3

Genetic susceptibility

Key points

- While some diseases, such as cystic fibrosis, are almost wholly genetic, genetic factors play a role in making us more or less vulnerable to the whole spectrum of respiratory disease.
- The search for genetic links to disease is two-pronged: linkage studies begin with a disease and look for genes associated with it, while association studies begin with polymorphisms or mutations, and look for associations with disease.
- Several genes have been identified that influence susceptibility to both asthma and COPD, reflecting similarities in disease presentation between the two conditions.
- Nondisease traits that influence respiratory health, such as tendency to nicotine addiction, and lung function, have also been related to genetic variations.

Respiratory diseases occur as a result of interactions between genotype and environment. Environmental influences include allergens, irritants, smoking, environmental tobacco smoke (ETS), diet, nutrients, drugs, infections and injuries. When a single gene has a very high impact on the development of a disease, this disease is called a "monogenic disease" (figure 1). Examples of such diseases are cystic fibrosis (CF) and α_1-antitrypsin deficiency, which are inherited in a classical "Mendelian" fashion, with recessive or dominant forms of the gene in question being passed from generation to generation. Other diseases are triggered mainly by major environmental exposures; examples include carbon monoxide poisoning, acute lung injury and acute respiratory distress syndrome (due to severe pneumonia or major trauma). However, in the most common lung diseases, such as asthma, chronic obstructive pulmonary disease (COPD), pulmonary fibrosis and sarcoidosis, both the genotype and the environment play major roles in disease susceptibility: these diseases are called "complex diseases".

Humans have 23 pairs of chromosomes (one pair of sex chromosomes and 22 pairs of autosomes). This provides every human with two versions of each gene: one on the maternally inherited chromosome and one on the paternally inherited chromosome. The human genome includes 3.3 billion base (nucleotide) pairs (the "building blocks" of DNA) and more than 25 000 genes, which code for proteins that build cells and tissues, and enzymes that catalyse biochemical

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> *The DNA sequence is more than 99% identical between different individuals; but this still leaves scope for more than 10 million potential differences or variations between the genomes of two humans*
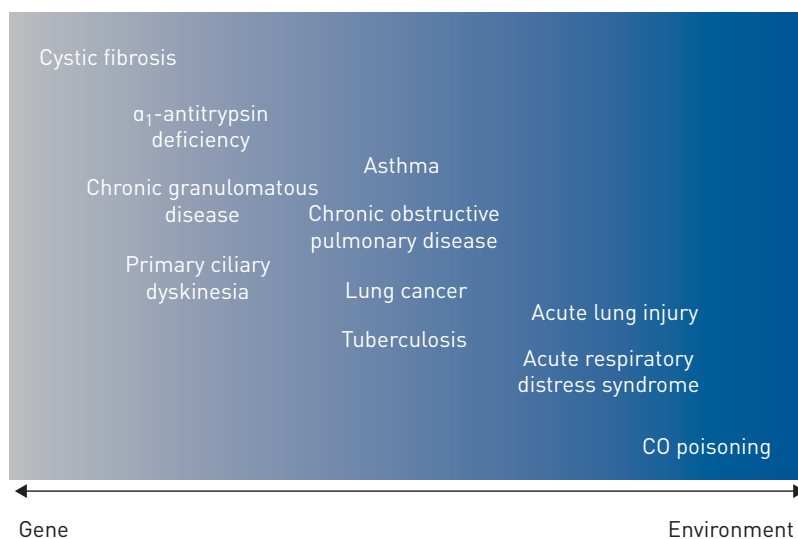

Figure 1 – Most common respiratory diseases are complex diseases. They arise as a consequence of interactions between an individual genotype and environmental exposures. CO: carbon monoxide.

Figure content: Cystic fibrosis; α_1-antitrypsin deficiency; Chronic granulomatous disease; Asthma; Chronic obstructive pulmonary disease; Primary ciliary dyskinesia; Lung cancer; Acute lung injury; Tuberculosis; Acute respiratory distress syndrome; CO poisoning. Axis: Gene — Environment.

reactions within cells. The DNA sequence is more than 99% identical between different individuals; but this still leaves scope for more than 10 million potential differences or variations between the genomes of two humans. Variations in gene structure that occur frequently in a population (1% or more of people) are called polymorphisms, whereas genetic variations that occur infrequently (less than 1%) are called mutations. There are several forms of polymorphism, of which single-nucleotide polymorphisms (SNPs) are by far the most common. SNPs constitute a single base-pair change in the DNA sequence at a particular point, relative to the common or "wild type" sequence. SNPs in parts of genes that code for proteins can lead to a change in the amino acid sequence of the protein, affecting its structure and/or function.

There are several methods to study the genetic factors that contribute to the development of an individual's specific characteristics (referred to as phenotypes; for example, height or lung function) or complex diseases, such as asthma and COPD. Linkage studies are performed in families: these are based on the tendency of genetic loci (the site on a chromosome at which one or several genes for a particular disease or trait are located) or alleles that are physically close to one another on a chromosome to be inherited together (this is known as genetic linkage). Once a genetic locus for the phenotype or disease of interest has been identified through linkage analysis, positional cloning is performed to further delineate the susceptibility gene(s). For many years, genetic linkage combined
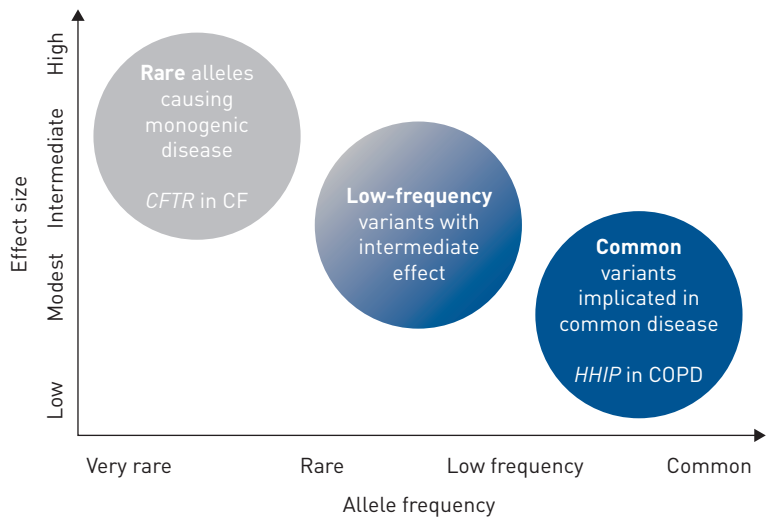
with positional cloning has offered a rational way of discovering gene mutations that cause monogenic diseases, such as CF. These searches have led to the discovery of rare mutations (present in less than 1% of the population) that alter the amino acid sequence of a protein and increase the risk of disease enormously (very high effect size) (figure 2).

In contrast, association studies begin with the polymorphism or mutation rather than with the disease. They are typically based on a case–control design (*i.e.* "cases" – people with the disease – are compared with healthy control subjects) in which SNPs are tested for association with a specific phenotype or disease. In single-candidate gene association studies, only one or a few SNPs near or in the gene under study are investigated for association with the disease of interest, based on an *a priori* hypothesis concerning the possible function and role of the particular gene. In genome-wide association studies, hundreds of thousands of SNPs across the entire human genome are genotyped and tested for association with the phenotype or disease of interest in hundreds or thousands of individuals. Without an *a priori* hypothesis, genome-wide association studies identify common genetic variants (which are present in more than 5% of the population) that confer a small risk of disease (small effect size, typically with odds ratios of 1.1 to 2.0).

This chapter on genetic susceptibility to respiratory diseases is neither exhaustive nor complete, but is intended as an introduction to the exponentially growing field of genetics and genomics in respiratory medicine and science.

Monogenic diseases

Monogenic diseases (table 1) are rare diseases attributable to genetic variants with large effects on disease status. Because

Figure 2 – Allele frequency *versus* disease risk. *CFTR*: cystic fibrosis conductance regulators; CF: cystic fibrosis; *HHIP*: hedgehog-interacting protein; COPD: chronic obstructive pulmonary disease.

of the high penetrance of such variants, the disease is typically inherited in a classical Mendelian fashion (*e.g.* dominant or recessive). The best-known monogenic respiratory diseases are CF and α_1-antitrypsin deficiency, but hundreds of rare monogenic diseases affecting the respiratory system have been described. We refer the interested reader to the Online Mendelian Inheritance in Man (OMIM) website, which is a comprehensive, authoritative and continuously updated compendium of human genes and genetic phenotypes (see Further reading).

Cystic fibrosis

CF is an autosomal recessive genetic disorder (*i.e.* both inherited copies of the gene need to be mutated in order for disease to result; or to put it another way, one healthy copy of the gene is enough to prevent CF), caused by mutations in the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene on chromosome 7. The CFTR protein is an ion channel that regulates transport of chloride ions (Cl^-) in epithelial cells in the airways, as well as in the pancreas, liver, intestine and skin. More than 1000 mutations of the *CFTR* gene have been described. In Europe, the most common is the ΔF508 mutation (a deletion of three DNA bases). The resulting CFTR protein has a missing amino acid (phenylalanine) in position 508. One in 25 people of European descent carries one mutant allele of CFTR, and one person in 2000–3000 is affected by CF. The various *CFTR* mutations cause different CFTR protein defects, which impair transport of chloride and sodium across epithelial surfaces, leading to thick viscous secretions (*e.g.* mucus or phlegm).

CFTR modulators and potentiators are drugs that aim to correct the underlying defect that leads to CF by modifying the function of the CFTR protein. Since the therapeutic effects of CFTR modulators are based on individual protein defects, knowledge of the genotype of both alleles of the *CFTR* gene is necessary for appropriate patient selection. As an example, ivacaftor, which was approved for use by the US Food and Drug Administration in January 2012, targets the specific *CFTR* mutation G551D (in which glycine in position 551 is substituted with aspartic acid), improves lung function and reduces respiratory symptoms and pulmonary exacerbations in patients with CF who have at least one G551D *CFTR* mutation.

α_1-antitrypsin deficiency

α_1-antitrypsin is a protease inhibitor, produced mainly in the liver, which protects the lungs against proteolytic damage by the enzyme neutrophil elastase. α_1-antitrypsin is encoded by the *SERPINA1* gene (also known as *PI*). Like CF, α_1-antitrypsin deficiency is an autosomal recessive inherited disorder affecting 1 in 2000–5000 persons in Europe. It increases the risk of liver disease, COPD and emphysema. Those with two copies of the most severe "Z" mutation (*PI* ZZ genotype) have very low serum protein levels of α_1-antitrypsin. Cigarette smoking greatly increases the risk of COPD in α_1-antitrypsin-deficient patients, leading to severe, early-onset emphysema due to destruction of alveolar septa in the lung as a consequence of the protease–antiprotease imbalance.

Primary ciliary dyskinesia

Primary ciliary dyskinesia (PCD), or immotile cilia syndrome, is a genetically heterogeneous autosomal recessive disorder, caused by loss of function of different parts of the cilia, which line the epithelial cells of the airway mucosa and are responsible for clearing secretions and foreign material. Patients with PCD suffer from recurrent upper and lower respiratory tract infections, often leading to bronchiectasis,

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Gene/locus	Gene name	Chromosomal location#	Gene product: protein function	Disease
CFTR	CF transmembrane conductance regulator	7q31.2	Ion channel: chloride transport	CF
SERPINEA1	α_1-antitrypsin	14q32.13	Serine protease inhibitor	α_1-antitrypsin deficiency (COPD, emphysema, liver disease)
DNAI1	Dynein, axonemal, intermediate chain 1	9p13.3	Dynein arm: ciliary function	CILD1, with or without situs inversus (Kartagener syndrome)
CYBB	p91-phox (phagocyte oxidase): beta subunit of cytochrome b, component of the phagocyte NADPH oxidase complex	Xp11.4	Killing of microbes in phagocytes by generation of reactive oxygen species	CGD, X-linked
CYBA	p22-phox (phagocyte oxidase): alpha subunit of cytochrome b, component of the phagocyte NADPH oxidase complex	16q24.3	Killing of microbes in phagocytes by generation of reactive oxygen species	CGD, autosomal recessive
SFTPC	Surfactant, pulmonary-associated protein C	8p21.3	Surfactant proteins are essential for lung function, preventing lung collapse by lowering surface tension	Respiratory distress syndrome of prematurity
SFTPB	Surfactant, pulmonary-associated protein B	2p11.2	Surfactant proteins are essential for lung function, preventing lung collapse by lowering surface tension	Respiratory distress syndrome of prematurity

Table 1 – Monogenic respiratory diseases (inherited in a Mendelian fashion). Only seven out of more than 100 known monogenic respiratory diseases are presented as illustration. #: p refers to the short arm of the chromosome. q refers to the long arm of the chromosome. The location numbers after p and q reflect the relative distance to the centromeres of the chromosomes (numbering by convention). CF: cystic fibrosis; COPD: chronic obstructive pulmonary disease; CILD1: ciliary dyskinesia, primary 1; NADPH: nicotinamide adenine dinucleotide phosphate; CGD: chronic granulomatous disease.

an abnormal widening of the airways. About half of people with PCD have Kartagener syndrome, in which PCD is combined with situs inversus (a condition in which the position of the major organs is a mirror image of the normal arrangement).

Other monogenic diseases encompass diseases caused by mutations in surfactant proteins, which are crucial in decreasing tension forces during breathing. Dysfunction of surfactant caused by mutations in surfactant protein genes leads to respiratory distress syndrome of prematurity. Mutations in cytochrome b, an enzyme involved in killing microbes in phagocytic cells, predispose individuals to recurrent respiratory infections (see the section on chronic granulomatous diseases later in this chapter).

Complex diseases

Asthma

Using the candidate gene approach (discussed earlier in this chapter), many genes have been associated with asthma or asthma-related traits such as allergy and high concentrations of immunoglobulin E (IgE) in serum (table 2). Not all of these suspected asthma susceptibility genes have been replicated in multiple independent studies. One group of (allergic) asthma susceptibility genes is involved in innate immunity responses, encompassing pattern-recognition receptors, immunoregulatory cytokines and molecules involved in antigen presentation. A second group of asthma susceptibility genes are key players in T-helper type 2 (Th2)-cell differentiation and Th2-cell effector function. Th2 cells are T-lymphocytes that drive the production of allergic immunoglobulins (IgE) and the chronic airway inflammation in (allergic) asthma.

Linkage studies in families have discovered several novel asthma susceptibility genes that are expressed in epithelial cells and/or smooth muscle cells in the airways (table 2). Although the functional role of these asthma susceptibility genes is not yet fully understood, they are thought to be involved in maintaining the integrity of the epithelial barrier, airway remodelling and bronchial hyperresponsiveness. These asthma susceptibility genes indicate the importance of altered communication between the epithelium and the underlying smooth muscle cells in the pathogenesis of asthma.

The first genome-wide association study of asthma showed that multiple markers at chromosomal location 17q21, encompassing genetic variants of *ORMDL3* and *GSDMB*, were strongly associated with childhood asthma. The association of the *ORMDL3/GSDMB* locus with early-onset asthma is further increased in children exposed to environmental tobacco smoke, implicating an interaction between gene and environment. In infancy, passive smoking does indeed significantly increase the risk of developing asthma. A large-scale genome-wide association study of asthma performed by the European GABRIEL consortium revealed that some genes involved in communication of epithelial damage to the adaptive immune system are susceptibility genes for asthma (table 2). This genome-wide association study of asthma confirmed the role of antigen presentation and of the Th2-cytokine gene *IL13* (interleukin 13) in the pathogenesis of asthma. Many of these asthma susceptibility genes have been confirmed by the American EVE consortium. Finally, several loci have been linked to increased serum total IgE levels in genome-wide association studies. These are *IL13*, *IL4R*, *STAT6* (signal transducer and activator of transcription 6), *FCER1A* (high-affinity Fc receptor for IgE) and *HLA-DRB1* (a human leukocyte antigen).

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Gene/locus	Chromosomal location#	Gene name	Mechanism
Candidate gene association studies			
TLR2	4q31.3	Toll-like receptor 2	Pathogen recognition/innate immunity
CD14	5q31.3	Cluster of differentiation 14: monocyte antigen	LPS signalling
IL10	1q32.1	Interleukin-10	Anti-inflammatory/regulatory T-cells
TGFB	19q13.2	Transforming growth factor-β	Anti-inflammatory/airway remodelling
HLA-DR	6p21.32	Human leukocyte antigens	Antigen presentation
HLA-DQ	6p21.32	Human leukocyte antigens	Antigen presentation
HLA-DP	6p21.32	Human leukocyte antigens	Antigen presentation
IL4	5q31.1	Interleukin-4	Th2 responses/IgE production
IL13	5q31.1	Interleukin-13	Mucus production/IgE production
IL4R	16p12.1	Interleukin-4 receptor	Th2 responses/IgE production
STAT6	12q13.3	Signal transducer and activator of transcription 6	Transcription factor (Th2 responses)
Genome-wide association studies			
ORMDL3	17q21	Orosomucoid like 3	Unknown
IL2R	10p15.1	Interleukin-2 receptor	T-cell proliferation Th1 responses
IL18R1	2q12.1	Interleukin-18 receptor 1	T-cell proliferation Th1 responses
IL13	5q31.1	Interleukin-13	Mucus production/IgE production
IL33	9p24.1	Interleukin-33	Innate immunity/danger signal
Linkage studies and positional cloning			
ADAM33	20p13	A disintegrin and metalloproteinase	Airway remodelling/bronchial hyperresponsiveness
DPP10	2q14.1	Dipeptidyl peptidase 10	
GPRA		G-protein coupled receptor for asthma susceptibility	Unknown

Table 2 – Genetic susceptibility to asthma. This is a partial list of selected genes intended as an illustrative example of genetic susceptibility to asthma. LPS: lipopolysaccharide; Th: T-helper type 2; IgE: immunoglobulin E. #: p refers to the short arm of the chromosome. q refers to the long arm of the chromosome. The location numbers after p and q reflect the relative distance to the centromeres of the chromosomes (numbering by convention).

Chronic obstructive pulmonary disease and emphysema

Since only about 20% of smokers develop COPD, genetic risk factors are thought to be involved in the pathogenesis of the disease. The best known genetic risk factor

for emphysema is α_1-antitrypsin deficiency, implicating an imbalance of protease (neutrophil elastase) and antiprotease (α_1-antitrypsin) in the pathogenesis of the disease. Two meta-analyses of candidate gene studies in COPD concluded that only a few other COPD susceptibility genes have been firmly identified. These include *TNFA* (tumour necrosis factor-α), *TGFB1* (transforming growth factor-β_1), *GSTP1* and *GSTM1* (glutathione S-transferases P1 and M1), and *SOD3* (superoxide dismutase 3).

Genome-wide association studies in COPD have identified three major susceptibility loci: the *FAM13A* locus on chromosome 4q22, the locus near *HHIP* on chromosome 4 and the *CHRNA3/CHRNA5* locus on chromosome 15 (see the nicotine addiction and smoking section later in this chapter). Recently, several of the genetic determinants of lung function, encompassing genes involved in lung development and growth, such as *HHIP* (hedgehog-interacting protein), have been confirmed as genetic risk factors for COPD (see the lung function section later in this chapter).

Since there are some similarities between the disease phenotypes and pathophysiological pathways of asthma and COPD, several susceptibility genes are suspected to be common to both diseases, whereas other susceptibility genes will be specific to asthma or COPD. Both asthma and COPD are very heterogeneous diseases with multiple distinct phenotypes, suggesting that the degree of overlap between the genetic susceptibilities will depend on the asthma or COPD phenotypes examined. Using the candidate gene approach, several genes, such as *TNFA*, *TGFB1*, *MMP12* (matrix metalloproteinase 12) and *ADAM33*, have been implicated as susceptibility genes for both asthma and COPD. Common pathogenetic pathways in airway inflammation and remodelling might explain this common genetic susceptibility. Some genes, such as *IL13*, have been specifically associated with allergy and allergic asthma, but not with COPD. In contrast, *SERPINE* (serine protease inhibitors) genes such as that for α_1-antitrypsin have been specifically implicated in the pathogenesis of emphysema, an important phenotype of COPD.

Pulmonary fibrosis

Although the cause of pulmonary fibrosis is unknown (*i.e.* it is idiopathic), it is estimated that 0.5–2.0% of cases of idiopathic pulmonary fibrosis (IPF) are familial. Several mutations and polymorphisms in different genes have been shown to increase susceptibility to IPF: mutations in *TERT* (the telomerase reverse transcriptase gene), the catalytic subunit of the telomerase enzyme; mutations in *TERC* (the telomerase RNA component gene); and a promoter mutation in the *MUC5B* gene, which codes for the mucin B protein. A polymorphism in the *SFTPA1* gene encoding pulmonary surfactant protein A1 influences susceptibility to IPF in nonsmokers, and a mutation in the *SFTPA2* gene encoding pulmonary surfactant protein A2 can cause IPF.

Sarcoidosis

Sarcoidosis is suspected to be caused by a combination of environmental exposure to a still-unknown agent (*e.g.* a microorganism or inorganic material) and genetic susceptibility. Class II molecules of the major histocompatibility complex (MHC), also called human leukocyte antigens (HLA), are cell surface proteins that present processed foreign antigens to T-lymphocytes. These T-lymphocytes are then stimulated to become effector cells of adaptive immune responses. There is a high degree of polymorphism in class II MHC genetic loci.

Variation in the *HLA-DRB1* gene on chromosome 6p21.3, affecting antigen presentation to T-lymphocytes, is a major contributor to susceptibility to sarcoidosis (the locus is called susceptibility locus for sarcoidosis 1 (SS1)). The second susceptibility locus for

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sarcoidosis, SS2, is on chromosome 6p21.32 and is associated with variation in the *BTNL2* (Butyrophilin-like protein 2) gene, which may regulate T-cell activation. The strongest association signal from a genome-wide association study for sarcoidosis mapped to the *ANXA11* gene, belonging to the annexin family, on chromosome 10q22.3.

Genetic variation of another MHC class II molecule, *HLA-DPB1*, has been shown to confer susceptibility to sarcoidosis and chronic beryllium disease, a hypersensitivity disorder of the lung caused by exposure to beryllium (used in diverse industries such as aerospace). Both sarcoidosis and chronic beryllium disease are characterised by chronic adaptive immune responses, leading to the formation of granulomas in the lung and lymph nodes.

Respiratory infections and pneumonia

Genetic factors can increase the risk of respiratory infections, including acute bronchitis and pneumonia. Most often, genetic polymorphisms underlie vulnerability to recurrent infections, but in rare cases monogenic defects are responsible (table 1). Repeated respiratory infections can be precipitated by structural defects of the lungs (*e.g.* bronchiectasis due to CF or PCD) or by genetic defects in the immune system. This defence system can be divided into the innate immune system, which recognises broadly conserved, generic structures of microbes *via* cell surface receptors (called pattern-recognition receptors), and the adaptive immune system, which recognises specific parts of microbial structures *via* very specific receptors on T-cells (which produce cytokines) and B-cells (which produce immunoglobulins (Ig)). These immunoglobulins, also called antibodies, are present in serum (*e.g.* IgM and IgG) and in sputum (IgA).

A disorder characterised by impaired immune responses towards infectious agents is called an 'immunodeficiency'. This can be either inherited or acquired (*e.g.* acquired immune deficiency syndrome (AIDS) caused by the human immunodeficiency virus (HIV)). Numerous genetic defects can impair the host's immune response to infection, leading to inherited immunodeficiencies. Genetic defects in innate immunity lead to several groups of immunodeficiencies. Firstly, chronic granulomatous diseases (table 1) are caused by immunodeficiencies due to impaired intracellular killing of microbes within phagocyte cells (neutrophils and macrophages). Secondly, defective recognition of microbes caused by genetic polymorphisms or mutations in pattern-recognition receptors can increase the risk of infection by particular micro-organisms. Deficiency of Toll-like receptor 3 (TLR3), which recognises double-stranded RNA, confers susceptibility to viral infections (*e.g.* herpesvirus), whereas deficiency of TLR5, which recognises

flagellin, increases the risk of *Legionella* infections (*e.g.* pneumonia due to *Legionella* (Legionnaires' disease)). Lastly, the common deficiency of mannose-binding lectin, which activates complement, increases the risk of infections with bacteria and fungi.

Genetic defects in adaptive immunity can affect the development and function of B-cells, leading to decreased levels of immunoglobulins (*e.g.* IgA deficiency), or of T-cells, impairing cellular immunity and predisposing to opportunistic infections. The most severe cases of inherited immunodeficiency are already apparent in infancy and are caused by impairment of both B- and T-cell immunity (*e.g.* X-linked severe combined immunodeficiency syndrome (SCID)).

Tuberculosis

One-third of the global population is latently infected with *Mycobacterium tuberculosis*. Exposure to *M. tuberculosis* can lead to asymptomatic 'latent' infection or to overt clinical tuberculosis. Why only 10% of individuals infected with *M. tuberculosis* develop active disease is not known, but variation in many genes has been associated with susceptibility to, or resistance against, *M. tuberculosis* (table 3). These genetic variants encompass a spectrum from causal susceptibility in rare cases, to very mild predisposition in the general population.

Lung cancer

Smoking is a major risk factor for lung cancer, and several studies have shown that a first-degree family history of lung cancer confers an approximately two-fold increased risk

Gene/locus	Location[#]	Name of gene or locus	Mechanism
Susceptibility to tuberculosis			
CISH	3p21.2	Cytokine-inducible SH2-containing protein	Adaptive immunity
CD209	19p13.2	DC-SIGN: membrane lectin receptor of dendritic cells	Pathogen recognition/cell adhesion
MCP1	17q12	Monocyte chemotactic protein 1 or CCL2	Chemo-attractant
VDR	12q13.11	Vitamin D receptor	Innate and adaptive immunity
MTBS1	2q35	*M. tuberculosis* susceptibility locus 1	Unknown
MTBS2	8q12-q13	*M. tuberculosis* susceptibility locus 2	Unknown
MTBS3	20q13.31-q33	*M. tuberculosis* susceptibility locus 3	Unknown
Protection against tuberculosis			
TIRAP	11q24.2	TIR domain-containing adaptive protein	TLR4 signalling
IFNG	12q15	Interferon-γ	Th1 adaptive immunity
IFNGR1	6q23.3	Interferon-γ receptor 1	Th1 adaptive immunity

Table 3 – Genetic susceptibility to, or protection against, *Mycobacterium tuberculosis*. This is a partial list of selected genes and loci intended as an illustrative example of genetic susceptibility to tuberculosis. [#]: p refers to the short arm of the chromosome. q refers to the long arm of the chromosome. DC-SIGN: dendritic cell-specific intercellular adhesion molecule 3-grabbing nonintegrin; CCL2: chemokine ligand 2; TIR: Toll/IL1R; TLR4: Toll-like receptor 4; Th1: T-helper type 1.

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> *The locus encompassing the* CHRNA3 *and* CHRNA5 *(nicotinic acetylcholine receptor) gene cluster on chromosome 15q24–25 has been associated with nicotine dependence*

of lung cancer, implicating a familial aggregation of lung cancer. Genome-wide association studies have identified a region on chromosome 15 (15q25.1), containing the nicotinic acetylcholine receptor subunit genes *CHRNA3* and *CHRNA5*, that is associated with nicotine addiction (*i.e.* number of cigarettes smoked per day) and lung cancer. Whether genetic variation in the nicotinic acetylcholine receptor increases the risk of lung cancer only indirectly *via* nicotine addiction or whether it also influences the lung epithelium directly in pulmonary carcinogenesis, is currently the subject of intense investigation (figure 3).

Both in small cell lung cancer and in nonsmall cell lung cancer, numerous somatic mutations and chromosomal aberrations have been described within the tumour cells. However, a detailed description of these is beyond the scope of this chapter. We refer the interested reader to one of the excellent reviews that are available on the genomics of lung cancer (see Further reading).

Pulmonary embolism

Most pulmonary embolisms arise from blood clots in the deep veins (*i.e.* deep vein thrombosis) of the legs. Risk factors for deep vein thrombosis and acute pulmonary embolism include immobilisation, surgery, stroke, malignancy, obesity and pregnancy, but also genetic susceptibility. If the former risk factors are absent (*i.e.* unprovoked venous thromboembolism), or if there is a positive family history of deep vein thrombosis or pulmonary embolism, then an inherited thrombophilia, or hypercoagulable state, should be suspected.

The most common inherited hypercoagulable state is due to a mutation in the coagulation factor V gene (called the factor V Leiden mutation), which causes resistance to the anticoagulation factor, activated protein C. Heterozygosity (one copy of the mutated gene) for the factor V Leiden mutation is present in approximately 5% of a Caucasian population, and
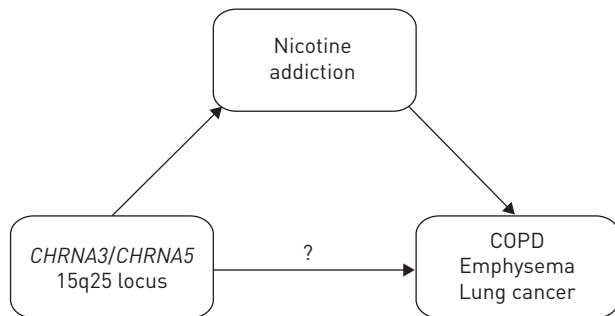

Figure 3 – Direct *versus* indirect effects of genetic variation in the nicotinic acetylcholine receptor cluster (including the *CHRNA3* and *CHRNA5* genes) on susceptibility to COPD, emphysema and lung cancer.

homozygosity (two copies of the mutated gene) in 1%. Homozygotes for the factor V Leiden mutation have a more than two-fold increased lifetime risk of developing deep vein thrombosis, with or without pulmonary embolism. Other inherited thrombophilias include a mutation in the prothrombin gene (coagulation factor II), antithrombin (ATIII) deficiency, protein C deficiency and protein S deficiency. Deficiencies of these anticoagulation factors increase the lifetime risk of venous thromboembolism seven- to eight-fold. Use of oral contraceptives (mainly third-generation oral contraceptives) is associated with an increased risk of venous thromboembolism, especially in heterozygote and homozygote carriers of the factor V Leiden mutation, implicating a gene–environment interaction.

Complex traits

Nicotine addiction and smoking

The locus encompassing the *CHRNA3* and *CHRNA5* (nicotinic acetylcholine receptor) gene cluster on chromosome 15q24–25 has been associated with nicotine dependence, as measured by the number of cigarettes smoked per day. This gene cluster has also been associated with smoking-related diseases such as peripheral arterial disease, lung cancer, COPD and emphysema. Whether the nicotinic acetylcholine receptor gene cluster confers an increased risk of developing smoking-related diseases such as COPD, emphysema and lung cancer, in addition to its major impact on smoking behaviour, is a matter of debate and intense investigation (figure 3).

Lung function

Asthma and COPD are classed as obstructive airway diseases. The ratio of a person's forced expiratory volume in 1 second (FEV_1) to forced vital capacity (FVC) (*i.e.* the FEV_1/FVC ratio) is an indicator of airflow obstruction; a reduced FEV_1/FVC ratio is the primary criterion for defining airway obstruction. The first genome-wide association study of pulmonary function, performed in the Framingham Heart Study in the USA, identified SNPs near the *HHIP* gene on chromosome 4q31 that were associated with the FEV_1/FVC ratio. Two large genome-wide association studies confirmed the *HHIP* locus and identified multiple novel loci associated with the FEV_1/FVC ratio (table 4). Thanks to collaboration between two large scientific research consortia, CHARGE (Cohorts for Heart and Aging Research in Genomic Epidemiology) and SpiroMeta, 16 additional genetic loci have been shown to be associated with lung function, including *RARB* (retinoic acid receptor B). Since several identified genes (*e.g. RARB* and *HHIP*) play crucial roles in lung development by regulating branching morphogenesis (the development of the bronchial 'tree') during fetal life, the results of these genome-wide association studies suggest that genetic variations associated with lung development and growth might be important genetic determinants of lung function in childhood and adulthood, both in healthy subjects and in patients with airway disease (asthma and COPD).

Conclusions and future prospects

The monogenic diseases CF and $α_1$-antrypsin deficiency are inherited in a recessive Mendelian fashion (*i.e.* mutations in both alleles are required for the disease to be present). However, the term 'monogenic' is an oversimplification, since the causal gene interacts both with other genes and with environmental exposures in the course of the

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disease. Indeed, several modifier genes influence the severity of the disease in CF, implicating gene–gene interactions in its development. Active and passive smoking have deleterious effects in subjects with α_1-antitrypsin deficiency, implicating important gene–environment interactions in the pathogenesis of panlobular emphysema.

The most common chronic respiratory diseases – asthma and COPD – are complex airway diseases that result from interaction between multiple environmental exposures and many genetic risk factors. Thanks to the development of novel, powerful tools for genetic studies, many genetic loci have been discovered that are associated with asthma, allergy, smoking behaviour, lung function and COPD. Despite the impressive advances in the genetics of asthma and COPD in the past decade, major challenges remain. Firstly, a large proportion of the genetic variance in disease risk remains unexplained. Most genetic variants identified so far by genome-wide association studies confer relatively small increments in risk, and explain only a small proportion of familial clustering. The remaining, 'missing' heritability can be attributed to additional genetic variation as yet unidentified, including structural variation (*e.g.* copy number variation of genes) and rare sequence variation. Secondly, the biological pathways and molecular mechanisms involved in the pathogenesis of chronic airway disease need to be elucidated in order to translate these new genetic insights into better strategies for prevention and treatment.

Gene	Gene name	Gene function
HHIP	Hedgehog-interacting protein	Lung development
GPR126	G-protein-coupled receptor 126	Unknown
ADAM19	A disintegrin and metalloproteinase 19	Cell migration and adhesion, cell-matrix interactions
AGER	Advanced glycation end products receptor	Receptor for danger signals, pro-inflammatory gene activation
FAM13A	Family with sequence similarity 13, member A	Signal transduction
GSTCD	Glutathione S-transferase, C-terminal domain containing	Detoxification
HTR4	5-hydroxytryptamine receptor-4	Receptor for serotonin, modulates release of neurotransmitters
PTCH1	Patched 1	Receptor for HHIP, lung development
MMP15	Matrix metalloproteinase 15	Breakdown of extracellular matrix
TGFB2	Transforming growth factor-ß2	Embryonic development
HDAC4	Histone deacetylase 4	Transcriptional regulation, cell cycle progression and development
RARB	Retinoic acid receptor, beta	Transcriptional regulation, limits cell growth

Table 4 – Genes associated with lung function.

Current and future applications of genetic testing in respiratory medicine encompass screening (*e.g.* newborn screening for CF), antenatal diagnosis, early diagnosis and prediction of disease risk (*e.g.* risk of recurrent venous thromboembolism according to underlying inherited thrombophilia). Pharmacogenetic and pharmacogenomic applications will improve our ability to use drugs more effectively and with less risk (*e.g.* optimising the dosing of the anticoagulant warfarin according to the genetic constitution of the patient). Finally, this genetic revolution will lead to the discovery of novel causal pathways, guiding mechanistic research in respiratory diseases and revealing new therapeutic targets.

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Early-life events

Key points

- Major early-life risk factors for respiratory disease include abnormal antenatal lung growth, low birthweight, prematurity and bronchopulmonary dysplasia, passive smoke exposure and viral infections.
- Abnormal antenatal lung development is common and has a high mortality risk.
- Low birthweight and prematurity are key risk factors for respiratory disease.
- Tobacco smoke exposure, during pregnancy and after birth, can have respiratory repercussions throughout childhood, and is a risk factor for asthma and infectious illness.
- Respiratory viral infections in early childhood can have a long-term impact on childhood lung function and asthma or wheezing.

Infants born very prematurely can require supplementary oxygen for many months. Rehospitalisation is common in the first 2 years after birth and the majority of admissions are for respiratory disorders. Rehospitalisation is particularly increased in infants with bronchopulmonary dysplasia (BPD) who require supplementary oxygen for more than 28 days after birth, and in infants who have a respiratory syncytial virus (RSV) lower respiratory tract infection (LRTI) (see chapter 16). Respiratory symptoms continue to be common in schoolchildren who were born prematurely, and the most severely affected remain symptomatic in adulthood; an adverse outcome that may be more common in females. Prematurely born infants, particularly those who wheeze at follow-up, have evidence of airway obstruction (raised airway resistance and gas trapping) in the first 2 years after birth. Their lung function improves with increasing age, but even in adolescence there is evidence of airflow limitation in those who had had BPD, particularly in those with ongoing recurrent respiratory symptoms. Gas transfer abnormalities and airway hyperreactivity have also been described, and fixed airway obstruction has been reported in young adults who had severe BPD.

It is more than 20 years since it was first reported that airway function was diminished in adults born with low birthweight and it was speculated that

> *Respiratory symptoms continue to be common in schoolchildren who were born prematurely; the most severely affected remain symptomatic in adulthood*

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pre-natal nutrition might program fetal lung growth. Low birthweight, however, is only one of a number of early-life factors that might influence respiratory disease in children and adults; other factors potentially include breastfeeding, post-natal weight gain, maternal paracetamol use during pregnancy, maternal obstetric complications, and indoor and outdoor air quality. This chapter will focus on the major risk factors.

Abnormal antenatal lung growth

Abnormal antenatal lung growth, which may result in pulmonary hypoplasia (incomplete lung development), is common: it has been reported to be present in 15–20% of early neonatal deaths. The mortality rate is high, particularly if the abnormal growth has occurred either as a consequence of oligohydramnios with rupture of the membranes between 14 and 19 weeks of gestation, or in association with a congenital diaphragmatic hernia (CDH). It may be primary, but more usually occurs as a consequence of a variety of problems, which can largely be divided into those conditions that reduce intra-thoracic space, fetal breathing movements or amniotic fluid volume. It is also found in association with trisomy 18 and 21. Pulmonary hypoplasia may have a genetic basis, as the condition occasionally occurs in twins and families. Both pre- and post-natal malnutrition can adversely affect lung growth. Vitamin A is essential for normal alveolar development and vitamin A deficiency decreases alveolar septal development.

Antenatal interventions

Determining whether a fetus has an important chromosomal abnormality is key to providing appropriate counselling to parents regarding antenatal intervention with the aim of promoting lung growth. In the first trimester, however, both amniocentesis and chorion villus sampling have been associated with an excess of infant respiratory symptoms and abnormal lung function at follow-up.

Antenatal interventions that aim to prevent abnormal antenatal lung growth include: amnio-infusion, which can facilitate ultrasound examination but has not been shown to improve lung growth; and thoraco-amniotic shunting, which results in effective drainage of pleural effusions, facilitating resuscitation, but is usually performed too late

in pregnancy to influence lung growth. *In utero* surgical repair of CDH has been attempted, but a more promising technique is obstruction of the normal egress of fetal lung fluid by placing a balloon in the trachea.

Pre-natal antioxidant supplementation might be expected to influence fetal lung growth and development, and to reduce the oxidative stress implicated in the development of BPD. However, follow-up of infants entered into a randomised trial did not demonstrate improved infant respiratory outcome following maternal high-dose vitamin C and E supplementation.

Low birthweight

Children and adults with a low birthweight have been reported to be at increased risk of wheezing, respiratory infection and lung function abnormalities. This is true regardless of whether the low birthweight was the result of *in utero* growth retardation or premature birth. Despite antenatal and post-natal prophylaxis, small-for-gestational age infants, compared with those born with an appropriate birthweight for their gestational age, had worse neonatal and infant respiratory outcomes. There are modifiable risk factors of respiratory disease in those born with low birthweight: for instance, smoking has been reported to be more common in low birthweight adults.

Prematurity and BPD

Prematurely born infants, particularly those who had BPD, are at increased risk of chronic respiratory morbidity. BPD is diagnosed in infants who are dependent on oxygen for at least 28 days after birth. Prematurely born infants are classified at 36 weeks' post-menstrual age as having mild, moderate or severe BPD according to their respiratory support requirement at that date. In the past, infants who developed BPD had frequently suffered severe respiratory failure, necessitating both high inflating pressures and supplementary oxygen. Nowadays, BPD can occur in very prematurely born infants who initially had minimal or even no signs of lung disease: the so-called 'new' BPD. In new, compared with 'old', BPD, there is less interstitial fibrosis, but there is an arrest in acinar development resulting in fewer and larger alveoli; there is also a reduction in the number of arteries. It has been suggested that abnormal

vascular development may lead to abnormalities in lung growth and that new BPD is a maldevelopment sequence resulting from interference with or interruption of normal developmental signalling for terminal maturation and alveolarisation of the lungs of very pre-term infants.

BPD has a multi-factorial aetiology (figure 1). It can occur in infants born at term who had severe respiratory failure, but it is commonest in very prematurely born infants. It was originally thought that BPD was caused by oxygen toxicity: prematurely born infants are deficient in antioxidant enzyme systems at birth and have low levels of antioxidants, making them more vulnerable to oxygen toxicity. High airway pressures have been associated with the development of BPD, with an inverse relationship between carbon dioxide levels and BPD development. Volutrauma in the first minutes after birth may be injurious to the lungs. BPD is commoner in infants who develop a patent ductus arteriosus, particularly if this is temporally related to infection. Chorioamnionitis can increase the risk of BPD, but only if associated with 'other hits' such as post-natal infection and a requirement for mechanical ventilation for more than 7 days. Some infants have a family history of BPD and certain genetic polymorphisms have been associated with the development of BPD.

Tobacco smoke exposure

Antenatal smoke exposure is an important risk factor for increased respiratory symptoms and lung function abnormalities in infants and children. In children less than 2 years of age, the risk for lower respiratory illness has been found to be increased by 72% if the mother smoked. Although the observed increase in risk is lower in older children, parental smoking may nevertheless account for
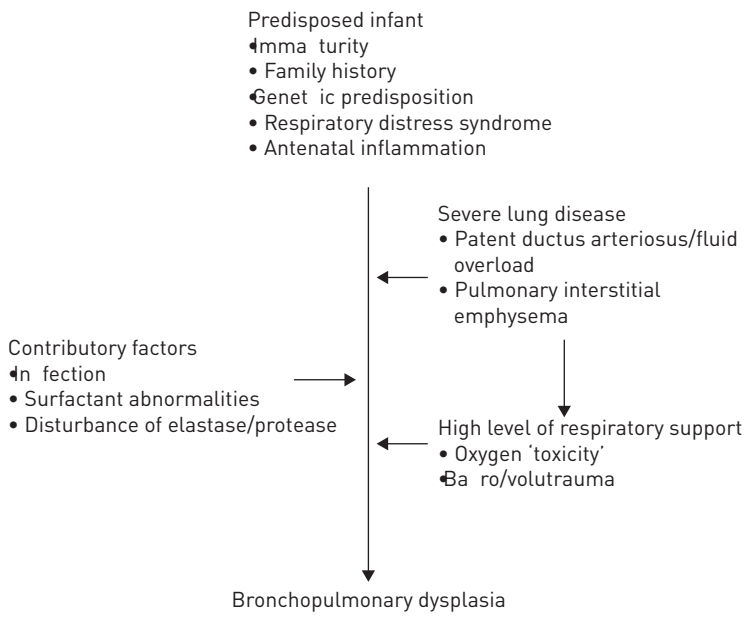
Predisposed infant
• Immaturity
• Family history
• Genetic predisposition
• Respiratory distress syndrome
• Antenatal inflammation

Severe lung disease
• Patent ductus arteriosus/fluid overload
• Pulmonary interstitial emphysema

Contributory factors
• Infection
• Surfactant abnormalities
• Disturbance of elastase/protease

High level of respiratory support
• Oxygen 'toxicity'
• Baro/volutrauma

Figure 1 – The multifactorial aetiology of bronchopulmonary dysplasia. Reproduced and modified from Rennie *et al.*, 2005, with permission from the publisher.

Bronchopulmonary dysplasia

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Pre-term birth	
Chronic illness	
	Bronchopulmonary dysplasia
	Other chronic lung disease
	Congenital heart disease
	Neurological disease
	Immunodeficiency
Maternal factors	
	Asthma
	Smoking during pregnancy
Environmental factors	
	Poverty
	Over-crowding
	Passive smoking

Table 1 – Risk factors for severe respiratory syncytial virus infection. Modified from GREENOUGH and BROUGHTON, 2005.

approximately 20% of all asthma in childhood. Maternal environmental tobacco smoke (ETS) exposure during the third trimester of pregnancy is associated with asthma and allergy-related symptoms in pre-school children. Certain infants may have a genetic susceptibility to the adverse effects of environmental smoke exposure, both maternal during pregnancy and in infancy. Antenatal smoking exposure has been demonstrated in some, but not all, studies to have an adverse effect on lung function in infancy. In older children, antenatal smoke exposure has been associated with a reduction in airway function. The effects of passive smoking exposure vary with genetic factors, sex, race and exposure to other pollutants. Exposure to ETS and subsequent active smoking both aggravate symptoms and have a negative effect on lung function. Passive smoke exposure in the first 3 months after birth also increases the risk of hospital admission for infectious illness. The association is strongest in the first 6 months after birth, but in vulnerable groups, such as prematurely born infants, the association has been shown to hold through to 8 years of age. Bronchiolitis also occurs more frequently in infants of mothers who smoke. Exposure in later childhood to ETS is associated with increased respiratory symptoms, although the effect appears to diminish with increasing age of the child.

Antenatal smoking exposure may have a more deleterious effect than passive smoke exposure after delivery. Analysis

of the British Births Survey data bank revealed that the incidences of admissions to hospital for a LRTI in the first 5 years after birth and of episodes of bronchitis were 2.3% and 14.1%, respectively, in infants of nonsmokers, 3.1% and 18.2% in infants whose mothers smoked only after birth, but 5.9% and 18.9% in infants whose mothers smoked only during pregnancy.

Viral infections in infancy

RSV is the most common respiratory pathogen in early childhood, with most children having had a RSV infection by 2 years of age. The majority of children suffer only a coryzal illness (common cold symptoms) requiring no medical intervention, but others develop bronchiolitis or RSV pneumonia requiring hospital admission and even intensive care. There are a number of risk factors for severe RSV infection (table 1) and therefore for increased respiratory illness at follow-up. Numerous studies have demonstrated that RSV infection in otherwise healthy infants born at term is associated with long-term respiratory sequelae. However, the effect appears to decrease with increasing age: in one cohort, although significantly more children who had had RSV LRTI wheezed up to 5 years of age compared to controls, there was no significant difference in children aged 5–10 years. Other studies report an increase in asthma in adults following RSV infection in infancy. However, the results of studies assessing bronchial hyperreactivity or allergic sensitisation following RSV infection in children born at term are conflicting. In prematurely born children who had BPD, hospitalisation due to RSV infection in the first 2 years after birth was associated with increased healthcare utilisation and associated costs up to 7 years of age. Lung function abnormalities at follow-up following RSV LRTI have been described in both term and prematurely born children.

The fact that 30–50% of children with viral-induced wheezing in infancy go on to develop asthma suggests that viral respiratory infections cause airway damage, promoting airway remodelling, leading to asthma. There is, however, evidence to suggest that infants who have symptomatic RSV LRTIs may have pre-existing diminished lung function, particularly small-airway abnormalities. In one study, however, the results were not significant and virology results were only available for the two infants who were hospitalised. Follow-up of the cohort highlighted that lung function level at 11 years of age was similar to the pre-infection level, suggesting that the infection had not had an adverse effect. In prematurely born infants, a higher resistance of the respiratory system at 36 weeks' post-menstrual age has been associated with more wheeze at follow-up following RSV LRTI and, in a larger cohort, with a greater requirement for RSV hospitalisation. Some single nucleotide polymorphisms (SNPs) have been associated with an increased risk of severe RSV infection as indicated by a need for hospitalisation. In addition, SNPs in genes coding for interleukin (IL)-8, IL-19, IL-20, IL-13, mannose binding lectin, interferon (IFN)-γ and RANTES (regulated upon activation, normal T-cell expressed, and secreted) have been associated with wheeze following RSV LRTI in term-born infants.

There is evidence that other respiratory viral infections may be associated with chronic respiratory morbidity in childhood. The chronic lung damage that can result

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> " _30–50% of children with viral-induced wheezing in infancy go on to develop asthma, which suggests that viral respiratory infections cause airway damage, promoting airway remodelling, leading to asthma_ "

from adenovirus infection in young children has frequently been reported. Asthma has been reported to be significantly more common in 5-year-old children who had been admitted to hospital with either human metapneumovirus (hMPV) or RSV bronchiolitis in infancy. Prematurely born infants with either a hMPV LRTI or a RSV LRTI have been found to be more likely to cough and wheeze at follow-up and have lung function abnormalities, particularly a higher airway resistance.

It may be that the impact of other viruses, particularly rhinovirus (RV), is even greater than that of RSV. Among children at increased risk of developing allergies and asthma, the most significant risk factor for the development of pre-school childhood asthma was the occurrence of a symptomatic RV illness during infancy. In another study, out of 14 respiratory viruses, RV was most likely to be associated with recurrent wheezing at 12 months in infants who had been hospitalised for their first episode of bronchiolitis.

A number of hypotheses have been put forward to explain the association of RV wheezing illnesses and asthma development. These include that predisposition by allergic sensitisation reduces IFN responses in infants with asthma. As a consequence, there is increased viral replication and impaired barrier function due to smoke exposure, pollution and/or virus infection, which again leads to enhanced viral replication, greater illness severity and airway damage. A 'double hit hypothesis' for atopy and viral infection has been proposed as, in the Perth Birth Cohort, there was an increase in the odds ratio of developing asthma at age 6 years in patients with a greater number of viral respiratory infections in the first year after birth who were atopic. In that cohort, RV was the most common pathogen associated with an acute respiratory infection in the first year after birth. Prospective follow-up of another cohort demonstrated that allergic sensitisation preceded RV wheezing but the converse was not true. Hence, the researchers suggested that the timing and plausible mechanisms by which allergic sensitisation led to more severe RV illness supported a causal role for allergic sensitisation in that developmental pathway.

It has been suggested that the development of asthma may be related to immature immune responses to respiratory viruses and that the timing of the viral respiratory infection is an important predictor of asthma. In the Tennessee Database study, infants born 4 months prior to the winter virus peak were 30% more likely to have asthma

than infants born 12 months before the winter virus peak. Viral infections, RV in particular, can activate a number of pro-inflammatory and airway remodelling pathways that might have deleterious effects on the rapidly growing airways of young children. There may also be a functional predisposition to RV-associated wheeze, as an increased risk of wheeze has been reported in infants with a higher pre-infection resistance of the respiratory system.

Wheezy bronchitis

Although children with wheezy bronchitis achieved normal lung function in early adulthood, when they were re-examined at age 45–50 years they had undergone a more rapid decline in lung function than controls. If such a rate of decline were to persist, it may predispose to the development of chronic obstructive pulmonary disease (COPD) in later life. COPD development is also related to indoor and outdoor pollutants.

Conclusion

There are many early-life risk factors for respiratory disease in children and adults, a number of which are preventable. It is important that prospective parents receive better advice about the adverse effects smoking could have on their infant. Effective prophylactic agents against respiratory viruses, particularly rhinovirus, need to be developed and evaluated appropriately. Invasive antenatal interventions, therapeutic or diagnostic, should only be introduced into routine clinical care after their impact on the infant has been carefully evaluated. Further, randomised trials with the outcome of respiratory status at follow-up are required to determine the best management of very prematurely born infants.

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Diet and nutrition

Key points

- Aspects of diet are risk factors for several respiratory diseases, but it does not always follow that dietary interventions are effective.
- Normal-weight and overweight people have lower respiratory mortality than underweight people.
- Intervention aimed at restoring fat-free mass is recommended in chronic obstructive pulmonary disease.
- A 'balanced diet' with plenty of fruit, vegetables and fish reduces the risk of developing lung diseases, particularly asthma and chronic obstructive pulmonary disease.

Most respiratory diseases result from complex interactions between genes and the environment. Since altering the former is currently impracticable, increasing attention has been given to the management of important environmental factors, such as physical inactivity, air pollution, smoking and diet. There is now a large body of evidence supporting the role of diet in the pathogenesis of respiratory disease, as well as the health value of certain nutritional interventions; for example, in the context of pulmonary rehabilitation.

This chapter summarises the evidence for poor nutrition as a risk factor for, and modulator of, chronic obstructive pulmonary disease (COPD), allergy and asthma, lung cancer, venous thromboembolism and respiratory infections. It reviews the field of nutritional assessment and the effect of nutritional interventions in respiratory diseases. It concludes with recommendations from the World Health Organization (WHO) and academic societies for primary and secondary prevention of respiratory disease.

Diet as a risk factor

Even in developed societies, populations and individuals are exposed to two main potential nutritional hazards: over-nutrition and

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> " *A major area of recent progress in cystic fibrosis has been the emphasis on the central role of under-nutrition* "

under-nutrition. In 2013, a large meta-analysis of data on healthy cohorts, which included 2.88 million subjects, showed that a body mass index (BMI) of up to 30 kg·m^{-2} – the boundary between 'overweight' and 'obese' – could have a protective effect against death. Furthermore, in a large population-based cohort of more than 1 million South Koreans aged 30–95 years, who were tracked for 12 years, over-nutrition had clear protective effects against death from respiratory causes in nonsmoking women and in both smoking and nonsmoking men. Diet surveys and, more recently, dietary pattern analysis have shown that in addition to abnormal overall calorie intake, the intake of individual nutrients and certain dietary behaviours can have protective or harmful effects. This approach has been used to investigate the role of diet in several chronic diseases, but so far there have been few studies relating to respiratory diseases. Study of dietary patterns may provide insight into combinations of foods and/or nutrients that have a positive or negative impact on the prevalence or severity of respiratory diseases. It should, however, be understood that the existence of an epidemiological link between a risk factor and a respiratory phenotype does not necessarily mean that interventions aimed at modifying diet are justified: large prospective and randomised controlled studies must be carried out first (table 1).

Obstructive lung diseases

Asthma

In asthma, both dietary exposures themselves (food, nutrients and dietary patterns) and the periods of exposure (antenatal, childhood, adulthood) are relevant to the pathogenesis and progress of the disease.

Dietary antioxidant intake has been associated with asthma throughout life. Cohort studies covering the antenatal period have suggested a link between childhood asthma and reduced maternal consumption of vitamin E, zinc, fruit and vegetables; however, randomised controlled trials (RCTs) are lacking. A recent meta-analysis of 62 studies on the effect of childhood food and nutrient intake on the risk of developing wheezing or asthma concluded that there was some evidence (although weak) of protective effects from vitamins A, D, and E, zinc, fruit and vegetables, and of a Mediterranean diet, against the development of asthma. In adults, an

Conditions	Epidemiological study data	Effectiveness of intervention, primary prevention#	Effectiveness of intervention, secondary prevention#	Available recommendations
Allergy and asthma	Risk factors: low level of antioxidants, low vitamin D status, high ratio of omega-6 to omega-3 polyunsaturated fatty acids. Protective factors: Mediterranean dietary pattern during childhood (but conflicting results in adults)	NA	NA	No specific recommendations
COPD and chronic respiratory failure	Risk factors: related to 'Western', 'traditional' dietary patterns, cured meat. Protective factors: fruit, vegetables and fibre	NA	Of three RCTs, one was positive for slowing the decline in FEV1. A meta-analysis (2012) showed a positive impact for oral supplementation on body composition and functioning in under-nourished patients with COPD	WHO recommendations on chronic diseases (2009). ATS/ERS guideline on pulmonary rehabilitation (updated 2013)
Lung cancer	Protective factors: fruit and vegetables	Two chemoprevention RCTs were negative for benefit, with higher risk in the β-carotene supplement arm; positive long-term prevention in subjects with high intake of fruit, vegetables and carotenoids	Negative results for nutritional support	No specific recommendations
Venous thromboembolism	Risk factor: high BMI	NA	NA	Obesity prevention in general population
Lung infections	Risk factors: low vitamin D status, under-nutrition	RCTs positive for vitamin D intake	RCTs positive for vitamin D intake	General recommendations for vitamin D intake
Cystic fibrosis	NA	NA	Positive cohort studies but no RCTs	Specific recommendations for nutritional support to prevent under-nutrition

Table 1 – Dietary risk factors, protective factors and interventions in respiratory diseases. COPD: chronic obstructive pulmonary disease; NA: not available; RCT: randomised controlled trial; FEV1: forced expiratory volume in 1 second; WHO: World Health Organization; ATS: American Thoracic Society; ERS: European Respiratory Society; BMI: body mass index. #: primary prevention is the prevention of a disease in healthy people; secondary prevention aims to halt or slow worsening of a disease in people who already have the disease.

association between asthma and lower intake of antioxidants has been reported but data from RCTs do not support supplementation with vitamin C or selenium.

During the antenatal period, and throughout life, observational studies have reported associations between asthma and a high intake of omega-6 polyunsaturated fatty acids, as well as a decreased intake of omega-3 polyunsaturated fatty acids. However, RCTs are either lacking or show minimal or no benefit for dietary intervention in adults.

Birth cohort studies to examine the association between maternal dietary intake of vitamin D during pregnancy and wheezing and asthma have yielded conflicting results. Studies on children already diagnosed with asthma have shown an association between low levels of vitamin D and asthma exacerbations. These studies have also shown that in patients with mild or moderate persistent asthma treated with inhaled corticosteroids, vitamin D sufficiency is associated with better lung function. These results suggest that vitamin D levels should be monitored in asthmatic children. A longitudinal study conducted in children in Australia reported that low vitamin D levels measured at 6 and 14 years of age were predictive of allergy phenotypes and bronchial hyperresponsiveness, but not of asthma, at those ages. However, low vitamin D levels at 6 years of age were predictive of later asthma and atopy phenotypes at 14 years of age. One RCT using data from the Northern Finland Birth Cohort 1966 reported that high-dose vitamin D supplementation in infancy was associated with an increased risk of atopy, allergic rhinitis, and asthma later in life (at age 31 years). Few studies have been conducted in adults, but a recent US study reported a strong protective effect of vitamin D against wheezing and exacerbations of asthma, supporting the notion that vitamin D status might influence the risk of respiratory disease.

Studies do not support an association between dietary pattern during pregnancy and asthma or wheezing in the child. Although research suggests an association between children's dietary patterns and asthma and wheezing, all such studies have been cross-sectional and therefore, in theory, prone to incorrect attribution of cause and effect. In adults, the overall results are conflicting: cross-sectional studies suggest that certain dietary patterns are associated with asthma, but these findings have not been confirmed in longitudinal surveys. Few studies relating asthma severity and control to diet have been performed, but 'Western'-type dietary patterns (*e.g.* refined grains, cured and red meats, desserts, French fries) are reported to be associated with a higher frequency of asthma attacks and with poor asthma control.

Chronic obstructive pulmonary disease
The main risk factor for COPD in the developed world is cigarette smoking, but up to one-third of patients with COPD (especially in developing countries) have never smoked, implying that other factors are also important. Diet is probably one such factor, but data on a diet–COPD association remain scarce.

Over the past decade, there has been growing research into dietary factors with antioxidant or anti-inflammatory properties that might affect lung function or COPD symptoms. Most of these epidemiological studies have been cross-sectional, but a

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few longitudinal studies have reported associations between specific dietary factors and a slower decline in lung function. In large prospective epidemiological studies in the USA, it was reported that a high intake of a 'prudent' dietary pattern (*e.g.* fruit, vegetables, fish, whole-grain products) decreased the risk of newly diagnosed COPD, whereas a high intake of a Western-type pattern increased risk. More recently, it has been reported that a 'traditional' dietary pattern (with high intake of red meat, processed meat, boiled vegetables, added fat, coffee, beer, and potatoes, but reduced consumption of soy products, low-fat dairy products, tea, breakfast cereal, brown rice, pizza, juice and fruit) was associated with reduced lung function and a higher prevalence of COPD. A high intake of refined foods was associated with an accelerated decline in lung function over 5 years.

In relation to specific foods, special attention has been paid to fibre intake. It has been reported among several groups that dietary fibre intake has independent inverse associations with the incidence and symptoms of COPD and with decline in lung function. In addition to foods and nutrients with potential beneficial effects, several studies have focused on those with potential harmful effects. Two studies have reported associations between frequent or high consumption of cured meats and the risk of developing COPD. A recent study has extended this association to include the evolution of the disease, revealing that high cured meat consumption is linked to a higher risk of readmission to hospital with COPD.

Nutritional factors are also important in relation to mortality from COPD, with reports from diverse clinical settings showing that a low BMI is a major predictor of mortality among patients with COPD. The poor prognosis for COPD patients with a low BMI has been confirmed by a study showing that mortality is higher among COPD patients with recent weight loss.

Other respiratory diseases

Lung cancer

Lung cancer is the leading cause of cancer-related death worldwide in men and the second-commonest cause in women. Evidence from several observational, retrospective and prospective studies strongly suggests that high consumption of fruit or vegetables, or both, reduces the risk of lung cancer by approximately 20–30%, with a similar magnitude of reduction for current smokers, ex-smokers and never-smokers.

However, vitamin supplementation has not been shown to decrease lung cancer risk. In fact, the results of two major primary randomised prevention trials of vitamin supplementation showed a higher lung cancer incidence in the group receiving high doses of beta-carotene. A re-analysis of data from the beta-Carotene and Retinol Efficacy Trial (CARET) showed that a high intake of fruit and vegetables decreased the risk of lung cancer in the placebo arm after 12 years of follow-up. Similarly, in the Alpha-Tocopherol Beta-Carotene (ATBC) trial, after 14 years of follow-up, higher dietary intake and serum levels of carotenoids, including carotene, were related to a lower risk of lung cancer. These findings suggest that other potentially protective dietary factors associated with fruit and vegetable intake are playing a part.

Venous thromboembolism

In a prospective cohort study of 87 226 female nurses, the risk of new cases of pulmonary embolism was nearly six-fold higher among those with a BMI of ⩾35 kg·m^{-2}. The risk was present in multiple subgroups and increased in linear fashion with BMI.
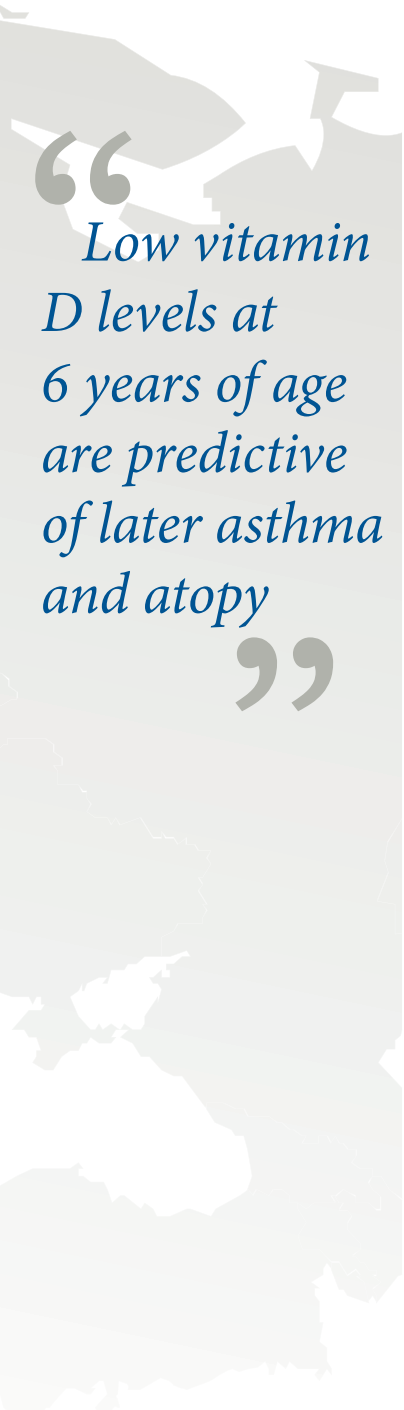
Respiratory infections

Although the respiratory tract is only the third-commonest site of infection in the body, it is the commonest site of fatal infections, which often represent the 'final common pathway' complicating the many effects of under-nutrition. For example, deaths among the malnourished are frequently due to pneumonia. The D vitamins have a demonstrated protective effect in preventing lung infections.

Nutritional status and interventions

Chronic obstructive pulmonary disease

As with other chronic diseases, COPD is often accompanied by abnormalities of body composition. This can mean loss of muscle bulk and cachexia ('wasting'), but also, increasingly, it means obesity. Various indices can signify under-nutrition in COPD: these include a BMI of <21 kg·m^{-2}, involuntary loss of more than 5% of total bodyweight in the past year, and a low fat-free mass index (<15 kg·m^{-2} in women or <16 kg·m^{-2} in men).

Nutritional depletion in COPD results from multiple and complex mechanisms, and nutritional intervention alone cannot address all of the issues raised. Consequently, clinical guidelines recommend nutritional intervention in the context of pulmonary rehabilitation in all patients with COPD, particularly in those who are already nutritionally depleted. After decades of scepticism, nutritional intervention aimed at restoring fat-free mass is now recommended and a recent meta-analysis of original data has shown a positive benefit from such supplementation. Nutritional intervention in COPD should be integrated into pulmonary rehabilitation, both at an early stage and in end-stage disease when patients are on long-term oxygen therapy and/or noninvasive ventilation.

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Allergies and asthma

Epidemiological findings underscore the importance of conducting prospective studies and clinical trials to clarify the role of antioxidants, omega-3 polyunsaturated fatty acids and vitamin D in asthma and wheezing, in both children and adults. Further studies are also needed to better understand how dietary habits might modulate asthma severity and/or control in adults. A recent exhaustive review of the association between asthma and diet concluded that until the results of forthcoming trials are available, the practical consequences of research linking diet with asthma are minimal, and, based on current evidence, people with asthma, pregnant women, parents, and children should not be advised to change or supplement their diet to treat or reduce the risk of developing asthma.

Clinical epidemiological studies suggest a strong relationship between obesity and poor control of asthma, and treatment by bariatric surgery has been advocated to control very severe cases.

Bronchial carcinoma

Nutritional principles indicate that a healthy diet should include at least moderate amounts of fruit and vegetables, but the available data suggest that general increases in fruit and vegetable intake would have little effect on cancer rates, at least in well-nourished populations. Advice in relation to diet and cancer should include the recommendation to consume adequate amounts of fruit and vegetables, but should put most emphasis on the well-established adverse effects of obesity and high alcohol intake. Specific nutritional intervention in patients treated for lung cancer has not resulted in a better quality of life.

Obstructive sleep apnoea syndrome and obesity hypoventilation syndrome

Obesity, especially affecting the trunk and neck, is a major risk factor for obstructive sleep apnoea syndrome (OSAS); although other factors may contribute to its pathogenesis, obesity is reported in 60–90% of individuals with OSAS. Patients with obesity hypoventilation syndrome (OHS) usually have very severe obesity, often in the 'morbid' range (a BMI of >40 $kg \cdot m^{-2}$). Although OHS is much less common than OSAS, its prevalence is increasing in many countries, in parallel with the 'epidemic' of obesity in the population. Either OSAS or OHS may coexist with COPD, particularly in

smokers, increasing morbidity. Weight loss may lead to resolution of OSAS or OHS but, even if successful, this is likely to take several months and in severely obese individuals, bariatric surgery may be indicated. Effective treatment of the breathing problems should not be delayed while waiting for weight loss to occur (see chapter 23).

Cystic fibrosis

A major area of recent progress in cystic fibrosis has been the emphasis on the central role of under-nutrition. The patient's diet and BMI are monitored very closely, and pancreatic enzyme supplementation should be used to combat pancreatic insufficiency.

Amyotrophic lateral sclerosis

Amyotrophic lateral sclerosis is a cause of severe weakness of the respiratory muscles. Enteral nutrition (feeding directly into the stomach or lower down the digestive tract), together with noninvasive ventilation can offer palliation and prolongation of life with acceptable side-effects. Percutaneous endoscopic gastrostomy (PEG) should be considered to stabilise weight and to prolong survival.

Clinical recommendations

The following are drawn from recommendations by WHO, the European Food Safety Authority (EFSA), the European Respiratory Society (ERS), the American Thoracic Society (ATS) and the Société de Pneumologie de Langue Française (SPLF).

Eating foods rich in antioxidants can counter the damage done to the body by oxidative stress, as antioxidants effectively 'mop up' free radicals and so prevent them from causing damage. Sources of vitamin C include citrus fruits (oranges, lemons, grapefruit), kiwi fruit, broccoli and green peppers; beta-carotene is present in apricots, mangoes, carrots, peppers and spinach; vitamin E can be found in grains, wheatgerm, almonds and peanuts; lycopene is found in tomatoes and processed tomato products; and grains, Brazil nuts, animal products (especially organ meats) and seafood contain selenium.

Magnesium is the fourth-most abundant mineral in the body and is essential for good health. Magnesium aids the action of the enzymes that facilitate the chemical reactions in the body. Magnesium may also help the airway smooth muscle to relax and help control the body's response to infection. It is found in nuts, cereals, seeds, carrots, spinach and seafood.

Omega-3 polyunsaturated fatty acids are essential for good health but are deficient in most people's diets. Omega-6 fatty acids are also essential but are over-consumed. The ideal ratio of omega-6 to omega-3 in the diet is 4 to 1. However, in the average modern diet the ratio is closer to 20 to 1. Omega-3 fatty acids are found in oily fish and shellfish, soy and leafy vegetables.

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A balanced diet

A balanced diet with a high intake of fruit, vegetables and fish reduces the risk of developing lung diseases, especially asthma and COPD. Although the effects of diet on the lungs are still under study, it is clear that the following advice can help to maintain good lung health:

- Eat a balanced diet with a lot of fruit, vegetables and fish.
- Reduce salt intake.
- Restrict the amount of trans- and omega-6 fatty acids in the diet.
- Maintain an ideal weight, with a BMI of 21–30 kg·m^{-2}.
- Undertake moderate exercise.

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Outdoor environment

Introduction ⓘ

Key points

- A large proportion of the European population lives in areas with unhealthy outdoor air quality, and is thus unable to avoid exposure to the harmful effects of pollution.
- The health effects of outdoor air pollution are the result of a mixture of gaseous and particulate pollutants, acting independently and in concert.
- The acute and chronic effects of outdoor air pollution are distinct from each other and must be studied independently.
- Daily variations in outdoor air pollution cause daily variations in mortality and respiratory symptoms.
- In the long term, outdoor air pollution can reduce life expectancy, affect lung development, increase asthma incidence and lead to other chronic respiratory diseases.

Like tobacco smoke, ambient air pollution is a well-established cause of morbidity and mortality. However, unlike smoking, air pollution is not a lifestyle choice but a ubiquitous involuntary environmental exposure, which can affect 100% of the population from the womb to death. Large parts of the European population continue to live in areas with unhealthy air quality. For some pollutants and in some regions, this situation is not improving and is even deteriorating. Changes in combustion and fuel technologies, industrial production, movement of goods and urban planning affect the constituents, and thus possibly the toxicity, of air pollution, in addition to the degree of exposure.

Pollution: composition/sources

Air pollution results from a complex mixture of thousands of pollutants. This mixture may include solid and liquid particles suspended in the air (particulate matter (PM)), and various gases such as ozone (O_3), nitrogen oxides (NO_2 or NO_x), volatile organic compounds (VOCs), and carbon monoxide (CO). The mixture varies with geographical location and the sources of the emissions. Particles vary in number, size, shape, surface area and chemical composition, while both particles and gases may vary in solubility and toxicity. The most important processes causing air pollution relate to the combustion of fossil fuels used in cars and

> *Air pollution is a ubiquitous involuntary environmental exposure, which can affect 100% of the population from the womb to death*

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trucks, aeroplanes, vessels or other engines, as well as in industries, power plants or household heating systems. Due to the close proximity of people to emissions, transport-related activities, particularly the use of cars and trucks, are an important source of air pollutants.

Traditionally, studies of the health effects of air pollution have measured some marker of air pollution, *e.g.* size-specific PM fractions, such as particles with an aerodynamic diameter of <10 µm (PM10) or <2.5 µm (PM2.5), respectively, or NO_2. Commonly used indirect markers of traffic-related pollutants are traffic density at the nearest road or residential distance from busy roads.

Pathophysiological effects of air pollutants

While experimental studies have shown a range of effects related to single pollutants, it should be emphasised that the effects of ambient air pollution cannot be assigned to a single pollutant in the mixture. As in the case of tobacco smoke, many pollutants act together in a series of partly interrelated mechanisms, which result in the observed associations between levels of air pollution and a range of health outcomes. Oxidative stress and both local and systemic inflammation are suggested to be the main harmful mechanisms set in train following the inhalation of these pollutants. A first step may be the generation of reactive oxygen species in the lung cells (*e.g.* from contact with the carbon core of inhaled particles where toxic substances such as sulfates, nitrates and metals are adsorbed). PM of various sizes and highly oxidative gases (*e.g.* O_3 or NO_x) have been shown to induce local pulmonary reactions related to oxidative stress. Both local and systemic inflammatory reactions, mediated through cytokines and chemokines, have been found in experimental studies in cellular systems and in animals, as well as in exposure-chamber studies with human subjects.

Claims that one specific aspect or constituent of ambient air pollution is 'more important' than others need to be interpreted with great caution. Such comparisons are inherently difficult to make, as the effect also depends on the health outcomes under study, the timescale (*e.g.* acute *versus* long-term effects) being considered, the underlying susceptibilities of the exposed individuals, and possibly the nature and concentrations of the co-pollutants.

> *The daily number of deaths tracks daily fluctuations in air pollution*

Marker of air pollution	Questionnaire-based respiratory health data	Objective respiratory markers	Biomarkers of effect	Health system use	Acute effects on mortality	Long-term effects on mortality/ life expectancy
Particulate matter	Respiratory symptoms	Diminished lung function, impaired growth of lung function	Airway inflammation, chronic lung disease	Emergency admissions for respiratory diseases, asthma	Increase in daily mortality	Increased mortality from cardiopulmonary diseases
Ozone	Respiratory symptoms	Diminished lung function	Airway inflammation	Emergency admissions for asthma	Increase in daily mortality	Suggestive for respiratory death
Nitrogen oxides	Respiratory symptoms	Increased bronchial reactivity, impaired growth of lung function	Airway inflammation alteration in lung immune defences	Emergency admissions for respiratory diseases	Increase in daily mortality	Increased long-term mortality from cardiopulmonary diseases

Table 1 – Examples of established associations between frequently used markers of ambient air pollution and various respiratory health outcomes. Markers of air pollution are often correlated with each other and the health effects are often nonspecific. While urban air pollution is considered a cause of these adverse health effects, specific effects cannot be assigned to single pollutants.

Respiratory health effects

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The respiratory tract is the portal of entry of air pollutants, and thus the lung is the first organ affected. The range of respiratory diseases that can be caused by air pollution exposure is large. Studies on the health impacts of air pollution differentiate between acute and chronic effects. The acute effects of pollution may be apparent within hours or days of exposure, but other health effects of air pollution result from long-term exposure, leading to chronic disease. While the acute and chronic effects of air pollution are partly interrelated, the distinction is important when planning and interpreting epidemiological studies as well as for policy making. Table 1 summarises the most important respiratory health effects of air pollution and how they can be measured.

Short-term respiratory effects of air pollution

Daily mortality
Several epidemiological studies have shown that the daily number of deaths, mainly from cardiovascular and respiratory diseases, tracks daily fluctuations in air pollution. A seminal European multi-city time-series analysis, APHEA (Air Pollution and Health: A European Approach), carried out in 29 study centres, found an increase of deaths from illness of 0.6% per 10 $\mu g \cdot m^{-3}$ increase in daily PM_{10} concentration, and data from hundreds of cities around the world have shown similar results. Studies on short-term mortality show that in general the air pollution-related relative risk is higher for respiratory outcomes than for cardiovascular ones, but since more people die from cardiovascular diseases, the absolute number of cardiovascular deaths related to air pollution is as large as, or larger than, the number of respiratory deaths attributable to air pollution.

Daily respiratory exacerbations
The daily variation in disease burden due to urban pollution is also shown by increases in the number of emergency hospital visits and admissions due to respiratory diseases, including asthma. The APHEA study reported increases per 10 $\mu g \cdot m^{-3}$ change in daily PM_{10} concentration of: 1.2% for asthma in children; 1.1% for asthma in adults aged up to 64 years; and 0.9% for all respiratory diseases (including chronic obstructive pulmonary disease (COPD), asthma and other respiratory diseases) in the elderly.

Patients with asthma, especially children who are not receiving anti-inflammatory or bronchodilator therapy, suffer more on or after days with higher pollution levels. Because of the large individual day-to-day variation in, and the many concomitant factors that influence, asthma symptoms, effects in asthmatic patients are not easily demonstrable without strict adherence to the study protocol and individualised exposure assessment. However, panel studies (longitudinal studies in which participants repeatedly provide information over some period of time) on asthmatic patients employing such rigorous methods have noted increased wheezing, cough and attacks of breathlessness, accompanied by poorer lung function and the need for additional medication, associated with daily variations in PM, NO_2 and/or O_3.

Weather influences the daily variation of pollutant concentrations considerably, with both unduly high (such as heatwaves) and low temperatures having consequences for health. Therefore, all studies on the short-term effects of air pollution need to take account of the effects of weather and other factors that vary over time. Modern

epidemiological methods enable the effects of such covarying factors to be disentangled from those attributable to the pollutants.

Long-term consequences

Long-term or lifetime exposure to ambient pollutants may also have pathological effects that eventually result in chronic ailments. The investigation of these effects usually requires large studies and, ideally, follow-up investigations over many years; consequently, fewer studies have investigated these types of effects. However, in the past 10 years, several studies have also confirmed the existence of chronic adverse effects of ambient air pollution.

Mortality and life expectancy

Mortality and life expectancy are important markers of lifetime morbidity and therefore play an important role in air pollution research. Studies conducted in Europe, the USA and Canada have confirmed that the overall effects of pollution on mortality are far larger than the fraction attributed to acute exposures. In general, respiratory disease is less often the cause of death than cardiovascular disease, and the two are often combined in the category of cardiopulmonary mortality. Cardiopulmonary mortality was associated with long-term differences in PM and sulfate concentrations between cities in the Harvard Six Cities Study and in the American Cancer Society (ACS) study. Comparison of community-level concentrations of fine PM with death rates 16 years later among more than 500 000 participants in the ACS study showed a 6% increase in cardiopulmonary deaths per 10 µg·m^{-3} of PM2.5 in models taking a range of other factors into account. In a further analysis of the data from the Los Angeles (USA) area after 18 years of follow-up, modelled PM2.5 concentrations were assigned to each residence. This more accurate assignment of exposure resulted in larger mortality estimates, with cardiopulmonary mortality increasing by 20% per 10 µg·m^{-3} increase in concentration of PM2.5. While traffic-related pollutants continue to play a dominant role in Europe, other sources of air pollution – including biomass burning or PM during Saharan dust episodes – also result in adverse effects.

Cohort studies in Europe have been able to confirm the relationship between cardiopulmonary death risk and pollution (figure 1). In three European studies, it was possible to analyse the data for respiratory and cardiovascular mortality separately. The results showed that urban air pollution, assessed individually for all participants by modelling traffic emissions of NO$_x$, was associated with overall mortality,

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mortality from ischaemic heart diseases, respiratory mortality, lung cancer mortality and (weakly) with cerebrovascular mortality. A Dutch cohort study with 20 years of exposure data observed weak associations of traffic density on the nearest main road with cardiopulmonary death. Respiratory deaths were related to NO_2, black smoke, traffic density within a radius of 100 m, and living near a main street.

Chronic respiratory disease in children

Children are more active and engage in more outdoor activities than adults. They breathe more rapidly and their metabolic rate is higher. Children's immune systems are not fully developed, so the incidence of respiratory infections is high. Their lungs are still growing and any deficit in growth will have an impact for the whole of the child's life. Moreover, possible confounding or modifying factors, such as active smoking, occupational exposure to dust and smoke or medical treatment, are largely absent, making the interpretation of epidemiological results more straightforward. Investigations into the development of lung function in children and the incidence of asthma – the most important chronic disease in children – are particularly relevant and interesting.

Symptoms

As early as the 1980s, several cross-sectional studies from Germany, Switzerland, France and the USA showed that school-age or pre-school children in communities exposed to higher levels of dust, sulfur dioxide (SO_2) and NO_2 suffered more from cough and acute bronchitis than children in less polluted regions. This phenomenon has been confirmed in recent studies.

Lung function (spirometry)

More recently, many cross-sectional studies have reported lower lung volumes in children living in more polluted areas. Of outstanding importance is the largest and most detailed long-term study ever conducted on air pollution and lung development in children, namely the University of Southern California (USC) Children's Health Study from the greater Los Angeles area. Several cohorts recruited during elementary or middle school and followed into adulthood confirm that ambient air pollution jeopardises the development of children's lungs, resulting in lower lung volumes and maximum expiratory flows at 18 years of age.
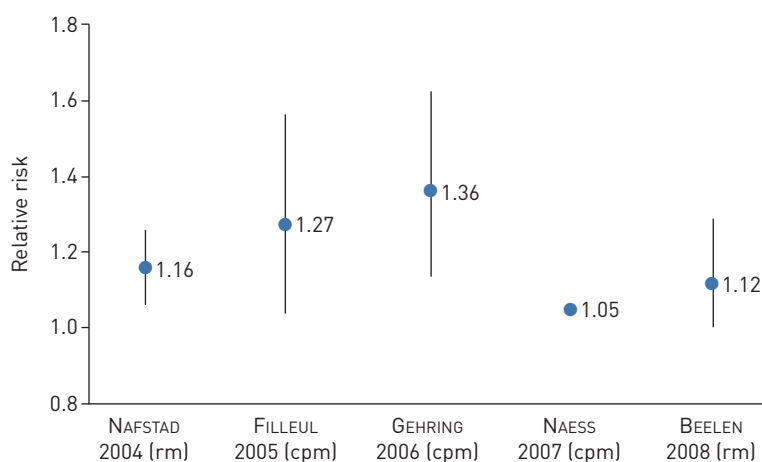

Figure 1 – Relative risks (RR) for respiratory (rm) or cardiopulmonary (cpm) mortality with 95% confidence intervals from European cohort studies on air pollution expressed per 10 µg·m^{-3} increase in NO_2 or NO_x.

Childhood asthma

While exacerbations of asthma clearly correlate with air quality, geographical comparisons of the prevalence of asthma or allergies do not follow differences in urban background levels of pollutants, such as PM2.5 or PM10. Novel approaches now integrate local measurements of traffic-related pollutants, geographic information systems, information about land use and spatial modelling techniques to characterise the local distribution of traffic-related pollutants within communities. People living alongside busy roads experience several-fold higher exposures to traffic-related primary pollutants than people living some 50–100 m further away. Epidemiological studies investigating the prevalence of childhood asthma as a function of proximity to traffic strongly suggest that living close to a busy road increases the risk of developing asthma in childhood, even with confounding factors taken into account. Despite rather different urban structures, traffic patterns and car fleets, this finding has now been confirmed in seminal cohort studies both in the USA (*e.g.* the USC Children's Health Study) and Europe. Most importantly, a European birth cohort, with children followed up to 8 years of age, has confirmed a higher incidence of asthma related to ambient air pollution. The results of the USC study are strongly suggestive that there is an interaction between genetic factors and exposure to traffic-related pollutants.

The contrasting lack of association between asthma onset and urban background pollution, and the strong associations between proximity to traffic arteries and asthma incidence – controlling for socioeconomic differences – suggests that those pollutants occurring at very high concentrations along street corridors (*e.g.* ultrafine particles, black carbon, particle-bound metals) play a key role in the genesis of asthma. Indeed, several recent reviews have concluded that near-road traffic-related air pollutants are causally related to the development of asthma in childhood. Urban planning decisions may therefore have major public health implications. The results place diesel cars, trucks and buses that emit particularly high concentrations of soot and large numbers of very toxic substances loaded on particles from exhaust, abrasion, and suspension, at the centre of the policy debate. While some believe that the impact of traffic-related air pollution on asthma prevalence is small, several health impact assessment studies have now confirmed that the public health burden of living close to a busy road is substantial. This is particularly the case in Europe, where a large proportion of urban citizens live along heavily trafficked street canyons.

Chronic respiratory disease in adults

The most important risk factor for chronic respiratory diseases in adults is smoking, and the health effects of
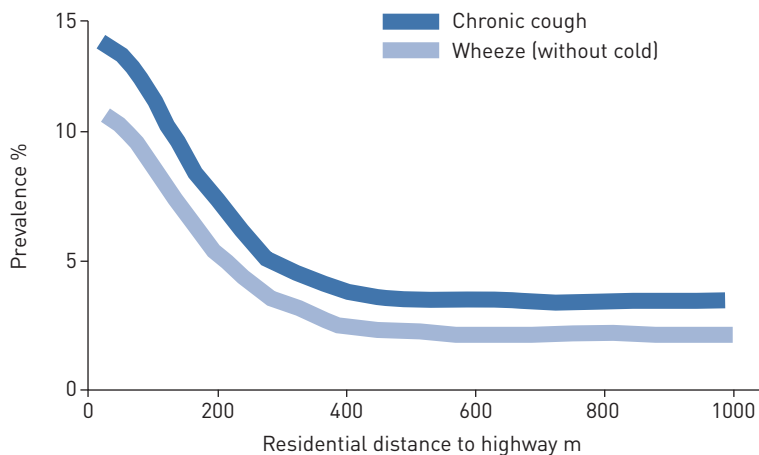
Figure 2 – Frequency of cough and wheeze is highest in Swiss adults living close to the highway. The spatial distribution of symptoms follows the spatial distribution of near-road traffic-related pollutants such as ultrafine particles, diesel soot, carbon monoxide and other primary pollutants. Associations are adjusted for other risk factors. Adapted from Hazenkamp-von Arx *et al.*, 2011.

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smoking and ambient air pollution have much in common. Studies evaluating the impact of outdoor air pollution on diseases such as COPD and asthma in adults need to take into account the inter-correlation of these factors, in addition to individual traits such as age, sex and genetic factors. Results based on people who have never smoked are particularly valuable.

Symptoms
Chronic cough and phlegm have been associated with long-term ambient PM exposure in several repeated cross-sectional studies in the USA and Europe. The Swiss study on Air Pollution and Lung Disease in Adults (SAPALDIA) confirmed that the prevalence of chronic symptoms declined as individually assigned home outdoor air quality improved. Some studies have shown that respiratory symptoms are more prevalent among participants living close to main streets, independently of background pollutant concentrations. As mentioned in the introduction to this chapter, air pollution is a complex mixture of constituents and such findings may indicate the independent role of some pollutants (or clusters of pollutants) in causing the same or similar health responses. Figure 2 shows the distribution of the prevalence of cough and wheeze among Swiss adults as a function of their residential distance from the highway. This cross-Alpine transit route is the dominant source of primary traffic-related pollutants in this rural valley. In contrast to more homogenously distributed fine particles, the distributions of traffic-related primary pollutants – such as ultrafine particles, diesel soot, CO, NO or metal-rich resuspended particles – follow the very same spatial patterns.

Lung function and COPD
Many studies (mostly cross-sectional, *i.e.* at a single time-point) have reported associations between lung function and air pollution, and there is a degree of inconsistency in the results, possibly for methodological reasons. Most importantly, reduction in exposure to pollutants has been shown to reduce age-related decline in lung function – a highly relevant finding observed in the SAPALDIA study where exposure to ambient air pollution was estimated at the individual level, taking full account of changes in residence during the 11-year follow-up. While a few studies support the notion that air pollution may also contribute to the development of COPD, further investigations are needed. Major difficulties with this assessment relate to more general challenges and uncertainties in COPD research. While air pollution is clearly

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associated with impaired development of lung function in children (as discussed previously), the way in which poor lung function in early life relates to later development of COPD is not clearly defined or understood. Moreover, air pollution triggers respiratory symptoms and enhances infections, but it is not known how these findings relate to the development of COPD, though cohort studies confirm that people with chronic symptoms and repeated infections are at higher risk of developing COPD. Last but not least, it is not well established whether COPD in nonsmokers and smokers can be considered as the same phenotype of disease.

Adult asthma incidence
As in children, asthma in adults is not correlated with urban background levels of pollution such as $PM_{2.5}$. However, the few studies investigating the contribution of local traffic-related air pollution to asthma onset in adults have produced similar findings to those looking at childhood asthma incidence. More research is needed to clarify these results and the interaction with atopy, genetics and other host factors.

Lung cancer

In nonsmokers, lung cancer is a relatively rare disease with a long latent period. The time from diagnosis to death is often short, and treatment has limited success. To look at lung cancer in population-based studies, the population sample needs to be large and the follow-up time long. Therefore, despite the coherence between experimental information, occupational studies and many results in population studies, not all long-term epidemiological studies have shown a link between ambient air pollution and lung cancer mortality. In the ACS cohort study, lung cancer incidence increased by 8% per 10 $\mu g \cdot m^{-3}$ increase in $PM_{2.5}$ levels, measured as between-city difference; in a Danish cohort study, lung cancer incidence increased by 3.7% per 10 $\mu g \cdot m^{-3}$ increase in NO_x, used as a marker of exposure to traffic-related pollutants. Most importantly, particles – in particular those from diesel engines – are loaded with carcinogens. The Californian Enironmental Protection Agency as well as the International Agency for Research on Cancer list diesel exhaust as an established carcinogen.

The large-scale European Study of Cohorts for Air Pollution (ESCAPE) will add to the evidence of long-term effects of air pollution on chronic diseases, including a range of respiratory ailments, such as the incidence of asthma and COPD and the symptoms of bronchitis, as well as the development of lung function and lung cancer (www.escapeproject.eu). Rigorous and standardised assessment of the exposure of European citizens to traffic-related pollution will highlight future policy requirements to tackle air quality along busy roads and highways.

> "*Living close to a busy road increases risk of developing asthma in childhood, even with confounding factors taken into account*"

The importance of susceptibility

To understand and interpret the observed respiratory health effects, it is crucial to acknowledge the relevance of susceptibility (or protective) factors that modulate individual reactions to exposure to ambient pollutants. The identification of susceptibility factors is subject to intense research. Given the relevance of the pathophysiological mechanisms mentioned previously, it is not surprising that an increasing number of studies report stronger effects of air pollutants in subjects with limited capacity to defend against oxidative stress and to balance inflammatory responses. Such modulating factors may relate to sex, age, underlying diseases and pro- and anti-oxidant intake, as well as a range of genetic characteristics. For example, a controlled trial in Mexican children not only confirmed the association between O_3 and respiratory health, but also revealed interactions related to oxidative stress pathways: children with anti-oxidant treatment were far less affected by O_3 than the placebo groups; and children with functional variants of the *GSTM* gene were protected against the adverse respiratory effects of ozone.

Relevance and outlook

Just as medicine should be based on evidence, public health action and policy should be grounded in science. Despite many unanswered questions, the evidence is sufficient to advocate sustained improvements of air quality across Europe. Thus, current scientific knowledge must reach policymakers in a comprehensible way. This is particularly urgent in the European Union, where air-quality standards are less stringent than in many individual member states and other areas of the world, and in conflict with research findings and the guidelines proposed by the World Health Organization (WHO). As with tobacco smoke, the voice of health professionals is instrumental in shaping the opinions of the public and policymakers. European research findings make a strong case for sustained improvements in air quality to support public health. In fact, the early tri-national European health impact assessment of air pollution emphasised what several local and trans-European analyses have since confirmed: the public health impact of air pollution is very substantial, thus, the benefits of a reduction in air pollution will be large, in terms of both cost-relevant morbidity and the summary health indicator of life expectancy. As shown in recent assessments on childhood asthma and air pollution, the benefits of clean air have, if anything, been substantially underestimated in the past.

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Occupational risk factors

Key points

- A detailed history is key when assessing a worker's occupational exposure risk and establishing a diagnosis. The latency of occupational respiratory diseases can range from a few hours to 50 years.
- National and international bodies set maximum allowable workplace concentrations for a wide range of substances. However, these limits are not usually set at a level designed to avoid sensitisation.
- The effects of workplace respiratory exposures can be life-changing, ranging from acute inhalation injuries to lung cancer, and running the full spectrum of pleural, interstitial and inflammatory respiratory disease.

Occupational lung diseases include a large number of respiratory disorders that result from inhalation of specific particles, gases, fumes or smoke. Before workplace safety guidelines were established, occupational diseases were a major cause of morbidity and mortality. In some areas, adequate workplace interventions have reduced exposure to, for example, inorganic dusts such as silica or asbestos. However, due to its long latency, the incidence of occupational lung cancer causally attributable to these particular agents is still very high. As another example, reduction of exposure to latex in hospital settings has resulted in a decrease in latex-induced asthma, but this reduction has been effected only in some countries and not in others. In many workplaces, exposure to a variety of irritative, sensitising, fibrogenic and carcinogenic agents is still a major challenge. Overall, occupational agents are responsible for about 15% (in men) and 5% (in women) of all respiratory cancers, 17% of all adult asthma cases, 15–20% of chronic obstructive pulmonary disease (COPD) cases and 10% of interstitial lung disease cases. Since occupational diseases are, in principle, preventable, it is very important that clinicians take occupational histories in order to identify potential causes and build the basis for prevention of future disease.

This chapter will focus on potentially hazardous exposures: the corresponding diseases are discussed in chapter 24.

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> *Immunological mechanisms underlying the effects of most low-molecular-weight agents have not been fully characterised*

The contribution of the workplace environment to diseases of the airways and lungs has been, and is still, changing in many countries. Disabling pneumoconiosis with associated tuberculosis has become uncommon in developed countries, but is still highly prevalent in places of rapid industrialisation. In developed countries, asbestos use has decreased considerably, but it is still used widely in developing countries (figure 1). Thus, the mortality toll in developing countries can be predicted. On the other hand, in Europe, exposure to (for example) diisocyanates and to beryl is still increasing, and the consequent cases of asthma and berylliosis are currently being seen in our clinics.

Exposure history and assessment

Many respiratory diseases, such as lung cancer, interstitial lung disease, asthma and COPD, can be caused by both nonoccupational and occupational factors. Therefore, an occupational exposure history is crucial in assessing the respiratory risks of a worker and in establishing a diagnosis of occupational lung disease. Unfortunately, many physicians do not have adequate knowledge and/or do not take the time to take an adequate exposure history.
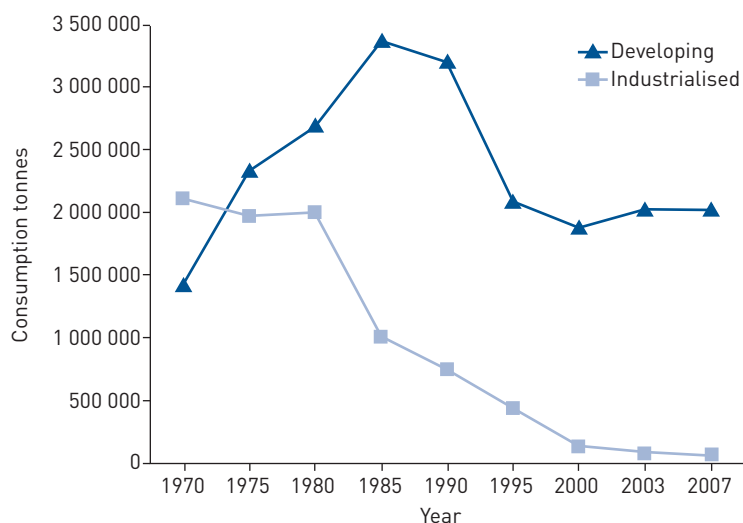

Figure 1 - Change in worldwide asbestos consumption, 1970–2007, in developing and industrialised nations. Reproduced from Rice, 2011, with permission from the publisher.
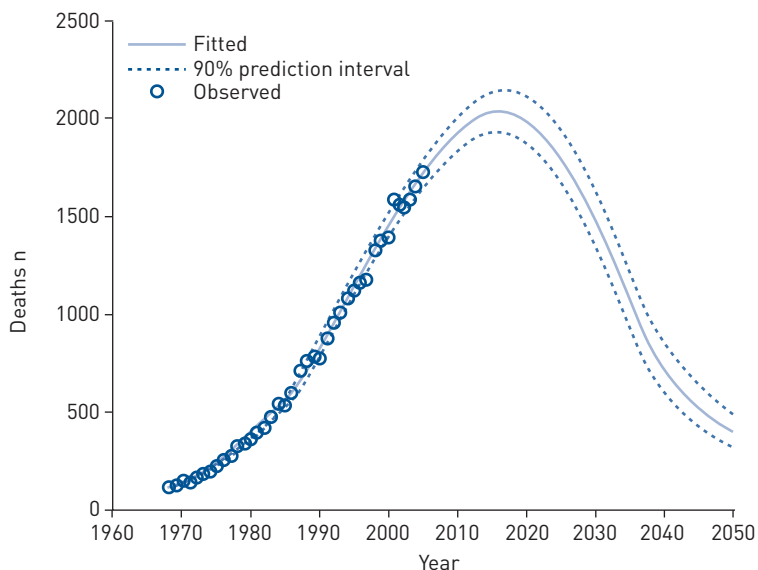
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Figure 2 - Observed and projected deaths from mesothelioma in the UK with fitted 50th percentile curve and 90% prediction interval. Reproduced from TAN *et al.*, 2010.

> *In many workplaces, exposure to a variety of carcinogenic agents is still a major challenge*

Timing

Some occupational lung diseases have a long latency and a critical cumulative level of exposure (for instance, lung cancer and interstitial lung diseases). Other conditions have short latency and thus the timing of symptom onset is critical. Particularly for the former group, an occupational exposure history should include every job since the patient started work.

Dose

High levels of dust over a long period are necessary to cause, for example, pneumoconiosis and COPD. Conversely, only a few weeks of asbestos exposure may lead to malignant mesothelioma 50 years later. Some allergic occupational diseases may occur even when exposure levels are within regulatory limits, because these limits are generally not defined to exclude sensitisation.

Cofactors

Smoking enhances the risk not only of occupational lung cancer, but also of some forms of occupational asthma and occupational COPD. Pre-existing allergies may increase the risk of becoming sensitised to occupational agents. Respiratory protective equipment, if used properly, can reduce the risk for some occupational lung diseases but efficacy is very limited with regard, for example, to protection against occupational asthma. In general, individual protective equipment is only the 'third line of defence' after technical and organisational approaches to reduce exposure to workplace agents.

Clinical approach

The components of a thorough occupational exposure history include:

- Job type and activities: employer, what products the company produces, job title, years worked, description of job tasks or activities, description of all equipment and materials the patient used, description of process changes and dates they occurred, any temporal association between symptoms and days worked.
- Exposure estimate: visible dust or mist in the air and estimated visibility, dust on surfaces, visible dust in sputum (or nasal discharge) at end of work shift, hours worked per day and days per week, open or closed work process system, presence and description of engineering controls on work processes (for instance, wet process, local exhaust ventilation), personal protective equipment used (type, training, testing for fit and comfort and storage locations), sick co-workers.
- Bystander exposures at work: job activities and materials used at surrounding work stations, timing of worksite cleaning (during or after shift), individual performing cleanup and process used (wet *versus* dry).
- Bystander exposure at home: spouse's job, whether spouse wears work clothes at home and who cleans them, surrounding industries.
- Other: hobbies, pets, problems with home heating or air-conditioning, humidifier and hot tub use, water damage in the home.

Latency between exposure and disease

Many inhaled agents cause symptoms at the time of exposure. These include 'Type I' allergens (those that provoke an immediate response, although they may also lead to a delayed response) and irritative agents. Latent periods of about 8–16 hours after exposure may occur in patients with toxic pulmonary oedema and extrinsic allergic alveolitis (hypersensitivity pneumonitis). At the other extreme, slow accumulation of mineral dusts may lead to disease symptoms many years later. Occupational respiratory cancer after exposure to carcinogens mostly occurs after a latent period of at least 10 years. With malignant mesothelioma, the latency is up to 50 years and, consequently the peak incidence of this disease has not yet been reached (figure 2).

Maximum workplace concentrations

In general, the primary aim of defining maximum workplace concentrations is to protect workers' health, based on scientifically sound evidence.

In Germany, MAK ('Maximale Arbeitsplatzkonzentration': maximum workplace concentration) values are derived by the DFG Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area, better known as the MAK Commission. This independent body has been mandated by the German Research Foundation (DFG) to determine the current state of research relating to the health risks posed by substances and materials used in the workplace, and to advise public authorities accordingly. The most important practical results of the Commission's work are scientific recommendations for the establishment of MAK values and BAT values (biological tolerance values for occupational exposure), for the classification of carcinogenic, embryotoxic/fetotoxic substances and germ cell mutagens, and for the evaluation of measurement methods. The recommendations are freely available online (see Further reading).

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Irritant gases

    High water solubility, *e.g.* ammonia, sulfur dioxide, hydrogen chloride

    Moderate water solubility, *e.g.* chlorine, hydrogen sulfide

    Low water solubility, *e.g.* ozone, nitrogen dioxide, phosgene

Organic chemicals

    Organic acids, *e.g.* acetic acid

    Aldehydes, *e.g.* formaldehyde, acrolein

    Isocyanates

    Amines. *e.g.* hydrazine, chloramines

    Tear (CS) gas, mustard gas

    Organic solvents, including some leather sprays

    Some agrochemicals (paraquat, cholinesterase inhibitors)

Metallic compounds

    Mercury vapours

    Metallic oxides, *e.g.* those of cadmium, vanadium, manganese, osmium

    Halides, *e.g.* zinc chloride, titanium tetrachloride, antimony pentachloride, uranium hexafluoride

    Nickel tetracarbonyl

    Hydrides of boron, lithium, arsenic, antimony

    Metal fumes

Complex mixtures

    Smoke from fires

    Pyrolysis products from plastics

    Solvent mixtures

    Spores and toxins from microorganisms

    Polymer fumes

Table 1 – Causes of chemical pneumonitis.

> *The latency of malignant mesothelioma is up to 50 years ... peak incidence has not yet been reached*

At the European level, the European Commission has set up the Scientific Committee on Occupational Exposure Limit Values (SCOEL), with a mandate to advise the Commission on occupational exposure limits for chemicals in the workplace. It does this by preparing scientific recommendations for the Commission, which are used to underpin regulatory proposals on occupational exposure limit values (OELVs) for chemicals in the workplace. During this procedure, draft recommendations from SCOEL undergo a stakeholder consultation to allow interested parties to submit health-based scientific comments and further data.

	Healthcare workers	Other occupations
Airborne, viral		
Varicella	All	
Measles	Physicians and nurses	
Rubella	All	
Mumps	Paediatricians and dentists	
Pertussis	All	
Parvovirus B19 infection	Nurses	
RSV infection	All	
Adenovirus infection	Staff in ophthalmology clinics, intensive care units and long-term paediatric care	
Influenza	Physicians and nurses	Office workers
SARS-coronavirus A	Physicians, nurses, healthcare assistants and others; nursing home attendants; housekeeping personnel, laboratory workers	Transport workers, business travellers, market for exotic animals
Avian influenza H5N1	Physicians, nurses, healthcare assistants	Poultry, farm and market workers
Mycoplasma infection	All	
Airborne, bacterial		
Tuberculosis	Nurses, physicians, pathologists, laboratory workers, housekeeping staff	
Anthrax	Hospital supply	Agricultural workers, wool sorters, mail sorters
Psittacosis		Turkey processing
Blood-borne, viral		
HIV infection	Physicians, nurses, dental workers and dentists, laboratory workers, technicians in dialysis unit, respiratory therapists	Embalmers or mortuary technicians
Ebola infection	Nurses	

Table 2 – Respiratory infections that may be occupationally acquired. RSV: respiratory syncyntial virus; SARS: severe acute respiratory syndrome. Reproduced from H0 *et al*., 2007, with permission from the publisher.

Recommendations adopted by the SCOEL are also available online (see Further reading).

In the USA, threshold limit values (TLVs) and biological exposure indices (BEIs), as defined by the American Conference of Governmental Industrial Hygienists, are determinations made by a voluntary body of independent knowledgeable individuals. They represent the opinion of the scientific community, after reviewing the available data, that exposure at or below the level of the TLV or BEI does not create an unreasonable risk of disease or injury (see www.acgih.org/TLV/).

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High-molecular-weight agents

    Acarians (ticks, mites)

    Algae

    Animal-derived antigens

    Arthropods

    Biological enzymes

    Crustacea, seafood, fish

    Flour

    Moulds/fungi

    Mushrooms

    Plants

    Plant-derived natural products

    Pollens

    Vegetable gums

Low-molecular-weight agents

    Aliphatic amines (ethyleamines and others)

    Anhydrides

    Aromatic amines

    Diisocyanates

    Drugs

    Fluxes

    Fungicides

    Metals

    Quaternary amines

    Reactive dyes

    Wood dust or bark

    Various chemicals

Table 3 – Causes of occupational asthma.

Minerals

    Coal

    Man-made vitreous fibres

    Oil mist

    Portland cement

    Silica

    Silicates

Metals

    Osmium

    Vanadium

    Steel dust

Organic dusts

    Cotton

    Grain

    Wood

Chemicals/gases/fumes

    Ammonia

    Firefighting exposures

    Cadmium

    Isocyanates

    Sulfur dioxide

    Welding fumes

    Environmental tobacco smoke

Table 4 – Agents which, under poor occupational hygiene conditions, may cause occupational bronchitis and chronic obstructive pulmonary diease.

Exposures and their effects

Acute inhalation injuries

Acute inhalation injury can have various clinical manifestations and may injure both the airways and the lung parenchyma. In principle, the site of damage depends on the nature of the inhaled agent. Causes of chemical pneumonitis may be grouped into four categories (table 1).

In addition, certain organic agents may cause (mainly) inhalation fever. Characteristically, high exposure to bacteria, fungi, and (endo)toxins in cotton mills, grain-handling facilities,

livestock farming and comparable settings is responsible for toxic pneumonitis due to organic agents.

Occupational infections

Compared with occupational lung diseases caused by exposure to gases, fumes and dusts at work, occupationally acquired lung infections received little attention until the 2003 epidemic of the viral infection severe acute respiratory syndrome (SARS), which affected more than 8000 individuals globally, one-fifth of whom were healthcare workers.

Many occupational infections have, however, been recognised for a long time. In recent years, some 'old' infections such as tuberculosis – particularly multidrug-resistant tuberculosis – and anthrax have re-emerged. Another occupational viral infection which has emerged in the past decade is avian influenza (H5N1) (table 2).

Occupational asthma

Workplace agents that are known to cause allergic occupational asthma include high-molecular-weight (glyco)proteins of vegetable or animal origin and low-molecular-weight compounds. High-molecular-weight proteins and a few low-molecular-weight compounds (such as platinum salts, reactive dyes, acid anhydrides, sulfonechloramide and some wood species) act *via* a recognised IgE-mediated mechanism. However, the immunological mechanisms underlying the effects of most low-molecular-weight agents (such as isocyanates, persulphate salts, aldehydes and wood dusts) have not been fully characterised.

The distribution of causal agents varies widely across geographical areas, depending on the pattern of industrial and/or agricultural activities. Between 350 and 400 agents have been reported to cause occupational asthma. Updated lists of causal agents and occupations are available online (see, for instance, www.asthme.csst.qc.ca). The commoner occupational causes of asthma are listed in table 3.

A major problem with occupational asthma is that the relevant agents are identified mainly by nonregulatory organisations, and most are not regulated with the aim of preventing asthma. About 10 new agents are recognised each year.

Occupational COPD

Some work-related obstructive airway disorders may be classified as COPD, but do not fit neatly into this category. For example, work-related variable airway limitation may occur with occupational exposure to organic dusts such as cotton (*i.e.* byssinosis), flax, hemp, jute, sisal and various grains (table 4). Such organic dust-induced airway disease is sometimes classified as an asthma-like disorder, but both chronic bronchitis (chronic cough and sputum production) and poorly reversible airflow limitation can develop with chronic exposure. Bronchiolitis obliterans and irritant-induced asthma are other conditions that may overlap clinically with work-related COPD.

The term 'nuisance dust' is frequently used to characterise exposures generally thought to be without adverse health effects. There is, however, abundant evidence that this is an inappropriate term. Although, *a priori*, there is no biological reason why a similar response to inhaled workplace irritants should not occur, it has until recently been somewhat more difficult to demonstrate an association between occupational exposures and COPD in epidemiological studies. For COPD, a population-attributable

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Inorganic fibrous dusts

      Asbestos

      Palygorskites (attapulgite and sepiolite)

      Wollastonite

      Zeolites

      Silicon carbide (carborundum)

      Aluminium oxide

      Nylon flock

Inorganic nonfibrous dusts

      Crystalline silica

      Coal dust

      Carbon compounds (graphite, carbon black, oil shale)

      Mica

      Kaolin

      Nepheline

      Diatomaceous earth

      Talc

Inhaled metals and metal compounds

      Beryllium

      Cobalt

      Aluminium

      Titanium

      Zirconium

      Rare earths (lanthanides)

      Iron, tin, barium (causes of 'benign' pneumoconioses)

Table 5 – Causes of pneumoconiosis.

> *Exposure to diisocyanates and to beryl is still increasing, and the consequent cases of asthma and berylliosis are currently being seen*

risk (PAR) of approximately 15–20% has been estimated to be due to occupational factors.

Occupational interstitial lung diseases

Many different agents are reported to cause occupational interstitial lung disease, some well described and others poorly characterised, and the list of causative agents continues to expand. These diseases were formerly thought of as the 'pneumoconioses', but the list of known causes of occupational interstitial lung disease extends far beyond the traditional coal, asbestos and silica (table 5). In large studies, about 10–15% of cases of interstitial lung disease turn out to be caused by occupational agents.

Another important form of interstitial lung disease is extrinsic allergic alveolitis (aka hypersensitivity pneumonitis – see also chapter 24). A large and expanding range of occupational agents are recognised as causes of this disease (table 6).

Disease	Exposure
Air conditioner lung	Humidifier water
Animal handlers' lung	Dust of dander, hair particles, dried urine of rats
Bagassosis	Mouldy sugar cane
Bird fanciers' lung	Droppings and feathers
Cheese washers' lung	Cheese mould
Farmers' lung	Mouldy hay, straw, grain
Hot tub lung	Bacteria in mist from hot tub
Maltworkers' lung	Mouldy malt
Maple bark strippers' disease	Mouldy maple bark
Mushroom workers' lung	Mouldy mushroom compost
Sequoiosis	Mouldy sawdust
Sewage sludge disease	Dust of heat-treated sludge
Wheat weevil lung	Mouldy grain, flour, dust
Suberosis	Mouldy cork dust
Wood pulp workers' disease	Mouldy wood chips

Table 6 – Causes of extrinsic allergic alveolitis/hypersensitivity pneumonitis.

Sufficient evidence	Limited evidence
Aluminium production	Acid mists, strong inorganic
Arsenic and inorganic arsenic compounds	Art glass, glass containers and pressed ware (manufacture of)
Asbestos (all forms)	Biomass fuel (primarily wood), indoor emissions from household combustion
Beryllium and beryllium compounds	
bis(chloromethyl)ether	Carbon electrode manufacture
Chloromethyl methyl ether (technical grade)	Alpha-chlorinated toluenes and benzoyl chloride (combined exposures)
Cadmium and cadmium compounds	
Hexavalent chromium compounds	Cobalt metal with tungsten carbide
Coal, indoor emissions from household combustion	Creosotes
Coal gasification	Engine exhaust, diesel
Coal tar pitch	Frying, emissions from high-temperature
Coke production	Insecticides, nonarsenical (occupational exposures in spraying and application)
Haematite mining (underground)	
Iron and steel founding	Printing processes
MOPP (vincristine-prednisone-nitrogen mustard-procarbazine mixture)	2,3,7,8-tetrachlorodibenzo-para-dioxin
	Welding fumes
Nickel compounds	
Painting	
Plutonium	
Radon-222 and its decay products	
Rubber production industry	
Silica dust, crystalline	
Soot	
Sulfur mustard	
Tobacco smoke, secondhand	
Tobacco smoking	
X radiation, gamma radiation	

Table 7 – Occupational causes of lung cancer. Adapted from Cogliano et al., 2011, with permission from the publisher.

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Occupational lung cancer

Following thorough scientific discussion, the International Agency for Research on Cancer has classified agents with sufficient and those with limited evidence of causing lung cancer (table 7). As can be seen, a huge variety of industries and occupations increase the risk of lung cancer. However, most occupational lung cancer is still caused by asbestos.

Occupational pleural diseases

Asbestos causes both malignant mesothelioma and various nonmalignant pleural diseases (diffuse thickening, noncalcified and calcified plaques, and benign pleural effusion). Even very low exposures and short periods of time are sufficient to cause malignant mesothelioma. Malignant mesothelioma is a signal tumour of asbestos exposure, both in an occupational and in an environmental setting, and, as discussed above, its latent period is up to 50 years. Therefore, a detailed occupational history is of highest importance in the work-up of patients with malignant mesothelioma. Checklists are helpful for patients and physicians (see also chapter 24).

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Passive smoking

Key points

- Environmental tobacco smoke is classed as a human carcinogen by the World Health Organization. There are no safe levels of exposure.
- Children exposed to second-hand smoke are at an increased risk of sudden infant death syndrome, acute respiratory infections, ear problems and more severe asthma. Parental smoking causes respiratory symptoms and slows lung growth in children.
- Smoke-free legislation results in significantly reduced respiratory symptoms and improved lung function.

Passive smoking is: 1) exposure to second- or third-hand smoke by breathing ambient air containing toxic substances resulting from the combustion of tobacco products after birth; or 2) exposure *in utero* to maternal blood contaminated with the combustion of tobacco smoking products.

Second-hand smoke (SHS) or environmental tobacco smoke (ETS) is the name given to the mixture of 'mainstream smoke' (smoke exhaled by a cigarette smoker), 'sidestream smoke' (emitted from the smouldering tobacco stick between puffs), contaminants emitted into the air during the puff and contaminants that diffuse through the cigarette paper and mouth-end between puffs. It is a complex mixture of gases and some 4000 particulate chemicals, which are generated during the burning and smoking of tobacco products. Of these, ⩾250 are known to be toxic or carcinogenic.

The majority of the compounds present in mainstream smoke are formed during combustion. The constituents of mainstream and sidestream smoke are broadly similar but there are important differences in their rates of emission into the air due to physical and chemical differences in the way cigarettes burn during and between puffs. Mainstream smoke is generated during inhalation at a temperature of approximately 800–900°C, which is higher than that seen in sidestream smoke generation (600°C), due to increased levels of oxygen passing through the cigarette. Mainstream smoke also has a pH of 6.0–6.7, making it more

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> " *Separating smokers from nonsmokers, cleaning the air and ventilating buildings cannot prevent nonsmokers being exposed to second-hand smoke* "

acidic than sidestream smoke (pH 6.7–7.5). The combustion process that generates sidestream smoke also produces smoke with much smaller particulate matter (PM) size and considerably higher concentrations of many carcinogens and toxins. However, dilution, chemical reactions, deposition and other removal processes may decrease the concentration of airborne SHS constituents, alter the size distribution of suspended particles and chemically modify some of the more reactive constituents of SHS (table 1). Third-hand smoke is the name given to substances that are re-emitted from solid surfaces having been initially deposited there during smoking.

Harmful effects of SHS on health

Many US government reports, going back to the 1972 Surgeon General's report 'The Health Consequences of Smoking', have discussed the harmful effects of SHS. The National Research Council and the Environmental Protection Agency (EPA) have also independently assessed the health effects of exposure to ETS (figure 1).

The EPA report, published in 1992, confirmed that the respiratory effects of ETS included:

- Lung cancer in nonsmoking adults. Passive smoking is causally associated with lung cancer in adults, and thus ETS, given the weight of evidence, belongs in the category of compounds classified by the EPA as Group A (known human) carcinogens.
- Non-cancer respiratory diseases and disorders.
    - Exposure of children to ETS from parental smoking is causally associated

Constituent	Emissions in SS per cigarette	Amount in SHS per m^3
Benzene	163–353 µg	4.2–63.7 µg
Benzo[a]pyrene	45–103 ng	0.37–1.7 ng
NNK	201–1440 ng	0.2–29.3 ng
4-Aminobiphenyl	11.4–18.8 ng	
2-Naphthylamine	63.1–128 ng	
1,3-Butadiene	98–205 µg	0.3–40 µg
Formaldehyde	233–485 µg	143 µg

Table 1 – Carcinogens in sidestream smoke (SS) and second-hand smoke (SHS) from cigarettes. NNK: 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone.

with: increased prevalence of respiratory symptoms of irritation (cough, sputum, and wheeze); increased prevalence of middle ear effusion (a sign of middle ear disease); and a small but statistically significant reduction in lung function as tested by objective measures of lung capacity.

– xposure to ETS is causally associated with additional episodes and increased severity of asthma in children who already have the disease.

– The epidemiological evidence is suggestive but not conclusive that ETS exposure increases the number of new cases of asthma in children who have not previously shown symptoms. Based on this evidence and the known effects of ETS on the immune system and lungs (*e.g.* atopy and airway hyperresponsiveness) the report concluded that ETS is a risk factor for the induction of asthma in previously asymptomatic children. Data suggest that relatively high levels of exposure are required to induce new cases of asthma in children.

• Subtle but significant effects of passive smoking on the respiratory health of nonsmoking adults, including coughing, phlegm production, chest discomfort and reduced lung function.

At the time that the early reports were published, there was some uncertainty about the relationship of SHS to sudden infant death syndrome (SIDS), upper respiratory tract infections and middle ear infections in children. However, by 2006, when the US Surgeon General published 'The Health Consequences of Involuntary Exposure to Tobacco Smoke', it was possible to state clearly that:

• SHS causes premature death and disease in children and in adults who do not smoke.
• Children exposed to SHS are at an increased risk of SIDS, acute respiratory infections, ear problems and more severe asthma. Smoking by parents causes respiratory symptoms and slows lung growth in their children.
• SHS has immediate adverse effects on the cardiovascular system of adults and causes coronary heart disease and lung cancer.
• The scientific evidence indicates that there is no risk-free level of exposure to SHS.
• Many millions of Americans, both children and adults, are still exposed to SHS in their homes and workplaces despite substantial progress in tobacco control.
• Eliminating smoking in indoor spaces fully protects nonsmokers from exposure to SHS. Separating smokers from nonsmokers, cleaning the air and ventilating buildings, however, cannot prevent nonsmokers being exposed to SHS.

"
Passive smoking is causally associated with lung cancer in adults
"

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Estimates of burden of disease due to SHS

Europe

Two major reports about the burden of disease due to SHS have been published in the past 10 years in Europe: the 'Analysis of the Science and Policy in Europe for the Control of Tobacco' (ASPECT) report in 2005; and 'Lifting the Smokescreen: 10 Reasons for a Smoke Free Europe' by the Smoke Free Partnership (SFP) in 2006. Both dealt with the extent of SHS health effects in European countries and with economic considerations. The SFP report estimated that 79 449 adults died because of SHS exposure in the European Union in 2002 and also estimated mortality for each separate member state. In March 2010, the Royal College of Physicians issued a report entitled 'Passive Smoking and Children'. It focused on the UK but also presented evidence from the world literature on the harmful effects of passive smoking on fetal and reproductive health. The report's authors estimated that in the UK, SHS causes 121 400 new cases of middle ear disease, 20 500 new lower respiratory tract infections and 22 600 new cases of wheeze, as well as 40 cases of SIDS each year.

USA

According to the 1992 EPA report, ETS is estimated to cause around 3000 lung cancer deaths per year among nonsmokers (never-smokers and former smokers) of both sexes in the USA. While there are statistical and modelling uncertainties in this estimate, and the true number may be higher or lower, the overall confidence in this estimate is medium to high, and the assumptions used when calculating it would tend to underestimate the actual population risk.

The ETS exposure of young children and particularly infants from parental (and especially maternal) smoking is causally associated with an increased risk of lower respiratory tract infections (pneumonia, bronchitis, and bronchiolitis). The EPA report estimated, with high confidence, that exposure to ETS in the USA causes 150 000–300 000 of these infections annually in infants and children less than 18 months old,
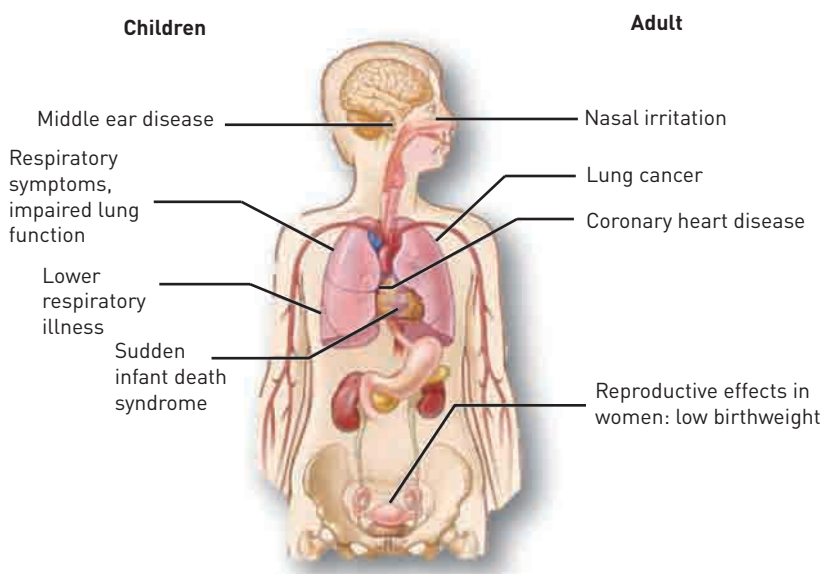

Children

Middle ear disease

Respiratory symptoms, impaired lung function

Lower respiratory illness

Sudden infant death syndrome

Adult

Nasal irritation

Lung cancer

Coronary heart disease

Reproductive effects in women: low birthweight

Figure 1. The dangers of second-hand smoke exposure. Reproduced from the US Surgeon General's report 'How Tobacco Smoke Causes Disease', 2010.

resulting in 7500–15 000 hospital admissions. Children up to 3 years of age were at increased risk of lower respiratory tract infections, but no estimated figures were derived for children over 18 months old.

The report also estimated that ETS exposure exacerbates symptoms in approximately 20% of the 2–5 million asthmatic children in the USA, and is a major aggravating factor in approximately 10%.

Measurement of SHS

The most direct and widely used method to measure ETS exposure is personal monitoring of respirable suspended particles and nicotine. Respirable suspended particles and nicotine give a good indication of cumulative exposure over a relatively short period of time. However, they have considerable limitations because of duration of measurements, representativeness of activity and cost.

Particles

Particulate matter, or PM, is the term given to the tiny particles of solid or semi-solid material found in the atmosphere. It consists of varying combinations of dry solid fragments, solid cores with liquid coatings and small droplets of liquid. In the case of airborne particles, the initial sizes of particles produced by cigarette smoking have been quoted to be 0.3–1.0 μm. This figure is not universally accepted, however: sidestream smoke particle size has been said to be typically 0.01–1.0 μm, with mainstream smoke particle size ranging from 0.1–1.0 μm.

Photometers, optical particle counters (OPCs) and condensation particle counters (CPCs) measure airborne particles in real time. Each technology has a unique sensitivity to specific particle characteristics such as size, mass and refractive index.

The instruments most commonly used for PM measurements are the Met One Aerocet 531 aerosol particulate profiler (Met One Instruments) and the TSI SidePak AM510 condensation particle profiler (TSI).

Nicotine

Nicotine vapour can be collected on filters by passive samplers and analysed using gas chromatography/mass spectrometry (GC/MS). Concentrations as low as 0.01 μg·mL^{-1} can be detected.

Biomarkers

Biomarkers are also useful for determining exposure to ETS because they enable us to predict potential health risks for exposed individuals, increasing our understanding of tobacco-related cancer mechanisms. Biomarkers offer a way to avoid many sources of bias or inaccurate reporting by study participants.

The most specific markers of exposure to SHS are thiocyanate and nicotine (in saliva, plasma or urine), and cotinine, a nicotine metabolite (in saliva, plasma, urine or hair). Cotinine is currently considered the marker of choice as thiocyanate is also influenced by diet, whereas cotinine appears to be the most specific and sensitive biomarker for smokers and nonsmokers as it reflects exposure to nicotine, which is almost wholly specific to tobacco.

Carboxyhaemoglobin in blood and carbon monoxide in exhaled air are also relatively easy-to-measure markers to quantify tobacco exposure, but they are not specific – road traffic or domestic emissions can affect them. Other substances that can be measured with more difficulty and variable specificity include: adducts of 4-aminobiphenyl to haemoglobin in red blood cells; adducts of benzo[a]pyrene to DNA in white blood cells; adducts of polycyclic aromatic hydrocarbons (PAHs) to plasma albumin; nicotine-derived nitrosamines in urine; hydroxyproline in urine; and *n*-nitrosoproline in urine.

Health benefits of smoke-free legislation

Respiratory health benefits

There is considerable experience and knowledge of the beneficial effects of comprehensive smoke-free legislation. Early studies from the USA showed that there were immediate respiratory health benefits in bar workers. The introduction of the Irish smoke-free legislation, and subsequently the Scottish and other national legislation,

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<blockquote>
Although children may benefit from smoke-free legislation in general, the laws do not prevent exposure in utero, in the home or in private vehicles
</blockquote>

has created an opportunity to measure health benefits at the level of individuals and populations. Various studies have confirmed the US results, showing significantly reduced respiratory symptoms and improved spirometry. In Irish studies, this was accompanied by a reduction in cotinine and exhaled breath carbon monoxide. The Irish research also found a significant improvement in gas exchange in the lung. These significant effects were seen in nonsmokers and ex-smokers but did not reach statistical significance in current smokers. It is also important to note that the subjects were not patients: they were in full-time employment with normal pulmonary function, yet they saw significant health benefits 1 year after the ban.

Cardiovascular health benefits

Studies on patients in the USA, Italy and Scotland have shown definite reductions in acute myocardial infarctions, varying from 17% in Scotland to 11% in Italy. Similar effects were seen in a small Irish regional study. More recently, an English study has shown a smaller, but nonetheless definite, reduction of 2.5%.

Other benefits

It is expected that the effects of smoke-free policies on lung cancer rates will take some time to be seen and reliably analysed.

There have been several recent reports of the beneficial effects of Irish and Scottish smoke-free legislation in pregnancy and in children.

Protection from exposure to SHS

Exposure to SHS is almost entirely preventable. Through Article 8 of the Framework Convention for Tobacco Control (FCTC) and a Council Recommendation, respectively, the World Health Organization (WHO) and the European Commission have declared that people have the right to be protected from SHS in public and indicated how this can be achieved. They have pointed out that they recognise the harmful effects of SHS, that comprehensive legislation is needed to prevent harm and that since there is no safe level of exposure (SHS is a Group 1 carcinogen according to the WHO), mechanical ventilation solutions are unacceptable. Many countries have now enacted comprehensive legislation since Ireland introduced its smoke-free law in March 2004. These countries include Norway, the UK, Sweden, Finland, Slovenia, Lithuania, Bulgaria and Turkey. Italy and France have laws that, in practice, are almost equivalent to comprehensive smoke-free legislation. Spain, Portugal and Greece initially introduced inadequate laws that did not meet the FCTC standard; Greece (2010) and Spain (2011) have already amended their laws, having shown that partial bans did not work.

Current smoke-free laws protect adults in the workplace and entertainment venues. Although children may benefit from smoke-free legislation in general, the laws do not prevent exposure *in utero*, in the home or in private vehicles. Legislation to protect children is needed and would be feasible in private vehicles, where we know levels of toxins can be very high in the presence of smoking, and that this causes disease in exposed children. Playgrounds in public parks are also increasingly smoke-free in Ireland and in the USA. Targeted smoking cessation services to help pregnant women stop smoking are also needed. Legislation to achieve smoke-free private housing may not be feasible or considered appropriate at present, but education and strong encouragement and advice should be offered. Legislation in municipal housing and in apartment blocks may well become commonplace if voluntary approaches fail.

In conclusion, SHS causes death and disability. It can be prevented, and health benefits due to the introduction of smoke-free legislation in children and adults have been widely reported.

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Tobacco smoking

Introduction

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Key points

- Smoking is habit-forming and physically addictive, and causes premature illness and death due to lung cancer, COPD, cardiovascular disease and a host of other ailments, as well as reducing lung function and complicating other diseases such as asthma and tuberculosis.
- Although there has been a decline in smoking prevalence in Europe, tobacco remains a huge problem, with at least one in four adults across Europe smoking and a rate in some countries exceeding 40%.
- Smoking cessation interventions, whether pharmaceutical or through advice and counselling, are highly cost-effective health measures among existing smokers.
- Smoking prevention policies such as advertising and marketing bans and high taxation play an invaluable role in preventing young people from taking up smoking: society will reap the benefits of these policies in future decades.

Tobacco smoking is the main preventable cause of morbidity and mortality from lung cancer, chronic obstructive pulmonary disease (COPD) and coronary artery disease, and it remains the most important health hazard in Europe. Today we have cost-effective tools to help smokers to quit and, thanks to political action, we have effective but still improvable legislation that helps to reduce the prevalence of smoking. The greatest effect on reducing morbidity and mortality in the next 10–20 years will come from cessation by current smokers, while intervention aimed at primary prevention – stopping people from taking up the habit at all – will mainly reduce smoking-induced disorders 20-plus years from now. However, the two interventions are complementary.

Epidemiology

Long-term trends in the prevalence of daily smoking in European countries where such data are available are illustrated in chapter 1. Overall, smoking is still a massive problem in Europe and there are large regional differences in smoking prevalence.

Figure 1 shows national smoking rates in Europe in 2010, based on data from the World Health Organization (WHO). It should be noted that the definition of smoking prevalence varies between countries: for many countries, the data are based on

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'daily smoking of any tobacco product', while in others the definition 'current smoking of any tobacco product' is used. Subject to these caveats, average prevalence of daily or any current smoking in the 28 countries of the European Union (EU) in 2010 was 27.8% in females and 41.4% in males, while overall in the WHO European region, the averages were 24.1% in females and 47.3% in males.

The most recent data on smoking prevalence come from the European Commission's (EC's) Eurobarometer survey, and are based on 26 751 interviews carried out in 2012 in 27 EU countries. Overall smoking prevalence was 28% (32% in males and 24% in females) and varied considerably with age (29% among 15–24-year-olds; 37% among 25–39-year-olds; 34% among 40–54-year-olds, and 17% among those aged 55 years or over.

Tobacco use is not high everywhere: according to 2011 data from the Organisation for Economic Co-operation and Development (OECD), Iceland has a notably low smoking prevalence of 14% in both sexes. Further afield, in California, comprehensive community legislation against smoking has contributed to a prevalence of less than 10% and to considerable savings in healthcare expenditure – an illustration of what can be achieved with the right political will.

The fight against tobacco use is making progress. The 2011 OECD data, from 26 European countries, show that between 1979 and 2010 the prevalence of smoking declined by an average of 36% in females and 32% in males, but with wide variation between countries from 0% to 71% (see chapter 1, figure 10). Among men, the overall tendency in European countries is for a gradual decline in smoking prevalence, which has levelled off in the past decade. Among women there has also been an overall decline, but in a minority of countries smoking prevalence has remained stubbornly constant for the past 30–40 years.

Reducing the health burden of tobacco smoking involves both treatment and prevention. In order to affect morbidity and mortality due to smoking during the next 20 years, the most powerful intervention is to persuade today's smokers to quit. Because it takes 20 years or more for most smoking-related disease to develop, the most effective means of reducing morbidity and mortality beyond that time is legislation now to reduce uptake of smoking among young people. In practice, we need to focus on both cessation and prevention.
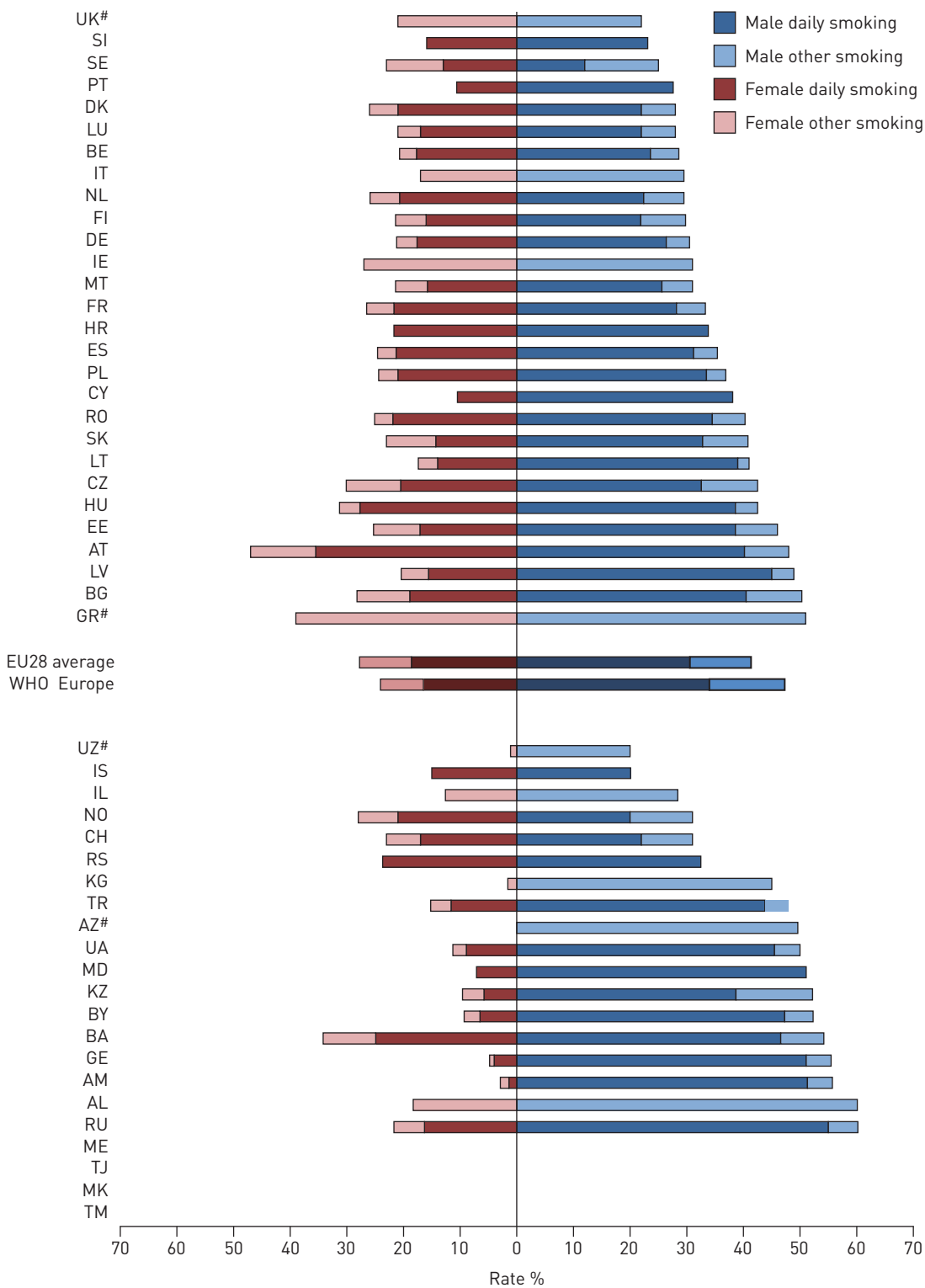
Figure 1 – Prevalence of daily and other current tobacco smoking in adults, 2010. #: current cigarette smoking. Source: World Health Organization Global Health Observatory.

Toxic effects of tobacco smoke

Tobacco smoke contains more than 4000 constituents, including carcinogens such as N-nitrosoamines and aromatic hydrocarbons, as well as toxic substances including ammonia, nitrogen oxides, hydrogen cyanide, carbon monoxide and nicotine. The carcinogens are the main cause of smoking-induced cancers – lung cancer, laryngeal cancer and urinary bladder cancer – and carbon monoxide has an important role in the aetiology of cardiovascular disease. However, it is not known precisely which constituents of smoke are responsible for the development of COPD. Nicotine plays no role in cancer or COPD and only a minor role in atherosclerosis. The constituents of smoke implicated in causing non-malignant disease are summarised in table 1 and the toxic effects of smoke are reviewed in more detail in chapter 8.

Disorders induced by tobacco smoking

Smoking is the main cause of many respiratory diseases and is one of the most important risk factors for cardiovascular diseases, cancers of several organs and many other pathological conditions. Estimates suggest that overall, approximately one-third of all cancers are caused by tobacco use. Of these, lung cancer is the prime example: in most societies, 80–90% of all lung cancers are attributable to tobacco. Lung cancer kills more people in the EU than any other cancer, accounting for about 20% of all cancer deaths. Tobacco smoking also plays a causal role in cancers of the mouth, larynx, pharynx, nose

Non-cancer effects	Smoke constituent	NCRI
Respiratory effects	**Acrolein**	**172**
	Acetaldehyde	**3.78**
	Formaldehyde	0.83
	Cadmium	0.52
	Chromium (hexavalent)	0.26
	Acrylonitrile	0.22
	Nickel	0.011
	Ammonia	0.006
Cardiovascular effects	**Hydrogen cyanide**	**1.97**
	Arsenic	**1.17**
	m-+p-Cresol	0.18
	O–Cresol	0.071
	Carbon monoxide	0.068
	Benzene	0.039
	Phenol	0.0022

Table 1 – Non-cancer risk indices (NCRI) for individual chemical constituents of mainstream cigarette smoke based on a single cigarette per day. Reference exposure levels (REL) are a guide to protect sensitive individuals against chronic effects over a long period of continuous exposure. The NCRI is equal to reported concentration as a fraction of the REL, assuming a total volume of 20 m^3 of air breathed daily. Bold numbers indicate an NCRI greater than 1.0, which signals that the threshold for adverse effects could be reached for some people by smoking a single cigarette per day. Reproduced from Fowles *et al.*, 2003, with permission from the publisher.
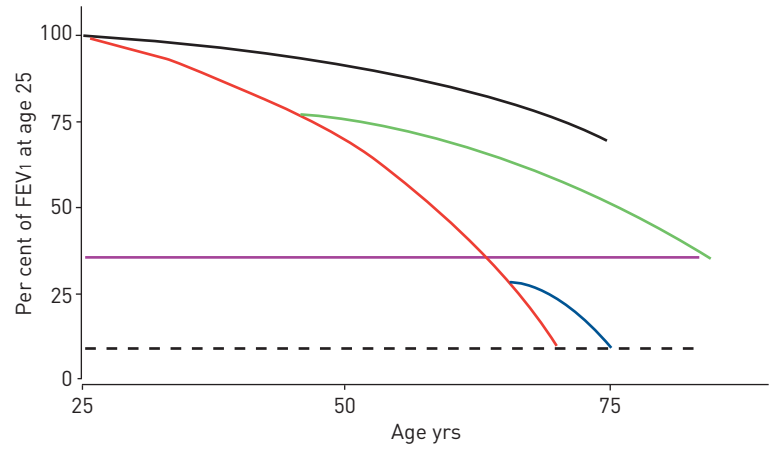
Figure 2 – Schematic diagram of the decline in lung function with age in nonsmokers, smokers and those who quit. Black: never-smoker or not susceptible to smoke; red: regular smoker and susceptible to smoke; green: quitter at age 45 years; blue: quitter at age 65 years. FEV1: forced expiratory volume in 1 s. The horizontal pink line indicates the level at which symptoms are likely to be disabling and the broken black line the level at which death is likely. Note that stopping smoking slows the rate of decline of lung function.

In Europe, smoking leads to more than 650 000 premature deaths every year

and sinuses, oesophagus, stomach, liver, pancreas, kidney, bladder, cervix and bowel, as well as one type of ovarian cancer and some types of leukaemia. Smoking is the main cause of COPD, particularly in Europe. (In some other parts of the world exposure to biomass fuels is relatively more important.) Smoking reduces the rate of growth of respiratory function during adolescence, resulting in a lower maximum forced expiratory volume in 1 s (FEV1) (a key measure of lung function) at maturity. Smoking then accelerates the decline of FEV1 in later adulthood and in old age. Figure 2 shows schematically the effect of smoking on FEV1 in healthy nonsmokers and susceptible smokers, as well as the effect of quitting smoking.

Smoking is also a cause of childhood asthma and a risk factor for the development of asthma in adults and is associated with increased risk of mortality, asthma attacks and exacerbations, greater severity and more difficulty in controlling asthma. Smoking predisposes to infection and is a serious complicating factor for tuberculosis.

Beyond the respiratory system, cigarette smoking is a risk factor for osteoporosis, reproductive disorders, adverse post-operative events and delayed wound healing, duodenal and gastric ulcers, periodontal disease and diabetes. It is a major modifiable risk factor for cardiovascular disease, including coronary artery disease, stroke, peripheral vascular disease and congestive heart failure. Studies of the relationship between cigarette smoking and cardiovascular disease show that cigarette smoking is associated with higher serum levels of cholesterol, coronary vasomotor reactivity, platelet aggregation and a pro-thrombotic state.

Societal costs of smoking

The burden of smoking-related diseases on society is enormous. It has been estimated that about 100 million people worldwide were killed by tobacco in the 20th century, and that the number will increase to 1 billion in the 21st century. It is estimated that in 2000, about 4.83 million deaths worldwide were attributable to tobacco smoking (12% of the estimated total global mortality among adults aged 30 years or older), with about 2.43 million of these in industrialised countries (19% of total adult mortality). The leading causes of death from tobacco smoking were cardiovascular diseases (1.69 million deaths), COPD (0.97 million) and lung cancer (0.85 million). In Europe, smoking leads to more than 650 000 premature deaths every year. Only 15% of the world's population live in Europe, but nearly a third of the burden of tobacco-related diseases occurs in Europe.

Smoking places a tremendous economic burden on society worldwide. The WHO estimates that the drain on the world economy is so large that it exceeds the total annual expenditure on health in all low- and middle-income countries. The total economic costs of tobacco reduce national wealth in terms of gross domestic product (GDP) by as much as 3.6%. In Europe, the burden from smoking, according to a report submitted to the EC in 2012, cost the economy €544 billion in 2009 – equivalent to about 4.6% of the EU's GDP.
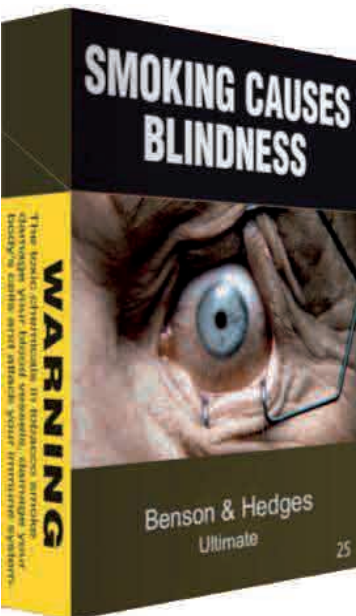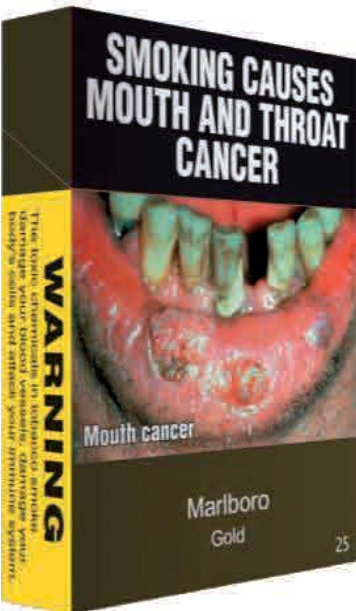
According to the WHO, the economic burden of tobacco is particularly high in the developing world and by 2030 four out of five tobacco-related deaths will occur in less developed countries. The poor are disproportionately affected, because buying tobacco diverts expenditure from necessities, including food, shelter, education and healthcare.

The economic costs of smoking extend beyond the direct costs of smoking-related illness and death and can be attributed to four elements:

1) Healthcare expenditures attributable to the treatment of smoking-related diseases in active smokers and those affected by second-hand smoke.
2) Loss of earnings, employee absence and reduced workplace productivity.
3) The monetised value of premature mortality and disability as assessed by disability-adjusted life-years lost.
4) Other indirect costs such as fire damage related to smoking and costs related to cleaning up after smoke. Smoking is the biggest cause of discarded litter in many cities. Tobacco growing results in widespread environmental harm from deforestation as well as pesticide and fertiliser contamination.

Dependence on tobacco

Cigarette smoking is a chronic relapsing disease. It is defined as a disorder or disease in the WHO International Statistical Classification of Diseases and Related Health Problems (ICD-10). One of the most important reasons for long-term smoking is physical dependence on nicotine although psychological components, habituation and genetic influences also are involved. Specific nicotine receptors have been identified in the brain and nicotine-dependent rats in which these receptors have been destroyed cease their intake of nicotine. When nicotine binds to these receptors, the neurotransmitter dopamine is released.

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Since nicotine dependence plays such an important role in continued smoking, it is not easy to quit and among those attempting to do so, a 1-year quit rate of 10–35% is the rule. Two simple questions can assess whether a smoker is dependent: whether he/she 1) smokes more than 8–10 cigarettes per day and 2) smokes the first cigarette within 30 minutes of waking. It is important to realise that smoking is not simply a lifestyle choice, but a disorder, and that quitting is not just a question of willpower, although motivation is an important factor for success.

Legislation and prevention of smoking

The 2005 WHO Framework Convention for Tobacco Control was the first international treaty negotiated by WHO and offers a blueprint for tobacco control. All EU countries are among the 176 nations that have signed it, but effective enforcement of the FCTC requires firm political commitment to achieve the WHO goal of a 40% reduction in global smoking prevalence between 2010 and 2025.

Taxation as a tool to prevent tobacco use

Price is probably the most powerful tool for reducing tobacco use. The relationship between price and reduction of demand for smoking is described by the price elasticity. Overall, there is a 3–4% fall in consumption for every 10% increase in price. A recent examination of this relationship in 11 EU countries carried out by the Pricing Policy and Control of Tobacco (PPACTE) project found it to be robust overall, but noted several further important aspects. For instance, lower socioeconomic groups and young people are most sensitive to price increases, while increases in income reduce price elasticity.

The tobacco industry usually opposes tax rises and often successfully persuades finance ministers that a price increase will lead to a loss of revenue through an increase in smuggling. There is evidence from many studies, including PPACTE, that this does not happen. Price is not the only – or even the main – cause of increases in smuggling. Smuggling depends on other factors such as the existence of established distribution networks, high levels of corruption, criminal involvement, low penalties for smuggling, and low probability of detection with poor implementation of controls. In the EU, these are compounded by nearness to land borders with countries where a high volume of cheap cigarettes is available.

Restriction of access to tobacco by minors

It is often argued that the sale of tobacco should be banned entirely. Some countries, such as Finland, foresee that they

may be able to ban its use in 2040 but no country in Europe is ready to ban tobacco outright today. There are much better data on the feasibility and usefulness of banning sale of tobacco to minors and properly applied restrictions do reduce teenage smoking. The importance of such measures is driven home by the fact that some 85% of smokers take up the habit in their teens.

The EU Tobacco Product Directive

The banning of advertising, sponsorship and promotion is obviously an important aspect of tobacco control, and such bans are widespread in the EU, backed by an EC directive on advertising. This directive is not universally adhered to and is of course not applicable outside the EU. In developing economies, tobacco advertising is still widespread.

In the EU, the battleground has shifted to tobacco packaging. Currently, Directive 2001/37/EC (the Tobacco Products Directive) is being revised with a view to further strengthening of the regulations. The use of health warnings and, more recently, graphic images of diseases caused by tobacco has become common on cigarette packages in many countries. Cancer images, usually showing advanced disease, are among the most often used. These images are thought to be effective in changing attitudes to smoking. Australia has led the world in introducing what is known as 'plain packaging', where the iconic logos of the tobacco industry are replaced by a simple description of the brand, and health warnings and images are used to discourage tobacco use. In Australia a law has been passed to end the general availability of cigarettes in 2035, after which they will only be available on prescription to buy in pharmacies. Similar proposals have been made in other countries. The European Respiratory Society (ERS) has been very active in the field of smoking prevention, with its Tobacco Control Committee focusing on the preventive and legislative aspects of tobacco control and lobbying the EU in this area.

Variation within Europe

Despite the universal ratification of the Framework Convention of Tobacco Control within the EU, tobacco control legislation varies widely across the continent. In 2011, the Association of European Cancer Leagues published a report into tobacco control activity in 31 countries, grading them on a 100-point scale according to their rules on pricing, smoke-free environments, tobacco advertising and promotion and packaging, as well as the provision of public information campaigns and smoking cessation services. Only five countries scored more than 60 points (figure 3), with the UK taking the top spot. Eight countries scored 40 points or fewer, with Austria and Greece having the least effective control measures in place.

Pharmacotherapy for smoking cessation

Several high-quality meta-analyses have investigated pharmaceutical interventions for smoking cessation, and guidelines have been published by several organisations. First-line pharmacological drugs for smoking cessation are nicotine replacement products (patch, gum, inhaler, nasal spray, lozenge/tablets, and oral spray), varenicline and bupropion, with scientifically well-documented efficacy when used for 2–3 months, mostly mild side-effects and at least a doubling of the 1-year quit rate compared with
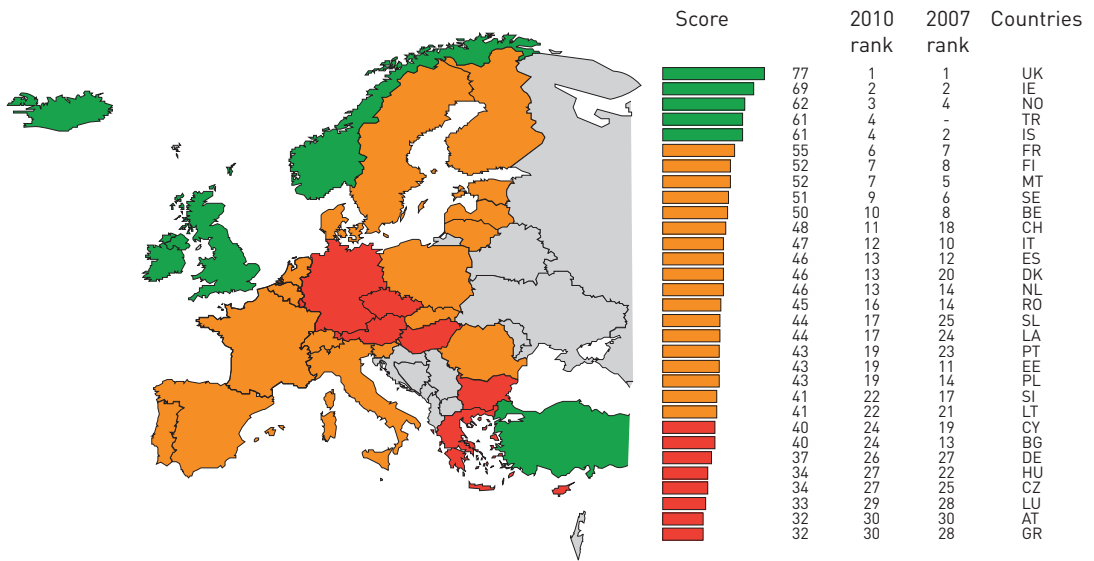
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Score	2010 rank	2007 rank	Countries
77	1	1	UK
69	2	2	IE
62	3	4	NO
61	4	-	TR
61	4	2	IS
55	6	7	FR
52	7	8	FI
52	7	5	MT
51	9	6	SE
50	10	8	BE
48	11	18	CH
47	12	10	IT
46	13	12	ES
46	13	20	DK
46	13	14	NL
45	16	14	RO
44	17	25	SL
44	17	24	LA
43	19	23	PT
43	19	11	EE
43	19	14	PL
41	22	17	SI
41	22	21	LT
40	24	19	CY
40	24	13	BG
37	26	27	DE
34	27	22	HU
34	27	25	CZ
33	29	28	LU
32	30	30	AT
32	30	28	GR

Figure 3 – The Tobacco Control Scale 2010. Countries are given a score out of 100, based on the strictness of their tobacco control rules. Stricter rules lead to higher scores. Reproduced from Association of European Cancer Leagues 2011, with permission from the publisher.

placebo (table 2). However, a 100% cure rate is not achievable and a typical finding in most studies of smoking cessation is a 1-year quit rate of about 25–35%, similar to the quit rates in other dependencies such as alchohol and opiates. To stop smoking is to break a complex habit and addiction and, to achieve reasonable quit rates, it is necessary to provide psychological support combined with pharmacological drugs.

Counselling for smoking cessation

With the most minimal intervention – provision of self-help materials for smoking cessation – the effect is only small. Telephone counselling is effective and can be used as well as, or instead of, face-to-face contact as an adjunct to self-help interventions.

Brief advice (less than 3 minutes) given by a general practitioner or nurse results in a small but significant increase in quit rates, of 2–3%. However there is a dose–response effect with person-to-person counselling in relation to the time taken in each session, as well as to the number of sessions. Group therapy seems to be as effective as individual counselling.

Benefits of quitting smoking

Compared to never-smokers, long-term daily cigarette smokers suffer higher early mortality from smoking-induced diseases. Ex-smokers have a longer average survival than

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	OR (95% CI)	1-year quit rate %
Placebo	1.0	13.6
Monotherapies		
Varenicline	3.1 (2.5–3.8)	33.2
High-dose nicotine patch	2.3 (1.7–3.0)	26.5
Nicotine gum (more than 14 weeks)	2.2 (1.5–3.2)	26.1
BupropionSR	2.0 (1.8–2.2)	24.2
Combination therapies		
Patch + *ad libitem* nicotine replacement therapy	3.6 (2.5–5.2)	36.5
Patch + BupropionSR	2.5 (1.9–3.4)	28.9
Patch + inhaler	2.2 (1.3–3.6)	25.8

Table 2 – Efficacy of first-line drugs for smoking cessation. Meta-analysis of data from placebo-controlled trials in smoking cessation reporting 1-year quit rates with the above drugs for smoking cessation used for 3 months in combination with counselling. The comparator is the placebo arm without drug but with counselling. The results are shown as odds ratios (OR) with 95% confidence intervals (CI) and as % of subjects who have stopped smoking at 1 year; OR is the proportional increase in quit rate compared to placebo (for example, with varencicline the average quit rate was 3.1 times that with placebo). Modified from Fiore *et al.*, 2008.

continuing smokers. Particularly convincing evidence comes from a longitudinal study of UK male doctors. It was found that the mortality of the smokers was almost double that of never-smokers and that COPD was 13 times more prevalent and lung cancer 15 times more prevalent among smokers compared with never-smokers. After a 50-year observation period it was concluded that smokers die about 10 years younger than nonsmokers. Cessation at ages 60, 50, 40 or 30 years results in gains of about 3, 6, 9 or 10 years of life expectancy, respectively. The effect of smoking cessation on the rate of decline of FEV_1 is illustrated schematically in figure 2.

To prove a causal relationship between smoking cessation and health benefits, an intervention study is necessary where smokers quit and outcome is observed. One of the best studies is the US Lung Health Study, a large randomised controlled trial in 5587 patients with mild COPD, which showed that repeated smoking cessation during 5 years resulted in a quit rate of 37%, and after 14.5 years the quitters had appreciably better lung function and a higher survival rate compared with those who continued to smoke. In another study, the quality of life of patients with moderate or severe COPD 1 year after quitting was significantly better than that of continuing smokers.

Cost-effectiveness of smoking cessation

Smoking cessation with counselling and drugs is one of the most cost-effective interventions in medicine for reducing ill health and prolonging life. More than 200 scientific studies have shown this, and the data also show that the more intensive the intervention, the more cost-effective it is. A directory of healthcare programmes which ranked the cost-effectiveness of interventions in relation to quality-adjusted life years (QALYs) gained showed that giving up smoking following the advice of a general practitioner was ranked third in a list of 21 medical and surgical interventions aimed at preventing or treating diseases.

The UK National Institute for Health and Clinical Excellence (NICE) has reported that smoking cessation interventions are highly cost-effective, at €1120–2800 per QALY gained. A recent meta-analysis from the Netherlands of studies in patients with COPD found that the cost per QALY gained was only €2400 for intensive counselling combined with pharmacotherapy.

Research from the USA has shown that insurance coverage of treatment for smoking cessation results in more frequent evidence-based counselling and drug provision and a higher overall cessation rate among the populations covered by this insurance.

Since 2000, the UK National Health Service has offered free counselling and smoking cessation drugs, and the issue of reimbursement is a matter of debate in most other European countries. Reimbursement for counselling and medicine for smoking cessation seems to increase adherence to clinical guidelines and results in more smokers becoming involved in cessation attempts.

ERS guidelines on smoking cessation ||||

In 2007, the ERS published guidelines on smoking cessation in patients with respiratory disorders. The most important conclusions were:

1) Patients with respiratory disease have a greater and more urgent need to stop smoking than the average smoker.
2) Smoking cessation treatment should be integrated into the management of the patient's respiratory condition.
3) Therapies should include pharmacological treatment (nicotine replacement therapy, bupropion or varenicline) combined with behavioural support.
4) Respiratory physicians should receive training to ensure that they have the knowledge, attitudes and skills necessary to deliver these interventions or to refer to an appropriate specialist.

According to a report by 'Europe Quitting: Progress and Pathways', more than 78 million smokers in Europe want to quit, but half of those surveyed who have tried to quit rate smoking cessation services as inadequate, poor or unacceptable. Education and training in cessation of tobacco use should be included in the curricula of all health professionals and medical students.

> *Smoking cessation interventions are highly cost-effective: €1120–2800 per QALY gained*

Future developments

Better primary prevention should be prioritised. It is also important to make smoking cessation interventions available to all patients with respiratory disorders who smoke. We have cost-effective interventions, but these are underused. Hospital administrators as well as national respiratory societies have a role to try to improve the quality of care in this area. The ERS, too, needs to continue to be a leader in this implementation process.

Conclusions

1) To prevent uptake of smoking amongst young people it is important to develop more smoke-free areas in public and to increase the price of cigarettes, in that way reducing morbidity and mortality from smoking 20 years hence and beyond.
2) Comprehensive community, country and EU interventions against smoking should be further strengthened, including plain packaging and the phasing-out of cigarettes.
3) To reduce the burden of tobacco-induced respiratory disorders – of which the most important are lung cancer and COPD – it is important to encourage all current smokers to quit in order to reduce morbidity and mortality from smoking over the next two decades.
4) Smoking cessation treatment (counselling in combination with drugs) is one of the most cost-effective interventions in medicine; it should be used more widely and its cost should be reimbursed completely. Education and training in cessation of tobacco use should be included in the curricula of all health professionals and medical students.
5) The UK model, with public smoking cessation clinics for every 150 000 of the population and reimbursement of smoking cessation therapy, could be a model for other European countries.
6) The proposals in the WHO Framework Convention of Tobacco Control should be further implemented across Europe.

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Indoor environment

Key points

- People spend most of their time indoors, so the quality of indoor air has major implications for health.
- Indoor air pollution can contribute to a wide spectrum of respiratory health effects, from allergic sensitisation to cancer.
- Indoor air pollution is largely the result of human activity, such as tobacco smoking, burning fuel for heat or cooking, the use of cleaning materials and solvents, and even breathing. Several pollutants may interact in a given environment.
- Natural pollutants such as allergens, dampness and mould, and radon, can also have significant health effects.
- Reflecting the complexity of indoor pollution, the most effective ways to reduce its impact are home-based, multi-component interventions.

Indoor environments contribute significantly to total human exposure to air pollutants, as people spend most of their time indoors. Indoor air quality is influenced by: penetrating outdoor air; specific indoor pollution sources; interactions between building system/construction techniques; and occupants. Some pollutants may be 2–5-fold more concentrated inside than outside buildings. Indoor pollutants may have an important biological impact even at low concentrations over long exposure periods. Indoor exposure occurs mainly at home and in schools, but also in day-care centres, social recreation settings or microenvironments, such as cars, buses, trains, subways and aeroplanes. Workplace indoor exposure is conventionally treated separately as 'occupational exposure' (see chapter 7).

The European Union (EU)-funded Towards Healthy Air in Dwellings in Europe (THADE) project showed that air pollution in dwellings is an important health problem across Europe. An EU-funded European Federation of Allergy and Airways Diseases Patients' Associations (EFA) project, Indoor Air Pollution in Schools, pointed out that the right to breathe good air at school is largely ignored in many countries, where high levels of common indoor pollutants are frequent because of poor building construction and maintenance, poor cleaning and poor ventilation. Indoor air quality is particularly important for vulnerable subpopulations, such as children (their defence mechanisms are still evolving, and they inhale a higher volume of air per bodyweight than adults), elderly people, subjects with cardiac and respiratory diseases and those with socioeconomic deprivation.

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> *Indoor air pollution is the eighth most important risk factor for disease, responsible for an estimated 2.7% of the global burden of disease*

Indoor pollutants and health effects

The Scientific Committee on Health and Environmental Risks (SCHER), one of the independent scientific committees managed by the Directorate-General for Health and Consumer Protection of the European Commission, reported that more than 900 different compounds have been detected in indoor air. Figure 1 shows the main indoor air pollutants and related sources. Most indoor pollutants derive from human activity (anthropogenic pollutants). Carbon dioxide (CO_2) is a product of human respiration, and elevated levels may be reached in crowded indoor environments with inadequate air exchange, thus altering indoor air quality. Allergens – mainly related to the presence of dust, damp, pets or insects, but also penetrating from outdoors – and infectious agents play an important role in indoor pollution. Indoor air pollution is the eighth most important risk factor for disease, responsible for an estimated 2.7% of the global burden of disease (4% in low-income countries). Conservative estimates show that 1.5–2 million deaths every year could be attributed to indoor air pollution, and there is consistent evidence that exposure to indoor pollutants increases the risk of several
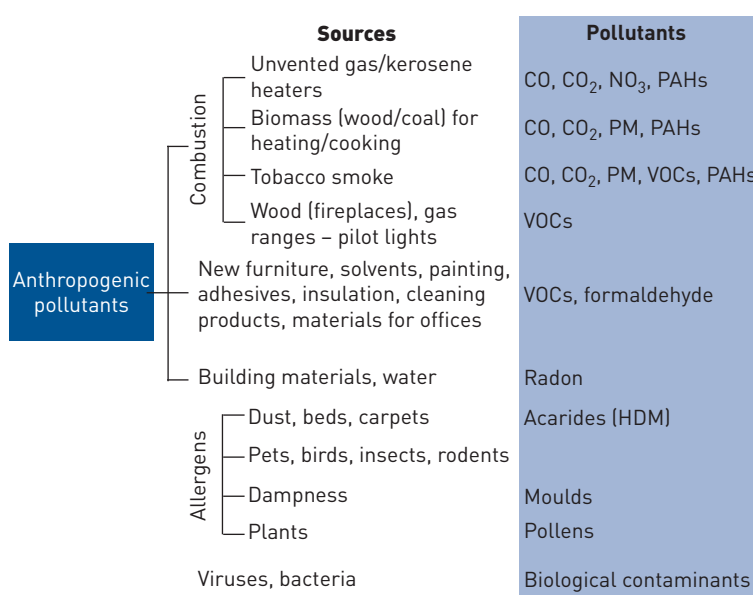

Figure 1 – The main indoor pollutants and their sources. CO: carbon monoxide; CO_2: carbon dioxide; NO_2: nitrogen dioxide; PAHs: polycyclic aromatic hydrocarbons; PM: particulate matter; VOCs: volatile organic compounds; HDM: house dust mite.

> *In infants and children, exposure to VOCs increases the risk of respiratory and allergic conditions such as asthma, wheezing, chronic bronchitis, reduced lung function, atopy and severity of sensitisation, rhinitis and respiratory infections*

respiratory/allergic symptoms or diseases. The commonest indoor risk factors with related health effects are shown in figure 2.

In indoor environments frequented by smokers, tobacco smoke is the major source of particulate matter (PM), accounting for as much as 50–90% of the total indoor PM concentration (see also chapter 8). It has, for example, been shown in Scotland and Ireland that among homes where solid fuels or gas are burned for heating and cooking, it is only in those where cigarette smoking occurs that the concentrations of fine particles with aerodynamic diameter <2.5 µm (PM2.5) are much higher than those recommended for good indoor air quality. In industrialised countries, few studies of measured indoor PM have been performed and those that do exist relate mainly to children. Positive associations of indoor PM with the risk of respiratory symptoms have been found; for example, an estimated increased incidence of nocturnal symptoms and wheezing in asthmatic children of 6–7% for each 10 $\mu g \cdot m^{-3}$ increment in indoor PM2.5. In another study, an increased prevalence of asthma in the previous year was found in schoolchildren exposed to high levels of PM2.5 in the classroom. Further research is needed to clarify whether indoor exposure to particles is associated with the severity of asthma or bronchitis in general populations, as well as with the development of respiratory diseases.
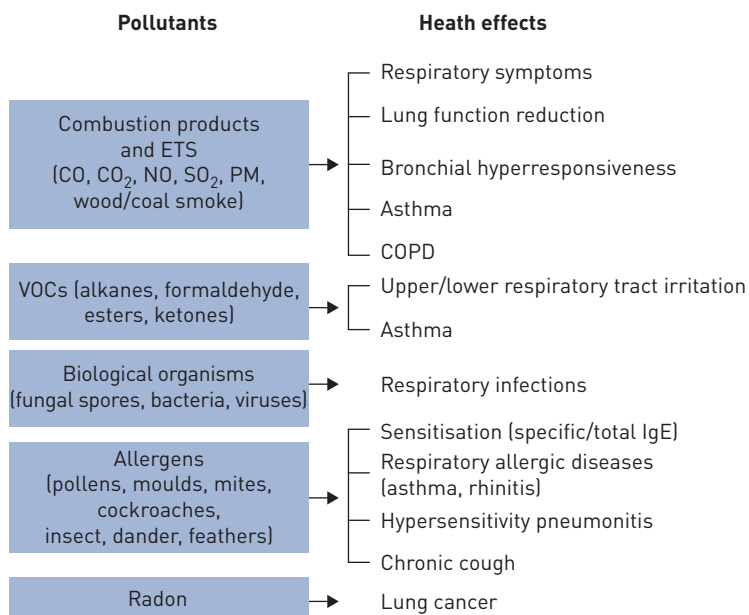

Figure 2 – The main respiratory health effects of common indoor pollutants. ETS: environmental tobacco smoke; CO: carbon monoxide; CO_2: carbon dioxide; NO_x: nitrogen oxides; SO_2: sulfur dioxide; PM: particulate matter; VOCs: volatile organic compounds; COPD: chronic obstructive pulmonary disease.

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Biomass fuels

About 50% of the world's population (about 3 billion people) have little or no access to modern forms of energy, and use biomass fuels for cooking, heating and lighting. These are frequently burned within the households in open fires or inefficient stoves.
In the rural areas of Latin America, 30–75% of households use biomass fuels for cooking, which have a dramatically high production of PM and carbon monoxide (CO). Solid fuels are still the dominant source of energy in households in rural China. In China, indoor air pollution from biomass fuels is responsible for approximately 1 000 000 premature deaths annually, compared with the 1 200 000 estimated to be caused in the country each year by outdoor PM pollution. A recent quantification of the disease burden caused by different risk factors globally indicates that in 2010, over 3.5 million deaths were attributable to household air pollution from solid fuels, representing more than 50% of the total deaths attributable to air pollution from particulate matter and ozone.

Figure 3 shows the main respiratory effects associated with biomass fuel smoke exposure. There is strong evidence of increased risk of acute lower respiratory infections in childhood (at least 2 million deaths annually in children under 5 years of age). There is also evidence of an association with the risk of developing chronic obstructive pulmonary disease (COPD), mostly for women, and with the risk of tuberculosis and asthma.

The International Agency for Research on Cancer has classified emissions from the indoor combustion of coal as a Group 1 carcinogen, *i.e.* a known carcinogen for humans. Indeed, there is strong evidence that women exposed to smoke from coal fires in the home have an elevated risk of lung cancer (the evidence is moderate for men) (figure 3).

Meta-analyses in low-income countries have estimated increased risks from solid fuel combustion averaging 3.5-fold for acute respiratory infections in children, 2.5-fold for chronic bronchitis in women, and 2.8-fold and 2.3-fold for COPD and chronic bronchitis in all adults, respectively.
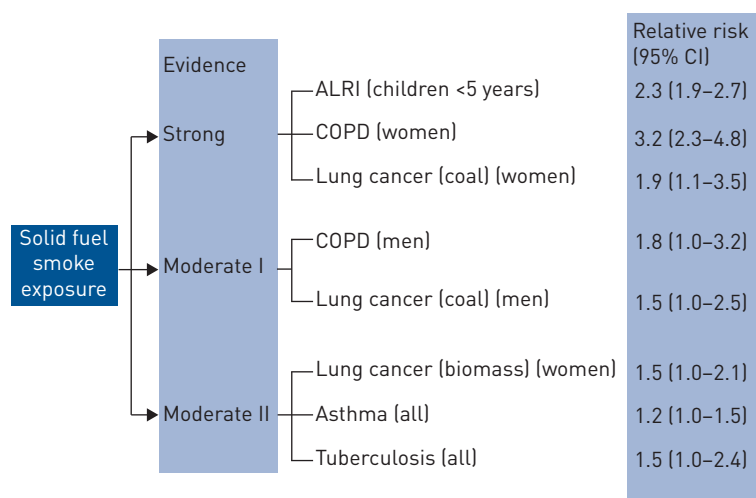

Figure 3 – The major respiratory health effects associated with exposure to biomass and solid fuel smoke. ALRI: acute lower respiratory infection; COPD: chronic obstructive pulmonary disease; CI: confidence interval. Reproduced and modified from Torres-Duque *et al.*, 2008.

Solid fuel smoke exposure	Evidence		Relative risk (95% CI)
	Strong	ALRI (children <5 years)	2.3 (1.9–2.7)
		COPD (women)	3.2 (2.3–4.8)
		Lung cancer (coal) (women)	1.9 (1.1–3.5)
	Moderate I	COPD (men)	1.8 (1.0–3.2)
		Lung cancer (coal) (men)	1.5 (1.0–2.5)
	Moderate II	Lung cancer (biomass) (women)	1.5 (1.0–2.1)
		Asthma (all)	1.2 (1.0–1.5)
		Tuberculosis (all)	1.5 (1.0–2.4)

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Nitrogen dioxide

Indoor nitrogen dioxide (NO_2) is generated mainly by gas-fuelled cooking and heating appliances. The results of longitudinal studies on the asthmatic population (mainly children), or those at risk of developing asthma, indicate positive associations between NO_2 concentration and respiratory symptoms, including wheezing, breathing difficulty, chest tightness, shortness of breath and cough. Adverse health effects in the general population are less evident. A recent study indicated that exposure to outdoor, but not indoor, NO_2 during the first year of life increases the risk of persistent cough. Conflicting results could in part be explained by the difficulty of determining the amount of exposure, as this can fluctuate depending mainly on the season or the use of specific NO_2 sources (*i.e.* peak concentrations occur during cooking or heating activities).

Volatile organic compounds

Exposure to volatile organic compounds (VOCs) may be related to a spectrum of illnesses ranging from mild (irritations) to very severe (cancer). Even the levels of exposure commonly found at the general population level are relevant. In infants and children, exposure to VOCs increases the risk of respiratory and allergic conditions such as asthma, wheezing, chronic bronchitis, reduced lung function, atopy and severity of sensitisation, rhinitis and respiratory infections. A recent meta-analysis estimated an average increase of 17% in the risk of asthma in children for each 10 $\mu g \cdot m^{-3}$ increase in formaldehyde concentration. In a national representative cross-sectional survey in France, high concentrations of VOCs in homes were associated with an increasing prevalence of asthma and rhinitis in adults.

The highest estimated risks between VOCs and health effects are: an approximately 8-fold increase for formaldehyde exposure with chronic bronchitis; 11- and 8-fold increases, respectively, for aromatic and aliphatic chemicals with increased specific immunoglobulin (Ig)E to milk; a 3.4-fold increase for plastics/plasticisers with persistent wheezing; and a 5.6-fold increase for painting with respiratory infections. The estimated increased risk for a diagnosis of asthma ranges from 1.2 to 2.9. Many of the effects observed in children have also been shown in adults. Exposure to VOCs generated by cleaning is a risk factor for asthma and it has been suggested that VOCs produced by microorganisms such as moulds (mVOCs) may contribute to asthma. At the population level, positive associations have been found between the exposure to mVOCs and nocturnal breathlessness, asthma, and chronic bronchitis-like symptoms. However, the role played by mVOCs is still controversial, due to their low specificity in relation to fungi and their very low concentrations in indoor air.

Phthalates also merit specific mention. These are semi-volatile organic compounds derived from the organic chemical compound phthalic acid. The main indoor sources of phthalate esters are plasticised polyvinyl chloride (PVC) materials, used in floor and wall coverings, shower curtains, adhesives, synthetic leather, toys, cosmetics and many other consumer products. There has been considerable concern about phthalates in relation to reproduction and human development; some recent studies have identified associations between phthalates in indoor dust and allergic respiratory symptoms. There is a need for large-scale epidemiological studies in different populations and housing conditions to investigate the respiratory effects of exposure to phthalates in homes.

Radon

In the early 1920s, in eastern Europe, miners working in mines with high levels of radon were found to have an elevated risk of lung cancer, suggesting a causal relationship. Subsequent studies on miners, including never-smokers, showed a strong association of radon exposure with lung cancer risk. The natural occurrence of radon in indoor environments, including homes, is therefore a public health concern. Numerous studies have shown that radon represents a risk at any level of exposure, irrespective of smoking. After cigarette smoking, radon is the second main cause of lung cancer in the general population with no occupational exposure, and it is a well-established cause of lung cancer in never-smokers. Indoor radon significantly increases the relative risk of lung cancer – probably in a linear dose–response relationship with no threshold – by 8–16% for every 100 $Bq \cdot m^{-3}$ increment in its concentration. In the USA, 2100–2900 cases of lung cancer in never-smokers each year are attributable to radon exposure, while in the UK, about 1100 deaths each year from lung cancer are related to radon. A pooled analysis of studies in North America showed that the risk of lung cancer increased by 10% for each concentration increment of 100 $Bq \cdot m^{-3}$ of residential radon; a similar result was found in a meta-analysis in Europe (a risk increase of 10.6% per 100 $Bq \cdot m^{-3}$).

Allergens

The exposure–response relationship between indoor allergens and respiratory/allergic conditions is complex, depending on several factors, such as genetic susceptibility or gene–environment interaction. The reported results are conflicting, with several studies reporting respiratory effects of indoor allergen exposure, including allergic sensitisation and the development of asthma.

Endotoxins are derived from the cell wall of Gram-negative bacteria and are ubiquitous in the environment. High exposure to endotoxins is significantly associated with the risk of COPD and COPD-like symptoms, as well as with bronchial hyperresponsiveness and wheezing. However, other studies have found that early or high exposure to cat allergens or dampness-related allergens have a protective effect against asthma/wheeze/atopy. This protective effect has been discussed extensively, and further studies are needed to better understand possible interactions with the immune system. A pooled analysis using a large database of European birth cohort studies (22 000 children) indicates that pet ownership in early life does not appear to either increase or reduce the risk of asthma or allergic rhinitis symptoms in children aged 6–10 years. However, a recent study found that asthmatic children sensitised and exposed to low levels of common household allergens, including mould, dust, cat and dog allergens, have an increased risk of illness.

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Dampness/mould

Dampness is present in 10–50% of houses. Moulds are a source of allergens, mVOCs and mycotoxins. Meta-analyses show associations of dampness/mould with increases of approximately 30–50% in respiratory and asthma-related health outcomes, including current asthma, ever-diagnosed asthma, upper respiratory tract symptoms, cough, wheezing and the development of asthma. According to the World Health Organization (WHO), dampness-related factors are also associated with dyspnoea, respiratory infections, bronchitis and allergic rhinitis. Positive associations, although not always statistically significant, have been found in children/infants or young adults between fungal concentration (expressed by culture colony counts) and risk of allergic sensitisation and asthma. Significant associations have also been found between exposure to moulds and respiratory symptoms or doctor-diagnosed asthma, regardless of atopy.

Some studies have found increased risks of wheezing and allergic sensitisation in relation to high exposure to ergosterol (a mould marker), whereas others found no such association. Other epidemiological studies have evaluated mould exposure based on β-glucans (components of the bacterial cell wall) or mycotoxins (fungal products). Exposure to β-glucans did not affect respiratory/allergic disorders, whereas there is insufficient evidence to implicate mycotoxins in mould-related respiratory effects. Recently, a new method has been developed to measure fungal DNA as a mould marker in dust/air. The main advantage of using DNA is the possibility of also identifying dead or dormant organisms. Significant positive associations have been reported between the quantity of DNA of certain fungi and wheezing, nocturnal dry cough, persistent cough, daytime breathlessness or a diagnosis of asthma.

Combined effects

Many studies have focused on the respiratory risks of exposure to a single pollutant. However, combined exposure to two or more agents is common. Indeed, indoor environments always contain complex mixtures of substances from different sources, which may jointly contribute to the toxic effects. There is evidence, mostly from *in vitro* or animal studies, of an interaction between air pollutants and allergens in the development of respiratory allergic diseases. In one human study addressing such interactions, a significant association between respiratory symptoms – consistent with asthma exacerbation – and PM was noted only in asthmatic children who owned a dog. Another study found that in mild asthmatics, exposure to a typical home concentration of NO_2 enhanced the decrease in airflow associated with inhaled allergen. In a recent study of children at high risk of asthma,

co-exposure to dog allergen and NO_2, or to dog allergen and environmental tobacco smoke, appeared to increase the risk of asthma.

In a large Indian study (about 100 000 women and 57 000 men, aged 20–49 years), living in a household using biomass for cooking and solid fuels showed a significantly higher risk of asthma in women, whereas tobacco smoking was associated with higher asthma prevalence in both sexes. The combined effects of biomass and solid-fuel use and tobacco smoke on the risk of asthma were higher in women. The combination of VOCs and allergens may also be of importance.

Indoor air quality in schools

Indoor air quality in schools has received particular attention in recent years, as children spend a large proportion of their indoor time at school. Indoor air pollution in schools is a combined effect of physical, chemical and biological factors, and depends on the level of environmental ventilation. The internal air within schools is often of poor quality. Schools are often poorly ventilated (as demonstrated by elevated CO_2 levels) and several pollutants have been found in classrooms, such as bacteria, moulds, VOCs and PM. Associations have been reported among the concentrations of pollutants and the onset of health problems in schoolchildren, mainly respiratory/allergic symptoms and diseases.

Direct comparison of studies is seldom possible because of different methodologies. However, two multicentre European studies using the same standardised procedure have provided data from different countries. Figure 4 shows the average 1-day indoor PM10 concentration, as measured inside the classrooms in the EU-funded Health Effects of School Environment (HESE) study and the School Environment And Respiratory Health of Children (SEARCH) study, promoted by the Regional Environmental Centre for Central and Eastern Europe (REC) (search.rec.org/search1/documents.html).

Interventions

Various intervention studies aimed at improving air quality have been performed. These include: a wood stove-exchange programme, which results in an overall reduction in
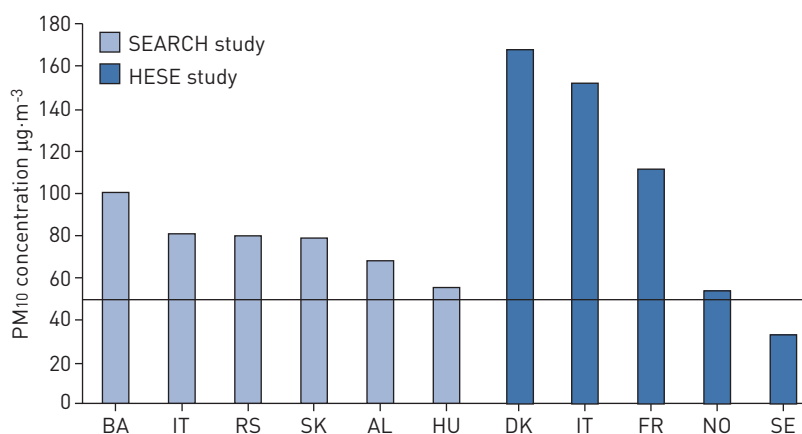
Figure 4 – Average 1-day indoor concentrations of particulate matter with an aerodynamic diameter <10 μm (PM10) measured in classrooms in various European countries. The line at 50 μg·m^{-3} represents the US Environmental Protection Agency annual standard. SEARCH: School Environment And Respiratory Health of Children; HESE: Health Effects of School Environment.

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indoor PM2.5 concentrations; nonpolluting home heating, which reduces the level of NO_2; education programmes that aim to decrease exposure to indoor allergens; displacement ventilation that may reduce CO_2, formaldehyde and viable bacteria; and electrostatic air cleaners to reduce the concentration of particles of all sizes. Evaluations of the effects of interventions that aim to reduce indoor exposure should take into account the impact on health in terms of dose–response relationships.

In summary, home-based, multi-trigger, multi-component interventions with an environmental focus are effective in improving the overall quality of life and productivity of children and adolescents with asthma. Allergen-reducing interventions (*i.e.* installation of mechanical ventilation and heat recovery systems) result in a significant decline in asthma symptoms, such as breathlessness during exercise, wheezing, and coughing during the day and night. In addition, the installation of non-polluting heating in the homes of children with asthma significantly reduces symptoms of asthma, days off school, healthcare utilisation and visits to a pharmacist. Education and remediation to reduce exposure to both indoor allergens and environmental tobacco smoke at home reduce asthma-associated morbidity in urban children with atopic asthma.

The effectiveness of interventions in adults is uncertain, as only a small number of studies have been performed and with inconsistent results. However, one experimental study in adults suggested that office workers with airway symptoms may benefit from installation of local air cleaners. In general, increasing ventilation above currently adopted standards and guidelines is likely to improve respiratory health. Programmes and public health initiatives to reduce exposure to indoor air pollution particularly need to be adopted in low- or middle-income countries. In developing countries, use of a chimney woodstove instead of a traditional indoor open fire significantly reduces CO exposure and the risk of all respiratory symptoms.

Conclusion

The adverse health effects of indoor air pollution exposure have been demonstrated in many epidemiological and experimental studies. Policies aimed at improving health quality both in public and private indoor settings are required in order to achieve relevant public health benefits.

> " *The installation of nonpolluting heating in the homes of children with asthma significantly reduces symptoms of asthma, days off school, healthcare utilisation and visits to a pharmacist* "

Further reading

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MAJOR RISK FACTORS

MAJOR RESPIRATORY DISEASES

RESPIRATORY MANAGEMENT

SPECIAL FIELDS OF RESPIRATORY CARE

PRACTISING RESPIRATORY MEDICINE IN EUROPE

CONCLUSIONS