Workplace interventions for treatment of occupational asthma (Review)

de Groene GJ, Pal TM, Beach J, Tarlo SM, Spreeuwers D, Frings-Dresen MHW, Mattioli S, Verbeek JH

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TABLE OF CONTENTS

[Intervention Review]

Workplace interventions for treatment of occupational asthma

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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 the outcome of occupational asthma.

Search strategy

We searched the Cochrane Central Register of Controlled Trials (CENTRAL); MEDLINE; EMBASE; NIOSHTIC-2; CISDOC and HSELINE up to February 2011.

Selection criteria

Randomised 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 trial quality, and extracted data.

Main results

We included 21 controlled before and after studies with 1447 participants that reported on 29 comparisons.

In 15 studies, removal from exposure was compared with continued exposure. Removal increased the likelihood of reporting absence of symptoms (risk ratio (RR) 21.42, 95% confidence interval (CI) 7.20 to 63.77), improved forced expiratory volume (FEV1 %) (mean

difference (MD) 5.52 percentage points, 95% CI 2.99 to 8.06) and decreased non-specific bronchial hyper-reactivity (standardised mean difference (SMD) 0.67, 95% CI 0.13 to 1.21).

In six studies, reduction of exposure was compared with continued exposure. Reduction increased the likelihood of reporting absence of symptoms (RR 5.35, 95% CI 1.40 to 20.48) but did not affect FEV1 % (MD 1.18 percentage points, 95% CI -2.96 to 5.32).

In eight studies, removal from exposure was compared with reduction of exposure. Removal increased the likelihood of reporting absence of symptoms (RR 39.16, 95% CI 7.21 to 212.83) but did not affect FEV1 % (MD 1.16 percentage points, 95% CI -7.51 to 9.84).

Two studies reported that the risk of unemployment after removal from exposure was increased compared with reduction of exposure (RR 14.3, 95% CI 2.06 to 99.16). Three studies reported loss of income of about 25% after removal from exposure.

Overall the quality of the evidence was very low.

Authors' conclusions

There is very low-quality evidence that removal from exposure improves asthma symptoms and lung function compared with continued exposure.

Reducing exposure also improves symptoms, but seems not as effective as complete removal.

However, removal from exposure is associated with an increased risk of unemployment, whereas reduction of exposure is not. The clinical benefit of removal from exposure or exposure reduction should be balanced against the increased risk of unemployment. We need better studies to identify which interventions intended to reduce exposure give most benefit.

PLAIN LANGUAGE SUMMARY

Workplace interventions to deal with occupational asthma

Occupational asthma is the most frequently reported work-related respiratory disease in many countries. It is defined as asthma that is caused by a specific workplace exposure to certain substances and not to factors outside the workplace. In a recent review the population attributable risk for adult onset asthma being caused by occupational exposures was 17.6%. Occupational asthma can lead to decreased quality of life, sickness absence and increased costs for the patient, the employer and society. Early removal from exposure has been reported to be important in the prognosis of occupational asthma in a number of papers and reviews, but is not universally accepted as an important part of management.

Twenty-one articles were included in this review, reporting on 29 studies of three different interventions with 1447 participants. Fifteen studies compared workers that were removed from exposure to those who continued to be exposed. In another six studies, reduction of exposure was compared to continued exposure and in again another eight studies workers who were removed from exposure were compared to those for whom exposure was reduced. Outcomes were asthma symptoms and lung function at follow up. The overall quality of the studies was very low. Both removal from and reduction of exposure reduced asthma symptoms significantly but removal did better. Lung function improved significantly after removal but not after reduction of exposure. However, removal from exposure came at the cost of a much higher risk of unemployment and a greater decrease of income. Therefore, it remains uncertain how much better removal of exposure is compared to reduction of exposure and the benefit of symptom improvement should be balanced against the much higher risk of job loss and income decrease.

Further randomised controlled trials are needed to find out which interventions most effectively reduce the impact of occupational asthma.

BACKGROUND

Occupational asthma is the most frequently reported work-related respiratory disease in most countries where there are reporting schemes (Meredith 1996). One commonly-used definition is asthma that is caused by a specific workplace exposure to certain substances and not to factors outside the workplace (Bernstein 1999). In a recent review the population attributable risk (PAR) for adult onset asthma being caused by occupational exposures was 17.6% (Toren 2009). Another study reported that 21% of all working asthma patients experience an aggravation of their symptoms due to work exposure at least weekly (Saarinen 2003). Data from surveillance schemes also suggest that there may be significant underreporting of occupational asthma (Cherry 2009). It has few specific features making it difficult to recognise; patients with occupational asthma do not always visit an occupational physician or chest physician, and those that do are not always diagnosed (McDonald 2000). Occupational asthma can lead to decreased quality of life, sickness absence and increased costs for the patient, the employer and society.

Common causes of occupational asthma include exposure to high molecular weight (HMW) agents such as wheat, latex and animal proteins, or low molecular weight (LMW) agents such as diisocyanates, acid anhydrides, platinum salts and plicatic acid. Two types of occupational asthma are generally recognised: 1) irritant-induced (with no latency period and symptoms and signs most often reported as starting within 24 hours of a spill or other very high exposure to a respiratory irritant, for example, chlorine) and 2) sensitiser-induced (often caused by an allergen such as wheat or animal proteins with a latent period ranging from a few weeks to years) (Nicholson 2010).

Effective management of workers suspected to have occupational asthma requires the identification and investigation of symptoms suggestive of asthma soon after they occur (Nicholson 2010). A clear diagnosis usually requires a combination of investigations. (Beach 2005).

A number of interventions have been studied as a way of effectively managing individuals with occupational asthma, including removal from exposure by relocating to another workplace, or providing personal protective equipment (Ameille 2005; Malo 1992; Paggiaro 1994; Vigo 2005). A number of reports have suggested that it is important to stop further exposure to the causal agent once the diagnosis has been established, as this can influence the prognosis (Tarlo 2002; Tarlo 2005; Tarlo 2008). There have also been several reviews on the management of occupational asthma (Beach 2005; Chan-Yeung 1995; Kogevinas 2007; Nicholson 2010; Rachiotis 2007; Tarlo 2008). Some authors from these earlier reviews found it difficult to draw conclusions about optimal management due, in part, to the heterogeneity of findings in the research available (Beach 2005).

OBJECTIVES

The objective of this review was to evaluate the effectiveness of workplace interventions on the clinical outcome of individuals with occupational asthma.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs) which included individual person-directed interventions such as providing personal protective equipment.

Exposure reduction in the workplace is often brought about at the group level therefore it is difficult to randomise at the individual level; we therefore also included controlled clinical trials (defined as inadequately randomised studies), controlled before and after studies (CBA) and interrupted time series (ITS) (according to the criteria of the Cochrane Effective Practice and Organisation of Care (EPOC) Group) (EPOC).

We accepted as controlled before and after studies all studies that included a concurrent control group and in which the outcome was measured before and after the intervention, both in the intervention and control group. The control group could receive either no intervention or an alternative intervention.

We excluded case studies.

Types of participants

Male or female workers with asthma and a work-related pattern of symptoms, pulmonary function changes, immunological or inflammatory changes, and/or changes in airway hyper-responsiveness, such that occupational asthma was considered to be the most likely diagnosis by their treating physician. For the determination of a work-related pattern of changes we accepted the following tests (some alone and some in combination): specific inhalation challenge, 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 chest physician or occupational physician (Beach 2005; Chan-Yeung 1995; Nicholson 2005; Tarlo 2008).

Types of interventions

We included any type of workplace intervention intended to reduce the symptoms or severity of occupational asthma by reducing the exposure at work. We compared actual interventions with no intervention or an alternative intervention. We did not include

studies studying the effects of medication only. We categorised the interventions into the groups below.

Removal from exposure

- Complete removal from exposure
- Substitution of causal agents

Reduction of exposure

- Introduction into use of personal respiratory protective equipment or more effective respiratory protective equipment
- The implementation of educational programmes designed to prevent or reduce exposure through increased worker awareness and knowledge
- Relocation to another work area with less exposure with the same or a different employer

Types of outcome measures

Primary outcomes

1. Asthma symptoms

We used improvement in asthma symptoms before and after the intervention as the primary outcome. Authors obtained information about asthma symptoms using interviews or questionnaires. Some reported numbers of symptomatic and asymptomatic individuals. Others described numbers of workers with improvement, or classified the symptoms into groups. We considered information obtained with all these various methods as equally valid.

2. Lung function

2a. FEV1 % predicted

Forced expiratory volume in the first second (FEV1) as a percentage of a predicted or reference value was used as the outcome measure of airway obstruction. A number of different reference values were used. We considered all to be equally valid.

2b. Non-specific bronchial hyper-reactivity (NSBH)

NSBH is an important hallmark of asthma. NSBH can be measured with different bronchoconstrictors and is reported in different ways, for example as a PC20 (predicted concentration of provocative agent causing a 20% decrement in FEV1) or PD20 (as for PC20 but utilising dose rather than concentration). We considered the information obtained with these various methods as equally valid.

Secondary outcomes

We intended to use 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) as secondary outcomes but no studies reported this outcome in this way. However, a number of papers reported information on changes in employment status and income following diagnosis. We decided to use this as a secondary measure.

Search methods for identification of studies

Electronic searches

We systematically searched the following databases: MEDLINE (January 1966 to January 2009); EMBASE (January 1980 to February 2011); the Cochrane Central Register of Controlled Trials(CENTRAL) (to January 2009); the Cochrane Airways Group Specialised Register of trials (to April 2010); the Cochrane Occupational Safety and Health Group Specialised Register; NIOSHTIC-2; CISDOC and HSELINE to February 2011. To identify papers on occupational asthma we used various terms indicating asthma, work and the combination of work and asthma. For locating randomised controlled trials we used the search strategy recommended by Lefebrve 2008. For locating non-randomised intervention studies we used the search strategy reported by Verbeek 2005 (Appendix 1).

Searching other resources

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

Data collection and analysis

Selection of studies

Two review authors assessed the title and abstract of all the papers identified in order to assess their relevance for inclusion, although this was not the same two authors for all papers. One author (GG) assessed all the studies. The second assessment was shared between the remaining authors. We obtained the full text of all papers considered relevant based on review of their title and abstract, and evaluated each against the inclusion criteria described above.

Data extraction and management

Two review authors performed data extraction independently. One author (GG) acted as one data extractor for all the papers. The remaining authors each acted as a second data extractor for a proportion of the papers. We used a consensus method to reconcile

differences in extracted information between authors where these occurred. A third author was asked to re-extract the data if differences could not be reconciled in this way. 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 additional information.

Assessment of risk of bias in included studies

We intended to assess risk of bias for randomised trials using the Cochrane Collaboration's tool, but no such trials were found. A number of non-randomised trials were included therefore we performed an additional evaluation of the quality of the studies using the checklist developed by Downs and Black (Downs 1998). For risk of bias assessment for these studies we used the 'Internal Validity' section of the Downs and Black assessment. We omitted question 18 on appropriate statistical tests as it was felt it could not be meaningfully interpreted and hence it did not add any value to the assessment of methodological quality. We interpreted a score of less than 50% for any study as 'high risk of bias'. For time series data we intended to use the quality checklist developed by the Cochrane EPOC group (EPOC) but no such studies were identified.

Measures of treatment effect

For controlled before and after studies (CBAs), 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, we described them in the table of Characteristics of included studies, or entered the data into 'other data tables'. For outcomes utilising continuous measures, we gave preference to analysing those results for which a mean difference (MD) between groups could be estimated. This was not possible for the results of the NSBH tests where the outcomes were measured on different scales. For these we used standardised mean differences (SMD) or effect sizes.

Asthma symptoms were reported in various ways. Some authors reported numbers of symptomatic and asymptomatic at follow up; others described numbers of subjects with improvement of symptoms, or symptoms were classified into groups with an indication of presence, severity or both. In each case, we analysed the data as a dichotomous outcome comparison and reported the risk ratio (RR) for both, absence of symptoms and for improvement (but no absence) of symptoms.

The most widely used parameter of lung function in the included papers was FEV1. FEV1 was reported in various ways but most commonly as a percentage of a predicted or reference value (FEV1 %) and this was used for comparison in these analyses. In order to minimise the influence of baseline differences, we used the mean difference 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 the baseline values and the values at follow up for completeness.

For measuring NSBH two different bronchoconstrictors were commonly used: methacholine and histamine. Results were most often presented as PC20, PC15 or PD20 and PD15. Some articles reported subjects with 'abnormal' values and other articles reported a continuous outcome in dose or concentration. The studies had used different test methods, therefore we used a standardised mean difference (SMD). The SMD is a measure used to combine study results when studies have used different instruments to measure the same construct. The SMD expresses the effect of the intervention in standard units 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 standard deviation 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 (Handbook 2009). We interpreted the SMDs in the following way: < 0.40 = small, 0.40 to 0.70 = moderate and > 0.70 = large.

Unit of analysis issues

It had been assumed that a number of studies might have used a cluster-randomised design without an allowance for the possible effect of this clustering, and we had intended to utilise a strategy which had previously been developed to deal with this (Campbell 2001; Ukoumunne 1999). However, we identified no studies with a cluster-randomised design.

Dealing with missing data

Where a paper was felt to be missing information that was needed for the meta-analysis we contacted the original authors to see if this information might be available. Where important statistical information was missing, for example the standard deviation or a correlation coefficient, we calculated this from other available statistics such as P values, using the methods described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Handbook 2009).

Some papers did not report whether the value used to describe the scatter of FEV1 % values was a standard deviation (SD) or a standard error (SE) (Chan-Yeung 1987; Lin 1996; Paggiora 1984). It was assumed that higher values indicated a SD, whereas lower values indicated a SE. For example below 5 we classified as low and above 20 as high.

Where the standard deviation could not be calculated for the change we estimated it from the correlation coefficient as recommended in the *Cochrane Handbook for Systematic Reviews of Interventions* Chapter 16.1.3.2.

In instances where the SE and no SD was provided, we calculated a SD so as to be able to enter the data into the meta-analysis.

We used the method recommended in the *Cochrane Handbook for Systematic Reviews of Interventions* Chapter 7.7.3.2.
Two articles reported data as a median and inter-quartile range. As the distribution of 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 the *Cochrane Handbook for Systematic Reviews of Interventions* Chapter 7.7.3.5 (Moscato 1999; Vandenplas 2002).
For the comparison 'change in FEV1 % baseline - follow up' we calculated the changes of the reported values FEV1 at baseline and follow up.

Assessment of heterogeneity

We defined clinical homogeneity as having similar interventions or exposure to the same kind of agent(s). Outcomes had to be measured at baseline and at follow up. We tested for statistical heterogeneity by means of the I^2 statistic in the meta-analyses graphs. We used a cut-off of $\geq$ 50% to indicate significant heterogeneity, as suggested in the *Cochrane Handbook for Systematic Reviews of Interventions* (Handbook 2009).

Assessment of reporting biases

We used a funnel plot to check for publication bias where more than five studies were available for inclusion in the analysis.
We excluded no papers on the basis of language.

Data synthesis

We pooled studies only when they included sufficient data, and were judged to be clinically homogeneous, using RevMan 5.1 software (RevMan 2011). When studies were statistically heterogeneous (I^2 > 50%) we used a random-effects model, otherwise we used a fixed-effect model. The outcomes 'improvement of symptoms' and 'absence of symptoms' yielded such statistically different results that these could not be combined. Therefore, we decided to consider these as different outcomes and classified asthma symptoms as either absence of symptoms or as improvement of symptoms. For the outcome improvement of symptoms we counted only those that improved and not those that had no symptoms any more.

Quality of evidence

We assessed the quality of evidence for each outcome by using the GRADE approach (GRADE working group). 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 which 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 (Appendix 2).

Subgroup analysis and investigation of heterogeneity

We intended to analyse subgroups of studies that included workers with different levels of exposure to see if this changed the effect of the intervention. In the included studies there was information about the levels of exposure or information about measurements in only two studies; consequently we could not meaningfully analyse data for subgroups with different exposure levels (Dressel 2007; Soyseth 1995).
We investigated whether heterogeneity could be caused by variations in the participant characteristics, interventions or outcome measurements used.

Sensitivity analysis

A sensitivity analysis had initially been planned to ascertain whether studies with a more stringent diagnosis of occupational asthma had different results to those studies with a lower diagnostic threshold. However, we did not perform this analysis because the majority of the studies used specific inhalation change (SIC) for diagnosis, the number of studies available using a different diagnostic threshold was limited, and the agents and interventions used were too heterogeneous to allow any meaningful analysis.

RESULTS

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies.

Results of the search

The total search including the update in February 2011 yielded 12,709 references. From a combined search of CENTRAL, MEDLINE, EMBASE and Nioshtic-2 we identified 9141 references, from CISDOC and HSELINE up to January 2009 we identified 1186, and we identified 276 from the Specialised Register of the

Cochrane Airways Group up to April 2010. An additional search of the Specialised Register of the Cochrane Airways Group in April 2010 identified one additional reference. Review of the references cited by speakers at the fourth Jack Pepys Workshop of experts on occupational asthma in May 2010 identified another two articles (Appendix 1; Appendix 3; Appendix 4; Appendix 5).

The screening of titles and subsequently abstracts of all references identified resulted in 161 articles for full-text evaluation. Full-text evaluation identified that, of these, 21 articles ultimately fulfilled our inclusion criteria.

Four of the 21 studies described two different interventions and a control group, so three comparisons were made for these studies (intervention 1 versus control; intervention 2 versus control; intervention 1 versus intervention 2). This resulted in a total of 29 comparisons. All included articles described occupational asthma due to exposure to sensitisers, except for one study of workers with pot room asthma (Soyseth 1995).

Included studies

See also the Characteristics of included studies and Characteristics of excluded studies.

Design

We did not identify any randomised studies nor interrupted time series. All comparisons were therefore based on a controlled before and after design.

In some of the controlled before and after (CBA) studies, it was apparent that the intervention and control group at baseline did not have the same severity of occupational asthma. It was not clear in 19 studies how patients were allocated to the intervention group or the control group. Only two studies were intentionally designed as an intervention study (Dressel 2007; Soyseth 1995). All the other studies were prospective or retrospective follow-up studies. The difference in severity of occupational asthma between intervention and control group might be due to the fact that the studies were not intentionally designed as an intervention study but were more reflections on experience.

Interventions

The interventions identified in the included studies were as follows.

Primary outcomes

Removal from exposure

'Removal from exposure' comprised interventions where the workers were completely removed from further exposure. This comprised relocation to another job and work area within the same companyor to another company where there was no exposure to the causal agent, or cessation of paid work. No studies were identified where the suspected causal agent was substituted with a different non-asthma causing alternative.

Reduction of exposure

'Reduction of exposure' comprised situations where personal protective equipment was introduced or enhanced, a worker was relocated to another job and work area with less exposure to the causal agent within the same companyor to another company, or an educational or training programme intended to reduce exposure was implemented. Change to the availability of personal protective equipment was identified as a method of reducing exposure in three of the included studies (Bernstein 2003 reduction; Rosenberg 1987 reduction; Vandenplas 2002). Reduction of exposure achieved by transferring workers to a different area (but the same or a similar job) within the same or another company or by assigning the worker to different tasks in the same general work area was the intervention in 10 of the included articles.

'An educational or training programme to reduce exposure' was identified as the intervention in one study (Dressel 2007).

Continued exposure

'Continued exposure' comprised those groups where no intervention in the workplace was made.

All interventions in the included studies were classified into one of these three categories: removal from exposure, reduction of exposure and continued exposure. Three direct comparisons could then be made:

- removal from exposure versus continued exposure;
- reduction of exposure versus continued exposure; and
- removal from exposure versus reduction of exposure.

One study (Moscato 1999) reported on an intervention group who ceased exposure and a control group who continued working with the same exposure. From the details published it appeared that the intervention group consisted of five workers who continued to be exposed, albeit intermittently or at lower levels of exposure, and seven who continued working with the same exposure. These 12 workers were included in the analysis as a single group with ongoing exposure, because the majority had ongoing exposure (Table 1).

1. Asthma symptoms

We compared asthma symptoms before and after the intervention in two separate ways: 1) for the number of subjects reporting an

absence of symptoms; and 2) for the number of subjects reporting improvement of symptoms.

Authors obtained information about asthma symptoms using a number of different methods. Nine studies used interviews (Chan-Yeung 1982; Chan-Yeung 1987 reduction; Mapp 1988; Marabini 1993; Moscato 1993 reduction; Moscato 1999; Munoz 2008; Padoan 2003; Paggiaro 1984). Others used questionnaires. Only minimal information about the content of interviews was given in those studies in which they were used. A number of different questionnaires were used. Results were reported in a number of different ways. Some authors reported numbers of symptomatic and asymptomatic individuals (Chan-Yeung 1982; Chan-Yeung 1987 reduction; Innocenti 1981; Lin 1996; Mapp 1988; Marabini 1994; Padoan 2003; Paggiaro 1984; 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 for each report an indication of presence, severity or both (Marabini 1993; Moscato 1999; Munoz 2008; 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.

Secondary outcome

Seven articles had information about employment, income or both at follow up. No papers were identified reporting disability or sickness absence as an outcome. Four articles had information about employment for the intervention group and five articles had information about income for the intervention group. Three articles had additional comments about the employment situation in their own countries (Table 3).

Agents

The agents reported as the cause of occupational asthma in the included studies comprised isocyanates (seven studies), western red cedar (four studies), natural rubber latex (three studies), several high molecular weight (HMW) and low molecular weight (LMW) agents combined (two studies), and cow dander and storage mite, persulphate salts, colophony, cobalt and pot room gases in one study each. Thus the causal agent was of HMW in four articles, LMW in 14 studies, both HMW and LMW in two studies and pot room gases in one study (Table 4; Table 5).

Follow-up time

Mean follow-up time of the studies was 3.8 years and ranged from five weeks to 11.5 years.

Within the individual studies the follow-up time varied considerably, for example 12 to 45 months (Burge 1982) or 26 to 83 months (Vandenplas 2002). Often the variability was described as a SD or standard error of the mean (SEM) (Table 6).

2. Lung function

2a. FEV1 % predicted

FEV1 % predicted was measured and presented as the percentage of a reference value in the following studies: 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; Paggiaro 1984; Rosenberg 1987 reduction; Rosenberg 1987 removal; Valentino 2002 and Vandenplas 2002.

2b. Non-specific bronchial hyperreactivity (NSBH)

NSBH was measured as PC20, PC15, PD20 or PC15. We considered the information obtained with these various methods as equally valid (Table 2).

Duration of exposure prior to diagnosis

Duration of exposure prior to diagnosis was reported in 10 studies. The mean was 7.2 years (range 2.9 to 15.6 years) (Table 6).

Duration of symptoms prior to diagnosis

Duration of symptoms prior to diagnosis was reported in 11 studies. The mean was 5.5 years (range 1.4 to 21.0 years) (Table 6).

Sample size

The number of participants in the included studies varied from nine participants (Pisati 1994) to 201 participants (Lin 1996). The number of participants in the intervention groups varied from seven (Moscato 1993 reduction; Munoz 2008; Rosenberg 1987 reduction) to 136 (Chan-Yeung 1987 reduction) and the number of participants in the control groups varied from one (Bernstein 2003 reduction; Pisati 1994) to 92 (Lin 1996) (Table 6).

Setting

Most studies were carried out at a university clinic or a hospital department specialising in occupational medicine or pulmonary medicine. Only one study was undertaken within a business or workplace setting (Soyseth 1995).

A source of funding was stated in only two articles. One study (Dressel 2007) was supported by two German statutory accident insurance institutions for agricultural workers. Another study (Vandenplas 2002) was supported by the Services Federaux des Affaires Scientifiques et Culturelles. We felt it unlikely that source of funding introduced a significant conflict of interest in any of these instances.

Studies were carried out in Europe (Italy 10, Belgium one, France one, Germany one, Great Britain one, Norway one, Spain one), Canada (British Columbia four) and the USA (Ohio one)

The included articles were published between 1984 and 2008, with 14 published prior to 2000.

All the included articles were written in English (17) or Italian (four).

Participants

All participants were workers in accordance with inclusion criteria. All the participants had acquired occupational asthma and were exposed to an agent with potential to cause asthma. Two articles (Bernstein 2003 removal; Vandenplas 2002) reported results for workers exposed to latex. In these articles some workers with pre-existing asthma were included, although no separation into occupational asthma and work-aggravated asthma was attempted in the results. One additional study included a single worker with probable work-aggravated asthma (Rosenberg 1987 removal).

The diagnosis of occupational asthma was based on specific inhalation challenge (SIC) with the suspected causative agent in 17 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 removal; Visentin 2003). In two studies the methods of diagnosis were not reported (Dressel 2007; Soyseth 1995).

The sex ratio differed between the studies from 100% male to 100% female. It appeared that this was probably due to differences in the workforces from which participants were identified. For example, in the studies of western red cedar workers (Chan-Yeung 1982; Chan-Yeung 1987 removal; Chan-Yeung 1987 reduction; Lin 1996; Marabini 1993), far more males were included, whereas females predominated in the studies of healthcare workers, hairdressers or cosmetic workers.

The mean age of the participants at the time of the baseline assessment was 39 years (range 32 to 50.2 years).

Type of asthma reaction

The type of asthma reaction was reported in 11 studies and was often only reported at baseline. At baseline an immediate reaction was found in 0% to 63% of the participants, a late reaction in 4% to 88% of the participants and a dual reaction in 13% to 50% of the participants (Table 6).

Atopy

Atopic status of participants was reported in 17 studies. Between 0% and 89% of participants were atopic in the included studies. In the studies with exposure to HMW agents between 56% and 89% of the participants were atopic, while in the studies with exposure to LMW agents between 0% and 49% of the participants were atopic (Table 6).

Smoking

Smoking status was reported in 17 articles. At baseline between 5% and 58% of the participants were smokers (Table 6).

Excluded studies

We excluded six studies. In three studies the control groups did not have occupational asthma. Two studies did not include a control group. One article (Dressel 2009) appeared to report results for the same subjects as had been described in a previous article two years before. The objective of this study was to evaluate the use of the fraction of exhaled nitric oxide in exhaled breath (FeNO). We chose to exclude this article because individuals who smoked or suffered a respiratory tract infection were excluded from this paper because of the potential for these to affect FeNO. A similar exclusion was not made in any of the other included studies and

consequently we felt it was difficult to compare this subject group with those from other included studies.

Risk of bias in included studies

We evaluated the internal validity of the included studies using the Downs and Black checklist (Downs 1998) and this generally showed low methodological quality. In none of the studies were the participants or those measuring the outcomes blinded. Only some studies adjusted for length of follow up. Compliance with the intervention was often unknown and there was frequently no

All studies were observational studies therefore we made an initial assessment that the evidence was of moderate quality. In addition, all studies had a high risk of bias which we considered an additional serious limitation. For this reason we downgraded the quality of evidence for all comparisons to 'very low'. Consequently, there was no need to use the other qualifiers to grade the quality of evidence, such as indirectness of evidence or publication bias (Appendix 2).

Effects of interventions

See: 'Summary of findings' table (Table 9).

Comparison 1: Removal from exposure versus continued exposure

Asthma symptoms at follow up

Of the 15 studies that reported asthma symptoms, 12 reported results for low molecular weight (LMW) agents, one for high molecular weight (HMW) agents and two for a combination of HMW and LMW agents.

Six studies reported the presence or absence of asthma symptoms. Nine studies reported numbers, percentages or symptom scores, from which it was possible to calculate the numbers of individuals with improvement in symptoms.

Absence of asthma symptoms

Asthma symptoms were significantly more often absent after complete removal with a risk ratio (RR) of 21.42 (95% confidence interval (CI) 7.20 to 63.77) based on six studies that were included in this comparison, with a greater risk ratio indicating a greater likelihood of absence of symptoms at follow up in the removal from exposure group.

Five of the six studies reported LMW agent studies. For these studies the pooled risk ratio for absence of symptoms was also significantly greater than one, with a RR of 24.02 (95% CI 7.21 to 79.94) (Analysis 1.1).

The very large risk ratios in these comparisons were mainly due to the three older studies carried out in the 1980s.

information on why or how participants were allocated to either the intervention group or control group. Most studies described the population the participants were recruited from. Most studies described the time period during which participants were recruited. None of the studies randomised participants to the different interventions. Only a few studies had adequate adjustment for confounders. Only a few studies had tried to take into account participants who were lost to follow up. The total score for included studies ranged from zero to seven out of 12 with a mean of 3.1 and SD 2.0 (Table 7; Table 8).

Improvement of asthma symptoms

The pooled risk ratio for improvement of asthma symptoms was 2.27 (95% CI 1.23 to 4.19) for all nine studies that were included in this comparison. There was considerable heterogeneity with I^2 = 65%.

For the LMW agent studies the pooled risk ratio for the seven studies reporting improvement was significantly greater than one with a RR of 2.58 (95% CI 1.15 to 5.75) (Analysis 1.2).

Change in FEV1 % (follow-up minus baseline values)

The pooled mean difference of change in FEV1 % between baseline and follow up (with a greater mean difference indicating a greater improvement in the removal from exposure group) was significantly different from zero with a mean difference (MD) of 5.52 percentage points (95% CI 2.99 to 8.06) for all eight studies that were included in this comparison. There was considerable heterogeneity in this comparison with I^2 = 76%.

Of the eight studies, seven reported results for LMW agents and one for a combination of HMW and LMW agents. For the LMW agent studies the pooled mean difference in change in FEV1 % between baseline and follow up was 6.23 percentage points (95% CI 3.83 to 8.62) for all seven studies (Analysis 1.3; Analysis 1.5; Analysis 1.6).

Change in non-specific bronchial hyper-reactivity (NSBH) (follow-up minus baseline values)

Change of NSBH between baseline and follow up differed significantly between complete removal from exposure and continued exposure with a pooled standardised mean difference of 0.67 (95% CI 0.13 to 1.21) for all five studies that were included in this comparison. (Note: a greater standardized mean difference indicated a greater improvement in favour of removal from exposure). Heterogeneity, as measured with the I^2 statistic, was 74%.
Of the five studies, four reported results for LMW agents and one for a combination of HMW and LMW agents. For the LMW agent studies the change in NSBH did not significantly differ between the intervention and the control group. The pooled standardised mean difference of change in NSBH between baseline and follow up was 0.53 (95% CI -0.03 to 1.08) for all four studies (Analysis 1.4; Analysis 1.7; Table 2).

Income/employment at follow up

Five of the 15 articles included in this comparison reported some information about income, employment or both. One article reported that 53 of 80 workers in the intervention group were unemployed at the time of follow up. Three articles reported a reduction in income for members of the intervention group varying between 25% and 50%. The other studies reported with statements in the text (Table 3).

Comparison 2: Reduction of exposure versus continued exposure

Asthma symptoms at follow up

Although six studies reported this comparison, one did not include sufficient data to be included in the pooled analyses (Chan-Yeung 1987 reduction) and one reported improvement of symptoms in the intervention group but did not mention the numbers of participants improved (Soyseth 1995).
Of the four studies, one reported results for LMW agents, two for HMW agents and one for a combination of HMW and LMW agents.
All studies reported the presence or absence of symptoms at follow up rather than improvement of symptoms.
Reduction of exposure increased the number of participants with absence of asthma symptoms significantly with a pooled RR of 5.35 (95% CI 1.40 to 20.48) for all four studies that were included in this comparison (Analysis 2.1).

Change in FEV1 % (follow-up minus baseline values)

Although three studies could potentially have been combined in this comparison, one did not include sufficient data to be included in the data analyses. The pooled mean difference of change in FEV1 % between baseline and follow up was 1.18 percentage points (95% CI -2.96 to 5.32) for the two studies that were included in this comparison.
Of the two studies, one reported results for LMW agents and one for HMW agents (Analysis 2.2; Analysis 2.3; Analysis 2.4).

Income/employment at follow up

Three of the five articles included in this comparison reported some information about income, employment or both, although no specific details about income or employment were given for the intervention group and control group. For details see Table 3.

Comparison 3: Removal from exposure versus reduction of exposure

Asthma symptoms at follow up

Of the eight studies that reported asthma symptoms, four reported results for LMW agents, three for HMW agents and one for a combination of HMW and LMW agents.
Three studies reported about absence of asthma symptoms. Five studies reported numbers, percentages or scores; from these we calculated the numbers of individuals with improvement.

Absence of asthma symptoms

Removal from exposure significantly increased the likelihood of a participant reporting the absence of asthma symptoms at follow up compared to reduction of exposure with a RR of 39.16 (95% CI 7.21 to 212.83) for the three studies that were included in this comparison (Analysis 3.1).

Improvement of asthma symptoms

Removal did not result in a significant increase of the number of participants with improvement of asthma symptoms compared to reduction of exposure with a RR of 1.27 (95% CI 0.84 to 1.92) for all five studies that were included in this comparison (Analysis 3.2). In this analysis the I^2 for heterogeneity was 83%.

Change in FEV1 % (follow-up minus baseline values)

There were five studies that included relevant data for this comparison, but one that reported results for a LMW agent did not include sufficient data to be included in analyses. The pooled mean difference of change in FEV1 % between baseline and follow up (with a greater mean difference indicating a greater improvement in the removal from exposure group) was 1.16 percentage points (95% CI -7.51 to 9.84) for all four studies that were included in this comparison.
Of the five studies, four reported results for LMW agents and one for HMW agents. For the three LMW agent studies that could

be included in the pooled analysis the pooled mean difference of change in FEV1 % between baseline and follow up was 3.14 (95% CI -7.25 to 13.53).

The I^2 for heterogeneity was 88% due to the influence of one study with opposite results (Analysis 3.3; Analysis 3.5; Analysis 3.6; Analysis 3.7; Table 2).

Income/employment at follow up

Five of the eight studies included in this comparison reported information about income, employment or both. Three studies reported employment status of the intervention group at follow up. In one study none of the four individuals in the removal from exposure group were employed at follow up; in another study seven of the 20 in the removal from exposure group were employed at follow up; and in the third study nine out of 16 subjects in the removal from exposure group were employed at follow up. A reduction in income of 20% to 25% was reported. In the control group, which in each case comprised a reduction of exposure group, no unemployment nor loss in income was reported. For the two studies that reported sufficient data, this resulted in an increased risk of unemployment for those that were removed from exposure with a RR of 14.3 (95% CI 2.06 to 99.16). For details see Analysis 3.4 and Table 3.

Explanation of heterogeneity

There was considerable heterogeneity in Analysis 1.2 of the effect of removal versus continued exposure on improvement of asthma symptoms (I^2 = 65%). This was almost fully explained by the inclusion of Munoz 2008 in which there was no additional effect of the intervention on asthma symptoms. Improvement of symptoms occurred in almost 100% of the individuals in both the removal from exposure group and the continued exposure group. It is unclear why the group with continued exposure behaved so differently to similar groups in other studies. An important feature of this study was that the duration of exposure since diagnosis was on average four years in the continued exposure group compared to three months for the removal group.

There was considerable heterogeneity in Analysis 1.3 of the effect of removal versus continued exposure on FEV1%. This was fully explained by the difference between HMW and LMW studies, which were analysed in separate subgroups.

In Analysis 1.4 of the effect of removal versus continued exposure on NSBH, much of the heterogeneity could be explained by the difference in effect between the HMW and LMW studies but for unclear reasons the study by Chan-Yeung 1982 also contributed substantially to the heterogeneity.

There was considerable heterogeneity in the comparison of removal from exposure versus reduction of exposure for the outcome improvement of asthma symptoms, which was explained by the greater effect in LMW studies than in HMW studies (Analysis 3.2).

For the Analysis 3.3 of the effect of removal from exposure versus reduction of exposure on the outcome change in FEV1 %, the heterogeneity was due to the study Valentino 2002 that had an effect in favour of removal while the other studies favoured reduction. We could not explain the reason.

Publication bias

In the funnel plot for the comparison of removal from exposure versus continued exposure for the outcome absence of asthma symptoms (Analysis 1.1; Figure 1), we did not see any indication of publication bias, but for improvement of symptoms there may have been some publication bias as small studies with negative non-significant findings were not apparent in the funnel plot (Figure 2). For the outcome FEV1 % it was unclear if studies were missing (Figure 3).

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

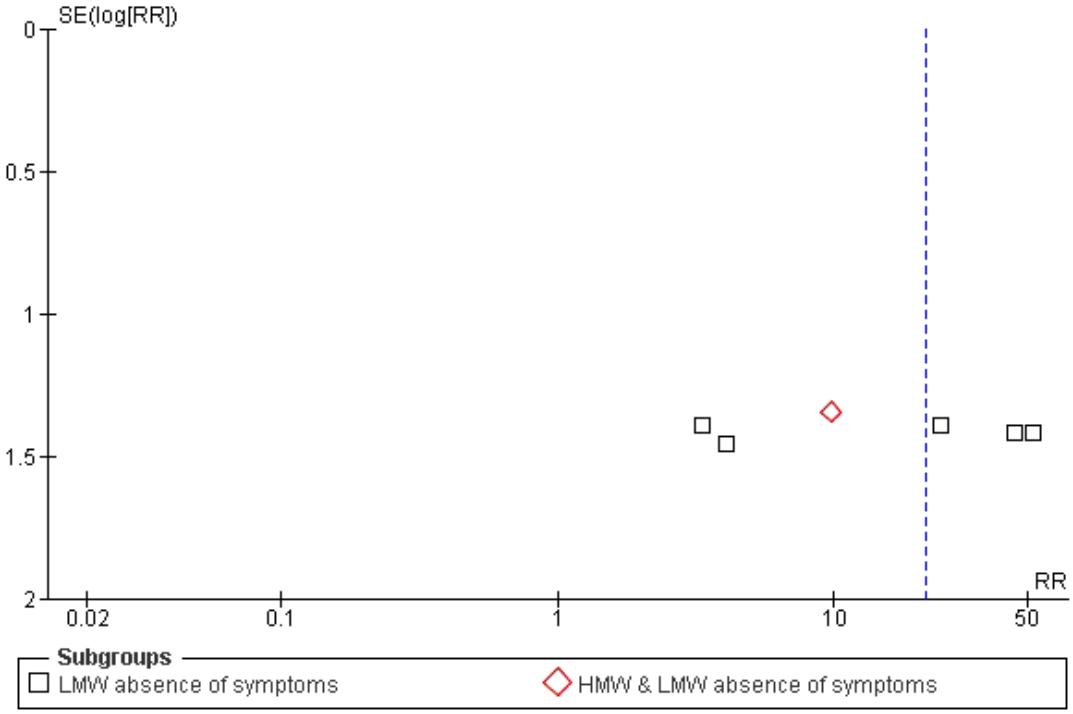


Figure 2. Funnel plot of comparison: 1 Removal from exposure versus continued exposure, outcome: 1.2 Improvement of asthma symptoms.

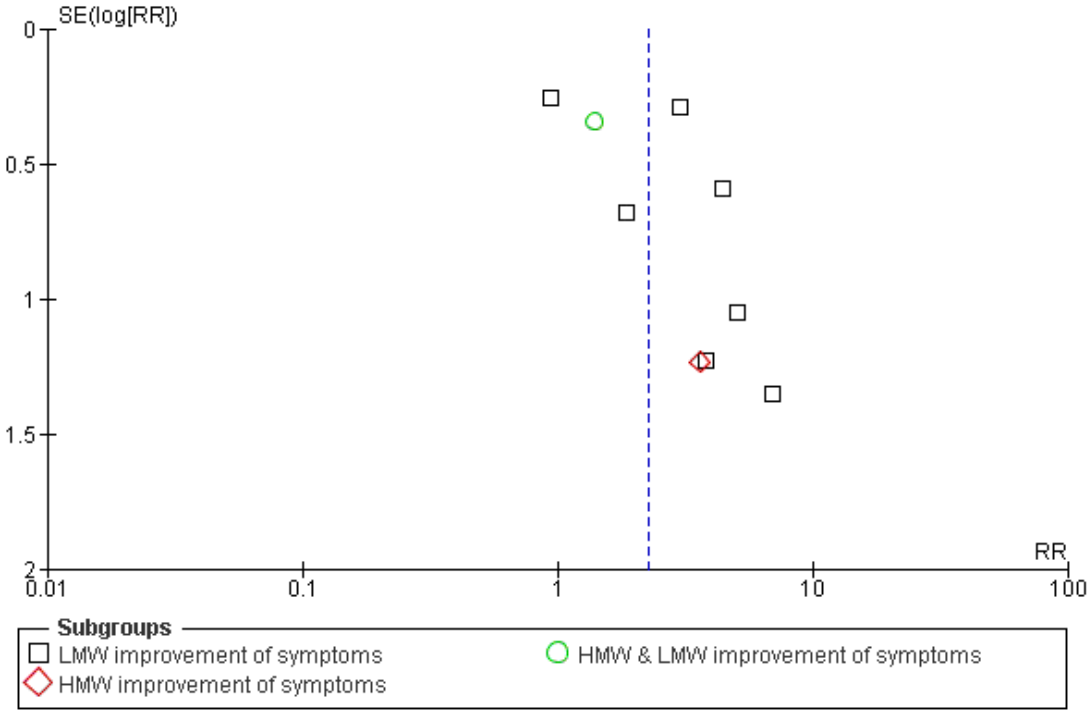
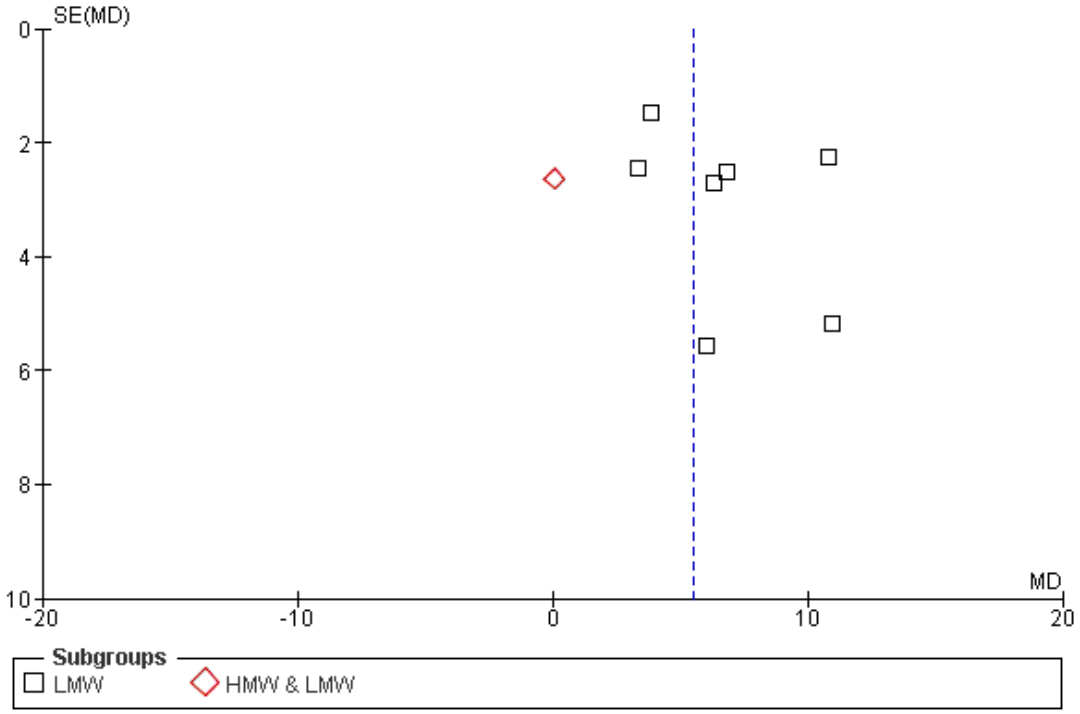


Figure 3. Funnel plot of comparison: 1 Removal from exposure versus continued exposure, outcome: 1.3 Change in FEV1 % follow-up minus baseline values



DISCUSSION

Summary of main results

Three comparisons of interventions were reported: removal from exposure versus continued exposure (15 studies); reduction of exposure versus continued exposure (six studies) and removal from exposure versus reduction of exposure (eight studies).

Asthma symptoms, measured either as absence of symptoms or improvement of symptoms, improved significantly more after removal from exposure and after reduction of exposure when compared to continued exposure. Forced expiratory volume in the first second (FEV1 %) improved significantly more following removal from exposure than with continued exposure, but not after reduction of exposure, although it is notable that there were fewer studies for the second comparison. Non-specific bronchial hyperreactivity (NSBH) improved with removal from exposure when compared with continuing exposure, but this outcome was not available for the other comparisons.

Total removal from exposure resulted in absence of asthma symptoms significantly more often than reduction of exposure, but there was no significant difference for improvement of symptoms or change in FEV1 % between these two interventions. The outcome NSBH was not available for this comparison.

Total removal from exposure led significantly more often to job loss or an appreciable loss of income than reduction of exposure.

The quality of the evidence for all outcomes was assessed as very low.

Overall completeness and applicability of evidence

Even though there are many reviews of management of occupational asthma, this review is, to our knowledge, the first to focus especially on different workplace interventions in comparison to a control group. Previous reviews have included case series which provided some evidence that removal from exposure resulted in symptom reduction. However, from these studies it was not possible to make a comparison of the relative magnitude of each intervention, such as the effect of removal from exposure versus reduction of exposure. While occupational asthma has traditionally

provided fertile ground for research and publication, as was shown by the more than 10,000 hits in our initial literature search, considerably less work has been published on the role of workplace interventions in managing occupational asthma. We included just 21 articles published over a timeframe of 27 years, from 1981 to 2008, with 14 published prior to 2000.

All studies were observational in nature. In only two studies (Dressel 2007; Soyseth 1995) the intervention was planned and allocated in a standardised way. The authors of these two studies described the criteria used for allocation to one group or the other. In all other studies it was unclear why subjects were allocated to either the intervention group or the control group and who initiated the intervention.

Reduction of exposure was generally achieved in a number of different ways. In the majority of studies the subjects were transferred to an area of the workplace with less, although still some, exposure to the agent causing occupational asthma. No measurements of exposure levels were reported in the articles. In some studies the reduction was achieved by a change in personal protective equipment (introduction of new equipment, or an improvement in existing equipment) (Bernstein 2003 reduction; Rosenberg 1987 reduction; Vandenplas 2002). In one study the reduction of exposure was achieved by an education and training programme (Dressel 2007). These studies were small, with largely non-significant outcomes, and yielded a significant outcome only for the absence of asthma symptoms in a pooled effect estimate.

It should be noted that most data were available for low molecular weight (LMW) agents and that studies for high molecular weight (HMW) agents were considerably more sparse. The causal agent was LMW in 14 studies, HMW in four studies, both HMW and LMW in two studies and pot room gases in one study. It is, therefore, difficult to draw conclusions for all groups of agents, and it is sensible to interpret these results with considerable caution when considering HMW agents. All articles, except possibly the one on pot room gases, reported on sensitiser-induced occupational asthma. No studies with irritant-induced occupational asthma (unless pot room gases are considered as irritants) were included and there were only four studies of the most commonly reported HMW causes of asthma, such as flour dust, animal proteins (Dressel 2007) and latex (Bernstein 2003 removal; Vandenplas 2002; Visentin 2003).

Not all studies reported all important outcomes and some of the studies presented results in a way that could not be used for meta-analysis. For asthma symptoms it is also important to note that in some studies symptoms were reported only as present or absent. An improvement in symptoms in these studies would not have been identified if some symptoms remained, and this may have led to some improvement not being reported.

It is notable that 10 of the 21 included studies came from Italy. One explanation for this might be, as suggested by Moscato 1999, that for example in Italy financial compensation for patients with occupational asthma was not guaranteed and the socioeconomic condition made it difficult to find another job. Probably as a result, many participants with occupational asthma continued to be exposed to the causative agent in their jobs, and could be followed up by their physicians.

All four studies about western red cedar workers came from the same research group at the University of British Columbia, Canada (Table 4).

Follow-up time, duration of exposure prior to diagnosis and duration of symptoms prior to diagnosis showed a wide variation if reported at all. This, together with the often small number of participants in a study, made it unrealistic to perform subgroup analyses.

Quality of the evidence

Overall, the quality of the available studies according to the GRADE approach was very low because nearly all the studies were observational studies and the risk of bias was considered high in all studies. No randomised controlled trials were found. There was no blinding and the overall evaluation of the included studies using the Downs and Black checklist was low, defined as a score less than 50%. The intervention and control groups in the same study were often hard to compare, because the FEV1 % predicted and the NSBH values at baseline often differed between groups. We tried to adjust for these baseline differences by using change values. It was not always clear when individual participants started the intervention; there was a wide variation in exposure times and in follow-up times. The methods to diagnose occupational asthma were not always specified and in two studies patients with work-aggravated asthma were also included. Selection of participants was not described in most of the articles and information on losses during follow up was also sparse.

Potential biases in the review process

We prevented language bias by including articles in all languages and translating foreign language articles using competent translators (usually natives of the relevant country). We avoided duplicate publication bias by using study data only once if they had been reported in more than one article. We tried to make our search as sensitive as possible which resulted in a fairly low specificity, with initially more than 10,000 hits. It is difficult to say categorically whether we might have missed some articles due to using insufficiently sensitive search terms, or missed publications in journals not included in the databases used. For example, due to time limitations we could not go through conference proceedings. However, we feel that it is highly unlikely that we would have missed important evidence from high-quality studies that would have altered the current results. It was not always possible to obtain missing data because authors often no longer had access to the original data. Some studies were supported by a company or insurance institution which could potentially give rise to a conflict of interest should they have a preference for a specific result, but we judged

such conflicts of interests likely to be only minor if present at all.

Agreements and disagreements with other studies or reviews

Nicholson 2005 et al reviewed 223 studies to produce evidence-based guidelines for the prevention, identification and management of occupational asthma. Although the objectives of that review differed from this review, and therefore a greater number of studies were included, these authors concluded similarly to this review, that complete avoidance of further exposure offered the best chance of recovery. Nicholson 2010 is an update of Nicholson 2005 incorporating an additional 90 studies.

Rachiotis 2007 performed a systematic review of case series of the outcome of occupational asthma after cessation of exposure. However, studies where patients had been relocated to low-exposure positions were excluded. The outcome measures comprised complete symptomatic recovery from asthma and improvement in NSBH. No assessment of study quality was applied. Only one-third of the patients with occupational asthma recovered fully from their disease despite avoidance of exposure to the initiating agent. The pooled prevalence of persistent NSBH at follow up was 73%. As in this review, these authors identified more studies of individuals with occupational asthma due to LMW (25) agents than HMW (14).

The review by Tarlo 2008 constituted a report of an American College of Chest Physicians (ACCP) expert panel and was a consensus document (to an extent based on a systematic review by Beach 2005) on the diagnosis and management of work-related asthma. These authors reported that removal of workers with sensitiser-induced occupational asthma from further exposure to the causative agent resulted in a better outcome.

All reviews to date appear in agreement that, once diagnosed, removal from exposure appears important to the outcome of occupational asthma, and that consequently periodic medical surveillance for workers in environments with possible exposure to sensitisers offers a number of potential advantages. Periodic surveillance leads to early detection and removal from exposure and this should increase the chances of complete reversal of symptoms. However, we did not find any studies that have evaluated this procedure in a controlled design.

AUTHORS' CONCLUSIONS

Implications for practice

Removal of individuals with occupational asthma from exposure is associated with a beneficial effect on asthma symptoms and lung function including both forced expiratory volume in the first second (FEV1) and non-specific bronchial hyper-reactivity (NSBH) when compared to continued exposure. This is especially apparent for occupational asthma due to low molecular weight agents.

Reduction of exposure is also associated with beneficial effects on symptoms but there was no significant effect on lung function when compared to continued exposure.

Removal from exposure improved asthma symptoms more than reduction of exposure but there was no significant difference in terms of effect on improvement of asthma symptoms, or on lung function.

However, one unintended consequence of removal from exposure is a much higher risk of loss of work and income than reduction of exposure.

Implications for research

The low quality of the evidence identified in the course of this review highlights the need for better quality research data in this area. Future studies should ideally be based on clear, possibly random, allocation of participants to either an intervention or a control group as these are likely to avoid bias in allocation of individuals to intervention groups. Future studies should include greater numbers of participants and collect better information on exposure, duration of symptoms before diagnosis, duration of symptoms before the intervention and report more fully on asthma symptoms, FEV1 and NSBH before, during and after the intervention. Studies are needed to fully evaluate the effect of reduction of exposure, through either personal protective equipment or education of workers after exposure is minimised, as far as reasonably achievable. Given the uncertainty of the effect of reduction of exposure and the beneficial effects of continued employment on health, these studies should randomise participants to reduction of exposure or removal from exposure. The effect of interventions can probably be increased if workers with occupational asthma are diagnosed at an earlier stage. Health surveillance or regular periodic health examinations would enable such an early diagnosis. The effect of interventions after health surveillance should be studied with a controlled and preferably randomised controlled design.

Further studies are also needed to identify whether exposure reduction, through changes in the working process and additionally the use of personal protective equipment (PPE), is effective in participants with a diagnosis of occupational asthma. Preferably these should be randomised studies and they would ideally compare PPE with the removal from exposure, the current best available workplace intervention.

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* *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.
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

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	High risk	

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-

Bernstein 2003 removal (*Continued*)

	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

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	High risk	

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

Burge 1982 (*Continued*)

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

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	High risk	

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 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 1982 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	High risk	

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

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	High risk	

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

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	High risk	

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

Dressel 2007 (*Continued*)

Interventions	Intervention: education programme: lecture about asthma, technical and organisational means of allergen avoidance and demonstration of use of protective equipment; 81 farmers Controls: no education programme; 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 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

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	High risk	

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
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

Innocenti 1981 (*Continued*)

	Duration of symptoms before diagnosis: not mentioned Place (country, city): Italy, Siena Article written in Italian language Sources of funding not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	High risk	

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 Sources of funding not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	High risk	

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

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	High risk	

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 3. FVC % predicted

Marabini 1993 (*Continued*)

	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

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	High risk	

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

Marabini 1994 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	High risk	

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 persulphate, 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

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	High risk	

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 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, phthallic anhydride, ammonium persulphate, 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

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	High risk	

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

Moscato 1999 (*Continued*)

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 persulphate, 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 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

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	High risk	

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

Munoz 2008 (*Continued*)

	3. Methacholine PC20 4. Skin test 5. Total IgE	
Notes	Exposed to: persulphate salts 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	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	High risk	

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 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	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**

Padoan 2003 (*Continued*)

Allocation concealment (selection bias)	High risk	

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

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	High risk	

Pisati 1994

Methods	Controlled before and after study; retrospective
Participants	9 participants; sex unknown Age unknown Occupations: cobalt workers Follow-up study of patients of their own hospital clinic Diagnosis of OA was based on specific inhalation challenge

Pisati 1994 (*Continued*)

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

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	High risk	

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 Intervention not planned Follow up: mean 24 months (6 to 54 months) Duration of exposure before onset of symptoms in months: mean 35.6

Rosenberg 1987 reduction (*Continued*)

	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

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	High risk	

Soyseth 1995

Methods	Controlled before and after study; prospective
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

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

Valentino 2002 (*Continued*)

	Place (country, city): Italy, Ancona Article written in Italian language Sources of funding not stated	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	High risk	

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	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	High risk	

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
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

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	High risk	

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
PEFR:
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
De Zotti 2000	No comparisons
Dressel 2009	Same study as Dressel 2007. Follow up 1 year. Many subjects excluded due to smoking, acute respiratory tract infections etc. So they achieved better results than mentioned in their article in 2007
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
Patovirta 2004	Controls were not from the same group. Controls did not have occupational asthma
Pohl 2003	No comparisons
Saetta 1992	Controls did not have occupational asthma

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	6	462	Risk Ratio (M-H, Fixed, 95% CI)	21.42 [7.20, 63.77]
1.1 LMW absence of symptoms	5	440	Risk Ratio (M-H, Fixed, 95% CI)	24.02 [7.21, 79.94]
1.2 HMW & LMW absence of symptoms	1	22	Risk Ratio (M-H, Fixed, 95% CI)	9.74 [0.70, 135.17]
2 Improvement of asthma symptoms	9	500	Risk Ratio (M-H, Random, 95% CI)	2.27 [1.23, 4.19]
2.1 LMW improvement of symptoms	7	470	Risk Ratio (M-H, Random, 95% CI)	2.58 [1.15, 5.75]
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	1	25	Risk Ratio (M-H, Random, 95% CI)	1.38 [0.71, 2.71]
3 Change in FEV1 % predicted: follow-up minus baseline values	8	806	Mean Difference (IV, Random, 95% CI)	5.52 [2.99, 8.06]
3.1 LMW	7	781	Mean Difference (IV, Random, 95% CI)	6.23 [3.83, 8.62]
3.2 HMW & LMW	1	25	Mean Difference (IV, Random, 95% CI)	0.10 [-5.09, 5.29]
4 Change in NSBP: follow-up minus baseline values	5	314	Std. Mean Difference (IV, Random, 95% CI)	0.67 [0.13, 1.21]
4.1 LMW	4	289	Std. Mean Difference (IV, Random, 95% CI)	0.53 [-0.03, 1.08]
4.2 HMW & LMW	1	25	Std. Mean Difference (IV, Random, 95% CI)	1.44 [0.54, 2.33]
5 FEV1 % predicted: follow up	8		Mean Difference (IV, Random, 95% CI)	Totals not selected
5.1 LMW	7		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
5.2 HMW & LMW	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
6 FEV1 % predicted: baseline	8		Mean Difference (IV, Random, 95% CI)	Totals not selected
6.1 LMW	7		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
6.2 HMW & LMW	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
7 NSBH: follow up	8		Std. Mean Difference (Fixed, 95% CI)	Totals not selected
7.1 LMW	7		Std. Mean Difference (Fixed, 95% CI)	0.0 [0.0, 0.0]
7.2 HMW & LMW	1		Std. Mean Difference (Fixed, 95% CI)	0.0 [0.0, 0.0]

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	5	244	Risk Ratio (M-H, Fixed, 95% CI)	5.35 [1.40, 20.48]
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	2	126	Risk Ratio (M-H, Fixed, 95% CI)	5.60 [0.89, 35.36]
1.3 HMW & LMW absence of symptoms	1	11	Risk Ratio (M-H, Fixed, 95% CI)	5.63 [0.38, 83.67]
2 Change in FEV1 % predicted: follow-up minus baseline values	3	192	Mean Difference (IV, Fixed, 95% CI)	1.18 [-2.96, 5.32]
2.1 LMW	2	99	Mean Difference (IV, Fixed, 95% CI)	1.10 [-4.32, 6.52]
2.2 HMW	1	93	Mean Difference (IV, Fixed, 95% CI)	1.3 [-5.12, 7.72]
3 FEV1 % predicted: follow up	3		Mean Difference (IV, Random, 95% CI)	Totals not selected
3.1 LMW	2		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
3.2 HMW	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
4 FEV1 % predicted: baseline	3		Mean Difference (IV, Random, 95% CI)	Totals not selected
4.1 LMW	2		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
4.2 HMW	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
5 NSBH follow up	2		Std. Mean Difference (Fixed, 95% CI)	Totals not selected
5.1 LMW	2		Std. Mean Difference (Fixed, 95% CI)	0.0 [0.0, 0.0]

Comparison 3. Removal from exposure versus reduction of exposure

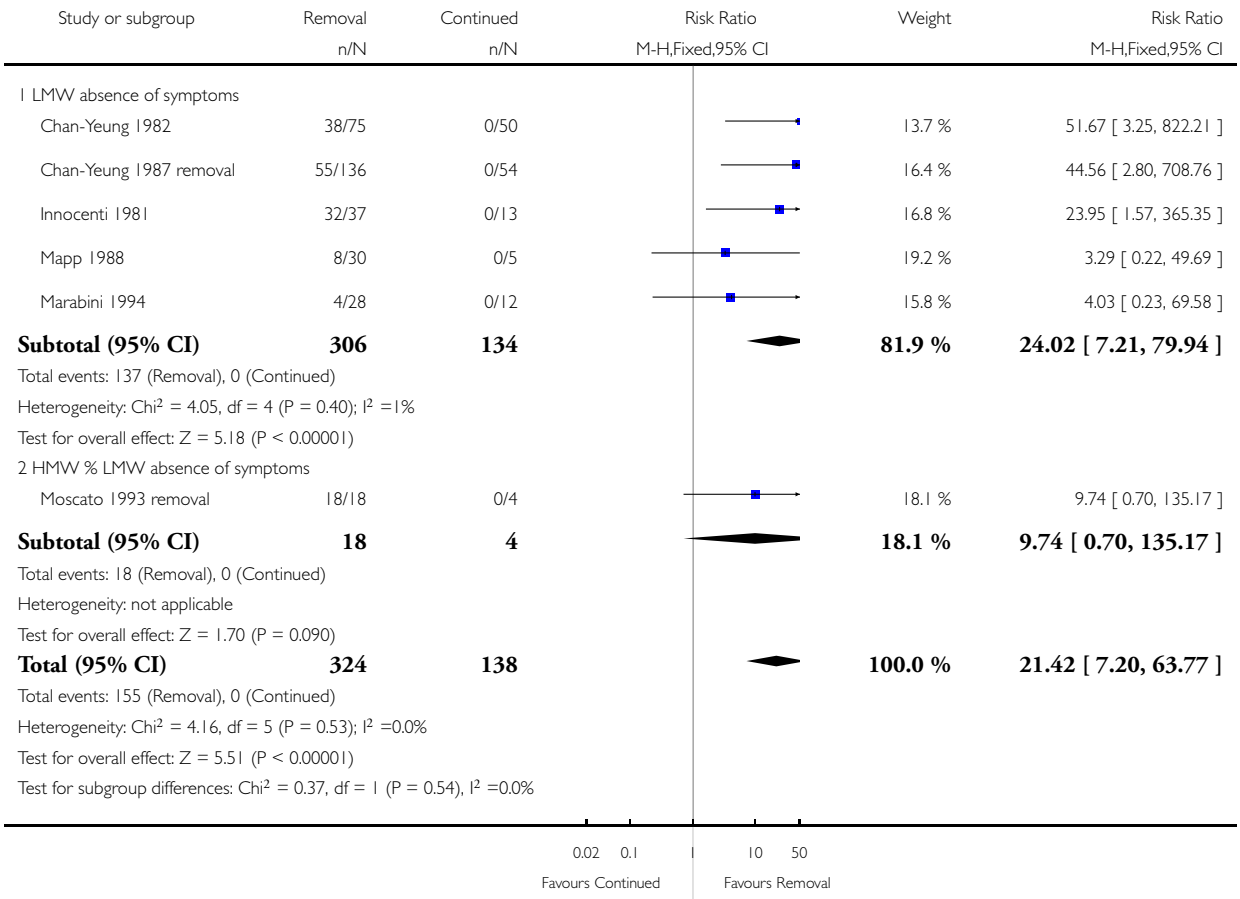
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Absence of asthma symptoms	3	257	Odds Ratio (M-H, Fixed, 95% CI)	39.16 [7.21, 212.83]
1.1 LMW absence of symptoms	2	228	Odds Ratio (M-H, Fixed, 95% CI)	48.53 [6.24, 377.68]
1.2 HMW absence of symptoms	1	29	Odds Ratio (M-H, Fixed, 95% CI)	17.86 [0.91, 350.85]
2 Improvement of asthma symptoms	5	140	Risk Ratio (M-H, Random, 95% CI)	1.27 [0.84, 1.92]
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)	1.73 [0.94, 3.20]
3 Change in FEV1 % predicted: follow-up minus baseline values	5	311	Mean Difference (IV, Random, 95% CI)	1.16 [-7.51, 9.84]
3.1 LMW	4	275	Mean Difference (IV, Random, 95% CI)	3.14 [-7.25, 13.53]
3.2 HMW	1	36	Mean Difference (IV, Random, 95% CI)	-4.0 [-9.80, 1.80]
4 Being unemployed	2	64	Risk Ratio (M-H, Fixed, 95% CI)	14.28 [2.06, 99.16]
5 FEV1 % predicted: follow up	5		Mean Difference (IV, Random, 95% CI)	Totals not selected
5.1 LMW	4		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
5.2 HMW	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
6 FEV1 % predicted: baseline	5		Mean Difference (IV, Random, 95% CI)	Totals not selected
6.1 LMW	4		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
6.2 HMW	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
7 NSBH follow up	3		Std. Mean Difference (Fixed, 95% CI)	Totals not selected
7.1 LMW	3		Std. Mean Difference (Fixed, 95% CI)	0.0 [0.0, 0.0]

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

Review: Workplace interventions for treatment of occupational asthma

Comparison: 1 Removal from exposure versus continued exposure

Outcome: 1 Absence of asthma symptoms



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

Review: Workplace interventions for treatment of occupational asthma

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 LMW improvement of symptoms					
Lin 1996	37/90	13/95		18.8 %	3.00 [1.71, 5.27]
Marabini 1993	22/80	3/48		12.5 %	4.40 [1.39, 13.92]
Munoz 2008	6/7	3/3		19.4 %	0.93 [0.56, 1.53]
Padoan 2003	21/74	2/13		10.9 %	1.84 [0.49, 6.94]
Paggiaro 1984	4/12	1/15		6.4 %	5.00 [0.64, 39.06]
Pisati 1994	8/8	0/1		5.0 %	3.78 [0.34, 41.88]
Rosenberg 1987 removal	14/20	0/4		4.3 %	6.90 [0.49, 97.25]
Subtotal (95% CI)	**291**	**179**		**77.4 %**	**2.58 [1.15, 5.75]**
Total events: 112 (Removal), 22 (Continued)					
Heterogeneity: Tau^2 = 0.68; Chi^2 = 21.77, df = 6 (P = 0.001); I^2 =72%					
Test for overall effect: Z = 2.31 (P = 0.021)					
2 HMW improvement of symptoms					
Bernstein 2003 removal	4/4	0/1		5.0 %	3.60 [0.32, 40.41]
Subtotal (95% CI)	**4**	**1**		**5.0 %**	**3.60 [0.32, 40.41]**
Total events: 4 (Removal), 0 (Continued)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.04 (P = 0.30)					
3 HMW % LMW improvement of symptoms					
Moscato 1999	9/13	6/12		17.6 %	1.38 [0.71, 2.71]
Subtotal (95% CI)	**13**	**12**		**17.6 %**	**1.38 [0.71, 2.71]**
Total events: 9 (Removal), 6 (Continued)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.95 (P = 0.34)					
Total (95% CI)	**308**	**192**		**100.0 %**	**2.27 [1.23, 4.19]**
Total events: 125 (Removal), 28 (Continued)					
Heterogeneity: Tau^2 = 0.44; Chi^2 = 22.66, df = 8 (P = 0.004); I^2 =65%					
Test for overall effect: Z = 2.61 (P = 0.0090)					
Test for subgroup differences: Chi^2 = 1.66, df = 2 (P = 0.44), I^2 =0.0%					

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

Review: Workplace interventions for treatment of occupational asthma

Comparison: 1 Removal from exposure versus continued exposure

Outcome: 3 Change in FEV1 % predicted: follow-up minus baseline values

Study or subgroup	Removal N	Mean(SD)	Continued N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 LMW							
Chan-Yeung 1982	75	6.3 (12.3)	50	-4.5 (12.3)		15.4 %	10.80 [6.40, 15.20]
Chan-Yeung 1987 removal	129	-0.5 (17.3)	47	-3.8 (13)		14.3 %	3.30 [-1.47, 8.07]
Lin 1996	122	-4.1 (12.1)	158	-7.9 (12.1)		21.1 %	3.80 [0.94, 6.66]
Mapp 1988	30	-1 (12.6)	5	-7 (11.3)		4.6 %	6.00 [-4.88, 16.88]
Marabini 1993	80	-2.7 (16.2)	48	-9.5 (12.1)		13.8 %	6.80 [1.87, 11.73]
Munoz 2008	7	-2.7 (6.7)	3	-9 (1.7)		12.7 %	6.30 [0.98, 11.62]
Paggiaro 1984	12	3 (14.2)	15	-7.9 (12.2)		5.1 %	10.90 [0.77, 21.03]
Subtotal (95% CI)	**455**		**326**			**86.9 %**	**6.23 [3.83, 8.62]**
Heterogeneity: Tau^2 = 3.32; Chi^2 = 9.06, df = 6 (P = 0.17); I^2 =34%							
Test for overall effect: Z = 5.10 (P < 0.00001)							
2 HMW % LMW							
Moscato 1999	13	-1 (8)	12	-1.1 (5)		13.1 %	0.10 [-5.09, 5.29]
Subtotal (95% CI)	**13**		**12**			**13.1 %**	**0.10 [-5.09, 5.29]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.04 (P = 0.97)							
Total (95% CI)	**468**		**338**			**100.0 %**	**5.52 [2.99, 8.06]**
Heterogeneity: Tau^2 = 5.81; Chi^2 = 13.27, df = 7 (P = 0.07); I^2 =47%							
Test for overall effect: Z = 4.27 (P = 0.000020)							
Test for subgroup differences: Chi^2 = 4.42, df = 1 (P = 0.04), I^2 =77%							

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

Review: Workplace interventions for treatment of occupational asthma

Comparison: 1 Removal from exposure versus continued exposure

Outcome: 4 Change in NSBP: follow-up minus baseline values

Study or subgroup	Removal N	Mean(SD)	Continued N	Mean(SD)	Std. Mean Difference IV,Random,95% CI	Weight	Std. Mean Difference IV,Random,95% CI
1 LMW							
Chan-Yeung 1982	33	6.03 (6.01)	22	-0.85 (1.54)		21.0 %	1.42 [0.82, 2.03]
Chan-Yeung 1987 removal	52	0.91 (5.6)	19	-0.25 (5.96)		22.5 %	0.20 [-0.33, 0.73]
Mapp 1988	30	0.19 (4.5)	5	0.03 (2.41)		15.2 %	0.04 [-0.91, 0.98]
Marabini 1993	80	2.71 (11.01)	48	-0.7 (4.82)		25.4 %	0.37 [0.01, 0.73]
Subtotal (95% CI)	**195**		**94**			**84.0 %**	**0.53 [-0.03, 1.08]**
Heterogeneity: $Tau^2 = 0.23$; $Chi^2 = 11.56$, df = 3 (P = 0.01); $I^2 = 74\%$							
Test for overall effect: Z = 1.86 (P = 0.063)							
2 HMW % LMW							
Moscato 1999	13	1.06 (1.23)	12	-0.78 (1.25)		16.0 %	1.44 [0.54, 2.33]
Subtotal (95% CI)	**13**		**12**			**16.0 %**	**1.44 [0.54, 2.33]**
Heterogeneity: not applicable							
Test for overall effect: Z = 3.14 (P = 0.0017)							
Total (95% CI)	**208**		**106**			**100.0 %**	**0.67 [0.13, 1.21]**
Heterogeneity: $Tau^2 = 0.26$; $Chi^2 = 15.48$, df = 4 (P = 0.004); $I^2 = 74\%$							
Test for overall effect: Z = 2.45 (P = 0.014)							
Test for subgroup differences: $Chi^2 = 2.84$, df = 1 (P = 0.09), $I^2 = 65\%$							

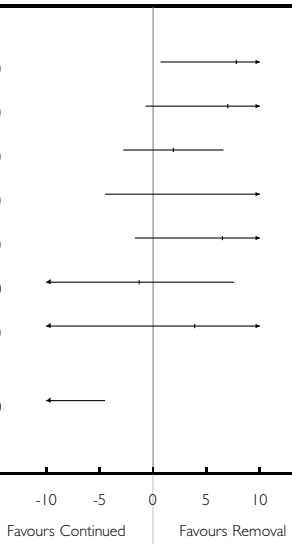
Analysis 1.5. Comparison 1 Removal from exposure versus continued exposure, Outcome 5 FEV1 % predicted: follow up.

Review: Workplace interventions for treatment of occupational asthma

Comparison: 1 Removal from exposure versus continued exposure

Outcome: 5 FEV1 % predicted: follow up

Study or subgroup	Removal N	Mean(SD)	Continued N	Mean(SD)	Mean Difference IV,Random,95% CI	Mean Difference IV,Random,95% CI
1 LMW						
Chan-Yeung 1982	75	98.7 (19.5)	50	90.9 (20.1)		7.80 [0.69, 14.91]
Chan-Yeung 1987 removal	129	93.4 (27.3)	47	86.4 (21.3)		7.00 [-0.70, 14.70]
Lin 1996	122	80.9 (19.9)	158	79 (20.1)		1.90 [-2.82, 6.62]
Mapp 1988	30	95.7 (18.6)	5	82.4 (18.8)		13.30 [-4.47, 31.07]
Marabini 1993	80	81.3 (26.8)	48	74.8 (20.1)		6.50 [-1.67, 14.67]
Munoz 2008	7	94.7 (11.1)	3	96 (2.9)		-1.30 [-10.15, 7.55]
Paggiaro 1984	12	96.7 (23.2)	15	92.8 (18.1)		3.90 [-12.11, 19.91]
2 HMW % LMW						
Moscato 1999	13	93 (10)	12	104.5 (7.8)		-11.50 [-18.50, -4.50]



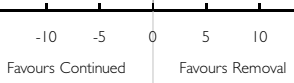
Analysis 1.6. Comparison 1 Removal from exposure versus continued exposure, Outcome 6 FEV1 % predicted: baseline.

Review: Workplace interventions for treatment of occupational asthma

Comparison: 1 Removal from exposure versus continued exposure

Outcome: 6 FEV1 % predicted: baseline

Study or subgroup	Removal N	Mean(SD)	Continued N	Mean(SD)	Mean Difference IV,Random,95% CI	Mean Difference IV,Random,95% CI
1 LMW						
Chan-Yeung 1982	75	92.4 (19.5)	50	95.4 (18.5)		-3.00 [-9.77, 3.77]
Chan-Yeung 1987 removal	129	93.9 (27.3)	47	90.2 (19.2)		3.70 [-3.53, 10.93]
Lin 1996	122	85 (17.7)	158	86.9 (16.3)		-1.90 [-5.94, 2.14]
Mapp 1988	30	96.7 (20.8)	5	89.4 (14.8)		7.30 [-7.66, 22.26]
Marabini 1993	80	84 (23.3)	48	84.3 (16.6)		-0.30 [-7.24, 6.64]
Munoz 2008	7	97.4 (8.7)	3	105 (2.2)		-7.60 [-14.51, -0.69]
Paggiaro 1984	12	93.7 (21.6)	15	100.7 (20.1)		-7.00 [-22.90, 8.90]
2 HMW % LMW						
Moscato 1999	13	94 (13.3)	12	105.6 (7.9)		-11.60 [-20.10, -3.10]



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

Review: Workplace interventions for treatment of occupational asthma

Comparison: 1 Removal from exposure versus continued exposure

Outcome: 7 NSBH: follow up

Study or subgroup	Std. Mean Difference (SE)	Std. Mean Difference IV,Fixed,95% CI	Std. Mean Difference IV,Fixed,95% CI
1 LMW			
Chan-Yeung 1982	1.14 (0.3)		1.14 [0.55, 1.73]
Chan-Yeung 1987 removal	0.15 (0.3)		0.15 [-0.44, 0.74]
Mapp 1988	0.03 (0.5)		0.03 [-0.95, 1.01]
Marabini 1993	0.17 (0.2)		0.17 [-0.22, 0.56]
Munoz 2008	0.65 (0.3)		0.65 [0.06, 1.24]
Paggiaro 1984	0.16 (0.2)		0.16 [-0.23, 0.55]
Rosenberg 1987 removal	0.65 (0.8)		0.65 [-0.92, 2.22]
2 HMW % LMW			
Moscato 1999	0.14 (0.4)		0.14 [-0.64, 0.92]

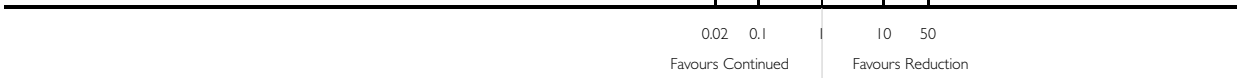
Analysis 2.1. Comparison 2 Reduction of exposure versus continued exposure, Outcome 1 Absence of asthma symptoms.

Review: Workplace interventions for treatment of occupational asthma

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	Risk Ratio M-H,Fixed,95% CI
1 LMW absence of symptoms				
Chan-Yeung 1987 reduction	0/42	0/54		0.0 [0.0, 0.0]
Rosenberg 1987 reduction	3/7	0/4		4.38 [0.28, 68.06]
Subtotal (95% CI)	**49**	**58**		**4.38 [0.28, 68.06]**
Total events: 3 (Reduction), 0 (Continued)				
Heterogeneity: Chi^2 = 0.0, df = 0 (P = 1.00); I^2 =0.0%				
Test for overall effect: Z = 1.05 (P = 0.29)				
2 HMW absence of symptoms				
Bernstein 2003 reduction	20/20	0/1		3.90 [0.35, 43.10]
Dressel 2007	12/81	0/24		7.62 [0.47, 124.22]
Subtotal (95% CI)	**101**	**25**		**5.60 [0.89, 35.36]**
Total events: 32 (Reduction), 0 (Continued)				
Heterogeneity: Chi^2 = 0.13, df = 1 (P = 0.71); I^2 =0.0%				
Test for overall effect: Z = 1.83 (P = 0.067)				
3 HMW % LMW absence of symptoms				
Moscato 1993 reduction	4/7	0/4		5.63 [0.38, 83.67]
Subtotal (95% CI)	**7**	**4**		**5.63 [0.38, 83.67]**
Total events: 4 (Reduction), 0 (Continued)				
Heterogeneity: not applicable				
Test for overall effect: Z = 1.25 (P = 0.21)				
Total (95% CI)	**157**	**87**		**5.35 [1.40, 20.48]**
Total events: 39 (Reduction), 0 (Continued)				
Heterogeneity: Chi^2 = 0.15, df = 3 (P = 0.99); I^2 =0.0%				
Test for overall effect: Z = 2.45 (P = 0.014)				
Test for subgroup differences: Chi^2 = 0.02, df = 2 (P = 0.99), I^2 =0.0%				



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

Review: Workplace interventions for treatment of occupational asthma

Comparison: 2 Reduction of exposure versus continued exposure

Outcome: 2 Change in FEV1 % predicted: follow-up minus baseline values

Study or subgroup	Reduction N	Mean(SD)	Continued N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
1 LMW						
Chan-Yeung 1987 reduction	41	-2.7 (12.9)	47	-3.8 (13)		1.10 [-4.32, 6.52]
Rosenberg 1987 reduction	7	6.1 (0)	4	-9.7 (0)		0.0 [0.0, 0.0]
Subtotal (95% CI)	**48**		**51**			**1.10 [-4.32, 6.52]**
Heterogeneity: Chi^2 = 0.0, df = 0 (P = 1.00); I^2 =0.0%						
Test for overall effect: Z = 0.40 (P = 0.69)						
2 HMW						
Dressel 2007	72	2 (13.2)	21	0.7 (13.2)		1.30 [-5.12, 7.72]
Subtotal (95% CI)	**72**		**21**			**1.30 [-5.12, 7.72]**
Heterogeneity: not applicable						
Test for overall effect: Z = 0.40 (P = 0.69)						
Total (95% CI)	**120**		**72**			**1.18 [-2.96, 5.32]**
Heterogeneity: Chi^2 = 0.00, df = 1 (P = 0.96); I^2 =0.0%						
Test for overall effect: Z = 0.56 (P = 0.58)						
Test for subgroup differences: Chi^2 = 0.00, df = 1 (P = 0.96), I^2 =0.0%						

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

Review: Workplace interventions for treatment of occupational asthma

Comparison: 2 Reduction of exposure versus continued exposure

Outcome: 3 FEV1 % predicted: follow up

Study or subgroup	Reduction N	Mean(SD)	Continued N	Mean(SD)	Mean Difference IV,Random,95% CI	Mean Difference IV,Random,95% CI
1 LMW						
Chan-Yeung 1987 reduction	41	97.8 (21.1)	47	86.4 (21.3)		11.40 [2.52, 20.28]
Rosenberg 1987 reduction	7	108.1 (0)	4	86.3 (0)		0.0 [0.0, 0.0]
2 HMW						
Dressel 2007	72	93.1 (21.2)	21	91.4 (20.2)		1.70 [-8.23, 11.63]

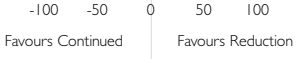
Analysis 2.4. Comparison 2 Reduction of exposure versus continued exposure, Outcome 4 FEV1 % predicted: baseline.

Review: Workplace interventions for treatment of occupational asthma

Comparison: 2 Reduction of exposure versus continued exposure

Outcome: 4 FEV1 % predicted: baseline

Study or subgroup	Reduction N	Mean(SD)	Continued N	Mean(SD)	Mean Difference IV,Random,95% CI	Mean Difference IV,Random,95% CI
1 LMW						
Chan-Yeung 1987 reduction	41	100.5 (19.2)	47	90.2 (19.2)		10.30 [2.26, 18.34]
Rosenberg 1987 reduction	7	102 (0)	4	96 (0)		0.0 [0.0, 0.0]
2 HMW						
Dressel 2007	72	91.1 (20.4)	21	90.7 (21.5)		0.40 [-9.93, 10.73]

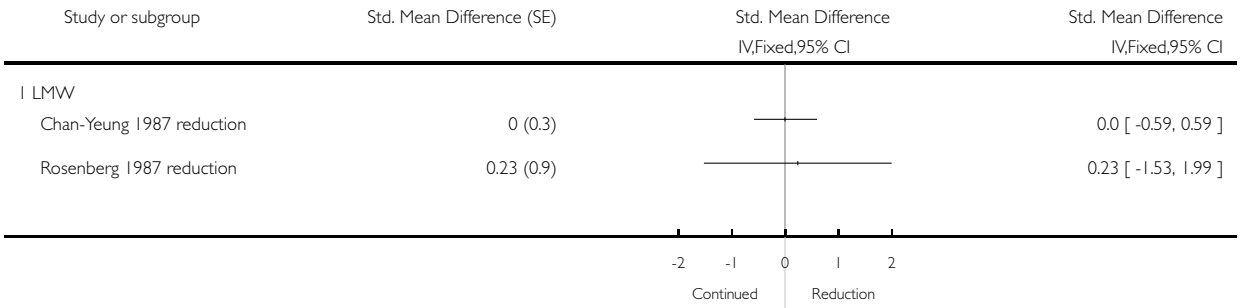


Analysis 2.5. Comparison 2 Reduction of exposure versus continued exposure, Outcome 5 NSBH follow up.

Review: Workplace interventions for treatment of occupational asthma

Comparison: 2 Reduction of exposure versus continued exposure

Outcome: 5 NSBH follow up

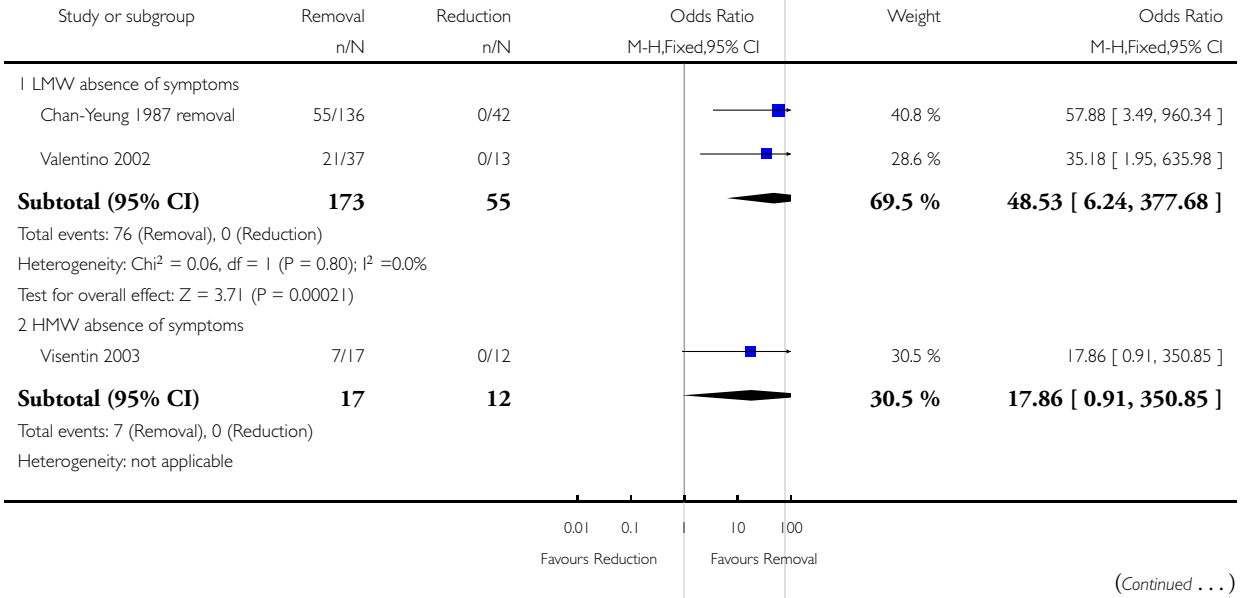


Analysis 3.1. Comparison 3 Removal from exposure versus reduction of exposure, Outcome 1 Absence of asthma symptoms.

Review: Workplace interventions for treatment of occupational asthma

Comparison: 3 Removal from exposure versus reduction of exposure

Outcome: 1 Absence of asthma symptoms



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Study or subgroup	Removal n/N	Reduction n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Test for overall effect: Z = 1.90 (P = 0.058)					
Total (95% CI)	**190**	**67**		**100.0 %**	**39.16 [7.21, 212.83]**
Total events: 83 (Removal), 0 (Reduction)					
Heterogeneity: Chi^2 = 0.35, df = 2 (P = 0.84); I^2 =0.0%					
Test for overall effect: Z = 4.25 (P = 0.000022)					
Test for subgroup differences: Chi^2 = 0.29, df = 1 (P = 0.59), I^2 =0.0%					

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

Review: Workplace interventions for treatment of occupational asthma

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
1 LMW improvement of symptoms					
Burge 1982	20/20	5/8		19.2 %	1.60 [0.94, 2.70]
Rosenberg 1987 removal	14/20	3/7		11.9 %	1.63 [0.66, 4.03]
Subtotal (95% CI)	**40**	**15**		**31.1 %**	**1.61 [1.02, 2.53]**
Total events: 34 (Removal), 8 (Reduction)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.00, df = 1 (P = 0.97); I^2 =0.0%					
Test for overall effect: Z = 2.05 (P = 0.041)					
2 HMW improvement of symptoms					
Bernstein 2003 removal	4/4	20/20		24.3 %	1.00 [0.74, 1.35]
Vandenplas 2002	16/16	20/20		27.4 %	1.00 [0.90, 1.11]
Subtotal (95% CI)	**20**	**40**		**51.7 %**	**1.00 [0.90, 1.11]**
Total events: 20 (Removal), 40 (Reduction)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.0, df = 1 (P = 1.00); I^2 =0.0%					
Test for overall effect: Z = 0.0 (P = 1.0)					
3 HMW % LMW improvement of symptoms					
Moscato 1993 removal	18/18	4/7		17.2 %	1.73 [0.94, 3.20]

(*Continued* . . .)

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Study or subgroup	Removal n/N	Reduction n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Subtotal (95% CI)	**18**	**7**		**17.2 %**	**1.73 [0.94, 3.20]**
Total events: 18 (Removal), 4 (Reduction)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.75 (P = 0.081)					
Total (95% CI)	**78**	**62**		**100.0 %**	**1.27 [0.84, 1.92]**
Total events: 72 (Removal), 52 (Reduction)					
Heterogeneity: Tau^2 = 0.16; Chi^2 = 23.78, df = 4 (P = 0.00009); I^2 =83%					
Test for overall effect: Z = 1.16 (P = 0.25)					
Test for subgroup differences: Chi^2 = 6.73, df = 2 (P = 0.03), I^2 =70%					

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

Review: Workplace interventions for treatment of occupational asthma

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	Mean(SD)	Reduction N	Mean(SD)	Mean Difference IV,Random,95% CI	Mean Difference IV,Random,95% CI
1 LMW						
Burge 1982	20	-3.5 (13.9)	8	2 (25.2)		-5.50 [-23.99, 12.99]
Chan-Yeung 1987 removal	129	-3.7 (17.3)	41	-2.7 (12.9)		-1.00 [-5.95, 3.95]
Rosenberg 1987 removal	20	4.2 (0)	7	6 (0)		0.0 [0.0, 0.0]
Valentino 2002	37	-0.2 (9.8)	13	-11.2 (4.7)		11.00 [6.94, 15.06]
Subtotal (95% CI)	**206**		**69**			**3.14 [-7.25, 13.53]**
Heterogeneity: Tau^2 = 63.63; Chi^2 = 14.98, df = 2 (P = 0.00056); I^2 =87%						
Test for overall effect: Z = 0.59 (P = 0.55)						
2 HMW						
Vandenplas 2002	16	3 (8.5)	20	7 (9.2)		-4.00 [-9.80, 1.80]
Subtotal (95% CI)	**16**		**20**			**-4.00 [-9.80, 1.80]**
Heterogeneity: not applicable						
Test for overall effect: Z = 1.35 (P = 0.18)						

(*Continued* . . .)

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Study or subgroup	Removal N	Mean(SD)	Reduction N	Mean(SD)	Mean Difference IV,Random,95% CI	Mean Difference IV,Random,95% CI
Total (95% CI)	**222**		**89**			**1.16 [-7.51, 9.84]**

Heterogeneity: $Tau^2 = 61.20$; $Chi^2 = 23.60$, df = 3 (P = 0.00003); $I^2 = 87\%$

Test for overall effect: Z = 0.26 (P = 0.79)

Test for subgroup differences: $Chi^2 = 1.38$, df = 1 (P = 0.24), $I^2 = 28\%$

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

Review: Workplace interventions for treatment of occupational asthma

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		61.0 %	11.57 [0.77, 174.35]
Vandenplas 2002	7/16	0/20		39.0 %	18.53 [1.14, 301.79]
Total (95% CI)	**36**	**28**		**100.0 %**	**14.28 [2.06, 99.16]**

Total events: 20 (Removal), 0 (Reduction)

Heterogeneity: $Chi^2 = 0.06$, df = 1 (P = 0.81); $I^2 = 0.0\%$

Test for overall effect: Z = 2.69 (P = 0.0071)

Test for subgroup differences: Not applicable

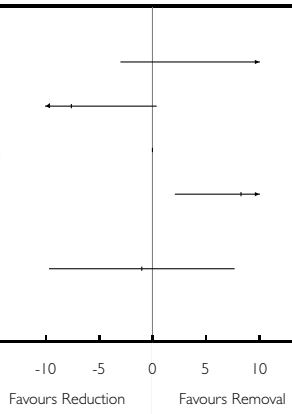
Analysis 3.5. Comparison 3 Removal from exposure versus reduction of exposure, Outcome 5 FEV1 % predicted: follow up.

Review: Workplace interventions for treatment of occupational asthma

Comparison: 3 Removal from exposure versus reduction of exposure

Outcome: 5 FEV1 % predicted: follow up

Study or subgroup	Removal N	Mean(SD)	Reduction N	Mean(SD)	Mean Difference IV,Random,95% CI	Mean Difference IV,Random,95% CI
1 LMW						
Burge 1982	20	86.3 (21.9)	8	74.8 (15.6)		11.50 [-2.96, 25.96]
Chan-Yeung 1987 removal	129	90.2 (27.3)	41	97.8 (21.1)		-7.60 [-15.59, 0.39]
Rosenberg 1987 removal	20	99.9 (0)	7	108 (0)		0.0 [0.0, 0.0]
Valentino 2002	37	96.9 (15.9)	13	88.6 (6.6)		8.30 [2.05, 14.55]
2 HMW						
Vandenplas 2002	16	99 (14.1)	20	100 (11.9)		-1.00 [-9.66, 7.66]



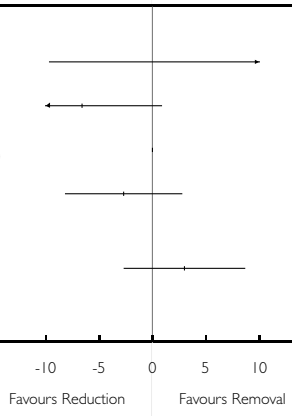
Analysis 3.6. Comparison 3 Removal from exposure versus reduction of exposure, Outcome 6 FEV1 % predicted: baseline.

Review: Workplace interventions for treatment of occupational asthma

Comparison: 3 Removal from exposure versus reduction of exposure

Outcome: 6 FEV1 % predicted: baseline

Study or subgroup	Removal N	Mean(SD)	Reduction N	Mean(SD)	Mean Difference IV,Random,95% CI	Mean Difference IV,Random,95% CI
1 LMW						
Burge 1982	20	89.8 (21.9)	8	72.8 (35.9)		17.00 [-9.66, 43.66]
Chan-Yeung 1987 removal	129	93.9 (27.3)	41	100.5 (19.2)		-6.60 [-14.13, 0.93]
Rosenberg 1987 removal	20	95.7 (0)	7	102 (0)		0.0 [0.0, 0.0]
Valentino 2002	37	97.1 (10.6)	13	99.8 (7.9)		-2.70 [-8.19, 2.79]
2 HMW						
Vandenplas 2002	16	96 (11.1)	20	93 (3.7)		3.00 [-2.68, 8.68]

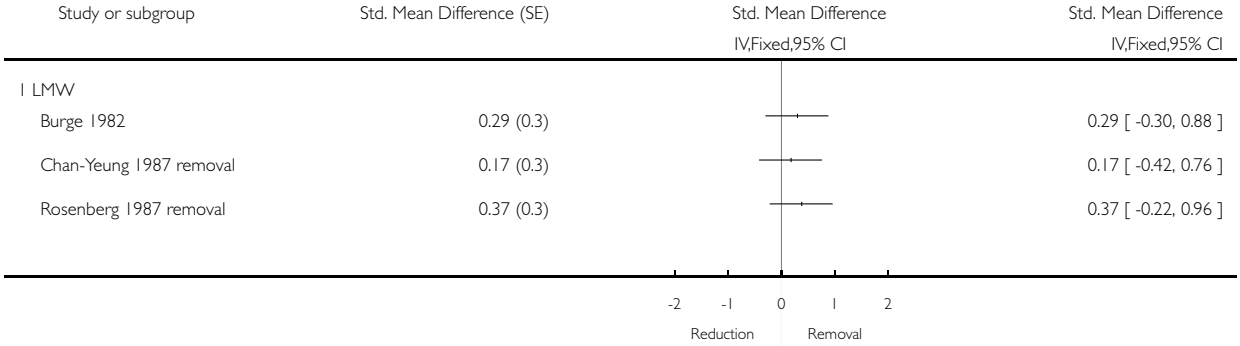


Analysis 3.7. Comparison 3 Removal from exposure versus reduction of exposure, Outcome 7 NSBH follow up.

Review: Workplace interventions for treatment of occupational asthma

Comparison: 3 Removal from exposure versus reduction of exposure

Outcome: 7 NSBH follow up



ADDITIONAL TABLES

Table 1. Interventions

	Removal from exposure	Reduction of exposure Moved to area with less exposure	Reduction of exposure Introduce/change use of PPE	Reduction of exposure Education/training programme
Bernstein 2003	+		+	
Burge 1982	+	+		
Chan-Yeung 1982	+			
Chan-Yeung 1987	+	+		
Dressel 2007				+
Innocenti 1981	+			
Lin 1996	+			

Table 1. Interventions (*Continued*)

Mapp 1988	+			
Marabini 1993	+			
Marabini 1994	+	+		
Moscato 1993	+	+		
Moscato 1999	+	+		
Munoz 2008	+			
Padoan 2003	+			
Paggiaro 1984	+			
Pisati 1994	+			
Rosenberg 1987	+	+	+	
Soyseth 1995		+		
Valentino 2002	+	+		
Vandenplas 2002	+	+	+	
Visentin 2003	+	+		

PPE: personal protective equipment

Table 2. Non-specific bronchial hyper-responsiveness (NSBH)

	Test	Removal from exposure					Reduction of exposure					Continued exposure				
		No.	Baseline	SD/SEM	Follow up	SD/SEM	No.	Baseline	SD/SEM	Follow up	SD/SEM	No.	Baseline	SD/SEM	Follow up	SD/SEM
Bernstein 2003	-															
Burge 1982	Histamine PD20 Nor-	20	6 abnormal		3 abnormal		8	4 abnormal		3 abnormal						

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

	mal > 4 um/ ml															
Chan-Ye-ung 1982	Metha-choline PC20	33	2.45	SD	8.48	SD						22	1.81	SD	0.96	SD
Chan-Ye-ung 1987	Metha-choline PC20	52	1.04	SD	1.95	SD	15	1.14	SD	0.64	SD	19	0.86	SD	0.61	SD
Dres-sel 2007	-															
In-no-centi 1981	-															
Lin 1996	-															
Mapp 1988	Metha-choline PD20	30	0.38	SEM	0.57	SEM						5	0.36	SEM	0.39	SEM
Mara-bini 1993	Metha-choline PC20	80	2.5	SEM	5.21	SEM						48	3.4	SEM	2.7	SEM
Mara-bini 1994	-															
Moscat 1993	Metha-choline PD20															

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

Moscat 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	
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	Acethycholine PC15	20	14/20 abnormal		7/12 abnormal		7	6 abnormal		5 abnormal		4	3 abnormal		4 abnormal	
Soyseth 1995	Methacholine PD20															
Valenti 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						
Visenti 2003	-															

SD: standard deviation
SEM: standard error of the mean

Table 3. Employment/income

Author	Outcome
Bernstein 2003	Removal from exposure group: 4/4 had a reduction in income. Mean reduction 25% in annual income (all 4 workers were forced to leave job due to symptoms)
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. 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

	Isocyanate	Latex	Western red cedar	Cow dander Storage mite	Pot room	Persulfate salts	Colophonium	Cobalt	Various
Bernstein 2003		+							
Burge 1982							+		

Table 4. Agents (*Continued*)

Chang-Yeung 1982			+						
Chang-Yeung 1987			+						
Dressel 2007				+					
Innocenti 1981	+								
Lin 1996			+						
Mapp 1988	+								
Marabini 1993			+						
Marabini 1994	+								
Moscato 1993									+
Moscato 1999									+
Munoz 2008						+			
Padoan 2003	+								
Paggiaro 1984	+								
Pisati 1994								+	
Rosenberg 1987	+								
Soyseth 1995					+				
Valentino 2002	+								

Table 4. Agents (*Continued*)

Vanden-plas 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	+			
Innocenti 1981		+		
Lin 1996		+		
Mapp 1988		+		
Marabini 1993		+		
Marabini 1994		+		
Moscato 1993			+	
Moscato 1999			+	
Munoz 2008		+		
Padoan 2003		+		
Paggiaro 1984		+		
Pisati 1994		+		
Rosenberg 1987		+		
Soyseth 1995				+

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

Valentino 2002		+		
Vandenplas 2002	+			
Visentin 2003	+			

Table 6. Baseline characteristics

Total & Groups	Participants	Age	Sex	Smoking (S)	Atopy	Type of reaction	Follow up	Exposure time before symptoms	Duration of symptoms before diagnosis
	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 mentioned**	**Not mentioned**	**2**		**2.5**
Removal from exposure	20	52	5%	35 - 15 - 50%	-	-	-	-	-
Reduction of exposure	8	45	12.5%	0 -25 - 75%	-	-	-	-	-

Table 6. Baseline characteristics (*Continued*)

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
Dressel 2007 - Total	**105**	**47.1**		**Not mentioned**	**Not mentioned**	**Not mentioned**	**5 weeks**	**Not mentioned**	**Not mentioned**
Reduction of exposure - education programme received	81	-	61%	-	-	-	-	-	-
Continued exposure - no education programme received	24	-	-	-	-	-	-	-	-
Innocenti 1981 - Total	**50**	***19-67***	**78%**	**S: 9/25**	**FU: 24%**	**Not mentioned**	**< 1**	**Not mentioned**	**Only mentioned for half of the subjects**

Table 6. Baseline characteristics (*Continued*)

Removal from exposure	37			S: 5/18	FU: 27%	-		-	-
Continued exposure	13			S: 4/13	FU: 15%	-		-	-
Lin 1996 - Total	**201**	**40.9**	**100**%	**5 - 28 - 67**%	**28**%	**Not mentioned**	**6.1**		
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			-	-	-	-	-	-

Table 6. Baseline characteristics (*Continued*)

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**	**21**
Removal from exposure	13	31	77%	23 - 23 - 54%	8%			6	20
Moscato 1999 - continue	12	35.5	66%	33 - 25 - 42%	25%			0.5	25.5
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%	-	-	-	-	-	-
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	-	-	-	-	-	-	-	-

Table 6. Baseline characteristics (*Continued*)

Paggiaro 1984 - Total	**27**	**50.2**	**59%**		**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	-	-	-	-	-	-	-	-
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%	-	-	-	-	-

Table 6. Baseline characteristics (*Continued*)

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%		-	-
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. Authors conclusions

Bernstein 2003	Asthma symptoms cleared in all asthmatic subgroups except the subject who continued to use latex gloves with no changes
Burge 1982	Only 2 of the 20 affected workers who left their original factories were symptom-free on follow up and most had a considerable reduction in their quality of life by continuing asthma. Lung function testing at presentation and follow up show no significant differences for any group. Histamine reactivity had returned to normal in half of the workers who had left their original factories, but in only one worker who had moved within her original factory. This suggested that the non-specific bronchial reactivity to histamine was the result rather than the cause of the OA, and that indirect exposure at work was sufficient to delay recovery of histamine reactivity
Chan-Yeung 1982	Early diagnosis and removal from red cedar exposure were found to be associated with recovery Only half of the patients of red cedar asthma recovered completely after their exposure ended. Early diagnosis and early removal from exposure were found to be associated with recovery
Chan-Yeung 1987	This study emphasises the importance of early diagnosis and early removal from exposure in patients with occupational asthma. The removal from exposure should be complete because partial removal did not prevent the deterioration of function of those who were continuously exposed. Early diagnosis and early removal are important for prognosis
Dressel 2007	After intervention work-related symptoms were reduced, FeNO was decreased, spirometric results were unchanged. Control group: none of the outcome measures showed a significant change over time
Innocenti 1981	The data suggest that TDI induces chronic and irreversible damage even if the exposure is discontinued and support the view that FVC is more impaired than FEV1
Lin 1996	Patients with red cedar asthma who continued to be exposed to cedar dust had a greater decline in FEV1. Patients with RCA who avoided the exposure after the diagnosis showed a similar rate of decline in FEV1 compared with sawmill workers
Mapp 1988	Conclusion: respiratory symptoms, isocyanate sensitisation and airway hyper-responsiveness to methacholine may persist after removal from occupational exposure to TDI 30/35 stopped exposure: 8 lost SIC to response to TDI, 5 had normal airway hyper-responsiveness to methacholine. TDI reactors on the follow-up challenge had persistent respiratory symptoms and airway hyper-responsiveness to methacholine At follow up significant difference with regard to FEV1: non-reactors showed improvement, reactors showed a deterioration. Methacholine PD20 was higher among the group of 8 non-reactors than in the group of reactors removed from exposure and in the group of the 5 reactors exposed to TDI
Marabini 1993	The results suggest that the severity of asthma is not the main determinant of working status. It was found that the persistence of exposure resulted in a deterioration in the asthma despite the use of more medication. Participants who were working were younger and had a larger number of dependents than subjects who were not working at the time of the follow-up examination. They conclude that the socioeconomic factors are important in determining the working status of subjects with red cedar asthma. To prevent severe impairment and disability, there should be more economic incentives for these subjects to choose other jobs
Marabini 1994	Despite removal from TDI exposure, OA can lead to permanent disability with important socio-economic consequences, and late response to SBPT may be a negative prognostic factor in TDI asthma

Table 7. Authors conclusions (*Continued*)

Moscato 1993	Patients with OA can recover completely if the diagnosis is made at an earlier stage of the disease and the patient is removed from exposure The data show that the complete cessation of exposure without loss of work occurs in only a proportion of patients and that in Italy the system for compensation acts slowly
Moscato 1999	In OA, cessation of exposure to the offending agent results in a decrease in asthma severity and in pharmaceutical expenses, but is associated with a deterioration of the individual's socioeconomic status (professional downgrading and loss of work-derived income)
Munoz 2008	Observations seem to indicate that the clinical and functional course for these patients will be favourable if they avoid exposure
Padoan 2003	The long-term follow up revealed that both asthmatic symptoms and airway hyper-responsiveness to methacholine persisted or improved slowly in subjects removed from exposure to TDI for > 10 years. A more favourable outcome was associated with a better lung function, a lower degree of airway hyporesponsiveness to methacholine and a longer interval from cessation of exposure
Paggiaro 1984	The study suggest that stopping occupational exposure to TDI frequently did not produce an improvement of the TDI bronchial asthma, and persistence of the occupational exposure causes a more rapid decline in the respiratory function
Pisati 1994	OA cobalt: early diagnosis and early removal from exposure after the onset of asthma are important factors for a favourable evolution of the disease and that specific and non-specific bronchial hyper-responsiveness can persist even in asymptomatic subjects no longer exposed to the cobalt
Rosenberg 1987	Confirms and extends previous results about the evaluation of OA. Respiratory symptoms often persist despite removal from exposure. Bronchial hyperreactivity lasts more than 4 years after cessation of exposure
Soyseth 1995	No improvement in lung function was found in the index group compared with the reference group. 49% of the improvement in bronchial responsiveness could be explained by removal from exposure
Valentino 2002	The present study confirms that early diagnosis and immediate removal from exposure are crucial, though not always sufficient, for a favourable evolution of the disease
Vandenplas 2002	In participants who reduced their exposure to latex, the improvement in asthma and rhinitis symptoms, as well as in the level of nonspecific bronchial hyper-responsiviness, was similar to what was observed in the participants who avoided exposure to latex. However, removal from exposure was associated with more pronounced work disability, income loss and perceived impairment of professional and social activities. When compensation benefits are taken into account, the final income loss did not differ between those who avoided exposure and those who reduced exposure. *(Different for other countries).*
Visentin 2003	The study shows that latex-induced occupational asthma improves after a follow up of 5 +/- 3 years, but a complete recovery occurs in a minority of subjects and is associated with cessation of exposure

FeNO: fraction of exhaled nitric oxide in exhaled breath
FEV1: forced expiratory volume in the first second
FVC: forced vital volume
OA: occupational asthma

RCA: red cedar asthma
SBPT: specific bronchial provocative test
SIC: specific inhalation change
TDI: toluene di isocyanate

Table 8. Methodological quality assessment

Items from the checklist of Downs and Black 1998																					
	Bern-stein 2003	Burg(1982	Chan Ye-ung 1982	Chan Ye-ung 1987	Dres-sel 2007	In-no-centi 1981	Lin 1996	Mapp 1988	Mara bini 1993	Mara bini 1994	Mosc 1993	Mosc 1999	Mun(2008	Pado: 2003	Pag-gioro 1984	Pisati 1994	Roser berg 1987	Soy-seth 1995	Valen 2002	Van-den-plas 2002	Visentin 2003
Re-port-ing 1 = Yes 0 = No																					
1. Is the hy-poth-esis clearl de-scrib(	1	1	1	1	1	1	1	1	1	1	1	0	1	1	1	1	1	1	0	1	0
2. Are main out-come clearl de-scrib(	1	1	1	1	1	0	1	1	1	0	1	1	1	1	1	1	1	1	0	1	0
3. Are pa-tient char-ac-ter-is-tics	0	1	1	1	1	0	1	1	1	0	0	0	1	1	1	0	0	1	0	1	0

Table 8. Methodological quality assessment (*Continued*)

clear de- scrib																					
4. Are in- ter- ven- tions clearl de- scribe	0	1	1	1	1	1	1	1	1	1	0	0	1	1	0	0	0	0	1	1	0
5. Are dis- tri- bu- tions of co- foun clearl de- scribe	0	0	0	1	0	0	1	1	1	1	0	1	1	0	1	0	0	1	1	1	0
6. Are main find- ings clearl de- scribe	0	0	1	1	1	0	1	1	1	1	0	1	1	0	1	0	0	0	0	1	0
7. Es- ti- mate of ran- dom vari- abil- ity in data for main	0	1	1	1	1	0	1	1	1	1	0	0	1	0	1	0	0	0	0	1	0

Table 8. Methodological quality assessment (*Continued*)

outcom																					
8. Have important adverse effects been reporte	1	1	0	1	0	0	0	0	1	0	0	1	0	0	0	0	0	0	0	1	0
9. Have characteristics of patients lost to follow up been describ	0	0	1	0	0	0	1	0	0	0	0	1	0	0	0	0	0	0	0	1	0
10. Have actual probabilities been reporte	0	0	0	0	1	0	1	0	0	0	0	0	0	1	0	0	0	1	0	1	0

Table 8. Methodological quality assessment (*Continued*)

Subtotal	**3**	**6**	*7*	**8**	*7*	**2**	**9**	*7*	**8**	**5**	**2**	**5**	*7*	**5**	**6**	**2**	**2**	**5**	**2**	**10**	**0**
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	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	0	0	0	0	0	0	0
16. If results were based on data	0	0	0	0	0	0	0	0	0	0	1	1	0	0	0	0	0	1	0	0	0

Table 8. Methodological quality assessment (*Continued*)

dred ing, was this mad clear																						
17. Anal- y- ses ad- juste for lengt of fol- low up?	0	0	0	1	1	0	1	0	0	1	0	1	0	0	0	0	0	1	0	0	0	
19. Was com- pli- ance with the in- ter- ven- tion re- li- able?	0	0	0	0	1	0	0	0	0	0	0	0	1	0	0	1	0	1	0	0	0	
20. Were the main out- come mea- sures used ac- cu- rate?	0	1	1	1	1	0	1	0	1	0	0	1	1	1	1	1	0	1	0	1	0	

Table 8. Methodological quality assessment (*Continued*)

21. Were patients recruited over the same population?	1	1	1	1	1	0	1	1	0	0	0	1	1	1	1	1	1	1	0	1	0	
22. Were patients recruited over the same period?	1	1	0	1	1	0	1	0	0	1	0	1	1	1	0	1	1	1	0	1	0	
23. Were subjects randomi to intervention group	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
24. Was randomisation concealed until	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	

Table 8. Methodological quality assessment (*Continued*)

re-cruitment was com-plete																						
25. Was there ad-e-quate ad-just-ment for con-found-ing fac-tors?	0	0	0	1	0	0	1	1	0	0	0	0	0	0	0	0	0	1	0	0	0	
26. Were losses of work-ers to fol-low up taken into ac-count	0	0	0	0	0	0	1	0	0	0	0	1	0	0	0	0	0	0	0	0	0	
TO-TAL	**2**	**3**	**2**	**5**	**5**	**5**	**6**	**2**	**1**	**2**	**1**	**6**	**4**	**3**	**2**	**4**	**1**	**7**	**0**	**3**	**0**	

Table 9. 'Summary of findings' table

COMPARISON:	Removal from exposure versus continued exposure				Reduction of exposure versus continued exposure				Removal from exposure versus reduction of exposure			
Number of included studies	15				6				8			
PRIMARY OUTCOMES:	Effect size	95% confidence interval	Number of studies	Number of participants	Effect size	95% confidence interval	Number of studies	Number of participants	Effect size	95% confidence interval	Number of studies	Number of participants
Absence of asthma symptoms	RR 21.42	7.20 to 63.77	6	462	RR 5.35	1.40 to 20.48	4	148	RR 39.16	7.21 to 212.83	3	257
Improvement of asthma symptoms	RR 2.27	1.23 to 4.19	9	500					RR 1.27	0.84 to 1.92	5	140
												283 89
Change in FEV1% predicted follow-up minus baseline values	MD 5.52	2.99 to 8.06	8	806	MD 1.18	-2.96 to 5.32	2	181	MD 1.16	-7.51 to 9.84	4	284

Table 9. 'Summary of findings' table (*Continued*)

Change in NSBH follow-up minus baseline values	SMD 0.67	0.13 to 1.21	5	314								

MD: mean difference
RR: risk ratio
SMD: standardized mean difference

APPENDICES

Appendix 1. Search strategies

Workplace interventions for treatment of occupational asthma: Search strategies

Elizabeth Arnold, Trials Search Co-ordinator, Cochrane Airways Group, January 2009

CENTRAL

#1 MeSH descriptor Asthma explode all trees
#2 asthma*
#3 wheez*
#4 (#1 OR #2 OR #3)
#5 MeSH descriptor Occupational Health, this term only
#6 MeSH descriptor Occupational Diseases, this term only
#7 MeSH descriptor Occupational Exposure, this term only
#8 MeSH descriptor Occupational Medicine, this term only
#9 MeSH descriptor Work explode all trees
#10 work*
#11 occupation*
#12 (#5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11)
#13 (#4 AND #12)

MEDLINE

Occupational asthma/RCT search	Occupational asthma/non-RCT search
1. exp Asthma/	1. exp Asthma/
2. asthma$.mp.	2. asthma$.mp.
3. wheez$.mp.	3. wheez$.mp.
4. or/1-3	4. or/1-3
5. Occupational Health/	5. Occupational Health/
6. Occupational Diseases/	6. Occupational Diseases/
7. Occupational Exposure/	7. Occupational Exposure/
8. Occupational Medicine/	8. Occupational Medicine/
9. exp Work/	9. exp Work/
10. work$.mp.	10. work$.mp.
11. occupation$.mp.	11. occupation$.mp.
12. or/5-11	12. or/5-11
13. 4 and 12	13. 4 and 12
14. (clinical trial or controlled clinical trial or randomized controlled trial).pt	14. effectiveness.mp.
15. (randomized or randomised).ab,ti.	15. effect$.ti.
16. placebo.ab,ti.	16. program.mp.
17. dt.fs.	17. intervention.mp.
18. randomly.ab,ti.	18. reduction.mp.
19. trial.ab,ti.	19. evaluation.mp.
20. groups.ab,ti.	20. decrease$.mp.
21. or/14-20	21. measures.mp.
22. Animals/	22. improve$.ab,ti.
23. Humans/	23. Comparative Study/
24. 22 not (22 and 23)	24. pc.fs.
25. 21 not 24	25. or/14-24.
26. 25 and 13	26. Animals/
	27. Humans/
	28. 26 not (26 and 27)
	29. 25 not 28
	30. 13 and 29

EMBASE

Occupational asthma/RCT search	Occupational asthma/non-RCT search
1. exp Asthma/	1. exp Asthma/
2. asthma$.mp.	2. asthma$.mp.
3. wheez$.mp.	3. wheez$.mp.
4. or/1-3	4. or/1-3
5. occupational health/	5. occupational health/
6. Occupational Exposure/	6. Occupational Exposure/

(*Continued*)

7. Occupational Disease/ 8. occupational medicine/ 9. occupational hazard/ 10. exp work/ 11. occupation$.mp. 12. work$.mp. 13. or/5-12 14. 4 and 13 15. Randomized Controlled Trial/ 16. Controlled Study/ 17. randomization/ 18. Double Blind Procedure/ 19. Single Blind Procedure/ 20. Clinical Trial/ 21. Crossover Procedure/ 22. follow-up/ 23. exp prospective study/ 24. or/15-23 25. (clinica$ adj3 trial$).mp. 26. ((singl$ or doubl$ or trebl$ or tripl$) adj5 (mask$ or blind$ or method$)).mp 27. exp Placebo/ 28. placebo$.mp. 29. random$.mp. 30. (latin adj3 square$).mp. 31. exp Comparative Study/ 32. ((control$ or prospectiv$ or volunteer$) adj3 (trial$ or method$ or stud$)).mp 33. (crossover$ or cross-over$).mp. 34. or/25-33 35. 24 or 34 36. exp ANIMAL/ 37. Nonhuman/ 38. Human/ 39. 36 or 37 40. 39 not 38 41. 35 not 40 42. 14 and 41	7. Occupational Disease/ 8. occupational medicine/ 9. occupational hazard/ 10. exp work/ 11. occupation$.mp. 12. work$.mp. 13. or/5-12 14. 4 and 13 15. effectiveness.mp. 16. effect$.ti. 17. program.mp. 18. intervention.mp. 19. reduction.mp. 20. evaluation.mp. 21. decrease$.mp. 22. measures.mp. 23. improve$.ab,ti. 24. pc.fs. 25. or/15-24 26. exp Animal/ 27. Nonhuman/ 28. Human/ 29. 26 or 27 30. 29 not 28 31. 25 not 30

NIOSHTIC-2

((effectiveness OR effect* OR program* OR compare* OR intervention OR reduction OR evaluation OR decrease* OR measures OR improve* OR prevention OR random*) AND asthma* or wheez*) AND occupation* or work*

CISDOC

ANY/
(**asthma*** or **wheez***) and **ANY/**(**effect*** or **control*** or **evaluation*** or **program*** or **prevention*** or **random***) and **ANY/**(**occupation)**

Cochrane Airways Groups Trials Register

For locating relevant studies in the Airways Groups trials register we used the following search strategy:
occupational OR *occupation* OR *workplace* OR *work-place* OR *farm** OR *swine* OR *baker* OR *flour OR wheat OR latex* OR *isocyanate** OR *glutaraldehyde* OR *textile** OR *solder** OR *welder** OR *"dust inhal*"* OR *"dust expos*"* OR *mining* OR *miner* OR *miners* OR *coal*

Appendix 2. Quality according to GRADE

Grades of Recommendation, Assessment, Development and Evaluation Working Group **(GRADE)**
Type of evidence
Randomised 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.

Appendix 3. Search results count April 2009

Workplace interventions for treatment of occupational asthma: Results count April 2009

Elizabeth Arnold, Trials Search Co-ordinator, Cochrane Airways Group

Search	Number of hits
CENTRAL	472
MEDLINE - RCT search	1931
MEDLINE - non-RCT search	3735 (2581 minus duplicates from RCT search)
EMBASE - RCT search	3132
EMBASE - non-RCT search	3701 (2105 minus duplicates from RCT search)
NIOSHTIC-2	1221
CISDOC	573
HSELINE	No access

(*Continued*)

Total (after de-duplication and not including CISDOC results)	9141
HSELINE and CISDOC	1186

Appendix 4. Search Strategy and Results April 2010

Susan Hansen, Trials Search Co-ordinator, Cochrane Airways Group
occupational or occupation or workplace or work-place or farm* or swine or baker or flour or wheat or latex or isocyanate* or glutaraldehyde or textile* or solder* or welder* or "dust inhal*" or "dust expos*" or mining or miner or miners or coal
Results: 8 hits

Appendix 5. Search strategies and results count February 2011

By Leena Isotalo, MSc, Information Specialist, Trials Search Co-ordinator, Cochrane Occupational Safety and Health Review Group
Central Search Results 10.2.2011/LI

ID	Search	Hits
#1	MeSH descriptor **Asthma** explode all trees	8814
#2	asthma*	21229
#3	wheez*	1131
#4	(#1 OR #2 OR #3)	21608
#5	MeSH descriptor **Occupational Health**, this term only	357
#6	MeSH descriptor **Occupational Diseases**, this term only	714
#7	MeSH descriptor **Occupational Exposure**, this term only	379
#8	MeSH descriptor **Occupational Medicine**, this term only	60
#9	MeSH descriptor **Work** explode all trees	242
#10	work*	29544
#11	occupation*	6193
#12	(#5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11)	32858

(*Continued*)

#13	(#4 AND #12)	1073
#14	(#13), from 2009 to 2011	41

MEDLINE (PubMed) search results 16 Feb 2011/LI

Search	Queries	Result
#22	Search **#14 OR #20**	571
#21	Search **#20 NOT #14**	327
#20	Search **#18 OR #19**	481
#19	Search **(#17) AND "2009/01/01"[Entrez Date] : "3000"[Entrez Date]**	463
#18	Search **#17** Limits: **Publication Date from 2009/01/01**	472
#17	Search **#16 NOT #8**	4223
#16	Search **#6 AND #15**	4351
#15	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]**	6283537
#14	Search **#11 OR #13**	244
#13	Search **(#10) AND "2009/01/01"[Entrez Date] : "3000"[Entrez Date]**	234
#11	Search **#10** Limits: **Publication Date from 2009/01/01**	235
#12	Search **#10**	2120
#10	Search **#9 NOT #8**	2120
#9	Search **#6 AND #7**	2173
#8	Search **animals[mh] NOT humans[mh]**	3536009
#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]**	2751417

(*Continued*)

#6	Search **#1 AND #5**	9799
#5	Search **#2 OR #3 OR #4**	883355
#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]**	883355
#3	Search **work[mesh]**	11286
#2	Search **"Occupational Health"[Mesh] OR "Occupational Diseases"[Mesh:NoExp] OR "Occupational Exposure"[Mesh:NoExp] OR "Occupational Medicine"[Mesh]**	130016
#1	Search **asthma[mh] OR asthma*[tw] OR wheez*[tw]**	122609

EMBASE (embase.com) Search results 16Feb 2011/LI

No.	Query	Results
#59	**#44** OR **#57**	**1217**
#58	**#57** NOT **#44**	**508**
#57	**#56** NOT **#43**	**917**
#56	**#17** AND **#55**	**940**
#55	**#45** OR **#46** OR **#47** OR **#48** OR **#49** OR **#50** OR **#51** OR **#52** OR **#53** OR **#54**	**6046507**
#54	**'prevention and control'**	**1115457**
#53	**improve***:ab,ti	**1179898**
#52	**measures**	**397644**
#51	**decrease***	**1530108**
#50	**'evaluation'**/exp	**155138**
#49	**reduction**	**840831**
#48	**intervention**	**335557**

(*Continued*)

#47	**program**	**654834**
#46	**effect***:ti	**1494989**
#45	**effectiveness**	**307753**
#44	**#40** NOT **#43**	**709**
#43	**#41** NOT **#42**	**4119663**
#42	**'human'**:de	**12301470**
#41	**'animal'**/exp OR **'nonhuman'**/exp	**5167288**
#40	**#17** AND **#39**	**753**
#39	**#27** OR **#38**	**5411372**
#38	**#28** OR **#29** OR **#30** OR **#31** OR **#32** OR **#33** OR **#34** OR **#35** OR **#36** OR **#37**	**2444817**
#37	**cross** NEXT/1 **over***	**17960**
#36	**crossover***	**51755**
#35	((**control*** OR **prospectiv*** OR **volunteer***) NEAR/3 (**trial*** OR **method*** OR **stud***)):ab,ti	**559218**
#34	**'comparative study'**/exp	**883255**
#33	**latin** NEXT/3 **square***	**3248**
#32	**random***:ab,ti	**618527**
#31	**placebo***:ab,ti	**156331**
#30	**'placebo'**/exp	**185268**
#29	(**singl*** OR **doubl*** OR **trebl*** OR **tripl***) NEXT/5 (**mask*** OR **blind*** OR **method***)	**189493**
#28	**clinical*** NEXT/3 **trial***	**957670**
#27	**#18** OR **#19** OR **#20** OR **#21** OR **#22** OR **#23** OR **#24** OR **#25** OR **#26**	**4324371**
#26	**'prospective study'**/exp	**156778**
#25	'follow-up':de	**502015**

(*Continued*)

#24	**'crossover procedure'**:de	**28872**
#23	**'clinical trial'**:de	**827304**
#22	**'single blind procedure'**:de	**12996**
#21	**'double blind procedure'**:de	**99000**
#20	**randomization**:de	**51765**
#19	**'controlled study'**:de	**3435065**
#18	**'randomized controlled trial'**:de	**278456**
#17	**#15** OR **#16**	**1914**
#16	**#14** AND [embase]/lim AND [1-1-2009]/sd	**1914**
#15	**#14** AND [embase]/lim AND [2009-2011]/py	**1776**
#14	**#4** AND **#13**	**14365**
#13	**#5** OR **#6** OR **#7** OR **#8** OR **#10** OR **#11** OR **#12**	**1076661**
#12	**work***:ab,ti	**838776**
#11	**occupation***:ab,ti	**117515**
#10	**'work'**/exp	**194387**
#8	**'occupational medicine'**:de	**20687**
#7	**'occupational disease'**:de	**49961**
#6	**'occupational exposure'**:de	**55019**
#5	**'occupational health'**:de	**40827**
#4	**#1** OR **#2** OR **#3**	**184113**
#3	**wheez***	**14012**
#2	**asthma***	**178835**
#1	**'asthma'**/exp	**150074**

NIOSHTIC-2 (OSH UPDATE) search result (118 references) 11.2.2011/LI

#1	GW{asthma* OR wheez*}
#2	GW{effect* OR program* OR compare* OR intervention OR reduction OR evaluation OR decrease* OR measures OR improve* OR prevention OR random*}
#3	#1 AND #2
#4	DC{OUNIOS}
#5	#3 AND #4
#6	PY{2008 OR 2009 OR 2010 OR 2011}
#7	#5 AND #6
#8	GW{occupation* OR work*}
#9	#7 AND #8

GW denotes All fields
DC denotes Database Code
CISDOC (OSH UPDATE) search result (19 references) 11.2.2011/LI

#1	GW{asthma* OR wheez*}
#2	GW{effect* OR control* OR evaluation* OR program* OR prevention* OR random*}
#3	DC{OUCISD}
#4	#1 AND #2
#5	PY{2008 OR 2009 OR 2010 oR 2011}
#6	#4 AND #5
#7	#3 AND #6
#8	GW{occupation* OR work*}
#9	#7 AND #8

GW denotes All fields
DC denotes Database Code
NUMBER OF HITS

Date	Database	Saved searches/ No. Query	number of hits	results/comments
7.2.2011	PubMed RCT Publication Date from 2009/01/01 OR 2009/01/01"[Entrez Date]	CR WORK-AST (RCT+non-RCT without time limits, My NCBI)	234 +7	results (in MEDLINE-format): pubmed˙result234.txt
	PubMed - non RCT		470 +6 (321+2)	pubmed˙result321.txt pubmed˙result9.txt
9.2.2011	EMBASE RCT [2009-2011/py] OR records added from [1-1-2009]	#44	644 + 61	Embase644.ris
	EMBASE RCT non-MEDLINE	#46	424	Embaseonly424.ris
	EMBASE NON-RCT	#61	845 + 67 (474 + 32)	EmbNON-RCT474.ris Embaseplus93.ris
	EMBASE NON-RCT non-MEDLINE	#63	(379)	EmbonlyNON˙RCT379.ris
10.2.2011	Central From 2009 to 2011		41	Centralfrom2009.txt (export from the Cochrane Library)
10.2.2011	COHF 2008- (asthma* OR wheez*)		0	
11.2.2011	NIOSHTIC-2 (OSH UPDATE) PY 2008-2011		118	NIOSHTIC-2.html NIOSHTIC-2RIS118.txt
11.2.2011	CISDOC (OSH UPDATE) PY 2008-2011		19	CISDOC.html CISDOCris19.txt
14.2.2011	yellow marked entrez date updates above			

WHAT'S NEW

Last assessed as up-to-date: 17 March 2011.

Date	Event	Description
6 May 2009	Amended	A new team of authors has conducted the review (change from protocol). Changes have been made to the methods

HISTORY

Protocol first published: Issue 1, 2007

Review first published: Issue 5, 2011

Date	Event	Description
1 October 2008	Amended	Converted to new review format.

CONTRIBUTIONS OF AUTHORS

GG conceived and co-ordinated the review process, selected studies, assessed quality, extracted data and wrote and edited the text of the review.

TP selected studies, assessed quality and extracted data.

JV advised on methodological aspects, such as quality assessment data extraction, data analysis and formulating conclusions.

JB selected studies, assessed quality, extracted data and edited the text of the review.

SM extracted the data from the articles written in the Italian language.

ST, SM and MFD participated in data extraction and commented on drafts of the review.

DECLARATIONS OF INTEREST

No conflicts of interest.

SOURCES OF SUPPORT

Internal sources

- Netherlands Center for Occupational Diseases, Netherlands.

External sources

- Grant, Dutch Government, Netherlands.
- Cochrane Occupational Health Field, Finland.
- Dutch Cochrane Centre, Netherlands.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We initially intended to include before and after studies that did not use a specific control group. We identified more than 50 such articles but found it was not possible to include them in our analyses. It would have required additional analyses to include these articles. As such analyses were performed quite recently by Rachiotis 2007 we decided to concentrate on articles with an intervention group and a control group.

Intervention: we included studies where the intervention comprised transferring the worker to a different area within the same or another company, or assigning the worker to different tasks as a reduction of exposure. This was the intervention in 10 of the included articles.

We considered employment outcomes as an adverse effect of the interventions.

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