



**Webinar Magistrali 2024**  
Italian Society of Occupational Medicine

**HUMAN HEALTH RISKS FROM THE WORKPLACE TO THE GENERAL ENVIRONMENT OF LIFE: WHAT LESSONS FOR RESEARCHERS AND PROFESSIONALS INVOLVED IN THEIR IDENTIFICATION, QUANTIFICATION, AND PREVENTION?**

The graphic features the SIML logo (Società Italiana di Medicina del Lavoro, founded in 1928) and an illustration of a globe, a sun, a wind turbine, and industrial smokestacks with people examining the scene.

1



**Harvard T.H. Chan School of Public Health**

ADVANCING PUBLIC HEALTH THROUGH EDUCATION, RESEARCH, AND PRACTICE

The image shows a low-angle view of the Harvard T.H. Chan School of Public Health building with a red banner across the facade.

2

## Overview

### Mission of the School

The mission of the Harvard T.H. Chan School of Public Health is to improve public health and prevent disease worldwide through education, research, and advocacy.

### Departmental Organization

The Harvard T.H. Chan School of Public Health is organized into ten departments, each dedicated to a specific area of public health, including epidemiology, biostatistics, nutrition, health policy and management, and environmental health.

### Groundbreaking Research

The Harvard T.H. Chan School of Public Health has conducted groundbreaking research in recent years, including studies on the effectiveness of vaccines, the impact of climate change on public health, and the prevention of chronic diseases.



3


## Quick Facts about Harvard School of Public Health

- Harvard School of Public Health currently has over 1,400 students
- The school has a diverse student body with over 80 countries represented
- The faculty at Harvard School of Public Health includes over 900 academic appointees

4


---

## Our Work



**Research from genes to globe**


Bench science, data science, social science  
Engagement with communities around the world



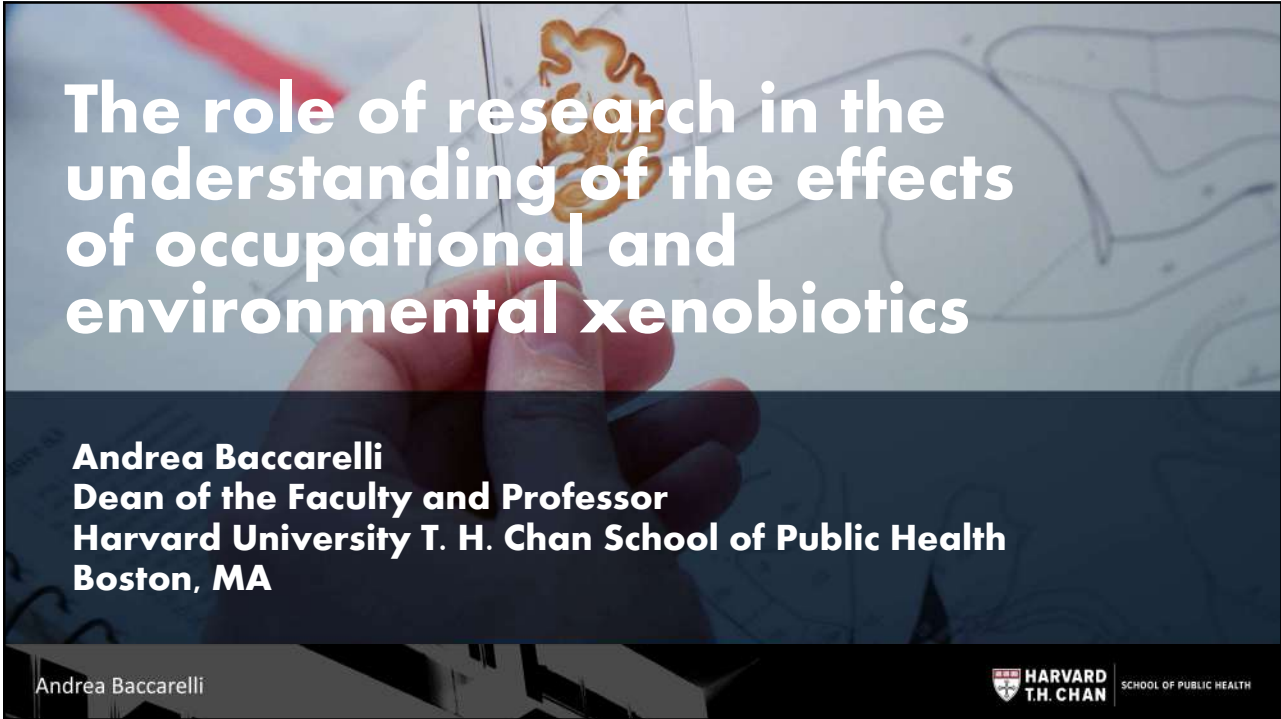
**Educational programs**

Professional degrees: MPH, DrPH  
Research degrees: SM, PhD  
Vast catalog of executive and continuing education

Andrea Baccarelli




5



# The role of research in the understanding of the effects of occupational and environmental xenobiotics

**Andrea Baccarelli**  
Dean of the Faculty and Professor  
Harvard University T. H. Chan School of Public Health  
Boston, MA

Andrea Baccarelli



6




**70-90% of human diseases are attributable to environmental causes**

Andrea Baccarelli

**HARVARD T.H. CHAN** SCHOOL OF PUBLIC HEALTH

7



**CENTRAL HARLEM**  
Life expectancy  
**75**

Your **neighborhood** shouldn't predict **your lifespan**, but it does

**UPPER EAST SIDE**  
Life expectancy  
**85**

8 Concept from calendow.org

**HARVARD T.H. CHAN** SCHOOL OF PUBLIC HEALTH

8

## Key Objectives of Environmental and Occupational Health Research



### Identify and quantify toxicity

Determine the toxic effects and potency of hazardous substances on human health and the environment.



### Characterize mechanisms

Understand the biological pathways and processes by which toxicants cause harm, enabling targeted interventions.



### Develop biomarkers

Establish measurable indicators of exposure, effect, and susceptibility to toxicants, for early detection and risk assessment.



### Influence public opinion and policymaking

Translate research findings into evidence-based recommendations for protecting public health and shaping regulatory policies.

By addressing these objectives, environmental and occupational health research aims to safeguard human health and promote a sustainable environment.

9

## Research Methods



### In vitro studies

Utilizes cell cultures or biological molecules to examine the direct effects of xenobiotics on cellular processes and mechanisms, providing insights into potential toxic responses and mechanisms of action.



### Animal studies

Involves administering xenobiotics to living organisms, typically rodents, to assess whole-body effects, toxicokinetics, and potential adverse effects, providing valuable data for risk assessment and extrapolation to human exposure scenarios.



### Epidemiological studies

Observational studies that investigate the association between exposure to xenobiotics and health outcomes in human populations, offering insights into real-world exposure scenarios and potential long-term effects.

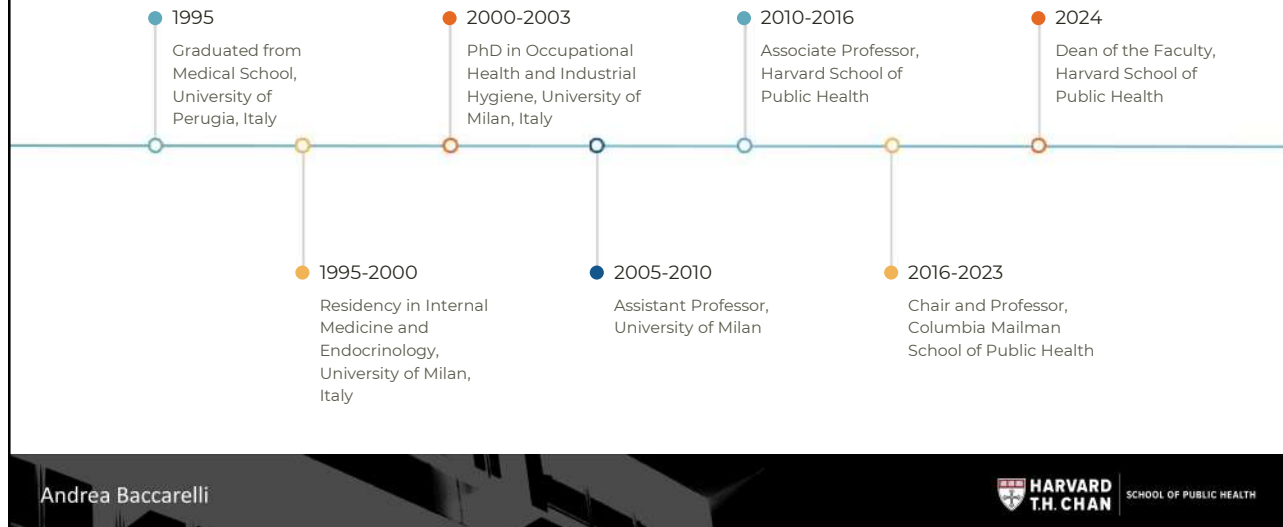


### Computational toxicology

Employs computational models and in silico techniques to predict the toxicity of xenobiotics based on their chemical structure and properties, providing a rapid and cost-effective screening approach for prioritizing further experimental testing.

10

## Intermission - about myself



11

## Three areas in one



### Environmental health/toxicology

Studying the health impacts of environmental exposures like air pollution, water contaminants, chemicals etc.



### Omics/genomics

Studying biological processes through various omics technologies like genomics, transcriptomics, proteomics etc.



### Data science

Applying computational and statistical methods to analyze large, complex biological and health data.

By combining expertise across these three areas, we can gain a deeper understanding of the interactions between the environment, genetics, and human health.

12

## Cost Comparison of Genetic Analysis, circa 2005

Costs in USD



Andrea Baccarelli



13

## My action plan

- **Contacted epigenetics experts worldwide**  
Reached out via email and conferences to connect with leading researchers
- **Created collaborations with statisticians and data scientists**  
Brought on experts in data analysis to maximize insights from epigenetic data
- **Learned technology, approaches, trends and fashions**  
Studied papers and attended talks to stay up-to-date on latest epigenetics methods
- **Connected all in my lab**  
Enabled open communication between team members across disciplines and roles
- **Created collaborations with existing cohorts and biobanks**  
Partnered with groups that have biological samples to analyze epigenetic data

14

## How I became an epigenetist

Faced with prohibitively expensive genetic analysis costs in Italy, I had to find a new path. I had what I needed to work in epigenetics: time and enthusiasm 😊



15

**My research uses  
molecular biology and  
data science to fingerprint  
chemical exposures**

17

# Environmental exposures leave many types of fingerprints on human cells

Peters, Nawrot, Baccarelli, Cell, 2021

Andrea Baccarelli

HARVARD T.H. CHAN SCHOOL OF PUBLIC HEALTH

18

# Challenge #1: Time

Andrea Baccarelli

HARVARD T.H. CHAN SCHOOL OF PUBLIC HEALTH

19



**Solution:  
epigenetics**

**Changes in DNA  
without alterations  
to the DNA  
sequence**

[genome.gov/genetics-glossary/Epigenetics](https://www.genome.gov/genetics-glossary/Epigenetics)

Andrea Baccarelli


 HARVARD  
T.H. CHAN SCHOOL OF PUBLIC HEALTH

20



**Our cells record  
their memories in  
the epigenome**

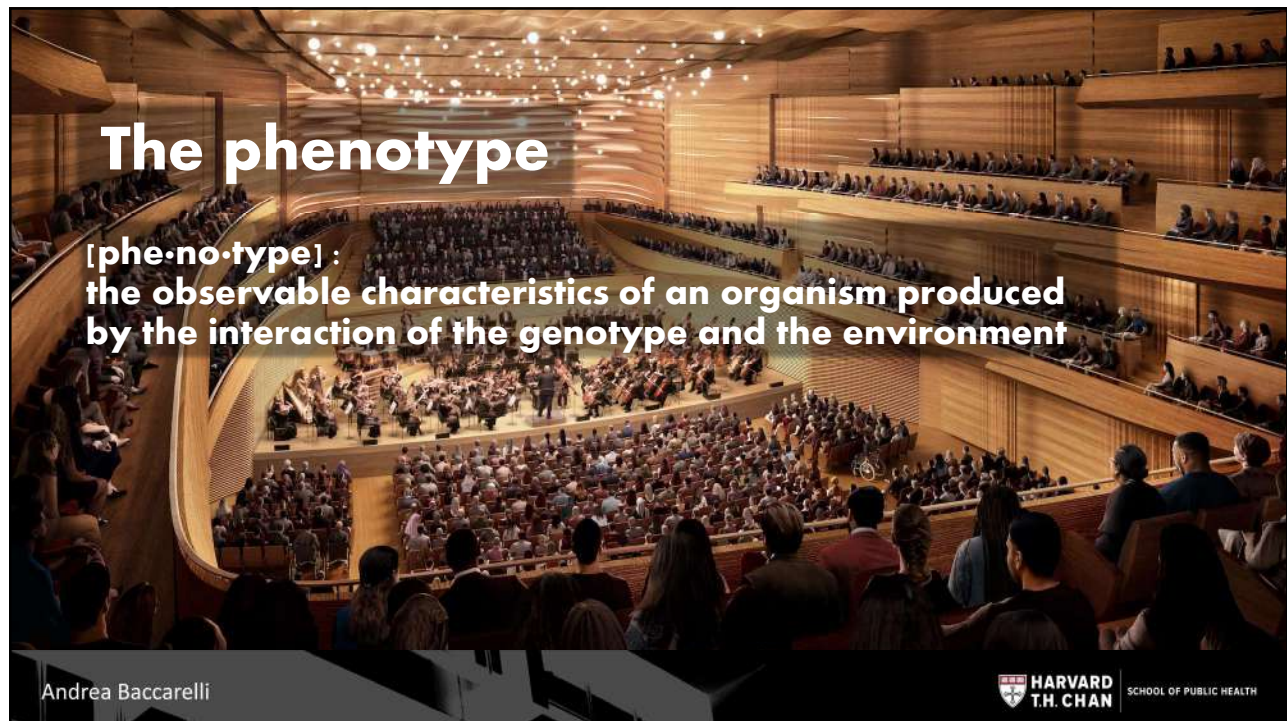
Andrea Baccarelli

 HARVARD  
T.H. CHAN SCHOOL OF PUBLIC HEALTH

21



22



23

**The epigenome**

**ink**

**hard pencil**

**soft pencil**

Andrea Baccarelli

HARVARD T.H. CHAN SCHOOL OF PUBLIC HEALTH

24

Methylation Pattern

DNA Sequence

**DNA methylation is a cellular program that controls genes**

garvan.org.au

25

# Blood DNA methylation records lifetime smoking

**15,907 blood DNA samples from 16 cohorts**

**Smoking associated with DNA methylation at >7,000 genes**

Joehanes et al., *Circ Cardiovascular Genet*, 2016

This slide by Unknown Author is licensed under CC BY

Andrea Baccarelli

27

# Blood DNA methylation records lifetime smoking

**Some genes never return to "non-smoker levels" after quitting**

Gene	Current	>5	>10	>15	>20	>25	>30
PRRT1	~5	~5	~5	~5	~5	~5	~5
TIAM2	~-5	~-5	~-5	~-5	~-5	~-5	~0
AHRR	~-10	~-10	~-10	~-10	~-10	~-10	~0


Joehanes et al., *Circ Cardiovascular Genet*, 2016

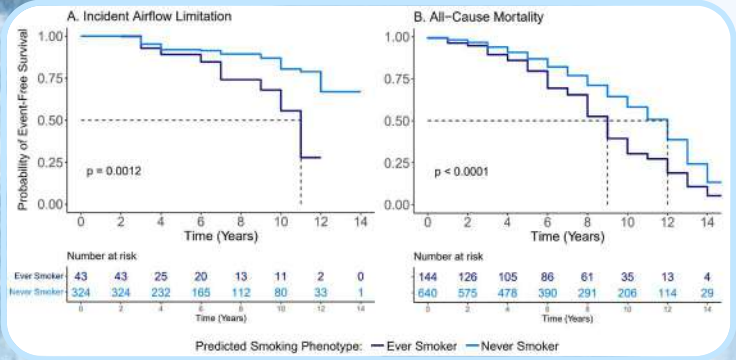
Andrea Baccarelli

28

## EpiSmokEr predicts lung function loss and death better than self reports

Christina Eckhardt





**A. Incident Airflow Limitation**  
p = 0.0012

**B. All-Cause Mortality**  
p < 0.0001

	0	2	4	6	8	10	12	14
Ever Smoker	43	43	25	20	13	11	2	0
Never Smoker	324	324	232	165	112	80	33	1


  

	0	2	4	6	8	10	12	14
Ever Smoker	144	126	105	86	61	35	13	4
Never Smoker	640	575	476	390	291	206	114	29

Predicted Smoking Phenotype: — Ever Smoker — Never Smoker

Eckhardt et al, Respir Med 2022

Andrea Baccarelli



30

## EpiSmokEr predicts lung function loss and death better than self reports

Christina Eckhardt



**Epigenetic classifier:**  
 HR=3.15, 95%CI 1.50, 6.59 airflow limitation  
 HR=2.11, 95%CI 1.56, 2.85 mortality

**Self-reported smoking:**  
 HR=2.21, 95%CI 1.13, 4.33 airflow limitation  
 HR=1.08, 95%CI 0.86, 1.36 mortality

Eckhardt et al, Respir Med 2022

Andrea Baccarelli



31

**We estimated bone lead levels by applying machine learning to blood DNA methylation data**

Estimated Pb levels (log scale)

Measured Pb levels (log scale)

*Colicino et al., IJEAS, 2019*

# Blood DNA methylation records long-term lead exposure

**Elena Colicino**

Andrea Baccarelli

32

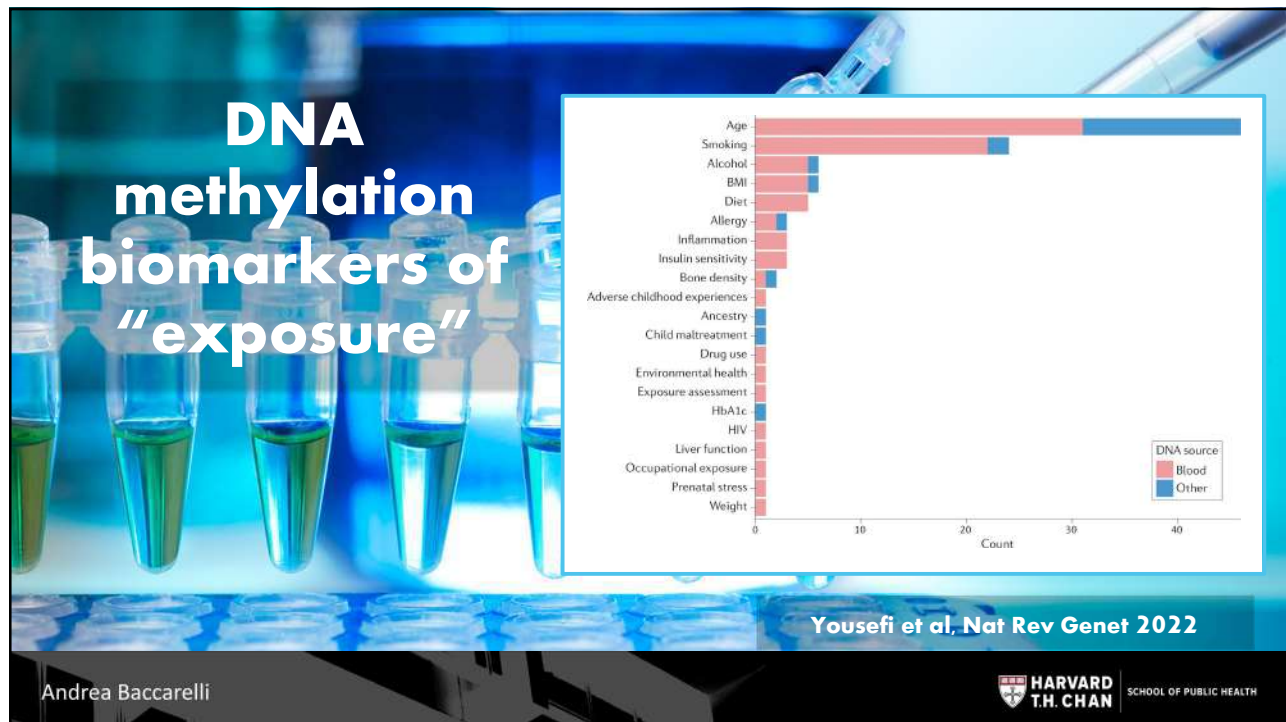
## Future Human's epigenomics lifestyle and environment blood testing

### Methylation profiling

<p><b>Air Pollution</b></p> <p>15 of 92 air pollution genes are activated</p>	<p><b>Tobacco smoking</b></p> <p>0 of 215 smoking genes are activated</p>	<p><b>Harmful metals</b></p> <p>4 of 13 metal genes are activated</p>	<p><b>Radiation</b></p> <p>2 of 145 radiation genes are activated</p>
<p><b>Alcohol</b></p> <p>25 of 165 alcohol genes are activated</p>	<p><b>Sedentary lifestyle</b></p> <p>4 of 59 sedentary lifestyle genes are activated</p>	<p><b>Unhealthy diet</b></p> <p>1 of 451 unhealthy diet genes are activated</p>	<p><b>Lung disease</b></p> <p>45 of 307 lung disease genes are activated</p>

You are in great shape! You have a healthy diet and kudos on your active lifestyle. Just not to leave any stones unturned, we see that your genes have been reacting to alcohol and some harmful pollutants that may come from air, water, or food. Your provider will discuss with you how to improve your scores and get you as healthy as you can possibly be!

34



35

## Limitations


- Different from exposure measures (downstream?)
- Specificity to each exposure still to be determined
- Not tissue specific

Andrea Baccarelli

HARVARD T.H. CHAN SCHOOL OF PUBLIC HEALTH

37

# Challenge #2: Tissues

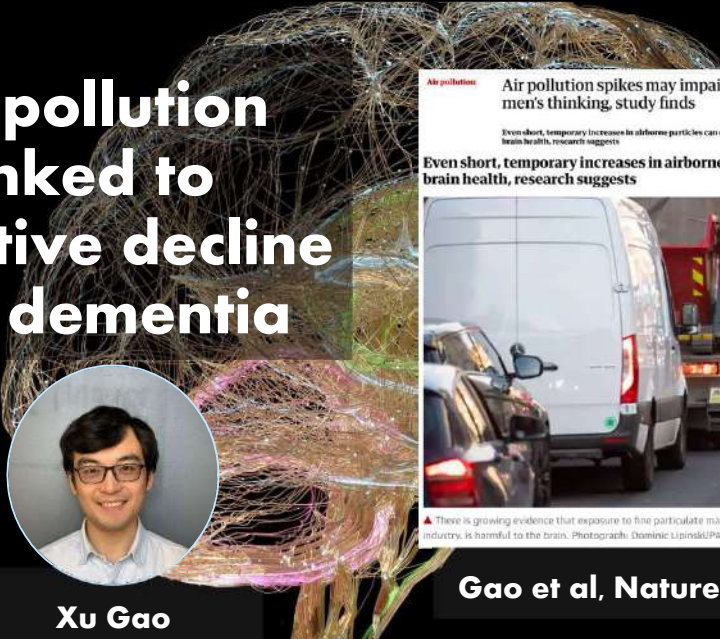



Andrea Baccarelli

HARVARD T.H. CHAN SCHOOL OF PUBLIC HEALTH

38

# Air pollution linked to cognitive decline and dementia

**Xu Gao**


**Gao et al, Nature Aging, 2021**

**Air pollution: Air pollution spikes may impair older men's thinking, study finds**

Even short, temporary increases in airborne particles can damage brain health, research suggests

**The Guardian** US edition  
17th 20th years

**Even short, temporary increases in airborne particles can damage brain health, research suggests**

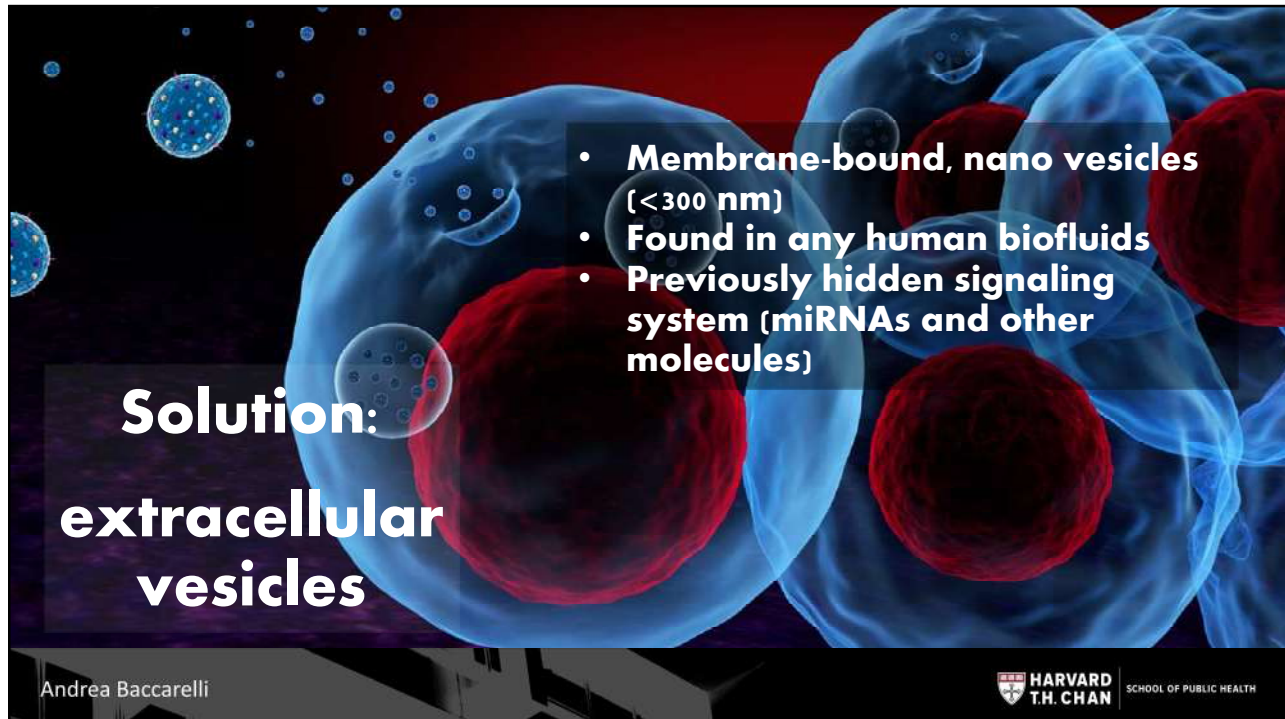


▲ There is growing evidence that exposure to fine particulate matter in the air, largely from road vehicles and industry, is harmful to the brain. Photograph: Dominic Lipinski/PA

Andrea Baccarelli

HARVARD T.H. CHAN SCHOOL OF PUBLIC HEALTH

39



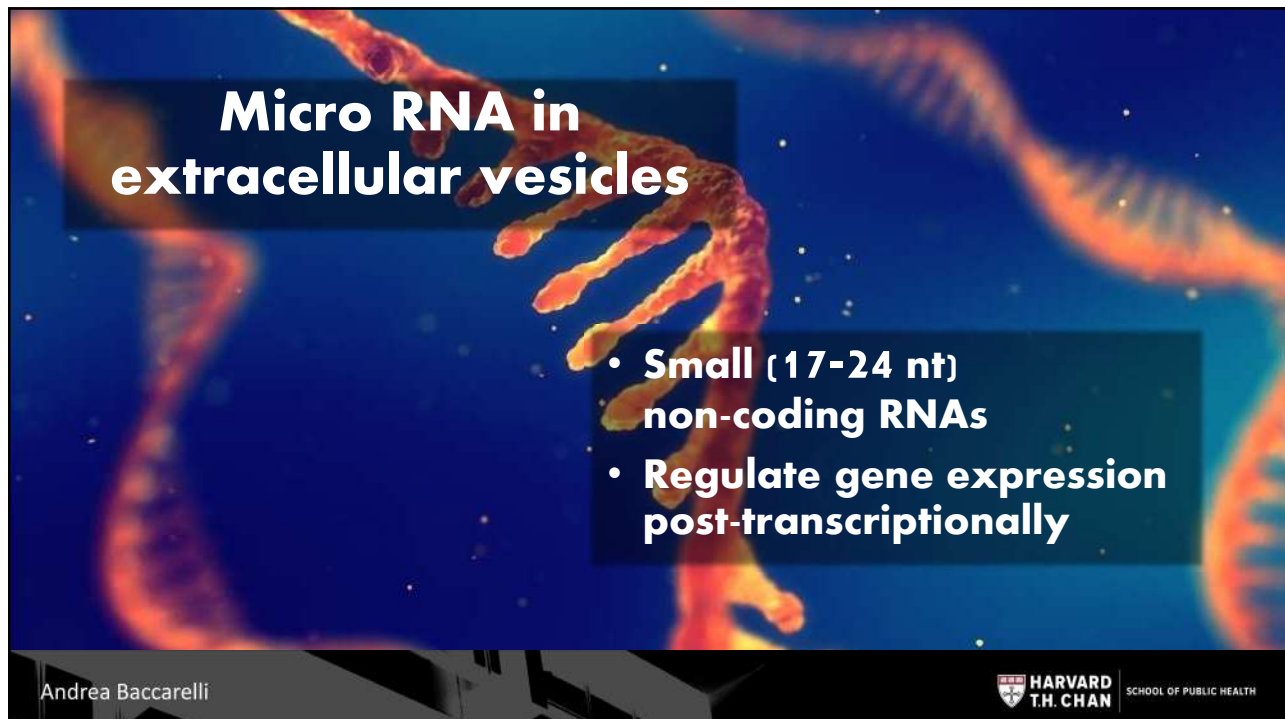
**Solution:**  
**extracellular vesicles**

- **Membrane-bound, nano vesicles (<300 nm)**
- **Found in any human biofluids**
- **Previously hidden signaling system (miRNAs and other molecules)**

Andrea Baccarelli

HARVARD T.H. CHAN SCHOOL OF PUBLIC HEALTH

41



**Micro RNA in extracellular vesicles**

- **Small (17-24 nt) non-coding RNAs**
- **Regulate gene expression post-transcriptionally**

Andrea Baccarelli

HARVARD T.H. CHAN SCHOOL OF PUBLIC HEALTH

42


## Our cells email each other

**To:** Blood neutrophils  
**Cc:** Lung alveolar cells; brain microglia  
**From:** Lung epithelial cells  
**Subject:** Response to air pollution


Dear Neutrophils,  
 As you are fully aware, over the last few days, we have been exposed to levels of particulate air pollution higher than usual.

Action is needed on your part in regard to this matter. Please see the attachment!

Yours,  
**LEP**  
 Epithelial Cells, Lung Office, Bronchi and Alveoli Division, email: [epicells@mylungs.ev](mailto:epicells@mylungs.ev)

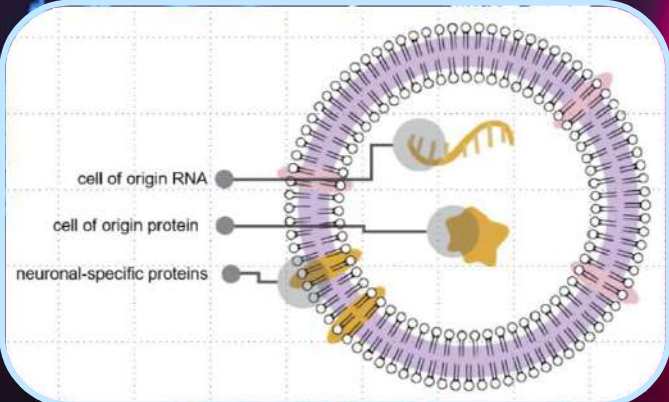
 [miRNAcargo.docx](#) (12K)

Andrea Baccarelli



43


## We can isolate in plasma vesicles released by neurons



Funded by R35ES031688

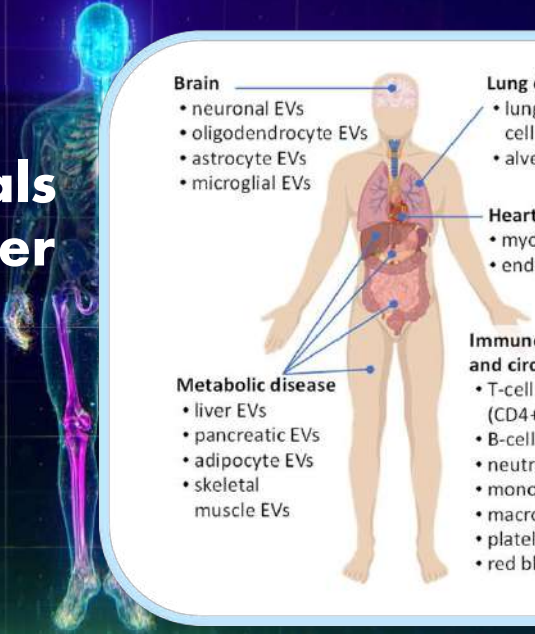
Courtesy of Neurodex

Andrea Baccarelli



47

**We can also measure chemicals where they matter**



**Brain**

- neuronal EVs
- oligodendrocyte EVs
- astrocyte EVs
- microglial EVs

**Lung disease**

- lung epithelial cell EVs
- alveolar cell EVs

**Heart disease**

- myocardial EVs
- endothelial EVs

**Metabolic disease**

- liver EVs
- pancreatic EVs
- adipocyte EVs
- skeletal muscle EVs

**Immune system and circulating cells**

- T-cell EVs (CD4+, CD8+, NK)
- B-cell EVs
- neutrophil EVs
- monocyte EVs
- macrophage EVs
- platelet EVs
- red blood cell EVs

**Diane Re**

Andrea Baccarelli

HARVARD T.H. CHAN SCHOOL OF PUBLIC HEALTH

49

**Future challenges**

**Many exposures to investigate**

**Lifetime data are needed to build lifetime molecular biomarkers**

**Validation across populations**

Andrea Baccarelli

HARVARD T.H. CHAN SCHOOL OF PUBLIC HEALTH

54




# Thanks!

- Thanks to my lab team and collaborators
- Our research is currently supported by multiple awards from the NIEHS and other NIH institutes
  - R35ES031688, PI: Baccarelli
  - R01ES032818, PIs: Baccarelli, Herbstman, Mason
  - R01ES032638, PIs: Navas-Acien, Baccarelli, Mason
  - R01AG069120, PIs: Baccarelli, Hou, Yaffe
  - R01ES032242, PIs: Colicino, Baccarelli
  - P30ES009089, PI: Baccarelli

**Andrea Baccarelli**  
 abaccarelli@hsph.harvard.edu  
 Twitter: @BaccarellIAA


55



## Pier Alberto Bertazzi

Pier Alberto Bertazzi was a renowned professor at the Università degli Studi di Milano, where he dedicated his career to advancing research in environmental and occupational health. His groundbreaking work has had a profound impact on understanding the links between environmental exposures and human health, particularly in the context of industrial disasters. Bertazzi's expertise and commitment to scientific rigor have inspired generations of researchers and students.

Andrea Baccarelli

 HARVARD T.H. CHAN SCHOOL OF PUBLIC HEALTH

56