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REVIEW



# The association between environmental tobacco smoke exposure and childhood respiratory disease: a review

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**ABSTRACT**

**Introduction**: Childhood respiratory illness is a major cause of morbidity and mortality particularly in low and middle-income countries. Environmental tobacco smoke (ETS) exposure is a recognised risk factor for both acute and chronic respiratory illness.

**Areas covered**: The aim of this paper was to review the epidemiology of ETS exposure and impact on respiratory health in children. We conducted a search of 3 electronic databases of publications on ETS and childhood respiratory illness from 1990–2015. Key findings were that up to 70% of children are exposed to ETS globally, but under-reporting may mask the true prevalence. Maternal smoking and ETS exposure influence infant lung development and are associated with childhood upper and lower respiratory tract infection, wheezing or asthma. Further, exposure to ETS is associated with more severe respiratory disease. ETS exposure reduces lung function early in life, establishing an increased lifelong risk of poor lung health.

**Expert commentary**: Urgent and effective strategies are needed to decrease ETS exposure in young children to improve child and long-term lung health in adults especially in low and middle income countries where ETS exposure is increasing.

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## 1. Introduction

Childhood respiratory illness remains a major challenge for global health. Pneumonia is the leading cause of under-5 mortality outside the neonatal period in low- and middle-income countries (LMICs) [1,2]. Asthma is the commonest chronic disease in children in high and LMIC settings [3]. Environmental tobacco smoke (ETS) exposure is a well-recognized risk factor for acute and chronic respiratory illness [4]; tobacco use is the leading global cause of preventable death [5]. Despite worldwide initiatives to reduce tobacco smoking, it is estimated that up to 40% of children are still exposed to tobacco smoke [6] and approximately 6 million deaths are tobacco related with half a trillion dollars in tobacco-related economic damage [5]. While the incidence of smoking is decreasing in certain regions [7], it is increasing in others, particularly in LMICs and especially amongst women [5,8]. Further, bans on tobacco smoking in public do not prevent smoking in homes where women and children may experience ETS exposure from household members [8], with the magnitude of exposure closely related to cohabitants' smoking habits [9].

ETS exposure often begins *in utero* with maternal smoking or exposure. Antenatal or early-life ETS exposure, from maternal, household, or community contacts, may impact on the susceptibility of the infant to develop respiratory disease and impair lung development [10,11]. However, the effects of postnatal tobacco smoke exposure may also be substantial, leading to poorer respiratory health [12].

Potential mechanisms for ETS-induced damage include impaired *in utero* lung growth from suppression of fetal breathing or direct genotoxicity [13]. Tobacco smoke comprises a large number of chemicals and carcinogens, all of which may affect the developing respiratory system [14]. Animal models suggest that nicotine is the component that has significant detrimental effects on lung growth and collagen deposition [15]. Nicotine affects lung branching through stimulation of alpha-7 nicotinic acetylcholine receptors during the pseudoglandular phase resulting in dysanaptic lung growth [16]. Changes in conducting airway structure can lead to decreased airflow and increased resistance, decreasing pulmonary function [15,16]. Prenatal nicotine may also alter peripheral and central chemoreception [14].

Further, there is evidence linking the effects of tobacco smoke exposure to impaired early-life immune function resulting in an imbalance in Th1 and Th2 responses increasing the susceptibility to allergic diseases and childhood respiratory infections [14,17].

The aim of this paper was to review the current data on the epidemiology of ETS exposure and the effects of this on lung health in children. Specific objectives were to investigate the effect of ETS exposure on acute respiratory infection, on chronic respiratory disease, and on lung function.

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## 2. Methods

Searches were conducted on three electronic databases: PubMed, Scopus, and Google Advanced Scholar. Keywords included, tobacco smoke or cigarette*, child*, respiratory or lung*, exposure or illnesses. Searches were limited to English language articles to include publications from 1990 to 2016. As this was not a formal meta-analysis, an adaption of the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guideline was used [18].

All papers including meta-analyses and systematic reviews were reviewed and included. Abstracts of identified documents were read and full texts of relevant documents were retrieved. Reference lists of retrieved documents were also searched to identify additional publications. Records were screened to identify the original articles, reviews, and meta-analyses relating to: epidemiology, ETS exposure, and respiratory tract infection in children; chronic lung diseases (asthma and chronic obstructive pulmonary disease (COPD); and lung function. The majority of these ($n$ = 4422) were excluded as they were either included in systematic reviews or meta-analyses, or assessed as being not relevant to the above criteria. When multiple reports on the same area of knowledge were encountered, the best quality article was selected for the review. From the 262 screened records, 123 were eligible for inclusion in the qualitative synthesis (Figure 1).

## 3. Results and discussion

### 3.1. Results

The 123 articles included were chosen to review the available literature on ETS exposure and childhood respiratory disease. In order to comprehensively review this extensive subject, literature pertaining to the epidemiology of ETS exposure, the acute and chronic sequelae, and preventative strategies to limit exposure was then explored as described later.

### 3.2. Epidemiology of ETS exposure in childhood

Recent global estimates report that worldwide 40–70% of children are exposed to tobacco smoke [6,19]. Further, the burden of antenatal exposure may be underestimated as smoking during pregnancy is often underreported [20,21]. There is large variability in smoking prevalence in different regions [20,22]. The reported overall pooled prevalence of smoking during pregnancy in LMICs is 1.3% (95% CI 0.9–1.8%) with Southeast Asia having the highest pooled regional prevalence of 2.7% (95% CI 1.1–4.8) [20]. However, this prevalence is based on self-reported smoking and may likely under estimate the true prevalence (Table 1). Smoking in pregnancy may also depend on societal acceptance as demonstrated by very disparate smoking prevalence found in two closely located South African communities of different ethnicities; 51% in pregnant women from one community compared to 14% in the other [23]. Even in high-income countries the prevalence of smoking in various regions within the United States of America before, during, and after pregnancy varied widely with smoking prevalence during pregnancy ranging from 2% to 30%. Overall smoking prevalence was highest in the 3 months preceding pregnancy (almost 25%), decreasing during pregnancy (12.3%) and after pregnancy (17.2%); however, tobacco-control efforts have achieved minimal reductions and much higher than national objectives of smoking within pregnancy (1.4%) [21].

### 3.3. ETS exposure and respiratory tract infection (RTI) in children

RTIs associated with ETS exposure include upper RTI (URTI) (otitis media, sinusitis, pharyngitis, tonsillitis) and lower respiratory tract infections (LRTIs) [26]. An increased risk of 1.2–1.6 of URTI or LRTI has been reported particularly in preschool children exposed to parental smoking [27]. When considering the impact of prenatal versus postnatal exposure on respiratory disease, postnatal paternal smoking is associated with increased otitis media while maternal smoking in

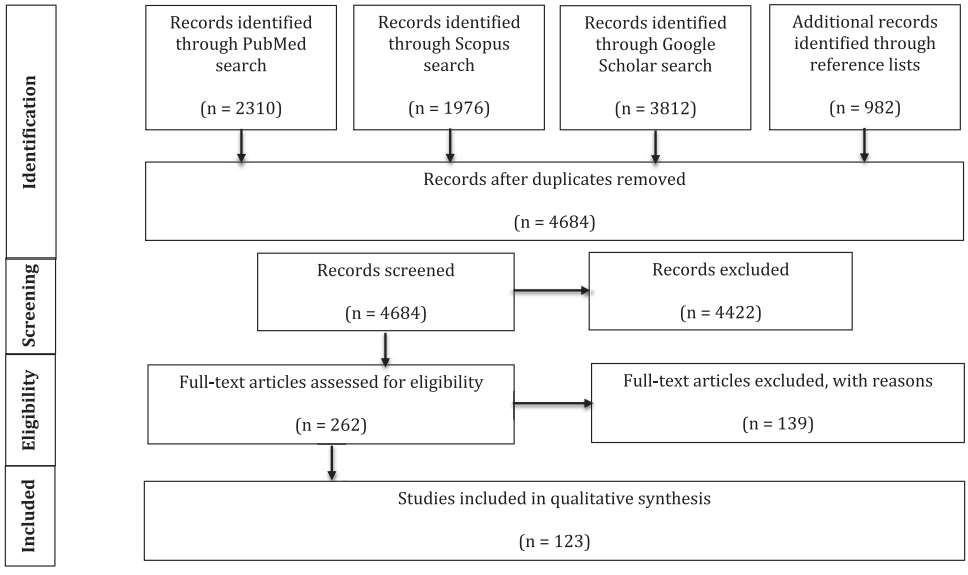


Figure 1. Flow diagram of literature review [18].

Table 1. Tobacco smoke exposure prevalence by WHO region [6,20,24,25].

| | | Exposure to second-hand smoke | | Active smoker | |
|---|---|---|---|---|---|
| WHO region and sub-region* | | Children <15 years (%) | Women (%) | Women (%) | Pregnant women in LMICs (%) |
| Africa | D | 13 | 11 | 3 | 0.0–4.5 |
| | E | 13 | 9 | | 0.0–5.4 |
| The USA | A | 25 | 15 | 16 | No data |
| | B | 29 | 22 | | 0.7–3.5 |
| | D | 22 | 19 | | 1.0–4.1 |
| Eastern Mediterranean | B | 37 | 25 | 4 | 6.8–13.4 |
| | D | 34 | 35 | | 0.4–3.8 |
| Europe | A | 51 | 32 | 22 | No data |
| | B | 61 | 54 | | 0.1–15.0 |
| | C | 61 | 66 | | 0.8–3.9 |
| Southeast Asia | B | 53 | 56 | 5 | 0.4–1.4 |
| | D | 36 | 19 | | 1.0–5.9 |
| Western Pacific | A | 51 | 54 | 4 | No data |
| | B | 68 | 51 | | 2.4–3.4 |
| Worldwide | | 41 | 35 | 8 | 0.9–1.8 |

* WHO region and subregional grouping, based on 2004 data. Categorization as follows: A = very low child mortality and very low adult mortality; B = low child mortality and low adult mortality; C = low child mortality and high adult mortality; D = high child mortality and high adult mortality; E = high child mortality and very high adult mortality. Adapted from WHO [24].
LMIC: low- and middle-income country.

pregnancy is associated with an increase in wheezing (odds ratio (OR) 1.41, 95% CI 0.99–2.01) or chestiness (OR 1.46, 95% CI 1.03–2.01) in the first year of life [28]. ETS is postulated to increase the risk of RTI by direct toxic effects on the mucosa, impaired ciliary function, and impaired local immune defences resulting in prolonged inflammation, congestion, or predisposition to infection [29,30].

### 3.3.1. Upper respiratory tract infection

ETS exposure is associated with recurrent otitis media and the increased need for tympanostomy tube placement with parental smoking reported to double the risk of recurrent acute otitis media [31,35]. Maternal smoking increased the risk of middle ear disease and the need for surgery (OR 1.86, 95% CI 1.31–2.63) [32]. Exposure to ETS was more common in children undergoing tonsillectomy for recurrent tonsillitis compared to a control group who underwent hernia repair surgery [33]. Children whose parents limited their exposure to ETS by enforcing smoke-free home environments experienced fewer URTIs and decreased health-care facility visits [34,35] (Table 2).

### 3.3.2. Lower respiratory tract infection

ETS exposure is reported as an important risk factor for childhood LRTI in several studies [2]. An updated systematic review found smoking by either parent (OR 1.22, 95% CI 1.10–1.35), both parents (OR 1.62, 95% CI 1.38–1.89), or a household member (OR 1.54, 95% CI 1.40–1.69) significantly increased the risk of LRTI [36] (Table 3).

In children hospitalized for community-acquired pneumonia, household ETS exposure was found to increase length of hospital stay and severity of pneumonia, particularly with more than two smokers in a household [37]. In a Canadian study, ETS exposure was also associated with severe LRTI in the first 2 years of life, predisposing to further respiratory morbidity in preschool years [38]. Other studies, from LMICs have also shown this association [39–41]. A high incidence of pneumonia (0.27 episodes per child-year (95% CI 0.23–0.32)) was reported in infants in the Drakenstein Child Health study, an African birth cohort study; maternal smoking was strongly associated with pneumonia (OR 2.36, 95% CI 1.45–3.82) [39]. Studies from Nepal and Indonesia confirm a similar risk [40,41], and in a large questionnaire-based study from Taiwan, prenatal ETS exposure or maternal smoking were significant risk factors for infantile pneumonia [42]. A Vietnamese study

Table 2. ETS exposure and URTI.

| First author and year of publication | Type and length of study | Sample size | Country and setting | Age of participants | Measurement of ETS exposure | Findings |
|---|---|---|---|---|---|---|
| Csákánya [31] | Cross-sectional, retrospective survey; 24 months | 412 | Hungary; pediatric hospital | 6 months to 18 years | Caregiver-reported ETS exposure | ETS exposure doubled risk of recurrent acute otitis media (OR 2.03, 95% CI 0.99–4.14), increased conductive hearing loss, and need for surgery |
| Jones [32] | Systematic review and meta-analysis | 61 studies | | | | Maternal smoking increased the risk of middle ear disease surgery (OR 1.86, 95% CI 1.31–2.63) |
| Straight [33] | Retrospective case-control study; 39 months | 497 | USA; hospital records | <15 years | Documented ETS exposure from household contacts | Exposure to ETS more common in children undergoing tonsillectomy (OR 2.49, 95% CI 1.5–4.11) |
| Spangler [34] | Cross-sectional survey | 208 | Hungary; pediatric hospital | 6 months to 18 years | Caregiver-reported ETS exposure | Limiting ETS exposure resulted in fewer URTI symptoms, health-care facility visits and adenoidectomy procedures (OR 3.2, 95% CI 1.43–6.38) |

ETS: environmental tobacco smoke; OR: odds ratio; URTI: upper respiratory tract infection.

Table 3. ETS exposure and LRTI.

| First author and year of publication | Type and length of study | Sample size | Country and setting | Age of participants | Measurement of ETS exposure | Findings |
|---|---|---|---|---|---|---|
| Jones [36] | Systematic review and meta-analysis | 60 studies | | <2 years | | Postnatal maternal smoking strongly associated with bronchiolitis (OR 2.51, 95% CI 1.58–3.97). Smoking by either parent (OR 1.22, 95% CI 1.10–1.35), both parents (OR 1.62, 95% CI 1.38–1.89), or household member (OR 1.54, 95% CI 1.40–1.69) increased risk of LRTI |
| Ahn [37] | Prospective surveillance study; 30 months | 2219 | USA; pediatric hospitals | <18 years | Caregiver-reported ETS exposure | ETS exposure increased hospital stay(hazard ratio 0.85, 95% CI 0.75–0.97) and severity of pneumonia, particularlywith >2 household smokers |
| Kovesi [38] | Cross-sectional survey | 388 | Canada; community survey | 3–5 years | Caregiver-reported ETS exposure | ETS exposure associated with severeLRTI in first 2 years (OR = 6.18 forbronchitis, OR = 14.6 for pneumonia); which then predisposed to increasedrespiratory morbidity in preschool years |
| le Roux [39] | Prospective cohort study; 24 months | 697 | South Africa; peri-urban community clinic | <1 year | Self-reported maternal smoking | High incidence of pneumonia – 0.27episodes per child-year (95% CI 0.23–0.32);maternal smoking a significant risk factor(incidence rate ratio 2.36, 95% CI 1.45–3.82) |
| Shibata [40] | Cross-sectional survey and case-control study | 461 | Indonesia; urban community | <12 years | Caregiver-reported indoor air pollution exposure and particle counter measurement | Acute respiratory infections in childhoodassociated with maternal ETS exposure(OR = 2.05; $p = 0.08$) and householdparticulate matter levels |
| Karki [41] | Case-control study; 12 months | 200 | Nepal; hospital | <5 years | Caregiver-reported ETS exposure | An increasing trend between bothparents smoking and childhoodpneumonia (OR 2.21, 95% CI 0.56–8.82) |
| Chen [42] | Prospective cohort survey; 24 months | 21,248 | Taiwan; stratified community survey | <6 months | Caregiver-reported ETS exposure | Prenatal ETS exposure(OR 1.7, 95% CI 1.06–2.69) andmaternal smoking (OR 2.43, 95%CI 1.16–4.72) significant riskfactors for infantile pneumonia |
| Suzuki [43] | Cross-sectional survey | 24,781 | Vietnam; community survey | <5 years | Caregiver-reported ETS exposure | Household ETS exposure (70.5%)associated with hospitaladmissions for pneumonia (OR 1.55, 95% CI 1.25–1.92) |
| Lanari [44] | Longitudinal cohort study; 38 months | 2210 | Italy; neonatology units | Neonates (≥33 weeks gestation) | Caregiver-reported *in utero* smoke (IUS) and ETS exposure | Prenatal ETS exposure increased risk of hospitalization for bronchiolitis (hazard ratio 3.5, 95% CI 1.5–8.1). Postnatal heavy smoking doubled this risk |
| Stevenson [45] | Prospective cohort study; 29 months | 2207 | USA; urban pediatric hospitals | <2 years | Caregiver-reported IUS and ETS exposure | Prenatal and maternal smoking and postnatal ETS increased the risk for ICU admission in children hospitalized for bronchiolitis (OR 1.95, 95% CI 1.13–3.37) |

IUS: *in utero* smoke; ETS: environmental tobacco smoke; LRTI: lower respiratory tract infection; OR: odds ratio; IAP: indoor air pollution.

of almost 25,000 children less than 5 years of age found that household ETS exposure to be independently associated with hospitalization for pneumonia (adjusted OR 1.55, 95% CI 1.25–1.92) [43].

Bronchiolitis is a major cause of respiratory morbidity in young children and while ETS exposure is a recognized risk factor, the source and timing of exposure varies. A systematic review found that postnatal maternal smoking was strongly associated with bronchiolitis (OR 2.51, 95% CI 1.58–3.97) [36]. More recently, prenatal ETS exposure and heavy postnatal maternal smoking were both associated with an increased risk of hospitalization for bronchiolitis in the first year of life; however, postnatal exposure increased the risk by twofold compared to prenatal ETS exposure [44]. Further, both prenatal and postnatal maternal smoking were associated with an increased risk for admission to ICU: OR = 1.51 (95% CI 1.14–2.00) for prenatal and OR = 1.95 (95% CI 1.13–3.37) for postnatal exposure [45].

#### 3.3.3. Pathogen-specific disease

Respiratory Syncytial Virus (RSV) is a leading cause of acute respiratory disease in children and may cause severe disease. ETS has been found to increase the risk of severe RSV disease as measured by hospitalization and hypoxia in both infants and children (adjusted OR 2.2–3.8) [46]. A recent systematic review and meta-analysis identifying risk factors for RSV-associated LRTI in children reported maternal smoking to be one of the most important risk factors (OR 1.36, 95% CI 1.24–1.50) [47] (Table 4).

Severe influenza virus disease has also been associated with ETS exposure, with ETS exposure associated with a 20% increased need for ICU admission and 12% increased risk of intubation compared to children without ETS exposure [48].

Pneumococcal nasopharyngeal carriage has also been associated with smoke exposure in Australian children [49]. However, in a systematic review of the association between ETS exposure and invasive bacterial disease, this association only occurred with meningococcal disease [50]. Another systematic review on the health effects of passive smoking also reported an increased risk for invasive meningococcal disease, pneumococcal carriage, and LRTI in children [51].

Tuberculosis (TB) remains a global health problem with young children particularly vulnerable to developing disease especially those living in LMICs. Studies from high burden TB regions demonstrate an association between ETS exposure and development of TB disease in adults [52,53]. While the effects of tobacco smoking and exposure on TB have been well described in adults, there are fewer studies focusing on children. A systematic review and meta-analysis found that ETS exposure caused an increase in both TB infection (OR 1.9, 95% CI 0.9–2.9) and disease (OR 2.8, 95% CI 0.9–4.8) in children [54].

### 3.4. ETS exposure and chronic lung disease in children

#### 3.4.1. Asthma

Childhood asthma is the commonest noncommunicable disease in children [55]. Findings from the International Study of Asthma and Allergies in Childhood (ISAAC) have confirmed the association between maternal smoking, and symptoms of asthma or rhinoconjuctivitis with an additive risk being paternal smoking [3]. Increasing number of maternal cigarettes smoked was associated with a higher prevalence of asthma symptoms. Further, maternal smoking in the first year of a child's life was associated with a greater risk of all asthma symptoms at 13–14 years, highlighting the impact of early exposure on long-term respiratory outcome [3]. ETS exposure has also been associated with more severe asthma attacks; children with asthma and ETS exposure were twice as likely to be hospitalized for asthma and had more emergency unit visits (OR 1.66, 95% CI 1.02–2.69) than unexposed asthmatics [56]. A 20% increased length of hospital stay was also found in ETS-exposed asthmatic children [57]. ETS exposure also impacts on asthma control with decreased response to inhaled corticosteroids and impaired histone deacetylase-2 function, possibly contributing to steroid resistance in asthmatic children [58]. *In utero* tobacco smoke exposure increased age-related airway hyperresponsiveness and reduced the efficacy of inhaled corticosteroids in asthmatic children [59]. Further, increased passive smoke exposure, as quantified by measuring urine cotinine, was also associated with more severe asthma exacerbations in Iranian children [60]. ETS-exposed children had increased comorbid conditions with significantly higher body mass index percentiles (>75%, OR 1.64, 95% CI 1.22–2.2) and were more likely to have more severe asthma then non-exposed controls [61].

In a recent meta-analysis, comparing antenatal and postnatal smoke exposure on the incidence of asthma and wheeze, children exposed to either antenatal or postnatal tobacco smoke exposure had a 30–80% increased risk of developing wheezing and a 21–85% increased risk of developing asthma [62]. However, the strongest risk for the development of wheezing was in children under 2 years with postnatal tobacco smoke exposure (OR 1.70, 95% CI 1.24–2.35) while the risk of developing asthma was associated with antenatal maternal smoking (OR 1.85, 95% CI 1.35–2.53) [62]. By contrast, in a large population-based prospective cohort study, continued maternal smoking during pregnancy led to increased risk of early and persistent wheezing (OR 1.24, 95% CI 1.01–1.52; OR 1.48, 95% CI 1.13–1.95) and asthma (OR 1.65, 95% CI 1.07–2.55) [63]. Postnatal paternal smoking was however not associated with an increased risk of wheezing [63].

This was confirmed in a recent meta-analysis focusing on smoke exposure and the development of wheezing and asthma in unselected birth cohorts. This analysis found a 36% increased risk of wheezing in early life of infants whose mothers smoked during pregnancy, while no clear exclusive postnatal effect could be demonstrated [64]. While maternal smoking and exposure increase the risk of asthma development, in nonsmoking mothers antenatal maternal ETS exposure also increased the risk of asthma development in their children [65].

#### 3.4.2. Chronic obstructive pulmonary disease

One of the first studies to explore the association between ETS exposure in childhood and the development of COPD in adulthood found an almost twofold increased risk of women developing COPD following childhood ETS exposure. There was also an increased risk of COPD symptoms in men exposed to ETS in childhood compared to those unexposed [66].

Table 4. ETS exposure and pathogen-specific disease.

| First author and year of publication | Type and length of study | Sample size | Country and setting | Age of participants | Measurement of ETS exposure | Findings |
|---|---|---|---|---|---|---|
| DiFranza [46] | Systematic review | 30 studies | | <5 years | | ETS increases risk of severe RSV disease as measured by hospitalization and hypoxia (adjusted OR = 2.2–3.8) |
| Shi [47] | Systematic review and meta-analysis | 20 studies | | <5 years | | Maternal smoking is a significant risk factor for RSV-associated acute LRTI in children (OR 1.36, 95% CI 1.24–1.50) |
| Wilson [48] | Retrospective cohort study; 7 years | 117 | USA; urban pediatric hospital | ≤15 years | Documented ETS exposure from household contacts | Children with an influenza virus infection and ETS exposure have a 20% increased need for ICU admission (OR 4.7, 95% CI 1.4–18.5) and are 12% more likely to be intubated (OR 8.8, 95% CI 0.9–232.4) |
| Mackenzie [49] | Cross-sectional survey | 551 | Australia; rural communities | 2–15 years | Caregiver-reported smoke exposure | Pneumococcal carriage associated with smoke exposure (OR 6.89, 95% CI 1.31–3.73) |
| Lee [50] | Systematic review and meta-analysis | 42 studies | | 1 month–19 years | | Association between ETS exposure and invasive meningococcal disease (OR 2.02, 95% CI 1.52–2.69) |
| Cao [51] | Overview of systematic reviews | 16 reviews | | | | Passive smoking associated with increased risk for invasive meningococcal disease (OR 2.18, 95% CI 1.63–2.92), pneumococcal carriage (OR 1.66, 95% CI 1.19–2.36), and LRTIs in infants (OR 1.42, 95% CI 1.33–1.51) |
| Sridhar [52] | Prospective cohort study | 714 | Turkey; community recruitment | 1 month–16 years | Caregiver-reported ETS exposure | ETS exposure associated with a significant increased risk of acquiring TB infection (OR 1.5, 95% CI 1.09–2.06) |
| du Preez [53] | Cross-sectional study | 196 | South Africa; impoverished urban community | 3–15 years | Caregiver-reported ETS exposure | Dose-response relationship between level of ETS exposure and risk of TB infection. Household member pack years associated with tuberculin skin test ≥15 mm (OR 1.09, 95% CI 1.01–1.17) |
| Jafta [54] | Systematic review and meta-analysis | 8 studies | | ≤15 years | | ETS exposure caused increase in both TB infection (OR 1.9, 95% CI 0.9–2.9) and disease (OR 2.8, 95% CI 0.9–4.8) |

RSV: respiratory syncytial virus; ETS: environmental tobacco smoke; LRTI: lower respiratory tract infection; OR: odds ratio; TB: tuberculosis.

Follow-up of participants from the Tucson Children's Respiratory birth cohort study through first 26 years of life has demonstrated that ETS exposure *in utero* and during early life increases the susceptibility to the harmful effects of active smoking in early adulthood and an accelerated decline in lung function [67].

A number of studies have reported the impact of early-life smoke exposure on the 'genetic programming' that control life-long lung development and aging with consequent susceptibility to obstructive lung diseases [68]. Studies investigating genetic determinants of obstructive lung disease and the effect of early-life smoke exposure on gene expression have found at least three COPD genes whose expression may be influenced by *in utero* tobacco smoke exposure [69,70]. Epigenetic changes may account for such generational effects [71]. Mice models show alterations in DNA methylation and airway hyperreactivity in response to *in utero* ETS [72]. Recent human studies have also found smoke-exposure-specific blood DNA methylation changes present in preschool children, which were comparable to those found at birth [73]. DNA methylation changes following *in utero* tobacco smoke exposure were also found in fetal lung and placental tissue suggesting a fetal origin for chronic diseases in later life [74].

#### 3.4.3. Bronchopulmonary dysplasia

While there are limited data on ETS exposure and bronchopulmonary dysplasia (BPD), the association between antenatal ETS exposure and preterm delivery is well recognized and there is a strong association between preterm delivery and BPD [75]. Gestational exposure of mice to cigarette smoke resulted in alveolar simplification and induction of a BPD-like condition in their offspring. This was mediated by down regulation of nicotinic receptors that in turn regulate other factors (hypoxia-inducible factor-1) involved in apoptosis control and angiogenesis in the developing fetal lung, which may explain the effects of ETS exposure on BPD [76]. In very low birth weight infants, intrauterine smoke exposure was also found to be an independent risk factor for BPD (OR 2.21; 95% CI 1.03–4.76) [77]. More recently, a case-control study looking at the respiratory outcomes of preterm infants with and without BPD exposed to both *in utero* smoking (IUS) and postnatal ETS showed that infants with BPD on home oxygen had the highest exposure to both [78]. Chronic tobacco smoke exposure as assessed by hair nicotine levels was common in children with BPD; relying on caregiver-reported smoke exposure underestimated this by almost 50%. Further, in children who required respiratory support (home oxygen or ventilation), higher log hair nicotine levels were associated with increased hospitalizations and limitation of activities [79].

#### 3.4.4. Cystic fibrosis

The deleterious effects of ETS exposure are likely to be more pronounced in children with chronic respiratory conditions including cystic fibrosis (CF) [80]. One of the few studies to look at the effects of ETS exposure in infants with CF found diminished growth as measured by length and weight/length at 4 and 12 months of age in smoke-exposed CF infants as compared to unexposed CF infants. Exposed CF infants also had increased air trapping (measured on CT scan), bronchodilator responsiveness (4.2-fold increase), and a higher prevalence of methicillin-resistant *S. aureus* and anaerobes on respiratory cultures [81]. *In utero* tobacco smoke exposure was also found to precipitate earlier structural lung disease in young CF children with increased CT scan diagnosed bronchiectasis (1.45 CF-CT score points (95% CI 0.35–2.56)) and air-trapping (1.39 CF-CT score points (95% CI 0.13–2.63)) as well as a shorter time to first infection. ETS-exposed CF children also had decreased forced expiratory volumes (FEV1s) at 6 years of age. These effects were strongest for maternal smoking; paternal smoking during gestation had a similar but milder effect [82]. The significant effects of maternal smoking on lower lung function in young CF patients warrant smoking cessation strategies targeting parents of this vulnerable group of children. Telephonic counseling and trained nurse-led interventions were found to be effective in enabling parents of children with CF to reduce or quit smoking in 12.5% of participants [83].

Both *in vitro* and *in vivo* studies have shown that cigarette smoke decreases the expression of cystic fibrosis transmembrane regulator (CFTR) gene, protein, and function contributing to the pathophysiology of existing CFTR deficiencies [84].

### 3.5. ETS exposure and lung function

The detrimental effects of ETS exposure on lung function have been well documented [11,85]. ETS exposure in children is associated with lower FEV1 values compared to matched unexposed children [86]. Antenatal maternal smoking has been associated with a reduction in early-life lung function suggesting that *in utero* smoke exposure may affect airway development and lung elasticity [87]. Maternal smoking during pregnancy and in early life is the most significant source of exposure affecting infant lung function [85].

Changes in infant lung function due to antenatal or early postnatal ETS can be detected very early in infants. In a South African birth cohort, the Drakenstein child health study, maternal smoking in pregnancy or postnatally was associated with a 19% lower compliance in exposed compared to unexposed infants at 6 weeks of age as measured by the forced oscillation technique [88]. In a large Chinese study of ETS exposure in preschool children, ETS exposure, as quantified by urine cotinine levels, was a significant risk factor for lung function impairment measured by spirometry [89].

Longitudinal cohort studies have shown that lung function trajectories are set in early life with a developmental window of susceptibility, which can be disrupted by both infectious and environmental exposures [10,90,91]. Maternal smoking reduces infant lung function which is associated with impaired lung volume in adulthood (both for FEV1 and forced vital capacity (FVC)), independent of smoking in adulthood, compounding the effect of smoking to reduce airflow limitation and increasing the risk of COPD [92]. Parental smoking was also responsible for a rapid decline in FEV1:FVC ratio in young adulthood even more (3%) than that of smokers not exposed to parental smoke [67]. The majority of studies focused on airflow limitation (FEV1 and FEV1:FVC) as a marker of ETS-exposure-related airway obstruction [92].

Even low levels of ETS exposure have been shown to affect lung function in preschool asthmatic children [93]. Further, ETS may increase airway inflammation in young children. ETS-exposed steroid naive preschool wheezers were found to have higher levels of exhaled nitric oxide (FeNO) and higher respiratory resistance, as measured by impulse oscillometary, compared to unexposed children [94].

### 3.6. The additive effect of indoor air pollution (IAP) and ETS exposure on lung health in children

The use of alternate fuel sources for cooking and heating is an important contributor to IAP particularly in LMIC [95]. The multiplicative effects of air pollution, from both indoor and outdoor sources and ETS exposures are important particularly as these countries carry the highest burden of child respiratory diseases [96]. ETS combined with other IAP, particularly antenatal exposure, affects lung growth that persists through adulthood [97]. There are numerous by-products of combustion; particulate matter (PM), carbon dioxide ($CO_2$), sulfur dioxide ($SO_2$), nitrogen dioxide ($NO_2$), and volatile organic compounds (VOC) are the most commonly assessed by-products of ETS and other combustions [95,98]. Recently it has been shown that sub- and nano-micron particles contribute to adverse effect of PM on the lung health of children [99]. A South African birth cohort study that evaluated the home environment and measured IAP in a peri-urban setting reported high passive tobacco smoke exposure (44%) and benzene (VOC) levels (median 5.6 μg/m$^3$ (IQR 2.6–17.1)) exceeding acceptable ambient standards. Significant associations between fossil fuel use and increased benzene (OR 3.4 (95% CI 2.1–5.4)), carbon monoxide (OR 2.9 (95% CI 1.7–5.0)), and $NO_2$ (OR 18.6 (95% CI 3.9–88.9)) levels were also found [100]. In an Italian study that examined the association between household cohabitants' smoking behaviors and urinary cotinine and benzene (a tobacco-related carcinogen) levels in children contacts found the levels of urinary benzene paralleled that of urine cotinine and were related to smoking behaviors such as smoking indoors versus outside the home [101]. Adverse respiratory outcomes are associated with a number of combustion by-products. A Chinese study of over 3000 preschool children showed that gestational and early life exposure to $NO_2$ from ambient air pollution was associated with asthma (OR 1.77; 95% CI 1.29–2.43) or allergic rhinitis (OR 1.67; 95% CI: 1.07–2.61) [102]. Indoor exposure to PM (PM 2.5) above levels of 100 μg/m$^3$ was independently associated with younger age of first LRTI (12% decrease (95% CI 2–21) in age) in Bangladeshi children [103]. Another African study assessing the effects of pollution from ETS, cooking, and heating fuels and outdoor traffic found an increased risk of wheezing from both indoor and outdoor air pollution sources. ETS exposure at home was associated with current wheeze (OR 1.36 95% CI: 1.06–1.77); use of gas for residential heating was associated with wheeze ever (OR 1.68 95% CI: 1.23–2.28) or current wheeze (OR 1.61 95% CI: 1.08–2.39); paraffin most frequently used for residential heating was associated with current severe wheeze (OR 1.85 95% CI: 1.04–3.28) [104]. The risk of LRTI mortality in LMIC is also increased by environmental exposures including ETS (OR 1.52, 95% CI 1.20–1.93) or IAP (OR 3.02, 95% CI 2.11–4.31) [105].

### 3.7. Prevention of exposure to ETS

The long-term burden of ETS exposure on respiratory morbidity and mortality is substantial. Public health programs that highlight not only the acute effects of ETS but also the long-term consequences on child health are needed. *In utero* and early-life ETS exposure remains an important risk factor for respiratory disease in young children with consequent long-term effects on respiratory health. Increasing evidence indicates that the roots of adult COPD lie in antenatal and early life exposures including ETS [106]. The generational effect of smoke exposure is important with evidence emerging of maternal smoking in pregnancy impacting on subsequent risk of asthma in grandchildren regardless of the mother's smoking status or of long-term COPD [107].

Global attempts to curb the tobacco epidemic include the World Health Organization's tobacco-free initiative, aimed at implementing smoke-free environments and legislation limiting tobacco advertising, particularly to prevent initiation of tobacco and nicotine addiction among youth [5,24,108]. While these measures aim to control tobacco smoke exposure in public places, household exposure remains problematic. Public health interventions require measures that target the tobacco industry through taxes on cigarette sales and warnings on cigarette packets but should also include local community involvement to ensure culturally acceptable interventions particularly in LMIC [25].

Key preventative strategies to protect children from tobacco smoke and nicotine exposure include a comprehensive ban on tobacco smoke, ban of smoking in multi-house units, and the ban on the use of nicotine delivery systems (e-cigarettes) [106].

It is essential that counselling and smoking cessation programs are offered to parents to address parental dependency and to reduce the impact of early life exposures' preconception, to promote child health, and prevent long-term sequelae [106,109]. Effective smoking cessation programs targeting vulnerable groups, especially women, pregnant women, and adolescents, particularly in LMICs are required to stem the smoking pandemic. A combination of motivational counselling, therapy, and pharmacological therapy is usually required. Interesting but yet unproven interventions might be using pharmacotherapy (bupropion and varenicline) and nicotine replacement therapy during pregnancy to reduce intra-uterine acquired lung disease [110,111].

However, the safety of pharmacological treatments in pregnant women is not established and alternative strategies including an individualized plan may be necessary [112,113]. Further research is required in these preventative strategies in pregnant mothers.

In LMICs, ETS and IAP are often found in the same households necessitating interventions which would benefit both exposures. Interventions that have been implemented to reduce household ETS or IAP include a combination of counselling, the installation of clean chimneys, and improved ventilation in the homes of smokers. A systematic

review and meta-analysis of the effectiveness of interventions to reduce ETS in homes as assessed by reduction in nicotine and PM levels found that although some benefits were documented, at follow-up, exposure was still present [114]. ETS exposure, as measured by cotinine levels, was consistently higher in children who lived in multiunit or attached housing compared to children living in detached homes, even if there were no smokers within the home [115]. Regulations to enforce smoke-free multiunit housing is a feasible intervention, particularly for new developments [114,116] that should be considered in LMIC regions, especially where government-subsidized housing may be provided. However, in LMIC, these interventions might not always be possible.

A novel strategy may be vitamin C supplementation to pregnant smokers who are unable to terminate smoking. A randomized double-blind trial showed that supplemental vitamin C improved newborn pulmonary function and decreased wheezing in the first year of life in infants of mothers who smoked [117]. While prevention or avoidance of smoking should be the optimal strategy in pregnancy and postnatally, this intervention needs to be further studied in pregnant mothers who are unable to refrain from smoking in pregnancy.

Electronic nicotine delivery systems (e-cigarettes) were designed to deliver nicotine without tobacco combustion and are used in smoke cessation; however, until recently they were unregulated by the US FDA [118,119]. While e-cigarettes are marketed as a safer alternative to tobacco smoking, they contain nicotine and flavorants and the long-term effects are unknown. Nicotine is a highly active chemical that affects many bodily cells and pathways and has both activating and desensitizing effects on receptors with a high risk of lethal poisoning when accidentally consumed orally by young children [120]. The attractive flavoring and active marketing of e-cigarettes also makes them appealing to the youth. Reducing tobacco use through campaigns that depict cigarette smoking as undesirable and harmful has been implemented; however, the promotion of e-cigarettes threatens this with the risk of increasing nicotine addiction [120]. A recent systematic review also found no strong evidence for e-cigarettes as a smoking cessation tool [121]. Urgent legislation and regulation of e-cigarettes is required to prevent another form of nicotine addiction targeted at vulnerable groups [122].

## 4. Conclusion

Children and adolescents remain the most vulnerable groups for both ETS exposure and initiation of cigarette smoking. Parental and family education to provide a smoke-free environment is vital to address this challenge [123]. Failure to do so will allow considerable morbidity of exposure to tobacco smoke in children and adults to continue.

## 5. Expert commentary

Childhood ETS exposure is an often under-recognized and reported problem particularly in LMIC where the burden of respiratory diseases is highest. ETS is associated with upper and lower respiratory disease including infections, wheezing, and chronic lung disease. Exposure antenatally may represent a particularly important period that affects lung development, with intergenerational effects. The increase in the incidence of women smokers in LMIC is of concern. Effective intervention strategies to combat the increasing exposure to ETS in LMIC are urgently needed, particularly for vulnerable populations such as adolescents and women of child-bearing age. However, tobacco control measures may be influenced by lobbyists and tobacco companies making regulation or legislation required to effectively implement nation-wide smoking cessation interventions difficult.

Pneumonia remains the leading cause of childhood mortality outside the neonatal period, in LMIC. ETS exposure is strongly associated with an increased risk for pneumonia and of severe disease. Further antenatal ETS is associated with childhood wheezing illness, asthma, more severe asthma attacks, and reduced lung function. With lung health trajectories set in this critical development period, interventions that target smoking cessation need to be broadened to include reducing not just maternal smoking but also ETS exposure from household contacts as differentiating prenatal from postnatal exposures as risk factors is difficult.

Interventions to reduce tobacco smoke pollution within homes have shown that individual-level programs are not effective enough to reduce contamination. Environmental risk factors from both ETS and other IAP exposures are potentially modifiable. However, addressing these requires both population-wide smoking cessation programs, as well as interventions to improve ventilation and decrease IAP, which may be difficult in LMIC where poverty results in poor infrastructure and high levels of air pollution within homes. In addition to the well-known exacerbating effect of poor ventilation on primary and second-hand smoking, impaired ventilation is a key factor in third-hand smoke exposure. Third-hand smoke describes pollutants that remain after the initial smoking event and react with other compounds to create secondary pollutants. These pollutants, such as carcinogenic nitrosamines, increase the risk of respiratory and non-respiratory diseases.

Electronic cigarettes provide a new risk for potential respiratory complications. This inconsistently regulated industry poses a hazard both from the often unknown constituents of the inhaled aerosol to the long-term complications associated with the use of such devices. The regulation of electronic cigarettes varies widely across different countries – from those having no specific regulation, to those who legislate it under pharmaceutical products, through to countries in which e-cigarettes are banned. While electronic cigarettes eliminate the by-products of tobacco combustion, the nicotine inhaled may still lead to significant problems. Currently, the effects of nicotine on the developing lung have mainly been studied in animal models with deleterious effects. Although passive vapor is considered safer that passive tobacco smoke exposure, the specific effects and safety levels are still being investigated. Systematic reviews on e-cigarettes have identified that some of the studies have methodological problems and/or are written by authors with conflicts of interest. Therefore, the effects of nicotine

exposure on human developing lungs is a research field that requires further exploration, as the potential harm from this may be substantial.

The early-life origins of adult chronic respiratory diseases are also increasingly recognized; however, the evidence from LMIC, particularly African countries, is lacking. Longitudinal studies, including birth cohort studies from these regions [23,88], may provide further insights. Collaboration between pediatric and adult health-care providers can only enhance patient care by early identification and monitoring of at-risk individuals.

Certain interventions, such as antenatal vitamin C supplementation, parental enforcement of smoke-free environments, and nurse-led or telephonic support in smoking cessation, have shown positive results in reducing respiratory disease in children. These relatively simple, cost-effective interventions should therefore be widely implemented, with ongoing monitoring to confirm effectiveness.

The body of evidence confirming the association between ETS exposure and childhood respiratory disease is substantial and unequivocal. Further research has the potential to identify specific underlying factors that contribute to ETS and IAP, as well as individual risk factors in children. The overall goal would be to develop targeted, cost-effective measures which would result in a tangible impact on both childhood and chronic adult respiratory diseases.

## 6. Five-year view

Effective anti-tobacco campaigns have to some extent reduce d smoking prevalence in high-income countries leaving LMIC more vulnerable to the tobacco industry. The consequent health effects need further exploration particularly as LMIC tend to face a multitude of environmental challenges.

The long-term effects of electronic cigarettes both from use and exposure will become more evident. This may contribute to better regulation of both the manufacture and distribution of these products, and will hopefully result in more consistent legislation across countries.

With the move toward personalized medicine, epigenetic factors may play a role in identifying tailored interventions for specific groups. Furthermore, the Genetic Test to Stop Smoking (GeTSS) trial has been developed to assess if the presence of a gene associated with lung cancer may be a motivating factor in smoking cessation. In the future, genetic factors are likely to play a role both in modifying risk factors and developing novel treatment approaches to ETS-related respiratory disease.

Further research into these factors may enhance our understanding of the association between ETS exposure and childhood respiratory disease.

## Key issues

- Global estimates of childhood environmental tobacco smoke (ETS) exposure are high (between 40–70%).
- Early life ETS exposure affects both lung development and subsequent respiratory disease, with the origins of certain adult chronic respiratory conditions beginning in childhood.
- Lifelong lung function trajectories are influenced by both prenatal and postnatal ETS exposures.
- Prevention of ETS exposure in childhood requires effective interventions to improve child and consequent adult respiratory health. Declaration of Interest

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