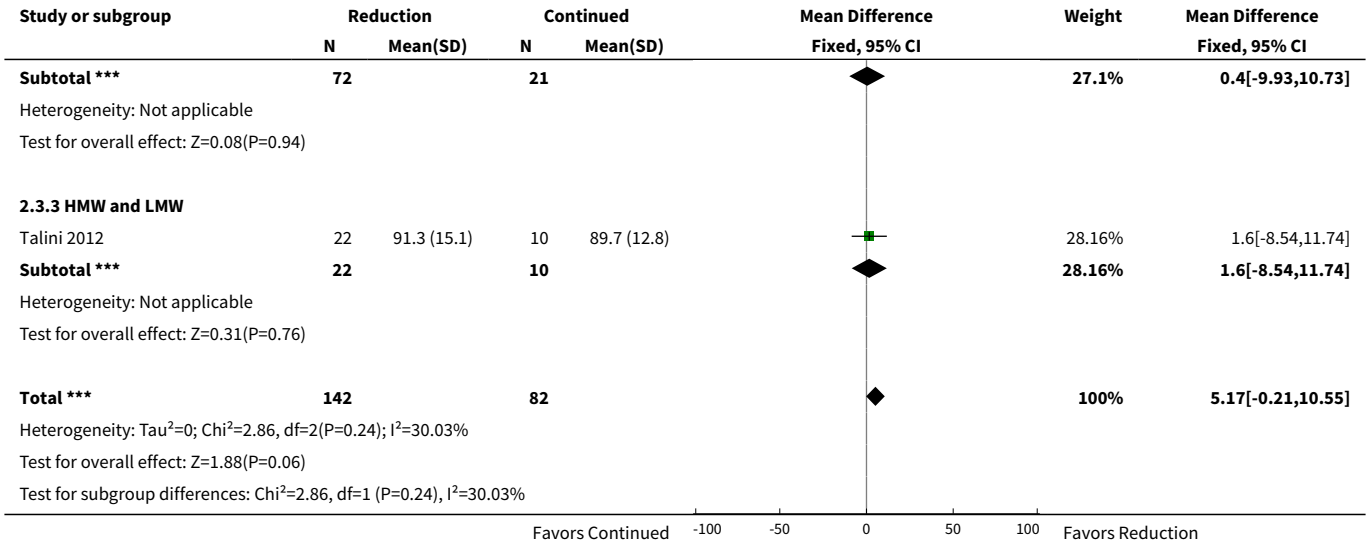


Analysis 2.2. Comparison 2 Reduction of exposure versus continued exposure, Outcome 2 Change in FEV1 % predicted: follow-up minus baseline values.

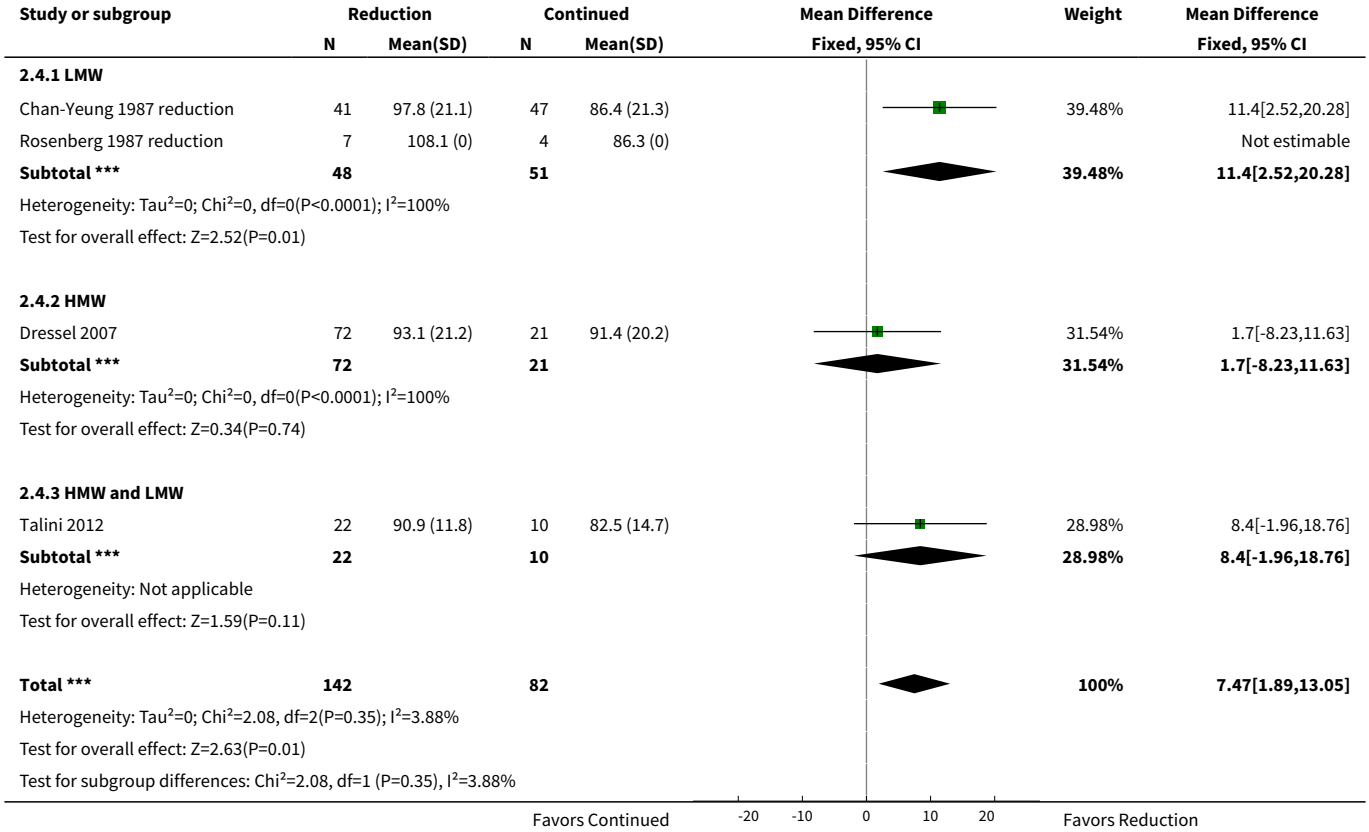


Analysis 2.3. Comparison 2 Reduction of exposure versus continued exposure, Outcome 3 FEV1 % predicted: baseline.





Analysis 2.4. Comparison 2 Reduction of exposure versus continued exposure, Outcome 4 FEV1 % predicted: follow up.

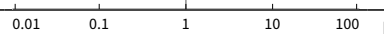


Comparison 3. Removal from exposure versus reduction of exposure

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Absence of asthma symptoms	6	359	Risk Ratio (M-H, Random, 95% CI)	6.05 [0.86, 42.34]
1.1 LMW absence of symptoms	3	274	Risk Ratio (M-H, Random, 95% CI)	9.31 [1.56, 55.73]
1.2 HMW absence of symptoms	1	29	Risk Ratio (M-H, Random, 95% CI)	10.83 [0.68, 173.30]
1.3 HMW and LMW absence of symptoms	2	56	Risk Ratio (M-H, Random, 95% CI)	2.08 [0.17, 25.76]
2 Improvement of asthma symptoms	5	140	Risk Ratio (M-H, Random, 95% CI)	1.11 [0.84, 1.47]
2.1 LMW improvement of symptoms	2	55	Risk Ratio (M-H, Random, 95% CI)	1.61 [1.02, 2.53]
2.2 HMW improvement of symptoms	2	60	Risk Ratio (M-H, Random, 95% CI)	1.0 [0.90, 1.11]
2.3 HMW & LMW improvement of symptoms	1	25	Risk Ratio (M-H, Random, 95% CI)	0.88 [0.40, 1.93]
3 Change in FEV1 % predicted: follow-up minus baseline values	7	388	Mean Difference (IV, Random, 95% CI)	2.58 [-3.02, 8.17]
3.1 LMW	5	321	Mean Difference (IV, Random, 95% CI)	5.79 [0.02, 11.56]
3.2 HMW	1	36	Mean Difference (IV, Random, 95% CI)	-4.0 [-10.52, 2.52]
3.3 HMW and LMW	1	31	Mean Difference (IV, Random, 95% CI)	-1.30 [-10.06, 7.46]
4 Being unemployed	2	64	Risk Ratio (M-H, Fixed, 95% CI)	14.28 [2.06, 99.16]
5 FEV1 % predicted: baseline	7	388	Mean Difference (IV, Fixed, 95% CI)	-2.42 [-5.52, 0.67]
5.1 LMW	5	321	Mean Difference (IV, Fixed, 95% CI)	-5.05 [-8.94, -1.16]
5.2 HMW	1	36	Mean Difference (IV, Fixed, 95% CI)	3.0 [-2.68, 8.68]
5.3 HMW and LMW	1	31	Mean Difference (IV, Fixed, 95% CI)	-1.70 [-13.63, 10.23]
6 FEV1 % predicted: follow up	7	388	Mean Difference (IV, Random, 95% CI)	0.62 [-5.12, 6.36]
6.1 LMW	5	321	Mean Difference (IV, Random, 95% CI)	1.90 [-6.71, 10.50]
6.2 HMW	1	36	Mean Difference (IV, Random, 95% CI)	-1.0 [-9.66, 7.66]
6.3 HMW and LMW	1	31	Mean Difference (IV, Random, 95% CI)	-3.0 [-13.39, 7.39]

Analysis 3.1. Comparison 3 Removal from exposure versus reduction of exposure, Outcome 1 Absence of asthma symptoms.

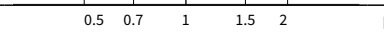
Study or subgroup	Removal n/N	Reduction n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
3.1.1 LMW absence of symptoms					
Chan-Yeung 1987 removal	55/136	0/42		15.19%	34.84[2.2,552.17]
Talini 2013	6/32	1/14		17.71%	2.63[0.35,19.82]
Valentino 2002	21/37	0/13		15.28%	15.84[1.03,244.39]
Subtotal (95% CI)	**205**	**69**		**48.18%**	**9.31[1.56,55.73]**
Total events: 82 (Removal), 1 (Reduction)					
Heterogeneity: Tau^2=0.91; Chi^2=3.13, df=2(P=0.21); I^2=36.16%					
Test for overall effect: Z=2.44(P=0.01)					
3.1.2 HMW absence of symptoms					
Visentin 2003	7/17	0/12		15.16%	10.83[0.68,173.3]
Subtotal (95% CI)	**17**	**12**		**15.16%**	**10.83[0.68,173.3]**
Total events: 7 (Removal), 0 (Reduction)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.68(P=0.09)					
3.1.3 HMW and LMW absence of symptoms					
Moscato 1993 removal	9/18	0/7		15.33%	8[0.53,121.59]
Talini 2012	5/9	13/22		21.32%	0.94[0.48,1.86]
Subtotal (95% CI)	**27**	**29**		**36.66%**	**2.08[0.17,25.76]**
Total events: 14 (Removal), 13 (Reduction)					
Heterogeneity: Tau^2=2.5; Chi^2=3.44, df=1(P=0.06); I^2=70.94%					
Test for overall effect: Z=0.57(P=0.57)					
Total (95% CI)	**249**	**110**		**100%**	**6.05[0.86,42.34]**
Total events: 103 (Removal), 14 (Reduction)					
Heterogeneity: Tau^2=4.5; Chi^2=27.5, df=5(P<0.0001); I^2=81.82%					
Test for overall effect: Z=1.81(P=0.07)					
Test for subgroup differences: Chi^2=1.07, df=1 (P=0.59), I^2=0%					



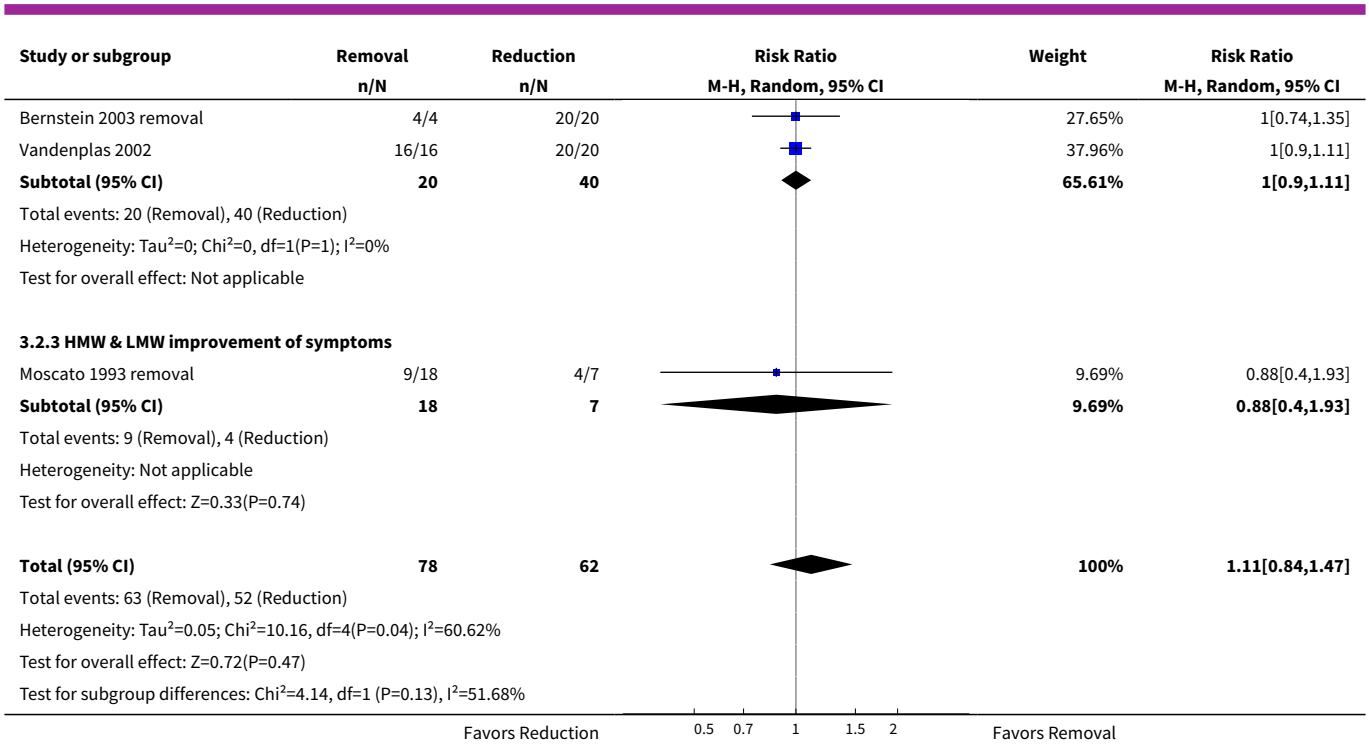
Favors Reduction — Favors Removal

Analysis 3.2. Comparison 3 Removal from exposure versus reduction of exposure, Outcome 2 Improvement of asthma symptoms.

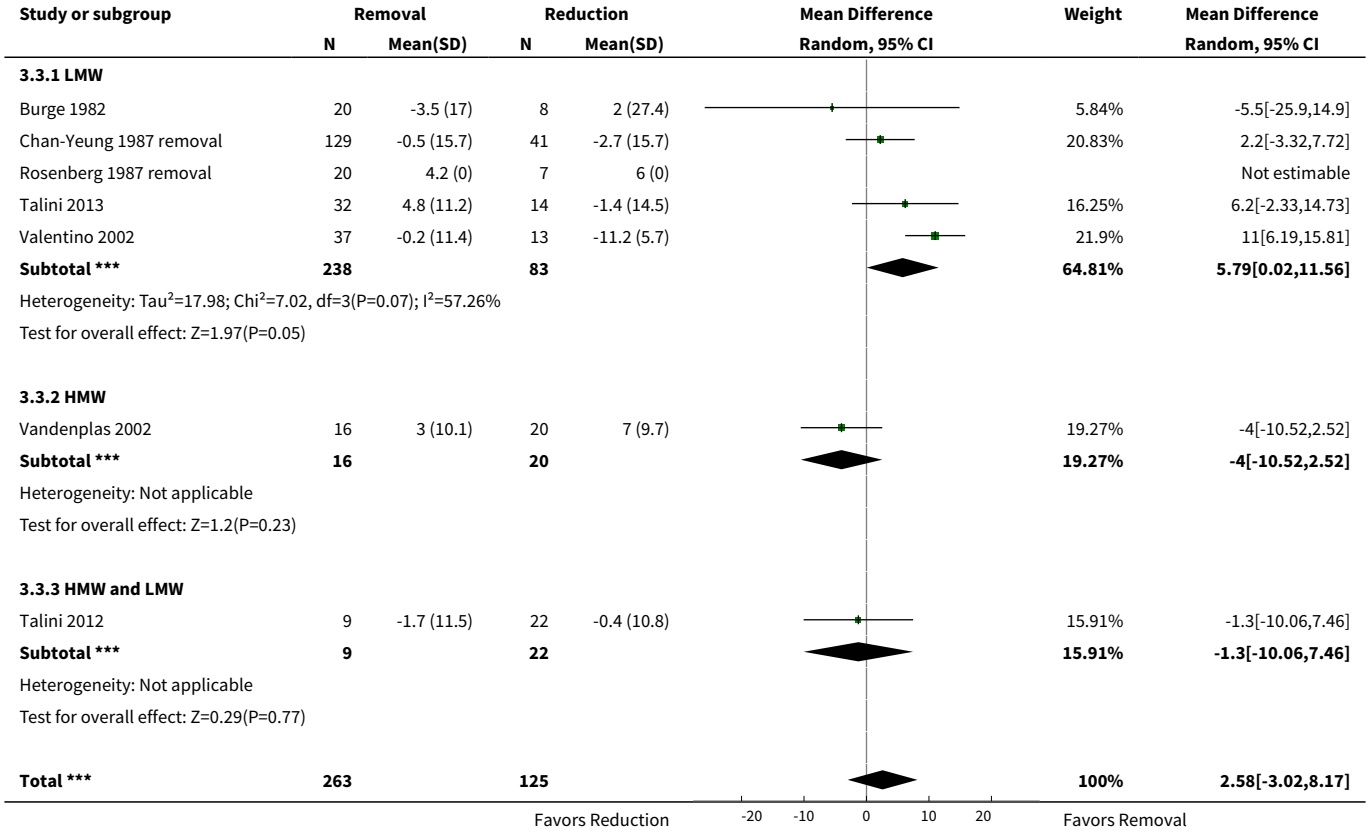
Study or subgroup	Removal n/N	Reduction n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
3.2.1 LMW improvement of symptoms					
Burge 1982	20/20	5/8		16.81%	1.6[0.94,2.7]
Rosenberg 1987 removal	14/20	3/7		7.89%	1.63[0.66,4.03]
Subtotal (95% CI)	**40**	**15**		**24.7%**	**1.61[1.02,2.53]**
Total events: 34 (Removal), 8 (Reduction)					
Heterogeneity: Tau^2=0; Chi^2=0, df=1(P=0.97); I^2=0%					
Test for overall effect: Z=2.05(P=0.04)					
3.2.2 HMW improvement of symptoms					



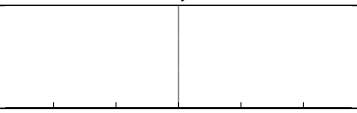
Favors Reduction — Favors Removal



Analysis 3.3. Comparison 3 Removal from exposure versus reduction of exposure, Outcome 3 Change in FEV1 % predicted: follow-up minus baseline values.

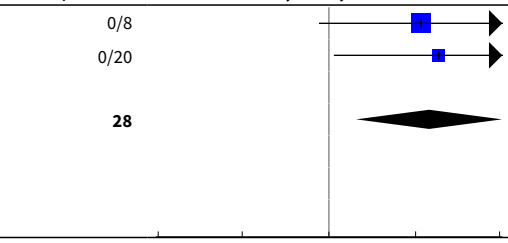


Study or subgroup	Removal N	Removal Mean(SD)	Reduction N	Reduction Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Heterogeneity: Tau²=31.17; Chi²=16.83, df=5(P=0); I²=70.29%							
Test for overall effect: Z=0.9(P=0.37)							
Test for subgroup differences: Chi²=5.17, df=1 (P=0.08), I²=61.3%							



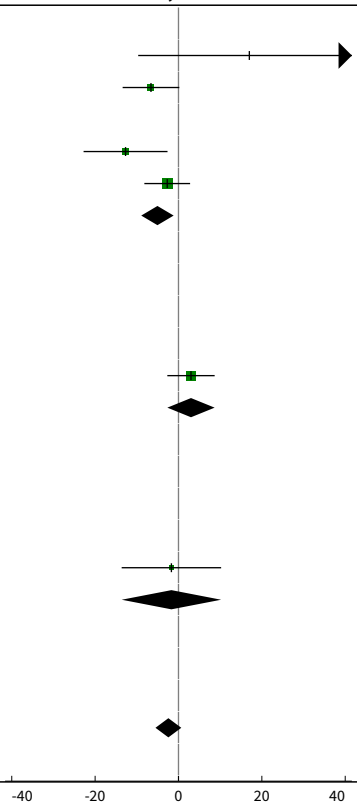
Analysis 3.4. Comparison 3 Removal from exposure versus reduction of exposure, Outcome 4 Being unemployed.

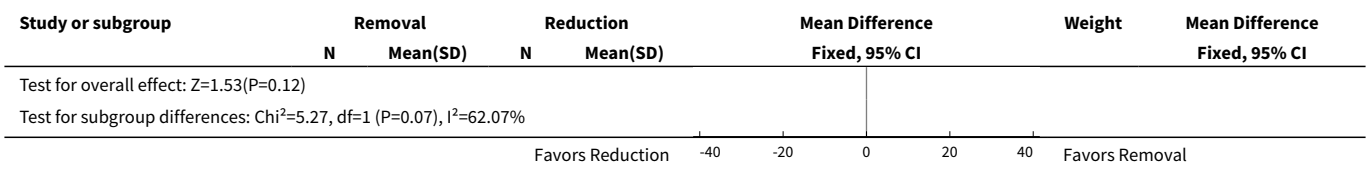
Study or subgroup	Removal n/N	Reduction n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Burge 1982	13/20	0/8		61.01%	11.57[0.77,174.35]
Vandenplas 2002	7/16	0/20		38.99%	18.53[1.14,301.79]
Total (95% CI)	**36**	**28**		**100%**	**14.28[2.06,99.16]**
Total events: 20 (Removal), 0 (Reduction)					
Heterogeneity: Tau²=0; Chi²=0.06, df=1(P=0.81); I²=0%					
Test for overall effect: Z=2.69(P=0.01)					



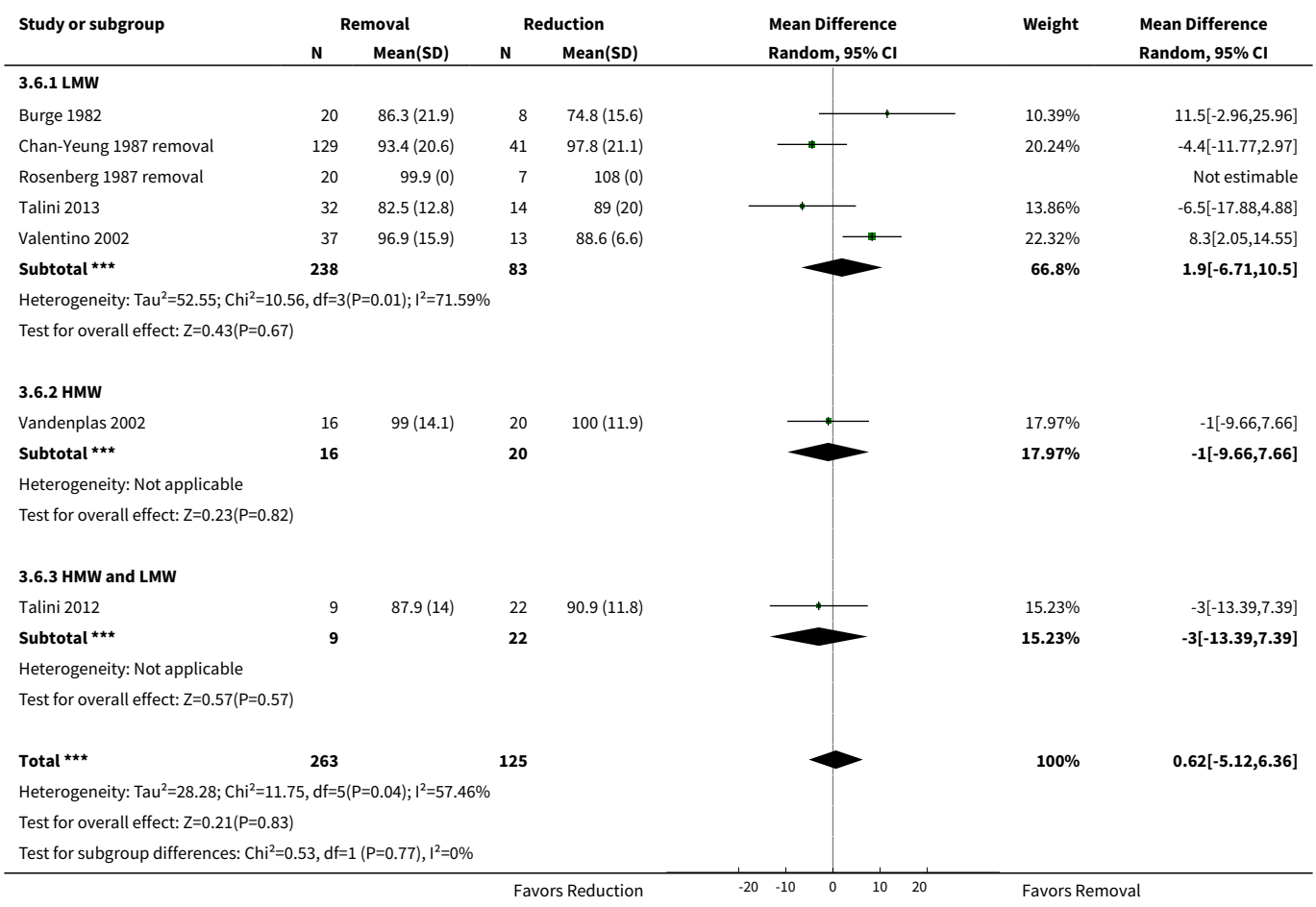
Analysis 3.5. Comparison 3 Removal from exposure versus reduction of exposure, Outcome 5 FEV1 % predicted: baseline.

Study or subgroup	Removal N	Removal Mean(SD)	Reduction N	Reduction Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
3.5.1 LMW							
Burge 1982	20	89.8 (21.9)	8	72.8 (35.9)		1.35%	17[-9.66,43.66]
Chan-Yeung 1987 removal	129	93.9 (19.8)	41	100.5 (19.2)		20.77%	-6.6[-13.4,0.2]
Rosenberg 1987 removal	20	95.7 (0)	7	102 (0)			Not estimable
Talini 2013	32	77.7 (15.4)	14	90.4 (16.3)		9.47%	-12.7[-22.77,-2.63]
Valentino 2002	37	97.1 (10.6)	13	99.8 (7.9)		31.88%	-2.7[-8.19,2.79]
Subtotal ***	**238**		**83**			**63.46%**	**-5.05[-8.94,-1.16]**
Heterogeneity: Tau²=0; Chi²=5.75, df=3(P=0.12); I²=47.82%							
Test for overall effect: Z=2.54(P=0.01)							
3.5.2 HMW							
Vandenplas 2002	16	96 (11.1)	20	93 (3.7)		29.8%	3[-2.68,8.68]
Subtotal ***	**16**		**20**			**29.8%**	**3[-2.68,8.68]**
Heterogeneity: Not applicable							
Test for overall effect: Z=1.04(P=0.3)							
3.5.3 HMW and LMW							
Talini 2012	9	89.6 (15.5)	22	91.3 (15.1)		6.74%	-1.7[-13.63,10.23]
Subtotal ***	**9**		**22**			**6.74%**	**-1.7[-13.63,10.23]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.28(P=0.78)							
Total ***	**263**		**125**			**100%**	**-2.42[-5.52,0.67]**
Heterogeneity: Tau²=0; Chi²=11.02, df=5(P=0.05); I²=54.64%							





Analysis 3.6. Comparison 3 Removal from exposure versus reduction of exposure, Outcome 6 FEV1 % predicted: follow up.



ADDITIONAL TABLES

Table 1. Interventions

	Removal from exposure	Reduction of exposure Moved to area with less exposure	Reduction of exposure Introduce/change	Reduction of exposure Education/training

Table 1. Interventions *(Continued)*

			use of PPE	program
Bernstein 2003	+		+	
Burge 1982	+	+		
Chan-Yeung 1982	+			
Chan-Yeung 1987	+	+		
Dressel 2007				+
Dressel 2009				+
DiGiampaolo 2012	+	+		
Innocenti 1981	+			
Lin 1996	+			
Mapp 1988	+			
Marabini 1993	+			
Marabini 1994	+	+		
Moscato 1993	+	+		
Moscato 1999	+	+		
Munoz 2008	+			
Munoz 2014	+			
Padoan 2003	+			
Paggiaro 1984	+			
Pisati 1994	+			
Rosenberg 1987	+	+	+	
Soyseth 1995		+		
Talini 2012	+	+	+	
Talini 2013	+	+		
Valentino 2002	+	+		
Vandenplas 2002	+	+	+	
Visentin 2003	+	+		

PPE: personal protective equipment

Table 2. Non-specific bronchial hyperreactivity (NSBH)

	Test	Removal from exposure				Reduction of exposure				Continued exposure			
		No.	Baseline	SD/ SEM	Follow-up	SD/ SEM	No.	Baseline	SD/ SEM	Follow-up	No.	Baseline	SD/ SEM	Follow-up	SD/ SEM
Bernstein 2003	-														
Burge 1982	Histamine PC20 Normal > 4 um/ml	20	6 abnormal		3 abnormal		8	4 abnormal		3 abnormal					
Chan-Yeung 1982	Methacholine PC20	33	2.45	SD	8.48	SD					22	1.81	SD	0.96	SD
Chan-Yeung 1987	Methacholine PC20	52	1.04	SD	1.95	SD	15	1.14	SD	0.64	19	0.86	SD	0.61	SD
Dressel 2007	-														
Dressel 2009	-														
DiGiampaolo 2012	-														
Innocenti 1981	-														
Lin 1996	-														
Mapp 1988	Methacholine PD20	30	0.38	SEM	0.57	SEM					5	0.36	SEM	0.39	SEM
Marabini 1993	Methacholine PC20	80	2.5	SEM	5.21	SEM					48	3.4	SEM	2.7	SEM
Marabini 1994	-														
Moscato 1993	Methacholine PD20														
Moscato 1999	Methacholine PD20	13	0.144	25-75 perc	1.200	25-75 perc					12	1.719	25-75 perc	1.936	25-75 perc
Munoz 2008	Methacholine PC20	7	4 abnormal		2 abnormal						3	2 abnormal		3 abnormal	

Table 2. Non-specific bronchial hyperreactivity (NSBH) *(Continued)*

Munoz 2014	Methacholine PC20	55	2	range 0.06-16	1.6	range 0.06-16			18	1.2	range 0.13-8	1.3	range 0.4-8.5
Padoan 2003	Methacholine PD20	74			1.10	SEM			13			0.855	SEM
Paggiaro 1984	Betacholine 15%	12	8 abnormal		7 abnormal				15	9 abnormal		11 abnormal	
Pisati 1994	Methacholine PD15	7	0.443		0.895				1	0.100		0.38	
Rosenberg 1987	Acethylcholine PC15	20	14/20 abnormal		7/12 abnormal	7	6 abnormal	5 abnormal	4	3 abnormal		4 abnormal	
Soyseth 1995	Methacholine PD20												
Talini 2012	Methacholine PD20	9	1.732		2.507	22	1.685	3.747	10	2.748		1.745	
Talini 2013, FEV1<82%	Methacholine PD20	17	0.20		1.01	5	0.09	0.06					
Talini 2013, FEV1>=82%	Methacholine PD20	15	0.21		0.25	9	0.49	0.58					
Valentino 2002	Methacholine PD20	37	0.373	in-app SD	0.957	in-app SD			12	0.383	in-app SD	0.382	in-app SD
Vandenplas 2002	Histamine PC 20	16	0.40		2.30	20	0.50	2.4					
Visentin 2003	-												

FEV1 < 82% and FEV1 ≥ 82%: Level of percent predicted FEV1 at baseline
PC20: Provocative concentration of methacholine causing a 20% fall in FEV1, mg/ml
PD20: Provocation dose causing a 20% decline in FEV1
SD: standard deviation
SEM: standard error of the mean
IQR: Interquartile range

Table 3. Employment/income

Author	Outcome
Bernstein 2003	Removal from exposure group: 4/4 had a reduction in income. Mean reduction 24% in annual income (all 4 workers were forced to leave job due to symptoms, but were employed by FU)
Burge 1982	Removal from exposure group: no employment at FU: 13/20. (Re-)employment at FU: 7/20 Reduction of exposure group: no employment at FU: 0/8. (Re-)employment at FU: 8/8
Chan-Yeung 1987	A higher percentage of non-white subjects remained in the industry compared to white subjects. This is due to the inability of non-white subjects to find other jobs because of the language difficulties.
Marabini 1993	Removal from exposure group: Unemployed 53/80. Mean reduction 50% in monthly income
Moscato 1993	At the time of FU only 5 patients had been contacted by the National Insurance Institute for Occupational Diseases, whereas 24 had not yet been contacted. In 2 out of 5 the diagnosis had been accepted by the National Insurance Institute for Occupational Diseases and the patients were waiting for compensation; 2 had already been granted disablement benefit; 1 had been examined but not accepted.
Moscato 1999	The Italian system for compensation did not guarantee prompt and automatic compensation of subjects with OA. Because of the delay with compensations, along with the current Italian socioeconomic condition that makes it difficult to find a job, a number of our patients who resigned after the diagnosis of OA remained without any financial support for a long period of time, with serious socioeconomic consequences Removal from exposure group: 25% reduction in annual income
Vandenplas 2002	Removal from exposure group: No Employment: 7/16. (Re-)employment at FU: 9/16. Median reduction in income 20% Reduction of exposure group: No Employment: 0/20. (Re-)employment at FU: 20/20

FU: follow-up
OA: occupational asthma

Table 4. Agents

	Iso-cyanate	Latex	West-ern red cedar	Cow dander Storage mite	Pot room	Persul-fates	Colo-phoni-um	Cobalt	Various
Bernstein 2003		+							
Burge 1982							+		
Chang-Yeung 1982			+						
Chang-Yeung 1987			+						
Dressel 2007				+					
Dressel 2009				+					
DiGiampaolo 2012									+
Innocenti 1981	+								
Lin 1996			+						
Mapp 1988	+								
Marabini 1993			+						
Marabini 1994	+								
Moscato 1993									+
Moscato 1999									+
Munoz 2008						+			
Munoz 2014									+
Padoan 2003	+								
Paggiaro 1984	+								

Table 4. Agents *(Continued)*

Pisati 1994					+	
Rosenberg 1987	+					
Soyseth 1995				+		
Talini 2012						+
Talini 2013	+					
Valentino 2002	+					
Vandenplas 2002		+				
Visentin 2003		+				

Table 5. Agents divided by mechanism

	HMW (high molecular weight)	LMW (low molecular weight)	HMW & LMW combined	Pot room
Bernstein 2003	+			
Burge 1982		+		
Chan-Yeung 1982		+		
Chan-Yeung 1987		+		
Dressel 2007	+			
Dressel 2009	+			
DiGiampaolo 2012			+	
Innocenti 1981		+		
Lin 1996		+		
Mapp 1988		+		
Marabini 1993		+		
Marabini 1994		+		
Moscato 1993			+	
Moscato 1999			+	
Munoz 2008		+		
Munoz 2014			+	
Padoan 2003		+		
Paggiaro 1984		+		
Pisati 1994		+		
Rosenberg 1987		+		
Soyseth 1995				+
Talini 2012			+	
Talini 2013		+		
Valentino 2002		+		

Table 5. Agents divided by mechanism *(Continued)*

Vandenplas 2002	+
Visentin 2003	+

Table 6. Baseline characteristics

Total & Groups	Partici-pants	Age	Sex	Smoking (S)	Atopy	Type of reaction	Fol-low-up	Expo-sure time before symp-toms	Dura-tion of symp-toms before diagno-sis
	No.	**Years**	**Male %**	**Smoker - ex-smoker - non-smoker**	**Positive**	**Immediate - late - dual**	**Years**	**Years**	**Years**
Bernstein 2003 - Total	**25**	**36.1**	**4.5%**	**Not mentioned**	**89%**	**Not mentioned**	**3.9**	**5.2**	**4.5**
Removal from exposure	4	-	-	-	-	-	-	-	-
Reduction of exposure	20	-	-	-	-	-	-	-	-
Continued exposure	1	-	-	-	-	-	-	-	-
Burge 1982 - Total	**28**	**50**	**7.1%**	**25 - 18 - 57%**	**Not men-tioned**	**Not mentioned**	**2**		**2.5**
Removal from exposure	20	52	5%	35 - 15 - 50%	-	-	-	-	-
Reduction of exposure	8	45	12.5%	0 -25 - 75%	-	-	-	-	-
Chan-Yeung 1982 - Total	**125**	**41.1**	**100%**	**5 - 26 - 69%**	**20.4%**	**10 - 43 - 47%**	**3.3**	**3.3**	**3.8**
Removal from exposure	75	41.6	100%	FU: 5 - 32 - 63%	17%	8 - 48 - 44%	3.5	3.5	5.1
Continued exposure	50	40.2	100%	FU: 2 - 22 - 76%	26%	8 - 36 - 56%	3.1	2.9	1.9
Chan-Yeung 1987 - Total	**232**	**41.9**	**98%**	**6 - 28 - 66%**	**31.4%**	**11 - 42 - 47%**	**4**	**4.1**	**2.2**
Removal from exposure	136	42.9	99%	6 - 29 - 65%	26%	11 - 42 - 47%	4.1	4.6	2.2
Reduction of exposure	42	39.8	100%	0 - 31 - 69%	32.4%	7.1 - 47.6 - 45.2%	4.3	3.8	1.7
Continued exposure	54	41.1	93%	6 - 24 - 71%	49.1%	13 - 37 - 50%	3.8	3.1	2.6

Table 6. Baseline characteristics *(Continued)*

DiGiampaolo 2012	**58**	**37.6**	**Not mentioned**	**0-52%-48%**	**Not mentioned**	**Not mentioned**	**12**	**Not mentioned**	**6.6**
Removal from Exposure	30	38.1	-	0 – 18 – 12 0-60%-40%	-	-	-	-	6.5
Continued exposure	28	37.0	-	0 – 12 – 16 0-43%-57%	-	-	-	-	6.8
Dressel 2007 - Total	**105**	**47.1**	65%	**Not mentioned**	**Not mentioned**	**Not mentioned**	**5 weeks**	**Not mentioned**	**Not mentioned**
Reduction of exposure - education program received	81	-	60%	-	-	-	-	-	-
Continued exposure - no education program received	24	-	79%	-	-	-	-	-	-
Dressel 2009 - Total	**55**	**45.6**	**67%**	**Not mentioned**	**Not mentioned**	**Not mentioned**	**1**	**Not mentioned**	**Not mentioned**
Reduction of exposure - education program received	43	46.5	63%						
Continued exposure - no education program received	15	44.1	80%						
Innocenti 1981 - Total	**50**	***19-67***	**78%**	**S: 9/25**	**FU: 24%**	**Not mentioned**	**< 1**	**Not mentioned**	**Only mentioned for half of the subjects**
Removal from exposure	37			S: 5/18	FU: 27%	-		-	-
Continued exposure	13			S: 4/13	FU: 15%	-		-	-

Table 6. Baseline characteristics *(Continued)*

Lin 1996 - Total	**201**	**40.9**	**100%**	**5 - 28 - 67%**	**28%**	**Not mentioned**	**6.1**		**2.0**
Removal from exposure	109	42.1	100%	7 - 30 - 64%	30%	-	5.3	-	1.83
Continued exposure	92	40	100%	3 - 27 - 70%	26%	-	6.9	-	2.3
Mapp 1988 - Total	**35**	**34.7**	**71%**	**9 - 27 - 63%**	**23%**	**12 - 33 - 50%**	**0.8**	**13.5**	**3.7**
Removal from exposure	30	33.9	66%	3 - 30 - 66%	27%	7 - 43 - 50%		13.2	3.7
Continued exposure	5	38.4	100%	40 - 20 - 40%	0%	0 - 40 - 60%		15	3.7
Marabini 1993 - Total	**128**	**47.3**	**100%**	**4 - 25 - 71%**	**36%**	**Not mentioned**	**5.6**	**Not mentioned**	**Not mentioned**
Removal from exposure	80	50	100%	3 - 27 - 70%	30%	-	5.9	-	-
Continued exposure	48	43	100%	6 - 21 - 72%	46%	-	4.8	-	-
Marabini 1994 - Total	**40**	**40**	**85%**	**35 - 30 - 35%**	**10%**	23 - 63 - 14%	**6.8**	**Not mentioned**	**Not mentioned**
Removal from exposure	28			-	-	-	-	-	-
Continued exposure	12			-	-	-	-	-	-
Moscato 1993 - Total	**29**	**36.4**	**72%**	**S: 17% NS: 42%**	**28%**	**FU: 62 - 7 - 31%**	**1,2**	**Not mentioned**	**8.5**
Removal from exposure	18	-	-	-	-	-	-	-	-
Moscato 1993 - reduce	7	-	-	-	-	-	-	-	-
Continued exposure	4	-	-	-	-	-	-	-	-
Moscato 1999 - Total	**25**	**34**	**72%**	**28 - 24 - 48%**	**16%**	**44 - 32 - 24%**	**1**	**3.8**	**1.75**
Removal from exposure	13	31	77%	23 - 23 - 54%	8%			6	1.67

Table 6. Baseline characteristics *(Continued)*

Moscato 1999 - continue	12	35.5	66%	33 - 25 - 42%	25%			0.5	2.13
Munoz 2008 - Total	**10**	**37.6**	**0%**	**S: 30% NS: 70%**	**30%**	**Not mentioned**	**5.3**	**Not mentioned**	**Not mentioned**
Removal from exposure	7	-	0%	-	-	-	-	-	-
Continued exposure	7	-	0%	-	-	-	-	-	-
Munoz 2014 - Total	**73**	**42**	**58%**	**21 - 14 - 66%**	**50%**	**32 - 40 - 22% + 7% other**	**>1.0**	**11.1**	**3.9**
Removal from exposure	55	41	64%	20 - 15 - 65%	42%	31 - 44 - 22% + 4% other	>1.0	6.0	4.0
Continued exposure	18	44	39%	22 - 11 - 67%	67%	33 - 28 - 22% + 17% other	>1.0	16.8	3.4
Padoan 2003 - Total	**87**	**38**	**72%**	**8 - 29 - 63%**	**23%**	**21 - 54 - 25%**	**11.5**	**12**	**3.8**
Removal from exposure	74	-	-	-	-	-	-	-	-
Continued exposure	13	-	-	-	-	-	-	-	-
Paggiaro 1984 - Total	**27**	**50.2**	**59%**	**S: 30% NS 70%**	**44%**	**22 - 41 - 37%**	**2**	**15.6**	
Removal from exposure	12	53	66%	S: 33% NS: 67%	-	-	-	-	
Continued exposure	15	48	53%	S: 27% NS: 73%	-	-	-	-	
Pisati 1994 - Total	**9**	**Not mentioned**	**Not mentioned**	**12.5 - 12.5 - 75%**	**0%**	**0 - 87.5 - 12.5%**	**3**	**Not mentioned**	**Not mentioned**
Removal from exposure	8	-	-	-	-	-	-	-	-
Continued exposure	1	-	-	-	-	-	-	-	-

Table 6. Baseline characteristics *(Continued)*

Rosenberg 1987 - Total	**31**	**35.9**	**Not clear**	**S: 19% - ENS: 81%**	**29%**	**Not mentioned**	**2**	**2.9**	**1.4**
Removal from exposure	20	38.4	Not clear	S: 30% - ENS: 70%	-	-	2.3	-	-
Reduction of exposure	7	37.6	Not clear	S: 14% - ENS: 86%	-	-	1.8	-	-
Continued exposure	4	48.8	Not clear	S: 50% - ENS: 50%	-	-	1.1	-	-
Soyseth 1995 - Total	**38**	**36.8**	**100%**	**S: 58% - NS: 42%**	**Not mentioned**	**Not mentioned**	**2**	**Not mentioned**	**Not mentioned**
Reduction of exposure	12	37.4	100%	S: 42% - NS: 58%	-	-	-	-	-
Continued exposure	26	36.5	100%	S: 65% - NS: 35%	-	-	-	-	-
Talini 2012 - Total	**41**	**40**	**80%**	**10 - 49 - 41%**	**37%**	**Not mentioned**	**>2, <3**	**Not mentioned**	**Not mentioned**
Removal from exposure	9	35	78%	11 - 56 - 33%	33%	-	3.2	-	-
Reduction of exposure	22	40	82%	14 - 36 - 50%	36%	-	2.9	-	-
Continued exposure	10	41	80%	0 - 70 - 30%	40%	-	1.7	-	-
Talini 2013 - Total	**46**	**47**	**70%**	**17 - 37 - 46%**	**22%**	**42 - 30 - 28%**	**11**	**Not mentioned**	**Not mentioned**
Removal from exposure	32	Not mentioned	Not mentioned	Not mentioned	Not mentioned	Not mentioned	Not mentioned	-	-
Reduction from exposure	14	-	-	-	-	-	-	-	-
Valentino 2002 - Total	**50**	**32.3**	**70%**	**FU. S: 36% NS: 64%**	**FU: 12%**	**28 - 56 - 16%**	**8.4**	**Not mentioned**	**Not mentioned**
Removal from exposure	37	33.3	73%	FU. S: 43% NS: 57%	FU: 11%	32 - 60 - 8%		-	-

Table 6. Baseline characteristics *(Continued)*

Reduction of exposure	13	29.3	62%	FU. S: 15% NS: 85%	FU: 15%	15 - 45 - 40%		-	-
Vandenplas 2002 - Total	**36**	**32**	**11%**	**Not clear**	**64%**	**63 - 4 - 33%**	**4.7**	**5.9**	**7.2**
Removal from exposure	16	32	6%		56%	44 - 12 - 44%		5.7	6.5
Reduction of exposure	20	32	15%		70%	70 - 5 - 25%		6.1	7.8
Visentin 2003 - Total	**29**	**32**	**10%**	**Not mentioned**	**Not mentioned**	**Not mentioned**	**5**	**Not mentioned**	**Not mentioned**
Removal from exposure	17			-	-	-	-	-	-
Reduction of exposure	12			-	-	-	-	-	-

Bernstein 2003: the 21 occupational asthma cases were part of a total group of 67 participants. Characteristics were mentioned for the total group of 67.
FU: follow-up
ES: ex-smoker
ENS: ex- and non-smokers
NS: non-smoker
S: smoker

Table 7. Methodological quality assessment - Part 1 of 2

Items from the checklist of Downs and Black 1998	Bernstein 2003	Burge 1982	Chan-Yeung 1982	Chan-Yeung 1987	Dressel 2007	Dressel 2009	Di Giampaolo 2010	Incorvaia 1981	Lin 1996	Mapp 1988	Maestrelli 1993	Malo 1994	Moscato 1993	Moscato 1999
Reporting														
1 = Yes adequate														
0 = No not adequate														
1. Is the hypothesis clearly described?	1	1	1	1	1	1	1	1	1	1	1	1	1	0

Table 7. Methodological quality assessment - Part 1 of 2 *(Continued)*

2. Are main outcomes clearly described?	1	1	1	1	1	1	1	0	1	1	1	0	1	1
3. Are patient characteristics clearly described?	0	1	1	1	1	1	1	0	1	1	1	0	0	0
4. Are interventions clearly described?	0	1	1	1	1	1	0	1	1	1	1	1	0	0
5. Are distributions of co-founders clearly described?	0	0	0	1	0	0	1	0	1	1	1	1	0	1
6. Are main findings clearly described?	0	0	1	1	1	1	0	0	1	1	1	1	0	1
7. Estimates of random variability in data for main outcome?	0	1	1	1	1	1	1	0	1	1	1	1	0	0
8. Have important adverse effects been reported?	1	1	0	1	0	0	1	0	0	0	1	0	0	1
9. Have characteristics of patients lost to follow-up been described?	0	0	1	0	0	0	0	0	1	0	0	0	0	1
10. Have actual probabilities been reported?	0	0	0	0	1	1	0	0	1	0	0	0	0	0
Subtotal	**3**	**6**	**7**	**8**	**7**	**7**	**6**	**2**	**9**	**7**	**8**	**5**	**2**	**5**
Internal validity														
14. Was attempt made to blind subjects to intervention?	0	0	0	0	0	0	0	0	0	0	0	0	0	0
15. Was attempt made to blind those measuring the outcome?	0	0	0	0	0	0	0	0	0	0	0	0	0	0
16. If results were based on data dredging, was this made clear?	0	0	0	0	0	0	0	0	0	0	0	0	1	1
17. Analyses adjusted for length of follow-up?	0	0	0	1	1	1	0	0	1	0	0	1	0	1
19. Was compliance with the intervention reliable?	0	0	0	0	1	1	1	0	0	0	0	0	0	0
20. Were the main outcome measures used accurate?	0	1	1	1	1	1	1	0	1	0	1	0	0	1
21. Were patients recruited over the same population?	1	1	1	1	1	1	0	0	1	1	0	0	0	1
22. Were patients recruited over the same period?	1	1	0	1	1	1	1	0	1	0	0	1	0	1
23. Were subjects randomized to intervention groups?	0	0	0	0	0	0	0	0	0	0	0	0	0	0
24. Was randomisation concealed until recruitment was complete?	0	0	0	0	0	0	0	0	0	0	0	0	0	0

Table 7. Methodological quality assessment - Part 1 of 2 *(Continued)*

25. Was there adequate adjustment for confounding factors?	0	0	0	1	0	0	1	0	1	1	0	0	0	0
26. Were losses of workers to follow-up taken into account?	0	0	0	0	0	0	1	0	1	0	0	0	0	1
TOTAL	**2**	**3**	**2**	**5**	**5**	**5**	**5**	**5**	**6**	**2**	**1**	**2**	**1**	**6**

Table 8. Methodological Quality Assessment - Part 2 of 2

Items from the checklist of Downs and Black 1998												
	Mun[illegible] 2008	Mu[illegible] 2014	Pad[illegible] 2003	Paggiaro 1984	Pisati 1994	Rosenberg 1987	Soyseth 1995	Talini 2012	Talini 2013	Valentino 2002	Vandenplas 2002	Visentin 2003
Reporting, 1 = Yes, adequate 0 = No, not adequate												
1. Is the hypothesis clearly described?	1	1	1	1	1	1	1	1	1	0	1	0
2. Are main outcomes clearly described?	1	1	1	1	1	1	1	1	1	0	1	0
3. Are patient characteristics clearly described?	1	1	1	1	0	0	1	1	1	0	1	0
4. Are interventions clearly described?	1	1	1	0	0	0	0	1	1	1	1	0
5. Are distributions of co-founders clearly described?	1	1	0	1	0	0	1	1	0	1	1	0
6. Are main findings clearly described?	1	0	0	1	0	0	0	1	1	0	1	0
7. Estimates of random variability in data for main outcome?	1	1	0	1	0	0	0	1	1	0	1	0
8. Have important adverse effects been reported?	0	0	0	0	0	0	0	0	0	0	1	0
9. Have characteristics of patients lost to follow-up been described?	0	1	0	0	0	0	0	0	0	0	1	0
10. Have actual probabilities been reported?	0	0	1	0	0	0	1	0	0	0	1	0
Subtotal	**7**	**7**	**5**	**6**	**2**	**2**	**5**	**7**	**6**	**2**	**10**	**0**

Table 8. Methodological Quality Assessment - Part 2 of 2 *(Continued)*

Internal validity												
14. Was attempt made to blind subjects to intervention?	0	0	0	0	0	0	0	0	0	0	0	0
15. Was attempt made to blind those measuring the outcome?	0	0	0	0	0	0	0	0	0	0	0	0
16. If results were based on data dredging, was this made clear?	0	0	0	0	0	0	1	0	1	0	0	0
17. Analyses adjusted for length of follow-up?	0	0	0	0	0	0	1	0	0	0	0	0
19. Was compliance with the intervention reliable?	1	0	0	0	1	0	1	0	1	0	0	0
20. Were the main outcome measures used accurate?	1	1	1	1	1	0	1	1	1	0	1	0
21. Were patients recruited over the same population?	1	0	1	1	1	1	1	1	1	0	1	0
22. Were patients recruited over the same period?	1	0	1	0	1	1	1	1	1	0	1	0
23. Were subjects randomized to intervention groups?	0	0	0	0	0	0	0	0	0	0	0	0
24. Was randomisation concealed until recruitment was complete?	0	0	0	0	0	0	0	0	0	0	0	0
25. Was there adequate adjustment for confounding factors?	0	0	0	0	0	0	1	1	1	0	0	0
26. Were losses of workers to follow-up taken into account?	0	0	0	0	0	0	0	0	0	0	0	0
TOTAL	**4**	**1**	**3**	**2**	**4**	**1**	**7**	**4**	**6**	**0**	**3**	**0**

APPENDICES

Appendix 1. Cochrane Central (Cochrane Library on Wiley) Search Strategies and Results Counts, by Date of Search

ID	Search	Jan 2010 to Dec 2015	December 2015 to April 2018	May 2018 to July 2019
#1	MeSH descriptor: [Asthma] explode all trees	9473	10827	10992
#2	asthma*	26573	30855	34858
#3	wheez*	1728	2162	2819
#4	#1 or #2 or #3	27168	31645	35918
#5	MeSH descriptor: [Occupational Health] this term only	436	555	621
#6	MeSH descriptor: [Occupational Diseases] this term only	777	835	1468
#7	MeSH descriptor: [Occupational Exposure] this term only	432	489	551
#8	MeSH descriptor: [Occupational Medicine] this term only	62	66	67
#9	MeSH descriptor: [Work] explode all trees	337	910	991
#10	work*	44128	64083	79156
#11	occupation* 8908	8908	11191	13514
#12	#5 or #6 or #7 or #8 or #9 or #10 or #11	48760	70173	87076
#13	#4 and #12	1793	1889	2212
#14	#13 Publication Year from first date to second date	939	470	595
#15	#14 Results from Cochrane Central Register of Controlled Trials	158	215	454

Notes: The December 2015 search was conducted by Barbara Landreth, MA, Librarian, National Institute for Occupational Safety and Health (NIOSH), Centers for Disease Control and Prevention (CDC), Morgantown, WV, USA. The April 2018 search was conducted by Joanna Taliano, MA MLS, Reference Librarian, and the July 2019 search was conducted by Yolanda Strayhorn, MLIS, Reference Librarian, both from the Library Science Branch, Division of Public Health Information Dissemination (DPHID), Center for Surveillance, Epidemiology, and Laboratory Services (CSELS), Office of Public Health Scientific Services (OPHSS), CDC, Atlanta, Georgia USA. Item ID #14 includes the text "from first date to second date," which varied with each of the three searches and was consistent with the dates indicated at the top of the columns with the results counts.

Appendix 2. Medline (PubMed) Search Strategies and Results Counts, by Date of Search

Search	Query	Jan 2010	December 2015	May 2018

(Continued)

		to Dec 2015	to April 2018	to July 2019
#21	Search #13 OR #20	1695	320	405
#20	Search #19 NOT #13	1048	187	250
#19	Search #17 OR #18	1421	639	350
#18	Search (#16) AND “first date”[Entrez Date] : “second date”[Entrez Date]	1392	591	308
#17	Search #16 Filters: Publication Date from 2015/12/01 to 2018/04/30	1405	615	335
#16	Search #15 NOT #8	5381	6079	6323
#15	Search #6 AND #14	5567	6298	6550
#14	Search effectiveness[tw] OR effect*[ti] OR program[tw] OR intervention[tw] OR reduction[tw] OR evaluation[tw] OR decrease*[tw] OR measures[tw] OR improve*[tiab] OR Comparative Study[pt] OR “prevention and control”[sh]	8212838	9648914	9958377
#13	Search #11 OR #12	647	320	155
#12	Search (#10) AND “2015/12/01”[Entrez Date] : “2018/04/30”[Entrez Date]	633	291	137
#11	Search #10 Filters: Publication Date from first date to second date	639	313	148
#10	Search #9 NOT #8	2645	3009	3134
#9	Search #6 AND #7	2728	3113	3246
#8	Search animals[mh] NOT humans[mh]	4063250	4487380	4605934
#7	Search randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized[tiab] OR placebo[tiab] OR drug therapy[sh] OR randomly[tiab] OR trial[tiab] OR groups[tiab]	3698201	4320968	4559364
#6	Search #1 AND #5	12237	13700	14224
#5	Search #2 OR #3 OR #4	1235525	1508627	1613207
#4	Search occupation*[tw] OR work[tw] OR works*[tw] OR work’*[tw] OR worka*[tw] OR worke*[tw] OR workg*[tw] OR worki*[tw] OR workl*[tw] OR workp*[tw]	1235525	1498824	1603264
#3	Search work[mesh]	14897	58042	60466
#2	Search “Occupational Health”[Mesh] OR “Occupational Diseases”[Mesh:NoExp] OR “Occupational Exposure”[Mesh:NoExp] OR “Occupational Medicine”[Mesh]	150095	162354	166177
#1	Search asthma[mh] OR asthma*[tw] OR wheez*[tw]	152101	170453	177218

Notes: The December 2015 search was conducted by Barbara Landreth, MA, Librarian, National Institute for Occupational Safety and Health (NIOSH), Centers for Disease Control and Prevention (CDC), Morgantown, WV, USA. The April 2018 search was conducted by Joanna Taliano, MA MLS, Reference Librarian, and the July 2019 search was conducted by Yolanda Strayhorn, MLIS, Reference Librarian, both from

the Library Science Branch, Division of Public Health Information Dissemination (DPHID), Center for Surveillance, Epidemiology, and Laboratory Services (CSELS), Office of Public Health Scientific Services (OPHSS), CDC, Atlanta, Georgia USA. Item IDs #11 and #18 mention "first date" and "second date," which varied with each of the three searches and were consistent with the dates indicated at the top of the columns with the results counts.

Appendix 3. Embase (Ovid) Search Strategies and Results Counts, by Date of Search

No.	Query	Jan 2010 to Dec 2015	December 2015 to April 2018	May 2018 to July 2019
1	exp Asthma/	152660	207284	221638
2	asthma$.mp.	174031	235422	251539
3	wheez$.mp.	20495	28003	30207
4	or/1-3	182327	247288	264460
5	Occupational Health/	27318	35557	37283
6	Occupational Exposure/	49148	68925	71772
7	Occupational Disease/	20490	30360	31397
8	Occupational Medicine/	3608	5770	6023
9	Occupational Hazard/	13128	16570	17292
10	exp Work/	199565	281962	304917
11	occupation$.ab,ti.	103233	147699	159921
12	work$.ab,ti.	1051102	1493731	1660697
13	or/5-12	1229047	1749708	1931913
14	4 and 13	16222	21960	23595
15	limit 14 to exclude medline journals	1581	1975	2214
16	15 and ((dates).dd,em,yr. OR (dates).dc)	1069	267	147
17	Randomized Controlled Trial/	345437	493298	548076
18	Controlled Study/	4192444	6006059	6780997
19	Randomization/	60751	76446	81108
20	Double Blind Procedure/	101240	142211	154330
21	Single Blind Procedure/	20058	31900	36019
22	Clinical Trial/	707089	915217	927541
23	Crossover Procedure/	41074	55822	59999

(Continued)

24	Follow-up/	899991	1273270	1412261
25	exp Prospective Study/	295905	457804	535467
26	or/17-25	5444465	7664302	8540771
27	(clinical$ adj3 trial$).mp.	1012327	1513214	1604834
28	((singl* or doubl* or trebl* or tripl*) adj5 (mask* or blind* or method*)).mp.	238780	282179	378942
29	exp Placebo/	221106	282179	300289
30	placebo$.ab,ti.	180126	253906	272777
31	random$.ab,ti.	910342	1267176	1390177
32	(latin adj3 square$).mp.	2747	4321	4621
33	exp Comparative Study/	721576	1020247	1101821
34	((control* or prospectiv* or volunteer*) adj3 (trial* or method* or stud*)).ab,ti.	847909	1196192	1313726
35	crossover$.mp.	59557	83648	89747
36	(cross adj over$).mp.	17181	25500	27289
37	or/27-36	2757787	3916644	4237032
38	26 or 37	6545133	9236026	10206596
39	16 and 38	360	101	86
40	exp Animal/ or exp Nonhuman/	14539607	21387440	23011866
41	Human/	11396565	16685222	18004916
42	40 not 41	3143042	4702218	5006950
43	39 not 42	323	93	82
44	effectiveness.mp.	448916	654288	732655
45	effect$.ti.	1061059	1569120	1689634
46	program.mp.	589324	780893	836865
47	intervention.mp.	522544	742721	832282
48	reduction.mp.	1044820	1438025	1553121
49	exp Evaluation/	28364	50790	60672
50	decrease$.mp.	1738088	2479199	2685496

(Continued)

51	measures.mp.	557399	776214	849948
52	improve$.ab,ti.	1777378	2543260	2830733
53	"prevention and control".mp. or pc.fs.	786619	1021172	1062988
54	or/44-53	6114791	8626876	9372161
55	16 and 54	482	124	65
56	55 not 42	462	118	60
57	56 not 43	284	67	25
58	43 or 57	607	160	107

Notes: The December 2015 search was conducted by Barbara Landreth, MA, Librarian, National Institute for Occupational Safety and Health (NIOSH), Centers for Disease Control and Prevention (CDC), Morgantown, WV, USA. The April 2018 search was conducted by Joanna Taliano, MA MLS, Reference Librarian, and the July 2019 search was conducted by Yolanda Strayhorn, MLIS, Reference Librarian, both from the Library Science Branch, Division of Public Health Information Dissemination (DPHID), Center for Surveillance, Epidemiology, and Laboratory Services (CSELS), Office of Public Health Scientific Services (OPHSS), CDC, Atlanta, Georgia USA. Item No. 16 mentions "dates" that varied with each of the three searches, and were consistent with the dates indicated at the top of the columns with the results counts

Appendix 4. NIOSHTIC-2 (Internet) Search Strategies and Results Counts, by Date of Search

	Query	Jan 2010 to Dec 2015	December 2015 to April 2018	May 2018 to July 2019
	(asthma* or wheez*) and (effect* or program* or compare* or intervention or reduction or evaluation or decrease* or measures or improve* or prevention or random*) and (occupation* or work*) - published from first date to second date	242	120	79

Notes: The December 2015 search was conducted by Barbara Landreth, MA, Librarian, National Institute for Occupational Safety and Health (NIOSH), Centers for Disease Control and Prevention (CDC), Morgantown, WV, USA. The April 2018 search was conducted by Joanna Taliano, MA MLS, Reference Librarian, and the July 2019 search was conducted by Yolanda Strayhorn, MLIS, Reference Librarian, both from the Library Science Branch, Division of Public Health Information Dissemination (DPHID), Center for Surveillance, Epidemiology, and Laboratory Services (CSELS), Office of Public Health Scientific Services (OPHSS), CDC, Atlanta, Georgia USA. The "first date to second date" indicated in the query varied with each of the three searches, and were consistent with the dates indicated at the top of the columns with the results counts.

Appendix 5. CISILO (CCOHS) Search Strategies and Results Counts, by Date of Search

	Query	Jan 2010 to Dec 2015	December 2015	May 2018 to July 2019

(Continued)

			to April 2018	
	(asthma* or wheez*) AND (effect* or control* or evaluation* or program* or prevention* or random*) AND (occupation* or work*) Publication Year from first date to second date	5	0	30

Notes: The December 2015 search was conducted by Barbara Landreth, MA, Librarian, National Institute for Occupational Safety and Health (NIOSH), Centers for Disease Control and Prevention (CDC), Morgantown, WV, USA. The April 2018 search was conducted by Joanna Taliano, MA MLS, Reference Librarian, and the July 2019 search was conducted by Yolanda Strayhorn, MLIS, Reference Librarian, both from the Library Science Branch, Division of Public Health Information Dissemination (DPHID), Center for Surveillance, Epidemiology, and Laboratory Services (CSELS), Office of Public Health Scientific Services (OPHSS), CDC, Atlanta, Georgia USA. The "first date to second date" indicated in the query varied with each of the three searches, and were consistent with the dates indicated at the top of the columns with the results counts

Appendix 6. Quality according to GRADE

Grades of Recommendation, Assessment, Development and Evaluation Working Group **(GRADE)**

Type of evidence

Randomized trial = high

Observational study = moderate

Any other evidence = very low

Decrease grade if:

- serious (- 1) or very serious (- 2) limitation to study quality;
- important inconsistency (- 1);
- some (- 1) or major (- 2) uncertainty about directness;
- imprecise or sparse data (- 1);
- high probability of reporting bias (- 1).

High = further research is very unlikely to change our confidence in the estimate of effect.

Moderate = further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low = further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low = any estimate of effect is very uncertain.

WHAT'S NEW

Date	Event	Description
25 September 2019	New citation required and conclusions have changed	We updated the systematic literature searches from January 2010 through July 2019. We added five new studies. With the new citation, the only change in conclusions compared to de Groene 2011 was that removal from exposure did not statistically significantly increase the likelihood of the absence of asthma symptoms compared to reduction of exposure.
9 September 2016	New search has been performed	Change in Author team – Stefania Curti replaced Stefano Mattioli

HISTORY

Protocol first published: Issue 1, 2007
Review first published: Issue 5, 2011

Date	Event	Description
18 March 2011	New search has been performed	Original review assessed as up-to-date

CONTRIBUTIONS OF AUTHORS

PH and JP coordinated the review process, selected studies, assessed quality of studies, extracted data, conducted data analyses, formulated conclusions, and wrote and revised the text of the review.

GG provided background on the initial review and critical methodological guidance, selected studies, assessed quality of studies, extracted data, and suggested changes to the text of the review.

JB, ST, TP, and SC selected studies, assessed quality of studies, extracted data, and suggested changes to the text of the review.

DECLARATIONS OF INTEREST

Paul K Henneberger: None known.

Jenil R Patel: None known.

Gerda J de Groene: None known.

Jeremy Beach: None known.

Susan M Tarlo: None known.

Teake M Pal: None known.

Stefania Curti: None known.

SOURCES OF SUPPORT

Internal sources

- No organization explicitly provided support for this review, Other.

External sources

- No organization explicitly provided support for this review, Other.

INDEX TERMS

Medical Subject Headings (MeSH)

*Workplace; Asthma [etiology] [*prevention & control]; Case-Control Studies; Occupational Diseases [etiology] [*prevention & control]; Occupational Exposure [adverse effects] [*prevention & control]; Protective Devices; Risk; Unemployment

MeSH check words

Humans