The relationship between cleaning product exposure and respiratory and skin symptoms among healthcare workers in a hospital setting: A systematic review and meta-analysis

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Abstract

Background and Aims: Several studies from multiple work settings have reported an increase in asthma and asthma-like respiratory symptoms in workers exposed to cleaning or disinfecting agents. Hospital workers perform many cleaning and disinfecting activities and may be vulnerable to respiratory and skin symptoms caused by these agents. This systematic review and meta-analysis aim to quantify the risk of asthma and asthma-like symptoms in hospital workers exposed to cleaning/disinfecting agents. A secondary aim is to assess associated risks of skin symptoms in those studies.

Methods: MEDLINE, EMBASE, CDSR, CENTRAL, CINAHL databases, and references of relevant review articles were searched. NHLBI quality assessment tools were used to assess the quality of the included studies. A total of 2550 articles were retrieved and 34 studies met criteria to be included. The software R version 4.0.5 was used to perform the meta-analysis. The random-effects model was used to pool the results due to within-studies heterogeneity.

Results: Meta-analysis of 10 studies evaluating the association between occupational cleaning exposures and asthma demonstrated a 35% increased risk in exposed hospital workers (meta-RR = 1.35, 95% CI: 1.09–1.68). The risk of asthma increased when workers were exposed to bleach compared with nonexposed workers (meta-RR = 1.51, 95% CI: 0.54–4.18), but was not statistically significant. Two studies investigated the relationship between respiratory and skin symptoms and produced mixed results.

Conclusions: The results suggest a need for preventive practices to reduce the risk of asthma and asthma-like symptoms in hospital workers exposed to occupational cleaning/disinfecting agents. Trial registration number: CRD42020137804.

KEYWORDS
asthma, cleaning, disinfecting agents, hospital workers, respiratory symptoms
1 INTRODUCTION

Cleaning and disinfecting tasks make up a significant portion of the duties of healthcare professionals and other workers in-hospital settings, especially to reduce risks of infection. These tasks can range from common housekeeping practices performed by cleaning staff, to surface and equipment cleaning and disinfection by healthcare workers such as nurses, respiratory therapists, physiotherapists, and radiographers. Multiple agents may be used for these tasks including quaternary ammonium compounds, bleach, and hydrogen peroxide. Cleaning and disinfection of endoscopes and surgical equipment may include use of potential respiratory sensitizers such as enzymes, and aldehydes such as glutaraldehyde or ortho-phthalaldehyde. Many of these tasks and agents have been associated with respiratory sensitization or irritation. Previous studies have reported an increased risk of asthma, asthma-like respiratory symptoms, as well as skin symptoms among healthcare workers exposed to cleaning or disinfecting agents. Specifically, bleach has been associated with asthma-like respiratory symptoms and hand dermatitis; however, few studies have evaluated the relationship between respiratory and skin symptoms. Additionally, previous evidence of increased respiratory and skin symptoms among this population was derived from self-reported measures of exposures. Therefore, there is a potential for bias toward reporting cleaning agents with stronger odors, causing uncertainty regarding the specific agents that may cause both respiratory and skin symptoms among hospital workers.

A recent systematic review conducted by Romero Starke et al. addressed a similar research question, the risk of obstructive respiratory diseases among healthcare workers exposed to cleaning or disinfecting agents compared with a nonexposed group; however, the review did not focus on all hospital workers and did not aim to evaluate skin symptoms among exposed healthcare workers with respiratory symptoms, nor to identify specific agents in the search strategy.

The aim of our study was to perform a comprehensive systematic review and meta-analysis of the available literature to quantify the risk of asthma and asthma-like symptoms in hospital workers exposed to cleaning or disinfecting agents. Furthermore, we aimed to identify risks of associated skin symptoms among the included studies, and the potential underlying causal agents.

2 METHODS

2.1 Literature search strategy and eligibility criteria

The systematic review was conducted following the PRISMA guidelines and the protocol was registered in PROSPERO (CRD42020137804) on April 28, 2020. The following electronic bibliographic databases were searched on October 5, 2017 and updated on August 9, 2021: Ovid MEDLINE, Ovid MEDLINE(R) ePUB Ahead of Print and In-Process & Other Non-Indexed Citations, EBM Reviews—Cochrane Database of Systematic Reviews (Ovid), EBM Reviews—Cochrane Central Register of Controlled Trials (Ovid), Embase (Ovid), and CINAHL (EBSCOhost). The search strategy consisted of using a combination of subject headings and free text terms for asthma, occupational exposures, healthcare personnel, and specific cleaning and disinfecting agents. Terms for asthma included such terms as asthma, wheeze, bronchial hyperreactivity, respiratory hypersensitivity, and airflow obstruction among others. Terms for workplace exposure included such terms as occupational disease, occupational exposure, work, occupation, job-site, and occupational air pollutants among others. Terms for healthcare workers included varied types of healthcare personnel and health facilities among others. Terms for cleaning products included terms for disinfectants, detergents, surface-active agents, ammonium compounds, anti-infective agents, acetic acid, 2-propanol, chloramines, phenols, and decontamination procedures among others (full search strategies are included in the Table S1). The search strategy was adapted for each database. Additional studies were found by examining the references of relevant reviews. All studies that evaluated respiratory outcomes, symptoms, diseases, or lung function measures in relation to occupational cleaning or disinfecting tasks or products in any hospital workers were included. Among the included studies, data regarding skin outcomes were also sought. Inclusion criteria were grouped according to the population-exposure-comparator-outcome (PECO) framework:

- Population—populations in which individuals worked in a hospital setting;
- Exposures—studies of individuals with exposure at work to cleaning and/or disinfecting agents;
- Comparators—studies reporting comparative effect estimates, specifically case-control or cohort studies reporting risk, rate, or odds across groups exposed to different levels of cleaning and/or disinfecting agents (including binary comparisons of exposed/unexposed), and across groups with and without asthma or asthma-like symptoms;
- Outcome—studies reporting incident asthma or asthma-like symptoms;
- Among subjects with asthma or asthma-like symptoms, the presence of reported skin symptoms was an additional outcome;
- English-language full-text available;
- Publication up to 6th August 2021.

We excluded studies that did not meet the inclusion criteria above. Randomized controlled trials, nonrandomized trials, cohort studies, and case control studies available in English were included. No restrictions regarding country, patient age, race, gender, and date were made. Case series, research in progress, conference proceedings, dissertations, books, editorials, letters, and review articles were excluded. Studies including occupational settings located outside of a medical centre or hospital were also excluded. A full list of inclusion and exclusion criteria is available in Table S2.
2.2 Selection process, data collection process, and quality assessment

Two reviewers independently screened the study titles and abstracts to exclude studies that did not meet the eligibility criteria. The full texts of the included studies were also screened independently by two reviewers. A consensus decision was made for disagreements regarding the inclusion of articles. If a disagreement was not resolved, a third reviewer was consulted for a final decision. Data extraction was completed independently by two reviewers using a modified form of the Cochrane Public Health Group Data Extraction and Assessment Template, adapted for this study according to the study aims and inclusion/exclusion criteria (Table S3). Two reviewers independently assessed the risk of bias in the included studies using the NHLBI quality assessment tools, suitable for the type of study, for example, observational cohort and cross-sectional studies (Table S4). A third reviewer was consulted for a final, deciding rating when there were quality assessment differences. The final scoring classification was ranked as poor, fair, or good.

2.3 Statistical methods for meta-analysis

Meta-analyses were considered to quantify the risk of respiratory and skin symptoms that are associated with cleaning and disinfecting agents. Studies included in the systematic review that received a “fair” or “good” quality score according to the NHLBI quality assessment tools were considered for the meta-analyses. The main reported effect measures between occupational exposure to cleaning or disinfecting products and asthma or asthma-like symptoms were pooled using the random-effects model. The random-effects model was chosen in consideration of the heterogeneity within the studies in terms of populations, age, and exposures. The Mantel-Haenszel method was used to calculate the weights of the studies. Higgins $I^2$ statistic was used to determine within-studies heterogeneity. A threshold of $I^2 \geq 50\%$ was used to determine substantial within-studies heterogeneity.$^7$ Subgroup analysis by study design was performed. Pooled risk ratio estimates were presented as meta-relative risks (RRs) and 95% CIs. Statistical significance was determined by a $p$-value of less than 0.05. The package “meta” in the software R version 4.0.5 was used to perform the meta-analysis.$^{10}$ Funnel plots and Egger’s test results were used to assess potential publication bias. Subgroup analyses were performed post-hoc to determine associations with different study classifications of asthma and asthma-like symptoms, and with specific reported exposures when comparable studies were available for meta-analyses.

3 RESULTS

A total of 2549 articles were retrieved from all databases, with one additional article identified through manual searching. There were 158 duplicate articles removed and 2315 articles excluded from title and abstract screening. The full texts of 77 articles were screened. A total of 34 articles met the study inclusion criteria. Reasons for the exclusion of studies are listed in the PRISMA flow diagram (Figure 1). Based on risk of bias assessments, most of the included studies received a “fair” quality score. Notably, one study received “poor” quality scores,$^4$ and four studies received “good” quality scores.$^{11-14}$ One study received a “good/fair” quality assessment score because it met 10 of 14 criteria, however, the participation rate and sample size was low, resulting in a “good/fair” quality assessment rating.$^{15}$ Overall, the quality of the studies was fair. There were no randomized controlled studies and most studies were cross-sectional. A quantitative meta-analysis was performed among ten “fair” or “good” quality studies evaluating the association between exposure to cleaning or disinfecting tasks or agents and asthma risk. A quantitative meta-analysis was also performed among three “fair” or “good” quality studies that evaluated the association between bleach exposure and asthma risk. Results of other studies could not be pooled due to important differences in how the exposures and outcomes were defined, or differences in the comparison groups used.

3.1 Asthma

Of the 34 studies meeting inclusion criteria, 23 studies investigated associations between occupational cleaning exposures and asthma. Tables 1 and 2 include the tasks and exposures reported in these studies. Only studies that investigated asthma as an outcome were included in this portion of the systematic review and Table 1. Twelve studies that investigated only asthma-like symptoms were summarized separately in Table 2. When studies investigated multiple outcomes, such as asthma, asthma-like symptoms, and skin symptoms, then they were included in each of the respective tables (Tables 1–3).

Five of the 23 studies were prospective and the remainder were cross-sectional or retrospective in design. Thirteen studies were performed in the United States of America,$^{12,13,15,16,18-20,23,24,27,29-31}$ and one study was performed in the United Kingdom$^{24}$ among healthcare and other hospital workers. Three studies were performed in Canada,$^{5,17,21}$ two studies were performed in France,$^{25}$ one study was performed in Sweden,$^{22}$ and one study collected data from participants located in ten European countries.$^{11}$ One study was performed in Australia$^{28}$ and one study was performed in the United States of America and Canada.$^{10}$ Occupational exposures to cleaning or disinfecting tasks or agents were assessed by self-report with the exception of five studies. Four studies used a job-exposure matrix (JEM) or a job task exposure matrix (JTEM) to estimate occupational exposure to cleaning agents$^{12,13,19,20}$ and one study used three methods to estimate exposure to cleaning agents: self-report, expert assessment, and an asthma-specific JEM.$^3$ With regard to outcome definitions for asthma, six studies used current asthma, described as presently having asthma.$^{1,16,23,26-28}$ Twelve studies used the definition of new-onset asthma, reported asthma, or post-hire asthma, that were defined as asthma onset diagnosed after entry into a healthcare profession.$^{5,11,12,17-21,24,25,29,35}$ One study used the definition of
adult-onset asthma, defined as asthma reported at 16 years of age or older. Two studies investigated asthma incidence in prospective cohort studies of female registered nurses. Last, one study assessed asthma control using the Asthma Control Test. All studies received a risk bias assessment score of “fair” or “good.”

Exposure to cleaning and disinfecting tasks or cleaning and disinfecting products was associated with increased asthma risk in most studies. An increase in the frequency of performed disinfection tasks from never or monthly to weekly or daily was associated with increased odds of new-onset asthma (odds ratio [OR] = 3.13, 95% CI: 1.05–9.35). The use of disinfectants to clean medical instruments was associated with poorly controlled asthma (OR = 1.37, 95% CI: 1.05–1.79) and very poorly controlled asthma (OR = 1.88, 95% CI: 1.38–2.56). Among asthmatic hospital workers, the most frequently reported exposure agents were glutaraldehyde (38%), latex (26%), and various cleaning products (15%). Latex is not a cleaning product; however, it may be used during cleaning tasks and can be a confounding factor when assessing the effects of cleaning and disinfecting agents on asthma risk. When considered separately, exposure to latex was associated with an increased risk of new-onset asthma and current asthma. Three studies reported that exposure to bleach significantly increased the risk of current, new-onset, or undiagnosed asthma among hospital workers. Similarly, one study also found that both latex and bleach exposures were associated with increased odds of new-onset asthma; however, these results were not statistically significant. Exposure to quaternary ammonium compounds was found to result in an increased risk of new-onset asthma among hospital workers. One study found that exposure to formaldehyde, glutaraldehyde, hypochlorite bleach, hydrogen peroxide, and enzymatic cleaners was associated with poor asthma control (p < 0.05 for all exposures), but exposure to alcohol and quaternary ammonium compounds was not associated with poor asthma control.

Several studies investigated glutaraldehyde as an occupational cleaning exposure. Dimich-Ward et al. found that hospital healthcare workers exposed to glutaraldehyde had an increased risk of new-onset asthma compared to unexposed healthcare workers.

![PRISMA flow diagram illustrating the process of screening and selecting articles related to occupational cleaning exposures and respiratory symptoms from a search of electronic bibliographic databases.](image-url)
| Author          | Country          | Period of data collection | Study design | Study population                                                                 | Type of exposure | Method of data collection | Covariates                          | Findings                                                                                     | Quality assessment score |
|-----------------|------------------|---------------------------|--------------|-----------------------------------------------------------------------------------|------------------|--------------------------|--------------------------------------|----------------------------------------------------------------------------------------------|--------------------------|
| Ellett et al.   | United States of America | 1995                      | Cross sectional | 3988 members of SGNA members exposed, 929 ASPAN members exposed, 830 ASPAN members nonexposed | Glutaraldehyde  | Questionnaire            | Age, gender, smoking status, prior health problems | No statistically significant differences in the number of respondents reporting asthma ($p < 0.592$) | Fair                     |
| Liss et al.     | Canada            | 2000–2001                 | Cross sectional | 1719 medical radiation technologists and a control group of 1848 physiotherapists | Cleaning tasks conducted by radiation technologists | Questionnaire, methacholine challenge test | Age, gender, smoking status           | Prevalence of new-onset asthma upon starting work in the profession was greater among medical radiation technologists: OR = 1.7 with a significant gender interaction ($p = 0.016$) Among females: age-adjusted OR = 1.3 (95% CI: 0.9–1.9) Among males: age-adjusted OR = 5.3 (95% CI: 1.4–20.2) | Fair                     |
| Dimich-Ward et al. | Canada           | 1999–2000                 | Cross sectional | 275 respiratory therapists and a control group of 628 physiotherapists | Occupation, work exposures (glutaraldehyde) | Questionnaire | Nasal allergies, time in profession, living with a smoker | Respiratory therapists tended to have a higher risk of having asthma attacks: OR = 2.6 (95% CI: 1.4–4.7) and asthma diagnosed after entering the profession: OR = 2.4 (95% CI: 1.2–4.7) Sterilizing instruments with glutaraldehyde-based instruments was associated with reported asthma: OR = 3.2 (95% CI: 11.1–9.3) | Fair                     |
| Pechter et al.  | United States of America | 1993–1997                | Cross sectional | 305 healthcare workers | Cleaning products (glutaraldehyde, formaldehydes, ammonia, bleach) | Interview | Age, gender, smoking status, occupation | Healthcare workers accounted for 16% of the confirmed cases of work-related asthma. Cases | Fair                     |
| Author          | Country          | Period of data collection | Study design     | Study population | Type of exposure                                                                 | Method of data collection                                        | Covariates                                                                 | Findings                                                                                                                                                                             | Quality assessment score |
|-----------------|------------------|---------------------------|------------------|------------------|----------------------------------------------------------------------------------|-------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------|
| Delclos et al.  | United States of America | 2003 | Cross sectional | 3650 health professionals | Cleaning products using an asthma risk factor JEM specifically for healthcare worker populations | Questionnaire, JEM, methacholine challenge test | Age, BMI, smoking status, occupation, race/ethnicity, atopy | Reported asthma medical instrument cleaning: OR = 2.22 (95% CI: 1.34–3.67); Surface cleaners: OR = 2.02 (95% CI: 1.20–3.40) | Good                     |
| Mirabelli et al. | 10 European countries | 1991–1999 | Population-based prospective cohort study (ECRHS-II) | 332 nurses and a reference population of 2481 administrative staff | Cleaning products (ammonia, bleach, liquid multiuse products, washing products, spray cleaning products) | Questionnaire | BMI, race/ethnicity | Compared with the reference group, an increased risk for new-onset asthma was observed among those using ammonia and/or bleach at work: RR = 2.16 (95% CI: 1.03–4.53); among those using liquid multi-use products at work: RR = 1.16 (95% CI: 0.61–2.19); among those using washing powders: RR = 1.65 (95% CI: 0.77–3.53); among any products in spray form: RR = 2.36 (95% CI: 0.99–5.64) | Good                     |
| Arif et al.     | United States of America | Not specified | Cross sectional | 3650 healthcare professionals | Cleaning tasks, use of powdered latex gloves, administration of aerosolised medications, use of adhesives/removers | Questionnaire | Age, gender, race/ethnicity, atopy, smoking status, BMI, seniority | Reported asthma Cleaning medical instruments: OR = 1.67 (95% CI: 1.06–2.62) General disinfectants and cleaning products: | Fair                     |
| Author                  | Country          | Period of data collection | Study design  | Study population | Type of exposure | Method of data collection | Covariates                              | Findings                                                                                      | Quality assessment                  |
|-------------------------|-------------------|---------------------------|---------------|------------------|------------------|--------------------------|------------------------------------------|---------------------------------------------------------------------------------------------|--------------------------------------|
| Delclos et al.\(^2\)    | United States of America | 2004                      | Cross sectional | 3650 healthcare workers | Occupational exposures (cleaning products, disinfectants) | Questionnaire | Age, seniority, gender, race/ethnicity, ever smoking, profession | As assessed by a JEM, current asthma was associated with cleaning products involved with instrument cleaning: PR = 1.19 (95% CI: 1.02–1.39) and powdered latex gloves: PR = 1.11 (95% CI: 0.95–1.32). | Fair |
| Author          | Country          | Period of data collection | Study design           | Study population                                                                 | Type of exposure                                                                 | Method of data collection | Covariates                                      | Findings                                                                 | Quality assessment score |
|-----------------|------------------|---------------------------|-------------------------|----------------------------------------------------------------------------------|----------------------------------------------------------------------------------|--------------------------|-----------------------------------------------|--------------------------------------------------------------------------|--------------------------|
| Kim et al.      | Sweden           | 2008                      | Cross sectional         | 429 healthcare workers exposed to cleaning tasks, 1727 healthcare workers not exposed to cleaning tasks, 10,030 nonhealthcare workers | Cleaning tasks                                                                 | Questionnaire            | Age                                           | Prevalence of adult-onset asthma was significantly higher among healthcare workers compared with nonhealthcare workers ($p = 0.003$) | Fair                     |
| Le Moual et al. | United States of America | 1992–2000                | Prospective cohort study| 1054 female operating room nurses and 7661 administrative nurses                  | Cleaning/disinfecting tasks                                                    | Questionnaire            | Age, race/ethnicity, smoking status, BMI, physician examinations | A significant association between operating room nursing and severe persistent asthma compared with administrative nursing: adjusted OR = 2.48 (95% CI: 1.06–5.77) | Fair                     |
| Walters et al.  | United Kingdom   | 1991–2011                 | Retrospective case series| 182 healthcare workers Glutaraldehyde, cleaning products, acrylates, formaldehyde, antimicrobial drugs | Specific allergen IgE, inhalation test, serial peak flow | Age, gender, BMI, occupation | There were 182 SHIELD notifications of occupational asthma in healthcare workers, representing 5%-19% of the annual notifications. | Fair |
| Author             | Country       | Period of data collection | Study design    | Study population | Type of exposure                                                                 | Method of data collection | Covariates                                                                 | Findings                                                                                                                                                                                                 | Quality assessment |
|--------------------|---------------|---------------------------|-----------------|------------------|----------------------------------------------------------------------------------|----------------------------|------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------|
| Gonzalez et al.    | France        | 2006–2007                | Cross sectional | 543 healthcare workers | Cleaning and disinfection tasks (quaternary ammonium compounds, chlorinated products/bleach, glutaraldehyde) | Questionnaire              | Age, gender, BMI, total number of years working in healthcare, smoking status | Healthcare workers had a higher risk of developing new-onset asthma when exposed to general disinfecting tasks: OR = 4.68 (95% CI: 1.08–20.22)                                                                 | Fair              |
| Casey et al.       | United States of America | Not specified            | Cross sectional | 78 disinfectant product users and 85 disinfectant product nonusers | Surface disinfectant product containing hydrogen peroxide, peracetic acid, and acetic acid | Questionnaire              | Age, gender, race/ethnicity, smoking                                          | No significant difference between current asthma diagnoses among product users and nonusers (p = 0.66). Highly exposed workers had a >3-fold excess of current asthma compared with the US population: SMR = 3.47 (95% CI: 1.48–8.13). | Fair              |
| Dumas et al.       | United States of America | 2014                     | Prospective cohort study | 4102 female registered nurses | Exposure to disinfectants (formaldehyde, glutaraldehyde, hypochlorite, bleach, hydrogen peroxide, alcohol, quats, enzymatic cleaners). | Questionnaires, Asthma Control Test, nurse-specific JTEM | Age, race, BMI, smoking status                                               | Disinfectant use to clean medical instruments was associated with poorly controlled asthma: OR = 1.37 (95% CI: 1.05–1.79) and very poorly controlled asthma: OR = 1.88 (95% CI: 1.38–2.56) (p<sub>prev</sub> = 0.004 after adjustment for potential confounders). Exposure to formaldehyde, glutaraldehyde, hypochlorite bleach, hydrogen peroxide, and enzymatic cleaners was | Good              |

Most frequently encountered agents: glutaraldehyde (38%), latex (26%), and cleaning products (15%).
| Author       | Country                  | Period of data collection | Study design         | Study population                                                                 | Type of exposure                                                                 | Method of data collection | Covariates                                           | Findings                                                                 | Quality assessment score |
|--------------|--------------------------|---------------------------|----------------------|----------------------------------------------------------------------------------|----------------------------------------------------------------------------------|---------------------------|------------------------------------------------------|--------------------------------------------------------------------------|--------------------------|
| Kurth et al. | United States of America | 2012–2014                 | Cross sectional      | 105 clinical nurses, 95 hospital office and administrative support workers, 51 patient care occupations | Sterilization/disinfection of medical instruments, cleaning equipment or surfaces, using chemicals in lab (alcohol, bleach, glass cleaner, detergent, quaternary ammonium compounds) | Questionnaire              | Age, race/ethnicity, gender, smoking status, seniority, days per week working | Participants exposed to cleaning equipment and environmental surfaces had a significantly higher prevalence of current asthma compared to nonexposed participants: PR = 1.83 (95% CI: 1.16–2.90). | Fair                     |
| Barnes et al. | Australia               | December 2016–June 2017  | Cross sectional      | 1112 healthcare workers                                                           | Chlorhexidine-based hand hygiene solutions                                          | Questionnaire              | Age, gender, race, work environment, occupation     | 128/1050 (12.2%) had current asthma during the previous year. Nurses and midwives reported asthma most frequently (13.7%). | Fair                     |
| Caridi et al. | United States of America | 2014                      | Cross sectional      | 2030 healthcare workers                                                           | Common healthcare tasks including cleaning fixed surfaces and sterilizing medical instruments | Questionnaire and telephone interviews | Age, gender, race/ethnicity, occupation, place of work, smoking | Cleaning fixed surfaces had statistically significant associations with post-hire asthma: OR = 1.76 (95% CI: 1.09 to 2.85) and current asthma: OR = 1.84 (95% CI: 1.26–2.68). | Fair                     |
| Author         | Country       | Period of data collection | Study design            | Study population | Type of exposure                                                                 | Method of data collection | Covariates                        | Findings                                                                                                                                                                                                 | Quality assessment score |
|----------------|---------------|---------------------------|--------------------------|------------------|----------------------------------------------------------------------------------|---------------------------|----------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------|
| Dumas et al. | United States of America | 2009–2013 | Prospective cohort study | 61,539 female nurses | Exposure to disinfectants (formaldehyde, glutaraldehyde, bleach, hydrogen peroxide, alcohol quats, or enzymatic cleaners) | Questionnaire            | Age, race, smoking habits, BMI | No significant association was observed between incident asthma and weekly use of disinfectants to clean surfaces: HR = 1.12 (95% CI: 0.87–1.43) or weekly use of disinfectants to clean medical instruments: HR = 1.13 (95% CI: 0.87–1.48). No association was observed between high-level exposure to specific disinfectants evaluated by the JTEM (formaldehyde, glutaraldehyde, bleach, hydrogen peroxide, alcohol quats, or enzymatic cleaners) and incident asthma. | Good                     |
| Su et al.    | United States of America | 2014       | Cross sectional          | 2030 healthcare workers | Cleaning and disinfecting activities                                              | Questionnaire, telephone interviews, hierarchical clustering | Age, gender, race/ethnicity, occupation, place of work, smoking | Undiagnosed/untreated asthma was associated with chlorine bleach: OR = 3.07 (95% CI: 1.75–5.39); enzymes: OR = 2.57 (95% CI: 1.18–5.58); detergents: OR = 3.04 (95% CI: 1.56–5.90). Disinfection products were associated with mild asthma symptoms: OR = 1.81 (95% CI: 1.09–2.99) and undiagnosed/untreated asthma: OR = 3.42 (95% CI: 1.24–9.39). | Fair                      |
| Author       | Country                  | Period of data collection | Study design  | Study population | Type of exposure                                      | Method of data collection | Covariates                                      | Findings                                                                                           | Quality assessment score |
|--------------|--------------------------|---------------------------|---------------|------------------|------------------------------------------------------|---------------------------|-----------------------------------------------|---------------------------------------------------------------------------------------------------|--------------------------|
| Patel et al. | United States of America | 2016–2017                 | Cross sectional| 413 certified nurse aids | Exposure to cleaning tasks and compounds             | Questionnaire             | Age, race, atopy, obesity, smoking, years at job | Mild asthma symptoms were associated with alcohols: OR = 1.34 (95% CI: 1.01–1.76) and chlorine bleach: OR = 1.44 (95% CI: 1.09–1.91). | Good/fair               |
| Dumas et al. | United States of America and Canada | 2010–present | Prospective cohort study | 17280 female nurses | Occupational use of high-level disinfectants (glutaraldehyde, ortho-phthalaldehyde, peracetic acid, hydrogen peroxide) | Questionnaire             | Age, race, ethnicity, smoking habits, BMI | Nurses with >5 years of HLD use had an increased risk of incident asthma: adjusted HR = 1.39 (95% CI: 1.04–1.86). Asthma risk was significantly increased among women with >5 years of HLD use but no current use: adjusted HR = 1.46 (95% CI: 1.00–2.12). No significant associations were observed between specific types of HLDs and incident asthma due to low numbers. | Fair                     |

Abbreviations: ASPAN, American Society of PeriAnaesthesia Nurses; BMI, body mass index; ECRHS, European Community Respiratory Health Survey; HLD, high-level disinfectant; HR, hazard ratio; JEM, job exposure matrix; JTEM, job task exposure matrix; OASYS, occupational asthma expert system; PEFR, peak expiratory flow rate; PR, prevalence ratio; RR, relative risk; SBPT, specific bronchial provocation test; SGNA, Society of Gastroenterology Nurses and Associates, SMR, standardized morbidity ratio; WSIB, Workplace Safety & Insurance Board.
| Author          | Country                | Period of data collection | Study design | Study population                                      | Type of exposure                  | Method of data collection                              | Covariates                                | Findings                                                                 | Quality assessment score |
|-----------------|------------------------|---------------------------|--------------|-------------------------------------------------------|-----------------------------------|--------------------------------------------------------|-------------------------------------------|-------------------------------------------------------------------------|-------------------------|
| Kern            | United States of America | 1988                      | Cross sectional | 51 clinical laboratory, phlebotomy, and radiology department employees | Acetic acid                      | Questionnaire, methacholine challenge test            | Age, gender, smoking status, history of atopy or asthma     | Risk of RADS was higher in subjects with high exposure to 100% acetic acid: OR = 9.8 (95% CI: 0.902–264.6). | Fair                    |
| Ellett et al.   | United States of America | 1995                      | Cross sectional | 3988 members of SGNA members exposed, 929 ASPAN members exposed, 830 ASPAN members nonexposed | Glutaraldehyde                    | Questionnaire                                         | Age, gender, smoking status, prior health problems       | More exposed SGNA respondents reported a worsening of nose/throat problems ($x^2 = 26.77, p < 0.002$) and breathing problems ($x^2 = 16.54, p < 0.011$) compared with either ASPAN group. No statistically significant differences in the number of respondents reporting rhinitis and chest pain. | Fair                    |
| Vyas et al.     | United Kingdom          | Not specified              | Cross sectional | 348 endoscopy nurses and 18 former employees who had left their jobs for health reasons | Airborne exposures of glutaraldehyde, succinaldehyde, and formaldehyde from cleaning tasks | Questionnaire, spirometry, pulmonary function tests, skin prick test, total serum IgE and IgE RAST | Age, gender, smoking status                        | Irritation of nose ($p < 0.01$) and eyes ($p < 0.05$) in current workers exposed to glutaraldehyde. No association between glutaraldehyde exposure to LRTs were found. | Fair                    |
| Liss et al.     | Canada                  | 2000–2001                  | Cross sectional | 1719 medical radiation technologists and a control group of 1,848 physiotherapists | Cleaning tasks conducted by radiation technologists | Questionnaire, methacholine challenge test            | Age, gender, smoking status                        | Medical radiation technologists had increased odds of reporting 2 or more work-related respiratory symptoms (cough, wheeze, chest tightness): adjusted OR = 3.9 (95% CI: 2.6–5.5). | Fair                    |
| Dimich-Ward et al. | Canada               | 1999–2000                  | Cross sectional | 275 respiratory therapists and a control group of 628 physiotherapists | Glutaraldehyde                    | Questionnaire                                         | Nasal allergies, time in profession, living with a smoker | Wheeze: OR = 2.1 (95% CI: 1.1–3.8) Woken by cough: OR = 2.3 (95% CI: 1.3–3.9) | Fair                    |
| Author            | Country         | Period of data collection | Study design | Study population | Type of exposure                                                                 | Method of data collection | Covariates                                      | Findings                                                                                                 | Quality assessment score |
|-------------------|-----------------|---------------------------|--------------|------------------|-----------------------------------------------------------------------------------|--------------------------|-------------------------------------------------|-----------------------------------------------------------------------------------------------------------|--------------------------|
| Delclos et al.    | United States of America | 2003                  | Cross sectional | 3650 health professionals | Cleaning products using an asthma risk factor JEM specifically for healthcare worker populations | Questionnaire, JEM, methacholine challenge test | Age, BMI, smoking status, occupation, race/ethnicity, atopy | Bronchial hyperresponsiveness-related symptoms were associated with general cleaning: OR = 1.63 (95% CI: 1.21–2.19) and exposure to a chemical spill: OR = 2.02 (95% CI: 1.28–2.31) | Good                     |
| Nayebzadeh        | Canada          | Not specified             | Cross sectional | 53 healthcare workers | Glutaraldehyde                                                                      | Interview                | Age, gender, race/ethnicity, BMI                | 3.7% of participants reported coughing as a symptom, and 53% reported itchy nose. 41% reported headache, 68% reported burning eyes, and 73% reported itchy eyes. A higher prevalence of these symptoms was observed where unsafe work practices were taking place. | Fair                     |
| Arif et al.       | United States of America | Not specified | Cross sectional | 3650 healthcare professionals | Cleaning tasks, use of powdered latex gloves, administration of aerosolised medications, use of adhesives/removers | Questionnaire            | Age, gender, race/ethnicity, atopy, smoking status, BMI, seniority | Nurses exposed to disinfectants and cleaning products were at significantly increased odds of having BHR-related symptoms: OR = 1.57 (95% CI: 1.11–2.21). | Fair                     |
| Arif and Delclos   | United States of America | 2004–2005             | Cross sectional | 3650 healthcare professionals | Exposures in the longest held job (cleaning agents, disinfectants, sterilants, general purpose cleaning, instrument cleaning/sterilization) | Questionnaire            | Age, gender, race/ethnicity, BMI, seniority, atopy, smoking status | Odds of work-related asthma symptoms (wheeze, shortness of breath) increased in a dose-dependent manner from OR = 2.64 (95% CI: 0.57–12.14) for once a week exposure to OR = 5.37 (95% CI: 1.43–20.16) for more than once a day exposure to cleaning agents. Work-related asthma symptoms | Fair                     |
| Author                      | Country        | Period of data collection | Study design | Study population                                                                 | Type of exposure                                                                 | Method of data collection | Covariates                                                                 | Findings                                                                                   | Quality assessment score |
|-----------------------------|----------------|---------------------------|--------------|----------------------------------------------------------------------------------|----------------------------------------------------------------------------------|--------------------------|------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------|--------------------------|
| Kim et al.                  | Sweden         | 2008                      | Cross sectional | 429 healthcare workers exposed to cleaning tasks, 1727 healthcare workers not exposed to cleaning tasks, 10,030 nonhealthcare workers | Cleaning tasks                                                                  | Questionnaire            | Age                                                                          | Healthcare workers exposed to cleaning products had significantly increased odds of having asthmatic symptoms (breathlessness, shortness of breath, cough, wheeze) in the past 12 months compared with nonhealthcare workers: OR = 1.9 (95% CI: 1.4–2.5). | Fair                     |
| Lee et al.                  | United States of America | Not specified            | Cross sectional | 183 cleaning workers employed at a university medical centre and affiliated health sciences campuses | Exposures during cleaning tasks (liquid multi-use cleaning products, polishes, waxes, disinfectants, bleach, solvents, glass cleaning, etc.) | Questionnaire            | Age, gender, race/ethnicity, education level, job title | Significant associations were found between respiratory symptoms and medium exposure to tasks using spray products: OR = 3.16 (95% CI: 1.24–8.04); high exposure to liquid multi-use cleaners: OR = 2.35 (95% CI: 1.02–5.43); carpet cleaners: OR = 2.33 (95% CI: 1.00–5.43). | Fair                     |
| Lipińska-Ojrzanowska et al. | Poland         | Not specified            | Cross sectional | 142 cleaning workers in health centres                                                   | Cleaning tasks (chloramine T, chlorhexidine, formaldehyde, glutaraldehyde, | Questionnaire, IgE serum, skin prick test, pulmonary function test | Age, gender, smoking status, presence of a pet at home | 47.2% of cleaners (67/142) developed at least one work-related respiratory symptom. Airway ailments were observed most | Poor                     |
| Author          | Country         | Period of data collection | Study design      | Study population                                                                 | Type of exposure                                                                 | Method of data collection       | Covariates                              | Findings                                                                                                           | Quality assessment score |
|-----------------|-----------------|---------------------------|-------------------|----------------------------------------------------------------------------------|-----------------------------------------------------------------------------------|---------------------------------|------------------------------------------|---------------------------------------------------------------------------------------------------------------------|--------------------------|
| El-Helaly et al. | Saudi Arabia    | 2012–2014                 | Prospective cohort study | 56 nurses responsible for disinfection and sterilization of medical instruments and equipment | Exposure to splashes, spills, mists, vapors, gases during use of cleaning chemicals (quaternary ammonium compounds, chlorhexidine, orthophthalaldehyde, glutaraldehyde, formaldehyde, bleach, endozyme1, ethylene oxide) | Questionnaire, spirometry       | Age, gender, smoking, BMI, education level | Prevalence of work-related cough increased from 5.4% in 2012 to 17.9% in 2014 (p = 0.06). All participants who had worked with cleaning chemicals for more than 10 years (60.7%) had significant decreases in spirometry parameters FEV₁ and FVC from 2012 to 2014. | Fair                     |
| Casey et al.    | United States of America | Not specified             | Cross sectional | 78 disinfectant product users and 85 disinfectant product nonusers | Surface disinfectant product containing hydrogen peroxide, peracetic acid, and acetic acid | Questionnaire                   | Age, gender, race/ethnicity, smoking | Product users had a higher prevalence of work-related wheeze than nonusers (p < 0.05). Disinfectant users also reported a higher prevalence of work-related asthma-like symptoms, shortness of breath, cough, chest tightness, and asthma attack, although these were not statistically significant. | Fair                     |
| Kurth et al.    | United States of America | 2012–2014                 | Cross sectional | 105 clinical nurses, 95 hospital office and administrative support workers, 51 patient care occupations | Sterilization/disinfection of medical instruments, cleaning equipment or surfaces, using chemicals in lab (alcohol, bleach, glass cleaner, detergent, quaternary ammonium compounds) | Questionnaire                   | Age, race/ethnicity, gender, smoking status, seniority, days per week working | Participants cleaning/disinfecting surfaces had a significantly higher PR of wheeze compared with nonexposed participants: PR = 1.50 (95% CI: 1.12–2.02) Participants exposed to cleaning and disinfecting products had significantly higher PRs for wheeze compared to nonexposed participants. | Fair                     |
| Author          | Country               | Period of data collection | Study design | Study population | Type of exposure                                      | Method of data collection                      | Covariates                        | Findings                                                                                           | Quality assessment score |
|-----------------|-----------------------|---------------------------|--------------|------------------|-------------------------------------------------------|-----------------------------------------------|------------------------------------|-----------------------------------------------------------------------------------------------|--------------------------|
| Bleach: PR = 1.57 (95% CI: 1.18–2.09); glass cleaner: PR = 1.64 (95% CI: 1.14–2.36); detergent: PR = 1.56 (95% CI: 1.14–2.13) | **Hawley et al.** | United States of America | 2015          | Cross sectional | 50 hospital cleaning staff | Hydrogen peroxide, peracetic acid, and acetic acid | Questionnaires, time-weighted average air samples | Age, gender, tenure, smoking status | 28.6% reported asthma-like symptoms in the previous 12 months. Shortness of breath was significantly associated with increased exposure to a total mixture of hydrogen peroxide, peracetic acid, and acetic acid (p = 0.022) and oxidant mixture of hydrogen peroxide and peracetic acid exposure (p = 0.017). Prevalence of wheeze in the previous 12 months was 2.5–2.8-fold higher in the highest exposure groups compared to the lowest exposure group. | Fair                     |
| Rangkooy et al. | Iran                  | Not specified             | Cross sectional | 30 persons of operation room with exposure to formaldehyde and 30 persons not usually exposed to formaldehyde in an educational hospital | Formaldehyde | NIOSH procedure No. 3500, respiratory symptoms, pulmonary function tests | Age, weight, gender, work experience | The prevalence of coughing, shortness of breath, and nasal irritation were significantly higher in the exposed group than the control (p < 0.05). Prevalence of wheezing was not significantly higher in the exposed group. | Fair                     |
| Barnes et al.   | Australia             | December 2016–June 2017   | Cross sectional | 1112 healthcare workers | Chlorhexidine-based hand hygiene solutions | Questionnaire | Age, gender, race, work environment, occupation | 37/1050 (3.5%) experienced wheeze/cough in the previous year. | Fair |
| Author       | Country            | Period of data collection | Study design | Study population          | Type of exposure                                                                 | Method of data collection       | Covariates                                   | Findings                                                                 | Quality assessment score |
|--------------|--------------------|--------------------------|--------------|----------------------------|---------------------------------------------------------------------------------|---------------------------------|---------------------------------------------|------------------------------------------------------------------------|--------------------------|
| Caridi et al. | United States of America | 2014                    | Cross sectional | 2030 healthcare workers | Common healthcare tasks including cleaning fixed surfaces and sterilizing medical instruments | Questionnaire and telephone interviews | Age, gender, race/ethnicity, occupation, place of work, smoking | Cleaning fixed surfaces was significantly associated with BHR-related symptoms: OR = 1.38 (95% CI: 1.08–1.77); wheeze: OR = 1.45 (95% CI: 1.08–1.94). | Fair                     |
| Patel et al.  | United States of America | 2016–2017               | Cross sectional | 413 certified nurse aids | Exposure to cleaning tasks and compounds                                        | Questionnaire                   | Age, race, atopy, obesity, smoking, years at job | The prevalence of BHR symptoms was 26.9%. Increased odds for BHR symptoms were associated with patient care cleaning: OR = 1.71 (95% CI: 0.45–6.51); instrument cleaning: OR = 1.33 (95% CI: 0.66–2.68); glutaraldehyde or orthophthalaldehyde: OR = 1.33 (95% CI: 0.66–2.68); latex glove use during 1992–2000: OR = 1.62 (95% CI: 0.84–3.12). | Good/fair                |
| Garrido et al. | Canada              | 2018–2019               | Cross sectional | 307 administrative staff, and nursing and cleaning staff | Exposure to disinfectants (bleach, hydrogen peroxide, isopropanol, quaternary ammonium compounds). | Questionnaire                   | Age, gender                                  | Exposed healthcare workers had an increased risk of respiratory symptoms: adjusted OR = 2.17 (95% CI: 1.18–4.14). Washing instruments manually, cleaning operating rooms, cleaning sanitary rooms, using aerosol products, preparing disinfectants, and filling devices with cleaning products were cleaning tasks associated with respiratory symptoms such as wheeze, shortness or breath, chest tightness, or cough. | Fair                     |
| Author          | Country | Period of data collection | Study design | Study population | Type of exposure | Method of data collection | Covariates                                                                 | Findings                                                                 |
|----------------|---------|---------------------------|--------------|------------------|------------------|-------------------------|----------------------------------------------------------------------------|-------------------------------------------------------------------------|
| Jalali et al.  | Iran    | 2019                      | Cross-sectional | 60 pathology laboratory staff | Formaldehyde     | Questionnaire, face-to-face interviews, NIOSH procedure No. 3500 | Age, weight, gender, work experience, type of work, daily working hours, exposure patterns | No specific cleaning agents had a statistically significant association with respiratory symptoms. Weezing (24%) and cough (21.7%) were the most prevalent respiratory problems in exposed workers. Occupational exposure in 28.3% (n = 17) of employees was above the range recommended by the OSHA. |

Abbreviations: ASPAN, American Society of PeriAnesthesia Nurses; BHR, bronchial hyperresponsiveness; ECRHS, European Community Respiratory Health Survey; FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity; JEM, job exposure matrix; LTRS, lower tract respiratory symptom; NIOSH, National Institute for Occupational Safety and Health; OASYS, occupational asthma expert system; OSHA, Occupational Safety and Health Administration; PR, prevalence ratio; RADS, reactive airways dysfunction syndrome; RAST, radio allergosorbent test; RR, relative risk; SGNA, Society of Gastroenterology Nurses and Associates; UTRS, upper tract respiratory symptoms.
| Author | Country | Period of data collection | Study design | Study population | Type of exposure | Method of data collection | Covariates | Findings |
|--------|---------|---------------------------|--------------|------------------|------------------|--------------------------|------------|----------|
| Ellett et al. | United States of America | 1995 | Cross sectional | 3988 members of SGNA members exposed, 929 ASPAN members exposed, 830 ASPAN members nonexposed | Glutaraldehyde | Questionnaire | Age, gender, smoking status, prior health problems | No statistically significant differences in the number of respondents reporting dermatitis ($p < 0.222$). Fewer exposed respondents showed an improvement in skin symptoms ($x^2 = 2.65, p < 0.002$). | Fair |
| Vyas et al. | United Kingdom | Not specified | Cross sectional | 348 endoscopy nurses and 18 former employees who had left their jobs for health reasons | Airborne exposures of glutaraldehyde, succinaldehyde, and formaldehyde from cleaning tasks | Questionnaire, spirometry, pulmonary function tests, skin prick test, total serum IgE and IgE RAST | Age, gender, smoking status | Work-related contact dermatitis was reported by 44% of endoscopy nurses exposed to glutaraldehyde and 56.7% of those exposed to a composite of succinaldehyde and formaldehyde. | Fair |
| Liss et al. | Canada | 2000–2001 | Cross sectional | 1719 medical radiation technologists and a control group of 1848 physiotherapists | Cleaning tasks conducted by radiation technologists | Questionnaire, methacholine challenge test | Age, gender, smoking status | Skin symptoms associated with latex: OR = 2.5 (95% CI: 1.9–3.4) | Fair |
| Lipińska-Ojrzanowska et al. | Poland | Not specified | Cross sectional | 142 cleaning workers in health centres | Cleaning tasks (chloramine T, chlorhexidine, formaldehyde, glutaraldehyde, benzalkonium chloride) | Questionnaire, IgE serum, skin prick test, pulmonary function test | Age, gender, smoking status, presence of a pet at home | 24% of cleaners (34/142) had work-related skin symptoms. Cleaners with respiratory symptoms had significantly greater odds of having skin symptoms compared with cleaners without respiratory symptoms: OR = 2.62 (95% CI: 1.11–6.21). | Poor |
| Lee et al. | United States of America | Not specified | Cross sectional | 183 cleaning workers employed at a University Medical Centre and affiliated | Exposures during cleaning tasks (liquid multi-use cleaning products, polishes, waxes, disinfectants, bleach, | Questionnaire | Age, gender, race/ethnicity, education level, job title | Chemical-related symptoms (respiratory, eye, nervous, skin, and gastrointestinal systems) were more common among hospital | Fair |
| Author       | Country         | Period of data collection | Study design | Study population | Type of exposure                                                                 | Method of data collection | Covariates                      | Findings                                                                                                                                                                                                 |
|--------------|-----------------|---------------------------|--------------|------------------|----------------------------------------------------------------------------------|---------------------------|---------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Casey et al. | United States of America | Not specified             | Cross sectional | 78 disinfectant product users and 85 disinfectant product nonusers | Surface disinfectant product containing hydrogen peroxide, peracetic acid, and acetic acid | Questionnaire               | Age, gender, race/ethnicity, smoking | Skin symptoms were reported by 19% of all participants (31/163), and 61% of skin problems (19/31) were described to be work-related. No statistically significant differences in the number of disinfectant product users and nonusers reporting skin problems in the last 12 months ($p = 0.32$). |
| Barnes et al. | Australia       | December 2016–June 2017   | Cross sectional | 1112 healthcare workers | Chlorhexidine-based hand hygiene solutions                                         | Questionnaire               | Age, gender, race, work environment, occupation | Of those with self-reported hay fever or asthma, 40.1% reported localized rash in the past 12 months, including 33.3% who experienced |

13.1% of participants (24/183) experienced dermal symptoms related to chemical exposure (itchy or burning skin, or rash) several times yearly. 2.7% of participants (5/183) experienced dermal symptoms related to chemical exposure daily. Contact dermatitis was significantly more frequent in workers with chemical-related symptoms than workers without ($p = 0.012$).
| Author          | Country   | Period of data collection | Study design | Study population                                      | Type of exposure                                      | Method of data collection | Covariates     | Findings                                                                 |
|-----------------|-----------|---------------------------|--------------|-------------------------------------------------------|-------------------------------------------------------|---------------------------|----------------|--------------------------------------------------------------------------|
| Garrido et al.   | Canada    | 2018–2019                 | Cross sectional | 307 administrative staff, and nursing and cleaning staff | Exposure to disinfectants (bleach, hydrogen peroxide, isopropanol, quaternary ammonium compounds) | Questionnaire             | Age, gender | Exposed healthcare workers had an increased risk of skin symptoms: adjusted OR = 1.77 (95% CI: 1.00–3.17). Actual disinfecting tasks were associated with hand dermatitis: adjusted OR = 2.19 (95% CI: 1.10–4.66). Bleach was the only specific cleaning agent that was significantly associated with hand dermatitis: adjusted OR = 2.54 (95% CI: 1.32–5.13). |

Abbreviations: ASPAN, American Society of PeriAnesthesia Nurses; RAST, radio allergosorbent test; SGNA, Society of Gastroenterology Nurses and Associates.
Ellett et al. and Gonzalez et al. found similar results; however, the risks reported in these studies were not statistically significant.\textsuperscript{16,25}

Two studies found contrasting results. Casey et al. evaluated the association between a surface disinfectant product containing hydrogen peroxide, peracetic acid, and acetic acid. No significant differences between current asthma diagnoses were found among product users and nonusers ($p = 0.66$).\textsuperscript{26} Last, Dumas et al. found no significant association between weekly use of disinfectants and incident asthma, and no significant association between high-level exposure to specific disinfectants and incident asthma.\textsuperscript{30}

3.2 | Meta-analyses for asthma

Ten studies evaluating asthma with fair or good quality scores were selected for a meta-analysis.\textsuperscript{1,5,6,11,16,17,22,25,26,29} When studies presented multiple risk estimates for asthma, the quantitative summary that defined occupational asthma the best was selected. For instance, quantitative summaries for new-onset asthma were selected over quantitative summaries for ever asthma diagnoses. The outcome definitions for the studies included in the meta-analysis included current asthma (ever asthma and report of asthma attacks, respiratory symptoms, or treatment of asthma in the past 12 months, or physician-diagnosed asthma that was still present),\textsuperscript{5,6,16,26} new-onset asthma, reported asthma, or post-hire asthma (reported onset of physician-diagnosed asthma after entering a healthcare profession),\textsuperscript{5,11,17,25,29} and adult-onset asthma (asthma reported at the age of 16 years old or later).\textsuperscript{22}

The pooled meta-analysis of the 10 studies demonstrated a significant 35\% increased risk for asthma among hospital healthcare workers exposed to cleaning or disinfecting tasks or agents (meta-RR = 1.35, 95\% CI: 1.09–1.68, $p = 0.01$, $I^2 = 30\%$) (Figure 2). The pooled risk estimate was higher among cross-sectional studies (meta-RR = 1.45; 95\% CI: 1.10–1.90, $p = 0.01$, $I^2 = 25\%$) (Figure 2). No evidence of publication bias was observed (Egger’s test $p = 0.66$) (Figure S1).

Before 2000, powdered latex gloves were used as personal protective equipment by most hospital staff, including cleaners.\textsuperscript{12} After 2000, there was a reduction in usage of powdered latex gloves due to increasing reports of latex allergy reactions.\textsuperscript{12} Therefore, latex may have been a confounding factor in estimating the risk from cleaning agents. A meta-analysis on studies conducted after 2000 was performed to identify any change in risks over time that may have been associated with decreased use of powdered latex gloves or other preventive exposure measures in hospitals since that time. The risk of asthma attributed to cleaning or disinfecting tasks or agents decreased from a 35\% increased risk to a 28\% increased risk after 2000 (meta-RR = 1.28, 95\% CI: 1.04–1.57, $p = 0.03$, $I^2 = 14\%$)

\textbf{FIGURE 2}  Forest plot illustrating a meta-analysis of 10 studies evaluating the association between exposure to cleaning or disinfecting tasks or agents and asthma risk; RR, relative risk.
(Figure 3). No evidence of publication bias was observed (Egger’s test \( p = 0.54 \)) (Figure S2).

Among cross-sectional studies, an additional subgroup analysis by study definition of asthma was performed. The results of five of the eight cross-sectional studies that evaluated new-onset asthma, reported asthma, or adult-onset asthma were pooled,\(^{3,6,11,15,17,19,22,26-29}\) excluding studies that evaluated current asthma.\(^{6,16,26}\) An additional subgroup analysis was performed to focus on new-onset asthma, adult-onset asthma, posthire asthma and post-hire reported asthma, since asthma caused by occupational cleaning exposures is more expected to occur within these subgroups. When focusing on new-onset asthma, adult-onset asthma, post-hire asthma, or reported asthma outcomes, a nonsignificant 46% increased risk was determined among healthcare workers exposed to cleaning or disinfecting agents or tasks (meta-RR = 1.46, 95% CI: 0.99–2.14, \( p > 0.05, I^2 = 20\% \)) (Figure 4). No evidence of publication bias was observed (Egger’s test \( p = 0.52 \)) (Figure S3).

### 3.3 | Bleach

The pooled meta-analysis of three studies evaluating asthma in relation to bleach exposure demonstrated a nonsignificant 51% increased risk among exposed healthcare workers (meta-RR = 1.51, 95% CI: 0.54–4.18, \( p = 0.23, I^2 = 48\% \)) (Figure 5).\(^{1,11,25}\) No evidence of publication bias was observed (Egger’s test \( p = 0.19 \)) (Figure S4).

### 3.4 | Asthma-like respiratory symptoms

Twenty-two studies assessed the associations between cleaning tasks or agents and lower and upper respiratory tract symptoms (LRTS and URTS respectively) (Table 2). All but one of the studies used a cross-sectional study design. All studies received a quality assessment score of “fair” or “good”: except for 1 study, which received a “poor” quality score.\(^{4}\) Nineteen of the 21 “fair” or “good” quality studies evaluated only LRTS or asthma-like symptoms, such as wheeze, cough, shortness of breath, and breathlessness.\(^{3,6,11,15,17,19,22,26-29,32,35-39}\) Most reported increased risks of LTRS associated with cleaning tasks and disinfectants.\(^{3,5,6,11,15,17,22,26,27,29,35-38}\) One study reported that the odds of work-related asthma symptoms such as shortness of breath and wheeze increased in a dose-dependent manner (OR = 2.64, 95% CI: 0.57–12.14 for once a week exposure to OR = 5.37, 95% CI: 1.43–20.16 for more than once daily exposure).\(^{35}\) One study found a nearly 10-fold risk of reactive airways dysfunction syndrome (RADS) in hospital workers exposed to 100% acetic acid (OR = 9.8, 95% CI: 0.902–264.6).\(^{32}\) Four studies reported increased odds of bronchial hyperresponsiveness (BHR)–related symptoms, such as trouble breathing, wheezing, shortness of breath, and chest tightness, associated with general cleaning tasks and cleaning and disinfectant products.\(^{12,15,19,29}\) In particular, Patel et al. found that BHR symptoms were associated with glutaraldehyde/orthophthalaldehyde (OR = 1.33, 95% CI: 0.66–2.68) and latex glove use during 1992–2000 (OR = 1.62, 95% CI: 0.84–3.12).\(^{15}\)

Four studies evaluated URTS in addition to LRTS.\(^{33,34,38,40}\) One study demonstrated a significant increase in worsening nose and
throat problems among nurses exposed to glutaraldehyde ($p < 0.002$). Similarly, a second study showed a significant increase in nose ($p < 0.01$) and eye irritation ($p < 0.05$) in nurses exposed to glutaraldehyde. Rankooy et al. found that the prevalence of nasal irritation was significantly higher in a group exposed to formaldehyde compared with a control group ($p < 0.05$). Last, Nayebezad et al. reported an increased prevalence of LRTS and URTS when unsafe work practices were occurring. Examples of unsafe work practices included leaving unused containers uncovered, the inappropriate storing or disposing contaminated linen and paper towels, and causing spills or leakages of solution from containers.

### 3.5 | Meta-analysis for wheeze

The pooled meta-analysis of four studies evaluating the risk of wheeze among healthcare workers exposed to cleaning or disinfecting tasks or agents demonstrated a nonsignificant 55% increased risk among exposed healthcare workers (meta-RR = 1.55, 95% CI: 0.85–2.82, $p = 0.10$; $I^2 = 49\%$) (Figure 6). No evidence of publication bias was observed (Egger's test $p = 0.80$) (Figure S5).

### 3.6 | Skin symptoms associated with respiratory symptoms

Only two studies directly investigated the risk of skin symptoms in relation to respiratory symptoms. Lipińska-Ojrzanowska et al. found that healthcentre cleaners with respiratory symptoms had significantly increased odds of having skin symptoms compared with healthcentre cleaners without respiratory symptoms (OR = 2.62, 95% CI: 1.11–6.21); however, this study received a poor quality assessment score, indicating a high risk of bias. Barnes et al. found that 40.1% of exposed healthcare workers with hay fever or asthma reported localized rash, 79.5% reported dry skin, and 36.6% reported eczema in response to chlorhexidine. No significant association was found between the respiratory symptoms and skin symptoms experienced among exposed healthcare workers with eczema or contact dermatitis. Last, Lee et al. evaluated the risk of skin symptoms in relation to more general chemical-related symptoms, which may include the respiratory, eye, nervous, skin, or gastrointestinal symptoms. This study reported that contact dermatitis was significantly more frequent in workers with chemical-related symptoms compared with workers without chemical-related symptoms ($p = 0.012$).

### 4 | DISCUSSION

This systematic review and meta-analysis found a 35% increased asthma risk among healthcare and other hospital workers exposed to cleaning and disinfecting tasks or cleaning and disinfecting agents, compared with other workers ($p = 0.01$). After 2000 the excess risk of asthma attributed to cleaning or disinfecting tasks or agents decreased to 28%, suggesting a possible earlier confounding effect of natural rubber latex exposure and/or other exposure changes. The risk of asthma attributed to cleaning and disinfecting tasks or agents increased (to 45%) when subgroup analysis was performed to focus on new-onset asthma and adult-onset asthma diagnoses; however, this increased risk was not statistically significant. Assessment of specific agents showed a nonsignificant 51% increased asthma risk associated with bleach exposure, and most studies also reported an increased asthma risk associated with exposure to glutaraldehyde, bleach, and quaternary ammonium compounds. No exposure-response relationships between potential causal agents and reported asthma could be determined due to the lack of quantitative exposure analysis. Four studies reported no statistically significant differences between current asthma diagnoses among disinfectant product users.
The meta-analysis for wheezing symptoms found a nonsignificant 55% increased risk among exposed healthcare workers.

Among the studies included in the systematic review, there were very limited results regarding the relationship between respiratory and skin symptoms. One study evaluated the relationship between respiratory and skin symptoms and found increased odds of skin symptoms in healthcare workers with respiratory symptoms; however, this study was given a "poor" quality assessment score, with a high risk of bias potentially affecting the reliability of the results. A second study found that exposed healthcare workers with hay fever or asthma also reported skin symptoms such as localized rash, dry skin, and eczema in response to chlorhexidine, suggesting a potential relationship between respiratory and skin symptoms; however, no significant association was found between the respiratory symptoms and skin symptoms experienced among exposed healthcare workers with eczema or contact dermatitis. Lee et al. reported that contact dermatitis was significantly more frequent in workers with chemical-related symptoms compared with workers without chemical-related symptoms; however, the outcome definition for chemical-related symptoms in this study included symptoms associated with respiratory, skin, gastrointestinal, eye, or nervous systems, making it difficult to discern the relationship between respiratory symptoms and contact dermatitis specifically. Due to the limited available data, no conclusions can be drawn about possible associations between respiratory and skin symptoms related to cleaning and disinfecting agents in hospital workers.

A strength of this systematic review was its comprehensiveness, as indicated by a lack of observed publication bias. Also, the systematic review included independent assessment from a minimum of two reviewers for the title and abstract screening, full-text screening, and risk of bias assessment stages of the methods. Another strength is that most of the included studies have a low risk of bias assessment, as deemed by a "fair" or "good" quality assessment score. Only one study received a "poor" quality assessment score, and the risk of bias in this study was considered in the interpretation of the results. Last, pooled risk estimates were obtained that quantify the risk of asthma among healthcare workers exposed to cleaning or disinfecting agents or tasks. The pooled risk estimates can be used to inform future public health interventions and research studies regarding similar topics.

One of the limitations of this systematic review is the exclusion of articles written in languages other than English. Additionally, almost all of the included studies used self-report measures to collect data, which is subject to recall bias. For instance, cleaning products and disinfectants that have a more pungent and noxious smell might be more memorable. In a study conducted in Arizona, participants with asthma were more likely to report feeling sick in the presence of compounds with a strong odor, such as cleaning agents. Studies using objective or quantitative assessments of occupational exposures and outcomes would be less susceptible to recall bias. In addition, this review did not include an assessment of preventive measures in each study setting. Potentially there may be significant differences in occupational hygiene measures in different settings that may have affected the extent of exposures and rates of respiratory symptoms in different studies (as was reported by Nayebozadeh).

Another weakness of this review involves the heterogeneity of the studies included in the meta-analyses. Although none of the meta-analyses had substantial heterogeneity ($I^2 \geq 50\%$), there was moderate heterogeneity within the included studies of each meta-analysis. Possible causes of within-studies heterogeneity could include the misclassification of outcomes and exposures, and how different studies may not have adjusted for the same potential confounders. Consequently, a fixed effect model could not be used to pool the studies. Also, several included papers assessed only one exposure without considering potential concurrent exposures. The results may be confounded by other unknown concurrent exposures, causing the results to be unreflective of any true relationships. Last, the possibility of the healthy worker effect was a limitation of our review. Many of the studies included in our review were cross-sectional in design and could have missed those who had left the healthcare workforce due to respiratory and/or skin symptoms. This could have resulted in an underestimation of the respiratory and skin symptoms in the study population. An association between asthma history and subsequent job changes in nurses was previously found, supporting the possibility of the healthy worker effect bias in cross-sectional studies regarding disinfectant exposures. More prospective cohort studies that follow healthcare workers from early stages of their career and examine the influence of exposure duration, similar to the study conducted by Dumas et al., would limit the healthy worker bias effect.

5 | CONCLUSIONS

In conclusion, this review found a higher risk of asthma among healthcare workers exposed to cleaning or disinfecting tasks or agents. These findings are consistent with the results of previously conducted systematic reviews. Compared with this review, both previous reviews determined a greater increase in asthma risk associated with cleaning or disinfecting tasks. The limitations found in this review may contribute to a potential underestimation of...
the risk. The findings highlight the importance of implementing safe work practices and control measures that protect healthcare workers from potentially harmful occupational cleaning and disinfecting exposures. The results of this review are especially relevant during the COVID-19 pandemic, when the use of cleaning and disinfecting agents has increased to prevent the transmission of the virus. Future studies using a prospective cohort design and quantitative exposure assessments of specific cleaning or disinfecting agents are recommended because they will decrease the potential of healthy worker effect bias and allow for the determination of an exposure-response relationship. Measuring exposure to specific cleaning or disinfecting agents in future studies will also help to further elucidate underlying causal agents. Also, further research regarding skin symptoms among healthcare workers with asthma-like respiratory symptoms is suggested. The studies that were included in this review evaluated asthma-like respiratory symptoms but have not fully explored the skin symptoms that may be concurrently occurring among healthcare workers with respiratory symptoms. Preventive measures that have been advised for those working with cleaning/disinfecting agents have included use of safe products when possible, safety education of workers, appropriate use of protective equipment, and good ventilation.44

Filling these gaps in knowledge could help with earlier prevention and treatment interventions to take place for these workers.

AUTHOR CONTRIBUTIONS
Kelly T.L. Dang: paper reviews; formal Analysis; writingReviewEditing. Kelly Dang performed formal analyses, wrote the original draft and contributed to review and editing of the final manuscript. Ameth Garrido contributed to the formal analyses, investigation, writing, and review of the manuscript. Shivonne Prasad contributed investigation, writing, and review of the manuscript. Marina Afanasyeva contributed to the project administration, review, and editing of the manuscript. Joshua Lipszyc contributed to the project conceptualization, investigation and review, and editing of the manuscript. Ani Orchanian contributed to the data curation, methodology, and writing, review, and editing of the manuscript. Susan M. Tarlo contributed to the project conceptualization, methodology, investigation, project administration, supervision, validation, and review and editing of the manuscript.

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CONFLICTS OF INTEREST
The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT
Additional data are available in the online supplement.

TRANSPARENCY STATEMENT
The lead author (manuscript guarantor) affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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Supporting Information
Additional supporting information can be found online in the Supporting Information section at the end of this article.

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