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Long term effect of air pollution on incident hospital admissions: Results from the Italian Longitudinal Study within LIFE MED HISS project

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ABSTRACT

Background: The LIFE MED HISS project aims at setting up a surveillance system on the long term effects of air pollution on health, using data from National Health Interview Surveys and other currently available sources of information in most European countries. Few studies assessed the long term effect of air pollution on hospital admissions in European cohorts.

Objective: The objective of this paper is to estimate the long term effect of fine particulate matter (PM2.5) and nitrogen dioxide (NO_2) on first-ever (incident) cause-specific hospitalizations in Italy.

Methods: We used data from the Italian Longitudinal Study (ILS), a cohort study based on the 1999–2000 National Health Interview Survey (NHIS), followed up for hospitalization (2001–2008) at individual level. The survey contains information on crucial potential confounders: occupational/educational/marital status, body mass index (BMI), smoking habit and physical activity.

Annual mean exposure to PM2.5 and NO_2 was assigned starting from simulated gridded data at spatial resolution of $4 \times 4\,km^2$ firstly integrated with data from monitoring stations and then up-scaled at municipality level.

Statistical analyses were conducted using Cox proportional hazard models with robust variance estimator.

Results: For each cause of hospitalization we estimated the hazard ratios (HRs) adjusted for confounders with 95% Confidence Interval (CI) related to a $10\,\mu g/m^3$ increase in pollutants. For PM2.5 and NO_2, respectively, we found positive associations for circulatory system diseases [1.05(1.03–1.06); 1.05(1.03–1.07)], myocardial infarction [1.15(1.12–1.18); 1.15(1.12–1.18)], lung cancer [1.18(1.10–1.26); 1.20(1.12–1.28)], kidney cancer [1.24(1.11–1.29); 1.20(1.07–1.33)], all cancers (but lung) [1.06(1.04–1.08); 1.06(1.04–1.08)] and Low Respiratory Tract Infections (LRTI) [1.07 (1.04–1.11); 1.05 (1.02–1.08)].

Discussion: Our results add new evidence on the effects of air pollution on first-ever (incident) hospitalizations, both in urban and rural areas. We demonstrated the feasibility of a low-cost monitoring system based on available data.

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1. Introduction

The association between the exposure to major airborne pollutants and several long term adverse effects on mortality has been well documented (Hoek et al., 2013) but relatively few studies focused on the long term effects of particulate (PM10 and PM2.5) or NO_2 on hospital admissions. Available studies have investigated the association between airborne pollution and some specific causes of hospitalizations: acute coronary events (Cesaroni et al., 2014), stroke (Andersen et al., 2012a; Kloog et al., 2012; Alimohammadi et al., 2016), asthma (Andersen et al., 2012a), respiratory illness or specifically Chronic Obstructive Pulmonary Disease (COPD) (Hruba et al., 2001; Andersen et al., 2011; Kloog et al., 2012; Atkinson et al., 2015), cerebrovascular diseases (Stafoggia et al., 2014; Kloog et al., 2012; Oudin et al., 2010), neurodegenerative diseases (Kioumourtzoglou et al., 2016) and diabetes (Kloog et al., 2012; Andersen et al., 2012b). These studies were mostly carried out in USA, where both the characteristics and susceptibility of the population exposed and the composition of air pollution mixture can be different from European context. Several cohorts are available in Europe, as the national English cohort (812,063 patients aged 40–89 years as reported by Atkinson et al., 2015), the Danish Diet, Cancer, and Health (DCH) cohort (57,053 people from Copenhagen or Aarhus aged 50–65 years, as reported by Andersen et al., 2012a) or the London cohort, which studied also combined effects of noise and air pollution (Halonen et al., 2015).

Earlier studies on long term effect had limitations on the exposure assessment, due to the lack of air quality monitoring networks able to represent large areas or countries, which led to study only restricted areas. In recent years, the quality of the exposure assessment has been improved, using prediction models for exposure which combine land use regression with physical measurements or using atmospheric Chemical Transport Models (CTMs) and satellite data. With these new techniques it is possible to investigate both long and short term effects on adverse health effect on wide areas; an example is the study of Kloog et al. (2012) and (2015) which investigated the effects of pollutants on hospital admissions across New-England or Cesaroni et al. (2013) for mortality. However, even though a large amount of population is involved in these studies, they are usually based on available health data from registers or on ecological data, with a consequent approximation in the control for individual potential confounders, such as diet, socioeconomic variables, physical activity, etc. For some of the investigated diseases, the debate on the real role played by the air pollutants on hospital admissions incidence is still ongoing: for COPD, an acute event, as the primary outcome, it cannot be unambiguously distinguished the role of air pollution in exacerbating COPD (developed due to other causes) from its etiological contribution to the development of COPD (Schikowski et al., 2014). Papers mentioned that asthma hospitalization could be a bad marker of asthma onset and thus could underrate the real asthma burden, with only a fraction of asthma patients hospitalized (Andersen et al., 2012a). For diabetes, an accurate and large study concluded that the risk for diabetes was only weakly associated with increasing mean levels of traffic-related air pollution, with indication of interaction, while the risks were higher in nonsmokers and physically active people (Andersen et al., 2012c).

The LIFE MED HISS project (LIFE MED HISS, 2013) is a pilot study aimed at estimating long-term effects of air pollution in four European Mediterranean countries (Italy, France, Slovenia and Spain), using already available or potentially available cohorts. These are based on the follow-up from the NHISs, a solution that offers wide information on almost all potential confounders needed. The aim of the project is to demonstrate the feasibility of this new approach and its possible application in other EU countries, since all perform regularly health interview and examination surveys (Hupkens et al., 1999). The approach is based on the linkage of individual survey's data, with mortality and hospitalization outcomes, where privacy regulations permit it, and with exposure data at the place of residence derived from national air pollution models. In countries where linkage was not possible because of privacy policy restrictions, the MED HISS project tested an ecological approach (Basagaña, 2015; de Keijzer et al., 2016). In both approaches, exposure to air pollution has been assigned using data coming from CTMs, where accuracy has been improved with monitoring station data by means of data fusion techniques (Gandini et al., 2016; Ghigo et al., 2017).

In this paper we present the results of MED HISS approach in Italy, where no privacy policy restrictions have arisen and linkage between survey's data and hospitalization outcomes has been possible. We used the data of the ILS, a cohort based on the NHIS followed up for mortality and hospitalization, and we evaluated the long term effects on hospital admissions related to air pollution exposure in the sample living in all the Italian national territory, covering both urban and rural areas. We studied the association between air pollution concentrations at municipal level and the risk of first-ever (incident) hospital admission for several causes, controlling for main individual confounders, including lifestyle and socioeconomic information. The use of first-ever hospitalization allows to approximate a measure of incidence of pathology. All results are stratified by gender and level of urbanization. Thanks to the nature of the ILS, we were able to analyze a wide list of causes, adding knowledge where few studies were available (like e.g. atherosclerosis or myocardial infarction).

2. Materials and methods

2.1. Health data

The ILS is a follow-up study based on the sample included in the 1999–2000 NHIS, carried out by the National Institute of Statistics, linked to mortality and hospital records (Marinacci et al., 2013). The original NHIS sample consists of 140,011 individuals belonging to 52,232 sampled families resident in 1449 municipalities in the whole national territory (Fig. 1). The NHIS contains, beside others, individual information on age, gender, occupational and educational status, marital status, residence, BMI, smoking habit and physical activity. Information on alcohol was not available in the survey, while information on diet was limited to particular conditions (e.g. macrobiotic diet) and therefore could not be used to assess lifestyles. Concerning residence, we had no information about home address due to privacy restrictions and we could only know the municipality of residence for each individual.

Due to the nature of the LIFE MED HISS project, variables included in the model are harmonized, according to the standard developed within the European EUROTHINE project (EUROTHINE 2005), ensuring a high degree of comparability with other European surveys, also considering levels chosen for categorical variables.

An individual record-linkage procedure was applied to the 128,818 individuals with complete personal data and giving consensus to be followed-up (92% of the total sample). Follow up for hospital admissions in this paper covers the period 2001–2008. Analyses on association between air pollution and adverse health effects are conducted on 74,989 individuals (belonging to 45,418 sampled families resident in 1442 municipalities) aged $>$ 35 years and alive at 2001: in this subcohort, 41,047 individuals experienced at least one hospital admission. We excluded non-accidental causes and repeated hospitalizations for the same subject (with the exceptions of myocardial infarction, angina pectoris and LRTI).

For each cause, we considered only the main cause of hospitalization out of six available, and, for each subject, only the first hospital admission, excluding all subsequent hospitalization for the same cause. This criterion permits to have a good approximation to an incidence measure. An exception to this rule was done for diabetes and COPD, which were searched among all six codes. A second type of exception was done for myocardial infarction, angina pectoris and LRTI: for the first two causes, a second event that occurred after 28 days or more

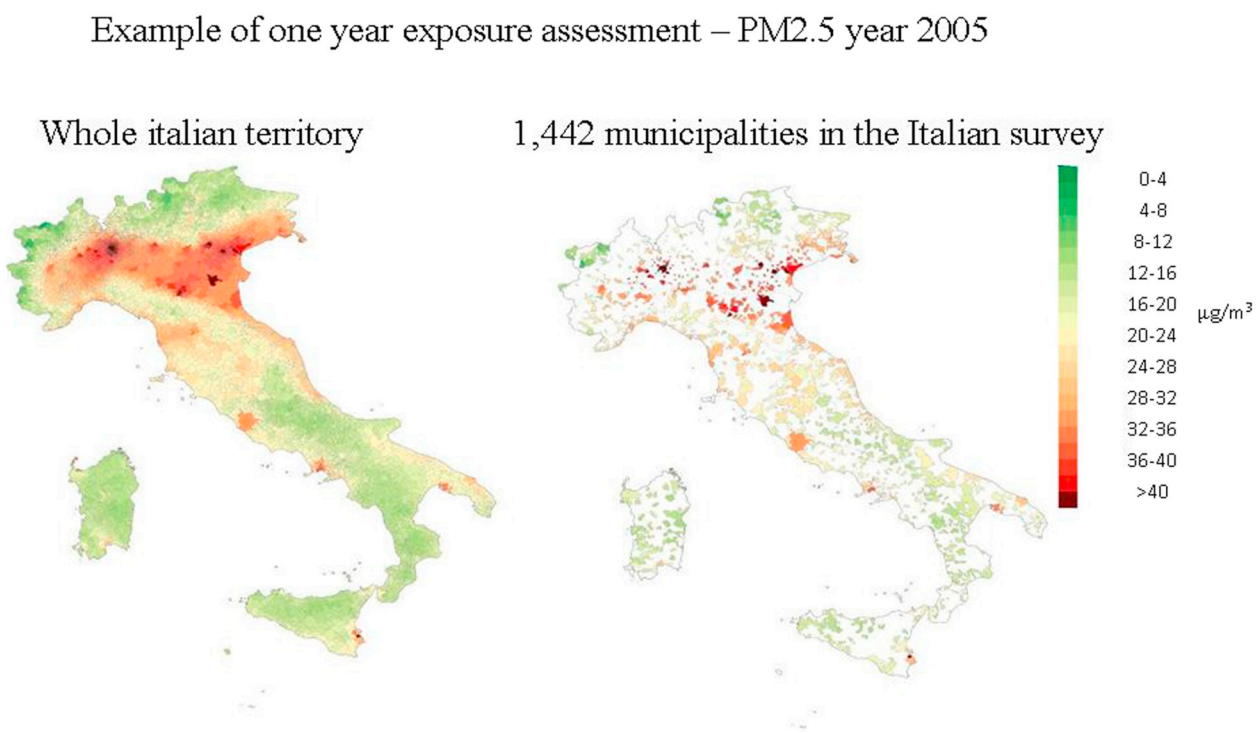

Fig. 1. PM2.5 data referred to year 2005 in all Italian municipalities and in the 1442 municipalities selected in the NHIS.

from the first episode was considered as a new event (Thygensen et al., 2012), whereas for LRTI the time elapsed from the first episode to consider it as a new event had to be 90 days or more.

We selected the following main group of causes: disease of the circulatory system (ICD-9 code 390–459), heart diseases (ICD-9 code 390–429), cerebrovascular diseases (ICD-9 code 430–438), diseases of the respiratory system (ICD-9 code 460–519), all neoplasm but lung cancer (ICD-9 code 140–239, with the exception of 162), mental, behavioural and neurodevelopmental disorders (ICD-9 code 290–319), diseases of the nervous system (ICD-9 code 320–359).

Moreover, we investigated the following specific causes: lung cancer (ICD-9 code 162), bladder cancer (ICD-9 code 188), kidney cancer (ICD-9 code 189), diabetes (ICD-9 code 250), Parkinson's disease (ICD-9 code 332), Alzheimer's disease (ICD-9 code 331), myocardial infarction (ICD-9 code 410), angina pectoris (ICD-9 code 413) atherosclerosis (ICD-9 code 440), LRTI (ICD-9 code 466, 480–487), chronic obstructive pulmonary disease (COPD) (ICD-9 code 490–492, 494, 496), asthma (ICD-9 code 493), and miscarriage (ICD-9 code 634).

2.2. Exposure to air pollution

The Italian exposure model takes into account data coming from the modeling system MINNI (National Integrated Modelling system for International Negotiation on atmospheric pollution), developed and validated by ENEA and the Italian Ministry of the Environment Land and Sea (Mircea et al., 2014; Mircea et al., 2016). MINNI includes an atmospheric chemical transport model (CTM) fed by emission data (national emission inventory of anthropogenic sources, biogenic VOCs, sea-salt, natural dust) and meteorological prognostic fields. MINNI outputs for PM2.5 and NO_2 were provided for years 1999, 2003, 2005 and 2007 at a spatial resolution representative of urban background pollution levels ($4 \times 4\,km^2$) at hourly resolution (Mircea et al., 2014). The CTM model included in the MINNI modeling system is called FARM (Gariazzo et al., 2007; Silibello et al., 2008) and the version used in the study is the 3.1.12.

In order to reduce model uncertainty, a data fusion technique is used to combine MINNI concentration fields and pollutant observations. Thus, it is possible to provide a more realistic representation of pollutant spatial distribution. Therefore, a Kriging with External Drift (KED, Van de Kassteele et al., 2009; Ignaccolo et al., 2013) procedure has been used to account for the observed data into MINNI fields. Specifically, the kriging is applied on the observed data and the external drift is constituted by the MINNI model output. Observations were interpreted as realizations of a Gaussian spatial process $Y(s)$ at spatial location s, in the domain S. $Y(s)$ has the following structure:

$$Y(s) = \mu(s) + w(s) + \varepsilon(s),$$

where in the trend component $\mu(s)$ the MINNI model output is introduced, $w(s)$ is a stationary Gaussian random process and $\varepsilon(s)$ is the error term. Regarding observed data introduced in the dispersion model outputs, we retrieved data from other Italian regional environmental agencies out of BRACE database (national system: http://www.brace.sinanet.apat.it/). Only background stations, whose spatial representativeness is consistent with the MINNI resolution, and only monitoring sites with > 80% of data have been considered and averaged to obtain annual observed values (Ghigo et al., 2017).

PM2.5 and NO2 are the most impacting pollutants on the Italian territory, in terms of long-term effect on human health. Also SO2 and CO have historically been of high impact, but their airborne levels have been drastically reduced before year 2000, therefore their impact is very low in the time span analyzed in this study. Black carbon was included in official EU emission inventories in 2017, so no national emission data were available at the time of this study.

Since the health data from the NHIS are aggregated at the municipal level, the exposure assessment has to rely on the same spatial scale. Therefore, following this data fusion approach, the Italian exposure assessment was carried out by up-scaling the gridded data at the municipality level (Ignaccolo et al., 2013). These annual exposure maps were obtained overlying gridded concentration data to municipality boundaries and then using a weighted average, where built-up area percentages were the weights. Built-up area information has been collected from Corine Land Cover data (CORINE, 2006) using land use classes belonging to Artificial Surfaces categories. In this way, for both

Table 1
Descriptive statistics of the Italian Longitudinal Study (considering individuals older than 35 years). For each category, mean levels of PM2.5 and NO_2 referred to year 2005 are reported.

		MED HISS (35 +) 74,989 individuals				PM2.5 μg/m^3 (year 2005)			NO_2 μg/m^3 (year 2005)		
		N (%)	Rural areas N (%)	Urban areas N (%)	Metropolitan areas N (%)	Rural areas mean (sd)	Urban areas mean (sd)	Metropolitan areas mean (sd)	Rural areas mean (sd)	Urban areas mean (sd)	Metropolitan areas mean (sd)
Gender	Men	35,466 (47.3%)	21,718 (61.2%)	10,887 (30.7%)	2861 (8.1%)	20.9 (7.0)	24.5 (7.2)	32.5 (7.4)	19.3 (8.0)	26.1 (9.7)	41.5 (11.6)
	Women	39,523 (52.7%)	23,740 (60.1%)	12,353 (31.2%)	3430 (8.7%)	20.9 (6.9)	24.6 (7.2)	32.6 (7.3)	19.3 (7.9)	26.1 (9.6)	41.6 (11.6)
Education level	Up to primary	34,978 (46.6%)	23,761 (67.9%)	9076 (26.0%)	2141 (6.1%)	20.6 (6.9)	24.5 (7.2)	32.2 (7.4)	18.7 (7.8)	25.8 (9.5)	41.2 (12.0)
	Lower secondary	18,518 (24.7%)	11,150 (60.2%)	5803 (31.3%)	1565 (8.5%)	21.0 (6.9)	24.8 (7.3)	32.8 (7.7)	19.6 (8.1)	26.6 (10.0)	41.8 (11.9)
	Upper secondary	16,683 (22.3%)	8737 (52.4%)	6195 (37.1%)	1751 (10.5%)	21.6 (6.8)	24.6 (7.2)	32.7 (7.1)	20.3 (8.1)	26.3 (9.5)	41.8 (11.1)
	Post secondary	4810 (6.4%)	1810 (37.6%)	2166 (45.0%)	834 (17.4%)	20.8 (6.6)	24.1 (7.2)	32.7 (7.1)	19.5 (7.7)	25.7 (9.2)	41.6 (11.1)
BMI	Underweight BMI < 18.5	1364 (1.8%)	797 (58.4%)	447 (32.8%)	120 (8.8%)	21.4 (7.1)	25.5 (7.6)	33.0 (8.1)	19.8 (8.1)	27.2 (9.9)	41.3 (11.9)
	Normal weight 18.5 ≤ BMI < 25	35,075 (46.8%)	20,457 (58.3%)	11,330 (32.3%)	3288 (9.4%)	21.1 (6.9)	24.7 (7.1)	32.7 (7.1)	19.5 (7.9)	26.3 (9.5)	41.6 (11.5)
	Overweight 25 ≤ BMI < 30	29,625 (39.5%)	18,366 (62.0%)	8999 (30.4%)	2260 (7.6%)	20.8 (6.8)	24.4 (7.3)	32.5 (7.3)	19.2 (8.0)	25.9 (9.7)	41.8 (11.7)
	Obese 30 ≤ BMI	8925 (11.9%)	5838 (65.4%)	2464 (27.6%)	623 (7.0%)	20.6 (6.8)	24.3 (7.4)	31.8 (7.2)	18.9 (7.9)	25.8 (9.9)	40.9 (11.8)
Occupational status	Not employed (retired included)	44,430 (59.3%)	27,175 (61.2%)	13,557 (30.5%)	3698 (8.3%)	20.7 (6.8)	24.6 (7.2)	32.5 (7.5)	19.0 (7.8)	26.1 (9.6)	41.7 (12.0)
	Employed	30,559 (40.7%)	18,283 (59.8%)	9683 (31.7%)	2593 (8.5%)	21.2 (7.0)	24.5 (7.2)	32.6 (7.1)	19.8 (8.2)	26.1 (9.6)	41.4 (11.0)
Smoking habit	Current smoker	17,113 (22.8%)	9800 (57.3%)	5621 (32.8%)	1692 (9.9%)	21.1 (6.9)	24.8 (7.3)	32.8 (7.5)	19.7 (8.1)	26.5 (9.9)	42.3 (11.8)
	Former smoker	18,194 (24.3%)	11,002 (60.5%)	5555 (30.5%)	1637 (9.0%)	21.5 (7.0)	25.1 (7.3)	32.8 (7.2)	19.8 (8.0)	26.7 (9.4)	41.4 (11.0)
	Never smoker	39,682 (52.9%)	24,656 (62.1%)	12,064 (30.4%)	2962 (7.4%)	20.6 (6.8)	24.2 (7.1)	32.2 (7.4)	18.9 (7.8)	25.7 (9.6)	41.3 (11.8)
Physical activity	Intense	3056 (4.1%)	1630 (53.3%)	1143 (37.4%)	283 (9.3%)	21.6 (6.8)	24.8 (7.1)	32.4 (7.1)	20.6 (7.9)	26.9 (9.9)	41.8 (10.7)
	Regular	13,609 (18.2%)	9490 (69.7%)	3391 (24.9%)	728 (5.3%)	21.5 (7.0)	26.1 (7.6)	33.2 (7.0)	19.8 (7.8)	27.6 (9.4)	41.4 (10.4)
	Light	23,291 (31.1%)	14,072 (60.4%)	7130 (30.6%)	2089 (9.0%)	20.7 (6.9)	25.1 (7.2)	32.4 (7.1)	19.1 (8.0)	26.5 (9.5)	40.0 (10.6)
	No physical activity	35,033 (46.7%)	20,266 (57.9%)	11,576 (33.0%)	3191 (9.1%)	20.7 (6.8)	23.8 (7.0)	32.5 (7.7)	19.1 (8.0)	25.4 (9.6)	42.6 (12.5)
Living with partner	Yes	62,493 (83.3%)	37,810 (60.5%)	19,717 (31.5%)	4966 (7.9%)	21.0 (6.9)	24.4 (7.2)	32.3 (7.3)	19.4 (8.0)	26.0 (9.7)	41.1 (11.5)
	No	12,496 (16.7%)	7648 (61.2%)	3523 (28.2%)	1325 (10.6%)	20.6 (6.8)	25.2 (7.2)	33.4 (7.6)	18.7 (7.5)	26.8 (9.3)	43.2 (11.9)
Age class	[35,45]	19,436 (25.9%)	11,879 (61.1%)	5933 (30.5%)	1624 (8.4%)	20.9 (7.0)	24.3 (7.2)	33.3 (6.8)	19.5 (8.2)	26.0 (9.7)	41.1 (10.9)
	[45,55]	17,716 (23.6%)	10,539 (59.5%)	5743 (32.4%)	1434 (8.1%)	21.1 (6.9)	24.3 (7.2)	32.1 (7.2)	19.6 (8.2)	25.9 (9.9)	40.8 (11.4)
	[55,65]	15,515 (20.7%)	9127 (58.8%)	5107 (32.9%)	1281 (8.3%)	21.2 (7.0)	24.9 (7.4)	32.8 (7.7)	19.7 (8.1)	26.5 (9.8)	42.0 (11.9)
	[65,75]	13,275 (17.7%)	8191 (61.7%)	3945 (29.7%)	1139 (8.6%)	20.6 (6.7)	24.6 (7.3)	32.9 (7.6)	18.7 (7.5)	26.1 (9.3)	42.3 (12.0)
	[75,85]	6973 (9.3%)	4400 (63.1%)	1931 (27.7%)	642 (9.2%)	20.5 (6.7)	24.7 (7.0)	32.9 (7.6)	18.4 (7.2)	26.1 (8.9)	42.2 (12.2)
	85 +	2074 (2.8%)	1322 (63.7%)	581 (28.0%)	171 (8.2%)	20.6 (6.7)	24.9 (6.9)	33.4 (7.9)	18.5 (7.4)	26.2 (9.0)	43.2 (12.7)

pollutants a mean annual value has been calculated for all Italian municipalities (Fig. 1).

2.3. Statistical analyses

For each of the analyzed outcomes, the individual effect of long-term exposure to air pollution on hospitalization is modelled using the Cox proportional hazard model, with air pollution levels and age class as time-varying variables, while adjusting for other variables. Robust variance estimates are produced to take into account the two-stage sampling strategy used by ISTAT (Istituto Nazionale di Statistica) in the survey (sampling municipalities at the first stage and households within each municipality at the second stage, and enrolling all the individuals of the sampled families).

We estimate hazard ratios (HRs) adjusted for gender, educational level (classified according to the international classification ISCED and grouped into the four classes: *up to primary*, corresponding to ISCED 0–1, *lower secondary*, ISCED 2 and 3C, *upper secondary*, ISCED 3A and 3B and *post secondary*, ISCED 4–6), marital status (living with partner/not living with partner), occupational status (employed/not employed), smoking habit (current smoker, former smoker, never smoker), physical activity (4 different levels combining information on type and frequency of activity) and BMI. The individual characteristics are known only at the time of the interview. For each subject we define the residence based on type of municipality according to the population size: *metropolitan areas* (municipalities with > 250,000 inhabitants), *urban areas* (between 20,000 and 250,000 inhabitants) and *rural areas* (municipalities with < 20,000 inhabitants).

The idea of LIFE MED HISS project is to obtain the maximum information from sources already available. Since we had four years of air pollution exposure (from 1999 to 2007), which were subsequent to the enrollment of the cohort, we did not find appropriate to use air pollution as time-dependent variable using only the most recent year of exposure, as done in other studies (Nafstad et al., 2004). Therefore, we divided the follow-up period in 4 risk sets and computed the annual exposure value of each risk set as the mean exposure of all the preceding years for which the data was available, as follows:

- 1999–2002 (exposure in 1999)
- 2003–2004 (mean exposure of 1999 and 2003)
- 2005–2006 (mean exposure of 1999, 2003 and 2005)
- 2007–2008 (mean exposure of 1999, 2003, 2005 and 2007)

Sensitivity analyses have been done using only one year of exposure (2005).

Due to the nature of data and consequently of the exposure assessment, which assigns one single value over the whole city, the results are presented also by municipality size population, according to the residence, for *rural, urban and metropolitan areas*.

The proportional hazard assumption was tested for all the fixed predictors and stratified Cox models were applied for predictors that did not meet the assumption.

For each outcome, we evaluated potential effect modification by adding into the model the proper interaction term of exposure by modifier. We used the likelihood ratio test to compare the models with and without interaction terms.

Due to the heterogeneous spatial coverage of monitoring stations in Northern and Central Italy (dense spatial coverage) and Southern Italy (sparse spatial coverage), sensitivity analyses are also presented restricted to the first domain.

All analyses were conducted using SAS, version 9.4 (SAS Institute Inc., 2013) and R, version 3.3.3 (R Core Team, 2017).

3. Results

Analyses on association between air pollution and hospital admissions are performed on 74,989 individuals aged > 35 years and alive at 2001.

Table 1 shows the distribution of sample characteristics, overall and stratified by size of the municipality of residence. Due to space constraints, pollutants are described only in 2005, but distributions do not change substantially in the other years.

Most individuals live in rural areas (60.6%), while only 8.4% of the population is resident in the twelve metropolitan cities with > 250,000 inhabitants (Rome, Milan, Naples, Turin, Palermo, Genoa, Bologna, Florence, Bari, Catania, Venice and Verona). In our cohort, 70.2% is between 35 and 65 years, with 2.8% of people aged over 85; 46.8% is normal weight and 11.9% is obese, with 0.2% with severe obesity. Most families are composed by person living with a partner (83.3%). Concerning physical activity, 46.7% is totally inactive. Educational level is categorized according to ISCED, with the highest percentage (46.6%) belonging to ISCED 0–1 (low education level), mainly concentrated in rural areas. Variables included in the analyses are compiled for all individuals. Mean and standard deviation of PM2.5 and NO_2 in 2005 are also shown in Table 1: the distribution of the pollutants looks invariant to each category of all the variables included in the analysis. If we consider only year 2005 for exposure, 76.3% and 79.1% of the individuals are exposed to concentration ranging between 10 and 30 $\mu g/m^3$, for NO_2 and PM2.5 respectively (Table 2).

Table 3 shows HRs with 95% CI of cause-specific hospitalization for 10 $\mu g/m^3$ increase in PM2.5 and NO_2. For PM2.5 and NO_2, respectively, we found positive associations for circulatory system diseases [1.05(1.03–1.06); 1.05(1.03–1.07)], myocardial infarction [1.15(1.12–1.18); 1.15(1.12–1.18)], lung cancer [1.18(1.10–1.26); 1.20(1.12–1.28)], kidney cancer [1.24(1.11–1.29); 1.20(1.07–1.33)], neoplasms (lung cancer excluded) [1.06(1.04–1.08); 1.06(1.04–1.08)] and LRTI [1.10 (1.04–1.15); 1.05 (1.01–1.10)]. Significant associations is also found with NO_2, and hospital admissions for atherosclerosis [1.10(1.03–1.17)]. We found negative associations for hospital admissions related to COPD [0.90(0.86–0.94); 0.94(0.90–0.97) for PM2.5 and NO_2 respectively].

Table 4 shows results stratified, for *rural areas*, *urban areas* and *metropolitan areas*. When main results are reported by municipalities' population size, metropolitan areas do not show significant results for most of causes.

Results stratified by gender are reported in Table 5. The risk of both lung, kidney and urinary cancer is higher in women than in men for both the air pollutants, on the contrary the effects of PM2.5 and NO_2 are the same for neoplasm (lung cancer excluded) hospitalization.

Table 2
Descriptive statistics of the Italian Longitudinal Study (considering individuals older than 35 years). Distribution of PM2.5 and NO_2 concentration referred to year 2005 data.

NO_2 levels - year 2005 data	N(%)	PM2.5 levels – year 2005 data	N(%)
$NO_2 < 10$ ($\mu g/m^3$)	793 (1.1%)	PM2.5 < 10 ($\mu g/m^3$)	277 (0.4%)
$10 \le NO_2 < 20$ ($\mu g/m^3$)	33,080 (44.1%)	$10 \le$ PM2.5 < 20 ($\mu g/m^3$)	29,917 (39.9%)
$20 \le NO_2 < 30$ ($\mu g/m^3$)	24,046 (32.1%)	$20 \le$ PM2.5 < 30 ($\mu g/m^3$)	29,390 (39.2%)
$30 \le NO_2 < 40$($\mu g/m^3$)	11,439 (15.3%)	$30 \le$ PM2.5 < 40 ($\mu g/m^3$)	13,726 (18.3%)
$40 \le NO_2 < 50$ ($\mu g/m^3$)	3603 (4.8%)	$40 \le$ PM2.5 < 50 ($\mu g/m^3$)	1174 (1.6%)
$NO_2 \ge 50$ ($\mu g/m^3$)	2028 (2.7%)	PM2.5 ≥ 50 ($\mu g/m^3$)	505 (0.7%)

Table 3
Association between exposure to pollutants (1999; 2003; 2005; 2007) and hospital admissions, using time dependent Cox model with robust variance estimator. Results expressed per HRs for 10 μg/m^3 increase. Model adjusted by age, gender, educational level, living with partner, occupational status, smoking habit, physical activity status, type of municipality (rural, urban, metropolitan areas) and BMI. Highlighted in bold statistically significant results (considering a 95% CI). In Italics we report the number of events.

Cause of hospitalization	Number of events	PM2.5	NO_2
		HR for 10 μg/m^3 increase	HR for 10 μg/m^3 increase
Diabetes	*3748*	0.97 (0.94–1.01)	0.98 (0.96–1.01)
Circulatory system diseases	*12,867*	**1.05 (1.03–1.06)**	**1.05 (1.03–1.07)**
Respiratory system diseases	4428	1.03 (1.00–1.07)	1.02 (0.98–1.05)
Neoplasm (lung cancer excluded)	*8138*	**1.06 (1.04–1.08)**	**1.06 (1.04–1.08)**
Behavioural disorders diseases	*1104*	0.98 (0.92–1.04)	0.99 (0.94–1.05)
Nervous system diseases	*2490*	**1.05 (1.01–1.09)**	**1.05 (1.01–1.09)**
Cardiac diseases	*7972*	1.02 (1.00–1.05)	**1.03 (1.01–1.05)**
Cerebrovascular diseases	*3380*	1.03 (0.99–1.07)	1.02 (0.99–1.06)
Atherosclerosis diseases	*546*	1.07 (0.99–1.15)	**1.10 (1.03–1.17)**
LRTI	*1540*	**1.10 (1.04–1.15)**	**1.05 (1.00–1.10)**
COPD	*2762*	**0.90 (0.86–0.94)**	**0.94 (0.90–0.97)**
Asthma	*138*	1.09 (0.92–1.30)	1.06 (0.89–1.25)
Lung cancer	*526*	**1.18 (1.10–1.26)**	**1.20 (1.12–1.28)**
Urinary bladder cancer	*501*	1.08 (1.00–1.17)	**1.09 (1.01–1.17)**
Kidney cancer	*196*	**1.24 (1.11–1.29)**	**1.20 (1.07–1.33)**
Parkinson	*149*	1.06 (0.91–1.23)	1.08 (0.94–1.24)
Alzheimer	*298*	1.03 (0.91–1.17)	1.06 (0.96–1.17)
Miscarriage	*78*	1.00 (0.80–1.23)	1.01 (0.84–1.22)
Stroke	*1505*	**1.15 (1.10–1.20)**	**1.14 (1.10–1.19)**
Angina pectoris	*851*	1.03 (0.96–1.10)	1.03 (0.97–1.10)

Focusing on lung cancer (Table 6), HRs are higher and robust even among non-smokers and former smokers [1.17 (1.04–1.31) and 1.16 (1.04–1.29) for PM2.5 and NO_2 for non-smokers; 1.16 (0.99–1.35) and 1.19 (1.03–1.38) for PM2.5 and NO_2 for former smokers]. Risks are also higher among sedentary people or who practice light physical activity, with about 20% excess of risk in both categories and for both pollutants. Considering BMI as a categorical variable, also obese and overweight people show higher HRs.

Since in the Southern part of Italy the spatial coverage of monitoring stations is lower, with potentially less accurate exposure assessment, a sensitivity analysis has been performed restricted to the northern and central regions of Italy. Considering overall results (reported in Table S1 of supplemental material), risks for hospital admissions for circulatory diseases are lower (respectively 1.03 (1.01–1.05) and 1.03 (1.01–1.05) for PM2.5 and NO_2), whereas risk estimates for asthma causes are higher [respectively 1.26 (1.06–1.50) and 1.27 (1.02–1.58) for PM2.5 and NO_2].

Sensitivity analyses have been performed also assigning to each subject only the year 2005 for exposure (Table S2 in supplemental material) in which spatial coverage of monitoring stations is robust also for PM2.5. HRs are similar to those estimated with time-dependent exposure assessment (1999–2007), only slightly attenuated for NO_2 and amplified for PM2.5.

4. Discussion

In this study we investigated the long term effect of air pollution on a wide series of causes of hospitalization using the follow-up of the 1999–2000 Italian Health Interview Survey.

PM2.5 and NO_2 were associated with an increased risk of hospitalization for cardiovascular diseases (in particular myocardial infarction), cancer (with a stronger effect for lung and kidney cancer), LRTI and nervous system diseases.

The proposed low-cost approach, suitable for surveillance, is based on linking resources like air pollution prediction models, mortality and hospital admissions registries and National Health Interview Surveys, the latter being already available and mandatory in all European countries. This record linkage has permitted the investigation of the impact of air pollution on a European cohort in the Mediterranean area. A peculiarity of this cohort is the availability of individual information, which naturally arises from the questionnaire. This allows controlling for individual potential confounders; besides, the NHIS contains a sample representative of the population spread in the whole national territory, covering both urban and rural areas. Thanks to the CTMs, the problem of having a limited number of PM2.5 monitors is overcome. MINNI system covers the whole national territory providing a measure of exposure for each municipality, including also rural and suburban populations which are far from monitoring stations.

As expected, a clear effect was seen for lung cancer hospital admissions. The focus on lung cancer confirms literature findings, ensuring the robustness of the use of the NHISs for epidemiological purposes in environmental field (Raaschou-Nielsen et al., 2011). The use of information on individual behaviours allowed showing risks for some categories: non-smokers experience the known risks, subject that do not perform physical activity and/or overweight or obese experience the highest risks.

However, the employment of land use regression models, as well as more detailed personal exposure assessment, which can include variables like distance from major roads (see for example Hystad et al., 2013), could be recommended to ensure more robust results in metropolitan areas, when more detailed information about home address is not limited by privacy regulation.

Significant risks are also seen considering all neoplasms, even excluding the contribution of lung cancer. Results also suggest a relationship between air pollution exposure and kidney cancer, indicating the potential effect of air pollutants on tissues more exposed to chemicals, also for their de-toxifying function.

Results obtained for circulatory diseases (both for PM2.5 and NO_2) confirm the putative biological mechanisms linking long term exposure to air pollution and cardiovascular diseases, which involves direct effects of pollutants on the cardiovascular system, blood, and lung receptors, and/or indirect effects mediated through pulmonary oxidative stress and inflammatory responses (Kloog et al., 2012). Risks are statistically significant also stratified by gender and by level of municipality population size. Results are substantially confirmed (with the exception of asthma) when restricted to the Northern and Central part of Italy, where the spatial coverage of monitoring stations is higher and improves CTMs data.

Table 4
Association between exposure to pollutants (1999; 2003; 2005; 2007) and hospital admissions, using time dependent Cox model with robust variance estimator. Results expressed per HRs for 10 μg/m^3 increase. Model adjusted by age, gender, educational level, living with partner, occupational status, smoking habit, physical activity status and BMI. Results divided by *metropolitan, urban and rural areas*. For each cell, the number of events is reported (in italics). Statistically significant results are highlighted in bold.

Cause of hospitalization	PM2.5						NO_2		
	Rural areas	Urban areas	Metropolitan areas	Rural areas	Urban areas	Metropolitan areas	Rural areas	Urban areas	Metropolitan areas
	Number of events	Number of events	Number of events	HR for 10 μg/m^3 increase	HR for 10 μg/m^3 increase	HR for 10 μg/m^3 increase	HR for 10 μg/m^3 increase	HR for 10 μg/m^3 increase	HR for 10 μg/m^3 increase
Diabetes	*2278*	*1150*	*320*	**0.93 (0.88–0.99)**	**0.94 (0.89–1.00)**	0.97 (0.87–1.08)	0.93 (0.88–0.98)	0.95 (0.90–1.01)	0.94 (0.84–1.06)
Circulatory system diseases	*7679*	*4008*	*1180*	1.02 (0.99–1.05)	1.02 (0.99–1.05)	1.04 (0.98–1.09)	1.02 (0.99–1.05)	**1.04 (1.01–1.07)**	1.00 (0.96–1.07)
Respiratory system diseases	*2668*	*1346*	*414*	1.05 (0.99–1.02)	1.02 (0.97–1.08)	1.02 (0.94–1.12)	1.01 (0.96–1.05)	1.02 (0.97–1.08)	**1.07 (1.01–1.13)**
Neoplasm (but lung)	*4798*	*2535*	*805*	**1.07 (1.03–1.11)**	1.02 (0.98–1.06)	1.03 (0.96–1.10)	**1.06 (1.03–1.10)**	1.03 (0.99–1.07)	1.03 (0.97–1.10)
Behavioural disorders	*637*	*352*	*115*	**0.85 (0.76–0.95)**	1.02 (0.91–1.13)	0.91 (0.77–1.09)	**0.86 (0.78–0.95)**	1.05 (0.95–1.16)	**0.81 (0.67–0.97**)
Nervous system diseases	*1460*	*810*	*220*	1.04 (0.97–1.11)	1.03 (0.96–1.10)	1.03 (0.91–1.17)	1.05 (0.99–1.12)	1.02 (0.96–1.09)	1.02 (0.89–1.17)
Cardiac diseases	*4750*	*2481*	*741*	0.96 (0.92–1.01)	1.01 (0.96–1.07)	0.92 (0.87–1.02)	**0.96 (0.92–1.00)**	1.01 (0.96–1.06)	0.98 (0.88–1.09)
Cerebrovascular diseases	*2069*	*1019*	*292*	1.03 (0.96–1.10)	0.98 (0.90–1.06)	0.94 (0.78–1.13)	0.99 (0.93–1.05)	0.98 (0.91–1.06)	1.01 (0.87–1.18)
Atherosclerosis	*310*	*172*	*64*	1.04 (0.91–1.20)	0.97 (0.85–1.12)	1.05 (0.84–1.29)	1.08 (0.95–1.23)	1.04 (0.91–1.18)	1.02 (0.80–1.30)
LRTI	*956*	*458*	*126*	1.08 (1.00–1.18)	**1.11 (1.01–1.22)**	**1.21 (1.06–1.38)**	1.06 (0.98–1.15)	1.06 (0.97–1.17)	1.17 (0.99–1.39)
COPD	*1727*	*788*	*247*	**0.82 (0.76–0.88)**	**0.89 (0.82–0.97)**	0.89 (0.79–1.00)	**0.82 (0.77–0.87)**	**0.91 (0.85–0.98)**	0.95 (0.85–1.06)
Asthma	*79*	*48*	*11*	1.07 (0.79–1.47)	1.09 (0.83–1.44)	1.08 (0.59–1.96)	0.93 (0.67–1.29)	1.13 (0.83–1.53)	1.17 (0.62–2.22)
Lung cancer	*293*	*171*	*62*	**1.18 (1.02–1.35)**	**1.17 (1.05–1.30)**	1.00 (0.79–1.25)	**1.21 (1.06–1.38)**	**1.22 (1.08–1.38)**	1.00 (0.80–1.25)
Urinary bladder cancer	*294*	*154*	*53*	1.18 (1.03–1.35)	0.93 (0.79–1.11)	0.99 (0.77–1.28)	**1.20 (1.06–1.37)**	0.93 (0.80–1.08)	0.98 (0.73–1.33)
Kidney cancer	*121*	*55*	*20*	**1.43 (1.18–1.72)**	1.16 (0.92–1.48)	1.13 (0.77–1.64)	**1.40 (1.15–1.70)**	1.11 (0.86–1.43)	1.20 (0.82–1.76)
Parkinson	*79*	*55*	*15*	0.96 (0.70–1.34)	1.06 (0.84–1.34)	0.67 (0.35–1.28)	0.91 (0.67–1.24)	1.13 (0.89–1.43)	0.69 (0.40–1.20)
Alzheimer	*169*	*96*	*33*	0.99 (0.79–1.24)	0.95 (0.74–1.22)	0.86 (0.53–1.41)	1.01 (0.83–1.22)	0.93 (0.74–1.16)	0.97 (0.67–1.39)
Miscarriage	*45*	*25*	*8*	1.11 (0.64–1.93)	1.03 (0.70–1.52)	1.19 (0.45–3.15)	1.04 (0.65–1.66)	1.10 (0.79–1.53)	5.39 (0.34–86.2)
Stroke	*848*	*523*	*134*	**1.16 (1.06–1.25)**	**1.12 (1.03–1.20)**	**1.19 (1.04–1.35)**	**1.15 (1.06–1.24)**	**1.16 (1.08–1.26)**	1.16 (0.99–1.36)
Angina pectoris	*496*	*284*	*71*	1.01 (0.89–1.13)	1.04 (0.92–1.18)	0.97 (0.78–1.21)	1.02 (0.92–1.13)	1.04 (0.93–1.17)	0.99 (0.79–1.23)

Results obtained for atherosclerosis (particularly for NO_2) confirm recent findings of coronary artery calcification within six metropolitan areas in the USA (Kaufman et al., 2016) and the results of ESCAPE on a preclinical marker of atherosclerosis (intima-media thickness of the common carotid artery) (Perez et al., 2015). Increased concentrations of PM2.5 and traffic-related air pollution within metropolitan areas are associated with progression in coronary calcification, consistent with acceleration of atherosclerosis. Considering myocardial infarction, few studies are available in the literature until now, whereas many studies focus on short-term effect (Bhaskaran et al., 2009). Our study supports the evidence of an effect of long-term exposure to air pollution on myocardial infarction.

It is known that the biological mechanisms linking long term exposure to air pollution and respiratory diseases include reduced lung function, pulmonary inflammation and oxidative stress.

Nevertheless, in our study no results are obtained for the whole group of respiratory diseases. If we investigate more specific causes of hospitalization, we see a clear effect of air pollution on LRTI and a suggestion on relationship with asthma, with all the known limitations to this type of hospital admissions. Risks for COPD are still an open issue with controversial results (Atkinson et al., 2015), while a causal role of air pollution in the induction of COPD would be biologically plausible (Schikowski et al., 2014). Following Schikowski, *in spite of plausible models of biological mechanisms, direct epidemiological evidence of the long-term effects of air pollution on COPD prevalence and incidence remains suggestive but not conclusive*. In LIFE MED HISS, a protective effect has been seen but this can also be due to competitive risks: since COPD, lung cancer and ischaemic diseases share a common risk factor (smoking) and in addition the hospitalization for COPD should not happen (it is considered inappropriate because this disease should be managed at home) it is likely that people who smoke and whose conditions are exacerbated by air pollution have been hospitalized for lung cancer or myocardial infarction rather than for COPD.

In contrast to what previously published (Kloog et al., 2012), we have not seen significant risk for diabetes and this could be an effect of the protective effect of Mediterranean diet which is spread among all the Italian population and could have mitigated the metabolic effect of chemicals. Concerning risks for urban and rural areas, there is no clear

Table 5
between exposure to pollutants (1999; 2003; 2005; 2007) and hospital admissions, using time dependent Cox model with robust variance estimator, divided by gender. Results expressed per HRs for 10 μg/m^3 increase. Model adjusted by age, educational level, living with partner, occupational status, smoking habit, physical activity status, type of municipality (rural, urban, metropolitan areas) and BMI. Number of events are reported in italics. Statistically significant results are highlighted in bold

Causes where number of events among men and women do not respect overall proportions are marked with an asterisk (*).

Cause of hospitalization	Number of events		PM2.5		NO_2	
	Women	Men	Women	Men	Women	Men
			HR for 10 μg/m^3 increase	HR for 10 μg/m^3 increase	HR for 10 μg/m^3 increase	HR for 10 μg/m^3 increase
Diabetes	*1784*	*1964*	0.97 (0.92–1.02)	0.98 (0.93–1.03)	0.98 (0.94–1.02)	0.99 (0.95–1.03)
Circulatory system diseases	*6100*	*6767*	**1.04 (1.01–1.06)**	**1.06 (1.03–1.08)**	**1.04 (1.02–1.06)**	**1.06 (1.04–1.09)**
Respiratory system diseases	*1833*	*2595*	1.03 (0.97–1.08)	1.04 (0.99–1.08)	0.99 (0.94–1.05)	1.03 (0.99–1.08)
Neoplasm (but lung)	*4326*	*3812*	**1.06 (1.03–1.09)**	**1.06 (1.03–1.09)**	**1.07 (1.04–1.10)**	**1.06 (1.03–1.09)**
Behavioural disorders	*626*	*478*	0.96 (0.89–1.05)	0.99 (0.90–1.09)	0.98 (0.92–1.05)	1.01 (0.94–1.09)
Nervous system diseases	*1507*	*983*	1.06 (1.00–1.11)	1.04 (0.98–1.11)	**1.05 (1.01–1.10)**	1.04 (0.99–1.10)
Cardiac diseases	*3508*	*4464*	1.01 (0.97–1.05)	**1.04 (1.00–1.08)**	1.02 (0.98–1.05)	**1.05 (1.02–1.08)**
Cerebrovascular diseases	*1654*	*1726*	1.04 (0.98–1.10)	1.02 (0.97–1.08)	1.03 (0.98–1.08)	1.02 (0.97–1.07)
Atherosclerosis	*190*	*356*	1.08 (0.95–1.22)	1.06 (0.97–1.17)	1.08 (0.96–1.21)	**1.11 (1.02–1.20)**
LRTI	*638*	*902*	**1.09 (1.00–1.18)**	**1.10 (1.03–1.18)**	1.05 (0.98–1.13)	1.05 (0.99–1.12)
COPD	*960*	*1802*	0.90 (0.83–0.96)	**0.91(0.86–0.96)**	**0.91 (0.86–0.97)**	**0.95 (0.91–0.99)**
Asthma	*90*	*48*	1.06 (0.85–1.31)	1.14 (0.84–1.55)	1.00 (0.81–1.24)	1.13 (0.85–1.51)
Lung cancer	*105**	*421**	**1.27 (1.11–1.46)**	**1.15 (1.07–1.25)**	**1.27 (1.11–1.46)**	**1.18 (1.09–1.27)**
Urinary bladder cancer	*89**	*412**	**1.24 (1.07–1.44)**	1.04 (0.95–1.14)	**1.24 (1.07–1.44)**	1.05 (0.97–1.13)
Kidney cancer	*62**	*134**	**1.32 (1.08–1.61)**	**1.20 (1.05–1.38)**	**1.26 (1.03–1.54)**	**1.17 (1.03–1.33)**
Parkinson	*68*	*81*	1.12 (0.91–1.38)	1.00 (0.80–1.25)	1.12 (0.93–1.36)	1.04 (0.86–1.27)
Alzheimer	*177**	*121**	1.05 (0.89–1.24)	0.99 (0.83–1.18)	1.03 (0.90–1.18)	1.07 (0.93–1.24)
Miscarriage	*78*		0.99 (0.80–1.23)		1.01 (0.84–1.22)	
Stroke	*517*	*988*	1.08 (0.99–1.18)	**1.17 (1.11–1.24)**	**1.13 (1.05–1.21)**	**1.15 (1.09–1.21)**
Angina pectoris	*283*	*568*	1.08 (0.96–1.21)	0.99 (0.91–1.09)	1.07 (0.97–1.18)	1.01 (0.94–1.09)

Table 6
Association between exposure to pollutants (1999; 2003; 2005; 2007) and hospital admissions for lung cancer, using time dependent Cox model with robust variance estimator. Results expressed per HRs for 10 μg/m^3 increase. Model adjusted by age, gender, educational level, living with partner, occupational status and type of municipality (rural, urban, metropolitan areas) smoking status, physical activity status, BMI when the variable is not used to show stratified results. Number of events are reported in italics. Statistically significant results are highlighted in bold

	Number of events	PM2.5	NO_2
		HR of hospital admissions for lung cancer for 10 μg/m^3 increase	HR of hospital admissions for lung cancer for 10 μg/m^3 increase
Overall	*526*	**1.18 (1.10–1.26)**	**1.20 (1.12–1.28)**
Rural areas	*293*	**1.18 (1.02–1.35)**	**1.21 (1.06–1.38)**
Urban areas	*171*	**1.17 (1.05–1.30)**	**1.22 (1.08–1.38)**
Metropolitan areas	*62*	1.00 (0.79–1.25)	1.00 (0.80–1.25)
Current smoker	*231*	**1.18 (1.07–1.32)**	**1.23 (1.11–1.36)**
Former smoker	*188*	1.16 (0.99–1.35)	**1.19 (1.03–1.38)**
Never smoker	*107*	**1.17 (1.04–1.31)**	**1.16 (1.04–1.29)**
Physical activity			
Intense	*13*	0.81 (0.46–1.42)	0.81 (0.47–1.04)
Regular	*89*	0.98 (0.79–1.22)	1.04 (0.86–1.25)
Light	*165*	**1.22 (1.09–1.37)**	**1.26 (1.12–1.41)**
No physical activity	*259*	**1.23 (1.12–1.35)**	**1.23 (1.12–1.34)**
Underweight BMI < 18.5	*8*	0.90 (0.51–1.48)	1.08 (0.68–1.70)
Normal weight 18.5 ≤ BMI < 25	*229*	1.11 (0.99–1.25)	1.09 (0.98–1.21)
Overweight 25 ≤ BMI < 30	*234*	**1.20 (1.08–1.32)**	**1.23 (1.11–1.35)**
Obese 30 ≤ BMI	*55*	**1.39 (1.15–1.67)**	**1.54 (1.31–1.80)**

evidence of higher risks in one of the two subgroups, but this seems to depend on the cause selected (Table 4). Information on alcohol and diet would have helped to clarify this topic, because of different behaviour among the two groups.

Controversial results obtained for metropolitan areas can be a combination of exposure misclassification and of the small amount of individuals sampled in these study areas. Considering not significant HRs obtained for lung cancer in cities with > 250,000 inhabitants, the use of a single concentration value for metropolitan areas could be a source of potential exposure misclassification, given the large within-city range. However, this source of bias is due to the lack of more detailed information about home address or residential postcode, avoidable if privacy policies would have permitted access to information at least on zip codes. The lack of permission has forced the use of concentration values at municipality level.

The lack of updated information for individual confounders and residential history is the major weakness of the use of Italian Longitudinal Study. Internal Italian mobility is about 1 million and a half every year, over a population of about 59 million of inhabitants (about 2.5%). In year 2009, 1,312,763 individuals changed their residence within Italian territory, whereas mobility outside Italian territory is 39,000 (ISTAT, 2016). Taking into account relatively low mobility rates of Italian people and providing that factors which influence mobility are not only related to environmental factors, an eventual non-differential misclassification is more likely to reduce the effect towards the null, as epidemiological literature generally suggests.

We used the exposure information as a proxy of past exposures. Having verified that in the Italian territory there were no differential temporal trends of the pollutants under investigation between metropolitan, urban and rural areas (Figs. 2 and 3), we trusted the use of the whole information available. The time-dependent approach aims at maximizing the information on exposure using available data. In this study the first year of the exposure available is contemporary to the time of the interview. Sensitivity analyses performed using only year 2005 (first year with an adequate spatial coverage of monitoring stations both for PM2.5 and for NO_2) seemed to show higher risks associated to particulate matter. This may suggest that the use of a time-dependent approach, including years in the past, could lead to conservative results due to less accuracy in particulate exposure measure. The adopted methodology correctly reproduces concentration mean

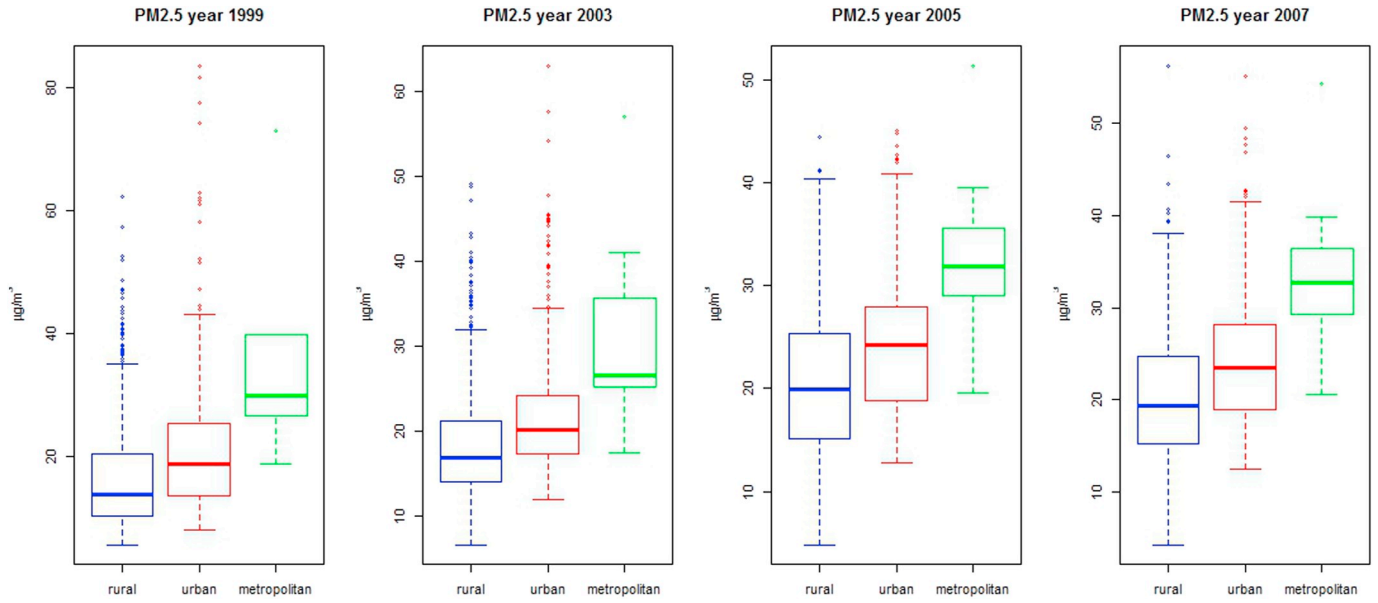

Fig. 2. Boxplot of PM2.5 for the four year considered divided by *metropolitan*, *urban* and *rural areas*.

levels typical of urban background stations, consistent with the MINNI spatial resolution. The system (MINNI-KED) underestimates observed levels at traffic stations in urban areas that are phenomena occurring at scales that cannot be solved at the adopted spatial resolution. This is a common problem of state-of-art national CTMs (Aguilera et al., 2013; Kiesewetter et al., 2014), likely to be solved in the future with routine application of more detailed modeling of urban areas. Moreover, up-scaling from gridded data to municipality level, needed to match the health data, preserves concentrations levels and main spatial patterns, but it amplifies the inability to capture spatial variations of small scale.

5. Conclusion

The MED-HISS project is a pilot study that tested the applicability of surveillance systems for European countries, thanks to relative cheapness in comparison to traditional cohort studies. Results obtained are consistent with the literature, as is the case for lung cancer, and demonstrated the feasibility of this approach, with the possibility to study a broad range of causes (IARC, 2013). The applied methodology provided consistent estimates useful to describe the exposure of large population for surveillance purposes.

To carry on this kind of studies it is necessary that privacy policies permit to link each individual of the survey with his health history.

European surveys are representative of population at some different level of urbanization. This permits to have a large amount of the cohort living in rural areas, which are less polluted, but usually also less studied.

Regarding exposure to air pollution we have implemented a methodology taking into account data coming from CTMs and air quality monitoring network. Firstly, trough KED, observations were fused in pollutant concentration fields and secondly a weighted average procedure was used to up-scale assimilated concentration fields at municipality scale. The adopted methodology produced satisfactory results and consistent exposure estimates at municipality level.

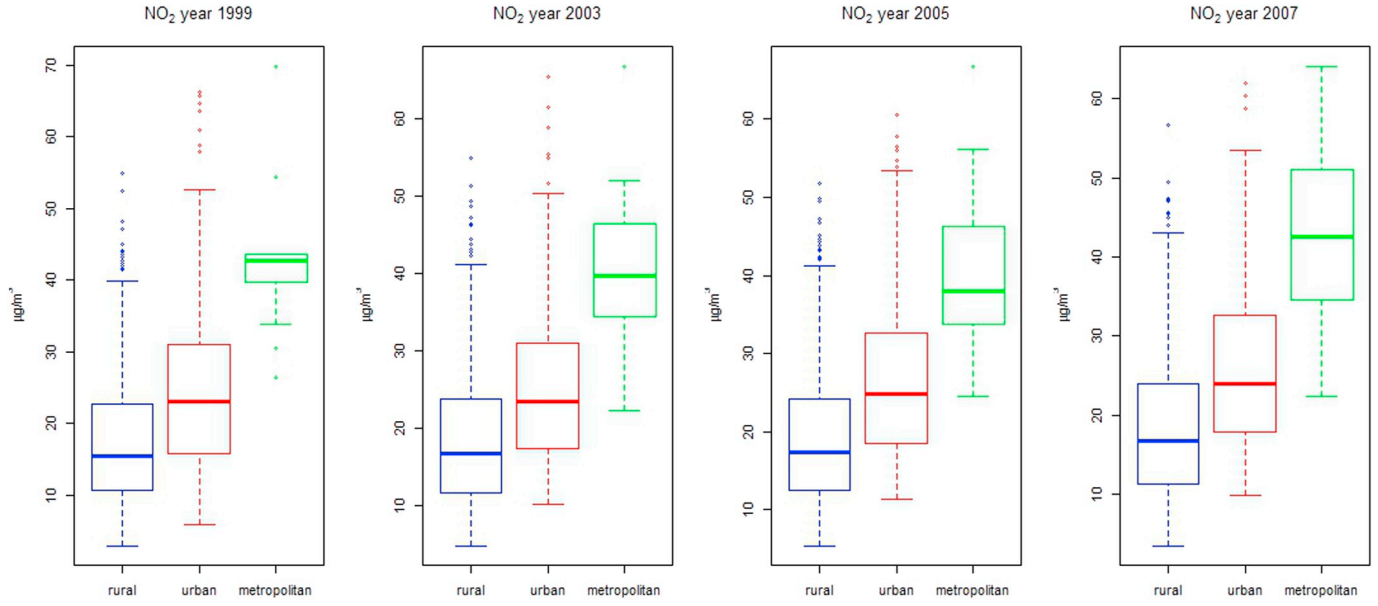

Fig. 3. Boxplot of NO_2 for the four year considered divided by *metropolitan*, *urban and rural areas*.

Due to the nature of the study, a wide list of causes has been analyzed, controlling for confounders at individual level. The availability of confounders depends on the survey. In this study we have identified a core set of variables which have a high degree of comparability with other European surveys. In the Italian Longitudinal Study, we have the strong limitation of having no information on alcohol consumption and on diet. However, subsequent surveys partially overcome this problem, but nowadays there is no follow-up with hospital admissions. Due to privacy restrictions we do not have more detailed information on residence than the municipality level, which could be a source of bias when studying metropolitan areas. Since only 8% of the cohort lives in metropolitan areas, this has a low impact on results from the Italian Longitudinal Study. A major source of misclassification is the lack of residential history before and after the interview, but the low rate of Italian mobility limits this problem.

Results obtained confirm the relationship measured in other studies on air pollution and hospital admissions, and add new evidence for causes with few studies available (e.g. myocardial infarction). Evidence arises for circulatory system, also when considering more specific causes like cerebrovascular disease, atherosclerosis, myocardial infarction and angina. Results for lung cancer confirm what already published. New issues are added considering all neoplasms (having excluded lung cancer) and kidney cancer. A study using a wider follow-up and using a cohort derived from a more recent survey is ongoing.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envint.2018.10.020.

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