New Avenues for Allergy and Asthma Prevention

The Exposome Approach

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Disclosures

Disclosures of Financial Relationships

• Isabella Annesi-Maesano
  – No relevant financial relationship to disclose

Learning Objectives

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• Understanding the exposome, its implementation and its applications
Why the environment and why the exposome?

THE ENVIRONMENT IS CRUCIAL

1. Environment more important than genetics in the development of diseases
2. Only the role of some environmental factors is known
3. Most diseases are multifactorial
The idea that there is a close link between health and the environment is not new.

- Hippocrates wrote in his treatise "Airs, waters, places": "To deepen medicine, we must first consider the seasons, know the quality of water, winds, study the various conditions of the soil and the way of life of the inhabitants."

- Ramazzini (XVIII century) completed this approach: "Listen Hippocrates: We must ask him (the patient) what he feels, what is the cause, how many days but to these questions, let me add: "and what profession does he do?"

Diseases results from gene and environment interactions

- Diseases are the result of interactions between genes and the environment.

- WHO report on Preventing diseases due to environmental exposures – towards an estimated environmental burden of disease.
Diseases result from gene and environment interactions

**ENVIRONMENT ROLE HAS STILL TO BE EXPLORED**
Risk factors for exposures that contribute to chronic diseases

- **Diseases result from gene and environment interactions.**

- **Need for a new paradigm:**
  - Most diseases are multifactorial diseases.
  - They cannot be explained by a unique factor.
The Complexities of Environment/Exposure

**LEAD:** Individuals are exposed to lead through air, water, soil, at home, work, during transportation, in early life, later... Through different penetration route. This can target different organs... and uses different pathways.

**Stressor:** Physical, Chemical, Biological, Psycho-social

**Source:** Air, Water, Soil, Food, Consumer Products, Drugs

**Place:** Home, School, Work, Neighborhood, Transports, Community, City, State, Region

**Time:** Fetal, Child, Adolescents, Young Adult, Adult, Older adults, Elderly

**Route of Contact:** Topical (Skin), Inhalation (Lungs), Ingestion (Diet or thow), Injection (Intravenous, Intramuscular, Subcutaneous, Intravenous), social patterns

**Organ distribution:** Lungs, Neuri, Skin, El, other organs

**Targets:** Biological pathways

Homo sapiens connects Leonardo da Vinci

Health consequences of this complexity has to be taken into account.

The Exposome...

It comprises processes in the individual: metabolism, genetic effects, external exposome, pathogens, chemical contaminants, social, economic and psychological influences.


INTERACTIONS AMONG THE 3 DOMAINS AT THE ORIGIN OF MULTIFACTORIAL DISEASES
From exposure to internal dose and health outcome considering the lifetime dimension: **8 ages**

DOHAD
(Developmental Origin of Health and Diseases)

Hypothesis

Developmental origin of multidisciplinary diseases
How assessing the exposome? 
The case of asthma and allergy

• Which stressors?
• Which assessments? Needs to take into account real life? How?
• Which exposure assessments?
• Relating the exposome to health outcomes
• Addressing prevention

Which stressors?

• **Bottom-up (targeted) approach** from known environmental exposures and connections to the molecular initiating event generating the disease

• **Top-down (untargeted) approach** from the disease and the initial molecular event aiming to discover novel environmental exposures and connections.

• **Hybrid approach**
1. Interactions amongst external and internal exposomes

Exposome data are heterogeneous, nonlinear variables that change over time and space.

2. Interactions amongst environmental risk factors belonging to the external exposomes

Call to action: Air pollution, asthma, and allergy in the exposome era
Assessing the exposome

The exposome can be assessed at various levels: populations, groups of people (susceptibles), individual

Technologies that can be applied to assess the external and internal exposome during lifetime

As many assessments as possible but at least in crucial life stages in several settings

Technologies avoiding exposure misclassification, not time-consuming and expensive. Statistical analysis considering the heterogeneity of the assessments and the multitude of testing in the context of big data.
Exemplary plot of the retrospective estimation of exposures for a random individual (woman, 75 years old) in the case of eight stressors.

Reliable assessment of the maximum number of environmental factors at different periods of life in the different settings attended by the individual (home, school, work, transportation, community, etc.), so to be representative of individual exposures across the entire lifespan, and at least in the life periods identified as critical in the lifespan.

- Early-life exposome is high dimensional and not easily reducible to fewer components.
- Correlations between exposures within the same exposure group can be high.
- Correlations between exposure groups are low.
- Exposome varies strongly by life period.
Assessing INDIVIDUAL EXPOSURE IN REAL TIME: air pollution

Assessments in real-time of:

- PM$_{10}$, PM$_{2.5}$, PM$_{10}$
- VOCs
- T
- Hum
- Pressure
- GPS

Laguille et al. STOTEN 2017
Dessimond et al. Sensor 2021
Connecting the dots between exposures and health

Environment-Wide Association Studies (EnvWAS) in asthma in HEALS twins (pre-existing data (HEALS))

~522 / 36 / 37 significant interactions (raw p-value / Bonferroni / FDR)

Significant interactions with correction for multiple hypotheses testing included: benzene derivatives, acyclic carbon derivatives, metals, particulate matter, and life habits
Metabolomics and pathway analysis

**Results:** The outcomes of birth cohorts with an exposomal approach improve our understanding of the association between environmental exposures and childhood diseases. For example, results from the Canadian Healthy Infant Longitudinal Development Study suggest an association between first trimester exposure to traffic-related air pollution and increased risk of allergic sensitization at 12 months of age ($P = .6$). In a smaller Canadian birth cohort study, it was found that regular use of air fresheners (adjusted $P = .04$) and presence of mold in the residence (adjusted $P < .001$) were associated with wheezing and cough. The application of emerging molecular omics technologies and has facilitated the comprehensive assessment of exposome in birth cohorts.
CONNECTING THE DOTS FOR EFFECTIVE PREVENTION OF DISEASES

EXPOSOME: A PROMISING POTENTIAL

Predictive model development for risk assessment

The promising potential of exposome is that it will provide the basis for evidence based health interventions: Both collective public health strategies and personalized intervention strategies.
Developed knowledge and technologies provide a range of opportunities for prevention:
- Several targets (patients, workers...)
- (Self) management and E-health solutions.

The last challenge consists in the identification of the avoidable exposome at the individual, family, and community level to promote prevention.

Public Health Perspectives: Insights from EWAS could have important policy implication

by Yves Parc Luy and Isabella Arpes-Marzano
Université Pierre et Marie Curie (UPMC)
Paris, France
Modifiable Exposome

A simplified exposome

Smoking
Diet
Physical activity behaviors
Infectious Agents
Accidents
Allergens
Organic food
Vitamins

Most things you see on TV or social media

Health-care access
Industrial toxicants
air/water

Individual

Major

Population/ societal

Minor

It's possible to plot the factors along axes that include the importance to health (minor to major) and the ability to control the factors at the individual, community or societal/population levels.

Résultats et faits marquants

Plateforme : Conception

Raw Data

Data acquisition

External Data Sources

Data Services

Ingestion
Cleaning
Integration
Representation

Data Analysis and Delivery

Data Processing and Enrichment

Transformation

Exposure Profiles

Health Risk Assessment

 Exposure Profile

Microenvironment Characterization

Canarin

The case of air pollution

Data Acquisition

Data Processing and Enrichment

Data Analysis and Delivery

Smart Apps

Professional Access / Business Analyst

External Data Services

Raw Data

Ingestion
Cleaning
Integration
Representation

Healthy College

Asthma & Immunology
CONCLUSIONS

- Exposome is needed to explain the development and the increase of many relevant diseases, particularly of chronic diseases like asthma and allergies (genome cannot do it)
- Exposome implementation needs validated methodologies and technologies and multidisciplinarity
- Exposome is useful in predicting trajectories and profiles of diseases and patients in view of several preventive actions at the population and personal level
- Avoidable exposome exists. Ad hoc actions are needed.
### Some pathways

| Biomarker | Source tissue | Lymphocytes (L) | Lymphocytes (N) | Susceptibility marker 
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<tr>
<td>Citrines</td>
<td>Blood, salivary, urine</td>
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| Polycyclic aromatic hydrocarbons (PAH) adducts | White blood cell DNA | Polycyclic aromatic hydrocarbons (PAH) | DNA damage | Increased FasL
| Odorant exposure | Sera, urine | Mint | Altered arcuate nucleus, increased FasL (reduction) | Mice, rat specific | 
| Ethylated cDNA (EDC) | Exhaled gas | Cigarette smoke | Acute inflammation, asthma control | Asthma, allergic rhinitis | 
| Bronchial epithelial cells | Sputum | Cigarette smoke | Acute inflammation, asthma control | Asthma, allergic rhinitis | 
| Atopic dermatitis | Sera, urine, urine | 
| Anti-IL-13 receptor | 
| DNA methylation | Blood, saliva, bronchial epithelium | 
| Cerulpolamin | Sera, urine | 
| Histone deacetylase (HDAC) | 
| NADPH oxidase (NOX) | 
| Nuclear magnetic resonance (NMR) metabolites | 
| Metabolic profile | 

*Note: The table above represents some pathways related to asthma and allergic rhinitis. The data includes various biological markers and their associated responses.*