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Industrial air pollution and mortality in the Taranto area, Southern Italy: A difference-in-differences approach

Simona Leogrande[a], Ester Rita Alessandrini[b], Massimo Stafoggia[b,*], Angela Morabito[c], Alessandra Nocioni[c], Carla Ancona[b], Lucia Bisceglia[d], Francesca Mataloni[b], Roberto Giua[c], Antonia Mincuzzi[a], Sante Minerba[a], Stefano Spagnolo[c], Tiziano Pastore[c], Annalisa Tanzarella[c], Giorgio Assennato[c], Francesco Forastiere[b,e,f], , on behalf of the CSA Puglia Study Group (see acknowledgements)

[a] Local Health Service Taranto, Viale Virgilio 31, Taranto, Italy
[b] Department of Epidemiology, Lazio Regional Health Service, Rome – ASL Roma 1, Via Cristoforo Colombo, 112, Italy
[c] ARPA Puglia, Corso Trieste 27, Bari, Italy
[d] AReS Puglia, Via G. Gentile 52, Bari, Italy
[e] Institute of Biomedicine and Molecular Immunology (IBIM), National Research Council, Via Ugo La Malfa 153, Palermo, Italy
[f] Environmental Research Group, King's College, Stamford Street, London, UK

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ABSTRACT

Background: A large steel plant close to the urban area of Taranto (Italy) has been operating since the sixties. Several studies conducted in the past reported an excess of mortality and morbidity from various diseases at the town level, possibly due to air pollution from the plant. However, the relationship between air pollutants emitted from the industry and adverse health outcomes has been controversial. We applied a variant of the "difference-in-differences" (DID) approach to examine the relationship between temporal changes in exposure to industrial PM_{10} from the plant and changes in cause-specific mortality rates at area unit level.

Methods: We examined a dynamic cohort of all subjects (321,356 individuals) resident in the Taranto area in 1998–2010 and followed them up for mortality till 2014. In this work, we included only deaths occurring on 2008–2014. We observed a total of 15,303 natural deaths in the cohort and age-specific annual death rates were computed for each area unit (11 areas in total). PM_{10} and NO_2 concentrations measured at air quality monitoring stations and the results of a dispersion model were used to estimate annual average population weighted exposures to PM_{10} of industrial origin for each year, area unit and age class. Changes in exposures and in mortality were analyzed using Poisson regression.

Results: We estimated an increased risk in natural mortality (1.86%, 95% confidence interval [CI]: −0.06, 3.83%) per 1 μg/m^3 annual change of industrial PM_{10}, mainly driven by respiratory causes (8.74%, 95% CI: 1.50, 16.51%). The associations were statistically significant only in the elderly (65 + years).

Conclusions: The DID approach is intuitively simple and reduces confounding by design. Under the multiple assumptions of this approach, the study indicates an effect of industrial PM_{10} on natural mortality, especially in the elderly population.

1. Introduction

In environmental epidemiology the exposures under study are exogenous and usually affect individuals across entire communities thus leading to potential residual confounding from unmeasured or mismeasured variables. The "causal inference" methods to observational

* Corresponding author.
E-mail addresses: simona.leogrande@asl.taranto.it (S. Leogrande), ester.alessandrini@gmail.com (E.R. Alessandrini), m.stafoggia@deplazio.it (M. Stafoggia), a.morabito@arpa.puglia.it (A. Morabito), a.nocioni@arpa.puglia.it (A. Nocioni), c.ancona@deplazio.it (C. Ancona), l.bisceglia@arespuglia.it (L. Bisceglia), f.mataloni@deplazio.it (F. Mataloni), robertogiua1956@gmail.com (R. Giua), antonia.mincuzzi@asl.taranto.it (A. Mincuzzi), sante.minerba@asl.taranto.it (S. Minerba), s.spagnolo@arpa.puglia.it (S. Spagnolo), t.pastore@arpa.puglia.it (T. Pastore), a.tanzarella@arpa.puglia.it (A. Tanzarella), assennatogiorgio@gmail.com (G. Assennato), fran.forastiere@gmail.com (F. Forastiere).

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studies, in the spirit of mimicking randomized experiments as a way to improve study design, have been applied to several fields in biomedicine (Gillespie et al., 2015; Hernán et al., 2008; Shimizu et al., 2016; Lu and Marcus, 2012; Jacob et al., 2013; Lu, 1999; Afendulis et al., 2011) with some applications also in environmental epidemiology (Galiani et al., 2005; Branas et al., 2011; Wang et al., 2016; Benmarhnia et al., 2016; Kioumourtzoglou et al., 2016). While any techniques commonly used in traditional epidemiology is able to control known and measured confounding factors (restriction, standardization, regression models), none can completely rule out the presence of residual confounding, i.e. lack of comparability between exposed and unexposed groups for factors that are not controlled at all or are (possibly partially) controlled for, but are measured inaccurately (Rothman, 2012). An alternative is to apply methods that try to remove confounding "by design", e.g. by trying to mimic randomized clinical trials. Such methods, however, usually make implicit assumptions about the confounding structure that are sometimes difficult, if not impossible, to test. On the other hand, it has been advocated that the use of different study designs/data sources, both traditional or innovative under the "causal inference" approach, may allow triangulation of different types of evidence within epidemiology in order to strengthen the confidence on a putative causal factor if evidence from different epidemiologic approaches provides the same conclusion (Pearce et al., 2019).

In this study we have adopted a "differences in differences" approach in order to investigate the relationship between ambient exposure to air pollution from a specific industrial source and mortality in the nearby population. The method has been applied in the past in the econometric literature and it can be seen as a "before/after study with a control group". The essence of the design is that differences in exposures across time are related to differences in rates of diseases in the same populations so that the role of potential individual and behavioral factors is canceled out as the comparisons are occurring within the same populations. Of course, the variability of exposure across time is essential to appreciate differences in disease occurrence. A recent study in the USA has used a variant of this method to evaluate the effects of long-term $PM_{2.5}$ exposure on mortality in New Jersey (Wang et al., 2016). Another study conducted in 207 US cities has used an extension of this method to assess the association between year-to-year fluctuations in $PM_{2.5}$ concentrations and year-to-year survival variations within cities (Kioumourtzoglou et al., 2016).

The present study has been conducted in the area of Taranto, South of Italy, where a large steel plant has been operating in close proximity of the resident population for several decades and the possible health effects due to the industrial pollution have been under scrutiny (Biggeri et al., 2004; Pirastu et al., 2011; Pirastu et al., 2010; Mataloni et al., 2012; Mincuzzi et al., 2013; Bustaffa et al., 2014; Iavarone et al., 2012; Serinelli et al., 2011) and debate (Bianchi, 2012; Michelozzi, 2012; *Epidemiol. Prev.*, 2012) in the last few years.

2. Methods

2.1. Study area and enrolment of the cohort

The study area is located in the Apulia region (South-East of Italy) (area of 445.17 km^2) and includes the municipalities of Taranto, Massafra and Statte. The municipality of Taranto (area: 249.86 km^2, population on 1st January 2014: 203,257, Source: Italian Institute of Statistics-Istat) is the main town of the province, overlooking the Ionian Sea and for its geographical location is known as the "municipality of the two seas"; in fact, it stretches between two seas: "Mar Grande" (Big Sea) and "Mar Piccolo" (Little Sea). Because of its location and geographical structure, it was considered a strategic point and became the location of an industrial, commercial and military harbor. It is characterized by the presence of a large industrial area which is placed in the northwest of the municipality and includes: a refinery, a cement plant, and the "ILVA" steel plant operating since 1965, which

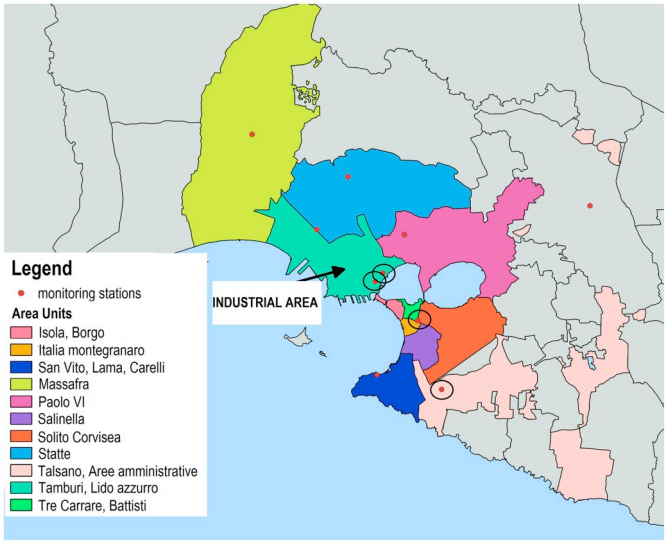

Fig. 1. Study area, monitoring stations (red dots, from North to South: "Machiavelli", "Archimede", "Alto Adige" and "Talsano") and area unit (colored polygons) of the study. The black arrow points to the "ILVA" steel plant. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

represents the largest European site for the steel production. As 1st November 2019 the plant is owned by the multinational steel manufacturing corporation ArcelorMittal.

The "ILVA" is an "integrated cycle" plant, so its main productions are: coke, sinter, pig iron, solid steel, hot rolled coils, cold rolled coils, hot galvanized coils, hot rolled heavy plates, black or coated welded pipes. A power plant is also integrated into the area. On 30th November 2015 it had 15,487 directly employed workers and a total of 8000 to 10,000 additional workers were estimated in the satellite activities (Source: "ILVA" website). The surface extension of the "ILVA" steel plant is about 15.45 km^2 of which about 10.45 km^2 in the municipality of Taranto and about 5 km^2 in the nearby municipality of Statte (Fig. 1) located in the northwest of the municipality of Taranto (area: 67.32 km^2, population on 1st January 2014: 14,190) close to the municipality of Massafra (area: 128 km^2, population on 1st January 2014: 32,780).

In a previous study (Mataloni et al., 2012), an open residential cohort was enrolled, including all residents in the study area at 01/01/1998 and those who entered in the three municipalities until 31/12/2010. Data on resident population (vital status, residential address and changes in address over time) were provided by the General Registry Offices of the three municipalities and were used after careful quality control procedures. Using the same sources, we updated the cohort and the vital status until 31/12/2014. Causes of death were provided by the Local Health Authority in Taranto. For the aims of the study, we retained only the latest period - 2008–2014 - as it matched the availability of environmental data and was short enough to reduce potential residual confounding from temporal covariates (see later for the assumption of the Difference-In-Differences [DID] model). All the residential addresses of the members of the cohort were geocoded using the ARCGIS software. On that basis, we assigned to each subject the corresponding district and census tract of residence for each year of the study. The list and a brief description of the nine districts (and the corresponding census tracts) are reported in the Supplemental material (Appendix A).

2.2. Exposure assessment

Our objective was to estimate levels to ambient particulate matter 10 μm or less in diameter (PM_{10}) from industrial origin for each year of

the study at each residential address of the cohort members and then to calculate annual population-weighted exposure to industrial PM_{10} by area unit (nine Taranto districts + Massafra and Statte). PM_{10} was chosen as the exposure variable instead of $PM_{2.5}$ since monitoring data for the entire period of the study were not available for $PM_{2.5}$. To this aim, we combined information from different sources. We considered four monitoring stations of the Regional Environmental Protection Agency (ARPA) network operating in the study area for the study period 2008–2014, which measured concentrations of nitrogen dioxide (NO_2) and PM_{10}. Those stations represented the different exposure conditions in the area. One station was located in the central urban area of Taranto ("Via Alto Adige") and another one was located in a sub-urban setting, south of the urban area and away from the industrial plant ("Via Ugo Foscolo" in the Talsano district), to measure background concentrations in the urban and rural area, respectively. The remaining two stations were located near the industrial area: "Via Machiavelli" and "Via Archimede", in the Tamburi district at the border of the industrial area. These data were used to describe temporal variability in exposure over the study area (see Fig. 1 where the monitoring locations are represented by red dots).

The Regional Environmental Protection Agency (ARPA) developed, for the year 2010, a dispersion model of PM_{10} emitted from the "ILVA" steel plant using a Lagrangian particle dispersion model (SPRAY) built on the available information about emissions sources, topography, land use and meteorology (ARPA Puglia, 2013). This model provided an estimate of the annual spatial distribution of "ILVA"-related PM_{10} concentrations, valid for the year 2010 (Fig. 2). We combined the PM_{10} annual average concentrations, measured by the monitoring stations, and the corresponding average concentrations modelled for the year 2010 by the dispersion model, to estimate industrial PM_{10} levels at the residential address of each individual and then at area unit level for each year of the period 2008–2014 according to a methodology illustrated in the Supplemental material - Appendix B. In brief, using a set of linear systems, we first evaluated the contribution from the industry to the measured PM_{10} at the monitoring site assuming a constant background and using NO_2 concentrations as a proxy measure for the contribution of traffic. Then, we evaluated industrial PM_{10} at the residential address of all the cohort members and, finally, we estimated the population-weighted exposure to industrial PM_{10} by year, area unit and age class.

Our approach had the following assumptions: 1) the background PM_{10} was the same in all the area units under study, since it represents background pollution levels originated from common large-scale sources, transboundary transport processes and secondary transformation; 2) the relative contributions of traffic to the overall PM_{10} concentration in different points can be estimated from the ratios between different NO_2 concentrations in those points; and, most importantly, 3) the relative contributions of industry to the overall PM_{10} concentration at different points could be inferred from the ratios between predicted industrial PM_{10} levels from the 2010 dispersion model in those points. In addition, we also assumed that the relative contribution of the "ILVA" steel plant in two points, as estimated by their ratio, remained constant over the years. Appendix B in the Supplemental material discusses the tenability of these assumptions.

2.3. Mortality data

Causes of death were ascertained using a record-linkage procedure with the mortality registry of the Local Health Authority in Taranto. In this registry, causes of death were coded using *International Classification of Diseases, 9th Revision* (ICD IX) for the period 2008–2010 and *10th Revision* (ICD X) for the period 2011–2014. We analyzed the following causes of death: natural causes (ICD IX 001–799, ICD X A00–R99), diseases of the circulatory system (ICD IX 390–459, ICD X I00–I99), heart diseases (ICD IX 390–429, ICD X I00–I51), and respiratory diseases (ICD IX 460–519, ICD X J00–J99).

2.4. Statistical analysis

For each year (seven: 2008–2014), area-unit (eleven: nine Taranto districts + Massafra and Statte) and age class (four: 0–34, 35–64, 65–74, > 74 years), we computed counts of cause-specific deaths. Furthermore, using cohort information and individual residential history, we estimated age-specific person-years to be used as denominators to calculate mortality rates or as "offset" in the multiple Poisson regression analysis described below. The person-years considered changes

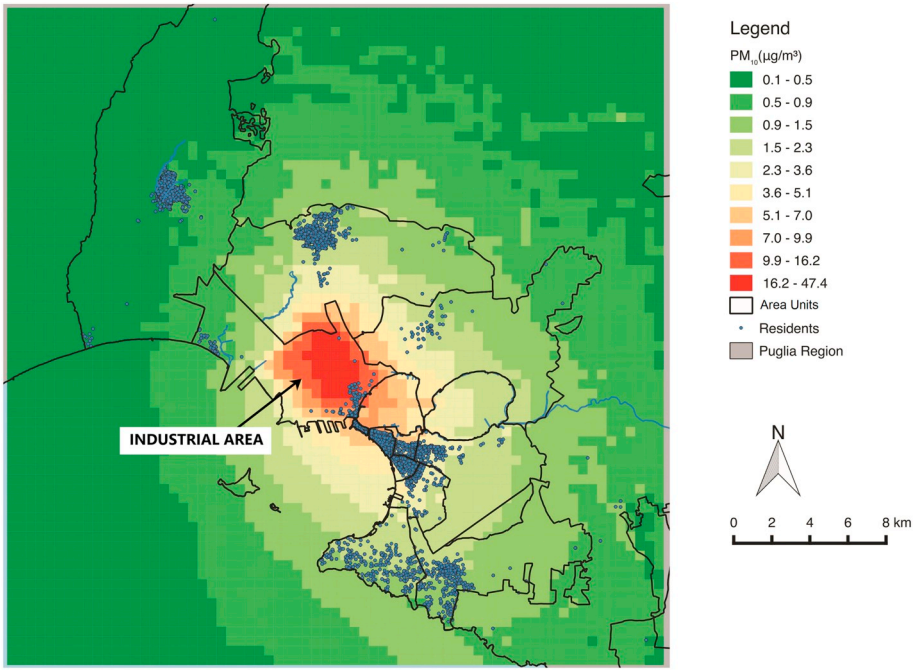

Fig. 2. Results of the 2010 dispersion model for "ILVA"-related PM_{10} (µg/m^3). The blue points are residential addresses of the study members, and the polygons are the districts under study.

of residential addresses.

We defined the following log-linear model:

$$\ln[E(Y_{q,t,e})] = \beta_0 + \beta_1 I_q + \beta_2 T + \beta_3 I_e + \beta_4 I_q * T + \beta_5 I_e * T + \beta_6 PM_{10\,q,t,e} + \ln(P_{q,t,e}) \quad (1)$$

where:

- $Y_{q,t,e}$ represents the number of deaths in area-unit q, year t and age class e;
- $PM_{10\ q,t,e}$ is the mean concentration of the industrial PM_{10} in the same stratum;
- $P_{q,t,e}$ is an offset term which represents person-years at risk;
- I_q, I_e define dummy variables for area units and age classes, respectively;
- T is a continuous variable for year, which we modelled linearly.

Furthermore:

- β_0 is the intercept term;
- β_1, β_2, β_3 are regression coefficients adjusting for confounding induced by factors varying across area units (β_1) and age classes (β_3) when T = 0, and over time (β_2) in the reference stratum of area unit and age group. Their meaning is of little interest;
- β_4 removes potential confounding introduced by factors, known or unknown, which might display different linear time trends across area units;
- β_5, similarly to β_4, adjusts for potential confounders which display different linear time trends across age groups;
- β_6 represents the association of industrial PM_{10} with mortality.

We can interpret the model in Eq. (1) as a variant of the difference-in-differences method, it is similar to the method proposed by Wang et al. (2016). The idea underlying model (1) is that an effect of PM on mortality is estimated by reducing confounding from spatio-temporal covariates by design. This is achieved with the introduction of age-specific and area unit-specific linear trends in the regression model. For example, if socio-economic status or lifestyle factors (smoking, diet, etc.) have changed differently across area units or age groups over 2008–2014, and if such changes have been collinear with concurrent changes in air pollution, the linear trends introduced in the model should account for that, provided that such changes have been linear. The drawback of the model, on the other side, is that only fluctuations of PM around linear trends are contrasted to concurrent fluctuations in mortality rates, with consequent decrease of statistical power.

Results were presented as percent increase risk of death, and 95% confidence intervals, relative to 1 μg/m^3 variation of industrial PM_{10}. This unit of measure has been chosen because it is easy to interpret, consistent with other reports (Vodonos et al., 2018), and close to the interquartile range at population level (1.6 μg/m^3). We tested whether the associations were modified by age. In this regard we considered two age groups: < 65 years, 65 + years. The effect modification was tested by stratification. Analytically, we calculated the difference between the strata coefficients. Assuming that the difference between the coefficients was distributed as a normal distribution with mean zero and variance equal to the sum of the strata variances (e.g. covariance = 0), we evaluated the p-value of the relative effect modification (REM).

For descriptive purposes only (see Figs. 5 and 6) we divided the study area into three sub-areas: “Tamburi, Lido azzurro”, close to the plant, “Isola, Borgo”, intermediate, and “Other areas” which includes all the districts and municipalities different from the previous two and away from the plant. For each of the three area units and each year we calculated the absolute change of industrial PM_{10}, as reported in Eq. (2).

$$AC_{q,t} = PM_{10\,q,t} - \frac{\sum_{t=2008}^{2014} PM_{10\,q,t}}{7} \quad (2)$$

- $AC_{q,t}$ absolute change in area-unit q, year t;
- $PM_{10\ q,t}$ is the mean concentration of the industrial PM_{10} in the same stratum.

For each of the three area units and each year we calculated the percent change of natural mortality rate (per 1000 person-years), as reported in Eq. (3).

$$PC_{q,t} = \frac{R_{q,t} - \frac{\sum_{t=2008}^{2014} R_{q,t}}{7}}{\frac{\sum_{t=2008}^{2014} R_{q,t}}{7}} * 100 \quad (3)$$

- $PC_{q,t}$ percent change in area-unit q, year t;
- $R_{q,t}$ is the natural mortality rate (per 1000 person-years) in the same stratum.

The follow-up and the statistical analysis were performed using SAS 9.0 (SAS Institute Inc., Cary, NC) and Stata 13 (StataCorp LLC, College Station, Texas) and geographical data were analyzed using Arcgis (Esri, Redlands, California) and Qgis (QGIS Development Team).

3. Results

Fig. 1 illustrates the study area, divided into eleven small area units: the two municipalities of Massafra and Statte and nine districts of the municipality of Taranto. The red dots represent the ARPA monitoring stations and there is a circle around the stations considered for the estimation of the industrial PM_{10}. Fig. 2 shows the 2010 PM_{10} ground concentrations estimated by the dispersion model for the “ILVA” steel plant. Fig. 3 displays the productivity (ktons/year) of the “ILVA” plant in the period under study divided by type: steel, coke, sinter, and pig iron. From a value of 8960 ktons of steel in 2008, there was a large decrease in productivity in 2009 due to the economic crisis, then an increase in 2010, 2011, and 2012 followed by a decrease in 2013 and 2014 due to a legal case. Fig. 4 illustrates the annual average PM_{10} measured concentrations assessed in the four monitoring stations. As expected, the PM_{10} values were higher close to the plant (Via Machiavelli and Via Archimede) and the pattern of the annual recorded concentrations somehow follows the “ILVA” productivity (shown in Fig. 3), with a peak in 2011 (the correlation coefficient between the annual productivity of steel and the annual PM_{10} values at the “Machiavelli” site was 0.61).

A total of 321,356 subjects in the study area were originally enrolled in the cohort; a total of 262,375 individuals were still alive and resident at the start of our study at January 1st, 2008. At 31/12/2014 the subjects in the original cohort were divided as follows: 238,473 people (74.2%) were alive and resident in the area, 37,736 subjects (11.7%) were dead, 45,147 individuals (14.1%) were emigrated outside

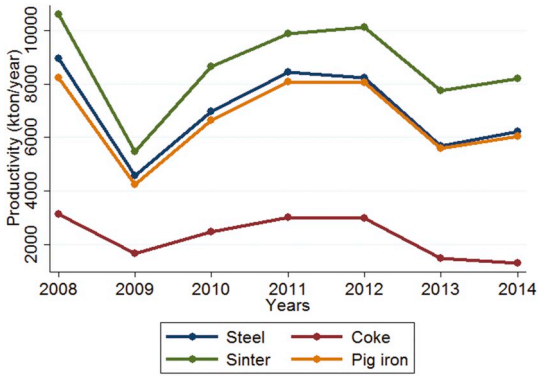

Fig. 3. Productivity (kton/year) of the “ILVA” Steel Plant by year and type of product.
(Source: IlVA.)

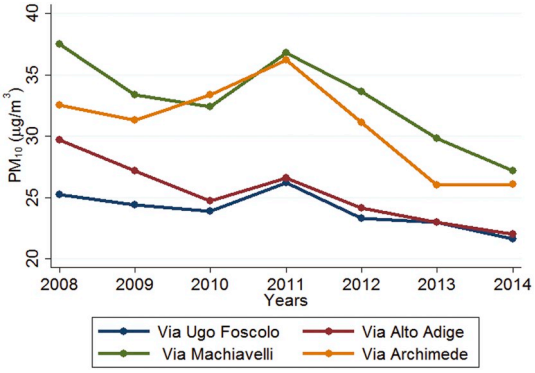

Fig. 4. PM_{10} ($\mu g/m^3$) concentrations at the fixed monitors by year ("Via Machiavelli" and "Via Archimede" were located in the Tamburi district close to the plant, "Via Alto Adige" was located in an urban area of Taranto and "Via Ugo Foscolo" in the Talsano district away from the industry and the town).

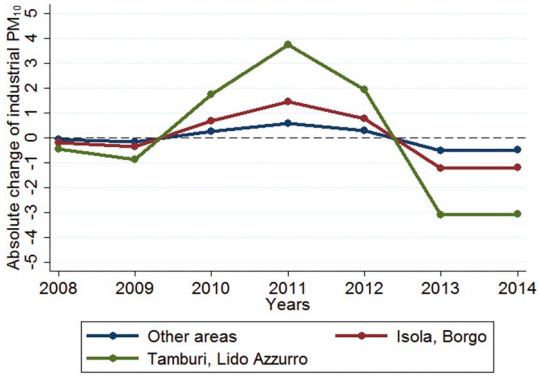

Fig. 5. Absolute change of population weighed exposure to industrial PM_{10} by year and area. Each value is the difference between the PM_{10} year and area unit-specific and the average of PM_{10} area-unit specific over years (see Eq. (2)).

the study area and so considered lost to follow up and censored at the time of loss. For the purposes of the present study, we only included residents in the period 2008–2014 (272,140 subjects), because we had concurrent data on air pollution monitoring stations only in the latest period.

Table 1 displays the number of deaths from natural causes and person-years of follow-up in the study period, by age, area unit and year. We estimated 1,726,353 person-years of follow-up, whose distribution is different across the area units. There were 15,303 natural deaths, 71.8% of which from subjects 75+ years old, and 0.8% from those below 35 years of age. Our enrolment period was up till 2010, therefore the cohort was open in the first three years of the study period (2008–2010) and closed afterward. In particular, in the year 2008, there were 262,375 people, with a percentage change in cohort residents between 2009 and 2008 of −0.23%. In contrast, for the last four years the changes were more significant albeit not extreme, in fact the percentage change in cohort residents between 2014 and 2013 was −2.07%.

While the later analysis on PM effects was based on the eleven areas separately, for descriptive purposes we divided the study area into three sub-areas only: "Tamburi, Lido azzurro", close to the plant, "Isola, Borgo", intermediate, and "Other areas" which includes all the districts and municipalities different from the previous two and away from the plant. For each of the three area units, we calculated the absolute change in the estimated industrial PM_{10} population exposure between the area yearly value and the area mean for the all period, as presented in Fig. 5. For example, the value represented in Fig. 5 for the year 2008 and the district "Tamburi, Lido azzurro" is the difference between the estimated industrial PM_{10} population exposure in the year 2008 in "Tamburi, Lido azzurro" and the average estimated industrial PM_{10} population exposure in "Tamburi, Lido azzurro" for the period 2008–2014. Fig. 6 illustrates the percent change of natural mortality rate (per 1000 person-years) between the area value for a specific year and the area mean for the all period. For example, the value represented in the Fig. 6 for the year 2008 and the district "Tamburi, Lido azzurro" is the difference of mortality rate in the year 2008 in "Tamburi, Lido azzurro" and the average of mortality rates in "Tamburi, Lido azzurro" for the period 2008–2014, divided by the average of mortality rates in "Tamburi, Lido azzurro" for the period 2008–2014, all multiplied by 100. It can be noted that the annual changes in mortality rates resemble the changes of the industrial PM_{10} population exposure in the "Tamburi, Lido azzurro" district and, to less extent, in the "Isola, Borgo" district, i.e. the districts mostly influenced by industrial emissions,

Table 1
Study population: number of deaths for natural causes and person-years of follow-up during the study period by age classes, area units and years.

	Number of deaths		Person-years of follow-up	
	n.	%	n.	%
Total	15,303	100.0	1,726,353	100.0
Age class (years)				
0–34	116	0.8	621,334	36.0
35–64	1771	11.6	737,862	42.7
65–74	2427	15.9	191,020	11.1
> 74	10,989	71.8	176,138	10.2
Area unit				
Isola, Borgo	2363	15.4	197,931	11.5
Italia montegranaro	2296	15.0	190,803	11.1
Lama, San Vito, Carelli	675	4.4	127,533	7.4
Massafra	1569	10.3	201,381	11.7
Paolo VI	710	4.6	122,082	7.1
Salinella	1192	7.8	160,348	9.3
Solito Corvisea	1391	9.1	157,536	9.1
Statte	664	4.3	96,152	5.6
Talsano, Aree amministrative	1129	7.4	176,840	10.2
Tamburi, Lido azzurro	1152	7.5	117,166	6.8
Tre Carrare, Battisti	2162	14.1	178,580	10.3
Year				
2008	2201	14.38	255,446	14.80
2009	2177	14.23	254,638	14.75
2010	2212	14.45	253,491	14.68
2011	2236	14.61	248,402	14.39
2012	2173	14.20	243,077	14.08
2013	2111	13.79	238,050	13.79
2014	2193	14.33	233,248	13.51

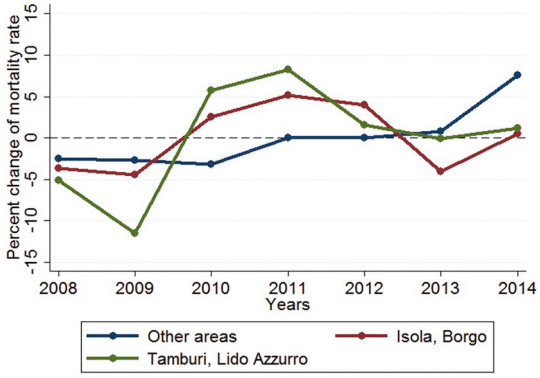

Fig. 6. Percent change of natural mortality rate (per 1000 person-years) by year and area.
Each value is the difference between the natural mortality rate year and area-unit specific and the average of natural mortality rate area-unit specific over years, divided by the average of natural mortality rate area-unit specific over years (see Eq. (3)).

Table 2
Number of deaths, percent increase of risk (I.R. %) and 95% confidence intervals (95% CI), relative to 1 μg/m^3 variation of industrial PM_{10} during the study period: 2008–2014.

Causes of death (ICD IX)	Number of deaths	I.R. %	95% CI	
Natural causes (001–799)	15,303	1.86	−0.06	3.83
Circulatory system diseases (390–459)	5721	0.70	−2.35	3.84
Heart diseases (390–429)	4346	1.91	−1.55	5.50
Respiratory diseases (460–519)	1150	8.74	1.50	16.51

whereas the patterns of exposure and mortality in the other areas deviate. In the Supplemental material – Appendix C, Table C.1 - population exposure to PM_{10}, number of deaths, person-years of follow-up and crude natural mortality rates in each of the three areas are reported.

Based on the model reported in Eq. (1), we estimated (Table 2) a percent increase of natural mortality of 1.86% (95% confidence interval (CI): −0.06, 3.83%) relative to 1 μg/m^3 variation of industrial PM_{10}. We found a 2.37% (95% CI: 0.31, 4.47%) increase in natural mortality (REM p-value = 0.22) among subjects 65+ years old (Fig. 7, Supplemental material – Appendix D - Table D.1). For respiratory mortality, the increase was 8.74% (95% CI: 1.50, 16.51%) with no evidence of effect modification by age (REM p-value = 0.96). Effect estimates for circulatory and cardiac diseases were positive but had large standard errors.

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4. Discussion

We found an association between industrial PM_{10} and mortality in the study area. In particular, changes in annual exposure to industrial PM_{10} were related to changes in mortality for natural and respiratory causes. Although the statistical tests for effect modification by age was far from statistical significance, the estimation of the effects for both natural and respiratory mortality had narrower confidence intervals in the elderly population consistently with other studies indicating that, at least for short-term exposure to particulate matter, older persons experience the highest risk of mortality (Bell et al., 2013).

Several studies conducted in the area of Taranto have found evidence of environmental pollution and impairment of the health of the resident population, in particular short-term effects of PM_{10} on mortality (Biggeri et al., 2004), increased mortality in Taranto for natural, cardiovascular, respiratory causes and lung cancer in ecological comparisons (Pirastu et al., 2011; Pirastu et al., 2010), increased mortality in the districts close to the industry in a retrospective cohort (Mataloni et al., 2012). Several descriptive investigations are also available (Mincuzzi et al., 2013; Berti et al., 2009; Martinelli et al., 2009; Comba et al., 2012; Vigotti et al., 2014), including biomonitoring studies (Bustaffa et al., 2014; Iavarone et al., 2012; Serinelli et al., 2011). However, the issue of the possible causal link between environmental exposures from the plant and adverse health outcomes has been disputed. We decided then to use a new method to assess the effect of exposure to industrial PM_{10} on mortality in the Taranto area as different study designs could be useful to address a causality issue in observational studies. The novelty of the approach has been the attempt to remove all known and unknown confounders “by design”. This has been at least partially achieved by focusing on annual fluctuations of industrial PM_{10} around area-specific and age-specific time trends, instead of exploiting the full range of PM_{10} variability over space and time. Also our analysis including only seven years of data might provide additional protection against long-term time trends. Therefore, in order for a variable to confound the studied association, it should display nonlinear different time trends across area units which covary with similar trends in PM_{10} exposure. While this seems unlikely, despite all these efforts, obviously we cannot completely rule out potential residual confounding due to the observational nature of our study design.

In this paper we used the cohort enrolled in a previous study (Mataloni et al., 2012) and we updated it using the same sources of information (General Registry Offices of the municipalities, local register of causes of death). The study has, to our judgment, several strengths: careful reconstruction of the individual residential histories, good quality geocoding, high completeness in the assignment of causes of death. However, it should be noted that the cohort lacks data on individual risk factors (such as smoking and other lifestyle

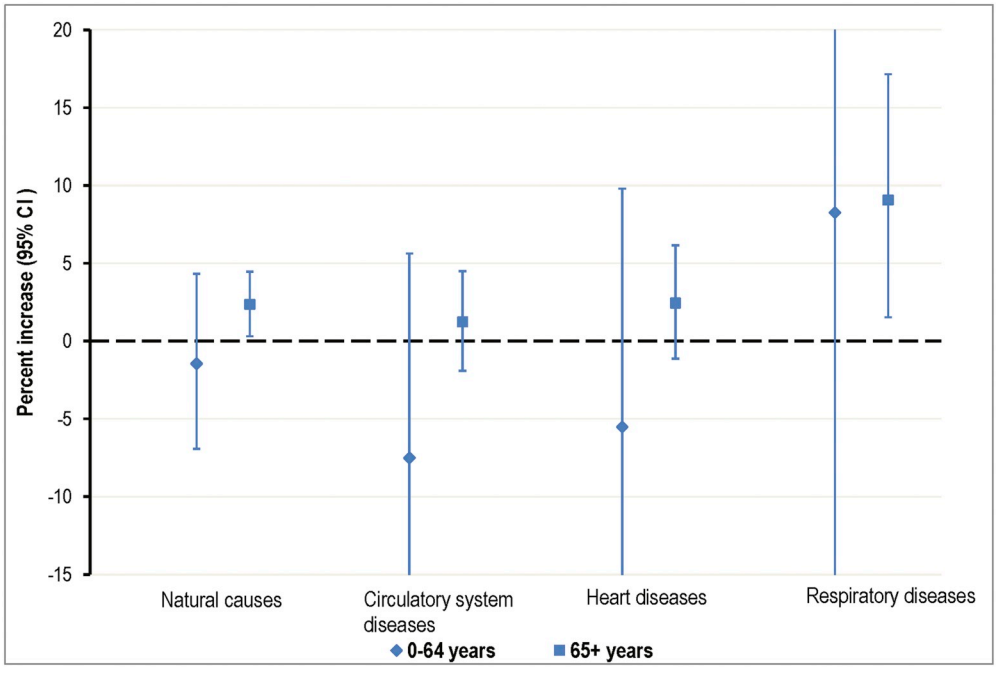

Fig. 7. Percent increase of risk of mortality (95% confidence intervals, 95% CI) relative to 1 μg/m^3 variation of industrial PM_{10} during the study period (2008–2014) by age group. Results from models stratified by age.

characteristics, individual estimates of exposure to meteorological parameters, etc.). However, such factors might have confounded the estimates under investigation only under the assumption that they varied differently across age groups and area units, and that such differences were not adequately captured by linear trends. Support against this possibility is provided by a recent re-analysis of the cohort study (Centro Salute Ambiente, 2016; Alessandrini et al., 2019), which applied indirect adjustment methods using ancillary data collected from an external survey. That study (Centro Salute Ambiente, 2016; Alessandrini et al., 2019) showed that the associations between industrial pollutants and mortality/morbidity were not biased by unmeasured individual confounders, including smoking.

Our analyses started from individual data, so for each subject of the cohort, we had information about his/her residential history and so about his/her ambient exposure to industrial pollution over the course of the study. Therefore, we took into account the variation in time and space of the person-years and we could estimate the ambient exposure for each year, area unit and age class. Some assumptions have been made. It was assumed that the changes over time in the temperature were the same in the area units (or, if different, were adequately described by linear shapes), so it was not necessary to control for this factor. Furthermore, we did not control for socioeconomic status, because it was assumed that the variations in time between area units were stable, or at least were captured by our linear time trends.

The exposure assessment of the industrial PM_{10} component was based on the assumption that NO_2 is a traffic indicator. However, NOx emissions from the industry also somehow contribute to local NO_2 and the main consequence is that the local PM_{10} component due to the industry may have been underestimated; such underestimation, on an annual basis, was likely proportional to the industrial productivity and to the PM emissions. The applicability of the PM_{10} spatial distribution estimated for 2010 to all the years of the study is also a critical aspect. As reported in the Supplemental material (Appendix B), the plots of the annual rose winds during 2008–2014 indicate a very similar pattern of prevailing winds that do not change on annual basis, thus supporting our approach. As an external validation of our exposure assessment method, an additional dispersion model was elaborated by the regional Environmental Protection Agency for the years 2012 using annual specific data. We assigned the 2012 PM_{10} values from the new dispersion model to each individual and compared the new results with our original estimate. The correlation coefficient between the two estimates was very high, 0.915 (our estimate: population-weighted mean 2.78 μg/m^3, sd 2.93; new estimate: mean 2.38 μg/m^3, sd 1.94) thus reassuring about the validity of our exposure estimates.

Other limitations of our study should be acknowledged. First, we could only analyze PM_{10}, and not $PM_{2.5}$, because only complete data on PM_{10} concentrations were available for the study period and only PM_{10} was modelled with a dispersion model when the study was conducted. Second, we considered only “ambient” (e.g. outdoor) exposures at the residential address, as we did not have information on either indoor sources nor occupational addresses or time-activity patterns. Third, we believe that the choice of considering the annual average PM concentrations (lag 0) as the reference exposure window might have partially underestimated the “true” effects due to the accumulation of several years of exposure. The choice was supported by several studies which showed that, especially for non-accidental and cardiovascular causes of death, exposure during the last year is the one most associated with the outcome (Schwartz et al., 2008; Brook et al., 2010). This might be different for respiratory causes, though.

In conclusion, under the model assumptions, the present investigation with new and original methods supports the results of traditional studies regarding the link between industrial emissions and mortality of the population living in the Taranto area.

Declaration of Competing Interest

Dr. Forastiere declares he has served as expert for the judge of the Taranto Court in a case involving the ILVA plant; there are no other competing financial interests. The other authors declare they have no actual or potential competing financial interests.

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CSA (Centro Salute e Ambiente) Study Group

Local Health Service Taranto, Italy: Simona Leogrande, Antonella Mincuzzi, Sante Minerba
Local Health Service Brindisi, Italy: Antonino Ardizzone, Susi Epifani, Giuseppe Spagnolo
ARPA Puglia, Bari, Italy: Giorgio Assennato, Roberto Giua, Angela Morabito, Alessandra Nocioni, Tiziano Pastore, Annalisa Tanzarella, Maria Serinelli, Stefano Spagnolo
AReS Puglia, Bari, Italy: Lucia Bisceglia, Anna Maria Nannavecchia, Vito Petrarolo
Department of Epidemiology, Lazio Regional Health Service, Rome – ASL Roma 1, Italy: Ester Alessandrini, Carla Ancona, Lisa Bauleo, Francesco Forastiere, Francesca Mataloni, Massimo Stafoggia.

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Appendix. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envint.2019.105030.

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