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Review

Influence of farming exposure on the development of asthma and asthma-like symptoms ☆

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ABSTRACT

Based upon age and type of farming exposures, a wide range of studies demonstrate either protective or deleterious effects of the farming environment on asthma. In this review, we highlight key studies supporting the concept that farming exposure protects children from asthma and atopy based on studies performed largely in European pediatric cohorts. Various types of farming in certain regions appear to have a greater effect on asthma protection, as does the consumption of unpasteurized milk. In the United State, where concentrated animal feeding operations (CAFOs) are more common, asthma is increased in children exposed especially to swine CAFOs; whereas, rates of atopy and allergy are lower in these children. We also review studies evaluating the role of farming exposures both as a child and/or as an adult on asthma seen in adults. The importance of microbes in farming environments and the contribution of various components of the innate immune system including toll-like receptors to the underlying mechanisms of asthma related to farming exposures are also reviewed.

Contents

1. Introduction

Asthma is a chronic inflammatory disease process involving the airways, which is characterized by recurrent airway hyper-responsiveness, bronchospasm, and reversible obstruction. Asthma is a heterogeneous group of conditions of potential genetic pre-disposition with environmental influence [1]. The heterogeneity of asthma results in a disease process that is variable in its severity and phenotype. Whereas asthma has historically been broadly categorized as IgE (allergic)-mediated allergic asthma or non-IgE mediated asthma, studies are now focusing on accurately capturing the multiple clinical phenotypes of this heterogeneous disorder [2]. The phenotypes of importance continue to include not only atopic status, but also factor in disease onset, clinical features, biomarkers such as eosinophilic inflammation and nitric oxide

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generation, genetics, and response to therapies [3–7]. Although it remains unclear how farming exposures affect these new clusters of asthma phenotypes, there have been recent advances into the understanding of how farming exposures might differentially affect various asthmatic phenotypes, which will be highlighted in this review. Based upon age and type of farming exposures, a wide range of studies have demonstrated protective or deleterious effects of the farming environment on asthma conditions. The evidence supporting the theory of farming exposures as variably protective against the development of asthma and in support of the "hygiene hypothesis" is strongest in several European pediatric cohorts. The impact of farming exposures in the development of "non-atopic" asthma remains present in children, but is less well described. In adult-focused studies, farming exposures are important risk factors in occupational and workplace-exacerbated asthma. The aim of this article is to review the recent literature to better appreciate current knowledge of the effects of farming and its influence upon asthma in both children and adults.

2. Farming exposures in children is protective: the evidence

Asthma and atopy have been shown to occur both independently and jointly in patient populations. In specific countries such as the United Kingdom and Australia, the prevalence of asthma and atopic skin reactivity has increased, while in other countries such as Hong Kong, Germany, and Italy there has been an increase in atopy, but not asthma [8]. Further, numerous studies report an inverse correlation for atopy for children who were raised on a farm versus non-farm children, suggesting that farming is protective of atopy [9–11]. Interestingly, asthma and farming exposures do not consistently follow a similar trend, which is likely explained by the multi-factorial clinical phenotypes of asthma and the heterogeneity of farming exposures [10].

In Europe, multiple large studies have investigated the effect of the farming environment with allergic disorders. The Allergy and Endotoxin study (ALEX) conducted from 1999 to 2004 and the Prevention of Allergy Risk factors for Sensitization in children related to Farming and Anthroposophic Lifestyle (PARSIFAL) project conducted from 2001 to 2004 have been important studies demonstrating farming exposures as protective against atopic and asthmatic conditions. We will highlight here the more recent GABRIELA (a multidisciplinary study to identify the genetic and environmental causes of asthma in the European Community) advanced surveys, which were conducted from 2006 to 2010.

2.1. ALEX study

The ALEX study team reported the protective nature of early exposure of children to stables and unpasteurized milk. Those being exposed to multiple factors including stables, farm life and unpasteurized milk had the most protection against development of asthma (OR: 0.14; 95% CI 0.14–0.48) [12]. Early life (prior to age 1 year) or increased frequency of farming exposure conferred greater protection from the development of asthma by age 5 years. For example, those who were exposed to farming environments and unpasteurized milk in their first year of life displayed protection from asthma; however, if children did not receive both of the exposures until after the first year of life, protection from development of asthma by age 5 years was not apparent (aOR 0.88 95% CI 0.42–1.86) [12]. Non-allergic asthma prevalence was 1% in those who frequently visited stables in the first year as compared with 4% in those who did not ($p = 0.034$) [12]. In allergic children, the incidence of non-allergic asthma in those who frequently visited stables in the first year of life was 8% compared with those who did not frequently visit stables, who had an incidence of asthma of 25% ($p = 0.029$) [12].

2.1.1. Strengths and weaknesses of the ALEX study

The ALEX study was retrospectively performed, which introduces potential for recall bias. This issue might have influenced the recall of the amount of time spent as infants (or as young children) in stables on the rural farms. The sample size of the ALEX study was quite large, with initially over 2500 parents completing a questionnaire on asthma and atopy from several European countries. Moreover, parents of nearly 1000 children consented to allowing their children to be tested for IgE antibodies to common local allergens, providing objective data. A potential weakness was that the diagnosis of asthma was elucidated by questionnaire data without complementary pulmonary function testing. However, core questions from the International Study of Asthma and Allergies in Childhood (ISAAC) questionnaire were utilized.

2.2. PARSIFAL study

The PARSIFAL studies sought to further define explanations for the possible protective effect of farming on asthma development. The PARSIFAL gathered its data on children from both rural and suburban areas of Europe, including Austria, Germany, Sweden, Switzerland, and the Netherlands. In this study, IgE levels to specific allergens were measured, and survey responses for atopy and asthma symptoms were expanded in comparison to the ALEX study. Similar to the ALEX study, a significantly lower prevalence of asthma for children exposed to farming environments was found (aOR, 0.49; 95% CI 0.35–0.69), but the protection with farming conferred for atopy was greater (aOR 0.24; 95% CI, 0.18–0.34) [13–15]. Consistent with the ALEX study, the PARSIFAL study found that unpasteurized farm milk consumption in the first year of life or ever in life was also associated with reduced risk for childhood atopic diseases [12–16].

2.2.1. Strengths and weakness of the PARSIFAL study

The PARSIFAL study expanded upon information gained in the ALEX study because the study population included comparisons among rural and farm children to suburban children. Similar to the ALEX study, the PARSIFAL study relied upon questionnaire data for the diagnosis of asthma as opposed to pulmonary function testing. However, the diagnosis of asthma included a previous doctor's diagnosis of asthma and wheezing in addition to the ISAAC questionnaire data. A strength of the PARSIFAL study included collection of allergen-specific IgE levels. A doctor's diagnosis of eczema or rhinoconjunctivitis was also included to help identify history of allergic symptoms for all participants in the study. Like the ALEX study, the PARSIFAL study limited questionnaires to children age 5–13 years. Another strength of the PARSIFAL study is that mattress dust in the German areas of the study was collected to provide exposure data on potential microbial influences (discussed later in this review).

2.3. GABRIELA study

The more recent GABRIELA studies demonstrate similar findings in relation to asthma and allergy as the ALEX and PARSIFAL studies. The GABRIELA study was a large European study, including 8334 school children in Germany, Switzerland, and Austria, and demonstrated decreased prevalence of asthma (aOR 0.76; 95%, CI 0.65–0.89) and atopy (aOR 0.51; 95% CI, 0.46–0.57) in children exposed to farming environments compared to children not exposed to farming environments. The GABRIELA study findings to date have also highlighted other factors which may be important in understanding the correlations with atopy, asthma, and degree of protection [9,11,14,17,18]. The GABRIELA study group has found that the protective nature of farm exposures in Europe is not universal. A subset of Polish farm children within the GABRIELA studies did not appear to gain as much protection against the development of asthma compared to those children who lived on a farm in the Alpine areas [9,17]. While some protection was conferred to those farmers' children in the Alpine regions, protection did not consistently reach significance, and it appeared to be counterbalanced by factors conferring increased risk for asthma, such as fruit cultivation or grain shred use [9,17]. These observations demonstrate