Inflammatory Markers, Environmental Tobacco Smoke (ETS) Exposure, and Childhood Asthma

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Prevalence of Childhood Asthma

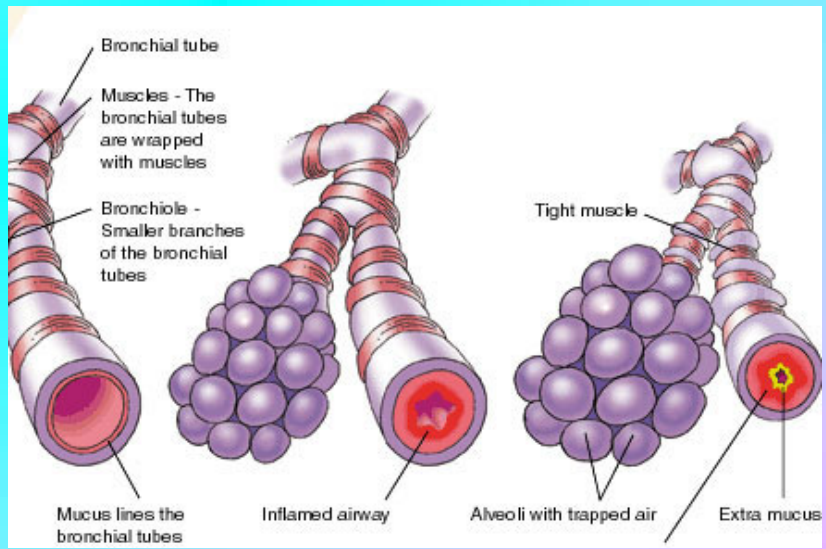
- Children ages 0-4 years have the highest asthma prevalence and hospitalizations.
- Over 60% of childhood asthma begins before age 3.
- Loss of lung function occurs within first 3 years of life.
- A total of 8 out of 10 children who die from asthma have very mild disease.

Prevalence of Childhood Asthma

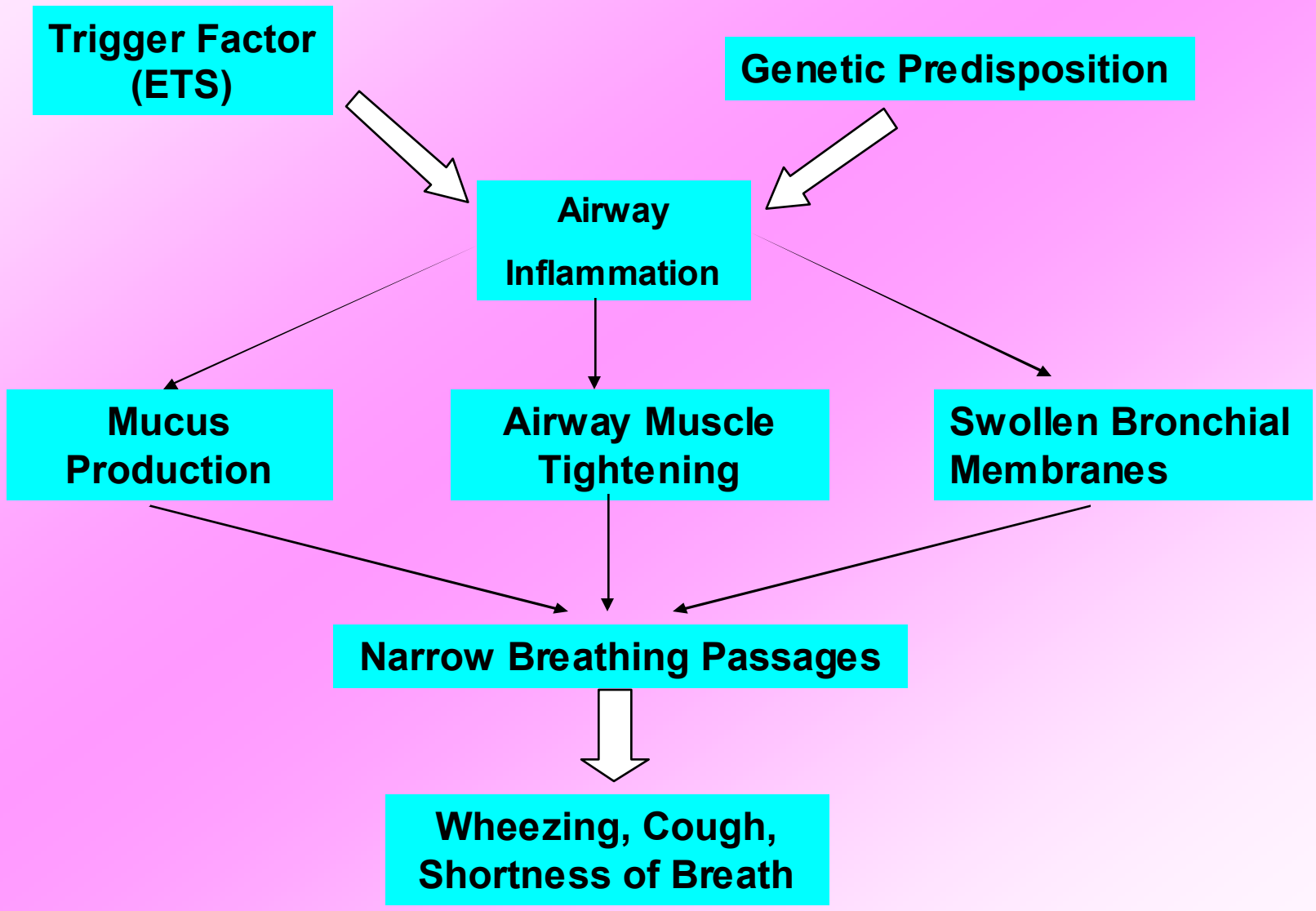
- 9.2 million children have been diagnosed with asthma (13%).
- 4 million children had an asthmatic attack in the past year (5.5%).

Classical Triad of Asthma

- Reversible obstructive airway disease due to:
  1) Inflammation of the airways (i.e., eosinophilia of the mucosa).
  2) Increased mucus secretion.
  3) Contraction of smooth muscle of airways with hyper-reactivity of the airways.



Development of Childhood Asthma



Major Risk Factors for Childhood Asthma

1) A positive family history (particularly maternal asthma with RR=2.0-7.5)

2) Atopy

3) Environmental exposure to allergens:

   -Outdoor air pollution: ozone, SO_2, NO_2, particulate matter, diesel exhaust

   -Environmental tobacco smoke: most powerful factor is parental smoking,

   -Indoor allergens: house dust mites, cockroaches, cats, dogs, fungus, and mold

   -Outdoor allergens: changes in weather, pollen

Major Risk Factors for Childhood Asthma

4) Respiratory tract infections
5) RSV
6) Food allergies
7) Day care settings
8) Breastfeeding
9) Urbanization
10) Stress
11) Wildfires

Facts about Asthma Diagnosis

- Accurate diagnosis of asthma is complex, and it is believed that the disease continues to be under-diagnosed and under-treated.
- There is no clear definition of asthma.

How to Currently Diagnose Childhood Asthma

i. Vitals, pulse oximetry, and chest x-ray.

ii. Any recurrent episodes of respiratory symptoms.

iii. Use of accessory muscles.

iv. Tachypnea.

v. Family history of asthma or allergic disorders.

vi. Any detailed symptoms:

   a. Frequency during the spring and fall allergy seasons
   b. Triggers (allergens, exercise, respiratory infections or cold air)

vii. An allergy skin or blood test (IgE).

How to diagnose childhood asthma in the future

Objective measures: Inflammatory markers

Classification of Asthma (5 years of age and younger)

Asthma classification	Symptom frequency
Step 1: Mild intermittent	Daytime: ≤ 2 days/week Nighttime: ≤ 2 nights/month
Step 2: Mild persistent	Daytime: > 2 days/week, but <1x/day Nighttime: > 2 nights/month
Step 3: Moderate persistent	Daytime: daily Nighttime: >1 night/week
Step 4: Severe persistent	Daytime: continual Nighttime: frequent

Research Agenda for ETS and Asthma

- The role of ETS (pre- or postnatal) in the development of allergy and in the potentiation of the immune response to asthma merits further investigation.
- Better markers for the development of IgE-mediated allergy in early childhood, and markers of specific genetic predisposition.

Environmental Tobacco Smoke (ETS) and Asthma

- In utero and postnatal exposures to environmental tobacco smoke have been implicated as risk factors for asthma.
- Tobacco exposure is implicated in the etiology and progression of childhood asthma.
- The association of maternal smoking and asthma is greatest among children diagnosed before 2 years.

ETS exposure and asthma in children (ages 2 months - 5 years)

- ½ of cases of early childhood asthma are due to secondhand cigarette smoke.
- 24 % of fetuses are exposed to maternal smoking during pregnancy.
- Children with prenatal exposure are 2x more likely to develop asthma.
- Children exposed to maternal smoke in the womb were 2x more likely to have ≥3 episodes of wheezing from 2 months – 2 yrs.

Inflammatory Markers

1) Reflect spontaneous changes in disease activity,
2) Mirror improvements due to therapy,
3) Have high sensitivity and specificity,
4) Have prognostic significance,
5) Be reproducible in steady state,
6) Be fast, easy to obtain, and non-invasive,
7) Be inexpensive,
8) Not be influenced by confounding factors.

Serum Eosinophil Cationic Protein (sECP)

- Early indicator of lung inflammation and asthma severity in children.
- Found in urine, serum, bronchial lavage, nasal secretion fluids, and sputum.
- Distinguishes between symptomatic and asymptomatic asthma
- Correlates with allergen exposure and active clinical disease
- Decreases with anti-inflammatory treatment

Serum Eosinophil Cationic Protein (sECP)

- Influenced by age (particularly < 2 years), daily maternal smoking, and diurnal variation.
- Increased with atopy (eczema, allergic rhinitis, and conjunctivitis), and respiratory tract infections in asthmatic children.
- Complicated by strict and time-consuming sampling procedures and the need for venipuncture.

Urinary Eosinophilic Protein X (uEPX)

- Most valuable biomarker of eosinophil activation in childhood asthma
- Easily measured in urine
- Undergoes no significant in vivo degradation
- Correlates inversely with nocturnal PEFRs, FEV1, and PFTs

Urinary Eosinophilic Protein X (uEPX)

- Not influenced by perennial allergy and polysensitization, and can differentiate symptomatic from asymptomatic patients.
- More concentrated than ECP in urine.

Why is uEPX preferable to sECP in children?

- Easily obtained, simple, non-invasive
- Higher release of EPX vs. ECP in asthmatics
- Not influenced by perennial allergy
- More concentrated in urine than ECP

Studies investigating the relationship between sECP, uEPX and Asthma

	Correlation	No correlation
Children:		
Total # of studies worldwide	3	0
Children (0-4 years):		
Total # of studies worldwide	0	0

Discrepancies among ECP/EPX Studies

- Asthma not clearly defined or subdivided
- Misclassification with other diagnoses (GERD)
- Included inhaled corticosteroid groups
- Retrospective or cross-sectional design
- Only Caucasians, no young children
- Markers not repeated throughout the study
- Duration of in utero or postnatal ETS exposure was not considered

Relevance/significance of this topic

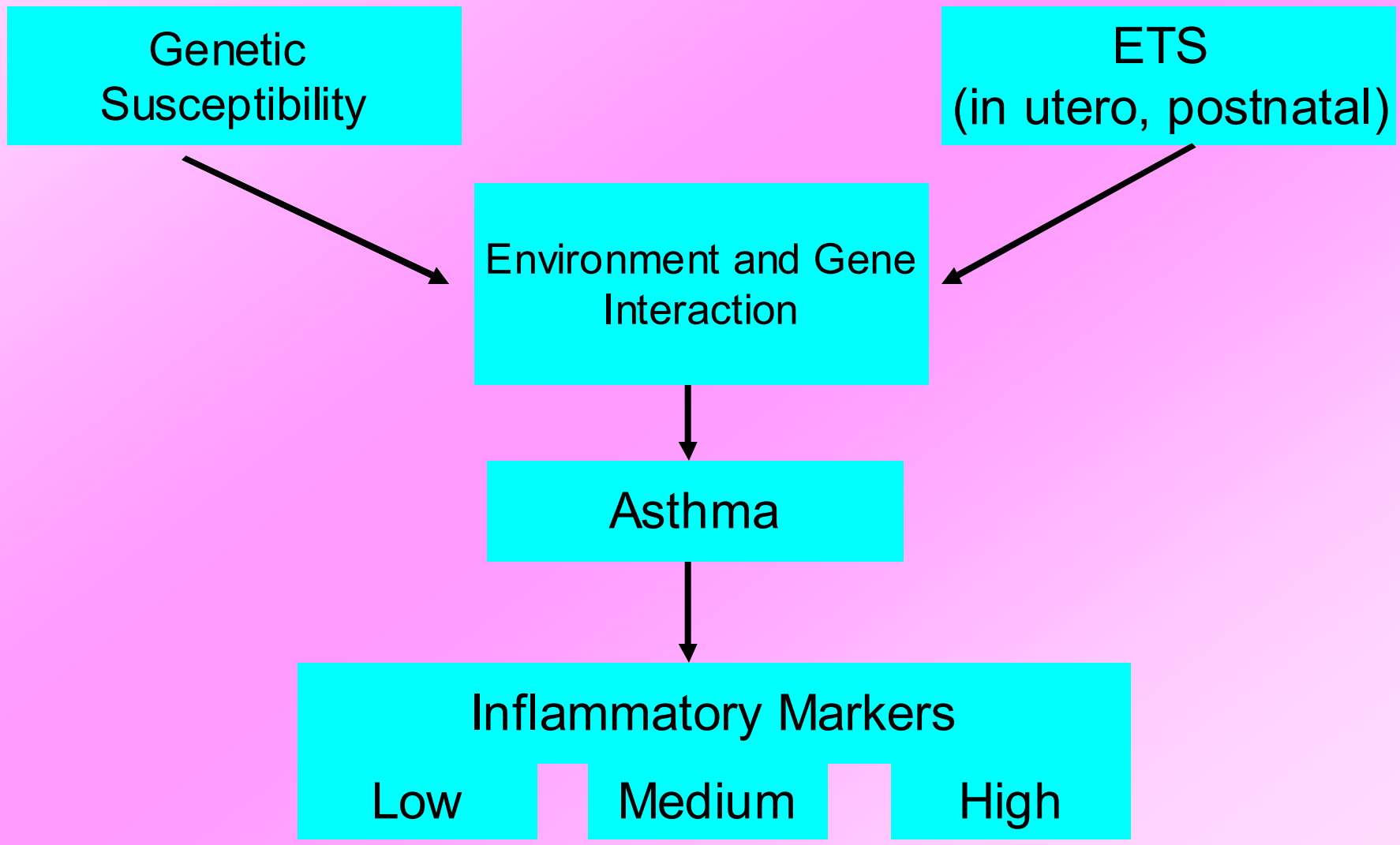
- One of the greatest challenges in pediatric respiratory medicine is to identify future asthmatics.
- Problems because of non-specific symptoms, and inability to obtain reliable PFTs in children <5 years.
- Invasive studies such as bronchoscopy, bronchial biopsies and pediatric lung function tests are not easily performed.
- Remarkably, no objective measures to predict which infants with *transient* wheeze will develop asthma.

Hypothesis

- Children with asthma will have higher levels of serum eosinophil cationic protein (sECP) and urinary eosinophil protein X (uEPX) compared to healthy children

- Children exposed to in utero and/or postnatal environmental tobacco smoke (ETS) will have the highest sECP and uEPX

Inflammatory Markers, ETS and Childhood Asthma



Definition of childhood asthma for this study

- Chronic inflammation of airways characterized by:
  - *wheeze, cough, breathlessness, and chest tightness (at night)*
- Responds to bronchodilators and anti-inflammatory meds
- Symptoms worsen with:
  - *cold air, dust, exercise, and mild respiratory illness*
- Family/parental history of asthma

Disease endpoints

- Number of asthma free days
- Peak Flow Assessment (≥3 years)
- PFT (≥3 years)

Human exposure assessment

- Cotinine
  - a nicotine metabolite and highly specific marker of ETS exposure found in serum, urine, and saliva.

Indicators of disease

- Eosinophilic cationic protein (ECP)
- Eosinophilic protein X (EPX)
  - Indicator of lung inflammation and asthma severity in children
  - Influenced by tobacco smoke and age

Study Population

- A 3-year prospective study in Southern California
- A total of 400 participants:

  200 asthmatic cases

  200 healthy controls matched on the basis of age (±3 months), sex, race, clinic/hospital
- All ethnic backgrounds

Inclusion Criteria for Cases and Controls

- Age 0 months - 4 years at study entry
- Birth weight > 2000 gm
- Gestational age >34wks
- Newly diagnosed asthmatics (steroid naïve, if possible) or healthy children

Exclusion Criteria for Cases and Controls

- Immunodeficient patients
- History of documented RSV or influenza in the past 3-6 months
- Any other illness which impairs respiration (i.e. BPD, cystic fibrosis, GERD, CVS disease, neuromuscular disease)
- Requiring assisted ventilation or oxygen therapy as newborn infants

Controls – Exclusion Criteria

- Personal or family history of asthma
- An intercurrent respiratory illness in the past month

Health Assessment
Baseline and follow-up visits* for Cases and Controls

1) History and Physical Examination
2) Vital signs (BP, HR, RR, T, pulse ox)
3) Blood Draws (¼ tsp.)
   for sECP, CBC w/ diff, RAST & IgE
4) Urine collection (3~5 ml)
   for uEPX and uCotinine
5) Daily diary (cases only)

Visit 1 (Continued)

6) Chest x-ray (posterior/anterior and lateral) (cases only at baseline)
7) Telephone Interview (45 min.)
8) Lung Function Tests (1 PFT) for children >3 years:

   (Daily PEFR for 1 year for cases and 1 time for controls)

* 4 months, 8 months, and 12 months

Conclusion

- **Expected Results**:
  - Asthmatic infants exposed to ETS in utero will have the highest sECP and uEPX values.
  - Healthy unexposed infants will have the lowest sECP and uEPX values at baseline.

Contribution of this Research

The contributions of this prospective study include:

1. A sample of 0-4 year olds
2. Atopic and non-atopic asthmatics
3. Comparison group of healthy infants
4. Racially diverse sample
5. Multiple ECP & EPX measurements
6. ETS exposure assessed with urinary cotinine
7. Conducting multivariate analyses
8. Data analysis separately on pre- and post-treatment

Limitations of the Study

- Identifying intermittent vs. persistent wheezers
- Extremely strict exclusion criteria:
  - URI
  - RSV
- Extremely strict inclusion criteria:
  - steroid naïve
  - severe asthmatics
- Length of visit for consultation

Benefits

- Inflammatory markers are simple, non-invasive tests
- Predict future asthmatics
- Identify susceptible infants/children who have been exposed to tobacco smoke during and/or after pregnancy

Policy Implications

1. Prevent irreversible lung damage
2. Remove stigma regarding asthma diagnosis for young children
3. Screen for asthma diagnosis using inflammatory markers:
   - All children?
   - What age?
   - How often?
4. Use inflammatory markers to measure asthma severity and control

Future Directions

- Diagnosis and monitoring of childhood asthma may implicate the use of different inflammatory markers
- Longitudinal studies of different markers are needed