Environmental Research 202 (2021) 111631

Contents lists available at ScienceDirect

Environmental Research

journal homepage: www.elsevier.com/locate/envres

Indoor PM2.5, VOCs and asthma outcomes: A systematic review in adults and their home environments

C.A. Paterson[a,*], R.A. Sharpe[b], T. Taylor[a], K. Morrissey[a]

[a] European Centre for Environment and Human Health, University of Exeter Medical School, University of Exeter, Knowledge Spa, Royal Cornwall Hospital, Truro, Cornwall, TR1 3HD, UK

[b] Public Health, Cornwall Council, 1E, New County Hall, Truro, TR1 3AY, UK

ARTICLE INFO

Keywords:
VOCS
PM2.5
Asthma
Indoor environment
Home environment

ABSTRACT

Introduction: As the amount of time people spend indoors increases globally, exposure to indoor air pollutants has become an important public health concern. Asthma is a complex disease caused and/or exacerbated by increased exposure to diverse chemical, physical and biological exposures from multiple indoor and outdoor sources. This review aims to investigate the relationship between increased indoor PM and VOC concentrations (i.e. objectively measured) and the risk of adult asthma in higher-income countries.

Methods: Eleven databases were systematically searched on the February 1, 2019 and again on the February 2, 2020. Articles were limited to those published since 1990. Reference lists were independently screened by three reviewers and authors were contacted to identify relevant articles. Backwards and forward citation chasing was used to identify further studies. Data were extracted from included studies meeting our eligibility criteria by three reviewers and assessed for quality using the Newcastle-Ottawa scale designed for case-control and cohort studies.

Results: Twelve studies were included in a narrative synthesis. We found insufficient evidence to determine the effect of PM2.5 on asthma in the indoor home environment. However, there was strong evidence to suggest that VOCs, especially aromatic compounds, and aliphatic compounds, were associated with increased asthma symptoms.

Discussion & conclusion: Although no single exposure appears to be responsible for the development of asthma or its associated symptoms, the use of everyday products may be associated with increased asthma symptoms. To prevent poor health outcomes among the general population, health professionals and industry must make a concerted effort to better inform the general population of the importance of appropriate use of and storage of chemicals within the home as well as better health messaging on product labelling.

1. Introduction

The prevalence of asthma among children and young people have been well documented (Asher et al., 2006, Pearce et al., 2007; Lai et al., 2009), but fewer studies have investigated asthma in adulthood. While rates vary (BLF, 2019; Mukherjee et al., 2016), it is thought that around 10% of adults have doctor-diagnosed asthma in the United Kingdom (U.K.). This represents one of the higher prevalence rates in the world (Netuveli et al., 2005) and poses a significant economic and societal burden (Takaro et al., 2011; Salo et al., 2014). Asthma is a complex heterogeneous disease characterised by airway inflammation, which can be caused and/or exacerbated by increased exposure to diverse chemical, physical and biological exposures (Sharpe et al., 2015b). Chemical, physical and biological exposures within the home are a public health concern as the amount of time people spend indoors increases. For example, Europeans now spend 89% of time indoors (McGratha et al., 2017). Around 70% of this time is in the home environment (Klepeis et al., 2001; Schweizer, 2007; Torfs et al., 2008), which increases to around 90% in vulnerable populations such as the very young, the infirm and elderly (Torfs et al., 2008; Spalt et al., 2016).

The interaction between indoor biological agents such as house dust mites and mould has been well documented (Sharpe et al., 2015a).

* Corresponding author.
E-mail addresses: C.b.paterson@exeter.ac.uk (C.A. Paterson), Richard.sharpe@cornwall.gov.uk (R.A. Sharpe), Timothy.J.Taylor@exeter.ac.uk (T. Taylor), K.Morrissey@exeter.ac.uk (K. Morrissey).

https://doi.org/10.1016/j.envres.2021.111631
Received 4 February 2021; Received in revised form 25 June 2021; Accepted 29 June 2021
Available online 2 July 2021

Fewer studies have investigated the potential impact of indoor particulates (PM2.5 and PM10) and volatile organic compounds (VOCs) such as formaldehyde (WHO, 2010). The concentrations of indoor PM and VOCs are largely dependent on resident behaviours (e.g. cooking, heating and environmental tobacco smoke), the presence of damp and mould (presence of microbial VOCs) and the reintroduction of chemicals into the home environment (e.g. new furnishings and building products (Sharpe et al., 2014). Increased exposure to indoor PM and VOC concentrations are thought to increase the risk of asthma (Arif and Shah, 2007a, Kwon et al., 2018; Guarnieri and Balmes, 2014, Hulin et al., 2012) and can enhance the bronchial responsiveness to other allergens in sensitised individuals (Casset et al., 2006). However, prior studies have reported inconsistent evidence between formaldehyde and VOCs and risk of asthma (Hussain et al., 2019; Mitha et al., 2013). The risk of childhood asthma and interest in these exposures (e.g. particulates increases oxidative stress and inflammation in the lungs (Mir, 2007)), has led to a number of prior reviews investigating elevated PM and VOCs and childhood asthma (Kelly and Fussell, 2015; Patelarou et al., 2015, Dick et al., 2014; AL-daghri et al., 2013). Fewer studies have focused on the interaction between indoor PM and VOCs and asthma in adulthood. Furthermore, prior studies have used a variety of proxy measures of indoor air quality (Jaakkola and Knight, 2008), rather than objective measures. To our knowledge, no prior studies have systematically reviewed studies concerning the indoor concentrations of elevated PM and VOCs (objectively measured) in higher income countries and the development and/or exacerbation of asthma in adulthood, which is the focus of this study. This is of public health interest because it provides an opportunity to inform future health intervention strategies.

2. Methods

2.1. Search strategy

In accordance with our study protocol (PROSPERO reference: CRD42018110070), electronic searches of 11 databases were conducted on the February 1, 2019 and again on the February 2, 2020. Searches were conducted across 11 databases (Cochrane Library (Wiley), MEDLINE (via the OVID platform), AMED, Web of Science, Scopus, Environment Complete (EBSCO), GreenFile (EBSCO), EMBASE (via the OVID platform), British Nursing Database, Applied Social Sciences Index and Abstracts (ASSIA), ScienceDirect and the TRIP Database). The World Health Organization (WHO) and the Department for Environment Food and Rural Affairs (DEFRA) were also searched. The search string included the following terms related to respiratory health; asthma, wheeze, cough, dyspnea, bronchitis, bronchial hyperactivity and bronchial spasm; and the following pollutants/exposures, particulate, PM2, PM10, volatile organic compounds, formoceresols and benzene. To fully understand the impact of indoor air quality on respiratory health, a systematic review of studies using objective measures of indoor air quality are needed. Observing this gap in the literature, we updated our protocol to include studies that used only objective measures of indoor concentrations of PM and/or VOCs'. The full search strategy is available on PROSPERO reference: CRD42018110070.

Forward and backward citation searches were conducted alongside contacting all authors of included studies to identify additional studies. The screening process was managed in Endnote version X8.2 (Thomas Reuters, New York, NY) and recorded using the PRISMA guidelines. Articles were independently screened by three team members (C.A.P, R.A.S and K.M) at title and abstract. The full text of articles meeting the inclusion criteria were obtained and screened by the three reviewers. Where there was any disagreement, a fourth reviewer (T.T) was consulted, and any discrepancies resolved through discussion.

2.2. Eligibility criteria and study selection

Included articles consisted of those reporting associations between the indoor home environment and objective measures of PM and VOCs exposure and risk of developing and/or the exacerbation of asthma (Fig. 1). The populations investigated encompassed adults aged over 18 years and both sexes. Studies deemed eligible for the analysis comprised:

1. Original peer-reviewed journal articles publishing primary data
2. English language studies
3. Cohort; case-control studies; randomised control trials; non-randomised control trials; cluster-randomised trials and cross over trials
4. Studies published in 1990 or later (due to rise in publications in this area of research after this date)
5. Investigation of the indoor home environment
6. Studies which identify objective measures of PM and/or VOCs and report level of risk as Odds Ratio or Relative Risk (crude and adjusted models)
7. Studies with outcomes of asthma ever and/or asthma symptoms in the last 12 months (including wheeze, whistling in the chest or a dry cough), doctor-diagnosed asthma (e.g. peak flow or spirometry), and initiation/development of asthma requiring newly diagnosed cases of asthma by a physician or doctor.

2.3. Data extraction

Relevant study and participant characteristics were extracted using a data extraction, which was adapted from the Cochrane guidelines for systematic review (Furlan et al., 2009). The data extraction form was subsequently used to populate data synthesis tables developed using the PROGRESS plus framework, which applies equity when reporting findings (O'neill et al., 2014).

2.4. Quality assessment

Included studies were assessed for quality by two review authors (C.A.P, R.A.S) using the Newcastle-Ottawa Scale (NOS) (Wells et al., 2009) customised for cross-sectional studies (Herzog et al., 2013). This scale assesses population selection, study comparability, and ascertainment of exposure and outcomes, to yield a maximum of ten points for cross-sectional studies (Herzog et al., 2013). A maximum of five points can be awarded for selection, two for comparability and three for the outcome. It was decided a priori that if disagreements persisted a third review author (KM) would be consulted. Studies were independently assigned an overall score out of 10. Consensus on the risk of bias scores was reached by two review authors (C.A.P, R.A.S) and a third reviewer was not required. Detailed notes on the decisions made with reference to the quality scoring for each paper is available from the authors on request.

3. Results

3.1. Synthesis

Due to significant heterogeneity, we provide an overarching synthesis of 12 studies that met our inclusion criteria; (Arif and Shah, 2007b, Balmes et al., 2014, Billionnet et al., 2011, Hulin et al., 2013, Jarvis et al., 1996, Levesque et al., 2001, Norbäck et al., 1995, Frisk et al., 2009; Simoni et al., 2002, 2004, Wieslander et al., 1997, Dales and Cakmak, 2019).

3.2. Risk of bias of individual studies

Included studies varied in terms of assessed NOS quality (Table 1). The majority were deemed medium quality according to the NOS, which suggests potential inclusion of bias. There is also significant heterogeneity between studies and therefore, the potential for reporting bias, resulting from studies collecting and reporting data inconsistently. For

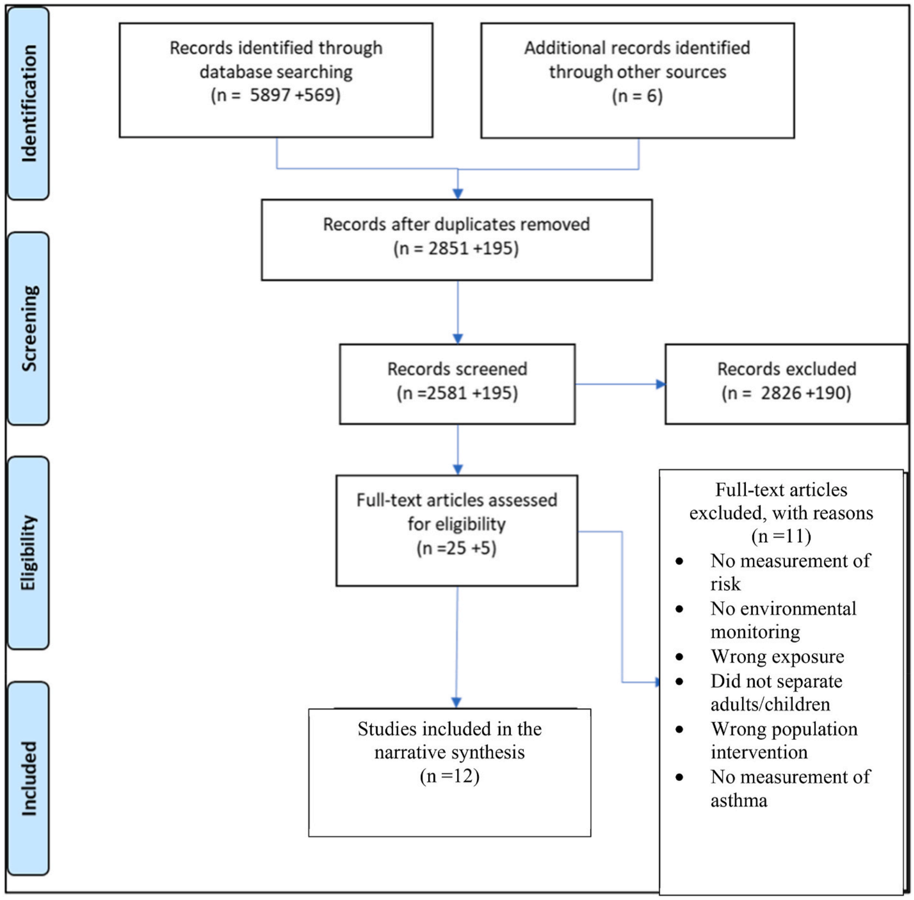

Fig. 1. Diagram of systematic search and included studies.

this reason, studies were prioritised according to their quality rating score and considered as low (<4), medium (5–7) and high (>8) quality. All 12 studies included studies measured VOCs (Simoni et al., 2002, 2004, Frisk et al., 2009, Levesque et al., 2001, Hulin et al., 2013, Billionnet et al., 2011, Bentayeb et al., 2013, Norbäck et al., 1995, Arif and Shah, 2007b, Wieslander et al., 1997, Dales and Cakmak, 2019); only one study measured just PM (Balmes et al., 2014). Studies have been grouped in our synthesis according to those reporting;

- Increased risk of spirometry-diagnosed asthma through exposure to particulate matter or VOCs
- Increased risk of self-reported asthma through exposure to particulate matter or VOCs
- Increased risk of asthma symptoms through exposure to particulate matter or VOCs

3.3. Study and participant characteristics

Three studies were performed before 1999 and nine after this time. Included studies were from five countries and included cross-sectional, cohort and case-control design methodologies (Table 1). Two studies were conducted in the USA, three in France, three in Sweden, two in Canada and two in Italy. Not all studies reported whether they had investigated rural or urban environments.

The characteristics of the participants were generally reported in detail across the studies (Table 1). The participants were all adults as defined by the inclusion criteria with the exception of the (Levesque et al., 2001 and (Dales and Cakmak, 2019)) study which included adult and child pairs, however, due to the focus of this review, only data relating to adults was considered. Recruitment was generally a random sample of the population designed to be representative of the general population. Six studies reported on ethnicity; however, this was not consistent across the studies. No studies reported any religion, disability or time-dependent relationships. Social-economic status (SES) was recorded in seven studies and reported in six. We grouped education and employment with SES as health opportunities, outcomes and SES are generally closely linked. Six of these studies reported on education and employment.

3.4. Study design characteristics of included studies

Eleven studies were cross-sectional, and one study was a case-control study with one day follow up. Recruitment, funding and statistical analyses differed between studies. Significant heterogeneity between study designs including the defined exposure and outcomes prevented the use of meta-analysis (described below).

In total, three studies measured PM 2.5 (Table 2). The study by Levesque et al. (2001) measured PM10. In terms of PM monitoring techniques, similar techniques were utilised in two of the studies (active sampling with Dorr Oliver type pre-selector) (Simoni et al., 2002) (Simoni et al., 2004), in one study sampling was via nephelometer and recorded three measurements of 3-min duration. Where VOCs were measured these were generally broken down into aldehydes, hydrocarbons and glycol ethers. VOC concentrations were monitored with reasonable consistency across studies in both duration and sampling location. For 10 studies, VOCs were measured continuously in either the bedroom and or living room for one week with the exception of Wieslander et al. (1997) and Arif and Shah (2007a, 2007b). Measures were collected via one measurement in the bedroom over 2 h and by personal exposure over 48–72 h in these cases. Sampling techniques for the VOCs

Table 1
Summary of participant characteristics of included studies.

Reference	Country	Study population	Non-respondents	Urban/rural, region	% Female	Ethnicity	SES	% Current Smokers	Current Asthma %	Final quality score
Frisk et al. (2009)	Sweden	Adults aged 19–54 y	No details	Orebro	63	Not reported	Occupation	24	No details	2/10
Levesque et al. (2001)	Canada	Adults aged 23–52 y	No details	Within 50 km Quebec	86.5	No details	Family income recorded but not reported	No details	No details	4/10
Arif and Shah (2007b)	USA	Adults aged 20–59 y	No details	No details	51.2	Non-Hispanic whites, Mexican-Americans, Non-Hispanic blacks, Other race/ ethnicity	13.7% below the poverty line	26.8	12.3	4/10
Norbäck et al., 1995	Sweden	Adults aged 20–44 y	14 who didn't attend medical investigation, 12 who were uncontactable, 14 refused exposure measurements	Urban, Uppsala	72	No details	No details	No details	30	6/10
Simoni et al. (2002)	Italy	Adults aged 15–72 y	No details	Po River Delta	51.4	No details	No details	No details	13.7 (f) 34.9 (m)	6/10
Simoni et al. (2004)	Italy	No details	No details	Urban, Pisa Rural, Po Delta	50.9 51.4	No details	No details	No details	25 24	6/10
Wieslander et al. (1997)	Sweden	Adults aged 20–44 y	Non-responders did not differ from participants in age, gender and smoking status	Uppsala	51.6	No details	No details	29 with symptoms 17 without symptoms	21	6/10
Balmes et al. (2014)	USA	Adults aged 18–50 y	Non-responders were younger and more likely smokers	Urban, Suburban, Rural, Northern California	73.5	Non-Hispanic white 58.9%	High school education	7.9	41.4	6/10
Bentayeb et al. (2013)	France	No details	No details	19 regions	52	French 96%	Education	27	No details	6/10
Billionnet et al. (2011)	France	Adults aged 15–89 y	No details	74 municipalities, 19 regions	52.1	French 96%	Employed 47.9% Higher education 52.25%	27	8.6	8/10
Dales and Cakmak (2019)	Canada	Adults aged 17–19 (children measured in the study but excluded from this analysis)	No details	Two sites in each of Atlantic Canada, the Prairies, and British Columbia, and four sites in Quebec, and six in Ontario.	50.9	Caucasian 76.5%	83.9% Household income above $1000 96.1% educated greater than high school	No details	9.3	8/10
Hulin et al. (2013)	France	Adults aged 26–60 y	Were younger, more of foreign nationality, and lower educational level	Urban, rural, periurban	51.6	Nationality	Recorded but not reported	26.2	8.4	9/10

were similar and consisted of diffusive sampling. While all studies measured concentrations of PM and/or VOCs, all studies (Levesque et al., 2001; Wieslander et al., 1997) reliably assessed the interaction between PM or VOC concentrations and health outcomes measured.

All studies used self-administered questionnaires to obtain data on the various health-related of interest. The majority of the health-based questions related to respiratory health. This meant the definition of asthma varied across included studies from using self-reported survey-based questions, to methacholine challenge, spirometry, reduced PEF and FEV (Table 2). Five measured peak expiratory flow (PEF) rate variability (Dales and Cakmak, 2019; Simoni et al., 2002, 2004; Wieslander et al., 1997; Frisk et al., 2009, Norbäck et al., 1995); five studies measured forced expiratory volume in 1 s (FEV1) (Dales and Cakmak, 2019; Balmes et al., 2014; Wieslander et al., 1997; Frisk et al., 2009, Norbäck et al., 1995). The same sampling techniques were utilised for all measurements of respiratory health; the Mini Wright peak flow meter for PEF and an EasyOne Spirometer for FEV1. A reduction in per cent predicted FEV1 is suggested to be more closely related to the incidence of chronic respiratory symptoms in the general population than other measures of lung function impairment (Jakeways et al., 2003), and therefore a useful measure in this review.

Objective measurements of the independent variables were used in six studies. Three studies examined formaldehyde separately from other included VOCs. Three studies also recorded temperature and relative humidity in the properties.

Table 2
Study design characteristics of included studies.

Reference	Study design	Study size	Follow up	Exposure of interest	Exposure measurement	Definition of asthma	Outcome measure	Final quality score
Frisk et al. (2009)	Cohort	49	13 months	Temp + RH Co2, No2, Formaldehyde ETS, 15 respirable allergens (not stated other than pets)	Diffusion sampling	A physician-diagnosed asthma, current use of asthma medicine, attacks of breathlessness and episodes of wheezing	Self-assessment diary, FEV1 and vital capacity (V. C.). Histamine provocation test, Blood samples, PEF, SPT	2/10
Balmes et al. (2014)	Cross-sectional	549 Interview 302 Home visit	N/A	Particulate Matter 2.5	Nephelometer	No clear definition	Spirometry, questionnaire	6/10
Simoni et al. (2004)	Cross-sectional	Pisa 707 Po Delta 383	N/A	PM2.5, No2	Passive sampling	Chronic bronchitic and/or asthmatic symptoms (i.e., sputum from the chest, shortness of breath, attack of shortness of breath, and wheeze) without the presence of fever and the reported presence of infection.	Symptom diary, PEF	6/10
Simoni et al. (2002)	Cross-sectional	383	N/A	Respirable suspended particulate (RSP) (<2.5μg/m3), NO2	Passive sampling	Chronic bronchitic and/or asthmatic symptoms (i.e., sputum from the chest, shortness of breath, attack of shortness of breath, and wheeze) without the presence of fever and the reported presence of infection.	PEF	6/10
Levesque et al. (2001)	Case-control	89	1 day	CO, NO, HCHO, PM10. Used self-reported presence of fumes in assessing health outcomes.	Gilian HFS 113 pump/Diffusion monitoring	Asthma defined as complicated lower respiratory tract illness which also included wheezing or respiratory difficulties, medical diagnoses of pneumonia, bronchitis or asthma attacks.	Questionnaire	4/10
Hulin et al. (2013)	Cross sectional	897	N/A	Total VOCs: 4 aldehydes (acetaldehyde, acrolein, formaldehyde, hexaldehyde), 12 hydrocarbons (benzene, 1,4-dichlorobenzene, ethylbenzene, n-decane, n-undecane, styrene, tetrachloroethylene, toluene, trichloroethylene, 1,2,4trimethylbenzene, m/p-xylene, o-xylene), and 4 glycol ethers (2-butoxyethanol, 2-butoxyethylacetate, 1-methoxy-2-propanol, 1-methoxy-2-propylacetate).	Passive diffusion sampling	A positive response to: “Have you had an attack of asthma in the last 12 months?” or “Are you currently taking medicines for asthma?” and “Have you been woken by an attack of shortness of breath at any time in the last 12 months?"	Questionnaire	9/10
Billionnet et al. (2011)	Cross-sectional	1612	N/A	20 VOCs including 4 aldehydes, 12 hydrocarbons ad 4 glycol ethers	Radial diffusive sampling	As suggested by ECRHS: (i) having an asthma attack in the last 12 months; (ii) having been woken by an attack of shortness of breath in the last 12 months; and (iii) currently using asthma medicine	Questionnaire	8/10
Bentayeb et al. (2013)	Cross-sectional	1012 Individuals 490 Homes	N/A	Aldehydes: formaldehyde, acetaldehyde, acroleine, hexaldehyde. - Aromatic hydrocarbons: benzene, toluene, m/p-xylenes, o-xylene, 1.2.4-trimethylbenzene, ethylbenzene, styrene. - Aliphatic hydrocarbons: n-decane, n-undecane; halogenated hydrocarbons:	Radial diffusive sampling	No clear definition	Questionnaire	6/10

(continued on next page)

Table 2 (*continued*)

Reference	Study design	Study size	Follow up	Exposure of interest	Exposure measurement	Definition of asthma	Outcome measure	Final quality score
				trichloroethylene, tetrachloroethylene, 1.4-dichlorobenzene; Glycol ethers: 1-metoxy2-propanol, 2 butoxy ethanol, 2-butoxyethylacetate, 1-methoxy-2-propylacetate.				
Norbäck et al., 1995	Cross-sectional	154	N/A	Temp, air humidity, VOCs, Co2, formaldehyde, and guanine from HDM	Direct reading instrument based on light scattering/ Diffusion sampling	Attacks of asthma during the past 12 months, nocturnal breathlessness in the past 12 months, or current use of asthma medication.	Blood samples, Interviews, SPT, FEV1, PEF, Methacholine challenge	6/10
Arif and Shah (2007b)	Cross-sectional	9965 Interview 9282 Physical exam 669 Exposure monitoring	N/A	Benzene Chloroform Ethylbenzene Tetrachloroethene (TCE) Toluene, trichloroethene, o-xylene, m-,p-xylene, 1,4-dichlorobenzene, and methyl tertiary butyl ether (MTBE)	Personal exposure via a passive monitoring device	Positive response to the question “Has your doctor or other health professional ever told you that you have asthma?"	PEF	4/10
Wieslander et al. (1997)	Cross-sectional	Interview, blood tests, SPT, bronchial provocation 699 Q’aire building characteristics, occupation, and symptoms 562 Subsample 62	N/A	Temperature, Humidity, VOCs, Formaldehyde	Passive sampling	A combination of bronchial hyper-responsiveness (BHR) and at least one symptom related to asthma. Symptoms related to asthma were recorded when subjects reported in previous 12 months: (1) wheezing or whistling in the chest or (2) at least one daytime attack of shortness of breath during exercise or while resting; (3) at least one night time awakening because of breathlessness or tightness in the chest	Questionnaire, SPT, FEV1, PEF, Methacholine challenge, blood	6/10
Dales and Cakmak (2019)	Cross-sectional	2846	N/A	Limonene	Diffusion sampling with Carbopack B 60/80®	Asthma: “We are interested in “long-term conditions” which are expected to last or have already lasted 6 months or more and that have been diagnosed by a health professional. Do you have asthma?"	FeNO FEV1 FVC Questionnaire	8/10

3.5. Results of studies included in our narrative synthesis

3.5.1. Increased risk of asthma through exposure to particulate matter

Conclusive evidence of the relationship between indoor PM2.5 and asthma outcomes in adults is lacking (Table 3). No high-quality evidence was found that measured risk of either development or exacerbation of asthma via a measure of spirometry in relation to exposure to PM2.5. Two medium-quality studies (Simoni et al., 2002, 2004) measured PM2.5 and found that high levels of exposure were associated with increased PEF maximum amplitude and variability. However, the studies primary outcome focus was on indoor pollution and associated acute respiratory symptoms and mild lung function impairment rather than asthma specifically. Although the studies are indicative of lung function changes, assumptions cannot be drawn between exposure to PM2.5 and increased PEF variability in this instance. Only one study of medium quality found that exposure to particulate matter in the kitchen at 21 μg/m3 was associated with increased odds of asthma-like symptoms, this was true in men but not women (Balmes et al., 2014).

3.5.2. Increased risk of asthma through exposure to volatile organic compounds

We found evidence to suggest that exposure to VOCs in the indoor home environment increases the risk of asthma and asthma-related symptoms (Table 3). One study of high-quality evidence (Dales and Cakmak, 2019) identified a 15% (95% CI: 1.14, 1.16) increased risk of asthma via measure of spirometry following a 100% increase in exposure to Limonene, a naturally occurring terpene (aliphatic compound). This may induce sensitisation and had been found to be associated with increased airway hyper-responsiveness in other studies (Norbäck et al., 1995). One medium quality study found wood and kitchen painting to be associated with an increased risk of asthma symptoms (OR 1.43; 95% CI: 1.01–2.06), bronchial hyper-reactivity, nocturnal breathlessness and current asthma via measure of spirometry. In this case, the most commonly detected compounds were aromatic compounds, aliphatic compounds and TXIB (Wieslander et al., 1997).

One study which was deemed to be of high quality and one of low-quality found an increased risk of asthma via measures of self-reported exposure to both aromatic and aliphatic compounds. An

Table 3
Health outcomes and associated risk.

Reference	Exposure	Exposure level (μg/m3)	Health measure	Health outcome	Risk ratio/ Odds Ratio Adjusted	Risk by Gender: Male	Risk by gender: Female	Final Quality Score
Frisk et al. (2009)	HDM	84.7 (SD 15.6)	FEV1 PEF	Reduced lung function	1.31 (0–8.72)	Not reported	Not reported	2/10
Balmes et al. (2014)	PM 2.5	39.1 ± 107.3 21 μg/m3 (kitchen)	FEV1	Self-rated "asthma bother"	N/A	2.52 (95%CI: 0.88–7.24)	Not reported	6/10
Simoni et al. (2004)	PM2.5	67/76	Self-reported daily diary PEF	Asthma symptoms PEF variability	1.39 (1.17–1.66) 1.37 (1.23–1.53)	Not reported	Not reported	6/10
Simoni et al. (2002)	Respirable suspended particulate (RSP) (<2.5μg/m3), RSP No2	68/45 winter/ summer 31/19 (ppb)	PEF	Asthmatic symptoms without a fever	1.23 (1.03–1.48)	Not reported	Not reported	6/10
Levesque et al. (2001)	Emission of fumes	Self-reported	Self-administered questionnaire and symptom diaries	Upper respiratory symptoms Complicated lower respiratory symptoms	P = 0.03 P = 0.08	Not reported	Not reported	4/10
Hulin et al. (2013)	Total VOCs	No details	ECRHS	Current asthma Chronic bronchitis Chronic bronchitis like symptoms	1.01 (0.99–1.03) 1.02 (0.99–1.05) 1.02 (0.98–1.02)	Not reported	Not reported	9/10
Billionnet et al. (2011)	Aromatic hydrocarbons Aliphatic hydrocarbons	No details	ECRHS	Asthma risk	N/A	Not reported	Not reported	8/10
Bentayeb et al. (2013)	Toluene o-xylene	8–20 3–5	ECRHS	Breathlessness	3.36 (1.13, 9.98) 2.85 (1.06, 7.68)	Not reported	Not reported	6/10
Norbäck et al., 1995	Toluene C8-Aromatics TVOC	120 (1–2330) 55 (5–690) 790 (90–9380)	PEF ECRHS	Nocturnal breathlessness	4.9 (1.1–22.8) 6.7 (1.0–45.1) 9.9 (1.7–58.8)	Not reported	Not reported	6/10
Arif and Shah (2007b)	Benzene Ethylbenzene Toluene o-Xylene m,p-Xylene	Geometric mean 1.21 (0.74–1.98) 2.55 (1.73–3.75) 14.33 (11.09–18.52) 2.16 (1.53–3.04) 5.97 (3.92–9.07)	Questionnaire	Asthma or Wheeze	1.33 (1.13–1.56) 1.34 (1.01–1.78) 1.21 (0.93–1.58) 1.32 (1.04–1.67) 1.33 1.08–1.64)	Not reported	Not reported	4/10
Wieslander et al. (1997)	Wood paint Kitchen Paint	Average TVOC in painted rooms = 413	PEF	Asthma (BHR + symptoms)	2.33 (1.22–4.46) 2.21 (1.09–4.51)	Not reported	Not reported	6/10
Dales and Cakmak (2019)	Limonene 100% increase	45 ppb (SD 61)	FeNo Fev1 FVC	Increase in asthma	1.16 (1.15, 1.16)	1.01 (1.01, 1.02).	1.42 (1.41,1.43)	8/10

additional two medium quality evidence studies found an increased risk of asthma-like symptoms following this exposure. High-quality evidence indicated that n-undecane and 1,2, 4-trimethylbenzene were significantly associated with asthma (OR 2.02; 95% CI: 1.18–3.46 and OR 2.10; 95% CI: 1.21–3.65 respectively). Using adjusted marginal models, positive associations between asthma and global VOC scores were also observed suggesting the risk of asthma to be 1.07 times higher for exposure to each additional VOC with a high exposure level (OR 1.07; 95% CI: 1.00–1.13). For individuals exposed to five additional VOCs, the risk was increased by 40%. There was no difference reported between sex.

Two specific VOC scores were significantly associated with an increased risk of asthma: aromatic hydrocarbons (OR 1.12; 95% CI: 1.01–1.24) and aliphatic hydrocarbons (OR 1.41; 95% CI¼1.03–1.93) (Billionnet et al., 2011). In contrast, a high quality study by Hulin et al. reported insignificant findings between measured exposures of total VOCs and risk of current asthma (OR 1.01; 95% CI; 0.99–1.03), chronic bronchitis (OR 1.02; 95% CI; 0.99–1.05) and chronic bronchitis like symptoms (OR 1.02; 95% CI; 0.98–1.02).

Arif and Shah (2007a, 2007b) conducted personal exposure monitoring of 669 individuals and found statistically significant odds of physician-diagnosed asthma for individuals exposed to aromatic compounds (OR 1.63; 95% CI: 1.17–2.27). When observing aromatic compounds individually, there was suggestive evidence that Toluene was associated with a 21% increased odds of physician-diagnosed asthma (OR 1.21 95% CI: 0.93–1.58) but the confidence intervals crossed unity. However, the study was deemed to be of a low-quality rating due to the definition used in the study to describe asthma and the outcome measures used.

A medium quality study, using personal exposure monitoring tools (Bentayeb et al., 2013), also identified that individuals without asthma were at increased risk for experiencing symptoms, with a significantly increased odds of one to two wheezing attacks observed following exposure to aromatic compounds (adj OR 1.68 95% CI: 1.08–2.61) and chlorinated hydrocarbons (adj OR; 1.50 95% CI: 1.01–2.23) compared to no wheezing. The odds of experiencing three or more wheezing attacks following exposure to benzene were nearly twofold (adj OR 1.85 95% CI: 1.13–3.04) (Arif and Shah, 2007b). The study further suggests a relationship between Toluene and o-xylene (aromatic compounds) and nocturnal breathlessness, a symptom of asthma, in the elderly (Bentayeb et al., 2013). Other VOCs related to increased asthmatic symptoms were formaldehyde but the evidence was limited. One medium quality study found formaldehyde in the bedroom to be associated with nocturnal breathlessness (Norback et al., 1995).

4. Discussion

To our knowledge, this is the first systematic review investigating the links between elevated indoor concentrations of PM and VOCs' and risk of asthma in adulthood. The current evidence linking increased indoor concentrations of PM to adult asthma is limited. Despite some mixed findings, this systematic review provides collective new evidence that in adults, aromatic and aliphatic compounds in the indoor home environment are associated with an increased risk of asthma in adulthood. Further, individuals without a diagnosis of asthma or history of respiratory illness are more likely to experience symptoms related to asthma such as wheeze and shortness of breath as a result of exposure VOCs, especially when exposure is at high concentration. We also found PEF variability in relation to respiratory symptoms that could be suggestive of asthma, but the evidence is inconclusive.

The risk of developing and/or exacerbating of asthma depends on a complex interaction between diverse environmental exposures. Resultant outcomes concerning both atopic and non-atopic asthma depends on the timing and extent of exposure resulting from exposure to diverse and overlapping interactions between physical, chemical and biological agents throughout the life course from early childhood into adulthood (Sharpre et al., 2015c). Each of these interactions and the potential impact on health relies on a number of largely modifiable environmental factors including leaks in building fabric, heating and ventilation patterns etc, but also, everyday indoor habits including for example from the presence of environmental tobacco smoke in the homes through to the use and choice of cleaning products (Sharpe et al., 2014). For example, previous authors have already highlighted the dangers of aerosolised domestic cleaning products on respiratory health, noting an increased incidence of asthma following exposure (Buckley, 2007; Zock et al., 2010). To raise awareness of the potential health risks, policymakers and industry alike need to take a more concerted effort in protecting public health by better informing them of the associated health risks by raising awareness and using more explicit health warnings on product labels detailing the importance of adequate ventilation specific to the product.

From a research perspective, there is a need for better exposure measures and case definition of asthma greater adoption of indoor sampling of diverse pollutants, asthma outcomes across the included studies because these were inconsistent and, in some cases, poorly defined. Better case definition must be adopted by future research to enable clearer and more thorough investigations into such vital areas. Furthermore, there is insufficient evidence to determine whether any increased risk of asthma is modified by sex at present. Given that the majority of caregivers are women (Sharma et al., 2016) and individuals spend a significant proportion of their time in the indoor environment, future investigations should attempt to address any gendered differences in risk reporting so targeted interventions can be implemented where needed most.

5. Limitations

The systematic review highlighted the limited evidence reporting objective exposure measurements for PM and VOCs, as well as the lack of objective outcomes measures for the outcome variable, asthma which can be measured objectively using spirometry tests. A reliance on non-objective measures can introduce an element of bias. With the widespread availability of indoor home environmental sensors, future studies need to be based on objectives measures of the exposures of interest (Moses and Morrissey, 2019). Furthermore, there is a need to consider the interaction between outdoor and indoor exposures when investigating the implications on health.

Furthermore, the mixed quality of included studies and significant heterogeneity with regard to the measurement of both the outcome and exposures of interest, meant we were unable to undertake a meta-analysis, which limited our evidence synthesis. The quantity of individual volatile organic compounds is vast. To date, there is limited knowledge to the extent in which inhalation of each can cause harm. The compounds measured and the way in which they are measured varies greatly both in and between studies. Whilst this review attempted to collect data from articles which have studied VOCs thought to be associated with adverse respiratory outcomes, there is an ever-evolving knowledge base of exactly which chemicals that consists of, and therefore the potential for some studies to have been inadvertently omitted. However, we also argue that given it is not just measurement differences and definitional differences that present a challenge in providing a meta-analysis, heterogeneity in susceptibility across different members of the population, as well as the diversity of environments that individuals spend their day in, means that a meta-analysis approach may not have been appropriate for such a review.

6. Conclusion

While advances in medicine and research mean that the heterogeneity of immunology of asthma is increasingly understood, there is a need for a greater understanding the role of diverse indoor exposures, risk of disease endotypes (Lotvall et al., 2011) and phenotypes (Darveaux and Busse, 2015). In response, this systematic review provides new evidence to suggest that VOCs such as aromatic and aliphatic compounds in the indoor home environment are associated with an increased risk of asthma and asthma-like symptoms (including wheeze) in adults. As noted, individuals are exposed to a complex mix of biological, chemical and physical agents across their life course. To prevent poor health outcomes individuals, health professionals and industry must make a concerted effort to better inform the general population of the importance of appropriate use of, and storage of chemicals, as well as better health messaging on product labelling. This review indicates the need for further investigation on the impacts of indoor air pollution on health and wellbeing using objective measures, and the need for consistency in the reporting of studies to ensure comparability.

CRediT author statement

C.A.Paterson: Conceptualisation, Methodology, Validation, Investigation, Formal analysis, Writing – original draft, Visualisation. Sharpe, R. A: Conceptualisation, Validation, Methodology, Investigation, review and editing, Supervision. Taylor, T: Conceptualisation, Validation, review and editing, Supervision, Funding acquisition. Morrissey, K: Conceptualisation, Validation, Investigation, review and editing, Supervision.

Funding

Funding for this research was provided through the Smartline project. The Smartline project (www.smartline.org.uk, based in Cornwall, UK) is receiving up to £3,780,374 of funding from the England European Regional Development Fund (Grant Numbers 05R16P00305, 05R18P02819) as part of the European Structural and Investment Funds Growth Programme 2014–2020. The Ministry of Housing, Communities and Local Government (and in London the intermediate body Greater London Authority) is the Managing Authority for European Regional Development Fund. Established by the European Union, the European Regional Development Fund helps local areas stimulate their economic development by investing in projects which will support innovation, businesses, create jobs and local community regenerations. For more information visit https://www.gov.uk/european-growth-funding.

The Smartline project is also funded by the South West Academic Health Science Network, Cornwall Council, and H.M. Government, and is a partnership between University of Exeter, Coastline Housing, Volunteer Cornwall, Cornwall Council, and the South West Academic Health Science Network.

The project funders had no involvement in the conduct of the research or preparation of the article.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

Al-daghri, N.M., Alokail, M.S., Abd-Alrahman, S.H., Draz, H.M., Yakout, S.M., Clerici, M., 2013. Polycyclic aromatic hydrocarbon exposure and pediatric asthma in children: a case-control study. Environ. Health : Glob. Access Sci. Source 12, 1-1.

Arif, A., Shah, S., 2007a. Association between personal exposure to volatile organic compounds and asthma among U.S. adult population. Int. Arch. Occup. Environ. Health 80, 711–719.

Arif, A.A., Shah, S.M., 2007b. Association between personal exposure to volatile organic compounds and asthma among U.S. adult population. Int. Arch. Occup. Environ. Health 80, 711–719.

Asher, M.I., Montefort, S., Björkstén, B., Lai, C.K., Strachan, D.P., Weiland, S.K., Williams, H., 2006. Worldwide time trends in the prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and eczema in childhood: ISAAC Phases One and Three repeat multicountry cross-sectional surveys. Lancet 368, 733–743.

Balmes, J.R., Cisternas, M., Quinlan, P.J., Trupin, L., Lurmann, F.W., Katz, P.P., Blanc, P. D., 2014. Annual average ambient particulate matter exposure estimates, measured home particulate matter, and hair nicotine are associated with respiratory outcomes in adults with asthma. Environ. Res. 129, 1–10.

Bentayeb, M., Billionnet, C., Baiz, N., Derbez, M., Kirchner, S., Annesi-Maesano, I., 2013. Higher prevalence of breathlessness in elderly exposed to indoor aldehydes and VOCs in a representative sample of French dwellings. Respir. Med. 107, 1598–1607.

Billionnet, C., Gay, E., Kirchner, S., Leynaert, B., Annesi-Maesano, I., 2011. Quantitative assessments of indoor air pollution and respiratory health in a population-based sample of French dwellings. Environ. Res. 111, 425–434.

BLF, 2019. Asthma statistics [Online]. Available: https://statistics.blf.org.uk/asthma, 2019.

Buckley, D.A., 2007. Fragrance ingredient labelling in products on sale in the U.K. Br. J. Dermatol. 157, 295–300.

Casset, A., Marchand, C., Purohit, A., Le Calve, S., Uring-Lambert, B., Donnay, C., Meyer, P., De Blay, F., 2006. Inhaled formaldehyde exposure: effect on bronchial response to mite allergen in sensitised asthma patients. Allergy 61, 1344–1350.

Dales, R.E., Cakmak, S., 2019. Is residential ambient air limonene associated with asthma? Findings from the Canadian Health Measures Survey. Environ. Pollut. 244, 966–970.

Darveaux, J., Busse, W.W., 2015. Biologics in asthma–the next step toward personalised treatment. J. Allergy Clin. Immunol. 3, 152–161. In practice.

Dick, S., Friend, A., Dynes, K., Alkandari, F., Doust, E., Cowie, H., Ayres, J.G., Turner, S. W., 2014. A systematic review of associations between environmental exposures and development of asthma in children aged up to 9 years. BMJ Open 4, e006554.

Frisk, M.L.A., Stridh, G., Ivarsson, A.-B., Kamwendo, K., 2009. Can a housing environmental index establish associations between indoor risk indicators and clinical tests in persons with asthma? Int. J. Environ. Health Res. 19, 389–404.

Furlan, A.D., Pennick, V., Bombardier, C., Van Tulder, M., GROUP, F. T. E. B. O. T. C. B. R, 2009. 2009 updated method guidelines for systematic reviews in the Cochrane back review group. Spine 34, 1929–1941.

Guarnieri, M., Balmes, J.R., 2014. Outdoor air pollution and asthma. Lancet 383, 1581–1592.

Herzog, R., Álvarez-Pasquin, M.J., Díaz, C., Del Barrio, J.L., Estrada, J.M., Gil, Á., 2013. Are healthcare workers' intentions to vaccinate related to their knowledge, beliefs and attitudes? A systematic review. BMC Publ. Health 13 (1), 1–17.

Hulin, M., Moularat, S., Kirchner, S., Robine, E., Mandin, C., Annesi-Maesano, I., 2013. Positive associations between respiratory outcomes and fungal index in rural inhabitants of a representative sample of French dwellings. Int. J. Hyg Environ. Health 216, 155–162.

Hulin, M., Simoni, M., Viegi, G., Annesi-Maesano, I., 2012. Respiratory health and indoor air pollutants based on quantitative exposure assessments. Eur. Respir. J. 40, 1033–1045.

Hussain, S., Parker, S., Edwards, K., Finch, J., Jeanjean, A., Leigh, R., Gonem, S., 2019. Effects of indoor particulate matter exposure on daily asthma control. Ann. Allergy Asthma Immunol. 123, 375–380 e3.

Jaakkola, J.J., Knight, T.L., 2008 Jul. The role of exposure to phthalates from polyvinyl chloride products in the development of asthma and allergies: a systematic review and meta-analysis. Environ. Health Perspect. 116 (7), 845–853.

Jakeways, N., Mckeever, T., Lewis, S.A., Weiss, S.T., Britton, J., 2003. Relationship between FEV1 reduction and respiratory symptoms in the general population. Eur. Respir. J. 21, 658.

Jarvis, D., Chinn, S., Luczynska, C., Burney, P., 1996. Association of respiratory symptoms and lung function in young adults with use of domestic gas appliances. Lancet 347, 426–431.

Klepeis, N.E., Nelson, W.C., Ott, J.P.R., W, R., Tsang, A.M., Switzer, P., Behar, J.V., Hern, S.C., Engelmann, W.H., 2001. The National Human Activity Pattern Survey (NHAPS): a resource for assessing exposure to environmental pollutants. Anal. Environ. Epidemiol. J. Expo. 11.

Kelly, F.J., Fussell, J.C., 2015. Air pollution and public health: emerging hazards and improved understanding of risk. Environ. Geochem. Health 37, 631–649.

Lai, C.K., Beasley, R., Crane, J., Foliaki, S., Shah, J., Weiland, S., ISAAC Phase Three Study Group, 2009. Global variation in the prevalence and severity of asthma symptoms: phase three of the International Study of Asthma and Allergies in Childhood (ISAAC). Thorax 64 (6), 476–483, 1.

Levesque, B., Allaire, S., Gauvin, D., Koutrakis, P., Gingras, S., Rhainds, M., Prud'homme, H., Duchesne, J.F., 2001. Wood-burning appliances and indoor air quality. Sci. Total Environ. 281, 47–62.

Lötvall, J., Akdis, C.A., Bacharier, L.B., Bjermer, L., Casale, T.B., Custovic, A., Lemanske Jr, R.F., Wardlaw, A.J., Wenzel, S.E., Greenberger, P.A., 2011. Asthma endotypes: a new approach to classification of disease entities within the asthma syndrome. J. Allergy Clin. Immunol. 127 (2), 355–360.

Mcgratha, J.A., Sheahan, J.N., Dimitroulopoulouc, C., Ashmored, M.R., Terrye, A.C., Byrnea, M.A., 2017. PM exposure variations due to different time activity profile simulations within a single dwelling. Build. Environ. 116, 55–63.

Mir, L., 2007. Indoor ultrafine particles and childhood asthma: exploring a potential public health concern. Environnement, Risques & Santé 6, 256-256.

Mitha, N., Levy, J., Annesi-Maesano, I., Lafortune, J., Magnier, A., Ibanez, G., 2013. Indoor air quality and adult asthma. Rev. Mal. Respir. 30, 374–413.

Moses, L., Morrissey, K., et al., 2019 Jan. Exposure to indoor mouldy odour increases the risk of asthma in older adults living in social housing. Int. J. Environ. Res. Publ. Health 16 (14), 2600.

Netuveli, G., Hurwitz, B., Levy, M., Fletcher, M., Barnes, G., Durham, S.R., Sheikh, A., 2005. Ethnic variations in U.K. asthma frequency, morbidity, and health-service use: a systematic review and meta-analysis. Lancet 365, 312–317.

Norbäck, D., Björnsson, E., Janson, C., Widström, J., Boman, G., 1995 Jun 1. Asthmatic symptoms and volatile organic compounds, formaldehyde, and carbon dioxide in dwellings. Occup. Environ. Med. 52 (6), 388–395.

O'neill, J., Tabish, H., Welch, V., Petticrew, M., Pottie, K., Clarke, M., Evans, T., Pardo Pardo, J., Waters, E., White, H., Tugwell, P., 2014. Applying an equity lens to interventions: using PROGRESS ensures consideration of socially stratifying factors to illuminate inequities in health. J. Clin. Epidemiol. 67, 56–64.

Patelarou, E., Tzanakis, N., Kelly, F.J., 2015. Exposure to indoor pollutants and Wheeze and asthma development during early childhood. Int. J. Environ. Res. Publ. Health 12, 3993–4017.

Pearce, N., Aït-Khaled, N., Beasley, R., Mallol, J., Keil, U., Mitchell, E., Robertson, C., 2007. Worldwide trends in the prevalence of asthma symptoms: phase III of the international study of asthma and allergies in childhood (ISAAC). Thorax 62, 758–766.

Salo, P.M., Arbes JR., S.J., Jaramillo, R., Calatroni, A., Weir, C.H., Sever, M.L., Hoppin, J. A., Rose, K.M., Liu, A.H., Gergen, P.J., 2014. Prevalence of allergic sensitisation in the United States: results from the national health and nutrition examination survey (NHANES) 2005-2006. J. Allergy Clin. Immunol. 134, 350–359.

Schweizer, C., 2007. Indoor time–microenvironment–activity patterns in seven regions of Europe. J. Expo. Sci. Environ. Epidemiol. 170–181.

Sharma, N., Chakrabarti, S., Grover, S., 2016. Gender differences in caregiving among family - caregivers of people with mental illnesses. World J. Psychiatr. 6, 7–17.

Sharpe, R.A., Thornton, C.R., Osborne, N.J., 2014. Modifiable factors governing indoor fungal diversity and risk of asthma. Clin. Exp. Allergy 44, 631–641.

Sharpe, R.A., Bearman, N., Thornton, C.R., Husk, K., Osborne, N.J., 2015a. Indoor fungal diversity and asthma: a meta-analysis and systematic review of risk factors. J. Allergy Clin. Immunol. 135, 110–122.

Sharpe, R.A., Thornton, C.R., Tyrrell, J., Nikolaou, V., Osborne, N.J., 2015b. Variable risk of atopic disease due to indoor fungal exposure in NHANES 2005-2006. Clin. Exp. Allergy 45, 1566–1578.

Simoni, M., Carrozzi, L., Baldacci, S., Scognamiglio, A., Pede, F.D., Sapigni, T., Viegi, G., 2002. The po river Delta (North Italy) indoor epidemiological study: effects of pollutant exposure on acute respiratory symptoms and respiratory function in adults. Arch. Environ. Health 57, 130–136.

Simoni, M., Scognamiglio, A., Carrozzi, L., Baldacci, S., Angino, A., Pistelli, F., Di Pede, F., Viegi, G., 2004. Indoor exposures and acute respiratory effects in two general population samples from a rural and an urban area in Italy. J. Expo. Anal. Environ. Epidemiol. 14, S144–S152.

Takaro, T.K., Krieger, J., Song, L., Sharify, D., Beaudet, N., 2011. The breathe-easy home: the impact of asthma-friendly home construction on clinical outcomes and trigger exposure. Am. J. Publ. Health 101, 55–62.

Torfs, R., Brouwere, K.D., Spruyt, M., Goelen, E., Nickmilder, M., Bernard, A., 2008. Exposure and Risk Assessment of Air Fresheners. Technical Report. Flemish Institute for Technological Research NV (VITO).

Wells, G.A., Shea, B., O'Connell, D.A., Peterson, J., Welch, V., Losos, M., Tugwell, P., 2009. The Newcastle-Ottawa Scale (NOS) for Assessing the Quality of Nonrandomised Studies in Meta-Analyses.
Who, 2010. WHO Guidelines for Indoor Air Quality: Selected Pollutants. World Health Organisation, Geneva.
Wieslander, G., Norbäck, D., Björnsson, E., Janson, C., Boman, G., 1997. Asthma and the indoor environment: the significance of emission of formaldehyde and volatile organic compounds from newly painted indoor surfaces. Int. Arch. Occup. Environ. Health 69, 115–124.
Zock, J.-P., Vizcaya, D., Le Moual, N., 2010. Update on asthma and cleaners. Curr. Opin. Allergy Clin. Immunol. 10, 114–120.
Kwon, Jae-Woo, Park, Hee-Won, Kim, Woo Jin, Kim, Man-Goo, Lee, Seung-Joon, et al., 2018. Exposure to volatile organic compounds and airway inflammation. Environ. Health: Global Access Sci. Source 17 (1). https://doi.org/10.1186/s12940-018-0410-1, 65–65, In press.
Mukherjee, Mome, Stoddart, Andrew, Gupta, Ramyani P, Nwaru, Bright I, Farr, Angela, Heaven, Martin, Fitzsimmons, Deborah, Bandyopadhyay, Amrita, Aftab, Chantelle, Simpson, Colin R, Lyons, Ronan A, Fischbacher, Colin, Dibben, Christopher, Shields, Michael D, Phillips, Ceri, Strachan, David P, Davies, Gwyneth A, McKinstry, Brian, Sheikh, Aziz, et al., 2016. The epidemiology, healthcare and societal burden and costs of asthma in the UK and its member nations: analyses of standalone and linked national databases. BMC Med. 14 (1), 113. https://doi.org/10.1186/s12916-016-0657-8. In press.
Spalt, Elizabeth, Curl, Cynthia, Allen, Ryan, Cohen, Martin, Williams, Kayleen, Hirsch, Jana, Adar, Sara, Kaufman, Joel, et al., 2016. Factors influencing time-location patterns and their impact on estimates of exposure: the Multi-Ethnic Study of Atherosclerosis and Air Pollution (MESA Air). J. Exp. Sci. Environ. Epidemiol. 26 (4), 341–348. https://doi.org/10.1038/jes.2015.26. In press.