

# Exercise-Induced Lung Disease: Too Much of a Good Thing?

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Exercise in children has important health benefits. However, in elite endurance athletes, there is an increased prevalence of exercise-induced bronchoconstriction and airway inflammation. Particularly at risk are those who practice in cold weather, ice rinks, swimming pools, and air pollution. The inflammation is caused by repetitive episodes of hyperventilation of cold, dry air, allergens, or toxins such as chlorine or air pollution. Children may be particularly at risk for lung injury under these conditions because of the immaturity and ongoing development of their lung. However, studies in pediatric athletes and exercising young children are sparse. Epithelial injury associated with hyperventilation of cold, dry air has not been described in children. However, exercise in the presence of air pollution and chlorine is associated with airway injury and the development of asthma in children; the effect appears to be modulated by both atopy and genetic polymorphisms. While management of exercise-induced bronchoconstriction and asthma is well established, there is little data to guide treatment or prevention of remodeling in athletes or inhalational lung injury in children. Studies underscore the need to maintain high levels of air quality. More investigations should be undertaken to better define the natural history, pathophysiology, and treatment of exercise-induced pulmonary inflammation in both elite athletes and exercising children.

## Introduction

APPROXIMATELY 30 MILLION children and adolescents in the United States participate in organized sports.<sup>1</sup> Exercise has widespread benefits. It improves physical fitness, self-esteem,<sup>2</sup> and cognitive and academic performance,<sup>3,4</sup> and reduces cardiovascular disease risk factors<sup>5</sup> and obesity.<sup>6</sup> In children with asthma, an exercise program improves quality of life and cardiovascular fitness,<sup>7</sup> decreases exercise dyspnea,<sup>8,9</sup> and decreases the need for medications such as inhaled corticosteroids.<sup>10</sup>

However, exercise can acutely precipitate bronchoconstriction and airway obstruction. In addition, in elite endurance athletes, there is an increased incidence of exercise-induced bronchoconstriction (EIB); 21%–69% demonstrate EIB and airway hyperresponsiveness (AHR), depending upon the specific sport demands.<sup>11–16</sup> Particularly at risk are those athletes who practice in the cold weather,<sup>17–20</sup> ice rinks,<sup>21–24</sup> and swimming pools.<sup>25,26</sup>

Atopy and lung inflammation have been shown to be cardinal features in the pathogenesis of EIB.<sup>17,27,28</sup> In endurance athletes, EIB has been associated with both eosinophilic<sup>29</sup> and neutrophilic inflammation,<sup>30–32</sup> increased airway vascular permeability,<sup>33,34</sup> and inflammatory mediators such as histamine, prostaglandin D<sub>2</sub>, tryptase, and cysteinyl leukotrienes<sup>31,35</sup> released from epithelial, eosinophil, and mast

cells. The airway injury and development of symptoms probably represent a complex interplay between the atopic response and epithelial injury due to repetitive episodes of hyperventilation of cold, dry air and allergens or toxins such as the chlorine bi-product trichloramine or air pollution<sup>36</sup>; the epithelial injury produced by exercising in the presence of toxins may produce allergic sensitization.<sup>37–39</sup> The risk of EIB and inflammation increases with the intensity of and amount of time spent in training for the sport.<sup>26,40,41</sup>

Children may be more sensitive than adults to exercise-induced lung injury because of the relative immaturity and continued growth of their lungs. Most of the studies on sports-related lung inflammation and EIB in elite athletes focus on young adults (18–20 years); however, they do include older adolescents (16–18 years). Unfortunately, there is little data on the relationship of exercise and lung inflammation in younger athletes and exercising children. The goal of this article is to review the literature on the interrelationship between exercise-induced lung injury, inflammation, and EIB in elite athletes and younger exercising children.

## Pathophysiology and Diagnosis of EIB

EIB is a common entity and is described by the transient narrowing of the airways during or most often after exercise.<sup>42–45</sup> It occurs in 10%–15% of children.<sup>46,47</sup> The preva-

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lence of EIB in asthmatic children is reported to be 45%–90%.<sup>48–50</sup> The incidence of EIB correlates with the clinical severity of asthma, but not consistently with the magnitude of the response.<sup>48</sup>

Data on the prevalence of EIB in competitive pediatric athletes are sparse, but it appears to be higher than in the general population. In varsity high school football players (14–18 years), the prevalence of EIB was 19% by submaximal step test<sup>16</sup> or free run.<sup>51</sup> In youth soccer players, the prevalence was 33% by symptoms (8–20 years)<sup>52</sup> and 40% by exercise challenge (8–13 years).<sup>53</sup> In a cohort of high school athletes, AHR was 38% by bronchial challenge.<sup>54</sup>

Symptoms of EIB include dyspnea, increased effort or work to breathe, chest tightness, shortness of breath, wheezing, chest congestion, or cough.<sup>55,56</sup> Often, EIB is diagnosed on the basis of these symptoms without objective lung function tests. However, the presence of EIB cannot be accurately determined on the basis of symptoms alone<sup>56</sup>; in children with exercise-induced dyspnea, only 7%–24% truly had EIB.<sup>47,57–59</sup> In college athletes, only 20% of those using bronchodilators had EIB.<sup>60</sup>

The diagnosis of EIB should be confirmed through standardized testing with spirometry and a formal challenge test. A clinical suspicion for asthma should be confirmed by a 12% or greater increase in forced expiratory flow in the first second of exhalation (FEV<sub>1</sub>) in response to a bronchodilator or a positive bronchoprovocation challenge. To diagnosis EIB, current guidelines require a 10% or greater decrease in FEV<sub>1</sub> in response to exercise<sup>61</sup> or eucapnic voluntary hyperpnea (EVH)<sup>62,63</sup> or a 15% or greater decrease in response to inhaled powder mannitol.<sup>64</sup> These challenges are particularly useful as they can correlate the symptoms that occur during exercise with objective data documenting bronchoconstriction.

The pathophysiology of EIB is not completely understood. During exercise, ventilation is increased. The increase in airflow through the intrathoracic airways causes evaporative water loss because inspired air must be humidified and warmed to body temperature. The water loss is associated with thermal cooling and increases in osmotic concentration because of drying.<sup>45,65,66</sup> EIB is likely initiated by the increase in osmolarity, which activates mast and epithelial cells and eosinophils and leads to a release of inflammatory mediators.<sup>67</sup> Alternatively, EIB may result from the heat loss, which leads to vascular dilation when the airways rewarm after exercise.<sup>68</sup> However, this theory does not account for the mediators released and the inhibition of bronchoconstriction through pharmacologic intervention.

Inflammation appears to play an important role in the pathogenesis of EIB in asthmatics. Exercise produces increases in histamine and tryptase (from mast cells) in induced sputum.<sup>31</sup> Cysteinyl leukotrienes likely play an important role in EIB; increases after exercise have been documented in asthmatic patients with EIB in induced sputum<sup>31</sup> and urine.<sup>69</sup> Treatment with a leukotriene receptor antagonist reduces the EIB response in adults<sup>70</sup> and children.<sup>71</sup> The severity of EIB in asthmatics correlates with eosinophilic inflammation,<sup>29</sup> airway vascular permeability,<sup>33</sup> and fractional exhaled nitric oxide (F<sub>E</sub>NO).<sup>72–74</sup> Inhaled corticosteroids improve EIB in asthmatic individuals<sup>75–77</sup> and are associated with an improvement in eosinophilic inflammation.<sup>29</sup>

## EIB in Elite Athletes

EIB in elite endurance athletes has unique characteristics. While studies focus on athletes 18–20 years, they do include older adolescents (16–18 years). Cold-weather athletes,<sup>17–20</sup> ice rink athletes,<sup>21–25,78</sup> and swimmers<sup>32,40,79,80</sup> have a particularly high prevalence of EIB. EIB in endurance athletes develops relatively late and occurs during their sports careers.<sup>19</sup> Unlike in “classic” asthmatics, EIB symptoms and mucosal inflammation often do not respond to corticosteroids.<sup>81</sup> Bronchial hyperresponsiveness and airway inflammation typically improve when the athletes finish their competitive careers<sup>26</sup> or decrease their training intensity.<sup>81</sup>

The pattern of inflammation seen in endurance athletes differs from those with classical asthma. Most endurance athletes have an increase in epithelial cells and neutrophils in induced sputum,<sup>26,32,82–84</sup> bronchoalveolar lavage<sup>85</sup> and bronchial biopsy,<sup>30</sup> which correlates with training intensity.<sup>86</sup> Eosinophils are seen in swimmers exposed to chlorine<sup>32</sup> and in cross-country skiers,<sup>30</sup> but are not as numerous as in asthmatics.<sup>30</sup> Accordingly, EIB in athletes has not consistently correlated to elevations in F<sub>E</sub>NO.<sup>60,82,87</sup> The data on sports-related lung injury and EIB in younger children is sparse, but will be evaluated by risk factor.

## Hyperventilation/cold air

In elite athletes, the high ventilatory rates that are achieved are theorized to cause lung injury; this is corroborated in animal models.<sup>88</sup> High ventilation with cold air (ie, low water content) is associated with more physiologic consequences than warm air. The larger the thermal energy that needs to be transferred, the more the airways narrow and the greater the drop in FEV<sub>1</sub> to challenge.<sup>45,65,89–91</sup> Healthy adults demonstrated an increase in bronchoalveolar lavage neutrophils and alveolar macrophages after 2 h of exercise in cold air but not at room air temperature.<sup>92</sup>

Endurance athletes demonstrate a high prevalence of EIB<sup>15,17,40,86,93,94</sup>; studies include a few older adolescents. In one study, 26% of Finnish National runners had EIB on exercise challenge; the occurrence of EIB increased with atopy.<sup>17</sup> The degree of inflammation has correlated with the intensity and duration of training.<sup>40,86</sup>

The highest incidence of EIB is seen in cold-weather endurance athletes<sup>18</sup> to which the term “ski asthma” has been applied. Elite skiers have demonstrated deterioration of lung function during the course of their careers.<sup>95</sup> In cross-country skiers, bronchoscopy revealed macroscopic inflammation of the proximal airways characterized by increased friability, vascularity and edema of the bronchial mucosa, and secretions; bronchoalveolar lavage has increased numbers of lymphocytes, myeloperoxidase, and tumor necrosis factor- $\alpha$ .<sup>85</sup> Endobronchial biopsies have revealed a prevalence of lymphoid aggregates,<sup>96</sup> elevated neutrophil, T-lymphocyte, macrophage, and eosinophil counts and tenascin expression in the subepithelial basement membrane, which is a marker for remodeling.<sup>30</sup>

There are no studies in children younger than 16 years on the acute inflammatory effects of hyperventilation with cold, dry air or on the presence of airway inflammation or remodeling in those that participate in cold-weather sports. More investigation is necessary to determine whether the changes seen in elite athletes have any correlate in younger

children who participate in cold-weather sports on either a competitive or a recreational level.

### *Air pollution*

Air pollution is primarily caused by the combustion of fossil fuels and is in part composed of sulfur oxides (such as sulfur dioxide, SO<sub>2</sub>), nitrogen oxides (such as nitrogen dioxide, NO<sub>2</sub>), ozone, and particulate matter (PM) that have been linked to respiratory disease. PM is further classified depending on its aerodynamic diameter into coarse (2.5–10 µm), fine (≤2.5 µm), and ultrafine (<0.10 µm). Other components include carbon dioxide, carbon monoxide, volatile organic compounds, and metals such as lead. It is often difficult to sort out which component of air pollution is responsible for deleterious respiratory effects. The size of the airborne particles and their surface area determine the potential to elicit inflammatory injury, oxidative damage, and other biological effects. These effects are stronger for fine and ultrafine PM because they can penetrate deeper into the airways of the respiratory tract.<sup>97</sup> Exercise increases lung deposition of PM.<sup>98,99</sup>

In children, high levels of air pollution have been positively associated with asthma,<sup>100</sup> rates of asthma exacerbations,<sup>101</sup> EIB symptoms,<sup>102</sup> impaired lung function<sup>103</sup> and growth,<sup>104</sup> and atopy.<sup>105</sup> Exercise in high air pollution environments is associated with the development of pulmonary dysfunction<sup>106</sup> and increased airway permeability.<sup>107</sup> In children, a 4 hour exposure to exercise in a mixture of ozone, SO<sub>2</sub>, and its oxidation product, sulfuric acid, produced symptoms in those with mild asthma and/or allergy.<sup>108</sup> Variants in arginase genes may modulate the expression of asthma and atopy when exposed to air pollution.<sup>109</sup>

Importantly, the risk of developing asthma increases with the number of sports that children play outdoors in communities with high ozone levels. In the study by McConnell et al., in communities with high ozone concentrations, the relative risk of developing asthma in children playing 3 or more sports was 3.3 (95% confidence interval 1.9–5.8) compared to those who played no sport; the risk increased with number of sports (relative risk 1.3 per sport, 1.1–1.6). The risk of asthma was increased for children playing at least one high activity sport.<sup>41</sup> Genetic polymorphisms of molecules involved in protection against oxidative stress have been shown to be important in the development of new-onset asthma in these children.<sup>110</sup>

Indoor air pollution is a potential health hazard for athletes who participate in ice rink sports. In combination with inadequate air exchange, fossil-fueled machines produce high levels of air pollutants.<sup>111–113</sup> The levels of NO<sub>2</sub> in many rinks far exceed the guidelines issued by the World Health Organization for indoor air quality both directly on the ice and in the spectator area. The highest levels of NO<sub>2</sub> were found when the resurfacers were powered by propane, followed by gasoline and then diesel; electric resurfacers did not have increased levels of NO<sub>2</sub>.<sup>111,112</sup> Ultrafine and fine PM concentrations in ice rinks, resurfaced with fossil-fueled machines, is 20-fold higher than outside areas.

There is a high incidence of EIB in elite ice rink athletes: hockey,<sup>56,78,114,115</sup> figure skaters,<sup>18,23,24</sup> and short track speed skaters.<sup>18</sup> Ice hockey players demonstrated a decay in lung function and increase in EIB symptoms when training in rinks with high levels of fine and ultrafine PM.<sup>114</sup> In the only

pediatric study, Thunqvist et al. found that the prevalence of physician-diagnosed asthma in children (9–16 years) who participated in ice hockey or figure skating was 15%. Of note, there was no difference in asthma prevalence between those that practiced in rinks with electric- or propane-powered resurfacing machines. However, children exposed to high levels of NO<sub>2</sub> were more likely to have wheezing and nasal symptoms.<sup>116</sup>

In cold-weather athletes, there are 2 additional potential sources of inhalational toxins. First, there is the widespread use of wood-burning stoves and fireplaces as a heating source. In adults, the use of wood-burning stoves has been associated with chronic bronchitis<sup>117</sup> and interstitial lung disease.<sup>118</sup> In preschool children, it is associated with increased lower respiratory tract symptoms<sup>119–124</sup> and pulmonary function abnormalities.<sup>125</sup> Second, ski and snowboard waxing produces fumes containing gaseous organofluorine compounds that cause pulmonary injury.<sup>126–129</sup> Elevated levels of these compounds are found in the blood of individuals chronically exposed to fluorinated ski wax fumes.<sup>130,131</sup> In a recent study, acute, short exposure to ski waxing did not alter pulmonary function<sup>132</sup>; however, the effect of repetitive exposures has not been studied, nor the effect on pulmonary function in children.

### *Chlorine*

Chlorine is the most common disinfectant used in swimming pools; it is associated with respiratory disease, asthma, and rhinitis.<sup>133,134,135</sup> Chlorine hydrolyzes to form hypochlorous acid, hydrogen ions, and chloride. It also reacts with nitrogen-containing compounds from swimmers' waste products (urine, sweat, and skin) to form inorganic chloramines (monochloramine, dichloramine, and trichloramine), which are primarily responsible for the smell and irritating properties of the swimming pool air.<sup>136</sup> These compounds, particularly trichloramine, are volatile and are released into the air. Their concentration depends on the level of water chlorination, density of bathers (and their hygiene), water temperature, ventilation, and air recirculation.<sup>136,137</sup> In outdoor pools, hypochlorous acid is the most likely irritant since the trichloramine would rapidly evaporate.

Acute exposure to high levels of chlorine is associated with oxidative injury and inflammation, epithelial injury, and AHR in both animals<sup>138,139</sup> and humans.<sup>133,140</sup> Acute respiratory distress syndrome and bronchiolitis may occur<sup>140</sup>; mortality after acute respiratory distress syndrome is high; however, the pulmonary effects usually improve over time.<sup>141</sup> In children, after an acute inhalational exposure, the most severe effects were seen in those with chronic respiratory disease and atopy.<sup>133</sup> In another study, lung function returned to normal after 15 days; however, elevations in leukotriene B<sub>4</sub> persisted up to 8 weeks postinjury.<sup>142</sup>

Swimming in chlorinated pools, especially indoor facilities, has been linked to lung epithelial injury and airways inflammation and hyperresponsiveness in elite athletes.<sup>32,40,79,80,84,143</sup> In adolescent swimmers, the prevalence of EIB by cardiopulmonary testing was 36%.<sup>79</sup> In induced sputum, swimmers have elevated levels of neutrophils, epithelial cells, and, also, eosinophils.<sup>32</sup> Eosinophil count has correlated with the severity of symptoms<sup>32</sup>; neutrophil count correlated with the number of training hours per week.<sup>40</sup> Training in an outdoor pool with low chlorine levels was

associated with high neutrophil levels, but normal eosinophil counts in induced sputum.<sup>83</sup> In swimmers who stopped high-level training, AHR, asthma symptoms, and sputum eosinophilia improved.<sup>26</sup>

The effects of chlorine are not confined to elite athletes; they occur in younger exercising children. In school children (ages 10–13 years), swimming in chlorinated pools is associated with the development of airway permeability and asthma in a dose-dependent manner; this effect is modulated by atopy.<sup>134,135,144</sup> Airway permeability, as measured by serum levels of surfactant protein A and surfactant protein B, was increased after 1 hour of exposure to chlorinated pool; it increased with cumulative pool exposure and correlated with immunoglobulin E (IgE) levels.<sup>144</sup> The risk of asthma, as defined by a positive EIB test or physician diagnosis, increased with cumulative pool exposure only in atopic children with serum IgE >100 kIU/L (odds ratio for each 100-hour increase in cumulative pool exposure = 1.79; 95% confidence interval, 1.07–2.72). All these effects were dose related and most strongly linked to pool attendance before 6–7 years of age.<sup>145,146</sup>

The use of outdoor chlorinated pools has also been associated with an increase in asthma prevalence,  $F_{E}NO$ , and sensitization to cat or house dust mite allergens in adolescents.<sup>145</sup> The risk of asthma increased with greater exposure; it was 4-fold higher when the lifetime exposure was over 500 hours. The risk of asthma was increased among atopic adolescents with total serum IgE >25 kIU/L.<sup>145</sup>

Infant swimming produced higher rates of infection in the first 2 years of life, including gastroenteritis, otitis media, and airway infections.<sup>146</sup> It has been associated with asthma,<sup>134,147</sup> atopy,<sup>145,147</sup> and increased airway permeability<sup>134</sup> in later childhood and adolescence. Attendance at indoor or outdoor chlorinated pools before the age of 2 years has been associated with an increased risk of bronchiolitis in those who spent >20 hours in chlorinated pools during infancy; those infants demonstrated higher risks of asthma and respiratory allergies later in childhood.<sup>147</sup>

## Air Quality Control Measures

It is clear that environmental toxins such as chloramine and air pollution, particularly in association with atopy, can contribute to airway inflammation and hyperresponsiveness in elite athletes and in younger children. The key to maintaining pulmonary health in exercising children is the control of environmental triggers and minimization of airborne toxins. In those that have established EIB, measures to avoid precipitating it are important. Exposure to environmental tobacco smoke should be avoided. In the atopic athlete, exposure to allergens should be minimized. For cold air endurance athletes, masks should be worn.<sup>148–150</sup> It may be beneficial to practice later in the day, when temperatures are warmer and to moderate practice in frigid temperatures.

Outdoor exercise should be moderated or avoided on days when the air quality is poor as reflected in an air quality index >50<sup>151</sup>; air quality is best in early morning and evening. In addition, practice near roads with a high volume of traffic, which have the highest level of air pollution, should be avoided.

In indoor rinks, it is important to minimize ambient levels of air pollutions.

Unfortunately, few states have laws that regulate air quality in indoor rinks. Ice rink operators should optimize

ventilation in the rinks and maintain their resurfacing machines. Obviously, resurfacing machines powered by electricity are the safest, but are expensive. Indoor ice rink operators should conduct air sampling for carbon monoxide and  $NO_2$  and take remedial actions if the levels are high.

For indoor chlorinated pools, efforts should be made to decrease the level of chloramines. It is important to optimize ventilation, encourage preswimming showers and good hygiene practices, and use the lowest possible level of chlorination. Chlorine level should be maintained at ~1 mg/L; chloramines should not be more than half of the free chlorine levels and should ideally be <0.2 mg/L.<sup>135</sup> The pH should be checked frequently. Infant swimming is of particular concern. However, until further data are obtained, no overt ban has been imposed. Obviously, if symptoms develop, then exposure should be limited.

If air quality cannot be improved, then a switch to a different ice rink or pool may be necessary. However, if that is not possible, then it may be necessary to limit exposure by decreasing exercise time. In theory, decreasing the intensity of the workout is an alternative, but few competitive athletes realistically have the ability to do so on a long-term basis and still succeed in their sports.

## Treatment

Treatment of the pediatric athlete with exercise-induced respiratory symptoms can be challenging. The first step is to assess whether there is evidence of persistent classical asthma characterized by early onset childhood asthma and atopy. Standardized testing with spirometry should be performed. If it is normal, then a formal challenge test should be performed to confirm EIB.

In the case of the athlete with classical asthma, daily treatment with inhaled corticosteroids is of proven efficacy to improve symptoms, pulmonary function, and attenuate bronchial hyperresponsiveness and EIB in a dose-dependent manner.<sup>75–77,152,153</sup> Pre-exercise short- and long-acting  $\beta_2$ -agonists are very effective at preventing EIB; however, tolerance to the protective effect occurs when they are taken daily.<sup>90,154–158</sup> In addition, chronic use of  $\beta_2$ -agonists appears to increase the severity of EIB.<sup>159,160</sup> Montelukast mildly reduces EIB, but does not induce tolerance; its effect with  $\beta_2$ -agonists is additive.<sup>70,161</sup> Pretreatment with cromolyn sodium (sodium cromoglycate) and nedocromil decrease EIB,<sup>162,163</sup> but they are increasingly difficult to obtain in the United States. In asthmatics, medications may be effective against the bronchoconstriction produced by exercising in high levels of air pollution. For atopic individuals with rhinitis, an antihistamine and topical nasal anti-inflammatory can be beneficial.<sup>164,165</sup> Antihistamines variably protect against EIB; the difference may have related to the intensity of the exercise and severity of asthma.<sup>31,164</sup> Topical nasal anti-inflammatory medications can improve EIB; they may decrease mouth-breathing, which circumvents the ability of the nasopharynx to warm the air, thus placing more stress on the lower airways.<sup>166</sup>

There are few clinical studies on the use of medications to prevent toxin-associated lung injury. In animal models, the injury associated with acute chlorine exposure has been attenuated variably with  $\beta_2$ -agonists,<sup>167</sup> inhaled and systemic corticosteroids,<sup>167</sup> and antioxidants.<sup>137,168,169</sup> No correlate clinical studies has been performed in humans for either

acute or chronic chlorine exposure. In asthmatics exposed to high SO<sub>2</sub> concentrations during exercise, pretreatment with a combination of  $\beta_2$ -agonists and anti-inflammatory medication<sup>170</sup> or montelukast<sup>171</sup> improves EIB and inflammation.

The competitive athlete without preexisting atopic asthma is more challenging to manage. Data are sparse on the efficacy of medications in this population in treating symptoms and attenuating inflammation and remodeling. It is clear that  $\beta_2$ -agonist pretreatment is effective against the bronchoconstriction evoked by exercise and EVH<sup>156</sup>; however, tachyphylaxis will develop with repeated daily use.<sup>90,156,158</sup> Inhaled budesonide for 22 weeks did not improve asthma symptoms, AHR, inflammation, or the remodeling seen in elite cross-country skiers.<sup>81</sup> In another study, pretreatment with a single high dose of inhaled beclomethasone did decrease the response to EVH.<sup>172</sup> In ice hockey players, treatment with montelukast for 4 weeks did not improve symptom scores, lung function, AHR, sputum eosinophil, or neutrophil counts or F<sub>E</sub>NO measurement.<sup>78</sup> However, Rundell et al. showed that pretreatment with a single dose of montelukast attenuated EIB when the exercise was performed in an ice rink with high PM<sub>1</sub>.<sup>173,174</sup> Fish oil supplementation decreased the response to exercise challenge in athletes with mild EIB.<sup>175</sup>

## Conclusion

Exercise has unarguable benefits. Even in children with asthma, exercise improves the quality of life and cardiovascular conditioning<sup>7</sup> and decreases the dyspnea associated with exercise<sup>8,9</sup> and the use of anti-inflammatory medications. However, elite endurance athletes, including older adolescents, who achieve high levels of ventilation may demonstrate evidence of "too much of a good thing"; in this population, chronic hyperventilation of cold, dry air seems to be associated with airway inflammation and remodeling in a dose-dependent manner. Similar effects have not been investigated in younger competitive athletes. It is unlikely that this degree of airway remodeling occurs in most exercising children because they do not attain the high levels of exercise intensity and duration achieved by the elite athletes. On the other hand, because their lungs are immature and are still developing, it is possible that they are more susceptible to epithelial injury. The effect of both chronic and acute exposure to exercise in the presence of cold, dry air needs to be further investigated in younger children.

Exercise in the presence of toxins such as chlorine and air pollutants is clearly associated with lung inflammation, EIB, and respiratory symptoms in both elite athletes and younger children. Atopy appears to modulate this effect; the epithelial injury produced by exercising in the presence of toxins may produce allergic sensitization. In addition, variants in genetic polymorphisms increase the susceptibility of certain individuals to injury associated with exercising in poor air quality. In elite athletes, the pulmonary deterioration and inflammation appears to resolve when they are "off-season" or retire from the sport. However, the data in young children suggest the possibility that the effects may be long-lasting and result in persistent pulmonary function abnormalities, asthma, and atopy.

Further studies are necessary in children to characterize the pathophysiology and natural history of lung inflammation associated with inhalational toxins, particularly in view

of children's requisite lung growth and development. Because of their higher activity levels and ventilation, children are more likely to be exposed than adults. Existing data underscore the need to maintain high indoor and outdoor air quality to minimize the risk of lung injury in children. Treatment of respiratory symptoms and EIB in elite athletes and children exposed to inhalational toxins is unclear; there is insufficient data to guide treatment. Further studies are necessary to determine the efficacy of medications in preventing the epithelial injury, and, in elite athletes, the remodeling.

## Author Disclosure Statement

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## References

1. National Institute of Health. Conference on sports injuries in youth: surveillance strategies, 1991. Bethesda, MD: National Institute of Health, 1992, NIH publication no. 93-3444.
2. Findlay LC, Bowker A. The link between competitive sport participation and self-concept in early adolescence: a consideration of gender and sport orientation. *J Youth Adolesc* 2009; 38:29–40.
3. Ruiz JR, Ortega FB, Castillo R, et al. Physical activity, fitness, weight status, and cognitive performance in adolescents. *J Pediatr* 2010; 157:917–922.e1–e5.
4. Trudeau F, Shephard R. Physical education, school physical activity, school sports and academic performance. *Int J Behav Nutr Phys Activity* 2008; 5:10.
5. Ortega FB, Ruiz JR, Castillo MJ, Sjostrom M. Physical fitness in childhood and adolescence: a powerful marker of health. *Int J Obes* 2007; 32:1–11.
6. Salcedo Aguilar F, Martínez-Vizcaíno V, Sánchez López M, et al. Impact of an after-school physical activity program on obesity in children. *J Pediatr* 2010; 157:36–42.e3.
7. Counil FP, Varray A, Matecki S, et al. Training of aerobic and anaerobic fitness in children with asthma. *J Pediatr* 2003; 142:179–184.
8. Cochrane LM, Clark CJ. Benefits and problems of a physical training programme for asthmatic patients. *Thorax* 1990; 45:345–351.
9. Fanelli A, Cabral AL, Neder JA, Martins MA, Carvalho CR. Exercise training on disease control and quality of life in asthmatic children. *Med Sci Sports Exerc* 2007; 39:1474–1480.
10. Neder JA, Nery LE, Silva AC, Cabral A, Fernandes A. Short term effects of aerobic training in the clinical management of moderate to severe asthma in children. *Thorax* 1999; 54:202–206.
11. Holzer K, Anderson SD, Douglass J. Exercise in elite summer athletes: challenges for diagnosis. *J Allergy Clin Immunol* 2002; 110:374–380.
12. Weiler JM, Layton T, Hunt M. Asthma in United States Olympic athletes who participated in the 1996 Summer Games. *J Allergy Clin Immunol* 1998; 102:722–726.
13. Weiler JM, Metzger WJ, Donnelly AL, Crowley ET, Sharath MD. Prevalence of bronchial hyperresponsiveness in highly trained athletes. *Chest* 1986; 90:23–28.
14. Parsons JP, Kaeding C, Phillips G, Jarjoura D, Wadley G, Mastronarde JG. Prevalence of exercise-induced bronchospasm in a cohort of varsity college athletes. *Med Sci Sports Exerc* 2007; 39:1487–1492.
15. Schoene RB, Giboney K, Schimmel C, et al. Spirometry and airway reactivity in elite track and field athletes. *Clin J Sport Med* 1997; 7:257–261.

16. Feinstein RA, LaRussa J, Wang-Dohman A, Bartolucci AA. Screening adolescent athletes for exercise-induced asthma. *Clin J Sport Med* 1996; 6:119-123.
17. Helenius IJ, Tikkanen HO, Haahtela T. Occurrence of exercise induced bronchospasm in elite runners: dependence on atopy and exposure to cold air and pollen. *Br J Sports Med* 1998; 32:125-129.
18. Wilber RL, Rundell KW, Szmedra L, Jenkinson DM, Im J, Drake SD. Incidence of exercise-induced bronchospasm in Olympic winter sport athletes. *Med Sci Sports Exerc* 2000; 32:732-737.
19. Heir T, Oseid S. Self-reported asthma and exercise-induced asthma symptoms in high-level competitive cross-country skiers. *Scand J Med Sci Sports* 1994; 4:128-133.
20. Helenius IJ, Tikkanen HO, Haahtela T. Exercise-induced bronchospasm at low temperature in elite runners. *Thorax* 1996; 51:628-629.
21. Rundell KW, Spiering BA, Evans TM, Baumann JM. Baseline lung function, exercise-induced bronchoconstriction, and asthma-like symptoms in elite women ice hockey players. *Med Sci Sports Exerc* 2004; 36:405-410.
22. Mannix ET, Manfredi F, Farber MO. A comparison of two challenge tests for identifying exercise-induced bronchospasm in figure skaters. *Chest* 1999; 115:649-653.
23. Mannix ET, Farber MO, Palange P, Galassetti P, Manfredi F. Exercise-induced asthma in figure skaters. *Chest* 1996; 109:312-315.
24. Provost-Craig MA, Arbour KS, Sestili DC, Chabalko JJ, Ekinci E. The incidence of exercise-induced bronchospasm in competitive figure skaters. *J Asthma* 1996; 33:67-71.
25. Helenius I, Lumme A, Haahtela T. Asthma, airway inflammation and treatment in elite athletes. *Sports Med* 2005; 35:565-574.
26. Helenius I, Ryttilä P, Sarna S, et al. Effect of continuing or finishing high-level sports on airway inflammation, bronchial hyperresponsiveness, and asthma: a 5-year prospective follow-up study of 42 highly trained swimmers. *J Allergy Clin Immunol* 2002; 109:962-968.
27. Frischer T, Meinert R, Karmaus W, Urbanek R, Kuehr J. Relationship between atopy and frequent bronchial response to exercise in school children. *Pediatr Pulmonol* 1994; 17:320-325.
28. Koh YI, Choi IS, Lim H. Atopy may be related to exercise-induced bronchospasm in asthma. *Clin Exp Allergy* 2002; 32:532-536.
29. Duong M, Subbarao P, Adelroth E, et al. Sputum eosinophils and the response of exercise-induced bronchoconstriction to corticosteroid in asthma. *Chest* 2008; 133:404-411.
30. Karjalainen EM, Laitinen A, Sue-Chu M, Altraja A, Bjermer L, Laitinen LA. Evidence of airway inflammation and remodeling in ski athletes with and without bronchial hyperresponsiveness to methacholine. *Am J Respir Crit Care Med* 2000; 161:2086-2091.
31. Hallstrand TS, Moody MW, Wurfel MM, Schwartz LB, Henderson WR Jr., Aitken ML. Inflammatory basis of exercise-induced bronchoconstriction. *Am J Respir Crit Care Med* 2005; 172:679-686.
32. Helenius IJ, Ryttilä P, Metso T, Haahtela T, Venge P, Tikkanen HO. Respiratory symptoms, bronchial responsiveness, and cellular characteristics of induced sputum in elite swimmers. *Allergy* 1998; 53:346-352.
33. Otani K, Kanazawa H, Fujiwara H, Hirata K, Fujimoto S, Yoshikawa J. Determinants of the severity of exercise-induced bronchoconstriction in patients with asthma. *J Asthma* 2004; 41:271-278.
34. Kanazawa H, Asai K, Hirata K, Yoshikawa J. Vascular involvement in exercise-induced airway narrowing in patients with bronchial asthma. *Chest* 2002; 122:166-170.
35. Pliss LB, Ingenito EP, Ingram RH Jr., Pichurko B. Assessment of bronchoalveolar cell and mediator response to isocapnic hyperpnea in asthma. *Am Rev Respir Dis* 1990; 142:73-78.
36. Sandra DA, Pascale K. Airway injury as a mechanism for exercise-induced bronchoconstriction in elite athletes. *J Allergy Clin Immunol* 2008; 122:225-235.
37. Wan H, Winton HL, Soeller C, et al. The transmembrane protein occludin of epithelial tight junctions is a functional target for serine peptidases from faecal pellets of *Dermatophagoides pteronyssinus*. *Clin Exp Allergy* 2001; 31:279-294.
38. Bernard A. Chlorination products: emerging links with allergic diseases. *Curr Med Chem* 2007; 14:1771-1782.
39. Li N, Hao M, Phalen RF, Hinds WC, Nel AE. Particulate air pollutants and asthma. A paradigm for the role of oxidative stress in PM-induced adverse health effects. *Clin Immunol* 2003; 109:250-265.
40. Bougault V, Turmel J, St. Laurent J, Bertrand M, Boulet LP. Asthma, airway inflammation and epithelial damage in swimmers and cold-air athletes. *Eur Respir J* 2009; 33:740-746.
41. McConnell R, Berhane K, Gilliland F, et al. Asthma in exercising children exposed to ozone: a cohort study. *Lancet* 2002; 359:386-391.
42. Anderson SD, Silverman M, Walker SR. Metabolic and ventilatory changes in asthmatic patients during and after exercise. *Thorax* 1972; 27:718-725.
43. Anderson SD, McEvoy JD, Bianco S. Changes in lung volumes and airway resistance after exercise in asthmatic subjects. *Am Rev Respir Dis* 1972; 106:30-37.
44. Godfrey S, Anderson SD, Silverman M. Physiologic aspects of exercise-induced asthma. *Chest* 1973; 63:Suppl:36S-7S.
45. McFadden ER Jr., Nelson JA, Skowronski ME, Lenner KA. Thermally induced asthma and airway drying. *Am J Respir Crit Care Med* 1999; 160:221-226.
46. Busquets RM, Anto JM, Sunyer J, Sancho N, Vall O. Prevalence of asthma-related symptoms and bronchial responsiveness to exercise in children aged 13-14 yrs in Barcelona, Spain. *Eur Respir J* 1996; 9:2094-2098.
47. Seear M, Wensley D, West N. How accurate is the diagnosis of exercise induced asthma among Vancouver schoolchildren? *Arch Dis Child* 2005; 90:898-902.
48. Cabral AL, Conceicao GM, Fonseca-Guedes CH, Martins MA. Exercise-induced bronchospasm in children: effects of asthma severity. *Am J Respir Crit Care Med* 1999; 159:1819-1823.
49. Jones RS, Buston MH, Wharton MJ. The effect of exercise on ventilatory function in the child with asthma. *Br J Dis Chest* 1962; 56:78-86.
50. Kattan M, Keens TG, Mellis CM, Levison H. The response to exercise in normal and asthmatic children. *J Pediatr* 1978; 92:718-721.
51. Kukafka DS, Lang DM, Porter S, et al. Exercise-induced bronchospasm in high school athletes via a free running test: incidence and epidemiology. *Chest* 1998; 114:1613-1622.
52. Macucci F, Guerrini L, Strambi M. Asthma and allergy in young athletes in Siena Province. Preliminary results. *J Sports Med Phys Fitness* 2007; 47:351-355.
53. Sidiropoulou M, Tsimaras V, Fotiadou E, Aggelopoulou-Sakadami N. [Exercised-induced asthma in soccer players ages from 8 to 13 years]. *Pneumologie* 2005; 59:238-243.
54. Mannix ET, Roberts MA, Dukes HJ, Magnes CJ, Farber MO. Airways hyperresponsiveness in high school athletes. *J Asthma* 2005; 41:567-574.
55. Rundell KW, Jenkinson DM. Exercise-induced bronchospasm in the elite athlete. *Sports Med* 2002; 32:583-600.
56. Rundell KW, Im J, Mayers LB, Wilber RL, Szmedra L, Schmitz HR. Self-reported symptoms and exercise-induced asthma in the elite athlete. *Med Sci Sports Exerc* 2001; 33:208-213.
57. De Baets F, Bodart E, Dramaix-Wilmet M, et al. Exercise-induced respiratory symptoms are poor predictors of bronchoconstriction. *Pediatr Pulmonol* 2005; 39:301-305.
58. Weinberger M. Exercise induced dyspnoea: if not asthma, then what? *Arch Dis Child* 2006; 91:543-544.
59. Joyner BL, Fiorino EK, Matta-Arroyo E, Needleman JP. Cardiopulmonary exercise testing in children and adolescents with asthma who report symptoms of exercise-induced bronchoconstriction. *J Asthma* 2006; 43:675-678.

60. Millward D, Paul S, Brown M, et al. The diagnosis of asthma and exercise-induced bronchospasm in division I athletes. *Clin J Sport Med* 2009; 19:482–486.
61. Crapo RO, Casaburi R, Coates AL, et al. Guidelines for methacholine and exercise challenge testing-1999. This official statement of the American Thoracic Society was adopted by the ATS Board of Directors, July 1999. *Am J Respir Crit Care Med* 2000; 161:309–329.
62. Anderson SD, Argyros GJ, Magnussen H, Holzer K. Provocation by eucapnic voluntary hyperpnoea to identify exercise induced bronchoconstriction. *Br J Sports Med* 2001; 35: 344–347.
63. Fitch KD, Sue-Chu M, Anderson SD, et al. Asthma and the elite athlete: summary of the International Olympic Committee's consensus conference, Lausanne, Switzerland, January 22–24, 2008. *J Allergy Clin Immunol* 2008; 122:254–260, 260e1–e7.
64. Brannan JD, Anderson SD, Perry CP, Freed-Martens R, Lassig AR, Charlton B. The safety and efficacy of inhaled dry powder mannitol as a bronchial provocation test for airway hyperresponsiveness: a phase 3 comparison study with hypertonic (4.5%) saline. *Respir Res* 2005; 6:144.
65. McFadden ER Jr., Gilbert IA. Exercise-induced asthma. *N Engl J Med* 1994; 330:1362–1367.
66. Anderson SD, Daviskas E. The mechanism of exercise-induced asthma is. *J Allergy Clin Immunol* 2000; 106:453–459.
67. Moloney ED, Griffin S, Burke CM, Poulter LW, O'Sullivan S. Release of inflammatory mediators from eosinophils following a hyperosmolar stimulus. *Respir Med* 2003; 97:928–932.
68. McFadden ER Jr. Hypothesis: exercise-induced asthma as a vascular phenomenon. *Lancet* 1990; 335:880–883.
69. Kikawa Y, Miyamoto T, Inoue Y, et al. Urinary leukotriene E4 after exercise challenge in children with asthma. *J Allergy Clin Immunol* 1992; 89:1111–1119.
70. Reiss TF, Hill JB, Harman E, et al. Increased urinary excretion of LTE4 after exercise and attenuation of exercise-induced bronchospasm by montelukast, a cysteinyl leukotriene receptor antagonist. *Thorax* 1997; 52:1030–1035.
71. Bonsignore MR, La Grutta S, Cibella F, et al. Effects of exercise training and montelukast in children with mild asthma. *Med Sci Sports Exerc* 2008; 40:405–412.
72. Menzies D, Nair A, Lipworth BJ. Non-invasive measurement of airway inflammation in asthma. *J Asthma* 2006; 43:407–415.
73. Nishio K, Odajima H, Motomura C, Nakao F, Nishima S. Exhaled nitric oxide and exercise-induced bronchospasm assessed by FEV1, FEF25–75% in childhood asthma. *J Asthma* 2007; 44:475–478.
74. Buchvald F, Hermansen MN, Nielsen KG, Bisgaard H. Exhaled nitric oxide predicts exercise-induced bronchoconstriction in asthmatic school children. *Chest* 2005; 128:1964–1967.
75. Subbarao P, Duong M, Adelroth E, et al. Effect of ciclesonide dose and duration of therapy on exercise-induced bronchoconstriction in patients with asthma. *J Allergy Clin Immunol* 2006; 117:1008–1013.
76. Jonasson G, Carlsen KH, Hultquist C. Low-dose budesonide improves exercise-induced bronchospasm in schoolchildren. *Pediatr Allergy Immunol* 2000; 11:120–125.
77. Hofstra WB, Neijens HJ, Duiverman EJ, et al. Dose-responses over time to inhaled fluticasone propionate treatment of exercise- and methacholine-induced bronchoconstriction in children with asthma. *Pediatr Pulmonol* 2000; 29:415–423.
78. Helenius I, Lumme A, Ounap J, et al. No effect of montelukast on asthma-like symptoms in elite ice hockey players. *Allergy* 2004; 59:39–44.
79. Clearie KL, Vaidyanathan S, Williamson PA, et al. Effects of chlorine and exercise on the unified airway in adolescent elite Scottish swimmers. *Allergy* 2010; 65:269–273.
80. Clearie KL, Williamson PA, Vaidyanathan S, et al. Disconnect between standardized field-based testing and mannitol challenge in Scottish elite swimmers. *Clin Exp Allergy* 2010; 40:731–737.
81. Sue-Chu M, Karjalainen EM, Laitinen A, Larsson L, Laitinen LA, Björmer L. Placebo-controlled study of inhaled budesonide on indices of airway inflammation in bronchoalveolar lavage fluid and bronchial biopsies in cross-country skiers. *Respiration* 2000; 67:417–425.
82. Bonsignore MR, Morici G, Riccobono L, et al. Airway inflammation in nonasthmatic amateur runners. *Am J Physiol Lung Cell Mol Physiol* 2001; 281:L668–L676.
83. Morici G, Riccobono L, Insalaco G. Markers of airway inflammation in non-asthmatic swimmers at rest and after exercise. *Eur Respir J* 2001; 18:491s.
84. Boulet LP, Turcotte H, Langdeau JB, Bernier MC. Lower airway inflammatory responses to high-intensity training in athletes. *Clin Invest Med* 2005; 28:15–22.
85. Sue-Chu M, Larsson L, Moen T, Rennard SI, Björmer L. Bronchoscopy and bronchoalveolar lavage findings in cross-country skiers with and without “ski asthma”. *Eur Respir J* 1999; 13:626–632.
86. Morici G, Bonsignore MR, Zangla D, et al. Airway cell composition at rest and after an all-out test in competitive rowers. *Med Sci Sports Exerc* 2004; 36:1723–1729.
87. Sue-Chu M, Henriksen AH, Björmer L. Non-invasive evaluation of lower airway inflammation in hyper-responsive elite cross-country skiers and asthmatics. *Respir Med* 1999; 93:719–725.
88. Davis MS, Freed AN. Repeated hyperventilation causes peripheral airways inflammation, hyperreactivity, and impaired bronchodilation in dogs. *Am J Respir Crit Care Med* 2001; 164:785–789.
89. Helenius IJ, Tikkanen HO, Haahtela T. Exercise-induced bronchospasm at low temperature in elite runners. *Thorax* 1996; 51:628–629.
90. Nelson JA, Strauss L, Skowronski M, Ciuffo R, Novak R, McFadden ER Jr. Effect of long-term salmeterol treatment on exercise-induced asthma. *N Engl J Med* 1998; 339:141–146.
91. Gilbert IA, McFadden ER. Airway cooling and rewarming—the 2nd reaction sequence in exercise-induced asthma. *J Clin Invest* 1992; 90:699–704.
92. Larsson K, Tornling G, Gavhed D, Muller-Suur C, Palmberg L. Inhalation of cold air increases the number of inflammatory cells in the lungs in healthy subjects. *Eur Respir J* 1998; 12:825–830.
93. Helenius IJ, Tikkanen HO, Haahtela T. Association between type of training and risk of asthma in elite athletes. *Thorax* 1997; 52:157–160.
94. Chimenti L, Morici G, Paterno A, et al. Bronchial epithelial damage after a half-marathon in nonasthmatic amateur runners. *Am J Physiol Lung Cell Mol Physiol* 2010; 298:L857–L862.
95. Verges S, Flore P, Blanche MP, Wuyam B. A 10-year follow-up study of pulmonary function in symptomatic elite cross-country skiers—athletes and bronchial dysfunctions. *Scand J Med Sci Sports* 2004; 14:381–387.
96. Sue-Chu M, Karjalainen EM, Altraja A, et al. Lymphoid aggregates in endobronchial biopsies from young elite cross-country skiers. *Am J Respir Crit Care Med* 1998; 158:597–601.
97. Valavanidis A, Fiotakis K, Vlachogianni T. Airborne particulate matter and human health: toxicological assessment and importance of size and composition of particles for oxidative damage and carcinogenic mechanisms. *J Environ Sci Health C Environ Carcinog Ecotoxicol Rev* 2008; 26:339–362.
98. Daigle CC, Chalupa DC, Gibb FR, et al. Ultrafine particle deposition in humans during rest and exercise. *Inhal Toxicol* 2003; 15:539–552.
99. Spiering BA, Wilson MH, Judelson DA, Rundell KW. Evaluation of cardiovascular demands of game play and practice in women's ice hockey. *J Strength Cond Res* 2003; 17:329–333.
100. Jerrett M, Shankardass K, Berhane K, et al. Traffic-related air pollution and asthma onset in children: a prospective cohort study with individual exposure measurement. *Environ Health Perspect* 2008; 116:1433–1438.

101. Ho WC, Hartley WR, Myers L, et al. Air pollution, weather, and associated risk factors related to asthma prevalence and attack rate. *Environ Res* 2007; 104:402–409.
102. McCormack MC, Breyse PN, Matsui EC, et al. In-home particle concentrations and childhood asthma morbidity. *Environ Health Perspect* 2009; 117:294–298.
103. Timonen KL, Pekkanen J, Tiittanen P, Salonen RO. Effects of air pollution on changes in lung function induced by exercise in children with chronic respiratory symptoms. *Occup Environ Med* 2002; 59:129–134.
104. Gauderman WJ, Vora H, McConnell R, et al. Effect of exposure to traffic on lung development from 10 to 18 years of age: a cohort study. *Lancet* 2007; 369:571–577.
105. Penard-Morand C, Charpin D, Raherison C, et al. Long-term exposure to background air pollution related to respiratory and allergic health in schoolchildren. *Clin Exp Allergy* 2005; 35:1279–1287.
106. Gong H Jr., Linn WS, Clark KW, et al. Exposures of healthy and asthmatic volunteers to concentrated ambient ultrafine particles in Los Angeles. *Inhal Toxicol* 2008; 20:533–545.
107. Broeckaert F, Arsalane K, Hermans C, et al. Serum clara cell protein: a sensitive biomarker of increased lung epithelium permeability caused by ambient ozone. *Environ Health Perspect* 2000; 108:533–537.
108. Linn WS, Gong H Jr., Shamoo DA, Anderson KR, Avol EL. Chamber exposures of children to mixed ozone, sulfur dioxide, and sulfuric acid. *Arch Environ Health* 1997; 52:179–187.
109. Salam MT, Islam T, Gauderman WJ, Gilliland FD. Roles of arginase variants, atopy, and ozone in childhood asthma. *J Allergy Clin Immunol* 2009; 123:596–602, e1–e8.
110. Islam T, Berhane K, McConnell R, et al. Glutathione-S-transferase (GST) P1, GSTM1, exercise, ozone and asthma incidence in school children. *Thorax* 2009; 64:197–202.
111. Brauer M, Lee K, Spengler JD, et al. Nitrogen dioxide in indoor ice skating facilities: an international survey. *J Air Waste Manag Assoc* 1997; 47:1095–1102.
112. Levy JI, Lee K, Yanagisawa Y, Hutchinson P, Spengler JD. Determinants of nitrogen dioxide concentrations in indoor ice skating rinks. *Am J Public Health* 1998; 88:1781–1786.
113. Rundell KW. High levels of airborne ultrafine and fine particulate matter in indoor ice arenas. *Inhal Toxicol* 2003; 15: 237–250.
114. Rundell KW. Pulmonary function decay in women ice hockey players: is there a relationship to ice rink air quality? *Inhal Toxicol* 2004; 16:117–123.
115. Leuppi JD, Kuhn M, Comminot C, Reinhart WH. High prevalence of bronchial hyperresponsiveness and asthma in ice hockey players. *Eur Respir J* 1998; 12:13–16.
116. Thunqvist P, Lilja G, Wickman M, Pershagen G. Asthma in children exposed to nitrogen dioxide in ice arenas. *Eur Respir J* 2002; 20:646–650.
117. Pandey MR. Domestic smoke pollution and chronic bronchitis in a rural community of the Hill Region of Nepal. *Thorax* 1984; 39:337–339.
118. Ramage JE Jr., Roggli VL, Bell DY, Piantadosi CA. Interstitial lung disease and domestic wood burning. *Am Rev Respir Dis* 1988; 137:1229–1232.
119. Honicky RE, Osborne JS 3rd, Akpom CA. Symptoms of respiratory illness in young children and the use of wood-burning stoves for indoor heating. *Pediatrics* 1985; 75:587–593.
120. Morris K, Morgenlander M, Coulehan JL, Gahagen S, Arena VC. Wood-burning stoves and lower respiratory tract infection in American Indian children. *Am J Dis Child* 1990; 144:105–108.
121. Belanger K, Beckett W, Triche E, et al. Symptoms of wheeze and persistent cough in the first year of life: associations with indoor allergens, air contaminants, and maternal history of asthma. *Am J Epidemiol* 2003; 158:195–202.
122. Naeher LP, Brauer M, Lipsett M, et al. Woodsmoke health effects: a review. *Inhal Toxicol* 2007; 19:67–106.
123. Honicky RE, Akpom CA, Osborne JS. Infant respiratory illness and indoor air pollution from a woodburning stove. *Pediatrics* 1983; 71:126–128.
124. Honicky RE, Osborne JS 3rd. Respiratory effects of wood heat: clinical observations and epidemiologic assessment. *Environ Health Perspect* 1991; 95:105–109.
125. Koenig JQ, Larson TV, Hanley QS, et al. Pulmonary function changes in children associated with fine particulate matter. *Environ Res* 1993; 63:26–38.
126. Johnston CJ, Finkelstein JN, Mercer P, Corson N, Gelein R, Oberdorster G. Pulmonary effects induced by ultrafine PTFE particles. *Toxicol Appl Pharmacol* 2000; 168:208–215.
127. Strom E, Alexandersen O. [Pulmonary damage caused by ski waxing]. *Tidsskr Nor Laegeforen* 1990; 110:3614–3616.
128. Bracco D, Favre JB. Pulmonary injury after ski wax inhalation exposure. *Ann Emerg Med* 1998; 32:616–619.
129. Sport S, Torgersen L. [Lung damage in connection with ski waxing]. *Tidsskr Nor Laegeforen* 1991; 111:1883–1884.
130. Nilsson H, Karrman A, Westberg H, Rotander A, van Bavel B, Lindstrom G. A time trend study of significantly elevated perfluorocarboxylate levels in humans after using fluorinated ski wax. *Environ Sci Technol* 2010; 44:2150–2155.
131. Nilsson H, Karrman A, Rotander A, van Bavel B, Lindstrom G, Westberg H. Inhalation exposure to fluorotelomer alcohols yield perfluorocarboxylates in human blood? *Environ Sci Technol* 2010; 44:7717–7722.
132. Hoffman MD, Clifford PS, Varkey B. Acute effects of ski waxing on pulmonary function. *Med Sci Sports Exerc* 1997; 29:1379–1382.
133. Agabiti N, Ancona C, Forastiere F, et al. Short term respiratory effects of acute exposure to chlorine due to a swimming pool accident. *Occup Environ Med* 2001; 58:399–404.
134. Bernard A, Carbonnelle S, Dumont X, Nickmilder M. Infant swimming practice, pulmonary epithelium integrity, and the risk of allergic and respiratory diseases later in childhood. *Pediatrics* 2007; 119:1095–1103.
135. Bernard A, Carbonnelle S, de Burbure C, Michel O, Nickmilder M. Chlorinated pool attendance, atopy, and the risk of asthma during childhood. *Environ Health Perspect* 2006; 114:1567–1573.
136. World Health Organization. Guidelines for safe recreational waters, volume 2-swimming pools and similar recreational-water environments. Geneva, Switzerland: World Health Organization, 2006.
137. Drobic F, Freixa A, Casan P, Sanchis J, Guardino X. Assessment of chlorine exposure in swimmers during training. *Med Sci Sports Exerc* 1996; 28:271–274.
138. Yadav AK, Bracher A, Doran SF, et al. Mechanisms and modification of chlorine-induced lung injury in animals. *Proc Am Thorac Soc* 2010; 7:278–283.
139. Tuck SA, Ramos-Barbon D, Campbell H, McGovern T, Karmouty-Quintana H, Martin JG. Time course of airway remodelling after an acute chlorine gas exposure in mice. *Respir Res* 2008; 9:61.
140. Parimon T, Kanne JP, Pierson DJ. Acute inhalation injury with evidence of diffuse bronchiolitis following chlorine gas exposure at a swimming pool. *Respir Care* 2004; 49:291–294.
141. Mohan A, Kumar SN, Rao MH, Bollineni S, Manohar IC. Acute accidental exposure to chlorine gas: clinical presentation, pulmonary functions and outcomes. *Indian J Chest Dis Allied Sci* 2010; 52:149–152.
142. Bonetto G, Corradi M, Carraro S, et al. Longitudinal monitoring of lung injury in children after acute chlorine exposure in a swimming pool. *Am J Respir Crit Care Med* 2006; 174: 545–549.
143. Carbonnelle S, Francaux M, Doyle I, et al. Changes in serum pneumoproteins caused by short-term exposures to nitrogen trichloride in indoor chlorinated swimming pools. *Biomarkers* 2002; 7:464–478.

144. Bernard A, Carbone S, Michel O, et al. Lung hyperpermeability and asthma prevalence in schoolchildren: unexpected associations with the attendance at indoor chlorinated swimming pools. *Occup Environ Med* 2003; 60:385–394.
145. Bernard A, Nickmilder M, Voisin C. Outdoor swimming pools and the risks of asthma and allergies during adolescence. *Eur Respir J* 2008; 32:979–988.
146. Schoefer Y, Zutavern A, Brockow I, et al. Health risks of early swimming pool attendance. *Int J Hyg Environ Health* 2008; 211:367–373.
147. Voisin C, Sardella A, Marcucci F, Bernard A. Infant swimming in chlorinated pools and the risks of bronchiolitis, asthma and allergy. *Eur Respir J* 2010; 36:41–47.
148. Beuther DA, Martin RJ. Efficacy of a heat exchanger mask in cold exercise-induced asthma. *Chest* 2006; 129:1188–1193.
149. Millqvist E, Bake B, Bengtsson U, Lowhagen O. Prevention of asthma induced by cold air by cellulose-fabric face mask. *Allergy* 1995; 50:221–224.
150. Nisar M, Spence DP, West D, et al. A mask to modify inspired air temperature and humidity and its effect on exercise induced asthma. *Thorax* 1992; 47:446–450.
151. Campbell M, Li Q, Gingrich S, Howard D, Macfarlane R, Cheng S. Air pollution and physical activity: examination of Toronto air data to guide public advice on smog and exercise. Toronto, Canada, 2003.
152. Pennings HJ, Wouters EF. Effect of inhaled beclomethasone dipropionate on isocapnic hyperventilation with cold air in asthmatics, measured with forced oscillation technique. *Eur Respir J* 1997; 10:665–671.
153. Pedersen S, Hansen OR. Budesonide treatment of moderate and severe asthma in children: a dose-response study. *J Allergy Clin Immunol* 1995; 95:29–33.
154. Edelman JM, Turpin JA, Bronsky EA, et al. Oral montelukast compared with inhaled salmeterol to prevent exercise-induced bronchoconstriction: a randomized, double-blind trial. *Ann Intern Med* 2000; 132:97–104.
155. Storms W, Chervinsky P, Ghannam AF, Bird S, Hustad CM, Edelman JM. A comparison of the effects of oral montelukast and inhaled salmeterol on response to rescue bronchodilation after challenge. *Respir Med* 2004; 98:1051–1062.
156. Anderson SD, Caillaud C, Brannan JD. Beta2-agonists and exercise-induced asthma. *Clin Rev Allergy Immunol* 2006; 31:163–180.
157. Ramage L, Lipworth BJ, Ingram CG, Cree IA, Dhillon DP. Reduced protection against exercise induced bronchoconstriction after chronic dosing with salmeterol. *Respir Med* 1994; 88:363–368.
158. Salpeter SR, Ormiston TM, Salpeter EE. Meta-analysis: respiratory tolerance to regular beta2-agonist use in patients with asthma. *Ann Intern Med* 2004; 140:802–813.
159. Inman MD, O'Byrne PM. The effect of regular inhaled albuterol on exercise-induced bronchoconstriction. *Am J Respir Crit Care Med* 1996; 153:65–69.
160. Hancox RJ, Subbarao P, Kamada D, Watson RM, Hargreave FE, Inman MD. Beta2-agonist tolerance and exercise-induced bronchospasm. *Am J Respir Crit Care Med* 2002; 165:1068–1070.
161. Coreno A, Skowronski M, West E, El-Ekiaby A, McFadden ER Jr. Bronchoprotective effects of single doses of salmeterol combined with montelukast in thermally induced bronchospasm. *Chest* 2005; 127:1572–1578.
162. Woolley M, Anderson SD, Quigley BM. Duration of protective effect of terbutaline sulfate and cromolyn sodium alone and in combination on exercise-induced asthma. *Chest* 1990; 97:39–45.
163. de Benedictis FM, Tuteri G, Pazzelli P, Bertotto A, Bruni L, Vaccaro R. Cromolyn versus nedocromil: duration of action in exercise-induced asthma in children. *J Allergy Clin Immunol* 1995; 96:510–514.
164. Baki A, Orhan F. The effect of loratadine in exercise-induced asthma. *Arch Dis Child* 2002; 86:38–39.
165. Henriksen JM, Wenzel A. Effect of an intranasally administered corticosteroid (budesonide) on nasal obstruction, mouth breathing, and asthma. *Am Rev Respir Dis* 1984; 130:1014–1018.
166. Mangla PK, Menon MP. Effect of nasal and oral breathing on exercise-induced asthma. *Clin Allergy* 1981; 11:433–439.
167. Wang J, Zhang L, Walther SM. Administration of aerosolized terbutaline and budesonide reduces chlorine gas-induced acute lung injury. *J Trauma* 2004; 56:850–862.
168. Zarogiannis SG, Jurkuvenaitis A, Fernandez S, et al. Ascorbate and deferoxamine administration post chlorine exposure decrease mortality and lung injury in mice. *Am J Respir Cell Mol Biol* 2010 Dec 3. [Epub ahead of print]; DOI: 10.1165/rcmb.2010-0432OC.
169. Leustik M, Doran S, Bracher A, et al. Mitigation of chlorine-induced lung injury by low-molecular-weight antioxidants. *Am J Physiol Lung Cell Mol Physiol* 2008; 295:L733–L743.
170. Linn WS, Shamoo DA, Peng RC, Clark KW, Avol EL, Hackney JD. Responses to sulfur dioxide and exercise by medication-dependent asthmatics: effect of varying medication levels. *Arch Environ Health* 1990; 45:24–30.
171. Gong H Jr., Linn WS, Terrell SL, Anderson KR, Clark KW. Anti-inflammatory and lung function effects of montelukast in asthmatic volunteers exposed to sulfur dioxide. *Chest* 2001; 119:402–408.
172. Kippelen P, Larsson J, Anderson SD, et al. Acute effects of beclomethasone on hyperpnea-induced bronchoconstriction. *Med Sci Sports Exerc* 2010; 42:273–280.
173. Rundell KW, Spiering BA, Baumann JM, Evans TM. Effects of montelukast on airway narrowing from eucapnic voluntary hyperventilation and cold air exercise. *Br J Sports Med* 2005; 39:232–236.
174. Rundell KW, Spiering BA, Baumann JM, Evans TM. Bronchoconstriction provoked by exercise in a high-particulate-matter environment is attenuated by montelukast. *Inhal Toxicol* 2005; 17:99–105.
175. Mickleborough TD, Murray RL, Ionescu AA, Lindley MR. Fish oil supplementation reduces severity of exercise-induced bronchoconstriction in elite athletes. *Am J Respir Crit Care Med* 2003; 168:1181–1189.

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