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Volatile organic compounds and risk of asthma and allergy: a systematic review

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ABSTRACT Volatile organic compounds (VOCs) are ubiquitous domestic pollutants. Their role in asthma/allergy development and exacerbations is uncertain. This systematic review investigated whether domestic VOC exposure increases the risk of developing and/or exacerbating asthma and allergic disorders.

We systematically searched 11 databases and three trial repositories, and contacted an international panel of experts to identify published and unpublished experimental and epidemiological studies.

8455 potentially relevant studies were identified; 852 papers were removed after de-duplication, leaving 7603 unique papers that were screened. Of these, 278 were reviewed in detail and 53 satisfied the inclusion criteria. Critical appraisal of the included studies indicated an overall lack of high-quality evidence and substantial risk of bias in this body of knowledge. Aromatics (*i.e.* benzenes, toluenes and xylenes) and formaldehyde were the main VOC classes studied, both in relation to the development and exacerbations of asthma and allergy. Approximately equal numbers of studies reported that exposure increased risks and that exposure was not associated with any detrimental effects.

The available evidence implicating domestic VOC exposure in the risk of developing and/or exacerbating asthma and allergy is of poor quality and inconsistent. Prospective, preferably experimental studies, investigating the impact of reducing/eliminating exposure to VOC, are now needed 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/allergy or living with established disease.



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Investigation of VOCs in relation to developing or exacerbating asthma or allergy indicates new studies are required <http://ow.ly/wEJ19>

Introduction

In westernised countries, asthma and allergic diseases are a public health concern because of their high prevalence, associated morbidity and substantial healthcare and societal costs [1, 2]. The prevalence of asthma and allergic disorders has increased since the early 1960s [3–12] and, although it is generally accepted that changes in the prevalence are a consequence of changing environmental influences, the identities of the relevant environmental exposures remain unclear.

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Volatile organic compounds (VOCs) are important indoor air pollutants produced by evaporation at room temperature from paints, wood, fabrics, cleaning agents, air fresheners, cosmetics, furnishings and floor and wall coverings. Indoor VOC levels exceed those outdoors [13–15], and are further increased by cigarette smoking and if a garage is attached to a house [16]. Greater use of VOC-containing products has, together with more effective insulation and less external ventilation of modern buildings, contributed to increased VOC exposure. The possible health effects of indoor VOC exposure are a cause for concern, given that people in general, and children in particular, now spend most of their time indoors [14, 17].

Several developments have led to a renewed interest in the possible effects of residential VOC exposure on asthma/allergy. These include the development of technologies that facilitate the quantification of individual VOC exposure, longitudinal cohort studies reporting associations consistent with a link between antenatal VOC exposure and childhood asthma/allergy [18, 19], and new approaches to reducing residential VOC exposure. Interventions to reduce VOC exposure are now feasible by, for example, avoiding redecoration, new furniture, air fresheners and perfumed items, and increasing ventilation [16]. The technology now also exists to construct so-called “nontoxic” houses, which are built without unplasticised polyvinyl chloride (uPVC) frames and using low-VOC paints and coverings.

We report here a systematic review investigating the possible effects of domestic VOC exposure on the development of asthma/allergy and the impact of VOCs on those with established disease.

Methods

We searched the following 11 international databases using a detailed search strategy (supplementary material, appendix 1): MEDLINE (1966–2012), EMBASE (1980–2012), Cochrane Library (1992–2012), LILACS (1986–2012), ISI Web of Science (1970–2012), BIOSIS (1969–2012), Global Health (1987–2012), AMED (1985–2012), TRIP (2003–2012), CAB (1910–2012) and CINAHL (1937–2012). Unpublished data and research in progress were identified using the key Internet-based databases www.clinicaltrials.gov, www.controlled-trials.com and www.anzctr.org.au, and by contacting international experts in the field (supplementary material, appendix 2). The bibliographies of included studies were scrutinised to identify further relevant studies. There were no language restrictions.

Observational studies (cross-sectional, case-control and cohort) and intervention studies (randomised controlled trials (RCTs), quasi-RCTs, controlled clinical trials (CCTs), controlled before-and-after (CBA) studies and interrupted time series) were eligible for inclusion; case reports/series and expert opinions were excluded.

Papers were included if they investigated the role of domestic (*e.g.* home, school, day care), objectively measured airborne exposure to VOCs occurring in real-life indoor environments, in the development of asthma/allergy and/or in exacerbating established disease. We therefore excluded papers reporting exposure to VOC sources, modelled or estimated exposure, and experimental exposure under laboratory conditions. Studies reporting only on exposure biomarkers were excluded on the grounds of their wide inter- and intra-individual variability, potential biological instability and because these measures reflect endogenous metabolites and routes of exposure, including those outside the scope of this review (*e.g.* digestive, dermal) (supplementary material, appendix 3). We also excluded studies that measured residential VOC concentrations to quantify exposure to environmental tobacco smoke.

Included studies reported ante- and post-natal exposures and outcomes in children and adults. The main outcomes of interest were: the incidence or prevalence of asthma, atopic eczema/dermatitis and allergic rhinitis/rhino-conjunctivitis; and evidence of allergic sensitisation. Secondary outcomes of interest were measures of increased disease activity by any objective measure (*e.g.* lung function, symptom scores, exacerbations, medication usage, healthcare utilisation and quality of life). Studies that reported nonspecific symptoms, such as throat/nasal irritation and symptoms associated with sick building syndrome, were excluded.

Two researchers independently reviewed titles and abstracts of identified studies, assessed the full text of potentially eligible studies against the inclusion criteria and carried out data extraction using customised forms (supplementary material, appendix 4). Disagreements were resolved through consultation between the two reviewers and discussion with other researchers if needed.

The methodological quality was assessed independently by two researchers using the Effective Public Health Practice Project (EPHPP) [20] for observational and the Cochrane Effective Practice and Organisation of Care (EPOC) criteria [21] for intervention studies.

For each publication, the method(s) used to quantify VOC exposure were assessed for the likelihood of providing a valid quantification of long-term individual domestic VOC exposure. This grading scheme is broadly based on the principle that longer averaging times are less susceptible to the influence of

short-term peaks and troughs, and the evidence that area or static sampling can under- or over-estimate personal exposure (table 1) [22].

Due to the substantial heterogeneity in populations, exposures and outcome measures, meta-analysis of the included studies was deemed inappropriate and was not conducted. A descriptive and narrative synthesis of the evidence was therefore undertaken. In interpreting the evidence we preferentially drew, wherever possible, on evidence from experimental studies and observational studies judged to be at low risk of bias.

Results

Description of studies

Our searches identified 8455 potentially relevant papers; 852 papers were removed after de-duplication, leaving 7603 unique papers that were subjected to screening. Of these, 53 satisfied our inclusion criteria (fig. 1).

We found eight interventional studies: one RCT [23], one CCT [24] and six CBA studies [25–30]. The majority (n=45) of studies employed observational designs. There were six cohort studies [31–36] and 11 case-control studies [37–47]. Among the observational studies, two-thirds (n=28) were cross-sectional studies [48–75].

30 studies investigated the role of VOCs in the context of developing asthma/allergy [25, 28, 31, 36, 37, 40–46, 48–54, 57, 59, 61–65, 67–69, 73]; five studies investigated the role of VOCs in exacerbating established asthma/allergy [24, 27, 32, 33, 56]; and the remaining 18 studies investigated the role of VOCs in both the development and exacerbation of asthma/allergy [23, 26, 29, 30, 34, 35, 38, 39, 47, 55, 58, 60, 66, 70–72, 74, 75] (table S1).

Quality assessment

Five studies, including one RCT [23], three cohort studies [33–35] and one case-control study [47], were graded as being at low risk of bias; 15 studies, including two cohort studies [31, 36], five case-control studies [37, 42–45] and eight cross-sectional studies [48, 50, 62, 65, 72–75], were graded as being at moderate risk of bias. The remaining 33 studies were judged to be at high risk of bias (tables S1 and S1A).

Studies investigating the role of VOCs in the aetiology of asthma/allergy

Six studies examined the association between total VOCs and asthma/allergy-related outcomes [36, 43, 45, 46, 49, 51]. While one cohort study at moderate risk of bias found no associations [36], two case-control studies at moderate risk of bias reported adverse associations between total VOCs and asthma [43, 45]. There was one further study that measured total VOC exposure but did not relate this to the outcomes of interest [63].

Total VOCs were also investigated in one case-control study [46] and two cross-sectional studies [49, 51] that were considered to be at high risk of bias (tables S1A and S2).

Aromatic VOCs

14 studies explored the associations between the aromatic group of VOCs and asthma/allergy-related health outcomes (table S1A) [31, 37, 40–43, 45, 46, 50, 51, 54, 61, 62, 73]. Among the studies at moderate risk of bias, one cohort study reported a significant association between exposure to benzene and decreased CD4 CD25 regulatory T-cells in cord blood [31], two case-control studies [43, 45] and two cross-sectional studies [50, 62] reported adverse associations between aromatic VOCs and asthma, wheezing, nocturnal breathlessness and cord blood T-cell parameters, while two other case-control studies

TABLE 1 Hierarchy of volatile organic compound exposure measurement

Exposure coding	Strength of the methodology
1 Repeated personal exposure sampling with each sample >24 h	Optimal
2 Repeated personal exposure sampling with each sample <24 h	Acceptable
3 Single personal exposure sampling >24 h	Acceptable
4 Single personal exposure sampling <24 h	Poor
5 Repeated area/static exposure sampling from several household locations	Poor
6 Single area/static exposure sampling from several household locations	Poor
7 Repeated area/static exposure sampling from one household location	Poor
8 Single area/static exposure sampling from one household location	Poor

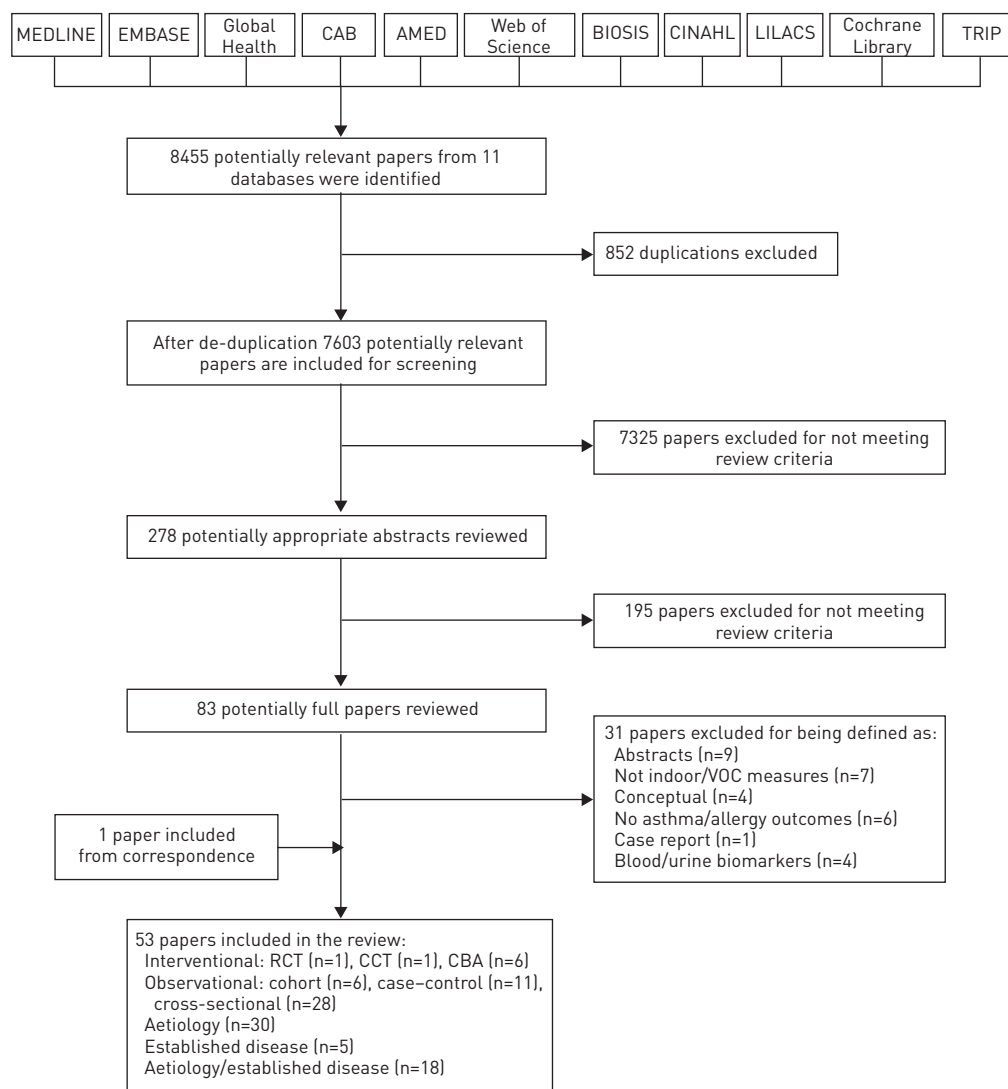


FIGURE 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram of studies identified to investigate the role of domestic volatile organic compound (VOC) exposure in risk of developing and/or exacerbating asthma and allergic disorders. RCT: randomised controlled trial; CCT: controlled clinical trial; CBA: controlled before-and-after.

[37, 42] and one cross-sectional study [73] found no association between aromatics and asthma, atopic eczema/dermatitis, allergic rhino-conjunctivitis or sensitisation. Aromatic VOCs were measured in two other studies, but exposure was not related to any of the outcomes of interest [63, 69].

Aromatic VOCs were also investigated in three case-control studies [40, 41, 46] and three cross-sectional studies [51, 54, 61] that were all considered to be at high risk of bias.

Chlorinated hydrocarbons

Two cross-sectional studies at moderate risk of bias examined chlorinated hydrocarbons as a group, or chloroethenes separately, and reported adverse association with wheezing and cord blood T-cell parameters [50, 62]. These types of VOCs were also investigated in two cross-sectional studies that were judged to be at high risk of bias [51, 61].

Propylene glycol and glycol ethers

One case-control study at moderate risk of bias reported adverse associations between propylene glycol and glycol ethers and asthma, rhinitis, eczema and IgE-sensitisation [37]. Another cross-sectional study also investigated this exposure; however, this study was at high risk of bias (table S1A) [51].

Alkanes

Alkanes were investigated in six studies (table S1A) [37, 42, 43, 51, 61, 62]. Three case-control studies at moderate risk of bias reported no associations between alkanes and asthma, atopic dermatitis, allergic rhino-conjunctivitis, sensitisation or nocturnal breathlessness [37, 42, 43]. One cross-sectional study at moderate risk of bias found adverse associations between methylcyclopentane and elevated percentages of interleukin-4-producing type 2 T-cells [62]. The remaining two cross-sectional studies were at high risk of bias [51, 61].

Alcohols

Alcohols were investigated in three cross-sectional studies; all were considered to be at high risk of bias [49, 53, 59].

Aldehydes

Two studies, one case-control [37] and one cross-sectional [48], at moderate risk of bias, found no association between aldehydes as a class and the outcomes of interest (table S1A). Formaldehyde was the most commonly reported individual aldehyde (17 studies) [25, 36, 40–44, 46, 48, 49, 51, 54, 57, 64, 65, 67, 68]. Among six studies at moderate risk of bias, one case-control study showed no associations with asthma [42], while one cohort study [36], two case-control studies [43, 44] and two cross-sectional studies [48, 65] at moderate risk of bias found adverse associations between formaldehyde exposure and asthma, allergic rhinitis, rhino-conjunctivitis, atopic eczema or nocturnal breathlessness. Four studies measured formaldehyde but did not relate exposure to the outcomes of interest [28, 52, 63, 69]. 11 remaining studies [25, 40, 41, 46, 49, 51, 54, 57, 64, 67, 68] on formaldehyde exposure were at high risk of bias.

Acrolein was investigated in one cross-sectional study at moderate risk of bias and found to be adversely associated with the prevalence of asthma in the past year in those with atopic asthma but not with nonatopic asthma [48]. A second cross-sectional study also assessed acrolein exposure; however, this study was at high risk of bias [51].

Acetaldehyde was investigated in four studies; all were considered to be at high risk of bias (table S1A) [41, 51, 57, 64].

Ketones

Ketones were investigated in three studies; all were considered to be at high risk of bias (table S1A) [49, 53, 59].

Terpenes

Terpenes were investigated in two studies at moderate risk of bias [43, 62]. In a case-control study, exposure to limonene was related to bronchial hyperresponsiveness and exposure to α -pinene and carenes (δ 2, δ 3) to a reduction in peak expiratory flow [43], while a cross-sectional study failed to relate any of these exposures to allergic sensitisation to food allergens [62]. Terpenes were also investigated in one study that was at high risk of bias (table S1A) [61].

VOCs only investigated in single studies

In one cross-sectional study at moderate risk of bias, chloroform as a single compound was associated with wheezing, and methyl t-butyl ether was associated with physician-diagnosed asthma and wheezing [50]. One case-control study at moderate risk of bias also reported that total terpene exposure was linked to nocturnal breathlessness [43].

Two other case-control studies at moderate risk of bias reported no association between exposure to organic acids as a class and asthma, eczema, allergic rhinoconjunctivitis and sensitisation [37], or between butanols as a class and asthma, sensitisation and lung function [43]. VOCs were also investigated in five other single studies at high risk of bias (table S5) [49, 51–53, 59].

Summary

Overall, we found a substantial body of evidence, the majority of which was judged to be at high risk of bias. Whilst it was therefore not possible to draw any conclusive assessment in relation to the aetiological role of VOCs in the development of asthma/allergy, the modest effect sizes and the heterogeneity of findings suggest that VOC exposure is unlikely to be a major risk factor for the development of asthma/allergy in the general population.

Studies investigating the effects of VOCs in established asthma/allergy

Total VOCs were investigated but not examined in relation to the outcome, in two studies, both of which were considered to be at high risk of bias (tables S1A and S3) [24, 27].

Aromatic VOCs

Total aromatic VOCs were investigated in four studies [27, 32, 33, 56]. One cohort study at low risk of bias reported that exposure to benzene, toluene and ethylbenzene was associated with a decrease in forced expiratory volume in 1 s (FEV₁) and with an increase in change of FEV₁ [33]. Exposure to these aromatics also leads to an increase in rescue medication and emergency department visits. Two studies measured toluenes [27, 56], two studies measured xylenes [27, 56], and one study measured styrenes [32], but none of these examined these exposures in relation to the outcomes of interest. These studies were judged as being at high risk of bias [27, 32, 56].

Aldehydes

Formaldehyde was investigated in one cohort study at low risk of bias that found no association with asthma/allergic disease exacerbation [33]. Two other studies also measured aldehydes but did not examine exposure in relation to the outcome of interest, and these were furthermore considered to be at high risk of bias [24, 27].

Summary

Overall, we found a much smaller body of evidence focusing on investigating the relationship between VOC exposure and asthma/allergy exacerbations in those with established disease. This evidence was highly heterogeneous and therefore inconclusive.

Studies investigating the role of VOCs in both aetiology and established disease

Out of eight studies that measured total VOCs, five did not relate exposure to outcomes [26, 29, 35, 58, 72]. The one case-control study at low risk of bias that analysed exposure-outcome relationships found no association [47]; the remaining two studies that also investigated total VOCs were at high risk of bias (see table S1A) [55, 70].

Four studies measured aromatics [26, 58, 70, 71], two studies measured chlorinated VOCs [26, 58], three studies measured alkanes [58, 70, 72], two studies measured alcohols [35, 38], three studies measured aldehydes [35, 71, 72], two studies measured ketones [35, 38], one study measured terpenes [70] and one study measured esters [72], but they did not examine these VOCs in relation to the outcome of interest.

Aldehydes

Formaldehyde was investigated in 14 studies [23, 30, 34, 35, 39, 47, 58, 60, 66, 70–72, 74, 75]. One RCT with low risk of bias reported adverse associations between formaldehyde and wheezing [23]. One cohort study at low risk of bias found no associations between formaldehyde and wheezing [34]; in contrast, one case-control at low risk of bias [47] and two cross-sectional studies at moderate risk of bias [74, 75] showed positive associations between formaldehyde and current asthma severity, wheezing/severity and nocturnal breathlessness (table S1A).

Esters

Assessment of 2,2,4-trimethyl-1,3-pentanediol diisobutyrate was carried out in two cross-sectional studies. One of these, at moderate risk of bias, did not relate exposure to asthma/allergy-related outcomes [72], while the second study was at high risk of bias (table S1A) [71].

Summary

The key additional insight from this body of work focusing on both asthma/allergy incidence and risk of exacerbation is that there was one well-conducted RCT which found that exposure to low-VOC (formaldehyde)-emitting heating resulted in reduced respiratory symptoms in children with atopic disease, but this had no impact on lung function.

Unpublished and ongoing studies

No relevant unpublished and/or ongoing studies were identified.

Discussion

This systematic review is probably the most comprehensive investigation undertaken to date of the role of VOCs in the development of asthma/allergic disease and in exacerbating established asthma/allergy. Most studies investigated the possible role of VOCs in the development of asthma and/or allergic disease, with relatively few studies relating VOCs to exacerbations/severity of established disease. The overwhelming majority of studies employed observational designs, with aromatics and formaldehyde being the main VOCs studied. Critical appraisal of included studies suggested that there was a substantial risk of bias in this body of knowledge. There were approximately equal numbers of studies reporting either adverse

associations of various VOCs or no association. Moreover, the numbers of studies supporting and not supporting the associations were also fairly balanced in terms of their methodological quality. In addition, only four of the included studies (one cohort [31], one case-control [42] and two cross-sectional [50, 65]) employed exposure assessment methodology that can be considered acceptable in generating the data for exposure-outcome analysis. Given the methodological concerns and the inconsistent results, these data do not provide sufficient evidence to unequivocally support or refute the hypothesis that domestic VOC exposure is associated with an increased risk of developing and/or exacerbating asthma/allergy.

A key strength of this systematic review is the comprehensiveness of the searches. We carefully identified all VOCs and then grouped and scrutinised them under several categories to find the effect of each compound on the development of asthma/allergy and exacerbating established disease. The methods used to quantify VOC exposure were carefully assessed and graded for methodological rigour. We note that the existing quality assessment tools do not incorporate assessment of the quality of the exposure information; consequently, studies rated as strong methodologically could have weak methods of quantifying personal VOC exposures. We believe this systematic review to have been more rigorous than the previous, frequently cited, systematic review [76], critical analysis [77] and literature review [78], which notably did not critically appraise study quality using validated tools or distinguish between studies investigating aetiology and those investigating established disease.

The main limitations of this review stem from the heterogeneity of populations, exposures and outcomes studied, and the overall limited body of high quality studies. The many limitations of the conducted studies include: inadequate sampling of VOCs at home or in schools; exposure assessment tending to be short-term (typically ≤ 24 h) and carried out by area sampling with very few personal sampling studies over extended periods; lack of standardisation in assessing asthma/allergy-related health outcomes; measurement of many VOCs that were not related to relevant health outcomes of interest; frequent inadequate adjustment for confounding factors; failure to adjust for clustering; failure to distinguish between disease aetiology, severity and treatment of established disease; and failure to adjust for or consider the consequence of multiple tests of statistical comparison. A potent source of indoor VOC exposure is environmental tobacco smoke, and a further limitation of our methodology was the deliberate exclusion of studies that had utilised VOC measurements as a proxy measure for environmental tobacco smoke exposure, because the focus of this study was residential VOC exposure from noncigarette sources. Notably, some studies failed to adjust for the smoking habits of household members.

Animal studies demonstrate that VOC exposure can influence the immune responses, increasing T-helper cell (Th) type 2 polarisation [79–81]. In humans, increased Th2 polarisation of neonatal immune responses has been associated with maternal VOC exposure during pregnancy [82]. Although little evidence exists suggesting that VOCs influence lung growth, embryotoxic effects from exposure to airborne VOCs on murine embryonic stem cells have been reported [83], and adverse effects on rat embryo/fetal development have been linked to VOC release from their cages [84].

Asthma and allergic diseases are a significant burden to the health services of industrialised countries and a potential threat to the health services of developing countries. The identification of environmental exposures that increase the risk of developing these conditions or exacerbating established disease is warranted. Whether VOCs have adverse effects on asthma/allergy is important to ascertain, given that intervention to reduce VOC exposure is feasible by lifestyle changes (*e.g.* avoiding redecoration, air fresheners and perfumed items; having a smoke-free home; increasing ventilation) and technological adaptation (*e.g.* use of low-emitting VOC materials). Despite the aforementioned shortcomings in the underpinning evidence base and the inconsistent findings, this work has demonstrated that it is not yet possible to exclude the possibility that VOCs, particularly aromatics, aldehydes (formaldehyde), alkanes and terpenes, may play a harmful role in the development of asthma/allergy and/or in exacerbating established disease.

Further work is required to clarify the impact of VOCs on the development/exacerbation of asthma/allergy. In the first instance, there is a need for well-designed, large cohort studies relating long-term, indoor, personal exposure measurements to validated asthma/allergy-related health outcomes with adequate adjustment for key potential confounding factors and effect modifiers. These observational studies may then need to be followed by well-conducted RCTs investigating the effectiveness and cost-effectiveness of interventions reducing VOC exposure on the risk of developing asthma/allergy and/or exacerbating established disease.

Conclusion

The overall body of evidence in relation to the role of VOCs in the development of asthma and allergic disease and the role of VOCs in exacerbating established asthma/allergy in children and adults is weak.

We found very few interventional studies and data were generally of poor quality, being derived mainly from observational studies. There is a need to develop a more definitive evidence base to examine the relationship between VOC exposure and asthma/allergy, in order to inform deliberations on public policy and clinical care.

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“Supplementary Material”

Volatile organic compounds and risk of asthma and allergy: a systematic review

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Short running title: VOC exposure and asthma and allergy

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SUPPLEMENTARY MATERIAL

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Supplementary Material, Appendix 1: Search strategy 1

Cochrane Library; MEDLINE; EMBASE; LILACS; ISI Web of Science; BIOSIS; Global Health; AMED; TRIP; CAB; and CINAHL.

For MEDLINE, EMBASE, GLOBAL HEALTH, AMED and CAB

1. Exp Hypersensitivity/
2. allerg*.mp.
3. atop*.mp.
4. or/1-3
5. exp Asthma/
6. asthma.mp.
7. Exp Respiratory Tract Diseases/
8. asthmatic children.mp.
9. acute asthmatic attack.mp.
10. night cough*.mp.
11. wheez*.mp.
12. Respiratory hypersensitivity/
13. bronchial disorder.mp.
14. hyper-responsiveness wheez*.mp.
15. Respiratory sounds/
16. Exp Respiration Disorders/
17. Exp Respiratory Function Tests/
18. lung function.mp.
19. ventilatory function.mp.
20. FEV.mp.
21. FEF.mp.
22. FVC.mp.
23. PEF.mp.
24. bronchial hyperreactivity.mp.
25. airway hyperreactivity.mp.
26. bronchial responsiveness.mp.
27. airway responsiveness.mp.
28. or/5-27
29. exp Food hypersensitivity/
30. food allerg*.mp.
31. food hypersensitivity.mp.
32. food hypersensitivities.mp.
33. allergy, food.mp.
34. or/29-33

35. exp Dermatitis, Atopic/
36. exp Eczema/
37. Neurodermatitis/
38. eczema.mp.
39. dermatitis.mp.
40. dermatitides.mp.
41. atopic dermatitis.mp.
42. atopic eczema.mp.
43. eczematous dermatiti*.mp.
44. dermatiti*, eczematous.mp.
45. besnier* prurigo.mp.
46. neurodermatitis.mp.
47. dermatitis, atopic.mp.
48. eczema, atopic.mp.
49. itching.mp.
50. Urticaria/
51. urticaria.mp.
52. or/35-51
53. exp Rhinitis/
54. Rhinitis Allergic Perennial/
55. Rhinitis Allergic Seasonal/
56. hayfever.mp.
57. hay fever.mp.
58. fever, hay.mp.
59. rhiniti*.mp.
60. poll?nosis.mp.
61. pollenosis.mp.
62. exp Nasal obstruction/
63. Conjunctivitis/
64. Conjunctivitis, Allergic/
65. conjunctivit*.mp.
66. rhino-conjunctivit*.mp.
67. or/53-66
68. Exp Anaphylaxis/
69. anaphylaxis react*.mp.
70. anaphylactic react*.mp.
71. anaphylactic shock*.mp.
72. anaphylactoid syndrome*.mp.
73. anaphylactoid react*.mp.
74. anaphylactic syndrome*.mp.
75. anaphylactoid shock*.mp.
76. acute systemic allergic react*.mp.
77. idiopathic anaphylaxis.mp.
78. systemic anaphylaxis.mp.

79. or/68-78
80. 3 or 28 or 34 or 52 or 67 or 79
81. analytical stud*.mp.
82. exp Epidemiologic Studies/
83. exp Intervention Studies/
84. exp Evaluation Studies/
85. exp Comparative Studies/
86. exp Follow-up Studies/
87. exp Prospective Studies/
88. prospectiv*.mp.
89. exp Cohort Studies/
90. exp Case-Control Studies/
91. control.mp.
92. healthy control children.mp.
93. exp Cross-sectional Studies/
94. cohort stud*.mp.
95. cohort.mp.
96. birth cohort.mp.
97. case-control stud*.mp.
98. cross-sectional stud*.mp.
99. etiology.mp.
100. trial.mp.
101. Clinical trial/
102. clinical trial.mp.
103. Controlled Clinical Trial/
104. controlled clinical trial.mp.
105. Randomized Controlled Trial/
106. Quasi-randomi?ed controlled trial
107. Controlled before and after studies
108. Interrupted time series
109. exp Placebos/
110. exp Random Allocation/
111. exp Double-Blind Method/
112. double-blind design.mp.
113. exp Single-Blind Method/
114. single-blind design.mp.
115. randomi?ed controlled trial.mp.
116. random*.mp.
117. exp Survey/
118. survey.mp.
119. questionnaire*.mp.
120. exp Primary prevention/
121. primary prevention.mp.
122. exp Secondary prevention/

123. secondary prevention.mp.

124. or/81-123

125. exp Ethanol/ or exp Propanols/ or exp Glycols/ or exp butanols/ or exp Heptanol/ or exp Hexanols/ or exp Octanols/ or exp Pentanols/ or exp Octanols/ or exp Aldehydes/ or exp Pyridines/ or exp Amines/ or exp Acetates/ or exp Acetic Acids/ or exp Phthalic Acids/ or exp Formic Acids/ or exp Citric Acid/ or exp Lactic Acid/ or exp Oxalic Acids/ or exp Esters/ or exp Hexanoic Acids/ or exp Trichloroacetic Acid/ or exp Carboxylic Acids/ or exp Isobutyric Acids/ or exp Polyurethanes/ or exp Hydrocarbons/ or exp Ethers/ or exp Ketones/ or exp Dioxins/ or exp Phenols/ or exp cresols/ or exp Hydroquinones/ or exp Azoles/ or exp carbon Disulfide/ or exp Acrylonitrile/ or exp Acetonitriles/ or exp Siloxanes/ or exp Isocyanates/ or exp Anhydrides/ or exp Furans/ or exp Picrates/ or exp Carbon Compounds, inorganic/ or exp Methylmethacrylates/ or exp Morpholines/ or exp Dimethylformamide/ or exp Pyrrolidinones/ or exp Formaldehyde/

126. (ethanol* or propanol* or glycol* or propanediol or butanol* or heptanol* or hexanol* or ethylhexanol or octanol* or octen* or octanon* or pentanol* or butoxyethanol or cellosolve or ethoxyethanol or methoxyethanol or dowanol or butoxydiglycol or butyl carbitol or butyl dioxitol or methylpropanol or isobutyl alcohol or isobutanol or aldehyde* or acetaldehyde* or isobutyraldehyde or isovaleraldehyde or valeraldehyde or formaldehyde or dimethylbenzaldehyde or benzaldehyde* or crotonaldehyde or furfural or hexanal* or hexanaldehyde or pentanal* or acrolein or acrylonitrile or propenal or propionaldehyde or propanal or butanal or butyraldehyde or methylbutanal or heptanal or furaldehyde* or octanal* or benzaldehyde or Decanal or nonanal or pyridine* or aromatic amine* or acetate* or acetic acid* or trichloroacetic acid or monoisobutyrate or diisobutyrate or ester* or dibutyl or formic acid* or hexanoic acid* or caproic acid* or carboxylic acid* or isobutyric acid* or texanol or polyurethan* or polyurethan\$ foam or diethyl phthalate or butyl benzyl phthalate or benzyl chloride or chlorotoluene or Octafluorotoluene or tetrahydrofuran or acid anhydride* or isopropanol or isopropyl alcohol or furan* or picric acid or trinitrophenol or isocyanobutan* or carbon monoxide or isobutane or methylpropane or isobutene or isobutylene or methylmethacrylat* or methacrylate* or cyclopropane* or ethanethiol or ethyl mercaptan or ethylene oxide or oxirane or propylene oxide or epoxypropane or dimethylaniline or dimethylacetamide or dimethyl acetamide or bromobenzene or bromochloromethane or bromomethane or chlorodibromomethane or chloromethane or methyl chloride or hydrocarbon* or halocarbon* or aromatic compound* or halogenated organic compound* or alkane* or alkene* or decane* or dodecane* or undecane* or hendecane* or heptane* or hexane* or nonan* or octan* or tridecane* or pentan* or trimethylpentane or isooctane or methylpentane* or methylhexane or tetradecane or trimethylhexane or hexadecan* or pentadecan* or ethane or dichloroethan* or dutch oil or freon or tetrachloroethan* or tetrachlorethan* or

- decene or butadiene* or hexachlorobutadiene or lindane).mp. [mp=title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
127. (acetylene or ethyne or chloroprene or isoprene or vinylidene chloride or chloroethan* or chlorethan* or ethyl chloride or dichloroethylen* or dichloroethen* or polyvinyl chloride or PVC or polyvinylchloride or vinyl chloride or chloroethen* or ethylbenzen* or ethyl benzen* or cyclohexanon* or hexanon* or Cycloalkane* or naphthene* or cyclopentan* or methylcyclopentan* or cyclohexan* or cyclohexene* or phenylcyclohexene or methylcyclohexan* or propylcyclohexan* or butylcyclohexan or benzene or benzol* or chlorobenzen* or trichlorobenzen* or dichlorobenzen* or xylen* or methylbenzene* or dimethylbenzen* or styrene* or toluen* or isopropyltoluen* or isopropylbenzene or isopropyl benzen* or propylbenzene or methylcyclopentane or cumene* or cymene or ethyl toluen* or ethyltoluen* or propylbenzen* or trimethylbenzen* or mesitylene or butylbenzene or hexafluorobenzene or perfluorobenzene or phenylcyclohexen* or naphthalene* or naphthalin* or moth balls or napht?ol* or pyrene* or chlorohydrocarbon* or organochlorid* or organochlorin* or chlorocarbon* or chloroalkan* or dichloropropane or dichloropropene or ethylene dibromide or dibromoethane or dibromomethane or methylene bromide or trichloropropane or trichloroethan* or chlorot?ene or methylchloroform or carbon tetrachloride or methane or paraffin or tetrachloromethan* or carbon chloride or tetrachloroethylen* or tetrachlorethylen* or tetrachloroethen* or perchloroethylen* or perchlorethylen* or trichloroethylen* or trichlorethylen* or trichloroethen* or trichlorethen* or trichlor or dichloromethan* or methylene chloride or trihalomethan* or dibromochloromethane or dibromochloropropane or chloroform or trichloromethan* or bromoform* or bromohydrocarbon* or bromomethan* or bromodichloromethane or terpen* or terpenoid* or camphor or allethrin* or pyrethrin* or pyrethroid* or carene or camphene or limonene or eucalyptol or pinene* or chlorofluorocarbon* or chlorofluorohydrocarbon* or trichlorofluoromethane* or trichloromonofluoromethane or trichlorofluoroethane* or dichlorodifluoromethane or ether* or epichlorohydrin or dioxan* or butoxyethanol* or butoxy ethanol* or ketone* or alkanone* or acetone or propanone or acetophenone* or phenylethanone or butanone* or pentanone or phenol* or carboic acid or cresol* or hydroxytoluen* or butylhydroxytoluen* or azole* or carbon disulfide or carbon disulphide or carbon bisulfide or siloxan* or heptanon* or ethenylpyridine or butylacetate or hydroquinon* or isocyanate* or diisocyanate* or isopentan* or methylbutan* or fenchon* or terpineol* or thujopsene*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
128. exp Volatile Organic Compounds/ or exp Volatilization/ or exp Odors/ or Volatile organic compound*.mp. or Volatile organic constituent*.mp. or

Volatile organic mixture*.mp. or Volatile chemical*.mp. or volatile compound*.mp. or volatile organic*.mp. or volatile agent*.mp. or Volatile organic chemical*.mp. or volatili?ation.mp. or organic gaseous.mp. or organic gas.mp. or organic gases.mp. or organic aerosol*.mp. or TVOC.mp. or TVOCs.mp. or VOC.mp. or VOCs.mp. or MVOC.mp. or MVOCs.mp. or odo?r\$1.mp.

129. aerosol.mp. or exp Aerosols/ or exp Deodorants/ or exp Household Products/ or Air freshener*.mp. or exp Aerosol Propellants/ or Cosmetic*.mp. or exp Cosmetics/ or exp Construction Materials/ or Building material*.mp. or Building product*.mp. or exp "Facility Design and Construction"/ or exp "Floors and Floorcoverings"/ or Carpet*.mp. or Chipboard.mp. or Chemical based product*.mp. or exp Disinfectants/ or exp Detergents/ or Cleaning agent*.mp. or Cleaning product*.mp. or Consumer product*.mp. or Decorat*.mp. or exp Disinfection/ or Disinfectant agent*.mp. or redecorat*.mp. or Deodorizer*.mp. or Domestic product*.mp. or Domestic chemical*.mp. or Flooring.mp. or exp Polyurethanes/ or Foam cushion*.mp. or exp "Interior Design and Furnishings"/ or Furnishing*.mp. or Furniture.mp. or Adhesive.mp. or exp Adhesives/ or Glue.mp. or exp Plasticizers/ or exp Household Articles/ or Household Article*.mp. or exp Household Products/ or exp Detergents/ or exp Cosmetics/ or Household Chemical*.mp. or Insect repellent.mp. or exp Insect Repellents/ or Insecticide.mp. or exp Insecticides/ or repellent.mp. or exp Mosquito Control/ or Mosquito coil*.mp. or exp Moths/ or Moth ball*.mp. or Lacquer.mp. or exp Lacquer/ or Solvent.mp. or exp Solvents/ or Surface material*.mp. or exp Solvents/ or exp Paint/ or Paint*.mp. or Perfume.mp. or exp Perfume/ or Plastic*.mp. or renovat*.mp. or exp Plasticizers/ or Plasticizer*.mp. or plasticiser*.mp. or Upholstery.mp. or Varnish*.mp. or Vinyl floor*.mp. or Wax.mp. or exp Waxes/ or exp Wood/ or Wood*.mp. or (freshener spray* or cleaning spray*).mp. or ((gas-phase or gas phase or gaseous-phase or gasphase) adj4 cigarette smoke).mp. or particleboard*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
130. exp Housing/ or Indoor*.mp. or household*.mp. or exp Air Pollution, Indoor/ or Air Pollutants/ or Air Pollution/ or indoor source*.mp. or residential.mp. or home.mp. or exp Residence Characteristics/ or residence.mp. or school*.mp. or exp Schools/ or domestic.mp. or housing.mp. or exp Ventilation/ or indoor pollutant*.mp.
131. exp Occupational Exposure/ or exp Air Pollutants, Occupational/ or outdoor pollution.mp. or occupational pollution.mp.
132. 125 or 126 or 127 or 128 or 129
133. (130 and 132) not 131
134. 80 and 124 and 133
135. 134 not (animals/not humans/)

Supplementary Material, Appendix 1: Search strategy 2

For The Cochrane Library, LILACS, TRIP, CINAHL, ISI Web of Science and BIOSIS

(volatile organic compound or VOC or total volatile organic compounds or TVOC or microbial volatile organic compounds or MVOC or volatile compound or “volatile organic mixture” or volatile chemical or volatile organic or volatile agent or “volatile organic chemical” or “volatile organic constituent” or volatilization or organic gas* or organic aerosol or “organic gaseous pollutant”)

AND

(“primary prevention” or “secondary prevention” or etiology or epidemiological stud* or intervention stud* or prospective stud* or cohort or cohort stud* or case-control stud* or cross-sectional stud* or trial or randomized controlled trial or quasi-randomized controlled trial or controlled clinical trial or “controlled before-after study” or “interrupted time series”)

AND

(hypersensitivity or allergy or asthma or atopy or “atopic dermatitis” or eczema or “hay fever” or “allergic rhinitis” or pollinosis or “food allergy” or anaphylaxis or “anaphylactic shock” or “systemic allergic reaction”)

Supplementary Material, Appendix 2: List of experts contacted

Name author	Country
Professor Patric N Breysse	USA
Professor Bert Brunekreef	The Netherlands
Dr. Derrick Crump	UK
Professor Ralph J Delfino	USA
Dr. Bruno Hubesch	Belgium
Professor Matti J Jantunen	Finland
Dr. Mark J Mendell	USA
Professor Jonathon M Samet	USA
Professor Giovanni Viegi	Italy
Professor Clifford P Weisel	USA
Professor H.-Erick Wichmann	Germany

Supplementary Material, Appendix 3: Description of excluded papers

No	Article	Reason for excluding
1.	Bornehag CG, et al. 2004	Abstract
2.	Brockow I, et al. 2008	No asthma/allergy outcomes
3.	Choi J, et al. 2011	Abstract
4.	Czaikowski R. 2000	Conceptual
5.	Drouet M, et al. 1985	Case report
6.	Elliot L, et al. 2006	Blood biomarkers
7.	Howard WA. 1979	Not indoor/VOC measures
8.	Huss-Marp J. 2004	Abstract
9.	Kamijima M, et al. 2005	No asthma/allergy outcomes
10.	Karmaus W, et al. 2005	Blood biomarkers
11.	Kerrebijn KF, et al. 1973	Not VOC measurements
12.	Kim JH, et al. 2005	Urinary biomarkers
13.	Kimmel R, et al. 2000	Not indoor/VOC measurements
14.	Kolossa-Gehring M, et al. 2007	Not indoor/VOC measurements
15.	Mayer PS, et al. 1972	Not indoor/VOC measurements
16.	Asthma triggers.2005	Conceptual
17.	Perrenoud D, et al. 1994	Not VOC measurements
18.	Rios JLM, et al. 2010 a	Abstract
19.	Rios JLM, et al. 2010 b	Abstract
20.	Rios JLM, et al. 2011	Abstract
21.	Roda C, et al. 2011	No asthma/allergy outcomes
22.	Rolle-Kampczyk UE, et al. 2002	Urinary biomarkers
23.	Rudnai P, et al. 2004	Conceptual
24.	Saijo Y, et al. 2004	No asthma/allergy outcomes
25.	Shimada T, et al. 1972	No asthma/allergy outcomes
26.	Son B, et al. 2011	Abstract
27.	Stewart L, et al. 2000	No asthma/allergy outcomes
28.	Tillett T. 2010	Conceptual
29.	Ware JH, et al. 1993	No indoor measurements
30.	Weisse K, et al. 2011	Abstract
31.	Yeatts KB, et al. 2011	Abstract

Supplementary Material, Appendix 4: Data extractions forms

* = fill in extraction sheet according to study design

Data extraction form RCTs, quasi RCTs, CCTS, ITS, CBA

<i>Full paper eligibility for review</i>	
<i>General information</i>	
Date of data extraction	
Author	
Article title	
Source (Year/Journal/Volume/ Pages)	
Country of origin	
Type of publication	
Identification of reviewer	
Notes	
Identification number	
Specific information	
<i>Methodological quality of study</i>	
Study design	
<u><i>Method</i></u>	
Method of allocation/randomisation	
Exclusions after randomisation	
Unusual study design	
<u><i>Population characteristics</i></u>	
Source of population	
Inclusion criteria	
Exclusion criteria	
Recruitment procedures used	
Total number of participants eligible/selected/contacted for study data collection and randomisation	
Total number of participants recruited	
Total number of participants responded/agreed to take part	
Number at follow up/Loss to follow up/Drop out rate	
Characteristics of cases - Age - Sex - Geographical region - Socio-economic status - Ethnicity - High risk (family history)	

- Others	
Symptoms/diagnosis cases/criteria	
<u>Assessments</u>	
Health	
Exposure of interest	
VOCs objectively assessed in the study	
Repeated personal exposure sampling with each sample >24 hours.	
Repeated personal exposure sampling with each sample <24 hours.	
Single personal exposure sampling > 24 hours.	
Single personal exposure sampling < 24 hours.	
Repeated biological monitoring data for VOC or VOC metabolite	
Single biological monitoring data for VOC or VOC metabolite	
Repeated area/static exposure sampling from several household locations	
Single area/static exposure sampling from several household locations	
Repeated area /static exposure sampling from one household location	
Single area /static exposure sampling from one household location	
Self-report of VOC producing activity with data on exposure modifiers and some method of quantification or semi-quantification	
Self-report of presence/absence of VOC producing activity	
Proxy-respondent report of either of the above two methods.	
<u>Intervention</u>	
Adherence	
Outcome measures	
<u>Primary prevention outcome measures:</u> Incidence or prevalence of asthma, eczema, hay fever (the number of new cases i.e. incidence of asthma, eczema, hay fever; Incidence of validated respiratory, dermal, nasal symptoms, lung function, atopic sensitisation	
<u>Secondary prevention outcome measures:</u> Measures of increased disease activity by any objective measure (lung function, symptom scores, exacerbations, medication usage, health care utilisation, quality of life	
Methods of assessment, sources of data + details	

<u>Analysis</u>	
A priori power calculation	
Method of analysis: statistical analysis used	
Confounding factors	
Subgroup analysis	
Missing data + how addressed	
<u>Results</u>	
General	
Differences between groups	
Primary outcome	
Other relevant outcomes	
VOCs found to have a significant impact	
Impact category – please choose one: 1) Aetiological – incidence/prevalence, risk of developing asthma/allergies 2) In established disease – markers of the disease severity 3) Both	
<u>Extra useful information</u>	
Limitations	
Interpretation	
Generalisability	
Is the methodology appropriate to provide valid and reliable answers to the study question/s?	
Funding	
Other	
<u>“Risk of bias table”</u> 1. Adequate sequence generation 2. Allocation concealment 3. Blinding of participants and personnel 4. Blinding of outcomes 5. Incomplete outcome data addressed 6. Free of selecting reporting 7. Free of other biases	<u>Judgement: (Yes/No/Unclear)</u> 1. 2. 3. 4. 5. 6. 7.

Data extraction cohort study

<i>Full paper eligibility for review</i>	
General information	
Date of data extraction	
Author	
Article title	
Source (Year /Journal / Volume/ Pages)	
Country of origin	
Type of publication	
Identification of reviewer	
Notes	
Identification number	
Specific information	
<i>Methodological quality of study</i>	
Study design	
<u>Population characteristics</u>	
<i>Cohort</i>	
Sources of subjects	
Inclusion criteria	
Exclusion criteria	
Recruitment procedures used	
Total number of subjects recruited	
Total number of subjects responded	
Total number of subjects eligible for study data collection	
Characteristics of cohort group - Age - Sex - Geographical region - Socio-economic status - Ethnicity - High risk (family history) - Others	
Exposure cohort	
Methods of follow up	
Follow up time cases/follow up duration	
<u>Assessments</u>	
Health	
Exposures of interest	
VOCs objectively assessed in the study	
Repeated personal exposure sampling with each	

sample >24 hours.	
Repeated personal exposure sampling with each sample <24 hours.	
Single personal exposure sampling >24 hours.	
Single personal exposure sampling <24 hours.	
Repeated biological monitoring data for VOC or VOC metabolite	
Single biological monitoring data for VOC or VOC metabolite	
Repeated area/static exposure sampling from several household locations	
Single area/static exposure sampling from several household locations	
Repeated area /static exposure sampling from one household location	
Single area /static exposure sampling from one household location	
Self-report of VOC producing activity with data on exposure modifiers and some method of quantification or semi-quantification	
Self-report of presence/absence of VOC producing activity	
Proxy-respondent report of either of the above two methods.	
<u>Analysis</u>	
A priori power calculation	
Method of analysis: statistical analysis used	
Confounding factors	
Subgroup analysis	
Missing data + how addressed	
<u>Results</u>	
<u>General</u>	
Primary outcome	
Other outcomes	
VOCs found to have a significant impact	
Impact category - <i>please choose one:</i> 1) Aetiological – incidence/prevalence, risk of developing asthma/allergies 2) In established disease - markers of the disease severity 3) Both	
Extra useful information	
Limitations	
Interpretation	
Generalisability	
Is the methodology appropriate to provide valid and reliable answers to the study question/s?	
Funding	
Other	

Quality assessment tool : EPHPP							
A) SELECTION BIAS							
(Q1) Are the individuals selected to participate in the study likely to be representative of the target population?	1. Very likely 2. Somewhat likely 3. Not likely 4. Can't tell						
(Q2) What percentage of selected individuals agreed to participate?	1. 80 - 100% agreement 2. 60 – 79% agreement 3. less than 60% agreement 4. Not applicable 5. Can't tell						
RATE THIS SECTION (See dictionary)	<table border="1"> <tr> <td>STRONG</td> <td>MODERATE</td> <td>WEAK</td> </tr> <tr> <td>1</td> <td>2</td> <td>3</td> </tr> </table>	STRONG	MODERATE	WEAK	1	2	3
STRONG	MODERATE	WEAK					
1	2	3					
B) STUDY DESIGN							
Indicate the study design	1. Randomized controlled trial 2. Controlled clinical trial 3. Cohort analytic (two group pre + post) 4. Case-control 5. Cohort (one group pre + post (before and after)) 6. Interrupted time series 7. Other specify _____ 8. Can't tell						
Was the study described as randomized? If NO, go to Component C.	No Yes						
If Yes, was the method of randomization described? (See dictionary)	No Yes						
If Yes, was the method appropriate? (See dictionary)	No Yes						
RATE THIS SECTION (See dictionary)	<table border="1"> <tr> <td>STRONG</td> <td>MODERATE</td> <td>WEAK</td> </tr> <tr> <td>1</td> <td>2</td> <td>3</td> </tr> </table>	STRONG	MODERATE	WEAK	1	2	3
STRONG	MODERATE	WEAK					
1	2	3					
C) CONFOUNDERS							
(Q1) Were there important differences between groups prior to the intervention?	1. Yes 2. No 3. Can't tell						

	The following are examples of confounders: 1. Race 2. Sex 3. Marital status/family 4. Age 5. SES (income or class) 6. Education 7. Health status 8. Pre-intervention score on outcome measure						
(Q2) If yes, indicate the percentage of relevant confounders that were controlled (either in the design (e.g. stratification, matching) or analysis)?	1. 80 – 100% (most) 2. 60 – 79% (some) 3. Less than 60% (few or none) 4. Can't Tell						
RATE THIS SECTION (See dictionary)	<table border="1"> <tr> <td>STRONG</td><td>MODERATE</td><td>WEAK</td></tr> <tr> <td>1</td><td>2</td><td>3</td></tr> </table>	STRONG	MODERATE	WEAK	1	2	3
STRONG	MODERATE	WEAK					
1	2	3					
D) BLINDING							
(Q1) Was (were) the outcome assessor(s) aware of the intervention or exposure status of participants?	1. Yes 2. No 3. Can't tell						
(Q2) Were the study participants aware of the research question?	1. Yes 2. No 3. Can't tell						
RATE THIS SECTION (See dictionary)	<table border="1"> <tr> <td>STRONG</td><td>MODERATE</td><td>WEAK</td></tr> <tr> <td>1</td><td>2</td><td>3</td></tr> </table>	STRONG	MODERATE	WEAK	1	2	3
STRONG	MODERATE	WEAK					
1	2	3					
E) DATA COLLECTION METHODS							
(Q1) Were data collection tools shown to be valid?	1. Yes 2. No 3. Can't tell						
(Q2) Were data collection tools shown to be reliable?	1. Yes 2. No 3. Can't tell						
RATE THIS SECTION (See dictionary)	<table border="1"> <tr> <td>STRONG</td><td>MODERATE</td><td>WEAK</td></tr> <tr> <td>1</td><td>2</td><td>3</td></tr> </table>	STRONG	MODERATE	WEAK	1	2	3
STRONG	MODERATE	WEAK					
1	2	3					

F) WITHDRAWALS AND DROP-OUTS				
(Q1) Were withdrawals and drop-outs reported in terms of numbers and/or reasons per group?	1. Yes 2. No 3. Can't tell 4. Not Applicable (i.e. one time surveys or interviews)			
(Q2) Indicate the percentage of participants completing the study. (If the percentage differs by groups, record the lowest).	1. 80 -100% 2. 60 - 79% 3. less than 60% 4. Can't tell 5. Not Applicable (i.e. Retrospective case-control)			
RATE THIS SECTION (See dictionary)	STRONG	MODERATE	WEAK	
	1	2	3	Not Applicable
G) INTERVENTION INTEGRITY				
(Q1) What percentage of participants received the allocated intervention or exposure of interest?	1. 80 -100% 2. 60 - 79% 3. less than 60% 4. Can't tell			
(Q2) Was the consistency of the intervention measured?	1. Yes 2. No 3. Can't tell			
(Q3) Is it likely that subjects received an unintended intervention (contamination or co-intervention) that may influence the results?	1. Yes 2. No 3. Can't tell			
H) ANALYSES				
(Q1) Indicate the unit of allocation (circle one)	community organization/institution practice/office individual			
(Q2) Indicate the unit of analysis (circle one)	community organization/institution practice/office individual			
(Q3) Are the statistical methods appropriate for the study design?	1. Yes			

	2. No					
	3. Can't tell					
(Q4) Is the analysis performed by intervention allocation status (i.e. intention to treat) rather than the actual intervention received?	1. Yes 2. No 3. Can't tell					
GLOBAL RATING						
COMPONENT RATINGS (Please transcribe the information from the boxes above onto this box. See dictionary on how to rate this section).						
A	SELECTION BIAS	STRONG	MODERATE	WEAK		
		1	2	3		
B	STUDY DESIGN	STRONG	MODERATE	WEAK		
		1	2	3		
C	CONFOUNDERS	STRONG	MODERATE	WEAK		
		1	2	3		
D	BLINDING	STRONG	MODERATE	WEAK		
		1	2	3		
E	DATA COLLECTION METHOD	STRONG	MODERATE	WEAK		
		1	2	3		
F	WITHDRAWALS AND DROPOUTS	STRONG	MODERATE	WEAK		
		1	2	3		
					Not Applicable	
<u>GLOBAL RATING FOR THIS PAPER (circle one):</u>		1 STRONG (no WEAK ratings) 2 MODERATE (one WEAK rating) 3 WEAK (two or more WEAK ratings)				
With both reviewers discussing the ratings: Is there a discrepancy between the two reviewers with respect to the component (A-F) ratings?		No Yes				
If yes, indicate the reason for the discrepancy		1 Oversight 2 Differences in interpretation of criteria 3 Differences in interpretation of study				
<u>Final decision of both reviewers (circle) one):</u>		1 STRONG 2 MODERATE 3 WEAK				

Data extraction case-control study

<i>Full paper eligibility for review</i>	
General information	
Date of data extraction	
Author	
Article title	
Source (Year /Journal/ / Volume/ Pages)	
Country of origin	
Type of publication	
Identification of reviewer	
Notes	
Identification number	
Specific information	
<i>Methodological quality of study</i>	

Study design	
<i>Population characteristics</i>	
Rationale for choice of cases and controls	
<i>Cases</i>	
Source of cases	
Inclusion criteria	
Exclusion criteria	
Recruitment procedures used	
Total number of cases recruited	
Total number of cases responded	
Total number of cases eligible/selected for study data collection	
Drop out rate	
Characteristics of cases - Age - Sex - Geographical region - Socio-economic status - Ethnicity - High risk (family history) - Others	
Symptoms/diagnosis cases/criteria	
<i>Controls</i>	
Source of controls	
Recruitment procedures used	
Inclusion criteria	
Exclusion criteria	
Total number of controls recruited	
Total number of controls responded	
Total number of controls eligible/selected for study data collection	
Drop out rate	
Characteristics of control groups - Age - Sex - Geographical region - Socio-economic status - Ethnicity	

- High risk (family history)	
- Others	
Matching of controls with cases	
<u>Assessments</u>	
Health	
Exposure of interest	
VOCs objectively assessed in the study	
Repeated personal exposure sampling with each sample >24 hours.	
Repeated personal exposure sampling with each sample <24 hours.	
Single personal exposure sampling >24 hours.	
Single personal exposure sampling <24 hours.	
Repeated biological monitoring data for VOC or VOC metabolite	
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Single area /static exposure sampling from one household location	
Self-report of VOC producing activity with data on exposure modifiers and some method of quantification or semi-quantification	
Self-report of presence/absence of VOC producing activity	
Proxy-respondent report of either of the above two methods.	
<u>Analysis</u>	
A priori power calculation	
Method of analysis: statistical analysis used	
Confounding factors	
Subgroup analysis	
Missing data + how addressed	
<u>Results</u>	
General	
Primary outcome	
Other outcomes	
VOCs found to have a significant impact	
Impact category – please choose one: 1) Aetiological – incidence/prevalence, risk of	

developing asthma/allergies 2) In established disease – markers of the disease severity 3) Both							
<u>Extra useful information</u>							
Limitations							
Interpretation							
Generalisibility							
Is the methodology appropriate to provide valid and reliable answers to the study question/s?							
Funding							
Other							
Quality assessment tool : EPHPP							
A) SELECTION BIAS							
(Q1) Are the individuals selected to participate in the study likely to be representative of the target population?	5. Very likely 6. Somewhat likely 7. Not likely 8. Can't tell						
(Q2) What percentage of selected individuals agreed to participate?	6. 80 - 100% agreement 7. 60 – 79% agreement 8. less than 60% agreement 9. Not applicable 10. Can't tell						
RATE THIS SECTION (See dictionary)	<table border="1"> <tr> <td>STRONG</td> <td>MODERATE</td> <td>WEAK</td> </tr> <tr> <td>1</td> <td>2</td> <td>3</td> </tr> </table>	STRONG	MODERATE	WEAK	1	2	3
STRONG	MODERATE	WEAK					
1	2	3					
B) STUDY DESIGN							
Indicate the study design	9. Randomized controlled trial 10. Controlled clinical trial 11. Cohort analytic (two group pre + post) 12. Case-control 13. Cohort (one group pre + post (before and after)) 14. Interrupted time series 15. Other specify _____ 16. Can't tell						
Was the study described as randomized? If NO, go to Component C.	No Yes						
If Yes, was the method of randomization	No						

described? (See dictionary)	Yes						
If Yes, was the method appropriate? (See dictionary)	No Yes						
RATE THIS SECTION (See dictionary)	<table border="1"> <tr> <td>STRONG</td><td>MODERATE</td><td>WEAK</td></tr> <tr> <td>1</td><td>2</td><td>3</td></tr> </table>	STRONG	MODERATE	WEAK	1	2	3
STRONG	MODERATE	WEAK					
1	2	3					
C) CONFOUNDERS							
(Q1) Were there important differences between groups prior to the intervention?	4. Yes 5. No 6. Can't tell The following are examples of confounders: 9. Race 10. Sex 11. Marital status/family 12. Age 13. SES (income or class) 14. Education 15. Health status 16. Pre-intervention score on outcome measure						
(Q2) If yes, indicate the percentage of relevant confounders that were controlled (either in the design (e.g. stratification, matching) or analysis)?	5. 80 – 100% (most) 6. 60 – 79% (some) 7. Less than 60% (few or none) 8. Can't Tell						
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STRONG	MODERATE	WEAK					
1	2	3					
D) BLINDING							
(Q1) Was (were) the outcome assessor(s) aware of the intervention or exposure status of participants?	4. Yes 5. No 6. Can't tell						
(Q2) Were the study participants aware of the research question?	4. Yes 5. No 6. Can't tell						
RATE THIS SECTION (See dictionary)	<table border="1"> <tr> <td>STRONG</td><td>MODERATE</td><td>WEAK</td></tr> <tr> <td>1</td><td>2</td><td>3</td></tr> </table>	STRONG	MODERATE	WEAK	1	2	3
STRONG	MODERATE	WEAK					
1	2	3					
E) DATA COLLECTION METHODS							

(Q1) Were data collection tools shown to be valid?	4. Yes 5. No 6. Can't tell								
(Q2) Were data collection tools shown to be reliable?	4. Yes 5. No 6. Can't tell								
RATE THIS SECTION (See dictionary)	<table border="1"> <tr> <td>STRONG</td> <td>MODERATE</td> <td>WEAK</td> <td></td> </tr> <tr> <td>1</td> <td>2</td> <td>3</td> <td></td> </tr> </table>	STRONG	MODERATE	WEAK		1	2	3	
STRONG	MODERATE	WEAK							
1	2	3							
F) WITHDRAWALS AND DROP-OUTS									
(Q1) Were withdrawals and drop-outs reported in terms of numbers and/or reasons per group?	5. Yes 6. No 7. Can't tell 8. Not Applicable (i.e. one time surveys or interviews)								
(Q2) Indicate the percentage of participants completing the study. (If the percentage differs by groups, record the lowest).	6. 80 -100% 7. 60 - 79% 8. less than 60% 9. Can't tell 10. Not Applicable (i.e. Retrospective case-control)								
RATE THIS SECTION (See dictionary)	<table border="1"> <tr> <td>STRONG</td> <td>MODERATE</td> <td>WEAK</td> <td></td> </tr> <tr> <td>1</td> <td>2</td> <td>3</td> <td>Not Applicable</td> </tr> </table>	STRONG	MODERATE	WEAK		1	2	3	Not Applicable
STRONG	MODERATE	WEAK							
1	2	3	Not Applicable						
G) INTERVENTION INTEGRITY									
(Q1) What percentage of participants received the allocated intervention or exposure of interest?	5. 80 -100% 6. 60 - 79% 7. less than 60% 8. Can't tell								
(Q2) Was the consistency of the intervention measured?	4. Yes 5. No 6. Can't tell								

(Q3) Is it likely that subjects received an unintended intervention (contamination or co-intervention) that may influence the results?	4. Yes 5. No 6. Can't tell																																																																												
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A	SELECTION BIAS	STRONG	MODERATE	WEAK																																																																									
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<u>GLOBAL RATING FOR THIS PAPER (circle one):</u>		1 STRONG (no WEAK ratings) 2 MODERATE (one WEAK rating) 3 WEAK (two or more WEAK ratings)																																																																											
With both reviewers discussing the ratings: Is there a discrepancy between the two reviewers with respect to the component (A-F) ratings?		No Yes																																																																											
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<u>Final decision of both reviewers (circle one):</u>		1 STRONG 2 MODERATE 3 WEAK																																																																											

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Data extraction cross-sectional study

<i>Full paper eligibility for review</i>	
General information	
Date of data extraction	
Author	
Article title	
Source (Year /Journal / Volume/ Pages/)	
Country of origin	
Type of publication	
Identification of reviewer	
Notes	
Identification number	
Specific information	
<i>Methodological quality of study</i>	
Study design	
<u><i>Population characteristics</i></u>	
Sources of subjects	
Inclusion criteria (diagnostic method?)	
Exclusion criteria	
Recruitment procedures used	
Total number of subjects recruited	
Total number of subjects responded	
Total number of subjects eligible/selected for study data collection	
Drop out rate	
Characteristics of study group - Age - Sex - Geographical region - Socio-economic status - Ethnicity - High risk (family history) - Others	-
<u><i>Assessments</i></u>	
Health	
Exposures of interest	
VOCs objectively assessed in the study	
Repeated personal exposure sampling with each sample >24 hours.	
Repeated personal exposure sampling with each sample <24 hours.	
Single personal exposure sampling >24 hours.	
Single personal exposure sampling <24 hours.	

Repeated biological monitoring data for VOC or VOC metabolite	
Single biological monitoring data for VOC or VOC metabolite	
Repeated area/static exposure sampling from several household locations	
Single area/static exposure sampling from several household locations	
Repeated area /static exposure sampling from one household location	
Single area /static exposure sampling from one household location	
Self-report of VOC producing activity with data on exposure modifiers and some method of quantification or semi-quantification	
Self-report of presence/absence of VOC producing activity	
Proxy-respondent report of either of the above two methods.	
<u>Analysis</u>	
A priori power calculation	
Method of analysis: statistical analysis used	
Confounding factors	
Subgroup analysis	
Missing data + how addressed	
<u>Results</u>	
General	
Primary outcome	
Other outcomes	
VOCs found to have a significant impact	
Impact category – please choose one: 1) Aetiological – incidence/prevalence, risk of developing asthma/allergies 2) In established disease – markers of the disease severity 3) Both	
<u>Extra useful information</u>	
Limitations	
Interpretation	
Generalisability	
Is the methodology appropriate to provide valid and reliable answers to the study question/s?	
Funding	
Other	
Quality assessment tool : EPHPP	
A) SELECTION BIAS	
(Q1) Are the individuals selected to	9. Very likely

participate in the study likely to be representative of the target population?	10. Somewhat likely 11. Not likely 12. Can't tell						
(Q2) What percentage of selected individuals agreed to participate?	11. 80 - 100% agreement 12. 60 – 79% agreement 13. less than 60% agreement 14. Not applicable 15. Can't tell						
RATE THIS SECTION (See dictionary)	<table border="1"> <tr> <td>STRONG</td> <td>MODERATE</td> <td>WEAK</td> </tr> <tr> <td>1</td> <td>2</td> <td>3</td> </tr> </table>	STRONG	MODERATE	WEAK	1	2	3
STRONG	MODERATE	WEAK					
1	2	3					
B) STUDY DESIGN							
Indicate the study design	17. Randomized controlled trial 18. Controlled clinical trial Cohort analytic (two group pre + post) Case-control Cohort (one group pre + post (before and after)) Interrupted time series Other specify _____ Can't tell						
Was the study described as randomized? If NO, go to Component C.	No Yes						
If Yes, was the method of randomization described? (See dictionary)	No Yes						
If Yes, was the method appropriate? (See dictionary)	No Yes						
RATE THIS SECTION (See dictionary)	<table border="1"> <tr> <td>STRONG</td> <td>MODERATE</td> <td>WEAK</td> </tr> <tr> <td>1</td> <td>2</td> <td>3</td> </tr> </table>	STRONG	MODERATE	WEAK	1	2	3
STRONG	MODERATE	WEAK					
1	2	3					
C) CONFOUNDERS							
(Q1) Were there important differences between groups prior to the intervention?	Yes No Can't tell The following are examples of confounders: Race Sex Marital status/family Age SES (income or class) Education Health status Pre-intervention score on outcome measure						
(Q2) If yes, indicate the percentage of relevant confounders that were controlled (either in the design (e.g. stratification, matching) or analysis)?	80 – 100% (most) 60 – 79% (some) Less than 60% (few or none) Can't Tell						
RATE THIS SECTION (See dictionary)	<table border="1"> <tr> <td>STRONG</td> <td>MODERATE</td> <td>WEAK</td> </tr> <tr> <td>1</td> <td>2</td> <td>3</td> </tr> </table>	STRONG	MODERATE	WEAK	1	2	3
STRONG	MODERATE	WEAK					
1	2	3					
D) BLINDING							

(Q1) Was (were) the outcome assessor(s) aware of the intervention or exposure status of participants?	Yes No Can't tell								
(Q2) Were the study participants aware of the research question?	Yes No Can't tell								
RATE THIS SECTION (See dictionary)	<table border="1"> <tr> <td>STRONG</td> <td>MODERATE</td> <td>WEAK</td> </tr> <tr> <td>1</td> <td>2</td> <td>3</td> </tr> </table>	STRONG	MODERATE	WEAK	1	2	3		
STRONG	MODERATE	WEAK							
1	2	3							
E) DATA COLLECTION METHODS									
(Q1) Were data collection tools shown to be valid?	Yes No Can't tell								
(Q2) Were data collection tools shown to be reliable?	Yes No Can't tell								
RATE THIS SECTION (See dictionary)	<table border="1"> <tr> <td>STRONG</td> <td>MODERATE</td> <td>WEAK</td> </tr> <tr> <td>1</td> <td>2</td> <td>3</td> </tr> </table>	STRONG	MODERATE	WEAK	1	2	3		
STRONG	MODERATE	WEAK							
1	2	3							
F) WITHDRAWALS AND DROP-OUTS									
(Q1) Were withdrawals and drop-outs reported in terms of numbers and/or reasons per group?	Yes No Can't tell Not Applicable (i.e. one time surveys or interviews)								
(Q2) Indicate the percentage of participants completing the study. (If the percentage differs by groups, record the lowest).	80 -100% 60 - 79% less than 60% Can't tell Not Applicable (i.e. Retrospective case-control)								
RATE THIS SECTION (See dictionary)	<table border="1"> <tr> <td>STRONG</td> <td>MODERATE</td> <td>WEAK</td> <td></td> </tr> <tr> <td>1</td> <td>2</td> <td>3</td> <td>Not Applicable</td> </tr> </table>	STRONG	MODERATE	WEAK		1	2	3	Not Applicable
STRONG	MODERATE	WEAK							
1	2	3	Not Applicable						
G) INTERVENTION INTEGRITY									
(Q1) What percentage of participants received the allocated intervention or exposure of interest?	80 -100% 60 - 79% less than 60% Can't tell								
(Q2) Was the consistency of the intervention measured?	Yes No Can't tell								
(Q3) Is it likely that subjects received an unintended intervention (contamination or co-intervention) that may influence the results?	Yes No Can't tell								
H) ANALYSES									
(Q1) Indicate the unit of allocation (circle one)	community organization/institution practice/office individual								

(Q2) Indicate the unit of analysis (circle one)	community organization/institution practice/office individual				
(Q3) Are the statistical methods appropriate for the study design?	Yes No Can't tell				
(Q4) Is the analysis performed by intervention allocation status (i.e. intention to treat) rather than the actual intervention received?	Yes No Can't tell				
GLOBAL RATING					
COMPONENT RATINGS (Please transcribe the information from the boxes above onto this box. See dictionary on how to rate this section).					
A	SELECTION BIAS	STRONG 1	MODERATE 2	WEAK 3	
B	STUDY DESIGN	STRONG 1	MODERATE 2	WEAK 3	
C	CONFOUNDERS	STRONG 1	MODERATE 2	WEAK 3	
D	BLINDING	STRONG 1	MODERATE 2	WEAK 3	
E	DATA COLLECTION METHOD	STRONG 1	MODERATE 2	WEAK 3	
F	WITHDRAWALS AND DROPOUTS	STRONG 1	MODERATE 2	WEAK 3	
		1	2	3	Not Applicable
<u>GLOBAL RATING FOR THIS PAPER (circle one):</u>		1 STRONG (no WEAK ratings) 2 MODERATE (one WEAK rating) 3 WEAK (two or more WEAK ratings)			
With both reviewers discussing the ratings: Is there a discrepancy between the two reviewers with respect to the component (A-F) ratings?		No Yes			
If yes, indicate the reason for the discrepancy		1 Oversight 2 Differences in interpretation of criteria 3 Differences in interpretation of study			
<u>Final decision of both reviewers (circle one):</u>		1 STRONG 2 MODERATE 3 WEAK			

Supplementary Material, Table S1: Description of included studies (n=53)

Authors	Country	Design	Exposure of interest measured						Outcomes assessed						Methodolog ical quality by risk of bias
			Formaldehyde	benzenes	toluenes	xylenes	TVOCs	Other	Asthma	AD/eczema	ARC	Sensitisation	Immunological	Other	
Interventional studies															
Marks 2010 ²³	Australia	RCT	✓						✓					Wheezing, lung function	Low
Tuomainen 2003 ²⁴	Finland	CCT	✓				✓	Acetaldehyde						Cough, nasal and skin symptoms; allergic symptoms	High
Broder 1988 ²⁵	Canada	CBA	✓						✓		✓			wheeze	High
Brugge 2003 ²⁶	USA	CBA					✓		✓			✓		Lung function	High
Kim 2010 ²⁷	South Korea	CBA	✓	✓	✓	✓	✓	Acetaldehyde, styrene, acetone, acrolein, propionaldehyde butyraldehyde		✓		✓			High
Norback 2011 ²⁸	Sweden	CBA	✓											Eye, nasal symptoms, throat symptoms, breathing difficulties, headache, tiredness	High
Putus 2004 ²⁹	Finland	CBA					✓	Branched hydrocarbons, 2-ethylhexanol, TXIB (trimethylpentanediol di-isobutyrate), 2-butoxyethoxy ethanol, 1-butanol, and 3-heptanone, diethyl phthalate, dimethylsulfide, and dimethyldisulfide	✓	✓	✓			Wheezing, dyspnea	High
Wantke 1996 ³⁰	Austria	CBA	✓									✓			High

Authors	Country	Design	Exposure of interest measured						Outcomes assessed						Methodological quality by risk of bias
			Formaldehyde	benzenes	toluenes	xylenes	TVOCs	Other	Asthma	AD/eczema	ARC	Sensitisation	Immunological	Other	
Observational studies															
Baiz 2011 ³¹	France	Cohort		✓	✓	✓							✓		Moderate
Diez 2000 ³²	Germany	Cohort		✓				Nonane, decane, undecane, dodecane, styrene				✓		Wheezing	High
Martins 2012 ³³	France	Cohort	✓	✓	✓	✓								Wheezing, lung function, rescue medication, emergency department visits	Low
Raaschou-Nielsen 2010 ³⁴	Denmark	Cohort	✓											Wheezing	Low
Smedje 2000 ³⁵	Sweden	Cohort	✓					MVOCs: 3-methylfuran, 3-methyl-1-butanol, 2-pentanol, 2-hexanone, 2-heptanone, 3-octanone, 3-octanol, 1-octen-3-ol	✓					Allergy, persistent cough, wheeze, shortness of breath	Low
Smedje 2001 ³⁶	Sweden	Cohort	✓						✓			✓		Self-reported pollen and pet allergy	Moderate
Choi 2010 ³⁷	Sweden	Case-control						Aromatics, alkanes, organic acids, aldehydes, methyl-alkanes, propylen glycol & PGEs, dimethyl-alkanes, texanols	✓	✓	✓	✓			Moderate
Dewey 1995 ³⁸	Germany	Case-control						MVOCs: 1-octen-3-ol, 3-methylfuran, 2-octen-1-ol, 1-butanol; 3-methyl-1-butanol; 2-pentanol; isobutanol; 3-octanol; 2-hexanone; 2-heptanone; 3-octanone	✓		✓				High
Garrett 1999 ³⁹	Australia	Case-control	✓						✓			✓		Cough, morning cough, dyspnoea, waking with dyspnoea, wheeze, chest tightness, morning chest	High

Authors	Country	Design	Exposure of interest measured						Outcomes assessed						Methodological quality by risk of bias
			Formaldehyde	benzenes	toluenes	xylenes	TVOCs	Other	Asthma	AD/eczema	ARC	Sensitisation	Immunological	Other	
														tightness, respiratory score	
Gee 2005 ⁴⁰	UK	Case-control	✓	✓			✓		✓						High
Hulin 2010 ⁴¹	France	Case-control	✓	✓	✓	✓		Acetaldehyde, BTEX	✓						High
Hwang 2011 ⁴²	South Korea	Case-control	✓	✓	✓	✓		Stylene, n-hexane, cyclohexane, methylcyclohexane	✓						Moderate
Norback 1995 ⁴³	Sweden	Case-control	✓		✓	✓	✓	Aromatics (Sum of ethylbenzene, m-sylene, o-xylene, and p-xylene), n-Alkanes (Sum of n-octane, n-nonane, n-decane, and n-undecane), Terpenes (Sum of a-pinene, 6-carene, and limonene), Butanols (Sum of n-butanol and iso-butanol), LVOC (Sum of unidentified compounds with a retention time below benzene), TVOC (Sum of all identified and unidentified compounds)	✓			✓		Lung function, BHR, eosinophilic cationic protein (S-ECP), blood eosinophil count	Moderate
Rumchev 2002 ⁴⁴	Australia	Case-control	✓						✓			✓			Moderate
Rumchev 2004 ⁴⁵	Australia	Case-control		✓	✓	✓	✓	Styrene	✓			✓		Wheeze, cough	Moderate
Tavernier 2006 ⁴⁶	UK	Case-control	✓	✓			✓		✓						High
Venn 2003 ⁴⁷	UK	Case-control	✓	✓	✓	✓		Limonene, undecane						Wheezing	Low

Authors	Country	Design	Exposure of interest measured					Other	Outcomes assessed					Other	Methodological quality by risk of bias
			Formaldehyde	benzenes	toluenes	xylenes	TVOCs		Asthma	AD/eczema	ARC	Sensitisation	Immunological		
Annesi-Maesano 2012 ⁴⁸	France	Cross-sectional	✓					Acetaldehyde, acrolein	✓		✓	✓			Moderate
Araki 2012 ⁴⁹	Japan	Cross-sectional	✓				✓	MVOC: 3-Methyl-1-butanol, 1-Pentanol, 2-Pentanol, 2-Hexanone, 2-Heptanone, 3-Octanone, 3-Octanol, 1-Octen-3-ol, and total for 29 VOCs	✓	✓	✓				High
Arif 2007 ⁵⁰	USA	Cross-sectional		✓	✓	✓		Chloroform, tetrachloroethene, trichloroethene, methyl tertiary butyl ether	✓					Wheezing	Moderate
Billionet 2011 ⁵¹	France	Cross-sectional	✓	✓	✓	✓		Acetaldehyde, acrolein, hexaldehyde, n-Decane, n-Undecane, styrene, tetrachlorethylene, 2-butoxyethanol, 2-butoxyethylacetate, 1-methoxy-2-propanol, methoxy-2-propylacetate	✓		✓				High
Chubirko 2005 ⁵²	Russian Federation	Cross-sectional	✓					Phenol	✓						High
Elke 1999 ⁵³	Germany	Cross-sectional						Microbial VOCs: 3-methylbutan-1-ol, 3-methylbutan-2-ol, fenchone, heptan-2-one, hexan-2-one, Nonan-2-one, octan-3-one, octan-3-ol, pentan-2-ol, α-terpineol, thujopsene	✓		✓			Wheezing	High
Erdei 2003 ⁵⁴	Hungary	Cross-sectional	✓	✓	✓	✓								Bacterial-specific IgGs	High
Fraga	Portugal	Cross-					✓		✓					Wheeze ever, wheeze last 12 months, , nocturnal	High

Authors	Country	Design	Exposure of interest measured						Outcomes assessed						Methodological quality by risk of bias
			Formaldehyde	benzenes	toluenes	xylenes	TVOCs	Other	Asthma	AD/eczema	ARC	Sensitisation	Immunological	Other	
2008 ⁵⁵		sectional												wheeze/cough, wheeze during exercise	
Gordian 2010 ⁵⁶	USA	Cross-sectional		✓	✓	✓			✓					Wheezing, exercise-induced asthma, dry cough, allergies	High
Hulin 2011 ⁵⁷	France	Cross-sectional	✓					Acetaldehyde	✓		✓	✓			High
Khalequzzaman 2007 ⁵⁸	Bangladesh	Cross-sectional	✓	✓	✓	✓	✓	Hexane, butyl acetate, methyl ethyl ketone, ethyl acetate, methyl isobutyl ketone, trichloroethylene, chloroform, butyl alcohol, 1,2 dichloroethane, 1,1,1-trichloroethane, carbon tetrachloride, tetrachloroethylene, p-dichlorobenzene	✓	✓				Wheezing	High
Kim 2007 ⁵⁹	Sweden	Cross-sectional						MVOCs: 3-methylfuran, 3-methyl-1-butanol, dimethyldisulfide, 2-hexanone, 2-heptanone, 1-octen-3-ol, 3-octanone, 2-methyl-1-butanol, ethyl-2-methylbutyrate, 2-pentylfuran, isobutylacetate, isobutanol, 1-butanol, 2-pentanol, ethylisobutyrate, 2-ethyl-1-hexanol, 2,2,4-trimethyl-1,3-pentanediol monoisobutyrate, 2,2,4-trimethyl-1,3-pentanediol diisobutyrate	✓			✓		Wheezing, nocturnal/day time breathlessness	High
Krzyzanowski 1990 ⁶⁰	USA	Cross-sectional	✓						✓					Wheezing, chronic cough	High

Authors	Country	Design	Exposure of interest measured						Outcomes assessed						Methodological quality by risk of bias
			Formaldehyde	benzenes	toluenes	xylenes	TVOCs	Other	Asthma	AD/eczema	ARC	Sensitisation	Immunological	Other	
Lehmann 2001 ⁶¹	Germany	Cross-sectional		✓	✓	✓		Hexane, Heptane, Octane, Nonane, Decane, Undecane, Dodecane, Tridecane, Methylcyclopentane, Methylcyclohexane, Styrene, Naphthalene, Trichloroethylene, Tetrachloroethylene, α -Pinene, Limonene, δ 3-Carene				✓		Specific IgE antibodies to food (milk, egg)	High
Lehmann 2002 ⁶²	Germany	Cross-sectional		✓	✓	✓		Hexane, Heptane, Octane, Nonane, Decane, Undecane, Dodecane, Tridecane, Methylcyclopentane, Cyclohexane, Methylcyclohexane, Styrene, Naphthalene, Trichloroethylene, Tetrachloroethylene, α -Pinene, Limonene, δ 3-Carene, δ 2-Carene					✓		Moderate
Liu 2010 ⁶³	China	Cross-sectional	✓	✓			✓		✓					Pneumonia, bronchitis, flu	High
Lovreglio 2009 ⁶⁴	Italy	Cross-sectional	✓					Acetaldehyde	✓	✓	✓				High
Matsunaga 2008 ⁶⁵	Japan	Cross-sectional	✓						✓	✓	✓				Moderate
Mi 2006 ⁶⁶	Sweden	Cross-sectional	✓						✓					Wheezing, shortness of breath, night-time awakening with breathlessness or tightness in the chest	High
Norback	Sweden	Cross-	✓											Eosinophil cationic protein, lysozyme in nasal lavage	High

Authors	Country	Design	Exposure of interest measured						Outcomes assessed						Methodological quality by risk of bias
			Formaldehyde	benzenes	toluenes	xylenes	TVOCs	Other	Asthma	AD/eczema	ARC	Sensitisation	Immunological	Other	
2000 ⁶⁷		sectional													
Palczynski 1999 ⁶⁸	Poland	Cross-sectional	✓						✓			✓		Lung function	High
Rudnai 1999 ⁶⁹	Hungary	Cross-sectional	✓	✓	✓	✓			✓					Allergic symptoms	High
Smedje 1997 ⁷⁰	Sweden	Cross-sectional	✓		✓	✓		14 common VOCs, including toluene, n-decane, n-undecane, limonene, xylene, 6-carene	✓						High
Villberg 2008 ⁷¹	Finland	Cross-sectional	✓					2,2,4-trimethyl, 1,3-pentanediol di-isobutyrate	✓						High
Wieslander 1997 ⁷²	Sweden	Cross-sectional	✓					TXIB, butanols, alifatics (C8-C11),	✓			✓	✓	Lung function, BHR, inflammatory biomarkers	Moderate
WU 2010 ⁷³	China	Cross-sectional		✓					✓					Wheezing	Moderate
Yeatts 2012 ⁷⁴	UAE	Cross-sectional	✓						✓					Wheezing, chest tightness/difficulty breathing, speech-limited wheeze	Moderate
Zhao 2008 ⁷⁵	China	Cross-sectional	✓						✓					Wheeze/whistling, nocturnal and daytime attacks of breathlessness, allergy	Moderate

Abbreviations:

AD	Atopic dermatitis
ARC	Allergic rhinoconjunctivitis
BHs	Branched hydrocarbons
BTEX	Benzene, toluene, ethylbenzene, and xylenes
COPSAC	The Copenhagen Prospective Study on Asthma in Childhood
DDA	Doctor-diagnosed asthma
ECP	Eosinophil cationic protein
EDEN	Pre and postnatal determinants of the child's development and health
FEF ₇₅	Flow rate at 75% of vital capacity
FERMA	Environmental Factors of Rural Environment and Respiratory and Allergic Diseases
FVC	Front Ventilation System
HCHO	Formaldehyde
IgE	Immunoglobulin E
LARS	Leipzig Allergy Risk Children Study
MTBE	Methyl tertiary butyl ether
MVOCs	Microbial volatile organic compounds
LVOC	Sum of unidentified compounds with a retention time below benzene
NHANES	National Health and Nutrition Examination Survey
OR	Odds Ratio
PGEs	Propylene glycol & glycol ethers
sIgE	Specific Immunoglobulin E
SPT	Skin Prick Test
TCE	Tetrachlorethene
TVOCs	Total Volatile Organic Compounds
TXIB	Trimethylpentanediol di-isobutyrate
UAE	United Arab Emirates
UFFI	Urea formaldehyde foam insulated

Supplementary Material, Table S1A: Associations between asthma/allergy outcomes and exposure to selected VOCs/ VOC groups that were examined in relation to health outcomes in more than one study

[illegible]

Investigating the role of VOCs in the severity/exacerbations of established asthma and allergic disease

Investigating the role of VOCs in both development of new and severity of established asthma and allergic disease

[illegible]

Footnotes

^bPGEs - Propylen glycol & glycol ethers^cTMPD-DIB - 2,2,4-trimethyl-1,3-pentanediol diisobutyrate

Adverse effect of exposure on the outcome: "+"

Protective effect of exposure on the outcome: "- "

No effect of exposure on the outcome: "0"

Measured exposure not examined in relation to the outcome: NE

Exposure not measured: blank

Not reported: NRs

Supplementary Material, Table S2: Detailed characteristics of included studies investigating the role of VOCs in the development of asthma and atopic disease

Study	Participants characteristics	Design	Exposure of interest	Outcomes			
				Asthma	AD /eczema	ARC	Sensitization
Broder 1988 ²⁵	The occupants of 231 control homes and 571 houses containing urea formaldehyde. ≥16 yrs -80%; 10-15 yrs–10%; <10yrs – 10%	CBA	HCHO	No difference		No difference in hay fever	
Norback 2011 ²⁸	Primary school children; Three elementary school classes (N=61), all with floor heating. Intervention group: fourth-grade class (n=26) front ventilation system (FVS); Control groups: third-grade and fifth-grade classes (n=35) mixing ceiling ventilation; Girls total: n 27 (44%) Boys total: n 34 (56%)	CBA	HCHO				
Baiz 2011 ³¹	370 mother-children pairs from in the EDEN (Pre and postnatal determinants of the child's development and health) prospective Birth Cohort Study in Nancy, France; mother's mean age 29.8 ± 4.7; new-bornboys 52. 6%,girls 47.5%; 56 women with personal exposure to VOCs	Cohort	Benzene, ethyl benzene, toluene, xylenes				
Smedje 2001 ³⁶	40 randomly selected schools in Uppsala, Sweden with pupils aged 7-13 years; 2034 pupils in total: 615 pupils aged 7 years; 657 aged 10 years and 762 aged 13 years; 48% boys and 52% girls; the mean age 10.3 years in 1993 and 14.3 years in 1997.	Cohort	HCHO	OR 1.7, 1.1-2.6 per 10 microgram/m ⁻³ increase in HCHO levels			

Study	Participants characteristics	Design	Exposure of interest	Outcomes			
				Asthma	AD / eczema	ARC	Sensitization
Choi 2010 ³⁷	Children, aged between 1-5; cases n=198: age 3-8 years, BMI 17 ± 2, females 43%; controls n=202: age 2-8 years, BMI 16 ± 2, females 44; blood sample (n=387) tested for 10 airborne allergens and two moulds	Case-control	8 classes of VOCs: aromatic hydrocarbons, alkanes, organic acids, aldehydes, methyl-alkanes, propylene glycol & glycol ethers (PGEs), dimethyl-alkanes, and texanol; individual PGE compounds	A natural –log unit of summed propylene glycol ethers (PGEs) in bedroom air (equal to interquartile range, or 3.43-15.65 µg/m ³) was associated with 1.5- fold greater likelihood of being a case (95% CI, 1.1-2.1), 1.5-fold greater likelihood of asthma (95% CI, 1.0-2.3)	A natural –log unit of summed propylene glycol ethers in bedroom air (equal to interquartile range, or 3.43-15.65 µg/m ³) was associated with 1.6-fold greater likelihood of eczema (95% CI, 1.1-2.3)	A natural –log unit of summed propylene glycol ethers in bedroom air (equal to interquartile range, or 3.43-15.65 µg/m ³) was associated with 2.8-fold greater likelihood of rhinitis (95% CI, 1.6-4.7)	When tested, analysis was restricted to the cases, same concentration was associated with 1.5-fold greater likelihood of IgE-sensitization (95% CI, 1.1-2.8) compared to the IgE sensitized cases
Gee 2005 ⁴⁰	Children aged 4-16 from two GP practices who have/have not asthma. Cases n=100; controls=100, matched for age and sex	Case-control	HCHO, VOCs	No associations			
Hulin 2010 ⁴¹	63 urban children (32 asthmatics and 31 controls) and 51 rural children (24 asthmatics and 27 controls) Cases: Age years: Urban: 13.7 ± 0.8 Rural 10.9 ± 0.9 (p <0.05 for diff urban/rural) All: 12.5 ± 1.6 Sex girls: Urban: 50% Rural: 50% All: 50% Controls: Age years: Urban: 14.2 ± 0.7 Rural 10.6 ± 0.8 (p <0.05 for diff urban/rural) All 12.6 ± 2.0 Sex girls: Urban: 55% Rural: 50% All: 53%	Case-control	Aldehydes (HCHO, acetaldehyde), benzene, toluene, ethylbenzene, and xylenes (BTEX).	Aldehyde OR 2.15, 1.01-4.58 and toluene OR 2.73, 1.28-5.83; Ethylbenzene OR 18.47 and xylenes OR 13.86 in current asthma, cases only; Acetaldehyde OR 1.09, 1.00-1.17 in rural children.			

Study	Participants characteristics	Design	Exposure of interest	Outcomes			
				Asthma	AD / eczema	ARC	Sensitivity
Hwang 2011 ⁴²	Children in asthma group (n=33); 8-9 years old 60.6%; 10-13 years old 39.4%; male 66.7%; female 33.3%; family asthma history 85.7%. Control group (n=40); 8-9 years old 75%; 10-13 years old 25%; family asthma history 96.3%.	Case-control	HCHO, benzene, toluene, ethylbenzene, styrene, m,p-xylene, o-xylene, n-hexane, cyclohexane methylcyclohexane	No significant differences between cases and controls			
Norback 1995 ⁴³	Cases (n=47), women 72% (p<0.01); Controls (n=41), women 32%; mean age of participants 32 ± 7 years	Case-control	HCHO, Toluene, C8-Aromaticst (Sum of ethylbenzene, m-sylene, o-xylene, and p-xylene), n-Alkanes (Sum of n-octane, n-nonane, n-decane, and n-undecane), Terpenes (Sum of a-pinene, 6-carene, and limonene), Butanols (Sum of n-butanol and iso-butanol), LVOC (Sum of unidentified compounds with a retention time below benzene), T VOC (Sum of all identified and unidentified compounds)	Significant associations with TVOCs (p<0.01)			
Rumchev 2002 ⁴⁴	Young children (between 6 months and 3 years old); males 65%; females 35%; cases (n=88), mean age 25 ± 7.46 months; controls (n=104), mean age 20 ± 7.54 months	Case-control	HCHO	Children exposed to HCHO levels 60 µg.m ⁻³ have a 39% increase in odds of having asthma compared to children exposed to HCHO levels <10 µg.m ⁻³			

Study	Participants characteristics	Design	Exposure of interest	Outcomes			
				Asthma	AD / eczema	ARC	Sensitization
Rumchev 2004 ⁴⁵	Cases (n=88), 6-12 m 6%; 13-24 months 50%; 25-36 months 44%; boys 69%; girls 31%. Controls (n=104), 6-12 months 23%; 13-24 months 51%; 25-36 months 26%; boys 62%; girls 38%	Case-control	Benzene, toluene, m-xylene, o,p-xylene, ethylbenzene, styrene, chlorobenzene, 1,3-dichlorobenzene, 1,2-dichlorobenzene and 1,4-dichlorobenzene. Total VOCs were defined as the sum of the 10 identified compounds	Adjusted ORs for the risk of asthma with each 10 µg/m ³ increase in exposure to: Benzene OR 2.92, 2.25-3.80; Ethylbenzene OR 2.54, 1.16-5.57; Toluene OR 1.84, 1.41-2.41; m-Xylene OR 1.61, 1.10-2.35; Dichlorobenzene OR 1.55, 1.27-1.89; 1,2-dichlorobenzene OR 1.30, 1.07-1.58			
Tavernier 2006 ⁴⁶	Children aged 4 to 17 years; Cases – asthmatic subjects (n=105), 50 male; 55 female; controls non-asthmatic subjects (n=95); 45 male; 50 female	Case-control	HCHO, VOCs	No differences between asthmatic and healthy children in their exposure to measured VOCs and HCHO			
Annesi-Maesano 2012 ⁴⁸	Children aged 9-10 years attending 108 primary schools in six cities in France; mean age 10.4 ± 0.7 years; male 49.3%	Cross-sectional	HCHO, acetaldehyde, acrolein	High concentrations of acrolein (>1.55 µg/m ³) OR 1.22, 1.09-1.38		High concentrations of HCHO (>28 µg/m ³) OR 1.19, 1.04-1.36	
Araki 2012 ⁴⁹	Subjects (n=609) aged from 6 to 60+ years old; from 182 detached houses in six regions of Japan; male 48.6%; female 51.4%	Cross-sectional	HCHO, 8 selected MVOC: 3-Methyl-1-butanol, 1-Pentanol, 2-Pentanol, 2-Hexanone, 2-Heptanone, 3-Octanone, 3-Octanol, 1-Octen-3-ol, and total for 29 VOCs	No associated with MVOCs	2-hexanone OR 2.71, 1.07-6.84; 1-octen-3-ol OR 2.64, 1.12-6.20	AR 1-pentanol OR 1.81, 1.08-3.05; 2-hexanone OR 2.38, 1.07-5.27; 1-octen-3-ol OR 5.0, 2.36-10.6; AC: 1-octen-3-ol OR 4.80, 1.72-13.4	

Study	Participants characteristics	Design	Exposure of interest	Outcomes			
				Asthma	AD / eczema	ARC	Sensitization
Arif 2007 ⁵⁰	Subjects (n=550) from NHANES 1999-2000; mean age 38.4 years (SE 0.81); female 51.2%; male 48.8%	Cross-sectional	Benzene, chloroform, ethylbenzene, tetrachloroethene (TCE), toluene, trichloroethene, o-xylene, m-,p-xylene, 1,4-dichlorobenzene, Methyl tertiary butyl ether (MTBE)	DDA: Aromatic compounds OR 1.63, 1.17-2.27; Benzene OR 1.33, 1.13-1.56; Ethylbenzene OR 1.34, 1.01-1.78; Toluene OR 1.21, 0.93-1.58; o-Xylene OR 1.32, 1.04-1.67; m,p-Xylene OR 1.33, 1.08-1.64; Chlorinated HC OR 0.93, 0.66-1.32; Tetrachloroethene OR 1.02, 0.90-1.15; Trichloroethene OR 0.94, 0.77-1.14; Never diagnosed asthma, ie 1-2 wheezing episodes in previous year vs zero aromatic compounds OR 1.68, 1.08-2.61; Ethylbenzene OR 1.76, 1.23-2.50; o-Xylene OR 1.39, 1.05-1.84; m,p-Xylene OR 1.47, 1.06-2.04 Chlorinated hydrocarbons OR 1.50, 1.01-2.23			

Study	Participants characteristics	Design	Exposure of interest	Outcomes			
				Asthma	AD / eczema	ARC	Sensitization
Billionet 2011 ⁵¹	1012 subjects from 490 dwellings in France; male 47.9%; female 52.1%; age ranged 15-89 years (median = 44 years)	Cross-sectional	Acetaldehyde, Acrolein, HCHO, Hexaldehyde, Benzene, 1,4-Dichlorobenzene, Ethylbenzene, n-Decane, n-Undecane, Styrene, Tetrachloroethylene, Toluene, Trichloroethylene, 1,2,4-Trimethylbenzene, m/p-Xylene, o-Xylene, 2-Butoxyethanol, 2-Butoxyethylacetate, 1-Methoxy-2-propanol, Methoxy-2-propylacetate	n-undecane OR 2.02, 1.18-3.46; 1,2,4-trimethylbenzene OR 2.10, 1.21-3.65; global VOC score, OR 1.07, 1.00-1.13; aromatic hydrocarbons OR 1.12, 1.01-1.24; aliphatic hydrocarbons OR 1.41, 1.03-1.93		Ethylbenzene OR 1.48, 1.09-2.02; trichloroethylene OR 1.54, 1.07-2.21; m/p- xylene OR 1.46, 1.07-2.00; o-xylene OR 1.43, 1.03-1.99; global VOC score OR 1.04, 1.00-1.08; one specific VOC score(halogenated hydrocarbons) associated OR 1.28, 1.07-1.54	
Chubirko 2005 ⁵²	100 apartments	Cross-sectional	HCHO and phenol	The prevalence of atopic disease, including asthma amongst occupant is 20% and 7% of them is perceived to be linked to the indoor environment, including HCHO and phenol			

Study	Participants characteristics	Design	Exposure of interest	Outcomes			
				Asthma	AD / eczema	ARC	Sensitivity
Elke 1999 ⁵³	The children (5- to 7 years old) from Eastern and Western Germany, no other details	Cross-sectional	Microbial VOCs 3-methylbutan-1-ol, 3-methylbutan-2-ol, fenchone, heptan-2-one, hexan-2-one, Nonan-2-one, octan-3-one, octan-3-ol, pentan-2-ol, α -terpineol, thujopsene	No associations		No associations	
Erdei 2003 ⁵⁴	3 rd grade (9-11 years old) schoolchildren from 16 schools across 6 Hungarian cities	Cross-sectional	Benzene, toluene, xylene, HCO				Bacterial specific levels v related significantly to HCHO concentrations
Hulin 2011 ⁵⁷	Urban subjects: schoolchildren from the French Six Cities Study from Clermont-Ferrand, in 63 classes 18 schools (n=1285) aged 10.6 $\pm$ 0.7 years; Rural subjects: schoolchildren in regular contact with farm animals from FERMA study in Auvergne, in 56 schools (n=357) aged 9.6 $\pm$ 0.9 years	Cross-sectional	HCHO and acetaldehyde	Asthma non atopic when rural children compared to all 6590 subjects in the French Six Cities Study: urban 2.2% vs rural 4.2% p<0.05			Urban 28.8% rural 14.8% p<0.05

Study	Participants characteristics	Design	Exposure of interest	Outcomes			
				Asthma	AD / eczema	ARC	Sensitivity
Kim 2007 ⁵⁹	Schoolchildren from 8 primary schools in Uppsala, Sweden (n=1014); median age 9 years, range 5-14 years, female 51%; male 49%	Cross-sectional	3-methylfuran, 3-methyl-1-butanol, dimethyldisulfide, 2-hexanone, 2-heptanone, 1-octen-3-ol, 3-octanone, 2-methyl-1-butanol, ethyl-2-methylbutyrate, 2-pentylfuran, isobutylacetate, isobutanol, 1-butanol, 2-pentanol, ethylisobutyrate, 2-ethyl-1-hexanol, plasticizers, TMPD-MIB, and TMPD-DIB	DDA: 2-Heptanone OR 1.03, 1.00–1.06, p<0.05; 2-Methyl-1-butanol OR 1.25, 1.05–1.50, p<0.05; TMPD-DIB OR 1.97, 1.14–3.42, p<0.05; Total MVOC OR 2.07, 1.09–3.93, p<0.05			

Study	Participants characteristics	Design	Exposure of interest	Outcomes			
				Asthma	AD / eczema	ARC	Sensitization
Lehmann 2001 ⁶¹	Cord blood and blood samples of infants from the cohort Leipzig Allergy Risk Children Study (LARS) (n=429); at the age of 36 months 200 children	Cross-sectional	Hexane, Heptane, Octane, Nonane, Decane, Undecane, Dodecane, Tridecane, Methylcyclopentane, Methylcyclohexane, Benzene, Toluene, Ethylbenzene, M_p-Xylene, o-Xylene, Styrene, 4-Ethyltoluene, 3-Ethyltoluene, 2-Ethyltoluene, Naphthalene, Chlorobenzene, Trichloroethylene, Tetrachloroethylene, α -Pinene, Limonene, δ 3-Carene				Exposure to alkylaromatics (C6,C9-C10), toluene, xylene, m+p-xylene, 3- and 4-ethyltoluene, chlorobenzene, m-xylene, significantly contributed to the development of allergic sensitization in the first 3 years of life to milk and egg white (ORs between 5.7 and 11.2)

Study	Participants characteristics	Design	Exposure of interest	Outcomes			
				Asthma	AD / eczema	ARC	Sensitivity
Lehmann 2002 ⁶²	Neonates cord bloods for T-cell cytokines (n=85) from a birth cohort study (LISA: Lifestyle-Immune System-Allergy); 43 boys and 42 girls	Cross-sectional	Hexane, Heptane, Octane, Nonane, Decane, Undecane, Dodecane, Tridecane, Methylcyclopentane, Cyclohexane, Methylcyclohexane, Benzene, Toluene, Ethylbenzene, m, p-Xylene, o-Xylene, Styrene, 4-Ethyltoluene, 3-Ethyltoluene, 2-Ethyltoluene, Naphthalene, Chlorobenzene, Trichloroethylene, Tetrachloroethylene, α -Pinene, Limonene, δ 3-Carene, δ 2-Carene				
Liu 2010 ⁶³	1000 schoolchildren in grade 2 to 4, aged 7-9 years in the primary schools in the Taian, China	Cross-sectional	HCHO, benzene, TVOC	Asthma, not analysed			
Lovreglio 2009 ⁶⁴	182 subjects (96 men and 86 women) aged from 1 to >60 years old living in 59 homes in Bari, Italy	Cross-sectional	HCHO, acetaldehyde	No associations	No associations	No associations	
Matsunaga 2008 ⁶⁵	998 pregnant women from Osaka Maternal and Child Health study; age range (<30 years old 47.2%; $\geq$ 30 52.8%)	Cross-sectional	HCO		HCHO levels of 47 ppb OR 2.25, 1.01-5.01		

Study	Participants characteristics	Design	Exposure of interest	Outcomes			
				Asthma	AD / eczema	ARC	Sensitization
Norback 2000 ⁶⁷	234 primary school personnel working in 12 randomly chosen primary schools in the municipality of Uppsala, Sweden; mean age ranged 45-47 years	Cross-sectional	HCHO				
Palczynski 1999 ⁶⁸	465 participants, living in apartment houses; 219 male; 246 female; 187 children aged 5-15 years (40.3%)	Cross-sectional	HCHO	No associations			
Rudnai 1999 ⁶⁹	Schoolchildren – 3 rd grade students (8-10 years old) from 6 towns in Hungary	Cross-sectional	HCHO, benzene, xylene, toluene	Fungi in the house OR 1.4, p=0.033; fungi in child's bedroom OR 2.02, p=0.002			
WU 2010 ⁷³	6551 schoolchildren selected from 8 primary schools, 6 middle and 2 kindergartens; age range 4.2-16.5 years; males 3381; females 3170; 197 completed the monitoring process (n=98 in winter-spring period; n=99 in summer – autumn period)	Cross-sectional	Benzene	No association			

Abbreviations:

AD	Atopic dermatitis
ARC	Allergic rhinoconjunctivitis
BHs	Branched hydrocarbons
BTEX	Benzene, toluene, ethylbenzene, and xylenes
COPSAC	The Copenhagen Prospective Study on Asthma in Childhood
DDA	Doctor-diagnosed asthma
ECP	Eosinophil cationic protein
EDEN	Pre and postnatal determinants of the child's development and health
FEF ₇₅	Flow rate at 75% of vital capacity
FERMA	Environmental Factors of Rural Environment and Respiratory and Allergic Diseases
FVC	Front Ventilation System

HCHO	Formaldehyde
IgE	Immunoglobulin E
LARS	Leipzig Allergy Risk Children Study
MTBE	Methyl tertiary butyl ether
MVOCs	Microbial volatile organic compounds
LVOC	Sum of unidentified compounds with a retention time below benzene
NHANES	National Health and Nutrition Examination Survey
OR	Odds Ratio
PGEs	Propylene glycol & glycol ethers
sIgE	Specific Immunoglobulin E
SPT	Skin Prick Test
TCE	Tetrachlorethene
TVOCs	Total Volatile Organic Compounds
TXIB	Trimethylpentanediol di-isobutyrate
UFFI	Urea formaldehyde foam insulated

Supplementary Material, Table S3: Detailed characteristics of included studies investigating the role of VOCs in severity/exacerbations of established asthma and atopic disease

Study	Participants characteristics	Design	Exposure of interest	Outcomes					
				Asthma	AD	ARC	Sensitisation	Immunological	Other
Interventional studies									
Tuomainen 2003 ²⁴	People moving into the two blocks flats in Finland; the total numbers of participants not described; two types of buildings, one low emission, one normal	CCT	TVOCs, HCHO, acetaldehyde						No statistical analysis,

Kim 2010 ²⁷	Nine patients with atopic dermatitis aged 6-18 years old (mean age 10.4 years); 3 males; 6 females	CBA	TVOCs and individual VOCs (benzene, toluene, ethylbenzene, styrene, xylene, formaldehyde, acetaldehyde, acetone, acrolein, propionaldehyde, butyraldehyde)		7 out of 9 patients showed objective and subjective improvements of clinical symptom				
Observational studies									
Diez 2000 ³²	475 premature children and children with allergic risk factors from the 1995-1996 birth cohort in the city of Leipzig, Germany	Cohort	25 VOCs, including nonane, decane, undecane, dodecane, benzene, styrene						Restoration and wheezing 1.1-3.5
Martins 2012 ³³	51 children aged 7.3 ± 1.1; males 54.9%; females 45.1% from Portugal	Cohort	HCHO, benzene, toluene, ethylbenzene, xylenes						For benzene, decrease of FEV1 (95% CI -7.13– -1.53), FEV1/FVC (-1.71, 95% CI -5.89, 2.47), FEF25–75% (-5.89, 95% CI -1.71, 9.51), increase of DFEV1 % (1.3, 95% CI 0.25, 2.47) p=0.013; increase of DFEV1 % (1.3, 95% CI 0.25, 2.47) p<0.001; For ethylbenzene, decrease of FEV1 (95% CI -0.25, 0.25) p=0.023; FEF25–75% (-1.71, 95% CI -5.89, 2.47) p=0.036; increase of DFEV1 (1.3, 95% CI 0.25, 2.47) p=0.036; EBC pH Benzene (-0.24, 95% CI -0.49, 0.01), ethylbenzene (-0.14, 95% CI -0.39, 0.11), FeNO, ethylbenzene (1.3, 95% CI 0.25, 2.47) p=0.039; Clinical outcomes toluene increase of rescue medication p=0.041; A&E visits 0.26 (95% CI 0.01, 0.51) p=0.039; Ethylbenzene rescue medication p=0.039

Gordian 2010 ⁵⁶	571 participants with age range (0-19 31%; 20-65 68%; 66+ 1%); female 51%; male 49% from family homes with attached garages in the state of Alaska, USA	Cross-section al	Benzene, toluene, ethylbenzene, xylene	High gasoline exposure (16%) where benzene levels exceeded the 9 ppb OR 2.49, 1.22-5.07					
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Supplementary Material, Table S4: Detailed characteristics of included studies investigating the role of VOCs in the development and severity of asthma and atopic disease

Participants characteristics	Design	Exposure of interest	Outcomes					
			Asthma	AD	ARC	Sensitisation	Immunological	Other
studies								
00 primary school students from 22 schools in New South Wales, Australia; males 55%; males 45%	RCT	HCHO						HCHO concentrations average, 9.4 ppb higher (5.7–13.1) during exposure to unflued gas versus flued gas heaters. Exposure to the unflued gas heaters was associated with increased cough reported the evening OR 1.16, 1.01–1.34; and wheeze reported in the morning OR 1.34, 1.04–1.83
ine families of a public housing development in Boston, USA	CBA	1,4-dichlorobenzene, 1,2-dichloropropane, methylt-butyl ether, and acrylonitrile 1,1,2,2-tetrachloroethane, 1,1,2-trichloroethane, carbon tetrachloride, 1,2-dichloroethane, and acrylonitrile, benzene, chloroform, 1,4-dichlorobenzene, toluene.	Not analysed					
74 children aged 12-16 years; boys 8%; girls 52% (spring 1999) before and 86 children after (spring 2002)	CBA	TVOC, branched hydrocarbons (BHs), 2-ethylhexanol, TXIB (trimethylpentanediol diisobutyrate), 2-butoxyethoxy ethanol , 1-butanol, and 3-heptanone, diethyl phthalate, dimethylsulfide, and dimethyldisulfide						Wheezing: previously OR 2.29, 1.1-5.0; occasionally OR 6.77, 3.2-14.5; common cold OR 5.89, 2.2-19.9; attacks of dyspnea and wheezing: last 12 months OR 2.51, 1.4-3.6; night cough OR 2.23, 1.4-3.6;

2 8-year old children (34 boys; 28 girls) attending a Viennese school for 2.5 years; control children: 19 healthy, non-atopic children (10 boys; nine girls; mean age 5 years, range 7-10 years)	CBA	HCHO				After transferral sIgE decreased from 1.7 ± 0.5 to 1.2 ± 0.2 (p<0.002) as did the incidence of symptoms		
studies								
11 infants and their mothers with asthma from the Copenhagen Prospective Study on Asthma in Childhood (COPSAC)	Cohort	HCHO						No associations between wheezing symptoms in infants and HCHO
732 children (1-7 grades) with mean age 10.4 in 1993; 1,476 children (1-7 grades) with mean age 12.3; boys 49%; girls 51%	Cohort	HCHO, MVOCs: 8 compounds (3-methyl furan, 3-methyl-1 -butanol, 2-pentanol, 2-hexanone, 2-heptanone, 3-octanone, 3-octanol, 1 -octen-3-ol)	Prevalence (%) in 1993 and 1995: DDA 6.3 vs 8.3 (p<0.001); current asthma 5.1 vs 6.3 (p<0.01); more than 1 asthmatic symptom 6.4 vs 8.5 (p<0.01); ORs for association between incidence and installation of a new ventilation system: any asthmatic symptoms OR 0.3, 0.1-0.8; (p<0.05); more asthma symptoms in 1995 than in 1993 OR, 0.5, 0.2-0.97; (p<0.05)					
3 flats with mould and 9 control flats without in Germany	Case-control	1-Octen-3-ol, 3-Methylfuran, 2-Octen-1-ol, 1-Butanol, 3-Methyl-1-butanol, 2-Pentanol, Isobutanol, 3-Octanol, 2-Hexanon, 2-Heptanon, 3-Octanon						In 3 people from mouldy flats allergic respiratory disease became worse and 4 people developed allergic disease; 1 allergen positive

48 children (7-14 years); 53 of whom asthmatic; equal numbers of girls and boys; 80 houses in the Latrobe Valley, Victoria, Australia	Case-control	HCHO	No association					
Cases: 193 children aged 9-11 years; boys 55%; girls 45%; Controls: 223 children aged 9-11 years; boys 51%; girls 49% from Nottingham, UK	Case-control	HCHO, TVOCs						No associations between persistent wheezing and HCHO or TVOCs
607 children aged 14.0 ± 0.3 from 9 schools in Porto, Portugal	Cross-sectional	VOCs, TVOCs						No association between VOC and any of respiratory outcomes
5 children from families using biomass fuel; 51 children using fossil fuel aged <5 years in urban slums Dhaka, Bangladesh	Cross-sectional	HCHO, 16 VOCs		No association				Biomass fuel use and wheezing, or wheezing chest OR 4.0, 1.1-16.2;
98 children aged 6-15 years (mean age 13); male 502%; 613 adults aged >15 years (mean age 37.0); male 43.4% from 102 households in Pima County, Arizona, USA	Cross-sectional	HCHO	prevalence of asthma: HCHO levels 60-120 ppb > less exposed; p<0.05; DDA HCHO ≤40 ppb 11.7%; ≥60ppb 23.8%, p<0.05					
414 children aged 13-14 years from 30 classes in 10 schools in Shanghai, China in winter time; male 50%; female 50%	Cross-sectional	HCHO						No associations between HCHO and any outcomes
27 children aged 13-14 years randomly selected from 11 schools in Uppsala, Sweden; boys 48%; girls 52%	Cross-sectional	HCHO, 14 common VOCs, including toluene, n-decane, n-undecane, limonene, xylene, 6-carene	HCHO OR 1.1, 1.01-1.2, p<0.042; VOC sampled by diffusion other VOCs OR 1.3, 1.1-1.5, p<0.001;					
79 case families; 137 patients selected from a hospital; 53 control families randomly selected from Helsinki area who living in similar types of houses as the cases	Cross-sectional	HCHO, 2,2,4-trimethyl,1,3-pentanediol di-isobutyrate	2,2,4-trimethyl,1,3-pentanediol di-isobutyrate and new asthma OR 2.844, 1.035-7.813					
62 subjects 20-44 years (272 men and 90 women) from Uppsala, Sweden	Cross-sectional	HCHO and VOCs	Newly painted surfaces OR 1.5, 1.0-2.4; particularly newly painted wood details OR 2.3, 1.2-4.5; kitchen painting OR 2.2, 1.1-4.5;					
28 Emirati households; female (51.8%); male 48.1%; urban 57.6%; rural 42.4%; adults (19-50 years) 59.4%; adolescents (11-18 years) 27.1%; children (6-10 years) 13.6%	Cross-sectional	HCHO						Speech-limiting wheeze OR 4.18, 1.23-14.22; shortness of breath ≥1/month OR 3.68, 1.11-12.27; chest tightness/difficulty breathing ≥1/month OR 6.52, 1.91-22.3; cough ≥1/month OR 3.59, 1.70-7.55

993 school children aged 12.8 ± 0.6; girls 50.7% in urban Taiyuan, China	Cross-sectional	HCHO	Cumulative asthma OR 0.79, 0.48-1.28					Wheezing/whistling OR 1.24, 1.03-1.48; night time attacks of breathlessness OR 1.40, 1.02-1.92
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Abbreviations:

AD	Atopic dermatitis
ARC	Allergic rhinoconjunctivitis
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COPSAC	The Copenhagen Prospective Study on Asthma in Childhood
DDA	Doctor-diagnosed asthma
ECP	Eosinophil cationic protein
EDEN	Pre and postnatal determinants of the child's development and health
FEF ₇₅	Flow rate at 75% of vital capacity
FERMA	Environmental Factors of Rural Environment and Respiratory and Allergic Diseases
FVC	Front Ventilation System
HCHO	Formaldehyde
IgE	Immunoglobulin E
LARS	Leipzig Allergy Risk Children Study
MTBE	Methyl tertiary butyl ether
MVOCs	Microbial volatile organic compounds
LVOC	Sum of unidentified compounds with a retention time below benzene
NHANES	National Health and Nutrition Examination Survey
OR	Odds Ratio
PGEs	Propylene glycol & glycol ethers
sIgE	Specific Immunoglobulin E
SPT	Skin Prick Test
TCE	Tetrachlorethene
TVOCs	Total Volatile Organic Compounds

TXIB	Trimethylpentanediol di-isobutyrate
UFFI	Urea formaldehyde foam insulated

Supplementary Material, Table S5: Associations between asthma/atopic outcomes and exposure to VOCs/ VOC groups that were examined in relation to health outcomes in single studies

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