

Review article

Passive smoking as a risk factor for development of obstructive respiratory disease and allergic sensitization

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In the Western industrialized countries, the number of cigarette-smoking women has steadily increased during the last decades. The number of heavy smokers has also become greater among pregnant women and mothers with infants and young children. As Table 1 shows, several studies have found that a very high proportion of unselected children are exposed daily to tobacco smoke at home. Thus, in Denmark, a recent study (31) found that 42% of mothers of infants smoked cigarettes daily. A total of 58% of the infants were exposed daily to tobacco smoke at home, 24% in day care outside home (day-care centers or private care-givers), and 66% of all the infants were exposed daily to tobacco smoke at home, in day care outside home, or both. Moreover, 42% of the private care-givers, working in their private homes, smoked cigarettes every day – also during daytime.

Previously, information concerning the extent of exposure to tobacco smoke was based only on personal or parental reports. Now it is possible to measure the nicotine metabolite, cotinine, in urine, serum, and saliva, thus obtaining a more objective measure of the exposure to tobacco smoke (15, 18, 30, 37, 77). In children, the level of urine cotinine has been shown to correlate with the number of cigarettes smoked by parents – especially by mothers (15, 18,

Table 1. Exposure of children to passive tobacco smoking

	≥ 1	M	F	M+F	None
Parental smoking (%)					
Ware et al. 1984 (73) n=10, 106, 6–16 yr	68	43	59		
Burchfiel et al. 1986 (8) n=3482, 0–19 yr	62	3*	27*	32	16
Magnusson 1986 (45) n=186, 0–18 mo	43	22	37	16	
Neuspiel et al. 1989 (52) n=9670, 0–10 yr		50	56		
Halken et al. 1991 (31) n=276, 0–18 mo	58	42	41	39	34
Wright et al. 1991 (79) n=847, 10–12 mo	39	26	30	16	61
Halken et al. 1992 (32) n=108 HR infants, 0–18 mo	45	25	38		44

M=Mother; F=Father; * M/F only; HR=high-risk infants – defined as having severe single atopic predisposition combined with cord-blood IgE≥0.05 kU/l or biparental atopic predisposition.

30, 37, 77). Cotinine and nicotine can also be measured in breast milk, and concentrations of nicotine increased 10-fold when the mother smoked just before nursing (15). In a recent study (68), cotinine

excretion in urine from non-breast-fed infants of smoking mothers (nicotine exposure via passive smoking only) was even higher than that of adult passive smokers. The urinary cotinine excretion in breast-fed infants of smoking mothers was at the same level as that of the mothers themselves.

The influence of passive smoking on acute and chronic respiratory disease (including asthma) has been reviewed previously by Fielding & Phenow (24) and Landau (41). These studies have varied greatly in study design and subject selection. Definitions have been ambiguous (or have not been stated at all), and diagnostic criteria have been vague. Moreover, the literature on the topic is characterized by inconsistent nomenclature and geographic differences. In addition to "wheezy bronchitis", other names for the disorder such as "obstructive bronchitis", "asthmatic bronchitis" and "recurrent wheezing" are also used. In infants and young children, it may be difficult to distinguish between recurrent wheezy bronchitis caused by infections and asthma; moreover, a syndrome called "wheezy bronchitis" in one study might be called "asthma" in another study.

Wheezy bronchitis occurs frequently in infants and young children, and it is often caused by an infection. It is characterized by wheezy respiration as a result of the small diameters of the bronchial system, edema of the mucous membranes, and bronchoconstriction. Recent studies have found a correlation between recurrent wheezy bronchitis in the first years of life and asthma later in childhood (26, 71, 75). These studies have shown that 30–50% of infants with recurrent wheezy bronchitis during their first years of life developed proven asthma later in childhood. Some authors contend that children suffering from recurrent wheezy bronchitis must be considered to be suffering from asthma until proven otherwise (21).

In this review, we will update the findings on a possible correlation between passive smoking and respiratory diseases including asthma. Moreover, we will review what is known about the influence of passive smoking on the development of allergic disease (sensitization to specific allergens, i.e., IgE-mediated reactions) and about immunologic reactions in children pre- or postnatally. It is important to recognize that a possible correlation between passive smoking and asthma does not necessarily imply a demonstrable allergic mechanism, but may be the result of a directly irritative, inflammatory reaction in the respiratory tract.

Wheezy bronchitis and asthma

Correlation between passive smoking and wheezy bronchitis/asthma

Most recent studies of the influence of passive smoking on respiratory health have shown a correlation between passive smoking and wheezy bronchitis and asthma in children. Only one study did not find a correlation between passive smoking and later persistent asthma (75). However, this study covered only a small, selected population ($n = 101$), data concerning exposure to tobacco smoke during the first years of life were gathered retrospectively, and the results were not adjusted for other risk factors (e.g., atopic predisposition) and confounding factors.

Unselected children

As Table 2 shows, several large cross-sectional studies of unselected children have found a significantly increased occurrence of asthma when at least one of the parents smoked cigarettes (1, 8, 12, 16, 25, 28, 29, 74).

Table 2. Passive tobacco smoking and wheezing/asthma

Study	<i>n</i>	Age (years)	Tobacco smoking	Risk of asthma (<i>P</i> /95% CI)
Cross-sectional studies – unselected children				
Gortmarker et al. 1982 (29)	3072	0–17	Mother	↑ RR 1.53–1.83; $P < 0.05$
Burchfiel et al. 1986 (8)	3482	0–19	≥ One parent	↑ OR 2.16; $P < 0.05$
Andrae et al. 1988 (1)	5301	0.5–16	Parents	↑ RR 2.5 (1.5–3.4)
Weitzman et al. 1990 (74)	4331	0–15	Mother	↑ OR 2.1; $P = 0.001$
			≥ 0.5 pack/day	
Chinn & Rona 1991 (12)	5002	5–11	Parents	↑ OR 1.35; $P < 0.05^*$
			> 20 cigarettes/day	
Goren & Hellman 1991 (28)	8259	7–11	Mother	↑ RR 1.24; $P < 0.05$
			Father	↑ RR 1.28; $P < 0.05^{**}$
Dekker et al. 1991 (16)	14495	5–8	One household	↑ OR 1.39 (1.17–1.65)
			Two households	↑ OR 1.72 (1.44–2.05)
Forastière et al. 1992 (25)	2929	7–11	Mother	↑ OR 1.7 (1.04–2.7)
			Two parents	↑ OR 1.5 (1.04–2.2)

* Persistent wheeze; ** wheeze without cold; OD = odds ratio; RR = relative risk; CI = confidence interval; ↑ = increased risk.

Prospective cohort studies (Table 3) of unselected children followed from birth found a significantly increased occurrence of wheezy bronchitis (2, 3, 6, 31, 52, 60, 72, 79) and asthma in children exposed to tobacco smoke at home. A prospective study of 276 unselected Danish infants (31) revealed that at least two episodes of wheezing before the age of 18 months were diagnosed in 25% of infants exposed to tobacco smoke every day at home, in day care, or both, and in 30% of children whose mothers smoked. The corresponding figure for infants who were not exposed to tobacco smoke was 15% ($P < 0.05\%$). A UK prospective study of 9670 children (52), followed from birth to the age of 10 years, found a 14% increase in childhood wheezy bronchitis/asthma when mothers smoked at least four cigarettes per day, and a 49% increase when mothers smoked more than 14 cigarettes per day. Another cohort study (49) of 153 children with or without a history of bronchiolitis also showed that maternal smoking was a powerful predictor of wheezing at 13 years with an odds ratio (OR) of 2.67 ($P < 0.01$) – the risk being higher in boys.

A recent study of 786 children followed prospectively from 2 to 12 years of age (47) found a significantly increased risk of developing asthma when the mother smoked at least 10 cigarettes per day and also had a low social status (fewer than 12 years of education). Some studies have shown that low social status correlates with an increased exposure to tobacco smoke at home as well as an increased occurrence of wheezy bronchitis (4, 31) and asthma (2, 43). One recent cohort study (2, 3) of 1174 infants followed from birth to 2 years of age used logistic regression analysis to adjust for confounding variables (maternal asthma, social class, bottle/breast-feeding, sex, etc.). It was found that maternal smoking significantly increased the prevalence of asthma when defined as three or more separate episodes of wheezing.

In most studies, maternal smoking seems to be especially important and correlates with an increased risk of developing wheezy bronchitis (6, 31, 79) and asthma (2, 8, 29, 47, 52, 74). Several studies do not show the same significant effect of paternal smoking alone (2, 47, 52, 79). Several studies found a positive correlation between the degree of passive smoking (number of cigarettes per day and number of smokers) and diagnosed asthma (8, 52, 74) and wheezy bronchitis (6, 79). The same correlation was found between the degree of exposure to tobacco smoke and respiratory infection (60, 72).

Children with atopic predisposition

In prospective follow-up studies of children with atopic predisposition (Table 4), a significant correlation was found between exposure to tobacco smoke and wheezing/persistent wheezy bronchitis. Atopic predisposition is defined as having atopic first-degree relatives (10, 14); biparental or severe single atopic predisposition, the latter combined with cord-blood IgE ≥ 0.5 kU/l (32); or wheezing children under 2 years of age combined with previous atopic disease, positive skin prick test, or atopic first-degree relatives (27). One study of 80 atopic children with wheezy bronchitis (27) showed a significantly increased risk (relative risk 2) of developing persistent wheezy bronchitis among passive smokers after 4 years. Furthermore, a four- to fivefold increased risk of having recurrent respiratory infections was found in the same group.

Children with atopic disease – asthma

A prospective study of 94 Canadian asthmatic children aged 7–17 years found significantly more asthma symptoms in those exposed to maternal tobacco smoking (49). Likewise, a US study of asthmatic children showed significantly more acute

Table 3. Passive tobacco smoking and wheezing/asthma

Study	n	Follow-up (years)	Symptoms	Tobacco smoking	Risk of RW OR/% (95% CI/P)
Prospective birth cohort studies – unselected children					
Rantakallio 1978 (60)	12 068	5	RW	Mother	↑ RR Br 4.7 (CI?)
Bisgaard et al. 1987 (6)	5953	1	Wh	Mother ≥ 3 cigarettes/day	↑ OR 2.7 (1.7–4.0)
Taylor & Wadsworth 1987 (72)	12 743	5	Br	Mother	↑ 20.3% $P < 0.01$
				None	14.1%
				Father	→
Neuspiel et al. 1989 (52)	9670	10	A	Mother	↑ RR 1.44 (1.24–1.68)
Halken et al. 1991 (31)	276	1.5	RW	Mother daily	↑ OR 2.6 (1.4–4.8)
					↑ OR 2.4 (1.2–4.9)
Wright et al. 1991 (79)	847	1	Wh	Mother > 20 cigarettes/day	↑ $P < 0.05$
Arshad & Hide 1992 (2)	1167	1	A	Mother	↑ OR 2.3 (1.34–3.92)
Arshad et al. 1993 (3)	1174	2	A	Mother	↑ OR 2.2 (1.5–3.4)

RW=recurrent wheezing $\geq$ twice; Wh=wheeze $\geq$ once; WB=wheezy bronchitis; A=asthma; Br=bronchitis.

Table 4. Passive tobacco smoking and wheezing

Study	n	Age (yr)		Symptoms	Smoking	Risk of RW
		Inclusion	Follow-up			
Prospective studies in children with atopic predisposition						
Cogswell et al. 1987 (13)	73 ^a	0	5	Wheeze ≥ x 1	Parental No parental	62%* 37%
Geller-Bernstein et al. 1987 (27)	80 ^b	<2	4	Persistent wheeze	Parental No parental	42%** 21%
Burr et al. 1989 (10)	483 ^c	0	1	Wheeze	Mother None	47%* 26%
Halken et al. 1992 (32)	54 ^c	0	1.5	Wheeze ≥ x 2	Daily Mother None	OR= 1.61 (1.03–2.52) 52%* 57% 17%

^a At least one atopic parent.

^b Atopic wheezing means wheezing plus at least two of following: 1) eczema/allergic rhinitis, 2) positive skin prick test, and 3) atopic first-degree relatives.

^c Severe single (first-degree relatives) atopic predisposition combined with cord-blood IgE $\geq$ 0.5 kU/l or biparental atopic predisposition.

* $P < 0.05$; ** $P < 0.01$.

asthma symptoms and more visits to emergency departments among passive smokers (20). Another recent retrospective study of 199 children with asthma (aged 8 months to 13 years) found that acute exacerbations of asthma increased with exposure to tobacco smoke, whether such exposure was reported by a parent or identified by cotinine level (11). In a longitudinal US study with a 5-year follow-up to the age of 13 years (48), a significantly increased frequency of persistent asthma was found among those exposed to maternal smoking (relative risk 2.7; $P < 0.01$). In two case-control studies (18, 77), maternal smoking was significantly more frequent among children with asthma than controls (OR = 2.0; 95% CI 1.1–3.4 and relative risk (RR) = 2.6; 95% CI 1.2–5.3). Another recent case-control study (17) found high levels of cotinine concentrations in saliva in children under 2 years of age. The geometric mean of cotinine determinations was significantly higher for wheezing patients in this age group than controls (9.8 and 4.3 ng/ml, respectively; $P < 0.05$). Moreover, significantly more hospital admissions and use of asthma medication were found among children exposed to tobacco smoke at home (74).

In children with past or present atopic dermatitis (50), asthma was found significantly more frequently in cases where the mother smoked cigarettes (79% and 52%). A recent prospective study (51) of 807 nonsmoking asthmatic children (1–17 years of age) found an improvement in adjusted measures of asthma severity (asthma scores 7.5 and 6.5; $P < 0.05$) and improved lung function (FEV₁) because of less exposure to tobacco smoke from parents. This study showed that although parents did not stop smoking when advised to do so, they smoked fewer cigarettes when in the house, and considerably fewer cigarettes when in the same room as their child.

The literature presents convincing evidence that exposure to tobacco smoke increases the risk for development of wheezy bronchitis and asthma in unselected children as well as in children with atopic predisposition. In addition to increased morbidity, increased need for medical treatment and increased use of asthma medication are found in asthmatic children who are exposed to tobacco smoking every day.

Respiratory tract infections

Viral infection might be an important factor in the development of obstructive respiratory disease (17); furthermore, respiratory tract infections often elicit or worsen asthma symptoms in asthma patients. The correlation between passive smoking and respiratory infections has been reviewed thoroughly by Fielding & Phenow (24). Several previous studies have found a consistent effect of parental smoking on upper and lower respiratory tract infections in children (tracheitis/bronchitis and pneumonia) (14, 22, 23, 34, 42, 58, 60, 61, 72). No information has been recorded on potential coexisting asthma symptoms. However, it is well known that asthmatic patients often have recurrent respiratory infections, and that some virus infections are often followed by asthma symptoms.

Exposure to parental smoking also significantly increases the risk of middle-ear effusions and related infections in young children (7, 19, 36, 39, 59, 65, 69). The occurrence of adenoid vegetations and adenotomia is up to four times more frequent among children exposed to tobacco smoke at home than children not exposed to tobacco smoke (65). A recent study (19) documented the exposure by measuring urine cotinine. It found that children with cotinine

values ≥ 2.5 ng/ml suffered new episodes of otitis media with effusion during the first 3 years of life at a rate 38% higher than in children showing lower values. Moreover, the duration of episodes of otitis media with effusion was significantly longer among passive smokers than in children not exposed to cigarette smoke.

Some studies found a correlation between passive smoking and an increased frequency of respiratory infections only during the first 1–2 years of life (14, 23), whereas others found a correlation up to the age of 14 years (61). In conclusion, there seems to be a positive correlation between passive smoking and an increased frequency of respiratory infections and middle-ear effusions in children. The risk seems to be greatest if the child's mother is a cigarette smoker.

Passive smoking and development of allergic sensitization/allergic disease

Prenatal exposure to tobacco smoking

Two previous retrospective studies found a correlation between maternal smoking during pregnancy and increased levels of the immunoglobulins IgG3 (46), IgE, and IgD (45) in cord blood. Also retrospectively, an increased occurrence of atopic symptoms at 18 months of age was found among children exposed to maternal smoking *in utero* (45). Recent prospective studies (54, 56) have not confirmed any correlation between maternal smoking during pregnancy and increased cord-blood IgE (54, 56) or increased cord-blood IgD (56). In the two latter studies, maternal smoking was verified by measuring cotinine in urine and cord blood.

By bronchial histamine provocation, a recent Australian study (80) found higher bronchial hyperreactivity in infants aged 2–10 weeks (mean 4.5 weeks) exposed to passive smoking at home than infants not exposed. Another recent study (33) found maternal smoking during pregnancy to be associated with a significant reduction in forced-expiratory-flow rates (helium-dilution measurement of functional residual capacity, followed by partial expiratory-flow-volume maneuvers) in young infants – both when the data were unadjusted and after controlling for infant size, age, sex, and passive smoking between birth and time of testing. The authors suggest a possible prenatal effect as well as a postnatal effect of passive smoking.

Postnatal exposure to tobacco smoking

Two studies (38, 64) showed a correlation between exposure to tobacco smoke and increased total serum IgE, while another study (57) did not confirm

this finding, finding instead a correlation between passive smoking and total serum IgD. In one of the former studies (64), a significantly increased occurrence of eosinophilia in blood, increased total IgE, and increased bronchial and skin-prick-test reactivity were found in sons of smokers. As Table 5 shows, four studies (1, 63, 76, 78) found a correlation between exposure to tobacco smoke and allergic sensitization in children.

In one of these studies (63), skin prick tests were, at a significant level, more frequently positive, and the reactions were significantly greater in boys exposed to parental tobacco smoking (63). In contrast to this, a German cross-sectional study (40) of 1470 6–8-year-old children showed that maternal smoking habits after birth did not influence the result of skin prick tests with common aeroallergens. However, the information on parental smoking habits and other risk factors was collected retrospectively by a questionnaire at the age of 6–8 years. A Swedish case-control study (53) found no correlation between exposure to tobacco smoking and a positive skin prick test; it found only a correlation between damp housing and sensitization to house-dust mite. In this study, the children's ages ranged from 3 to

Table 5. Passive tobacco smoking and sensitization

Study	Patients (age range)	Sensitization
Correlation with parental smoking		
Wittig et al. 1978 (78)	2190 unselected	↑ SPT pollen ↑ SPT lactalbumin Earlier debut AA, AR
Andrae et al. 1988 (1)	5301 unselected (3–17 yr)	↑ BHR ↑ AA (↑↑ if also damp home)
Ronchetti et al. 1992 (63)	166 unselected (13 yr)	↑ SPT index in boys (aeroallergens)
Wickman et al.* 1992 (76)	115 SPT aeroallergens 54 controls (3–17 yr)	↑ SPT HDM** ↑↑ if also damp home → SPT others
No correlation with parental smoking		
Nordvall et al.* 1988 (53)	60 HDM sensitized 60 controls 3–17 yr	→ SPT HDM
Kuehr et al. 1992 (40)	1470 unselected 6–8 yr	→ SPT aeroallergens

* Case control study; ** environmental tobacco smoke exposure 0–2 yr.

SPT: skin prick test; HDM: house-dust mite; AA: allergic asthma; AR: allergic rhinitis; BHR: bronchial hyperreactivity.

17 years, but no information was provided on the age at which the child was exposed to tobacco smoke, or the degree or duration of the exposure to tobacco smoking.

A recent German study (67) showed that exposure to parental tobacco smoking significantly correlated with a reduced number of T-helper cells (CD4) in infants. A recent Swedish case-control study (77) reported significantly more passive smokers among asthmatic children allergic to house-dust mites than among a control group – a finding even more pronounced when the child lived in a damp home as well. A US study (78) of 2190 children has shown a significantly earlier onset of allergic respiratory illnesses (asthma and rhinitis) in children exposed to tobacco smoking. The same study also reported a significantly higher frequency of positive skin prick tests to pollen and lactalbumin in passive smokers. An epidemiologic cross-sectional study (1) of 5300 children in Sweden found a significantly higher prevalence of bronchial hyperreactivity and pollen allergy when the parents were smokers. In children who were also exposed to outdoor pollution, the prevalence was even more pronounced. This suggests that different kinds of pollution may act synergistically.

Thus, passive tobacco smoking seems to affect the immune system in children – possibly also prenatally. Some data indicate that children exposed to tobacco smoke may run an increased risk of developing allergy with sensitization to specific allergens. There might be a synergistic effect between tobacco smoke and other risk factors.

Passive smoking and allergic diseases in adults

In adults it is much more difficult to detect a correlation between passive smoking and the development of allergic diseases and asthma. Adults are often exposed to an abundance of competitive factors which might explain a disease or mask the potential effect of passive smoking.

While the studies and documentation on the effect of passive smoking in childhood are numerous and convincing, similar studies in adults have never been done. At present, no existing study documents a correlation between passive smoking and development of asthma in adults.

Asthmatic patients with bronchial hyperreactivity may develop asthmatic symptoms when exposed to unspecific irritants including exposure to tobacco smoke. Moreover, Barbee et al. (4) found that the prevalence of wheezing decreased in adults who stopped smoking, especially in those who had a negative skin test to common airborne allergens.

Passive smoking – possible mechanisms and consequences

Development of an allergic disease seems to be a consequence of a combination of genetic factors and several environmental factors. Environmental factors include potential allergens, inhalant allergens as well as food allergens, but also possible adjuvant environmental factors that might facilitate sensitization. The latter include tobacco smoke in particular, but also other pollutants such as sulfur dioxide, nitrogen dioxide, and carbon monoxide. Several studies indicate that air pollution increases the risk of sensitization against potential allergen sources such as pollen (35, 62). These findings are supported by results from experiments of sensitization in rats (81) and mice (55).

Some authors (5, 66, 82) have proposed that a person can develop a true allergy to tobacco smoke. However, this theory has never been proved, and the studies in question seem to be controversial. Lehrer et al. (44) showed that the sensitivity to tobacco smoke in asthmatic patients was not caused by an IgE-mediated reaction against antigens in tobacco smoke.

In the last decades, a true increase in the occurrence of allergic diseases has been reported in industrialized countries (9, 83). This increase cannot be explained by a change in the genetic material alone. Therefore, it is likely that altered environmental factors may be important, and that indoor air pollution probably plays a major role. Tobacco smoke is the main source of indoor pollution (77). At the same time that the number of female cigarette smokers increased in the Western industrialized countries, the energy crisis of 1970s led to improved insulation of homes. Reduced ventilation and increased humidity indoors resulted. Thus, conditions were optimized in our homes for growth of airway allergen sources such as house-dust mites and molds. The combination of exposure to an increased amount of allergens and an increased concentration of tobacco smoke and other airway irritants may have a synergistic effect on the development of allergic airway diseases. Tobacco smoke may act in several ways. Eventually, it has a directly irritative effect on the mucous membrane and thereby damages its surface, allowing penetration of potential allergens and causing an increased risk of sensitization. Another possibility is that tobacco smoke has a direct effect – an alteration of the allergen making it more allergenic. Furthermore, tobacco smoke may have a direct immunomodulating effect, possibly initiated already prenatally *in utero*. A true allergy against components of tobacco smoke seems to be irrelevant (44).

Conclusion

Many people are passive smokers, but infants and young children especially cannot choose whether or not to be so. There is now convincing evidence that daily passive tobacco smoking results in an increased risk of developing airway diseases including wheezy bronchitis, asthma, and bronchial hyperreactivity in unselected children as well as children with atopic predisposition. Moreover, passive smoking results in increased morbidity, increased need for medical treatment, and increased use of asthma medication in asthmatic children. Furthermore, in children, passive smoking seems to be associated with an increased risk of developing allergic sensitization against specific allergens. Exposure to maternal smoking seems to have the greatest effect – perhaps because the mother is the parent more often at home and spending more time with the infant during the first years of life. Moreover, an intrauterine effect might be a cause. Further studies are necessary on both the pre- and postnatal effects of passive smoking on the immune system.

References

- ANDRAE S, AXELSON O, BJÖRKSTÉN B, FREDERIKSSON M, KJELLMAN N-IM. Symptoms of bronchial hyperreactivity and asthma in relation to environmental factors. *Arch Dis Child* 1988; 63: 473–8.
- ARSHAD SH, HIDE DW. Effect of environmental factors on the development of allergic disorders in infancy. *J Allergy Clin Immunol* 1992; 90: 235–41.
- ARSHAD SH, STEVENS M, HIDE DW. The effect of genetic and environmental factors on the prevalence of allergic disorders at the age of two years. *Clin Exp Allergy* 1993; 23: 504–11.
- BARBEE RA, HALONEN M, KALTENBORN WT, BURROWS B. A longitudinal study of respiratory symptoms in a community population sample: correlations with smoking, allergen skin-test reactivity to IgE. *Chest* 1991; 99: 20–6.
- BECKER CG, DUBIN T, WIEDEMAN HP. Hypersensitivity to tobacco antigen. *Proc Natl Acad Sci U S A* 1976; 73: 1712–16.
- BISGAARD H, DALGAARD P, NYBOE J. Risk factors for wheezing during infancy. A study of 5953 infants. *Acta Paediatr Scand* 1987; 76: 719–26.
- BLACK N. The aetiology of the glue ear – a case-control study. *Int J Pediatr Otorhinolaryngol* 1985; 9: 121–33.
- BURCHFIEL CM, HIGGINS MW, KELLER JB, HOWATT WF, BUTLER WJ, HIGGINS ITT. Passive smoking in childhood. Respiratory conditions and pulmonary function in Tecumseh, Michigan. *Am Rev Respir Dis* 1986; 133: 966–73.
- BURNEY PGJ, CHINN S, RONA RJ. Has the prevalence of asthma increased in children? Evidence from the national study of health and growth 1973–86. *BMJ* 1990; 300: 1306–10.
- BURR M, MISKELLY FG, BUTLAND BK, MERRETT TG, VAUGHAN-WILLIAMS E. Environmental factors and symptoms in infants at high risk of allergy. *J Epidemiol Community Health* 1989; 43: 125–32.
- CHILMONCZYK BA, SALMUN LM, MEGATHLIN KN, et al. Association between exposure to environmental tobacco smoke and exacerbations of asthma in children. *N Engl J Med* 1993; 328: 1665–9.
- CHINN S, RONA RJ. Quantifying health aspects of passive smoking in British children aged 5–11 years. *J Epidemiol Community Health* 1991; 45: 188–94.
- COGSWELL JJ, MITCHELL EB, ALEXANDER J. Parental smoking, breastfeeding, and respiratory infection in development of allergic diseases. *Arch Dis Child* 1987; 62: 338–44.
- COLLEY JR, HOLLAND WW, CORKHILL RT. Influence of passive smoking and parental phlegm pneumonia and bronchitis in early childhood. *Lancet* 1974; ii: 1031–4.
- DAHLSTRÖM A, LUNDELL B, CURVALL M, THAPPER L. Nicotine and cotinine concentrations in the nursing mother and her infant. *Acta Paediatr Scand* 1990; 79: 142–7.
- DEKKER C, DALES R, BARLETT S, BRUNEKREEF B, ZWANENBURG H. Childhood asthma and indoor environment. *Chest* 1991; 100: 922–6.
- DUFF AL, POMERANZ ES, GELBER LE, et al. Risk factors for acute wheezing in infants and children: viruses, passive smoke, and IgE antibodies to inhalant allergens. *Pediatrics* 1993; 92: 535–40.
- ERLICH R, KATTAN M, GODBOLD J, et al. Childhood asthma and passive smoking. Urinary cotinine as a biomarker of exposure. *Am Rev Respir Dis* 1992; 145: 594–9.
- ETZEL RA, PATTISHALL EN, HALEY NJ, FLETCHER RH, HENDERSON FW. Passive smoking and middle ear effusion among children in day care. *Pediatrics* 1992; 90: 228–32.
- EVANS D, LEVISON MJ, FELDMAN CH, et al. The impact of passive smoking on emergency room visits or urban children with asthma. *Am Rev Respir Dis* 1987; 135: 567–72.
- FADEN H, ELIOT E. Acute bronchopulmonary infections. In: BIERMAN CW, PEARLMAN DS, eds. *Allergic diseases of infancy, childhood and adolescence*. Philadelphia: Saunders, 1980: 572–80.
- FERGUSON DM, HORWOOD LJ. Parental smoking and respiratory illness in infancy. *Pediatr Pulmonol* 1985; 1: 99–106.
- FERGUSON DM, HORWOOD LJ, SHANNON FT, TAYLOR B. Parental smoking and lower respiratory illness in the first three years of life. *J Epidemiol Community Health* 1981; 35: 180–4.
- FIELDING J, PHENOW JK. Health effects of involuntary smoking. *N Engl J Med* 1988; 319: 1452–60.
- FORASTIERE F, CORBO GM, MICHELOZZI P, et al. Effects of environment and passive smoking on the respiratory health of children. *Int J Epidemiol* 1992; 21: 66–73.
- FOUCARD T, SJÖBERG O. A prospective 12-year follow-up study of children with wheezy bronchitis. *Acta Paediatr Scand* 1984; 73: 577–83.
- GELLER-BERNSTEIN G, KENETT R, WEISGLASS L, TSUR S, LAHAV M, LEVIN S. Atopic babies with wheezy bronchitis. *Allergy* 1987; 42: 85–91.
- GOREN AI, HELLMAN S. Passive smoking among schoolchildren in Israel. *Environ Health Perspect* 1991; 96: 203–11.
- GORTMARKER SL, KLEIN WALKER D, JACOBS FH, RUCH-ROSS H. Parental smoking and the risk of childhood asthma. *Am J Public Health* 1982; 72: 574–9.
- GREENBERG RA, HALEY NJ, ETZEL R, LODA FA. Measuring the exposure of infants to tobacco smoke. *New Engl J Med* 1984; 310: 1075–8.
- HALKEN S, HØST A, HUSBY S, HANSEN LG, ØSTERBALLE O, NYBOE J. Recurrent wheezing in relation to environmental risk factors in infancy. A prospective study of 276 infants. *Allergy* 1991; 46: 507–14.
- HALKEN S, HØST A, HANSEN LG, ØSTERBALLE O. Effect of an allergy prevention programme on incidence of atopic symptoms in infancy. A prospective study of 159 “high-risk” infants. *Allergy* 1992; 47: 545–53.
- HANRAHAN JP, TAGER IB, SEGAL MR, et al. The effect of

- maternal smoking during pregnancy on early infant lung function. *Am Rev Respir Dis* 1992; 145: 1129–35.
34. HARLAP S, DAVIS AM. Infant admissions to hospital and maternal smoking. *Lancet* 1974; i: 529–32.
 35. ISHIZAKI T, KOIZUMI K, IKEMORI R, ISHIYAMA Y, KISHIBIKI E. Studies of prevalence of Japanese cedar pollinosis among residents in a densely cultivated area. *Ann Allergy* 1987; 8: 265–70.
 36. IVERSEN M, BIRCH L, LUNDQVIST GR, ELBRØND O. Middle ear effusion in children and the indoor environment: an epidemiological study. *Arch Environ Health* 1985; 40: 74–9.
 37. JARVIS MJ, RUSSEL MA. Measurement and estimation of smoke dosage to nonsmokers from environmental tobacco smoke. *Eur J Respir Dis* 1984; 133 (Suppl. 65): 68–75.
 38. KJELLMAN N-IM. Effect of parental smoking on IgE levels in children. *Lancet* 1981; i: 993–4.
 39. KRAEMER MJ, RICHARDSON MA, WEISS NS, et al. Risk factors for persistent middle-ear effusions. Otitis media, catarrh, cigarette smoke exposure, and atopy. *JAMA* 1983; 249: 1022–5.
 40. KUEHR J, FRISCHER T, KARMAUS W, et al. Early childhood risk factors for sensitization at school age. *J Allergy Clin Immunol* 1992; 90: 358–63.
 41. LANDAU LI. Editorial. Smoking and childhood asthma. *Med J Aust* 1991; 154: 715–16.
 42. LEEDER SR, CORKHILL R, IRWIG LM, HOLLAND WW, COLLEY JRT. Influence of family factors on the incidence of lower respiratory illness during the first year of life. *Br J Prev Soc Med* 1976; 30: 203–12.
 43. LEEDER SR, CORKHILL R, IRWIG LM, HOLLAND WW. Influence of family factors on asthma and wheezing during the first five years of life. *Br J Prev Soc Med* 1976; 30: 213–18.
 44. LEHRER SB, BARBANDI F, TAYLOR JP, et al. Tobacco smoke "sensitivity" – is there an immunologic basis? *J Allergy Clin Immunol* 1984; 73: 240–5.
 45. MAGNUSSON CGM. Maternal smoking influences cord serum IgE and IgD levels and increases the risk for subsequent infant allergy. *J Allergy Clin Immunol* 1986; 78: 898–904.
 46. MAGNUSSON CGM, JOHANSSON SGO. Maternal smoking leads to increased cord serum IgG3. *Allergy* 1986; 41: 302–7.
 47. MARTINEZ FD, CLINE M, BURROWS B. Increased incidence of asthma in children of smoking mothers. *Pediatrics* 1992; 89: 21–6.
 48. MCCONNOCHIE KM, ROGHMAN KJ. Wheezing at 8 and 13 years: changing importance of bronchiolitis and passive smoking. *Pediatr Pulmonol* 1989; 6: 138–46.
 49. MURRAY AB, MORRISON BJ. The effect of cigarette smoke from the mother on bronchial responsiveness and severity of symptoms in children with asthma. *J Allergy Clin Immunol* 1986; 77: 575–81.
 50. MURRAY AB, MORRISON BJ. It is children with atopic dermatitis who develop asthma more frequently if the mother smokes. *J Allergy Clin Immunol* 1990; 86: 732–9.
 51. MURRAY AB, MORRISON BJ. The decrease in severity of asthma in children of parents who smoke since the parents have been exposing them to less cigarette smoke. *J Allergy Clin Immunol* 1993; 91: 102–10.
 52. NEUSPIEL DR, RUSH D, BUTLER NR, GOLDING J, BURR PE, KURZON M. Parental smoking and post-infancy wheezing in children: a prospective cohort study. *Am J Public Health* 1989; 79: 168–71.
 53. NORDVALL SL, ERIKSSON M, RYLANDER M, SCHWARTZ B. Sensitization of children in the Stockholm area to house dust mites. *Acta Paediatr Scand* 1988; 77: 716–20.
 54. ORYSZCZYN M-P, GODIN J, ANNESI I, HELLIER G, KAUFFMANN F. *In utero* exposure to parental smoking, cotinine measurements, and cord blood IgE. *J Allergy Clin Immunol* 1991; 87: 1169–74.
 55. OSEBALD JW, CHUNG ZEE Y, GERSHWIN LJ. Enhancement of allergic lung sensitization in mice by ozone inhalation. *Proc Soc Exp Biol Med* 1988; 188: 259–64.
 56. OWNBY DR, JOHNSON CC, PETERSON EL. Maternal smoking does not influence cord serum IgE or IgD concentrations. *J Allergy Clin Immunol* 1991; 88: 555–60.
 57. OWNBY DR, MCCULLOUGH J. Passive exposure to cigarette smoke does not increase allergic sensitization in children. *J Allergy Clin Immunol* 1988; 82: 634–7.
 58. PEDREIRA FA, GUANDOLO VL, FEROLI EL, et al. Involuntary smoking and incidence of respiratory illness during the first year of life. *Pediatrics* 1985; 75: 594–7.
 59. PUKANDER J, LUOTONEN J, TIMONEN M, KARMA P. Risk factors affecting the occurrence of acute otitis media among 2–3-year-old urban children. *Acta Otolaryngol (Stockh)* 1985; 100: 260–5.
 60. RANTAKALLIO P. Relationship of maternal smoking to morbidity and mortality of the child up to the age of five. *Acta Paediatr Scand* 1978; 67: 621–31.
 61. RANTAKALLIO P. A follow-up study up to the age of 14 of children whose mothers smoked during pregnancy. *Acta Paediatr Scand* 1983; 72: 747–53.
 62. REHSTEINER R. Beitrage zur Kenntnis der Verbreitung des Heuschnupfens. Thesis. Medical University of Zurich, 1926.
 63. RONCHETTI R, BONCI E, CUTRERA R, et al. Enhanced allergic sensitization related to parental smoking. *Arch Dis Child* 1992; 67: 496–500.
 64. RONCHETTI R, MACRI F, CIOFETTA G, et al. Increased serum IgE and increased prevalence of eosinophilia in 9-year-old children of smoking parents. *J Allergy Clin Immunol* 1990; 86: 400–7.
 65. SAID G, ZALOKAR J, LELLOUCH J, PATOIS E. Parental smoking related to adenoidectomy and tonsillectomy in children. *J Epidemiol Community Health* 1978; 32: 97–101.
 66. SAVEL H. Clinical hypersensitivity to cigarette smoke. *Arch Environ Health* 1970; 21: 146–8.
 67. SCHMITT M, GRUTERS A, BECK H, et al. Does passive smoking lead to a decrease of CD4 + lymphocytes in infants? *Allergy* 1992; 47 (Suppl. 12): 17.
 68. SCHULTE-HOBEIN B, SCHWARTZ-BICKENBACH D, ABT S, PLUM C, NAU H. Cigarette smoke exposure and development of infants throughout the first year of life: influence of passive smoking and nursing on cotinine levels in breast milk and infant's urine. *Acta Paediatr* 1992; 81: 550–7.
 69. STÄHLBERG MR, RUUSKANEN O, VIROLAINEN E. risk factors for recurrent otitis media. *Pediatr Infect Dis* 1986; 5: 30–2.
 70. STEDMAN RL. The chemical composition of tobacco smoke. *Chem Rev* 1968; 68: 153–207.
 71. STORM K, HAAHR J, KJELLMAN N-IM, ØSTERBALLE O. The occurrence of asthma and allergic rhinitis, atopic dermatitis and urticaria in a 1-year cohort of Danish children [in Danish]. *Ugeskr Laeger* 1986; 148: 3295–9.
 72. TAYLOR B, WADSWORTH J. Maternal smoking during pregnancy and lower respiratory tract illness in early life. *Arch Dis Child* 1987; 62: 786–91.
 73. WARE JH, DOCKERY DW, SPIRO A III, SPEIZER FE, FERRIS BG Jr. Passive smoking, gas cooking, and respiratory health of children living in six cities. *Am Rev Respir Dis* 1984; 129: 366–74.
 74. WEITZMAN M, GORTMAKER S, KLEIN WALKER D, SOBOLO A. Maternal smoking and childhood asthma. *Pediatrics* 1990; 85: 505–11.
 75. WENNERGREN G, HANSSON S, ENGSTRÖM I, et al. Characteristics and prognosis of hospital-treated obstructive bronchitis in children aged less than two years. *Acta Paediatr* 1992; 81: 40–5.
 76. WICKMAN M, NORDVALL SL, PERSHAGEN G. Risk factors

- in early childhood for sensitization to airborne allergens. *Allergy* 1992; 47 (Suppl. 12): 39.
77. WILLERS S, SVENONIUS E, SKARPING G. Passive smoking and childhood asthma. *Allergy* 1991; 46: 330-4.
78. WITTIG HJ, McLAUGHLIN ET, LEIFER KL, BELLOIT JD. Risk factors for the development of allergic disease: analysis of 2190 patients' records. *Ann Allergy* 1978; 41: 84-8.
79. WRIGHT AL, HOLBERG C, MARTINEZ FD, TAUSSIG LM, GROUP HEALTH MEDICAL ASSOCIATES. Relationship of parental smoking to wheezing and nonwheezing lower respiratory tract illnesses in infancy. *J Pediatr* 1991; 118: 207-14.
80. YOUNG S, LE SOUEF PN, GEELHOED GC, et al. The influence of a family history of asthma and parental smoking on airway responsiveness in early infancy. *N Engl J Med* 1991; 324: 1168-73.
81. ZETTERSTRÖM O, NORDVALL SL, BJÖRKSTÉN B, et al. Increased IgE antibody responses in rats exposed to tobacco smoke. *J Allergy Clin Immunol* 1985; 75: 594-8.
82. ZUSSMAN BM. Tobacco sensitivity in the allergic population. *Asthma Res* 1974; 11: 159-67.
83. ÅBERG N. Asthma and allergic rhinitis in Swedish conscripts. *Clin Exp Allergy* 1989; 19: 59-63.