MODENA PNEUMOLOGICA

Update in tema di pneumopatie interstiziali diffuse

IPF e inquinamento: una relazione da scoprire

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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?

Methodologies in epidemiological research in IPF

- *National registry databases*
- *Questionnaire-based studies*
- *Analysis of the health care systems databases*

Methodologies in epidemiological research in IPF

- *National registry databases*

***CON**: Registry studies rely on the activity of physicians in reporting patient numbers and data and result in underestimation of patient numbers*

***PRO**: Registry cohorts are important in the determination of patient clinical course and the possible differences in the management*

Methodologies in epidemiological research in IPF

- *Questionnaire-based studies*

Due to the low response rates and lack of monitoring of the centers that have attended the study, data derived from these studies should be interpreted with caution

Methodologies in epidemiological research in IPF

- *Analysis of the health care systems databases*

This approach provides information from a large population without the expenditure required by the creation of a national registry

It is critical for accruing a sufficient sample size for epidemiological studies for rare diseases such IPF

Methodological issues in studies using pre-existing databases

- Selection bias due to healthcare system or insurance that provide data concerns only a portion of the population
- Different disease coding and selection criteria
- Different diagnostic criteria (evolution of guidelines)
- True disease onset is unknown
- Methodological aspects in rate calculation
- Automated claims data used without validation and without correction for misclassification would overestimate incidence and prevalence

Esposito DB et al. Am J Respir Crit Care Med 2015

Caminati et al. Eur Respir Rev 2015

Methodologies in epidemiological research in IPF

- *National registry databases*
- *Questionnaire-based studies*
- *Analysis of the health care systems databases*

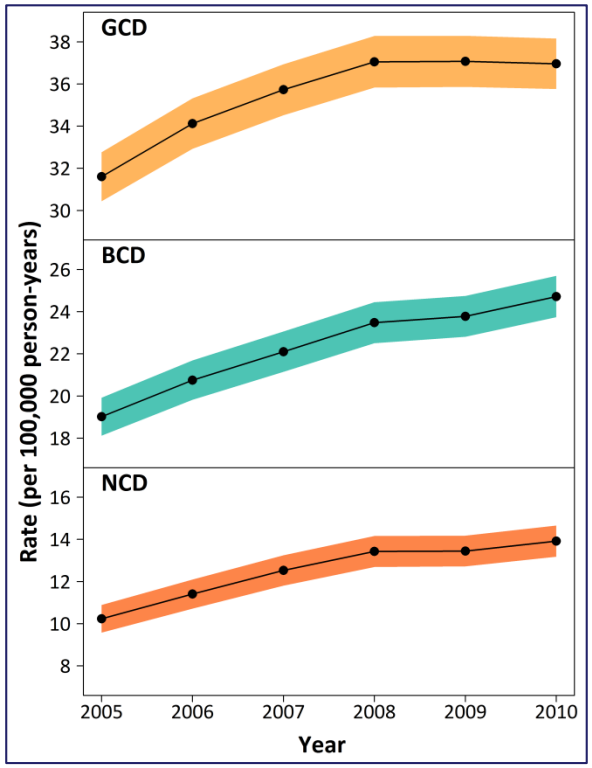
The results published from these studies are very different

Epidemiology of idiopathic pulmonary fibrosis in Northern Italy

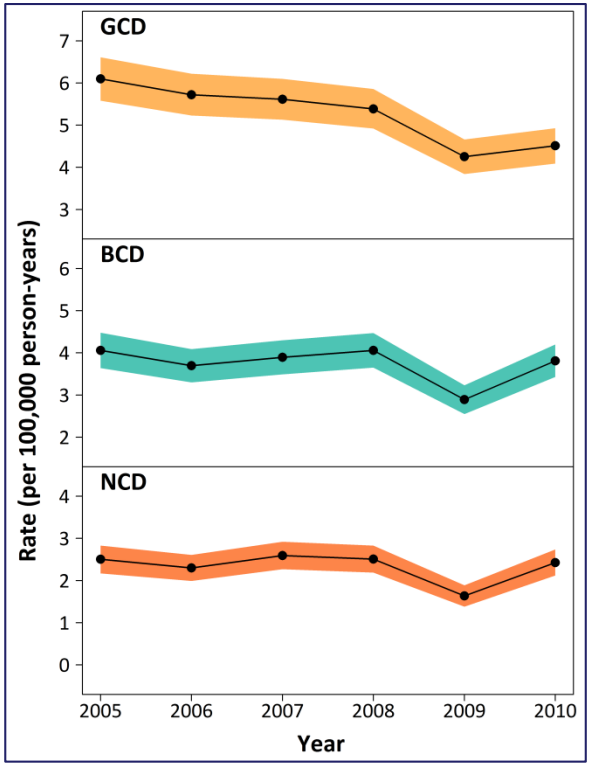
Harari S. et al PlosOne 2016

Case Definition	Criteria
Generic	An 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

Harari S. et al. PlosOne 2016

Authors	Cauntry	Study period	Pop	Age pop.	Mortality*	Incidence*	Prevalence*
Harari et al	Italy (Lombardia)	2005-2010	~10,000,000	-	-	General: 5.3 (5.1-5.4) Broad: 3.7 (3.6-3.9) Narrow: 2.3 (2.2-2.5)	General: 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

Harari S. 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

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

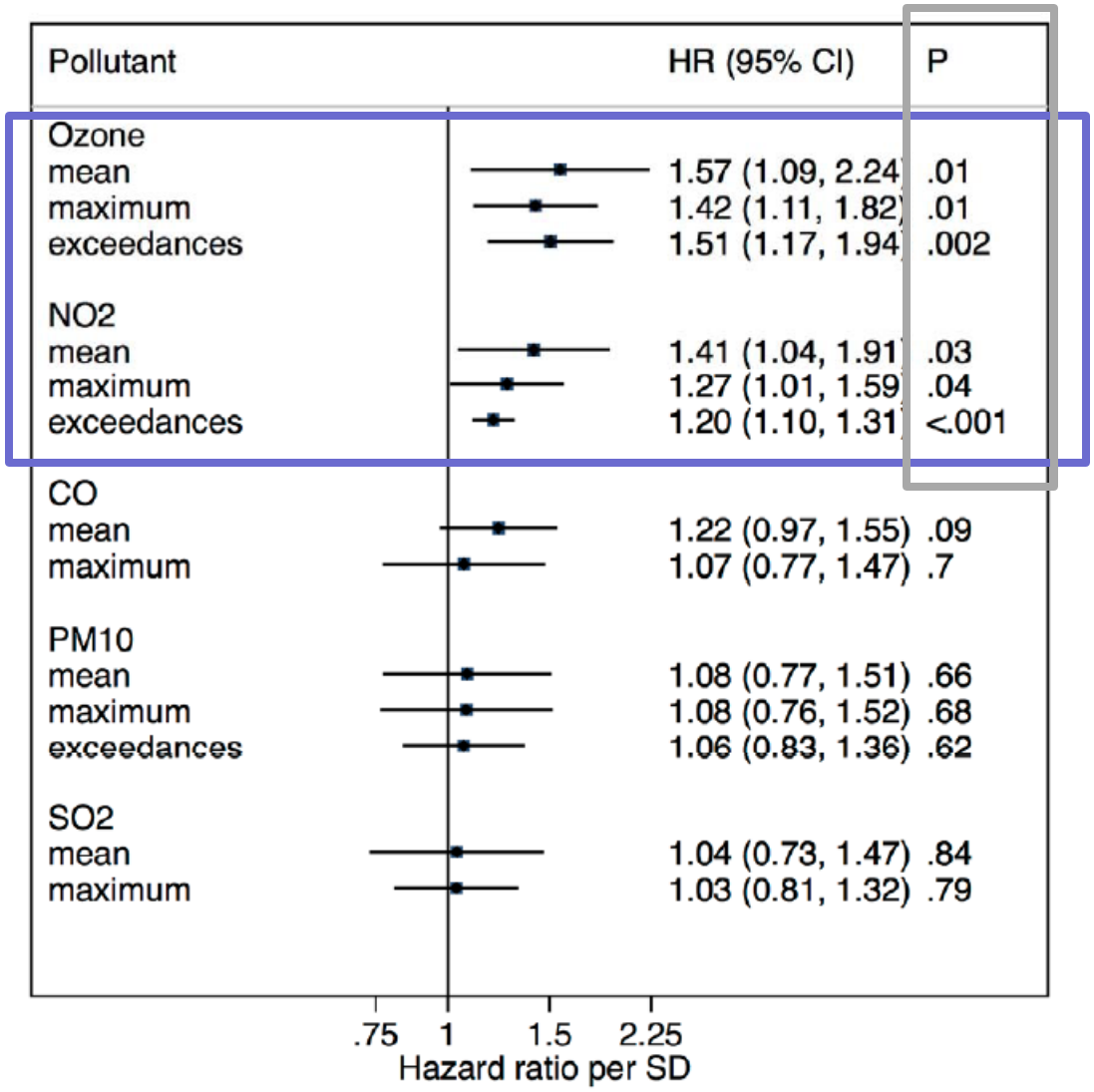
“Our study demonstrates a significant relationship between ambient O3 and NO2 levels and acute exacerbation of IPF.

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 L, Annesi-Maesano I, Thorax 2017 ; doi: 10.1136/thoraxjnl-2017-209967

- 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.

Air pollution and subclinical ILD

Sack C, Kaufman JD, Eur Respir J 2017 ; 50

- Ambient air pollution exposures were associated with subclinical ILD.
- The odds of ILAs increased 1.77-fold per 40 ppb increment in NOx (95% CI 1.06 to 2.95, p = 0.03).
- There was an overall trend towards an association between higher exposure to NOx and greater progression of HAAs (0.45% annual increase in HAAs per 40 ppb increment in NOx; 95% CI −0.02 to 0.92, p = 0.06).
- No association with Pm 2,5 – NO2 and O3 was detected

Exposure to ambient particulate matter is associated with accelerated functional decline in IPF

Winterbottom CJ, et al. Chest 2017

- Ambient air pollution, as measured by average PM10 concentration, is associated with an increase in the rate of decline of FVC in IPF, suggesting a potential mechanistic role for air pollution in the progression of disease.

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

Regenerative organs

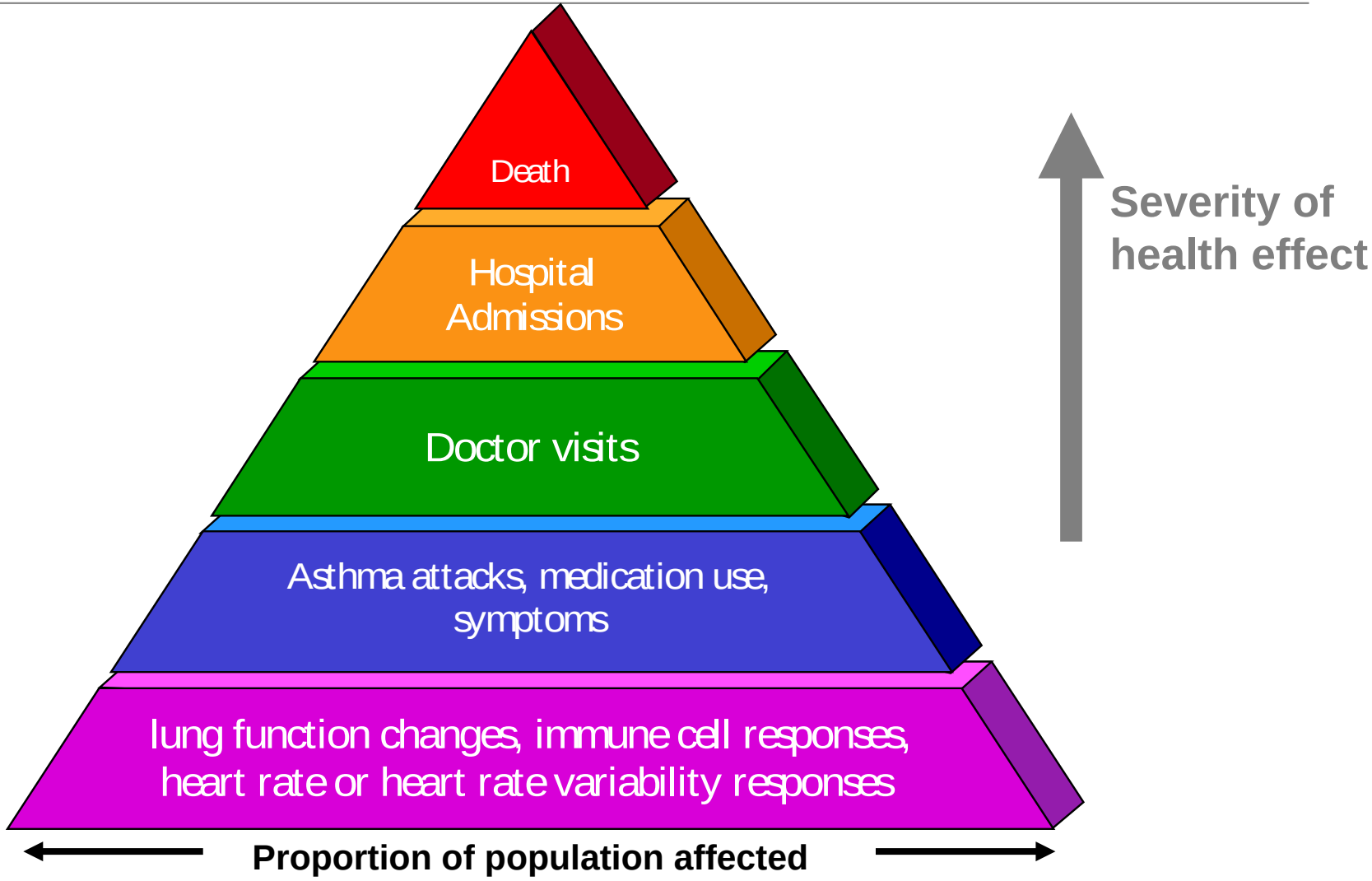
- ***Premature Birth***
- ***Decreased Birth Weight***
- *Decreased foetal growth*
- *In uterine growth retardation*
- *Decreased sperm quality*
- *Preclampsia*

Vascular system

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

Joint ERS / ATS statement (ERJ 2017)

Air pollution respiratory effects pyramid



Source: American Thoracic Society, 2000

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

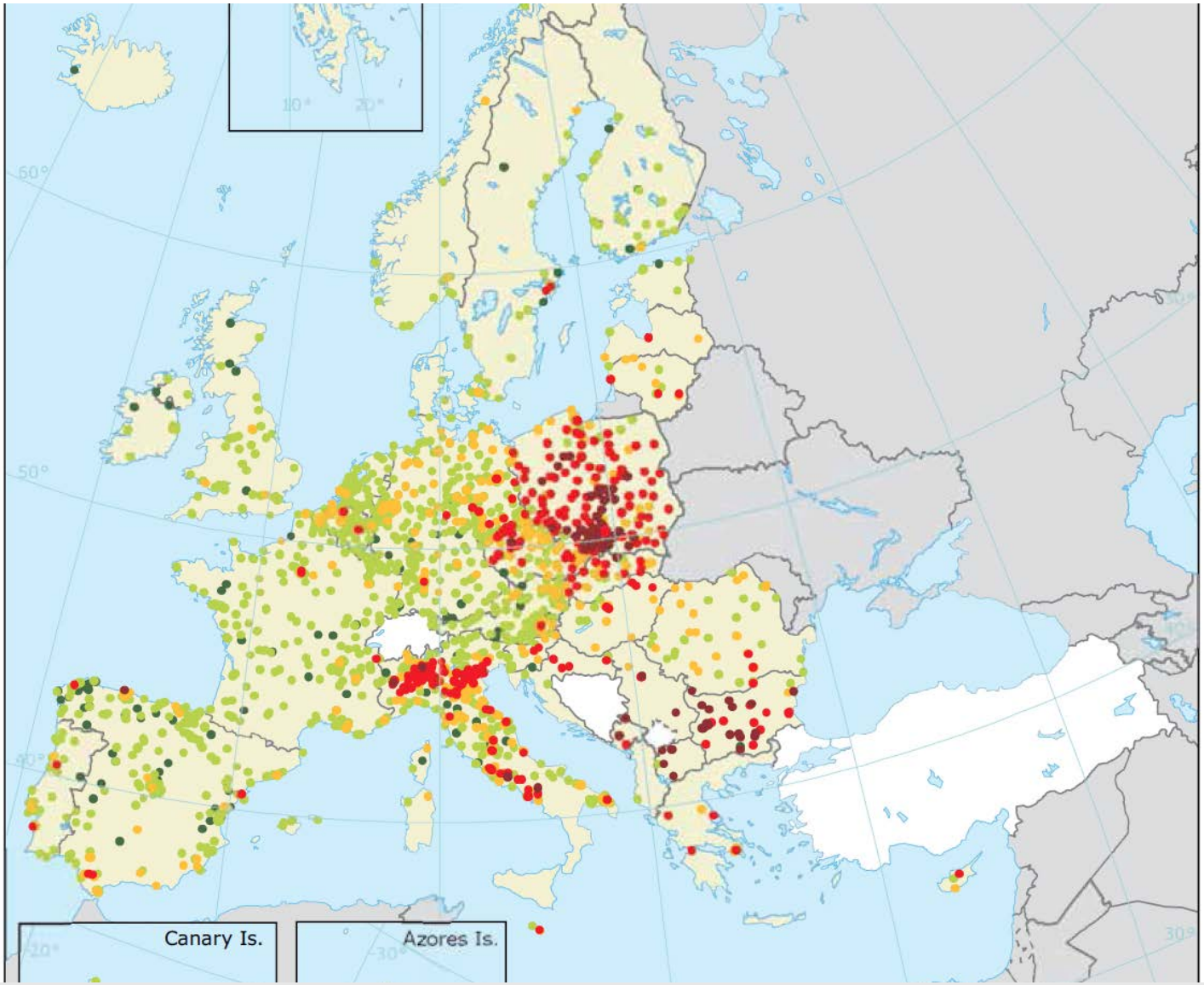
Milan

Po Valley

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.

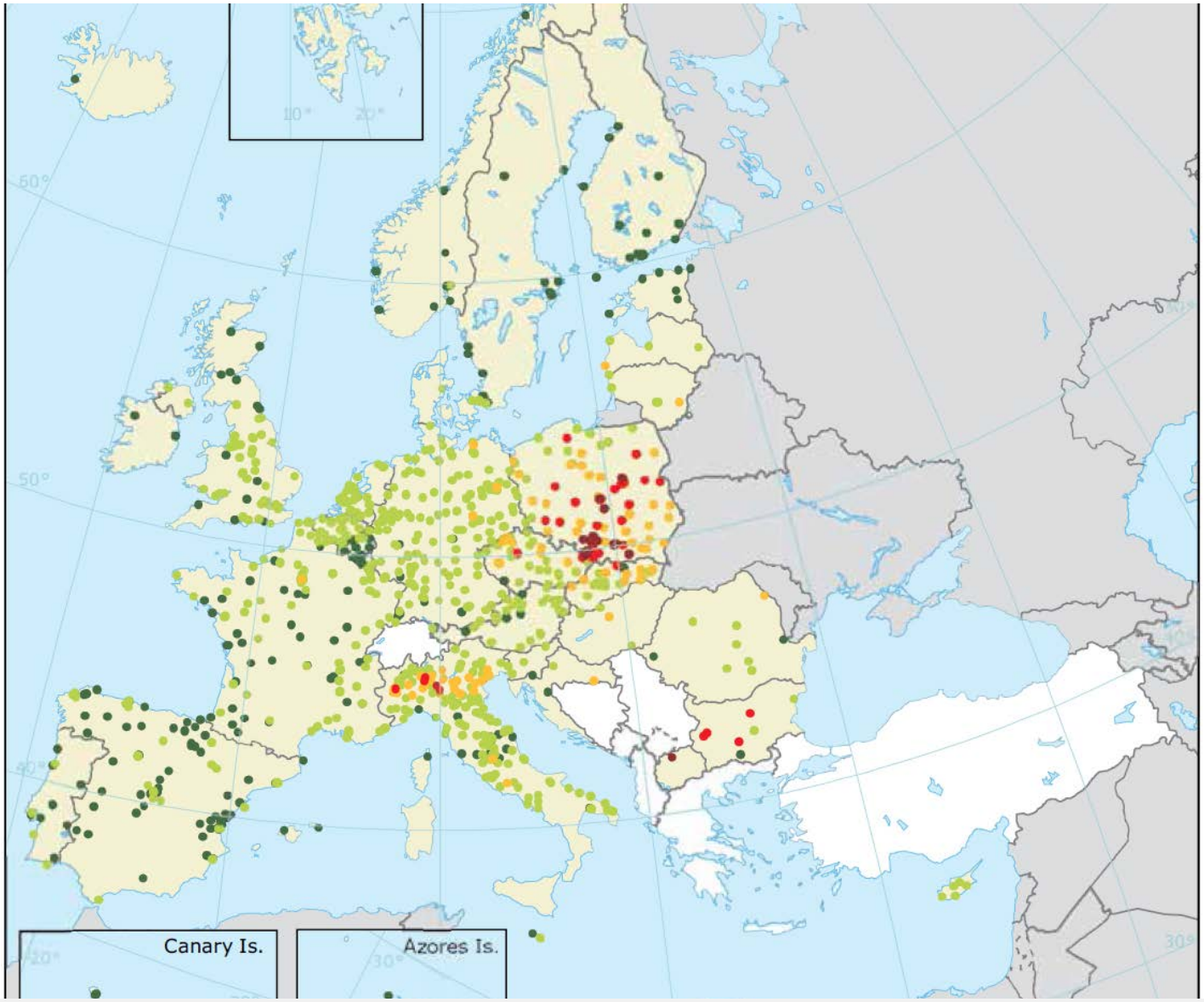
Daily mean concentrations of PM_{10} in 2014



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/m³ threshold over 1 year

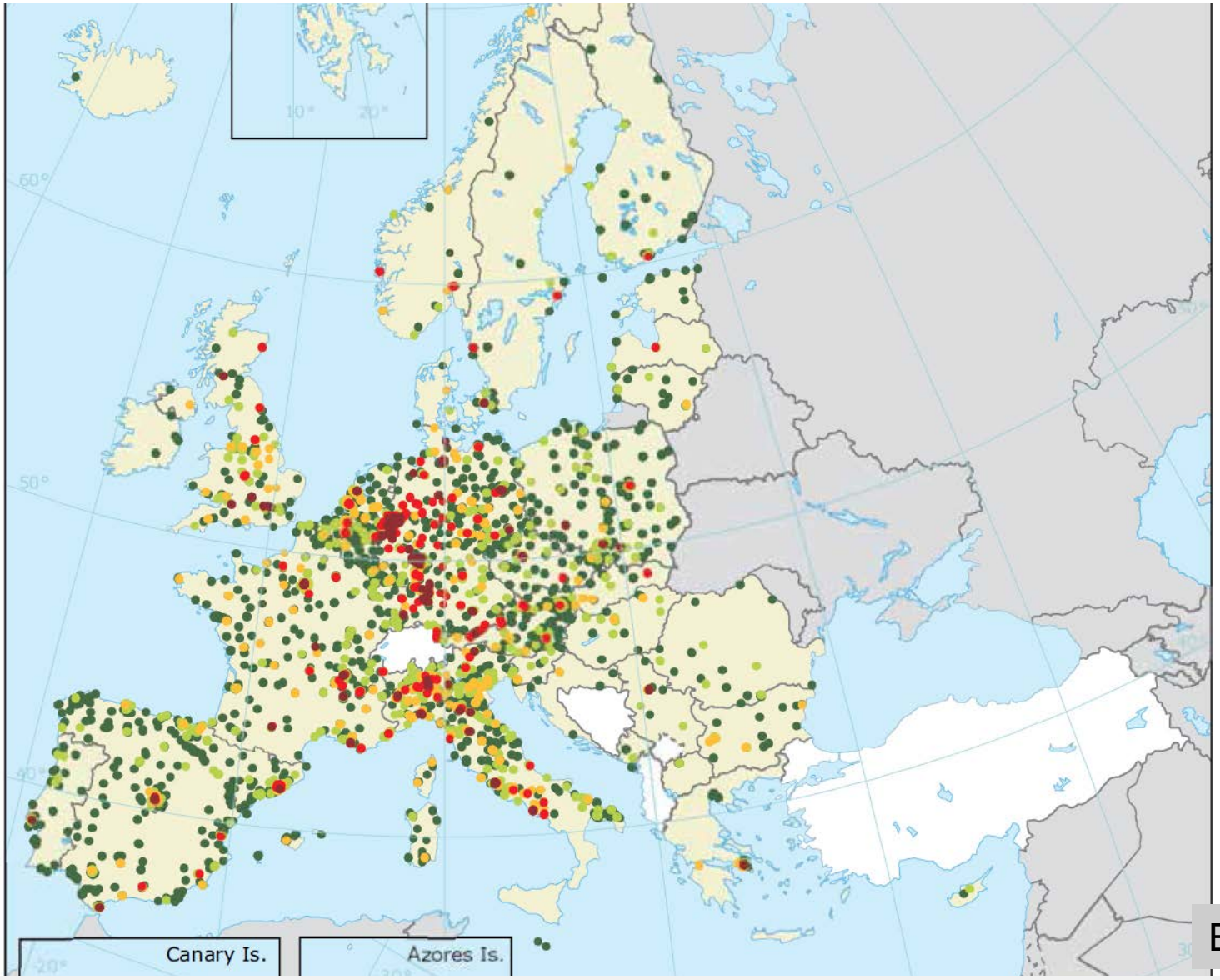
Daily mean concentrations of $PM_{2.5}$ in 2014



EEA, 2016

The red and dark-red dots indicate stations reporting exceedances of the EU annual target value (25 µg/m³) plus at least 5µg/m³

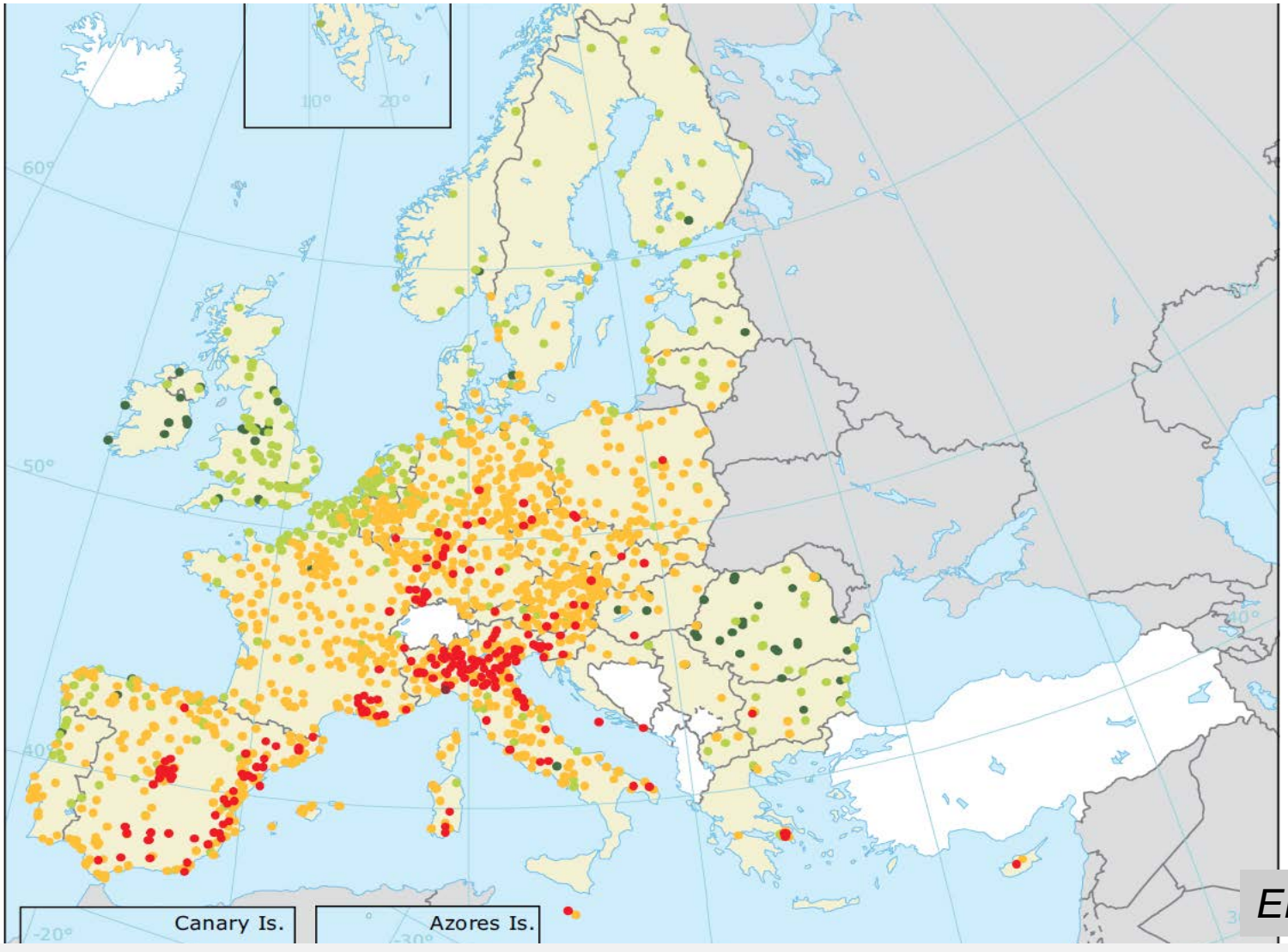
Annual mean concentrations of NO_2 in 2014



EEA, 2016

Red and dark-red dots correspond to exceedances of the EU annual limit value and the WHO AQG (40µg/m³)

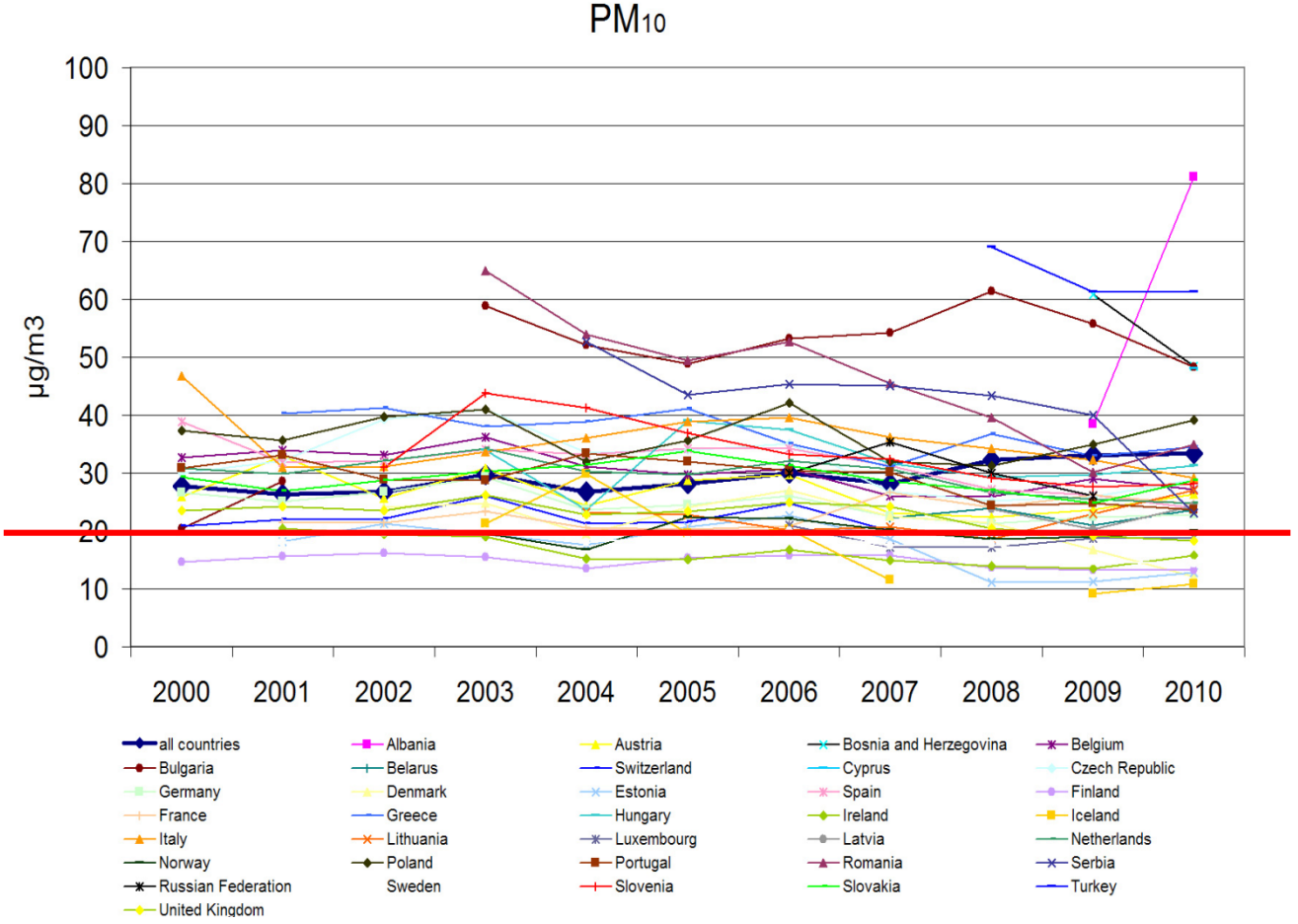
Maximum daily 8-hour means of O_3 in 2014



EEA, 2016

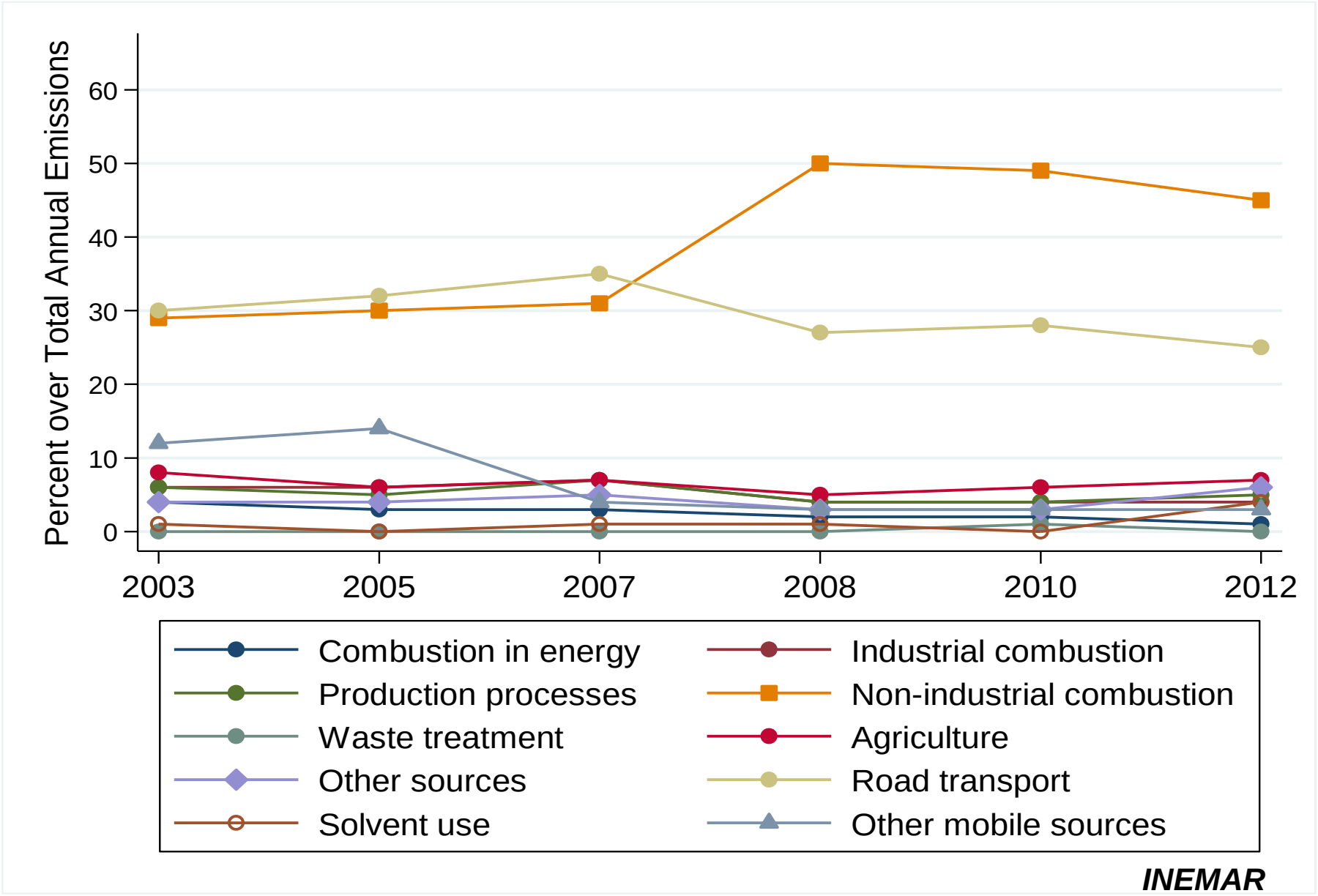
For O_3 the target value allows 25 exceedances over the 120-µg/m^3 threshold. At sites marked with red and dark-red dots, the 26th highest daily O_3 concentration exceeded the threshold

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

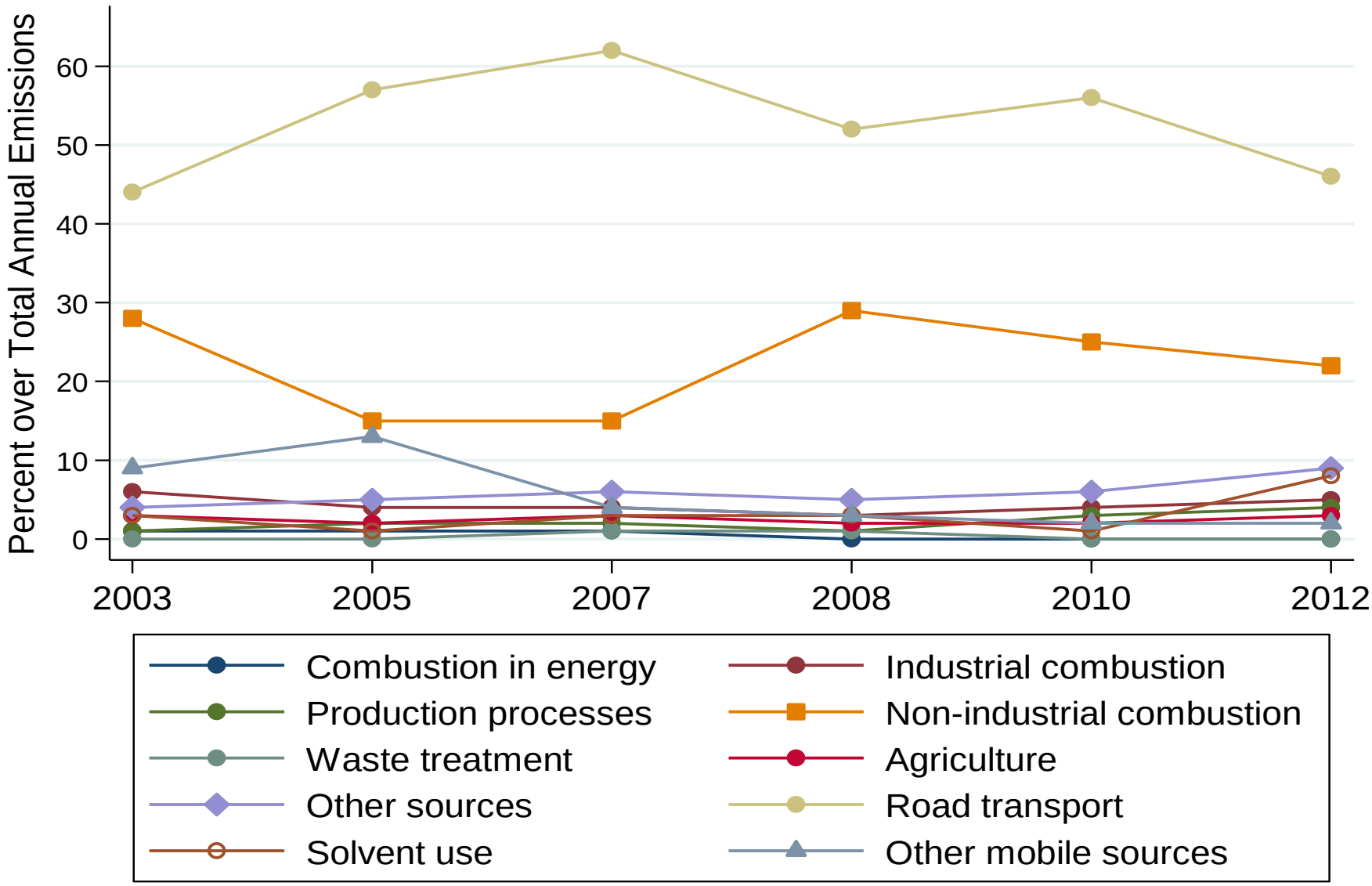


PM_{10} levels in the European Region of WHO

Temporal trend of PM_{10} different emission sources in the entire Lombardy region (%)



Temporal trend of PM_{10} emission sources in the city of Milan (%)



INEMAR

The association between air pollution and the incidence of idiopathic pulmonary fibrosis in Northern Italy

S. Conti, S. Harari, A. Caminati, A. Zanobetti, Schwartz JD, Bertazzi PA, Cesana GC, F. Madotto, *Eur Respir J 2018; 51:1700397;doi:10.1183/13993003.00397-2017*

Aim of the study

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

Cross-sectional study

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

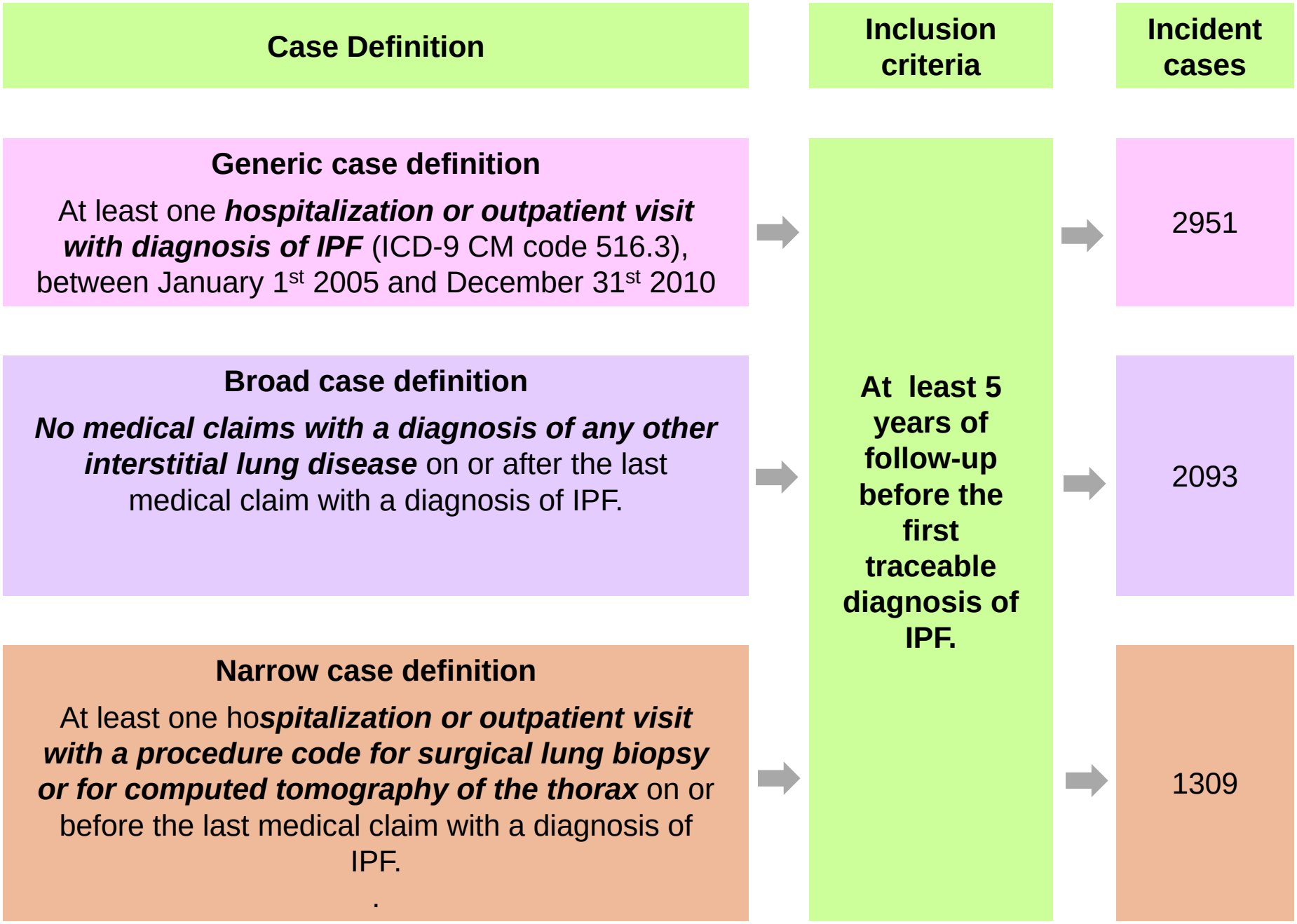
For each municipality, we estimated the chronic exposure to NO_2 using the average daily overall and seasonal NO_2 levels from 2005 to 2010:

- all background monitors located within 10 km from the municipality limits and all traffic monitors located within 5 km

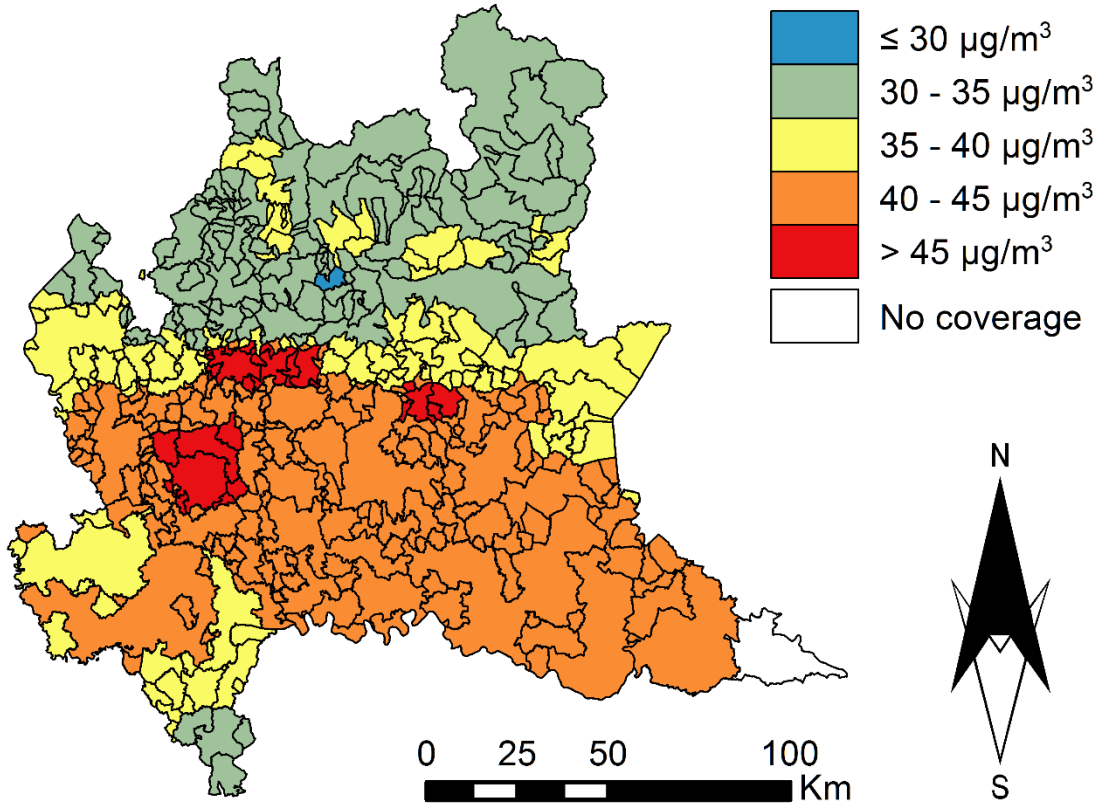
Incident cases of IPF (2005-2010)

	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
CVǁ	8.23	8.37	8.23

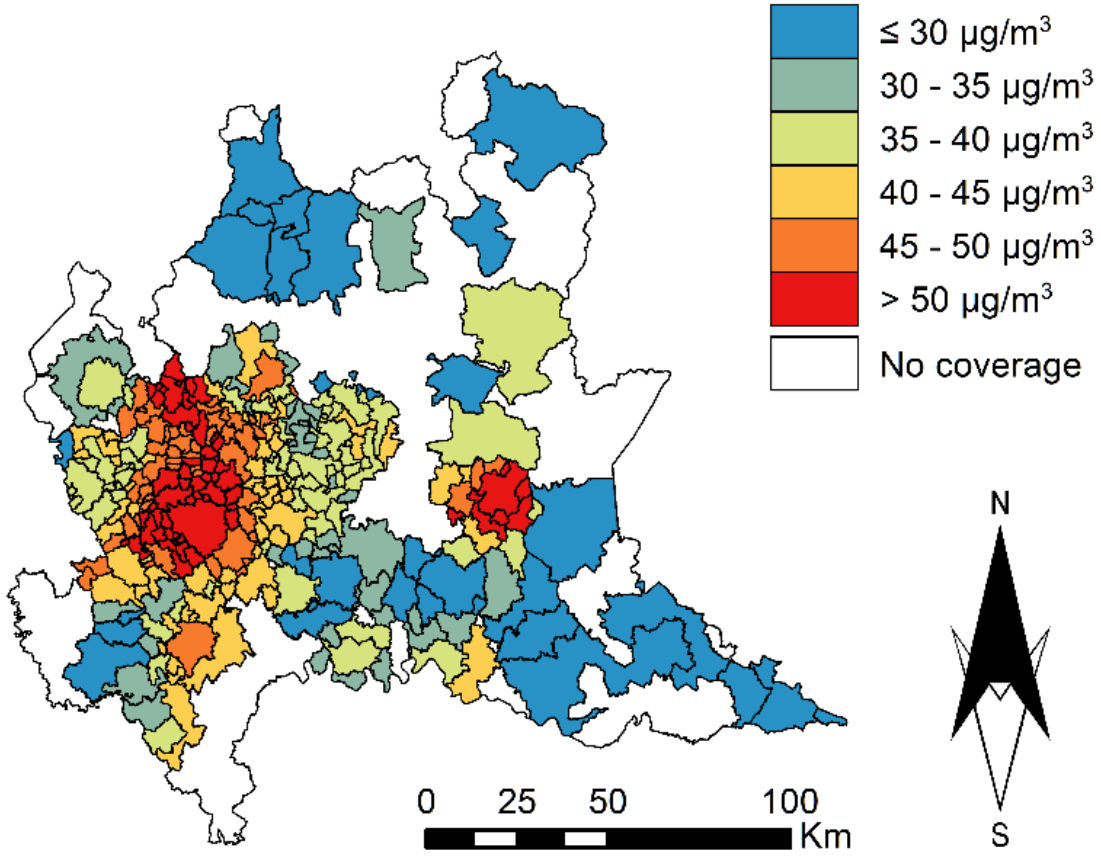
** *p-value of Wilcoxon test vs GCD <0.05*
†† *p-value of Wilcoxon test vs BCD <0.05*


Case Definition
Inclusion criteria
Incident cases
Generic case definition
At least one hospitalization or outpatient visit with diagnosis of IPF (ICD-9 CM code 516.3), between January 1st 2005 and December 31st 2010
Broad case definition
No medical claims with a diagnosis of any other interstitial lung disease on or after the last medical claim with a diagnosis of IPF.
Narrow case definition
At least one hospitalization or outpatient visit with a procedure code for surgical lung biopsy or for computed tomography of the thorax on or before the last medical claim with a diagnosis of IPF.
.
At least 5 years of follow-up before the first traceable diagnosis of IPF.
2951
2093
1309

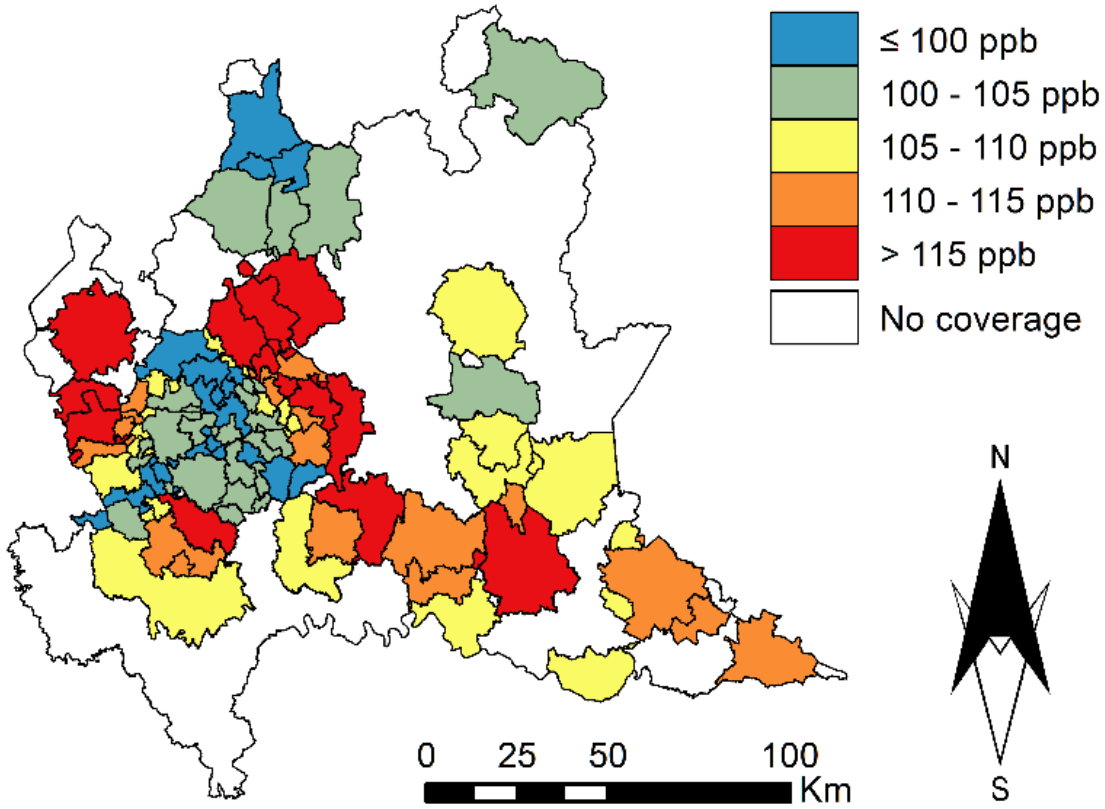
Results – Map of the daily average PM10 concentration (2005-2010)



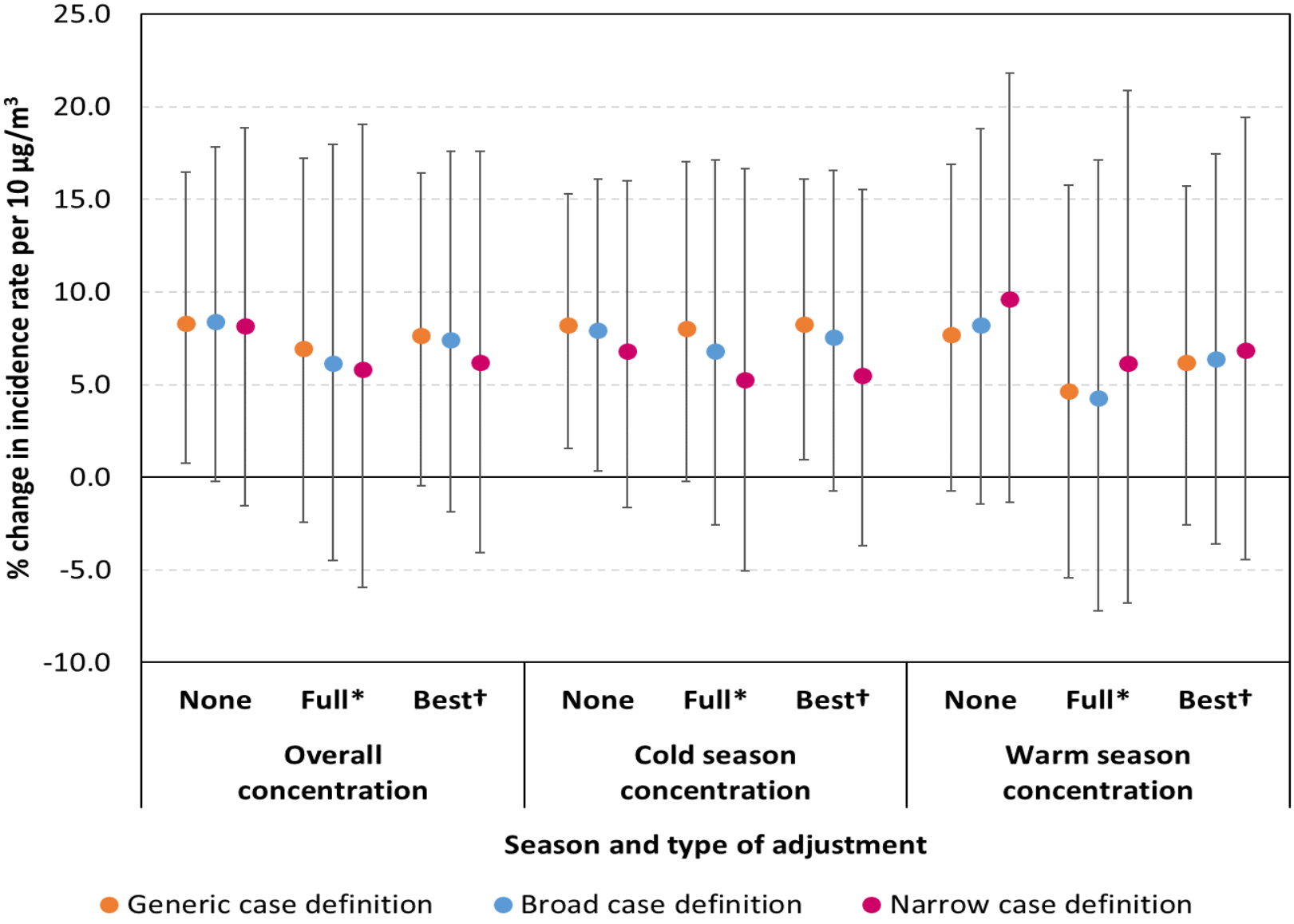
Results – Map of the estimated daily average NO2 concentration (2005-2010)

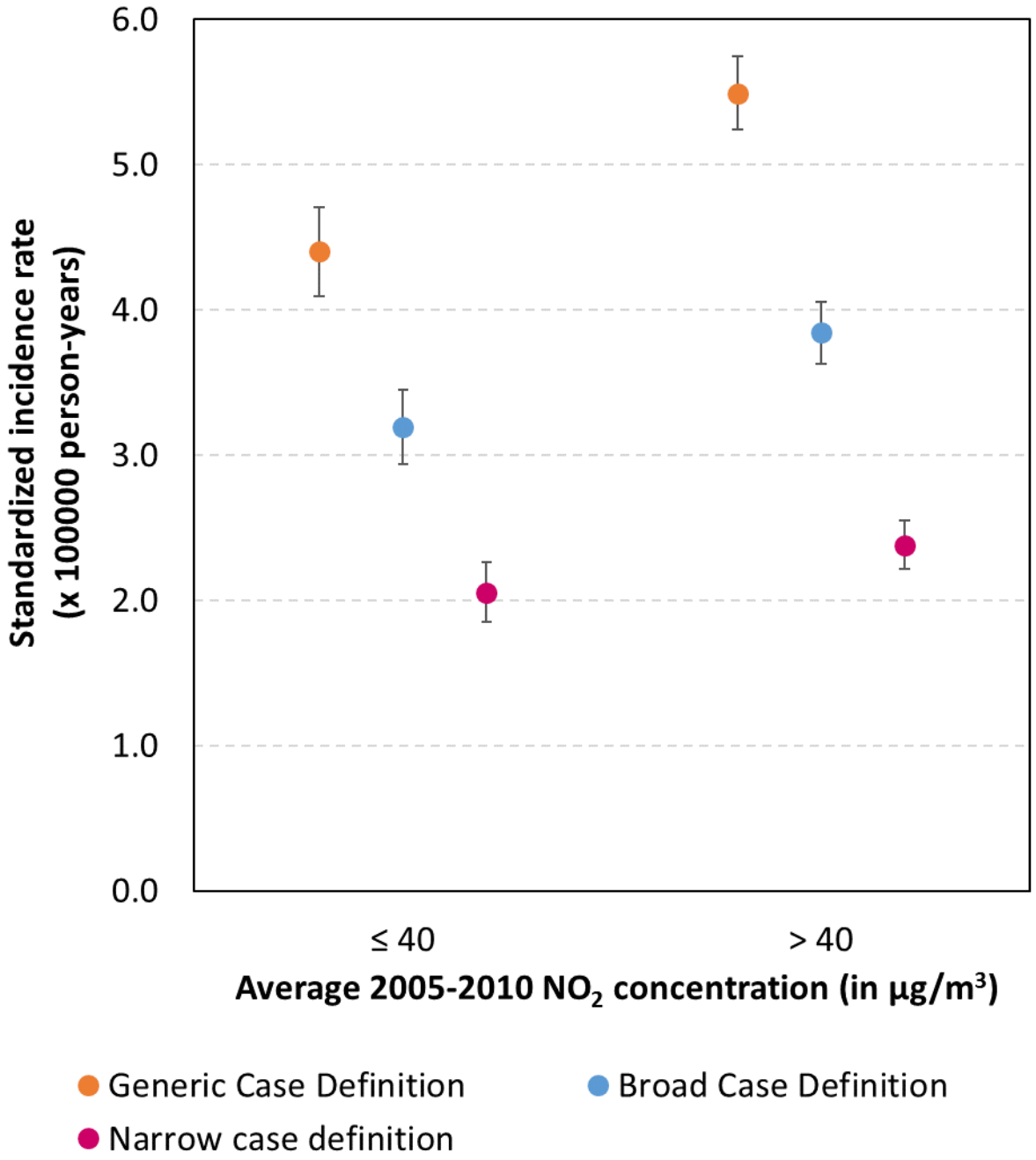


Results **– *Map of the estimated daily average* 8-hour maximum O_3 *concentration (2005-2010)***

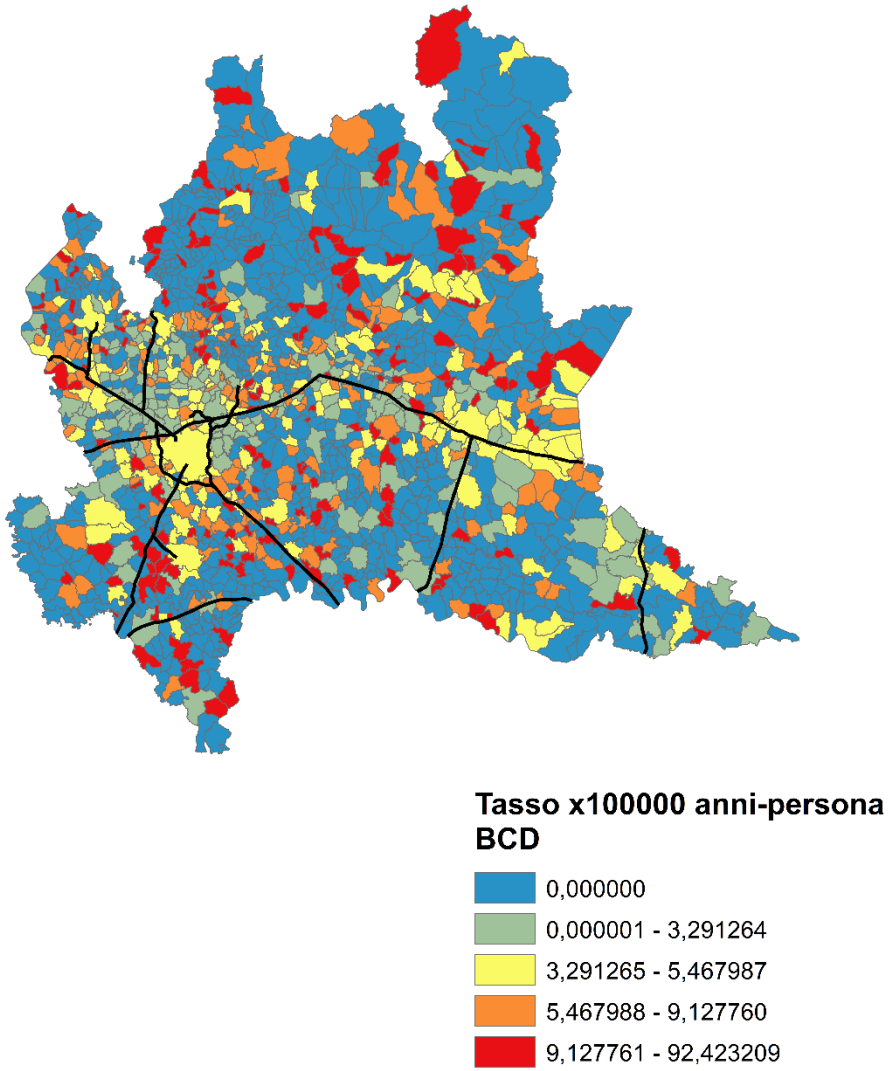


Estimated % change in the incidence rate, with related 95% confidence interval, for a 10 µg/m³ increase in the average NO_2 concentration.





Age and gender adjusted incidence rates. Comparison between areas with an average NO_2 concentration above and below 40 µg/m³.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0,000000
0,000001 - 3,291264
3,291265 - 5,467987
5,467988 - 9,127760
9,127761 - 92,423209

Conclusions

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

Positive association between incidence and the concentration of NO2

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

Conclusions

This is the first study showing that traffic-related pollution, traced by NO_2, might have a role in the development of IPF.

The precision of the estimates can be improved using subject-specific rather than aggregated data.

The use of administrative databases allowed us to study a large and unselected population and consequently a large sample of cases, an essential condition to grant sufficient power in studies of environmental epidemiology.

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

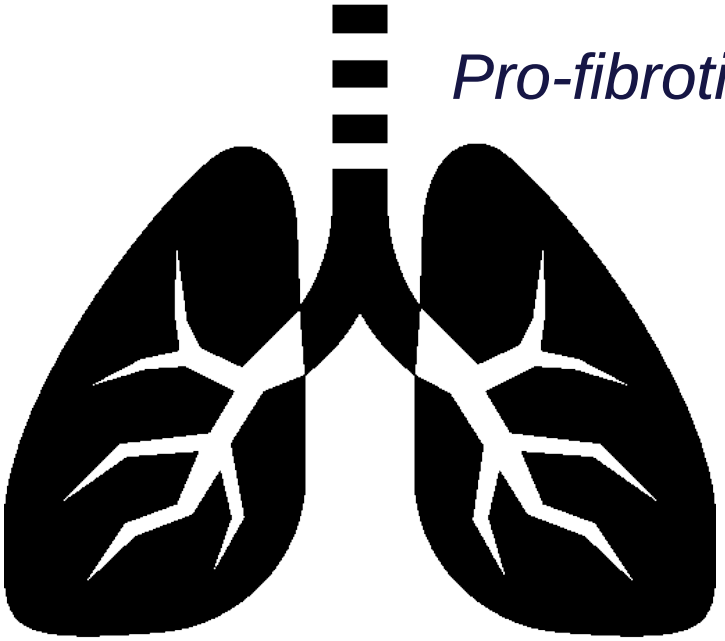
NO2 exposure has been associated with increased risk of respiratory hospitalization in COPD and asthma, and traffic-related air pollution exposure increases the risk of post lung transplant bronchiolitis obliterans syndrome

Inflammation

Oxidative stress

TGF-β1

Pro-fibrotic activity



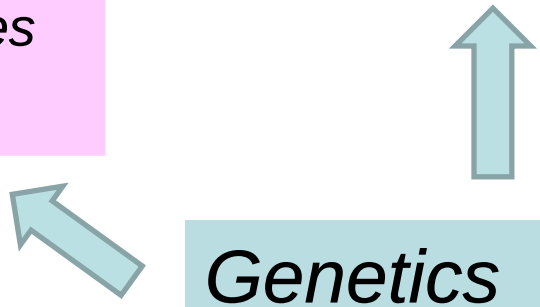
Aberrant wound healing

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



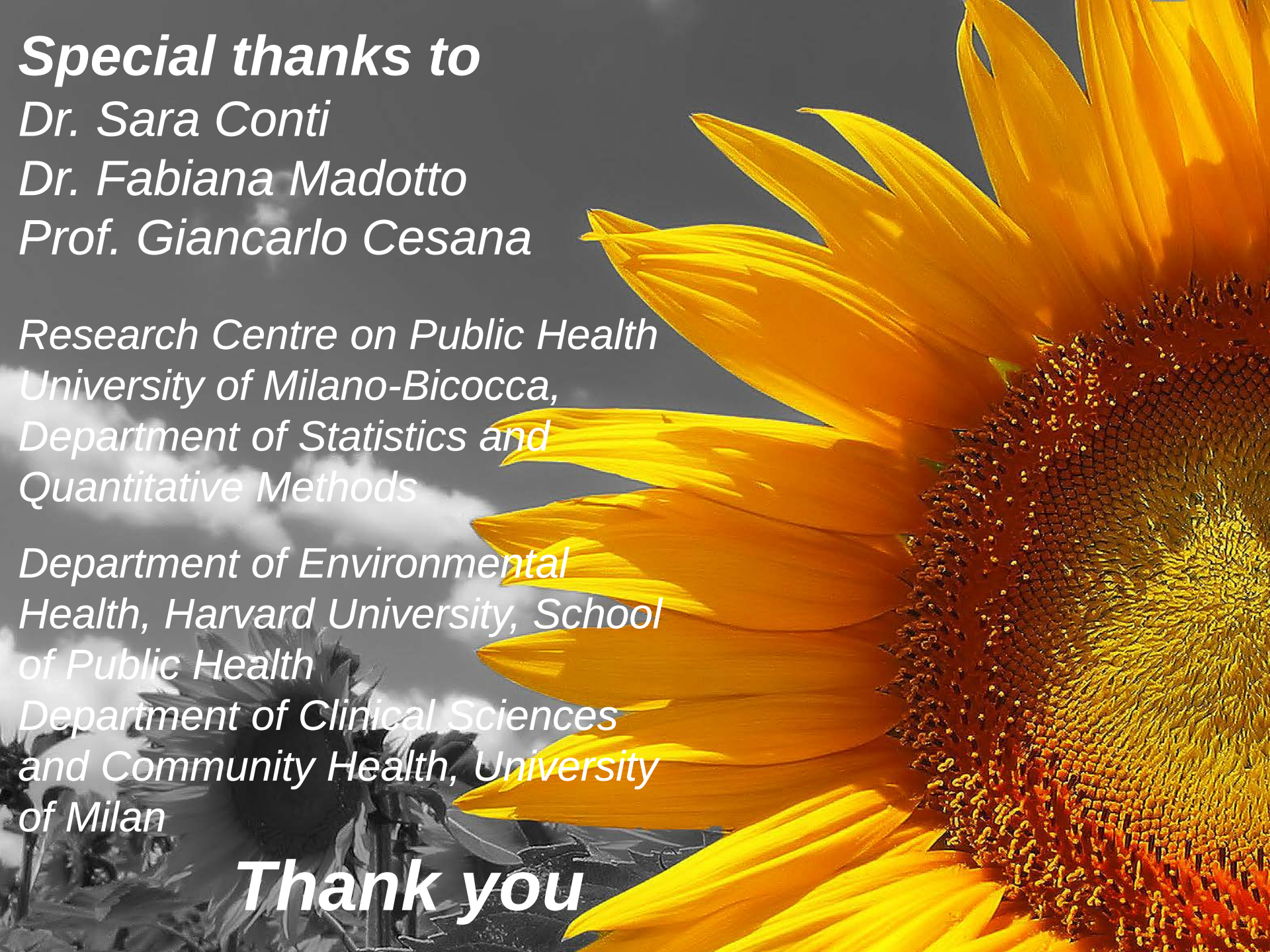
Genetics

Review

Are IPF patients fragile and vulnerable people?

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



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Department of Environmental Health, Harvard University, School of Public Health
Department of Clinical Sciences and Community Health, University of Milan

Thank you