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Ozone short-term exposure and acute coronary events: A multicities study in Tuscany (Italy)

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A B S T R A C T

Objective: Many studies have investigated the potential role of ozone exposure in cardiovascular mortality and morbidity. The effects on specific cardiovascular outcome and the role of individual susceptibility are less studied. This paper focuses on the short-term effects of ozone on acute coronary events and it investigates comorbidities as indicators of personal susceptibility.
Setting and patients: This study was conducted in five urban areas of the Tuscany region (Italy) covering the period January 2002–December 2005. Air quality and meteorological data from urban background monitoring sites were collected. Hospital admissions for acute myocardial infarction and out-of-hospital coronary deaths were extracted from administrative database.
Design: Both time series and case-crossover designs were applied. The confounding effects of some time-dependent variables, such as temperature, were taken into account. Some potential susceptibility factors were investigated. Pooled estimates were derived from random-effect meta-analysis.
Results: During the warm season 4555 hospitalized acute myocardial infarctions and 1931 out-of-hospital coronary deaths occurred. Authors estimated a 6.3% (95% confidence interval, 1.2%, 11.7%) increase in out-of-hospital coronary deaths for a 10 μg/m^3 increase in ozone (lag 0–5). Results also suggested higher risks for females, elderly, and patients previously hospitalized for cerebrovascular and artery diseases.
Conclusions: This study adds further evidence to the relation between cardiovascular diseases and ozone exposure, showing an adverse effect on out-of-hospital coronary deaths, but not on hospitalized acute myocardial infarctions. Some susceptible subgroups, such as females, elderly, and patients affected by some chronic diseases, are likely to be at major risk.

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1. Introduction

Ozone (O_3) is an oxidant pollutant naturally present in the troposphere. During the warm season, in some areas (i.e. around urban areas) ground level O_3 concentration may be increased by photochemical reactions in the presence of sunlight and precursor pollutants, such as nitrogen oxides (NOx) and volatile organic compounds (VOCS) (World Health Organization, 2005). Despite efforts to mitigate O_3 pollution, in many countries ground-level ozone concentration exceeds standards for protecting human health (European Environment Agency, 2011). During summer 2011 European Union threshold for protecting human health (120 μg/m^3 maximum daily eight-hour mean for no more than 25 days a year) was exceeded in a significant part of Europe, mainly in the Mediterranean area. A recent World Health Organization (WHO) report evaluated that current policies are insufficient to significantly reduce ozone levels in Europe in the next decade (Amann et al., 2008). In the USA many counties exceeded the 2008 ozone standard of 0.075 ppm (8-hour averaging time, corresponding to 147 μg/m^3 at 25 °C), and some of them are expected not to attain this limit in 2020 (Environmental Protection Agency, 2011).

Ozone pollution affects human health leading to a wide range of adverse effects, from respiratory symptoms to hospitalizations, and mortality. Meta-analyses and large multi-city epidemiological studies have strengthened the evidence that daily exposure to

Abbreviations: O_3, Ozone; NOx, oxides of nitrogen; VOCs, volatile organic compounds; PM_{10}, particulate matter with a diameter ≤ 10 μm; NO_2, CO, carbon monoxide; WHO, World Health Organization; RISCAT, Cardiovascular risk and air pollution in Tuscany study

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high levels of O_3 increases all-causes mortality and cardiovascular mortality (Bell et al, 2004; Stafoggia et al., 2010; Gryparis et al., 2004; Samoli et al., 2009). On the other hand, the association with hospital admissions for cardiovascular diseases is less clear and contrasting findings have been reported (Mustafic et al., 2012; Ruidavets et al., 2005; Von Klot et al., 2005; Henrotin et al., 2010; Lanki et al., 2006).

Coronary heart diseases, and specifically acute myocardial infarction, are leading causes of morbidity and mortality in Europe (Graham et al., 2007). Effects of major cardiovascular risk factors (i.e. smoking, cholesterol and blood pressure levels, diet, physical activity, diabetes) have been widely assessed (Graham et al., 2007). The identification of other risk factors, such as air pollutants, with small effects sizes but to which entire populations are exposed, could contribute to implement preventive measures with wide effects in term of reduction of the burden of disease.

This study allows to investigate in the same setting the effects of O_3 level both on cardiovascular mortality, and on hospitalizations. This could help to better understand cardiovascular adverse effects of ozone, improving the comparability of results for both cardiac outcomes. Other aspects regarding the relationship between O_3 level and cardiovascular adverse effects, such as individual susceptibility to cardiovascular damage and the potential confounding/modification effects of other pollutants or meteorological variables are still open.

In Tuscany (Italy), the Cardiovascular Risk and Air Pollution in Tuscany (RISCAT) study investigated the relationship between air pollutants and cardiovascular adverse events. A previous paper by same authors reported risk estimates for particulate matter with a diameter $\leq 10\ \mu m$ (PM_{10}), nitrogen dioxide (NO_2) and carbon monoxide (CO) (Nuvolone et al., 2011). The present study examines the short-term association between O_3 levels and a specific group of cardiovascular events (hospital admissions for acute myocardial infarction and out-of-hospital cardiovascular deaths). This study also investigates the role of comorbidities as indicators of individual susceptibility. From a public health perspective, the identification of subgroups of population more susceptible to O_3 adverse effects is crucial to improve specific preventive measures.

2. Materials and Methods

2.1. Air quality and meteorological data

The Tuscany Regional Agency for Environmental Protection provided air quality data covering the study period, January 2002 - December 2005. All monitoring sites ($n=29$) classified as “urban background” (based on European and Italian air quality legislation), representing exposure of general population in urban areas were included. In a first step daily 8-hour maximum moving average for O_3 and CO, and daily average for PM_{10}, and NO_2 were calculated for each site. In a second step, in order to define areas with homogeneous air quality levels, a correlation analysis between sites was conducted: each pair of sites was compared by means of Pearson and Lin concordance coefficients. Five urban areas (about 1,350,000 inhabitants, 38% of total population of the region) with homogeneous air quality levels were identified. Some areas include only one municipality (Arezzo, area 1; Pistoia, area 4; Prato, area 5). The other areas include more than one municipality (metropolitan area of Florence, area 2; Pisa and Livorno coastal area, area 3). In the areas where more than one monitoring site was available, a daily area value was calculated by averaging daily mean data. Monitoring sites with at least 75% daily data availability were included; days with missing data have been excluded from the analyses. During the study period, methods and instruments of environmental monitoring were homogeneous and consistent with quality assurance criteria.

Meteorological data (air temperature, Celsius degrees - °C, and relative humidity, %) obtained from one meteorological station for each area were provided by Tuscany Regional Agency for Environmental Protection. Apparent temperature was calculated from daily mean air temperature, relative humidity, and dew point temperature (O'Neill et al., 2003). Apparent temperature is a measure of discomfort due to combined exposure to heat and high humidity, and it is often used in the studies on adverse health effects of hot temperature and air pollution (O'Neill et al., 2003; Stafoggia et al., 2010).

2.2. Health data

Data on hospitalized acute myocardial infarctions and out-of-hospital coronary deaths were obtained from the Tuscany Regional Registry of Acute Myocardial Infarction. The population-based registry, operating in Tuscany since the late 1990s, is based on the record-linkage between hospital discharge and mortality databases. Details on the registry's structure and validation are presented elsewhere (Barchielli et al., 2010). In summary, patients are identified by a personal identification number, which allows to perform anonymously the electronic record linkage among data sources. The registry identifies hospitalized acute myocardial infarctions (ICD9-cm code 410 as primary discharge diagnosis) and out-of-hospital coronary deaths (ICD9 codes 410–414 as underlying cause of death) as first and recurrent events. A new case of hospitalized acute myocardial infarction or out-of-hospital coronary death was defined as occurring 28 days after a previous event. For each subject the first event was included in the analyses and information on age, sex, municipality of residence, and date of the event were available. According to primary or secondary diagnoses of hospital admissions in the previous 3 years, patients were classified as affected by some cardiovascular and non cardiovascular chronic comorbidities.

2.3. Statistical analyses

Two study designs were used to evaluate the association between O_3 levels and coronary events. Time series of daily counts of coronary events study design was implemented and Poisson generalized additive models (GAM) were fitted to include non-linear effects of temperature and to fit distributed lag models. A case-crossover design was applied to investigate individual susceptibility (Levy et al., 2001), and conditional logistic regression models were fitted adjusting for a set of time-dependent variables, such as population decrease during vacation periods, holidays, and meteorological data. The analyses have been restricted to warm season (April-September).

The lag structure in the ozone-cardiovascular outcome association was evaluated fitting single-lag models and distributed lag models. Single-lag models were fitted from lag 0 to lag 5, by adding to the model each lag term one at a time. Cubic polynomial distributed lag models were fitted from lag 0 to lag 5 by adding to the model all lag terms simultaneously, and constraining the corresponding coefficients to follow a third-degree polynomial shape. Cumulative lags were also evaluated, and three different lag structures were a priory chosen to represent “immediate” effects (lag 0 to 1), “delayed” effects (lags 2 to 5), and “prolonged” effects (lags 0 to 5). Moving averages (0–1 days, 2–5 days and 0–5 days) of ozone levels were included in the models one at a time (single-lag model), and compared with corresponding estimates obtained by distributed lag models (Schwartz, 2000).

The potential confounding effect of high temperature has been controlled using a spline function of the apparent temperature. Different lag structures for apparent temperature were also tested.

The presence of an effect modification in patients with or without a specific condition was assessed using the case cross-over design. The effect estimate in each category of the potential effect modifier was compared with the effect estimate in the reference category for that variable. Statistical significance (at $\alpha=0.05$ level) of the effect modification was formally evaluated, and p-values of relative effect modification (p-REM) computed and reported. Variables used for effect modification analyses were gender, age (<75, 75–85 and ≥ 85 years), and presence of some comorbidities, such as cardiovascular and respiratory diseases, potentially associated with air pollution and generally investigated in susceptibility analyses (Stafoggia et al., 2010).

In each area we also estimated bi-pollutant models including simultaneously with ozone other pollutants (PM_{10}, CO, and NO_2) as linear terms at the same lag selected for ozone.

Area-specific estimates were combined using meta-analysis methods. Heterogeneity among areas was tested using both Q statistic and I^2 statistic. Conservatively, area-specific results were combined using a random effects meta-analysis whether or not there was a significant heterogeneity among areas.

All effect estimates were expressed as the percent increase in risk (and the corresponding 95% Confidence intervals – CI), relative to a 10 $\mu g/m^3$ O_3 increase.

3. Results

Table 1 summarizes data on populations, coronary events, O_3, and meteorological variables levels for each participating area.

3.1. Study population and coronary events

Overall, 4,555 hospitalized acute myocardial infarctions and 1,931 out-of-hospital coronary deaths occurred during the study period. Table 2 reports individual characteristics for the two dataset: in the hospitalized acute myocardial infarctions group,

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