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ORIGINAL PAPER

Meteorological factors, air pollutants, and emergency department visits for otitis media: a time series study

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Abstract

Otitis media (OM) is a very common disease in children, which results in a significant economic burden to the healthcare system for hospital-based outpatient departments, emergency departments (EDs), unscheduled medical examinations, and antibiotic prescriptions. The aim of this retrospective observational study is to investigate the association between climate variables, air pollutants, and OM visits observed in the 2007–2010 period at the ED of Cuneo, Italy. Measures of meteorological parameters (temperature, humidity, atmospheric pressure, wind) and outdoor air pollutants (particulate matter, ozone, nitrous dioxide) were analyzed at two statistical stages and in several specific steps (crude and adjusted models) according to Poisson's regression. Response variables included daily examinations for age groups 0–3, 0–6, and 0–18. Control variables included upper respiratory infections (URI), flu (FLU), and several calendar factors. A statistical procedure was implemented to capture any delayed effects. Results show a moderate association for temperature (T), age 0–3, and 0–6 with $P < 0.05$, as well as nitrous dioxide (NO_2) with $P < 0.005$ at age 0–18. Results of subsequent models point out to URI as an important control variable. No statistical association was observed for other pollutants and meteorological variables. The dose–response models (DLNM—final stage) implemented separately on a daily and hourly basis point out to an association between temperature (daily model) and RR 1.44 at age 0–3, CI 1.11–1.88 (lag time 0–1 days) and RR 1.43, CI 1.05–1.94 (lag time 0–3 days). The hourly model confirms a specific dose–response effect for T with RR 1.20, CI 1.04–1.38 (lag time range from 0 to 11 to 0–15 h) and for NO_2 with RR 1.03, CI 1.01–1.05 (lag time range from 0 to 8 to 0–15 h). These results support the hypothesis that the clinical context of URI may be an important risk factor in the onset of OM diagnosed at ED level. The study highlights the relevance of URI as a control variable to be included in the statistical analysis in association with meteorological factors and air pollutants. The study also points out to a moderate association of OM with low temperatures and NO_2, with specific risk factors for this variable early in life. Further studies are needed to confirm these findings, particularly with respect to air pollutants in larger urban environments.

Keywords Otitis media · Biometeorology · Air pollution · Upper respiratory tract infections · Emergency department database · Epidemiology

Introduction

OM is a very common disease in children, which results into a significant economic burden to the healthcare system. Its prevalence is highest in the first 3 years of life, particularly with acute episodes (AOM) (Hoffman et al. 2013; National Center for Health Statistics, Centers for Disease Control and Prevention 2011; Bluestone and Klein 2001; Marchisio et al. 2012). The onset of an inflammatory disease of the middle ear is connected with genetic, anatomical, and environmental factors (Rovers et al. 2004; Hoffman et al. 2013). Studies were carried out to identify potential associations between OM and

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sociodemographic, ethnic, and genetic susceptibility as risk factors (Casselbrant et al. 2009; McCormick et al. 2011; Vakharia et al. 2010; Lasisi et al. 2007). An increased risk of middle ear disease was observed in children with craniofacial anomalies, including cleft palate (Sheahan et al. 2003). Studies were focused, in particular, on upper respiratory infections as the most common comorbidities, generally deemed to pose the highest risk of OM, particularly in the acute form. Several studies confirmed the association between URI and the onset of OM (Patel et al. 2007; Kalu et al. 2011), also suggesting a significant statistical association. Other studies point out to a seasonal trend of OM connected with cold-like illnesses, in most cases due to viral upper respiratory infections. There is additional scientific evidence of the important role of respiratory viruses in the development of OM, demonstrating a significantly high risk following influenza virus infections (Stockmann et al. 2013; Fleming et al. 2016). Several studies stressed the role of anti-flu vaccines in reducing the onset of OM in children (Block et al. 2011). These works on cold-like illnesses generally consider OM episodes in children as complications of URI, with a 40 to 70% recorded incidence (Winther et al. 2007; Chonmaitree et al. 2008; Mandel et al. 2008).

In recent decades, the influence of meteorological and climate factors on different aspects of human disease developed into solid and progressive scientific evidence. A broad range of documented adverse health outcomes were observed after short-term and long-term exposure to several climate factors (Michelozzi et al. 2009; Xu et al. 2014; Lin et al. 2009; Barnett et al. 2012). In particular, a number of studies investigated a potential relationship between respiratory infections and exposure to low temperatures. The number of general practitioner examinations (Athens) for respiratory infections was investigated (Nastos and Matzarakis 2006), with cold temperature and absolute humidity as risk factors. One study (Mäkinen et al. 2009) supports the hypothesis that low temperature and low humidity may be associated with an increased prevalence of respiratory tract infections. A potential role of relative humidity is further confirmed by a study (Falagas et al. 2008) demonstrating a positive correlation between meteorological variables and the prevalence of upper and lower respiratory infections ($P = <0.001$). The same work highlights a negative correlation for temperature ($P = <0.001$).

While a limited number of studies were carried out to investigate the possible associations between meteorological factors and OM, no specific studies seem to have considered RH as a risk factor for the prevalence of OM. The rates of hospitalization for OM (Sprem and Branica 1993) were shown to increase as temperature decreases. By contrast, average annual temperature changes (Miller et al. 2012) do not seem to influence the prevalence of OM or respiratory allergy.

In addition to meteorological and climate factors, indoor and outdoor environmental pollution factors are also important. These were the object of recent scientific research carried out through the epidemiological analysis of the risk of respiratory disease and of the prevalence of OM in the population (Brauer et al. 2006; Zemek et al. 2010; MacIntyre et al. 2011; Hoffman et al. 2013; Darrow et al. 2014); the effects of passive tobacco smoke on breast-fed infants exposed to maternal smoking were demonstrated by a study (Håberg et al. 2011). A study conducted on Greenland children (Koch et al. 2011) shows that preventive measures in case of attendance of childcare centers and exposure to passive smoking may reduce the frequency of chronic suppurative OM. By contrast, this finding is still not unanimously confirmed by the scientific literature, which shows no statistically significant association between passive smoking and the onset of OM (Salah et al. 2013). This study also confirms URI as a major risk factor for the onset of OM.

Lots of studies were carried out both on mortality and morbidity in view of identifying statistically significant associations between air pollutants and an increased risk of disease onset. Consistent historical multicenter studies, such as NMMAPS (USA) I and II (Samet et al. 2000), APHEA (Europe) I and II (Katsouyanni et al. 2001), and MISAI–II and Epiair 2 (Italy) (Biggeri et al. 2001; Scarinzi et al. 2013), demonstrated that the cardiovascular and respiratory districts are more sensitive to short-term air pollutants, including particulate matter (PM_{10}), carbon monoxide (CO), nitrous dioxide (NO_2), and ozone (O_3). Scanty information is available on potential associations between several climate covariates and/or different air pollutants in the onset of OM. A specific review indicates that exposure to passive tobacco smoke is a major risk factor; additional and specific effects of exposure to air pollutants are uncertain (Heinrich and Raghuyamshi 2004). However, recent studies observed a statistically significant association with certain species of air pollutants (Brauer et al. 2006; Zemek et al. 2010). Another work (Macintyre et al. 2011) analyzed the relationship between indoor air pollutants and the onset of OM in children, with statistical evidence of NO_2 and CO as risk factors. Further confirmation comes from a study carried out in the USA on CO, NO_2, SO_2, and PM_{10} significantly associated with recurrent ear infections in children (Bhattacharyya and Shapiro 2010). Traffic-related air pollution was investigated as a risk factor for several respiratory infections in early childhood (Macintyre et al. 2014); this study shows no effect for most air pollutants, except NO_2 with OR = 1.09; 95% CI 1.02, 1.16 per 10 $\mu g/m^3$ increase in NO_2. An Italian birth cohort study on exposure to air pollution reported an OR = 1.08, 95 CI%, 0.89 to 1.32 risk of OM for NO_2 (Ranzi et al. 2014). With specific reference to O_3, several recent studies explored the interaction between ozone and temperature on human health. There is scientific consensus on the impact of extreme heat on mortality and on a potential specific combined role of O_3 (heat–ozone–mortality relationship) (Ren et al. 2008; Colleen et al.

2012). Research carried out on respiratory illnesses, ear infections, eczema, and early life exposure in infants identified an association between air pollutants and the diseases under study, however without identifying a specific age group as being at risk (Aguilera et al. 2013). As to the importance of URI as a factor for comorbidity in OM, reference is made to the study which points out to a higher number of ED visits for URI following exposure to traffic pollutants and ozone in the first 4 years of age (Darrow et al. 2014).

The aim of this work is to test the hypothesis that the ED visits for OM performed at the S. Croce and Carle Hospital of Cuneo may be influenced by climate and air pollutant covariates, with URI, FLU, and calendar factors as control variables, in a specific geographic region of the Cuneo Province.

ED visit database

The ED visits database was released by the S. Croce and Carle Hospital of Cuneo over the years 2007–2010. The ED database includes a numeric code for each medical record; age; gender; year, day, hour, and minute of access; municipality of residence; and hospital discharge mode (sent back home, refused admission, removed, or hospitalized). Diagnoses were coded according to the ICD classification-ninth revision. The symptoms reported by the patients and the triage code of access (white, green, yellow, red) are stated in specific fields of clinical interest. The first field contains the diagnosis and the corresponding ICD-9 code, described as DIA-1; there follows five more fields (from DIA-2 to DIA-6), where any subsequent ICD-9 reclassifications are indicated. Two more text fields contain a description of the physical examination and the patient's medical history, with optional distinctions among different subtypes of OM (unilateral, bilateral, with or without effusion). Additional clinical data available for each patient include maximum and minimum pressure, respiratory rate, inhaled oxygen fraction, tympanic temperature, and oximetry.

Climate and air pollutant databases

Three specific climate and air pollutant databases were used:

(a) The database containing the climate time series of Cuneo (Collana di Studi Climatologici in Piemonte 1998), with thermometric time series from 1951 to 1986 and rainfall observations from 1913 to 1986. Data is calculated as a monthly average.

(b) The climate databases (from 2004 to 2015) of five meteorological variables: temperature (*T*), relative humidity (RH), atmospheric pressure (BAR), maximum daily gust of wind (*W*), and rainfalls. The weather stations selected for monitoring include Cuneo Camera di Commercio (44° 23′ 16″ N, 7° 32′ 50″ E, 550 m a.s.l.) for BAR, *W*, and rainfalls and Cuneo Cascina Vecchia (44° 22′ 14″ N, 7° 31′ 39″ E; 575 m a.s.l.) for *T* and RH, as well as stations located in different cities within a short distance, namely Bra (44° 42′ 08″ N, 7° 51′ 09″ E, 285 m), Alba (44° 42′ 22″ N, 8° 01′ 43″ E, 164 m), Fossano (44° 32′ 23″ N, 7° 47′ 18″, 403 m), and Boves (44° 20′ 10″ N, 7° 33′ 47″ E, 560 m).

(c) Air pollutant variables from 2003 to 2016: PM_{10}, sampled according to UNI EN 12341. The reference method is based on the 24-h collection of the PM_{10} fraction of ambient particulate matter on a filter, as well as on gravimetric mass determination: NO_2 (μg/m^3—hourly observations), O_3 (μg/m^3—hourly observations), and CO (mg/m^3—hourly observations).

The selected stations include Cuneo-Alpini (44° 22′ 54″, 7° 32′ 17″, 551 m), Alba-Tanaro (44° 42′ 13″, 8° 01′ 59″, 164 m), Bra-Madonna dei Fiori (44° 42′ 22″, 7° 50′ 35″, 283 m), Borgo San Dalmazzo-Giovanni XXIII (44° 20′ 17″ N, 7° 29′ 38″ E, 631 m), and Saliceto-Moizo (44° 24′ 49″ N, 8° 10′ 03″ E, 388 m).

The climate and air pollutant databases were released by the Regional Environmental Protection Agency of Piedmont. Each variable is recorded based on hourly observations, except PM_{10} (daily observations).

The geographic area under study

The geographic area under study borders with southeast France to the west (Departments of Hautes-Alpes, Alpes de Haute-Provence, and Alpes-Maritimes, in the region Provence-Alpes-Côte d'Azur), the Turin province to the north, the Asti Province to the east, and Liguria (Imperia and Savona Provinces) to the south. With a 6903-km^2 surface, it is the third largest province in Italy. According to data as at January 01, 2015, the number of residents is about 600,000, with a density of 63 inhabitants/km^2. It includes 250 municipalities with an average altitude of 558,112 m. Cuneo has 56,141 inhabitants, plus 64,356 in the nine municipalities bordering with the city, for a total of 120,497 inhabitants.

According to the classification system developed by W. Koeppen, from the climate point of view, the Cuneo Province, characterized by hills and high plains, is located in the mesothermal C band (mild mid-latitude climate). The geographic context of the province and the specific area under study are shown in two maps (Figs. 1 and 2). Figure 2 highlights the specific portion of the geographic region under study. In particular, the yellow line marks the borders of the province; the red line indicates isoaltimetry, with an altitude ≥1000 m in accordance with the exclusion criteria that follow (point f); the blue line identifies the area under study within which most EDs are located (>90%), and the white line shows the borders of the urban belt of Cuneo. The study area is generally characterized by a quite homogeneous hilly plateau. The calculated geodetic distances from Cuneo to the other weather and air pollutant stations are as follows: Alba 51.8 km, Bra 41.8 km, Fossano 22.3 km, and Boves 7.2 km

Fig. 1 Geographical contest of Cuneo and its province at the national scale

(located within the urban belt of Cuneo); Borgo San Dalmazzo 8.5 km (air pollutants only); and Saliceto 49.6 km. The average distance among the reference stations is 30.7 km (climate) and 27.9 km (air pollutants). Altitude ranges from 164 to 631 m for all the stations, with an average of 433 m.

Ethics

The ED visit database is fully anonymized according to the privacy code. It is a completely de-identified data set that, as such, was not subject to the approval of the ethics committee. No patient contact was made, and patients could not be traced.

Patient inclusion/exclusion criteria and URI inclusion as a control variable

Patients aged 0 to 18 were selected according to the following criteria:

Inclusion criteria:

(a) ICD-9 codes 382.9, 381.00, 381.01, 381.02, 382.00, 383.00 (DIA-1—first diagnosis): fully included in the study.

(b) ICD-9 codes 382.9, 381.00, 381.01, 381.02, 382.00 (DIA-2—second diagnosis): inclusion confirmed based on medical history and physical examination, with symptoms or clinically related diseases observed at DIA-1.

(c) ICD-9384.20: tympanic perforation at DIA-1, only if associated with OM at DIA-2 or if diagnosis is confirmed by clear signs of acute suppurative OM upon the examination.

Exclusion criteria:

(a) ICD-9 codes 382.9, 381.00, 381.01, 381.02, 382.00 at DIA-2, with symptoms or diseases observed at DIA-1 not related to the clinical group under study, of greater importance and clearly at the origin of the ED visits (diagnosis, medical history, and examination cross-data).

(b) OM patients at second ED visit within 5 days from first.

(c) ICD-9 code 384.20: (tympanic perforation) at DIA-1 without an associated diagnosis of OM, non-specified otoscopic observation of OM, barotrauma, or other traumatic factors described in medical history.

(d) Patients with an impaired immune system, malformations (cleft palate), or neoplastic rhino-pharyngeal diseases.

(e) Non-residents and all patients whose municipality of residence does not appear in the corresponding ED database fields.

(f) People living in municipalities at an altitude >1000 m, for obvious differences in terms of mean air pollutant concentrations and climatic characteristics of the geographic area.

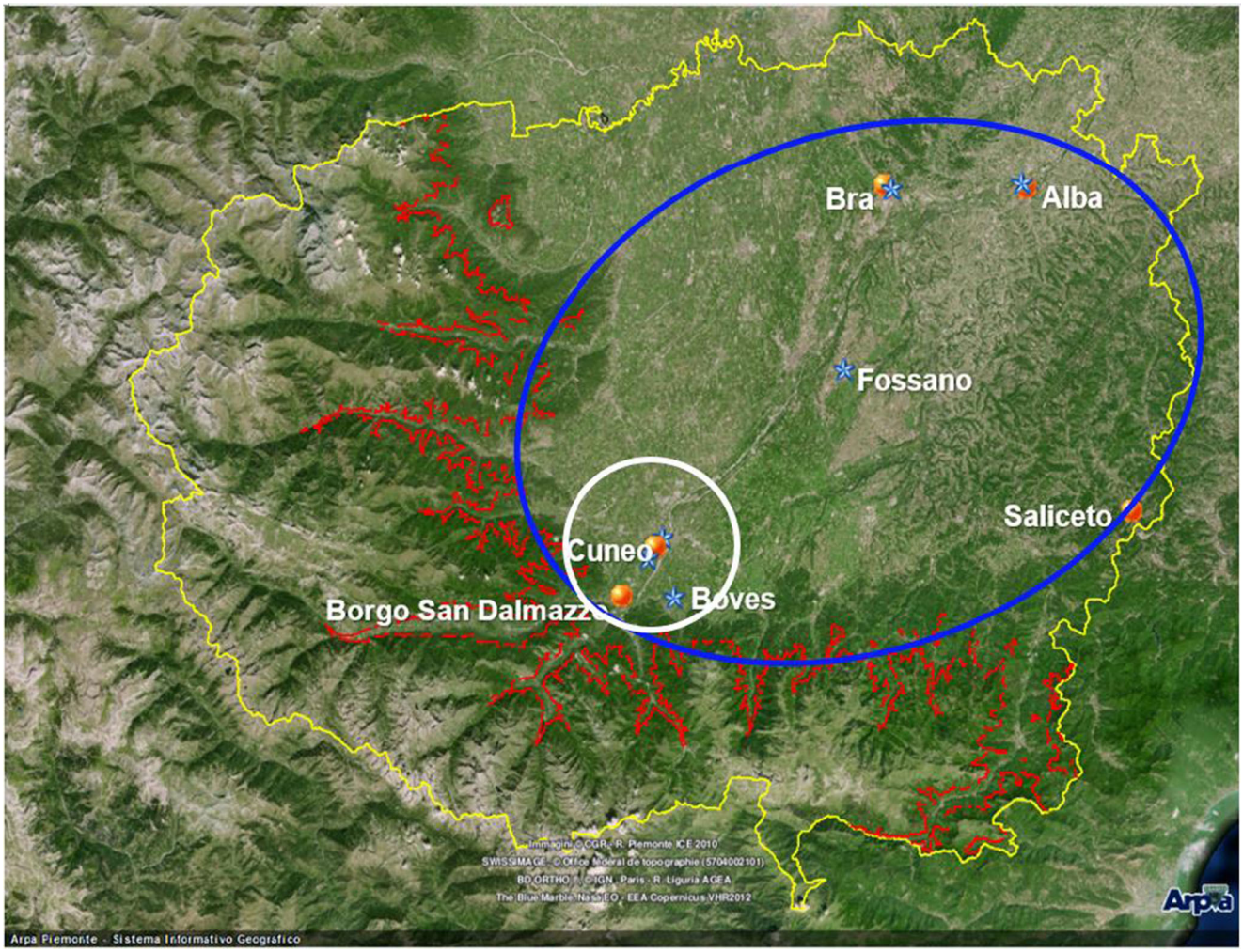

Fig. 2 Geographical contest of Cuneo and its province. Geographical contest: province border (*yellow line*), isoaltimetric line (*red line*), study area (*blue line*), and conurbation of Cuneo (*white line*). Sampling sites: Meteo sampling sites (*blue stars*) and air pollutant sampling sites (*yellow circles*)

Diagnosis and related history and clinical signs of URI to study the association with OM:

(a) ICD-9 codes at DIA-1, DIA-2, and DIA-3: 463, 462, 461.9, 464.0, 460.0, 465.9, 487.1.

(b) Signs and symptoms of acute upper respiratory tract inflammation in medical history and upon physical examination.

Statistical methods

The first step in the statistical methodology focuses on the control of geographic variability for climate and air pollutants. The 2007–2010 database was used as a thermometric, hygrometric, barometric, and wind reference time series (RTS) to test three candidate stations (CS). The stations selected as CSs are Cuneo Camera di Commercio and Cuneo Cascina Vecchia (climatic CS), as well as Cuneo Alpini (for air pollutants). The reference series was created on the basis of the geotopographic characteristics of the monitoring stations (see previous climate and air pollutant databases), with certain minimum criteria for inclusion and exclusion, namely a minimum of three reference stations, a 200-km distance from the CS to other stations, and an altimetric variation of about 450 m (Peterson and Easterling 1994), using the Bravais–Pearson correlation coefficient.

In order to ascertain whether trends play a specific long-term role and whether statistically significant developments occur, W. Koppen's classification was tested and applied for the thermometric profile. More specifically, the Theil–Sen estimator (Theil 1950; Sen 1968) and the R Open air library were used for PM_{10}, NO_2, and O_3.

A recent panel study (Hoffman et al. 2013) points out to the need to improve statistical methods of analysis that take into account the complexity of data and expand knowledge about the risk factors for OM. In order to investigate the complicated risk associations with OM, a statistical modeling approach is recommended, organized in two progressive stages and multiple steps.

The response variables (structured as cumulative age groups) include the number of daily ED visits at age 0–3 (age group 1) as the baseline, at age 0–6 (age group 2) as the first control, and at age 0–18 (age group 3) as the second control. Different covariates were included in the models: climate covariates *T*, RH, BAR, and *W*; air pollutants NO_2, O_3, and PM_{10}. These covariates were treated as explanatory variables in the entire statistical sequence. Furthermore, several calendar factors were added to all the statistical routines: time with natural cubic spline (7df × 4 years), days of week (DOW—1 Monday…7 Sunday), and summer holidays with three categories: 1 = July 15–31 and August 16–31, 2 = August 1–15, 0 = all the other days. Concomitant URI was identified through the combined analysis of additional ICD-9 diagnoses (from DIA-2 to DIA-6) and two ED fields for medical history and physical examination. Additionally, an interaction analysis was planned for different combinations of covariates, with a focus on possible interactions between T and O_3 according to previous publications that point out to such connection (Ren et al. 2008; Kahle et al. 2015). The variable URI was fitted to adjust the statistical modeling approach. A potential confounding variable related to the peaks of influenza (FLU), obtained from Centro Interuniversitario di Ricerca sull'Influenza e le altre Infezioni Trasmissibili 2012 (http://www.cirinet.it/jm/), was included in the models. The weekly incidence rate for each categorized week was calculated using a variable dummy (0 = <4‰, 1 = ≥4‰) as a criterion.

Stage1:

Developed through four subsequent procedures, it is based on the construction of a standard Poisson generalized additive model (PGAM) regression applied to the time series. In the first steps, all the air pollutant and climate covariates were included. The third step was performed by adding URI (clinical context) and FLU (epidemiological context) as control variables. All the statistical routines were performed by applying stepwise regression in two progressive ways—before backward procedure (BBP) and after backward procedure (ABP). Lastly, the Akaike information criterion (AIC) was used to find the best model fit (goodness of fit).

Stage2:

Several studies, particularly in the last decade, reported a delayed effect of air pollutants or climate factors on a variety of diseases and on mortality. Specifically for OM, recent studies based on investigation methods aimed at exploring the delayed effects of different pollutants as related to the onset of OM (Zemek et al. 2010) highlighted statistically significant associations. OM shows a consistent time relation with upper respiratory tract infections, with a peak 3 to 4 days after the onset of nasal symptoms and upper respiratory tract infection (Kousha and Castner 2016). For this reason, a complex sequential statistical procedure was programmed. A PGAM was used in combination with the distributed linear and nonlinear lag models (DLNM) (Gasparrini 2013, 2014), as well as the libraries R statistics mgcv, dlnm, and splines to estimate the lagged effects through a natural spline with 5 df and internal knots placed at equally spaced quantiles, with a centered point.

To correct the effects for seasonality and long-term trends, a smooth function was also included, as for the previous statistical steps, with 7df/year and DOW. The DLNM methodological framework was implemented in four progressive lag steps—lag time at 0–1, 0–3, 0–5, and 0–10 days—specifically for each statistically significant air pollutant and climate covariate in the previous stage 1, using a PGAMs in two ways: without URI and FLU as control variables (crude DLNM) and with URI and FLU (adjusted DLNM). The estimated RR (95% CI) was the final outcome of the DLNM procedure. According to the information on the patient access time contained in the database, the analysis of possible delayed effects was expanded to the hourly scale (hourly approach), with methods similar to those used in the DLNM (daily approach). Due to the type of monitoring used for PM_{10} (see the units and metrics used for this pollutant), no possible delayed effects on the hourly scale could be programmed. Lastly, in the light of possible overdispersion in this final routine, the use of the quasi-Poisson model—if confirmed by data—as an alternative to the standard Poisson model was considered.

To consolidate the statistical results of the dose–response models, a sensitivity analysis was performed, having the following general characteristics: variations in reference point with 25th and 75th (baseline 50th or min or general mean, depending on the specific covariate); natural spline with 5, 6, 8, and 9 df/year (baseline 7 × 4 year); and lag range with 0–2, 0–4, and 0–6 (baseline, 0–1, 0–3). The sensitivity analysis (hourly approach) included the execution of Poisson or quasi-Poisson models and had the same structure implemented in the daily models.

Results

The analysis of temperature and rainfalls from the time series (series from 1951 to 1986) related to the climate data of Cuneo showed a $T < +18$ °C, with $T > -3$ °C in the mid-winter season. According to W. Koppen's climate methodology and climate classification, the city of Cuneo is classified as CF, however with the possibility of inclusion in both subgroups CFb and CFa. In fact, according to the climate data set, the city can be classified as CFb with $T < 22$ °C in the hottest month. On the other hand, the results of the analysis performed from 2004 to 2015 only suggest the existence of a transition regime with the prevalence of the CFa type characterized by an average temperature >22 °C in the hottest month. The same climate trend was observed for all the weather stations used to test the CS. This result is more formally confirmed by the application of the Theil–Sen estimator, which shows a

statistically significant trend, with $P = 0.05$, for the 2004–2015 period. These results are consistent with some thermometric time series reviewed on a global scale (GissTemp:// http://data.giss.nasa.gov/gistemp/ and HadCRU: http://www.metoffice.gov.uk/hadobs/hadcrut4/).

The rainfall pattern has two maximum peaks—one in spring with the highest values recorded in May and one in autumn, with the highest values recorded in October—and two minimum peaks—one in winter (January) and one in summer (July or August). During winter, snowfalls are the most abundant among all major cities in Italy. The correlation coefficient calculated between the thermometric reference time series (RTS) and the candidate station (CS) was $r = 0.98$. The same was observed for BAR with $r = 0.94$ and RH with $r = 0.91$, while the wind field shows a moderate correlation with $r = 0.68$. The missing values of the total observations were <0.03% for all the weather and air pollutant stations. Air pollutant correlation terms: NO_2 with $r = 0.88$, O_3 $r = 0.86$, and PM_{10} with $r = 0.76$. Table 1 summarizes the climate and air pollutant results for the 2007–2010 period, including both the CS and the RTS.

As shown for T, attempts were made to understand whether the trends for the three pollutant species were specifically important for the purpose of the analysis. The results of the Theil–Sen estimator calculated on the Cuneo Station for the 2003–2016 period show a strongly significant trend for NO_2 and PM_{10} in all seasons: NO_2 with $P = 0.001$ (autumn) and $P = 0.01$ (winter), PM_{10} with $P = 0.001$ (autumn) and $P = 0.01$ in winter. No significant trends were observed for O_3 in any season, with a constant $P > 0.1$. Similar results are obtained from the other three observation stations for NO_2 and PM_{10} with $P = 0.001$ or $P = 0.01$ according to the measurement site and to seasons, whereas O_3 does not show any specific trend signs ($P > 0.1$). In particular, the analysis for the 2003–2010 period, which is most relevant to trend analysis (excluding the 2011–2016 period), is aligned with prior results, with trends between $P = 0.01$ and $P = 0.05$, however less important compared to the 2003–2016 period. Figure 3a (NO_2), b (PM_{10}) provides a comprehensive summary of statistical results.

Table 2 shows the number of cases admitted in the ED, grouped by gender and age. A preliminary analysis of the different pollutants allowed to estimate the inconsistency of the observed values of CO with mean ≤0.77, max ≤1.4, and min ≤0.2 for all days. In the light of the limit value set as the maximum average over 8 h (10 mg/m^3) in Italy, this pollutant was excluded from the statistical analysis. Preliminarily, the Bravais–Pearson correlation was performed (cross-correlation matrix) between climate and outdoor air pollutant covariates. This matrix suggests some terms of moderate collinearity, in particular T: O_3 ($r = 0.71$) and T: NO_2 ($r = -0.71$). Otherwise, there are no specific terms of correlation between T and PM_{10} with $r = -0.17$. The collinearity terms for the individual pollutants show O_3: PM_{10} ($r = -0.21$), O_3: NO_2 ($r = -0.60$), and NO_2: PM_{10} ($r = 0.47$).

The total number of ED visits was 304,040, with a daily average of 208 and an average age of 42.30 years. The annual number of ED visits was 71,689 (2007), 76,645 (2008), 78,009 (2009), and 77,697 (2010). Before applying the exclusion criteria, 2817 ED visits for OM were isolated, with a daily average of 2.44 and an annual average of 704.5. Annual ED visits totalled 604 (2007), 760 (2008), 740 (2009), and 713 (2010), with a daily average of 2.1, and included 1570 males (55.7%) and 1247 females (44.3%).

After applying the exclusion criteria, the recorded daily number of ED visits is 2532, including 1132 females and 1400 males, aged 15.39 on average, SD ± 19.68 for females (44.46%) and 13.29 ± 18.34 for males (55.54%). This result is in accordance with previous research (Teele et al. 1989). The seasonal OM distribution for the entire period shows 792 ED visits in winter (31.28%), 679 in spring (26.82%), 446 in summer (17.61%), and 615 in autumn (24.29%). The covariate URI is observed in a large number of cases (1273), including 549 females and 724 males. The age-specific result for URI is 769 ED visits for age group 0–3 (60.41%), 305 for age group 4–6 (23.96%), 148 for age group 7–18 (11.63%), and 54 for age group >18 (54.24%). Additionally, the specific frequency of access by time slots points out to a maximum peak between 9 and 11 a.m. and a secondary peak between 4 and 8 p.m.

The first statistical steps were carried out including all air pollutant and climate covariates. The results of the first crude step (step 1) are shown in Table 3 (BBP), with NO_2 ($P < 0.001$), PM_{10} ($P < 0.05$ in age groups 2 and 3), and T ($P < 0.05$ in age group 1). In step 2 (ABP), results show NO_2 with $P < 0.001$ (Table 4) and T with $P < 0.04$ in age group 1. In this statistical phase, we observed a specific relation of BAR with $P < 0.019$ in age group 1.

No statistically significant association was observed for O_3, W, and RH with a constant $P > 0.25$; these variables were excluded according to the backward procedure. A specific interaction analysis performed for different combinations of explanatory variables ($T \times NO_2$, $T \times PM_{10}$, $NO_2 \times PM_{10}$, and $T \times O_3$) showed no evidence of a multiplier effect with $P = >0.05$, more specifically interaction $T \times NO_2$ ($P = >0.89$), $T \times PM_{10}$ ($P = >0.43$), $T \times O_3$ ($P = >0.98$), $NO_2 \times PM_{10}$ ($P = 0.38$), and $NO_2 \times O_3$ ($P = >0.17$).

Steps 3 and 4 are part of a model that includes URI and FLU as control variables. The results of these steps are shown in Table 5 (BBP) and in Table 6 (ABP). This modeling approach confirms the role of URI, which can significantly modify the effects shown in the previous steps. It is still significant in both steps ($P < 0.05$) for age group 1; NO_2 is only significant in step 3 ($P < 0.05$) for age group 3. The statistical procedure was repeated by including the calendar variable DOW with $P < 0.001$ in all steps.

The outcome of stage 2 (PGAMs combined with DLNM) is expressed in terms of RR (95% CI). As provided for by the

Table 1 Statistical summary for CS and RTS (outdoor air pollutants and climatological variables)

Variables	Units	Mean	SD	Min	25th	50th	75th	Max
CS[a] O_3 ($\mu g/m^3$)	1461	60.86	27.34	8	39.00	61.00	81.00	149
RTS[b] O_3 ($\mu g/m^3$)	1461	51.05	26.03	7	27.00	53.00	74.00	130
CS PM_{10} ($\mu g/m^3$)	1461	28.23	18.89	1	15.00	24.00	36.00	121
RTS PM_{10} ($\mu g/m^3$)	1461	36.78	21.98	5	21.00	31.00	48.00	125
CS NO[b] ($\mu g/m^3$)	1461	34.39	13.20	8	25.00	32.00	43.00	86
RTS NO[b] ($\mu g/m^3$)	1461	29.40	11.47	7	20.00	27.00	37.00	73
CS *T* (°C)	1461	12.10	8.01	−7.6	5.04	12.10	19.10	26.9
RTS *T* (°C)	1461	12.33	8.16	−7.3	5.27	12.37	19.45	27.3
CS RH (%)	1461	67.85	16.81	27	56.00	68.50	81.00	100
RTS RH (%)	1461	73.39	15.37	31	62.67	73.00	85.33	100
CS BAR (hP)	1461	949.01	7.41	914.0	945.10	949.84	953.80	972.10
RTS BAR (hPa)	1461	971.00	7.38	937.30	966.65	971.70	975.80	994.10
CS[c] *W* (km/h)	1461	1.59	0.45	0.4	1.30	1.60	1.90	3.5
RTS[c] *W* (km/h)	1461	1.50	0.39	0.5	1.27	1.47	1.70	4.4
CS winter	48	2.07	3.16	−7.20	−.15	2.20	4.20	13.40
RTS winter	48	2.03	3.14	−7.30	−.05	2.32	4.32	13.10
CS spring	48	12.34	4.85	−1.90	8.90	12.00	16.00	25.00
RTS spring	48	12.58	4.80	−1.05	9.22	12.36	16.24	25.10
CS summer	48	21.87	2.75	12.80	20.40	22.20	23.80	27.00
RTS summer	48	22.11	2.72	13.00	20.60	22.42	24.02	27.30
CS autumn	48	11.86	5.40	−0.50	7.90	11.75	16.50	23.00
RTS autumn	48	12.20	5.39	−0.01	8.27	12.06	18.84	23.80

[a] Candidate station

[b] Reference time series

[c] Statistical summary for monthly temperature all seasons 2007–2010 (CS and RTS)

statistical methodology, some statistically non-significant covariates were excluded from the DLNM analysis in all the steps and age groups (*W*, RH, and BAR), while *T*, NO_2, O_3, and PM_{10} were included separately. The estimated RR for *T* was significant in age group 1, age group 2, and lag times 0–1 and 0–3. In age group 1, the model displays RR 1.44, CI 1.11–1.88 (lag time 0–1), and RR 1.43, CI 1.05–1.94 (lag time 0–3 days). Age group 2 shows RR 1.29, CI 1.03–1.61 (lag time 0–1) and RR 1.31, CI 1.02–1.7. The DLNM does not display a significant RR for NO_2, PM_{10}, and O_3. The DLNM results for *T*, NO_2, PM_{10}, and O_3 are shown in Tables 7 and 8. The analysis of delayed effects (quasi-Poisson approach for overdispersion) performed on an hourly basis with age group 1 and total count of OM as response variables (Table 9) provided statistically significant results for *T* starting from lag range 0–11 (RR 1.20, CI 1.04–1.38) and subsequent ones up to lag range 0–15 and, to a lesser extent, for NO_2 from lag range 0–8 (RR 1.03, CI 1.01–1.05) to lag range 0–15. This analysis did not highlight any statistically significant results for O_3, with constant RR < 1 throughout the progressive lag range sequence.

In conclusion, the results of the sensitivity analysis performed on *T* and NO_2, PM_{10}, and O_3 are consistent with the evidence obtained in the different DLNM steps. Twelve graphic representations are provided, including a bidimensional plot for *T*, NO_2, PM_{10}, and O_3, in Figs. 4a (T), b (NO_2) and 5a (PM_{10}), d (O_3), and a chart of the exposure-related response to a specified value in Fig. 6a, b, c, d.

Discussion

The correlation coefficient calculated between CS and RTS for several climate and air pollutants suggests an overall consistent homogeneity of the compared series. However, results on correlation terms show differences for certain covariates, including *W*. More specifically, *W* and PM_{10} (though statistically consistent) can be interpreted as the result of partial variability on the space scale.

Early step results showed statistical evidence in the evaluation of the short-term effects of certain variables, air pollutants, and climate covariates. These results are further confirmed by the modeling adjusted for URI, where the importance of this factor in the onset of OM is confirmed with great emphasis.

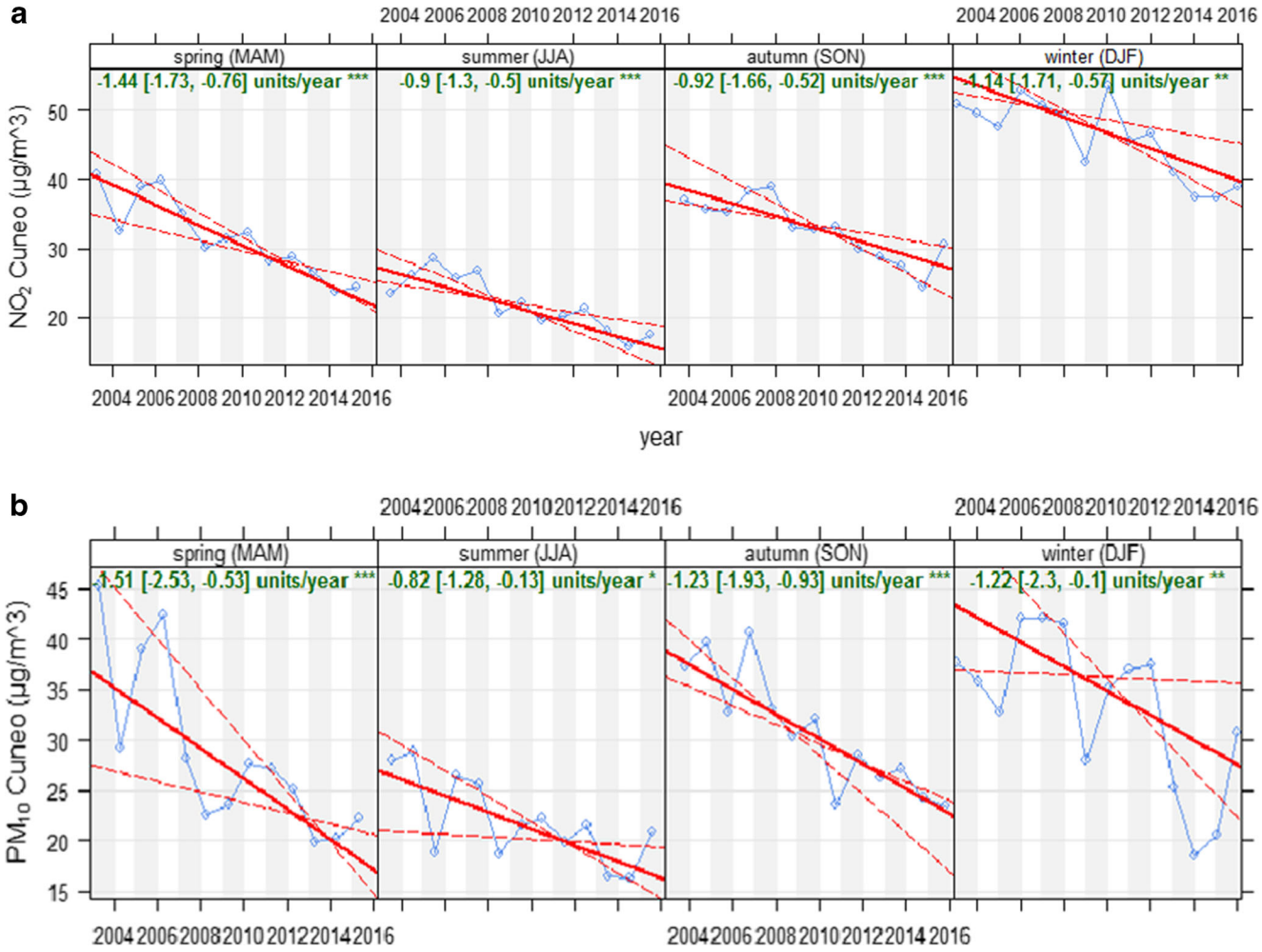

Fig. 3 **a**, **b** Trend analysis from 2003 to 2016 (from January 2003 to February 2016) for NO_2 and PM_{10} at the seasonal scale. Signif. codes: ***0, **0.001, *0.01, .0.05, and +0.1

Of particular interest was the research carried out through the National Health Interview Survey (NHIS, USA) in view of determining whether average temperature (annual average) between 1998 and 2006 influenced the probability of recurrent OM (≥3 OM in a year). Mean temperature experienced 1.5° fluctuations over the period under study, with no significant impact on OM rates (Miller et al. 2012). Our study highlighted a moderate association of the *T* parameter, which seems to point out to a greater involvement of age group 1. The *T*–OM association confirms a typical seasonal pattern, already observed in previous studies and related to cold-like illnesses.

As to the correlation term between *T* and PM_{10} with $r = -0.17$, a possible interpretation of this result is that rainfalls are effective to reduce particulate matter. In addition, the correlation term between CS and RTS for PM_{10} ($r = 0.76$) reflects some degree of variability of this pollutant between stations compared to the other pollutants (NO_2 $r = 0.88$, O_3 $r = 0.86$).

The collinearity terms between the three pollutant species do not show any specific criticalities, with O_3/PM_{10} and O_3/NO_2 seemingly countercorrelated, and can be accounted for as the result of two pollutant species that reach their peak concentrations in different seasons. Partial collinearity recorded for NO_2 and PM_{10} ($r = 0.47$) does not prevent using these variables in statistical modeling.

The results obtained from the stage 2 execution (daily approach) also confirmed a dose–response effect of *T* in the DLNM, with statistically significant RR in lag ranges 0–1 and 0–3, age group 1, and age group 2.

Table 2 Statistical summary of all ED visits, sex, and specific age groups

Variables	Units	Mean	SD	Min	Sum	25th	50th	75th	Max
ED visits	1461	1.73	1.69	0	2532	0.5	1	3	10
Sex males	1461	0.96	1.16	0	1400	0	1	1	7
Sex females	1461	0.77	0.97	0	1132	0	1	1	5
Age group 1	1461	0.73	1.06	0	1070	0	0	1	7
Age group 2	1461	1.05	1.36	0	1538	0	1	2	9
Age group 3	1461	1.16	1.43	0	1699	0	1	2	10

Table 3 (Stage 1–step 1) Poisson regression model with air pollutants and climatological covariates adjusted for seasonal and calendar factors (long[a] and short time)—before backward procedure (BBP)

Covariates	Response variable Age group 1 (count 0–3 years) Age 1 Pr(>|z|)	Response variable Age group 2 (count 0–6 years) Age 2 Pr(>|z|)	Response variable Age group 3 (count 0–18 years) Age 3 Pr(|z|)
Intercept	0.045835*	0.168648	0.177288
PM_{10}	0.245903	0.026025*	0.004341**
NO_2	0.000443***	3.97e−06***	1.51e−07***
O_3	0.240288	0.453304	0.948242
T	0.019699*	0.038502*	0.078966†
BAR	0.051787†	0.160899	0.156104
RH	0.979246	0.370737	0.295638
W	0.827999	0.858777	0.714904
DOW	<2e−16***	<2e−16***	<2e−16***
Holidays	0.239462	0.487190	0.880106

[a] Natural splines on covariate time (7df × 4 years)

Signif. codes: ***0, **0.001, *0.01, † 0.05, 0.1 ‘’ 1

Table 4 (Stage 1–step 2) Poisson regression model with air pollutants and climatological covariates adjusted for seasonal and calendar factors (long[a] and short time)—after backward procedure (ABP)

Covariates	Age group 1 (count 0–3 years) Pr(>|z|)
Intercept	0.0086**
PM_{10}	0.29825
NO_2	1.47e-05***
T	0.03749*
BAR	0.01910*
DOW	<2e−16***
Holidays	0.2137
Covariates	Age group 2 (count 0–6 years) Pr(>|z|)
Intercept	0.0546†
PM_{10}	0.0443*
NO_2	2.23e-07***
T	0.0808†
BAR	0.0559†
DOW	<2e−16***
Holidays	0.4337
Covariates	Age group 3 (count 0–18 years) Pr(>|z|)
Intercept	0.0730†
PM_{10}	0.0058**
NO_2	2.51e−08***
T	0.1179
BAR	0.0728†
DOW	<2e−16***
Holidays	0.8341

[a] Natural splines on covariate time (7df × 4 years)

Signif. codes: ***0, **0.001, *0.01, † 0.05, 0.1 ‘’ 1

The increased risk observed in age group 1 could be related to specific anatomical and functional characteristics of the Eustachian tube, which was smaller and more horizontal than in adults (Swarts et al. 2013; Takasaki et al. 2007) and often showed partial obstruction due to adenoidal hypertrophy. In the early stages of a cold-like illness, inflammation may cause, most often in infants, decreased fluid drainage and ventilation of the middle ear. This adds up to the immature state of the immune system early in life, which results in greater susceptibility to infections.

NO_2, a risk factor for respiratory distress, shows some evidence of association with OM in several steps (see tables) and, unlike the *T* parameter, in all the age groups under study. NO_2 also stands out more clearly as a risk factor, with statistical significance in the period from 8 to 15 lags. Considering long-term trends that point out to a constant decline of NO_2, this result is even more valuable if compared against similar studies carried out on broader urban contexts, where NO_2 pollution rates are much higher. Results for O_3 confirm the findings of previous statistical steps. As to results on the trends that point out to a transitional regime for *T* and a clearly significant trend for NO_2 and PM_{10}, the recorded ED visits appear substantially stable (604 in 2007, 760 in 2008, 740 in 2009, and 713 in 2010). This result suggests that trends do not seem to influence the number of ED visits. However, the analysis of health data should best be continued over a longer period of time. This further shows that exposure to NO_2, albeit moderate as in the case of Cuneo, may impair the mucociliary clearance of the upper respiratory tract and middle ear and alter the inflammatory response to infections, with a likely secondary role in the pathogenesis of URI and OM (Helleday et al. 1995; Frampton et al. 2002; Chauhan and Johnston 2003). However, the daily DLNM models—both

Table 5 (Stage 1–step 3) Poisson model with air pollutants and climatological covariates adjusted for URI and FLU, seasonal and calendar factors (short and long[a] time)—BBP

Covariates	Age group 1 Pr(>|z|)	Age group 2 Pr(>|z|)	Age group 3 Pr(>|z|)
Intercept	0.33890	0.66709	O.7540
PM_{10}	0.64885	0.86217	0.3748
NO_2	0.24534	0.12204	0.0420*
T	0.03092*	0.07566†	0.1066
BAR	0.43422	0.80245	0.8908
URI	<2e−16***	<2e−16***	<2e−16***
FLU	0.13673	0.09139†	0.2386
DOW	0.01960*	7.24e−05***	2.63e−06***
Holidays	0.64233	0.88514	0.4991

[a] Natural splines on covariate time (7df × 4 years)

Signif. codes: ***0, **0.001, *0.01, † 0.05, 0.1 ‘’ 1

crude and adjusted—do not show any effects of NO_2 in terms of RR.

The results of the dose–response model implemented on an hourly basis for *T*, NO_2, and O_3 are particularly interesting and confirm the role of temperature (lag range 0–11...0–15 with significant RR). Additionally, a specific statistical significance of RR (lag range from 0 to 8 to 0–15) with a more limited risk profile, which the daily approach had not revealed, was found for NO_2.

This result for NO_2 can be accounted for by the short-term toxicity of the pollutant, which interacts with the respiratory epithelial membranes generating free radicals that adversely affect mucociliary clearance (Helleday et al. 1995; Chauhan and Johnston 2003). A study highlighted such a strong effect of NO_2 on rhinitis, a very frequent inflammation associated with the onset of otitis (Cesaroni et al. 2008). In the light of the above, the dose-dependent pathophysiological impact of NO_2 on the epithelial membranes of the upper respiratory tract and of the Eustachian tube may promote progression towards otitis media within a few hours when anatomopathological conditions are already affected by an incipient or full-blown viral or bacterial infection. This hypothesis is supported by studies suggesting that exposure to NO_2 may enhance the cytotoxic effect of respiratory viruses and of other pathogenic agents on the epithelial cells (Frampton et al. 2002). Addressing this possibility will require further research.

Table 6 (Stage 1–step 4) Poisson regression models with air pollutants and climatological covariates adjusted for URI and FLU, seasonal and calendar factors (short and long[a] time)—ABP

Covariates	Age group 1 Pr(>|z|)	Age group 2 Pr(>|z|)	Age group 3 Pr(|z|)
Intercept	0.0544†	0.0502†	0.0490*
NO_2	0.1290	0.1021	0.0687†
T	0.0299*	0.0805†	0.1428
URI	<2e−16***	<2e−16***	<2e−16***
FLU	0.1076	0.0854†	0.2464
DOW	0.0199*	5.64e−05***	1.31e−06***
Holidays	0.6425	0.8836	0.4968

[a] Natural splines on covariate time (7df × 4 years)

Signif. codes: ***0, **0.001, *0.01, † 0.05, 0.1 ‘’

Statistically, the effects of O_3 and PM_{10} remain negligible. While PM_{10}, in step 2 (crude model), denotes a $P < 0.05$ in age groups 2 and 3, this result is not confirmed in subsequent statistical routines (adjusted models and DLNM daily and for the O_3 hourly approach). The lack of hourly data on PM_{10} (an approach to OM that is quite seldom used in scientific literature) poses a specific limit that prevents drawing final conclusions on the role of this pollutant in OM. Reference is made to future works considering hourly dose–response approaches. More generally, the limited number of studies carried out so far on the possible association between pollutant species and OM suggests that further research is needed to draw more solid conclusions.

The interaction analysis does not provide significant results for the different combinations of *T* and air pollutants. More specifically with respect to the interaction between *T* and O_3, the result should be reasonably interpreted as a consequence of the typical trend of this pollutant, with maximum concentrations in summer and minimum in winter, whereas the prevalence of OM is highest in winter. On the other hand, there is substantial scientific agreement about the role of high temperatures and of the T × O_3 interaction (Ren et al. 2008; Colleen et al. 2012).

General OM–air pollutant associations mentioned in this study need further investigation, particularly through research on large urban areas, by reason of the lack of investigable values of CO in Cuneo, highlighted in publications as respiratory risk factors, and of moderate local exposure to other pollutants (Heinrich and Raghuyamshi 2004; Brauer et al. 2006; Zemek et al. 2010; Macintyre et al. 2011). The variable RH is statistically non-significant in all the models used. Our investigations carried out on PubMed and Cochrane Library (key words used: otitis media, relative humidity, absolute

Table 7 (Stage 2) Results of DLNM—RR for *T* and EDs adjusted for URI and FLU, seasonal and calendar factors (centered point at 15 °C as baseline)

Lag steps	Lag ranges (days)	RR	95% CI low	95% CI high
Step 1-age group 1 (*T*)	0–1	1.44*	1.11*	1.88*
Step 2-age group 1 (*T*)	0–3	1.43*	1.05*	1.94*
Step 3-age group 1 (*T*)	0–5	1.40	0.99	1.98
Step 4-age group 1 (*T*)	0–10	1.45	0.91	2.32
Step 1-age group 2 (*T*)	0–1	1.29*	1.03*	1.61*
Step 2-age group 2 (*T*)	0–3	1.31*	1.02*	1.70*
Step 3-age group 2 (*T*)	0–5	1.26	0.94	1.68
Step 4-age group 2 (*T*)	0–10	1.19	0.81	1.77
Step 1-age group 3 (*T*)	0–1	1.20	0.98	1.48
Step 2-age group 3 (*T*)	0–3	1.18	0.92	1.50
Step 3-age group 3 (*T*)	0–5	1.13	0.85	1.48
Step 4-age group 3 (*T*)	0–10	1.00	0.69	1.45

Signif. codes: ***0, **0.001, *0.01, † 0.05, 0.1

humidity, temperature, air pollutants) did not identify any studies exploring potential associations between RH and OM. Only few studies (Nastos and Matzarakis 2006; Mäkinen et al. 2009; Falagas et al. 2008) evaluated the risk profile for RH; however, such studies were carried out on upper respiratory diseases, rather than on OM. A recent study, carried out specifically on EDs and respiratory diseases (asthma, chronic obstructive pulmonary disease, upper respiratory infection, and pneumonia), confirms relative humidity as an autonomous risk factor (Qin et al. 2014). The result of our study for relative humidity should be further explored, with future research carried out on OM. A possible interpretation of the result is that RH may play a role in URI. However, further research should be carried out, particularly in different environmental settings, in view of obtaining a clear and detailed overview of a possible role of RH in the onset of OM.

The variable DOW showed clear statistical importance in both the stages and steps, with specific close control on weekends ($P < 0.001$). This result can be accounted for by the absence of general practitioners on weekends, which leads parents to choose the ED option. The adjustment of statistical modeling with the inclusion of holiday periods, essentially tied to the summer season, did not show any specific relevance.

The inclusion of the variable BAR in modeling is in line with other studies, which highlighted possible associations between atmospheric pressure and several human diseases (Danet et al. 1999; Funakubo et al. 2011). Our research highlights no significance of BAR ($P > 0.05$) with URI and FLU as variables under control. The results ($P = 0.019$) observed in age group 1 (step 2) could be related to the development of a low-pressure area, a meteorological context that is often associated with low winter temperatures, to which the group is sensitive. On the other hand, an involvement of the Eustachian tube peculiar to this age group, as described above, can be assumed. Upon abrupt changes in barometric pressure, this functional defect may cause a failure of compensation mechanisms to balance pressure in the middle ear (Takasaki et al. 2007). More detailed studies are needed to confirm this

Table 8 (Stage 2) Results of DLNM—RR for NO_2 and EDs adjusted for URI and FLU, seasonal and calendar factors and centered point at 10 μg/m^3 as baseline)

Lag steps	Lag ranges (days)	RR	95% CI low	95% CI high
Step 1-age group 1 (NO_2)	0–1	0.93	0.89	0.97
Step 2-age group 1 (NO_2)	0–3	0.98	0.93	1.04
Step 3-age group 1 (NO_2)	0–5	1.03	0.96	1.10
Step 4-age group 1 (NO_2)	0–10	0.99	0.91	1.07
Step 1-age group 2 (NO_2)	0–1	0.94	0.90	0.97
Step 2-age group 2 (NO_2)	0–3	0.98	0.94	1.03
Step 3-age group 2 (NO_2)	0–5	1.04	0.99	1.11
Step 4-age group 2 (NO_2)	0–10	1.02	0.96	1.10
Step 1-age group 3 (NO_2)	0–1	0.94	0.90	0.97
Step 2-age group 3 (NO_2)	0–3	0.98	0.93	1.02
Step 3-age group 3 (NO_2)	0–5	1.03	0.97	1.08
Step 4-age group 3 (NO_2)	0–10	1.01	0.94	1.08

Table 9 (Stage 3) Results of DLNM—RR (hourly approach) for *T* (centered point 15 °C), NO_2 (centered point 10 μg/m^3), and EDs adjusted for URI and FLU, seasonal and calendar factors

Temperature (15 h)	Lags	RR	95% CI low	95% CI high
	1	0.66	0.60	0.73
	2	0.67	0.60	0.74
	3	0.66	0.59	0.73
	4	0.65	0.57	0.73
	5	0.67	0.59	0.75
	6	0.70	0.62	0.80
	7	0.78	0.68	0.90
	8	0.87	0.76	0.99
	9	0.97	0.84	1.11
	10	1.10	0.96	1.26
	11	1.20*	1.04	1.38
	12	1.26*	1.09	1.48
	13	1.29*	1.12	1.50
	14	1.29*	1.11	1.49
	15	1.25*	1.07	1.45
NO_2 (15 h)	1	0.97	0.96	0.98
	2	0.97	0.95	0.98
	3	0.98	0.96	0.99
	4	0.99	0.97	1.01
	5	0.99	0.98	1.02
	6	1.01	0.99	1.03
	7	1.02	0.99	1.04
	8	1.03*	1.01	1.05
	9	1.04*	1.01	1.06
	10	1.04*	1.02	1.07
	11	1.05*	1.03	1.07
	12	1.06*	1.03	1.08
	13	1.06*	1.04	1.09
	14	1.06*	1.04	1.09
	15	1.06*	1.03	1.09

Variable response total count of OM

Signif. codes: ***0, **0.001, *0.01, † 0.05, 0.1

finding and to investigate correlations between barometric variations and middle ear pressure homeostasis in infants under normal and inflammatory conditions.

The research has some limits, in particular: (a) in the case of Cuneo, there are relatively low-risk profiles due to the pollution rates of individual pollutant species, much less important than in big conurbations; (b) only ED visits lack of outpatient data on OM cases; (c) inability to provide specific data (indoor air pollution) for the patients; (d) lack of data on the use and duration of breastfeeding (as a protective factor) or of bottle feeding alone (as a negative factor); and (e) lack of data on the socioeconomic factors capable to influence the onset of OM. A further limit is due to the lack of specific information on the practice of smoking during pregnancy.

The pathogenesis of OM is the result of an interaction among several factors, including intrinsic ones, connected with the host, and external ones, derived from the environment. Some of these factors, as stated in the limits, are not included in the database. However, the observational study on risk factors connected with meteoclimatic agents, pollutants, and OM cases reported to EDs is deemed to be significant, also in the light of the above-described limits. The main limit to this kind of studies is the possible existence of observation biases of exposures and outcomes. With reference to exposures, our aims included appropriate characterization and definition of the geographic region under study and maximum homogeneity. Moreover, with reference to the outcomes, OM cases were selected according to strict inclusion/exclusion criteria. Based on these assumptions, ED visits for OM can be considered as representative of acute pathological events in response to the exposure to acute environmental changes in meteoclimatic and/or polluting agents.

Preference for reporting to an ED is often motivated by the severity of acute clinical conditions or by other unpredictable time-related factors (festivities, weekends). This choice makes the lack of outpatient data less significant.

The lack of data on intrinsic factors, including feeding modes and indoor pollution, is important for the purpose of the epidemiological analysis. However, notwithstanding this

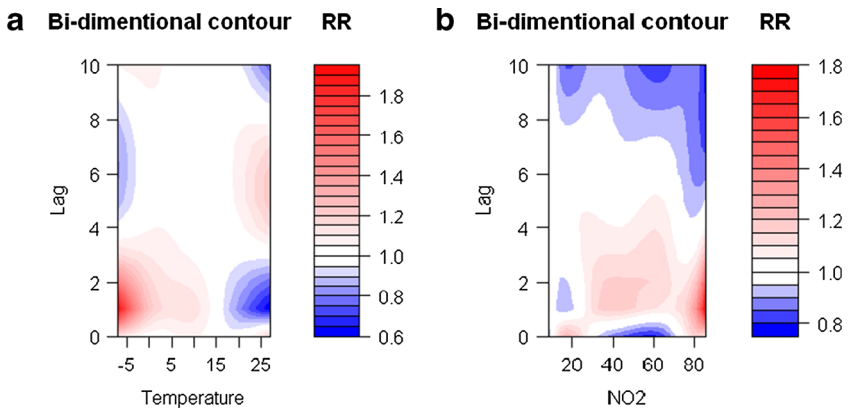

Fig. 4 **a**, **b** Bidimensional plot for temperature and NO_2 (lag ranges 0–10) adjusted for URI and FLU—age 1

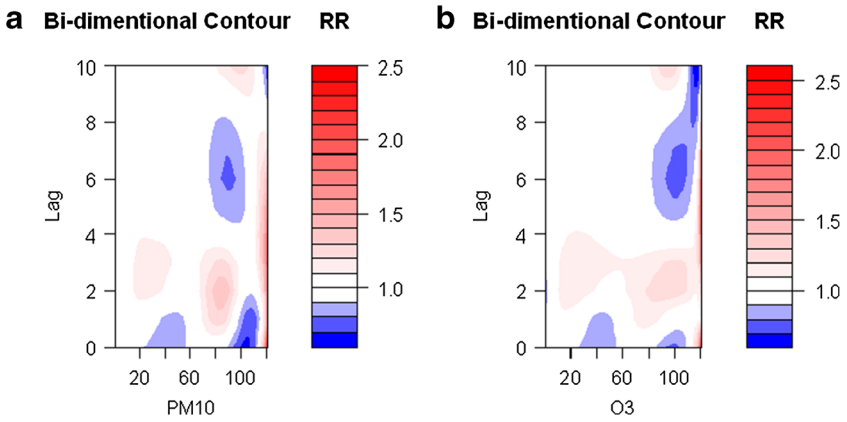

Fig. 5 **a**, **b** Bidimensional plot for PM_{10} and O_3 (lag ranges 0–10) adjusted for URI and FLU—age 1

limit, data on the seasonal trend of acute OM events is important and connected with the climate and atmospheric peculiarities of the geographic region, which could be defined as "local geoclimatic factors." This data, if available, can provide guidelines in terms of medical care, education, and parent care, in view of a prevention and care strategy aimed both at children with no intrinsic risk factors and, even more so, at children that show some of these in their medical history. A prevention and care strategy should also be recommended in case of chronic or recurring otitis, where an exacerbation or worsening of the clinical conditions is promoted by the acute seasonal meteoclimatic and/or polluting event. The results of the study highlight the effect of low temperatures, typical of the region of Cuneo.

Conclusion

These results support the assumption that URI is an important control factor in the onset of OM diagnosed in EDs. As to major risk factors, shared with URI, our study highlights low temperatures and the exposure to NO_2 as additional risk factors with different lag times, suggesting the appropriateness of using models and incorporating calendar and meteorological data to help EDs ensure a more effective allocation of the resources needed to treat children with URI and OM. Further studies are needed, particularly in large urban environments, to confirm the results of OM factor risk/association with other pollutants, particularly fine and ultrafine PM.

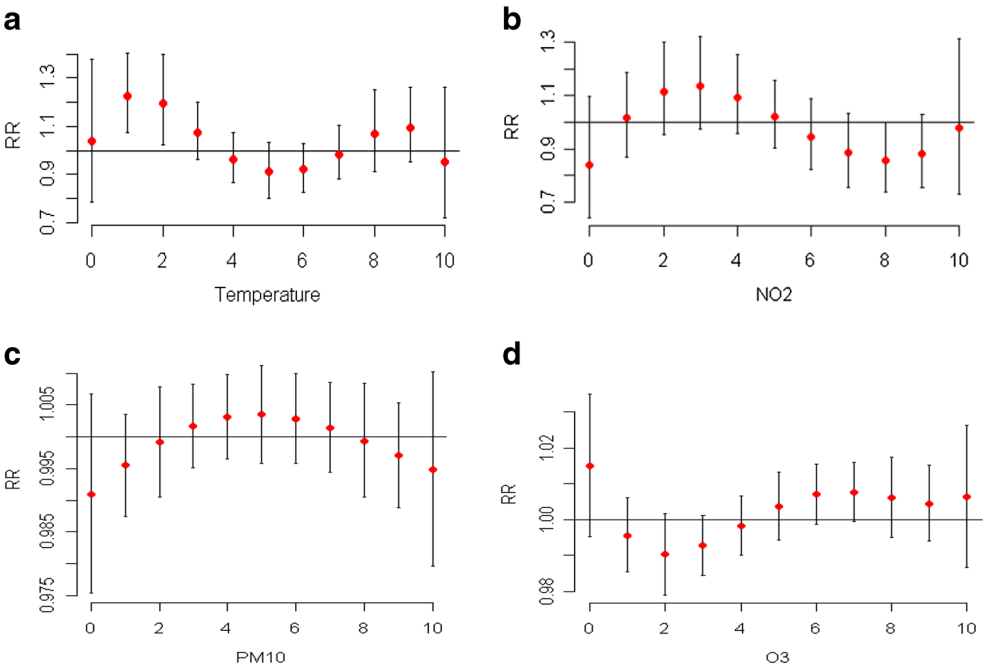

Fig. 6 **a**, **b** Exposure response specific to a temperature of 5 °C (25th) and NO_2 at 58 μg/m_3 (95th) adjusted for URI and FLU—age 1–lag range 0–10. **c**, **d** Exposure-response specific to PM_{10} of 15 μg/m_3 (25th) and O_3 at 20 μg/m_3 (10th) adjusted for URI and FLU—age 1–lag range 0–10

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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