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*Roma, Istituto Superiore di Sanità  
16 Novembre 2018*

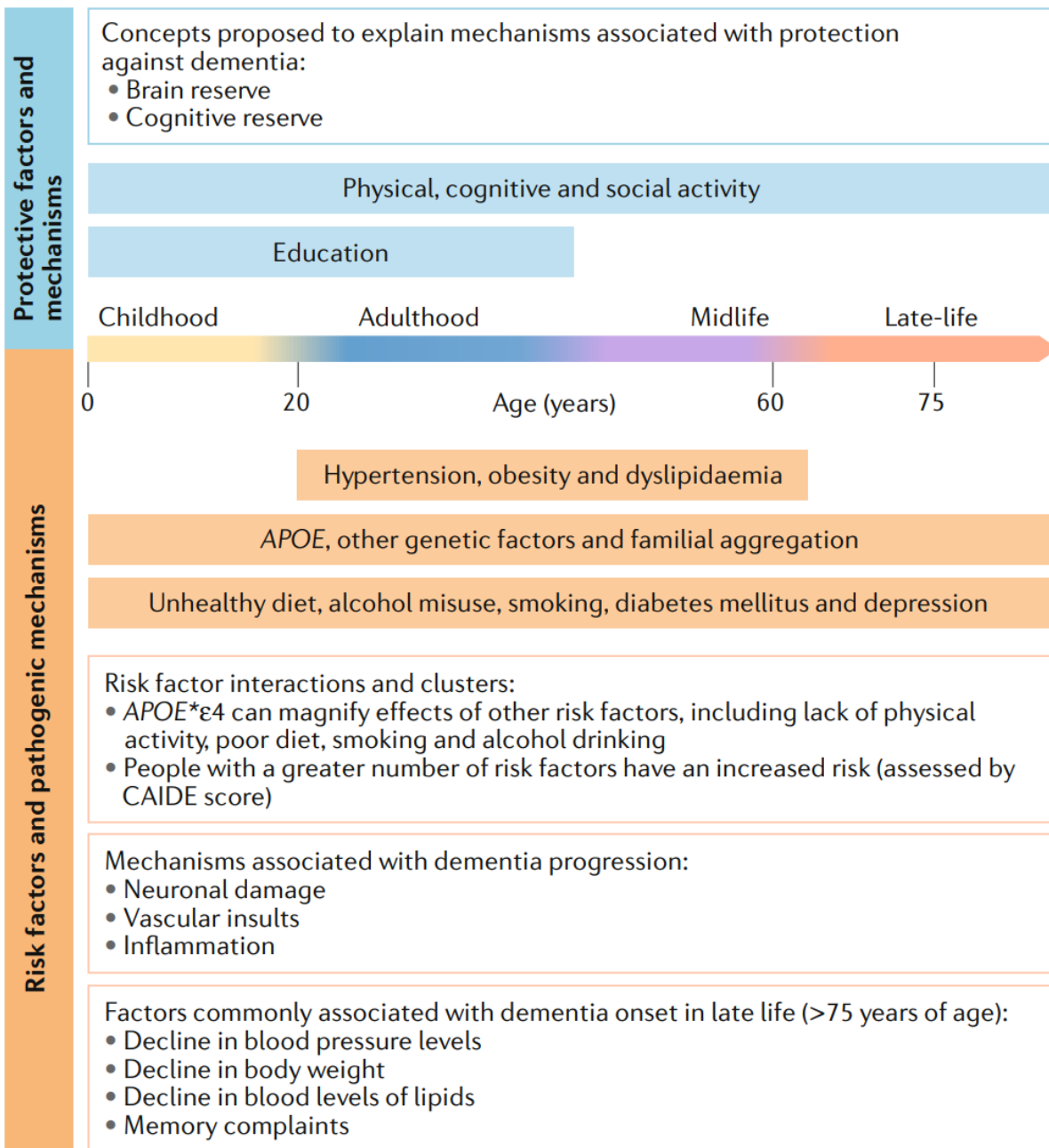
# **INQUINAMENTO ATMOSFERICO E RISCHIO DI DEMENZA**

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Department of Neurobiology, Care Sciences and Society  
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# Risk and protective factors for dementia across the lifespan



# Potential for primary prevention of AD



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	Prevalence	PAR (95% CI)
Diabetes mellitus	6.4%	2.9 (1.3-4.7)
Midlife hypertension	8.9%	5.1 (1.4-9.9)
Midlife obesity	3.4%	2.0 (1.1-3.0)
Physical inactivity	17.7%	12.7 (3.3-24.0)
Depression	13.2%	7.9 (5.3-10.8)
Smoking	27.4%	13.9 (3.9-24.7)
Low educational attainment	40.0%	19.1 (12.3-25.6)
<b>Adjusted combined</b>		<b>28.2 (14.2-41.5)</b>



**Hearing loss**  
**Traumatic brain injuries**  
**Diet**  
**Anticholinergic burden**  
**Air pollution**



**70%?**

# The polluted brain

Road traffic noise, air pollution, and risk of dementia – results from the Betula project

John Andersson<sup>a,\*</sup>, Anna Oudin<sup>b</sup>, Anna Sundström<sup>a,c</sup>, Bertil Forsberg<sup>b</sup>, Rolf Adolfsson<sup>d</sup>, Maria Nordin<sup>a</sup>

**BMJ Open** Are noise and air pollution related to the incidence of dementia? A cohort study in London, England

Iain M Carey,<sup>1</sup> H Ross Anderson,<sup>1,2</sup> Richard W Atkinson,<sup>1</sup> Sean D Beevers,<sup>2</sup> Derek G Cook,<sup>1</sup> David P Strachan,<sup>1</sup> David Dajnak,<sup>2</sup> John Gulliver,<sup>3</sup> Frank J Kelly<sup>2,4</sup>

**Living near major roads and the incidence of dementia, Parkinson's disease, and multiple sclerosis: a population-based cohort study**

Hong Chen, Jeffrey C Kwong, Ray Copes, Karen Tu, Paul J Villeneuve, Aaron van Donkelaar, Perry Hystad, Randall V Martin, Brian J Murray, Barry Jessiman, Andrew S Wilton, Alexander Kopp, Richard T Burnett

**Increased Risk of Dementia in Patients Exposed to Nitrogen Dioxide and Carbon Monoxide: A Population-Based Retrospective Cohort Study**

Kuang-Hsi Chang<sup>1,2</sup>, Mei-Yin Chang<sup>3</sup>, Chih-Hsin Muo<sup>4</sup>, Trong-Neng Wu<sup>1</sup>, Chiu-Ying Chen<sup>1</sup>, Chia-Hung Kao<sup>5,6\*</sup>

**Long-term PM<sub>2.5</sub> Exposure and Neurological Hospital Admissions in the Northeastern United States**

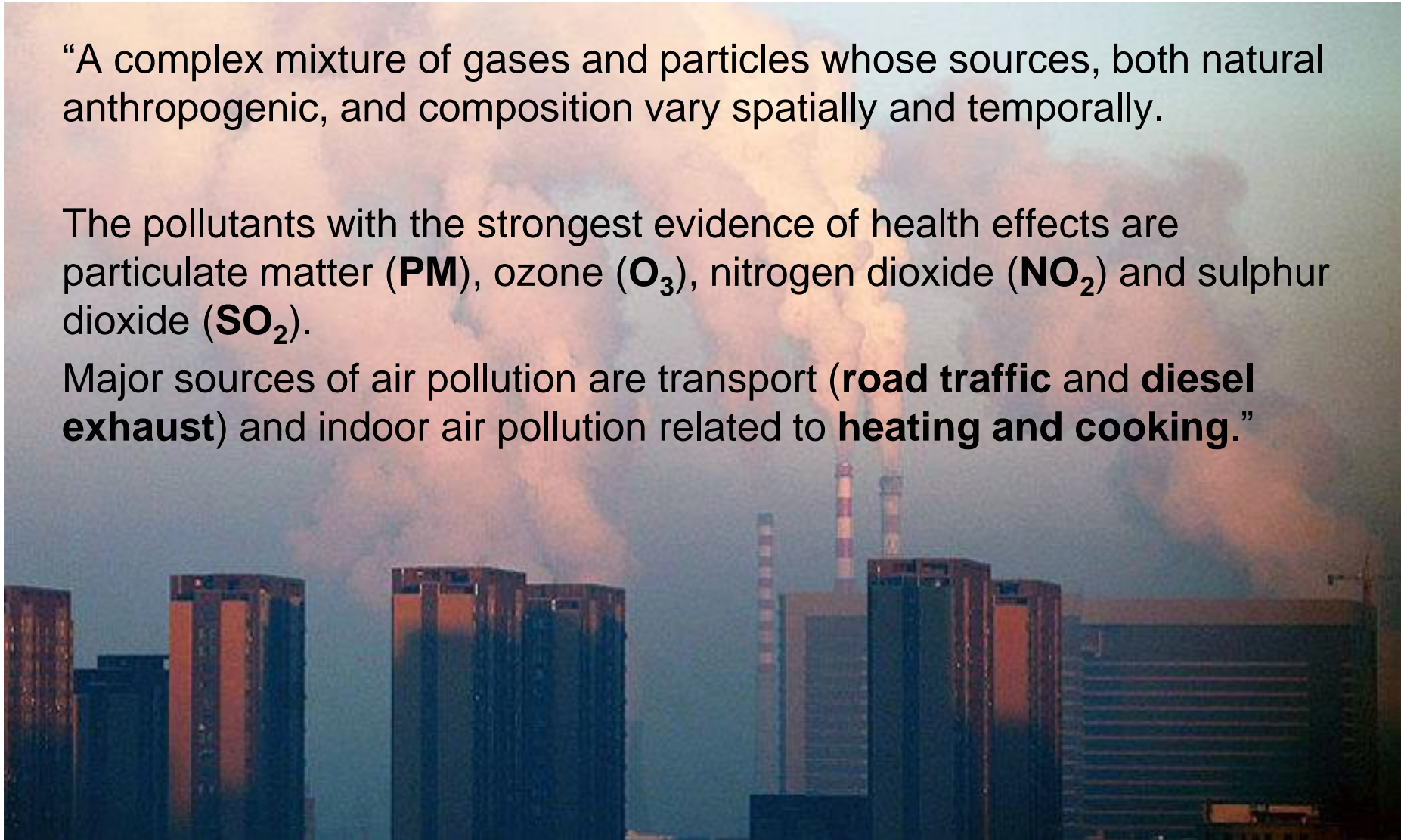
Marianthi-Anna Kioumourtoglou,<sup>1</sup> Joel D. Schwartz,<sup>1,2</sup> Marc G. Weisskopf,<sup>1,2</sup> Steven J. Melly,<sup>1</sup> Yun Wang,<sup>3</sup> Francesca Dominici,<sup>3</sup> and Antonella Zanobetti<sup>1</sup>

# What is air pollution?

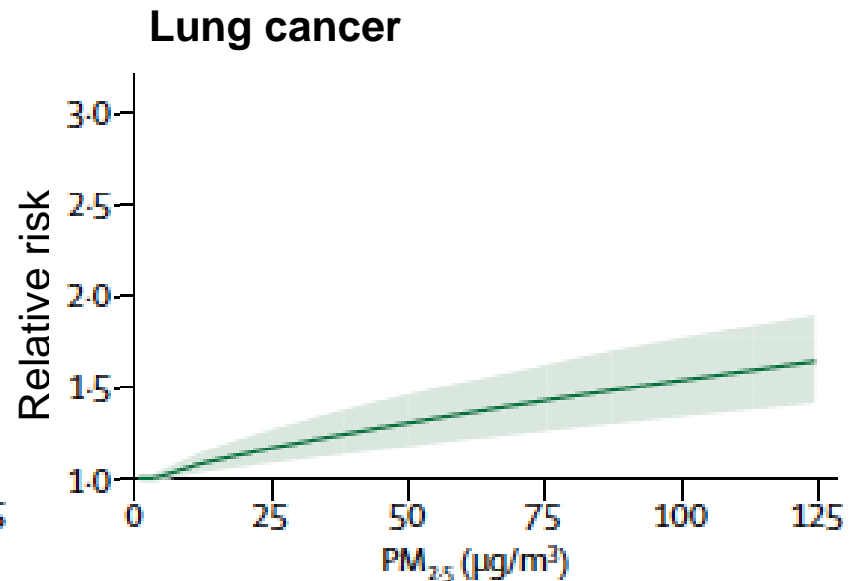
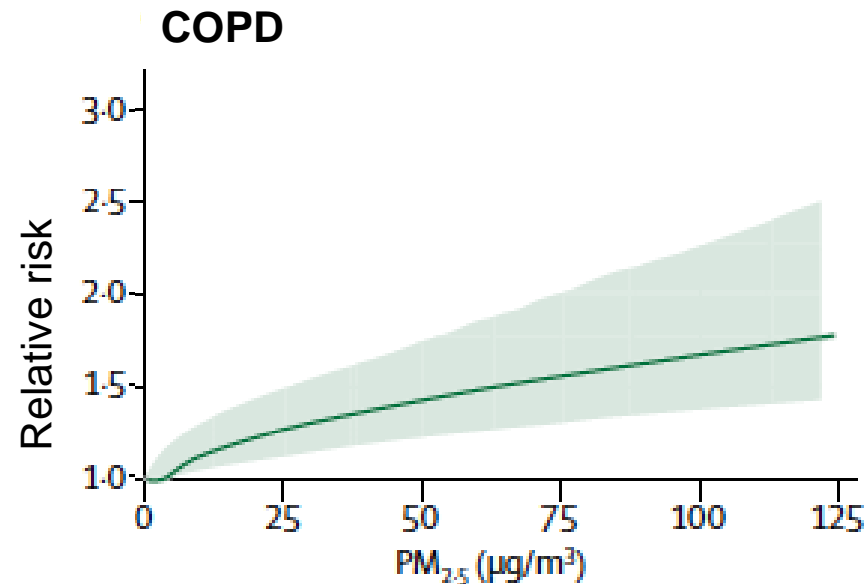
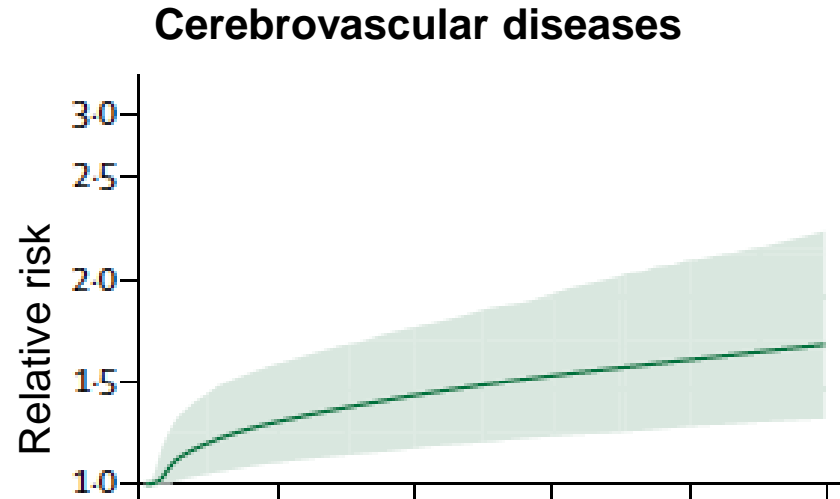
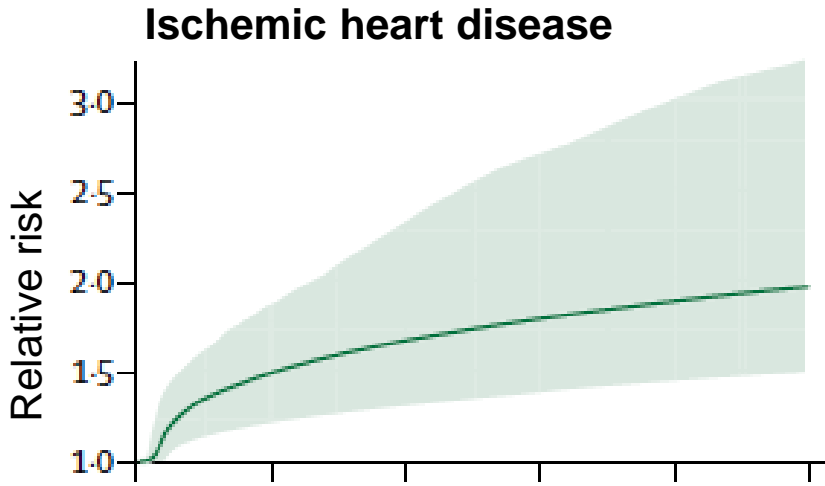
“A complex mixture of gases and particles whose sources, both natural anthropogenic, and composition vary spatially and temporally.

The pollutants with the strongest evidence of health effects are particulate matter (**PM**), ozone (**O<sub>3</sub>**), nitrogen dioxide (**NO<sub>2</sub>**) and sulphur dioxide (**SO<sub>2</sub>**).

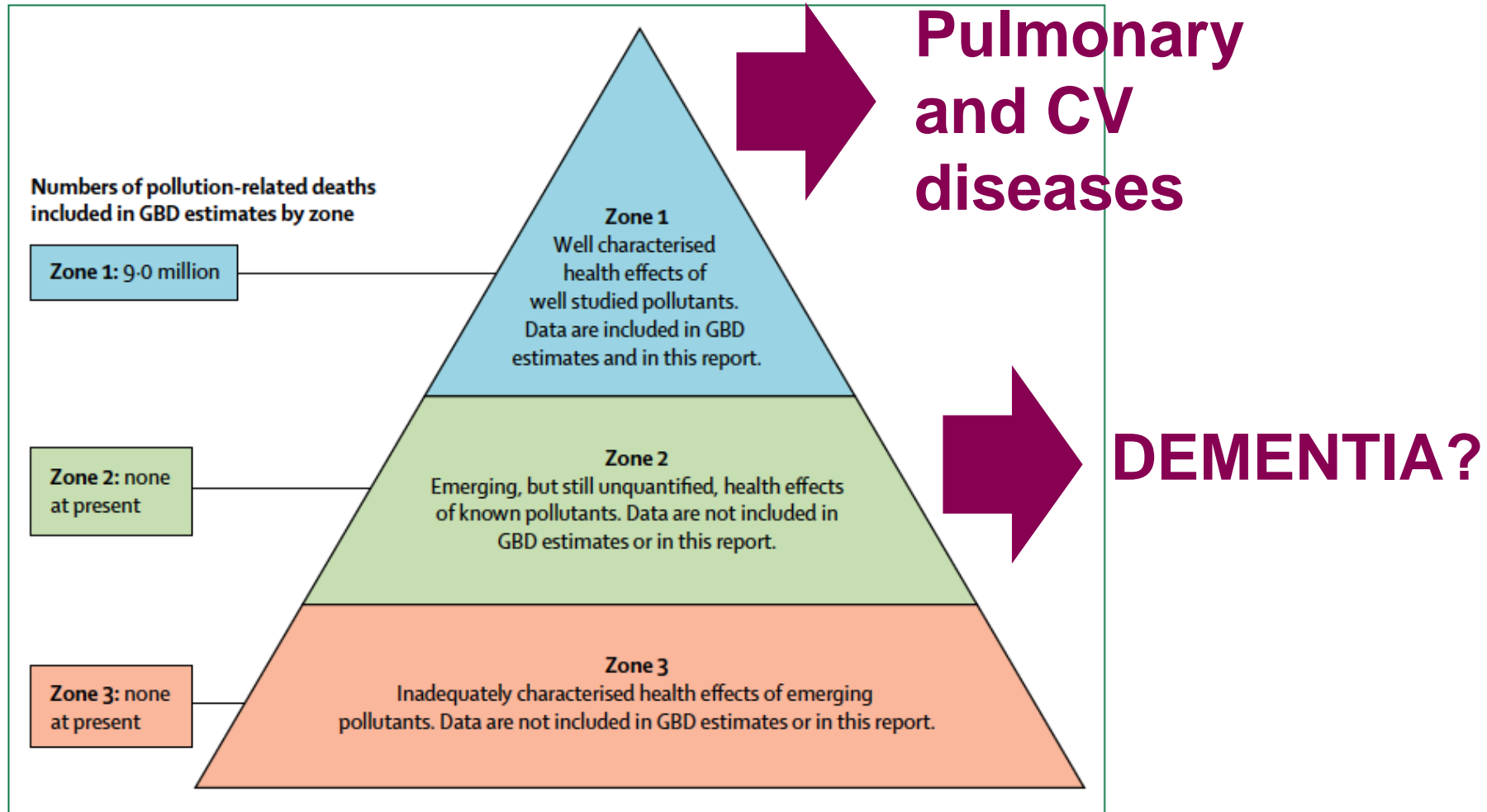
Major sources of air pollution are transport (**road traffic** and **diesel exhaust**) and indoor air pollution related to **heating and cooking**.”



# Integrated exposure-response functions

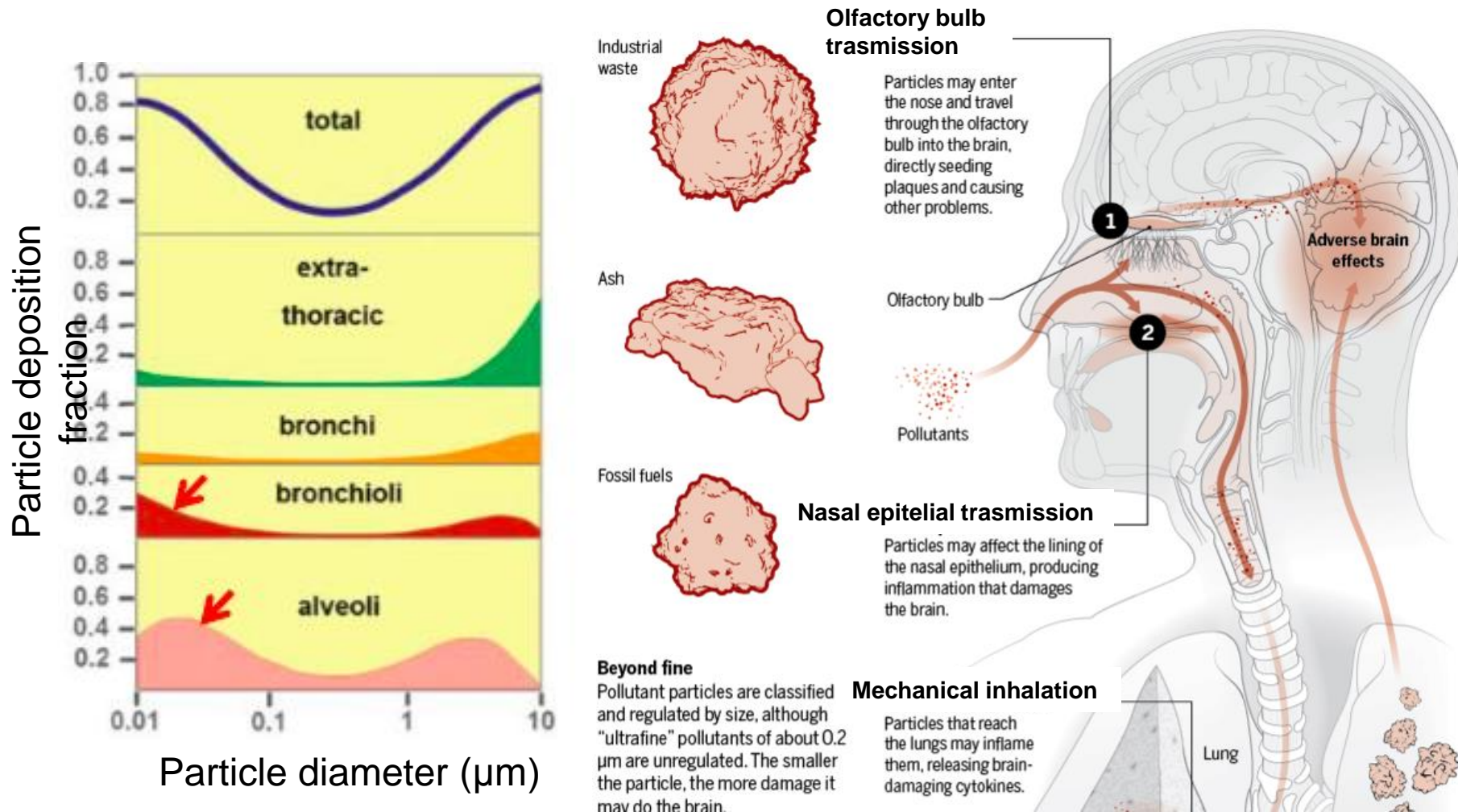


# The pollutome





# Particular Matter (PM) and the brain





# Aim-1

To systematically review, summarize and quantify the available evidence concerning the effect of air pollution on:

1. Cognitive impairment/decline
2. Dementia

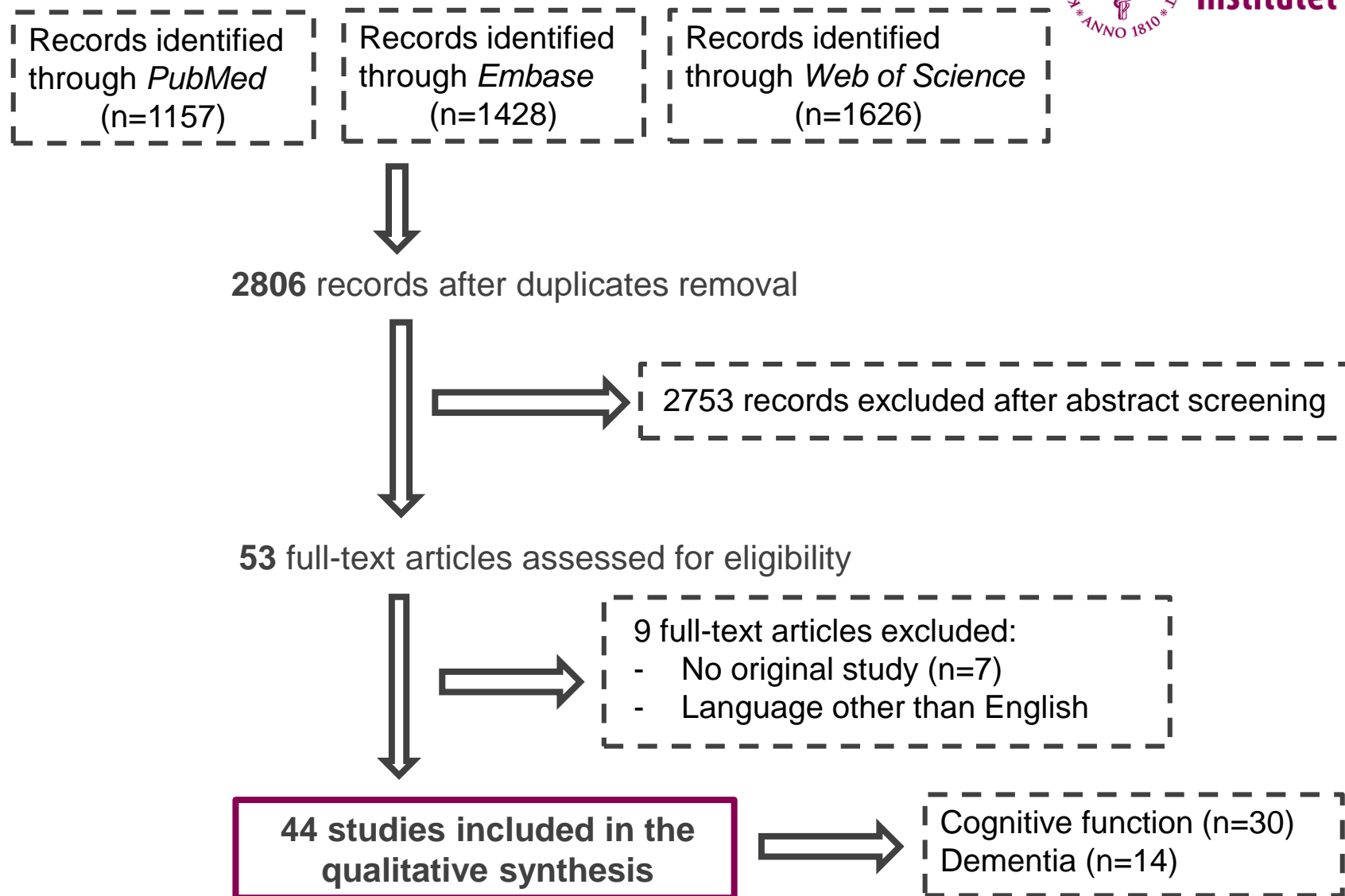
...regardless of the study setting, study design, or assessment of air pollution and cognitive function/dementia.

- PubMed, Web of Science and Embase
- Free words and MeSH terms referred to air pollution and cognitive impairment/dementia
- Two assessors screened abstracts/titles and full text articles
- Newcastle-Ottawa Scale (NOS) for risk of bias

## **Exclusion criteria**

- Cross-sectional/intervention design
  - Did not present original data
  - Studies conducted in vitro or on animals
  - Studies including persons younger than 18
-

# Results-I: PRISMA flowchart



# Results - II

- ✓  $N \approx 3$  million people
- ✓ Age range 55-100 years
- ✓ Females 44 to 65%
- ✓ Longitudinal study-design ( $N=13$ ); case-control study ( $N=1$ )
- ✓ NOS: 7-8



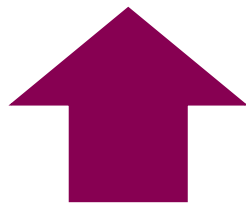
# Results-III

## Air pollution:

- Air pollutants: PM<sub>10</sub>, PM<sub>2.5</sub>, O<sub>3</sub>, NO<sub>x</sub>, NO<sub>2</sub>
- Range in years of assessment: 1
- Methods of assessment: 1
- Different groups: continuous or categorical

## Dementia

- Diagnostic: register-, hospital-, or administrative- based (N=10); DSM-IV criteria (N=4)
- Mean follow-up time: 10 yrs



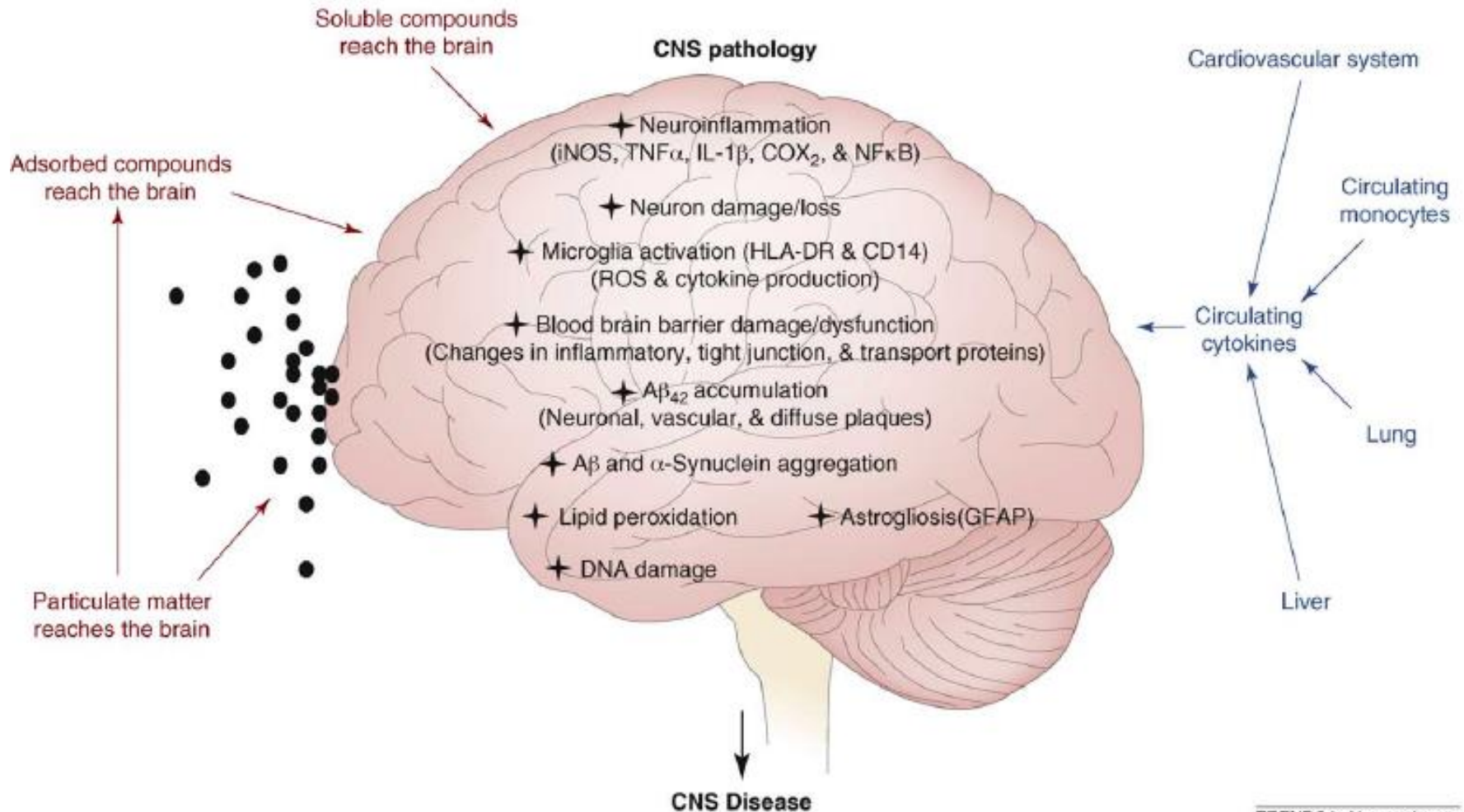
**RISK OF DEMENTIA**

**HETEROGENEITY**

# Possible mechanisms- I Neuroinflammation

## Direct mechanisms

## Peripheral mechanisms

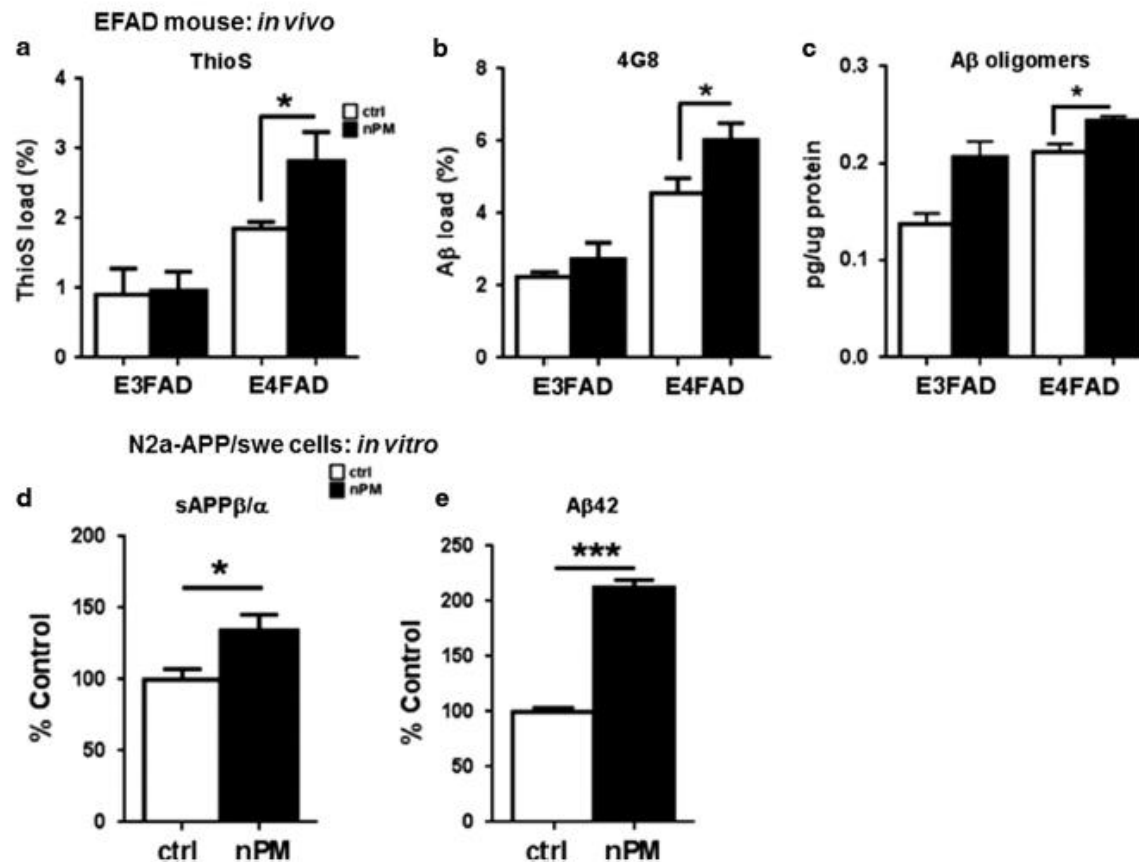




# Possible mechanisms- II

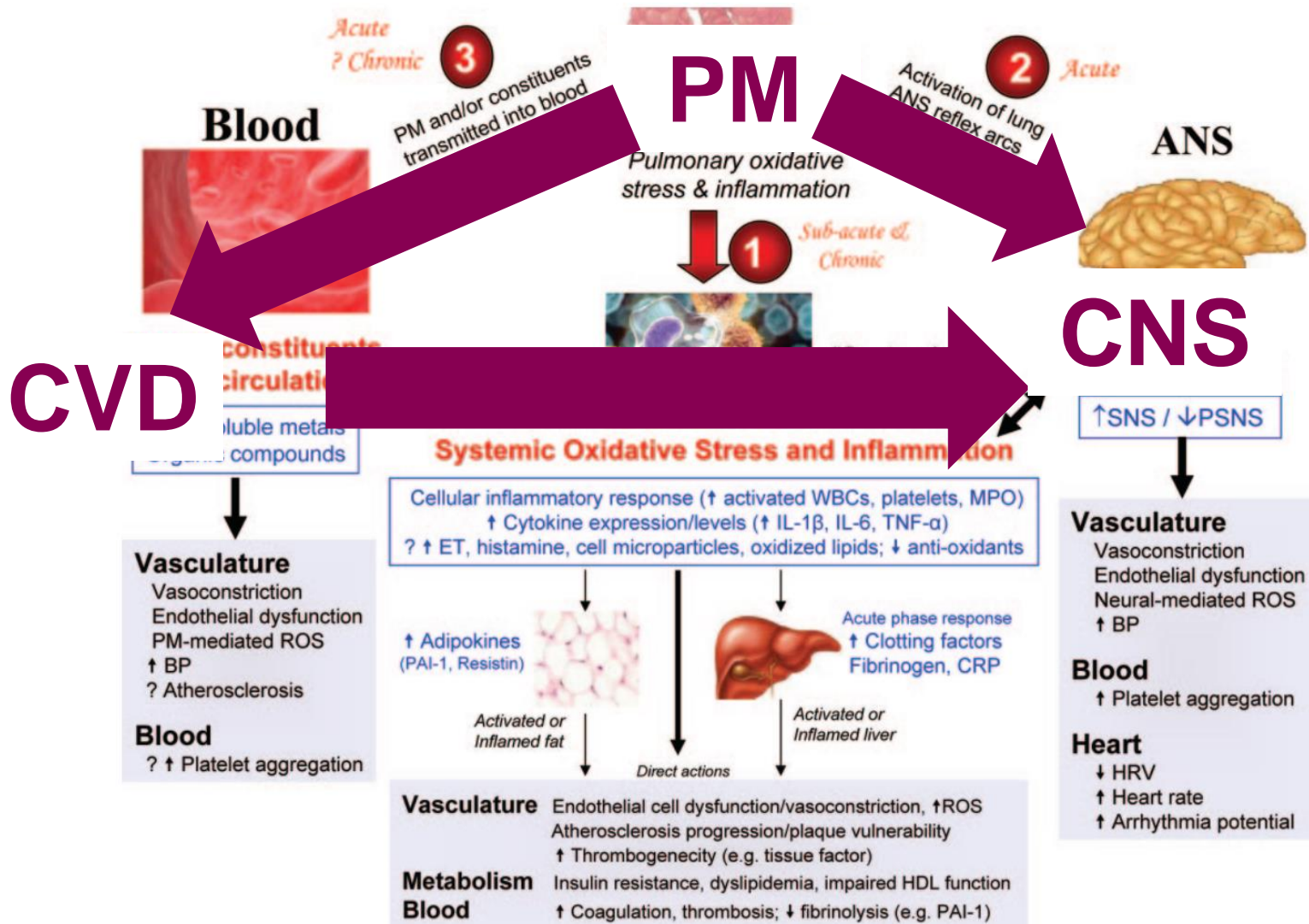
## Amyloidogenesis

Particulate air pollutants, APOE alleles and their contributions to cognitive impairment in older women and to amyloidogenesis in experimental models



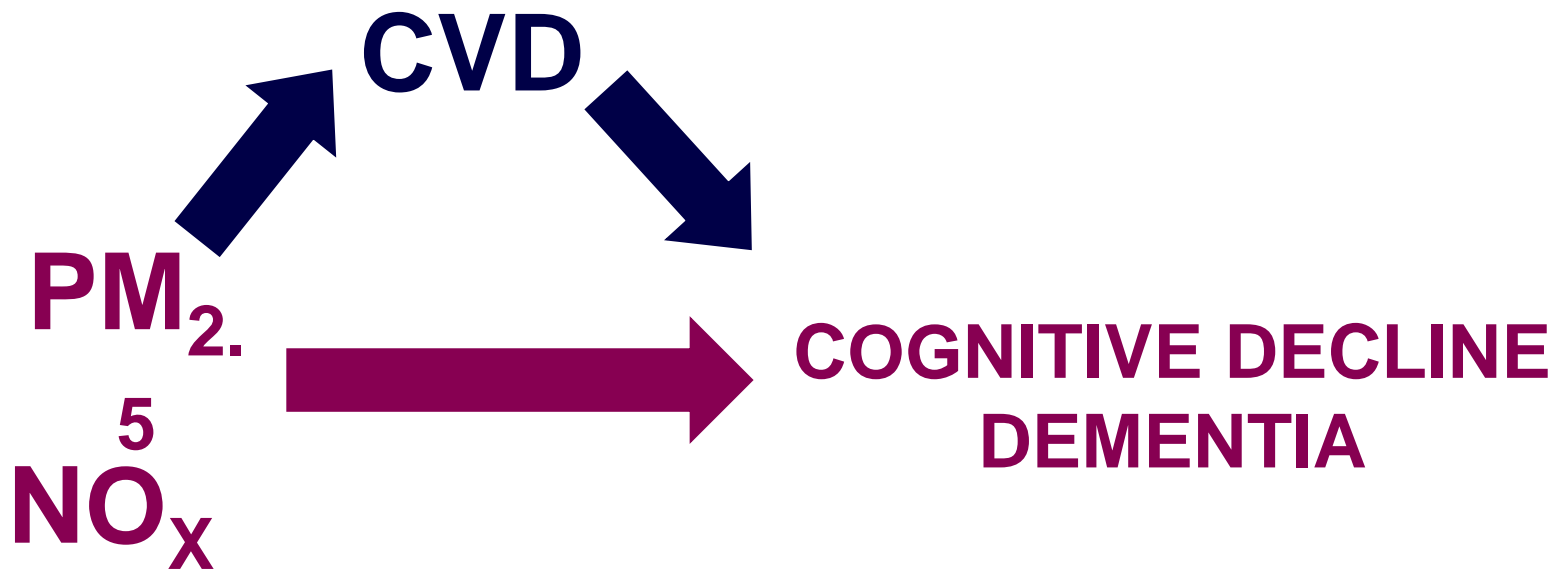
# Possible mechanisms- III

## The role of cardiovascular diseases (?)



# Aims-II

1. To investigate the association between long-term air pollution from road traffic and cognitive decline and dementia
2. To clarify the role of cardiovascular diseases (CVD) on the studied association

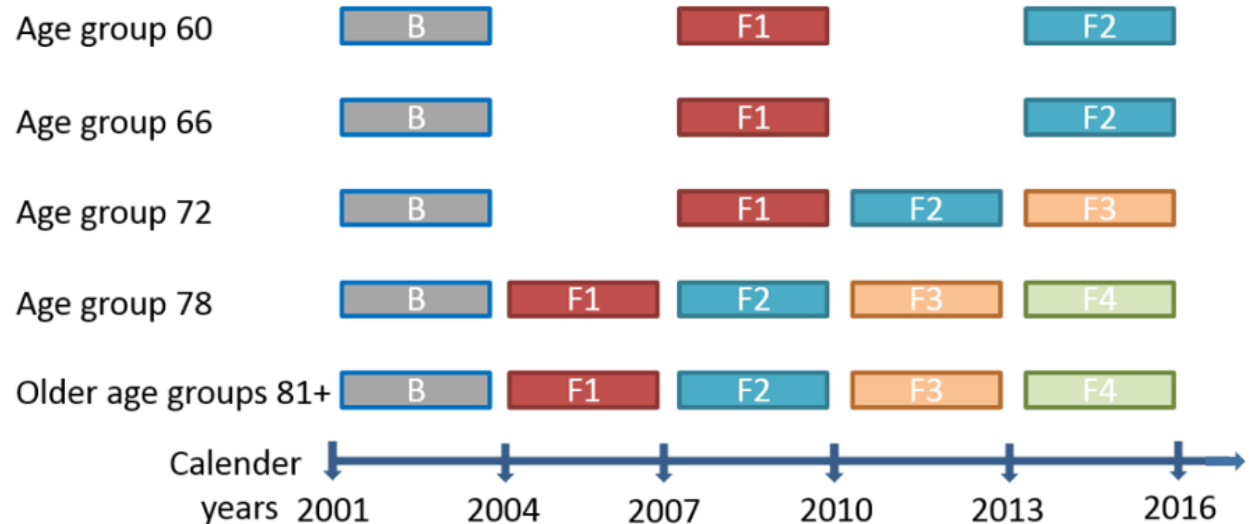


# Study population

## Swedish National Study on Aging and Care-Kungsholmen



**SNAC-K**  
N=3363



*B=baseline, F1=first, F2=second, F3=third, F4=fourth.*

**POPULATION**  
-11 cohorts 60+  
-Kungsholmen  
District  
-FU 3-6 yrs

### ASSESSMENT

- Nurse: Interview, blood and performance tests
- Physician: Interview, clinical examination
- Psychologist: Cognitive tests

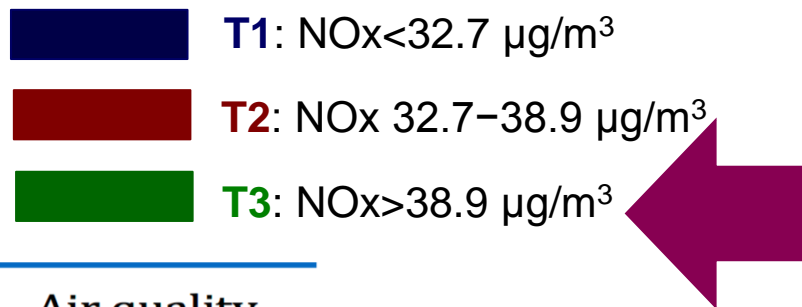
### OTHER SOURCES

- National patient registry
- National death registry

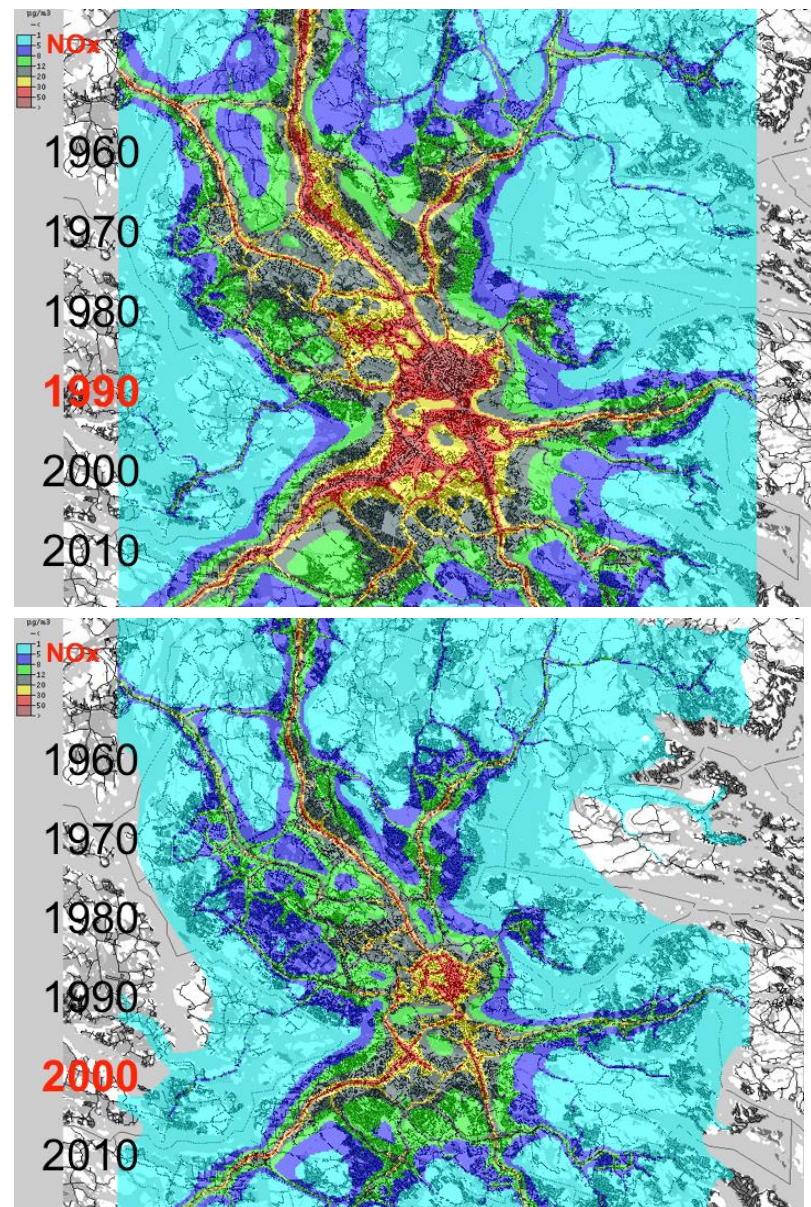


# Exposure assessment

- ✓ We estimated air pollutants (**PM<sub>2.5</sub>**, **NO<sub>x</sub>**) at the residential addresses of study participants with dispersion modeling.
- ✓ Annual average air pollution levels were calculated covering the period 1990–2001 (prior to the baseline assessments).
- ✓ The estimated PM<sub>2.5</sub> and NO<sub>x</sub> concentration at the residential address at baseline has been tertitized.



**NO<sub>x</sub> = 40 μg/m<sup>3</sup>**



## Air quality

Pollution sources and impacts, EU legislation and international agreements

Maps of the concentration of **NO<sub>x</sub>** in Stockholm in **1990** and **2000**

# Definitions of outcomes and covariates

## Outcomes

- ✓ **Cognitive decline**, MMSE scores
- ✓ **Dementia**, DSM-IV criteria following a three-step procedure

## Covariates/mediators

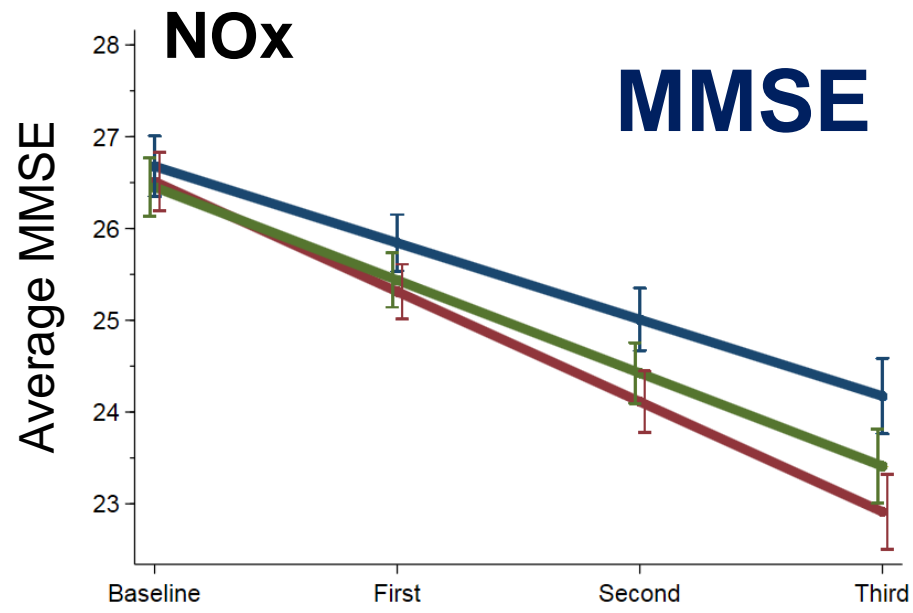
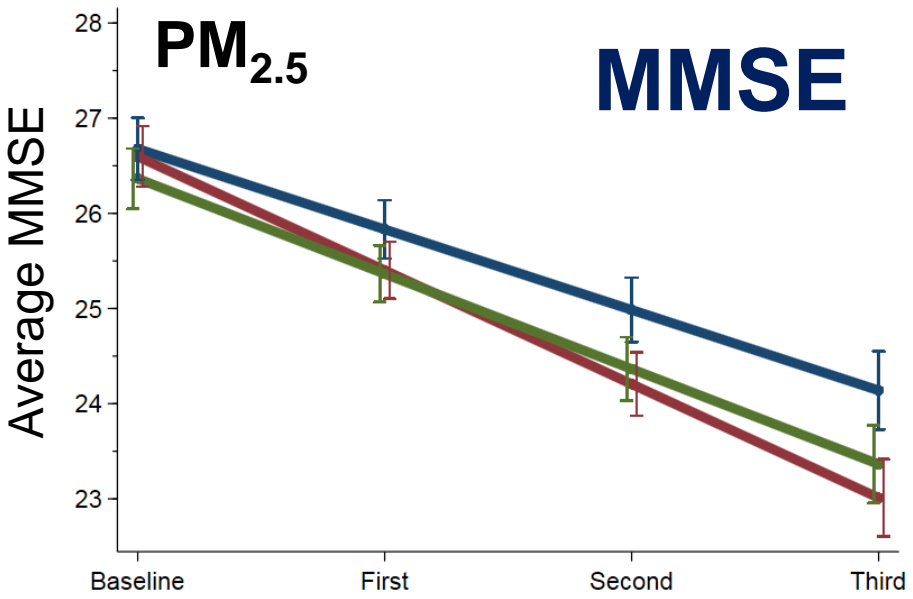
- ✓ Demographic: age, sex, education
  - ✓ Lifestyle habits: smoking.
  - ✓ **CVD**: atrial fibrillation, ischemic heart disease, heart failure
-



# Analytic approach

1. **Linear mixed-effect models** to assess the change in cognitive performance over 13 years.
  2. **Multinomial logistic regression models** were used to estimate adjusted odds ratios (OR) and 95% confident intervals (CI) between air pollutants exposure and all-type dementia, taking into account death as competing event.
  3. **The mediating effect** was analyzed through a generalized structural equation modeling, which allowed us to estimate the direct and indirect effect of the pollutants on dementia risk.
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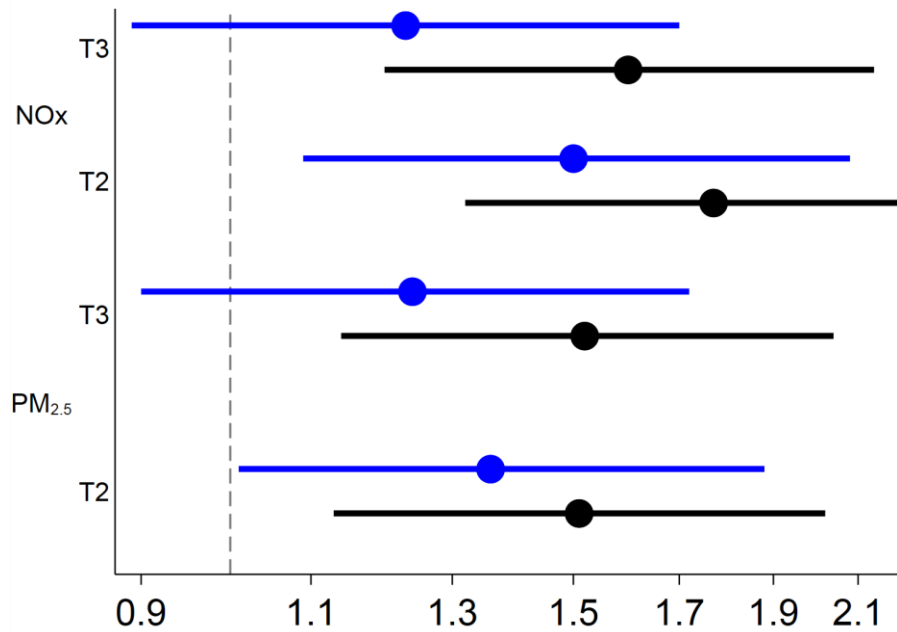
# Preliminary results-I: Cognitive decline



Linear mixed models adjusted for: age, sex, education, and smoking.

- T1:** NOx < 32.7  $\mu\text{g}/\text{m}^3$ , PM<sub>2.5</sub> < 8.6  $\mu\text{g}/\text{m}^3$
- T2:** NOx 32.7–38.9  $\mu\text{g}/\text{m}^3$ , PM<sub>2.5</sub> 8.6–8.9  $\mu\text{g}/\text{m}^3$
- T3:** NOx > 38.9  $\mu\text{g}/\text{m}^3$ ; PM<sub>2.5</sub> > 8.9  $\mu\text{g}/\text{m}^3$

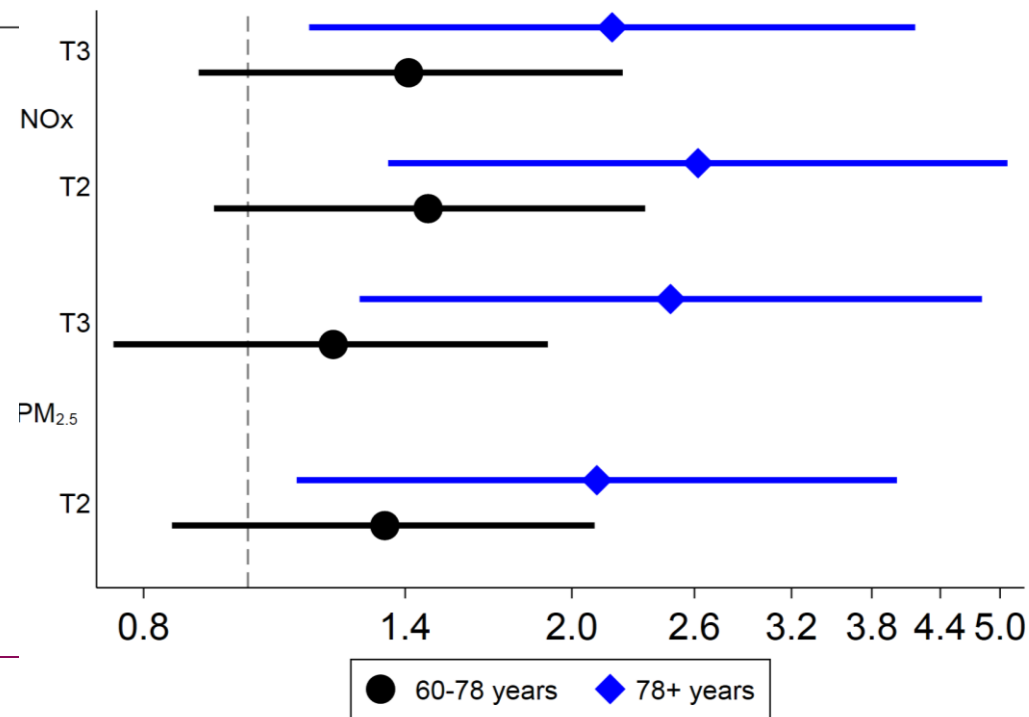
# Preliminary results-II: Dementia



Multinomial logistic regression models, considering death as a competing event.

**Model 1:** crude effect.

**Model 2:** sex, age, education, and smoking.

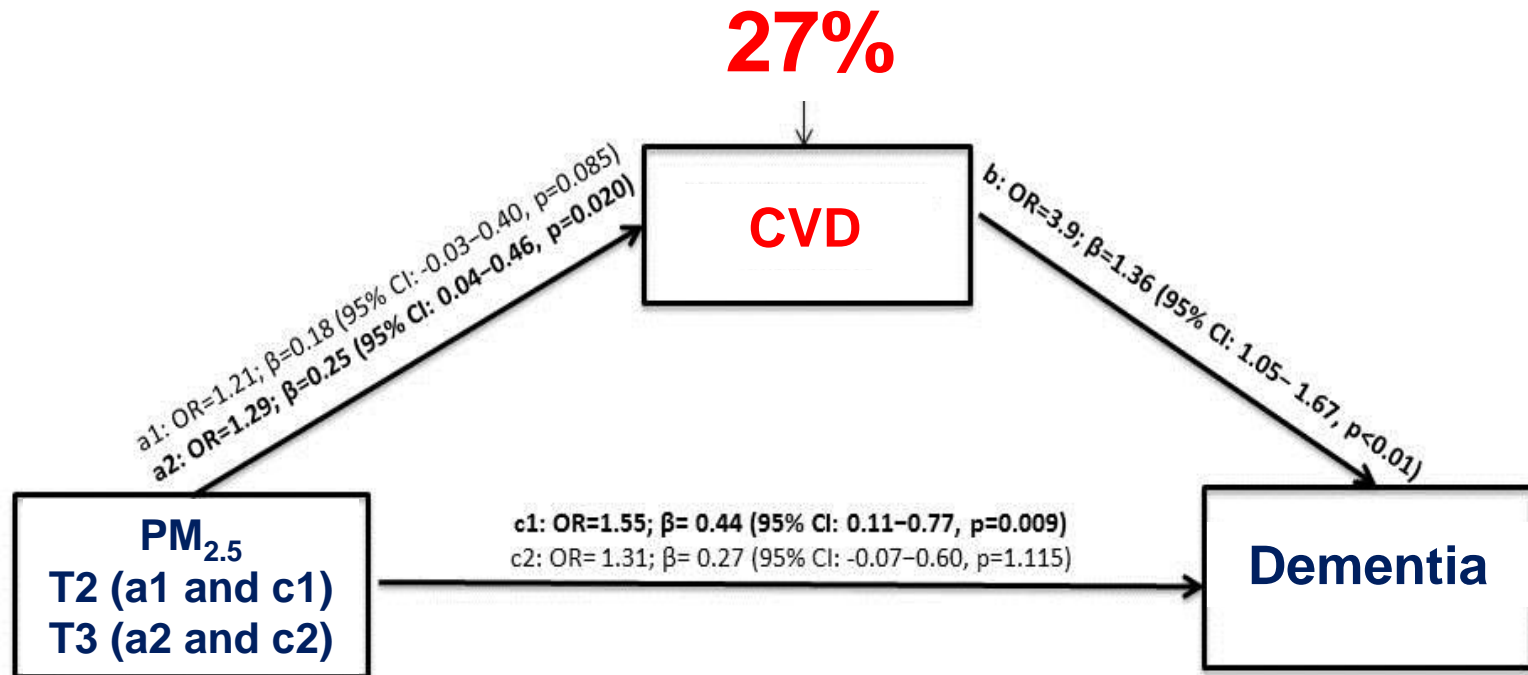


● 60-78 years    ◆ 78+ years

# Preliminary results-IV: The role of CVD

The mediating effect of **CVD** (i.e. ischemic heart disease, atrial fibrillation and heart failure) is analyzed through a generalized structural equation modeling, to estimate the direct and indirect effect of the pollutants on dementia risk.

Model is adjusted for age, sex, education, and smoking status.



# Conclusions and future research directions

1. Long-term exposure to air pollution is associated with a steeper cognitive decline and a higher risk of dementia.
2. Cardiovascular diseases might play a role in such association.



- Further explore the time relationship between air pollution and dementia.
  - Investigate the possible mechanisms behind this association.
-

# Recommendations: Lessons from the AHA



1. Evidence-based appropriate **treatment** of the traditional cardiovascular risk factors should be emphasized. This may also **lessen the susceptibility** of patients to air pollution exposures.
2. Citizens should be **educated** about the cardiovascular risks posed by air pollution.
3. Create *ad hoc* prevention policies and national **surveillance network**.



**DEMENTIA?**



# Acknowledgments



SNAC-K staff in data collection and management.  
SNAC-K participants and caregivers.

Debora Rizzuto<sup>1</sup>  
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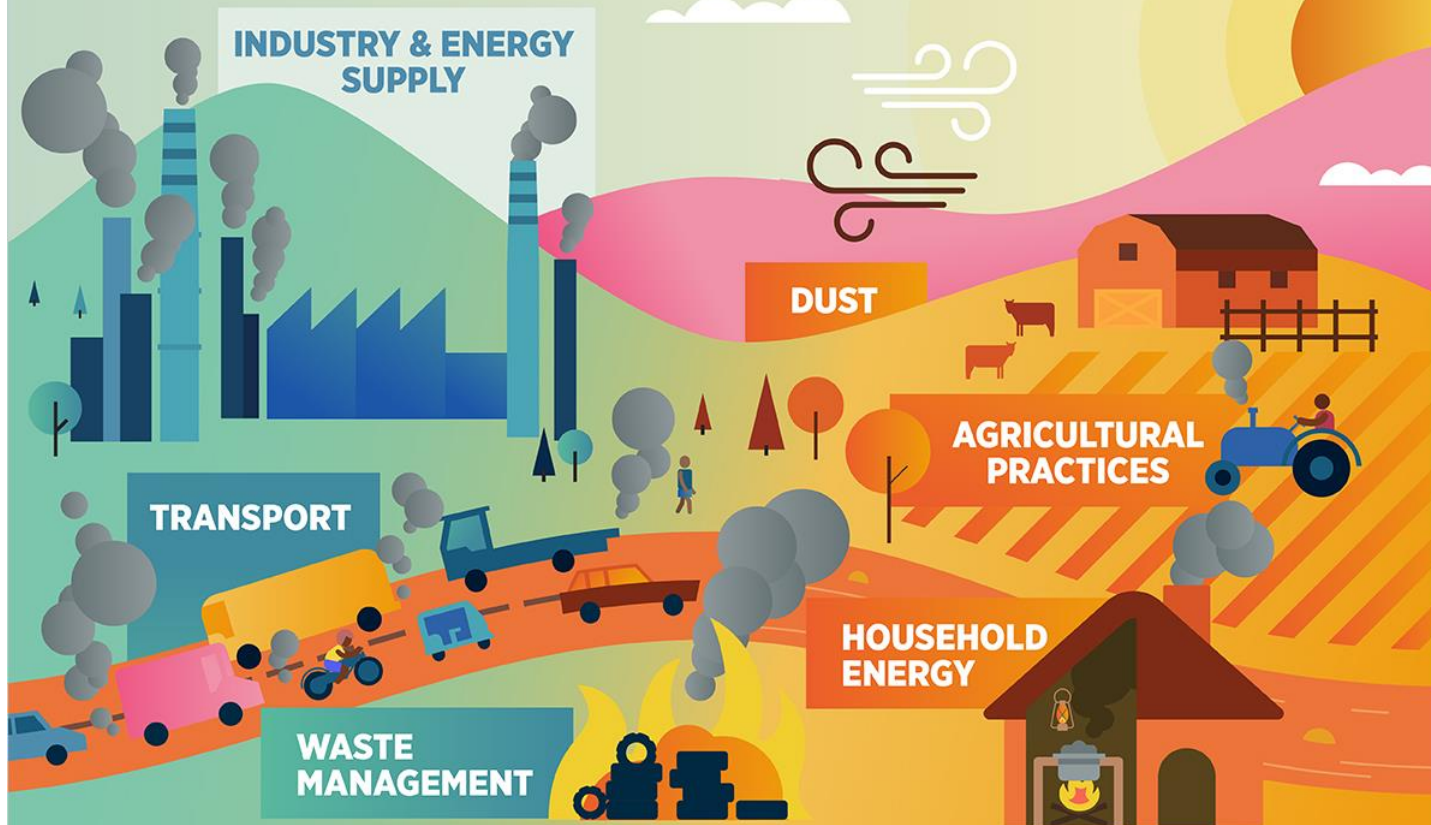


*Thank you for your attention*

# EXTRA SLIDES

# WHAT ARE THE SOURCES OF AIR POLLUTION?

Outdoor air pollution affects urban and rural areas and is caused by multiple factors:



**Countries cannot tackle air pollution alone.**  
It is a global challenge we must all combat together.

# AIR POLLUTION – THE SILENT KILLER



Every year, around **7 MILLION DEATHS** are due to exposure from both outdoor and household air pollution.

**Air pollution is a major environmental risk to health.** By reducing air pollution levels, countries can reduce:



Stroke

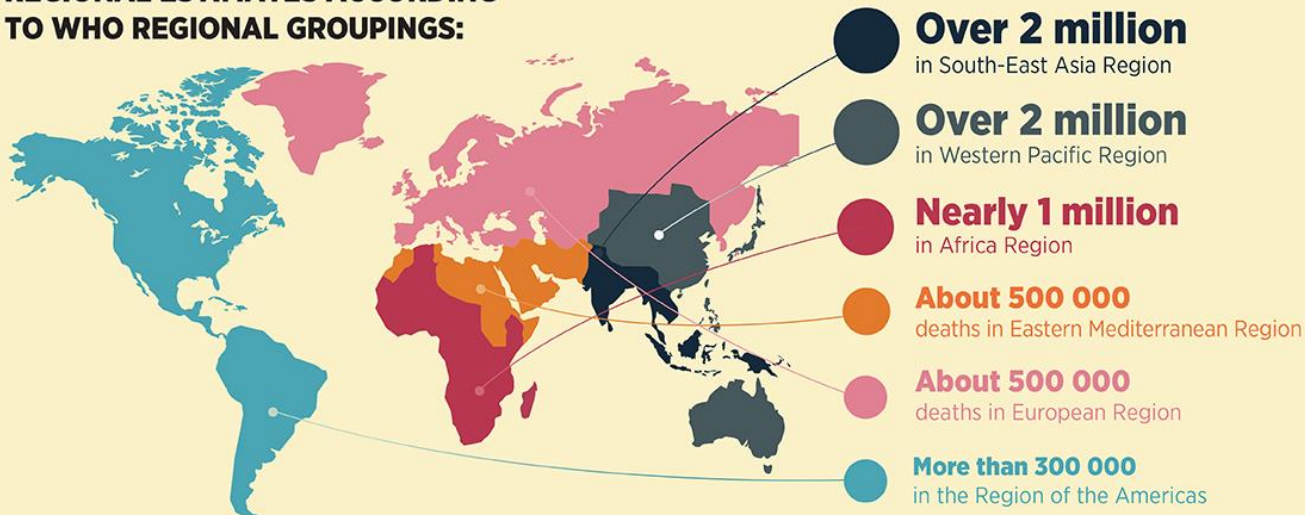


Heart disease



Lung cancer, and both chronic and acute respiratory diseases, including asthma

## REGIONAL ESTIMATES ACCORDING TO WHO REGIONAL GROUPINGS:



# Possible pathways through the CNS

