Nutrition and Asthma in Children

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Disclosure

- I have no relevant financial relationships with any commercial products and/or providers of commercial services discussed in this presentation.
- I do not intend to discuss an unapproved or investigative use of a commercial product or device in my presentation.

Nutrition’s Role in Asthma

- Asthma, particularly among children, has grown in prevalence and is a worldwide public health burden.
- Many new pharmaceutical approaches have been developed for treating asthma with success in decreasing hospitalizations and deaths resulting from asthma exacerbations.
- However, asthma has been an elusive target for public health interventions including nutrition and diet.

Asthma Status in USA

- Asthma-related deaths increased in the 90’s but have since leveled off or even decreased.
- Highest prevalence: children 11-17 yrs but the highest rates of asthma-related health care visits: 0-4 yrs olds. Lifetime prevalence 13%.
- Burden of asthma: great-school/work absenteeism and restriction of activity (12.8 million days of missed school days, 2003).
- 159,000 hospitalizations (3% of all admissions) and 750,000 ED visits (2.8% of all Peds visits) in 2004.
- Geographical differences are significant.

Mechanisms of Asthma

- Inflammation
- Clinical symptoms
- Mechanisms of Asthma

Asthma = Reversibility (even partial) with or without treatment
Immunology of Asthma

- Asthma and the allergic diseases of atopy are characterized by inflammatory processes, with T helper (Th) cell responses of the Th2 phenotype being considered crucial for the initiation and maintenance of inflammation.
- Cytokines such as IL-4, IL-5 and IL-13 secreted by Th2 cells are important mediators of inflammation that is characterized by elevated IgE, mast cell degranulation and eosinophilic inflammation.
- Although inflammation plays a central role in asthma, it appears that the airway epithelium contributes to the airway inflammatory response.
- The airway epithelium of individuals with asthma appears to be intrinsically abnormal, with increased susceptibility to injury resulting in a chronic pro-inflammatory milieu.

Variability of Asthma

- Genetic Factors
  - Atopy and Asthma Hyperresponsiveness
  - Defects in Target Organs
  - Bronchial epithelium
  - Presence of specific HLA alleles
  - Polymorphisms of the interleukin-4 receptor (IL-4R)
  - Polymorphisms of the FcεRI-β receptor for immunoglobulin E (IgE).
  - Polymorphisms of the interleukin-4 family of cytokine genes
  - Polymorphisms of CD14
  - Polymorphisms at other loci

- Environmental Factors
  - Atopic triggers
  - Stress/vocal cord dysfunction
  - Chronic lung disease of prematurity
  - Menstrual and pregnancy-related asthma
  - Chronic nasal drainage/sinusitis
  - Obesity
  - Weather change

- “Asthma” Triggers
  - Atopic triggers (IgE-mediated): pollen, mold, dust mite, pet dander, foods
  - Viral infections: RSV, rhinovirus, adenovirus
  - Lower respiratory infections: chlamydia, mycoplasma
  - Environmental: dust, pollution, diesel fuels
  - Exercise
  - Gastroesophageal reflux
  - Stress/vocal cord dysfunction
  - Chronic lung disease of prematurity
  - Menstrual and pregnancy-related asthma
  - Chronic nasal drainage/sinusitis
  - Obesity
  - Weather change

Genetics and Asthma

- It is known that environmental factors affect gene expression and manifestation of disease.
- Early fetal exposures to nutrition and other environmental factors may program organ development and future development of asthma.
- Nutrition and diet may be important to the development of asthma through epigenetic effects.
- With significant changes in diet occurring in industrial nations, dietary factors may play a key role in affecting the complex genetics and developmental pathophysiology of asthma.
Nutrition and Airway Development

- Airway development is nearly complete by birth and in subsequent years airway development is limited to increases in length and diameter.
- Potential exposures that impair fetal and early childhood airway development may have major effects on airway function during childhood into adulthood.
- Lung and airway development is regulated by numerous genetic and epigenetic factors such as lung fluid volume, mechanical strain, and hyperoxia.
- It is likely that other environmental influences such as maternal nutrient status may have the potential to influence lung and airway organogenesis.

Changing Diet and Asthma

- It has been hypothesized that the increase in asthma may, in part, be a consequence of changing diet.
- In industrialized countries, the modern diet differs considerably from that of previous generations, and is now dominated by foods that have been processed, stored and transported great distances.
- The nutrient content of food may also have changed. These changes may have arisen because of changes in food processing (open air vs indoor or green house farming) and location of production.
- The distance traveled for many foods has increased and this increased storage and transportation can affect the nutrient content.

Intrauterine Nutrition and Asthma

- Maternal nutrient status during pregnancy may have the potential to promote neonatal T-helper (Th1) cell responses to allergens leaning toward Th2-cell responses, which increase the risk of developing asthma.
- This may be due, in part, to the intake of n-3 polyunsaturated fatty acids (n-3 PUFAs), eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), which can affect immune function.
- The incorporation of EPA and DHA in cell membranes leads to decreased availability of arachidonic acid, and increased competition for both the cyclooxygenase and lipoygenase enzymes, resulting in decreased synthesis of arachidonic acid-derived eicosanoids.
- Prostaglandin E2 (PGE2) is reduced, which could alter the balance of Th1 and Th2 cytokines, as well as the production of leukotrienes, which play an important role in asthma.

Diet Types and Asthma

- This content of food and the types of diet may have influenced the rise of asthma prevalence.
- Observational studies showed that consumption of foods rich in antioxidants had decreased in the United Kingdom diet while asthma prevalence rose.
- Dietary intake of saturated fats (butter and lard) has decreased and consumption of n-6 polyunsaturated fatty acids (n-6 PUFAs) present in vegetable oils has increased along with a decrease in n-3 PUFAs from sources such as fish.
- Lack of antioxidants and the increase in n-6 PUFAs has promoted the theory of an "inflammatory diet" as a potential cause leading to an increase in inflammatory disorders including asthma.
Maternal Diet-PUFAs

• Several retrospective observational studies have supported the possibility that increasing n-3 PUFAs in pregnancy might prevent atopy and even asthma in offspring. Other studies have been less supportive including a large prospective RTC.
• Recent study in Japan looked at the 533 women who took either olive oil or fish oil during the 3rd trimester of pregnancy. (Started in 1990 to study differences in pregnancy outcomes)
• In the group who took fish oil, asthma occurred at lower rates during the first 15–16 yr of life in children compared to the group who took olive oil (n=528)

Maternal Diet & Nutrients

• Some studies investigating the relationship between maternal diet during pregnancy and asthma in the offspring have found beneficial effects of higher intake of Vit E, Vit D, zinc, selenium and iron, and higher consumption of fish and apples.
• Prevention and incidence of Asthma and Mite Allergy (PIAMA), 4,146 women were enrolled and follow-up of their children took place at 3 mo and yearly from 1 to 8 yrs of age.
• Investigated the associations between maternal consumption of fresh fruit, vegetables, fish, egg, dairy, nuts and nut products (e.g., peanut butter) during pregnancy and childhood symptoms of asthma longitudinally.
• Results showed no consistent associations between the maternal intake of the investigated food groups during pregnancy and childhood asthma symptoms until 8 years of age, except for nut products (was a small beneficial effect of daily fruit consumption on wheeze)

Maternal Diet & Antioxidants

• Role of antioxidants has been mentioned their role in the maternal diet may be more important then PUFAs
• Recent study investigated the association between maternal intake of vegetables, fruit, and selected antioxidants during pregnancy and the risk of wheeze and eczema in Japanese infants at 16-24 months of age using data from the Osaka Maternal and Child Health Study (OMCHS).
• 763 mothers and infants participated and completed three surveys (prenatal till 24 mo postnatal) and showed that maternal consumption of green and yellow vegetables, citrus fruit, and β-carotene during pregnancy affords protection against the development of eczema in the offspring.
• The present study also provides further evidence for the preventive role of maternal Vit E intake during pregnancy in the development of infantile wheeze.

Breastfeeding and Asthma

Five mechanisms have been proposed
1. A breastfed infant is less exposed to foreign dietary antigens
2. Human milk contains factors that promote gastrointestinal mucosa maturation thereby allowing early ‘closure’ of macromolecular absorption
3. Oligosaccharides in human milk may promote the development of bifidus flora by the provision of substrate for lactobacillus bifidus, the ‘healthy’ bacteria, while limiting the growth of potentially pathogenic bacteria.
4. Human milk has functional immunomodulatory and anti-inflammatory factors that decrease macromolecular uptake, may have more effective immune function, and an ability to a targeted response to a potential pathogen.
5. Cytokines and growth factors in human milk may play an important role in modulating the development of asthma.

Children’s Diet & Fatty Acids

• Perhaps changing diet in young children has contributed to increase in asthma
• In Japan, diet has changed dramatically with a decrease from 1958 to 1999 (in adults) in the intake of carbs from 84% to 62% and an increase in intake of fat from 5% to 20%, protein from 11% to 18%, fish from 56 to 71 g/day and meat from 13 to 92 g/day.
• Study of >25,000 school age children in Japan found intake of polyunsaturated fatty acids -n-3 and n-6 polyunsaturated fatty acids and linoleic acid (18:2 n-6) was independently associated with an increased prevalence of wheeze
• Not clear as to the ratio of PUFAs or possible other areas of concern in a population with a high fish intake. However, this study could not establish a clear cause and effect of dietary fatty acid intake
Children & Maternal - Mediterranean Diet

- Several recent studies conducted in Mediterranean countries (Spain, Greece) and one conducted in Mexico evaluated the association between childhood Mediterranean diet and asthma outcomes in children.
- All of the studies reported beneficial associations between a high level of adherence to the Mediterranean diet during childhood and symptoms of asthma or allergic rhinitis.
- Two studies focused on prenatal Mediterranean diet: one showed benefit and the other did not.

Mediterranean Diet-Review

- The traditional Mediterranean diet refers to a dietary pattern in the Mediterranean olive grove areas.
- The diet is characterized by increased intake of plant foods such as fruits and vegetables, bread and cereals (whole grain), legumes and nuts. Has low to moderate amounts of dairy products and eggs, and only little red meat.
- The results of these studies, indicate a protective effect of maternal and children’s adherence to the Mediterranean diet on asthma and allergic disorders.
- This may reflect a high exposure to several antioxidant compounds and n-3 PUFAs and their effect on the oxidative stress damage and the inflammation of lung tissues.
- The timing of such dietary exposure is becoming a key aspect in the study of diseases involving systems with a long developmental length such as those affecting the immunological and respiratory systems.

Vitamin D and Asthma

- Where does this “hot topic” fit in?
  - In 1999 it was hypothesised that the increase in asthma and allergy is a consequence of widespread rickets prophylaxis with vitamin D supplements in Westernized countries since vitamin D may promote Th-cell differentiation towards the Th2 phenotype.
  - However more recently, increasing vitamin D insufficiency in industrial countries has been noted and perhaps the increase in asthma is a consequence of widespread vitamin D insufficiency.
  - The effects of vitamin D on promoting regulatory Tcell populations suggests that vitamin D insufficiency promotes the development of asthma and allergy by reducing the inhibitory effect of regulatory Tcells on Th2 immune differentiation.

Vitamin D-Not Clear

- Observational studies have reported conflicting results. Two birth cohort studies have reported potentially beneficial associations between maternal dietary vitamin D intake during pregnancy and childhood wheeze.
  - One study showed vitamin D intake during pregnancy was found to be associated with an increased risk of recurrent wheeze at age 3 years.
  - In a large northern Finnish study (04') regular high dose (>50 mg/d) vitamin D supplementation during infancy has been associated with an increased likelihood of allergic outcomes at 31 yrs of age but this was not consistent after adjustment adherence to supplementation were made.
  - A UK birth cohort (08') has reported that elevated maternal blood 25-hydroxyvitamin D in the third trimester is associated with an increased likelihood of childhood asthma at 9 yrs.

Vitamin D

- Recent Study looked at disease variables in children with asthma and low vitamin D levels.
  - Found that corticosteroid use and worsening airflow limitation were associated with lower vitamin D serum levels.
  - Also noted that vitamin D enhances glucocorticoid action in peripheral mononuclear blood cells from asthmatic patients and enhanced immunosuppressive function of dexamethasone.
  - Vitamin D supplementation might potentiate the anti-inflammatory function of steroids and improve control.
  - Needless to say, more studies are needed.

More on Antioxidants

- Many observational epidemiological studies have related dietary antioxidants to asthma and allergic outcomes.
  - These observational studies have the usual problems of quantifying dietary intake, plus, many children and adults may alter their diet because of asthma and/or allergies.
  - In addition, reduced blood antioxidant levels may be a consequence of the systematic oxidant stress associated with the inflammatory processes of asthma.
  - Studies of low Vit E, Vit C, Selenium, carotenoids, and flavonoids intake in addition to fruits/vegetables have been done evaluating wheeze, lung function and asthma rates.
  - Most have shown that there is more asthma, more wheeze and lower lung function if these nutrients are low in the diet.
**Nutrition and Asthma: Summary**

- There is evidence of an association between nutrition and asthma; however, the clinical and public health relevance of the associations remains unclear.
- There is insufficient evidence to advise individuals with asthma, pregnant women, parents and children to change or supplement their diet in order to treat or reduce the risk of developing asthma.
- There is little evidence that antioxidant or PUFAs supplementation can be used as an adjunct to conventional therapy for asthma.
- However there is a need for well-designed randomized controlled trials of nutrient intervention in children with asthma and for trials of combinations of nutrients.
- The maternal intake of Vit E, Vit D and PUFAs during pregnancy provides the most promising evidence that nutritional supplementation in the developmental period may have a role in the primary prevention of asthma in children.

**Obesity and Asthma**

- Obesity and asthma prevalence have increased over the last several decades, and studies over the last 15 years have suggested that obesity is related to asthma.
- Recent study using the National Health and Nutrition Examination Survey (NHANES) examined the relationship of weight to current asthma.
- The analysis included children age 219 (n=16,074) from the 1999-2006.
- Obesity was significantly related to current asthma among children and adolescents.
- The association was stronger in non-atopic children than in atopic children.
- C-reactive protein (CRP) levels were associated with current asthma in non-atopic children, but not after adjusting for BMI.

**Obesity and Asthma: How?**

- Current evidence favors the association that obesity precedes asthma in adults, however in children inconsistent findings have been observed.
- Early childhood is a dynamic period for growth, as well as for disease development. Inadequate nutrition during infancy, the period with most rapid growth, could result in lifelong problems.
- During infancy, human lung parenchyma undergoes a substantial structural remodeling because of alveolar formation and septal restructuring. Insults during this critical time period can have profound effects on subsequent development of respiratory systems and lung disease processes, including asthma.

**Childhood Origin of Asthma (COAST)**

- 285 COAST children (who had at least one parent with allergies and/or asthma) were enrolled at birth and followed up to age 1 year, 259 (91%) at age 6 years and 238 (84%) at age 8 years were evaluated for asthma.
- These children, who were at high risk for developing asthma, were monitored for being overweight and development of asthma.
- If overweight and <1 yr, there was a decrease incidence of asthma, this was gone from 2-5 yrs of age.
- In fact, later onset of being overweight was found to have an increase incidence of having asthma at age 6 and 8.
- These findings provide evidence of the complex relationships between age, overweight status, and wheezing/asthma development.
**COAST Conclusions**

- Findings suggest that association between weight and childhood asthma changes with age.
- Although obesity might promote asthma in later life, these findings suggest the possibility that nutrition during infancy should be optimized to promote lung growth and development and that this could have effects in reducing asthma risk later in childhood.
- However, after the first year of life, attention should be focused on balanced nutrition to prevent becoming overweight and obese beyond infancy, which might be a potential risk factor for asthma.

**Wheezing Infant and Obesity**

- In adults, obesity decreases both function using commonly measured parameters.
- In children, high BMI has shown different results when lung function is measured.
- 100 children who were hospitalized <24 months for wheezing illness were prospectively followed along with lung function, height and weight at ages 4 (n=83), 7 (n=80) and 12 yrs (n=79).
- Overweight was present in 6.0% of children at 4.0 years, in 22.2% at 7 yrs and in 33.3% at 12 yrs of age (about 20% were obese at age 12).
- Being overweight was associated with decreased FEV1/FVC at both 7.2 and 12.3 years of age.
- Being overweight and obese at early school age preceded reduced FEV1/FVC at age 12 yrs.

**Why?**

- The mechanisms leading to lung function disorders in association with overweight or obesity may be narrowing of the small peripheral airways.
- In addition, decreased compliance of either the lungs due to narrow peripheral airways or the chest wall due to body adiposity may lead to subnormal lung function, including both decreased airway flows.
- The effect of excessive weight gain on lung function may be age dependent, which means that different mechanisms may influence in children and in adults and in children at different ages.
- Being “mildly” overweight before age 7, showed some protection from “asthma”
- The results suggest the importance of the prevention of excessive weight gain at preschool and school age in children with early childhood wheezing.

**Dietary Supplementation as Treatment**

- Most studies have not been supportive of using supplements or even nutrition in treating established asthma.
- Novel nutritional formula (NNFs) using NNF enriched eicosapentaenoic acid and linoleic fatty acids with antioxidants were given to asthmatic children.
- NNF group had reduced biomarkers of disease activity and the gene/environmental exposure important.
- The peripheral mononuclear blood cells (PMBC) fatty acid composition changes reflected an antiinflammatory profile.
- Both the NNF group and the control, did show improvement in asthma free days.

**Conclusions**

**IT IS COMPLICATED!**

- Nutrition likely plays an important role in both the development and control of asthma.
- The earlier the intervention (prenatal) may be the best time to change the diet/supplements.
- The genetic interaction is even more complex with gene/environmental exposure important.
- Breastfeeding is still good.
- Diet may have less impact on improving established asthma.
- Obesity and Asthma relationship is real but also complex.

**Bibliography**

Bibliography


