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Mortality and morbidity in a population exposed to multiple sources of air pollution: A retrospective cohort study using air dispersion models



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ABSTRACT

Background and aims: A landfill, an incinerator, and a refinery plant have been operating since the early 1960s in a contaminated site located in the suburb of Rome (Italy). To evaluate their potential health effects, a population-based retrospective cohort study was conducted using dispersion modeling for exposure assessment.

Methods: A fixed cohort was enrolled in the Rome Longitudinal Study in 2001, mortality and hospitalizations were followed-up until 2010. Exposure assessments to the landfill (H_2S), the incinerator (PM_{10}), and the refinery plant (SO_X) were performed for each subject using a Lagrangian dispersion model. Individual and small-area variables were available (including exposures levels to NO_2 from traffic and diesel trucks). Cox regression analysis was performed (hazard ratios, HRs, 95% CI) using linear terms for the exposures (5th–95th percentiles difference). Single and bi-pollutant models were run.

Results: The cohort included 85,559 individuals. The estimated annual average exposures levels were correlated. H_2S from the landfill was associated with cardiovascular hospital admissions in both genders (HR 1.04 95% CI 1.00–1.09 in women); PM_{10} from the incinerator was associated with pancreatic cancer mortality in both genders (HR 1.40 95% CI 1.03–1.90 in men, HR 1.47 95% CI 1.12–1.93 in women) and with breast morbidity in women (HR 1.13 95% CI 1.00–1.27). SO_x from the refinery was associated with laryngeal cancer mortality in women (HR 4.99 95% CI 1.64–15.9) and respiratory hospital admissions (HR 1.13 95% CI 1.01–1.27).

Conclusions: We found an association of the pollution sources with some cancer forms and cardio-respiratory diseases. Although there was a high correlation between the estimated exposures, an indication of specific effects from the different sources emerged.

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1. Introduction

In the Malagrotta area, located in the suburb of Rome (Italy), a large landfill for municipal solid waste (MSW), an incinerator of medical wastes, and a petrochemical refinery are situated within just a few kilometers of each other. Limited evidence of increased risk of cancer has been suggested among people living close to incinerators (Porta et al., 2009; Forastiere et al., 2011; WHO, 2007) and several uncertainties limit the interpretation of the available epidemiological studies on landfills (Porta et al., 2009). There is no clear indication that living close to a refinery is associated with cancer incidence or cause-specific mortality (Simonsen et al., 2010). An old study suggested an increase in lung cancer mortality

among women living close to major industries (Bhopal et al., 1998), while a more recent study (Cirera et al., 2013) has documented an association with haematological cancers.

Most of the studies conducted in contaminated sites have methodological problems, including the use of health data at the aggregate level, the limited possibility of adjusting for socioeconomic status, (Floret et al., 2003; Viel et al., 2008) or the distance from the source used as a proxy for population exposure. In 2011, the European Environmental Agency (EEA) suggested applying dispersion models to provide a better exposure assessment (European Environmental Agency, 2014). Recently, an assessment of air pollution exposure from incinerator emissions was performed in the UK and a review on exposure assessment methods in epidemiological studies of incinerators was published (Ashworth et al., 2013; Cordioli et al., 2013).

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Previous studies conducted in the Malagrotta area detected an excess of stomach cancer among workers at the medical waste incinerator and an increase of lung, bladder, brain cancers and multiple myeloma among petroleum refinery workers (Rapiti et al., 1997; Lo Presti et al., 2001). A study on the resident population did not indicate an excess mortality in people living close to the landfill, except for laryngeal cancer among men (Michelozzi et al., 1998).

This study aimed at evaluating the morbidity and mortality effects of exposures to the three sources of air pollution (landfill, incinerator, and refinery plant) in the cohort of people living in the Malagrotta area. Dispersion models were used for exposure assessment considering urban traffic and individual factors (e.g. educational level, occupation, area-based socioeconomic status) as potentially confounding variables.

2. Methods

2.1. The study plants and the area of investigation

The landfill, one of the largest in Europe (15 ha of surface, 1.46 million t MSW/year), began officially in 1984 receiving unprocessed municipal waste; however, the unofficial use of the landfill dates back at least 10-15 years. The closure of the landfill was announced in 2004 but actually occurred at the end of 2013, after Italy received a notice from the EU Commission for infringement of the Landfill Directive (1999/31/EC). The incinerator for medical waste (stack height 80 m, stack diameter 1.13 m, exit velocity 15.5 m/s, capacity 60 t/day) began its activity in 1996, replacing the old MSW incinerator that had burnt waste from 1964 to 1985 and then closed because of failure to comply with pollution standards as no emissions control measures were operating. The petrochemical refinery (97 ha of surface, 15 stacks ranging from 25 to 72 m in height, stacks diameter ranging from 0.8 to 2.9 m, exit velocity ranging from 1 to 5.9 m/s) has been refining 4.3 million t/year of crude oil since 1964 and is the most important refinery plant in central Italy.

The study area was defined as a 7 km radius from the boundary of the landfill defined using GIS software to allow a proper comparison among subjects with a wide range of contrasting exposure values The petrochemical refinery and the waste incinerator were located by their chimneys coordinates. The World Geodetic System of 1984, with the Universal Transverse Mercator zone 33Nord projection (WGS84_UTM33N) was the reference for the geographical coordinates.

2.2. Exposure assessment

We used a Lagrangian particle model (SPRAY ver.5) to simulate the concentration of air pollutants (ARIANET, 2014). The SPRAY model simulates the transport, dispersion and deposition of pollutants emitted (2005 emission inventories) using the orography, the meteorological data (managed by RAMS 2005 (RAMS, 2014)), the turbulence and the hourly spatial distribution (horizontal and vertical) of the emissions, based on the characteristics of the single source and on the mass fluxes (g/h). The model follows the path of fictitious particles in the atmospheric turbulent flow, and it is able to take into account complex situations, such as the presence of obstacles, breeze cycles, strong meteorological non homogeneities and non-stationary, wind calm conditions.

The domain for estimating pollutants concentrations was a square of $30\times30~\text{km}^2$ and the resolution chosen was 500 m (consistent with the meteorological fields). A single concentration value was estimated as the annual average for a square cell of 500 m \times 500 m. For each source, a pollutant was selected as the

exposure marker: hydrogen sulphide (H_2S) for the landfill, sulphur oxides (SO_X) for the petrochemical refinery, and airborne particulate matter of diameter less than 10 μ m (PM_{10}) for the incinerator.

The landfill emissions (H_2S) were generated using Landfill Gas Emissions Model (Landfill Gas Emissions Model, 2014). Using the dates of starting and ending of the operation for each sector of the landfill, the waste capacity and the waste acceptance rate, the emission rates for H_2S were calculated using a first-order decomposition rate equation. The Emission Manager software EMMA was used to approximate the landfill shape as a regular grid with a resolution of 125 m \times 125 m and to estimate the hourly emissions of the H_2S emission in each landfill allotment (Calori and Radice, 2004).

We obtained the hourly emission values of SO_X (refinery) and PM_{10} (incinerator) assuming uniform time modulation and using information about the chimney geographic coordinates, its internal diameter, the percentage of release of gases, the temperature and speed of the flue gas. Estimated annual average concentration maps of current H_2S , SO_X , and PM_{10} levels were produced. Although it can be assumed that significant changes occurred in relation to the activity in the area and the specific emissions, i.e. increasing and decreasing of the landfill activity, change in the activity of the incinerator, emission control from the refinery, no emission data from the past were available so to consider time-changes in the exposure variables in the analysis. Therefore, no attempt was made to back extrapolate concentration levels.

2.3. Enrollment of the cohort and follow-up procedures

The Rome Longitudinal Study (RoLS) (a population-based cohort enrolled from the 2001 Italian census) was the source for the study cohort (Cesaroni et al., 2010). The RoLS is part of the National Statistical Program for the years 2011–2014 and was approved by the Italian Data Protection Authority. All residents, living in the study area at the same baseline address for at least 5 years before October 2001, and who did not move during the course of the follow-up, were enrolled. Vital status was assessed using the Rome municipal register during the period October 2001 to December 2010. We considered subjects as lost to follow-up if they died or moved out of the city. Each subject in the cohort was assigned a value of H_2S , SO_X , and PM_{10} corresponding to the estimated map values at their residence.

2.4. Health outcomes

We analyzed natural and cause-specific mortality and hospital admissions. We considered cancer types for which there were some possible hypotheses of an association with environmental factors: stomach, colon and rectum, liver, pancreas, larynx, lung, bladder, kidney, brain, and lymphatic and haematopoietic cancer (see appendix for ICD IX codes) (Porta et al., 2009; Bhopal et al., 1998; Michelozzi et al., 1998; Ranzi et al., 2011; Rushton 2003; Elliott et al., 1996; Bhopal et al., 2009). The underlying cause of death for deceased subjects was retrieved from the regional Registry of Causes of Death, while hospital admissions were obtained from the regional Hospital Information System. For each subject only the principal diagnoses cause of hospitalization were used and the event was defined at the time of the first hospitalization for a specific cause that occurred in the study period.

2.5. Covariates

We considered for each subject age, gender, region of birth (north, center, south, out of Italy) educational level (high: university, medium: high school and low: elementary school),

occupation (non manual labor, manual labor, retired, unemployed, housewife), civil status (married, single, separated/divorced, widowed), and an area-basedsocio-economic position (SEP) index (high, medium, low) (Cesaroni et al., 2006).

Outdoor concentrations of NO $_2$ ($\mu g/m^3$) at the residential addresses of the cohort participants were available from a Land Use Regression (LUR) model built for the city of Rome (Cesaroni et al., 2012). We categorized the NO $_2$ estimated concentration of $\mu g/m^3$ in three levels: low (NO $_2$ < =30), medium (30 < NO $_2$ < =40) and high (NO $_2$ > 40). We also considered NO $_2$ (in $\mu g/m^3$) related to the municipal solid waste transport system (diesel trucks) from the city of Rome to the landfill in 2008 (low: NO $_2$ < =0.101, medium: 0.101 < NO $_2$ < =0.856, and high: NO $_2$ > 0.856) (further details in http://www.integrated-assessment.eu/content/health_effects_waste_management).

As an alternative surrogate of long term exposure to air pollution at the baseline address, we used the Functional Road Class (FRC) attribute (included in the TeleAtlas MultiNet road network) to classify the type of street: motorway (FRC=0) and major traffic roads (FRC=1-5).

2.6. Statistical analyzes

We investigated the correlation between exposure to H_2S , SO_X , and PM_{10} using Pearson's correlation coefficient. We used gender-specific Cox proportional hazard regression models [hazard ratios (HRs)] to study the association between air pollution exposures and the study outcomes, with age as the underlying time variable. To take into account possible time-related changes in mortality and hospitalization rates during the study period, the analyzes were performed stratifying by calendar period (2001–2004; 2005–2007; 2008–2010).

Exposure to the different pollution sources was modeled (single-pollutant models) as a fixed continuous variable using the value of the annual mean exposure at the residence. Because of the varying magnitude of the exposure indicator, the linear associations were estimated for an increment equal to the difference between the 95th and the 5th percentiles of the distribution of each pollutant. HRs were estimated considering as confounders all the individual covariates, the GIS variables, and the other environmental factors. More parsimonious models were built using a backward elimination strategy for variables with a p-value > 0.20(this was done for major outcomes like non-accidental mortality). The final models included the following variables: education, occupation, civil status, area-based SEP index, and the outdoor NO₂ concentration (from the LUR model). In order to disentangle the role of each pollutant/source of emission, single and multipollutant (bi-pollutant) models were performed. We considered as candidate for the multipollutant analyzes all the possible positive associations between the pollutants and the outcomes that had more stable effect estimates.

The potential spatial autocorrelation of health outcomes was taken into account because people that are geographically close are more similar to each other than to people who live far away and therefore tend to experience more similar outcome rates. In order to adjust for this phenomenon, each address was classified according to a $500~\text{m} \times 500~\text{m}$ grid, and the Cox regression model was extended by including a random intercept of the grid cells. Although we always considered spatial autocorrelation in our analysis, the only condition where this correlation was statistically significant was for non accidental mortality among men (p-value of the random intercept < 0.015).

All tests were based on the likelihood ratio test statistic. Two-sided 95% confidence intervals (CIs) were calculated on the basis of the Wald test of the Cox regression parameter on the log ratio scale. STATA and R softwares were used for the statistical analyzes.

3. Results

Fig. 1 illustrates the study area (a) and results of the dispersion model for H_2S originating from the landfill (b), SO_X , from refinery (c), and PM_{10} from the incinerator (d). The dispersion model for H_2S shows the highest concentration of the pollutant on the landfill itself with a regular dispersion in the surrounding area. The dispersion of SO_X originated from multiple point sources at the refinery plant (with heights ranging from 25 m-responsible for a more local dispersion-to 72 m with wider dispersion) had overall a larger impact in the area. The dispersion of PM_{10} from the incinerator was mainly influenced by chimney height (80 m) and prevailing winds (SW-NE direction). The results were a relatively wide dispersion of particles in the area in two directions, one on the southwest and one on the northeast of the chimney.

A total of 85,559 individuals were enrolled in the cohort in 2001 (48.2% males), and the concentrations of the pollutants were estimated for each of them at their residential address at baseline. Online supplementary Fig. S1 shows the population distribution of exposure levels for H₂S, SO_X, and PM₁₀. The annual average exposure levels of the population [mean (SD, 50th percentile, 95th–5th percentiles)] were generally low: 0.02 μ g/m³ (0.03, 0.01, 0.04) for H₂S (landfill), 1.67 μ g/m³ (0.92, 1.52, 2.88) for SO_X (petrochemical refinery), and 0.02 ng/m³ (0.02, 0.02, 0.04) for PM₁₀ (incinerator). The three exposure indicators were highly correlated: the correlation coefficient between H₂S and SO_X was 0.78, between H₂S and PM₁₀ was 0.75, and between SO_X and PM₁₀ was 0.81. The cut-offs for the upper 90th percentile were 0.03 ng/m³ for H₂S, 2.52 μ g/m³ for SO_X, and 0.03 mg/m³ for PM₁₀. (Table S1)

In addition to the pollution produced by the industrial plants, air quality in the area was greatly affected by traffic as it is located close to important roads: the Ring Road of Rome, two highways (one leading to the airport), and a local road network mainly devoted to MSW transport to the landfill. Online supplementary Fig. S2 shows the location of the highways, the high traffic roads, and estimated NO_2 concentration levels from road traffic, and from waste transport.

The main characteristics of the 85,559 subjects according to three exposure sources (divided by 50th and 90th percentile cutoffs) are described in Table 1.

The distribution of gender, age classes, birth place, and civil status was rather similar over the exposure categories for all pollutants. However, people living in areas with high concentrations of H₂S, SO_X, or PM₁₀ were more likely to be less educated, to be manual workers, and of low SEP compared with their reference groups (p < 0.05). In addition, people in the high exposure categories tended to live closer (500 m) to highways, but more distant from the high traffic roads; therefore, traffic-related NO2 concentrations were lower in these groups compared with those in the low exposure category (p < 0.05). No differences between the cohort and the general population living in Rome was observed for gender, age, level of education, civil status, and occupation. The main difference between Roman citizens and residents in this area is that in this cohort 62% of people lived in low and medium-low SEP areas compared to 41.1% observed in Rome, in addition the mean NO2 level in Rome was $43.6 \,\mu g/m^3$ (SD 8.4) whereas the mean level in this area was lower, i.e. $37.8 \mu g/m^3$ (SD 5.02).

During the study period (October 2001–December 2010) we observed 6187 deaths and, after excluding trauma, we considered 5878 (3233 men and 2645 women) deaths from non accidental causes (38.8% from cancer, 38.1% from cardiovascular diseases, and 6.5% from respiratory diseases); 45514 subjects were admitted to the hospital (13.2% for cancer, 25.2% for cardiovascular diseases, and 12.6% for respiratory diseases).

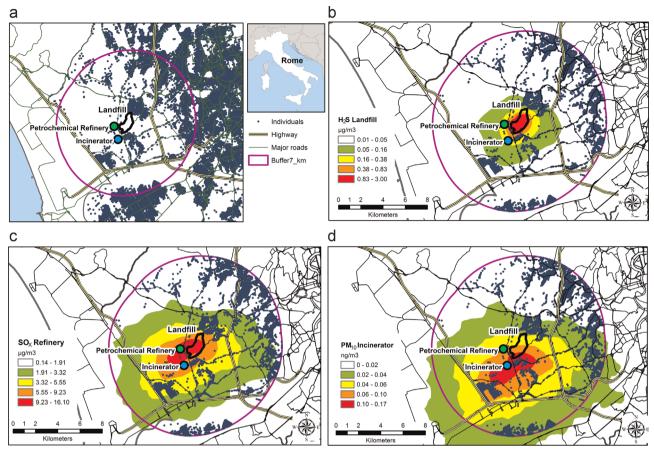


Fig. 1. Study area (panel a) and results of the dispersion models for H_2S (panel b), SO_X (panel c) and PM_{10} (panel d).

We found an association between the linear term of H_2S exposure and laryngeal cancer (HR=1.36; 95% CI 1.02–1.83, based on 6 cases) as well as bladder cancer (HR=1.35; 95% CI 1.00–1.82) in women. Mortality for pancreatic and laryngeal cancer was associated with SO_X from the refinery, again only among women (HR=1.75, 95% CI 1.02–3.01 and HR= 4.99, 95% CI 1.64–15.2, respectively). A clear association between PM_{10} and pancreatic cancer was observed in both genders (HR=1.40; 95% CI 1.03–1.90 men; HR=1.47; 95% CI 1.12–1.93 women). PM_{10} was also associated with laryngeal cancer among women (HR=1.92; 95% CI 1.16–3.19) (Table 2).

Table 3 shows the results for hospital admissions. There was an association of H₂S exposure and hospitalizations for laryngeal cancer (HR=1.36; 95% CI 1.08-1.72, based on 9 cases with a clear overlap with mortality) only among women, and for cardiovascular diseases in both genders (HR=1.02; 95% CI 0.98-1.05 in men and HR=1.04; 95% CI 1.00-1.09 women). H₂S exposure was also associated with hospital admissions for respiratory diseases among men (HR=1.02 95% CI 0.97-1.07). SO_X from the refinery was associated with hospital admissions for laryngeal cancer among women (HR=4.19; 95% CI 1.36-12.9) and for respiratory diseases among men (HR=1.13; 95% CI 1.01-1.27). There was an association between the linear term of PM₁₀ exposure and for pancreatic cancer hospitalizations (HR=1.35; 95% CI 1.01-1.81) among men. PM₁₀ was also associated with hospitalizations for liver (HR= 1.55; 95%1.02-2.35), laryngeal (HR= 1.83; 95%1.09-3.06), and breast cancers (HR= 1.13; 95%1.00-1.27) among women. PM₁₀ exposure was also associated with hospital admission for respiratory diseases among men (HR=1.05 95% CI 0.99-1.12).

It should be noted that there were few inverse associations among women, namely for SO_x and PM₁₀ and hospitalizations for

cancer of the lymphatic and haematopoietic tissue and for PM_{10} and hospitalizations for genitourinary diseases.

Since only some confounders were used in our main models (education, occupation, civil status, area-based SEP index, and outdoor NO_2 concentrations from the LUR model), we repeated the analyzes considering all sets of confounding variables and the results were very similar.

Supplemental Tables S2 and S3 report the results of the multipollutant models. In interpreting these results the high correlation among the pollutants should be noted, making some of the effect estimates unstable. For pancreatic cancer mortality, the strongest and most stable associations were found for PM₁₀ in both gender and the adjustment for SO_X or H₂S did not alter the main results. The limited number of laryngeal cancer cases precluded meaningful multivariate analyzes, however the strong association for SO_x in females remained after multiple adjustment. The association of H₂S with bladder cancer in females was sensitive to the adjustment for the other variables. For hospitalizations, PM₁₀ was associated with liver cancer but the confidence intervals were wider after adjustment whereas only limited changes were seen for PM₁₀ and pancreatic cancer in males or breast cancer in females. The associations of H₂S with cardiovascular morbidity in both males and females, as well as the association of SO_x with respiratory diseases hospitalization in males, were not changed after adjustment for other pollutants. In summary, PM₁₀ (incinerator) was the strongest factor for pancreatic mortality and hospital admissions and for breast cancer morbidity; SO_x (refinery) was the strongest factor for laryngeal cancer mortality in women and for respiratory hospital admissions in males; H2S (landfill) was associated with cardiovascular hospital admissions in both genders.

4. Discussion

Overall and all cancer mortality were not associated with the exposure indicators. However, we found a positive association between the emissions from the incinerator and pancreatic cancer mortality in both genders and, among women, an association with breast cancer morbidity. Emissions from the refinery were associated with laryngeal cancer mortality in women and with respiratory hospital admissions in males; $\rm H_2S$ from the landfill was associated with cardiovascular hospital admissions in both genders.

Our results for cancers are difficult to be interpreted in etiological terms and a review of previous knowledge is useful. Laryngeal cancer has risk factors such as cigarette smoking, occupational exposure to certain substances (eg asbestos), and alcohol consumption. An association of contaminated sites with laryngeal

cancer has already been observed in two studies conducted in the 1990s, one conducted in the Malagrotta area (Michelozzi et al., 1998; Elliott et al., 1992). Two recent studies found associations between living close to incinerators and laryngeal cancer while a Canadian study did not detect any association (Ranzi et al., 2011; Federico et al., 2010; Williams and Jalaludin 1998). It is to note that the excess laryngeal cancer that we found among women was based on few cases (six of the nine cases hospitalized for larynx cancer were also observed deaths). A large ecological study, carried out in the UK, analyzed the incidence of bladder cancer in populations living at various distances from a landfill site and did not detect any association (Jarup et al., 2002). However, bladder cancer has been associated with residence in a polluted city area in a case-control study of the general population in Spain (Castaño-Vinyals et al., 2008). Pancreatic cancer was the site in excess in

 Table 1

 Descriptive individual and environmental characteristics of the cohort members.

			H ₂ S				SO_X			PM_{10}				
			< 50th	50°-90°	> 90th	< 50th	50°-90°	> 90th	< 50th	50°-90°	> 90th			
Total	85,559		45,175	31,742	8,642	43,635	33,282	8,642	42,266	34,651	8,642			
Gender														
Females	44,181	51.6	52.0	51.4	50.6	52.0	51.5	50.6	51.9	51.4	51.2			
Males	41,378	48.4	48.0	48.6	49.4	48.0	48.5	49.4	48.1	48.6	48.8			
Age class (yrs)														
5–14	2,815	3.3	3.2	3.3	3.8	3.2	3.3	3.8	3.2	3.4	3.4			
15-44	32,659	38.2	37.5	38.4	41.0	37.7	38.0	40.9	37.6	38.2	41.2			
45-64	26,844	31.4	30.9	32.1	31.0	31.1	31.8	31.1	31.1	32.2	29.3			
65–106	23,241	27.2	28.4	26.2	24.1	28.0	26.9	24.1	28.2	26.2	26.2			
Level of education														
Low	53,213	62.2	61.8	61.2	68.2	62.0	61.0	68.0	61.5	60.9	71.1			
Medium	25,892	30.3	30.2	31.2	27.1	30.1	31.3	27.3	30.5	31.5	24.2			
High	6,454	7.5	8.0	7.6	4.7	7.9	7.7	4.8	8.1	7.6	4.7			
Occupation														
Non manual worker	18,069	21.1	20.9	22.3	17.8	20.7	22.4	18.0	21.1	22.5	15.8			
Manual worker	14,839	17.3	16.9	17.0	20.9	17.0	16.9	20.8	17.0	17.1	19.8			
Retired	12,913	15.1	15.7	14.6	13.7	15.5	14.9	13.7	15.6	14.8	14.1			
Not working	17,158	20.1	20.2	20.1	19.2	20.3	19.9	19.2	20.1	19.4	22.4			
Housewife	13,975	16.3	16.6	15.9	16.8	16.6	15.9	16.7	16.4	15.9	17.4			
Missing	8,605	10.1	9.8	10.0	11.6	9.8	10.0	11.6	9.8	10.3	10.4			
Civil status	,,,,,,,													
Married	45,074	52.7	52.8	51.8	55.0	52.9	51.8	55.2	52.9	52.5	52.5			
Single	31,355	36.6	36.4	37.2	36.1	36.5	37.1	36.1	36.4	36.9	37.0			
Separated/divorced	3,440	4.0	3.8	4.5	3.7	3.8	4.4	3.7	3.7	4.3	4.4			
Widow	5,690	6.7	7.0	6.5	5.1	6.9	6.8	5.1	7.0	6.3	6.2			
SEP (Socioeconomic position)	3,030	0.7	7.0	0.5	5.1	0.5	0.0	5.1	7.0	0.5	0.2			
High-medium high	14,447	16.9	21.7	13.2	5.4	21.6	13.7	5.3	20.7	13.8	10.4			
Medium	18,514	21.6	16.3	32.7	9.0	15.1	33.3	9.9	17.3	30.5	7.1			
Low-medium low	52,598	61.5	62.0	54.2	85.6	63.4	52.9	9.9 84.8	62.0	55.6	82.4			
Vicinity to high traffic road	32,330	01.5	02.0	34.2	05.0	05.4	32.3	04.0	02.0	33.0	02.4			
Within 150 m	40,298	47.1	62.1	31.5	25.7	61.4	33.9	25.5	62.6	33.7	24.9			
	40,296	47.1	02.1	31.3	25.7	01.4	33.9	23.3	02.0	33.7	24.9			
Vicinity to motorways	0.200	10.9	13.5	5.8	15.7	14.0	5.4	16.5	14.0	4.1	18.8			
Within 500 m	9,309	10.9	13.5	5.8	15.7	14.0	5.4	16.5	14.8	4.1	18.8			
NO ₂ (ug/m ³):														
Land Use Regression model	14705	17.3	12.0	16.5	37.3	140	15 1	27.0	14.2	14.5	42.1			
≤ 30	14,705	17.2	13.9	16.5		14.8	15.1	37.6	14.3	14.5	42.1			
$> 30 \text{ and } \le 40$	41,790	48.8	52.1	41.6	58.4	53.9	39.8	58.2	52.5	43.4	52.9			
> 40	29,064	34.0	34.0	41.9	4.3	31.3	45.2	4.3	33.2	42.2	5.0			
Trucks for waste transport														
≤ 0.101	76,960	89.9	85.3	98.6	82.5	85.2	98.4	81.7	83.8	99.0	83.8			
0.101-0.856	6,877	8.0	11.9	1.1	13.6	12.0	1.2	14.3	13.1	0.9	11.9			
> 0.856	1,722	2.0	2.9	0.3	4.0	2.8	0.4	4.0	3.1	0.1	4.3			
Vital Status														
Alive	70,397	82.3	81.9	82.5	83.6	82.0	82.3	83.8	82.1	82.4	82.9			
Dead	6,187	7.2	7.6	7.0	6.1	7.5	7.2	6.1	7.5	6.9	7.2			
Migrant	8,975	10.5	10.5	10.5	10.3	10.5	10.5	10.1	10.5	10.7	9.8			
Person years														
2001-2004	266,908	36.8	36.9	36.7	36.7	36.8	36.8	36.6	36.8	36.8	36.7			
2005-2007	237,552	32.7	32.7	32.8	32.7	32.7	32.8	32.7	32.8	32.8	32.7			
2008-2010	220,942	30.5	30.4	30.5	30.7	30.4	30.5	30.7	30.4	30.5	30.6			

Table 2 Association between H₂S (municipal waste landfill), SO_X (petrochemical refinery), and PM₁₀ (waste incinerator) exposure and cause–specific mortality by gender. Adjusted hazard ratios (HRs, and 95% CI) per a linear increase equal to the difference between the 95th and 5th percentiles of each pollutant (0.043 μ/m³ for H₂S, 2.882 μ/m³ for SO_X, and 0.027 n/m³ for PM₁₀)-Malagrotta area (Rome) 2001–2010.

			H ₂ S					SO_x						PM ₁₀						
	No. of cases		Men		Women			Men			Women			Men			Women			
	Men	Women	omen HR ^a 95% CI HR ^a		95%	CI	HR ^a	IC 95% H		HR ^a	95% CI		HR ^a	IC 95%		HR ^a 95%		CI		
Natural Mortality	3233	2645	1.00	0.94	1.06	0.98	0.91	1.06	1.04	0.92	1.18	0.93	0.81	1.07	1.04	0.98	1.11	1.02	0.94	1.09
All cancers	1303	893	0.93	0.83	1.03	1.00	0.89	1.13	0.95	0.79	1.14	0.97	0.77	1.22	1.02	0.92	1.12	1.04	0.92	1.17
Stomach	82	63	0.89	0.58	1.38	0.91	0.54	1.52	0.85	0.41	1.77	1.07	0.49	2.33	0.89	0.60	1.34	0.97	0.62	1.50
Colon and rectum	149	95	0.86	0.59	1.25	0.84	0.48	1.48	0.68	0.38	1.24	0.79	0.36	1.70	0.82	0.58	1.16	0.69	0.40	1.19
Liver	40	17	0.77	0.30	1.95	1.10	0.52	2.30	0.62	0.17	2.23	1.61	0.38	6.87	0.66	0.29	1.50	1.32	0.63	2.77
Pancreas	52	64	1.11	0.86	1.43	1.13	0.88	1.44	1.62	0.80	3.26	1.75	1.02	3.01	1.40	1.03	1.90	1.47	1.12	1.93
Larynx	26	6	0.53	0.10	2.95	1.36	1.02	1.83	0.82	0.18	3.85	4.99	1.64	15.2	1.01	0.49	2.09	1.92	1.16	3.19
Lung	416	155	0.93	0.76	1.13	1.11	0.91	1.34	0.94	0.68	1.30	1.38	0.84	2.26	1.04	0.88	1.23	1.24	0.96	1.60
Breast		155				0.65	0.38	1.13				0.72	0.39	1.33				0.97	0.71	1.33
Bladder	61	12	0.88	0.51	1.52	1.35	1.00	1.82	1.14	0.54	2.43	2.82	0.76	10.4	1.05	0.70	1.57	1.53	0.70	3.36
Kidney	39	15	1.00	0.60	1.69	0.03	0.00	2.50	1.17	0.44	3.14	0.04	0.00	1.47	1.08	0.63	1.86	0.14	0.02	1.15
Brain	26	18	0.88	0.35	2.23	0.93	0.37	2.31	0.69	0.15	3.18	1.12	0.25	5.05	0.68	0.22	2.07	1.00	0.41	2.43
Lymphatic and haematopoietic tissue	113	67	0.83	0.51	1.35	0.56	0.21	1.48	0.89	0.47	1.69	0.40	0.13	1.23	1.11	0.83	1.49	0.61	0.31	1.19
Cardiovascular diseases	1145	1095	1.01	0.93	1.11	1.01	0.90	1.13	1.08	0.89	1.31	1.00	0.81	1.25	1.02	0.91	1.13	1.03	0.92	1.16
Ischemic heart disease	491	356	1.00	0.86	1.16	1.09	0.94	1.26	1.05	0.79	1.41	1.25	0.89	1.75	0.96	0.81	1.13	1.06	0.87	1.30
Respiratory diseases	230	154	1.04	0.89	1.23	0.68	0.37	1.24	1.31	0.88	1.95	0.64	0.32	1.28	1.12	0.91	1.38	0.86	0.59	1.25
Digestive system diseases	140	99	1.09	0.92	1.29	0.94	0.61	1.43	1.21	0.75	1.94	0.84	0.40	1.78	1.09	0.85	1.40	1.10	0.78	1.56
Genitourinary diseases	47	42	0.89	0.46	1.73	0.90	0.41	1.98	0.92	0.34	2.48	0.77	0.23	2.61	0.81	0.42	1.54	0.69	0.30	1.58

^a Adjusted for gender, age, education, occupation, civil status, area-based SEP index, and outdoor NO₂ concentration (from LUR model).

both men and women in our study. The etiologic factors of pancreatic cancer include smoking and alcohol abuse and the literature does not support a potential effect of environmental chemicals (Schottenfeld and Fraumeni, 2006). A Finnish study found a strong excess of pancreatic cancer among men living in a former dump area, but the authors concluded that the observed excess was more likely explained by clustering of males with diabetes and pancreatitis-related behavior (Pukkala and Pönkä, 2001). However,

a report of cancer incidence among persons living near a waste landfill site in Montreal, Canada, found increased incidence of cancers of the liver, kidney, pancreas, and non-Hodgkin's lymphomas (Goldberg et al., 1999).

Among women residents in this area we also observed an increase in the risk of hospital admissions for breast cancer, particularly for those exposed to high concentrations of PM_{10} (incinerator). These results confirm those recently found among

Table 3 Association between H_2S (municipal waste landfill), SO_X (petrochemical refinery), and PM_{10} (waste incinerator) exposure and cause-specific hospital admissions by gender. Adjusted hazard ratios (HRs and 95% CI) per a linear increase equal to the difference between the 95th and 5th percentiles of each pollutant (0.043 μ/m³ for H_2S , 2.882 μ/m³ for SO_X , and 0.027 n/m³ for PM_{10})-Malagrotta area (Rome) 2001–2010.

			H ₂ S						SO _x						PM ₁₀						
	No. of cases		Men		Women			Men			Women			Men			Women				
	Men	Women	HR ^a	95%	CI	HR ^a	95%	CI	HR ^a	HR ^a 95% CI		HR ^a 95% CI		HR ^a 95%		HR ^a	R ^a 95% CI		HR ^a	95%	CI
All causes	21.917	23.957	1.00	0.98	1.03	0.99	0.97	1.02	1.00	0.95	1.05	0.97	0.93	1.02	0.99	0.96	1.02	0.97	0.94	0.99	
All cancers	3.258	2.796	0.97	0.91	1.03	0.99	0.93	1.06	0.90	0.80	1.02	0.92	0.80	1.04	0.95	0.89	1.02	0.96	0.89	1.03	
Stomach	111	97	0.81	0.51	1.28	0.87	0.53	1.43	0.71	0.36	1.38	1.00	0.50	2.01	0.86	0.59	1.23	1.07	0.76	1.52	
Colon and rectum	370	269	0.93	0.76	1.14	0.89	0.66	1.20	0.95	0.67	1.34	0.93	0.60	1.43	0.89	0.72	1.11	0.87	0.67	1.14	
Liver	65	28	0.66	0.30	1.46	1.22	0.97	1.54	0.62	0.25	1.55	1.80	0.68	4.80	0.73	0.42	1.27	1.55	1.02	2.35	
Pancreas	69	74	1.10	0.85	1.42	1.03	0.74	1.44	1.46	0.75	2.83	1.21	0.61	2.40	1.35	1.01	1.81	1.11	0.76	1.63	
Larynx	64	9	0.90	0.51	1.58	1.36	1.08	1.72	1.21	0.56	2.60	4.19	1.36	12.9	1.13	0.76	1.67	1.83	1.09	3.06	
Lung	444	156	0.94	0.79	1.13	0.99	0.73	1.33	0.85	0.61	1.17	1.05	0.62	1.78	1.01	0.86	1.18	0.98	0.72	1.33	
Breast		731				1.04	0.93	1.15				1.13	0.89	1.43				1.13	1.00	1.27	
Bladder	388	89	0.90	0.73	1.11	0.99	0.67	1.46	1.01	0.72	1.40	0.80	0.34	1.85	1.04	0.87	1.23	0.75	0.43	1.29	
Kidney	111	53	0.87	0.58	1.31	0.76	0.33	1.72	0.73	0.38	1.40	0.71	0.26	2.00	0.87	0.60	1.24	0.99	0.59	1.63	
Brain	51	40	0.95	0.56	1.61	1.04	0.66	1.62	0.68	0.24	1.94	0.94	0.32	2.73	0.97	0.56	1.68	0.49	0.20	1.24	
Lymphatic and haematopoietic tissue	301	205	0.86	0.67	1.11	0.73	0.46	1.15	0.80	0.54	1.19	0.51	0.28	0.92	0.92	0.74	1.14	0.66	0.45	0.95	
Cardiovascular diseases	6.324	5.220	1.02	0.98	1.05	1.04	1.00	1.09	1.01	0.93	1.10	1.02	0.92	1.12	0.99	0.94	1.03	1.00	0.95	1.05	
Ischemic heart disease	1.786	815	0.98	0.90	1.06	1.01	0.86	1.08	0.87	0.74	1.02	0.83	0.64	1.07	0.89	0.81	0.98	0.91	0.79	1.06	
Respiratory diseases	3.244	2.563	1.02	0.97	1.07	0.95	0.88	1.02	1.13	1.01	1.27	0.91	0.79	1.05	1.05	0.99	1.12	0.98	0.91	1.06	
Digestive system diseases	6.079	5.021	0.99	0.95	1.03	0.99	0.94	1.03	0.97	0.89	1.05	1.01	0.92	1.10	0.98	0.94	1.02	0.98	0.93	1.03	
Genitourinary diseases	1.444	1.015	0.84	0.65	1.08	0.93	0.82	1.05	1.05	0.89	1.23	0.81	0.65	1.01	0.99	0.90	1.08	0.85	0.75	0.97	

^a Adjusted for gender, age, education, occupation, civil status, area-based SEP index, and outdoor NO₂ concentration (from LUR model).

women living near the incinerator in Coriano (North of Italy) and are in line with other results previously published (WHO 2007; Ranzi et al., 2011).

The increased risk for cardio-respiratory diseases, observed particularly among residents exposed to emissions from the incinerator and the refinery, can be considered a plausible effect of air pollution typical of industrial areas. There is a body of scientific evidence to substantiate the findings with regard to cardio-respiratory effects of air pollution (Forastiere et al., 2011; WHO 2005; Brook et al., 2010).

From the results of this study it is not easy to determine which specific agent emitted from the plants could have an etiological role in the excess risks found. PM₁₀ and SO_x have been already used as surrogate markers for exposure to a complex mixture of the pollutants produced by combustion processes: particles, gases, metals, and organic compounds (Ranzi et al., 2011; Smargiassi et al., 2009). Gases emitted from landfills consist of methane and carbon dioxide, and other gases, such as hydrogen sulphide and a mixture of volatile organic compounds (VOCs) are emitted at low concentrations that comprises approximately 0.5% of the total emissions. We chose H₂S as the landfill tracer because MSW landfills are potential sources of offensive odors that disturb nearby communities and this emission can be well characterized (Palmiotto et al., 2014; Sarkar et al., 2003). Overall, the estimated concentrations of PM₁₀, SO_X and H₂S were low and highly correlated (correlation 0.75-0.81) which make it more difficult to identify emissions (and consequently the plants) most responsible for the observed effects.

The strength of this work is the cohort size (85,559 residents) and the longitudinal study design adopted: individuals were followed for over ten years, exposure was assessed with advanced modeling techniques, and individual SEP, urban and waste truck traffic were also considered as potential confounders. We defined the study population as people living up to 7 km away from the plants, based on previous studies and on the estimated profile of the distribution of pollutants emitted (Elliott et al., 1992). This choice provided a good contrast of exposure conditions and increased the comparability of the population groups.

Pollutant levels estimated at residence may not adequately represent exposure because people do not spend all their time at home, and we did not provide any information regarding daily or occupational activities. However, the excesses we detected in the areas with higher exposure levels were observed mainly among women, a more stable population then men, suggesting that misclassification of exposure is less likely to have occurred. The inaccuracy of individual exposure would lead to non-differential misclassification and would tend to mask the detected association, leading to results biased towards the null, but we cannot exclude a chance finding given the multiple testing we performed.

We could not take into account individual risk factors such as cigarette smoking, alcohol use and physical activity, however those individual characteristics are strongly associated with SEP. It is therefore reasonable to assume that the adjustment we made in the statistical analysis for education, occupation, and area-based

SEP also adjusted for those unmeasured individual variables. However, we found no excess risk of lung, stomach or colon and rectum cancers. We noticed few inverse associations (cancer of the lymphatic and haematopoietic tissue and genitourinary diseases) for which we do not have an explanation other than chance.

We took into account the effect of exposure to vehicular traffic using predicted NO_2 levels; the dispersion model for NO_2 showed no overlap between the areas of high NO_2 and the areas of high PM_{10} , SO_X , or H_2S concentrations. The associations observed in the present study, if causal, represent the effects of long-term exposures to a pollutant mixture even after statistical control for the background pollutant levels. Indeed, the SO_X exposure estimates used in this study are likely correlated with other stack and/or fugitive refinery emissions such as $PM_{2.5}$ and volatile organic compounds.

We studied a closed population and therefore, immigrants, and all children born after October 2001 were not included. For this reason, it was not possible to assess the health of children residents. However, the analysis carried out on 2815 children present to October 2001 revealed no special increases in the risk of mortality or hospital admission related to the estimated concentration of the pollutant tracers of the plants (data not shown).

Monitoring campaigns conducted during the study period shows that SO_X , PM_{10} , and NO_2 concentrations in the Malagrotta area were below the limits established by law, and the H_2S measured concentrations were also below the reference value of $150~\mu g/m^3$ set by the WHO guidelines for air quality (WHO, 2005; ISPRA, 2011). In this study we used authorized emission values to simulate dispersion from the industrial plants, which overestimated concentration values; nevertheless the shape of the fallout and the gradients of exposure were not sensitive to this choice. It should be noted that we considered only exposure to air pollution whereas soil contamination or food and water consumption could have importance but detailed data on these aspects were lacking.

In conclusion, the study suggests an association between air contamination and some cancers and cardio-respiratory diseases. Although there was a high correlation between pollutants estimates, some specific effects from the single sources emerged.

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Appendix

International Classification of Diseases, 9th Revision (ICD-IX) codes

Health outcomes	ICD-9 codes
Natural mortality	001-799
Total hospital admission	001-999
All cancers	140-208

Stomach	151
Colon and rectum	153-154
Liver	155.0
Pancreas	157
Larynx	161
Lung	162
Breast	174
Bladder	188
Kidney	189
Brain	191
Lymphatic and haematopoietic tissue	200-208
Cardiovascular diseases	390-459
Ischemic heart disease	410-414
Respiratory diseases	460-519
Digestive system diseases	520-579
Genitourinary diseases	580-599

Appendix A. Supplementary material

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.envres.2014.10.036.

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