Received: 10 September 2020 | Revised: 20 November 2020 | Accepted: 24 November 2020

DOI: 10.1002/ajim.23208

BRIEF REPORT

AMERICAN JOURNAL OF INDUSTRIAL MEDICINE WILEY

The effectiveness of removal from exposure and reduction of exposure for managing occupational asthma: Summary of an updated Cochrane systematic review

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

[1]Respiratory Health Division, National Institute for Occupational Safety and Health, Morgantown, West Virginia, USA

[2]Department of Epidemiology, Human Genetics and Environmental Sciences, School of Public Health, The University of Texas Health Science Center at Houston, Houston, Texas, USA

[3]Department of Epidemiology, Fay W. Boozman College of Public Health, University of Arkansas for Medical Sciences, Little Rock, Arkansas, USA

[4]Netherlands Center of Occupational Diseases, Academic Medical Center, Coronel Institute of Occupational Health, Amsterdam, The Netherlands

[5]Department of Medicine, University of Alberta, Edmonton, Alberta, Canada

[6]Department of Medicine and Dalla Lana School of Public Health, University of Toronto, Toronto, Ontario, Canada

[7]Department of Medical and Surgical Sciences, University of Bologna, Bologna, Italy

Correspondence

Paul K. Henneberger, MPH, ScD, Respiratory Health Division, National Institute for Occupational Safety and Health, 1000 Frederick Ln, Morgantown, WV 26508, USA.
Email: phenneberger@cdc.gov

Abstract

Background: The objective was to update the 2011 Cochrane systematic review on the effectiveness of workplace interventions for the treatment of occupational asthma.

Methods: A systematic review was conducted with the selection of articles and reports through 2019. The quality of extracted data was evaluated, and meta-analyses were conducted using techniques recommended by the *Cochrane Handbook for Systematic Reviews of Interventions*.

Results: Data were extracted from 26 nonrandomized controlled before-and-after studies. The mean number of participants per study was 62 and the mean follow-up time was 4.5 years. Compared with continued exposure, removal from exposure had an increased likelihood of improved symptoms and change in spirometry. Reduction of exposure also had more favorable results for symptom improvement than continued exposure, but no difference for change in spirometry. Comparing exposure removal to reduction revealed an advantage for removal with both symptom improvement and change in spirometry for the larger group of patients exposed to low-molecular-weight agents. Also, the risk of unemployment was greater for exposure removal versus reduction.

Conclusions: Exposure removal and reduction had better outcomes than continued exposure. Removal from exposure was more likely to improve symptoms and spirometry than reduction among patients exposed to low-molecular-weight agents. The potential benefits associated with exposure removal versus reduction need to be weighed against the potential for unemployment that is more likely with removal from exposure. The findings are based on data graded as very low quality, and additional studies are needed to generate higher quality data.

KEYWORDS

asthma management, exposure reduction, exposure removal, interventions at work, work-related asthma

Paul K. Henneberger and Jenil R. Patel are joint first authors.

1 | INTRODUCTION

Work-related asthma includes (i) occupational asthma (OA), which is caused by workplace exposures, and (ii) work-exacerbated asthma, in which workplace exposures worsen existing or concurrent asthma. A recent literature review concluded that 16% of adult-onset asthma is attributable to occupation,[1] although this is likely an underestimate. Both sensitizers and irritants are known to cause OA. Sensitizer-induced asthma is characterized by an immunologic-mediated sensitization to a workplace agent and can result from exposure to either high-molecular-weight (HMW) agents (e.g., animal or vegetable proteins) or low-molecular-weight (LMW) agents (e.g., diisocyanates, plicatic acid from western red cedar).[2] Irritant-induced OA has typically been characterized by onset shortly after high-level exposure to respiratory irritants (e.g., chlorine gases),[3] although it might also result from chronic low- to moderate-level irritant exposures.[4] Over 300 workplace agents are known to cause OA and can occur in a variety of occupations and industries.[5] OA can have a profound adverse impact on a patient's quality of life, employment status, and income.[6,7]

A 2011 Cochrane systematic review evaluated the effectiveness of workplace interventions on the outcome of OA.[8] When compared with continued exposure, both removal from exposure and reduction of exposure increased the likelihood of subsequently reporting an absence of symptoms, but only removal was associated with improvement in the forced expiratory volume in 1 s as the percentage of a predicted or reference value (FEV1%). When compared with reduction of exposure, removal from exposure increased the likelihood of an absence of symptoms but not of improvement in FEV1%. Unfortunately, unemployment was also more likely after removal from exposure compared with exposure reduction.

Several studies of workplace interventions for OA were published after the 2011 review. With a comprehensive approach of including recently published studies,[9–12] along with those studies already identified in the 2011 Cochrane review, we produced an updated systematic review of evidence on the effectiveness of workplace interventions for the treatment of OA.[13]

2 | MATERIALS AND METHODS

We searched relevant publications in the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE (PubMed), EMBASE (Ovid), NIOSHTIC-2, and CISILO (CCOHS) up to July 31, 2019. We looked for but did not find any randomized controlled trials or interrupted time-series of workplace interventions. However, we identified nonrandomized controlled before-and-after studies. We included studies evaluating workplace interventions that eliminated or reduced OA patients' exposure at work and excluded studies that investigated the effects of medication only or medical monitoring/surveillance. The primary health outcomes of interest were changes in asthma symptoms, FEV1%, and nonspecific bronchial hyperreactivity (NSBH) from baseline to follow-up. Two authors worked independently to assess study eligibility and risk of bias, and extract data.

We combined the extracted health results from eligible studies in meta-analyses and calculated statistics using techniques recommended by the *Cochrane Handbook for Systematic Reviews of Interventions*.[14] Most results from the meta-analyses were reported as a risk ratio (RR), mean difference (MD), or a standardized mean difference (SMD), each with a 95% confidence interval (95% CI). We contacted authors if their publications lacked required statistical information or did not clearly describe the calculations in their studies. We used the I^2 statistic to test statistical heterogeneity in the meta-analyses, interpreting values of $I^2 > 50\%$ to indicate substantial heterogeneity. We used funnel plots to evaluate publication bias when at least five studies were available for this analysis and checked whether papers had overlapping study samples. We evaluated the quality of evidence for the different outcomes using the GRADE approach.[15]

3 | RESULTS

We included 26 observational, non-randomized controlled before-and-after-studies with 1695 participants that reported on 36 comparisons used in the meta-analyses. Only three of the 26 studies were designed as intervention studies. For different comparisons, we identified 18 studies of removal from exposure versus continued exposure; 7 reduction of exposure versus continued; and 10 removal from exposure versus reduction. The types of agents investigated were HMW in 5 studies, LMW in 15 studies, both HMW and LMW in 5 studies, and pot room gases in 1 study. Sample sizes ranged from nine to 232 participants with a median of 41 and a mean of 62. The follow-up times for the 26 studies had a mean of 4.5 years, median of 3.2 years, and range 5 weeks to 12 years. Median durations were 5.6 years for exposure before symptoms (reported by 10 studies) and 3.8 years for symptoms before diagnosis (reported by 13 studies). The diagnosis of OA was based on a specific inhalation challenge with the suspected workplace agent in 20 studies.

The relative effects of workplace interventions on health outcomes are presented in Table 1. When compared with continued exposure, removal from exposure had a greater likelihood of the absence of symptoms (RR, 4.80; 95% CI, 1.67 to 13.86), improvement of symptoms (RR, 2.47; 95% CI, 1.26 to 4.84), better change in FEV1% (MD, 4.23 percentage points; 95% CI, 1.14 to 7.31), and improved NSBH (SMD, 0.43; 95% CI, 0.03 to 0.82; Table 1). The comparison of reduction of exposure to continued exposure revealed a greater likelihood of absence of symptoms (RR, 2.65; 95% CI, 1.24 to 5.68) and no difference for change in FEV1%. No data were available to analyze symptom improvement and change in NSBH. Based on all available studies, the comparison of removal from exposure to the reduction of exposure showed no statistically significant differences for symptoms or FEV1%, and a lack of data for NSBH (Table 1). However, the subset of studies on exposure to LMW agents showed more favorable results for exposure removal versus

TABLE 1 Relative effects of workplace interventions for occupational asthma on the absence of asthma symptoms, improvement of asthma symptoms, change in FEV1%, and change in NSBH, for three different comparisons[a]

	Comparisons					
	Removal from exposure versus continued exposure		Reduction of exposure versus continued exposure		Removal from exposure versus reduction of exposure	
Outcome	Relative effect (95% CI)	Number of participants (studies)	Relative effect (95% CI)	Number of participants (studies)	Relative effect (95% CI)	Number of participants (studies)
Absence of asthma symptoms	RR, 4.80 (1.67 to 13.86)	641 (9 observational studies)	RR, 2.65 (1.24 to 5.68)	334 (7 observational studies)	RR, 6.05 (0.86 to 42.34)	359 (6 observational studies)
Improvement of asthma symptoms	RR, 2.47 (1.26 to 4.84)	435 (9 observational studies)	[b]	[b]	RR, 1.11 (0.84 to 1.47)	140 (5 observational studies)
Change in FEV1% predicted: FU minus baseline values	MD, 4.23 percentage points (1.14 to 7.31)	898 (10 observational studies)	MD, 2.76 percentage points (−1.53 to 7.04)	224 (4 observational studies)	MD, 2.58 percentage points (−3.02 to 8.17)	388 (7 observational studies)
Change in NSBH: FU minus baseline values	SMD, 0.43 (0.03 to 0.82)	387 (6 observational studies)	[b]	[b]	[b]	[b]

Abbreviations: CI, confidence interval; FEV1%, forced expiratory volume in one second as the percentage of a predicted or expected value; FU, follow-up; MD, mean difference; NSBH, nonspecific bronchial hyperreactivity; RR, risk ratio; SMD, standardized mean difference.

[a]Contents of table based on the three tables in the Summary of Findings section of the 2019 Cochrane review "Workplace interventions for treatment of occupational asthma."[13] We rated the quality of the evidence as very low for all outcomes in this table. See original document for details.

[b]No studies reported or enabled the calculation of the outcome for this comparison.

reduction for the absence of symptoms (RR, 9.31; 95% CI, 1.56 to 55.73), improvement of symptoms (RR, 1.61; 95% CI, 1.02 to 2.53), and change in FEV1% (MD, 5.79 percentage points; 95% CI, 0.02 to 11.56; Table 1).

Based on data from two studies, the risk of unemployment after removal from exposure was increased compared with the reduction of exposure, with RR, 14.28 (95% CI, 2.06 to 99.16). Also, four studies reported a decrease in income varying from 20% to 50% after removal from exposure.

4 | DISCUSSION

All studies in the current systematic review were observational and had a high risk of bias along with unexplained heterogeneity in study results. Therefore, we graded the quality of this evidence as "very low" for all outcomes.

We concluded that both removal from exposure and reduction of exposure for OA patients may improve asthma symptoms compared with continued exposure. While not observed for reduction of exposure, studies of removal from exposure indicated improved lung function compared with continued exposure. The direct comparison of removal from exposure to the reduction of exposure revealed that removal may improve symptoms and lung function among OA patients exposed to LMW agents, but this was not apparent among the relatively small group of reported cases exposed to HMW agents or both HMW and LMW agents. Due to the smaller sample size and overall lower graded quality of evidence, we do not recommend any change to clinical practice advice to remove exposure in HMW OA based on our findings. Unfortunately, removal from exposure may also increase the risk of unemployment compared with reduction of exposure. Considering these findings, care providers should carefully balance the potential clinical benefits of removal from exposure or reduction of exposure with potentially detrimental effects of unemployment while addressing management options.

Additional high-quality studies are needed to evaluate the effectiveness of workplace interventions for OA. Randomizing OA patients to removal from exposure, reduction of exposure, and continued exposure would likely be rejected by most ethics committees and treating physicians. Alternatively, improvements in methods for before and after studies are possible if not always easy. For example, there are opportunities to improve the methods for gathering information about respiratory symptoms. Summary estimates for improvement of symptoms (Table 1) were based on 9 articles for removal versus continued exposure and 5 articles for removal versus reduction of exposure, which together accounted for 11 unique articles. Three investigations used questions based on a validated questionnaire, three used questionnaires of unclear origin, and five used interviews with no mention of the questions used. Subsequent studies could produce more reliable results by using validated and standardized questions about respiratory symptoms. Examples of additional improvements include prospective enrollment of newly diagnosed OA cases for longitudinal follow-up, following all participants at the same intervals since diagnosis, and collecting more details about socioeconomic impact.

While the current review addressed the treatment of OA, it is important to note that primary prevention is possible. Recommendations from the European Respiratory Society Task Force on the Management of Work-Related Asthma identified exposure elimination as the preferred approach to primary prevention of OA, with exposure reduction as the next best option.[16]

ACKNOWLEDGMENTS

The authors thank the Cochrane organization for innumerable acts of support during the preparation of the 2019 systematic review. The only funding the study received was from the National Institute for Occupational Safety and Health, Morgantown, WV, The University of Texas Health Science Center at Houston, Houston, TX, University of Arkansas for Medical Sciences, Little Rock, AR, Coronel Institute of Occupational Health, Amsterdam, The Netherlands, University of Alberta, Edmonton, Alberta, Canada, University of Toronto, Toronto, Ontario, Canada, and University of Bologna, Bologna, Italy that supported the salaries of the authors.

CONFLICTS OF INTEREST

The authors declare that there are no conflicts of interest.

DISCLOSURE BY AJIM EDITOR OF RECORD

John D. Meyer declares that he has no conflict of interest in the review and publication decision regarding this article.

AUTHOR CONTRIBUTIONS

Paul K. Henneberger and Jenil R. Patel contributed equally to writing, reviewing, and finalizing this report, which is based on the original Cochrane review that is referenced. Gerda J. de Groene, Jeremy Beach, Susan M. Tarlo, Teake M. Pal, and Stefania Curti reviewed and contributed to the content, wording, and finalization of this report.

DATA AVAILABILITY STATEMENT

Data used in this brief summary of a systematic review are available from published articles that are referenced in the current article or the parent document.

DISCLAIMER

The findings and conclusions in this report are those of the authors and do not necessarily represent the views of the National Institute for Occupational Safety and Health.

ORCID

Paul K. Henneberger http://orcid.org/0000-0001-8796-5005
Jenil R. Patel http://orcid.org/0000-0002-4875-7390
Gerda J. de Groene https://orcid.org/0000-0002-3797-6571
Susan M. Tarlo https://orcid.org/0000-0002-4746-5310

REFERENCES

1. Blanc PD, Annesi-Maesano I, Balmes JR, et al. The occupational burden of nonmalignant respiratory diseases: an official American Thoracic Society and European Respiratory Society statement. *Am J Respir Crit Care Med*. 2019;199(11):1312-1334. https://doi.org/10.1164/rccm.201904-0717ST
2. Cormier M, Lemiere C. Occupational asthma. *Int J Tuberc Lung Dis*. 2020;24(1):8-21. https://doi.org/10.5588/ijtld.19.0301
3. Brooks SM, Weiss MA, Bernstein IL. Reactive airways dysfunction syndrome (RADS). Persistent asthma syndrome after high level irritant exposures. *Chest*. 1985;88(3):376-384. https://doi.org/10.1378/chest.88.3.376
4. Dumas O, Le Moual N. Do chronic workplace irritant exposures cause asthma? *Curr Opin Allergy Clin Immunol*. 2016;16(2):75-85. https://doi.org/10.1097/ACI.0000000000000247
5. CNESST. Occupational asthma. List of agents causing occupational asthma with references. http://www.csst.qc.ca/en/prevention/reptox/occupational-asthma/Documents/AgentsAnglais.pdf. Accessed November 17, 2018.
6. Knoeller GE, Mazurek JM, Moorman JE. Health-related quality of life among adults with work-related asthma in the United States. *Qual Life Res*. 2013;22(4):771-780. https://doi.org/10.1007/s11136-012-0206-7
7. Vandenplas O. Socioeconomic impact of work-related asthma. *Expert Rev Pharmacoecon Outcomes Res*. 2008;8(4):395-400. https://doi.org/10.1586/14737167.8.4.395
8. de Groene GJ, Pal TM, Beach J, et al. Workplace interventions for treatment of occupational asthma. *The Cochrane Database Syst Rev*. 2011;5:CD006308. https://doi.org/10.1002/14651858.CD006308.pub3
9. Di Giampaolo L, Cavallucci E, Braga M, et al. The persistence of allergen exposure favors pulmonary function decline in workers with allergic occupational asthma. *Int Arch Occup Environ Health*. 2012;85(2):181-188. https://doi.org/10.1007/s00420-011-0653-4
10. Munoz X, Viladrich M, Manso L, et al. Evolution of occupational asthma: does cessation of exposure really improve prognosis? *Respir Med*. 2014;108(9):1363-1370. https://doi.org/10.1016/j.rmed.2014.08.001
11. Talini D, Novelli F, Bacci E, et al. Mild improvement in symptoms and pulmonary function in a long-term follow-up of patients with toluene diisocyanate-induced asthma. *Int Arch Allergy Immunol*. 2013;161(2):189-194. https://doi.org/10.1159/000338993
12. Talini D, Novelli F, Melosini L, et al. May the reduction of exposure to specific sensitizers be an alternative to work cessation in occupational asthma? Results from a follow-up study. *Int Arch Allergy Immunol*. 2012;157(2):186-193. https://doi.org/10.1159/000327550
13. Henneberger PK, Patel JR, de Groene GJ, et al. Workplace interventions for treatment of occupational asthma. *Cochrane Database Syst Rev*. 2019;10:CD006308. https://doi.org/10.1002/14651858.CD006308.pub4
14. Higgins J, Green S. *Cochrane Handbook for Systematic Reviews of Interventions (version 5.1.0)*. The Cochrane Collaboration; 2011. http://handbook-5-1.cochrane.org/
15. Balshem H, Helfand M, Schünemann HJ, et al. GRADE guidelines: 3. Rating the quality of evidence. *J Clin Epidemiol*. 2011;64(4):401-406. https://doi.org/10.1016/j.jclinepi.2010.07.015
16. Heederik D, Henneberger PK, Redlich CA. Primary prevention: exposure reduction, skin exposure and respiratory protection. *Eur Respir J*. 2012;21(124):112-124. https://doi.org/10.1183/09059180.00005111

How to cite this article: Henneberger PK, Patel JR, de Groene GJ, et al. The effectiveness of removal from exposure and reduction of exposure for managing occupational asthma: Summary of an updated Cochrane systematic review. *Am J Ind Med*. 2021;64:165–169. https://doi.org/10.1002/ajim.23208