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Review

Risk and Protective Factors for the Development of Childhood Asthma

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EDUCATIONAL AIMS

1. Asthma, as a complex disease, has a broad spectrum of potential determinants ranging from genetics to environmental and lifestyle-related factors.
2. Despite evidence indicating that many factors are probably associated with the onset of childhood asthma, the relationships are not considered causal.
3. Only environmental tobacco smoke has been associated with an increased risk for the development of childhood asthma.

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SUMMARY

Childhood asthma prevalence worldwide has been increasing markedly over several decades. Various theories have been proposed to account for this alarming trend. The disease has a broad spectrum of potential determinants ranging from genetics to lifestyle and environmental factors. Epidemiological observations have demonstrated that several important lifestyle and environmental factors including obesity, urban living, dietary patterns such as food low in antioxidants and fast food, non-breastfeeding, gut flora imbalance, cigarette smoking, air pollution, and viral infection are associated with asthma exacerbations in children. However, only environmental tobacco smoke has been associated with the development of asthma. Despite epidemiological studies indicating that many other factors are probably associated with the development of asthma, the relationships are not considered causal due to the inadequate evidence and inconsistent results from recent studies. This may highlight that sufficient data and exact mechanisms of causality are still in need of further study.

INTRODUCTION

Over recent decades, the prevalence of childhood asthma has been dramatically increasing globally, but the etiology of the disease is still not well understood. Asthma incidence among U.S. children increased from 3.6% in 1980 to 5.8% in 2003, and it is the third highest cause of hospitalization, exceeded only by pneumonia and injuries [1]. Increases in the prevalence of asthma with similar or even greater magnitude were also reported from many other developed countries such as the U.K., Germany, Canada, and Australia [1]. Although asthma is generally less common in developing countries than in developed countries, the prevalence is increasing as they become more westernized or communities become urbanized. Such a transition is currently taking place in China at a much higher speed and during a shorter period than in many other countries [2]. The second nationwide survey in 2000 revealed that the prevalence of asthma among Chinese children 0–14 years old was 1.97%, nearly 2 times of that in 1990 (1.00%), suggesting an increasing trend [3]. Asthma, as a complex disease, has a broad spectrum of potential determinants ranging from genetics to environmental and lifestyle factors. However, this rapidly increasing incidence worldwide cannot be explained by genetic causes alone, as genetic changes require many generations for population-wide effects to occur. Evidence

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has shown that environmental and lifestyle factors are likely to be key events in explaining the overall increasing trend toward asthma prevalence [4]. In this report, we aimed to provide the data relating several important lifestyle and environmental factors, and to discuss their possible association with the development of childhood asthma.

Lifestyle Factors

Overweight/obesity

Recently, the prevalence of both asthma and obesity in children have increased substantially in many countries. The parallel rise in prevalence of both disorders and the coexistence of both asthma and obesity has led interest in the association between the two epidemics [5]. A number of epidemiological studies in children have examined the relationship of obesity or overweight with asthma, and many studies support a positive association between body mass index (BMI) and asthma. Chinn performed a comprehensive review and found that obesity increases the risk of subsequent asthma, although no evidence supports the hypothesis that asthma leads to increased obesity [6]. Flaherman and Rutherford conducted a meta-analysis and found that high birth weight had a pooled relative risk of 1.2 for the subsequent development of asthma, and further calculated a population attributable risk of 0.066 [7].

It should be noted that children and adolescents or boys and girls were considered together in many previous studies which did not divide children on age or gender. One problem exists here that does not exist in the adult studies, which is in the definition of weight for height in children and, more particularly, in the cut-off points used to define overweight and obesity [8]. In children, adult BMI cut-off points are not an accurate measure of body fatness because BMI changes with age, requiring age-specific cut-off points [5]. Unfortunately, until now there has been no standardized definition of overweight and obesity in children to correspond with the adult cut-off points. The other problem is that sex may be an important confounding factor in the study of obesity and asthma. However, the data is conflicting as to whether the association of BMI with asthma is affected by gender. A prospective study revealed that among overweight children, the risk of new-onset asthma was evident among boys but not in girls [9]. In contrast, another birth cohort study showed that, girls, but not boys, who became overweight were seven times more likely to develop asthma [10].

Urban/rural area

Many epidemiological studies in the past decade have consistently documented that children living in rural areas seem to be at lower risk of asthma than their urban counterparts; moreover, children living in a rural areas are at decreased risk of developing asthma [11]. For example, rural Chinese children had significantly lower prevalence of asthma and atopic sensitization than urban children, using the validated ISAAC (International Study of Asthma and Allergies in Childhood) questionnaire and objective skin-prick tests [12]. Another large study in the U.S. pediatric Medicaid population found that the rural children had increased asthma prevalence and similar asthma morbidity compared with urban children [13]. These results support the hygiene theory, early exposure to infection for children may confer an advantage by regulating the immune system to protect against allergies so as to reduce the future risk of asthma.

Although the underlying mechanisms behind this apparent protective effect of rural/farm living are not well understood, the overall consensus is that environmental factors and socioeconomic issues predispose people to asthma. It appears that places that share similar environmental and socioeconomic risk factors may have comparable prevalence of asthma regardless of whether it is in a rural or urban location [11]. These factors may partly explain why there were no differences in asthma prevalence in rural and urban areas from several studies [14,15]. However, not all farming environments are associated with protection against allergies. The multicenter PARSIFAL study revealed that exposure to sheep farming was associated with increased risk of allergies, but the explanation for this association remained to be explored [16].

Diet (antioxidants)

The antioxidant hypothesis was first proposed in 1994 by Seaton et al., who suggested that alteration in diet associated with westernization may be responsible for the increase in asthma prevalence [17]. Observations showed that consumption of foods rich in antioxidants had decreased in the UK diet while asthma prevalence concurrently rose. The transition from a traditional diet to a modern diet appeared to have resulted in a decrease in antioxidant intake [17]. Subsequently, many observational studies have focused on vitamin C, vitamin E, carotenoids, flavonoids, and minerals such as selenium and zinc, and typically these have reported low antioxidant intake to be associated with an increased incidence of childhood asthma [18,19]. However, not all studies on the role of antioxidants have been positive. A meta-analysis concluded that dietary intake of antioxidant vitamins C and E and β–carotene does not significantly influence the risk of asthma [20]. In addition, the potential role of antioxidants as supplements has been explored, but a number of studies have been inconclusive. A Cochrane review of vitamin C supplementation in asthma showed that there is insufficient evidence to recommend vitamin C supplementation in the treatment of asthma [21]. It should be noted that overall the body of observational evidence is inherently weak because of the biases and limitations of cross-sectional and case-control studies that predominate. These limitations include the difficulties in quantifying dietary intake, reverse causation, and lack a temporal element. Unfortunately, longitudinal data are very limited for antioxidants highlighted in studies of asthma. There is an urgent need for longitudinal studies to fill the gaps of information on the association of antioxidants with asthma.

Diet (lipids)

Black and Sharpe in 1997 proposed that the rise of asthma prevalence may stem from increased consumption of polyunsaturated fatty acids (PUFAs) and decreased consumption of saturated fat [22]. The ω-6 PUFAs may particularly have a role in regulating immune response and inflammation. These PUFAs are found largely as linoleic acid in foods such as margarine and vegetable oils, which have increased in consumption with westernization [23]. Linoleic acid is a precursor of prostaglandin E_2 that inhibits interferon-γ and promotes an inflammatory environment which favors the development of asthma. Meanwhile, ω-3 PUFAs from oily fish may have an anti-inflammatory role [23]. Therefore, atopic sensitization and inflammation could be promoted by increasing dietary intake of ω-6 PUFAs and decreasing intake of ω-3 PUFAs.

A small number of epidemiological studies have examined the lipid hypothesis, but they reported inconsistent results. For example, in children aged 12 to 15 years, atopic disease and atopic sensitization were associated with reduced ω-3 PUFA and an increase in ω-6/ω-3 PUFA ratio. In addition, serum IgE levels were positively associated with ω-6 PUFAs and negatively associated with serum eicosapentaenoic acids (EPAs) [24]. In contrast, Griese et al reported that plasma and mononuclear cell phospholipid EPA levels were positively associated with atopic asthma and serum IgE in children [25]. Although there is increasing interest in the use of dietary PUFA supplementation to prevent the development of asthma and atopic disease, it is disappointing that intervention studies have not found consistent results nor provided sufficient support for dietary supplementation with PUFAs [26,27].