7TH INTERNATIONAL MEETING ON PULMONARY RARE DISEASES AND ORPHAN DRUGS

PROGRAM

ENDORSED BY ERS EUROPEAN RESPIRATORY SOCIETY

MILANO – ITALY
CONGRESS CENTER
PALAZZO DELLE STELLINE
FEBRUARY 24 - 25, 2017

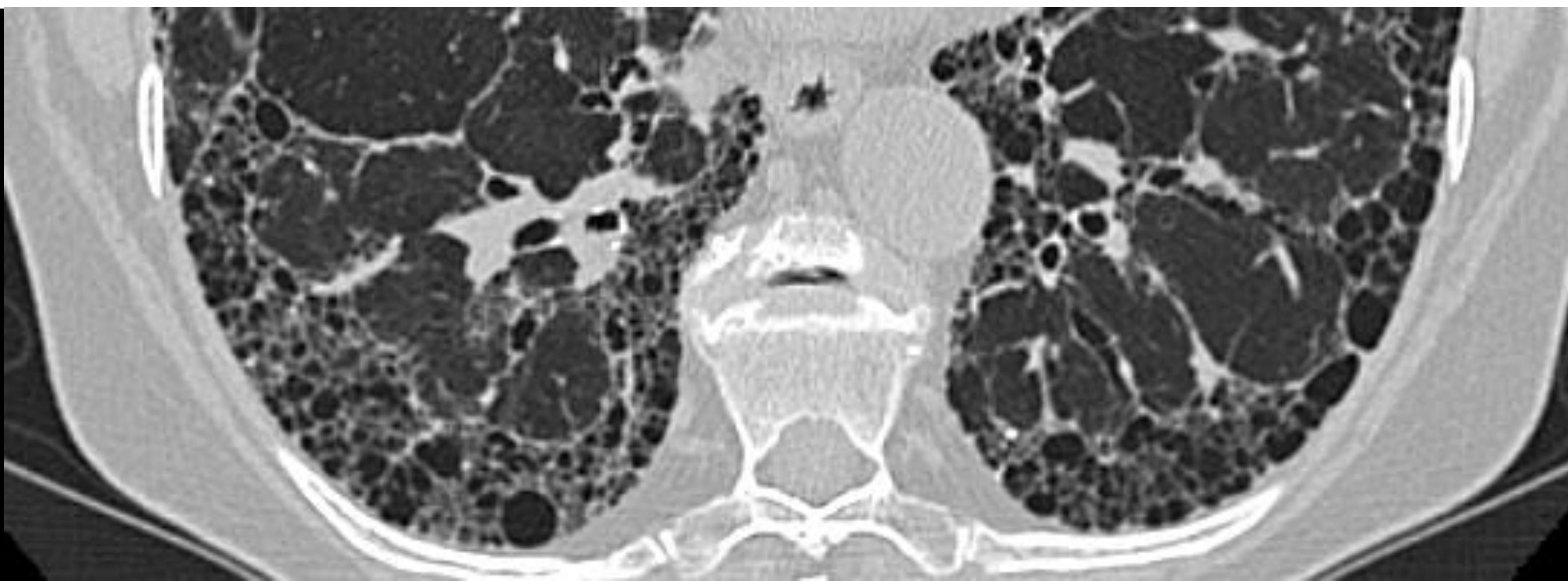
Epidemiology of IPF and air pollution

Antonella Caminati

U.O. di Pneumologia e Terapia Semi Intensiva-Servizio di Fisiopatologia Respiratoria ed Emodinamica Polmonare
Osp. San Giuseppe – MultiMedica IRCCS Milano

The epidemiology of IPF has not been completely investigated

Estimated incidence and prevalence rates are highly variable



Incidence and prevalence of IPF varies across studies

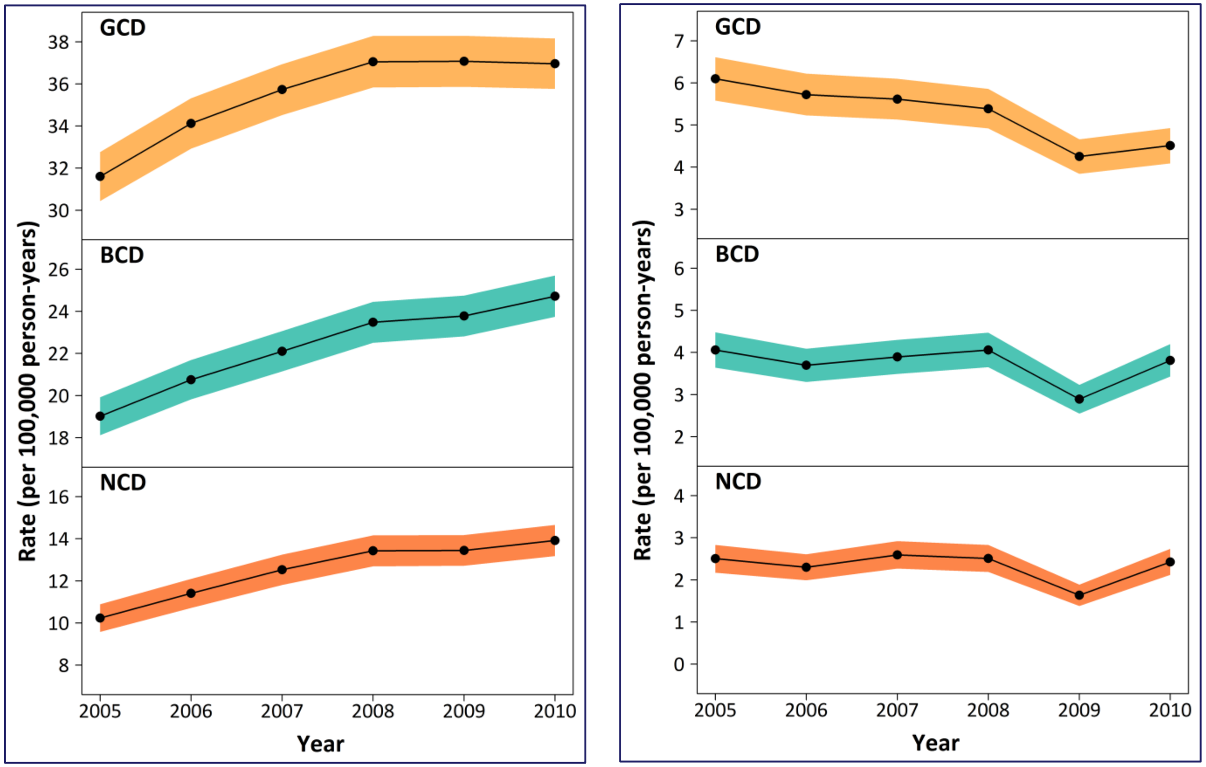
Is it due to real geographic variation (differences between races or environmental factors, etc.) or due to the differences in case finding methodologies, study designs and diagnostic criteria?

Epidemiology of idiopathic pulmonary fibrosis in Northern Italy

S. Harari et al PlosOne 2016

Case Definition	Criteria
Generic	A hospitalization or an outpatient visit with diagnosis of IPF
Broad	Meet GCD; No medical claims with a diagnosis code for any other type of ILDs
Narrow	Meet BCD One or more medical claims with a procedure code for surgical lung biopsy, or transbronchial lung biopsy or computed tomography of the thorax

Prevalence *Incidence*



Epidemiology of idiopathic pulmonary fibrosis in Northern Italy

S. Harari et al. PlosOne 2016

Authors	Cauntry	Study period	Pop	Age pop.	Mortality*	Incidence*	Prevalence*
Harari et al	Italy (Lombardia)	2005-2010	~10,000,000	-	-	Generic: 5.3 (5.1-5.4) Broad: 3.7 (3.6-3.9) Narrow: 2.3 (2.2-2.5)	Generic: 35.5 (35.0-36.0) Broad: 22.4 (22.0-22.8) Narrow: 12.6 (12.3-12.8)

** rates per 100000 person-year*

Epidemiology of idiopathic pulmonary fibrosis in Northern Italy

S. Harari et al PlosOne 2016

- In the period 2005-2010 in Northern Italy IPF prevalence is increasing and incidence is stable
- Prevalence and incidence of IPF are clearly higher in older age groups, a finding consistent with the role of aging in the pathogenesis of IPF
- IPF also appears to be more common in men compared to women, however, some postulate this may be due to sex differences in historical smoking patterns rather than an inherent sex-related risk for IPF

- The differences in epidemiological parameters might be a result of the heterogeneous methods used than true geographical differences in IPF epidemiology
- It is unknown if the incidence and prevalence of IPF are influenced by **geographic**, ethnic, cultural or racial factors

ATS/ERS/JRS/ALAT guidelines 2011

- ***Evidences about the role of air pollution in the development and course of IPF are scarce***
- Increased ozone and nitrogen dioxide exposure over the preceding 6 weeks was associated with an increased risk of acute exacerbation of IPF

Johannson KA et al. Eur Respir J 2014; 43:1124

Acute exacerbation of idiopathic pulmonary fibrosis associated with air pollution exposure

Johannsson KA et al Eur Respir J 2014; 43:1124

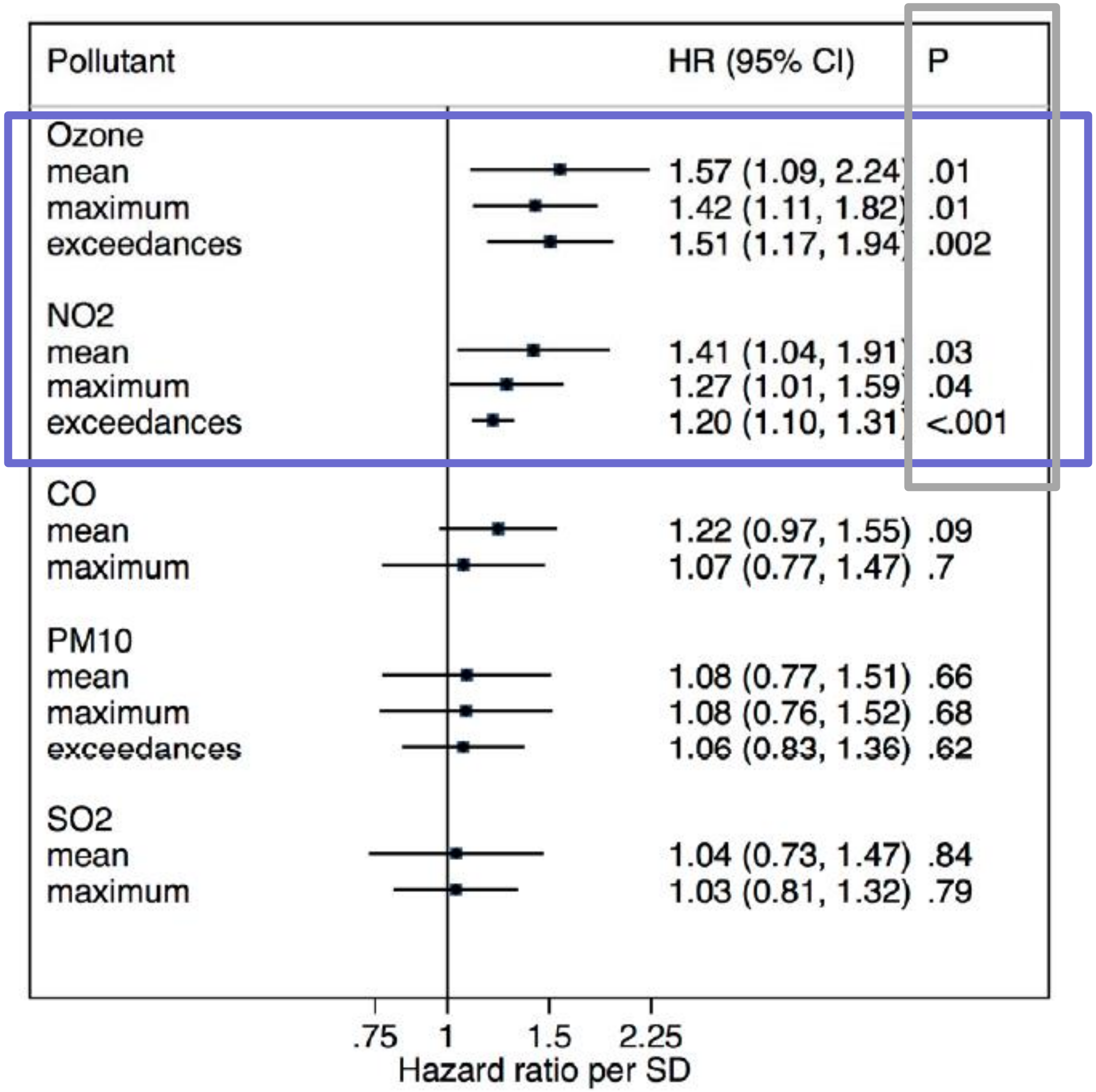
“Our study demonstrates a significant relationship between ambient O3 and NO2 levels and acute exacerbation of IPF.

The magnitude of the associated risk is comparable to what has been reported for exacerbation of other chronic lung diseases

Air pollution is a potentially modifiable risk factor either via behavioural adaptation of the patient or community-level reductions in exposure through environmental policy”

Acute exacerbation of idiopathic pulmonary fibrosis associated with air pollution exposure

Johannson KA et al Eur Respir J 2014; 43:1124



IPF and air pollution

Sesé, Annesi-Maesano, Thorax 2017 In press

- Increased mean level of ozone in the 6 weeks before an AE and in the 16 weeks before an SAE (HR= 1.0234, 95%CI: 1.0005-1.0468, p=0.045).

- Mortality was significantly associated with increased levels of exposure to PM_{10} (HR=2.0117, 95%CI: 1.0723-3.7728) per 10 μg/m^3, and $PM_{2.5}$ (HR=2.815, 95%CI: 1.7125-4.6185) per 5 μg/m^3

  – Cumulative levels of exposure to particulate matter PM_{10} and $PM_{2.5}$ were above WHO recommendations in 34% and 100% of patients, respectively.

What's the role of chronic air pollution exposure in the development of IPF?

Global risk factor ranking

1. High blood pressure
2. Smoking
3. Alcohol use
4. Household air pollution
5. Low fruit consumption
6. High BMI
7. High plasma glucose
8. Childhood underweight
9. Ambient air pollution
10. Physical inactivity

*Air pollution is a **major risk factor** for public health*

The Global Burden of Disease Study 2010
Lancet 2013, January 4

Air pollution affects multiple organs immediately and has long-term consequences

Lung

- **Respiratory Disease Mortality**
- **Respiratory Disease Morbidity**
- **Lung Cancer**
- **Pneumonia**
- Upper and lower respiratory symptoms
- Airway inflammation
- Decreased lung function
- Decreased lung growth

Brain

- **Stroke**
- Neurological development
- Mental Health
- **Neurodegenerative diseases**

Heart

- ***Cardiovascular Disease Mortality***
- ***Cardiovascular Disease Morbidity***
- ***Myocardial Infarction***
- ***Arrhythmia***
- ***Congestive Heart Failure***
- *Changes in Heart Rate Variability*
- *ST-Segment Depression*

Metabolism

- Insulin Resistance
- **Type 2 diabetes**
- **Type 1 diabetes**
- Bone metabolism

Vascular system

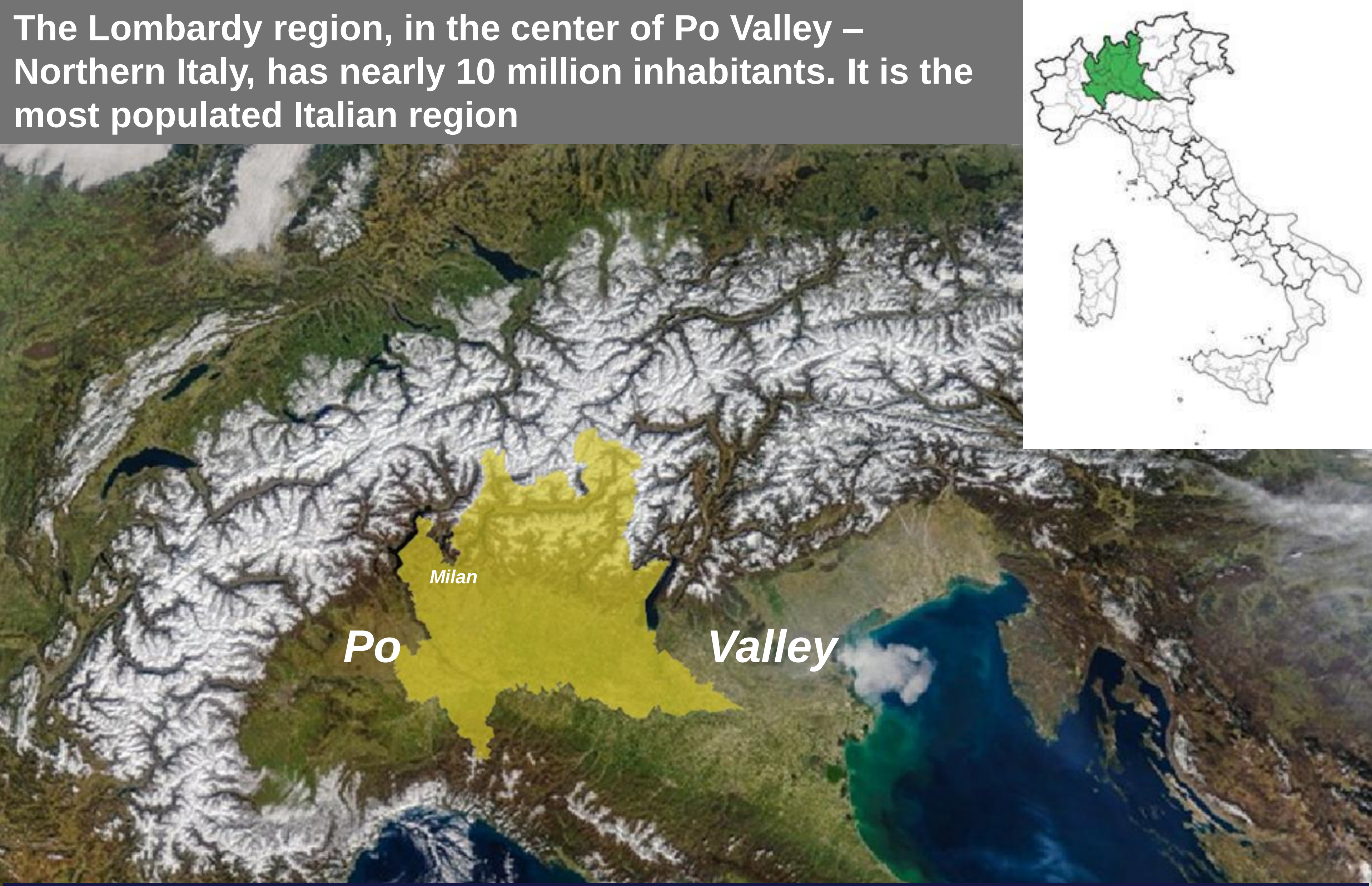
- **High blood pressure**
- Endothelial dysfunction
- Increased blood coagulation
- Systemic inflammation
- **Deep Venous Thrombosis**

Regenerative organs

- ***Premature Birth***
- ***Decreased Birth Weight***
- *Decreased foetal growth*
- *In uterine growth retardation*
- *Decreased sperm quality*
- *Preclampsia*

Joint ERS / ATS statement (ERJ 2017)

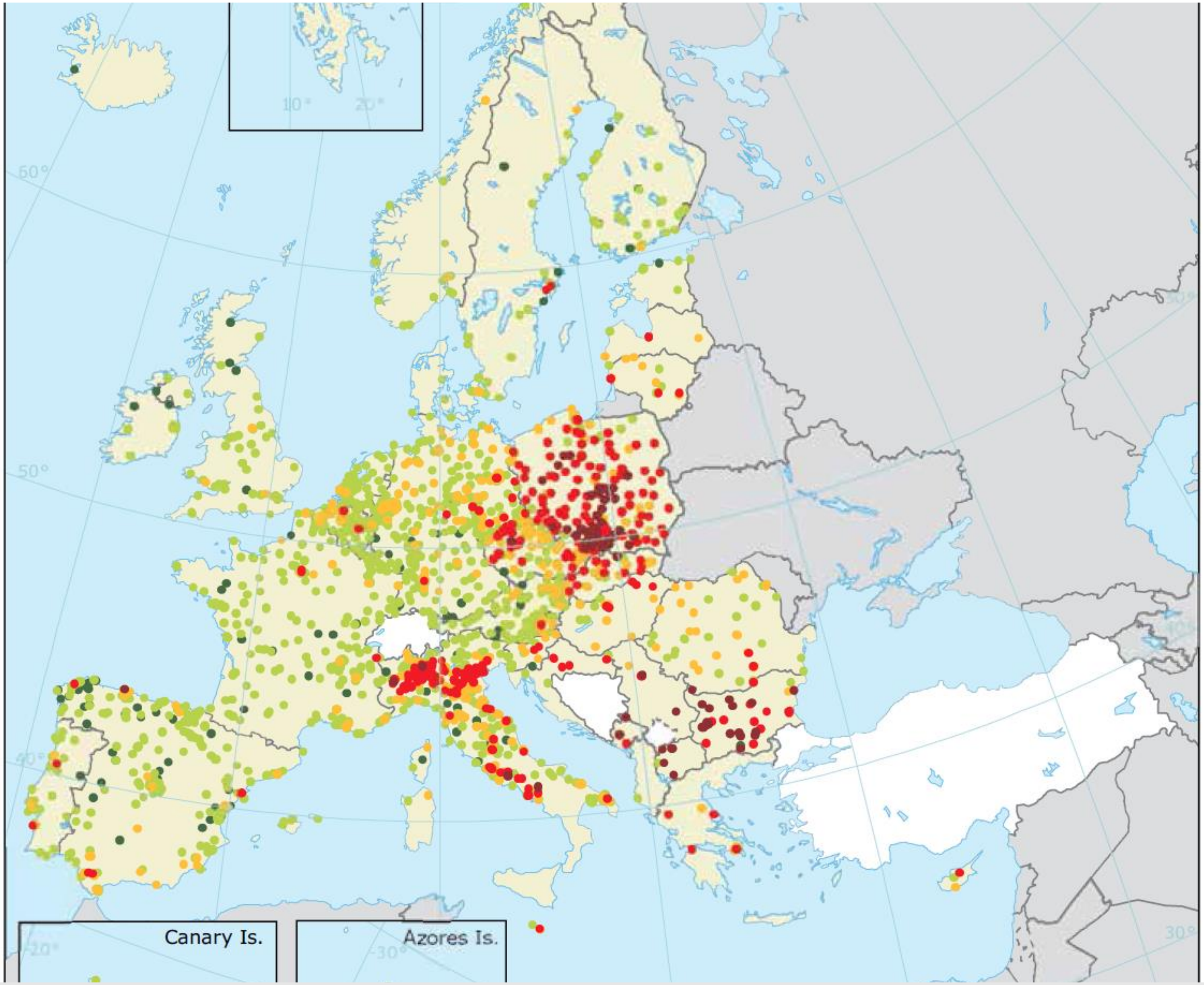
The Lombardy region, in the center of Po Valley – Northern Italy, has nearly 10 million inhabitants. It is the most populated Italian region



One of the most polluted areas in Europe because of industrial plants, intensive agriculture and high population density. The presence of the Alps and Apennines acts as a barrier favoring stagnation conditions and accumulation of pollutants

The Po River basin is bordered on three sides by mountains. Weather disturbances are frequently unable to cross the Alpine barrier. Poor air mass exchange causes frequent phenomena of thermal inversion, with smog and pollution being trapped close to the ground.

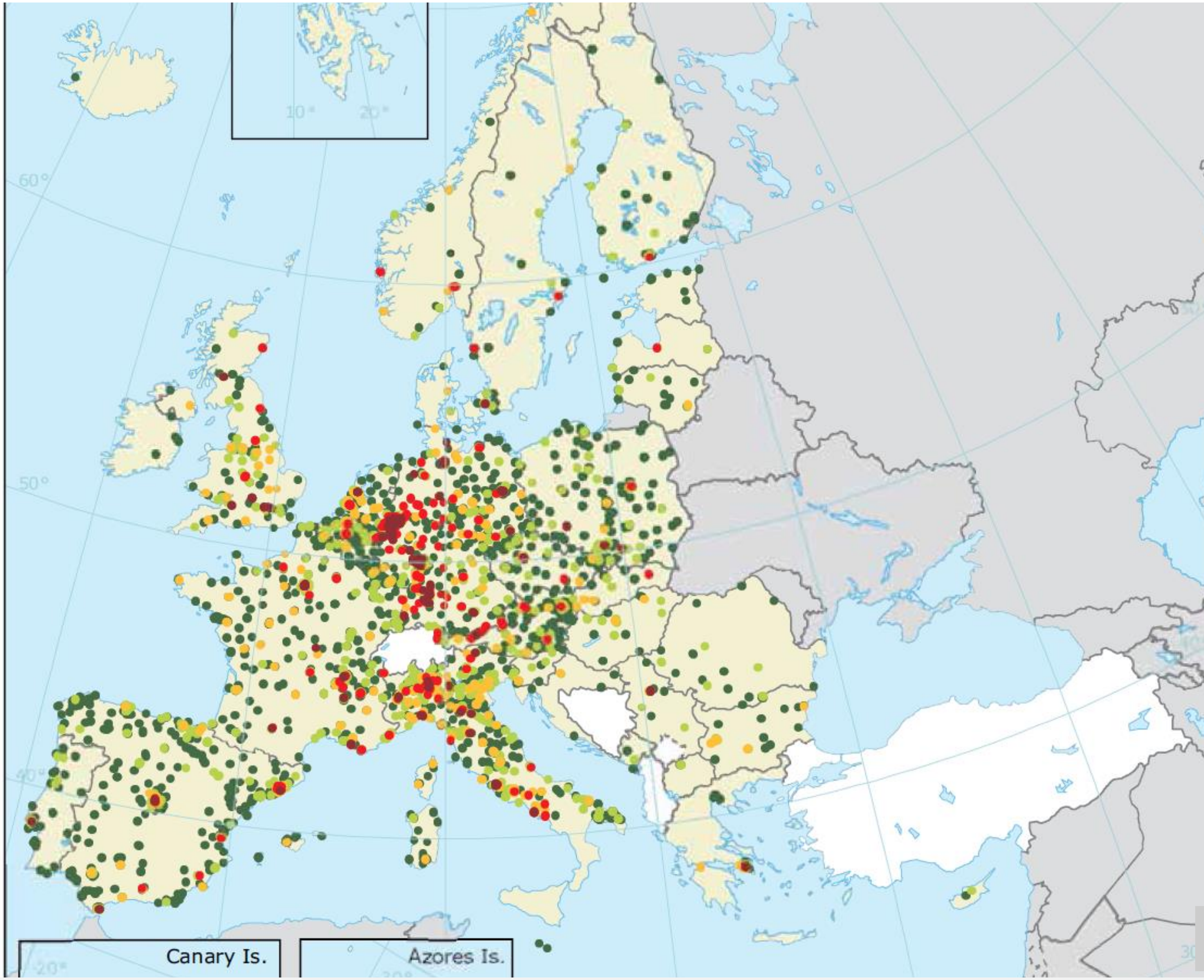
Daily mean concentrations of PM_{10} in 2014



EEA, 2016

The red and dark-red dots indicate stations with exceedances of the PM_{10} daily limit value, allowing 35 exceedances of the 50µg/m^3 threshold over 1 year

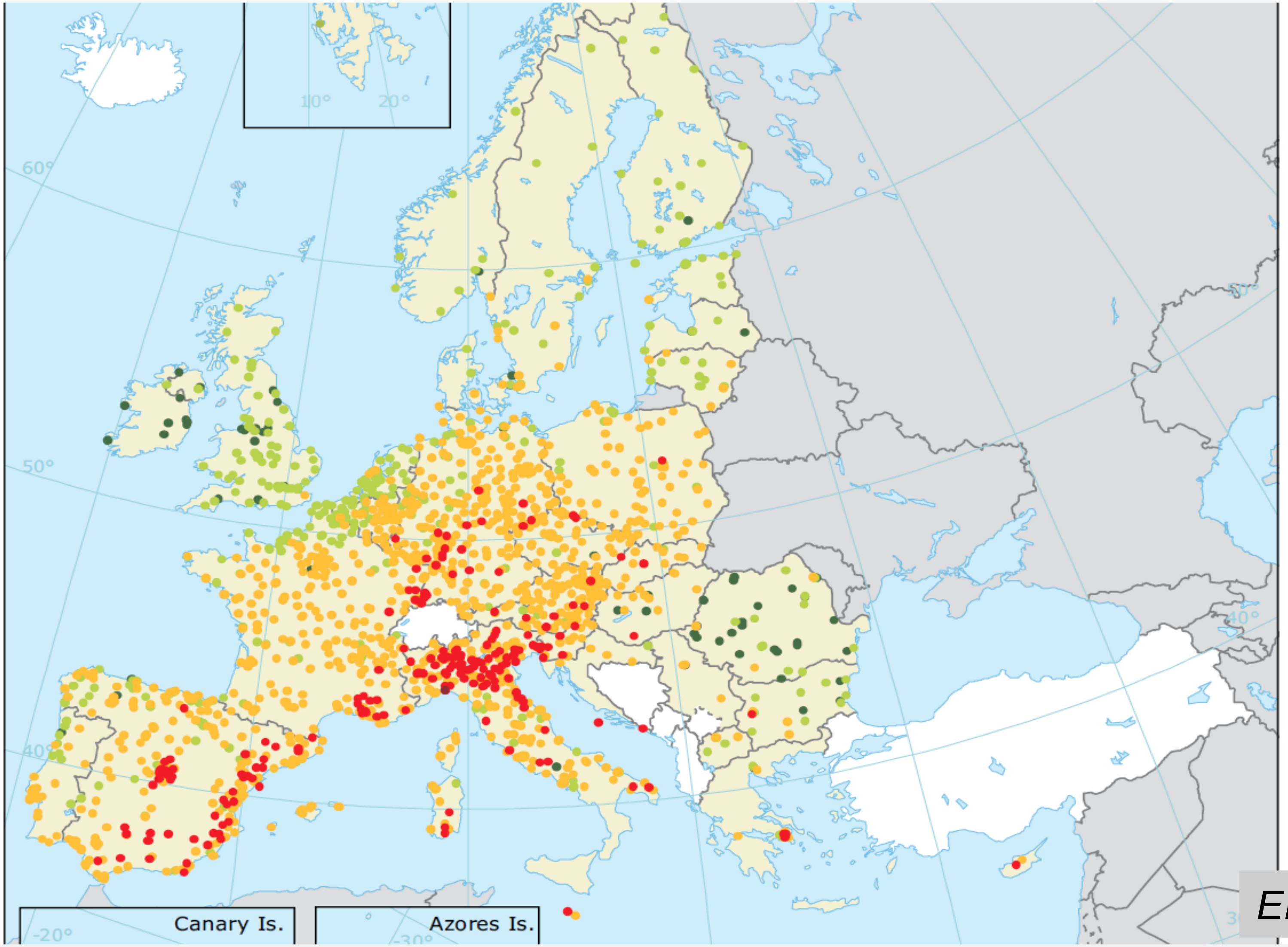
Annual mean concentrations of NO_2 in 2014



EEA, 2016

Red and dark-red dots correspond to exceedances of the EU annual limit value and the WHO AQG (40µg/m^3)

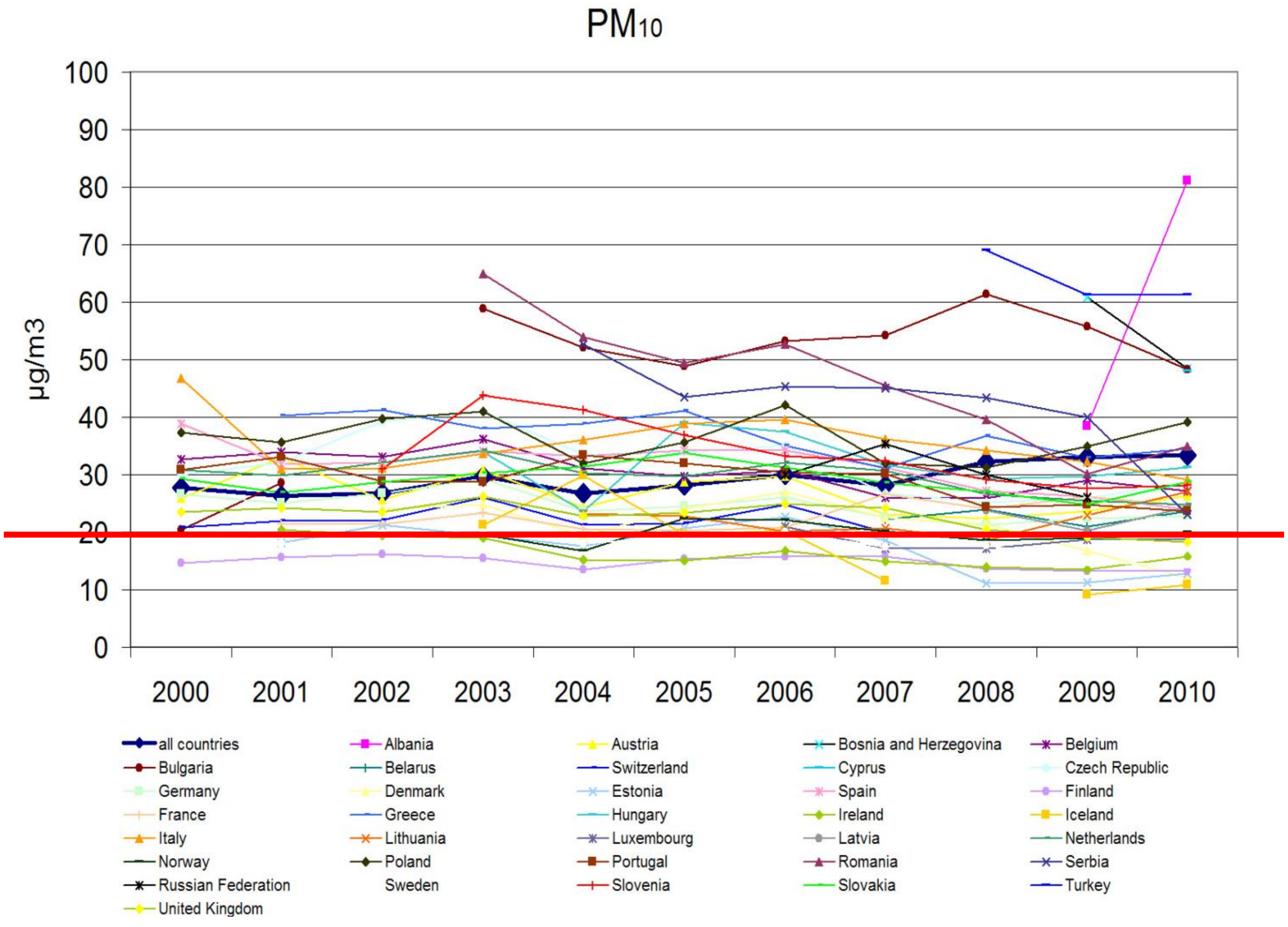
Maximum daily 8-hour means of O_3 in 2014



EEA, 2016

For O_3 the target value allows 25 exceedances over the 120-µg/m^3 threshold. At sites marked with red and dark-red dots, the 26th highest daily O_3 concentration exceeded the threshold

Over the last decade, PM10 levels have remained overall stable and well above WHO guidelines...



PM_{10} levels in the European Region of WHO

The association between air pollution and the incidence of Idiopathic Pulmonary Fibrosis in Northern Italy

Conti S et al; submitted

Aim of the study

To investigate the relationship between **chronic exposure** to three criteria pollutants – PM_{10}, NO_2 and O_3 – and the incidence of IPF in Lombardy from 2005 to 2010

Methods

The 2005-2009 average PM_{10} daily overall, warm (April – September) and cold (October – March) season concentrations were computed for each municipality, based on Aerosol Optical Depth measures

We requested hourly NO_2 and O_3 concentrations measured from 2005 to 2010 at background and traffic monitoring stations (ARPA)

Methods

For each municipality, we estimated the chronic exposure to NO_2 using three strategies to compute the average daily overall and seasonal NO_2 levels from 2005 to 2010:

- all background monitors located within 10 km from the municipality limits (monitor selection A);
- all background monitors located within 10 km from the municipality limits and all traffic monitors located within 5 km (monitor selection B);
- all background and traffic monitors located within 10 km from the municipality limits (monitor selection C).

Incident cases of IPF (2005-2010)

	GCD[*] N=2951	BCD[†] N=2093	NCD[‡] N=1309
Incident cases of IPF from 2005 to 2010			
Males - N(%)	1674 (56.7%)	1252 (59.8%)	772 (59.0%)
Age at IPF onset			
Mean (SD)	69 (13.0)	70 (13.0)	69 (12.9)
Median (IQR[§])	72 (63; 79)	72 (64; 79)	72 (63; 79)
Min; Max	6; 98	6; 98	6; 95
N° cases per municipality		**	** ††
Mean (SD)	1.9 (15.7)	1.4 (11.3)	0.8 (7.0)
Median (IQR[§])	1 (0; 2)	0 (0; 1)	0 (0; 1)
Min; Max	0; 602	0; 433	0; 265
CV[II]	8.23	8.37	8.23

*** p-value of Wilcoxon test vs GCD <0.05*

†† p-value of Wilcoxon test vs BCD <0.05

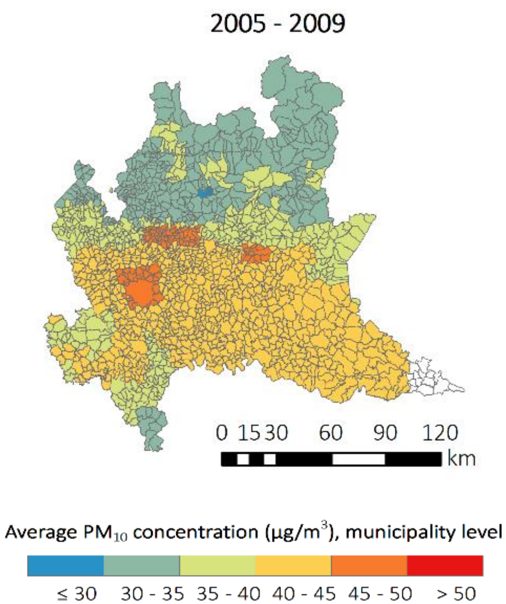
	Descriptive measure
Average population per municipality	
Mean (SD)	6,249 (34,855)
Median (IQR*)	2,609 (1,152; 5,666)
Min; Max	36; 1,311,775
CV†	5.58
Percentage of males per municipality	
Mean (SD)	49.6 (1.4)
CV†	0.03
Mean age per municipality	
Mean (SD)	42.6 (3.1)
CV†	0.07
Municipalities with assessed exposure to PM_{10} – N (%)	1,531 (99.1%)
Municipalities with assessed exposure to NO_2 – N (%)	
Monitor selection A‡	988 (63.9%)
Monitor selection B§	1,062 (68.7%)
Monitor selection C‖	1,162 (75.2%)
Municipalities with assessed exposure to O_3 – N (%)	891 (57.7%)

‡ All background monitors within 10km from the city limits
§ All background monitors within 10km and all traffic monitors within 5 km from the city limits
‖ All background and traffic monitors within 10km from the city limits

	Overall	Warm season	Cold season
Average PM_{10} concentration ($\mu g/m^3$)*			
Mean (SD)	39 (4.3)	27 (3.1)	52 (5.8)††
Median (IQR‡)	40 (35.8; 42.4)	28 (24.7; 29.5)	53 (46.7; 56.0)
Minimum; Maximum	30; 50	20; 34	40; 66
Average NO_2 concentration ($\mu g/m^3$)†			
Monitor selection A§			
Mean (SD)	36 (8.5)	24 (6.8)	47 (10.4)††
Median (IQR‡)	35 (29.8; 42.5)	24 (18.9; 28.4)	45 (39.9; 53.5)
Minimum; Maximum	16; 58	9; 51	24; 70
Monitor selection B‖			
Mean (SD)	37 (9.0)	26 (7.9)	48 (10.3)††
Median (IQR‡)	38 (30.0; 43.4)	25 (20.7; 31.3)	48 (41.1; 55.3)
Minimum; Maximum	16; 65	9; 55	24; 74
Monitor selection C**			
Mean (SD)	39 (9.7)	29 (9.0)	50 (10.7)††
Median (IQR‡)	39 (31.5; 46.4)	28 (21.5; 34.6)	50 (42.6; 57.3)
Minimum; Maximum	16; 65	9; 55	24; 75
Average O_3 concentration (ppm)†			
Mean (SD)		109 (7.2)	
Median (IQR‡)		110 (103.6; 116.4)	
Minimum; Maximum		91; 120	

†† p-value Wilcoxon rank-signed test vs "Warm season" <0.05

Mean concentration of PM10

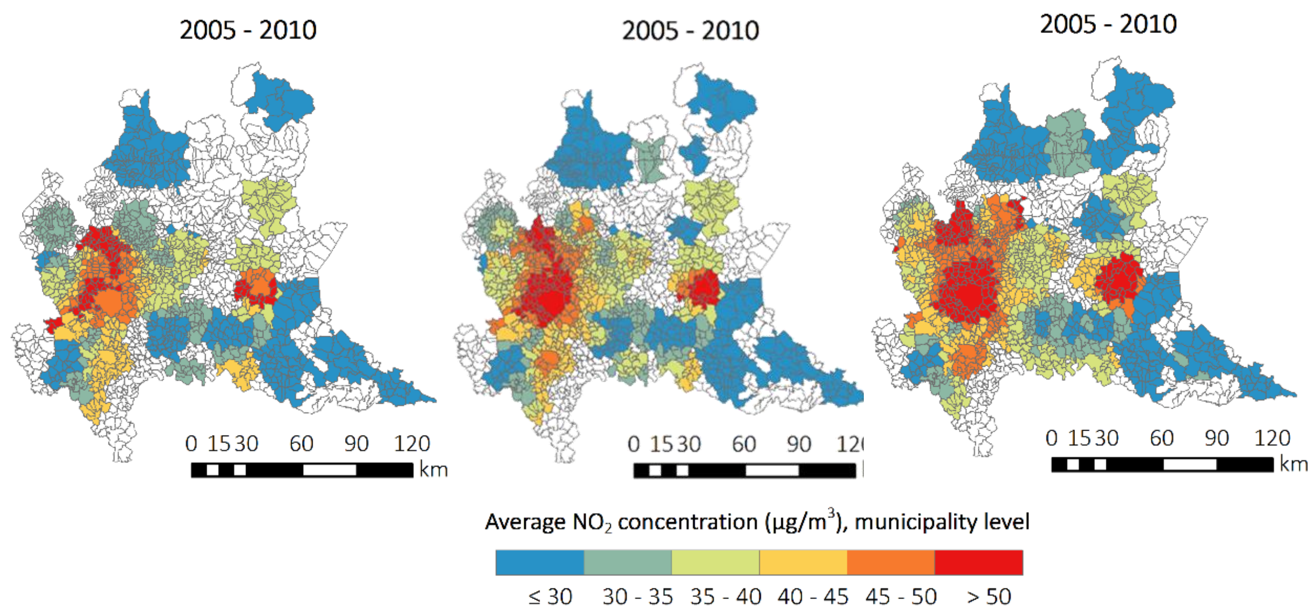


Mean concentration of NO2

All background monitors[1]
Monitor selection A

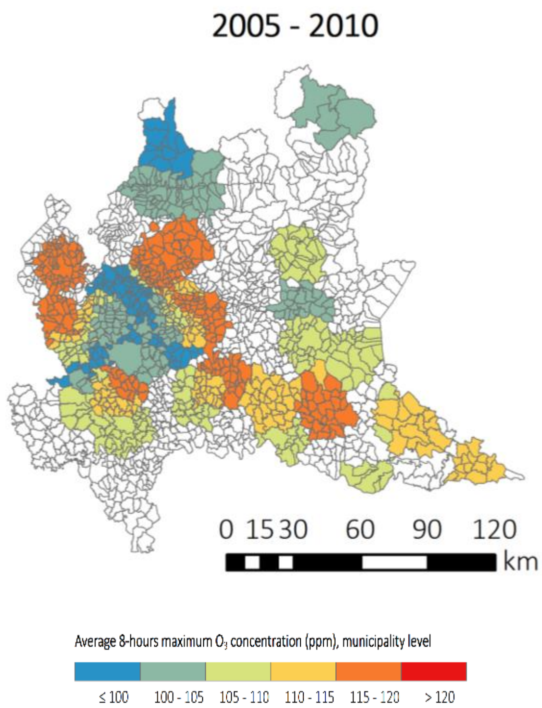
All background monitors[1] and traffic stations[2]
Monitor selection B

All background monitors[1] and traffic station[1]
Monitor selection C



1. Located within 10 km from the municipality limits
2. Located within 5 km from the municipality limits

Mean concentration of O_3



1. Located within 10 km from the municipality limits
2. Located within 5 km from the municipality limits

Estimated % change in the Incidence Rate (IR), with related 95% Confidence Interval (CI), for an unit increase in the daily average pollutants concentrations.

	GCD	BCD	NCD
Daily average PM_{10} (1 μg/m³increase)			
	-0.64 (-1.96; 0.69)	-0.19 (-1.76; 1.39)	-0.55 (-2.36; 1.30)
Daily average NO_2 concentration (1 μg/m³increase)			
Monitor selection A[1]	0.49 (-0.15; 1.13)	0.38 (-0.38; 1.14)	0.17 (-0.70; 1.05)
Monitor selection B[2]	0.61 (0.02; 1.21)†	0.55 (-0.15; 1.26)	0.41 (-0.39; 1.22)
Monitor selection C[1]	0.61 (0.06; 1.17) †	0.64 (-0.01; 1.29)††	0.40 (-0.34; 1.15)
Daily 8-hour average O_3 concentration (1 ppm increase)			
Warm season	-0.50 (-1.29; 0.30)	-0.36 (-1.30; 0.60)	-0.58 (-3.40; 2.32)

† p-value <.0.05; †† p-value <0.1

Conclusions

No association was detected with PM_{10} and O_3 chronic exposure

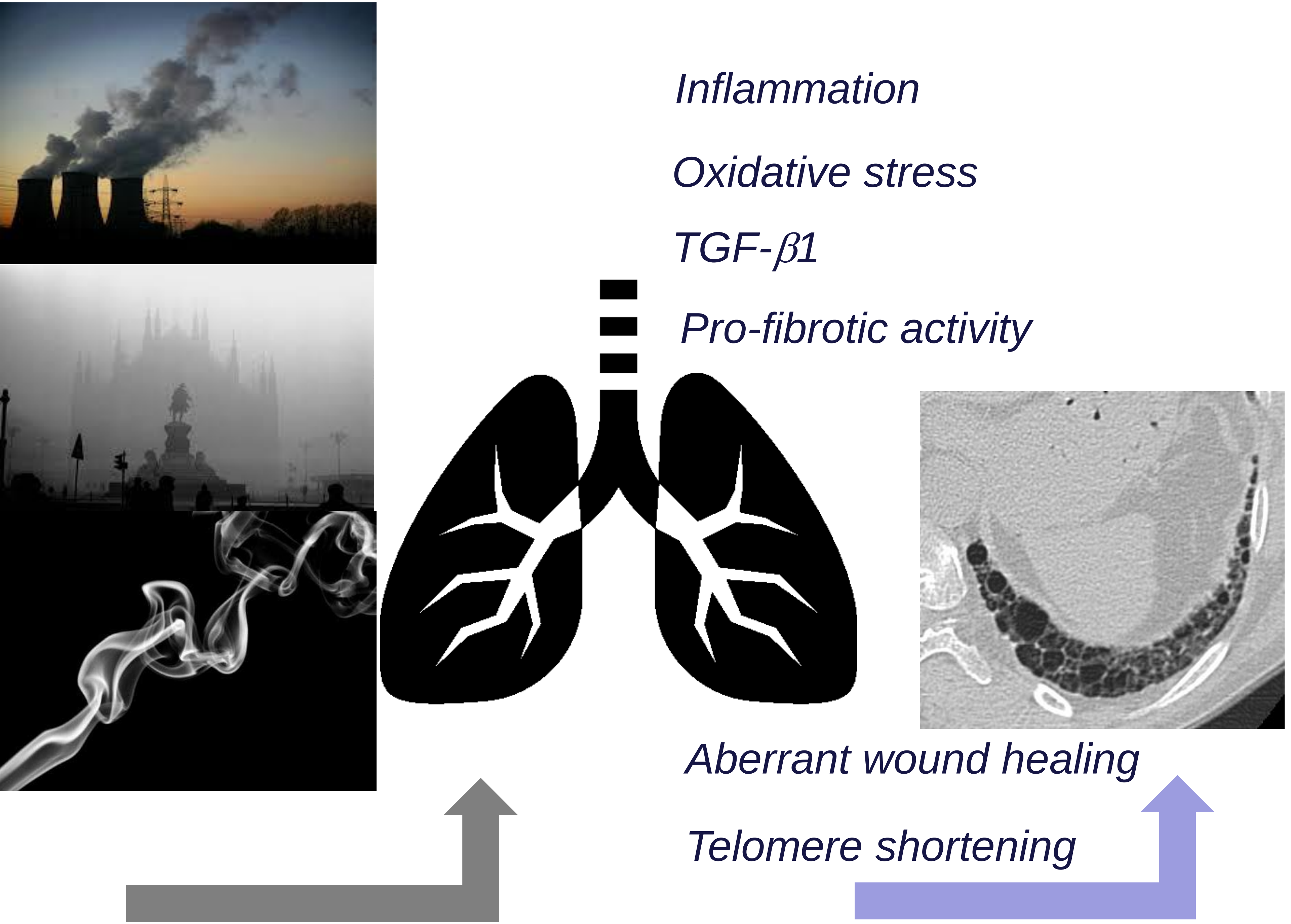
We observed that for each 1 μg/m^3 increment in the chronic NO_2 concentration, the incidence rate of IPF increased between 0.49% (95% CI: -0.15; 1.13) and 0.66% (95% CI: 0.17;1.15) depending on the IPF case definition used, the monitor selection strategy for exposure assessment and the season considered

What's the rationale?

Air pollution induces oxidative stress, telomere shortening and cellular senescence, dysregulated fibrogenesis and inflammation.

The development of diseases with "telomere dysfunction" like IPF needs the contribution of both genetic and environmental factors in order to develop the entire disease phenotype

NO2 exposure has been associated with increased risk of respiratory hospitalization in COPD and asthma, and traffic-related air pollution exposure increases the risk of post lung transplant bronchiolitis obliterans syndrome



Inflammation
Oxidative stress
TGF-β1
Pro-fibrotic activity
Aberrant wound healing
Telomere shortening

Potential factors of susceptibility and vulnerability

Older age
Younger age
Gender
BMI
Pre-existing CVDs
Pre-existing Asthma
Pre-existing Diabetes

Lower socio-economic status
Smoking habits
Unbalanced diet

Genetics

Review

Are people with IPF fragile and vulnerable?

Particulate Matter–Induced Health Effects: Who Is Susceptible?

Jason D. Sacks, Lindsay Wichers Stanek, Thomas J. Luben, Douglas O. Johns, Barbara J. Buckley, James S. Brown, and Mary Ross

Special thanks to

Dr. Sara Conti

Dr. Fabiana Madotto

Prof. Giancarlo Cesana

Research Centre on Public Health University of Milano-Bicocca, Department of Statistics and Quantitative Methods

Department of Environmental Health, Harvard University, School of Public Health

Department of Clinical Sciences and Community Health, University of Milan

Thank you