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# Early-life risk factors for chronic nonrespiratory diseases

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**ABSTRACT** We have witnessed a change in disease patterns contributing to the global burden of disease, with a shift from early childhood deaths due to the classic infectious communicable diseases to years lived with disability from chronic noncommunicable diseases. In both developing and developed countries, the years lived with disability attributable to chronic disease have increased: cardiovascular diseases by 17.7%; chronic respiratory disease by 8.5%; neurological conditions by 12.2%; diabetes by 30.0%; and mental and behavioural disorders by 5.0% over the past 20 years. Recognition of the contribution made by adverse environmental exposures in early life to noncommunicable diseases in later life is increasing. These early-life exposures appear to contribute to both chronic respiratory and chronic nonrespiratory diseases. In this State of the Art article, we aim to examine early-life environmental exposures that have an epidemiological association with chronic nonrespiratory diseases, such as obesity and type II diabetes, cardiovascular disease, and neurocognitive and behavioural problems. We will highlight the potential overlap in environmental risks with respiratory diseases, and point out knowledge gaps and research opportunities.



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Respiratory diseases are linked to obesity/diabetes/metabolic syndrome, CVD and neurocognitive/behavioural disorders <http://ow.ly/CGbea>

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## Introduction

Publication of the 2010 Global Burden of Disease estimates has shown a marked shift away from communicable towards noncommunicable diseases (NCDs) over the past 20 years [1], with an associated increase in both morbidity and mortality from these conditions. Early childhood deaths have declined and years lived with disability have increased [1]. Premature deaths do still occur, especially in low-income developing countries. Indoor air pollution, associated with cooking and heating with solid fuels (*i.e.* wood, crop residue, charcoal, coal and dung) in open fires, unflued stoves or poorly maintained and leaky stoves, is a major global problem affecting an estimated 3 billion people and causing 4.3 million premature deaths annually [2]. Among these deaths: 12% are from pneumonia, many of which are in children; 34% from stroke; 26% from ischaemic heart disease; 22% from chronic obstructive pulmonary disease (COPD); and 6% from lung cancer.

In both developing and developed countries, the years lived with disability attributable to chronic disease have increased: cardiovascular diseases (CVDs) by 17.7%; chronic respiratory disease by 8.5%; neurological conditions by 12.2%; diabetes by 30.0%; and mental and behavioural disorders by 5.0% over the past two decades [3]. These estimates and assessments of the hazards posed by underlying risk factors are based on conservative methodology that requires a very high level of proof before a risk factor can be included [4]. Table 1 shows the changes in risk factors recognised over the past 20 years. While several of the top risks have a clear environmental link, the present approach creates a structural bias by excluding newly recognised and emerging risk factors that have not yet achieved the full weight of evidence required for inclusion in the Global Burden of Disease estimates [6]. Adverse environmental exposures in early life are among the risk factors systematically excluded from consideration in the current methodology. Yet understanding is increasing that many chronic NCDs are initiated by early-life exposures to toxic chemicals together with nutritional imbalances and psychosocial stress [7].

The fetal and developmental origins of adult disease [8] currently generate much interest. Exposure to toxic or endocrine-disrupting chemicals in early life can influence metabolism to alter brain growth [9] or promote obesity [10–12], and play a substantial role in initiation and/or progression of diseases [13] including: respiratory diseases such as asthma, COPD and lung cancer; neurobehavioural disorders, including attention deficit hyperactivity disorder [14] and autism spectrum disorders; depression and other mental disorders; and obesity and type II diabetes [15]. While the mechanisms involved are not known with certainty, individual genetic susceptibility, gene-by-environment interactions and epigenetic mechanisms are likely to be involved [16]. An increasing body of evidence from animal studies suggests that environmental exposures increase disease susceptibility *via* epigenetic mechanisms [17]. Environmental toxicants have the potential to alter gene expression and modify disease susceptibility through induction of methylation of CpG dinucleotide sequences in promoter regions regulating common genes, in transposable elements adjacent to genes with metastable epialleles, and in regulatory elements of imprintable genes [17]. Solid data from human studies have been lacking but with the rapid advances in technology for assessing the “methyloome” and “epigenome”, this is an area of active current research.

TABLE 1 Top 10 risk factors contributing to the global burden of disease and how they have changed over the past 20 years

Rank	1990	2010	
	Risk factor	Risk factor	Change <sup>#</sup> % (95% UI)
1	Childhood underweight	High blood pressure	27 (19–34)
2	Household air pollution <sup>¶</sup>	Smoking <sup>*</sup>	3 (–5–11)
3	Smoking <sup>*</sup>	Alcohol use	28 (17–39)
4	High blood pressure	Household air pollution <sup>¶</sup>	–37 (–44– –29)
5	Suboptimal breast feeding	Low fruit consumption	29 (25–34)
6	Alcohol use	High body mass index	82 (71–95)
7	Ambient PM pollution	High fasting blood glucose	58 (43–73)
8	Low fruit consumption	Childhood underweight	–61 (–66– –55)
9	High fasting blood glucose	Ambient PM pollution	–7 (–13– –1)
10	High body mass index	Physical inactivity	

UI: uncertainty interval; PM: particulate matter. <sup>#</sup>: in contribution to global burden of disease for the 2010 risk factor over the past 20 years; <sup>¶</sup>: predominantly due to burning solid or biomass fuel; <sup>\*</sup>: excluding second-hand smoke. Data from [5].

Several factors contribute to the lack of recognition of early-life exposure to environmental toxicants as risk factors for NCDs. The contribution made by early-life environmental exposures to NCDs has only recently been recognised. Given the relatively long time between low-dose exposures in early life and disease expression many years later, there is a natural barrier in obtaining the appropriate data to establish this relationship. This can be solved either by very long-term studies or by shorter studies that demonstrate environmental contribution to recognised risk factors for NCDs; for example, low lung function is a recognised risk factor for COPD. Thus, studies linking environmental exposures during fetal development or infancy to low lung function at birth or in early childhood provide evidence for early-life contributions to COPD. Similarly, studies demonstrating early-life environmental exposures resulting in rapid weight gain and increased adiposity in infancy, both known risk factors for subsequent obesity, will help to bridge the evidence gap.

Another problem is that most, if not all of the population, are likely to be exposed to the environmental toxicants suspected as risk factors for NCDs. For example, a recent summary of human biomonitoring studies concluded that the exposure to bisphenol A (BPA), a synthetic compound with oestrogen-like activity that is used in the construction of polycarbonate plastics widely used in food and beverage containers, was ubiquitous [18]. Thus, traditional epidemiology methods that rely on comparing exposed with unexposed populations are not suitable for examining early-life exposure to BPA as a risk factor for NCDs in later life. Finally, as is becoming increasingly clear, age- and species-dependent susceptibility and metabolism confound translation of results of animal studies to humans or from studies in adults to infants. The consequence is that environmental exposures have not been accorded due consideration in public health planning and resource allocation [6].

In this State of the Art article, we aim to examine the evidence that early-life environmental exposures have adverse impacts on chronic nonrespiratory diseases, especially obesity and type II diabetes, CVD, and neurocognitive and behavioural problems. We will highlight links to chronic respiratory disease and potential common early-life exposures and risk factors, and point out knowledge gaps and research opportunities. While a full discussion of early-life exposures and risk factors for chronic respiratory disease is beyond the scope of this article and covered elsewhere in this series [19], a brief summary is warranted of exposures and risk factors that are common between respiratory and nonrespiratory disease. These factors are summarised in table 2.

## Obesity and type II diabetes

There is a growing body of evidence that shows that environmental chemical exposures increase the risk of development of obesity and type II diabetes [20]. The strongest associations are with persistent lipophilic pollutants. However, one reason why these associations have not received wide-spread acceptance is that, as lipophilic chemicals, they are stored in fat and obese people have a higher fat mass. However, the most convincing data come from a re-presentation of data from the US National Health and Nutrition

TABLE 2 Links between chronic respiratory and nonrespiratory diseases through common early-life exposures and risk factors

Respiratory risk factor	Obesity	Type II diabetes/ metabolic syndrome	Cardiovascular disease	Neurocognitive and behavioural disorders
<b>Prenatal</b>				
Genetic susceptibility	Overlap with asthma <sup>#</sup>	Not studied	Overlap with COPD	Overlap with asthma
Maternal smoking	Asthma, COPD <sup>¶</sup>	Asthma, COPD	Asthma, COPD	Asthma, COPD
Maternal stress	No link	Asthma	Not studied	Asthma
Maternal undernutrition	Asthma, COPD	Asthma, COPD	Asthma, COPD	Asthma
Environmental chemical exposure	Asthma <sup>+</sup>	Asthma	Asthma	Asthma
<b>Postnatal</b>				
Breast feeding, early weaning, diet	Asthma	Via obesity <sup>§</sup>	No link	Asthma
Low birth weight and catch-up growth	Asthma	Via obesity	Asthma, COPD	Asthma
Environmental tobacco smoke	Asthma, COPD	Asthma, COPD	Asthma, COPD	Asthma
Low socioeconomic status	Asthma, COPD	Asthma, COPD	Asthma, COPD	Asthma, COPD
GIT microbiota dysbiosis	Asthma	Asthma	No link	No link
Air pollution	Asthma, COPD	Asthma, COPD	Asthma, COPD	No link

GIT: gastrointestinal tract; COPD: chronic obstructive pulmonary disease. <sup>#</sup>: in the genes of interest and chromosomal regions linking to both conditions; <sup>¶</sup>: exposures increasing risk are similar to those for both asthma and COPD; <sup>+</sup>: exposures increasing risk are similar to those for asthma but not COPD; <sup>§</sup>: exposure increases risk indirectly.

Examination Survey, which originally showed a strong dose–response relationship between serum concentrations of persistent organic pollutants and diabetes [21]. In re-presenting the data, PORTA and LEE [22] clearly demonstrated an influence of the serum concentrations of persistent organic pollutants on diabetes, independent of body mass index (BMI). They showed that people with the lowest chemical concentrations had almost zero risk of diabetes regardless of their BMI (fig. 1). In addition, the risk of diabetes climbed progressively with increasing pollutant levels, even in normal-weight individuals (BMI <25 kg·m<sup>-2</sup>) [22]. There is also increasing evidence suggesting that BPA may be diabetogenic [23, 24]. Urine levels of BPA have been positively correlated with CVD and type II diabetes [25]. In animal studies, BPA exposure has been shown to cause the metabolic syndrome, including insulin resistance [23, 26–28].

While the associations between exposure to a variety of environmental chemicals and obesity and diabetes have been seen across the life span, recent studies implicate exposure before birth as an important factor that increases the risk of obesity later in life. The impact of prenatal exposure increasing the risk of obesity has been demonstrated in humans for maternal tobacco smoke [29]; dichlorodiphenyldichloroethylene (DDE), the metabolite of dichlorodiphenyltrichloroethane (DDT) [30, 31]; hexachlorobenzene [32]; and polychlorinated biphenyls [33, 34]. There is some indication that different polychlorinated biphenyl congeners may have different associations, and that sex and height may be confounders [35]. Animal studies have demonstrated that environmental chemicals, especially those with endocrine-disrupting activity, act prenatally on adipocyte precursors to increase the number of adipocytes; to modify the way adipocytes store and metabolise fat postnatally, especially in the presence of a high-fat diet; and increase the secretion of pro-inflammatory cytokines from adipocytes [28, 36, 37]. Similar data are lacking for humans.

Studies in adolescents have implicated associations between obesity and serum concentrations of perfluoroalkyl chemicals [38] and urinary BPA [39]. Associations with various phthalates [40] and metals [41] have shown either positive, negative or no relationship with obesity. In addition, at least one study has shown a relationship between increasing BPA concentrations and reduced BMI/adiposity in girls at 9 years of age [42], which suggests these relationships are quite complex.

The gastrointestinal microbiota is a key component of human homeostasis and “peripheral metabolism” (*i.e.* occurring in the gut) increases energy extraction from food [43]. Alterations to the gastrointestinal microbiota (dysbiosis) have been described in a variety of chronic inflammatory diseases, such as inflammatory bowel disease, obesity and asthma. These changes commonly involve a reduction in so-called probiotic species, including *Lactobacillus* and *Bifidobacterium*, as well as outgrowth of potentially pathogenic bacteria [44]. The gastrointestinal microbiota is susceptible to environmental influences, include place and mode of delivery [45], and the presence of siblings and pets in the home in early life [46]. The composition of the microbiota may protect or predispose individuals to obesity [43]. The infant bowel is sterile at birth and the microbiota is established in early postnatal life [47, 48]. The composition of the microbiota is different in breast- and formula-fed infants, and the timing of cessation of breastfeeding is an important event in establishing the microbiota [47]. Infants with more short-chain fatty

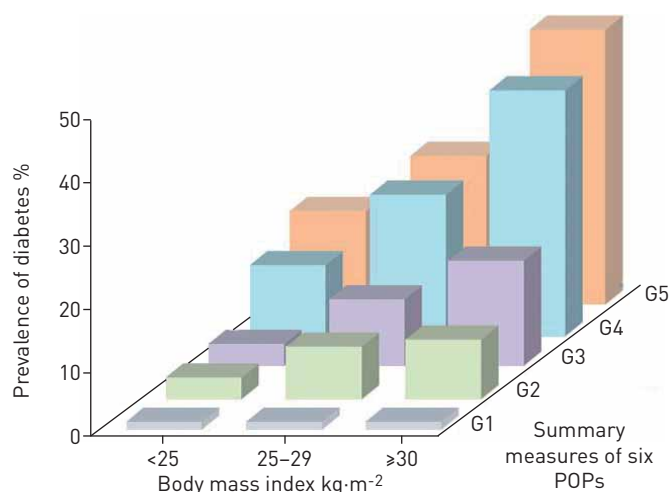


FIGURE 1 Influence of serum levels of persistent organic pollutants (POPs) on risk of diabetes. The population is divided into quintiles of serum levels of six POPs (from G1 (lowest) to G5 (highest) levels) and by body mass index. Reproduced from [22] with permission from the publisher.

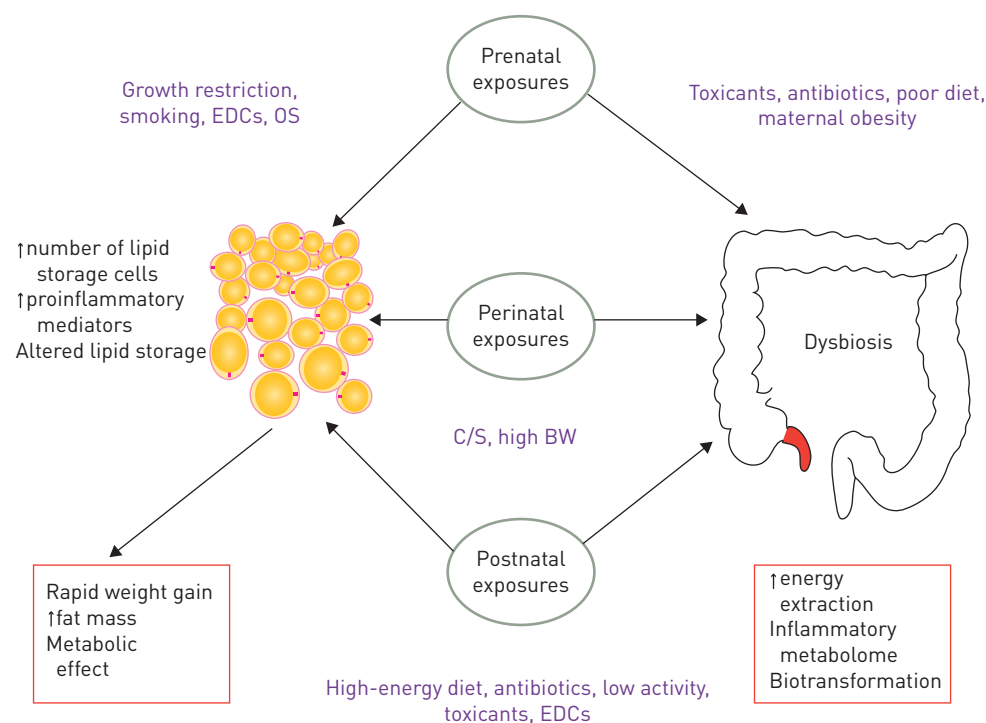


FIGURE 2 Schematic representation of the potential roles of environmental exposures in early life in increasing the risk of obesity/type II diabetes. Common exposures influencing two “target organs”, adipocytes and the gastrointestinal microbiota, are shown. EDC: endocrine-disrupting chemical; OS: oxidative stress; C/S: caesarean section; BW: birth weight.

acid-producing bacteria have a more rapid increase in BMI in early life [47]. The gastrointestinal microbiota is also involved in the biotransformation of environmental toxicants [49] and may increase or decrease the toxicity of the chemical. There is little direct knowledge to determine what contribution biotransformation of such chemicals may make to human disease. Figure 2 depicts a schema linking prenatal and early-life environmental exposures with the risk of obesity/type II diabetes. The main targets of environmental exposures are adipocyte precursors and adipocytes, and the gastrointestinal microbiota. While direct evidence in humans is not available for some aspects of this schema, it does suggest an agenda for fruitful research.

Perinatal exposure to a variety of environmental toxins has been associated with low birth weight, including phthalates [50], perfluorinated compounds [51–53] and occupational exposures to pesticides [54]. Furthermore, there appear to be relationships of environmental toxins with birth at lower gestational age, and phthalates [55, 56] and perfluorinated compounds [51, 53] with preterm birth.

Reduced gestational age and preterm birth have been shown to be associated with insulin resistance, and future obesity and type II diabetes. DARROW *et al.* [52] also found a relationship between serum levels of perfluorinated compounds, such those found in non-stick cookware, and pregnancy-induced hypertension, which has been shown to be associated with future maternal obesity and diabetes [57, 58]. Babies born to mothers with gestational diabetes are more likely to be born large for gestational age [59]; these babies have an increased risk of future obesity and type II diabetes. Few studies have investigated links between environmental toxicants and gestational diabetes. One study failed to show a relationship between maternal BPA exposure and gestational diabetes [60]. Exploration of the role that environmental toxins may have in the development of gestational diabetes and the role this plays on the development of fetal macrosomia would be a fruitful area for future research.

Overweight in adults is a major risk factor for development of diabetes, hypertension, heart disease and stroke [61]. There is strong evidence that obesity during childhood increases risk of type II diabetes [62], hypertension [63], ischaemic heart disease and stroke later in life [64, 65]. The Bogalusa Heart Study found that the critical factor was central obesity, even in children of “normal” weight, and that these children were at significantly elevated risk of hyperlipidaemia and elevated insulin levels [66]. Many of the same contaminants that increase the risk of obesity following early-life exposure also increase risk of diabetes, although these studies have usually been conducted in adults, for example polychlorinated biphenyls and organochlorine pesticides [67, 68].

TABLE 3 Environmental links to obesity/type II diabetes

**What is known?**

- Chemicals with endocrine-disrupting activity increase the risk of diabetes, independently of obesity
- Prenatal exposure to environmental chemicals increase the risk of obesity, especially in early life
- Dysbiosis increases the risk of obesity
- Prenatal exposure to environmental chemicals is associated with low birth weight

**Emerging evidence**

- Adipocyte precursors may be more susceptible than mature adipocytes to environmental chemicals
- Central obesity in early life may predispose to insulin resistance regardless of body mass index

**Speculation**

- The immunological and metabolic consequences of the pattern of dysbiosis seen in adults with obesity or type II diabetes are likely to have life-long effects, especially if encountered during fetal development or in early life
- The pattern of dysbiosis that is detrimental in obesity/type II diabetes is also detrimental to respiratory health

Environmental links to obesity/type II diabetes are summarised in table 3.

**Link to respiratory disease**

The association between asthma and obesity has been demonstrated in many cross-sectional and prospective epidemiological studies published in diverse populations [69]. The consistency of the obesity–asthma link suggests that this association is not spurious. A number of early-life factors may predispose individuals to expressing both phenotypes including those discussed below. HALLSTRAND *et al.* [70] reported genetic analyses of monozygotic and dizygotic twin pairs, and showed that 8% of the genetic component of obesity is shared with asthma. Several linkage analyses have revealed genome regions that may harbour susceptibility genes for both asthma and obesity, including overlaps noted at positions 5q, 6p, 11q and 12q [71–73]. Polymorphisms in five genes have been associated with both asthma and obesity: *ADRB2* ( $\beta_2$ -adrenergic receptor), *TNFA* (tumour necrosis factor (TNF)- $\alpha$ ) [74, 75], *LPA* (lymphotoxin- $\alpha$ ) [76–78], *VDR* (vitamin D receptor) [79–81] and *PRKCA* (protein kinase C $\alpha$ ). These findings suggest that certain genetic variants may have pleiotropic effects on both obesity and asthma, and/or influence pathways that are common to both. However, further studies will be required to investigate whether specific genetic variants influence both obesity and asthma.

Rapid early-life weight gain, independent of birth weight, is associated with adult obesity [82, 83]; however, whether this contributes to the associations between asthma and obesity is not clear from the current literature. In addition, as highlighted later, fetal growth restriction may change these relationships.

A Western diet may increase the risk of obesity and of asthma. Obese children and adults have been reported to have low serum concentrations of antioxidants [84–87]. Maternal diet and the specific nutrients have not been explored in relation to childhood obesity or in the context of both asthma and obesity.

The effects of alterations in gastrointestinal tract (GIT) flora, including reduced diversity and the absence of “beneficial” organisms in infancy, can have long-term effects on allergic diseases [88]. While evidence in this field is sparse and still emerging, the microbes thought to be beneficial for allergic diseases and obesity appear to overlap. However, whether this apparent overlap in beneficial microbes indicates common mechanisms for allergic diseases and obesity is unknown. The GIT microbiome also differs in adults with and without type II diabetes, with changes in the relative proportions of various microorganisms [89] that were associated with plasma glucose levels [90]. However, direct links with respiratory disease are lacking.

The relationship between other respiratory diseases such as COPD and obesity is increasingly being recognised in the literature. The overall prevalence of obesity in a population of primary care patients with COPD in the Netherlands was reported as 18%, compared with 10% in the general population, with the prevalence of obesity being highest in those with mild disease (Global Initiative for Chronic Obstructive Lung Disease (GOLD) stages 1 and 2) and lowest in those with severe disease (GOLD stage 4). When emphysema and chronic bronchitis are reported separately, a significantly increased prevalence of obesity is reported in chronic bronchitis (25%) compared with controls (16%), while underweight was more prevalent in patients with emphysema [91]. There are no data jointly linking early-life influences on both obesity and COPD.

Obesity plays a major role in the development of metabolic syndrome and has been identified as an important risk factor for chronic diseases such as type II diabetes. There are no studies specifically

examining early-life influences in the inception of both asthma and type II diabetes, except *via* obesity. There are several variations to the definition of metabolic syndrome but most include abdominal obesity, atherogenic dyslipidaemia, hypertension and insulin resistance. An association between asthma and the metabolic syndrome has been suggested in a large cross-sectional analysis that indicated children diagnosed with asthma tend to have higher rates of insulin resistance and serum triglyceride levels [92], independent of the children's weight, sex and history of exposure to tobacco smoke [92]. Similarly, lung function was lower in nondiabetic adults with insulin resistance after controlling for BMI [93]. This suggests that those in the normal weight range may be more susceptible to developing asthma secondary to the metabolic derangements of increasing triglyceride or blood glucose levels, independently of BMI. Asthma symptoms are reported more frequently in subjects with metabolic syndrome [94]. Insulin resistance and diabetes are associated with reduced lung function [92, 95]. Associations have also been reported between COPD and the metabolic syndrome. Large population-based studies have demonstrated a higher prevalence of type II diabetes, hypertension, dyslipidaemia and resultant CVD in COPD [96, 97]. The prevalence of type II diabetes in COPD is estimated at 1.6–16%, increasing with COPD severity [97, 98].

Maternal smoking during pregnancy and exposure to environmental tobacco smoke (ETS) are risk factors for obesity [29] and type II diabetes [99, 100] in later life. Maternal stressful events have also been associated with insulin resistance in the offspring in later life, even after accounting for birth weight and family history of diabetes [101]. A retrospective study of mothers who experienced bereavement during pregnancy had increased risk of having diabetic adult offspring [102]. Low socioeconomic status (SES) during childhood is a risk factor for adult type II diabetes even after correcting for SES in adult life and personal obesity [103, 104]. The risk was amplified when childhood low SES was combined with adult obesity.

Various epidemiological studies describe an association between air pollution and type II diabetes. Although the findings have been inconsistent, when assessed as a whole, the majority of observations support the association [105].

### Cardiovascular disease

The major traditional risks for CVD, tobacco smoking, high-fat diets, dyslipidaemia, obesity and exposure to ambient air pollution, have been well established through large-scale epidemiological studies conducted in adults. Environmental chemicals, including polyaromatic hydrocarbons, aldehydes and metals, are recognised as increasing the risk of CVD [106]. Fewer studies of environment contributions to CVD risks have focused on early-life exposures beyond the relationships with development of obesity. However, LAMERRILL *et al.* [107] found that prenatal exposure to DDT and its metabolites was associated with an increased risk of hypertension at ages 37–47 years. A recent study that combined data from the Cardiovascular Risk in Young Finns study (Finland) with the Childhood Determinants of Adult Health Study (Tasmania, Australia) demonstrated that exposure to parental smoking during childhood or adolescence was associated with greater carotid intima-media thickness up to 25 years later [108]. The effect was greater if both parents smoked, and was independent of personal smoking in adulthood and uniform across categories of age, sex and cohort. Interest is increasing in the early-life origins of CVD, with an adverse intrauterine environment and fetal growth restriction becoming recognised as increasing the risk of atherosclerosis [109]. A number of early-life biomarkers of future CVD risk are emerging, including indicators of: increased vascular stiffness (carotid and aortic intima-media thickness, arterial distensibility and pulse wave velocity); endothelial dysfunction (flow-mediated vasodilatation, serum intercellular adhesion molecule 1 and vascular cell adhesion molecular 1); and of systemic inflammation (highly sensitive C-reactive protein), as well as indicators of dyslipidaemia and insulin resistance. Longitudinal birth cohorts are currently studying the influence of early-life environmental exposures on long-term cardiovascular health using such early-life biomarkers of the effects of exposure, with a major concentration of presumed epigenetic mechanisms [109]. We await the results of such studies with interest.

Environmental links to CVD are summarised in table 4.

### Link to respiratory diseases

There is now considerable evidence of an association between respiratory disease, such as asthma and COPD, and CVD. Figure 3 shows a schematic representation of common risk factors that may link these diseases. CVD is a major contributor to morbidity and mortality in patients with COPD [110–112]. In a large cohort study of patients with COPD, the prevalence of coronary artery disease was 33.6%, compared with 27.1% in an age- and sex-matched cohort without COPD [113]. In addition, a number of population studies have shown that airflow limitation (low forced expiratory volume in 1 s (FEV<sub>1</sub>)) or FEV<sub>1</sub>/forced vital capacity ratio is a predictor of cardiovascular risk [112]. In the Lung Health Study of 5887 patients with COPD patients, CVD was the leading cause of death [114].

TABLE 4 Environmental links to cardiovascular disease

**What is known?**

Traditional risk factors for cardiovascular disease in adults are well established

**Emerging evidence**

Adverse intrauterine environments increase life-long risks of cardiovascular disease

Biomarkers of vascular stiffness and endothelial dysfunction in early life predict future cardiovascular disease

**Speculation**

Environmental exposures in early life increase the risk of cardiovascular disease more than similar exposures in later life

ETS exposure in adults is associated with impaired arterial endothelial function [115], increased arterial wall thickness [116] and lipid alterations [117] that favour atherosclerosis. The same effects have been demonstrated in some [118, 119] but not all studies [120] in children. Passive smoke inhalation has also shown to increase the likelihood of fatal and nonfatal myocardial infarction [120]. Large prospective cohort studies looking at children and adults exposed to maternal smoking during pregnancy have reported an increased CVD risk profile including obesity [121–124], higher systolic blood pressure [125], higher atherogenic lipoproteins and triglycerides [126]. While the role of maternal smoking on the subsequent susceptibility to cardiovascular disease is recognised, the mechanism underlying this effect is not well understood and is an area of research need. There are no studies investigating the effect of *in utero* cigarette smoke exposure and the direct links between CVD and COPD.

The associations between low birth weight and CVD, type II diabetes, hypertension and obesity in later life are well recognised [127–129]. The associations seem to be consistent and stronger among subjects with postnatal catch-up growth. Well-designed epidemiological studies that take into account confounding factors are needed to further elucidate the associations of lung disease and low birth weight and the link with CVD.

Exposure to air pollution may be causally linked to CVD. All commonly measured ambient air pollutants are positively associated with increased hospitalisation [130, 131] and mortality due to CVD [132–134]. Particulate matter exposure in animal studies induced more advanced and larger coronary lesions, more extensive atherosclerosis in the aorta, and more unstable plaques [135]. Studies of the effect of particulate matter exposure in humans have shown it causes tachycardia and hypertension, and increases in blood viscosity [136], coagulation factors [137], inflammatory mediators [137] and endothelial injury/dysfunction [138]. Collectively, these responses may result in adverse cardiovascular events by causing myocardial ischaemia [139], malignant ventricular arrhythmias [140], increased plaque vulnerability and enhanced potential for acute thrombosis triggering acute coronary syndromes. Despite the growing evidence of the deleterious effects of early-life ambient air pollution on COPD and CVD, there are no studies linking the two directly.

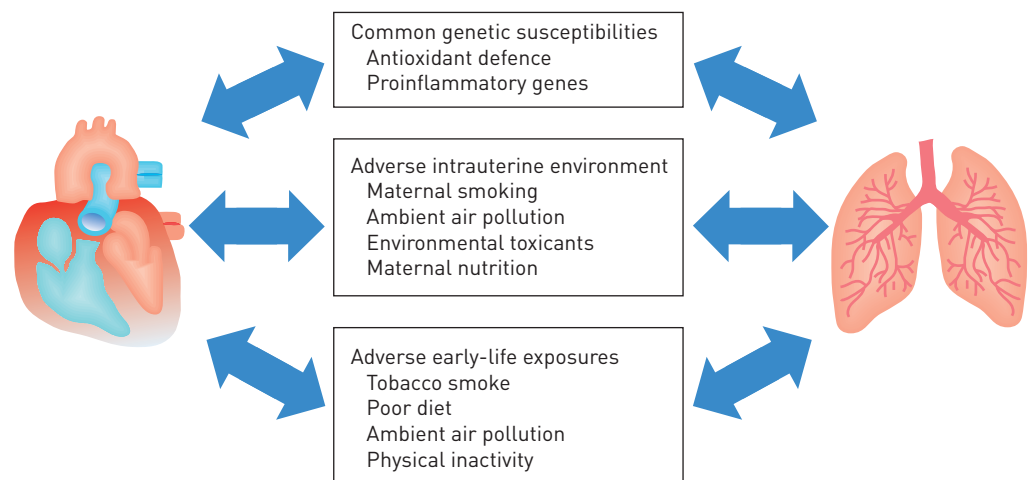


FIGURE 3 Schematic representation of the common risk factors underlying the associations between cardiovascular disease and respiratory disease.

There may be a shared genetic susceptibility between COPD and CVD in antioxidant defence system genes. Complex polygenic interactions of the matrix metalloproteases [141–143] and polymorphisms of epoxide hydrolase [144, 145] have been identified as a possible genetic link between COPD and CVD. The adverse health consequences of exposure to ambient air pollution are magnified in those less able to defend against oxidative stress. Several studies have also demonstrated an association between asthma and CVD. Subjects with adult-onset asthma are at increased risk of CVD including carotid atherosclerosis, coronary heart disease or stroke [146–149].

### Neurocognitive disorders

There is an increasing recognition of the major impact that mental health disorders, in the broadest use of the term, have on society. In children, neurocognitive disorders, such as autism spectrum disorder, attention deficit hyperactivity disorder, mental retardation, dyslexia and other biological disorders of the brain, are common [150], with between 400 000 and 600 000 of the 4 million babies born each year in the USA affected. Globally, childhood behavioural disorders contribute 5.75 million disability-adjusted life-years, a substantial proportion of the total burden of disease. They are particularly prominent in terms of nonfatal burden, accounting for 0.8% of the years lived with disability across all ages [151]. Attention deficit hyperactivity disorder is diagnosed in mid-childhood and the prevalence declines with age, being 5–10% in childhood, 2.5–4% in adolescents and 2.5% in adults [152, 153]. A recent pooled analysis suggested a global prevalence of 5.3% for attention deficit hyperactivity disorder in children and adolescents, although parental reports of symptoms consistent with attention deficit hyperactivity disorder often give higher estimates, with 7.2% of American children 4–17 years of age reported by parents to have a current diagnosis of attention deficit hyperactivity disorder [154]. By any measure neurocognitive disorders in children and adolescents impose a huge burden on society.

Attention deficit hyperactivity disorder often co-occurs with other neurobehavioural disorders. AGUIAR *et al.* [152] reported that the most common comorbidities in boys are oppositional defiant disorder (>32%) and conduct disorders (>7%), while anxiety disorders (33%) are more common in girls, and depression and bipolar disorders are common in adolescents. There is less certainty over whether attention deficit hyperactivity disorder is associated with decreased cognitive function and lower intelligence quotient (IQ), although several of the environmental exposures associated with attention deficit hyperactivity disorder (see later), including lead [155], polychlorinated biphenyls [155], organochlorine pesticides [155], organophosphate pesticides and tobacco smoke [156], are associated with lower IQ. A recent meta-analysis that included 137 comparisons of full-scale IQ among children with attention deficit hyperactivity disorder and controls concluded that a reduction of 9 points was seen with attention deficit hyperactivity disorder [154].

Attention deficit hyperactivity disorder is considered to be a highly heritable disorder, with pooled data from twin studies suggesting a heritability of 76% [157]. Considerable evidence suggests that neurocognitive disorders result from complex interactions of genetic, environmental and social factors [158]. The developing human brain is exquisitely sensitive to toxic chemicals [150] and early-life exposure to environmental toxicants has major impacts on neurocognitive disorders. Substantial evidence links loss of cognition (IQ), dyslexia and attention deficit hyperactivity disorder to lead, methyl mercury, organophosphate and organochlorine insecticides, polychlorinated biphenyls, arsenic, manganese, polyaromatic hydrocarbons, BPA, brominated flame retardants, and perfluorinated compounds [150]. Additional risk factors identified by longitudinal cohort studies or epidemiological studies include: low birth weight [159, 160]; head trauma [161]; low parental education level [161]; family psychosocial adversity [162–165]; family dysfunction [166]; prenatal exposure to drugs of abuse and tobacco smoke [164, 167, 168]; Western diet and no or short duration breastfeeding [164, 169]; and maternal vitamin D insufficiency during pregnancy [170].

Environmental links to neurocognitive disorders are summarised in table 5.

### Link to respiratory disease

Despite being debated for a long time, there are large epidemiological studies that have now shown an association between asthma and symptoms consistent with attention deficit hyperactivity disorder [171–173], with more severe symptoms in severe asthma [171]. A schematic representation of the common risk factors for neurocognitive disorders and respiratory disease is shown in figure 4. Shared genetic susceptibilities may be involved in the link between attention deficit hyperactivity disorder and asthma. A prospective twin study indicated that 68% of the phenotypic correlation between asthma and the hyperactivity–impulsivity dimension of attention deficit hyperactivity disorder was because of genetic influences [173]. Possible shared hereditary influences could involve inflammatory pathways, including the various cytokines central to the pathogenesis of asthma. Polymorphisms of *IL2* (interleukin (IL)-2), *IL6*

TABLE 5 Environmental links to neurocognitive disorders

**What is known?**

Adverse intrauterine exposures decrease IQ and increase risk of neurobehavioral disorders  
 Prenatal exposures are associated with greater effects than exposures in later life

**Emerging evidence**

Common genetic susceptibilities underlie the link between asthma and attention deficit hyperactivity disorder  
 Maternal stress during pregnancy may contribute to the link between asthma and attention deficit hyperactivity disorder

**Speculation**

The patterns of gastrointestinal dysbiosis differ between asthma and neurocognitive dysfunction, suggesting separate mechanism may be involved  
 Vitamin D deficiency affecting both brain and lung development may contribute to the association between asthma and attention deficit hyperactivity disorder

IQ: intelligence quotient.

(IL-6) and *TNFA* [173], and increased levels of cytokines IL-2, IL-6, TNF- $\alpha$ , IL-16, IL-10 and IL-13 [175] have been shown to be associated with attention deficit hyperactivity disorder.

Pre- and postnatal tobacco smoke exposure may be a risk factor for behavioural and neurodevelopmental problems, including reduced general intellectual ability, skills in language and auditory tasks, and academic achievement, and attention deficit hyperactivity disorder [176]. Animal studies have shown that nicotine is a prenatal neuroteratogen, resulting in abnormalities of neuronal cell proliferation and differentiation, eliciting abnormalities in the number of cells and, eventually, altered synaptic activity, and could account for the neurodevelopmental deficits observed in humans [177]. Prenatal nicotine exposure alters airway growth and alters receptor expression on airway cells. Whether the mechanisms invoked are similar is not known.

Prenatal stress may provide a link between attention deficit hyperactivity disorder and asthma. Prospective studies have documented that maternal stress is positively linked to attention deficit hyperactivity disorder in the offspring [178]. This association has also been demonstrated in animal models, particularly with rodents and nonhuman primates [179, 180], although the mechanisms involved are not known; neither are the mechanisms underlying maternal stress and asthma, although blaming effects on the hypothalamic–pituitary–adrenal axis and on cortisol secretion is popular.

The gut microbiota has been reported to differ between healthy (“neurotypical”) children and those with autism spectrum disorder [181–183], with supportive mechanistic studies in animal models [184]. However, not all human studies support a role for intestinal flora in neurocognitive disorders [185]. In addition, the patterns of gastrointestinal dysbiosis implicated in neurocognitive disorders differ from that seen in obesity/type II diabetes and allergic disorders.

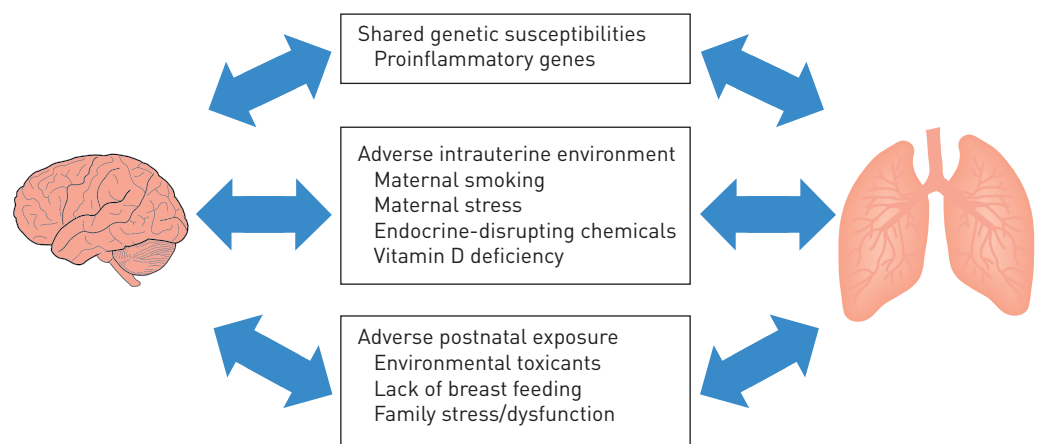


FIGURE 4 Schematic representation of the common risk factors underlying the associations between neurocognitive disorders and respiratory disease.

## Conclusion

The global burden of disease associated with both chronic respiratory and nonrespiratory diseases is substantial and increasing. As highlighted in this article, epidemiological evidence linking respiratory diseases with obesity, type II diabetes and metabolic syndrome, CVD, and neurocognitive and behavioural disorders is substantial, but few studies specifically examining direct mechanistic links exist in the human literature. Common environmental exposures in early life and shared risk factors may underlie these associations, and warrant specific study.

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