The Relationship between Urban Airborne Pollution and Short-term Mortality

Introduction

The influence of airborne pollutants on mortality indexes has been extensively examined since the famous episodes of high pollution during 1930 in the Meuse Valley, 1948 in Pennsylvania and 1952 in London. The majority of studies confirm the existence of a significant correlation between airborne pollution and mortality. During the last decades the improvement of environmental conditions dramatically decreased the levels of urban airborne pollution. Anyway, still nowadays the study of the pollution-mortality relationship constitutes a pivotal challenge for epidemiologists involved in environmental medicine. Three different epidemiological approaches are commonly used: transversal studies, time series studies, prospective studies.

Transversal studies compare mortality rates referred to a preset timespan (usually years) between areas having different pollution levels. Typically, urban areas are compared to rural areas. Results of these studies are greatly affected by long term variables influencing the characteristics of the populations under comparison. These variables are diet, smoking habits, cultural level, race, lifestyle, etc. Therefore, populations under examination should be carefully selected and standardized to correct the possible confounding effect of these variables. Such a goal cannot be easily obtained because long lasting variables significantly influence the place of residence of populations. On the whole, the main pitfall of this approach is that mortality increases determined by differences among the above reported variables are erroneously attributed to pollution.

Studies retrospectively evaluating changes in pollution indexes and mortality rates are named 'time series studies' or 'studies analyzing historic series'. They examine changes in daily mortality rates and daily pollution level during a defined time-span. Mortality is evaluated in the same population at different pollution levels and times using short time intervals (i.e., 1–3 days) between pollution and mortality. Therefore, such an approach estimate only short-term pollution related mortality. Long lasting variables affecting population characteristics (i.e., cigarette consumption, social and cultural status, etc.) do not influence in a relevant manner these studies because the comparison is performed on the same population. On the contrary, short lasting variables, such as extreme macroclimatic situations and short lasting infective epidemics, can be important biases of this approach. Whenever these confounding factors are not exhaustively considered, mortality changes due to these causes can be erroneously attributed to concomitant pollution episodes.

Prospective studies represent the most complete and reliable approach, checking individually by questionnaire or laboratory techniques the influence of both long and short lasting confounding factors. This epidemiological approach is the only one able to estimate long-term pollution related mortality. These studies imply a great practical complexity, a relevant size of subjects recruitment, a very long time to be completed. Because of these reasons only few exhaustive cohort study concerning the association between pollution and mortality has been so far performed. The large majority of published articles apply the time series analysis approach.

Quantitative Aspects of Pollution-Mortality Relationship

The time series analysis approach examines the influence of pollution level on global mortality as excess of mortality in more polluted vs. less polluted days. Transversal studies describe the mortality excess in residents of a polluted area as compared to residents of a less polluted area. In any case results can be expressed as relative risks. These relative risks range between 1.02 and 1.13 in some of the most representative time-series studies examined in this review, with a mean value of 1.083 (Figure 1). Only some rare studies, report a relative risk lower than 1.0. An exhaustive prospective study performed in 6 US cities involving...
Table 1: Epidemiological methods used to study pollution-mortality relationships.

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<th>Type of study</th>
<th>Description</th>
<th>Advantages</th>
<th>Disadvantages</th>
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<tr>
<td>Transversal studies</td>
<td>Comparison of mortality rates between populations undergoing different levels of pollution (e.g., urban vs. rural areas)</td>
<td>Not affected by short lasting confounding factors (e.g., extreme climatic situations, accidents, etc.)</td>
<td>Influenced by long lasting confounding factors (e.g., demographic characteristics, cultural social and life-style related factors, etc.)</td>
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<td>Time-series analysis</td>
<td>Retrospective evaluation on the same population of mortality trends as compared to pollution levels in a defined period</td>
<td>Not affected by long-lasting confounding factors; low cost and complexity</td>
<td>Influenced by short-lasting confounding factors</td>
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<tr>
<td>Prospective studies</td>
<td>Prospective evaluation of mortality in a population using an individual control of confounding factors by questionnaires, lab analyses, medical controls, etc.</td>
<td>Lowest influence of confounding factors</td>
<td>High complexity; long time requested; high cost</td>
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ing 8111 subjects followed for up to 16 years established a relative risk of 1.26 in the most polluted city as compared to the least polluted city. Pollution level differed of about 3 orders of magnitude among the examined cities. It is of relevance that highly reliable prospective studies estimate relative risks concerning long-term mortality remarkably higher than those concerning short-term mortality obtained by the less complex time-series studies. One of the most complete study analyzing time series data in 12 European cities, accounting for over 23 millions of people involved, is the APHEA project. This study estimated that the relative risk of all-causes death in the general population for a $50 \, \mu g/m^3$ increase is 1.020 for sulfur dioxide and 1.022 for airborne particulate matter having a particle size lower than 10 $\mu m$ (PM$_{10}$).

On this basis, it could be argued that airborne pollution does not influence the global mortality rate in a dramatic manner. It should be considered that moderate changes affecting global mortality indexes when referred to the general population imply a not negligible excess of deaths. As an example, in a town having 1,000,000 of dwellers with an average amount of deaths per year of 10,000, an excess of mortality of 1,083 implies an excess of 830 deaths per year. Therefore, it could be estimated that pollution could approximately contribute to an excess of 200–1300 deaths per million of urban residents per year.

Interestingly, the previously reported prospective study estimated, after correction of confounding factors, that the percentage of survival after 14 years was 88% in the least polluted city and 78% in the most polluted city. Therefore, a difference of 10% in survival percentage could presumably be related to pollution. Referring to a town of 1,000,000 dwellers with 10,000 deaths per year this would imply an excess of 14,000 deaths in 14 years. These estimates clearly suggest that urban airborne pollution is a relevant problem for public health.

Intriguing findings can be achieved by studying the correlation between air pollution and single cause mortality rates. It is well established that airborne pollution mainly influence mortality rates as related to chronic obstructive pulmonary diseases (COPD) and cardiovascular diseases, as demonstrated since the severe pollution episode of London in 1952. More recently, high pollution levels in Birmingham (Alabama) have been associated with a relative risk of 1.16 for COPD related death causes (i.e., bronchitis, emphysema, asthma, other occlusive bronchitis, and alveolitis). Similarly, a relative risk of 1.17 was determined for cardiovascular diseases related death causes (i.e., carditis, heart ischemic syndromes, myocardiopathies, arrhythmia and cardiac failure). The relative risk of death for causes other than cardiovascular and COPD origin was only 1.06. Similar data have been also reported by other authors.

Particular problems arise from the possible association between air pollution and increases in death rates related to neoplastic causes. The analysis of historic series takes into account only short periods of interval between pollution levels and death rate changes. Due to the very long latency of neoplasms, increases in cancer incidence occur only after decades of continuous exposures to carcinogenic factors. This interval is further increased when cancer occurrence is re-
lated to exposures to low doses of environmental carcinogens, as in the case of airborne pollution. Therefore, time series approach is not a suitable epidemiological method to evaluate the relationship between cancer and pollution. Long lasting prospective cohort studies constitute the ideal tool to evaluate this relationship. One of the most important prospective study concluded that airborne pollution is related only to lung tumors deaths, with a relative risk of 1.37 in most vs. least polluted city. Transversal studies comparing the number of cancer related deaths between urban and rural areas constitute a more practical tool to evaluate cancer-pollution relationship. The large majority of these studies is mainly focused on lung cancer, but an overwhelming influence of cigarette smoke has been established. It has been reported that risk for cancer development in urban areas over countryside areas is higher by a factor up to 1.5; however, the extent to which urban air pollution contributes to this excess remains unknown. At this regard, one other fruitful approach is the case-control retrospective study. A retrospective cohort study conducted in Copenhagen (Denmark) concluded that the influence of outdoor air pollution on lung cancer death cannot be distinguished from that induced by cigarette smoke or working exposures.

A main problem is that all these studies really need an exhaustive evaluation of individual clinical history. In fact, it has been determined that the previous presence of any lung disease increases the risk of lung cancer development in nonsmokers with a relative risk of 1.56. In addition, an important influence of birthplace on the level of risk for lung cancer development has been also established. Subjects born in rural areas migrating to urban areas possess a significantly decreased relative risk for lung cancer development as compared to individuals born in urban areas. This fact can represent a critical bias affecting transversal studies comparing cancer incidence in urban and rural areas because immigration is by far prevalent in urban districts. Therefore, the real incidence of pollution on lung cancer development could be underestimated in towns having a high immigration rate.

On the whole, the influence of pollution on cancer deaths seems to exist but its entity remains uncertain from the quantitative point of view due to the presence of overwhelming confounding factors.

Qualitative Aspects of the Pollution-Mortality Relationship

As previously reported, mortality is increased at increased pollution levels. Plotting together mortality and pollution data a dose-response mortality-pollution curve can be described (Figure 2). There is a general agreement concerning the morphology of this curve. All main studies describe a linear relationship between mortality and pollution, as expressed by different indicators (Figure 2). On this basis, it could be argued that does not exist any threshold pollution level under which pollution does not influence mortality rates. Therefore, at least from the epidemiological point of view, any no-effect pollution level can be established.

At a variance with the initial part of the curve, whose linearity has been unequivocally defined
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Figure 2: Morphology of the mortality-pollution curve. The correlation is linear at low doses, tending to a plateau at high pollution levels. Pollution is reported as the air concentration of particulate matter having a size lower than 10 µm (PM\textsubscript{10}). A 20 µg/m\textsuperscript{3} increase of PM\textsubscript{10} significantly affects mortality rate mainly at low PM\textsubscript{10} values. (Figure 2, left), controversies exist regarding the morphology of the upper part (Figure 2, right). Studies performed in USA suggest that the linearity of the curve persists also at high pollution level. On the contrary, European but also Chinese studies suggest that mortality rate increases more slowly at high pollution levels, describing a 'hockey stick' curve tending to a 'plateau' at high pollution values. This difference between American and European studies is probably due to the different levels of pollution considered. Usually, pollution levels in US cities are by far lower than in European cities. As an example, a mean level of 89 µg/m\textsuperscript{3} of total particulate matter has been detected in 6 US cities, as compared to the value of 163 µg/m\textsuperscript{3} detected in Athens, Greece or of 139 µg/m\textsuperscript{3} in Milan, Italy. American and European studies examine the same curve, but focusing on different pollution levels. Therefore, it can be established that the pollution-mortality curve tend to a plateau whenever its range includes sufficiently high pollution levels.

The existence of the 'plateau effect' on mortality at high pollution levels implies that mortality is greatly affected by pollution increases at relatively low pollution levels, less affected at high pollution levels. Referring to Figure 2 an increase of 20 µg/m\textsuperscript{3} of PM\textsubscript{10}, (i.e., from 20 to 40 µg/m\textsuperscript{3} on the x-axis) increases the relative risk of mortality for all causes from 1.02 to 1.04; an increase of 20 µg/m\textsuperscript{3} (i.e., from 160 to 180 µg/m\textsuperscript{3}) does not significantly affect mortality. This phenomenon can be attributed to the existence of particular population subcategories mainly contributing to the increase of pollution related mortality.\textsuperscript{3} These susceptible individuals are progressively depleted moving towards the upper part of the curve. When the highest pollution levels are reached, the number of persons particularly sensitive to pollution effects is considerably decreased and cannot contribute any more to increase the mortality rate.

The time interval between the reaching of a pollution level and the arising of related health consequences in the exposed population is defined as latency period. In terms of mortality it should be distinguished between long latency pathologies and sudden clinical episodes. In the first category are included chronic degenerative diseases such as chronic obstructive or restrictive respiratory diseases, tumors, cardiovascular diseases. It is generally well established that pollution constitute an important risk factor contributing to the development of COPD. The finding of polycyclic aromatic hydrocarbon-DNA adducts in human atheromas does not rule out a possible role of pollution also in the development of atherosclerosis and its clinical consequences. Anyway, it has not been established whether polycyclic aromatic hydrocarbons arise from exposure to cigarette smoke, inhalation of polluted air, or consumption of contaminated food.

All these degenerative diseases require years or decades of exposure to their environmental risk factors to became clinically relevant. Therefore, the latency period between exposure to pollution and related chronic degenerative disease appearance is particularly long. In addition to pollution, many other risk factors can exert their influence on the development of chronic degenerative diseases during this time interval. For this reason, it is particularly difficult to establish a causal relationship between pollution and the

\textsuperscript{3} emphasis added. This phenomenon is sometimes called the 'harvesting' effect.—CLS
appearance of chronic degenerative diseases. Of course, it is by far easier to observe short-term effects of pollution in terms of unbalance of previously existing severe clinical situations. Pollution health effects can be studied evaluating the induction of heart failure in patients affected by cardiomyopathies, asthma attacks appearance in susceptible subjects previously affected by respiratory failure. Most studies refer to the short-term increase of mortality as related to pollution level increase. The timespan latency between pollution increase and the short-term mortality rate change has been accurately examined in Birmingham, Alabama. The best correlation exist when daily mortality rate is compared to the mean of PM$_{10}$ (airborne particulate matter having a particle size lower than 10 $\mu$m) concentrations of the 3 previous days. Other authors, referring to Milan (Italy), obtained the best mortality-pollution correlation after one day of interval. They suggest that the higher level of correlation found using the average pollution levels registered during longer intervals constitute an artifact caused by the artificial decrease of pollution data variance.

On the whole, it can be accepted that the latency period between pollution increase and short-term mortality changes, falls in the 1–3 days interval range.

**Regression Curves between Mortality and Specific Pollutants**

Referring to the pollution-mortality curve, the indicator used to describe pollution level should be always specified because the characteristics of this curve greatly change depending on the applied indicator. The best correlation is usually found using the fine airborne particulate matter concentration, which is the air concentration of suspended particles smaller than 10 $\mu$m (PM$_{10}$). This fraction of the total particulate matter possesses the highest biological activity. In fact, particles with a medium size greater than 10 pm are entrapped in the epithelial lining fluid of the upper aerodigestive tract undergoing to expectoration by cough, ingestion, or macrophage phagocytosis, therefore being almost completely devoid of relevant biological effects. Accordingly to these considerations, the correlation between mortality and total particulate matter (PM > 10 $\mu$m + PM$_{10}$) is usually significantly worse than those with PM$_{10}$ alone. Comparing PM$_{10}$ and PM$_{2.5}$ (air concentration of suspended particles smaller than 2.5 $\mu$m) related mortality indexes a stronger association was found with PM$_{2.5}$. It should also be noted that ultrafine particles, having an average size lower than 0.05 $\mu$m, presumably possess low biological activity because they are almost completely emitted during expiration without being retained into the lung. Therefore, the best pollution indicator to be considered for the study of pollution-mortality relationship is the particulate matter with an average particle size of 0.05–10 $\mu$m.

Use of other pollution indicators strictly depends on the specific characteristics of the area under study. In case of winter-like pollution, mainly related to house warming emissions, mortality is significantly related to the level of sulfur dioxide, as demonstrated in Berlin (Germany). In case of summer-like pollution, involving the occurrence of high temperatures, strong sun irradiance and consequent increases in pollutant photoactivation phenomena, good results can be obtained by comparing mortality with the levels of ozone and nitric oxides, as demonstrated in San Paolo (Brazil), and Mexico City (Mexico). A statistically significant correlation between ozone levels and mortality has been found only during May–October 1995, and not in the other months of the same year in Genoa (Italy).

These data suggest that macroclimate related factors greatly influence pollution characteristics and its consequences on the exposed population. Wind speed is inversely related to pollution levels, raining can modify air-suspended pollutants composition, sun irradiance causes photochemical modifications of several pollutants, etc. The climate factor mainly affecting mortality indexes is the environmental temperature. Mortality is significantly increased in day characterized by excessively low or high temperatures. It has been demonstrated in Milan, Italy, that the relative mortality risk related to respiratory diseases progressively increases from 1.0 at 23 °C up to 2.6 at > 29 °C. Similarly, it has been reported in Athens (Greece) a dramatic increase of the daily number of deaths when the mean daily temperature exceed 30 °C. These data suggest that mortality increases in an exponential manner at high levels of temperature (Figure 4). The increasing level of oxidative pollutants induced by the increased sun irradiance during the hottest days probably contributes to the occurrence of this phenomenon. It has been demonstrated that air pollution and temperature synergistically interact to increase mortality during summertime. Of course, possible direct influences of temperature on previously com-
promised cardiovascular apparatus could represent an additive mechanism contributing to the mortality increase. Probably, a similar trend occurs also at extremely low temperatures. It has been verified an antagonistic effect of temperature increase towards mortality rates during wintertime. In particular, a 5 °C increase in temperature is associated with a 2% decline in daily mortality. The increase of house-warming pollution at low temperature probably contributes to the occurrence of this phenomenon.

On the whole, available data suggest that the influence of temperature on daily mortality is partially mediated by its effects on pollution. From the quantitative point of view, the correlation between temperature and mortality rate can be described by a U curve, characterized by exponential mortality increases at lowest and highest temperature values (Figure 3).

Pollution-Mortality Correlation in Particular Population Categories

It has been established that pollution-related mortality increase does not involve the whole exposed population but mainly affects several population categories. The 'plateau' morphology of the upper part of the pollution-mortality curve (Figure 2) is caused by the previously referred depletion of individuals highly susceptible to pollution related health effects. The category possessing the highest risk has been identified in the elderly. It has been reported during highly polluted days a significant increase in mortality due to respiratory causes only in subjects older than 65 years, both in South America and Europe.

An increased pollution-related mortality in subjects previously affected by cardiovascular diseases or COPD has been also reported, thus indicating that also these subjects are particularly susceptible to pollution induced health effects.

Other factors increasing individual susceptibility towards pollution effects are represented by respiratory infective diseases, with particular reference to influenza. Influenza epidemics can determine a 15% increase in monthly mortality rate. It is highly presumable that Orthomyxoviridae infected subjects constitute a subcategory at high risk for the appearance of pollution-induced health effects, as following discussed.

As far as concern the youngest population and children, unfortunately retrospective epidemiological studies performed in this category are usually affected by confounding variables of great relevance, such as the high incidence of infective diseases, hampering the clear evaluation of pollution effects on mortality. In addition, it should be considered that in developed countries pediatric mortality is by far lower than mortality in subjects older than 65 years. Therefore, studies concerning the influence of pollution on mortality rate possess the highest power in the elderly, the lowest in young and middle aged subjects.

Hypotheses of Causality of Pollution-Mortality Relationship

The existence of a correlation between pollution and mortality is almost undoubtedly established. However, it remains to be clarified whether or not this relationship fits the causality criterion. For this purpose, several characteristics of the association should be taken into account including: (a) dose-response association (b) epidemiological evidence (c) time course occurrence (d) biological plausibility. Epidemiological studies affirmatively answer to points (a), (b), and (c), as previously reported. Toxicological studies examine point (d). Several pathogenetic mechanisms have been described by experimental studies to explain the increase of respiratory and cardiovascular mortality induced by pollution (Table 2).

As far as concern cardiovascular diseases, it is well documented that mixtures of airborne genotoxicants exert the highest genotoxic effects in the heart. Toxicokinetic and toxicodynamic reasons justifying the particular susceptibility of the heart to inhaled pollutants has been extensively analyzed. They include a low mitoses rate, low DNA repair capability, high perfusion-mass rate, metabolic attitudes of this organ. Therefore, pollution-induced heart DNA damage could overwhelm DNA repair capacities thereby affecting myocardial inotropism or specific myocardial cell function, thus worsening pre-existing heart failures or arrhythmia situations. Type I immunopathological reactions and acute inflammatory episodes, such as those occurring in susceptible subjects exposed to airborne pollution, induce the systemic release of tromboxane, which increases blood coagulation rate getting easier the occurrence of heart infarctions. A study involving a population of 3256 randomly selected individuals established an increase in plasma viscosity during severe air pollution episodes.
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As far as concern COPD, it is well established that airborne pollution favors chronic bronchitis. In addition, oxidative pollutants can peroxidize mastcell membranes determining the release of vasoactive histamine-related mediators inducing acute bronchi obstruction and asthma attacks. Oxidative pollutants are also involved in the inhibition of proteolytic enzyme suppressors, such as α-1-antitrypsin. This mechanism has been involved in lung emphysema development. A particular situation occurs in the respiratory apparatus during Orthomyxoviridae infection. These viruses disrupt the ciliated epithelia thereby allowing airborne pollutants to bypass this fundamental defensive mechanism. Therefore, it seems reliable that influenza affected or convalescent patients constitute a category highly susceptible to pollution-related health consequences.

On the whole, reported data support the hypothesis that the influence of pollution on mortality fits a causality relationship. It should be emphasized that short-term pollution related mortality mainly affects diseases recognizing a great number of other environmental and lifestyle related risk factors. Pollution is only one of them, and although may cause a sudden death, this happens only in patients who have been undergoing for years the influence of many other risk factors. 4 In this light, it is very difficult to quantify pollution-related life-shortening in affected peo-

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Table 2: Data supporting the causality of the association between airborne pollution and cardiovascular disease related mortality

<table>
<thead>
<tr>
<th>Experimental data</th>
<th>Description</th>
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<tbody>
<tr>
<td>Indirect influence of airborne pollutants on cardiovascular apparatus</td>
<td>Immunopathological reactions and inflammatory phenomena induced by airborne pollutants in the respiratory apparatus release biological mediators increasing blood coagulability and viscosity. An increase in blood viscosity in urban dwellers during days with high levels of airborne pollutants has been demonstrated.</td>
</tr>
<tr>
<td>Direct influence of airborne pollutants on cardiovascular apparatus</td>
<td>Heart is the most susceptible organ to genotoxic damage induced by exposures to airborne pollutants mixture, such as cigarette smoke. This data has been demonstrated both in animal and humans. Increase of genotoxic damage in heart could affect myocardial functions worsening preexisting arrythmias and heart failures. It has been demonstrated in humans that exposure to mixtures of airborne genotoxicants is related to an increase of DNA damage in aortic smooth muscle cells. It is not clear whether or not environmental pollution is able to induce similar phenomena.</td>
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4 another aspect of the ‘harvesting’ effect of pollution episodes.—CLS
Conclusions

On the basis of the above mentioned considerations, airborne pollution can be undoubtedly considered an important hazard for the health of urban populations. However, pollution is not per se sufficient to induce short-term mortality increases, but moreover contributes to significantly worsen preexisting severe clinical situations. This conclusion is supported by the existence of a prevalent pollution related mortality in patients previously affected by cardiovascular diseases, COPD or older than 65 years.

Mortality evaluation is a fundamental epidemiological tool for the monitoring of pollution induced health effects. It is of great importance to look at population mortality rates not only evaluating the effects of high pollution levels, but, moreover, checking the biological impact of relatively low pollution levels. In fact, because of the linearity of pollution-mortality relationship, no threshold pollution level devoid of biological consequences on the exposed population can be established. The frequent use of threshold values in pollution evaluation is mainly a practical tool for health public interventions but does not possess a serious meaning from the epidemiological point of view. As a consequence, pollution levels should be always maintained at the lowest possible level and not only under ‘threshold’ values. On this basis, mortality can be retained as a sensitive indicator for the continuous monitoring of population exposed not only to high but moreover to low pollution levels.

Questions

1. External research. What is epidemiology?

2. External research. The authors mention ‘famous episodes’ of localized, transient high air pollution; such are sometimes called killer smog episodes. Construct a list of the most famous killer smogs, including place, date, and an estimate of the mortality for each episode.

3. What exactly are ‘confounding factors’?

4. What exactly are the relative risks that the authors quote for various studies?

5. Describe the three major epidemiological methods, along with their advantages and disadvantages.

6. The most common epidemiological method used to study the health effects of air pollution is the time series study. Why do you suppose that is?

7. Why is the study of the connection between air pollution and lung cancer so complicated?

8. What is the explanation put forth for the ‘plateau’ in the dose-response curve for air pollution mortality?

9. What pollutant is most strongly correlated with mortality rate in the epidemiology studies surveyed by the authors? What other pollutants are also significant?