Applications of the difference-in-differences approach to study the health effects of air pollution

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Outline

- Denial of the health effects of air pollution
- Causality determination
- Application of the GRADE system
- New approches in the study design
- Epidemiological «triangulation»
- Difference in differences
- Applications: Taranto, Lazio

Air pollution science under attack

EUROPEAN RESPIRATORY *journal*

Urban air quality and health: two steps forward, one step back Frank J. Kelly


Jim West/Science Photo Library

THE LANCET
Respiratory Medicine

Promoting clean air: combating fake news a denial

**Annette Peters, Nino Künzli, Francesco Forastiere, Barbara Hoffmann*

Lancet Respir Med 2019
Published Online
June 20, 2019

Pneumologi tedeschi, scienziati americani e ministri italiani:
il negazionismo sull'inquinamento atmosferico diventa internazionale!

German pulmonologists, American scientists, and Italian ministers:
denial of atmospheric pollution becomes international!

Francesco Forastiere,[1] Carla Ancona[2]

EPIDEMIOLOGIA & PREVENZIONE
Rivista dell'Associazione italiana di epidemiologia

Synthesis and science integration for causal determination

Combination of the degrees of evidence in humans and animals taking into account other relevant data (if any) to provide an “Overall Evaluation”

- IARC Monographs
- EPA Integrated Science Assessment

TABLE 6-3 Categories of Evidential Weight for Causality

Category	Conditions
Causal relationship	Sufficient evidence to conclude that there is a causal relationship. Observational studies cannot be explained by plausible alternatives, or they are supported by other lines of evidence, for example, animal studies or mechanistic information.
Likely to be a causal relationship	Sufficient evidence that a causal relationship is likely, but important uncertainties remain. For example, observational studies show an association but co-exposures are difficult to address or other lines of evidence are limited or inconsistent; or multiple animal studies from different laboratories demonstrate effects and there are limited or no human data.
Suggestive of a causal relationship	At least one high-quality epidemiologic study shows an association but other studies are inconsistent.
Inadequate to infer a causal relationship	The studies do not permit a conclusion regarding the presence or absence of an association.
Not likely to be a causal relationship	Several adequate studies, covering the full range of human exposure and considering susceptible populations, are mutually consistent in not showing an effect at any level of exposure.

Source: EPA 2013a, p. B-9.

Joint Glyphosate Task Force Issues Statement on IARC Monograph

The Joint Glyphosate Task Force (JGTF) reiterates its call for the World Health Organization (WHO) to clarify how the International Agency for Research on Cancer (IARC) arrived at vastly inconsistent classification on glyphosate.

https://www.youtube.com/watch?t=6&v=CbBkB81ySxQ

IARC 2015

Glyphosate 2A

POLICY

16 | NATURE | VOL 568 | 4 APRIL 2019

Pollution rules under siege at US environment agency

Adviser attacks EPA decision-making ahead of major review of air-pollution standards.

BY JEFF TOLLEFSON

research. The head of CASAC, Tony Cox, is a statistician who has long questioned the evidence linking fine particulate pollution to premature deaths, and the draft letter reflected this scepticism. It also called on the EPA to do another research assessment looking at the uncertainties and inconsistencies in the scientific literature on air pollution.

Science

POLICY FORUM

Cite as: G. T. Goldman and F. Dominici, *Science* 10.1126/science.aaw9460 (2019).

Don't abandon evidence and process on air pollution policy

Gretchen T. Goldman[1] *and* Francesca Dominici[2]

[1]Center for Science and Democracy, Union of Concerned Scientists, Cambridge, MA, USA. [2]Harvard T. H. Chan School of Public Health, Boston, MA USA.
Email: ggoldman@ucsusa.org

Who decides how to establish causality?

Randomized Controlled Trials versus Observational studies

- In the clinical realm, evidence-based review has become the starting point for establishing guidelines for clinical practice.
- Much of the evidence considered in the clinical context comes from randomized clinical trials (RCT), where exposures are assigned at random by the investigator, providing some assurance that potential confounders and modifiers, both known and unknown, are balanced across treatment groups.

Environmental health and clinical medicine are two different disciplines

- Clinical medicine

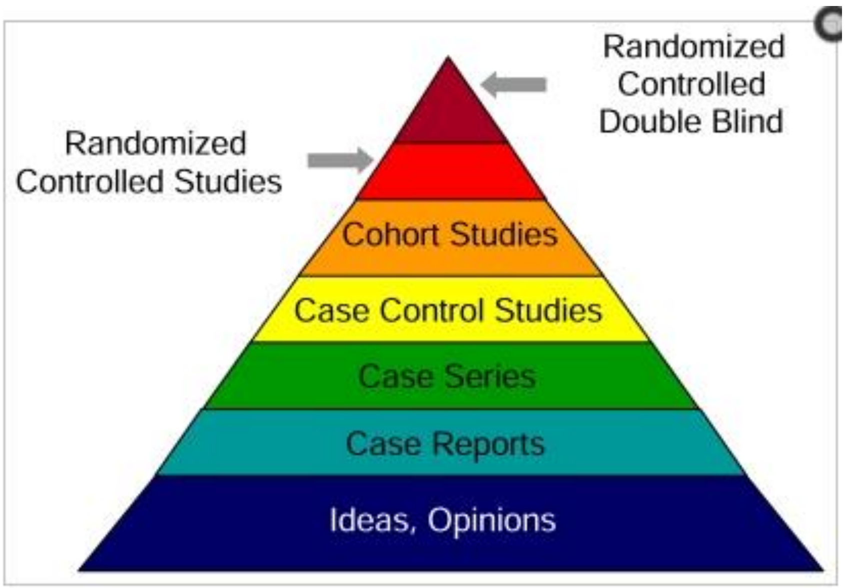


FIGURE 2-1 Evidentiary hierarchy of weighing evidence

- Environmental health

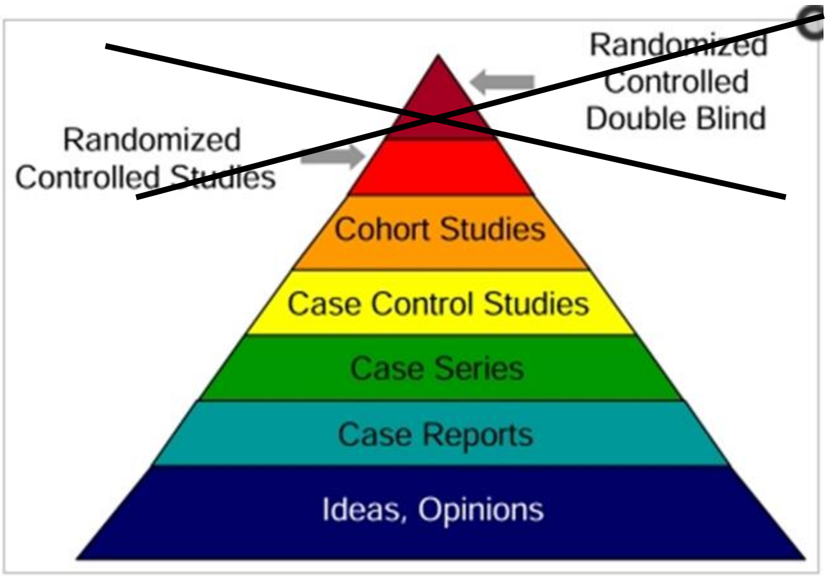


FIGURE 2-1 Evidentiary hierarchy of weighing evidence

"As per the current GRADE guidance, evidence from Non-Randomized Studies starts with a default initial certainty of "Low" due to concerns of confounding and selection bias when randomization is lacking" Morgan et al, Env Int 2019

ELSEVIER

Contents lists available at ScienceDirect

Environment International

journal homepage: www.elsevier.com/locate/envint

GRADE: Assessing the quality of evidence in environmental and occupational health

CrossMark

Rebecca L. Morgan [a], Kristina A. Thayer [b], Lisa Bero [c], Nigel Bruce [d], Yngve Falck-Ytter [e], Davina Ghersi [f,g], Gordon Guyatt [a], Carlijn Hooijmans [h], Miranda Langendam [i], Daniele Mandrioli [j], Reem A. Mustafa [a,k], Eva A. Rehfuess [l], Andrew A. Rooney [b], Beverley Shea [m], Ellen K. Silbergeld [n], Patrice Sutton [o], Mary S. Wolfe [b], Tracey J. Woodruff [o], Jos H. Verbeek [p], Alison C. Holloway [q], Nancy Santesso [a], Holger J. Schünemann [a,r,*]

[a] Department of Clinical Epidemiology & Biostatistics, McMaster University, Health Sciences Centre, Room 2C14, 1280 Main Street West, Hamilton, ON L8S 4K1, Canada

1. Establish initial level of certainty

Study design	*Initial certainty in an estimate of effect*
Randomized trials →	High certainty
Observational studies →	Low certainty

2. Consider lowering or raising level of certainty

Reasons for considering lowering or raising certainty	
↓ Lower if	↑ Higher if*
Risk of Bias Inconsistency Indirectness Imprecision Publication bias	Large effect Dose response All plausible confounding & bias • would reduce a demonstrated effect or • would suggest a spurious effect if no effect was observed

3. Final level of certainty rating

Certainty in an estimate of effect across those considerations
High ⊕⊕⊕⊕
Moderate ⊕⊕⊕◯
Low ⊕⊕◯◯
Very low ⊕◯◯◯

*upgrading criteria are usually applicable to observational studies only.

Adapted from "Methodological idiosyncracies, frameworks and challenges of non-pharmaceutical and non-technical treatment interventions" (Schünemann 2013)

Environmental health and clinical medicine are two different disciplines

Clinical medicine

- Evaluation of patients' benefit (positive effects)
- Worry of false positive
- Exposure is well defined
- Human studies
- Effectiveness

Environmental Health

- Evaluation of population risk (negative effects)
- Worry about false negative
- Exposure is estimated
- Human, animal, in vitro studies
- Susceptible groups
- Uncertainties evaluation

In defense of observational studies

- “It is important that we not treat these [observational] studies as second-class citizens; they have the advantage of being conducted in the natural habitat of the target population…and they can be “pure” in the sense of not being contaminated by issues of ethics or feasibility”

  (Pearl J, Mackenzie D. *The Book of Why: The New Science of Cause and Effect.* Penguin Books Limited; 2018)

Well established **study designs** in air pollution epidemiology

- **Episode analysis**
- **Population-based time-series**
- **Case- crossover analysis**
- **Population-based cross-sectional studies**
- **Ecological design**
- **Cohort-based mortality**
- **Cohort- and panel-based morbidity**
- **(Intervention/natural/quasi-experimental studies)**

(Pope A, ISEE, 2016)

All these studies adjust for confounders in the analysis stage (usually by regression)

«Causal inference» methods

Extension of traditional methods:

- Instrumental variable analysis (IV)
- Regression discontinuity
- Negative control outcomes
- Difference in differences (DD)

Adjust for confounders by design!

ISEE COMMENTARY

Causal Inference in Environmental Epidemiology: Old and New Approaches

Neil Pearce,[a] Jan P. Vandenbroucke,[a,b,c] and Deborah A. Lawlor[a,d,e]

Epidemiology, 2019

International Journal of Epidemiology, 2017, 1–21
doi: 10.1093/ije/dyw314
Original Article

Original Article

Triangulation in aetiological epidemiology

Debbie A. Lawlor,[1,2,*] Kate Tilling[1,2] and George Davey Smith[1,2]

[1]MRC Integrative Epidemiology Unit at the University of Bristol, Bristol, UK and [2]School of Social and Community Medicine, University of Bristol, Bristol, UK

"The practice of strengthening causal inferences by integrating results from several different approaches, where each approach has different (and assumed to be largely unrelated) key sources of potential bias."

The most famous shape in football: the triangle

Consistency of Findings (Hill's criteria)

Has this association been seen with other studies, with other study designs, and in different groups of people?

- If so, this strengthens the findings

ISEE COMMENTARY

Causal Inference in Environmental Epidemiology: Old and New Approaches

Neil Pearce,[a] Jan P. Vandenbroucke,[a,b,c] and Deborah A. Lawlor[a,d,e]

Epidemiology, 2019

Triangulation refers to triangulation of different types of evidence within epidemiology, which might be called "epidemiologic triangulation".

Criteria for its use in causal inference in epidemiology have been proposed recently, and these specify that *results from at least two (but ideally more) methods that have differing key sources of unrelated bias be compared.*

If evidence from such different epidemiologic approaches all point to the same conclusion, this strengthens confidence that is the correct causal conclusion, particularly when the key sources of bias of some of the approaches would predict that the findings would point in opposite directions

Difference in differences

- The difference-in-difference (DID) technique originated in the field of econometrics, but the logic underlying the technique has been used in the past. It is called the 'controlled before-and-after study' in some social sciences.

- DID is a quasi-experimental design that makes use of longitudinal data from treatment and control groups to obtain an appropriate counterfactual to estimate a causal effect.

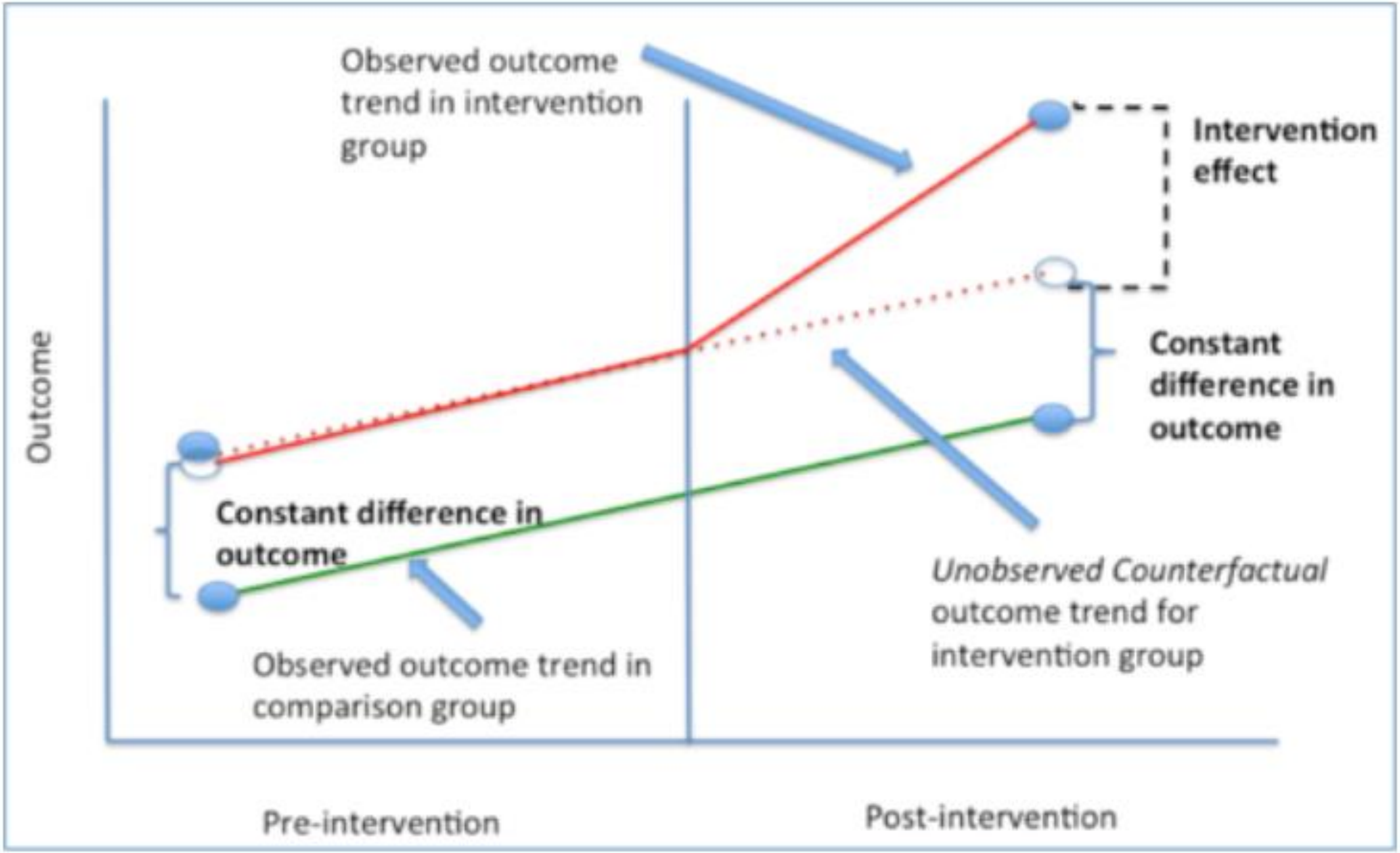


Figure 1. Difference-in-Difference estimation, graphical explanation

Difference in differences

- This approach controls for unobserved differences between the two groups which are
  - fixed over time
  - as well as differences which vary through time but which affect both control and treatment groups equally (for example economy wide factors).

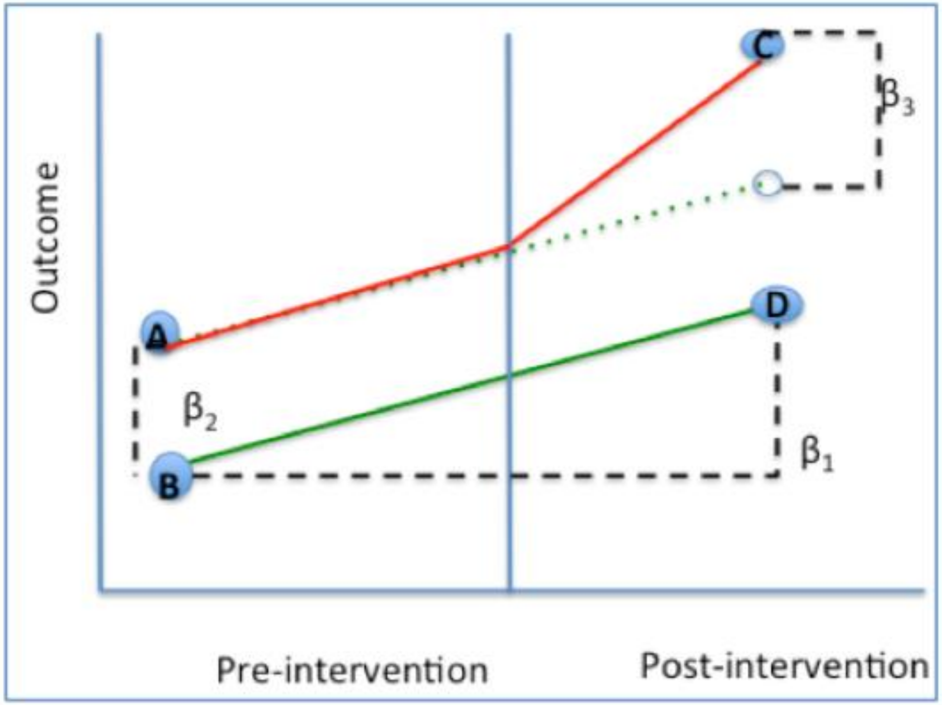
- DID estimation requires that:
- Intervention is unrelated to outcome at baseline (allocation of intervention was not determined by outcome)
- Treatment/intervention and control groups have Parallel Trends in outcome
- Composition of intervention and comparison groups is stable

Regression Model

DID is usually implemented as an interaction term between time and treatment group dummy variables in a regression model.

$Y = \beta 0 + \beta 1 * [\text{Time}] + \beta 2 * [\text{Intervention}]$
$+ \beta 3 * [\text{Time} * \text{Intervention}] + \beta 4 * [\text{Covariates}] + \varepsilon$

Coefficient	Calculation	Interpretation
β_0	B	Baseline average
β_1	D-B	Time trend in control group
β_2	A-B	Difference between two groups pre-intervention
β_3	(C-A)-(D-B)	Difference in changes over time



Strengths and Limitations

Strengths

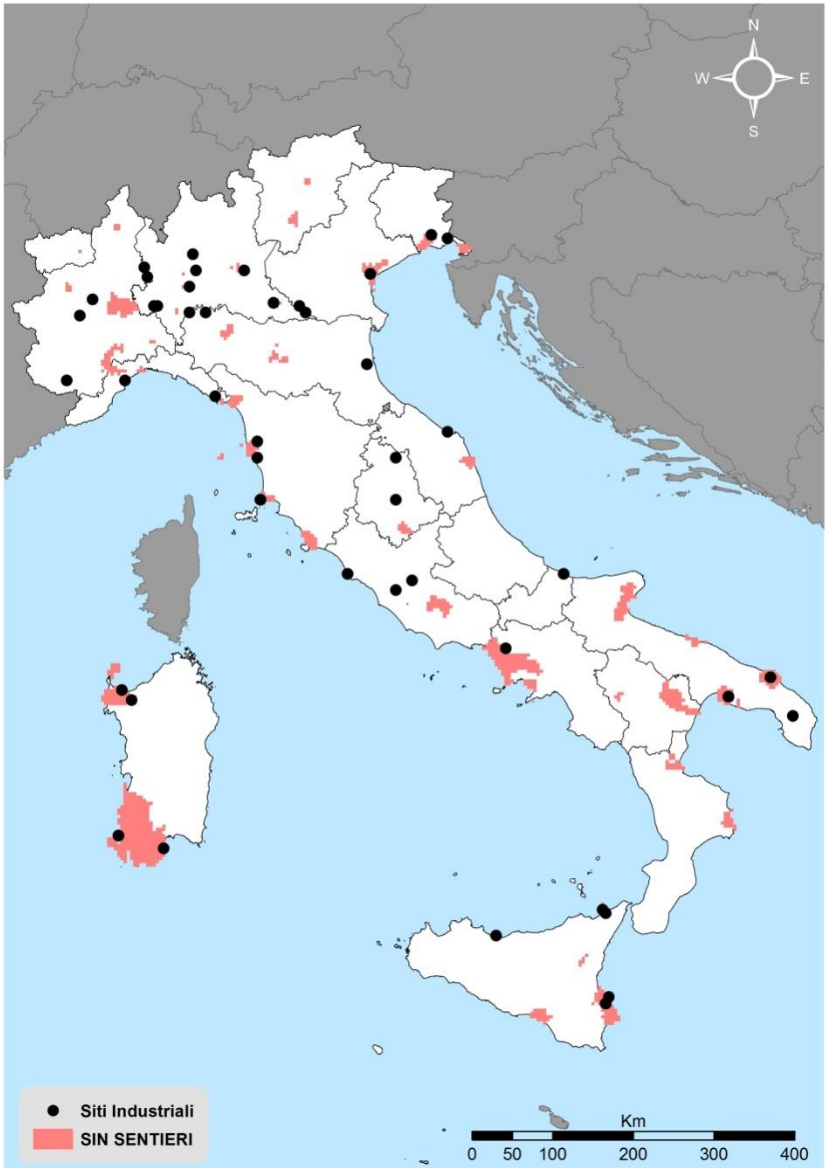
- Intuitive interpretation
- Can obtain causal effect using observational data if assumptions are met
- Can use either individual and group level data
- Comparison groups can start at different levels of the outcome (DID focuses on change rather than absolute levels)
- Accounts for changes due to factors other than intervention

Limitations

- Requires baseline data & a non-intervention group
- Cannnot use if intervention allocation determined by baseline outcome
- Cannot use if comparison groups have different outcome trend
- Cannot use if composition of groups pre/post change are not stable

Application 1: industrial emissions

Industrial sites in Italy

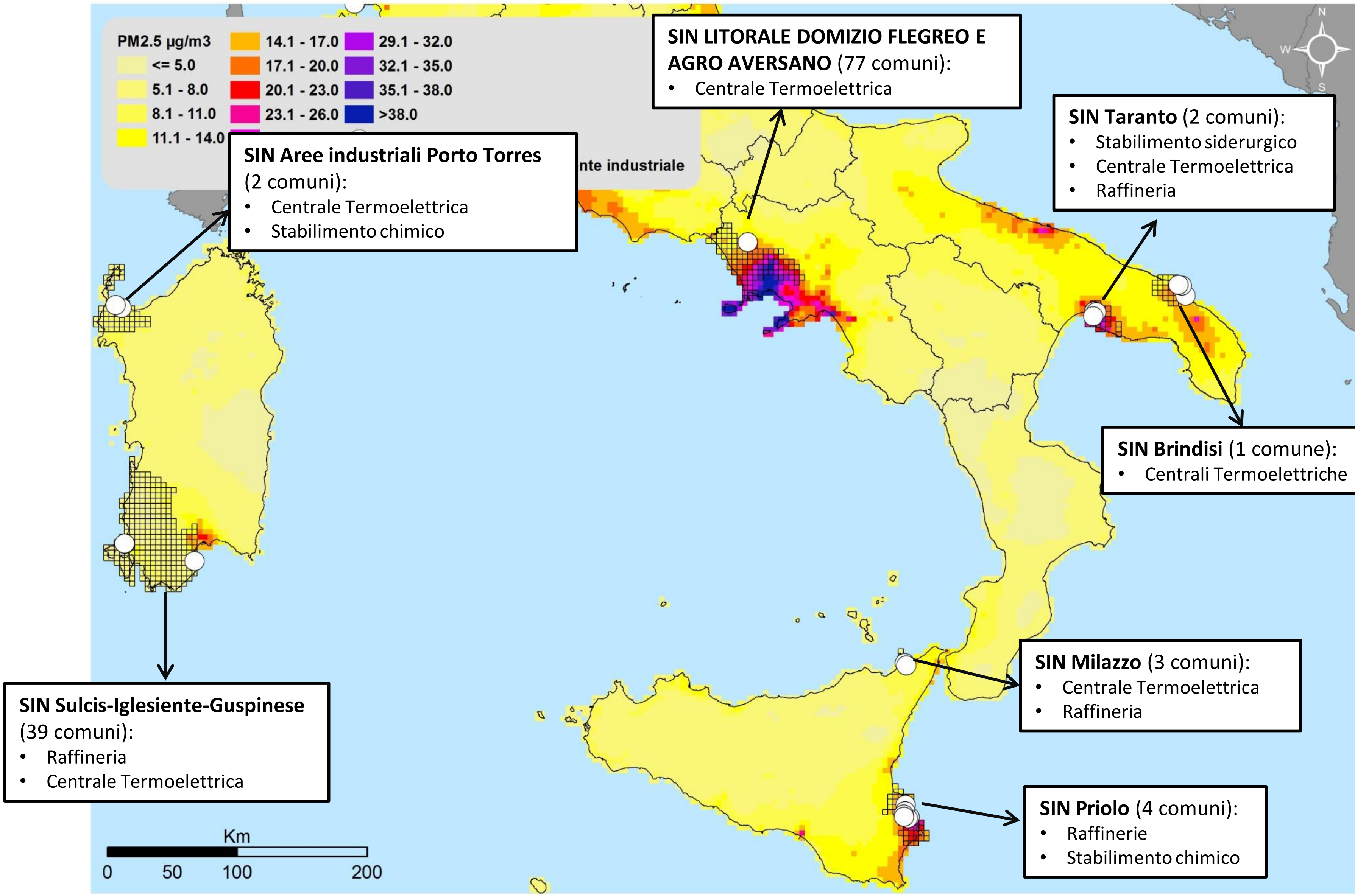


61 industrial sites
(**44** municipalities)

European Pollutant Release and Transfer Register (E-PRTR)

”Revealing the costs of air pollution from industrial facilities in Europe”
European Environmental Agency, 2011

Industrial sites



A case study in Taranto, Italy

Study area

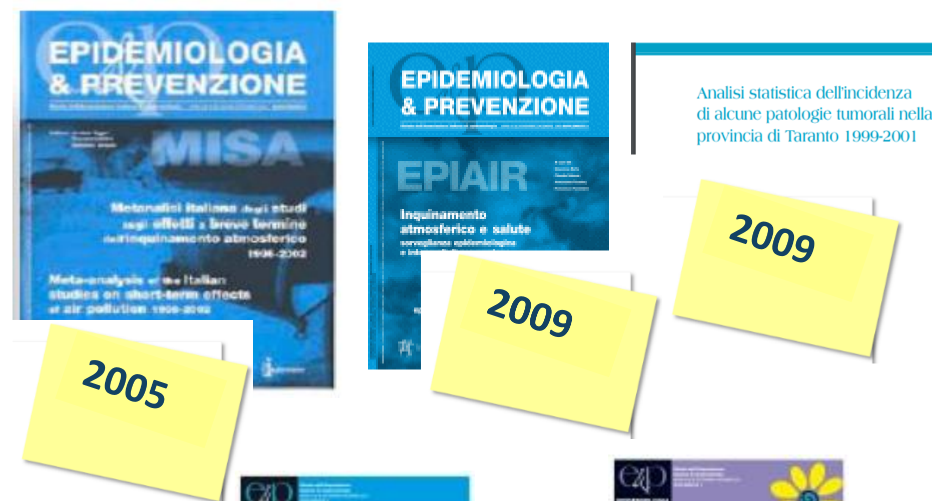
Epidemiological studies in Taranto

"MORTALITA' per CARCINOMA del POLMONE a TARANTO,

CITTA' SEDE di POLO SIDERURGICO"

- INDAGINE CONOSCITIVA

Primo rapporto
Ambiente e Salute in Italia
pubblicato nel 1997 (dati 1980-87);



ASL TA - O.E.R. PUGLIA
ANALISI GEOGRAFICA di MORTALITA'
1998-2004 per TUMORI MALIGNI

Background

- **24 July 2012, the Taranto Court ordered the partial closure of the ILVA plant and immediate remedial actions**
- Top executives, including Emilio Riva, chairman at ILVA’s owner Gruppo Riva SpA, were arrested because of neglected environmental controls at the plant
- For more than 6 years, the Italian government directly managed the plan; finally, in 2019 it was sold to an Indian company.

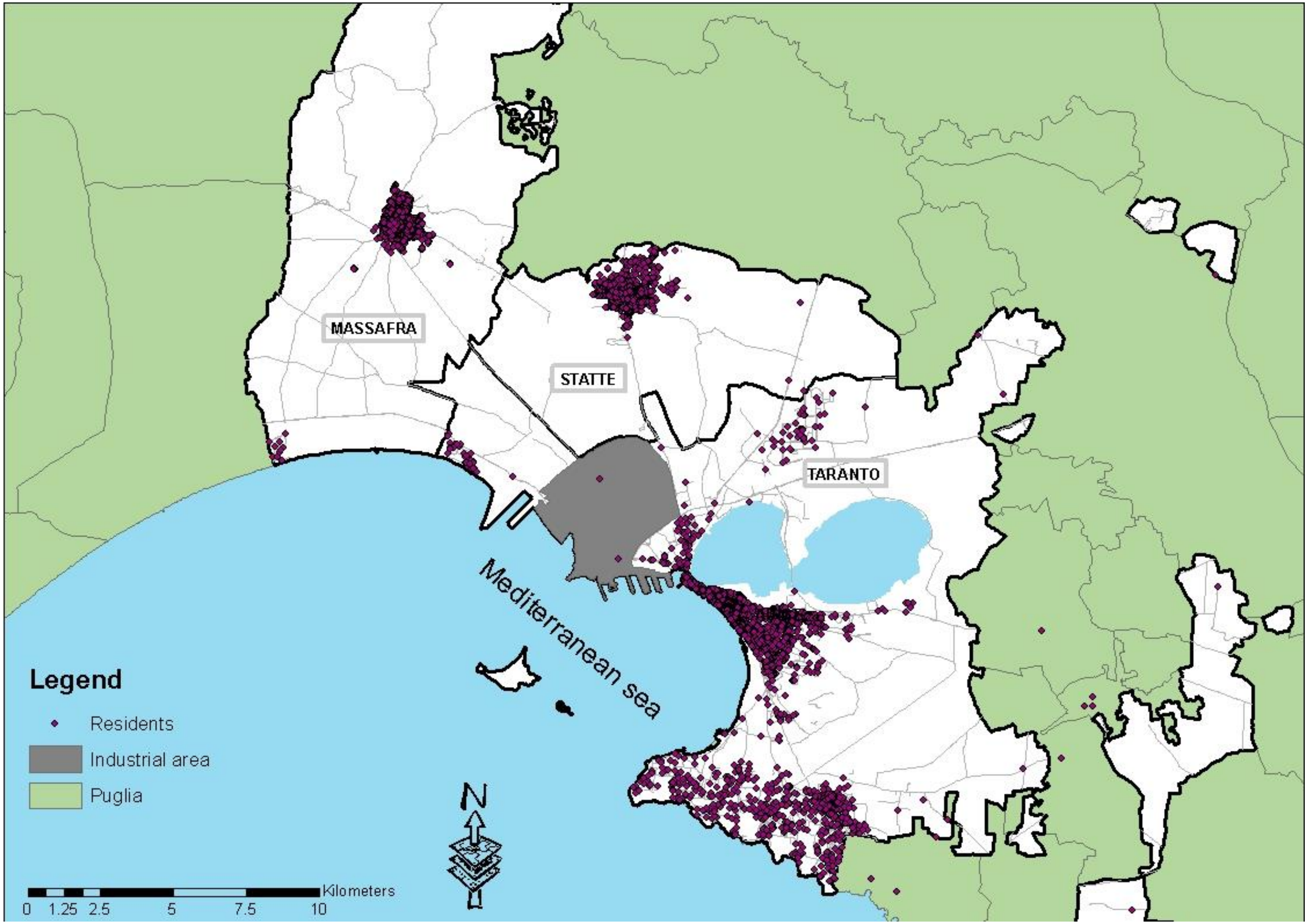
The evidence: traditional cohort study

Alessandrini et al, submitted for publication

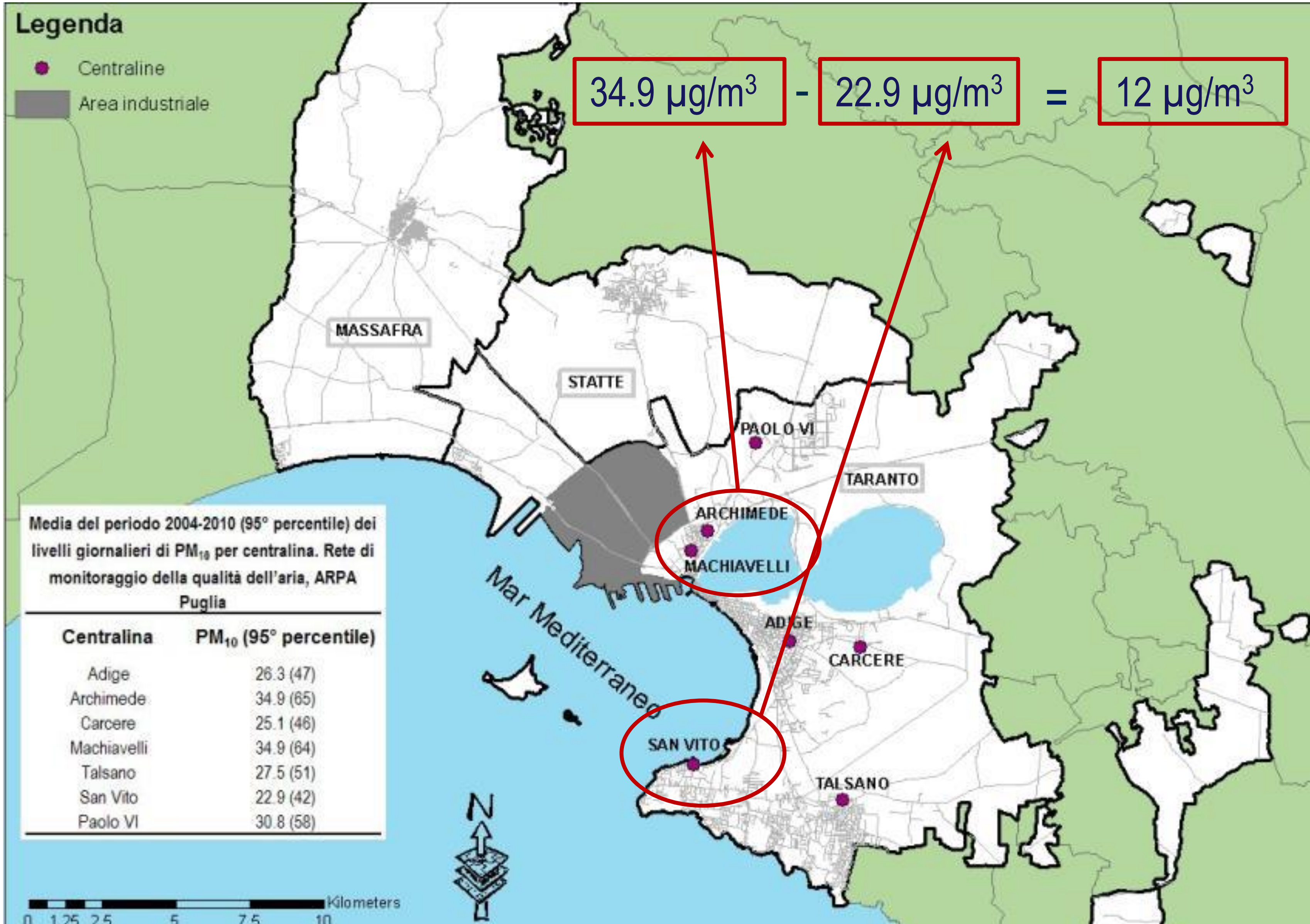
Methods

- *Cohort of residents in Taranto, Massafra and Statte (1998-2010)* ⇨ *Municipality data*
- *Mortality and hospitalization (1998-2013)* ⇨ *Regional Health database*
- *PM_{10} and SO_2 concentration from industry* ⇨ *Lagrangian particle model (2010)*
- *Backward estrapolation PM10 and SO2* ⇨ *Production and emissions: lagged exposure*

Geocoding of the cohort members

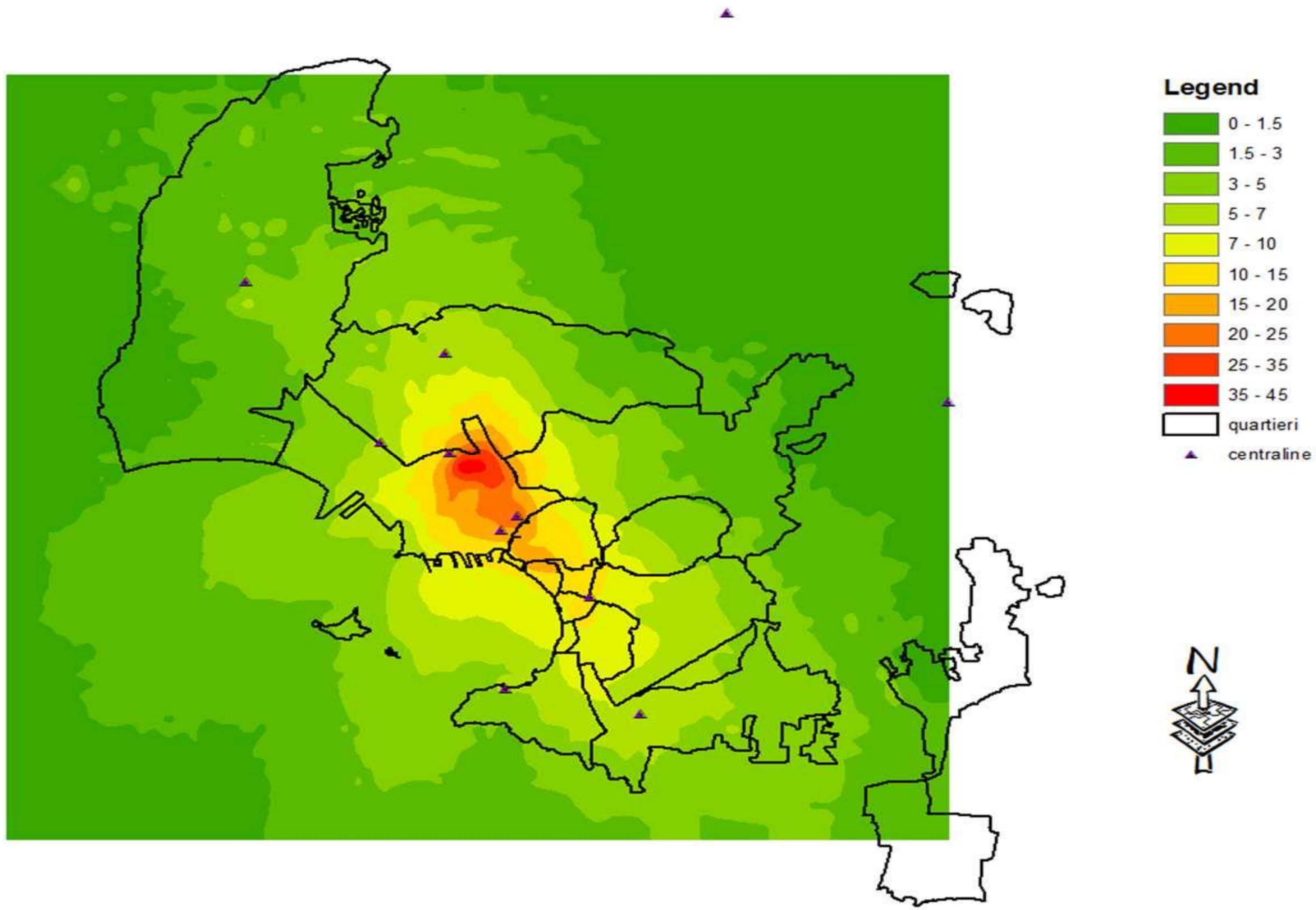


PM10 from fixed monitors (2004-2010)

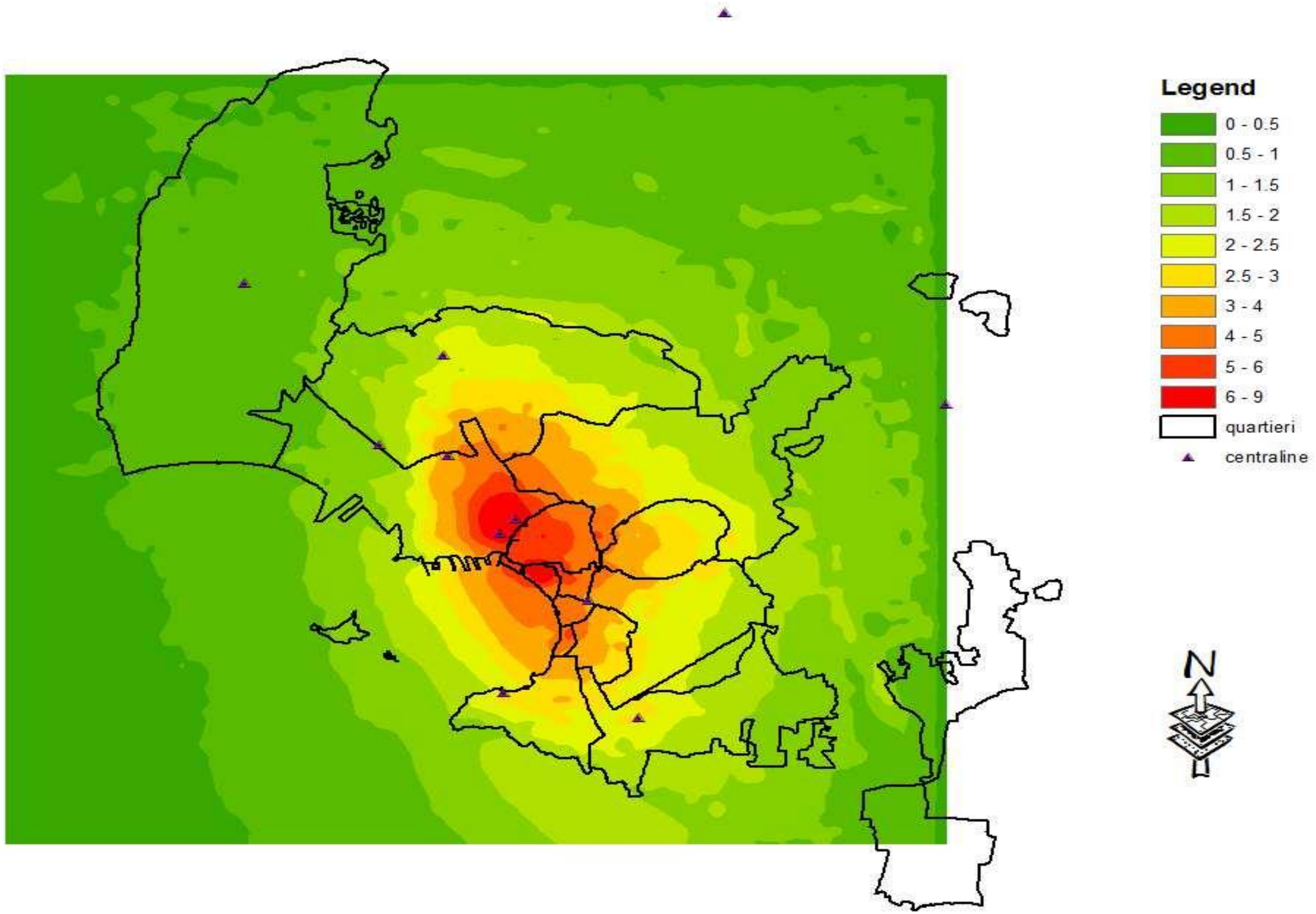


Centralina	PM_{10} (95° percentile)
Adige	26.3 (47)
Archimede	34.9 (65)
Carcere	25.1 (46)
Machiavelli	34.9 (64)
Talsano	27.5 (51)
San Vito	22.9 (42)
Paolo VI	30.8 (58)

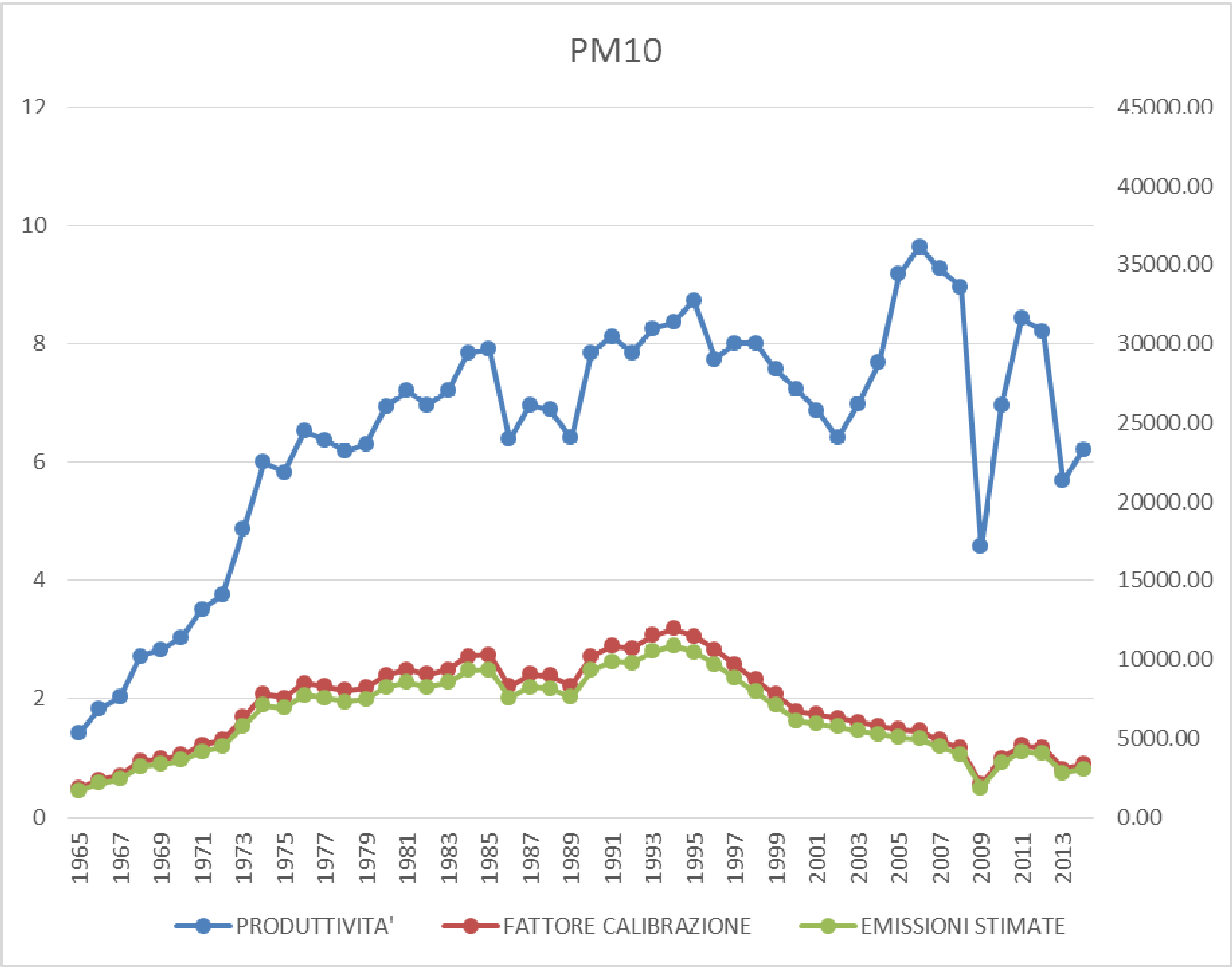
PM_{10} industrial, 2010 (Spray model)



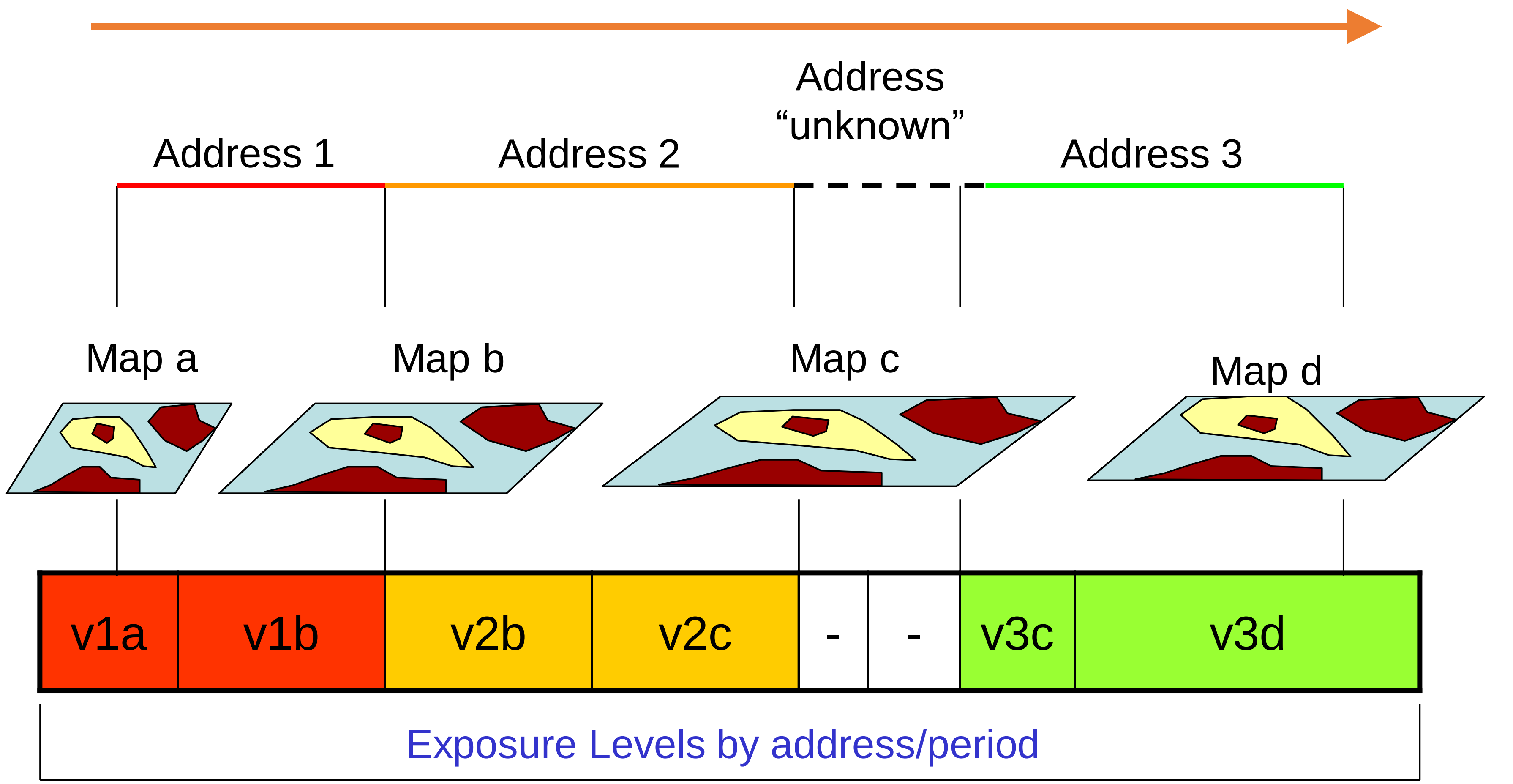
SO_2 industrial, 2010, Spray model



Productivity and emissions ILVA: PM_{10}



Long-term exposure since 1965



$$Ec = \sum v_{ij} * time_{ij}$$

Andrea Ranzi courtesy

Statistical analyses

Hazard Ratio ⇒ *Cox proportional model*

annual exposure = PM_{10} o SO_2 industrial(10µg/m^3)

Confounders = age, sex, calendar period, SES, occupation

321,356 subjects

35,358 deaths

Associations between annual average exposure to industrial PM_{10} and SO_2 at lag 0 and cause-specific mortality. Adjusted Hazard Ratios (HRs and 95% CI) per 10 $\mu g/m^3$ increase of each pollutant, 1998-2013

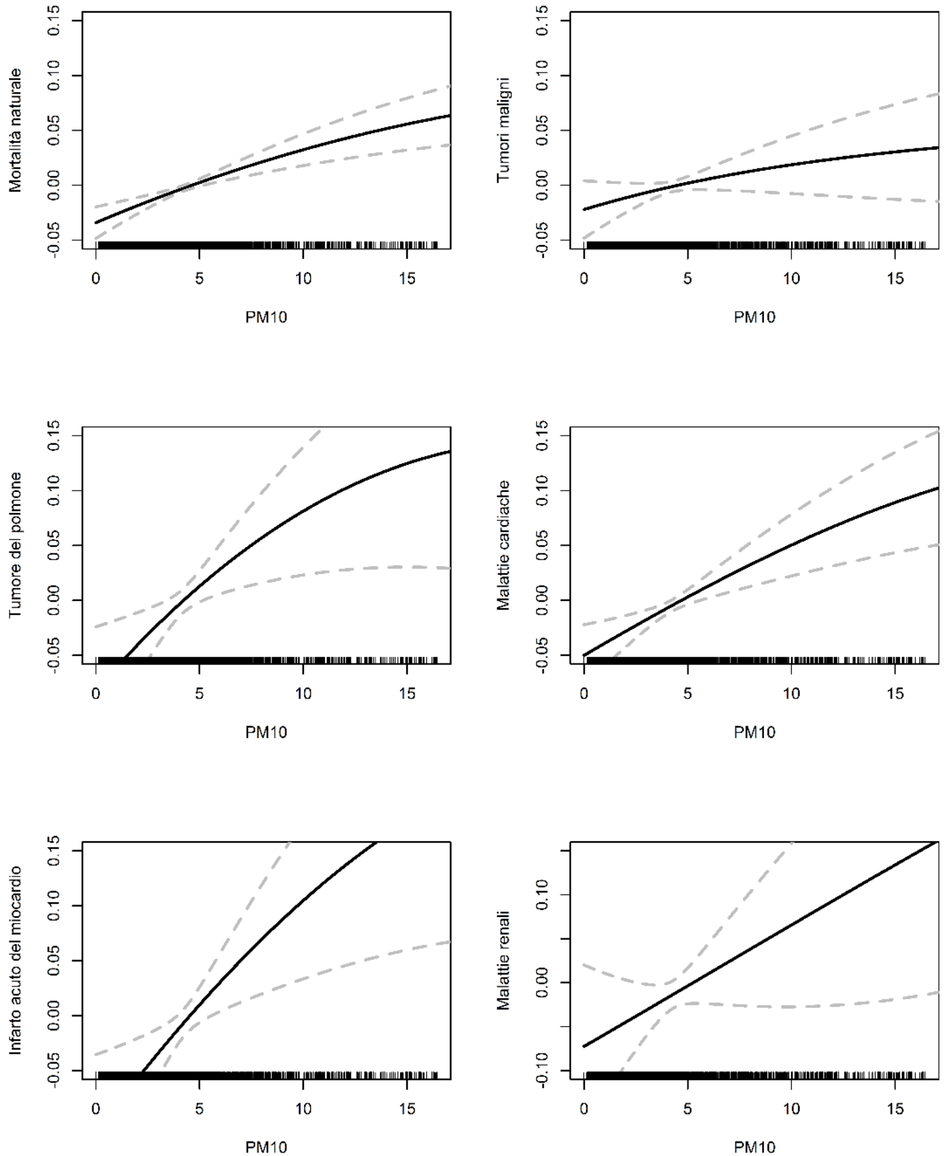
Causes of death (ICD-9CM)	PM_{10}			SO_2	
	N	HR*	95%CI	HR*	95%CI
Natural mortality (001-799)	33042	**1.04**	**1.02-1.06**	**1.09**	**1.05-1.12**
Malignant neoplasms (140-208)	10210	**1.03**	**1.00-1.06**	**1.08**	**1.02-1.15**
Trachea, bronchus, and lung (162)	2164	1.05	0.99-1.12	**1.17**	**1.03-1.34**
Bladder (188)	476	1.03	0.90-1.18	0.98	0.74-1.29
Kidney (189)	116	0.95	0.70-1.30	0.81	0.46-1.45
Lymphatic and hematopoietic tissue (200-208)	879	0.98	0.87-1.09	1.04	0.85-1.28
Diseases of the central nervous system (330-349)	1014	1.05	0.951.16	1.05	0.86-1.29
Diseases of the circulatory system (390-459)	12527	1.02	1.00-1.05	1.04	0.99-1.10
Heart diseases (390-429)	8857	**1.05**	**1.02-1.09**	**1.11**	**1.04-1.18**
Acute myocardial infarction (410-411)	1275	**1.10**	**1.02-1.19**	**1.29**	**1.10-1.52**
Cerebrovascular disease (430-438)	2903	0.90	0.85-0.96	0.80	0.72-0.89
Diseases of the respiratory system (460-519)	2741	1.02	0.97-1.08	1.02	0.91-1.14
Respiratory infections (460-466, 480-487)	751	0.90	0.80-1.02	0.85	0.69-1.04
COPD (490-492, 494, 496)	1618	1.03	0.95-1.10	1.04	0.90-1.21
Kidney disease (580-599)	707	**1.13**	**1.02-1.25**	1.16	0.93-1.45

*Hazard Ratio (HR) from a Cox model stratified for period of follow-up (3 categories) and sex, adjusted for age (temporal axis), socioeconomic position and occupational status

Dose-response relationship

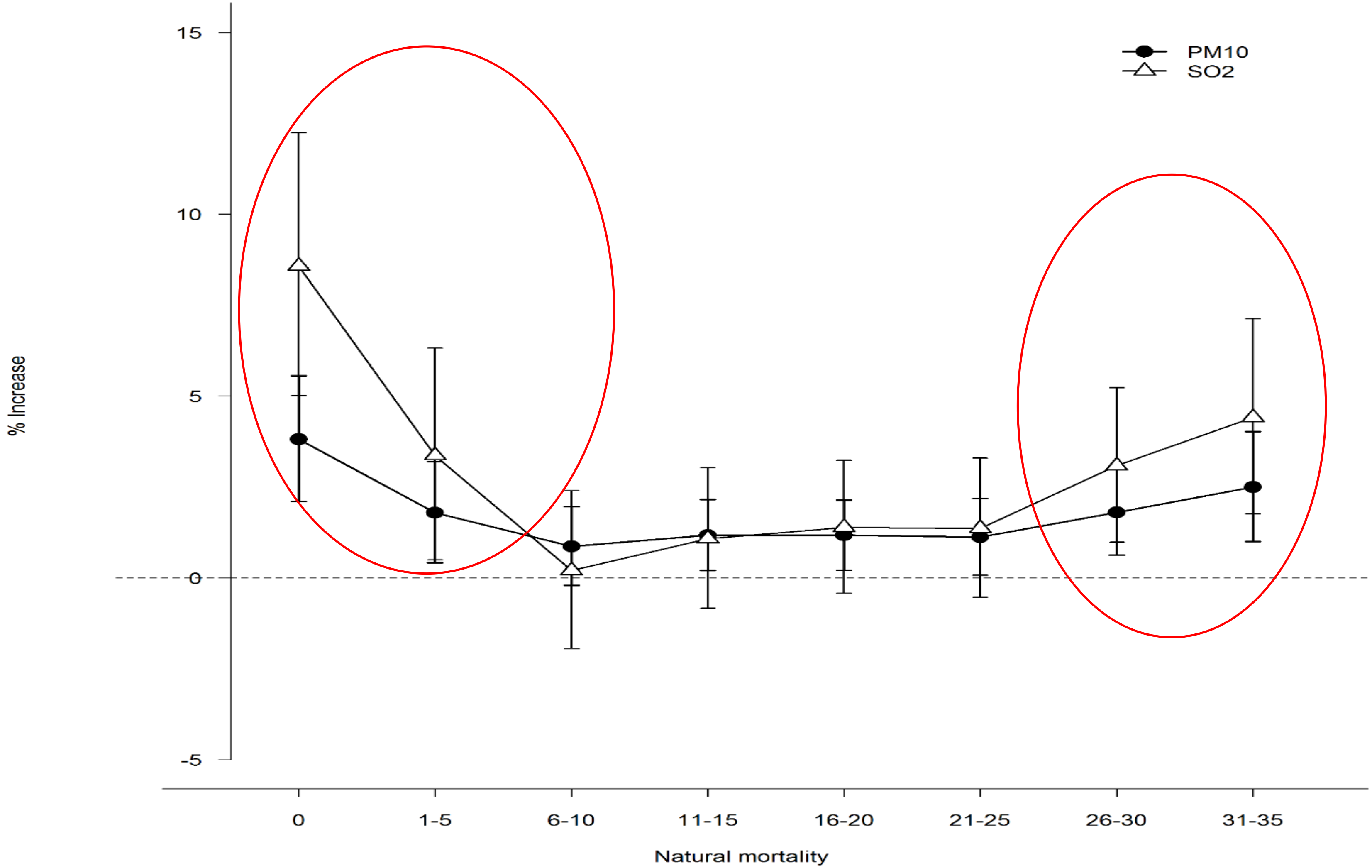
Penalized splines (95%CI) of the relationship between annual exposure to industrial PM_{10} at lag 0 and natural mortality, mortality from malignant neoplasms, from lung cancer, heart diseases, acute myocardial infarction and kidney diseases

PM10



The latency of the effects

Association of industrial PM_{10} and SO_2 and natural mortality by 5-year time windows. Results expressed as percent increase for 10 µg/m^3 increment



The evidence: difference in differences

Leogrande et al, Env Int (under revision)

Study design

- Select a short study period (2008-2013)
- Select all the cohort members
- Estimate for each year (6 years), for each area (11 districts), and for each age class (4) PM10 due to industrial emissions
- Calculate mortality rates for each year, area, age class
- Contrast fluctuations of PM10 around linear trends to concurrent fluctuations in mortality rates.
- Limited statistical power, but confounders adjusted by design (same population).

ILVA production 2008-2013

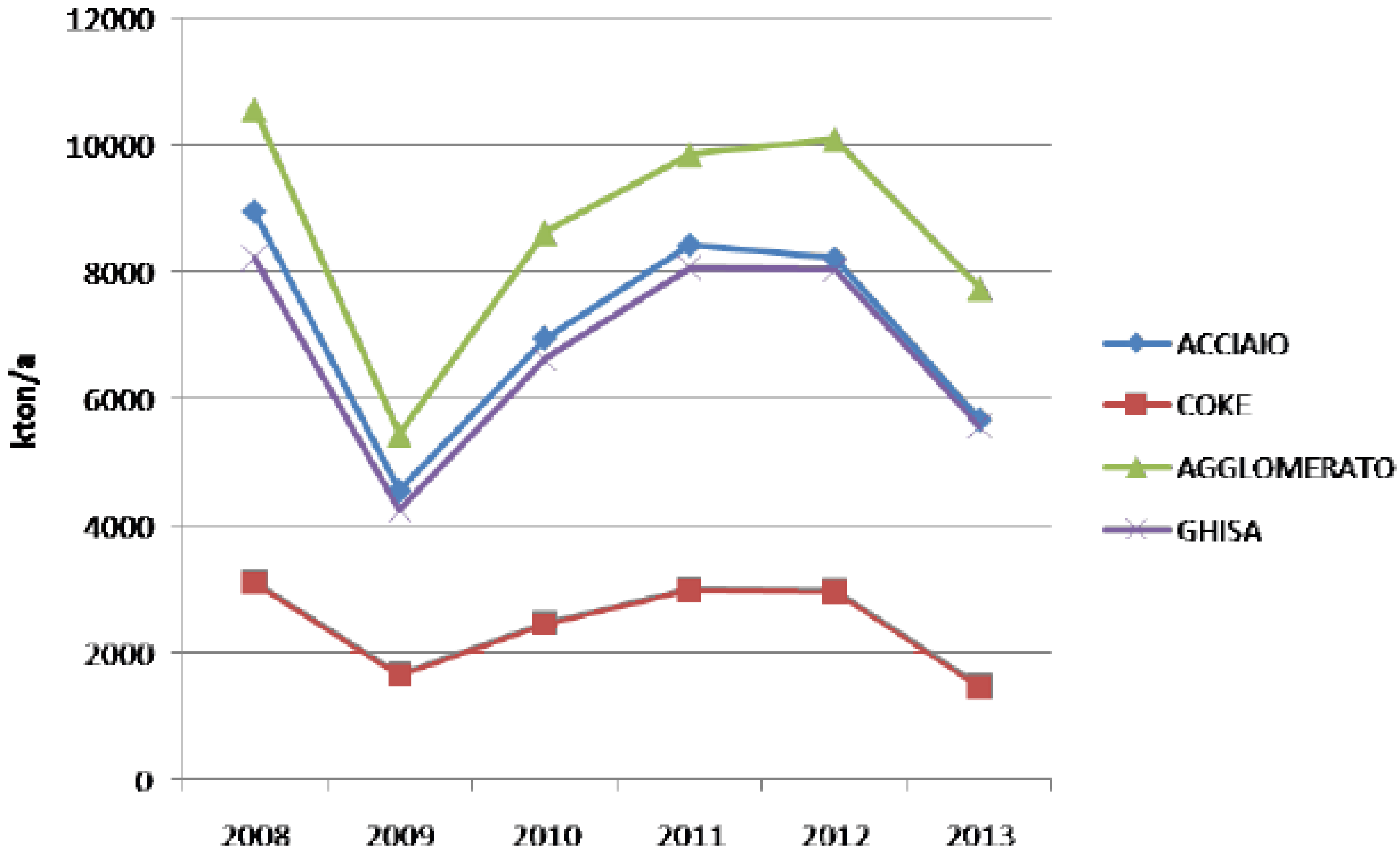
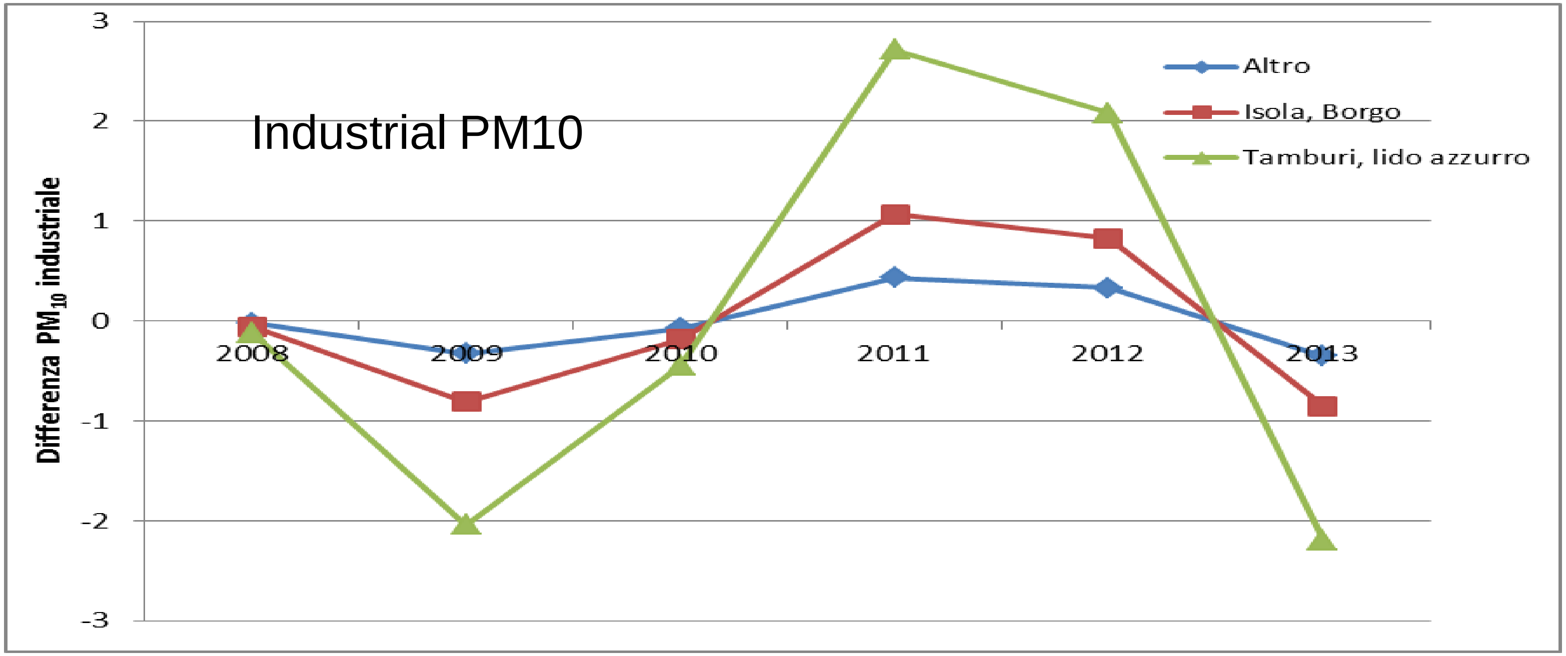
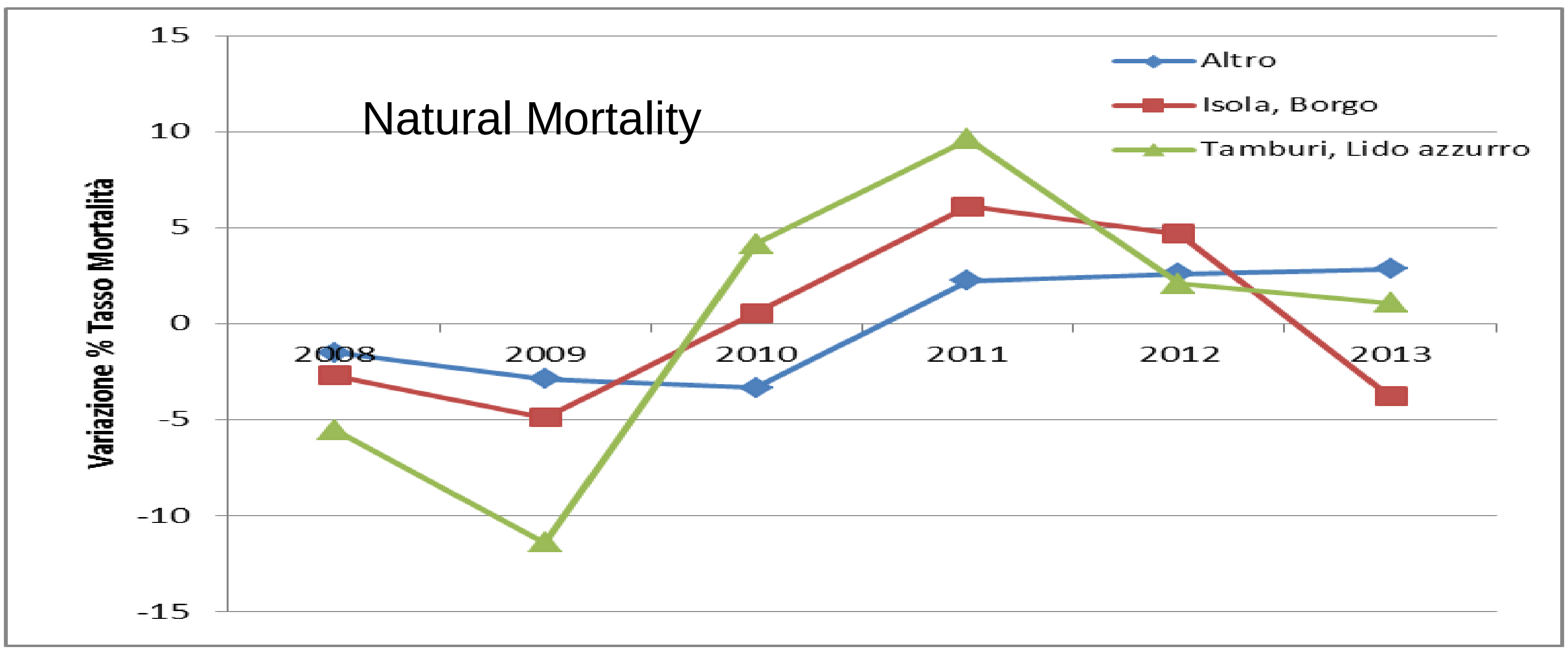


Figura. Produzioni ILVA per gli anni 2008-2013

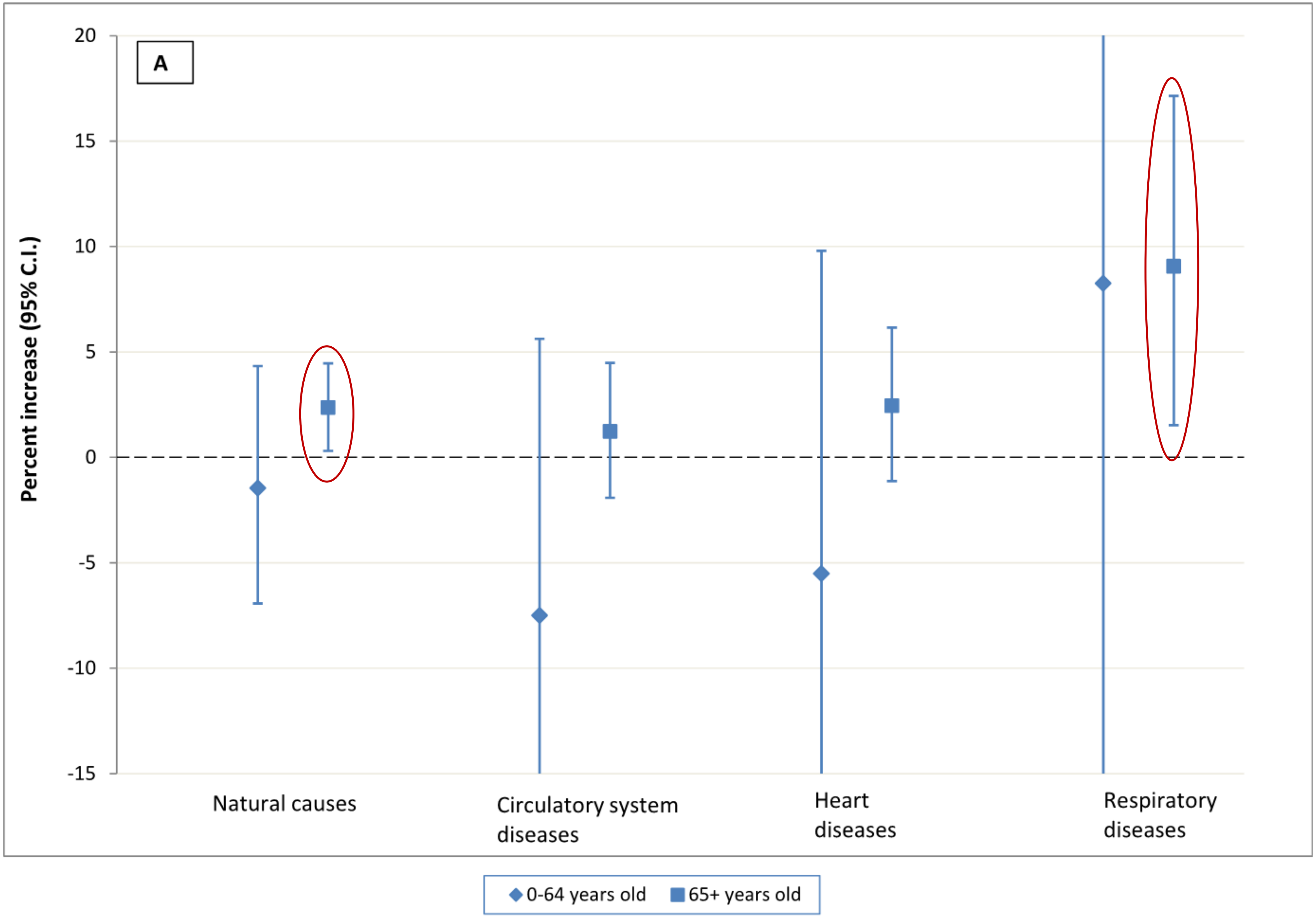

Industrial PM10
Differenza PM_{10} industriale
3
2
1
0
-1
-2
-3
2008
2009
2010
2011
2012
2013
Altro
Isola, Borgo
Tamburi, lido azzurro


Natural Mortality
Variazione % Tasso Mortalità
15
10
5
0
-5
-10
-15
2008
2009
2010
2011
2012
2013
Altro
Isola, Borgo
Tamburi, Lido azzurro

Results: percent increase of risk and 95% C.I., relative to 1 $\mu g/m^3$ variation of industrial PM_{10} (IQR=1.6 $\mu g/m^3$)

Causes of death (ICD IX)	Number of deaths	I.R. %	95% C.I.	
Natural causes (001-799)	15,303	1.86	-0.06	3.83
Circulatory system diseases (390-459)	5,721	0.70	-2.35	3.84
Heart diseases (390-429)	4,346	1.91	-1.55	5.50
Respiratory diseases (460-519)	1,150	8.74	1.50	16.51

Results: Percent increase of risk of mortality and 95% C.I., by age class



Conclusions: evidence from different study designs

- Exposure to emissions of industrial origin is associated with increased mortality/morbidity in Taranto (*possibility of residual confounding by individual factors*)
- Fluctuations of PM10 - around the linear trends - are associated to concurrent fluctuations in mortality rates (*confounding removed by design*)
- The findings reinforce the interpretation of a *casual relationship*

Application 2: Long-term effects of PM on mortality

The evidence: traditional cohort study

Cesaroni et al, EHP 2013

Air pollution and mortality in the Rome Longitudinal Study

Research

EHP 2013

Long-Term Exposure to Urban Air Pollution and Mortality in a Cohort of More than a Million Adults in Rome

Giulia Cesaroni,[1] Chiara Badaloni,[1] Claudio Gariazzo,[2] Massimo Stafoggia,[1] Roberto Sozzi,[3] Marina Davoli,[1] and Francesco Forastiere[1]

[1]Department of Epidemiology, Lazio Regional Health Service, Rome, Italy; [2]Italian Workers' Compensation Authority (INAIL), Rome, Italy; [3]Regional Environmental Protection Agency, Rome, Italy

		10 ug/m³ NO2			10 ug/m³ PM2.5		
	Cases	HR	95%CI		HR	95%CI	
Non accidental mortality	144,441	**1.03**	1.02	1.03	**1.04**	1.03	1.05
Cardiovascular mortality	60,318	**1.03**	1.02	1.04	**1.06**	1.04	1.08
IHD mortality	22,562	**1.05**	1.03	1.06	**1.10**	1.06	1.13
Respiratory mortality	8,825	**1.03**	1.00	1.06	**1.03**	0.97	1.08

The evidence: difference in differences

Long-Term PM_{10} Exposure and Cause-Specific Mortality in the Latium Region (Italy): A Difference-in-Differences Approach

Matteo Renzi,[1] Francesco Forastiere,[2,3] Joel Schwartz,[4] Marina Davoli,[1] Paola Michelozzi,[1] and Massimo Stafoggia[1,5]

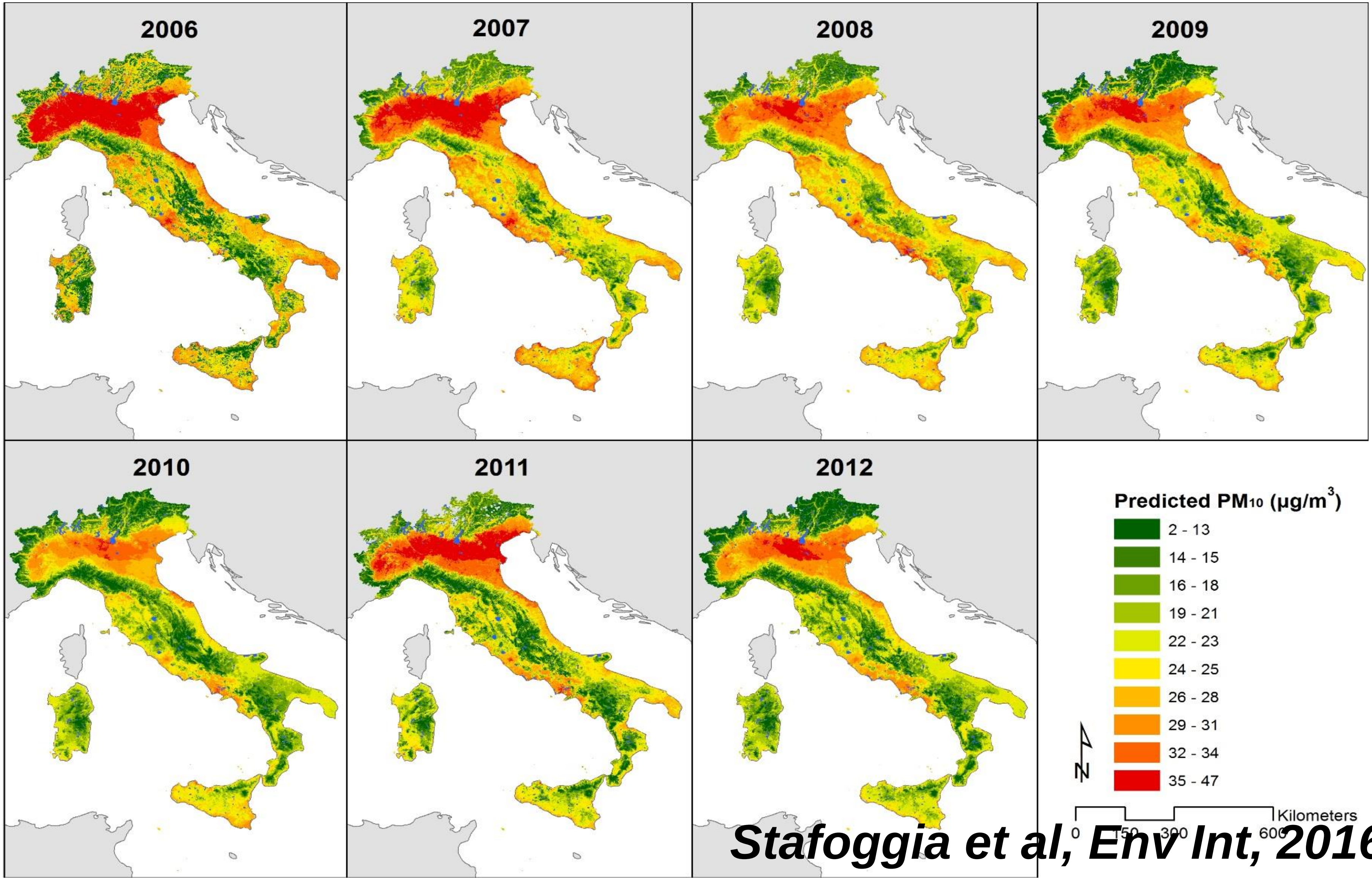
[1]Department of Epidemiology, Lazio Region Health Service/ASL Roma 1, Rome, Italy
[2]Institute of Biomedicine and Molecular Immunology (IBIM), National Research Council, Palermo, Italy
[3]Environmental Research Group, King's College, London, UK
[4]Department of Environmental Health, Harvard T.H. Chan School of Public Health, Boston, Massachusetts, USA
[5]Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden

EHP 2019

Aims

- To assess the association between long-term exposure to PM10 and cause-specific mortality (nonaccidental,cardiovascular,and respiratory) in the Latium region (central Italy), in the 2006–2012 period.
- To exclude by design confounding effects by individual and spatio-temporal factors
- To evaluate differential effects of PM on cause-specific mortality in urban, suburban,and rural areas of the region.

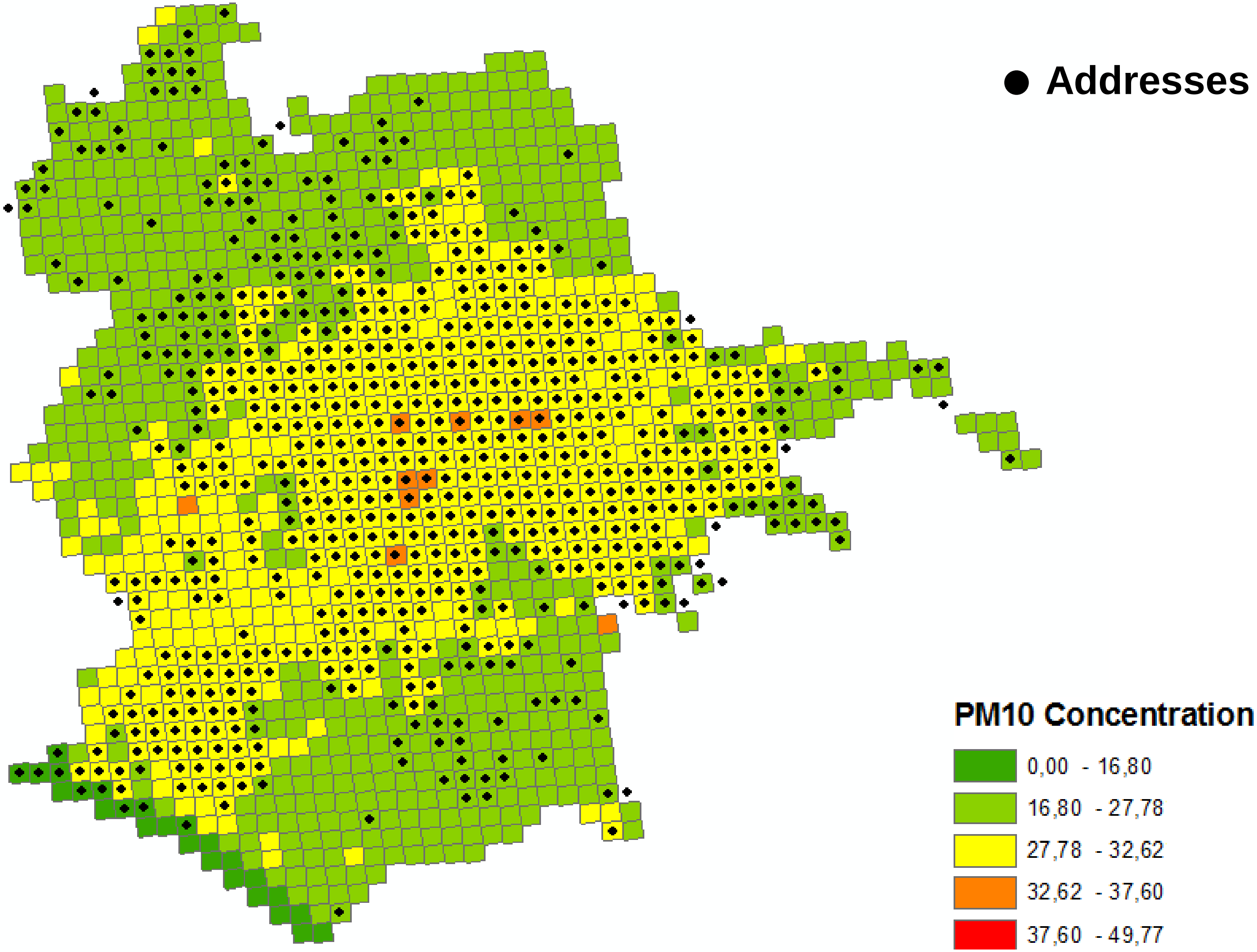
Estimation of daily PM10 concentrations in Italy (2006-2012) using finely resolved satellite data, land use variables and meteorology (1-km^2 grid)



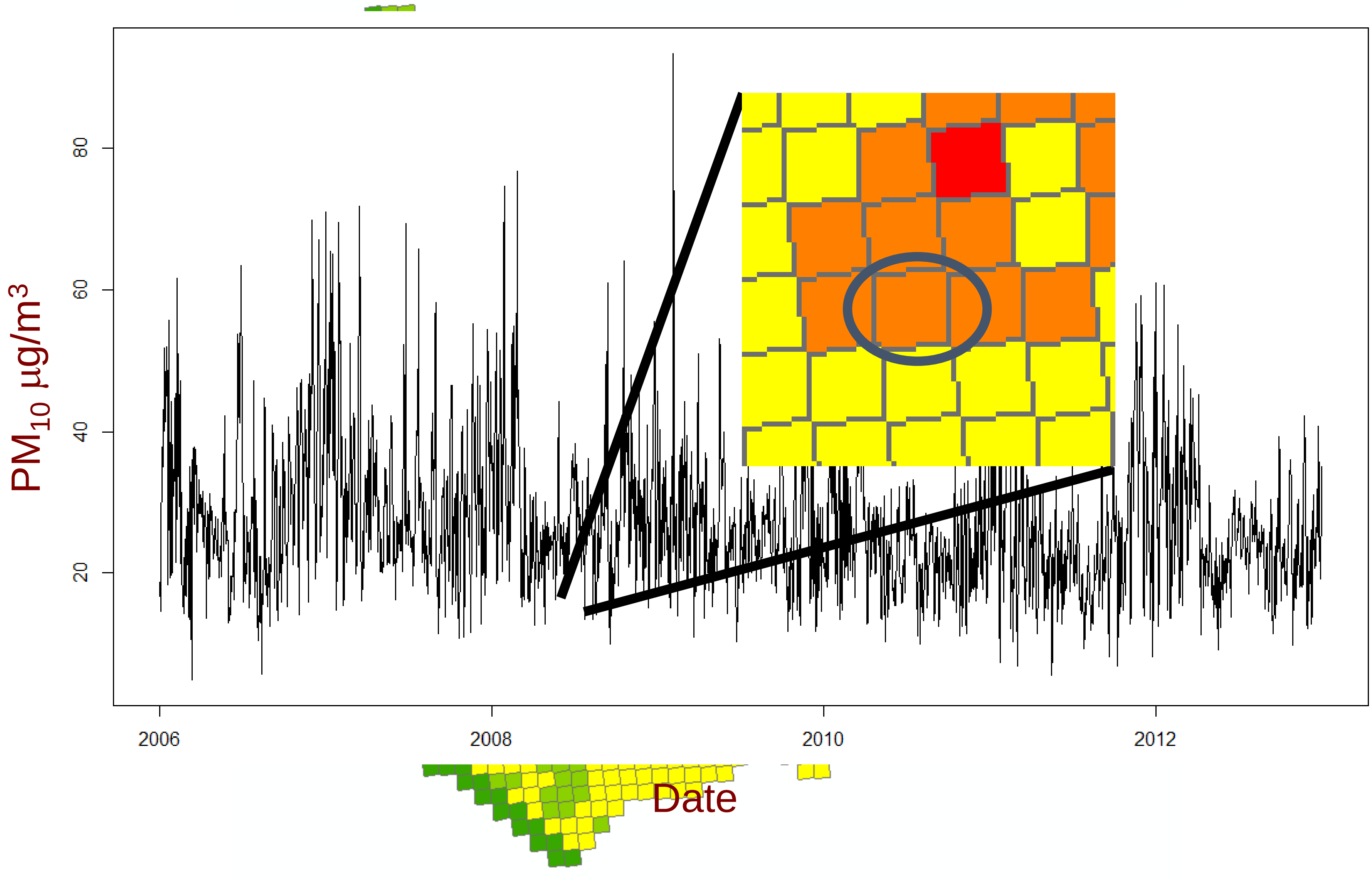
Stafoggia et al, Env Int, 2016

Exposure assessment – Spatial

2009



Exposure assessment – Temporal



The Lazio region

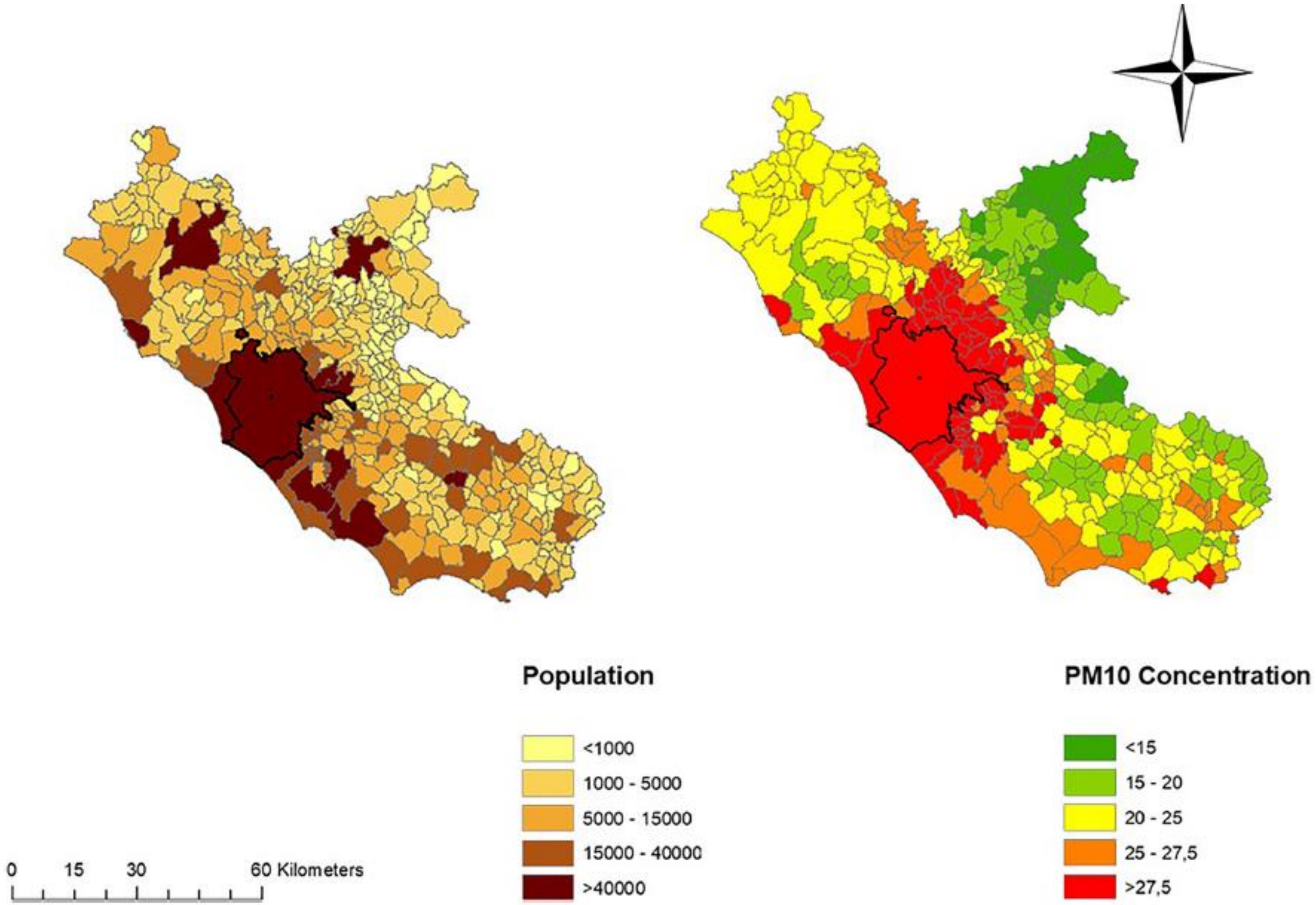


Figure 1. Population size and PM_{10} concentration in 378 municipalities of the Latium Region during the study period. The population size is reported for the year 2006, and the PM_{10} concentration is the average in the whole period.

Variability (SD) of the PM10 concentration in the Lazio Region (2006-2012)

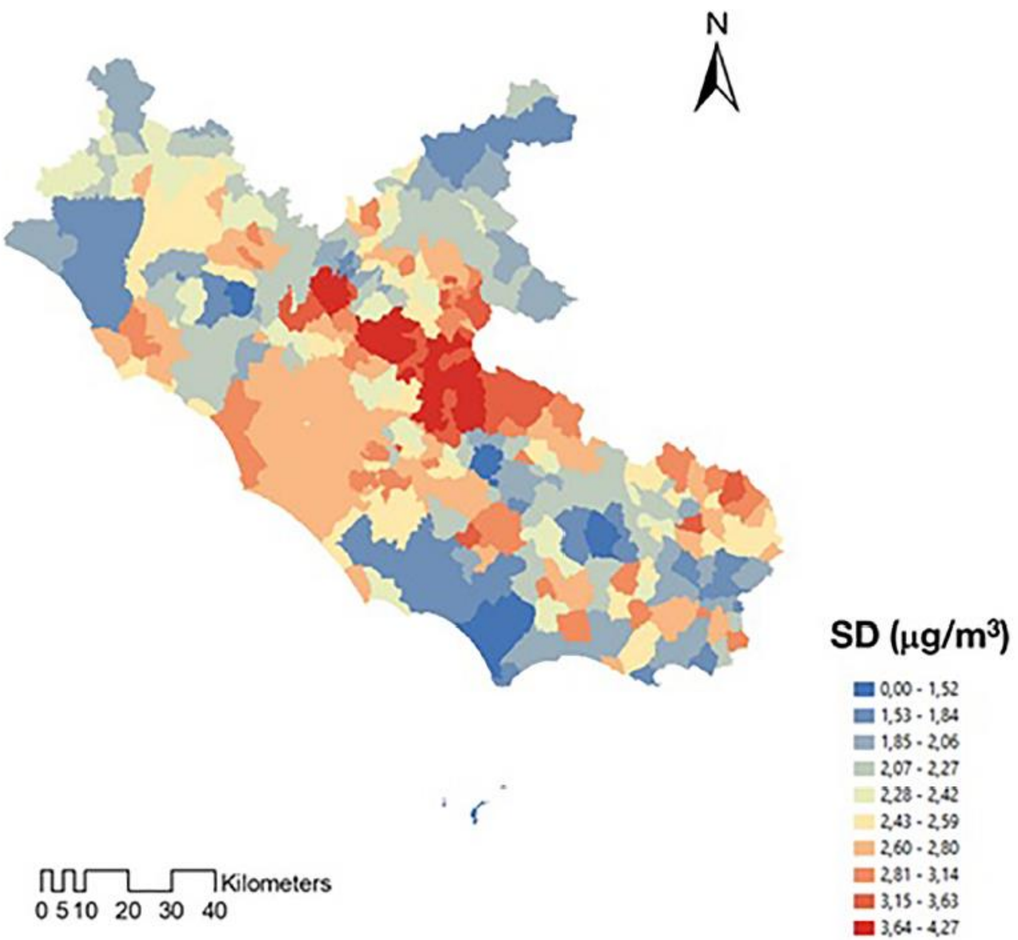


Figure 3. Standard deviation of the annual PM_{10} concentrations for each municipality in the whole region over the period 2006–2012.

Statistical analysis: conditional Poisson regression models :

- Model:

pm10 + i.year + i.municipality + temp_summer + temp_winter + sd_summer + sd_winter and offset (ln_pop)

- Exposure:
    - PM_{10} annual average
    - Warm temperatures (April to September)
    - Cold temperatures (October to March)
    - Standard deviation of warm temperatures
    - Standard deviation of cold temperatures

- Covariates:
    - Calendar year (dummy)
    - Municipality (dummy)

- Offset:
    - Population (natural logarithm)

Table 3. Associations between long-term exposures to environmental variables and cause-specific mortality. Results are expressed as percent increase of risk and relative 95% confidence intervals (CI) per 1-μg/m^3 increase of PM_{10}.

	Mortality		
Area/cause-specific mortality	IR%	95% CI	
Latium Region			
Nonaccidental	0.75	0.17	1.34
Cardiovascular	0.93	0.03	1.83
Respiratory	1.42	−0.38	3.25
Latium region without Rome			
Nonaccidental	0.57	−0.07	1.22
Cardiovascular	0.59	−0.38	1.57
Respiratory	2.02	0.05	4.04
Rome (155 urbanistic zones)			
Nonaccidental	0.53	−0.05	1.12
Cardiovascular	0.22	−0.64	1.08
Respiratory	0.57	−1.43	2.62

Conclusions: evidence from different study designs

- Exposure to PM2.5 from various sources is associated with increased mortality in Rome in an administrative cohort (*possibility of residual confounding by individual factors*)
- Fluctuations of PM10 - around the linear trends - are associated to concurrent fluctuations in mortality rates in the Lazio region (*confounding removed by design)*
- The findings reinforce the interpretation of a *casual relationship*

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