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A joint ERS/ATS policy statement: what constitutes an adverse health effect of air pollution? An analytical framework

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ABSTRACT   The American Thoracic Society has previously published statements on what constitutes an adverse effect on health of air pollution in 1985 and 2000. We set out to update and broaden these past statements that focused primarily on effects on the respiratory system. Since then, many studies have documented effects of air pollution on other organ systems, such as on the cardiovascular and central nervous systems. In addition, many new biomarkers of effects have been developed and applied in air pollution studies.

This current report seeks to integrate the latest science into a general framework for interpreting the adversity of the human health effects of air pollution. Rather than trying to provide a catalogue of what is and what is not an adverse effect of air pollution, we propose a set of considerations that can be applied in forming judgments of the adversity of not only currently documented, but also emerging and future effects of air pollution on human health. These considerations are illustrated by the inclusion of examples for different types of health effects of air pollution.

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Background

The human health effects of exposure to tropospheric outdoor air pollutants, which include both particulate matter and gaseous contaminants, have gained prominence as a global public health concern. Indeed, the most recent Global Burden of Disease (GBD) report lists outdoor air pollution as a leading cause of death and lost disability-adjusted life years, accounting for an estimated >3 million premature deaths per year globally [1, 2], as well as similarly large numbers of deaths associated with indoor air pollution exposures (*e.g.* biomass and coal burning smoke). However, outdoor air pollution exposures and trends are quite disparate in different parts of the globe: the principal community air pollutants monitored for regulatory purposes, including carbon monoxide, nitrogen dioxide (NO_2), sulfur dioxide, particulate matter (PM) and ozone, have generally (but not universally) shown declining concentrations in the developed nations in recent years, while in the low- and middle-income countries (LMIC) pollutant levels have risen dramatically in some (*e.g.* China and India) [3], but have declined in others (*e.g.* Mexico).

The contrasting situations (*i.e.* improvement *versus* deterioration of air quality) around the globe present differing challenges to the evaluation of air pollution health effects. In the developed world, a critical question is whether adverse effects occur at lower air pollution concentrations and still warrant further regulation below the current national standards and guidelines of the World Health Organization (WHO). In contrast, in other countries there is uncertainty as to whether the concentration–response functions for adverse health effects estimates (*e.g.* increased risk of death per $\mu g \cdot m^{-3}$ particulate matter with a 50% cut-off aerodynamic diameter of 2.5 μm ($PM_{2.5}$)) derived in the developed world are directly applicable to the differing pollution mixes and concentrations, as well as the differing demographic compositions (*e.g.* higher percentages of young people), found in many LMICs. In these developing countries, the existence of a health hazard may also be questioned in the absence of relevant local scientific documentation of associations between air pollution and health.

Whether in the high-income countries or LMICs, the aim of air quality management is to limit or avoid adverse impacts of air pollution on the public's health. Thus, there is a need to identify those effects that are considered "adverse", and to separate them from those effects not considered adverse, thereby focusing control measures on the pollutants causing, and populations experiencing, the most severe health impacts. However, while the United States Clean Air Act (www.gpo.gov/fdsys/pkg/USCODE-2013-title42/html/ USCODE-2013-title42-chap85-subchapI-partA-sec7409.htm) requires that the administrator of the US Environmental Protection Agency (EPA) promulgate, for certain "criteria" pollutants, standards that will be sufficient to protect against adverse effects of the air pollutants on health, the Act is silent on the definition of "adverse effect", leaving flexibility for consideration of new knowledge. In Europe, the preamble of the Air Quality Standards also mentions the word "adverse" without further classification: "Humans can be adversely affected by exposure to air pollutants in outdoor air. In response, the European Union has developed an extensive body of legislation which establishes health based standards and objectives for a number of pollutants in air" (http://ec.europa.eu/environment/air/quality/standards.htm). Thus, guidance as to what the latest science indicates to constitute an adverse effect is essential to developing and implementing the most effective air pollution control policies in all parts of the world [4].

The American Thoracic Society (ATS) has previously provided such guidance on the definition of adverse health effects of air pollution, beginning with a statement made in 1985, followed by the most recent 2000 ATS statement, *What Constitutes an Adverse Health Effect of Air Pollution* [5], both of which focused largely on impacts to the respiratory system. However, since that time, new toxicological, clinical and epidemiological studies have identified significant human health effects of air pollution beyond the respiratory tract, and at lower levels of exposure. New types of data streams and approaches to toxicity assessments have also become relevant, generated by the various emerging "omics" and exposure technologies, as well as newly developed systems approaches to toxicity and exposure assessment [6, 7]. Since 2000, substantial evidence has also accumulated on air pollution and the cardiovascular system. As a result, it is now clear that excess morbidity and mortality related to cardiovascular effects of air pollution occur, in addition to respiratory effects [8]. Additionally, new evidence is accumulating for the occurrence of adverse effects of air pollution on the central nervous system (CNS), reproduction and development, and certain metabolic outcomes, as well as cancer [9]. In this document, the ATS and the European Respiratory Society (ERS) now cooperatively update the ATS 2000 statement to address these new scientific findings.

Methods

To develop a new statement, we have assembled, from the ERS and ATS membership, a group of clinicians, toxicologists, epidemiologists and public health specialists, encompassing a broad range of expertise in studies of air pollution and health. Working group meetings were held in Brussels (Belgium; March 12–13, 2015), Denver (CO, USA; May 16, 2015) and San Francisco (DA, USA; May 16, 2016). Draft report sections were prepared by subgroups, and then discussed at the meetings and by e-mail under the leadership of GDT, HK and BB. At an early stage it was decided that a systematic review of all literature on air pollution and health would not be provided, but instead appropriate examples would be chosen to illustrate considerations of adversity. This statement, like the 2000 statement, is intended to provide guidance to policymakers, clinicians and public health professionals, as well as others who interpret the scientific evidence on the health effects of air pollution for risk management purposes. Because we now can consider a wider, and still growing, range of biomarkers of exposure and health effects of air pollution, this statement first includes a list of general considerations as to what constitutes an adverse health effect, in order to provide guidance to researchers and policymakers when new health effects markers or health outcome associations might be reported in future. These considerations, as summarised in table 1, are applied within this statement to a number of illustrative examples of effects to help in the general assessment as to whether or not specific outcomes can be considered adverse. It is hoped that this approach allows this statement to be a guidance document that is applicable to future assessments as to whether an effect is adverse or not, analogous to the broad applicability of BRADFORD HILL's [10] considerations for assessing causality of associations between environment and disease. As such, this statement does not offer strict rules or numerical criteria, but rather proposes considerations to be weighed in setting boundaries between adverse and nonadverse health effects.

The scope of this statement is limited to adverse health effects of direct exposure to outdoor air pollutants. While the committee recognised the wide-ranging and serious secondary and higher order adverse health effects attributable to climate change from rising atmospheric concentrations of greenhouse gases and black carbon, their consideration was not included in this statement. For additional consideration of the effects of climate change, the reader is referred to recent reviews, including those of the Intergovernmental Panel on Climate Change [11] and US National Climate Assessment [12].

TABLE 1 Considerations for assessing adversity of clinical or pathological effects

Consideration	Pertinent questions
1. Fatality	Does air pollution exposure lead to an increase of short-term or long-term mortality?
2. Persistence of effect	How persistent over time is the effect? (Generally, chronic effects such as the induction of new disease are given greater weight, although short-term exposures may lead to changes that increase risk for triggering acute adverse events, such as myocardial infarction)
3. Population risk	Is there a shift in the population risk distribution of an adverse event?
4. Susceptibility	Are the very young, older adults or individuals with pre-existing health conditions or specific genetic characteristics more likely to be affected?
5. Medical/functional significance	Is there evidence of one or more of the following? 1) severe interference with a normal activity of the affected person or persons; 2) incapacitating illness; 3) permanent injury; 4) progressive dysfunction; 5) reduced quality of life

All of the task force members submitted conflict of interest disclosures that were vetted and managed in accordance with ATS and ERS policies.

Adverse effects of air pollution on health: elements of an analytic framework

Introduction

In this joint statement, we seek to update past ATS statements discussing what constitutes an adverse health effect of outdoor air pollution [5, 13]. Since 2000, additional useful statements on the topic have been produced [14]. As discussed, we do not attempt to provide an exact definition or fixed list of health impacts that are, or are not, adverse. Instead, we propose a number of generalisable "considerations", with examples, to evaluate whether or not an effect is adverse. We aim to provide guidance for evaluation of effects that may be identified in the future, not just the ones seen "under the lamppost" of today's knowledge. How we evaluate whether the literature supports an assessment of adversity is key to our discussion of guidelines. There cannot be precise numerical criteria, as broad clinical knowledge and scientific judgments, which can change over time, must be factors in determining adversity. The WHO [15] has provided one practical framework, categorising evidence of adversity according to benchmarks. The first is that single, not (yet) verified observations by themselves only indicate a need for further research, while the benchmark of adversity is the availability of clear verified evidence for clinical or pathological change. In between these extremes, to which most of our discussion will apply, are those changes where exposure–response relationships and adversity can be posited and assessed in terms of multiple lines of evidence, despite an absence of overt or clinical disease. The more strongly such changes (including most human "biomarkers") are linked to a clinical condition, a pathological change or a pathway to those changes, and the more multiple biomarkers converge on a mechanistic pathway, the stronger the evidence for an adverse effect.

The global burden of disease

As a starting scope of adverse health effects, we include effects on any condition that contributes to the global burden of disease, as published in the *Lancet* GBD issues of December 2012 and September 2015 [1, 2, 16]. In the GBD reports, indoor and outdoor air pollution is already considered to be a significant risk factor for ischaemic heart disease, chronic obstructive pulmonary disease (COPD), lung cancer, stroke and childhood respiratory infections [1, 2, 16].

The GBD project is an ongoing effort that does not provide a final list of every possible health condition contributing to the burden of disease. Therefore, in addition, the committee considers certain clinically relevant conditions that are not (yet) listed in the GBD, but which have been associated with air pollution exposure (*e.g.* low birthweight, lowered lung function and biomarkers of cardiovascular risk) to be potentially adverse effects of air pollution.

Effects of air pollution on biomarkers of exposure and disease

In recent decades, many biomarkers of exposure, susceptibility and disease have been identified and studied epidemiologically in relation to air pollution exposure, and it is important to also consider changes in them as potentially adverse health outcomes [17]. Genetic susceptibility, such as the null variant of GSTM1, can enhance susceptibility to biomarker change associated with air pollution [18], and epigenetic changes are garnering increased attention in air pollution research [19].

Biomarkers have been defined, in a report for the US Food and Drug Administration by the Institute of Medicine (IOM) [20], as follows:

> Biomarkers are characteristics that are objectively measured and evaluated as indicators of normal biological processes, pathogenic processes, or pharmacologic responses to an intervention. Cholesterol and blood sugar levels are biomarkers, as are blood pressure, enzyme levels, measurements of tumor size from magnetic resonance imaging (MRI) or computed tomography (CT), and the biochemical and genetic variations observed in age-related macular degeneration… they can help public health professionals to identify and track health outcomes.

While it is recognised that not all biomarkers are in the causal pathway for development of a disease, they can nevertheless be valuable indices of a change in disease status or disease risk. The IOM [20] suggested that the BRADFORD HILL considerations [10] can be used to assess the prognostic value or degree of association between a biomarker and a clinical end-point [21]. Temporality, strength of association, consistency and biological plausibility were recognised to be of particular importance. Of major importance to the present document, the IOM recognised that acceptance and use of biomarkers may be different for clinical risk prediction and treatment in individuals, *versus* planning and evaluation of public health programmes in populations, as also emphasised by other National Academy of Sciences committees [6, 7].

Since the list of biomarkers studied to date [22] is extensive, with new biomarkers constantly being added, we cannot review the detailed evidence for or against adversity for each of these. Rather, in line with previous expert committee reports [6, 7] we provide a number of specific factors to evaluate when considering effects of air pollution on human biomarkers, and their potential for associated adverse health outcomes.

The IOM suggested a three-stage framework for the development and validation of biomarkers [20], as follows. 1) Analytical validation: to ensure reliability, reproducibility, sensitivity, and specificity of the measurement of the biomarker; 2) qualification: to confirm a strong association with the clinical outcome of concern; and 3) utilisation: contextual analysis to determine that the biomarker is appropriate for the proposed use.

Of these, stages 2 and 3 seem especially relevant to consideration of biomarkers as metrics of adverse health effects of air pollutants. The concluding section of the 2000 ATS statement establishes a baseline of understanding [5], stating that "the committee cautions that not all changes in biomarkers related to air pollution should be considered as indicative of injury that represents an adverse effect". Therefore, here we include illustrative examples of biomarkers that are most strongly associated with adverse effects in this statement's various sections on each respective organ system.

When multiple biomarkers reflective of a particular pathophysiological pathway (e.g. pulmonary inflammation) have been demonstrated to change together, it is deemed that this gives greater credibility to their individual and joint relevance. For instance, in a study of subacute responses to large governmentally imposed changes in air pollution emissions during the 2008 Beijing Summer Olympics, investigators showed that forced exhaled nitric oxide fraction (a measure of airway inflammation) and multiple exhaled breath condensate measures (pH, nitrite, nitrate, 8-isoprostane and malondialdehyde) all responded in unison to decreases in pollutant concentrations, followed by opposite responses to subsequent increases in pollutant levels [23, 24]. Such collective coherence (a Bradford Hill causality consideration factor) among various biomarkers strengthens the evidence for a shared pathophysiological process: in this case, oxidative stress and inflammation, which have been associated with various adverse health effects (although health effects as such were not measured in this particular panel study). For example, additional measures in the aforementioned study showed significant changes in nonrespiratory biomarkers of systemic inflammation, coagulation, heart rate and blood pressure, suggesting that changes in these biomarkers were indeed related to air pollution, and that they also collectively indicate that adverse effects occurred on a population level, if supported by evidence that the biomarkers are risk factors for adverse outcomes at the population level [25]. Such collective pathophysiological support need not come from within a single study, but the above study does illustrate how considerations for causality, such as consistency, coherence and biological plausibility can also be incorporated into the assessment of adversity. The importance of all of the above pathways, and their respective markers, underlies much of the growing recognition of the range of cardiovascular, systemic/metabolic and developmental effects of air pollution.

The pollution exposures associated with the Beijing Olympics provide an illustrative example of how biomarkers can show substantial changes when ambient pollution levels change dramatically. Approximate 50% reductions in ambient pollution attained in Beijing during the 2008 Olympics resulted in 30–60% reductions in multiple biomarkers of respiratory oxidative and stress and inflammation, and even greater increases when strict pollution controls were relaxed [23]. In these young healthy subjects, individual risk of a clinical event is minimal, but population risk, including that of susceptible subpopulations, such as the elderly, is probably substantial.

Population health effects

As discussed in the 2000 ATS statement, the effects of air pollution can be viewed in terms of an increment in an individual's risk of disease or injury, or in terms of an additional public health risk incurred by a population [26]. Both perspectives are pertinent: any health risk or change beyond some critical boundary, incurred by an exposed individual, could be deemed adverse, while exposure to air pollution beyond an acceptable degree could also enhance risk for a portion of the population. In the case where the relationship between a risk factor and the disease is deemed causal, the 2000 ATS committee considered (and we concur) that "such a shift in the risk factor distribution, and hence the risk profile of the exposed population should be considered adverse, even in the absence of the immediate occurrence of frank illness". Further, considerations of health equity and environmental justice (e.g. socioeconomically disadvantaged populations being more exposed to air pollutants) are also similarly relevant to an assessment of adversity at the population level, with a similar shift in exposure and risk being of greater adversity to such vulnerable populations. These issues have received increased recognition and research funding from US EPA and National Institutes of Health [27].

The context of application to individuals versus populations may also affect interpretation of the validity of biomarkers as predictors of adverse health effects. This is illustrated by the emergence of biomarkers of

inflammation as potential indicators of either cardiovascular disease or disease risk. For example, C-reactive protein (CRP) is an independent predictor of cardiovascular risk, and is considered to be the best inflammatory marker available at this time [28]. However, it is not known to be in the causal pathway for cardiovascular disease, and it is not clear if reductions of CRP alone are consistently associated with better clinical outcomes. Thus, the IOM [20] concluded that CRP is not appropriate for use as a surrogate end-point, but may still be useful for population risk prediction.

General considerations for assessing adversity of effects

Overall, considerations of health outcomes and biomarkers, as indicators of adverse effects, are complex.

Table 1 lists several general factors for consideration of adversity. Table 2 complements table 1 by providing a number of considerations for assessing reliability and adversity of biomarker changes. For example, in the case of pollution in Beijing during the Olympics, considerations 1, 2, 3, 4 and 5 in table 2 are all met to a greater or lesser degree for most of the studied biomarkers which showed hypothesised changes, with consideration 6 of requiring analysis of further data.

Assessment of adversity by biological system

Here we discuss the evidence for adverse health effects of air pollution, considering several organs and outcomes. Figure 1 presents the committee's assessment of established air pollution adverse effects, as well as noting those for which evidence of an association with air pollution and/or adversity is emerging. Outcomes noted in bold in figure 1 are those presently included in the GBD estimates of the health effects of air pollution.

A further issue in the consideration of toxicity or adversity is the rapid development of new methods for toxicity testing and risk assessment [29], as addressed by the IOM in 2007. Here, animal models of toxicity are being replaced by new *in vitro* approaches to define toxicity, many of which can be seen as analogues of webs of mechanistically informed biomarkers, often relying on "omics" approaches [30]. Detailed consideration of these methods are beyond the scope of this review, but they should be considered further as these innovative approaches are validated in future studies.

Respiratory effects

The respiratory tract is the primary portal of entry for air pollutants; consequently the respiratory effects of pollutants have been studied for decades. In the >15 years since publication of the prior ATS version of this document, much progress has been made in understanding the pathogenic processes and pathophysiology involved in chronic respiratory diseases. For example, both asthma and COPD, as well as other lung diseases, involve airway inflammation, airway remodelling, changes in airway responsiveness, reduced airway clearance and impaired host defence against infection. It is reasonable to posit that air pollution effects on any of these processes may contribute to the underlying disease itself, and examples of such candidate effect biomarkers are provided later.

Effects of air pollution on the onset and/or clinical course of any of the respiratory clinical conditions assessed in the GBD are considered here to constitute adverse effects, as are effects on quality of life. The 2000 ATS document provided a list of respiratory health effects that included adverse clinical outcomes, symptoms and diseases, most of which are now included in the GBD disease list. Similarly, table 3 provides examples of common respiratory conditions and outcomes that have been associated with air pollution exposure. This list is illustrative, and not intended to be exhaustive.

There is convincing epidemiological evidence that both short-term and long-term exposures to air pollutants, including PM, ozone, black carbon and nitrogen oxides are associated with increases in respiratory mortality [32, 33]. PM exposure also increases the risk of lung cancer [34–36]. Clearly, the

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TABLE 2 Considerations for assessing validity and adversity of biomarker changes

1. Analytical validation
2. Relevance to a clinical condition
3. Appropriateness for proposed use: population *versus* individual characterisation
4. Presence of multiple converging biomarkers
5. Degree of adherence to Bradford Hill considerations for judging a causal link to air pollution (especially dose/response, replication, biological plausibility and cessation of exposure)
6. Adversity considerations as in table 1 (including adversity of associated clinical end-points)
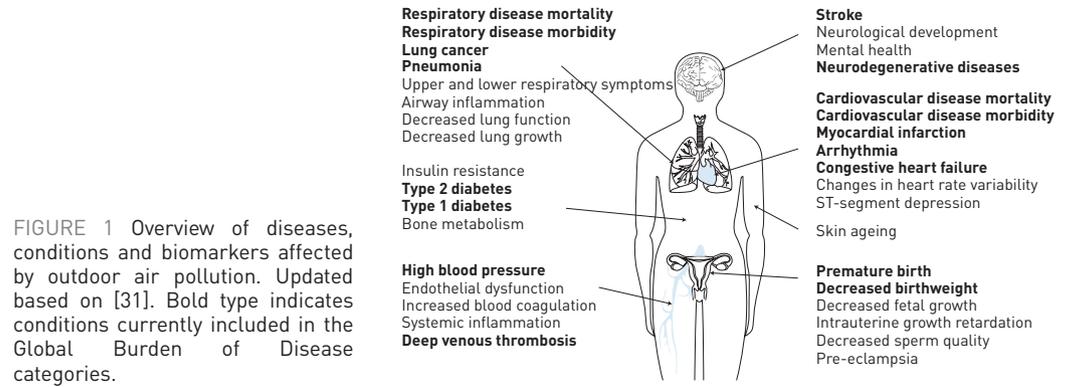
FIGURE 1 Overview of diseases, conditions and biomarkers affected by outdoor air pollution. Updated based on [31]. Bold type indicates conditions currently included in the Global Burden of Disease categories.

Respiratory disease mortality
Respiratory disease morbidity
Lung cancer
Pneumonia
Upper and lower respiratory symptoms
Airway inflammation
Decreased lung function
Decreased lung growth

Insulin resistance
Type 2 diabetes
Type 1 diabetes
Bone metabolism

High blood pressure
Endothelial dysfunction
Increased blood coagulation
Systemic inflammation
Deep venous thrombosis

Stroke
Neurological development
Mental health
Neurodegenerative diseases

Cardiovascular disease mortality
Cardiovascular disease morbidity
Myocardial infarction
Arrhythmia
Congestive heart failure
Changes in heart rate variability
ST-segment depression

Skin ageing

Premature birth
Decreased birthweight
Decreased fetal growth
Intrauterine growth retardation
Decreased sperm quality
Pre-eclampsia

increased mortality associated with higher exposure to air pollution is considered adverse; this is the first and foremost consideration mentioned in table 1.

It is also well established that increased exposures to various air pollutants contribute to exacerbations in patients with chronic respiratory disease, such as asthma, COPD and cystic fibrosis [37]. Exposure to traffic-related air pollution (TRAP) has been associated with worsening of asthma and wheezing [38]. A review of the evidence by the US-based Health Effects Institute [39] found that "sufficient" evidence existed to conclude that TRAP causes respiratory symptoms and exacerbations in children with asthma. However, evidence that TRAP actually causes asthma in children or COPD/asthma in adults was considered insufficient [40, 41]. Another, more recent review found additional evidence for a link between TRAP and incidence of asthma [42].

Long-term improvements in air quality are associated with clinically significant positive effects on lung function growth in children [43]. There is also increasing evidence of associations between increased long-term exposure to TRAP and lung function decline in adults [44], as well as attenuation of this decline with reductions in air pollution [45]. For example, an increased rate of long-term decline in lung function in adults, or a decrease in lung function growth in children, are considered adverse, as these would be deemed "progressive dysfunction", in the terms of table 1.

The previous ATS statement addressed the important question of whether small, transient reductions in lung function, as can be seen in susceptible subjects following acute exposure to ozone, should be considered adverse. The document concluded that small transient changes in forced expiratory volume in 1 s (FEV_1) alone were not necessarily adverse in healthy individuals, but should be considered adverse when accompanied by symptoms. We support the conclusion that, in otherwise healthy individuals, "a small, transient loss of lung function, by itself, should not automatically be designated as adverse" [46]. However, such small lung function changes should be considered adverse in individuals with extant compromised function, such as that resulting from asthma, even without accompanying respiratory symptoms.

Moreover, in considering the magnitude of change and clinical significance, there must also be a distinction made between population changes and individual changes in lung function measures. As discussed in the previous ATS statement, a small but statistically significant mean reduction in FEV_1 in a population means that some people had larger reductions, with the likelihood that reductions in a subset of susceptible subjects can have passed a threshold for clinical importance. For example, re-analysis of data from a study by ADAMS [47, 48], involving 30 subjects exposed to 0.06 ppm ozone for 6.6 h, showed a ~3%

TABLE 3 Examples of respiratory clinical effects associated with air pollution

Increased respiratory mortality
Increased incidence of malignancies of the respiratory tract
Increased incidence, prevalence or frequency of exacerbations in chronic pulmonary disease: asthma, COPD and cystic fibrosis
Increased incidence or severity of upper and lower respiratory tract infections
Increased respiratory symptoms that affect quality of life: cough, phlegm, wheezing, dyspnoea and nasal drainage
Increased incidence of preterm birth, low birthweight or growth restriction leading to adverse respiratory outcomes
Reduced growth of lung function in children
Transient (hours) reductions in lung function associated with symptoms in healthy individuals
Transient (hours) reductions in lung function without symptoms in especially susceptible individuals (*e.g.* children with severe asthma)
Persistent or chronic (weeks, months or years) reductions in lung function

COPD: chronic obstructive pulmonary disease.

mean decrease in FEV_1. However, two of the subjects had declines in FEV_1 >10% [49]. The more recent literature on long-term effects of air pollution on lung function decline in adults provides further examples on the complexities of defining "adverse effects" for individuals, because effects may depend on a variety of susceptibility factors such as genetic make-up, medication, diet, physical activity or varying metabolic states as seen in diabetics or the obese [50–52].

Given the marked expansion of biomarkers of respiratory disease and pathobiology since the 2000 ATS statement, there is a need to consider the interpretation of changes in biomarkers as potentially adverse, even in the absence of measurable clinical effects. Table 4 provides examples of biomarkers of respiratory health or function that have been used in studies of the respiratory effects of air pollution.

Similar to the considerations for measures of lung function, a small transient change in one of these biomarkers by itself may not be adverse in otherwise healthy individuals. However, such a biomarker change should be considered adverse when additional evidence provides a context for clinical adversity, including changes in complementary biomarkers (as enumerated earlier for the Beijing Olympics study), as well as associations with respiratory symptoms or adverse health outcomes in people with respiratory disease or associations with any adverse effect of air pollution. For example, a small increase in leukocytes in induced sputum following ozone exposure that resolves in <48 h may not, by itself, be considered adverse. Yet when such evidence for transient airway inflammation is considered in the context of acute decrements of lung function and/or increases in respiratory symptoms, as well as increased risk of exacerbations in people with respiratory disease, this may constitute evidence of adversity (see considerations 2, 4 and 6 in table 2).

Some pollutant exposures have been shown to transiently increase airways responsiveness [53, 54]. Is this adverse if there are no symptoms or other clinical effects? Airways hyperresponsiveness (AHR) to a specific allergen or a nonspecific challenge (such as methacholine, mannitol or cold air) is an almost universal finding in asthma. AHR gets worse during asthma exacerbations, and improves with treatment. There is evidence that recurrent episodes of bronchoconstriction in people with asthma promote airways remodelling [55], which may lead to irreversible airways obstruction. Based on the applicability of considerations 2–5 in table 1, we conclude that clinically relevant increases in AHR in asthmatics following pollutant exposure may appropriately be considered adverse, even without accompanying symptoms or other clinical effects.

AHR is frequently found in healthy people without airways disease. Such individuals have an increased risk for reduced lung function and the development of asthma [56]. Worsening of AHR by air pollution in this group may be deemed adverse, especially if persistent or accompanied by symptoms. However, it is less clear, based on the considerations listed in table 1 whether transient increases in airways responsiveness alone are adverse in healthy people with normal airways responsiveness at baseline. Similar to the considerations for FEV_1, as discussed earlier, we propose that small, transient changes in airways responsiveness following air pollution exposure in healthy people, without symptoms or clinical illness, are not always adverse. However, small mean population changes can encompass larger effects in some individuals as was the case for FEV_1. If the magnitude of the airways responsiveness increase is sufficient for a subject with previously normal airways responsiveness to cross the threshold of AHR (*e.g.* provocative concentration causing a 20% fall in FEV_1 <8 $mg \cdot mL^{-1}$), adversity is evidenced, even in the absence of symptoms [57]. Thus, although this effect is not necessarily adverse in healthy individuals, it may be deemed an adverse population-based risk, as it will probably include susceptible individuals.

Early effects on the respiratory system

Effects of air pollution on lung function in the first weeks of life, including respiratory rate and tidal breathing flows have been reported [58] and are of concern, since poor neonatal airway function is a risk factor for airflow obstruction in young adults [59]. Subtle changes in infant lung function associated with

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TABLE 4 Examples of biomarkers of potentially adverse respiratory health effects

Increased levels of markers of airway inflammation (*e.g.* PMNs or inflammatory cytokines in BAL or sputum)
Increased levels of markers of airway injury or inflammation in exhaled breath (*e.g.* increased acidity of exhaled breath condensate or increased F_{eNO} in asthmatics)
Increased levels of blood markers of lung injury (*e.g.* 8-isoprostanes, club cell secretory protein)
Imaging evidence for lung injury or reduced lung volume
Reduced pulmonary gas exchange (*e.g.* D_{LCO}, D_{LNO}, P_{aO_2}, pulse oximetry)
Increased airways responsiveness to nonspecific challenge
Increased airways hyperresponsiveness in asthmatic patients

PMN: polymorphonuclear leukocyte; BAL: bronchoalveolar lavage; F_{eNO}: exhaled nitric oxide fraction; D_{LCO}: diffusing capacity of the lung for carbon monoxide; D_{LNO}: diffusing capacity of the lung for nitric oxide; P_{aO_2}: arterial oxygen tension.

maternal exposure to air pollution are putative biomarkers for long-term consequences of maternal exposure on children's lung function. Additionally, evidence for long-term effects of intrauterine and early postnatal exposure on lung function at 4.5 years of age has been reported [60]. If this association is substantiated by further studies, we consider long-term reduced lung function to be an adverse effect of exposure to air pollution in early life.

Cardiovascular effects

Since the previous ATS statement, numerous studies have examined associations between acute and chronic exposures to outdoor air pollutants and acute cardiovascular events, as well as biomarkers of relevant cardiovascular pathogenetic mechanisms [8, 61]. Here we provide examples of how to apply the analytic framework described above for both acute and chronic pollutant/cardiovascular event associations and acute and chronic pollutant/biomarker associations. These examples should not be interpreted as providing arguments for or against causal effects on each outcome, but are the committee's interpretations of the literature, providing a demonstration of how this statement's framework regarding adversity of effects can be applied. Table 5 provides examples of common cardiovascular conditions that have been linked with air pollution in studies, as discussed later.

Myocardial infarction

Multiple studies have reported acute triggering of myocardial infarction associated with increased pollutant concentrations in the previous few days/hours [62, 63]. Although a meta-analysis using data from 22 European cohort studies reported no clear association between deaths from cardiovascular diseases and long-term concentrations of several PM metrics [64], many other studies have reported associations between long-term averages of air pollutant concentrations and increased cardiovascular mortality and morbidity [65–72] or increased risks of coronary heart disease or coronary events [66, 73, 74]. As an example, in a study of 11 European cohorts, the risk of coronary events was increased by 13% for each 5 $\mu g \cdot m^{-3}$ increase in $PM_{2.5}$. In all those exposed, the attributable fraction is calculated as the relative risk (RR) minus 1 divided by the RR, so 0.13/1.13=0.12. On a population basis, this implies that 12% of coronary events could be prevented by reducing $PM_{2.5}$ population exposure by 5 $\mu g \cdot m^{-3}$. Thus, acute fatal and/or nonfatal myocardial infarction represents an adverse effect of air pollution on both the acute and chronic timescales of exposures, as per considerations 1 (fatality) and 5 (medical/functional significance) in table 1.

Heart failure and stroke

Both heart failure exacerbations and mortality and stroke have been associated with exposure to air pollution levels experienced over the prior few days, as documented in systematic reviews and meta-analyses [75, 76]. While longer-term exposures have been associated with an increased risk of stroke, few studies have evaluated the risks of heart failure. Thus, such increased risks of heart failure and stroke (particularly of ischaemic aetiology) can be defined as adverse effects of air pollution on an acute timescale. While the risk of stroke can probably be considered an adverse event due to long-term exposures, the risk of heart failure has not yet been conclusively investigated in this regard.

Arrhythmia

While some studies have reported increased risks of ventricular and atrial arrhythmias associated with outdoor air pollutant levels over the previous few hours and days, the findings are not consistent [77–81]. Should future studies corroborate the indications that air pollution may prompt cardiac arrhythmias, such events would be considered adverse.

High blood pressure

High blood pressure is the leading risk factor for morbidity and mortality worldwide, accounting for nearly half of all myocardial infarctions and strokes [1, 82]. It is listed in the GBD risk assessment [1, 83, 84]. Mounting epidemiological and mechanistic evidence from human and animal studies demonstrates that air

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TABLE 5 Cardiovascular clinical effects associated with air pollution

Cardiovascular disease mortality
Myocardial infarction
Stroke
Increased blood pressure
Arrhythmias
Hospital admissions for congestive heart failure

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pollution is an additional environmental factor capable of increasing blood pressure [85–87]. The ensuing health consequences are demonstrated by a recent meta-analysis whereby short-term increases in outdoor $PM_{2.5}$ trigger an elevation in blood pressure (1–2 mmHg per 10 $\mu g \cdot m^{-3}$) over a 5-day period, while longer-term exposures in the order of 30 days to 1 year prompt even larger pro-hypertensive responses (5–10 mmHg) [86]. Perhaps most importantly, a growing number of studies further demonstrate that living in regions with higher levels of $PM_{2.5}$ may also promote the genesis of the chronic hypertensive disease state *per se* [86, 87]. While some studies indeed support this pathway, firm conclusions cannot be established, given the relative paucity of published evidence on this end-point. Given the well-established linkages between higher blood pressure and the long-term risk of multiple cardiovascular events, chronically increased blood pressure induced by air pollution can itself be considered adverse, while the adversity of more transient increases are less clear, and qualify as a concern that will benefit from further research.

Atherosclerosis is the primary long-term disease mechanism leading to myocardial infarction and stroke [61]. A change in a single biomarker of vascular dysfunction, potentially leading to reduced blood flow may or may not be relevant to a specific ultimate vascular adverse event. However, as discussed above, the effects of air pollution on biomarkers are considered more adverse when such effects occur in a suite of related pathophysiological biomarkers that, together, increase the risk of the clinical outcomes listed in table 5. Such a possible chain of biomarker changes can be seen for many of the biomarkers listed in table 6. For example, substantial progression of arterial calcification indicates progression of atherosclerosis and increased risk for ischaemic events. Experimental studies in humans have indicated that a collection of related pathophysiological biomarkers may be adversely affected by air pollution exposures (*e.g.* increased arterial stiffness, reduced bioavailability of vascular nitric oxide, reduction of flow-mediated and endothelial-dependent vasodilatation, reduced fibrinolytic capacity/tissue plasminogen activator release, increased thrombocyte adhesiveness, increased *ex vivo* thrombogenicity and ECG ST–T segment depression).

We now discuss in more detail some of the cardiovascular biomarkers for which there is specific evidence of an association with air pollution.

Heart rate variability

Heart rate and heart rate variability (HRV) are regulated, in part by the parasympathetic and sympathetic nervous systems. Decreased HRV has been associated with cardiovascular mortality and morbidity in older populations and those at higher risk of cardiovascular events [8, 88]. While acute changes in HRV over hours to days have convincingly been linked to air pollution exposures [88], the relevance to health is uncertain. It may be postulated that the change in this biomarker reflects an underlying autonomic imbalance that could play a role in triggering clinically significant arrhythmias and other acute cardiovascular events; however, this remains speculative at present. The linkages between changes in HRV and a worsened prognosis have generally been documented in association with presumed chronic reductions in HRV. However, associations between long-term exposure and chronic markers of autonomic function has been a research subject in only a few studies, which indicate possibly complex interactions between long-term exposure to air pollution, HRV and individual susceptibility factors [89–91]. Thus, it is uncertain at this time whether alterations in individual HRV metrics after short-term or long-term exposure can themselves be considered adverse biomarkers or effects of air pollution.

Carotid intima-media thickness

Carotid intima-media thickness (CIMT), measured using ultrasound, is an established marker of atherogenesis. Since its first use [92], several cross-sectional studies have reported associations between

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TABLE 6 Illustrative examples of biomarkers of cardiovascular effects

Decreased heart rate variability
Changes in ECG depolarisation and repolarisation
Increased carotid intima-media thickness
Increased coronary artery calcification
Carotid artery stenosis
Increased aortic calcification
Increased arterial stiffness
Impaired vascular endothelial function
Impaired vascular fibrinolysis
Increased platelet adhesiveness or activation
Increased thrombogenicity
Increased markers of systemic inflammation, endothelial function, nitric oxide metabolism, oxidation *etc*.

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home outdoor levels of air pollution and CIMT, including one which combined data from four cohort studies [93]. As summarised in a meta-analysis [94], both the cross-sectional and longitudinal associations between CIMT and air pollution were significant, although the associations between CIMT progression and long-term exposure were based on only three studies. However, another review [95] has not been able to demonstrate a clear association between CIMT progression and incident cardiovascular disease events, and so further work is needed to establish whether an increase in CIMT can be considered an indicator of adverse effects of air pollution on a chronic timescale.

Carotid arterial stenosis

Carotid artery stenosis (CAS) has been assessed using bilateral carotid artery duplex ultrasound. This important risk factor for cerebrovascular disease and stroke is clearly adverse. A recent study from the USA has indicated that long-term $PM_{2.5}$ air pollution exposures are independently associated with increased CAS [96].

Vascular function

Several air pollutants have been associated with impaired microvascular and conduit vascular function in human panel and controlled exposure studies, as well as in animal experiments [97–99]. Chronic endothelial dysfunction is an important biomarker that is both predictive of and causally related to cardiovascular diseases and events [100]. In addition, $PM_{2.5}$ exposures in the prior few days can impair flow-mediated dilatation of conduit arteries [97]. This probably occurs as a consequence of air pollution-mediated tissue oxidative stress and inflammation, reducing bioavailability of NO while potentiating vasoconstrictive mediators (*e.g.* endothelin) and pathways [99]. The independent associations between endothelial dysfunction and heightened cardiovascular risk are all in the chronic timescale, and assume that a persistent impairment in vascular health is ongoing, which would indicate adversity as specified by consideration 5 (medical/functional significance) in table 1 and consideration 2 (relevance to a clinical condition) in table 2. In this regard, evidence supports the position that long-term air pollution exposures over months to years are linked to a chronic impairment in vascular endothelial function [97]. Chronic endothelial and vascular dysfunction is judged to be a biomarker of adverse air pollution effects on health. The health relevance of acute reductions in endothelial function induced by air pollution is less certain.

Other biomarkers

Numerous other biomarkers, intermediate health end-points and pathophysiological changes associated with heightened cardiovascular risk have been investigated in relation to air pollution exposures [8]. A short list of examples is provided in table 6, as a comprehensive list is beyond the scope and focus of this statement. Further to that which has already been noted, changes in markers of inflammation (*e.g.* high-sensitivity CRP, interleukin-6 and tumour necrosis factor-α), coagulation (*e.g.* prothrombin time, fibrinogen and *ex vivo* thrombus formation time), thrombosis (*e.g.* CD40L, p-selectin and platelet activation metrics), adipocytokines (*e.g.* leptin and adiponectin), endothelial activation, haemodynamic markers (*e.g.* Von Willebrand factor, endothelin and nitrite) and lipid oxidation (low-density lipoprotein oxidation status and high-density lipoprotein dysfunction) have been noted. In addition to blood-based biomarkers, markers of heightened arrhythmia potential (*e.g.* repolarisation abnormalities), and myocardial ischaemia (ST depression) have been associated with air pollution exposure in human studies. Many of these end-points are indeed linked to a greater cardiovascular risk in the long run. However, most of the associations with air pollution have only been shown to occur over short timescales of exposures, *i.e.* in the order of days. Assessing changes in multiple biomarkers, as discussed earlier, may strengthen the case for adversity. While it is possible that acute or transient perturbations in these biomarkers might play a role in triggering an acute event, no firm conclusion can be made at this time to determine that these other acute biomarker changes individually constitute adverse health effects.

Emerging adverse effects of outdoor air pollution

The assessment of adverse health effects of outdoor air pollution initially focused on respiratory health outcomes, and, more recently, cardiovascular outcomes. However, associations have also been reported between outdoor air pollution and systemic or metabolic effects, involving multiple pathophysiological pathways. These have included systemic inflammation, oxidative stress, immune modulation and epigenetic alteration. This suggests that multiple health outcomes, not necessarily detectable by short-term studies (*e.g.* daily time series), may also be relevant.

Diabetes and obesity

There is an emerging body of evidence linking outdoor air pollution to type 2 diabetes, as suggested by a recent systematic review and meta-analysis [101]. This review specifically indicated that the observed associations were stronger among females than males. These findings are well supported by animal experiments, which have indicated that systemic inflammation, immune responses in adipose tissue and

peripheral insulin resistance can be induced by exposure to particulate matter [102]. This evidence is further supported by reports of insulin resistance and elevated haemoglobin A1c concentrations associated with air pollution [103, 104]. Epidemiological studies of short-term exposure to outdoor air pollution have indicated changes in systemic inflammation markers in individuals with diabetes or impaired glucose tolerance. A few prospective cohort studies have also suggested that environmental pollutants contribute to the development of childhood obesity [105], and a variety of mechanisms that may contribute to obesity and enhanced insulin resistance have been demonstrated. These possible mechanisms include glucose and lipid dysregulation in tissues such as adipose and hepatic tissue and skeletal muscle and brown adipose through pathways well known to be altered in insulin resistance [105]. In line with this observation, associations between air pollution exposures at the place of residence and liver enzymes have also been observed [106]. Immunomodulatory effects of outdoor air pollution are further hypothesised to promote an earlier onset of type 1 diabetes [107, 108]. Clearly, development of these systemic/metabolic outcomes would be considered adverse, as per consideration 2 (persistence) in table 1; however, their associations with air pollution are not sufficiently robust at this time to consider them to be adverse effects of air pollution.

Epigenetic alterations

Emerging evidence suggests that outdoor air pollution alters the epigenetic regulation of white blood cells and other tissues, potentially resulting in transient, as well as permanent changes in gene regulation in various tissues [109]. Such epigenetic changes suggest a mechanism for understanding the links between outdoor air pollution exposure and impaired function of multiple organs. Furthermore, changes in micro-RNA and other RNA species may constitute important signalling pathways, orchestrating an interplay between different organs that may indicate impairment by outdoor air pollution exposures. Clear evidence of adversity is still evolving.

Pregnancy and developmental outcomes

The 2000 ATS statement identified infants as a susceptible group, but did not directly address the question of adverse effects of *in utero* exposures. In this section, we consider the emerging evidence that maternal exposure to air pollution results in a wide range of adverse effects that may resolve after birth or continue or increase susceptibility to disease in later life [110, 111].

Birthweight and prematurity

A number of epidemiological studies report associations between maternal exposure to air pollution and newborn infant outcomes. Among these are reductions in overall birthweight, low birthweight (<2500 g at any gestational age), low birthweight at term (<2500 g at ⩾37 weeks gestation) and preterm birth (<37 weeks gestation). Preterm birth and low birthweight are well-known for their association with neonatal morbidity and mortality and have also been associated with adult morbidity [112–114]. A systematic review and meta-analysis published in 2012 reported reduced birthweight and increased risk for low birthweight associated with exposure to NO_2, PM_{10} and $PM_{2.5}$ for entire-pregnancy exposures [115]. The meta-analysis also reported positive associations between air pollutant exposures and increased risk of preterm birth. Following this review, two recent multicohort studies have focused on the association between maternal exposure and "low birthweight at term", because infants in this weight category are considered to have suffered fetal growth restrictions. One of these studies [116] estimated that 11% of term low birthweight cases would be avoided were $PM_{2.5}$ concentrations reduced by 5 µg·m^{-3}. Low birthweight at term is known to be associated with increased risk of neonatal death and has been associated with other adverse outcomes [116–121]. In addition, two so-called "natural experiments" found community-level air pollution interventions to reduce pollution and affect preterm birth or birthweight [122, 123]. Results from these studies and meta-analysis indicate that maternal exposure to air pollution is associated with increased risk of low birthweight, but there was considerable variability in risk estimates by specific gestational period. We conclude that low birthweight at term and prematurity are adverse effects, when caused by maternal air pollution exposure, in view of the shifts in population risk for later adverse medical conditions associated with low birthweight (consideration 3 in table 1).

Stillbirth

Stillbirth has been associated with maternal exposure to PM and NO_2 [124–127]; however, not all studies agree [127]. Stillbirth is clearly an adverse outcome (consideration 1 in table 1), but its association with air pollution is still not sufficiently proven.

Congenital abnormalities

A study completed in the San Joaquin Valley (CA, USA) reported that the highest quartile of maternal NO_2 exposure was associated with neural tube defects [128]. However, evidence for an association between air pollution and congenital abnormalities has been inconsistent to date [129, 130]. Congenital

abnormality is clearly an adverse outcome in terms of both persistence and medical significance, but its association with air pollution exposure is still uncertain.

Neurological and psychiatric outcomes

Substantial evidence points to a potential role for air pollution in diseases of the CNS [131–133] and psychiatric disorders [134] (table 7). Biological mechanisms underlying these possible pollution effects are presently not well understood, and relevant epidemiological investigations are still at an early stage. Cognitive function and psychiatric conditions were discussed upon briefly under the heading of "quality of life" in the 2000 statement, but are substantially expanded upon in this statement.

Neurodegenerative disorders

Dementia is a general term for loss of memory and other mental abilities severe enough to interfere with daily life. Alzheimer's disease and vascular dementia, previously known as multi-infarct or post-stroke dementia, are the most common forms of dementia. Higher estimated annual exposure to PM2.5 has been associated with worse performance in cognitive function tests, in particular tests evaluating episodic memory [135]. An increased rate of decline in cognitive function may also be associated with higher air pollution exposures [136]. Some studies have reported associations between exposure to air pollutants and dementia [137, 138], but not all study results support such a relationship [139].

Several pathways leading from inhalation of air pollutants to adverse effects in the CNS have been postulated: direct transport *via* the olfactory epithelium, traversing metabolic barriers in the olfactory epithelium, systemic transport *via* the blood–brain barrier and sensory afferent signalling from the gastrointestinal tract [132]. Evidence of changes in innate immune response, disruption of synaptic function and neuroinflammation has been observed in response to air pollution [140, 141]. Alternatively, adverse CNS health effects from air pollution may be secondary to systemic impacts mediated by other body systems. Subclinical and clinical cardiovascular and metabolic disease are established risk factors for cognitive decline and dementia [142], and it is likely that at least part of the observed impact of air pollutants on cognitive disease risk occurs as a result of air pollution-induced ischaemic effects. Whether mediated by systemic disease or due to the direct impact of air pollution on the CNS, neurodegenerative disease outcomes are clearly adverse.

Neurodevelopment and behavioural disorders in children

Pioneering studies of exposure to lead have clearly documented effects on children's neurodevelopment, with end-points such as increased hyperactivity, reduced attention and several cognitive deficits [143]. Maternal or child exposure to air pollutants during pregnancy, infancy or childhood (when the brain neocortex develops rapidly) has been related to delays in cognitive development in children [144–148]. Recent studies have evaluated the association between prenatal and perinatal exposures to air pollutants and childhood behavioural disorders, but with conflicting results [149–151]. Impaired neurodevelopment in childhood is clearly adverse.

Psychiatric disorders

It has been postulated that air pollution induced oxidative stress can be related to dopaminergic neurotoxicity, and therefore to depressive moods. The association between exposure to outdoor air pollution and depressive symptoms has been evaluated, with mixed results [1, 152]. Other studies on the mental health effects of air pollution suggest a link between short-term variability in air pollution and suicide [153], although confounding from meteorological conditions, including rainfall and visibility, could not be excluded. POWER *et al.* [154] reported an exposure-dependent association between higher levels of PM2.5 and anxiety, especially

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TABLE 7 Neurological and psychiatric conditions tentatively associated with air pollution and examples of markers of neurological effects

Conditions	Alzheimer's disease and other dementias
	Parkinson's disease
	Reduced cognitive function in adults
	Delayed neurodevelopment in children
	Depression
	Anxiety disorders
Markers	Structural brain damage at functional magnetic resonance imaging
	Neurobehavioral testing
	Cognitive function testing

in the month immediately preceding the scoring of anxiety. Depression and anxiety disorders are clearly adverse conditions.

Imaging and biomarker studies

Advances in functional imaging, such as functional MRI and positron emission tomography scanning, have begun to be applied to air pollution health studies. A study of brain imaging and function in pre-adolescence showed structural brain damage related to pulmonary arterial hypertension exposure *in utero* [155]. Using MRI among those aged ⩾60 years, WILKER *et al.* [156] have examined the associations between residential long-term exposure to outdoor air pollution and markers of brain ageing, free from dementia and stroke. Exposure to elevated levels of $PM_{2.5}$ was statistically associated with smaller total cerebral brain volume and with higher odds of covert brain infarcts, indicating that air pollution is associated with evidence of structural brain ageing. Such structural brain ageing changes would clearly constitute an adverse effect, because of their relevance to clinical conditions (consideration 2 in table 2), but specific pollution-associated abnormalities have yet to be identified.

Cognitive impacts

This committee has concluded that any detectable level of transient or permanent loss of cognitive function, measured by a validated test, should be considered adverse. Thus, decrements in cognitive function are treated differently to decrements in respiratory function, for which the committee concluded that, in otherwise healthy individuals, "a small, transient loss of lung function, by itself, should not automatically be designated as adverse". Subtle, but important, deficits in cognition or other neurobehavioral functions may be asymptomatic, and repeated episodes of transient cognitive deficits, even if completely reversible, could have cumulative effects on educational attainment and achievement. Under a broad definition of health, the committee determined that a decrement in educational achievement due to air pollution exposure would be considered an adverse health effect. The committee was also in agreement that any detectable permanent decrement in cognitive function attributable to air pollution should be considered an adverse health effect.

Discussion and conclusions

The authors of this statement have recognised and discussed substantial new areas of human health effects from air pollution, choosing the GBD reports as a starting point for the identification of health effects to be considered adverse when convincingly associated with exposure to air pollution. In addition, we have identified a series of considerations to help define adversity of effects of air pollution on subclinical changes short of disease, and provide illustrative examples of their application. These include alterations in some biomarkers that contribute to the development of clinical disease. Effects on the respiratory system listed in the previous ATS statement are elaborated upon, and newly recognised respiratory effects of exposure to air pollution during pregnancy are detailed. Cardiovascular end-points were especially considered, as an important expansion of the previous ATS statement, in large part because cardiovascular disease is so widespread and increasing around the globe, but also because of the enormous volume of new literature now supporting the adverse effects of air pollution on cardiovascular disease development and exacerbation. Systemic conditions are a new area of concern in which ample evidence for effects of air pollution on biomarkers of systemic effects is available. Wholly new sections on metabolic dysfunction, pregnancy and developmental outcomes, as well as CNS and psychiatric effects, have now been included. It is clear from the vantage point of 2016, more than 15 years since the previous statement, that the list of detectible air pollution health effects and their indices continues to expand, making a determination of the adversity of these numerous effects more and more important.

Future statements should continue to build upon the considerations for adversity presented here, investigating areas such as systemic effects, reproductive effects and CNS effects, while advancing our understanding of the best uses of biomarkers across the wide spectrum of outcomes affected by outdoor air pollution.

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