EARLY LIFE ORIGIN OF CHRONIC OBSTRUCTIVE LUNG DISEASES

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MODEL OF CHANGES OF LUNG FUNCTION ACROSS THE LIFE

Maximal Level of FEV₁ (%)

Age (yr)

Healthy subjects

Symptoms

Disability
EARLY INSULTS MAY CAUSE FAILURE TO ACHIEVE MAXIMAL LUNG FUNCTION AND EXPOSE INDIVIDUALS TO THE RISK OF CHRONIC RESPIRATORY DISEASES LATER IN LIFE.

Lung immaturity
Viral infections (RSV, HRV)
Atopy
Passive smoking

Baraldi & Filippone NEJM 2007
Early-life origins of chronic respiratory diseases: understanding and promoting healthy ageing

Carraro S, Scheltema N, Bont L, Baraldi E
Early-life origins of chronic respiratory diseases: understanding and promoting healthy ageing

Carraro S, Scheltema N, Bont L, Baraldi E
FACTORS ACTING IN THE INTRAUTERINE LIFE MAY HAVE EFFECTS ON LIFELONG RESPIRATORY HEALTH

It may be necessary to intervene in utero or in early postnatal life
‘80-’90 Barker: link between events occurring in the fetal environment and long-term health and lifespan consequences in adults

Barker DJ et al *Lancet* 1986
THE “FAMILY TREE” OF CHRONIC RESPIRATORY DISEASE SYNDROMES

- premature birth
- respiratory infection
- respiratory allergy
- smoking (1st, 2nd hand)

Susceptibility
Inception

Common genotype

atopic asthma

non-atopic asthma

COPD

Birth
School age
Young adulthood
≥ Middle age

Holt & Sly CEA 2009 modified
EARLY INSULTS MAY CAUSE FAILURE TO ACHIEVE MAXIMAL LUNG FUNCTION AND EXPOSE INDIVIDUALS TO THE RISK OF COPD LATER IN LIFE

- Lung immaturity
- Infections (RSV, HRV)
- Atopy
- Passive smoking

![Graph showing the impact of early insults on maximal FEV1 levels and the development of COPD over age.](image)
TOBACCO SMOKE EXPOSURE AND CHANGES OF LUNG FUNCTION ACROSS THE LIFE
TOBACCO SMOKE EXPOSURE AND CHANGES OF LUNG FUNCTION ACROSS THE LIFE
Smoking in pregnancy is associated with an increased risk for asthma and lower lung function at age 14.
**SPEGNI LA SIGARETTA, PROTEGGI IL TUO BAMBIN!**

**FUMO DI “PRIMA MANO”**
Fumo inalato direttamente da un fumatore.

**FUMO DI “SECONDA MANO”**
Fumo inalato da chi è vicino ad un fumatore.

**FUMO DI “TERZA MANO”**
Residui tossici di fumo su vestiti e tessuti che vengono rilasciati nell’ambiente anche a sigarette spente.

**DANNI DA FUMO ATTIVO E PASSIVO**
Basso peso alla nascita e ridotto calibro delle vie aeree del neonato
Riacutizzazioni asmatiche e infezioni respiratorie
Bronchite cronica ed enfisema
Cancro del polmone
Aumentata incidenza di malattie cardiovascolari

*Iniziativa promossa da:*

**forza**

**Con il patrocinio di:**

**SIMRI**
Società italiana per lo studio e la ricerca pediatrica

**Più voli più bassi**
Associazione a favore dei bambini affetti da sindrome di Down, malattia spastica e sindrome di Down - croce.

**Chiesi**
Ricerca svolta in conformità ai linee guida dell'EFPIA.
Uso in aumento – percezione che sono sicure (meno catrame) – aumento accettabilità sociale del fumo

L’aerosol di e-cig non è solo "vapore acqueo", come viene affermato nella commercializzazione. Effetti dannosi della nicotina

Prove insufficienti a concludere che le e-cigarettes aiutino gli utenti a smettere di fumare.

Il loro uso può essere una minaccia per i bambini e per il feto di madri incinte.

E’ necessario impedire la promozione delle e-cigarettes tra i non fumatori e i più giovani.
EARLY INSULTS MAY CAUSE FAILURE TO ACHIEVE MAXIMAL LUNG FUNCTION

Lung immaturity
Infections (RSV, HRV)
Atopy
Passive smoking

Maximal Level of FEV₁ (%)

Age (yr)

Healthy subjects
Susceptible smokers
COPD
Symptoms
Disability
PREMATURITY IS A MAJOR HEALTH PROBLEM
IN THE DEVELOPED COUNTRIES

Preterm delivery rate:
- 5-9% Europe
- 12-13% USA

PRETERM DELIVERY RATE IS INCREASING

Goldenberg, Lancet 2008
**BPD:** Any form of lung injury of the newborn determining the need for supplemental $O_2$ at 36 weeks’ postmenstrual age

Stages of lung development:
- **Canalicular stage:** 16 w
- **Saccular stage:** 23 w
- **Alveolar stage:** 32 w
- **Premature delivery**
- **Normal development:** 38 w

New BPD:
- Developmental arrest/delay
- Structural injury

Baraldi & Filippone NEJM 2007
Despite the huge improvement in neonatal intensive care, BPD remains a major cause of morbidity and mortality among premature infants.
Effect of preterm birth on later FEV$_1$: a systematic review and meta-analysis

Kotecha Thorax 2013

59 studies: 28 preterm-born, 24 with BPD

BPD group

Born 1964-2000
Ages 5-23 years
G.A. 24-36 weeks

PRETERM group

Mean Difference

Study or Subgroup | Mean | IV, Random, 95% CI
--- | --- | ---
1984 Wheeler | 82 | 106
1987 Bader | 73 | 82.37
1990 De Kleine | 73 | 90.34
1990 Northway | 74.8 | 90.9
1991 Ahrens | 77.11 | 85.9
1995 Santuz | 93 | 98
1998 Mitchell | 78 | 98
2000 Kennedy | 78.4 | 98
2000 Pianosi | 86 | 98
2001 Doyle | 88.5 | 98
2003 Barker | 90 | 98
2004 Korhonen | 90 | 98
2005 Baraldi | 77.8 | 98
2005 Halvorsen | 86.4 | 98
2006 Vrijlandt | 90.1 | 98
2007 Abreu | 99 | 98
2009 Karila | 79.1 | 98

-16.2%

Mean Difference

Study or Subgroup | Mean | IV, Random, 95% CI
--- | --- | ---
1984 Wheeler | 106 | 106
1989 Galdes-Sebaldt | 82.37 | 106
1990 De Kleine | 90.34 | 106
1997 Giacoia | 85.9 | 106
1998 Gross | 98 | 106
1998 Jacob | 86.1 | 106
1998 Mitchell | 85 | 106
2000 Kennedy | 95.4 | 106
2000 Pianosi | 83 | 106
2001 Doyle | 96.7 | 106
2002 Mieskonen | 89.8 | 106
2003 Barker | 101 | 106
2003 Kilbride | 89 | 106
2004 Korhonen | 95 | 106
2005 Baraldi | 90.3 | 106
2005 Halvorsen | 94.7 | 106
2006 Doyle | 87.1 | 106
2006 Vrijlandt | 99.2 | 106
2007 Abreu | 100 | 106
2007 Pahta | 88 | 106
2010 Fawke | 90 | 106

-7.2%
INDIVIDUAL WHO ENTER ADULT LIFE WITH LUNG-FUNCTION DEFICITS ARE AT RISK OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE LATER IN LIFE

Baraldi & Filippone NEJM 2007

Concern that a subset of BPD survivors may be susceptible to a new COPD-like phenotype
When Does BPD Start?

Maximal Level of FEV$\text{1}$ (%)

- Healthy subjects
- Survivors of broncho-pulmonary dysplasia

Lung immaturity
Prolonged oxygen supplementation
Mechanical ventilation
Infections
Patent ductus arteriosus

Symptoms
Disability

Age (yr)
‘-OMIC’ SCIENCES

ENVIRONMENT

Drugs
Diet
Commensal microorganisms
Pollutants
Toxic agents

PHENOTYPE

Genome (DNA)

Trascriptome (RNA)

Proteome (proteins)

Metabolome (metabolites)

Post-genomic techniques

Carraro J Pediatr 2009
Metabolomics: A New Frontier for Research in Pediatrics

Silvia Carraro, MD, Giuseppe Giordano, PhD, Fabiano Reniero, PhD, Giorgio Perilongo, MD, and Eugenio Baraldi, MD

SYSTEMS BIOLOGY AND ‘OMIC’ SCIENCES

METABOLITE FINGERPRINTING

Metabolomics allows the characterization of the metabolite fingerprint of a biological sample without any “a priori” hypothesis allowing hypothesis free profiling of biomarkers, rather than a traditional hypothesis-driven approach.

J Pediatr 2009;154:638-44
METABOLIC PROFILING OF THE AMNIOTIC FLUID PREDICTS THE RISK OF PRETERM DELIVERY AND BPD DEVELOPMENT

Amniotic fluid

Biomarker Target

Work-flow

Pathways Analysis

Identification & quantification of metabolites

PCA, PLS-DA, O2PLS-DA

Features Selection

n (data matrix)
p (data points)
METABOLIC PROFILING OF THE AMNIOTIC FLUID PREDICTS THE RISK OF PRETERM DELIVERY AND BPD DEVELOPMENT

AF collected between the 21\textsuperscript{th}-28\textsuperscript{th} week of gestation

<table>
<thead>
<tr>
<th>group</th>
<th>R2</th>
<th>Q2</th>
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<tbody>
<tr>
<td>BPD</td>
<td>0.71</td>
<td>0.37</td>
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<tr>
<td>CMPD</td>
<td>0.80</td>
<td>0.62</td>
</tr>
<tr>
<td>CMTD</td>
<td>0.81</td>
<td>0.59</td>
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</tbody>
</table>

Baraldi et al ERS 2014
METABOLIC PROFILING OF THE AMNIOTIC FLUID PREDICTS THE RISK OF PRETERM DELIVERY AND BPD DEVELOPMENT

Suggesting that BPD begins during fetal life

Baraldi et al  ERS 2014
EARLY LIFE ORIGIN OF CHRONIC RESPIRATORY DISEASE

• Prematurity and BPD

• Recurrent wheezing and asthma

• Viral infections and subsequent airway obstruction

• COPD?
ATOPIC CHILDREN ARE MORE LIKELY TO CONTINUE WHEEZING BY THE TIME THEY REACH ADOLESCENCE

MAS study – Illi et al Lancet 2006
Airflow limitation in asthma is related to 2 components:
- **congenital** (1/3)
- **acquired** (2/3)

This leaves open a “window of opportunity” to prevent the acquired component.

**Bisgaard AJRCCM 2012**
Airflow limitation in asthma is related to 2 components:
- **congenital** (1/3)
- **acquired** (2/3)
This leaves open a “window of opportunity” to prevent the acquired component.

*Bisgaard AJRCCM 2012*
At birth, different metabolic profiles characterize AF of children who will or won’t develop recurrent wheezing.

\[ R^2 = 0.80 \quad Q^2 = 0.48 \]
EARLY INSULTS MAY CAUSE FAILURE TO ACHIEVE MAXIMAL LUNG FUNCTION AND EXPOSE INDIVIDUALS TO THE RISK OF COPD LATER IN LIFE.
Post-RSV-bronchiolitis recurrent wheeze

A UNIQUE MODEL!
Infants hospitalized for RSV bronchiolitis: 18 years follow-up

Asthma & recurrent wheeze

- RSV (n=46): 39%
- Control (n=92): 9%

Atopy

- RSV (n=46): 43%
- Control (n=92): 17%

Sigurs, Thorax 2010
ASTHMA 30 YEARS AFTER HOSPITALIZATION FOR BRONCHIOLITIS

- 70 bronchiolitis children enrolled in 1981-1982 evaluated at the age of 28-31 years (Finland)
- 138 matched controls

Asthma was present in 1/3 of the former bronchiolitis patients

Backman Ped Pulm 2013
Healthy preterm (33-35 ga) infants “late preterm”
214 Palivizumab vs 215 placebo

61% reduction in the number of wheezing days in the first year of life (hospitalization 12% vs 22%)

Figure 2. Cumulative Wheezing Days for 429 Preterm Infants during the First Year of Life.
EARLY LIFE ORIGIN OF CHRONIC RESPIRATORY DISEASE

• Prematurity and BPD
• Recurrent wheezing and asthma
• Viral infections and subsequent airway obstruction
• COPD?
Chronic Obstructive Pulmonary Disease
COPD

A PEDIATRICIAN TALKING ABOUT COPD?
“Any model of COPD which does not take into account early life influences is likely to be fatally flawed”

“COPD is a disease of childhood that becomes manifest in adults”
# COPD – RISK FACTORS

**ENVIRONMENTAL FACTORS**
- Cigarette smoking
- Second hand smoke
- Maternal smoking
- Pollution
- Occupational exposure
- Lung growth
- Nutrition
- Respiratory infections

**INDIVIDUAL FACTORS**
- ALFA1-AT deficiency
- Oxidative stress
- Low birth weight
- Reduced lung function in the first months of life
Early life origins of chronic obstructive pulmonary disease

Follow-up study from general population (7,738 subjects) Enrolled at 20-45 yrs – followed 9 years

People with early life disadvantages (asthma, respiratory infections < age 5, maternal smoking...) have low lung function when adults, no catch-up with age and an increased COPD risk.

The impact of childhood disadvantages was as large as that of heavy smoking!!

Svanes et al. Thorax 2010
COPD PHENOTYPES

- COPD smokers
- COPD-Asthma
- Poor lung function at birth and in the first years of life (transient wheeze ?)
- Prematurity and BPD
- Recurrent respiratory infections in infancy
NATURAL HISTORY OF WHEEZING ACROSS THE LIFE
A common “at risk” genotype probably predispose to chronic respiratory disease syndromes.

Deficit in airway function shortly after birth predisposes to flow limitation in adult life.

Environmental experiences during infancy (prematurity, respiratory infections, allergy, smoking exposure) may determine the progression towards specific phenotypes.
EARLY LIFE EVENTS ARE CRUCIAL IN THE GENERATION OF CHRONIC OBSTRUCTIVE LUNG DISEASES

Investment in Paediatric Research warrants to save lives (and money) for adult respiratory health