Asthma, pollution and altitude

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Denis CHARPIN – Faculté de Medicine de Marseille Aix-en- Provence - FRANCE
Why is it important to speak about air pollutants?

- In 2010, WHO estimated >6 million people die prematurely every year because of air pollution (1).
- In 2012 the estimated numbers are about 7 million deaths as a result of (indoor and outdoor) air pollution.
- Few controlled human exposure studies that can provide irrefutable evidence of adverse effects after acute exposure to an individual pollutant (1).
- Difficulty to understand the mechanisms and the role of different pollutants in respiratory morbidity (2).

• Indoor air pollution:
  - Accounted for 4.3 million deaths (South-East Asia and Western Pacific regions).
  - Respiratory illnesses made up 40% of the death toll.
  - Children < 5 years are particularly vulnerable.
  - In 2012 over 500 000 deaths from acute lower respiratory infections related to indoor air pollution in this age groups (4)

• Outdoor air pollution:
  - Accounted for 3.7 million deaths, concentrated in low-income and middle-income countries.
  - 389 000 of these deaths were from chronic obstructive respiratory disease.
  - 227 000 from lung cancer (emissions from diesel engines are particularly culpable) (5).

4 - www.thelancet.com/respiratory Vol 3 February 2015
5 - www.thelancet.com/respiratory Vol 2 May 2014
Why is it important to speak about air pollutants?

- 680,000 premature deaths each year (for 2000)
- Total external costs estimated to 803 bn Euro/yr for 2000 reduced to 537 bn Euro/yr by 2020

### Air pollution issues in Europe

<table>
<thead>
<tr>
<th>European emission sector</th>
<th>Europe</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>bn euros</td>
</tr>
<tr>
<td>EU/1 Combustion in energy and transf. industries</td>
<td>185</td>
</tr>
<tr>
<td>EU/2 Non-indus. combustion plants/wood</td>
<td>73</td>
</tr>
<tr>
<td>EU/3 Combustion in manufacturing industry</td>
<td>60</td>
</tr>
<tr>
<td>EU/4 Production processes</td>
<td>50</td>
</tr>
<tr>
<td>EU/5 Extr. and distr. of fossil fuels/geoth. energy</td>
<td>10</td>
</tr>
<tr>
<td>EU/6 Solvents and other product use</td>
<td>13</td>
</tr>
<tr>
<td>EU/7 Road transport</td>
<td>138</td>
</tr>
<tr>
<td>EU/8 Other mobile sources and machinery</td>
<td>50</td>
</tr>
<tr>
<td>EU/9 Waste treatment and disposal</td>
<td>7.8</td>
</tr>
<tr>
<td>EU/10 Agriculture</td>
<td>180</td>
</tr>
<tr>
<td><strong>Sum EU/1-10</strong></td>
<td>766</td>
</tr>
</tbody>
</table>

Several studies have been done in order to confirm the positive influence of “resting” in altitudes and its effect in children, adolescents and adults. The majority of those, have been done in clinics located in the Alps, such as:

- Misurina (Itália) 1756 m
- Davos (Suissa) 1560 m
- Briançon (França) 1360 m

These studies have demonstrated the beneficial effects in asthmatic patients when staying in high altitudes, clearly showing a reduction in symptoms, less necessity of medication as well as a lower risk for being hospitalized.

Why is it important to speak about asthma

- 300 million people suffer from asthma conditions.
  - 5 to 7% are adults
  - 7 to 9% children of 6-7 years old (ISAAC)
  - 10 to 15% young adults 13-14 years old (ISAAC)
- It’s estimated that by 2025 there will be 400 million asthmatics.

- Represents 1% of the world health expenses.
- The total cost of respiratory pathologies is (in the EC) 100 billion Euros/year.
  - (120 Euros per person per year).
- Asthma itself in the EC costs 20 billion Euros/year
- Asthma is responsible for 250,000 deaths per year worldwide (mostly female adults)
  - (> 800 Euros per patient and per year).
Asthma, pollution and altitude

Agenda

• Physical air pollutants (PM)
• Chemical air pollutants (NO, NO2 and SO2)
• Biological air pollutants (Pollens, molds and HDM)
• Conclusion: The beneficial effect of altitude on respiratory and allergic diseases.
Results are calculated for a total of about 1870 monitoring stations reporting to AirBase.

**CONCLUSION:**

Rural and urban background concentrations are on average modeled well, while the model may be slightly pessimistic for future roadside concentrations.
Swiss SALPADIA study

- Was initiated in 1991.
- Participants, 18–60 years of age, were randomly selected from the population registries.
- Eight geographic Swiss regions, with varying degrees of urbanization and different environmental and cultural characteristics.
- Participants of the baseline examination \( (n = 9,651) \) were invited in 2002 \( (n = 8,047) \) for a second examination.
Physical air pollutants: Different concentrations

[Graph showing different concentrations of PM_{10} in various locations.]
By 2050 (outdoor) air pollution will become the biggest environmental cause of premature death worldwide.

[Organization for Economic Cooperation and Development, OECD, Environmental outlook to 2050]
Physique pollutants and mortality

London Smog, December 1952

[Graph showing deaths, sulphur dioxide, and smoke levels during the period of the London Smog in December 1952.]
Physical air pollutants and lung function


Swiss SALPADIA study

Figure 3. Estimated Effect of Interval Exposure between 1991 and 2002 (Expressed as Mean Annual PM$_{10}$) on Mean Annual Decline in FEV$_1$. 
Physical air pollutants and lung function
Physical air pollutants and lung function
Conclusion:
DEPs induced AHR independent of their adjuvant effects, suggesting the use of these models to study the mechanism or mechanisms of acute asthma exacerbation by means of PM.

Physical air pollutants and IgE


Patients allergic to pollens (n = 25)

<table>
<thead>
<tr>
<th></th>
<th>Day 0</th>
<th>Day 14</th>
<th>Day 28</th>
<th>Day 32</th>
</tr>
</thead>
<tbody>
<tr>
<td>KLH</td>
<td>1 mgr</td>
<td>100 mgr</td>
<td>100 mgr</td>
<td>-</td>
</tr>
<tr>
<td>Nasal washes</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
</tbody>
</table>

KLH: Keyhole limpet hemocyanin

<table>
<thead>
<tr>
<th></th>
<th>Day 0</th>
<th>Day 14</th>
<th>Day 28</th>
<th>Day 32</th>
</tr>
</thead>
<tbody>
<tr>
<td>KLH + DEP (0.3 mgr)</td>
<td>1 mgr</td>
<td>100 mgr</td>
<td>100 mgr</td>
<td>-</td>
</tr>
<tr>
<td>Nasal washes</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
</tbody>
</table>

DEP: Diesel exhaust particle

DEPs can act as mucosal adjuvant to an IgE response and may increase allergic sensitization
Physical air pollutants and allergy

Patients allergic to Ambrosia


- Nasal provocation with: **Amb a1 (1000 U / ml) - Amb a1 + 0.3 mg of DEP**
- Nasal washes at 18 hours post challenge (day 1) and at day 4th and 8th
- Specific IgE were measured against Ambrosia (nasal wash).
Physical air pollutants (DEP) and allergy
Particulate matter may affect health

How inhalation of particulate matter may affect our health

- PM Inhalation
  - Lungs
    - Inflammation
    - Oxidative stress
    - Accelerated progression and exacerbation of COPD
    - Increased respiratory symptoms
    - Effected pulmonary reflexes
    - Reduced lung function
  - Systemic Inflammation Oxidative Stress
    - Increased CRP
    - Proinflammatory mediators
    - Leukocyte & platelet activation
  - Heart
    - Altered cardiac autonomic function
    - Oxidative stress
    - Increased dysrhythmic susceptibility
    - Altered cardiac repolarization
    - Increased myocardial ischemia
  - Blood
    - Altered rheology
    - Increased coagulability
    - Translocated particles
    - Peripheral thrombosis
    - Reduced oxygen saturation
  - Vasculature
    - Atherosclerosis, accelerated progression and destabilization of plaques
    - Endothelial dysfunction
    - Vasoconstriction and hypertension
  - Brain
    - Increased cerebrovascular ischemia

Based on Pope and Dockery (J Air & Waste Management Association, 2006)
Particulate matter may affect health

60 adults (mild and moderate asthmatics) in a 2 hour walking trip in Oxford Street Hyde Park

McCreanor et al NEJM 2007; 357: 2348
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• Conclusion: The beneficial effect of altitude on respiratory and allergic diseases.
Regarding *environmental pollution* and gaseous pollutants, it is well known that NO, NO$_2$ and SO$_2$ are considered risk factors for the development of severe respiratory diseases.

Gaseous air pollutants

- Clear reduction since late 80s when 3-ways catalyst were introduced
- Annual mean limit of 30µ/m³ still exceeded at urban sites.
Gaseous air pollutants
Munich “vs” Davos

- Munich
  - O3: 38
  - NO2: 68
  - NO: 53
  - SO2: 3

- Davos
  - O3: 79
  - NO2: 40
  - NO: 30
  - SO2: 0
Data established on many years by ppb (part for billion in volume).

We observed that the difference is highly significant between Briançon (10 ppb), London (1400 ppb), Paris (1000 ppb), Lyon (260 ppb), and Genoa (230 ppb).

<table>
<thead>
<tr>
<th>Location</th>
<th>SO$_2$ (ppb)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LONDON fog</td>
<td>1400 ppb</td>
</tr>
<tr>
<td>PARIS</td>
<td>1000 ppb</td>
</tr>
<tr>
<td>LYON</td>
<td>260 ppb</td>
</tr>
<tr>
<td>GENES</td>
<td>230 ppb</td>
</tr>
<tr>
<td>BRIANÇON</td>
<td>10 ppb</td>
</tr>
</tbody>
</table>
Gaseous air pollutants - SO$_2$
Challenge to mites after exposure to ozone compared to a similar challenge after exposure to filtered air.

Figure 2. Geometric mean values and standard errors of mean of provocative doses of allergen, PD_{20}FEV₁, in the subjects with asthma, after filtered air or ozone exposure on Study Days 4 and 5 and without previous exposure on Day 3 (control).
The effect of 3h exposure to 200 ppb O₃, 400 ppb NO₂, and 200 ppb O₃ + 400 ppb NO₂, compared with air, on allergen PD2₀FEV₁ in mild asthmatics.
Gaseous air pollutants
Health consequences

Effect of six hours of exposure to 400 ppb NO2 + 200 ppb SO2 on the dose of inhaled allergen require to decrease the FEV1 by 20% in mild asthmatic

C. Rusznak and col. Thorax 1996;51:1105-1108
Gaseous air pollutants
Health consequences

Figure 2: Effect of exposure to pollutant gases on PD_{20}FEV\_1
Individual results and mean are shown. Significance testing was done after log transformation of data. CBU=dose of inhaled allergen expressed as cumulative breath units.
Ozone (O3):
- Irritates the nose and throat; causes wheezing, coughing, pain when taking a deep breath; causes breathing difficulties during exercise or outdoor activities
- Reduces lung capacity
- Aggravates asthma
- Increases vulnerability to respiratory diseases, increases the risk of dying from lung and heart diseases
- Increases hospital admissions for lung diseases

Sulphur dioxide (SO2)
- Contributes to respiratory diseases (especially in children and elderly)
- Aggravates cardiovascular and respiratory diseases (particularly in asthmatics)

Nitrogen dioxide (NO2)
- Increases incidence of asthma
- Increases the risk of dying from lung diseases
- Increases hospital admissions for lung conditions
Asthma, pollution and altitude

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Climatic factors and atmospheric pollens

Pollen per m3

Birch pollen 2004

Grass pollen 2003

Basel

Davos

[Graphs showing pollen levels over time for Birch and Grass pollens, differentiated by location and time of year.]
We observed that pollination in altitude is characterized by later starting and shortened season as well as lower density is in plain and lower littoral.
Increased pollen allergenicity?

There is hypothesis that air pollutants promote airways sensitization by inducing changes in the allergenic contents of airborne particles carrying antigens such as pollens.

WJ Gauderman and col. NEJM 2004
D’Amato and col CEA 2005
Climatic factors and atmospheric molds

Characteristics of high altitude: DRY

Lower spore concentration

Cladosporium spp
25-50 %

Alternaria spp
1-3 %

compared to sea level

Leuschner Grana 1981
Climatic factors and atmospheric molds

ALTERNARIA
Mean 1994 - 1999

From May to September:

<table>
<thead>
<tr>
<th>Location</th>
<th>Min.</th>
<th>Max.</th>
<th>Av.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brussels</td>
<td>5</td>
<td>700</td>
<td>97.84</td>
</tr>
<tr>
<td>Nice</td>
<td>5</td>
<td>460</td>
<td>62.83</td>
</tr>
<tr>
<td>Briançon</td>
<td>1</td>
<td>46</td>
<td>15.83</td>
</tr>
</tbody>
</table>

Brussels / Nice : p<10^-2
Brussels / Briançon : p<10^-9
Nice / Briançon : p<10^-9

Evaluated by the Burkard Volumetric Spore Sampler
(Analysis center : C.E.M.B.R.E.U.)
Climatic factors and atmospheric molds

CLADOSPORIUM
2004

May to Septembre

<table>
<thead>
<tr>
<th></th>
<th>Min.</th>
<th>Max.</th>
<th>Av.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brussels</td>
<td>10</td>
<td>26530</td>
<td>5183.75</td>
</tr>
<tr>
<td>Nice</td>
<td>680</td>
<td>10060</td>
<td>2781.98</td>
</tr>
<tr>
<td>Briançon</td>
<td>184</td>
<td>5235</td>
<td>1568.45</td>
</tr>
</tbody>
</table>

Brussels / Nice : p < 10⁻⁶
Brussels / Briançon : p < 10⁻⁹
Nice / Briançon : p < 10⁻⁹

Quantifié avec le capteur volumétrique Burkard
(Centre d’analyse : C.E.M.B.R.E.U. - Briançon, ISP-IHE - Bruxelles)
Climatic factors and House Dust Mites

HDM concentration (Der-p-1) in different climes and altitudes

Menz 1987
FIG. 2—Geometrical means of numbers of house-dust mites over a one-year period in dust from four houses in Davos (1967-8), three houses in Basle (1967-8), and three houses in Leiden (1964-5). Mean values are plotted logarithmically.
Asthma and Allergy to House-dust Mites in Populations Living in High Altitudes*

Denis Charpin, M.D.; Jean-Pierre Kleibauer M.D.; André Lanteaume, B.S.; Hassan Razzouk, M.D.; Daniel Vervloet, M.D.; Mondher Toumi, M.D.; Fadel Faraj M.D.; and Jacques Charpin, M.D.

<p>| Table 1—Distribution of Studied Population, in Each Town, According to Age and Gender |
|---------------------------------|-------------------------------|-------------------------------|</p>
<table>
<thead>
<tr>
<th>Age Range</th>
<th>Marseille</th>
<th>Briançon</th>
<th>Marseille</th>
<th>Briançon</th>
</tr>
</thead>
<tbody>
<tr>
<td>18-34</td>
<td>756</td>
<td>847</td>
<td>205</td>
<td>232</td>
</tr>
<tr>
<td>35-49</td>
<td>431</td>
<td>623</td>
<td>148</td>
<td>170</td>
</tr>
<tr>
<td>50-65</td>
<td>540</td>
<td>810</td>
<td>131</td>
<td>169</td>
</tr>
<tr>
<td></td>
<td>1727</td>
<td>2281</td>
<td>484</td>
<td>571</td>
</tr>
<tr>
<td>Total</td>
<td>4,008</td>
<td>1,055</td>
<td></td>
<td></td>
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</table>

<table>
<thead>
<tr>
<th>Table 3—Number of Persons Having Skin Test*</th>
</tr>
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<tbody>
<tr>
<td></td>
</tr>
<tr>
<td>Briançon</td>
</tr>
<tr>
<td>Overall</td>
</tr>
<tr>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>Asymptomatic subjects</td>
</tr>
<tr>
<td>Asthmatic subjects</td>
</tr>
</tbody>
</table>

*Hay fever patients are not mentioned. In parentheses is the percentage of positive skin test to HDM—p values refer to the comparison of the proportion of positive skin test to HDM in the two towns.
### Table 6. Estimates of dampness/mould prevalence by type of exposure indicator and climate

<table>
<thead>
<tr>
<th></th>
<th>Cold climate</th>
<th>Moderate/warm climate</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Water damage</strong></td>
<td>18% (Bornehag et al., 2005)</td>
<td>9% (Zhang et al., 2005)</td>
</tr>
<tr>
<td></td>
<td>5% (Jaakkola et al., 2005)</td>
<td>8.9% (Lee et al., 2003)</td>
</tr>
<tr>
<td></td>
<td>10% (Spengler et al., 2004)</td>
<td></td>
</tr>
<tr>
<td><strong>Condensation</strong></td>
<td>14% (Bornehag et al., 2005)</td>
<td>28% (Zhang et al., 2005)</td>
</tr>
<tr>
<td></td>
<td>15% (Jaakkola et al., 2005)</td>
<td></td>
</tr>
<tr>
<td><strong>Dampness</strong></td>
<td>15% (Wickman et al., 2003)</td>
<td>6-10% (du Prel et al., 2005)</td>
</tr>
<tr>
<td></td>
<td>18% (Rönmark et al., 1999)</td>
<td>19-27% (Baker, Henderson, 1999)</td>
</tr>
<tr>
<td><strong>Mould</strong></td>
<td>1.2% (Turunen et al., 2008)</td>
<td>19% (Zhang et al., 2005)</td>
</tr>
<tr>
<td></td>
<td>1.5% (Bornehag et al., 2005)</td>
<td>24% (Lee et al., 2003)</td>
</tr>
<tr>
<td></td>
<td>3.5% (Jaakkola et al., 2005)</td>
<td>21-29% (Baker, Henderson, 1999)</td>
</tr>
<tr>
<td></td>
<td>10% (Spengler et al., 2004)</td>
<td></td>
</tr>
<tr>
<td><strong>Any combination of above</strong></td>
<td>5% (Turunen et al., 2008)</td>
<td>5.5-7% (Simoni et al., 2007)</td>
</tr>
<tr>
<td></td>
<td>20% (Jaakkola et al., 2005)</td>
<td>23% (Salo et al., 2004)</td>
</tr>
</tbody>
</table>
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Conclusions

Air pollution issues in Europe
respiratory effects depend on particle size and physical properties of the pollutant

- **nose, throat**: particles < 30 μm
- **trachea, bronchia**: particles < 10 μm
  - **SO₂, NO₂, O₃**
- **lung, pulmonary alveoli**: particles < 2-3 μm
  - **NO₂, O₃**
- **lung tissue, blood circulation**: ultrafine particles < 0.1 μm

*Source: European Respiratory Society, 2010*
Conclusions

What May Play a Role in Today’s Respiratory Allergy and Asthma?

- **Climate Change and Air Pollution**
  - Aggressive allergens
  - Severe symptoms

- **Indoor Lifestyle**
  - Persistent allergen exposure
  - Persistent symptoms

- **New Allergens**
  - More and different allergens
  - Frequent symptoms

- **Stressful Lifestyle**
  - Neuro-immune responses
  - Susceptive to allergy
‘Asthmatic persons are so capricious that each patient has to find out for himself; a given asthmatic may lose his asthma at Davos. Only young persons should try the experiment, and persons free from emphysema’.
Conclusions

- Environmental pollution is associated with loss of lung function.
- Environmental pollution worsens asthma and induces lung inflammation.
- Environmental pollution is a likely factor contributing to symptoms and exacerbations.
Several studies have been done in order to confirm the positive influence of “resting” in altitudes and its effect in children, adolescents and adults. The majority of those, have been done in clinics located in the Alps, such as:

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- Davos (Suissa) 1560 m
- Briançon (França) 1360 m

These studies have demonstrated the beneficial effects in asthmatic patients when staying in high altitudes, clearly showing a reduction in symptoms, less necessity of medication as well as lower risk for being hospitalized.
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