Long-term exposure to air pollution and hospitalization for dementia in the Rome longitudinal study

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Abstract

Background: Few studies have explored the role of air pollution in neurodegenerative processes, especially various types of dementia. Our aim was to evaluate the association between long-term exposure to air pollution and first hospitalization for dementia subtypes in a large administrative cohort.

Methods: We selected 350,844 subjects (free of dementia) aged 65–100 years at inclusion (21/10/2001) and followed them until 31/12/2013. We selected all subjects hospitalized for the first time with primary or secondary diagnoses of various forms of dementia. We estimated the exposure at residence using land use regression models for nitrogen oxides (NOx, NO2) and particulate matter (PM) and a chemical transport model for ozone (O3). We used Cox models to estimate the association between exposure and first hospitalization for dementia and its subtypes: vascular dementia (Vd), Alzheimer’s disease (Ad) and senile dementia (Sd).

Results: We selected 21,548 first hospitalizations for dementia (7497 for Vd, 7669 for Ad and 7833 for Sd). Overall, we observed a negative association between exposure to NO2 (10 μg/m3) and dementia hospitalizations (HR = 0.97; 95% CI: 0.96–0.99) and a positive association between exposure to O3, NOx and dementia hospitalizations, (O3: HR = 1.06; 95% CI: 1.04–1.09 per 10 μg/m3; NOx: HR = 1.01; 95% CI: 1.00–1.02 per 20 μg/m3). Exposure to NOx, NO2, PM2.5, and PM10 was positively associated with Vd and negatively associated with Ad. Hospitalization for Sd was positively associated with exposure to O3 (HR = 1.20; 95% CI: 1.15–1.24 per 10 μg/m3).

Conclusions: Our results showed a positive association between exposure to NOx and O3 and hospitalization for dementia and a negative association between NO2 exposure and hospitalization for dementia. In the analysis by subtype, exposure to each pollutant (except O3) demonstrated a positive association with vascular dementia, while O3 exposure was associated with senile dementia. The results regarding vascular dementia are a clear indication that the brain effects of air pollution are linked with vascular damage.

Keywords: Dementia, Air pollution, Cohort analysis, Rome longitudinal study, Alzheimer’s disease, Vascular dementia
Background
The estimated number of people living with dementia worldwide in 2015 was 46.8 million. This number will almost double every 20 years, resulting in problems for individuals, families, and society [1]. Among the several types of dementia, Alzheimer’s disease is the most common and accounts for an estimated 60 to 80% of cases [2], whereas Vascular dementia, caused by cerebrovascular diseases, is the second most common form of dementia, accounting for 10 to 20% of cases [3]. Dementia is a syndrome characterized by a cognitive and functional decline. It is usually preceded by mild cognitive impairment, and generally, it is difficult to distinguish between the two conditions [4]. Dementia commonly occurs later in life as a consequence of the cerebrovascular and neurodegenerative processes that begin earlier in life [5]. Alzheimer’s disease is characterized by a progression in cognitive decline and in ability to function. It is often characterised also by behavioural disturbances, which tend to become more frequent as the severity of dementia increases. People can lose their independence, becoming unable to take care of themselves. Although there can be plateaus during the illness, the decline tends to accelerate and increase [6]. Vascular dementia can manifest soon after a vascular event that can cause a sudden deterioration in cognitive function, or can manifest slowly after multiple cerebral infarctions or diffuse white matter disease. The course of vascular dementia is less predictable than Alzheimer’s disease, since if underlying vascular disease can be stabilised, a relative stability may be seen for a period [3, 6].

Age is the most important known risk factor for dementia [2], and given the increasing elderly population, dementia will represent one of the most relevant public health issues. Diabetes [7, 8], mid-life obesity [9, 10], smoking [11, 12], brain injury [13], and depression [14, 15] are associated with a higher dementia risk [16]. There are also factors associated with a decreased risk of dementia, including physical activity [17, 18] and years of formal education [16, 19]. However, the aetiology of dementia is not fully understood, because genetic factors [20] and the most common risk factors do not fully explain dementia risk [21, 22]. Taking into account of non-independence between potentially modifiable risk factors, Norton and colleagues estimated that one third of Alzheimer’s disease cases might be attributable to education, physical inactivity, hypertension, diabetes, obesity, depression, and smoking [21].

The role of long-term exposure to air pollution in the onset of dementia is still controversial. In last decade, there has been increased interest in the effects of air pollution on the central nervous system and neurodegeneration. According to both epidemiological and toxicological studies, exposure to air pollution, particularly particulate matter, seems to be associated with decreased cognitive function [23–27]. Potential biological pathways, such as systemic inflammation, have been highlighted in order to explain this relationship [25, 27]. In particular, it is recognized that older brains are more vulnerable to pro-inflammatory stimuli, and one of the possible mechanisms of air pollution’s adverse effects on brain health is oxidative stress [25, 27]. Few studies have analysed the role of air pollution exposure in the development of dementia, using different study designs and different measures of exposure, and showed an association between air pollution exposure and dementia [28–34]. Only two studies differentiated between types of dementia, studying Alzheimer’s disease and vascular dementia [28, 32]. The Swedish cohort study found similar results by dementia types [28], while the case control study by Wu and colleagues found stronger associations between O₃ and PM₁₀ and Alzheimer’s disease compared to vascular dementia [32].

The aim of the present study was to evaluate the association between air pollution exposure (PM₁₀, coarse PM (particles with a size fraction between 2.5 and 10 μm), PM₂.₅, PM₂.₅ absorbance, NO₂, NOₓ, summer O₃, and distance to high-traffic roads) and first hospitalization for dementia in a large cohort of residents in Rome [35, 36]. Furthermore, we separately investigated the effect of air pollution on hospitalization for three types of dementia: vascular dementia, Alzheimer’s disease and senile dementia.

Methods
Study population
We defined the study population from the Rome Longitudinal Study, an administrative cohort [35, 36] that included all residents in Rome who filled out the questionnaire of the population census from 2001 on October 21st, 2001 and followed them using administrative data. The Rome Longitudinal Study included all subjects who had resided in Rome for at least 5 years and were not living in institutions (prisons, hospitals, or nursing homes) at the time of the census. For this study, we selected all subjects aged 65 years or older at inclusion and followed them until December 31st, 2013 or until 100 years of age, death, migration or hospitalization for dementia, whichever came first.

Individual information, recorded at the 2001 census, was available, including gender, age, educational level, occupational status, marital status, and place of birth. Residential history and vital status were available from the Municipal Register data.

Study outcomes
We used data from the Hospital Discharge Registry (HDR), included in the Regional Health Information System (HIS), which covers both public and private health
care providers and collects up to six diagnoses and procedure codes (ICD-9-CM) for each hospital discharge.

We used the HDR to identify dementia hospitalizations from October 21st, 2001 to December 31st, 2013. We selected from the HDR subjects hospitalized for the first time during the follow-up in the Lazio Region with a primary or a secondary diagnosis of Jakob-Creutzfeldt disease (ICD9-CM: 046.1), senile dementia (ICD9-CM: 290.0, 290.2, 290.3), presenile dementia (ICD9-CM: 290.1), vascular dementia (ICD9-CM: 290.4), persistent mental disorders due to conditions classified elsewhere (ICD9-CM: 294), Alzheimer’s disease (ICD9-CM: 331.0), Pick’s disease (ICD9-CM: 331.1), or Dementia with Lewy bodies (ICD9-CM: 331.82). We studied first dementia hospitalizations overall (including all the mentioned codes) and for subtypes: vascular dementia (ICD9-CM: 290.4), Alzheimer’s disease (ICD9-CM: 331.0), and senile dementia (ICD9-CM: 290.0, 290.2, 290.3), which were the most frequent dementia codes in discharge records. The codes for senile dementia are likely used for elderly when a more specific diagnosis is difficult to be determined.

To study the first hospitalization for dementia and dementia subtype, we excluded from the analyses the subjects hospitalized for dementia before the beginning of the follow-up (from January 1st, 1996 to October 21st, 2001).

Exposure assessment
To assess environmental exposure at the residential address at the time of inclusion, we used the Land Use Regression (LUR) models developed within the European Study of Cohorts for Air Pollution Effects (ESCAPE project) for the city of Rome. The pollutants of interest were particulate matter (size fraction < 10 μm: PM10, < 2.5 μm: PM2.5, soot (PM2.5 absorbance), and 2.5–10 μm: coarse PM), and nitrogen oxides (NOx and NO2) [37, 38]. The models’ R² values ranged from 71% (PM2.5) to 86% (NO2), and the cross-validated R² values ranged from 59% (PM10) to 79% (PM2.5 absorbance). Details on the models and measurement campaigns can be found elsewhere [37–40]. Briefly, particulate matter was measured in 20 sites, and nitrogen oxides were measured in 40 sites in three two-week periods during 2010. Measures were averaged using a continuous background monitoring site operating for the entire year in order to estimate an annual average measure of the concentration of pollutants at each site. To predict the concentration of pollutants, several traffic and land use variables were used. Following a strict protocol based on a multilinear regression model, an equation for each pollutant was identified. The produced equations were applied to estimate the pollutant concentration at each individual address.

To estimate summer (from May to September) daily ozone (8 h) exposure, we used the Flexible Air quality Regional Model (FARM), a chemical transport model. The FARM is a three-dimensional Eulerian model used to simulate the transport and multiphase chemistry of pollutants in the atmosphere. This model was applied over the city of Rome with a grid resolution of 1 x 1 km, using emission inventory data, modelled meteorology and measurements taken in 2005 [41].

Furthermore, as a proxy measure of exposure to traffic, we analysed the distance between residential addresses and the nearest high-traffic road (HTR; roads with > 10,000 vehicles per day) [36]. Distance (m) was measured using ArcGIS software.

Statistical analysis
We calculated standardized incidence rates for the first hospitalization for dementia using four age groups (65–74, 75–84, 85+) and the Italian population in 2008 as the standard population. We used the Cox proportional hazards models, with age as the time scale, to estimate the association between long-term air pollution exposure (PM10, coarse PM, PM2.5, PM2.5 absorbance, NO2, NOx, and summer O3) and first hospitalization for dementia. To explore the effects of air pollution on the subtypes of dementia, we conducted a separate analysis for the first hospitalization for each classification: vascular dementia, Alzheimer’s disease and senile dementia (a subject could have been classified as having more than one type).

We considered several variables as possible confounders or effect modifiers: age, sex, place of birth (Rome or other), marital status (married, single, separated/divorced or widowed), and educational level (primary school or less, junior high school, high school or university). We used a small area (census block, average 500 inhabitants) composite index of socioeconomic position (SEP, five levels: from very high to very low) that allowed us to better characterize residential deprivation [42]. We considered as potential confounders the hospital discharges occurred before the inclusion for diabetes, brain injuries and, since we did not have information on smoking habit, the discharges for chronic obstructive pulmonary disease (see Additional file 1 with ICD-9-CM codes for selection).

We stratified the baseline hazard function by sex, which was the only variable that did not satisfy the proportional-hazards assumption (tested by Schoenfeld’s residuals). Air pollutants were included as continuous variables. We expressed hazard ratios (HR) and relative 95% confidence intervals per fixed increases of each pollutant: 10 μg/m³ for PM10, NO2 and Summer O3, 5 μg/ m³ for PM2.5 and coarse PM, 20 μg/m³ for NOx and 1
unit \(10^{-5}/m\) for PM\(_{2.5}\) absorbance. We defined five categories of distance to an HTR: less than 50 m, 50–100 m, 101–200 m, 201–300 m, and more than 300 m from an HTR. In order to address possible confounding between pollutants, for the first hospitalization for dementia we performed two pollutants models, when the correlation was < 0.70 and the main analyses showed statistical significant results.

We evaluated a possible effect modification adding an interaction term between the exposures and the effect modifiers (sex, age, SEP, or education), and we performed the likelihood ratio test to compare the goodness of fit of the models with and without the interaction term.

To account for the possible bias due to deaths that occurred before dementia onset, we performed a competing risks analysis using the Fine and Grey method, where we considered death as a competing event [43]. Only study participants with no missing information from any of the exposures and confounders in the main model were included in analyses.

Finally, to explore possible misclassification, we performed additional sensitivity analyses. We selected narrower subgroups of cases. The first subgroup was composed by the first of at least two hospitalizations of the same subtype. The second subgroup included hospitalizations with only primary diagnosis of dementia and subtypes. To explore the possible misclassification of exposure we performed the analysis on subjects who did not change residence during the entire follow-up.

Analyses were performed using STATA13 (StataCorp. 2013. Stata Statistical Software: Release 13. College Station, TX: StataCorp LP).

**Results**

After the exclusion of prevalent cases of dementia (\(N = 4292\); 1%) and subjects with missing exposure information (\(N = 4417\); 1%), we selected 350,844 subjects.

Table 1 shows the characteristics of the study population at the beginning of the follow-up and first hospitalization for dementia. Our study population was composed of 145,994 men (42%) and 204,900 women (58%). The mean age at inclusion was 74.5 years (standard deviation (SD) 6.9). A proportion of 51% of the population had a primary school or less education, 58% were married, and 33% were born in Rome. During the follow-up (10.6 years), 21,548 subjects were hospitalized for the first time for dementia (7916 men and 13,632 women). The standardized hospitalization rates were higher in women, in those living without a partner, in less educated people and in subjects with a very low or low socioeconomic position.

Table 2 shows the characteristics of the first hospitalization for different types of dementia considered. We selected 7497 first time hospitalized people for vascular dementia (3083 men and 4414 women), 7669 for Alzheimer’s disease (2679 men and 4990 women) and 7833 for senile dementia (2654 men and 5179 women). The mean age at the baseline was approximately 76 years (SD 6) for subjects who developed Alzheimer’s disease, whereas it was 78 (SD 7) for subjects who developed vascular or senile dementia. The standardized hospitalization rate was 24 per 10,000 person-years for each types of dementia. The distribution of this rate was similar in all types of dementia by place of birth, educational level and socio-economic position. Higher rates were observed in widowed and single subjects for vascular and senile dementia and in married and widowed subjects for Alzheimer’s disease.

Table 3 shows the average exposure levels of the population (mean (SD and interquartile range)) at inclusion, which were 36.9 \(\mu\)g/m\(^3\) (5.3 and 4.9) for PM\(_{10}\), 17.4 \(\mu\)g/m\(^3\) (3.4 and 1.8) for coarse PM, 19.7 \(\mu\)g/m\(^3\) (2.0 and 3.4) for PM\(_{2.5}\), 2.76 \(10^{-5}/m\) (0.48 and 0.33) for PM\(_{2.5}\) absorbance, 43.9 \(\mu\)g/m\(^3\) (10.3 and 12.7) for NO\(_x\), 87.4 \(\mu\)g/m\(^3\) (24.1 and 32.6) for NO\(_x\), and 97.6 \(\mu\)g/m\(^3\) (5.9 and 4.6) for O\(_3\).

The average distance to an HTR was 203 m (198 and 201). We found a relatively high correlation between particulate matter and nitrogen oxides (ranging from 0.52 [NO\(_x\)-PM\(_{2.5}\) absorbance] to 0.71 [coarse PM - NO\(_x\)]), likely due to similar emission sources, while the correlation was lower between O\(_3\) and other pollutants (ranging from \(-0.12\) [NO\(_x\)-O\(_3\)] and \(-0.02\) [PM2.5 - O\(_3\)]) (see Additional file 2).

Table 4 shows the association (adjusted Hazard ratios, HRs) between long-term exposure to air pollution and first hospitalization for dementia, vascular dementia, Alzheimer’s disease and senile dementia. Unadjusted HRs are presented in Additional file 3. Overall, we found a negative association between long-term exposure to NO\(_2\) and dementia (HR = 0.98, 95% CI: 0.96, 0.99 per 10 \(\mu\)g/m\(^3\) increases) and a positive association between exposure to O\(_3\) and dementia (HR = 1.06, 95% CI: 1.03, 1.08 per 10 \(\mu\)g/m\(^3\) increases). The associations of dementia with coarse PM and NO\(_x\) exposures were negative and positive, respectively (HR = 0.98, 95% CI: 0.96, 1.00 per an increase of 5 \(\mu\)g/m\(^3\) of coarse PM and HR = 1.01, 95% CI: 1.00, 1.02 per an increase of 20 \(\mu\)g/m\(^3\) of NO\(_x\)). There was no evidence of associations between hospitalization for dementia and exposure to the other pollutants nor to distance to HTR.

We found an overall statistically significant positive association between first hospitalization for vascular dementia and each pollutant (with the exception of O\(_3\)) and distance to HTR. In contrast, for Alzheimer’s disease, opposite results emerged. We found a negative
Table 1 Baseline characteristics of the study population and first hospitalization for dementia

| Characteristics                  | Population | First hospitalization for dementia |
|----------------------------------|------------|------------------------------------|
|                                  | N          | %                                  | N          | %       | SHR* (10,000 P-Y) |
| Total                            | 350,844    | 100                                | 21,548     | 100     | 88       |
| **Age class**                    |            |                                    |            |         |          |
| 65–69                            | 110,334    | 31.5                               | 3214       | 14.9    |          |
| 70–74                            | 95,602     | 27.3                               | 5367       | 24.9    |          |
| 75–79                            | 73,421     | 20.9                               | 6332       | 29.4    |          |
| 80–84                            | 38,620     | 11.0                               | 3883       | 18.0    |          |
| 85–89                            | 23,299     | 6.6                                | 2116       | 9.8     |          |
| 90+                              | 9568       | 2.7                                | 636        | 3.0     |          |
| **Age mean (SD)**                | 74.5 (6.8) |                                    | 77.1 (6.5) |         |          |
| **Gender**                       |            |                                    |            |         |          |
| Men                              | 145,944    | 41.6                               | 7916       | 36.7    | 85       |
| Women                            | 204,900    | 58.4                               | 13,632     | 63.3    | 90       |
| **Place of Birth**               |            |                                    |            |         |          |
| Rome                             | 114,112    | 32.5                               | 6685       | 31.0    | 92       |
| Other                            | 236,732    | 67.5                               | 14,863     | 69.0    | 87       |
| **Marital Status**               |            |                                    |            |         |          |
| Married                          | 202,004    | 57.6                               | 10,787     | 50.1    | 83       |
| Single                           | 24,626     | 7.0                                | 1585       | 7.4     | 91       |
| Separated                        | 12,043     | 3.4                                | 642        | 3.0     | 97       |
| Widowed                          | 112,171    | 32.0                               | 8534       | 39.6    | 98       |
| **Education**                    |            |                                    |            |         |          |
| Primary School or less           | 178,062    | 50.8                               | 12,423     | 57.7    | 100      |
| Junior high School               | 72,823     | 20.8                               | 4146       | 19.2    | 85       |
| High School                      | 60,861     | 17.4                               | 3044       | 14.1    | 69       |
| University                       | 39,098     | 11.1                               | 1935       | 9.0     | 72       |
| **Area-based SEP**               |            |                                    |            |         |          |
| Very High                        | 75,772     | 21.6                               | 4271       | 19.8    | 78       |
| High                             | 75,595     | 21.6                               | 4556       | 21.1    | 84       |
| Medium                           | 72,325     | 20.6                               | 4459       | 20.7    | 89       |
| Low                              | 68,080     | 19.4                               | 4321       | 20.1    | 96       |
| Very Low                         | 59,072     | 16.8                               | 3941       | 18.3    | 101      |
| **CVD prevalent**                |            |                                    |            |         |          |
| Yes                              | 89,054     | 25.4                               | 6650       | 30.9    | 113      |
| No                               | 261,790    | 74.6                               | 14,898     | 69.1    | 80       |
| **Stroke prevalent**             |            |                                    |            |         |          |
| Yes                              | 6560       | 1.9                                | 638        | 3.0     | 168      |
| No                               | 344,284    | 98.1                               | 20,910     | 97.0    | 87       |
| **COPD**                         |            |                                    |            |         |          |
| Yes                              | 19,472     | 94.5                               | 1402       | 6.5     | 123      |
| No                               | 331,372    | 5.6                                | 20,146     | 93.5    | 87       |
| **Brain injury**                 |            |                                    |            |         |          |
| Yes                              | 2257       | 0.6                                | 194        | 0.9     | 121      |
| No                               | 348,587    | 99.4                               | 21,354     | 99.1    | 88       |
strong association between air pollution exposure and vascular dementia, and not clear results for Alzheimer’s disease and senile dementia. The results were confirmed by sensitivity analyses performed on the subgroup of subjects with narrower case definitions and in analyses including death as the competing event.

Only recently, seven studies have explored the role of air pollution exposure on dementia (see Additional file 8). Six were cohort studies, including five studies on disease incidence and one on hospital admissions in the United States [28–31, 34, 44]. Our results regarding the relationship between residential exposure to air pollution and hospitalization for dementia are inconsistent with previous reports [28, 29, 34]. This could depend mainly by the different outcomes chosen; most of the previous studies analysed the incidence of the disease as the outcome, whereas we studied the first hospitalization. The access to hospital does not represent the onset of neurodegeneration; it partly represents the severity of neurocognitive disorders, and partly the severity of important comorbid conditions, that require a hospital admission. Our findings are in contrast with the only study on hospital admissions for dementia [44]. We found null results for particulate matter, while the hazard ratio reported in the US was 1.08 (1.05–1.11) per 1 μg/m³ increase in PM_{2.5} [44]. However, in their study, Kioumourtzoglou and colleagues analysed data from 50 cities and found some geographical variability in their results [44].

To our knowledge, only a Canadian study investigated the association of exposure to O₃ on overall dementia and showed an absence of association [34], while in our data we found a 6% higher hospitalization rate per 10 μg/m³ in summer ozone exposure.

The findings on vascular dementia, with a strong association with all pollutants (except O₃ but including traffic exposure) are comparable to those reported in the literature. A case-control study in Taiwan showed a strong positive significant association with PM_{10} [32], and a Swedish cohort study including 1806 adults
| Characteristics | Vascular dementia | Alzheimer's disease | Senile dementia |
|-----------------|------------------|---------------------|-----------------|
|                 | First hospitalization SHR | First hospitalization SHR | First hospitalization SHR |
|                 | N % (10,000 P-Y) | N % (10,000 P-Y) | N % (10,000 P-Y) |
| Total           | 7497 100 32     | 7669 100 28        | 7833 100 32     |
| Age             |                 |                     |                 |
| 65–69           | 983 13.1        | 1347 17.6           | 1033 13.2       |
| 70–74           | 1721 23.0       | 2244 29.3           | 1806 23.1       |
| 75–79           | 2185 29.1       | 2319 30.2           | 2295 29.3       |
| 80–84           | 1507 20.1       | 1182 15.4           | 1490 19.0       |
| 85–89           | 837 11.2        | 493 6.4             | 907 11.6        |
| 90+             | 264 3.5         | 84 1.1              | 302 3.9         |
| Age mean (SD)   | 77.7 (6.5)      | 75.8 (5.8)          | 77.7 (6.6)      |
| Gender          |                 |                     |                 |
| Men             | 3083 41.1       | 2679 34.9           | 2654 33.9       |
| Women           | 4414 58.9       | 4990 65.1           | 5179 66.1       |
| Place of Birth  |                 |                     |                 |
| Rome            | 2326 31.0       | 2336 30.5           | 2453 31.3       |
| Other           | 5171 69.0       | 5333 69.5           | 5380 68.7       |
| Marital Status  |                 |                     |                 |
| Married         | 3690 49.2       | 4200 54.8           | 3629 46.3       |
| Single          | 603 8.0         | 416 5.4             | 649 8.3         |
| Separated       | 227 3.0         | 206 2.7             | 265 3.4         |
| Widowed         | 2977 39.7       | 2847 37.1           | 3290 42         |
| Education       |                 |                     |                 |
| Primary School  | 4445 59.3       | 4445 58.0           | 4475 57.1       |
| Junior high School | 1452 19.4     | 1483 19.3           | 1463 18.7       |
| High School     | 970 12.9        | 1087 14.2           | 1193 15.2       |
| University      | 630 8.4         | 654 8.5             | 702 9           |
| Area-based SEP  |                 |                     |                 |
| Very High       | 1355 18.1       | 1510 19.7           | 1605 20.5       |
| High            | 1579 21.0       | 1605 20.9           | 1714 21.9       |
| Medium          | 1639 21.9       | 1537 20.0           | 1578 20.1       |
| Low             | 1552 20.7       | 1565 20.4           | 1512 19.3       |
| Very Low        | 1372 18.3       | 1452 18.9           | 1424 18.2       |
| CVD prevalent   |                 |                     |                 |
| Yes             | 2722 36.3       | 2046 26.7           | 2354 30.1       |
| No              | 4775 63.7       | 5623 73.3           | 5479 69.9       |
| Stroke prevalent|                 |                     |                 |
| Yes             | 354 4.7         | 115 1.5             | 193 2.5         |
| No              | 7143 95.3       | 7554 98.5           | 7640 97.5       |
| COPD            |                 |                     |                 |
| Yes             | 583 7.8         | 392 5.1             | 526 6.7         |
| No              | 6914 92.2       | 7277 94.9           | 7307 93.3       |
| Brain injury    |                 |                     |                 |
| Yes             | 75 1.0          | 62 0.8              | 71 0.9          |
| No              | 4647 99.0       | 638 9.2             | 729 99.1        |

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showed a positive effect of NOx exposure [28]. In contrast to Wu and colleagues, we did not find any association between ozone exposure and vascular dementia, but we found higher hospitalization risks with the increase of all traffic-related pollutants (PM$_{2.5}$ absorbance, NOx, NO$_2$ and decreasing distance to high-traffic roads). Vascular dementia is characterized by a different pathogenesis in respect to other dementias, such as Alzheimer’s disease. Vascular damages triggered by large vessel atherosclerosis and small vessel arteriosclerosis cause cortical and subcortical infarcts, sub-infarct ischaemic lesions and large and small cerebral haemorrhages that are responsible for the onset of vascular dementia [45]. Moreover, it is well established that long-term exposure to air pollution is linked to atherosclerosis and vascular diseases [46]. Despite the fact that vascular dementia patients share similar neurological symptoms with subjects affected by other types of dementia, they present different subclinical conditions as described above. Those different pathogenesis mechanisms could explain our results. In fact, patients affected by vascular dementia should receive different treatment, provided only by hospitals, compared to Alzheimer’s patients who are usually treated at home or in nursing facilities (as described in detail below).

We found statistically significant negative associations between Alzheimer’s disease and all pollutants, with the exception of O$_3$. These results contrast with previous reports: Kioumourtzoglou et al. reported a HR = 1.15 (1.11, 1.19) per 1 $\mu$g/m$^3$ increase in PM$_{2.5}$, Oudin et al. found a HR = 1.02 (0.92, 1.14) per 10 $\mu$g/m$^3$ increase in NOx, and the case control study showed an association between both ozone and PM$_{10}$ and Alzheimer’s disease [28, 44]. However, independently of previous research, our results have important limitations. In contrast to other cohort studies on the incidence of dementia, we analysed hospital admissions as the outcome, which do not reflect the onset of the disease, nor the gravity, but indicates access to services. Alzheimer’s disease and dementia are not conditions that systematically require hospital admissions. In Italy, they are usually treated at home, with a large burden on familial components, and at a later stage in nursing homes.

To our knowledge, there are no other studies that have investigated the possible role of air pollution in senile dementia. Similar to Alzheimer’s disease, we found...
negative associations with all traffic-related pollutants (soot, NO₂, NOx) and closer distances to high traffic roads. One possible explanation could rely on the same hypothesis of the Alzheimer’s results. Despite the fact that some mechanisms of the onset of senile dementia are still unknown, these diseases share the same risk factors and subjects could present similar clinical conditions. We found a strong association between long-term O₃ exposure and hospitalizations for senile dementia, with a 20% higher risk of being hospitalized per 10 μg/m³ increase in summer ozone. Socioeconomic position was an effect modifier in the association between ozone and hospital admissions for senile dementia, with a higher risk in disadvantaged groups compared to subjects with high socioeconomic levels. The differences we found between socioeconomic levels can be attributed to behavioural changes arising from adaptive strategies [47].

During the last years, several epidemiological and toxicological studies highlighted the potential impact of air pollution on the central nervous system. The pathways involved in brain responses are those identified for responses in the circulatory system, as stated by Block and colleagues (2012): “(1) the release of inflammatory and oxidative stress mediators by the lungs into the systemic circulation; (2) interactions between pollutants and pulmonary neuronal afferents resulting in autonomic imbalance; and (3) direct translocation of particle constituents or particles from the respiratory tract into the systemic circulation” [25]. The role of particulate matter and nitrogen oxides in cardiovascular disease is well-established [48–50], hence the association we found between air pollution exposure and vascular dementia is not surprising. The evidence of long-term exposure to ozone has been less studied compared to other pollutants. However, ozone activates pro-inflammatory genes [51] Both acute and long-term impacts of ozone on mortality have been reported in humans [52, 53], as the adverse neurobehavioral effects in adults, reducing coding ability, attention and short-term memory, characteristics common to all types of dementia [54].

This is the largest population-based cohort study in Europe investigating the role of long-term exposure to air pollution in dementia and to our knowledge, no other studies have investigated senile dementia in particular. The exposure was estimated at residential addresses, with the exception of ozone where a 1 km² area was used for all subjects, and several individuals’ information was available. The study size allowed us to carry out analysis by type of dementia, whereas in the literature, studies generally focus either on overall dementia or on Alzheimer’s disease.

The main limitation of this analysis is the use of dementia hospitalizations as outcome, with a possible misclassification of cases. Generally, the identification of dementia cases is based on different sources ranging from hospital discharge registry to drug registry or neurological reports. In our study, data from drug registries were not available for the entire period of interest, thus we limited case collection to only hospital discharge registries. The possible misclassification is due to the fact that subjects who are hospitalized for dementia are

| Characteristics | Dementia | Vascular dementia | Alzheimer’s disease | Senile dementia |
|-----------------|----------|-------------------|--------------------|-----------------|
| N=21,548        | N=7500   | N=7671            | N=7835             |                 |
| PM₁₀ (10 μg/m³) | 1.00     | 1.06              | 0.95               | 0.98            |
| Coarse PM (5 μg/m³) | 0.98     | 1.06              | 0.91               | 0.97            |
| PM₂₅ (5 μg/m³) | 0.99     | 1.07              | 0.91               | 0.98            |
| PM₂₅ abs (10⁻³/m) | 1.00     | 1.15              | 0.91               | 0.93            |
| NO₂ (10 μg/m³) | 0.97     | 1.05              | 0.91               | 0.96            |
| NOx (20 μg/m³) | 0.97     | 1.05              | 0.91               | 0.96            |
| O₃ (10μg/m³)   | 0.97     | 1.05              | 0.91               | 0.96            |

Distance to HTR (m)

- < 50
  - 1.01  | 0.97  | 1.06  | 1.17  | 1.10  | 1.24  | 0.97  | 0.90  | 1.04  | 0.90  | 0.83  | 0.97  |
- 50–100
  - 0.98  | 0.93  | 1.02  | 1.11  | 1.03  | 1.19  | 0.96  | 0.89  | 1.04  | 0.88  | 0.80  | 0.95  |
- 101–200
  - 0.99  | 0.95  | 1.03  | 1.10  | 1.03  | 1.17  | 0.99  | 0.92  | 1.05  | 0.87  | 0.80  | 0.93  |
- 201–300
  - 1.00  | 0.95  | 1.04  | 1.02  | 0.94  | 1.09  | 1.00  | 0.93  | 1.08  | 0.94  | 0.87  | 1.02  |
- > 300
  - 1.00  | ref.  | 1.00  | ref.  | 1.00  | ref.  | 1.00  | ref.  |

p-trend b 0.827 0.001 0.206 0.001

a Models adjusted for age, education, place of birth, marital status, area-based socioeconomic position with baseline hazard function stratified by sex
b Wald test across categories of exposure
Conclusions

We found a positive association between residential exposure to NOx and ozone with first hospitalization for dementia in Rome. Exposures to particulate matter and nitrogen oxides were associated with hospitalizations for vascular dementia. We could not find a reasonable explanation for the negative associations we found in Alzheimer’s disease, and the results need to be interpreted cautiously, because on one side residual confounding of unmeasured lifestyle risk factors could play an important role, and on the other side using hospitalizations to identify dementia cases could lead to possible misclassification of cases.

Air pollution is pervasive, global, and harmful for health. Further efforts to reduce exposure in big cities are needed and have also the potential for beneficial effects on neurological health in elderly.

Additional files

- **Additional file 1:** ICD9-CM codes for comorbid conditions. (DOCX 13 kb)
- **Additional file 2:** Pearson correlation coefficients of exposure to air pollutants. (DOCX 14 kb)
- **Additional file 3:** Association between long-term exposure to air pollution and dementia, vascular dementia, Alzheimer disease and senile dementia. Rome 2001–2013. (DOCX 16 kb)
- **Additional file 4:** Association between long-term exposure to air pollution and first hospitalization for dementia. Sensitivity analyses, Rome 2001–2013. (DOCX 16 kb)
- **Additional file 5:** Association between long-term exposure to air pollution and first hospitalization for vascular dementia. Sensitivity analyses, Rome 2001–2013. (DOCX 16 kb)
- **Additional file 6:** Association between long-term exposure to air pollution and first hospitalization for Alzheimer’s disease. Sensitivity analyses, Rome 2001–2013. (DOCX 16 kb)
- **Additional file 7:** Association between long-term exposure to air pollution and first hospitalization for senile dementia. Sensitivity analyses, Rome 2001–2013. (DOCX 20 kb)
- **Additional file 8:** Previous studies on Dementia disease (overall dementia, Alzheimer’s disease and vascular dementia) and air pollution. (DOCX 16 kb)

Authors’ contributions

FC, GC, FF conceived the idea and designed the study in collaboration with MR. FC and MR were responsible for the acquisition of the data. CG provided data on ozone exposure. FC was responsible for undertaking the data analysis and producing the tables and graphs, together with MR and GC. CG, MD, PM, FF provided input into the data analysis. All authors contributed to the interpretation of the results. The manuscript was drafted by FC, GC and MR and then shared with all authors for critical revision. All authors read and approved the final manuscript.

Funding

None

Availability of data and materials

Not applicable

Ethics approval and consent to participate

Not applicable
Consent for publication
Not applicable

Competing interests
The authors declare that they have no competing interests

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Received: 28 March 2019 Accepted: 1 August 2019

Published online: 09 August 2019

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