

Exercise-Induced Bronchoconstriction and the Air We Breathe



Kenneth W. Rundell, PhD^{a,*}, James M. Smoliga, DVM, PhD^b,
Valérie Bougault, PhD^c

KEYWORDS

- Air pollution • Particulate matter • Ozone • Trichloramines • Nitrogen dioxide
- Sulfur dioxide • Exercise-induced bronchoconstriction • Asthma

KEY POINTS

- Environmental factors that influence mediator release and airway pathology include ambient air humidity and airborne pollutants, including chemical irritants and particulate matter.
- The high ventilatory demands of exercise exacerbates total exposure to noxious stimuli and allows particulate matter to deposit at deeper levels within the lungs.
- Subjects with and without respiratory pathologies may present respiratory symptoms in polluted environments or cold, dry air.
- The prevalence of exercise-induced bronchoconstriction and asthma in competitive athletes is attributed to training and competing in adverse environmental conditions.
- New-onset asthma from chronic inhalation of pollutants and the acute exercise-induced bronchoconstriction response is a major health concern for individuals training, competing, working, and recreating in high pollution environments.

INTRODUCTION

Exercise-induced bronchoconstriction (EIB) is defined as the transient abnormal constriction of the airways in response to vigorous exercise.¹ Key mediators in this response are histamine, leukotrienes, and prostaglandins that are released from mast cells, eosinophils and neutrophils in the airways.^{2,3} These mediators are released in response to the airway mucosa being exposed to various triggers related to air

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^a Department of Basic Sciences, Geisinger Commonwealth School of Medicine, 525 Pine Street, Scranton, PA 18510, USA; ^b Department of Physical Therapy, High Point University, 1 University Parkway, High Point, NC 27262, USA; ^c Pluridisciplinary Research Unit Sport, University of Lille, Health Society (URePSSS), EA7369, Lille, France

* Corresponding author. 605 Skyline Drive South, South Abington Township, PA 18411.

E-mail address: kwrundell@gmail.com

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quality. Environmental factors that influence mediator release include ambient air humidity and airborne pollutants, including chemical irritants and particulate matter (PM).^{4,5} The high ventilatory demands of exercise exacerbates total exposure to these noxious stimuli, while also allowing PM to deposit at deeper levels within the lungs.⁶

Although acute exposure to these environmental triggers is capable of initiating an EIB event, chronic exposure is epidemiologically linked to the development of asthma and other allergic/immunologic conditions. The prevalence of EIB and asthma in competitive athletes exceeds that found in the recreational athlete, and has been attributed to training and competing in adverse environmental conditions,¹ such as the high pollution conditions found in ice rinks, indoor swimming pools, and high vehicular traffic areas.⁷ New-onset asthma from the chronic inhalation of pollutants and the acute EIB response present a major health concern for individuals training, competing, working, and recreating in these high pollutant environments. Thus, this paper aims to explore the relationship between EIB and asthma with specific environmental exposures commonly encountered during exercise, in the hopes that a greater understanding of these associations can lead to improved prevention and clinical management of airway disease.

GENERAL PATHOGENESIS OF POLLUTION-INDUCED AIRWAY DYSFUNCTION

Oxidative Stress

There is increasing evidence supporting the notion that oxidative stress caused by the inhalation of environmental pollutants during exercise promotes the development of asthma and enhances the EIB response.^{8–12} Oxidative stress is a key feature in the pathogenesis of asthma¹³ and is likely involved in the production and release of inflammatory mediators in the EIB response.¹⁴ The oxidative stress in the airways includes the increase in reactive oxygen/nitrogen species (RONS) concomitant with a decrease in resident antioxidants. Increased concentrations of 8-isoprostane, a marker of airway oxidative stress, in exhaled breath condensate are associated with EIB.¹⁴ Additionally, plasma and exhaled breath condensate concentrations of biomarkers associated with lipid peroxidation, such as malondialdehyde, are increased after exercise in athletes with EIB.¹⁵

Inflammation

The biologic response to the inhalation of air pollution has been shown to stimulate airway inflammation through oxidative stress and is characterized by an increase in airway inflammatory cells and inflammatory mediators (**Fig. 1**). Pollution exposure (fine particles, particles $<2.5\ \mu\text{m}$ and $>0.1\ \mu\text{m}$ in diameter, $[\text{PM}_{2.5}]$, diesel exhaust, ozone) has been associated with increased neutrophils, eosinophils, eosinophil cationic protein, interleukin (IL)-8, and IL-33 in nasal lavage, in vitro animal studies, and human bronchial lavage samples.^{16–19} Increases in myeloperoxidase, neutrophils, mast cells, CD4^+ and CD8^+ T lymphocytes, and the upregulation of adhesion molecules (eg, intercellular adhesion molecule-1 and vascular cell adhesion molecule-1) have been associated with ultrafine particle exposure,^{20,21} supporting neutrophilic inflammation in the airways.^{18,22,23}

Glutathione Depletion

Reduced glutathione (GSH) plays a central role in protection against airway oxidative stress and has been shown to decrease in asthmatics²⁴ and after PM exposure in airway epithelial cells in vitro.²⁵ Conversely, GSH may increase in healthy subjects after exposure to mild levels of diesel exhaust, indicating that the air–lung interface in

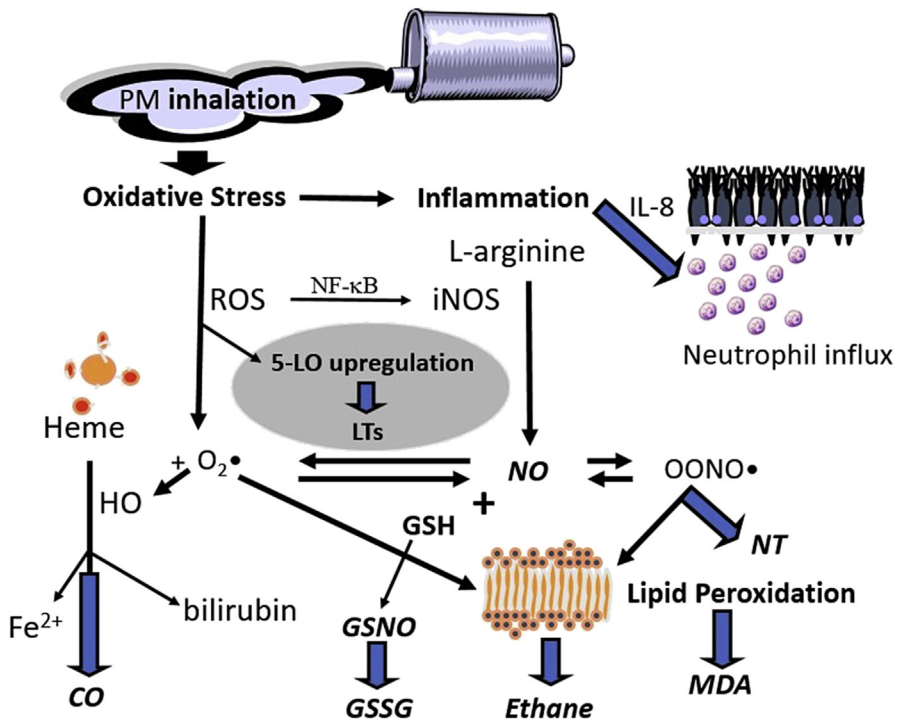


Fig. 1. Possible pathways from particulate matter (PM)-induced oxidative stress initiating airway inflammation, damage, and bronchoconstriction. GSH, glutathione; GSNO, nitroso-glutathione; GSSG, oxidized glutathione; IL-8, interleukin-8; iNOS, inducible nitric oxide; LTs, leukotrienes; MDA, malondialdehyde; NF-κB, nuclear factor κB; NO, nitric oxide; NT, nitrotyrosine; ROS, reactive oxygen species. (Adapted from Paredi P, Kharitonov SA, Barnes PJ. Analysis of expired air for oxidation products. *Am J Respir Crit Care Med* 2002;166(12 Pt 2):S32; Reprinted with permission of the American Thoracic Society. Copyright © 2018 American Thoracic Society. The American Journal of Respiratory and Critical Care Medicine is an official journal of the American Thoracic Society.)

healthy subjects is capable of counteracting an acute mild oxidative challenge.²⁶ Thus, GSH is a critical antioxidant in the airways. Decreased GSH has been shown in various lung dysfunctions, whereas oxidized GSH has been found to be high in the bronchial fluids of asthmatics.²⁴ It has been suggested that low GSH in the lung may amplify inflammation and airway hyperresponsiveness (AHR).²⁷ It seems likely that the airway dysfunction attributed to PM exposure is related to GSH status.

Antioxidant defense pathways²⁸ and GSH homeostasis²⁹ are controlled by GSH S-transferase, which is found in high concentrations in the lung. The single nucleotide polymorphism of GSH S-transferase π (GSTP1) *ile*¹⁰⁵ has been linked to the development of new-onset asthma and EIB in children who participate in team sports in high ambient ozone, demonstrating a hazard ratio for new-onset asthma of 6.15 (95% confidence interval, 2.2–7.4).³⁰ Thus, genotypic variation can account for some of the interindividual variation in respiratory responses to pollution exposure.

Evidence supporting the clinical importance of airway GSH can be found in studies using the GSH precursor *N*-acetyl-L-cysteine. Treatment with the cysteine donor (in the synthesis of GSH) *N*-acetyl-L-cysteine has been used therapeutically to reduce inflammation in various lung diseases. Results have been promising; Meyer and

colleagues³¹ have shown a significant increase in GSH in alveolar lavage fluid and other studies^{32–35} have demonstrated beneficial effects of *N*-acetyl-L-cysteine on oxidant mediated lung inflammation and inhibition of nuclear factor κ B and IL-8 upregulation. The cysteine donor *N*-acetylcystein has also been shown to increase lung epithelial cell GSH levels and inhibit RONS production.³⁴ Kasielski and Nowak³⁵ demonstrated that long-term oral administration of *N*-acetyl-cysteine attenuated H_2O_2 formation in the airways of patients with chronic obstructive pulmonary disease. Rubio and colleagues³⁶ demonstrated oral *N*-acetyl-cysteine attenuated elastase-induced pulmonary emphysema in rats. Blesa and associates³² demonstrated that oral *N*-acetyl-cysteine attenuates pulmonary inflammation in response to antigen in the rat. Several in vitro studies have demonstrated similar effects by the cysteine donors.^{37,38} All of these studies are suggestive of RONS having a key role in airway dysfunction, which can potentially be attenuated through therapeutics that support GSH function.

Nitric Oxide

Marginal associations between increased exhaled nitric oxide (NO) and particle exposure have been shown.³⁹ NO is an unstable free radical that is proposed to be important in vasodilation and airway inflammation. On the contrary, a decrease in exhaled NO, alveolar NO, and NO_3 , with an increase in lipid peroxidation, has been shown after high PM exercise¹⁵; these findings support a particle-induced downregulation of NO synthase and the formation of peroxynitrite (ONOO⁻) by the reaction between NO and super oxide anions ($O_2^{\cdot -}$) (Fig. 2). Peroxynitrite, a highly reactive oxidant species, is involved in lipid peroxidation. The formation of peroxynitrite results in decreased availability of NO, and diminishes the provasodilatory effects of NO. A more than 200% increase in malondialdehyde found in this study¹⁵ supports peroxynitrite initiated lipid peroxidation.⁴⁰ The significant correlations between lung function and change in NO_3 and exhaled NO in this study¹⁵ support a mechanism of decreased NO availability causing a sympathetic-induced bronchoconstriction or vasoconstriction. That finding provides a plausible explanation for the reduction in carbon monoxide diffusing capacity and decreased mid expiratory flow rates after ultrafine particle inhalation noted by Pietropaoli and colleagues.⁴¹

Likewise, NO reacts with GSH to form a potent airway bronchodilator, S-nitrosoglutathione (GSNO).^{42,43} It has been proposed that GSNO is critical in the AHR characteristic of asthma.⁴³ An in vitro study⁴⁴ using cultured alveolar macrophage cells demonstrated pronounced interaction between S-nitrosothiol metabolism and leukotriene metabolism. This study found that low levels of GSNO (0.5–1.0 μ mol/L) increase 5-lipoxygenase expression, whereas levels exceeding 5 μ mol/L inhibit 5-lipoxygenase expression and activity.⁴⁴ 5-Lipoxygenase is the rate-limiting enzyme in the biosynthesis of the potent bronchoconstrictors, cysteinyl leukotrienes. In support of this finding, Que and colleagues⁴³ demonstrated that endogenous GSNO (when not broken down by GSNO reductase) protects against methacholine-induced AHR and augments β_2 -adrenergic agonist airway relaxation. A decrease in GSNO may in part explain why leukotrienes are predominant mediators in PM-induced bronchoconstriction.⁵

EXPOSURE-SPECIFIC PATHOPHYSIOLOGY

Exercise-Induced Bronchospasm and Environmental Humidity and Temperature

Ambient air humidity is a key factor in the onset of bronchoconstriction. Generally speaking, this constriction occurs as a result of local changes in airway surface liquid osmolarity from conditioning large volumes of inspired air to body temperature and

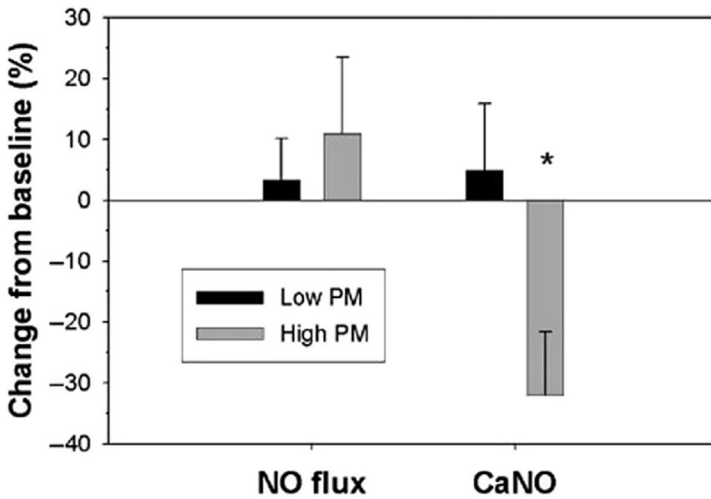


Fig. 2. The small decrease in exhaled nitric oxide (eNO) after high PM₁ (PM < 1 micrometer diameter) exercise was not different from the small decrease after low PM₁ exercise. Conducting airways nitric oxide (NO) flux was also not different between exposures, but fractional alveolar contribution to eNO (CaNO) significantly decreased 32% after high PM₁ exercise ($P = .02$). Exhaled NO was determined at 5 flow rates to calculate NO flux (nL s^{-1}) and CaNO (parts per billion). A plot of NO output (nL s^{-1}) versus expiratory flow rate (mL s^{-1}) was used to calculate NO flux and CaNO. The volume of eNO (VeNO) was calculated by multiplying the fraction of eNO plateau values by the expiratory flow rates. Linear least squares method was used to determine the best fit line through a plot of VeNO versus flow rate. NO flux was indicated as the y intercept and CaNO was indicated as the slope of the line. The decrease in eNO was attributed to CaNO, but not to conducting airway NO flux and the decrease in NO₃ and eNO combined with a large increase in malondialdehyde could provide a plausible pathway for peroxynitrite-mediated lipid peroxidation. * $P < .05$ (From Rundell KW, Slee JB, Caviston R, et al. Decreased lung function after inhalation of ultrafine and fine particulate matter during exercise is related to decreased total nitrate in exhaled breath condensate. *Inhal Toxicol* 2008;20(1):5; with permission.)

99% relative humidity during exercise.^{45,46} The change in osmolarity causes resident inflammatory cells to degranulate, releasing inflammatory cell mediators that act on responsive bronchial smooth muscle receptors.⁴⁷ Cold air is generally associated with EIB, but this is generally due to the low water content of cold air rather than the temperature itself. Even if air is warmed to body temperature, an EIB response can be observed in asthmatics; however, the response is attenuated when the air is humidified.⁴⁸ Thus, endurance athletes training in cold environments (eg, cross-country skiers) are at increased risk of EIB, as well as the development of asthma.^{49,50} Cross-country skiers without a history of EIB or asthma experience airway inflammation and remodeling similar to individuals with frank asthma.⁵¹ Such macroscopic inflammatory changes have been observed in a cohort adolescent skiers (mean of 7 years of experience) compared with controls, and this inflammation was worse in skiers with asthma.⁵² Airway remodeling and consequent signs and symptoms of pulmonary dysfunction in these athletes may occur in the presence⁵³ or absence of bronchial hypersensitivity.⁵⁴ This remodeling may result in progressive decreases in pulmonary function, as evidenced by an increased prevalence of self-reported asthma with age in skiers.⁴⁹ Additionally, Stensrud and coworkers⁵⁵ reported that exercise

performance is decreased by approximately 5% in dry air (40% relative humidity) compared with humid air (95% relative humidity) in athletes with EIB. However, in a recent systemic review by Price and colleagues,⁵⁶ the authors concluded that, although it is reasonable to suspect that EIB impacts athletic performance, there is currently insufficient evidence to provide a definitive answer.

Particulate Matter

Airborne PM consists of a mixture of small particles of organic and inorganic compounds, acids, metal, dust, and carbon. PM is categorized as course particles (PM_{10} ; 2.5–10 μm diameter), fine particles ($PM_{2.5}$), and nano/ultrafine size ($PM_{0.1}$; <0.1 μm diameter; **Fig. 3**). The primary source of $PM_{2.5}$ and ultrafine particles is from fossil fuel combustion emissions such as motor vehicles, furnaces, and gas cooking stoves. Greater than 90% of the particles from diesel emissions are in the ultrafine size range,⁵⁷ and current thinking supports the concept that PM toxicity is related to smaller particle size and number count.^{20,58} The 24-hour average National Ambient Air Quality Standards established by the US Environmental Protection Agency for PM_{10} and $PM_{2.5}$ are 150 $\mu\text{g}/\text{m}^3$ and 35 $\mu\text{g}/\text{m}^3$, respectively. There are no standards for $PM_{0.1}$ because a mass metric for these does not provide practical information; these nano/ultrafine particles are best described by a number metric (particles/ cm^3). However, the small size and mass of these smallest particles allows them to have the greatest alveolar deposition, which is exacerbated by the high ventilations of exercise.^{6,59} Daigle and colleagues⁶ examined lung deposition of ultrafine carbon black particles (mean diameter, 26 ± 1.6 nm) at rest and during moderate exercise; the number of particles deposited during exercise was 4.5-fold greater than at rest and was attributed to the combined increase in deposition fraction during exercise (from 0.66 ± 0.11 to 0.83 ± 0.04) and increased minute ventilation during exercise (from 9.0 ± 1.3 to 38.1 ± 9.5 L/min). This may have implications to respiratory health of those exercising in areas of high airborne PM. PM generated from combustion emissions can be associated with the formation of RONS and influence mediators released from airway cells involved in EIB.^{15,60,61} Exposure to PM has been associated with emergency department visits,^{62,63} increased bronchodilator use,⁶⁴ and bronchoconstriction after exercise in asthmatics and nonasthmatics.²²

High levels of airborne nano/ultrafine PM have been identified at indoor ice rinks use fossil-fueled (gas, propane, or natural gas) Zambonis for ice resurfacing (**Fig. 4**)^{65–67} and at athletic fields that are in close proximity to major roadways.⁶⁸ The prevalence of asthma and EIB in skating athletes has been documented to be between 20% and 50%. Several groups^{69–71} evaluating elite figure skaters found that 29% to 35% tested positive for EIB by challenge test and Wilber and colleagues⁷¹ reported that 50% of

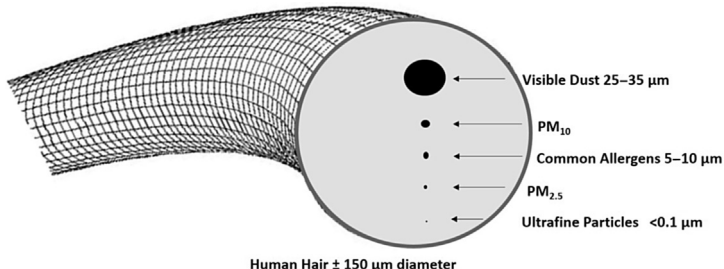


Fig. 3. Particle diameters in relation to diameters of human hair, visible dust, and common allergens. PM, particulate matter.

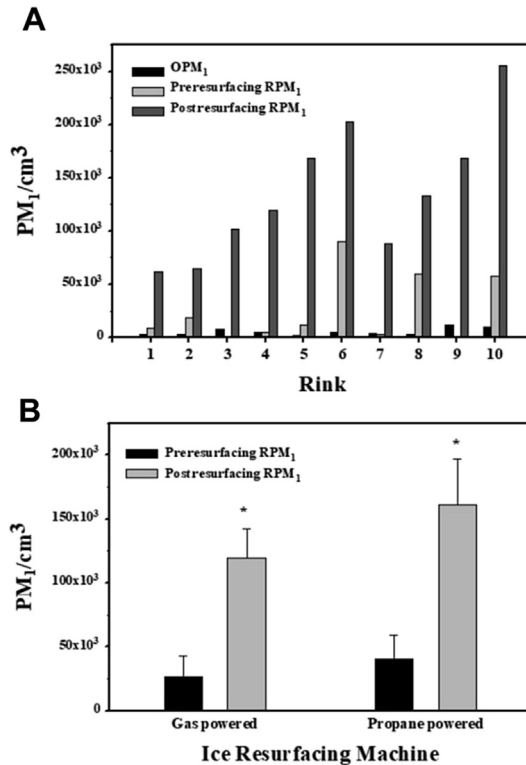


Fig. 4. (A) Comparing outside PM₁ (OPM) with preresurfacing and postresurfacing rink PM₁ (RPM) in 10 indoor ice rinks. The OPM values were from immediately outside each rink. (B) Comparing RPM between rinks serviced with gasoline-powered resurfacing machines ($n = 6$) with those using propane-powered resurfacing machines ($n = 4$). Differences between the preresurfacing and postresurfacing RPM₁ were evident within rinks ($P < .05$). Ice rinks resurfaced by fossil-fueled machines had higher baseline particulate levels, which became elevated during and immediately after each hourly resurfacing. (From Rundell KW. High levels of airborne ultrafine and fine particulate matter in indoor ice arenas. *Inhal Toxicol* 2003;15(3):237–50; with permission.)

female and 33% of male Olympic short track speed skaters and 25% of female long track speed skaters tested positive for EIB. Likewise, 21% of elite women ice hockey players tested positive for EIB⁷² and showed a significant decrease in lung function over 4 years.⁶⁶ Exposure to high PM from fossil-fueled ice resurfacing machines during high ventilation exercise coupled with a genetic susceptibility could account for the observed high prevalence of asthma and EIB in ice rink athletes.^{66,67,69–71}

Likewise, outdoor athletic fields and playgrounds in areas near high traffic roadways should be cause for concern because of traffic emissions. High levels of PM₁ (PM < 1 micrometer diameter) have been recorded at college soccer fields adjacent to major highways⁶⁸ and have been implicated in both acute^{5,15,20–22,62} and chronic^{66,72–74} effects on the pulmonary system.

Ozone

Ozone (O₃) is considered a secondary pollutant because it is formed from a photochemical reaction in atmosphere between nitrogen oxides, especially nitrogen dioxide

(NO₂), sunlight, and hydrocarbons, and is a key oxidant that can cause EIB.^{75–77} Ozone is one of the most widespread global air pollutants; it travels with the wind, tending to reach high concentrations in big cities, downwind distant peripheries, and surrounding hills or mountains, especially during hot and sunny weather.⁷⁷ The current standards for O₃ is between 100 and 140 µg/m³ (0.05–0.07 ppm) 8-hour mean, according to the World Health Organization and the US Environmental Protection Agency, respectively. Additional cutoffs include 160 µg/m³ (0.08 ppm) that may affect health of susceptible exercising people, and a higher level of 240 µg/m³ (0.12 ppm) defined as potentially having significant health effects, especially in vulnerable populations.⁷⁷ High concentrations of O₃ are a major problem in America and in Europe, and in hot climate megacities, the level of O₃ may exceed 400 µg/m³ (0.20 ppm) for several days, constituting a significant threat to public health.⁷⁷

Exercise in high levels of O₃ may provoke cough and substernal pain, and is correlated with O₃ concentration,^{78,79} but depends on the ventilation rate and exercise duration. Although an O₃ concentration of less than 0.16 ppm may provoke small changes in the forced expiratory volume in 1 second (FEV₁) and forced vital capacity, higher concentrations result in an increased number of healthy subjects developing acute decreased lung function and more severe response.^{78,79} Exposure to O₃ has been shown to decrease FEV₁ up to 48% from preexposure values.^{79,80} Likewise, McDonnell and colleagues⁷⁹ observed that some healthy subjects without EIB had a 40% to 45% decrease in FEV₁ after moderate intermittent 2-hour exercise (ventilatory equivalent [VE] of 35 L/min/body surface area) in a concentration of O₃ greater than 0.24 ppm compared with the same exercise performed in a filtered air environment. This finding is of concern, because some healthy subjects without known EIB may be sensitive to O₃ and develop mild to severe decreases in lung function during a single exercise exposure to O₃.^{79,81}

It is now recognized that the decreased lung function and respiratory symptoms from exercise in high [O₃] is primarily caused by stimulation of sensory nerves along conducting airways.^{82–85} Inhaled O₃ reacts with epithelial fluid lining substrates, such as antioxidant molecules, membrane phospholipids, cholesterol, and macrophages to cause inflammatory mediator release and stimulation of airway sensory nerve endings.⁸⁶ The consequent release of neuropeptides, such as substance P, stimulates the axon reflex, which inhibits full inspiration, and causes reduced lung function and a rapid shallow breathing pattern.^{87,88} The metabolites of cyclooxygenase-2 may in part mediate the stimulation of the nociceptive respiratory tract afferents and their inhibition may prevent the lung function changes owing to O₃.^{89–92} Asthmatics with a lower baseline FEV₁ and uncontrolled asthma as well as susceptible healthy subjects may have an additional bronchoconstriction after exercise in O₃.⁹³

Repeated daily exposure to O₃ combined with daily exercise periods causes a marked attenuation of discomfort from respiratory symptoms and the decreases in forced vital capacity and FEV₁ in a majority of subjects.^{80,94–98} Some studies found no observable change in FEV₁ after O₃ exposure exercise, suggesting individual variability in the response to O₃.^{99,100} In communities with high O₃ concentrations, the relative risk of developing asthma in children is related to time spent outside, and the number of outdoor sports played.¹⁰¹ McConnell and colleagues¹⁰¹ found that the relative risk of developing asthma in children playing 3 or more sports was 3.3 (95% confidence interval, 1.9–5.8), compared with children playing no sports in communities with high [O₃] or to children in areas of low O₃. Repeated episodes of O₃ inhalation may attenuate airway inflammation and neuropeptides release; rapid and shallow breathing occurs during the first days of exposure, and remodeling of the

centriacinar airways is observed.¹⁰² This finding suggests that O₃ exposure may contribute to the development of asthma and AHR in children and elite endurance summer sport athletes.

The O₃-induced bronchoconstriction may be partially reversed by albuterol.¹⁰³ Previous treatment with inhaled corticosteroids, or inhaled corticosteroids and long-acting beta agonists, does not prevent the neutrophilic airway inflammation or AHR owing to O₃ exposure in exercising mild asthmatics or healthy subjects who are susceptible to AHR.^{104,105}

Nitrogen Dioxide

NO₂ is a reddish-brown gas with a characteristic pungent odor that can be noticeable during episodes of vehicular pollution. It is a key precursor of a range of secondary photochemically generated pollutants, such as ozone, and organic nitrate and sulfate particles measured as PM₁₀ or PM_{2.5}. The major source of nitrogen oxides is from the combustion processes in stationary sources (power generation of the cities, heating) and in mobile sources (internal combustion, ie, vehicle emissions). Annual mean NO₂ concentrations in urban areas throughout the world are generally in the range of 20 to 90 µm³ (0.01–0.05 ppm).⁷⁷ The World Health Organization standard levels for NO₂ are a 40 µm³ (0.021 ppm) annual mean or a 200 µm³ 1-hour mean (0.106 ppm).⁷⁷ Hourly averages near very busy roads may exceed 940 µm³ NO₂ (0.50 ppm).⁷⁷

Mild asthmatics may be more susceptible to the potential effects of high [NO₂] than healthy subjects, with respect to airway responsiveness and lung function. In healthy subjects, short-term exposure of up to 2 hours, comprising periods of 10 to 30 minutes exercising at light to moderate intensity, does not provoke respiratory symptoms and shows no evidence of impaired pulmonary function when exposed to 0.12 to 4.00 ppm NO₂.^{106–113} Mean airway narrowing after exercise does not seem to be different between filtered air or NO₂ inhaled during exercise in mild asthmatics.^{109,112,114–118} However, similar to O₃, there is a great interindividual airway response to NO₂, especially in mild asthmatics.^{119,120} NO₂ inhalation at [0.30 ppm] may potentiate EIB compared with a controlled exposure at similar workloads and ventilation rates.^{119,120} Bauer and colleagues¹¹⁹ observed a decrease in the FEV₁ of 9.4% after exercising for 10 minutes at a VE of 30 L/min in a filtered air environment, compared with a decrease of 37% when exercising with a concentration of 0.30 ppm of NO₂ in a particularly susceptible mild asthmatic who was treated with only short-acting beta agonists as needed. Jorres and Magnussen¹¹⁴ observed that a mild asthmatic had a decrease in FEV₁ of 20%, whereas another had no change in FEV₁ after a 3-hour exposure to 1 ppm NO₂ while exercising for 10 minutes every 20 minutes at a VE of approximately 30 L/min.

Many studies have reported no increase in airway reactivity after exposure to NO₂,¹¹⁴ whereas others found an increase in airway reactivity after low-dose exposure in the majority of mild asthmatics (0.10–0.20 ppm over 1–2 hours).^{115,121} During a second day of exposure to 1 ppm NO₂ during 25 minutes of mild intensity exercise (2-fold the resting VE) every 30 minutes during a 2-hour period, Hackney and colleagues¹²² observed an increase in respiratory symptoms despite finding no change in lung function. The increase in airway responsiveness after NO₂ exposure could be partially explained by the increase in thromboxane B₂, prostaglandin D₂, and various leukotrienes observed in mild asthmatics exposed to NO₂ while exercising, whereas 6ketoPGF1α, a metabolite of prostaglandin I₂ that is associated with bronchodilation, was decreased in all subjects.¹²³ Sandstrom and colleagues¹²⁴ also noted a decrease in subset of lymphocytes after repeated exposure of 20 minutes NO₂, with 15 minutes of light exercise, possibly increasing susceptibility to airway infections.

This finding is of concern, especially in those with airway disease or athletes. Combined exposure to NO₂ and O₃ or PM does not seem to have additional or synergistic effects on airway function.^{125,126}

Sulfur Dioxide

Sulfur dioxide (SO₂) is a gas originating from natural volcanic activity and industrial activities, such as the combustion of coal, petroleum, gasoline, and nondesulfurized natural gas.⁷⁷ The World Health Organization standards for SO₂ are 20 µg/m³ (0.0075 ppm) for 24 hours or 500 µg/m³ for a 10-minute mean (0.19 ppm).⁷⁷ Urban and rural concentrations are generally similar and the annual mean in European countries and is less than 50 µg/m³ (0.019 ppm), with daily mean concentrations of less than 100 µg/m³ (0.038 ppm). In the Baltimore, Maryland area, from June to September 2013, maximal 5-minute values of 229 ppb (600 µg/m³) and 1-hour values of 134 ppb (351 µg/m³) have been registered.¹²⁷ In the majority of healthy subjects, there are no significant effects on pulmonary function during exercise when exposed to SO₂ at ambient levels of less than 2 ppm, but exposure may accentuate the response to other pollutants such as O₃, especially in susceptible subjects, and when the concentration of both pollutants is high.^{128–131} In asthmatics, SO₂ inhalation before or during exercise may elicit or aggravate bronchoconstriction and increase airway resistance at concentrations observed during ambient pollution episodes (0.4–0.6 ppm).^{132–134} After a 10-minute exercise session with 1 ppm SO₂ exposure at a ventilation rate 6 times greater than resting values, asthmatics with EIB had a mean 23% decrease in FEV₁, whereas no change in pulmonary function was observed when exercising in filtered air.¹³⁵ Oral-nasal breathing of SO₂ during exercise may decrease the amplitude of response compared with oral breathing.^{132,136} However, inhaled cromolyn or antileukotrienes has been shown to decrease SO₂-induced airway resistance and bronchoconstriction in asthmatics during exercise by preventing degranulation of airway mast cells and inhibiting the action of leukotrienes.^{137,138}

Trichloramines

Trichloramines (NCl₃) belong to a family of byproducts from the reaction between chlorine disinfection products used in swimming pools and nitrogenous contaminants from swimmers, such as sweat, urine, soap residues, or cosmetics.^{139–141} NCl₃ is the most volatile compound among the chloramines, is airborne at the water surface, and is strongly suspected to cause respiratory symptoms in swimmers. The characteristic chemical odor accompanying high levels of NCl₃ in the air^{139,141} is often associated, in a dose-response manner, with the report of eye, nasal, and respiratory symptoms during training in swimmers, trainers, and lifeguards, and may trigger bronchoconstriction in asthmatics.^{142–146} Although the high humidity conditions present at swimming pools are beneficial for asthmatics,¹⁴⁷ individuals should avoid swimming pools with a strong chlorine odor. The concentration of NCl₃ in swimming pool atmosphere is strongly dependent on the hygiene, activities of swimmers, water exchange rate, and swimming pool ventilation.¹⁴⁸ To avoid eye and respiratory tract infections, standards for chlorinated-disinfected swimming pool ambient air NCl₃ suggest not exceeding 0.3 to 0.5 mg/m³.^{145,148,149} However, NCl₃ is not routinely measured at most indoor swimming pools. Studies at municipal swimming pools in various countries report concentrations of NCl₃ in the atmosphere exceeding 0.5 mg/m³,^{150,151} despite within-standard levels in the water.

There is an association between regular indoor chlorinated pool attendance and the development of allergic diseases, bronchiolitis, and asthma in infants, young children, leisure adolescent swimmers, and adult swimmers,^{152–166} but this relationship

remains debatable.^{167–169} Chronic exposure to chlorine N,N diethyl-1,4 phenylenediamine sulfate is responsible for occupational asthma in lifeguards and pool workers.^{142,143,170,171} Recently, Rosenman and colleagues¹⁷¹ reported that exposure to airborne chlorine byproducts by individuals who work at indoor swimming pools, water parks, or hydrotherapy spas was associated with the development of new onset asthma and triggering the EIB response in existing asthmatics.

The high-intensity exercise during swim training seems to be a major risk factor for the appearance of asthmatic symptoms.¹⁷² In young competitive swimmers, the exercise load has been suggested to correlate with an increased AHR to histamine after swim training.¹⁷³ Years of NCl_3 exposure during repeated intense swimming sessions (ie, ≥ 10 h/wk) is implicated in development of atopy and allergies, AHR, and asthma in young adult competitive swimmers.^{174–177} Bronchial biopsies from national-level competitive swimmers also showed similar airway remodeling and inflammation compared with mild asthmatic nonathletes, independent of airway responsiveness.¹⁷⁸ Because of a predominantly neutrophilic inflammation, corticosteroids may be ineffective in many swimmers.¹⁷⁹ Interestingly, this group does not typically have an exacerbation while swimming, likely because the high humidity at the pool surface provides a degree of protection. Castricum and colleagues¹⁸⁰ found that only 1 of 33 elite swimmers tested positive for EIB after an 8-minute swim challenge at an intensity of 85% or greater of the maximal heart rate, whereas 18 tested positive by a 6-minute dry air EVH challenge (Fig. 5), demonstrating the low asthmogenicity of swimming but high prevalence of EIB among this population.

Simultaneous Exposure to Multiple Environmental Triggers

It is clear that exposures to specific pollutants cause acute and chronic airway dysfunction, but it is also important to recognize that athletes are often simultaneously exposed to various combinations of each of these. For instance, the 20% to 50% prevalence of EIB reported in skaters far exceeds the approximate 8% to 12% prevalence in other athletes in the United States.^{1,69–71} Chronic ventilation of the dry ice

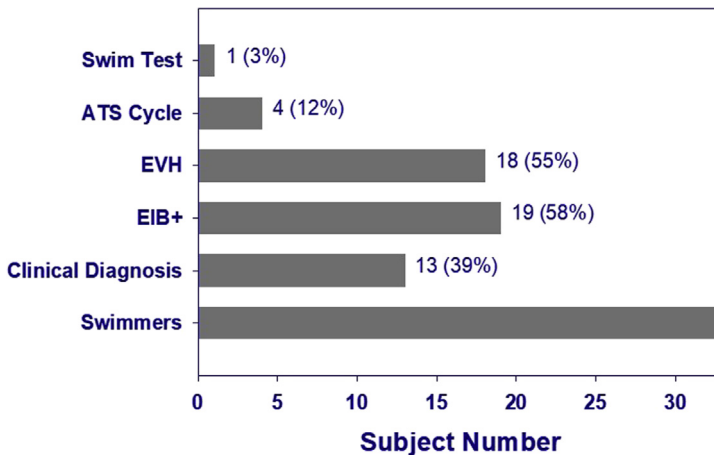


Fig. 5. Of 19 competitive swimmers who tested positive for exercise-induced bronchospasm (EIB), only 1 tested positive to a swim challenge test, likely owing to the high humidity at the water surface. (Data from Castricum A, Holzer K, Brukner P, et al. The role of the bronchial provocation challenge tests in the diagnosis of exercise-induced bronchoconstriction in elite swimmers. *Br J Sports Med* 2010;44(10):736–40.)

rink air by skating athletes during training and competition, coupled with high levels of PM₁ from fossil-fuel powered ice resurfacers, may exaggerate the EIB response, or directly cause airway damage that leads to new-onset asthma.⁶⁵ Ice rink air quality has been shown to be associated the high prevalence of airway dysfunction in skating athletes.^{69,70} Likewise, urban athletic fields and school playgrounds can present a major health concern. College soccer players, both with and without a diagnosis of asthma, whose practice fields are in close proximity to major highways have shown significant decreases in lung function over the course of a season.⁶⁸

SUMMARY AND PUBLIC HEALTH RECOMMENDATIONS

The prevalence of EIB and asthma among cold weather endurance athletes, ice rink sport athletes, and competitive swimmers is higher than in nonathletes and summer athletes, and has been related to repetitive inhalation of dry air and/or pollutants. In the United States, ozone, PM, and pool trichloramines are the pollutants most commonly encountered by training and competing athletes. Acute hyperpnoea of these pollutants during exercise have been shown to increase oxidative stress and trigger airway inflammation and decrease lung function. Acute effects on the respiratory system from pollution exposure have been documented in both the nonasthmatic and the asthmatic, with increased emergency department visits for respiratory distress during outbreaks of high pollution. Likewise, chronic exercise while breathing cold/dry air and/or these pollutants has been related to the development of new-onset asthma, EIB, and low resting lung function.

Despite the overwhelming evidence that air quality has a significant impact on respiratory health, many areas are not aware of the high ozone and PM that can be found at urban playgrounds and athletic fields along high traffic roadways and as such present a risk to young athletes. Only a few states do regulate where these recreation areas can be developed, and only 1 state does not allow the development of new athletic fields within 100 m of major highways; that particular state monitors ice rink pollution levels and allows only electric resurfacing in new rinks. Likewise, appropriate ventilation systems for indoor swimming pools should be in place and monitoring chlorine levels and sanitary conditions of the pool water should be enforced. Given the importance of exercise training for the prevention of chronic disease, there is substantial public health benefit in addressing air quality problems in sports and recreational areas.

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