

# BMJ Open A systematic review of associations between environmental exposures and development of asthma in children aged up to 9 years

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## ABSTRACT

**Objectives:** Childhood asthma is a complex condition where many environmental factors are implicated in causation. The aim of this study was to complete a systematic review of the literature describing associations between environmental exposures and the development of asthma in young children.

**Setting:** A systematic review of the literature up to November 2013 was conducted using key words agreed by the research team. Abstracts were screened and potentially eligible papers reviewed. Papers describing associations between exposures and exacerbation of pre-existing asthma were not included. Papers were placed into the following predefined categories: secondhand smoke (SHS), inhaled chemicals, damp housing/mould, inhaled allergens, air pollution, domestic combustion, dietary exposures, respiratory virus infection and medications.

**Participants:** Children aged up to 9 years.

**Primary outcomes:** Diagnosed asthma and wheeze.

**Results:** 14 691 abstracts were identified, 207 papers reviewed and 135 included in the present review of which 15 were systematic reviews, 6 were meta-analyses and 14 were intervention studies. There was consistent evidence linking exposures to SHS, inhaled chemicals, mould, ambient air pollutants, some deficiencies in maternal diet and respiratory viruses to an increased risk for asthma (OR typically increased by 1.5–2.0). There was less consistent evidence linking exposures to pets, breast feeding and infant dietary exposures to asthma risk, and although there were consistent associations between exposures to antibiotics and paracetamol in early life, these associations might reflect reverse causation. There was good evidence that exposures to house dust mites (in isolation) was not associated with asthma risk. Evidence from observational and intervention studies suggest that interactions between exposures were important to asthma causation, where the effect size was typically 1.5–3.0.

**Conclusions:** There are many publications reporting associations between environmental exposures and modest changes in risk for asthma in young children, and this review highlights the complex interactions between exposures that further increase risk.

## Strengths and limitations of this study

- This is the first systematic review of the whole literature relating early life environmental exposures to childhood asthma causation.
- A high level of evidence was available (ie, systematic reviews, meta-analyses and/or intervention studies) for many exposure classes.
- More than 70% of papers identified described associations observed within single populations.
- The observational literature is likely to be affected by publication bias, reverse causation and confounders.
- Studies describing outcomes in children where the mean age was >9 years were not included.

## INTRODUCTION

Asthma is a common chronic condition in children where environmental and genetic factors are implicated in causation. The rapid rise in asthma during the 1980s and 1990s<sup>1</sup> was too abrupt to be explained solely by change in prevalence of genetic variations. Changing environmental exposures appear to be relevant to the high prevalence of asthma in the Western world,<sup>2</sup> although some exposures are likely to be effective via epigenetic mechanisms.<sup>3</sup>

Many environmental exposures have been linked to asthma causation, including allergens,<sup>4</sup> smoking,<sup>5</sup> dietary factors<sup>6</sup> and respiratory infections.<sup>7</sup> Recently, evidence has emerged to suggest that asthma causation may involve interactions between different environmental exposures<sup>8–9</sup> and/or environmental exposures and atopy.<sup>10</sup> Owing to the many challenges of relating even a single exposure to asthma causation, there is very little synthesis in the literature of multiple environmental exposures and asthma causation.

The Environmental Determinants of Public Health in Scotland (EDPHiS) was commissioned in 2009 to quantify the evidence on the connections between the environment and

key aspects of health of children in order to inform the development of public policy. Asthma was identified as a priority along with obesity, unintentional injury and mental health. The overall aim of this systematic review was to capture all of the literature associating early environmental exposures and asthma development in children up to 9 years of age; this cut-off was chosen to avoid the effects of puberty and active smoking on asthma causation. A recent paper describes associations between environmental exposures and asthma control and exacerbation.<sup>11</sup> Our specific aims were (1) to describe the magnitude of association between the development of asthma and environmental exposures and (2) to explore evidence of interactions between environmental exposures.

## METHODS

### Study design

A workshop attended by senior researchers from government and academia, and health practitioners and policy professionals identified environmental influences considered important on causation and exacerbation of asthma (previously described,<sup>11</sup> box 1). By extrapolation from approaches to assessment of causation in workplace exposures for compensation purposes (<http://iiac.independent.gov.uk/about/index.shtm>), we considered an exposure that increased the risk for asthma by at least twofold as having at least a modest effect size.

### Search strategy and data sources

The search strategy for MEDLINE is provided in the online supplementary material and has also been described previously.<sup>11</sup> Two reviewers (SD and ED) searched the electronic databases (including MEDLINE, EMBASE, Cochrane controlled trials register (CCTR) and CINHAI) and reference lists of other studies and reviews between January 2010 and April 2010. Updated searches were carried out in July 2011 and November 2013. No date limits were applied to the search strategy.

#### Box 1 Areas for environmental determinants of causation and exacerbation of asthma derived from stakeholder workshop

- ▶ Environmental tobacco smoke (antenatal and postnatal);
- ▶ Domestic combustion (cooking, heating and candles);
- ▶ Inhaled chemicals (volatile organic compounds, Chlorine, phthalates);
- ▶ Damp housing/mould;
- ▶ Inhaled allergens (house dust mite, pets, pollens);
- ▶ Air pollution;
- ▶ Dietary exposures (maternal diet, breast feeding, diet in childhood);
- ▶ Respiratory virus infection;
- ▶ Medications (antibiotics and paracetamol);
- ▶ Industrial combustion (incinerators);
- ▶ Fireworks and bonfires;
- ▶ Vacuuming;
- ▶ Air conditioning or humidifiers.

Studies identified from searching electronic databases were combined, duplicates removed and papers were screened for relevance to the review based on the information contained in the title and abstract. Abstracts were screened by a second reviewer (SWT) and potentially eligible papers were identified.

### Inclusion/exclusion criteria

Studies were included if (A) they captured exposure to an environmental factor identified as potentially relevant to the development of asthma; (B) the mean age of asthma outcome was  $\leq 9$  years. (C) Outcomes include diagnosis of asthma or data related to healthcare utilisation (hospital admissions, drug use), (D) the study design was either a meta-analysis, systematic review, randomised control trial, non-randomised control trial or cohort study. If no evidence was apparent for an exposure, then studies meeting the lower Scottish Intercollegiate Guidelines Network criteria were considered, that is, case-control and case report studies (<http://www.sign.ac.uk/guidelines/fulltext/50/annexb.html> 21 Jun 2014).

### Study selection and data extraction

The full text of references identified as potentially relevant was obtained and papers included by applying the inclusion criteria, sometimes after discussion between reviewers (SD and SWT). Papers that were included in a systematic review were not included. For cohort studies where outcomes were reported at increasing ages after one exposure, only the most recent paper was included. A summary table included the following details from studies: study design, characteristics of the study population, study objectives and the key outcome(s) reported including what the primary asthma outcome was, for example, wheeze, physician diagnosed asthma, etc.

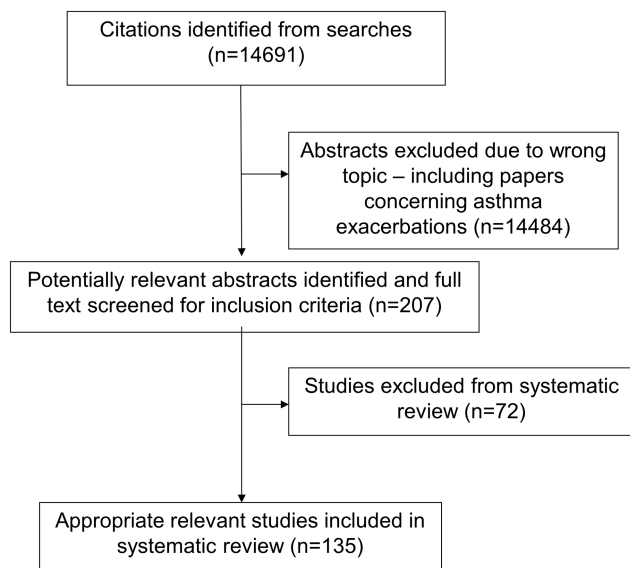
### Quality assessment

Quality assessment of included papers was carried out using "Effective public health practice project quality assessment tool for quantitative studies" ([http://www.ephpp.ca/PDF/Quality%20Assessment%20Tool\\_2010\\_2.pdf](http://www.ephpp.ca/PDF/Quality%20Assessment%20Tool_2010_2.pdf) accessed Jun 2014). Results are presented in the online supplementary material; due to the relatively large number of studies identified, a random 10% were chosen for quality assessment.

## RESULTS

### Literature search

There were 14 691 references identified from electronic databases and other studies. There were 207 full papers reviewed and 135 studies met the inclusion criteria (figure 1). There were 15 systematic reviews, 6 meta-analyses, 92 cohort studies, 14 intervention studies included, 5 case-control studies and 3 cross-sectional studies. No case series were included. There were 62 studies from Europe (including 3 meta-analyses), 32 from North America, 13 studies from Australia or New



**Figure 1** QUOROM statement flow chart.

Zealand, 3 from Japan and single remaining papers from UAE, India, Qatar, South Korea, Mexico, Taiwan and Brazil. There were 84 (63%) studies published in the past 5 years, that is, from 2009. **Box 1** in the online supplementary file presents details of the included studies, including number and mean age of children included, the respiratory outcome reported and the effect size. No studies were identified for industrial combustion, fireworks, bonfires, vacuuming, air conditioning or air humidifiers. **Table 1** presents the effect size of the exposures on asthma risk from the studies identified. **Table 2** presents results from studies where interactions between exposures were associated with altered asthma risk

## Secondhand smoke

### Antenatal exposure

One meta-analysis and five cohort studies were identified and most found exposure was associated with increased risk for asthma. The meta-analysis<sup>12</sup> identified 735 exposed children and concluded that exposure was associated with an increased risk for asthma at 6 years (OR 1.7). The cohort studies found that risk was increased by 1.13<sup>13</sup> and 2.1<sup>14</sup> at 2 years, and 1.4 at 7 years.<sup>15</sup> One study of infants born 3–4 weeks prematurely found increased risk for wheeze at 3 years only among those exposed to secondhand smoke (SHS; OR 4.0, **table 2**).<sup>16</sup> One study found no association between antenatal exposure and risk for symptoms.<sup>17</sup>

### Postnatal exposure

One systematic review and six cohort studies were identified and all reported that exposure was associated with increased asthma risk. The systematic review concluded that exposure to tobacco smoke was associated with an increased risk of 1.3 among children aged 6–18 years.<sup>5</sup> Postnatal exposure was associated with increased risk for

wheeze between 1.2<sup>18</sup> and 2.9,<sup>17</sup> and 1.7 for asthma at 5 years (**table 2**).<sup>19</sup> The study from Japan<sup>17</sup> found a link between postnatal but not antenatal maternal smoking and wheeze at 16–24 months. One study<sup>18</sup> found that postnatal paternal smoking was a risk factor for wheeze (RR 1.14 (1.04 to 1.24)) independent of maternal smoking. Another study reported an interaction between short duration of maternal education and SHS exposure.<sup>19</sup> A final study found that increasing exposure to fine particulates (PM<sub>2.5</sub>) and urinary cotinine, products of tobacco combustion, was positively linked to risk for infant wheeze.<sup>20</sup>

## Domestic combustion

Two cohort, one cross-sectional and two case-control studies were identified and there was inconsistent evidence between exposure and asthma risk. One cohort study retrospectively modelled exposure to gas cooking at 5 years to asthma in 4-year-olds and found no association.<sup>21</sup> In a second cohort study, increasing exposure to domestic PM<sub>2.5</sub> was associated with increased risk for new onset wheeze over the next 3 years (OR 1.5 per quartile increase in exposure), adjusting for SHS exposure.<sup>22</sup> A cross-sectional study found an association between detectable indoor air sulfur dioxide (SO<sub>2</sub>) and risk for wheeze (OR 1.8) at age 6–10 years.<sup>23</sup> This study found no link between burning incense and asthma symptoms<sup>23</sup> and this was consistent with a case-control study that found no evidence for exposure to Bakhour incense and risk for asthma.<sup>24</sup> A case-control study from India<sup>25</sup> found evidence for increased asthma among children (OR 4.3) living in homes where biomass was used for cooking compared with other homes.

## Inhaled chemicals

One meta-analysis, one cohort study, one cross-sectional study and two reports from one case-control study were identified and all found evidence of exposure being associated with increased asthma risk. The meta-analysis of data from seven studies concluded that increasing formaldehyde exposure was associated with increased asthma risk (OR 1.2 per 10 µg/m<sup>3</sup> increase).<sup>26</sup> A cohort study<sup>27</sup> used redecoration of the apartment as a proxy for exposure to volatile organic compounds (VOCs) and found an increase in risk for obstructive bronchitis (OR 4.2). Simultaneous exposure to SHS and cats added to the risk of obstructive bronchiolitis in the second year (OR 5.1, **table 2**).<sup>27</sup> One cross-sectional study<sup>28</sup> found an association between indoor exposure VOC of microbial origin (MVOCs) and plasticisers, and risk of asthma (mean increased risk for asthma 2.1/µg/m<sup>3</sup> of total MVOC). Two scientific papers on the same study<sup>29 30</sup> found domestic exposure to formaldehyde, benzene and its compounds, and toluene, was positively associated with asthma risk (3% increase per 10 µg/m<sup>3</sup> increase in formaldehyde exposure).

**Table 1** Magnitude of effect of environmental exposure on respiratory symptoms

Exposure	Magnitude of effect (95% CI)
<b>SHS</b>	
Antenatal exposure	1.7 (1.2 to 2.3) <sup>†12</sup> 1.13 (1.04 to 1.23) <sup>*13</sup> 2.1 (1.2 to 3.7) <sup>†14</sup> 1.35 (1.13 to 1.62) <sup>†15</sup> 4.0 (1.9 to 8.6) <sup>*16</sup> No association <sup>17</sup>
Postnatal exposure	1.3 (1.1 to 1.6) <sup>††5</sup> 1.2 (1.0 to 1.3) <sup>*18</sup> 2.9 (1.1 to 7.2) <sup>*17</sup> 1.7 (1.1 to 2.58) <sup>†19</sup> 4.2 (1.4, 13.0) for exposure to high fine particulate <sup>*20</sup>
<b>Domestic combustion</b>	
Gas cooking	No association <sup>21</sup>
Fine particulates (PM <sub>2.5</sub> )	1.5 (1.1 to 2.2) per quartile PM <sub>2.5</sub> increase <sup>*22</sup>
Detectable Sulfur Dioxide	OR 1.8 (1.1 to 3.1) <sup>*23</sup>
Incense	No association <sup>24</sup> 17 <sup>23</sup>
Biomass	4.3 (3.0 to 5.0) <sup>†25</sup>
<b>Inhaled chemicals</b>	
VOC	1.2 (1.01 to 1.4) per 10 µg/m <sup>3</sup> increase <sup>†26</sup> 4.2 (1.4 to 12.9) <sup>††27</sup> 2.1 (1.1 to 3.9) per µg/m <sup>3</sup> of total MVOC <sup>*28</sup> 1.39 (no CI given) <sup>†29</sup> 2.92 (2.25 to 3.75) <sup>†30</sup>
Chlorinated swimming pools	0.5 (0.3 to 0.9) <sup>†31</sup> No association $\nexists$ <sup>32</sup>
Other chemicals	1.7 (1.2 to 2.4) <sup>*34</sup> (cleaning agents) 1.6 (1.2 to 2.1) <sup>††33</sup> (PVC) 1.9 (1.1 to 3.2) <sup>†35</sup> (pyrene) 0.7 (0.5 to 0.9) <sup>*36</sup> (maternal BPA) 1.4 (1.0 to 1.9) <sup>*36</sup> (child BPA) 2.8 (2.0 to 3.9) <sup>†37</sup> and 1.7 (1.01 to 2.9) <sup>*38</sup> (oil refinery)
<b>Damp housing/mould</b>	
	1.5 (1.3 to 1.7) <sup>††39</sup> 1.4 (1.1 to 1.8) <sup>*†40</sup> (no association at 6–8 years) 7.1 (2.2 to 12.6) <sup>†41</sup> 2.4 (1.1 to 5.6) <sup>†42</sup> for exposure 2.6 (1.1 to 6.3) <sup>43</sup> per unit increase in mould index 1.8 (1.5 to 2.2) <sup>44</sup> per unit increase in mould index
<b>Multiple exposures</b>	
	0.7 (0.5 to 0.9) <sup>†48</sup> 0.4 (0.3 to 0.8) <sup>†49</sup> 3.0 (1.1 to 7.9) for high HDM <sup>†</sup> and 1.2 (1.1 to 1.4) <sup>*</sup> per quartile LPS increase <sup>50</sup> 1.8 (1.02 to 3.0) <sup>*</sup> increasing cockroach allergen <sup>55</sup> and 0.3 (0.1 to 0.98) <sup>*</sup> for dog and 0.6 (0.4 to 1.01) <sup>*</sup> for cat exposure <sup>55</sup> 2.6 (1.3 to 5.4) <sup>†</sup> for high cat exposure <sup>51</sup> 2.7 (1.1 to 7.1) <sup>†</sup> dog and SHS to 4.8 (1.1 to 21.5) <sup>†</sup> dog and elevated NO <sub>2</sub> <sup>56</sup> 3.1 (1.8, 5.2) <sup>*</sup> for exposure to SHS, infection and no breast feeding <sup>57</sup> No association <sup>†45</sup> $\nexists$ <sup>46</sup> $\nexists$ <sup>47</sup> 52–54
<b>Inhaled allergens/particles</b>	
Pet	0.7 (0.6 to 0.9) <sup>††</sup> cat exposure <sup>59</sup> 1.1 (1.0 to 1.3) <sup>††</sup> dog exposure <sup>59</sup> 4.7 (1.2 to 18.0) <sup>†</sup> cat exposure <sup>61</sup> 0.6 (0.4 to 0.9) <sup>*</sup> cat exposure <sup>62</sup> 0.3 (0.1 to 0.81) <sup>*</sup> cat exposure <sup>63</sup> 1.2 (1.1 to 1.3) <sup>*</sup> cat exposure <sup>64</sup> No association <sup>†60</sup> 65 66
Other exposures	1.5 (1.1 to 2.1) <sup>*</sup> highest vs lowest quartile LPS exposure <sup>68</sup> 1.4 (1.1 to 1.7) <sup>*</sup> mouse allergen <sup>69</sup>

Continued

Table 1 Continued

Exposure	Magnitude of effect (95% CI)
HDM	0.4 (0.2 to 0.6)† feather quilt <sup>70</sup>
	1.8 (1.0 to 3.2)† number of synthetic bedding items <sup>71</sup>
Outdoor allergens	No association cockroach <sup>52</sup>
	No association‡ <sup>72 73 74</sup>
Air pollution	OR 3.1 (1.3 to 7.4)* birthday during fungal spore season <sup>75</sup> OR 1.4 (1.1 to 1.7)† grass pollen exposure <sup>76</sup>
	RR 1.2 (1.02 to 1.3)† tree canopy cover <sup>77</sup>
	1.05 (1.00 to 1.11)†‡ per ppm increased NO <sub>2</sub> <sup>78</sup>
	1.02 (1.00 to 1.04)†‡ per ppm increased NO <sub>2</sub> <sup>78</sup>
	1.06 (1.01 to 1.12)†‡ per ppm increased CO <sup>78</sup>
	1.04 (1.01 to 1.07)*‡ per ppm increased SO <sub>2</sub> <sup>78</sup>
	1.05 (1.04 to 1.07)*‡ per unit increase particulates <sup>78</sup>
	1.04 (1.01 to 1.07)* per ppm increased CO <sup>79</sup>
	1.2 (1.0 to 1.31)† per 5ppb increase NO <sub>2</sub> <sup>80</sup>
	2.0 (1.2 to 3.6)† traffic-related particles <sup>82</sup>
Dietary exposures	1.3 (1.0 to 1.6)† higher traffic density <sup>84</sup>
	3.1 (1.3 to 7.4)† high exposure to PM <sub>2.5</sub> <sup>85</sup>
	No association <sup>81</sup>
	Maternal dietary components during pregnancy
	0.2 (0.08 to 0.6)†‡ Mediterranean diet <sup>86</sup>
	0.6 (0.4 to 1.0)* Western diet <sup>88</sup>
	0.6, (0.3 to 0.96)* fish consumption <sup>89</sup>
	0.8 (0.7 to 1.0) peanuts and 0.8 (0.7 to 0.8) tree nuts† <sup>90</sup>
	1.6 (1.2 to 2.0) low vegetables 1.5 (1.2 to 1.8) low fruit and chocolate 1.4 (1.1 to 1.7)† <sup>91</sup>
	No association fish oil <sup>87</sup> ‡, butter and margarine <sup>92</sup>
Specific nutrient intake during pregnancy	
0.6 (0.4 to 0.7)*‡ increased vitamin D intake <sup>86</sup>	
0.7 (0.5 to 0.9)*‡ increased vitamin E intake <sup>86</sup>	
0.3 (0.1 to 0.4)*‡ increased plasma vitamin A <sup>86</sup>	
0.95 (0.91 to 0.99)* per 10 nmol/L increase cord vitamin D <sup>97</sup>	
No association vitamin D (plasma) <sup>93–95</sup> (intake) <sup>96</sup> , dietary antioxidants <sup>99</sup> or folate <sup>100</sup> or vitamin A <sup>101</sup> supplements	
Breast feeding	
OR 0.92 (0.86 to 0.98)*‡ <sup>102</sup>	
OR 1.1 (1.0 to 1.2)†‡ <sup>102</sup>	
1.4 (1.2 to 1.7)* never breast feeding <sup>103</sup>	
0.9 (0.8 to 0.96)† exclusive breast feeding <sup>104</sup>	
2.0 (1.0 to 3.8)† maternal margarine intake during lactation <sup>98</sup>	
No association‡ <sup>105</sup>	
Cow's milk formula	
RR 0.4, (0.2 to 0.9)*‡ hydrolysed vs standard <sup>106</sup>	
OR 0.3 (0.1 to 1.0)* fatty acid supplementation <sup>108</sup>	
No association <sup>109</sup>	
Infant diet	
0.4 (0.2 to 0.9) for youngest vs oldest age at introduction of wheat† <sup>111</sup>	
0.6 (0.4 to 0.9) for early vs delayed introduction of fish <sup>115</sup>	
No association with age at introduction of solids <sup>112 113</sup> prebiotic supplementation† <sup>117</sup>	
‡ <sup>118</sup> or vitamin supplementation <sup>119</sup>	
Child diet	
0.6 (0.4 to 0.9)† full cream milk <sup>121</sup>	
1.5 (1.04 to 2.1) Western diet <sup>124</sup>	
0.93 (0.85 to 1.00) per fruit item consumption/day/week <sup>125</sup>	
0.5 (0.3 to 0.6) for highest vs lowest tertile plasma vitamin D <sup>126</sup>	
No association milk supplementation‡ <sup>120</sup> , organic food <sup>122</sup> , dietary anti oxidant <sup>123</sup>	
Respiratory virus infection	
Respiratory infection±wheeze	
0.5 (0.3 to 0.9)† for infant lower respiratory tract infection <sup>127</sup>	
9.8 (4.3 to 22.0)* wheeze with rhinovirus <sup>128</sup>	
2.9 (1.2 to 7.1)† wheeze with rhinovirus <sup>129</sup>	
2.2 (1.5 to 3.3)† RSV infection 6–11 months previously <sup>130</sup>	
0.9 (0.7 to 1.0)† early day care <sup>132</sup>	
No association early day care <sup>131</sup>	

Continued

Table 1 Continued

Exposure	Magnitude of effect (95% CI)
Medications	
Antibiotics	1.2 (1.0 to 1.5)†† antenatal exposure <sup>135</sup> 1.5 (1.3 to 1.8)†† postnatal exposure <sup>135</sup> No association†† <sup>136</sup>
Paracetamol	1.3 (1.1 to 1.4)†† <sup>139</sup> 1.2 (1.0 to 1.4)*†† <sup>138</sup> No association <sup>140</sup>
Other medications	1.1 (1.0 to 1.2) for antibiotics, 1.3 (1.1 to 1.6) gastro-oesophageal reflux treatment, 1.6 (1.1 to 2.3) opiates, 1.3 (1.2 to 1.4) thyroid supplements <sup>140</sup>
Other maternal exposures during pregnancy	2.7 (1.2 to 6.0)* dietary dioxins and polychlorinated biphenyl <sup>141</sup> 2.3 (1.3 to 4.1)* highest vs lowest BPA exposure <sup>142</sup> 0.7 (0.5 to 0.9)* BPA exposure <sup>36</sup> 1.1 (1.0 to 1.2)* per 10% increase in DDT metabolite <sup>143</sup> 1.2 (1.0 to 1.3) for increasing electromagnetic exposure <sup>144</sup>

No effect size and/or confidence intervals were identified for studies with the following citations: <sup>58, 67, 83, 107, 110, 114, 116 and 137</sup>.

Magnitude of effect of environmental exposure on respiratory symptoms including wheeze (\*), asthma (†), obstructive bronchitis (††) or atopic disease (¥) in children aged up to 9 years. Details of when the exposure occurred are presented in the text and the supplemental table.

†Indicates a randomised clinical trial, systematic review or meta-analysis.

BPA, bisphenol A; DDT, dichlorodiphenyltrichloroethane; HDM, house dust mite; LPS, lipopolysaccharide; MVOC, VOC of microbial origin; PVC, polyvinyl chloride; RSV, respiratory syncytial virus; SHS, secondhand smoke; VOC, volatile organic compound.

### Chlorinated swimming pools

Two cohort studies were identified. Exposure to chlorinated swimming pools in infancy and childhood was associated with reduced risk for current asthma at 7 years (OR 0.5).<sup>31</sup> A second study found no link between exposure to chlorine through swimming and asthma at 6 years of age;<sup>32</sup> those who did not attend swimming during the first year of life were more likely to have asthma.

### Other chemicals

In this broad category, there was one systematic review, two cohort studies, two cross-sectional studies and a case-control study; all found evidence of exposures being linked to increased asthma symptoms. A systematic review of seven studies of children aged up to 12 years found a positive association between polyvinyl chloride exposure in dust samples and asthma (OR 1.6).<sup>33</sup> One study (using the same cohort aforementioned<sup>31</sup>) created a composite household chemicals exposure score (including chlorine/chloride exposure), and found a positive association between exposure and risk of incident wheeze after 2.5 years of age (OR 1.7).<sup>34</sup> Two cohort studies related antenatal and current exposures to asthma risk: high exposure to pyrene was associated with increased asthma risk in 5–6-year-olds (OR 1.9),<sup>35</sup> and this association was only apparent in non-atopic children, and maternal exposure during pregnancy was not related to asthma (table 2); maternal bisphenol A (BPA) exposure during pregnancy was inversely associated with wheeze at 5 years (OR 0.7) but not at 7 years; however, the child's current exposure was positively associated with this outcome (OR 1.4).<sup>36</sup> Living close to a petrochemical plant was associated with an increased risk for asthma (OR 2.8).<sup>37</sup> A case-control study found increased wheeze in

6–14-year-olds living close to an oil refinery compared with controls (OR 1.7).<sup>38</sup>

### Damp housing/mould

One systematic review, one meta-analysis plus four cohort studies were identified and early exposure was consistently associated with increased risk for later asthma symptoms. The systematic review included data from 16 studies and concluded that exposure to visible mould was associated with increased risk for asthma (OR 1.5).<sup>39</sup> The meta-analysis of eight European birth cohorts found an association between exposure to visible mould or dampness and increased wheeze at 2 years (OR 1.4) but this was not significant at 6–8 years (OR 1.1).<sup>40</sup> The cohort studies found mould exposure in early life to be associated with increased risk for asthma at 3 years (OR 7.1)<sup>41</sup> and 7 years (RR 2.4 for presence of any mould,<sup>42</sup> and OR of 2.6<sup>43</sup> and 1.8<sup>44</sup> per unit increase in mouldiness index).

### Inhaled allergens

#### Indoor exposures

Multiple exposures: There were five intervention studies and eight cohort studies identified. One intervention randomised newborns to house dust mite (HDM) reduction measures, avoidance of cow's milk or both or neither and found no difference in asthma incidence at age 5 years across the four groups.<sup>45</sup> A second study also modified postnatal exposure to cow's milk protein (and other dietary allergens) and HDM and the intervention group had trends for reduced wheeze (OR 0.4 (0.2 to 1.08)) at 8 years.<sup>46</sup> A third intervention study reduced exposures to SHS, inhaled and ingested allergens and promoted breast feeding but found no difference in asthma outcome age 6 years.<sup>47</sup> The fourth intervention modified exposures to antenatal and postnatal oily fish,

**Table 2** Magnitude of effect of main effect on asthma aetiology and magnitude of interaction with other factor

Study	Interaction between	Magnitude of interaction (95% CI)
Robison <i>et al</i> <sup>16</sup>	Late premature delivery (<37 weeks) and antenatal SHS exposure	OR for wheeze 2.0 (1.3 to 3.1) associated with prematurity and 1.1 (0.5 to 2.4) with in utero SHS exposure. OR for wheeze 3.8 (1.8 to 8.0) if both premature and SHS exposed
Martinez <i>et al</i> <sup>19</sup>	Smoke exposure from mother	OR 2.6 (1.4 to 4.6) if exposed and mother $\leq$ 12 years education OR 1.7 (1.1 to 2.6) for asthma by 5 years
Diez <i>et al</i> <sup>27</sup>	Redecoration Pet exposure Dampness	Redecoration associated with OR for obstructive bronchiolitis at 2 years 4.1 (1.4 to 12.9). OR 5.1 (1.6 to 15.6) if also exposed to ETS or pets
Jung <i>et al</i> <sup>85</sup>	Pyrene exposure Atopy	High exposure was associated with increased risk for asthma 1.9 (1.1 to 3.2) and this was increased to 2.9 (1.8 to 5.7) among non-atopic children
Carlsten <i>et al</i> <sup>56</sup>	Dog exposure SHS High NO <sub>2</sub>	No association with dog exposure per se OR 2.7 (1.1 to 7.1) for dog and SHS OR 4.8 (1.1 to 21.5) for dog plus high NO <sub>2</sub>
Karmus <i>et al</i> <sup>67</sup>	Recurrent lower respiratory tract infection Breast feeding SHS	OR 2.5 (1.8 to 3.4) for asthma at ages 4 and 10 years. OR 3.1 (1.8 to 5.2) with antenatal exposure to products of tobacco smoke
Melen <i>et al</i> <sup>61</sup>	Smoke exposure Pets Window pane condensation	OR for 1 to 2 and 3 exposures (compared to none) were 1.1, 4.4 (1.0 to 18.6) and 10.8 (2.0 to 59.6)
Celedon <i>et al</i> <sup>62</sup>	Early cat exposure Maternal asthma	Exposure associated with reduced risk for wheeze (OR 0.6 (0.4 to 0.9)) but only in those with no maternal asthma
Trevillian <i>et al</i> <sup>71</sup>	Synthetic bedding Bedroom heating Recent bedroom painting	Exposure to >1 synthetic item of bedding was associated with increased asthma (OR 1.8 (1.0 to 3.2)). Co-exposure to room heating was associated with OR 7.1 (0.1 to 23.9), recent painting OR 7.2 (2.3 to 23.2)
Kim <i>et al</i> <sup>81</sup>	Ambient air pollution (ozone, CO, NO <sub>2</sub> , SO <sub>2</sub> and PM <sub>10</sub> ) Previous bronchiolitis	Asthma at 5 years not associated with higher exposures but among bronchiolitis subset ozone exposure associated with OR 7.5 (2.7 to 21.3), CO exposure OR 8.3 (2.9 to 23.7) and NO <sub>2</sub> exposure OR 7.9 (0.97 to 64.8)
Ryan <i>et al</i> <sup>82</sup>	Traffic-related particles (elemental carbon attributable to traffic) Domestic LPS	A positive asthma predictive index at 36 months was associated with exposure to increased levels of particles before 12 months (OR=2.0 (1.2 to 3.6)). Co-exposure to high concentrations of endotoxin increased the risk (OR=3.4 (1.3 to 8.9))
Kusel <i>et al</i> <sup>129</sup>	Atopy Virus positive wheezing illness	OR 3.1 (1.5 to 6.4) if atopic for wheeze at 5 years. OR 3.9 (1.4 to 10.5) if also wheezy illness

LPS, lipopolysaccharide; SHS, secondhand smoke.

SHS and dampness and observed reduced asthma risk at 2 years for the intervention group (OR 0.7).<sup>48</sup> The fifth study modified antenatal and postnatal exposures to HDM, pets, SHS, promoted breast feeding and delayed weaning, and asthma risk at 7 years was reduced in the intervention group (OR 0.4).<sup>49</sup> Five observational studies related early life HDM exposure plus other 'dust' exposures to asthma: increased HDM and lipopolysaccharide (LPS) exposures were independently associated with increased symptoms by 7 years; HDM  $\geq$ 10  $\mu$ g/g was associated with increased risk for asthma (OR 3.0) and each quartile increase in LPS was associated with increased risk for lifetime wheeze (OR 1.2).<sup>50</sup> Exposure to higher concentrations of cat allergen (but not HDM) was associated with increased asthma risk by 6 years of age OR for third versus lowest exposure quartile 2.6 (1.3 to 5.4);<sup>51</sup> other studies found no association between (1) infantile exposure to HDM and cat and cockroach

allergen and wheeze at 2 years,<sup>52</sup> (2) HDM, cat and dog allergen exposure and wheeze at 4 years,<sup>53</sup> and (3) HDM and cat exposure and asthma at 7 years.<sup>54</sup> One study reported increasing cockroach allergen exposure in infancy was positively associated with wheeze by age 5 years (OR 1.8) and, independently, the presence of a dog and higher concentrations of cat allergen exposure were associated with reduced wheeze risk (OR 0.3 and 0.6).<sup>55</sup> Dog allergen exposure in infancy was not associated with asthma at 7 years per se but was associated with asthma in combination with exposure to SHS (OR 2.7) or elevated NO<sub>2</sub> (OR 4.8).<sup>56</sup> A final study observed interactions between exposures to SHS, breast feeding and recurrent respiratory infections and asthma.<sup>57</sup>

Pet exposure: There were two systematic reviews, one meta-analysis and six cohort studies identified and the results were highly inconsistent. One systematic review of nine studies concluded that exposure to pets around the

time of birth may reduce risk for allergic disease (including asthma) where there is no family history of asthma, but no effect size was given.<sup>58</sup> The second systematic review concluded that exposure to cats reduced the risk for asthma (OR 0.7) and to dogs increased asthma risk (OR 1.1).<sup>59</sup> The meta-analysis found no evidence for cat exposure in early life being linked to asthma risk at age 6–10 years; there was a non-significant trend for dog ownership to be associated with reduced asthma risk (OR 0.8 (0.6 to 1.0)).<sup>60</sup> The cohort studies found early cat exposure to be associated with increased severe asthma at 4 years (OR 4.7),<sup>61</sup> and reduced wheeze by age 5 years (OR 0.6<sup>62</sup> and 0.3<sup>63</sup>), increased wheeze at 7 years (OR 1.2)<sup>64</sup> and no association with asthma risk at 4<sup>65</sup> or 8 years;<sup>66</sup> in a post hoc analysis, early exposure to dog was linked to reduced late onset wheeze at 4 (OR 0.4 (0.2 to 1.0)).<sup>65</sup> There was apparent synergy between exposure to high concentrations of cat allergen, SHS exposure and window pane condensation and increased risk for severe asthma at 4 years (OR 10.8 (2.0 to 59.6)).<sup>61</sup>

**Other exposures:** There was one systematic review identified relating exposure to farm living to asthma risk; data from 39 studies were identified, and despite differences in definitions for asthma and associations with exposure to living on a farm, there was a 25% reduction in risk of asthma for children living on a farm compared with controls (no CIs presented).<sup>67</sup> A cohort study found an association between LPS concentration in mother's mattress when the infant was 3 months old and repeated wheeze by 2 years of age (OR 1.5 comparing highest with lowest quartile for exposure).<sup>68</sup> A second cohort study reported an association between increased current exposure to mouse allergen and wheeze at 7 years of age (OR 1.4)<sup>69</sup>; there was no association between mouse allergen exposure in infancy and later wheeze. A third small cohort reported no association between exposure to cockroach allergen in infancy and wheeze in the first 2 years of life.<sup>52</sup> Observational studies report associations between exposure to feather quilt in infancy and reduced asthma at 4 years compared with non-feather quilt (OR 0.4)<sup>70</sup> and that a greater number of synthetic items of bedding (known to be HDM rich) during infancy was associated with increased risk for a history of asthma by 7 years (OR 1.8).<sup>71</sup>

**HDM exposure:** There were two intervention studies<sup>72 73</sup> and one observational study,<sup>74</sup> and none found an association between exposure in infancy<sup>72 73</sup> or by 2 years of age<sup>74</sup> and asthma at 3,<sup>73</sup> 6–7<sup>74</sup> or 8 years of age.<sup>72</sup>

**Outdoor allergens:** Three cohort studies were identified and all found exposure was related to increased asthma risk. One study related fungal spores and pollen concentrations at the time of birth to wheeze at age 2 years and those born in autumn to winter (the fungal spore season) were at increased risk for wheezing (OR 3.1).<sup>75</sup> A second study reported an association between increased grass pollen exposure between 4 and 6 months of age and increased asthma at 7 years of age (OR 1.4).<sup>76</sup>

The third study related tree canopy cover (a source of tree pollen and also of altered airflow and air quality) in infancy to asthma at 7 years and found a positive association (RR 1.2).<sup>77</sup>

### Air pollution

One meta-analysis and eight additional cohort studies were identified, and while pollutants associated with combustion were associated with increased asthma risk, no single pollutant was consistently identified. The meta-analysis found that exposure to Nitrogen Dioxide (NO<sub>2</sub>, OR 1.05), Nitric Oxide (OR 1.02) and Carbon Monoxide (CO, OR 1.06) were associated with higher prevalence of diagnosis of childhood asthma. Exposures to SO<sub>2</sub> (OR 1.04) and particulates (OR 1.05) were associated with a higher prevalence of wheeze in children.<sup>78</sup> Ambient lifetime CO exposure, but not NO<sub>2</sub>, ozone or particulates with mass less than 2.5 microns (PM<sub>2.5</sub>), was associated with increased risk for wheeze at 5 years (OR 1.04 per ppm increased CO).<sup>79</sup> A second cohort study found that ambient exposure to NO<sub>2</sub>, but not ozone, SO<sub>2</sub>, PM<sub>2.5</sub> and PM<sub>10</sub>, was associated with increased asthma risk at 3 years (OR 1.2 per 5ppb increase).<sup>80</sup> A third study related averaged lifetime exposure to ozone, CO, NO<sub>2</sub>, SO<sub>2</sub> and PM<sub>10</sub>, and found no association with asthma in 7-year-olds for the whole population, but among the 10% with previous bronchiolitis, asthma risk was increased (OR approximately 7) in association with higher exposures to ozone, CO and NO<sub>2</sub> (table 2).<sup>81</sup> Exposure to traffic-related particles (elemental carbon attributable to traffic) during infancy was associated with increased risk for asthma in 3-year-olds (OR 2.0) and co-exposure to high concentrations of domestic endotoxin increased the risk (OR 3.4).<sup>82</sup> One study found increased wheeze prevalence in 4-year-olds among those exposed to stop/go traffic compared with unexposed children (23% vs 11%)<sup>83</sup> and the second found that children with a lifetime exposure to higher traffic density were more likely to be diagnosed with asthma (OR 1.3).<sup>84</sup> Exposure to high (>4.1 µg/m<sup>3</sup>) levels of PM<sub>2.5</sub> during infancy were associated with increased risk for asthma in a small cohort (OR 3.1).<sup>85</sup>

### Dietary exposures

#### Maternal diet—food items

There was one systematic review, one intervention study and five cohort studies identified, and some food items were linked to childhood asthma risk. The systematic review of 62 studies concluded that there was more convincing evidence for maternal fruit (compared with vegetable) intake during pregnancy to be associated with reduced risk for childhood asthma;<sup>86</sup> there was only one study that identified maternal Mediterranean diet to outcome (persistent wheeze (OR 0.2) at age 6.5 years) and maternal exposure to fish was not included. A small intervention study where pregnant mothers took placebo or fish oil supplement found no difference in respiratory symptoms between treatment groups at 1 year.<sup>87</sup> A study from



Japan found reduced risk for wheeze at 16–24 months for children whose mother's diet had been least 'Westernised' (OR 0.6 for comparison with most 'Westernised').<sup>88</sup> A Mexican study found a protective effect of fish consumption during pregnancy on atopic wheeze (OR 0.6).<sup>89</sup> In Denmark, maternal intake of peanuts (OR 0.8) and tree nuts (OR 0.8) was inversely associated with asthma in children at 18 months of age.<sup>90</sup> In Finland, low maternal consumption of leafy vegetables (OR 1.6), malaceous fruits (eg, apple, pear, OR 1.5) and chocolate (OR 1.4) were positively associated with the risk of wheeze in 5-year-old children.<sup>91</sup> A final study found no association between maternal butter and margarine intake and asthma outcomes in children aged 5–6.<sup>92</sup>

### Maternal diet-specific nutrients

There was one systematic review and eight cohort studies identified, and reduced exposure to some nutrients was associated with increased asthma risk. Meta-analysis within the systematic review found that (1) increasing maternal vitamin D intake was associated with reduced risk for wheeze in the last year (OR 0.6, 4 studies) but not asthma at 5 years; (2) increasing maternal vitamin E intake was associated with reduced wheeze at 2 years (OR 0.7, 3 studies); (3) increased maternal plasma vitamin A was associated with reduced asthma risk (OR 0.3, 2 studies); and (4) there was no evidence for associations between maternal plasma zinc or selenium and asthma outcomes.<sup>86</sup> Of five cohort studies published after the systematic review, four found no evidence linking maternal plasma vitamin D<sup>93–95</sup> or vitamin D intake<sup>96</sup> and asthma; one study found an inverse association between cord plasma vitamin D and risk for wheeze, but not asthma, by age 5 years (OR 0.95 per 10 nmol/L increase).<sup>97</sup> One study found maternal fatty acid intake during the third trimester was associated with asthma outcome at 5 years (eg, higher  $\alpha$ -linoleic acid and palmitic acid intake associated with ~40% reduced risk).<sup>98</sup> Other studies found no association between maternal dietary antioxidants<sup>99</sup> or folate<sup>100</sup> and vitamin A<sup>101</sup> supplementation and childhood asthma outcomes.

### Exposure to milk during infancy

In addition to the previously described complex interventions where milk exposure was modified, a number of studies were identified where only milk was the exposure of interest and there was evidence that early milk exposure was related to altered asthma risk.

**Breast milk:** One systematic review with meta-analysis, two cohort studies and one intervention study were identified. Meta-analysis of 31 studies found any breast feeding reduced risk for wheeze (OR 0.92) but increased risk for asthma (OR 1.10).<sup>102</sup> Never breast feeding was associated with increased wheeze by 4 years (OR 1.4)<sup>103</sup> and exclusive breast feeding was associated with reduced asthma risk at 5 (OR 0.9)<sup>104</sup> but not at 6 years of age. The intervention study found that prolonged breast feeding (up to the age of 12 months) was

associated with reduced asthma at 4 but not at 6 years of age.<sup>105</sup> Maternal margarine intake (but not fatty acid or fish intake) while breast feeding was associated with increased risk for asthma at 5 years (HR 2.0).<sup>98</sup>

**Cow's milk formula:** One systematic review, two intervention studies and one observational study were identified. A systematic review of 10 trials concluded that hydrolysed cow's milk formula, but not soya-based milk, reduced risk of wheezing in infancy (RR 0.4) compared with standard cow's milk formula.<sup>106</sup> Modification of cow's milk formula either by a non-hydrolysing fermentation process or supplementation with fatty acids (arachidonic acid or docosahexaenoic acid) was associated with reduced risk for wheeze by 2 (13% vs 35%)<sup>107</sup> and 3 years of age (OR 0.3)<sup>108</sup> compared with standard cow's milk formula. An observational study found no evidence for hydrolysed feed for the first 6 months reducing asthma risk at 3 years.<sup>109</sup>

### Dietary exposures during infancy

There were two systematic reviews, two clinical trials and five observational studies identified; there were some associations between exposure to some dietary components and altered risk reported. Four observational studies related first dietary exposures to asthma outcomes, and one found evidence for early introduction of cereals by 6 months, and egg by 11 months was associated with 30–40% reduced risk for asthma at 5 years,<sup>110</sup> and a second study found a direct relationship between age at introduction of oats and risk for asthma at 5 years (OR 0.4 for earliest vs latest age at introduction).<sup>111</sup> Two other studies found no association between early or delayed introduction of any solids and asthma risk at 5<sup>112</sup> and 6 years.<sup>113</sup> A systematic review of 14 studies relating fish oil exposure during infancy and asthma (and other allergic outcomes) concluded that exposure was linked to a reduced risk of between 5% and 75%.<sup>114</sup> One cohort study found an association between the introduction of fish between 6 and 12 months and decreased risk for wheezing at 48 months (OR 0.6),<sup>115</sup> however, the two previously discussed studies found no association between fish exposure and asthma<sup>112 113</sup> and an intervention study of fish oil supplements in the first 6 months of life did not change risk for asthma symptoms at 12 months.<sup>116</sup> A systematic review of two trials found no link between infant diet supplementation prebiotics and asthma risk,<sup>117</sup> and a trial where infants were randomised to supplement with probiotic ( $\pm$ prebiotic) or placebo also found no difference in asthma risk.<sup>118</sup> One cohort study found no evidence for association between infant vitamin supplements and asthma risk, although among African-Americans, supplementation was associated with increased risk (OR 1.3).<sup>119</sup>

### Dietary exposure in childhood

One RCT and six cohort studies were identified, and there was limited evidence linking early exposure to later increased asthma risk. Supplementation of milk with

fermented milk containing lactobacillus during the first 2 years did not alter risk for asthma compared with placebo.<sup>120</sup> One observational study found daily exposure to full cream milk at 2 years reduced risk for asthma 1 year later (OR 0.6 (0.4 to 0.9)).<sup>121</sup> Exposure to organic food during the first 2 years<sup>122</sup> and dietary oxidant at 5<sup>123</sup> were not associated with altered risk for wheeze at 2 years or asthma at 8 years, respectively. Studies from the Netherlands found exposure to a 'western' diet at 14 months was associated with an increased risk for frequent wheeze at 3 years (RR 1.5),<sup>124</sup> exposure to fruit in early childhood reduced risk for asthma at 8 years (OR 0.93 per item consumed day per week)<sup>125</sup> and that increased plasma vitamin D at 4 years was associated with reduced asthma risk at 8 years (OR for highest vs lowest tertile 3 0.5)<sup>126</sup> but serum vitamin D levels at 8 years were not associated with current asthma risk.<sup>126</sup>

### Respiratory virus infection

There were six cohort studies identified and there was consistent evidence for infection associated with wheeze or that hospitalisation increased asthma risk. Parent reported lower respiratory tract infections during infancy were negatively associated with the risk of asthma at 7 years of age in one cohort (OR 0.5).<sup>127</sup> A cohort study demonstrated that wheeze before 4 years of age was associated with increased risk for asthma at 6 years if rhinovirus (OR 9.8) was present;<sup>128</sup> there was a borderline increase in risk if respiratory syncytial virus (RSV) was present (OR 2.6). A second cohort selected for familial risk for atopy also found rhinovirus positive (but not RSV positive) wheezing lower respiratory tract infection during infancy was associated with increased risk for asthma at age 5 years (OR 2.9).<sup>129</sup> A third study observed an increased risk of asthma following infection with RSV, and this risk was higher in the months following the hospitalisation and lower with longer duration since hospitalisation (eg, RR 6.2 within 2 months of hospitalisation and RR 2.2 6–11 months after hospitalisation).<sup>130</sup> Early daycare, a proxy for respiratory infections, was not associated with altered risk for asthma at age 8 years<sup>131</sup> in one cohort but was associated with reduced asthma risk at 8 years in a second study (HR 0.9).<sup>132</sup>

### Other infections

One small cohort study observed reduced risk for wheeze at 18 months for children whose parents cleaned their dummy/pacifier by sucking it (OR 0.1 (0.01 to 1.0)) compared with other cleaning practices.<sup>133</sup> A second cohort study found no evidence for infection in preschool children (either serologically proven or isolated from stool samples) and wheeze by 11 years.<sup>134</sup>

### Medications

#### Antibiotics

Three systematic reviews were identified that related antenatal<sup>135</sup> and postnatal<sup>135–137</sup> exposure to antibiotics and asthma outcomes. There was evidence that

antenatal and postnatal exposures were associated with increased risk for early asthma symptoms (eg, OR 1.2 for antenatal exposure and 1.5 for postnatal exposure)<sup>135</sup> but all three systematic reviews concluded that this association was explained by reverse causation. One systematic review demonstrated that the OR fell from 1.3 to 1.1 when reverse causation was considered.<sup>136</sup>

#### Paracetamol

Three systematic reviews were identified and these linked antenatal<sup>138</sup> and postnatal<sup>137–139</sup> exposure to paracetamol to the risk of asthma symptoms. There were associations between paracetamol exposure and the development of asthma OR 1.3<sup>139</sup> and wheeze OR 1.2.<sup>138</sup> The third systematic review did not present an effect size and suggested that any association was by reverse causation.<sup>137</sup>

#### Other maternal exposures during pregnancy

A whole-population study found treatment during the second and third trimester with the following were associated with increased risk for asthma: antibiotics (OR 1.1); drugs for gastro-oesophageal reflux (OR 1.3); opiates (OR 1.6); and thyroid drugs (OR 1.3). There was no association with paracetamol prescribing.<sup>140</sup> Five cohort studies related various maternal exposures during pregnancy to early childhood wheeze and reported the following associations: exposure to dietary dioxins and polychlorinated biphenyls was associated with increased wheeze by 3 years (OR 2.7);<sup>141</sup> exposure to BPA was positively associated with a transient increase in wheeze in one study (OR for wheeze at 6 months 2.3, highest vs lowest exposure)<sup>142</sup> and inversely associated with transient wheeze in a second study (OR for wheeze at 5 years 0.7 per increase in log transformed BPA)<sup>36</sup>; each 10% increase in exposure to dichlorodiphenyldichloroethylene (a product of the pesticide dichlorodiphenyltrichloroethane (DDT)) was associated with increased wheeze at 12–14 months of age (RR 1.11);<sup>143</sup> each unit increase in in utero electromagnetic exposure was linked with increased risk for asthma at 13 years (HR 1.15).<sup>144</sup>

## DISCUSSION

The aim of this systematic review was to provide an overview of the literature describing associations between environmental exposures in early life and asthma outcomes by 9 years of age. This review is mostly based on observational studies and is likely to be influenced by submission bias (where investigators do not submit papers that find no associations which challenge current paradigms) and/or publication bias. In addition, reverse causation or confounding may explain some associations reported, for example, postnatal exposures to antibiotics, paracetamol and perhaps pets. Moreover, observational studies cannot prove causation and most intervention studies found no effect on outcome even where studies indicated a potentially important mechanism, for

example, HDM interventions. Given these caveats, we believe that three major conclusions can be drawn. First, there was a moderately strong level of evidence (ie, RCT, systematic review or meta-analysis) for the presence of associations between most exposures and asthma risk but the literature remains relatively deficient for exposures to infection and domestic combustion (both of which are likely to be important on a global basis). Second, where associations were present, these were of small-moderate effect size by our predefined standard. Third, we identified interactions between exposures (most commonly SHS) and/or atopy which increased the risk of that exposure being associated with asthma. Given that there is no prospect of a cure for asthma, modification of the environment in early life currently offers the best hope of reducing the burden of asthma in the population and an overview of all exposures such as we present here may be of use to policymakers, healthcare workers and lobbying groups.

There is no single exposure which seems likely to cause asthma and even 'single' exposures are invariably contaminated by other exposures. There was consistent evidence in the literature for associations between exposures to SHS, inhaled chemicals, mould, respiratory viruses, ambient air pollutants and maternal dietary components, and increased asthma risk. However, each of these is a complex exposure and there was evidence of interaction between all these exposures. There is evidence that asthma risk may be related to diversity of exposure to fungus and not exposure per se<sup>145</sup> and our findings are consistent with this idea. There were inconsistent associations between asthma and exposures to pets, breast feeding and infant diet when considered separately but those intervention studies where asthma risk was successfully reduced often included modifications to some or all of these exposures. There is further evidence that asthma risk can be reduced by early exposure to an environment that is diverse in many inhaled and ingested factors common to the human environment for millennia, such as animal dander, LPS, fungi and breast milk (but not including man-made chemicals).

There are a number of limitations to this systematic review in addition to those already described. First, in the absence of a gold standard definition of asthma, different outcomes have been used, for example, asthma or wheeze; these may not be interchangeable and have different associations with a given exposure. Second, associations reported may not be persistent: exposure to breast feeding is an example of a waning effect of a given exposure over time, presumably as current exposures modify the effect of past exposures. Third, the upper age of study participants was 9 years and this meant that many highly cited studies describing associations between exposure and asthma risk in older children were not included.<sup>146</sup> Fourth, in our methodology we included only the latest paper from cohorts where associations may have been reported at several different ages and this will mean that transient associations are

not captured; for example, we have interpreted an intervention study where breast feeding was successfully prolonged as having no effect on asthma at 6 years<sup>105</sup> but the exposure was associated with reduced asthma symptoms in this cohort at ages 2<sup>147</sup> and 4<sup>148</sup> years. Finally, it is possible that a given exposure may have a different effect on asthma risk between populations where different genetic and/or epigenetic factors may be acting.

In summary, we have reviewed the literature for associations between all environmental exposures and the development of asthma in children aged under 9 years. Early life exposures to exhaled tobacco smoke, VOCs, mould, breast feeding, pets and many dietary factors appear to be important to the development of asthma and interactions between these exposures further increase this risk, particularly in individuals with allergic parents. Complex interventions in early life are challenging<sup>149</sup> but the evidence in the observational literature and from small intervention studies demonstrates that approaches using this study design may lead to stronger public health advice stating that interventions which alter multiple early life environmental encounters are able to modify asthma risk in this age group.

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