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REVIEW ARTICLE

The impact of indoor pollution on asthma-related outcomes: A systematic review for the EAACI guidelines on environmental science for allergic diseases and asthma

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Abstract

Systematic review using GRADE of the impact of exposure to volatile organic compounds (VOCs), cleaning agents, mould/damp, pesticides on the risk of (i) new-onset asthma (incidence) and (ii) adverse asthma-related outcomes (impact). MEDLINE, EMBASE and Web of Science were searched for indoor pollutant exposure studies reporting on new-onset asthma and critical and important asthma-related outcomes. Ninety four studies were included: 11 for VOCs (7 for incidenceand 4 for impact), 25 for cleaning agents (7 for incidenceand 8 for impact), 48 for damp/mould (26 for incidence and 22 for impact) and 10 for pesticides (8 for incidence and 2 for impact). Exposure to damp/mould increases the risk of new-onset wheeze (moderate certainty evidence). Exposure to cleaning agents may be associated with a higher risk of new-onset asthma and with asthma severity (low level of certainty). Exposure to pesticides

Abbreviations: ACQ, asthma control questionnaire; ACT, asthma control test; AHR, airway hyper-responsiveness; CI, confidence interval; EAACI, European Academy of Allergy and Clinical Immunology; ECRHS, European Community Respiratory Health Survey.; ED, emergency department; FEV1, forced expiratory flow in the first second; GDG, guideline development group; GINA, Global Initiative for Asthma; HR, hazard ration; NOS, Newcastle–Ottawa Scale; OR, odds ratio; PEF, peak expiratory flow; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; Q, question; QoL, quality of life; RCT, randomized control trial; ROB, risk of bias; ROBINS-E, Risk Of Bias In Non-randomized Studies - of Exposure; RR, risk ratio; SoF, summary of findings; SR, systematic review; VOCs, volatile organic compounds; WHO, World Health Organization.

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and VOCs may increase the risk of new-onset asthma (very low certainty evidence). The impact on asthma-related outcomes of all major indoor pollutants is uncertain. As the level of certainty is low or very low for most of the available evidence on the impact of indoor pollutants on asthma-related outcomes more rigorous research in the field is warranted.

KEYWORDS
asthma, GRADE, guideline, indoor pollution, systematic review

1 | INTRODUCTION

Asthma is a heterogeneous condition shaped by genetics and heavily driven by environmental factors acting, especially in early life, acting within the complex scaffold of the exposome.[1–7]

Around 90% of human activities are performed indoors, thus there is an increased risk of exposure to indoor air pollutants such as cleaning agents, damp and mould, pesticides, volatile organic compounds (VOCs), cooking and biofuels and many more, all of which can significantly impact respiratory health.[8–14]

Ongoing studies primarily aim to gain a deeper understanding of the mechanisms by which indoor exposure can cause or aggravate pre-existing asthma.[5,15–23] Indoor exposure to damp and mould can lead to the fungal colonization of airways and significantly increase levels of eosinophils.[24] VOCs have also been linked to the development of asthma,[8,10] however, their effects can vary greatly depending on their source (e.g. tobacco smoke, furniture polish or cleaners and lack of proper ventilation). Cleaning agents and indoor pesticides cause mucous epithelial damage and may initiate or aggravate pre-existing asthma through different mechanisms, however their clinical relevance is still yet to be proven.[25–39]

The aim of this systematic review (SR) and meta-analysis is to synthesize and update the current scientific evidence of the on the risk of developing asthma upon exposure to specific indoor pollutants and their impact on asthma-related outcomes. This SR was conducted in support of the recommendations enclosed in the clinical care guidelines developed by the European Society of Allergy and Clinical Immunology (EAACI) on the environmental science for allergic diseases and asthma. The SR includes most of the major indoor pollutants with the exception of tobacco smoke that is reviewed separately. Other components of the indoor exposome such as airborne allergens were not included, although we acknowledge their reciprocal interaction with the exposures assessed in this SR.

2 | METHODS

This SR follows the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[40]

2.1 | Structured question and outcome prioritization

The Guideline Development Group (GDG) framed four clinical questions (Q), as follows: 'Is indoor exposure to VOCs associated with development of asthma and/or asthma related outcomes?' (Q1), 'Is indoor exposure to cleaning agents associated with development of asthma and/or asthma related outcomes? (Q2)', 'Is indoor exposure to damp/mould associated with development of asthma and/or asthma related outcomes?' (Q3) and 'Is indoor exposure to pesticides associated with development of asthma and/or asthma related outcomes?' (Q4).

The GDG prioritized the outcomes using a 1-to-9 scale (7–9: critical; 4–6: important; 1–3: of limited importance), as suggested by the GRADE approach. For all questions, the population was defined as children or adults (i) without asthma to assess the risk of developing asthma; (ii) and with asthma to evaluate the impact on the disease-related outcomes. For assessing new-onset asthma the critical outcomes were incident asthma, incident recurrent wheezing and low lung function. For assessing the impact on pre-existing asthma, the critical outcomes were moderate and severe asthma exacerbations, asthma control (asthma control test (ACT) and asthma control questionnaire (ACQ)) and asthma-related quality of life (QoL; Table 1).

2.2 | Search methodology

Electronic search queries with a combination of controlled vocabulary and search terms were performed in the following databases: (i) MEDLINE (up until July 29, 2022); (ii) EMBASE (up until July 29 2022) and (iii) Web of Science Core (up until June 6 2022). Search queries were adapted to each database using validated filters to retrieve appropriate designs as needed (Table S1). The GDG checked the included/excluded studies for any missing studies or for those that could potentially be included in the SR.

2.3 | Eligibility criteria and selection of studies

For all clinical questions, the SR included observational studies (namely cohort, case control and cross-sectional studies) or

TABLE 1 Clinical questions and prioritization of outcomes for the systematic review.

	Q1	Q2	Q3	Q4
P (population)	Children or adults, (i) without asthma (incidence) and (ii) with asthma (impact)	Children or adults, (i) without asthma (incidence) and (ii) with asthma (impact)	Children or adults, (i) without asthma (incidence) and (ii) with asthma (impact)	Children or adults, (i) without asthma (incidence) and (ii) with asthma (impact)
E (exposure)	Indoor exposure to VOCs measured through air sampling including: benzene, ethylene glycol, formaldehyde, methylene chloride, tetrachloroethylene, toluene, xylene, and 1,3-butadiene	Indoor exposure to cleaning agents measured through air sampling including: bleach, ammonia, chlorohydric acid, quaternary ammonium products, laundry detergents, disinfectants, dishwashers	Indoor exposure to dampness or mould measured through air sampling including: water damage, damp stains or other dampness indicators, visible mould and mould odour	Indoor exposure to pesticides measured through air sampling including: carbamates, organophosphates, thiocarbamates, dithiocarbamates, organochlorines, pyrethroids, fungicides, fumigants, insecticides, pesticides and herbicides
C (comparison)	No exposure	No exposure	No exposure	No exposure
O (outcome) - incidence	(i) Critical: Incident doctor-diagnosed asthma, incident recurrent wheezing (for infants or pre-school children), low lung function (FEV1)	(i) Critical: Incident doctor-diagnosed asthma, incident recurrent wheezing (for infants or pre-school children), low lung function (FEV1)	(i) Critical: Incident doctor-diagnosed asthma, incident recurrent wheezing (for infants or pre-school children), low lung function (FEV1)	(i) Critical: Incident doctor-diagnosed asthma, incident recurrent wheezing (for infants or pre-school children), low lung function (FEV1)
O (outcome) - impact	(ii) Critical: severe or moderate asthma exacerbations, asthma control, asthma-related QoL	(ii) Critical: severe or moderate asthma exacerbations, asthma control, asthma-related QoL	(ii) Critical: severe or moderate asthma exacerbations, asthma control, asthma-related QoL	(ii) Critical: severe or moderate asthma exacerbations, asthma control, asthma-related QoL
O (outcome) - impact	(ii) Important: lung function (FEV1, PEF), asthma symptoms/well days, asthma medication	(ii) Important: Lung function (FEV1, PEF), asthma symptoms/well days, asthma medication	(ii) Important: lung function (FEV1, PEF), asthma symptoms/well days, asthma medication	(ii)Important: lung function (FEV1, PEF), asthma symptoms/well days, asthma medication

Note: Severe asthma exacerbations: ED visit or hospitalization for asthma and/or systemic corticosteroid use for >3 consecutive days.

Moderate asthma exacerbations: any change in symptoms or asthma medications not warranting ED visit or hospitalization for asthma and/or systemic corticosteroid use for >3 consecutive days.

Low lung function: FEV1 < 80% LLN.

experimental studies (i.e. randomized clinical trials (RTC)) that (i) assessed children or adults with or without asthma, (ii) measured objectively airborne exposure to VOCs (Q1), cleaning agents (Q2), damp/mould (Q3) or pesticides (Q4) occurring in indoor environments and (iii) assessed any of the outcomes of interest for incident asthma or for pre-existing asthma (Table 1). The SR for Q1 excluded studies that (i) defined exposure to VOCs based only on potential sources (i.e. carpet, furnishing and paint) or (ii) modelled the exposure but did not directly measure the concentration of VOC or (iii) defined exposure based on endogenous biomarkers. For all the questions abstracts or conference communications not published as full articles in peer reviewed journals, and publications in languages other than English were excluded.

Based on eligibility criteria, two reviewers independently screened the search results by title and abstract. Records which had not been excluded were then subsequently independently assessed by full-text reading by two reviewers. Disagreements were solved by consulting with a third reviewer.

2.4 | Data extraction and risk of bias assessment

After calibration, one reviewer used a pre-designed extraction form to obtain relevant data from eligible studies, including: study design, method of analysis, study location and exposure period, mean age and number of participants, exposure measurement and definitions/thresholds, outcome definition, effect estimates and their 95% confidence intervals (CI). The second reviewer then performed a quality control of the process (cross-check) and disagreements were solved by consulting a third reviewer. Publications were carefully analyzed to exclude the risk of including data from the same study more than once.

A similar approach for risk of bias (ROB) assessment was used with one reviewer assessing each study included, and the second reviewer performing the quality control, with disagreements solved by consensus. For observational studies, the risk of bias assessment was performed using the Risk Of Bias In Non-randomized Studies - of Exposures (ROBINS-E) tool.[41] This tool includes the following domains: (i) bias due to confounding, (ii) bias in selection of participants, (iii) bias in classification of exposures, (iv) bias due to departures from intended exposures, (v) bias due to missing data, (vi) bias in measurement of outcomes and (vii) bias in selection of reported results. The GDG prioritized the most significant confounders, including sex, age, smoking exposure, and allergy, which included parents' allergy in the case of the paediatric population. For randomized controlled trials (identified in Q3 and Q4), we assessed the risk of bias using the ROB 2.0 tool.[41] This tool includes the following domains: (i) random sequence generation (selection bias), (ii) allocation concealment (selection bias), (iii) blinding of participants and personnel (performance bias), (iv) blinding of outcomes assessment (detection bias), (v) incomplete outcome data (attrition bias) and (vi) selective reporting (reporting bias). The Newcastle–Ottawa Scale (NOS) was used for longitudinal studies. This scale was developed to assess the quality of non-randomized studies with its design, content and ease of use directed to the task of incorporating the quality assessments in the interpretation of results. The three domains included in NOS are (i) selection of the study groups, (ii) comparability of the groups and (iii) ascertainment of the outcome. These domains were classified with a 'star system'. Longitudinal studies (cohort and incidence case control) can be awarded a maximum of one star for each numbered item within the selection and outcome categories, and a maximum of two stars can be given for comparability. Studies scoring 8 or 9 were categorized as high quality.

2.5 | Data synthesis and analysis

Results were narratively described and tabulated in summary of findings (SoF) tables. Risk ratios (RR) and odds ratios (ORs) adjusted for confounders were used as the main measures of effect.[42] However, results expressed with other measures of effects were also described.

In the presence of studies of the same design and with similar methodological and clinical characteristics, effect estimates were pooled across studies using the generic inverse variance method. Heterogeneity was assessed using the I^2 statistic[11] and the Q Cochran test p-value, with $I^2 > 50\%$ and a p-value <.10 indicating substantial heterogeneity.[43] In the presence of substantial heterogeneity, the random-effects model was used; otherwise, meta-analysis was performed using the fixed-effects model. Subgroup analyses were conducted according to participants' age group (0–11, 12–17 and ≥ 18 years) and ROB. Publication bias statistics and funnel plots were not assessed, as we included less than 10 studies for each outcome. All statistical analyses were conducted with RevMan 3.5 software.

2.6 | Certainty of the evidence

The certainty (quality) of the evidence was rated for each outcome as high, moderate, low or very low, following the GRADE approach, and the synthesis of evidence is presented using summary of finding (SoF) tables.[44] Grading started from high certainty in randomized controlled trials and low certainty in observational studies. Quality was downgraded or upgraded according to the standard GRADE domains (ROB, imprecision, inconsistency, indirectness and publication bias).[45] In SoF tables the reporting of the adjusted estimations provided by longitudinal studies was prioritized.

3 | RESULTS

The search retrieved a total of 14,507 individual records from databases across all questions, which corresponds to 1507 records for Q1 (Figure 1a), 5509 records for Q2 (Figure 1b), 5549 records for Q3 (Figure 1c) and 1942 records for Q4 (Figure 1d). For

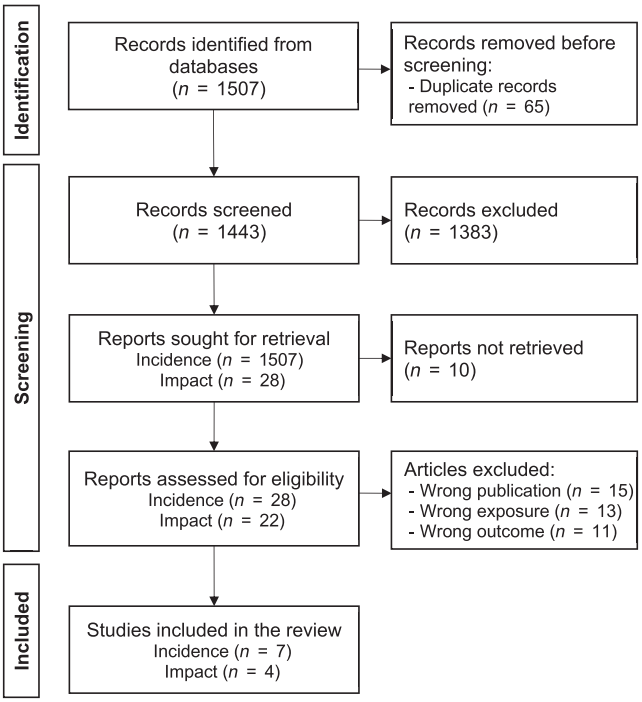

FIGURE 1 Study selection flow chart. (a) VOCs. (b) Cleaning agents. (c) Cleaning agents. (d) Pesticides.

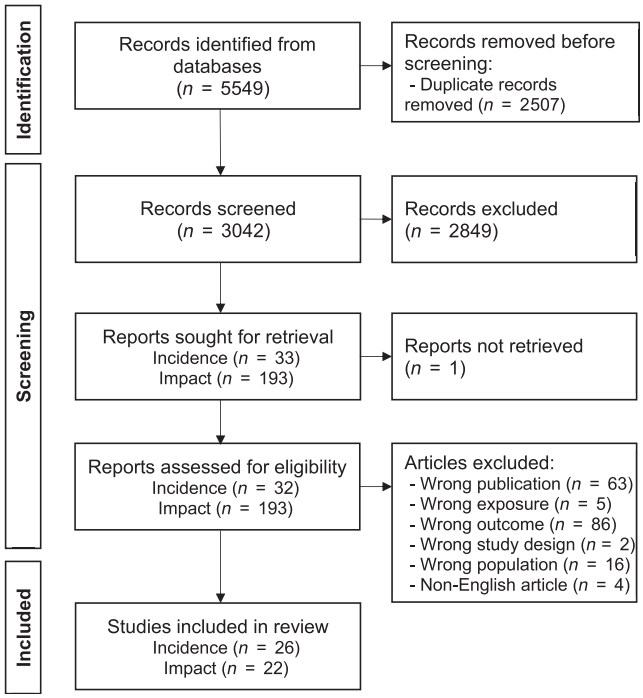

FIGURE 1 (Continued)

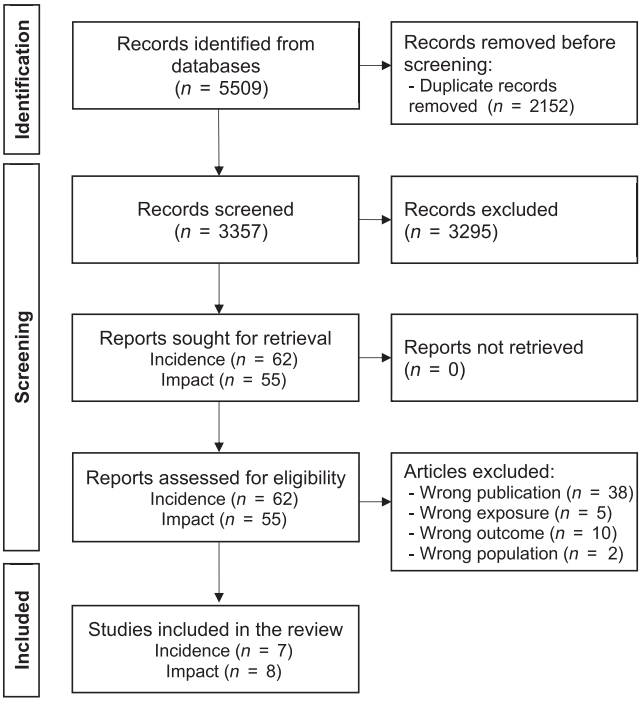

FIGURE 1 (Continued)

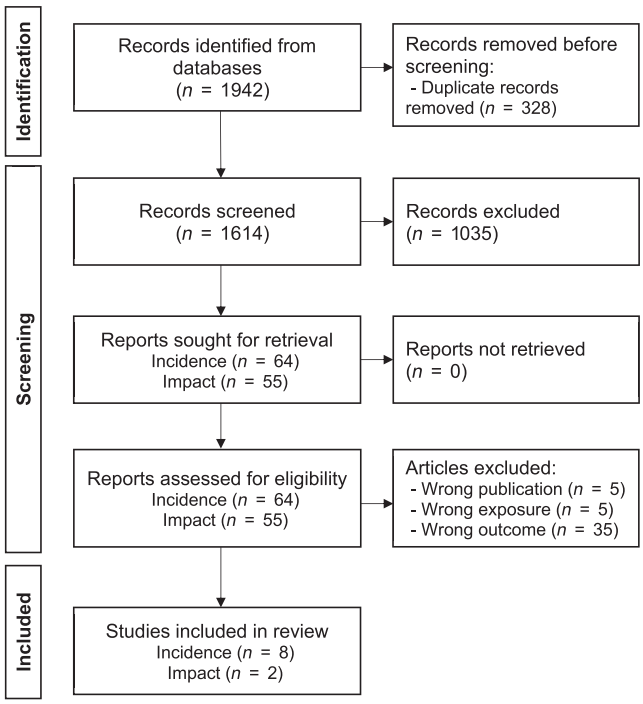

FIGURE 1 (Continued)

indoor exposure to VOCs, 7 studies were included for new-onset asthma[8,13,23,46–49] and 4 studies for the impact on asthma-related outcomes[50–53] (Tables 2.1 and 2.2). For exposure to cleaning agents, 7 studies were included for new-onset asthma[54–59] and 8 for the impact on asthma-related outcomes[31,60–66] (Tables 2.3 and 2.4). For damp/mould exposure, 26 studies were included for new-onset asthma[67–92] and 22 studies for the impact on asthma-related outcomes[93–114] (Tables 2.5 and 2.6). For pesticide exposure, 8 studies were included for new-onset asthma[115–122] and 2 studies for the impact on asthma-related outcomes[123,124] (Tables 2.7 and 2.8). Studies excluded at full text assessment and reasons for exclusion are described in Table S2.

TABLE 2.1 Characteristics of the studies included in the systematic reviews. Studies included for the risk of new-onset asthma following indoor VOC exposure.

Study	Study design	Country	Population (age range)	*N* participants	Exposure	Outcome
Smedje 2001	Cross-sectional	Sweden	Children (7–13 y)	1258	Formaldehyde, TVOCs	Incidence of physician-diagnosed asthma
Venn 2003	Case–control	UK	Children (6–8 y)	416	Formaldehyde, TVOCs	Persistent wheezing, frequent nighttime and daytime symptoms
Hulin 2010	Cross-sectional	France	Children (9–11 y)	114	Formaldehyde, Benzene, Toluene, Xylenes	Risk of developing asthma
Rawi 2015	Cross-sectional	Malaysia	Children (5–6 y)	111	TVOCs	FVC, FEV1, respiratory symptoms
Yu 2018	Cohort	China	Infants (≥4 m)	1414	Formaldehyde	New onset of wheeze
Maesano 2019	Cross-sectional	France	Adults (>15 y)	109	Benzene, Tetrachloroethylene, Toluene, Xylene	Presence of asthma
Rodrigues 2020	Cross-sectional	Portugal	Children (0–36 m)	131	TVOCs	Wheezing episodes

Abbreviations: FEV1, forced expiratory volume in one second; FVC, forced vital capacity; m, months; TVOCs, total volatile organic compounds; y, years.

TABLE 2.2 Studies included for the impact of indoor exposure to VOCs on asthma-related outcomes.

Study	Study design	Country	Population (age range)	*N* participants	Exposure	Outcome
Norback 1995	Cohort	Sweden	Adults (20–45 y)	47	Formaldehyde, Toluene, TVOCs	Asthma symptoms
Uba 1989	Before-after	USA	Adults (>18 y)	12	Formaldehyde	FEV1
Rive 2013	Cohort	France	Children (mean age 13.9 ± 0.78 y)	32	Benzene	Asthma symptoms
Harving 1990	Randomized controlled trial	Denmark	Adults (15–36 y)	15	Formaldehyde	FEV1

Abbreviations: FEV1, forced expiratory volume in one second; FVC, forced vital capacity; m, months; TVOCs, total volatile organic compounds; y, years.

3.1 | Exposure to indoor VOCs as risk factor to developing asthma

3.1.1 | Characteristics of studies included

Five studies were conducted in European countries and two were conducted in Asia. The number of participants ranged from 109 to 1414 per study. Most studies included children (up to 13 years old), while one study included only adults. Five studies were cross-sectional, one a case–control and one a cohort study (Table 2.1).

Four studies assessed exposure to total VOCs, while five assessed specific VOCs, such as formaldehyde, benzene, toluene, xylene and tetrachloroethylene. Six studies reported the VOCs assessment method as glass fibre filters, charcoal absorbent tubes, passive diffuser samplers, VOC monitors, PerkinElmer type sampling tubes and radial diffuse samplers. VOCs measuring periods (1 week) was defined and clearly reported in just two studies. The recruitment period was well defined in all the studies. All the studies assessed the outcomes with validated and standardized questionnaires (Table 2.1).

Four studies were classified as having a 'high ROB' and three as having a 'very high ROB'. This classification followed concerns about biases in potential confounding factors, exposure assessment and outcome assessments (Table S3).

3.1.2 | New-onset physician-diagnosed asthma

For physician-diagnosed asthma, three cross-sectional studies evaluated the association with total VOCs, two with formaldehyde, one with tetrachloroethylene and two with benzene, toluene and xylenes. Significant associations were inconsistently found, and only for benzene, formaldehyde, toluene and xylenes (in atopic patients). In all cases, the certainty of evidence was very low (Table 3.1).

TABLE 2.3 Studies included for the risk of new-onset asthma following indoor exposure to cleaning agents.

Study	Study design	Country	Population (age range)	*N* participants	Exposure	Outcome
Dumas 2020	Prospective cohort	USA and Canada	Female nurses (mean age 34 y)	17,280	High level of disinfectants	New clinician-diagnosis of asthma
Dumas 2019	Prospective cohort	USA	Female nurses (mean age 55 y)	61,539	Disinfectants	New clinician-diagnosis of asthma
Karjalainen 2002	Prospective cohort	Finland	Female cleaners (25–59 y)	54,000	Indirect exposure to cleaning products by industry	Incident cases of asthma
Kogevinas 2007	Population-based study	13 European countries	Cleaners (20–44 y)	410	Cleaning products	New-onset asthma
Mirabelli 2007	Prospective cohort	13 European countries	Female nurses (27–56 y)	332	Cleaning products	New-onset asthma
Sejbaek 2022	Population-based study	Denmark	Professional cleaners (16–50 y)	360,479	Cleaning products	Incident cases of asthma
Zock 2007	Prospective cohort	10 European countries	Household cleaners (20–48 y)	3503	Cleaning products	Physician-diagnosed asthma

Abbreviations: m, months; y, years.

TABLE 2.4 Studies included for the impact of indoor exposure to cleaning agents on asthma-related outcomes.

Study	Study design	Country	Population (age range)	*N* participants	Exposure	Outcome
Bernstein 2009	Prospective cohort	US	Adult women (18–65 y)	44 (25 with asthma)	Cleaning products	Lung function
Dumas 2014	Prospective cohort	France	Adult women (mean 48 y)	391 (73 with adult-onset asthma)	Cleaning products	Asthma severity Asthma control
Dumas 2021	Prospective cohort	France	Elderly women (70–76 y)	2223	Household cleaning products	Asthma control
Le Moual 2005	Case–control	France	Adults (mean 43 y)	148	Industrial cleaning products	Asthma severity
Le Moual 2012	Case–control	France	Adult women (mean 44 y)	683	Eight types of sprays included cleaning products	Asthma control
Le Moual 2014	Case–control	France	Adults (mean 43 y)	545	JEM (22 substances at risk of inducing asthma including cleaning agents)	Asthma control Asthma symptoms
Vizcaya 2013	Nested case–control	Spain	Adults (mean 42 ± 10 y)	42	Cleaning products	Lung function
Vizcaya 2015	Prospective cohort	Spain	Women adults (mean 45 y)	21	Cleaning products	Lung function

Abbreviations: JEM, job-exposure matrix; m, months; y, year.

3.1.3 | Persistent wheezing

For persistent wheezing, two cross sectional-studies and one case control study evaluated total VOCs and formaldehyde. In all studies except one (in which a protective association between total VOCs and persistent wheezing was observed), no association between exposure to VOCs and persistent wheezing was observed (very low certainty). Only exposure to formaldehyde was found to be potentially associated with a higher risk of new-onset wheeze (low certainty; Tables 3.1.1–3.1.4).

3.1.4 | Lung function

For lung function, a cross-sectional study reported no association with exposure to total VOCs (very low certainty; Table 3.1).

TABLE 2.5 Studies included for the risk of new-onset asthma following indoor exposure to dampness/mould.

Study	Study design	Country	Population (age range)	N participants	Exposure	Outcome
Nafstad 1998	Incident case control	Norway	Infants	502	Dampness and mould	New onset of asthma
Gent 2002	Cohort	USA	Infants	880	Dampness and mould	New onset of asthma
Jaakkola 2002	Incident case control	Finland	Adults (21–63 y)	1453	Dampness and mould	New onset of asthma
McConnell 2002	Cohort	USA	Children (9–11 y)	3535	Dampness	New onset of asthma
Ronmark 2002	Cohort	Sweden	Children (7–8 y)	3247	Dampness	New onset of asthma
Belanger 2003	Cohort	USA	Infants (2–4 m)	849	Mould	New onset of asthma
Emenius 2004	Incident case control	Sweden	Infants	540	Dampness and mould	New onset of asthma
Jaakkola 2005	Cohort	Finland	Children (1–7 y)	1916	Dampness and mould	New onset of asthma
Gunnbjornsdottir 2006	Cohort	5 European countries	Adults	15,995	Dampness and mould	New onset of asthma
Pekkanen 2007	Incident case control	Finland	Infants (12–92 m)	362	Dampness and mould	New onset of asthma
Karvonen 2009	Cohort	Finland	Infants	396	Dampness and mould	New onset of asthma
Rosenbaum 2010	Cohort	USA	Infants	103	Dampness and mould	New onset of asthma
Schroer 2009	Cohort	USA	Infants (12–14 m)	570	Dampness and mould	New onset of asthma
Hwang 2011	Incident case control	Taiwan	Children	564	Dampness and mould	New onset of asthma
Larsson 2011	Cohort	Sweden	Children (6–8 y)	4799	Dampness	New onset of asthma
Reponen 2011	Cohort	USA	Children	176	Dampness and mould	New onset of asthma
Norback 2013	Cohort	Europe, Australia, and USA	Young adults	7104	Dampness and mould	New onset of asthma
Behbod 2013	Cohort	USA	Infants	499	Mould	New onset of asthma
Hedman 2014	Cohort	Sweden	Children (7–8 y)	3151	Dampness	New onset of asthma
Rosenbaum 2014	Cohort	USA	Infants	103	Dampness	New onset of asthma
Karvonen 2015	Cohort	Finland	Infants	391	Dampness and mould	New onset of asthma
Thacher 2016	Cohort	Sweden	Infants	3293	Dampness and mould	New onset of asthma
Norback 2018	Cohort	China	Children (3–6 y)	39,782	Dampness and mould	New onset of asthma
Graff 2019	Cohort	Sweden	Adults	353	Dampness	New onset of asthma
Cox 2020	Cohort	USA	Children	556	Dampness	New onset of asthma
Saijo 2022	Cohort	Japan	Children	60,529	Mould	New onset of asthma

Abbreviations: m, months; y, years.

3.2 | Impact of indoor exposure to VOCs on asthma-related outcomes

3.2.1 | Characteristics of studies included

Three studies were conducted in Europe and one in the United States. One was a cohort study, one before-after study and one randomized controlled trial. The number of participants per study ranged from 12 to 47. Two studies included only adults, one only assessed children and another included both children and adults. Two studies assessed indoor exposure to VOCs (total VOCs, formaldehyde, toluene or benzene), one assessed exposure to formaldehyde in medical students attending an anatomy laboratory and one reported on experimental exposure to formaldehyde in a chamber with different concentrations (Table 2.2). None of the included studies evaluated the pre-specified SR critical outcomes, thus only important outcomes, namely asthma symptoms and lung function were available for the analysis (Table 2.2).

The randomized control trial was considered to have an unclear risk of bias (as details on the randomization and allocation concealment were not clear), the observational studies were considered to have a moderate ROB (mostly due to concerns in participant selection and in confounding; Table S3).

3.2.2 | Asthma symptoms

One cohort study reported that a 10-fold increase of VOCs may be associated with more self-reported episodes of nocturnal breathlessness or chest tightness in the previous 12 months, either considering total VOCs (OR = 9.9; 95% CI = 1.7–58.8), formaldehyde (OR = 12.5; 95% CI = 2.0–77.9) and toluene (OR = 4.9; 95% CI = 1.1–22.8) (evidence of very low certainty; Tables 3.2, 3.2.1 and 3.2.2). Another cohort study found no significant association between high exposure to benzene and self-reported

TABLE 2.6 Studies included for the impact of indoor exposure to dampness/mould on asthma-related outcomes.

Study	Study design	Country	Population (age range)	*N* participants	Exposure	Outcome
Burr 2007	RCT	UK	Adults (mean 26.8 ± 16.07 y)	232	Mould	Changes in variability of peak expiratory flow rate
Ross 2000	Cohort	USA	Adults and children (5–49 y)	57	Dampness and mould	Emergency room visit Speech limiting
Wever-Hess 2000	Cohort	Netherlands	Infants (mean 11 ± 5.7 m)	113	Dampness	Asthma exacerbation Hospitalization Recurrent exacerbation
			Infants (mean 38 ± 8.2 m)	144		
Belanger 2006	Cohort	USA	Children (0–12 y)	728	Dampness and mould	Shortness of Breath
Hagmolen 2007	Cohort	Netherlands	Children (mean 11 ± 2.5 y)	526	Dampness and mould	Severe airway hyper-responsiveness Asthma symptoms Peak Expiratory Flow Variability
Bundy 2009	Cohort	USA	Children (6–12 y)	225	Mould	Peak Expiratory Flow Variability
Gent 2012	Cohort	USA	Children (mean 7.47 ± 1.7 y)	1233	Mould	Rescue medication use Asthma severity score
Ciebiada 2014	Cohort	Poland	Adult	68	Mould	Persistent airflow obstruction
Baxi 2019	Cohort	USA	Children (mean 7.9 y)	351	Mould	Asthma symptom days
Bonner 2006	Cross-sectional	USA	NR	149	Dampness and mould	Hospitalizations
Teach 2006	Cross-sectional	USA	Children (1–17 y)	488	Mould	Asthma emergency visit Persistent asthma symptoms Quality of life
Ly 2008	Cross-sectional	Costa Rica	Children (mean 8.7 y)	439	Mould	Airway hyper-responsiveness
Deger 2010	Cross-sectional	Canada	Children (6 m - 12 y)	980	Dampness and mould	Asthma control
Visser 2010	Cross-sectional	Netherlands	Infant (mean 13.3 ± 1.8 m)	1105	Dampness and mould	Recurrent wheeze Emergency room visit
Gomes de Souza 2013	Cross-sectional	Brazil	Children (mean 10 ± 1.6 y)	59	Mould	Quality of life
Zubairi 2014	Cross-sectional	Pakistan	Adult (mean 46 ± 18 y)	391	Mould	Asthma exacerbation
Vesper 2006	Cross-sectional	USA	Children (6–14 y)	60	Mould	Persistent Asthma Emergency room visit Hospitalization
Wang 2017	Cross-sectional	Sweden	Adults	639	Dampness and mould	Current asthma medication Asthma exacerbation
Hsu 2018	Cross-sectional	USA	Adults	14,076	Mould	Hospitalization Emergency room visit
Cowan 2022	Cross-sectional	Puerto Rico	Adults	931	Mould	Asthma control
			Children (0–17 y)	177		
Strachan 1995	Case–control	USA	Children (11–16 y)	486	Dampness and mould	Frequent attacks Speech limiting
Hernberg 2014	Case–control	Finland	Children (21–63 y)	487	Dampness and mould	FEV1 levels FVC level

Abbreviations: FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; m, months; NA, not apply; NR, not reported; RCT, randomized controlled trial; y, years.

episodes of wheezing, wheezing after effort, dry cough and at least four wheezing episodes in the previous 12 months (wheezing: OR = 1.89, 95% CI = 0.39–9.23; dry cough: OR = 1.25, 95% CI = 0.19–7.88; wheezing after effort: OR = 10.38, 95% CI = 0.63–170.44; at least four wheezing episodes per year: OR = 2.95, 95% CI = 0.46–18.64; very low certainty; Table 3.2.3).

TABLE 2.7 Studies included for the risk of new-onset asthma following indoor exposure to pesticides.

Study	Study design	Country	Population (age range)	*N* participants	Exposure	Outcome
Alhanti 2022	Cross-sectional	Costa Rica	Pregnant women (>15 y; mean 29 y)	266	Multiple pesticides	Self-reported asthma (ever-diagnosed by physician)
Bukalasa 2018	Cross-sectional	Netherlands	Children (14 y)	1473	Herbicides, fungicides and plant regulators	Self-reported asthma (ever-diagnosed by physician)
Hallit 2017	Case–control	Lebanon	Children (3–16 y)	1503	Unspecified pesticide(s)	Self-reported asthma (ever-diagnosed by physician)
Salam 2004	Case–control	USA	Children (8–18 y)	691	Herbicides and pesticides	Self-reported asthma (diagnosed by physician before 5 years)
Salameh 2003	Cross-sectional	Lebanon	Children (5–16 y)	3291	Unspecified pesticide(s)	Self-reported asthma (ever-diagnosed by physician)
Salameh 2006	Case–control	Lebanon	Adults and children (12–99 y)	507	Unspecified pesticide(s)	Self-reported asthma (ever-diagnosed by physician)
Schneider 2004	Cross-sectional	Israel	Children (7–12 y)	6579	Unspecified pesticide(s)	Self-reported asthma (ever-diagnosed by physician)
Raherison 2019	Cohort prospective	France	Children (3–10 y)	281	Multiple pesticides	Self-reported asthma (ever-diagnosed by physician)

Abbreviation: y, years.

TABLE 2.8 Studies included for the impact of indoor exposure to pesticides on asthma-related outcome.

Study	Study design	Country	Population (age range)	*N* participants	Exposure	Outcome
Salome 2000	RCT	Australia	Adults (>16 y)	25	Insecticide aerosols	Lung function
Newton 1983	Quasi-experimental study	Australia	Adults (>18 y)	7	Insecticide aerosols	Lung function

Abbreviations: RCT, randomized control trial; y, years.

3.2.3 | Lung function

One before-and-after study assessing exposure to formaldehyde in medical students after a 7-month follow-up found no differences in the forced expiratory lung volume in the first second (FEV1) values (very low certainty). One RCT reported no significant changes in FEV1 values 90 min after the experimental chamber exposure to formaldehyde (Table 3.2.1).

3.3 | Exposure to cleaning agents as risk factor for developing asthma

3.3.1 | Characteristics of studies included

Five studies were performed in Europe and two in North America. All studies were prospective cohorts and included only adults. The number of participants included ranged from 332 to 360,479. Six studies focused on occupational exposure to cleaning products or disinfectants and one assessed household cleaners (residential use). All studies assessed the outcomes with validated and standardized questionnaires (namely, 2002–2006 Global Initiative for Asthma (GINA) guidelines, Asthma Control Test (ACT) and European Community Respiratory Health Survey (ECRHS I and II); Table 2.3).

Since all studies included subjects from other primary studies they were classified as having a moderate ROB arising from measurement of the exposure (Table S3).

3.3.2 | New-onset asthma

Three observational studies assessed the association between exposure to detergents and new-onset asthma in nurses followed over 5 years, with inconsistent results (low certainty of evidence). Only

TABLE 3.1 Summary of findings. Total volatile organic compounds (VOCs) exposure and risk of new-onset asthma.

Outcomes	*N* studies	Certainty of the evidence (GRADE)	Narrative
New-onset physician-diagnosed asthma	1 observational study	⨁◯◯◯ Very low[a,b]	The study did not find association between exposure to VOCs and incidence of physician-diagnosed asthma
Lung function (FVC and FEV1)	1 observational study	⨁◯◯◯ Very low[a,b]	The study did not find association between exposure to VOCs (concentrations between 0.08 and 0.11 ppm) and lung function when measured with FVC% and FEV1%
Persistent wheezing	3 observational studies	⨁◯◯◯ Very low[a,b,c]	Two studies reported no association, while one study reported a protective association between VOC exposure ≥0.103 ppm and asthma OR = 0.23 (95% CI = 0.09–0.61)

The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

Explanations: [a]Very serious risk of bias due to lack of adjusting for potential confounders (periodicity, other pollutants like pollen, indoor pollutants' interaction), missing data and potential misclassification during ascertainment of events. [b]Serious imprecision due to small sample size. [c]Serious imprecision because may be both harmful and beneficial.

TABLE 3.1.1 Exposure to benzene and risk of new-onset asthma.

Outcomes	*N* studies	Certainty of the evidence (GRADE)	Narrative
New -onset physician-diagnosed asthma	2 observational studies	⨁◯◯◯ Very low[a,b,c]	At a median concentration of 1.8 μg/m^3, one study did not find an association between benzene exposure and asthma (OR = 1.3; 95% CI = 0.4–3.8) At a median concentration of 10 μg/m^3 the other study found a higher risk of asthma associated with benzene exposure (OR = 6.64; 95% CI = 1.56–28.27)

Explanations: [a]Very serious risk of bias. Studies did not include potential confounders (periodicity, other pollutants like pollen, indoor pollutants' interaction); missing data and misclassification bias during ascertainment of events. [b]Serious imprecision due to the small sample size. [c]Serious imprecision due to the effect may be both harmful and beneficial.

TABLE 3.1.2 Exposure to formaldehyde and risk of new-onset asthma.

Outcomes	*N* studies	Certainty of the evidence (GRADE)	Narrative
New- onset physician-diagnosed asthma	3 observational studies	⨁◯◯◯ Very low[a,b,c]	Two cross-sectional studies in children reported a significant association between asthma incidence and an increment of 10 μg/m^3 of formaldehyde (OR = 1.90; 95% CI = 1.08–3.50 and OR = 1.7; 95% CI = 1.1–2.6). Another study reported no association, probably due to missing values (OR 0.31; 95% CI = 0.04–2.51)
New onset of wheeze	1 observational study	⨁⨁◯◯ Low [b]	One cohort study reported that indoor exposure to formaldehyde in infants significantly increased the risk of new onset of wheeze by 4% (95% CI = 1%–7%) per 10 units (μg/m^3) of exposure
Persistent wheezing	1 observational study	⨁◯◯◯ Very low[b,c]	No association was found at different formaldehyde concentrations according to a case–control study performed in children

The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

Explanations: [a]Very serious risk of bias due to not including potential confounders (periodicity, other pollutants like pollen, indoor pollutants interaction); missing data and misclassification bias during ascertainment of events. [b]Very serious imprecision due to the small sample size. [c]Serious imprecision due to the effect may both be harmful or beneficial.

one cohort study reported that cleaning products may be associated with the development of asthma in nurses exposed to cleaning agents (adjusted hazard ratio (HR) = 1.38; 95% CI = 1.03–1.85),[24] but this association was not found in the other two other studies (Table 3.3).

Another three observational studies assessed the association between exposure to cleaning agents and the new asthma risk among professional cleaners, with similarly low certainty of evidence. Two cohort studies that followed professional cleaners over 5 years (adjusted RR = 1.71; 95% CI = 0.92–3.17) and over 10 years (adjusted

TABLE 3.1.3 Exposure to toluene and risk of new-onset asthma.

Outcomes	N studies	Certainty of the evidence (GRADE)	Narrative
New- onset physician-diagnosed asthma	2 observational studies	⨁◯◯◯ Very low[a,b,c,d]	One cross-sectional study in children reported a positive association between a 10 μg/m^3 increase in toluene exposure and asthma (OR = 2.73, 95% CI = 1.28–5.83). The other cross-sectional study (in adults) did not find an association (adjusted OR = 0.37; 95% CI = 0.07–1.97)

Explanations: [a]Very serious risk of bias due to not including potential confounders (periodicity, other pollutants like pollen, indoor pollutants interaction); missing data and misclassification bias during ascertainment of events. [b]Very serious imprecision due to a small sample size. [c]Serious imprecision due to the effect may both be harmful or beneficial. [d]Serious inconsistency due to large variability.

TABLE 3.1.4 Exposure to xylenes and risk of new-onset asthma.

Outcomes	N studies	Certainty of the evidence (GRADE)	Narrative
New- onset physician-diagnosed asthma	2 observational studies	⨁◯◯◯ Very low[a,b,c,d]	Two cross-sectional studies evaluated the association between a 10 μg/m^3 increase in xylenes exposure and asthma. The study performed in adults reported no significant association (OR = 0.36; 95% CI = 0.08–1.72), The paediatric study showed a positive association only when the analysis was restricted to atopic cases (OR = 3.39; 95% CI = 1.21–7.80)

Explanations: [a]Very serious risk of bias due to not including due to not including potential confounders (periodicity, other pollutants like pollen, indoor pollutants interaction); missing data and misclassification bias during ascertainment of events. [b]Very serious imprecision due to a small sample size. [c]Serious imprecision due to the effect may both be harmful or beneficial. [d]Serious inconsistency due to large variability.

TABLE 3.2 Impact of total VOCs exposure on asthma-related outcomes.

Outcomes	N studies	Certainty of the evidence (GRADE)	Relative effect (95% CI)
Asthma symptoms	1 observational study	⨁◯◯◯ Very low[a,b]	OR 9.9 (1.7 to 58.8)

The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

Explanations: [a]Serious risk of bias. [b]Very serious imprecision due to a small sample size.

TABLE 3.2.1 Impact of indoor formaldehyde exposure on asthma-related outcomes.

Outcomes	N studies	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Narrative
Asthma Symptoms	1 observational study	⨁◯◯◯ Very low[a,b]	OR 12.5 (2.0 to 77.9)	–
Lung Function (FEV1)	2 studies; one before and after and another an RCT	⨁◯◯◯ Very low[a,b]	-	No significant changes in FEV1 after exposure to formaldehyde in a 90 min chamber challenge (RCT with different formaldehyde concentrations) or after 7 months follow-up (before-after study in medical students with mean peak exposure of 1.9 ppm)

The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

Explanations: [a]Serious risk of bias. [b]Very serious imprecision due to a small sample size.

RR = 1.50; 95% CI = 1.43–1.57) reported a possible excess asthma risk in comparison to administrative workers. Additionally, one study showed that 6 cumulative years of cleaning may be associated with an increase in the risk of new-onset asthma (adjusted incident rate ratio = 2.53; 95% CI = 1.38–4.64; Table 3.3).

For residential exposure one study found that the use of cleaning sprays (at least 4 days per week) in residential settings may be associated with an increase in the risk of physician-diagnosed new-onset asthma (adjusted HR = 2.11; 95% CI = 1.15–3.89; low certainty)[29] (Table 3.3).

TABLE 3.2.2 Impact of indoor toluene exposure on asthma-related outcomes.

Outcomes	*N* studies	Certainty of the evidence (GRADE)	Relative effect (95% CI)
Asthma symptoms	1 observational study	⨁◯◯◯ Very low[a,b]	OR 4.9 (1.1 to 22.8)

The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

Explanations: [a]Serious risk of bias. [b]Very serious imprecision due to a small sample size.

TABLE 3.2.3 Impact of indoor benzene exposure on asthma-related outcomes.

Outcomes	*N* studies	Certainty of the evidence (GRADE)	Relative effect (95% CI)
Asthma Symptoms - Wheezing in the past 12 months	1 observational study	⨁◯◯◯ Very low[a,b,c]	OR 1.89 (0.39 to 9.23)
Asthma Symptoms - Dry cough in the past 12 months	1 observational study	⨁◯◯◯ Very low[a,b,c]	OR 1.25 (0.19 to 7.88)
Asthma Symptoms - Wheezing after effort in the past 12 months	1 observational study	⨁◯◯◯ Very low[a,b,c]	OR 10.38 (0.63 to 170.44)
Asthma Symptoms - 4+ wheezing crises in the past 12 months	1 observational study	⨁◯◯◯ Very low[a,b,c]	OR 1.89 (0.46 to 18.64)

The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

Explanations: [a]Serious risk of bias. [b]Very serious imprecision due to a small sample size. [c]Serious imprecision due to the effect may both be harmful or beneficial.

TABLE 3.3 Exposure to cleaning agents and the risk of developing asthma.

Outcomes	*N* studies	Certainty of the evidence (GRADE)	Narrative
New-onset physician-diagnosed asthma in nurses	3 observational studies	⨁⨁◯◯ Low[a,b]	One study reported a positive significant association between >5 year use of detergents and incidence of asthma in female nurses (adjusted HR = 1.38; 95% CI = 1.03–1.85), but similar results were not found for shorter exposures A second study did not find an increased asthma risk associated with weekly use of disinfectants (adjusted HR = 1.11; 95% CI = 0.91–1.37) or sprays (adjusted HR = 1.11; 95% CI = 0.76–1.60) A third study showed that disinfection activities were not significantly associated with new-onset asthma (adjusted RR = 1.29; 95% CI = 0.70–2.36)
New-onset physician-diagnosed asthma in cleaners	3 observational studies	⨁⨁◯◯ Low[a,b]	Two studies reported that cleaners—compared to administrative workers—may have higher risk of new-onset asthma: adjusted RR = 1.50 (95% CI = 1.43–1.57) and adjusted RR = 1.71 (95% CI = 0.92–3.17) A third study found an association for those who had a 6-year exposure of cleaning (adjusted incidence-rate ratio = 2.53; 95% CI = 1.38–4.64), but not for shorter exposures or recent employed cleaners
New-onset physician-diagnosed asthma after residential exposure	1 observational study	⨁⨁◯◯ Low[a]	The study found that the use of house cleaning sprays at least 4 days/week in residential settings may be associated with increased incidence of asthma (adjusted HR = 2.11; 95% CI = 1.15–3.89). Such results were not observed for the use of less regular cleaning sprays. A higher risk of asthma was associated with the daily use of three or more types of cleaning spray

The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

Explanations: [a]Downgraded by one level due to missing data and risk of bias arising from measurement of the exposure and outcomes. [b]The effect may be both harmful and beneficial.

Regarding exposure to specific cleaning agents, the SR also found low or very low-quality evidence. In one study nurses exposed to ammonia and/or bleach were found at increased risk of new-onset asthma (adjusted RR = 2.16; 95% CI = 1.03–4.53; low certainty of evidence). The risk was not observed for glutaraldehyde (very low certainty of evidence). In the residential context, ammonia or bleach was not associated with increased risk of asthma development (low certainty of evidence; Tables 3.3.1 and 3.3.2).

TABLE 3.3.1 Exposure to glutaraldehyde and the risk of developing asthma.

Outcomes	*N* studies	Certainty of the evidence (GRADE)	Narrative
Incidence of physician-diagnosed asthma in nurses	2 observational studies	⨁◯◯◯ Very Low[a,b,c]	One study reported a positive (but not significant) association between glutaraldehyde and asthma incidence (adjusted HR = 1.55; 95% CI = 0.96–2.49); The second study showed that the use of glutaraldehyde was not associated with incident asthma (adjusted HR = 1.11; 95% CI = 0.88–1.41)

The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

Explanations: [a]Downgraded by one level due to missing data and risk of bias arising from measurement of the exposure and outcomes. [b]Downgraded by one level due to small sample size and wide confidence intervals. [c]The effect may be both harmful and beneficial.

TABLE 3.3.2 Exposure to ammonia and/or bleach and the risk of developing asthma.

Outcomes	*N* studies	Certainty of the evidence (GRADE)	Narrative
Incidence of physician-diagnosed asthma in nurses	1 observational study	⨁⨁◯◯ Low[a,b]	The study found that the use of ammonia and/or bleach increases the risk of new asthma-onset (adjusted RR = 2.16; 95% CI = 1.03–4.53)
Incidence of physician-diagnosed asthma (residential exposure)	1 observational study	⨁⨁◯◯ Low[a]	The study found that the use of bleach (adjusted RR = 1.10; 95% CI = 0.56–2.17) or ammonia (adjusted RR = 0.98; 95% CI = 0.52–1.86) was not associated with increased risk of new-asthma onset

The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

Explanations: [a]Downgraded by one level due to missing data and risk of bias arising from measurement of the exposure and outcomes. [b]Downgraded by one level due to small sample size and wide confidence intervals.

3.4 | Impact of exposure to cleaning agents on asthma-related outcomes

3.4.1 | Characteristics of studies included

All eight studies were performed in Europe and included adult patients with asthma. Study designs were prospective cohorts or case–controls. The number of participants included ranged from 21 to 2223. Five studies assessed occupational exposure to cleaning products and three evaluated residential exposure to common household detergents. Five studies included only female participants and one of them, exclusively, elderly women. Exposure was assessed by using different questionnaires and validated tools such as job-exposure-matrix or the ECRHS. Asthma control was assessed based on the GINA 2006–2010 guidelines or ACT (Table 2.4).

One study was classified as having 'low ROB', with the remainder having a moderate ROB (due to potential cofounding, measurement of the exposure, selection of participants and/or measurement of the outcomes; Table S3).

3.4.2 | Severe asthma exacerbations

One cohort study reported that the household use of cleaning sprays may increase the odds of severe asthma exacerbation in women (OR = 2.20; 95% CI = 1.20–4.04; low certainty; Table 3.4).

3.4.3 | Asthma control

Two studies reported on the association between occupational exposure to cleaning agents and poorly controlled asthma, one suggesting a possible association between 10 years of exposure to cleaning agents and poorly controlled-asthma in adult cleaners (OR = 2.30; 95% CI = 1.40–3.60) and the other reporting increased odds of poorly controlled-asthma following cleaning product exposure in female workers (OR = 2.19; 95% CI = 0.87–5.49). Both had low certainty of evidence (Table 3.4).

For residential exposures, two studies reported an association between the use of cleaning products and poorly controlled asthma in women of all ages (OR = 2.05 95% CI = 1.25–3.35) and in elderly women only (OR = 1.74; 95% CI = 1.13–2.70; low certainty). The latter study mentions that the weekly use of bleach may increase the odds of having poorly controlled asthma (OR = 1.34 95% CI = 1.03; 1.74; low certainty; Table 3.4).

3.4.4 | Asthma symptoms

One study reported a potential (but not significant) association between occupational exposure to cleaning agents and having ≥2 symptoms of asthma (OR = 2.19; 95% CI = 0.87–5.49)[31] (low certainty). For residential exposure, using ≥2 types of cleaning spray ≥1 day per week was associated with increased odds of ≥2 symptoms of asthma (OR = 2.50; 95% CI = 1.54–4.03)[34] (low certainty; Table 3.4).

TABLE 3.4 Impact of exposure to cleaning agents on asthma-related outcomes.

Outcomes	*N* studies	Certainty of the evidence (GRADE)	Narrative
Severe exacerbations (domestic exposure)	1 observational study	⨁⨁◯◯ Low[a]	The study found that the household use of cleaning sprays may increase the odds of severe asthma exacerbation in women (OR = 2.20, 95% CI = 1.20–4.04)
Asthma control (occupational exposure)	2 observational studies	⨁⨁◯◯ Low[a,b]	One study suggests a possible association between 10-year exposure to cleaning agents and poorly controlled-asthma in adult cleaners (OR = 2.30; 95% CI = 1.40–3.60) The second study reported that exposure to cleaning agents may increase the odds of having poorly controlled-asthma in female workers (adjusted OR = 2.19; 95% CI = 0.87–5.49)
Asthma control (residential exposure)	2 observational studies	⨁⨁◯◯ Low[a,b]	Two studies report an association between use of cleaning products and poorly-controlled asthma in women (OR = 2.05; 95% CI = 1.25–3.35) and in elderly women (OR = 1.74; 95% CI = 1.13–2.70) The latter study mentions that the weekly use of bleach may increase the odds of having poorly controlled asthma (adjusted OR = 1.34; 95% CI = 1.03–1.74), but the same impact was not observed for ammonia or furniture sprays
Asthma symptoms (occupational exposure)	1 observational study	⨁⨁◯◯ Low[a]	There may be an association between occupational exposure to cleaning products and ≥2 asthma symptoms (OR = 2.19, 95% CI = 0.87–5.49)
Asthma symptoms (residential exposure)	1 observational study	⨁⨁◯◯ Low[a]	The study suggests that using ≥2 types of cleaning spray ≥1 day per week may increase the odds of ≥2 asthma symptoms (OR = 2.50; 95% CI = 1.54–4.03)
Lung Function (occupational exposure)	2 observational studies	⨁◯◯◯ Very Low[a,b,c]	One study found that exposure to cleaning products is associated with decrease in the mean FEV_1/FVC (adjusted regression coefficient = −4.4, 95% CI = −7.4; −1.5) and FEV_1 (adjusted regression coefficient = −6.80, 95% CI = −14.0; 0.3) The second study reports decrease of FEV_1 after exposures to cleaning agents, with the largest drop occurring in relation to exposure to hydrochloric acid and powder soap/detergent
Lung Function (residential exposure)	1 observational study	⨁◯◯◯ Very Low[a,b,c]	Change in pre-cleaning and post-cleaning peak expiratory flow rates in asthmatic patients ranging from 123 to 95 L/s.
Asthma severity (occupational exposure)	2 observational studies	⨁⨁◯◯ Low[a,b]	The cohort study found that exposure to cleaning products is possibly related to severe persistent asthma (adjusted OR = 5.10, 95% CI = 1.70–15.3) The case–control study showed that the use of industrial cleaning agents was associated with severe asthma (adjusted OR = 7.20, 95% CI = 1.30–39.9)

The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

Explanations: [a]Downgraded by one level due to risk of bias arising from measurement of the exposure. [b]Downgraded by one level due to risk of bias in selection of participants into the study. [c]Downgraded by one level due to small sample size and wide confidence intervals.

3.4.5 | Lung function

There was very low certainty of evidence for an association between cleaning agents and impact on lung function, both for occupational and residential exposure. A case–control study in professional cleaners with asthma assessing the effect of detergents on FEV1 reported that asthma may be associated with an 8% decrease in post-bronchodilator FEV1 (95% CI = 1%–15%). A second study evaluating the short-term impact of exposure to cleaning agents on lung function among professional female cleaners with asthma reported decreases of 174 mL in FEV1 (95% CI = 34–314) and 37 L/min in the peak expiratory flow (PEF; 95% CI = 4–70), particularly in the days when three or more cleaning sprays are used. A prospective study assessing the effects of residential exposure to cleaning agents on PEF rates reported a change in pre-cleaning and post-cleaning PEF rates from 123 to 95 L/s in patients with asthma and 154 to 96 L/s in controls (Table 3.4).

3.4.6 | Asthma severity

Two studies that reported results for the association between occupational exposure to cleaning agents and asthma severity (low certainty of evidence). The cohort study reported that severe persistent

asthma may be associated with higher occupational exposure to cleaning products in women (OR = 5.10; 95% CI = 1.70–15.30). The case–control study suggested that the exposure to industrial cleaning agents may associate with increased odds of severe asthma in cleaners (OR = 7.20; 95% CI = 2.40–23.50).

3.5 | Exposure to mould/damp as a risk factor for developing asthma

3.5.1 | Characteristics of studies included

Thirteen studies were conducted in Europe, 10 in the United States, 3 in Asia and 1 study included European countries, Australia and the United States. All 26 studies were longitudinal, with 21 cohorts and 5 incident case–control studies. For most of the studies the follow-up periods ranged from 1 to 20 years. Twenty-two studies included children and 4 studies assessed adults. The number of participants per study ranged from 103 to 60,529 individuals. In 11 studies, exposure was evaluated through self-administered questionnaires, while 15 studies included visual inspection and sampling for exposure measurements (Table 2.5).

3.5.2 | New-onset asthma

Exposure to damp was evaluated as water damage exposure or any indicators of damp. Mould exposure was assessed through visible mould or mould odour (Tables 3.5.1–3.5.4). Most of the study results were adjusted for potential confounding factors.

Exposures to any damp indicator, moisture and visible mould were all associated with increased probability of new-onset asthma (moderate certainty; Tables 3.5.1, 3.5.3 and 3.5.4). For exposure to any damp the calculated OR for new-onset asthma was 1.43 (95% CI = 1.22–1.67), with no heterogeneity detected (I^2 = 0%; Q-Cochran test p-value = .56; Figure S1B,C). A stronger association was observed for studies assessing children (OR = 1.54; 95% CI = 1.24–1.91; I^2 = 0%; Q-Cochran test p-value = .93) than for those assessing adults (OR = 1.32; 95% CI = 1.05–1.65; I^2 = 78%; Q-Cochran test p-value = .03), even though that difference between subgroups was not significant (p = .33; Figure S2A,B). By including only high-quality studies similar overall risk was observed (meta-analytical OR = 1.32; 95% CI = 1.07–1.63; I^2 = 35%; Q-Cochran test p-value = .20; Figure S4). Type of exposure measurement did not influence the overall calculated risk (Figure S3A,B).

Exposure to moisture has meta-analytical OR = 1.48 (95% CI = 1.19–1.84) for developing new-onset asthma, although with

TABLE 3.5.1 Exposure to any dampness indicator and the risk of developing asthma.

Outcomes	*N* studies	Certainty of the evidence (GRADE)	Baseline risk	Meta-analytical relative effect (95% CI) [I^2]	Absolute effect (95% CI)
New-onset asthma	11 cohort studies	⨁⨁⨁◯ Moderate[a,b,c]	8.2%*	OR 1.43 (1.22 to 1.67) [0%]	+31 per 1000 (+16 to +48)
			9.4%*		+35 per 1000 (+18 to +54)

*We considered the incidence of asthma previously reported in adults and children in the European Union population (https://err.ersjournals.com/content/24/137/474).

Explanations: [a]The majority of the included studies have limitations in terms of the representativeness of the exposed cohort and the measurement of the exposure and outcome, which may have affected the accuracy of the estimates. Additionally, some studies did not conduct a sufficient follow-up to capture the outcome of interest. [b]The majority of studies show an increase in the risk of developing asthma, with overlapping confidence intervals. [c]Despite the asymmetry observed in the funnel plot, we do not have a strong suspicion of significant publication bias.

TABLE 3.5.2 Exposure to water damage and the risk of developing asthma.

Outcomes	*N* studies	Certainty of the evidence (GRADE)	Baseline risk	Meta-analytical relative effect (95% CI) [I^2]	Meta-analytical absolute effect (95% CI)
New-onset asthma	6 cohort studies	⨁⨁◯◯ Low[a,b,c,d]	8.2%*	OR 1.13 (0.98 to 1.30) [0%]	+10 per 1000 (−2 to +22)
			9.4%*		+11 per 1000 (−2 to +25)

*We considered the incidence of asthma previously reported in adults and children in the European Union population (https://err.ersjournals.com/content/24/137/474).

Explanations: [a]The majority of the included studies have limitations in terms of the representativeness of the exposed cohort and the measurement of the exposure and outcome, which may have affected the accuracy of the estimates. Additionally, some studies did not conduct a sufficient follow-up to capture the outcome of interest. [b]The majority of studies show an increase in the risk of developing asthma, with overlapping confidence intervals. [c]We considered an important variation of one case as clinically relevant. The confidence interval included a clinical relevant point. [d]Despite the asymmetry observed in the funnel plot, we do not have a strong suspicion of significant publication bias.

TABLE 3.5.3 Exposure to mould moisture and the risk of developing asthma.

Outcomes	*N* studies	Certainty of the evidence (GRADE)	Baseline risk	Meta-analytical relative effect (95% CI) [I^2]	Meta-analytical absolute effect (95% CI)
New-onset asthma	9 cohort studies	⨁⨁⨁◯ Moderate[a,b,c]	8.2%*	OR 1.48 (1.19 to 1.84) [42%]	+35 per 1000 (+14 to +59)
			9.4%*		+39 per 1000 (+16 to +66)

*We considered the incidence of asthma previously reported in adults and children in the European Union population (https://err.ersjournals.com/content/24/137/474).

Explanations: [a]The majority of the included studies have limitations in terms of the representativeness of the exposed cohort and the measurement of the exposure and outcome, which may have affected the accuracy of the estimates. Additionally, some studies did not conduct a sufficient follow-up to capture the outcome of interest. [b]The majority of studies show an increase in the risk of developing asthma, with overlapping confidence intervals. [c]Despite the asymmetry observed in the funnel plot, we do not have a strong suspicion of significant publication bias.

TABLE 3.5.4 Exposure to visible mould and the risk of developing asthma.

Outcomes	*N* studies	Certainty of the evidence (GRADE)	Baseline risk	Meta-analytical relative effect (95% CI) [I^2]	Meta-analytical absolute effect, (95% CI)
New-onset asthma	14 cohort studies	⨁⨁⨁◯ Moderate[a,b,c]	8.2%*	OR 1.34 (1.12 to 1.61) [65%]	+25 per 1000 (+9 to +44)
			9.4%*		+28 per 1000 (+10 to +49)

*We considered the incidence of asthma previously reported in adults and children in the European Union population (https://err.ersjournals.com/content/24/137/474).

Explanations: [a]The majority of the included studies have limitations in terms of the representativeness of the exposed cohort and the measurement of the exposure and outcome, which may have affected the accuracy of the estimates. Additionally, some studies did not conduct a sufficient follow-up to capture the outcome of interest. [b]Statistical ($p = .0004$, $I^2 = 65\%$) but unimportant heterogeneity. The majority of studies show an increase in the risk of development of asthma, with overlapping confidence intervals. [c]Despite the asymmetry observed in the funnel plot, we do not have a strong suspicion of significant publication bias.

moderate heterogeneity ($I^2 = 42\%$; Q-Cochran test p-value = .09). Heterogeneity ceases to be observed by considering only studies performed in children (meta-analytical OR = 1.87; 95% CI = 1.43–2.45; $I^2 = 35\%$; Q-Cochran test p-value = .56). No significant risk is observed however for mould moisture and new-onset asthma when considering only high-quality studies (OR = 1.01; 95% CI = 0.73–1.39; $I^2 = 0\%$; Q-Cochran test p-value = .69; Table 3.5.3).

For exposure to visible mould a meta-analytical OR = 1.34, (95% CI = 1.12–1.61) for developing asthma was calculated, with substantial heterogeneity ($I^2 = 65\%$; Q-Cochran test p-value < .001; Figure S5). Similar results were observed if (i) only studies performed in children were included (meta-analytical OR = 1.38; 95% CI = 1.11–1.71; $I^2 = 65\%$; Q-Cochran test p-value < .001) (Figure S6) or (ii) if only high-quality studies were included (meta-analytical OR = 1.34; 95% CI = 1.06–1.70; $I^2 = 50\%$; Q-Cochran test p-value = .07; Figure S7; Table 3.5.4). Type of exposure measurement did not influence the overall calculated risk (Figure S8).

Exposure to water damage was found to possibly increase the risk of new-onset asthma (meta-analytical OR = 1.13; 95% CI = 0.98–1.30; $I^2 = 0\%$; Q-Cochran test p-value = .63), with low certainty of evidence (Figure S1A). Similar results were observed in subgroup analyses if considering only paediatric studies (OR = 1.16; 95% CI = 0.92–1.46; $I^2 = 0\%$; Q-Cochran test p-value = .57) or only adult studies (OR = 1.11; 95% CI = 0.93–1.34; $I^2 = 28\%$; Q-Cochran test p-value = .25) or only high-quality studies (meta-analytical OR = 1.14; 95% CI = 0.98–1.32; $I^2 = 0\%$; Q-Cochran test p-value = .66; Table 3.5.2).

Ten studies assessing the association between damp/mould (not differentiated) and risk of new-onset asthma yielded a meta-analytical OR = 1.42 (95% CI = 1.20–1.69; $I^2 = 59\%$; Q-Cochran test p-value = .01; Figure S9).

3.6 | The impact of exposure to damp/mould on asthma-related outcomes

3.6.1 | Characteristics of studies included

Of the 22 studies identified, twelve were conducted in the United States, 1 in Canada, 7 in Europe, 1 in South America and 1 in Asia. There was one randomized controlled trial, 8 cohort studies, 2 case–control studies and 11 cross-sectional studies. Nine studies evaluated exposure to mould and damp combined, while 12 evaluated exposures to mould and 1 evaluated exposure to damp. More than half of the studies were performed in the paediatric population. Sample sizes ranged from 57 to 14,076 individuals. All studies except that of Bundy et al. were classified as having a high risk of bias (Table 2.6).

3.6.2 | Asthma exacerbations

The association between damp exposure and moderate asthma exacerbation was explored in four studies. The cohort studies suggested that damp exposure may increase the odds of moderate asthma exacerbation in children aged 0–1 years (adjusted OR = 7.60, 95% CI = 2.00–28.60) and 2–4 years (unadjusted OR = 1.63, 95% CI = 0.78–3.39), as well as increase the odds of recurrent exacerbation (adjusted OR = 3.80, 95% CI = 1.10–12.80). The case–control studies reported no significant association (adjusted OR = 1.31, 95% CI = 0.84–2.05). Given the diversity of study designs and of the populations assessed, meta-analysis was not performed. Evidence was considered as of very low certainty, with all studies having been classified as having a high risk of bias (Table 3.6.1).

One cohort study evaluated damp exposure and the risk of severe asthma exacerbation, with results displaying low precision (OR = 7.13; 95% CI = 0.83–61.28; very low evidence certainty; Table 3.6.1).

Five studies reported on the association between mould exposure and moderate asthma exacerbation (Table 3.6.2). Cross-sectional studies did not find an association between mould exposure or asthma exacerbations (adjusted OR = 1.21; 95% CI = 0.55–2.64).

For severe exacerbations following mould exposure three studies found increased adjusted odds of hospitalization but had less consistent results on emergency department visits (Figure S10). Overall, certainty in the obtained evidence was considered to have very low certainty (Table 3.6.2).

3.6.3 | Asthma control

Cross-sectional evidence suggests that damp and mould may be associated with higher odds of poor asthma control, but evidence was deemed as of very low certainty (Tables 3.6.1 and 3.6.2, Figure S11).

3.6.4 | Asthma-related QoL

We identified one cross-sectional study that assessed the association between mould exposure and asthma-related QoL.[101] The study

TABLE 3.6.1 Impact of dampness exposure on asthma-related outcomes.

Outcomes	*N* studies	Certainty of the evidence (GRADE)			
Moderate asthma exacerbation	4 observational studies*	⨁◯◯◯ Very Low[a,b,c]	In the cohort studies exposure to dampness increased the odds of moderate asthma exacerbation by 1.63 (95% CI = 0.78–3.39) in children aged 2–4 years old or 7.60 times (95% CI = 2.00–28.60) in children aged 0–1 year old. A positive association was found for recurrent exacerbation in children 0–1 year old Case–control studies and cross-sectional studies did not find significant impact of dampness exposure on asthma exacerbation risk		
			Baseline risk	Relative effect (95% CI)	Absolute effect (95% CI)
Severe asthma exacerbation	1 observational study	⨁◯◯◯ Very Low[d,e]	72.7%	OR 7.13 (0.83 to 61.28)	+223 per 1000 (−38 to +267)
Asthma control**	1 observational study	⨁◯◯◯ Very Low[f,b]	38.3%	OR 1.06 (0.91 to 1.23)	+23 per 1000 (−34 to +88)
Lung function	1 observational study	⨁◯◯◯ Very Low[f,b,c]	Case–control study suggested that exposure to dampness was not significantly associated with FEV1 or FVC decrease		
Asthma medication	1 observational study	⨁◯◯◯ Very Low[f,e]	38.3%	OR 1.35 (0.84 to 2.19)	+456 per 1000 (−40 to +193)

*The outcome included different study design; however, the SR prioritized the results of the cohort studies.

**The outcome of 'asthma control' is defined such that relative estimates greater than 1 indicate a higher probability of experiencing poor control.

Explanations: [a]The majority of estimates included in the outcome are based on study designs that may introduce selection bias or a lack of certainty regarding the temporal relationship between exposure and asthma outcomes. Most studies did not account for potential confounding factors and had missing data that could have impacted the estimates. Additionally, many studies show a high risk of bias in terms of the measurement of exposure and the selection of reported outcomes. [b]The confidence intervals of the included studies were wide, and most of them included trivial point. [c]The majority of studies had small sample sizes for this outcome, with less than 500 participants. [d]The study did not account for potential confounding factors and may have been subject to measurement errors, which could have influenced the estimates. [e]The confidence interval was wide and encompassed points of trivial and small relevant benefit (100 events). [f]The estimate included in the outcome is based on study design that may introduce selection bias or a lack of certainty regarding the temporal relationship between exposure and asthma outcomes. The study has a high risk of bias in terms of the measurement of exposure that probably underestimated the effect.

TABLE 3.6.2 Impact of mould exposure and asthma-related outcomes.

Outcomes	*N* studies	Certainty of the evidence (GRADE)	Basal risk	Relative effect (95% CI)	Absolute effect (95% CI)
Moderate asthma exacerbation	5 observational studies*	⨁◯◯◯ Very Low[a,b]	Cross-sectional studies did not find significant associations between mould exposure and asthma exacerbations		
Severe asthma exacerbation	4 observational studies*	⨁◯◯◯ Very Low[c,d,e]	The cohort study reported that the mould exposure associated with higher odds of emergency room visits (OR = 2.80; 95% CI = 0.70–11.10). This trend was also reported in two out of three cross-sectional studies		
Asthma control**	2 observational studies)	⨁◯◯◯ Very Low[a,f]	38.3%	Rate of prevalences 1.39 (1.04 to 1.86) [I^2 = 57%]	466 more per 1000 (395 more to 538 more)
Quality of life***	(1 observational study)	⨁◯◯◯ Very Low[g,b]	27.3%	PR 1.13 (0.95 to 1.33)	35 more per 1000 (14 fewer to 90 more)
Lung function	5 observational studies*	⨁◯◯◯ Very Low[a,h,i]	One cohort study suggested that mould exposure may increase the odds of persistent airways obstruction (OR = 2.25, 95% CI = 1.00–5.05) but other did not find an association with PEF variability (OR = 1.48, 95% CI = 0.32–6.87) Case–control and cross-sectional studies suggested that mould exposure decreased FVC but there were no changes in the FEV1 or airway hyper-responsiveness		
Asthma symptoms	5 observational studies*	⨁◯◯◯ Very Low[a,b]	One cohort study suggests that mould exposure associates with higher odds of shortness of breath (OR = 1.77; 95% CI = 1.22–2.55), with other reporting an association with speech limiting (OR = 2.20; 95% CI = 0.70–6.70). Another cohort study did not find an association between mould exposure and asthma symptom days (OR = 0.91; 95% CI = 0.63; 1.30). Cross-sectional studies did not find significant associations between mould exposure and asthma exacerbations		
Asthma medication	1 observational study	⨁◯◯◯ Very Low[j,b]	38.3%	OR 0.82 (0.37 to 1.79)	46 fewer per 1000 (197 fewer to 143 more)

*The outcome included different study design; however we prioritized the results of the cohort studies.

**The outcome of 'asthma control' is defined such that relative estimates greater than 1 indicate a higher probability of experiencing poor control.

***Evaluated with the Asthma quality of life score (categorized than less of 3 and more and equal of 3 points).

Explanations: [a]The majority of estimates included in the outcome are based on study designs that may introduce selection bias or a lack of certainty regarding the temporal relationship between exposure and asthma outcomes. Most studies did not account for potential confounding factors and had missing data that could have impacted the estimates. Additionally, many studies show a high risk of bias in terms of the measurement of exposure and the selection of reported outcomes. [b]The confidence intervals of the included studies were wide, and most of them included trivial point. [c]The majority of estimates included in the outcome are based on study designs that may introduce selection bias or a lack of certainty regarding the temporal relationship between exposure and asthma outcomes. All of the studies included have a high risk of bias or concerns related to confounding factors that may impact the results. Additionally, most of the studies have a high risk of bias in the measurement of exposure. [d]The confidence intervals of the included studies were wide, and most of them included trivial point. [e]The majority of studies had small sample sizes for this outcome, with less than 500 participants. [f]The confidence interval was wide and encompassed a moderate relevant benefit point (400 events). [g]The estimate included in the outcome is based on study design that may introduce selection bias or a lack of certainty regarding the temporal relationship between exposure and asthma outcomes. The study has a high risk of bias in terms of the measurement of exposure and the adjusting of confounding factors that probably affect the estimation. [h]We downgraded the evidence by one level because it is a surrogate outcome. [i]The confidence intervals of the included studies were wide, and included trivial or a small relevant benefit points (+1 point of the measure). [j]The estimate included in the outcome is based on study design that may introduce selection bias or a lack of certainty regarding the temporal relationship between exposure and asthma outcomes. The study has a high risk of bias in terms of the measurement of exposure that probably underestimated the effect.

suggests that mould exposure increases the prevalence of lower quality of life (prevalence ratio = 1.13, 95% CI = 0.95–1.33; very low certainty; Table 3.6.2).

3.6.5 | Asthma symptoms

Among cohort studies, one study reported that mould exposure may be associated with shortness of breath (unadjusted OR = 1.77, 95% CI = 1.22–2.55; data for paediatric patients). No association was found in relation to speech limiting (unadjusted OR = 2.20, 95% CI = 0.70–6.70) or asthma symptom days (unadjusted OR = 0.91, 95% CI = 0.63–1.30). Cross-sectional studies did not find either an association between mould exposure and persistent asthma symptoms (unadjusted OR = 1.00; 95% CI = 0.83–1.02; Table 3.6.2).

3.6.6 | Asthma medication

One cross-sectional study evaluated the association between damp and mould exposure and current asthma medication use. The study did not find a significant association for damp (OR = 1.35, 95%

CI = 0.84–2.19) or moulds exposure (OR = 0.82, 95% CI = 0.37–1.79), and the evidence had very low certainty (Tables 3.6.1 and 3.6.2).

3.6.7 | Lung function

The impact of damp exposure on lung function is uncertain based on one case–control study that evaluated the effect on FEV1 and FVC in adults (≥18 years old) who self-reported being exposed at home or work to water damage or visible damp. This study did not find an association between damp and decrease in FEV1 (adjusted regression coefficient = −0.04; 95% CI = −0.27; 0.18) or FVC (adjusted regression coefficient = 0.09; 95% CI = −0.06; 0.24; Table 3.6.1).

The impact of mould exposure on lung function was assessed in five studies, including two cohort studies, which suggested that mould exposure may increase the odds of persistent airways obstruction (OR = 2.25, 95% CI = 1.00–5.05), but not of PEF variability (OR = 1.48, 95% CI = 0.32–6.87). Case–control and cross-sectional studies suggested that mould exposure decreased FVC but there were no changes in the FEV1 or airway hyper-responsiveness. Overall, evidence displayed very low certainty (Table 3.6.2).

3.7 | Exposure to pesticides as a risk factor for developing asthma

3.7.1 | Characteristics of studies included

There were eight studies assessing the association between indoor exposure to pesticides and asthma development, four of which were performed in the Middle East, two in Europe, one in North America and one in Latin America. Four were cross-sectional studies, three studies were case–control studies and one was a prospective cohort study. All studies included children, and only two also assessed adults. The number of included participants ranged from 266 to 6579. Five studies assessed the outcomes with validated standardized questionnaires (Table 2.7).

3.7.2 | Incidence of new-onset asthma

Seven studies assessed the incidence of new-onset asthma following indoor exposure to pesticides. Four studies found that pesticides may be associated with the development of asthma, two studies did not find any association and one study found a potential protective association against developing asthma. Overall, the evidence certainty was classified as 'very low' (Table 3.7).

For fungicides exposure one study reported that exposure to mancozeb (OR = 1.28; 95% CI = 0.59–2.78), chlorothalonil (OR = 1.33; 95% CI = 0.53–3.31) or triadimenol (OR = 0.95; 95% CI = 0.41–2.21) did not significantly increase the risk of new-onset asthma (Table 3.7.1).

For insecticides, one study found that the exposure to chlormequat may be associated with asthma (OR = 1.75; 95% CI = 0.78–3.90; Table 3.7.2). The same study reported that herbicides may be associated with asthma (OR = 2.12; 95% CI = 0.94–4.75). However, these results were not significant and evidence was classified as low quality (Table 3.7.3).

3.7.3 | Lung function

One observational study did not find an association between exposure to spray or powder pesticides and PEF < 75% of predicted values (OR = 1.12; 95% CI = 0.88–1.41). The certainty of evidence was considered 'very low' (Table 3.7.1).

TABLE 3.7 Indoor exposure to pesticides and the risk of developing asthma.

Outcomes	*N* studies	Certainty of the evidence (GRADE)	Narrative
Incidence of new-onset asthma (ever-diagnosed by physician)	7 observational studies	⨁◯◯◯ Very Low[a,b,c]	Four studies reported a positive association (OR = 1.99, 95% CI = 1.05–3.87; OR = 2.39, 95% CI = 1.17–4.89; OR = 2.78, 95% CI = 1.18–6.67; OR = 1.99, 95% CI = 1.00–3.99) Two studies did not find a significant association (OR = 0.36, 95% CI = 0.09–1.55 and OR = 3.93, 95% CI = 0.40, 38.44) One study found a negative association (OR = 0.50, 95% CI = 0.34–0.74)
Lung function	1 observational study	⨁◯◯◯ Very Low[a,b,d]	The exposure to spray or powder pesticides was not significantly associated to PEF < 75% of predicted values (OR = 1.12, 95% CI = 0.88–1.41)

The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

Explanations: [a]Downgraded by one level due to missing data and risk of bias arising from measurement of the exposure and outcomes. [b]Downgraded by one level due to small sample size and wide confidence intervals. [c]The effect may be both harmful and beneficial. [d]Downgraded by one level due to not including potential confounders (atopy, measure of asthma severity, allergic status, etc.).

TABLE 3.7.1 Indoor exposure to fungicides and the risk of developing asthma.

Outcomes	*N* studies	Certainty of the evidence (GRADE)	Narrative
Incidence of new-onset asthma (ever-diagnosed by physician)	1 observational study	⨁⨁◯◯ Low[a,b]	The exposure to mancozeb (OR = 1.28, 95% CI = 0.59–2.78), chlorothalonil (OR = 1.33, 95% CI = 0.53–3.31) or triadimenol (OR = 0.95, 95% CI = 0.41–2.21) were not associated with asthma

The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

Explanations: [a]Downgraded by one level due to missing data and risk of bias arising from measurement of the exposure and outcomes. [b]Downgraded by one level due to small sample size and wide confidence intervals.

TABLE 3.7.2 Indoor exposure to insecticides and the risk of developing asthma.

Outcomes	*N* studies	Certainty of the evidence (GRADE)	Narrative
Incidence of new-onset asthma (ever-diagnosed by physician)	1 observational study	⨁⨁◯◯ Low[a,b]	Exposure to chlormequat was not significantly associated to asthma (OR = 1.75, 95% CI = 0.78–3.90)

The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

Explanations: [a]Downgraded by one level due to missing data and risk of bias arising from measurement of the exposure and outcomes. [b]Downgraded by one level due to small sample size and wide confidence intervals.

TABLE 3.7.3 Indoor exposure to herbicides and the risk of developing asthma.

Outcomes	*N* studies	Certainty of the evidence (GRADE)	Narrative
Incidence of self-reported asthma (ever-diagnosed by physician)	1 observational study	⨁⨁◯◯ Low[a,b]	Herbicides may be associated with asthma (although non-significantly) (OR = 2.12, 95% CI = 0.94–4.75)

The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

Explanations: [a]Downgraded by one level due to missing data and risk of bias arising from measurement of the exposure and outcomes. [b]Downgraded by one level due to small sample size and wide confidence intervals.

3.8 | Impact of indoor exposure to pesticides on asthma-related outcomes

3.8.1 | Characteristics of included studies

Both studies included were conducted in Australia. One was a randomized clinical trial with a cross-over design, while the other had a before and after exposure design. The number of participants included ranged from 7 to 25. Both studies included adults. Both studies were classified as having a high ROB. The studies included only assessed the impact of pesticide exposure on lung function (FEV1; Table 2.8).

3.8.2 | Lung function

The certainty for the available evidence is 'very low'. The double blind randomized clinical trial compared the impact of standard and 'low irritant' insecticide aerosols on lung function and found that the use of insecticides produced a maximum fall in FEV1 in comparison to negative control of 3.3 ± 3.6% for aerosol 5.1 ± 4.7% for aerosol B and 5.1 ± 2.1% for the 'low irritant' aerosol. The before and after study reported that after exposure to standard insecticides, the FEV1 fell more than 20% compared to baseline values in 14% of patients (Table 3.8).

4 | DISCUSSION

4.1 | Main findings

The current SR critically appraised the evidence from 94 studies: 11 studies for exposure to VOCs (7 for new-onset asthma and 4 for impact on asthma-related outcomes), 25 studies for exposure to cleaning agents (7 for new-onset asthma and 8 for impact on asthma-related outcomes), 48 studies for damp/mould exposure (26 for new-onset asthma and 22 for impact on asthma-related outcomes) and 10 studies for indoor exposure to pesticides (8 for new-onset asthma and 2 for impact on asthma-related outcomes).

Low certainty evidence shows that exposure to formaldehyde may be associated with a higher risk of new onset of wheeze. There is very low certainty of evidence on exposure to VOCs and risk of

TABLE 3.8 Impact of indoor exposure to pesticides on asthma-related outcomes.

Outcomes	*N* studies	Certainty of the evidence (GRADE)	Narrative
Lung function (occupational exposure)	One RCT and one before and after design	⊕◯◯◯ Very Low[a,b]	The RCT study reported a higher maximum fall in FEV_1 was for older insecticide formulation (mean difference fall = 3.3 ± 3.6%) and for aerosol B (mean difference fall = 5.1 ± 4.7%) in comparison to the negative control The other study reported that 14.2% of patients had a clinically relevant fall in FEV_1 (greater than 20% compared to baseline value) after standard exposure to insecticide

The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

Explanations: [a]Downgraded by two levels due to risk of bias in selection of participants into the study and random sequence generation, allocation concealment, blinding of participants, personal, and outcomes, and unclear reporting. [b]Downgraded by one level due to small sample size and wide confidence intervals.

new-onset physician-diagnosed asthma and persistent wheeze, and on its impact on asthma symptoms and lung function.

Similarly, low certainty of evidence was encountered for exposure to cleaning agents, and the risk of new-onset asthma or exacerbation of asthma.

Based on moderate certainty of evidence, exposure to visible mould/mould odour and damp, as evaluated by any indicator, probably increases the risk of developing asthma. The evidence for the impact of water damage exposure on risk of asthma onset has low certainty. There is uncertain evidence for the impact of damp and mould exposure on the asthma-related outcomes.

The evidence of the effect of exposure to indoor pesticides on the risk of developing asthma is of low certainty, while for the impact of indoor pesticides on lung function is unclear with very low certainty of evidence.

4.2 | Results in the context of previous published SR and key trials

Our results are well aligned with the SR of Nurmatov et al.[10] that showed that the available evidence implicating domestic VOC exposure in the risk of developing and/or exacerbating asthma and allergy is of poor quality and inconsistent. Different from our SR Nurmatov et al. used the Effective Public Health Practice Project for observational and the Cochrane Effective Practice and Organisation of Care criteria for intervention studies to assess the methodological quality. The search for eligible studies was until 2012. Unfortunately, the inclusion of 10 years of additional research in our SR did not change the quality of the data available and there is still a high unmet need for prospective studies, investigating the impact of reducing/eliminating exposure to VOCs, in order to generate a more definitive evidence base to inform policy and clinical deliberations in relation to the management of the now substantial sections of the population who are either at risk of developing asthma or living with established disease. A more recent SR which reviewed a similar number of studies reviewed concluded that indoor exposure to VOCs increases the risk of asthma and asthma-related symptoms, even when they reported mixed findings from each primary study.[9] This SR performed for the EAACI guidelines differs as it rigorously assessed the risk of bias of the studies included and the certainty of the findings, and thus found that the evidence on the impact of exposure to VOCs on both asthma incidence and asthma-related outcomes is very uncertain. Another SR published in 2017 reported that each 10 μg/m^3 increase in formaldehyde exposure was associated with a significant increase in the risk of asthma in children, but not in adults.[8] Although our results are in line with this review, our confidence in the results is very low due to the very serious risk of bias of the studies. The most recent SR by Maung et al.[12] evaluated categories of risk (children and patients with respiratory diseases) and looked specifically at major VOC sources and on the factors increasing the likelihood of a negative impact on respiratory health. This SR concluded that high VOCs were associated with upper airways and asthma symptoms and as well as cancer. It also showed that formaldehyde levels were particularly high in new houses and that personal exposure related to both indoor and outdoor pollutant levels, home characteristics and air exchange rates, temperature, humidity, educational level, air purifiers and time near sources. Different from our SR Maung et al. carried out quality assessment of the studies according to the Joanna Briggs Institute Critical Appraisal Tool[125] which contrarily to GRADE generally found the studies included at low risk of bias, which is not surprising as this appraisal tool does not check for risk of bias, imprecision, inconsistency, indirectness or publication bias.

A previous SR found a positive association between the level of exposure to cleaning products and specific job tasks and the risk of asthma, but the authors did not asses the quality of evidence.[126] Another SR reported in line with the previous one, that cleaners have a 50% increased pooled relative risk of developing asthma, however the quality of evidence reported is unclear.[127] In our review we also found a positive association, but the quality of evidence is low. Similar results were recently reported in a nationwide Danish population-based study where asthma risk was increased in the inception cohort for cumulative years of cleaning but decreased in the full cohort and the study could not confirm that recent work within cleaning products was associated with an increased risk of asthma.[28] The multicentre Respiratory Health in Northern Europe,

Spain and Australia generation study showed that mother's occupational exposure to indoor cleaning agents starting before conception, or around conception and pregnancy, was associated with more childhood asthma and wheeze in offspring.[29] Similarly, the Canadian Healthy Infant Longitudinal Development Cohort Study showed that frequent use of household cleaning products in early life was associated with an increased risk for childhood wheeze and asthma but not atopy at age 3 years.[30] These pivotal trials published after our SR was performed showed the importance of good quality data from longitudinal well characterized cohorts and provide hope for the next appraisal of the literature on exposure to cleaning agents, which is planned for the upcoming EAACI guidelines update in 2028.

There is consistent evidence from previous SRs linking mould and damp exposure to increased risk (1.09–2 times) for new-onset asthma.[128–130] Our SR yielded similar results reporting and increased risk from 1.13 to 1.48 times. However, it is important to note that all of these findings are based on observational studies, which are susceptible to confounding bias, as previously reported.[130] This issue is particularly relevant for asthma, which has a multifactorial pathogenesis that involves multiple exposures within the frame of the exposome. In addition, assessing mould and damp exposure can be challenging because different indicators are measured across studies using various methods. This variability can affect the way estimates are analyzed and reported for each indicator and does not provide an overall risk. A previous SR reported that exposure to damp indicators is associated with a less certainty as compared to mould indicators.[129] The difference in effect size may be attributed to less extensive damage or damage of shorter duration. However, it is important to note that the estimation of damp exposure may be more difficult than that of mould, as it often relies on subjective perceptions reported by study participants. The absence of longitudinal evidence on the impact of damp or mould creates uncertainty about their impact on asthma-related outcomes, highlighting the need for further research. Moreover, the causal relationship between exposure to mould and damp and asthma symptoms remains unclear, including the specific microbiological agents involved and the time frame for exposure.[24,131]

Two SRs on pesticides exposure were run in parallel and published in 2022 and 2023, suggesting an association between pesticide exposure and childhood wheeze and asthma[37] or claiming a twofold greater risk of developing or exacerbating asthma in children and adolescents.[39] Gilden et al.[37] included 25 studies, 8 for prenatal pesticide exposure ($n=8407$), 12 for postnatal exposures ($n=50,488$) and 5 for pre-and postnatal exposures ($n=20,919$). The main pesticides investigated were dichlorodiphenyldichloroethylene (14 studies) and organophosphates (7 studies). Different from our SR primary methods of outcome assessment were questionnaire-based (84%), followed by spirometry (16%), registry data and blood measures. Quality of data was not appraised using GRADE. Similarly, the Rodriguez SR[39] used for quality analysis the Methodological Items for Non-Randomized Studies tool that does not account for ROB, imprecision, inconsistency, indirectness and publication bias.

4.3 | Limitations and strengths

This systematic review has several strengths. It is based on an exhaustive electronic search in three large databases. The GDG was consulted for studies potentially relevant to answer each clinic question. More importantly, strict methods were used to evaluate the quality of the available evidence regarding the exposures of interest: (i) we first selected and prioritized the outcomes of interest for the population and for the clinical question; (ii) the GRADE approach was used to evaluate the certainty of the evidence for each outcome, considering the risk of bias of the included studies, inconsistency, imprecision and indirectness; (iii) findings are presented in a format that facilitates clear communication with all stakeholders.

However, only observational studies were available, so the quality of the evidence was moderate at its best. In addition, cross-sectional and case–control studies were used to assess the association between pesticide indoor exposure and asthma incidence, which is of course not ideal. As the studies included reported only asthma-related outcomes we could not conduct a subgroup analysis based on the presence or absence of asthma comorbidities, such as rhinitis, that might clearly impact asthma-related outcomes.

Another inherent limitation is the difficulty of quantifying chronic exposure, particularly at the personal level. Measurements suffer from their own imprecision, often cross-sectional nature and a wide variability depending on external characteristics (e.g. the room, vertical dispersion and rhythm of ventilation and more). Taking into account that the pathophysiological effects may depend upon different models (e.g. thresholds or persistence), we can only expect a very rough estimation of true exposure at a personal level.

Another important gap stems from the fact that pollutants are more often evaluated individually, while the possibility of between-pollutant interactions has been neglected.[132] In the same line interactions with other components of the indoor exposome like allergens were not evaluated.

4.4 | Implications for practice and research

Indoor air pollution is becoming an increasing proportion of the problem as improvements in outdoor air pollution occur, yet indoor air quality has been studied much less than outdoors. According to the UK Chief Medical Officer's annual report 2022, a better understanding of how we can prevent and reduce indoor air pollution should now be a priority.[22,133,134]

This systematic review shows that there is very limited evidence about exposure to indoor pollutants and risk of developing asthma or impact on asthma-related outcomes. Thus, only conditional recommendations for clinical practice or for policy makers and regulators can be formulated. High-quality interventional studies using better and consistent exposure measures, as well as clearer outcome definitions are urgently needed to assess with certitude the impact of exposure to indoor pollutants.

An improved methodological approach proving causality instead of associations together with an integrated surveillance network for the overall environmental impact on asthma-related outcomes is a key pillar to move this field forward. More can be achieved by validated criteria for selecting the best assay(s) to assess exposure and the biological response for the research question of interest, by easy-to-implement guidelines for sample collection, by shared repositories and biobanks and by implementing the exposomics, cross-omics approach and system biomedicine.

5 | CONCLUSION

It is hypothesized that exposure to indoor pollutants has a significant impact on asthma inception and severity. In support of the EAACI guidelines recommendations extensive and systematic reviews were conducted providing a structured summary incorporating GRADE assessments. Our findings suggest trends that indicate a potential link between indoor exposure and an increased incidence and impact of asthma outcomes. However, there is a high level of concern about the certainty of the evidence, highlighting the need for more rigorous cohort studies to better understand the risks.

AUTHOR CONTRIBUTIONS

Ioana Agache, Carlos Canelo-Aybar, Wendy Nieto-Gutierrez, Marek Jutel and Cezmi A. Akdis drafted the detailed protocols for the systematic reviews, supervised the overall research process and wrote the manuscript. Josefina Salazar, L. Yesenia Rodríguez-Tanta, Yahveth Cantero, Camila Montesinos, Yang Song, Giancarlo Alvarado-Gamarra, Ivan Sola conducted the searches and the analysis under the supervision of Pablo Alonso-Coello. All the other authors revised and approved the search protocols, revised the data from the systematic reviews and the final manuscript.

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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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