

# The Impact of Air Pollution on Chronic Respiratory Diseases

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## Abstract

Air pollution is one of the world's most serious environmental problems. Air pollutants continue to be major contributing factors to chronic respiratory diseases (such as chronic obstructive pulmonary disease and asthma), cardiovascular diseases, and cancer. We conducted a systematic literature review to provide some insight into what we currently know about the health problems associated with various air pollutants (especially ozone and particulate matter) and their relationship in promoting chronic respiratory diseases. Additionally, an overview of methodology used for evaluating the impact of air pollution on chronic respiratory diseases was done. A literature search targeted studies on the association between the effects of air pollution and respiratory health endpoints published between January 2000 and June 2010.

**Keywords:** air pollution, chronic obstructive pulmonary disease, asthma, morbidity, mortality

## Introduction

In the last two decades epidemiological research has shown the significant impact of air pollution on population health. Growing evidence indicates that increasing levels of ambient air pollution are associated with exacerbation of chronic diseases, like chronic pulmonary diseases and respiratory health effects [1-3]. The adverse health effects associated with air pollution may be attributable to short-term (a few minutes to 24 h) exposure or long-term (months to decades) exposure, and different pollutants may have widely different exposure-response characteristics [2, 4].

Ambient air pollution consists of a highly variable, complex mixture of different substances that may occur in

gas, liquid, or solid phase. Common outdoor pollutants, identified as being of greatest concern from a health perspective, are particulate matter (PM), nitrogen dioxide (NO<sub>2</sub>), carbon monoxide (CO), volatile organic compounds, and ozone (O<sub>3</sub>). Urban ambient air pollution is the result of emissions from multiple sources, mainly stationary, industrial, and domestic fossil fuel combustion, and petrol and diesel vehicle emissions [2].

Among all air pollutants, PM is the type of air pollution that causes the most serious effects on human health, because it contains a broad range of diverse toxic substances [5]. The term PM is used to describe airborne solid particles and/or droplets. These particles may vary in size, composition and origin. Based on size, urban PM tends to be divided into three groups: coarse (larger than 1 µm, usually defined as the difference between PM<sub>10</sub> and PM<sub>2.5</sub>),

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fine, (smaller than 1  $\mu\text{m}$ , usually measured as  $\text{PM}_{2.5}$ ) and ultrafine particles (UFP) smaller than 0.1  $\mu\text{m}$ . In the air pollution regulations of PM there are two main categories,  $\text{PM}_{2.5}$  and  $\text{PM}_{10}$ , which refer to particles with aerodynamic diameter smaller than 2.5  $\mu\text{m}$  and 10  $\mu\text{m}$ , respectively [6]. Chemical composition of ambient PM varies widely as a function of its main emission sources and of the chemical reactions that take place in the atmosphere. The major components of PM are transition metals, ions (sulfate, nitrate), organic compound, quinoid stable radicals of carbonaceous materials, minerals, reactive gases, and materials of biologic origin. The health effects associated with ambient exposure to  $\text{PM}_{10-2.5}$  (coarse particles) differ from those of  $\text{PM}_{2.5}$  (fine particles) according to the sites of deposition in the respiratory tract and chemical composition. Coarse particles, which are produced primarily by processes such as mechanical grinding, windblown dust, and agricultural activities, deposit preferentially in the upper and larger airways. Particles  $\text{PM}_{2.5}$  in size, which are more likely to result from combustion processes, can reach smaller airways and alveoli [5, 7]. Numerous epidemiological studies [5, 7-9] have found a strong exposure-response relationship between PM for short-term effects (premature mortality, hospital admissions) and long-term or cumulative health effects (morbidity, lung cancer, cardiovascular, and cardiopulmonary diseases).

Ozone, a highly reactive form of oxygen that is the primary component of urban smog, is commonly known as an irritant air pollutant. In several studies respiratory morbidity, including asthma and chronic obstructive pulmonary disease (COPD), has been linked with the short-term changes in  $\text{O}_3$  levels [10, 11]. Results of epidemiological studies addressing long-term effects of ozone are not entirely consistent. Several studies indicate that an increase in ground-level ozone may actually cause asthma [12-14].

## Method

### Data Source and Literature Search Strategy

We performed a systematic review of the literature focused on the short-term and long-term effects of outdoor air pollution (in particular PM and  $\text{O}_3$ ) on respiratory health outcomes, published between January 2000 and June 2010. The data source was the MEDLINE electronic database searched via PubMed, using topic-related search terms, either alone or in combination, both for exposure and for health outcomes.

**Key words and search strategy:** The search strings consisted of next words: (“Ozone” or “Particulate Matter”) and (“Pulmonary Disease” or “Respiratory Disease” or “Asthma”) and (“Incidence” or “Prevalence” or “Morbidity” or “Mortality”). The search was restricted to humans and to articles published in English.

**Data processing and quality assessment:** Eligible studies were appraised by two independent reviewers who also extracted data. Discrepancies were resolved through a third reviewer. Titles and abstracts of the identified citations were

screened to select articles according to the rating relevance, based on the following criteria:

1. Extremely relevant papers – if data about incidence, prevalence or mortality are presented in the abstract.
2. Quite relevant papers – data about incidence, prevalence or mortality are not presented in the abstract, but a researcher can conclude from the title and abstract that they are presented in the full text paper.
3. Marginally relevant papers – data about incidence, prevalence or mortality are not presented in the abstract, and a researcher can conclude from the title and abstract that they are probably also not presented in the full text.

Out of 318 identified papers, 68 were selected as extremely relevant, 100 as quite relevant, and 150 articles were of marginal relevance. Only extremely relevant papers were recommended for further reading.

The full text papers were rated for quality of research as high, medium, or low. The quality assessment was based on the following criteria:

- clearly stated aims
- appropriate methods are used
- well constituted context of the study
- clearly described, valid, and reliable results
- clearly described analysis
- possible influences of the outcome are considered
- conclusion is linked to the aim, analysis, and interpretation of results of the study
- limitations of research are identified

Based on previous criteria, the best-rated articles [36] were recommended for final analysis.

Number of identified papers through data processing and quality assessment are presented in Fig. 1.

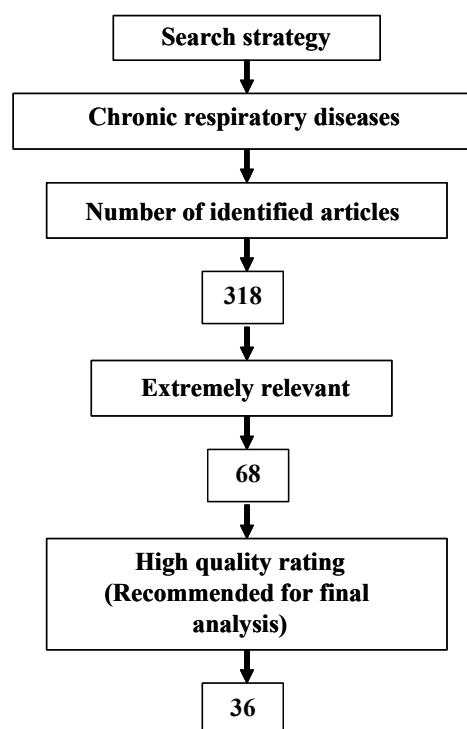


Fig. 1. Search strategy for systematic review of air pollution adverse effects on the respiratory system.

## Results

### Methods Used in the Reviewed Studies

Assessing the health effects of ambient air pollution on individuals in a population is the primary goal of air pollution epidemiology studies. Epidemiologic studies of air pollution look for association between the exposure of interest (levels of O<sub>3</sub>, particulates, and other pollutants) and health outcome using statistical methods. In practice, most of the air pollution studies on humans have been observational studies: ecological time-series, case-crossover, panel, and cohort studies, while cross-sectional studies are less common. The time-series, case-crossover, and panel studies are best suited for estimating the acute effects of air pollution, while cohort studies estimate acute and chronic effects combined [6].

The time-series studies associate time-varying pollution exposure to time-varying event counts [10, 15-17]. The time-series studies of PM examine association over time in one area, between daily changes in PM<sub>10</sub> and daily counts of mortality or hospitalizations, controlling for other factors [17]. These studies can control for effects of weather and season [15].

The case-crossover design is used to estimate the risk of a respiratory event associated with a short-term exposure. The case-crossover design is a variant of the matched case-control design in which a case subject becomes a control subject on days when no event (hospital admission) occurs. It has been shown that the case-crossover design is best suited to study intermittent exposures inducing immediate and transient risk, and abrupt rare outcomes [11, 18]. For example, to evaluate the effect of short-term exposure of O<sub>3</sub> and PM<sub>10</sub> on respiratory hospital admissions for pneumonia and COPD, a large multi-city study was conducted [11]. The case-crossover analysis in which a case subject becomes a control subject on days when no hospital admission occurs was used. Study confirmed that short-term increases in PM<sub>10</sub> and O<sub>3</sub> ambient concentrations are related to hospital admissions for COPD and pneumonia, especially during seasonally warm periods.

Panel studies enroll a cohort or panel of individuals and follow them over time to investigate changes in repeated outcome measures [1]. They are most effective for studying short-term health effects of air pollutants, particularly in the susceptible subpopulation. The panel study design is commonly used to study chronic disease exacerbations such as daily asthma symptoms, COPD, or lung function [1].

Air pollution cohort studies associate long-term exposure with health outcome. Either a prospective or retrospective design is possible. In the prospective design participants are followed over time for mortality or other health events [9, 14, 19, 20]. A measure of cumulative air pollution is often used as an exposure variable. Cohort studies might estimate a combination of acute and chronic effects because the outcomes accumulate over long time periods and could be triggered by either cumulative or short-term peak exposures. Thus, although estimation of chronic effects is one goal of cohort studies, these may not be separable from the acute effects of exposure [3].

### Effects of Air Pollution on Morbidity and Mortality of Chronic Respiratory Diseases

Although the mechanisms are not fully explained, epidemiological evidence suggests that outdoor air pollution is a contributing cause of morbidity and mortality of chronic respiratory diseases all over the world [3, 7, 9, 18, 20].

Results from toxicological research have shown several mechanisms of adverse effects, such as cytotoxicity through oxidative stress mechanisms, oxygen-free radical-generating activity, DNA oxidative damage, mutagenicity, and stimulation of proinflammatory factors [1, 6]. Air pollution exposure involves the contact of pollutants with the respiratory tract, such exposure being measured according to two parameters: intensity and duration. The pathogenic effects of environmental pollution on the organism fall into two categories: acute or short-term effects, and chronic or long-term effects, depending on the time required from exposure to the manifestation of its effect [5].

#### Short-Term Effects

##### *Hospital Admission*

Air pollution has been associated with hospital admissions for respiratory diseases in cities all over the world. The most common and consistent associations have been found with PM and ozone [11, 15].

Relatively few studies of the association between air pollution and emergency department visits have been conducted [10, 15]. In the large multicenter analysis of Stieb et al. [15] associations were examined between CO, NO<sub>2</sub>, O<sub>3</sub>, SO<sub>2</sub>, and PM<sub>10</sub> and PM<sub>2.5</sub>, and visits for various cardiac and respiratory conditions (asthma, COPD and respiratory infections). Daily average concentrations of CO and NO<sub>2</sub> exhibited the most consistent associations with emergency department visits for cardiac conditions, while O<sub>3</sub> exhibited the most associations with visits for respiratory conditions. PM<sub>10</sub> and PM<sub>2.5</sub> were strongly associated with asthma visits during warm periods. Significant associations between O<sub>3</sub> concentrations and asthma-related emergency department visits among children were also found in the study of Babin et al. [10].

In a large-scale epidemiological study of respiratory hospital admissions in children, carried out in the largest cities in Australia and New Zealand, positive associations were observed for PM<sub>2.5</sub> and PM<sub>10</sub>, for several childhood respiratory diseases including pneumonia, bronchitis and asthma [21].

Halonen et al. [17] found that most particle fractions had positive associations with hospital admissions for pneumonia, asthma, and COPD among the elderly ( $\geq 65$  years). The overall associations were stronger for respiratory than for cardiovascular outcomes.

Lung function and exacerbations of COPD have been associated with short-term exposure to air pollution. In a large case-crossover study of Medicare recipients in 36 U.S. cities, Medina-Ramon et al. [11] found that the risk of

daily hospital admissions for COPD and pneumonia increased with short-term increases in ozone concentrations during the warm season. Findings suggest that some city characteristics modify the effect of air pollution on respiratory hospital admissions. It was shown that use of central air conditioning decreases the effect of air pollution and that variability of summer temperature decreases the effect of ozone on COPD [11].

In the study of Sauerzapf et al. [22], no associations were observed between O<sub>3</sub> or particulates and the risk of hospital admission for COPD.

Yamazaki and coauthors conducted case-crossover design study to examine the association between short-term exposure to outdoor air pollution and nighttime primary care visits due to asthma attack [18]. They found the association between ozone and visits for asthma attack in warm months, which was greater among preschool children. There was no association between ozone and primary care visits among adults. Similar results were reported by Halonen et al. [23] who found that ambient O<sub>3</sub> exacerbated asthma and COPD among the elderly, and asthma among children during the warm season, and that adults seem to be less sensitive to the effects of O<sub>3</sub>.

In a systematic review and meta analysis Weinmayr et al. [2] found clear evidence of effects of PM<sub>10</sub> on the occurrence of asthma symptom episodes, and to a lesser extent on cough and Peak Expiratory Flow (PEF).

Epidemiological studies also have shown that short-term effects of O<sub>3</sub> can be enhanced by PM, and vice versa, and that O<sub>3</sub> may facilitate responses to allergens [12, 13, 23].

Kiechl-Kohlendorfer et al. [24] reported that living at higher altitude was associated with an enhanced risk of hospitalization for atopic asthma (RRs 2.08, 95%CI (1.45-2.98) and 1.49 (1.05 to 2.11) for the comparison between altitude categories ( $\geq 1200$ , 900-1199 m vs  $<900$  m;  $p < 0.001$ ). The risk for asthma hospitalization increased by 7% to each 100 m increase in altitude ( $p = 0.013$ ). Altitude characteristics (declining with outdoor temperature, air humidity, and ozone levels) could be operative in underlying mechanisms of triggering and attenuating lung function.

There is evidence that low birth weight (LBW) and prematurity are associated with reduced lung function, higher levels of airway reactivity, and increased susceptibility to lung damage. Large multicenter study of inner-city children with asthma evaluated a series of demographic, host, and home environment characteristics that may modify response (symptomatic and pulmonary functional) to urban air pollution [25]. Asthmatic children born prematurely or with LBW have the greatest response to ozone. Children of LBW or of premature birth appear to be more susceptible to the effects of air pollution than children of normal birth weight or full-term gestation.

Experimental data suggest that asthma exacerbation by ambient air pollutants is enhanced by exposure to endotoxins and allergens. McConnel et al. [26] found a strong association between bronchitic symptoms and air pollutants

like PM<sub>10</sub>, PM<sub>2.5</sub>, and PM<sub>10-2.5</sub> among asthmatic children owning a dog (indicator of allergen and endotoxin exposure). Results suggest that exposure to endotoxins and allergens may worsen the relationship between air pollution and respiratory symptoms in asthmatic children [26]. An interaction between endotoxin and oxidant air pollutants is a plausible explanation.

The relationship between air pollution concentrations and total IgE levels in adult asthmatics was examined in a study of 369 asthmatic adults from the French Epidemiological study on Genetics and Environment of Asthma (EGEA). Ozone concentrations were positively related to total IgE levels and an increase of 10 mg/m<sup>3</sup> of O<sub>3</sub> resulted in an increase of 20.4% (95% CI=3.0-40.7) in total IgE levels. Ozone and ambient pollutants may up-regulate total IgE levels among asthmatic adults. Adjustment for age, gender, smoking habits, and previous life in the countryside did not change the results [27].

### Mortality

Numerous studies have shown associations between ambient air pollution and daily mortality [5, 23]. It was shown that outdoor air pollution is also associated with respiratory premature mortality. A short-term link between the levels of ozone and PM<sub>10</sub> and mortality for respiratory causes was found in a study by Siccard et al. [4]. By considering the ozone mean values in urban areas during 1997-2005, an increase of 3.0% year<sup>-1</sup> was obtained with annual averages and 3.9% year<sup>-1</sup> with median values. A clear increasing trend for PM<sub>10</sub> ambient concentrations was also obtained. Over the same period an annual change rate of +0.31% year<sup>-1</sup> for "airway diseases" was identified. Fischer et al. [16] found that the elderly (over 65 years) are at higher risk for acute mortality effects of air pollution compared to younger age groups. Statistically significant associations were found for O<sub>3</sub> (total and COPD mortality), PM<sub>10</sub> (pneumonia), NO<sub>2</sub> (pneumonia), and CO (pneumonia). Children are uniquely predisposed to the potentially harmful effects of PM and O<sub>3</sub> [2, 15].

The main characteristics and results of the above-mentioned short-term studies are presented in Table 1.

### Long-Term Effects

#### Morbidity in Adults

Strong epidemiological evidence suggests that exposure to PM air pollution causes exacerbations of pre-existing lung conditions, such as COPD, resulting in increased morbidity and mortality. However, little is known whether chronic low-grade exposure to ambient PM can cause the development and progression of COPD [28]. Vulnerable groups (COPD) and the elderly seem to be susceptible to air pollution at lower levels than the general population.

According to the Swiss Study on Air Pollution and Lung Disease in Adults (SAPALDIA), a -3.14% decrease in forced vital capacity (FVC) per 10 µg/m<sup>3</sup> increment in PM<sub>10</sub>



Table 1. Main results from selected short-term studies.

| Authors and year of publication | Study design                            | Year(s) of study | Site of study             | Population                        | Pollutant(s)                    | Health outcome               | Main results (Odds Ratio or Hazard Ratio 95% Confidence Intervals)    |
|---------------------------------|---|------------------|---------------------------|-----------------------------------|---------------------------------|------------------------------|---|
| Medina-Ramon et al., 2005 [11]  | Case-crossover                          | 1986-99          | USA                       | Adults (≥ 65y)                    | O <sub>3</sub> (lag 2)          | COPD HA                      | 0.27% 95%CI: 0.08-0.47% increase per 5 ppb, worm s.                   |
|                                 |   |                  |                           |                                   | O <sub>3</sub> (lag 2)          | Pneumonia HA                 | 0.41% 95%CI: 0.26-0.57% increase per 5 ppb, worm s.                   |
|                                 |   |                  |                           |                                   | PM <sub>10</sub> (lag 1)        | COPD HA                      | 1.47% 95%CI: 0.93-2.01% increase per 10 µg/m <sup>3</sup> , worm s.   |
|                                 |   |                  |                           |                                   | PM <sub>10</sub> (lag 0)        | Pneumonia HA                 | 0.84%, 95%CI: 0.50-1.19% increase per 10 µg/m <sup>3</sup> , worm s.  |
| Stieb et al., 2009 [15]         | Time-series                             | 1990-2000        | Canada                    | Children and adults (all ages)    | O <sub>3</sub> (lag 2)          | Asthma EDV                   | 3.2% 95%CI: 0.3-6.2% increase per 18.4 ppb                            |
|                                 |   |                  |                           |                                   | O <sub>3</sub> (lag 2)          | COPD EDV                     | 3.7% 95%CI: -0.5-7.9% increase per 18.4 ppb                           |
|                                 |   |                  |                           |                                   | PM <sub>10</sub>                | Asthma EDV                   | 14.4% 95%CI: 0.2-30.7% increase per 20.6 µg/m <sup>3</sup> worm s.    |
|                                 |   |                  |                           |                                   | PM <sub>2.5</sub>               | Asthma EDV                   | 7.6% 95%CI: 5.1-10.1 increase per 8.2 µg/m <sup>3</sup> worm s.       |
| Babin et al., 2007 [10]         | Time-series                             | 2001-04          | USA                       | Children (5-12y)                  | O <sub>3</sub>                  | Asthma EDV                   | 3.2% 95%CI: 1.4-5.0% increase per 0.01 ppm                            |
|                                 |   |                  |                           |                                   | O <sub>3</sub>                  | Asthma EDA                   | 8.3% 95%CI: 2.6-14.4% increase per 0.01 ppm                           |
|                                 |   |                  |                           |                                   | PM <sub>2.5</sub>               | Asthma EDV                   | n.s.  |
|                                 |   |                  |                           |                                   | PM <sub>2.5</sub>               | Asthma EDA                   | n.s.  |
| Barnett et al., 2005 [21]       | Meta-analyses of case crossover studies | 1998-2001        | Australia and New Zealand | Children (1-14y)                  | PM <sub>10</sub>                | Respiratory HA               | OR=1.7-1.9 95%CI: 0.1-3.8   |
|                                 |   |                  |                           |                                   | PM <sub>2.5</sub>               | Respiratory HA               | OR=1.7-2.4 95%CI: 0.7-3.8   |
|                                 |   |                  |                           |                                   | PM <sub>2.5</sub>               | Pneumonia+ac.br.             | OR=1.7-2.4 95%CI: 0.0-4.7   |
| Halonen et al., 2009 [17]       | Time-series                             | 1998-2004        | Europe, Finland           | Adults (≥ 65y)                    | PM (lag 5)                      | Pneumonia, HA                | 3.1% 95%CI: 0.43-5.8  |
|                                 |   |                  |                           |                                   | PM (lag 0)                      | Asthma/COPD HA               | 3.8% 95%CI: 1.3-6.3   |
|                                 |   |                  |                           |                                   | PM (lag 0)                      | Respiratory Mt               | 5.1% 95%CI: 1.2-9.0   |
| Sauerzapf et al., 2009 [22]     | Case-crossover                          | 2006-07          | UK                        | Adults (≥18y)                     | O <sub>3</sub>                  | COPD, HA                     | n.s.  |
|                                 |   |                  |                           |                                   | PM <sub>10</sub>                |                              | n.s.  |
| Yamazaki et al., 2009 [18]      | Case-crossover                          | 2002-03          | Japan                     | Children (0-14y)                  | O <sub>3</sub>                  | Asthma EDV                   | OR=1.16 95%CI: 1.00-1.33% increase per 10 ppb, worm s.                |
|                                 |   |                  |                           |                                   | PM <sub>2.5</sub>               | Asthma EDV                   | OR=1.29 95%CI: 1.08-1.55% increase per 10 µg/m <sup>3</sup> , worm s. |
| Weinmayr et al., 2010 [2]       | Systematic review – Meta-Analysis       | 1990-2008        | Europe and other          | Children (15-19y)                 | PM <sub>10</sub>                | Asthma symptoms              | OR=1.028 95%CI: 1.006-1.051   |
|                                 |   |                  |                           |                                   | O <sub>3</sub>                  | Asthma (bronchitic symptoms) | OR=1.41 95%CI: 1.05-1.88% per 4.3 ppb                                 |
| McConnell et al., 2006 [26]     | Cohort follow-up                        | 1996-99          | USA                       | Children owning dog               | PM <sub>10-2.5</sub>            |                              | OR=1.30 95%CI: 0.91-1.87% per 4.2 µg/m <sup>3</sup>                   |
|                                 |   |                  |                           |                                   | PM <sub>10</sub>                |                              | OR=1.60 95%CI: 1.12-2.30% per 4.2 µg/m <sup>3</sup>                   |
| Friedman et al., 2001 [12]      | Time-series                             | 1996             | Atlanta                   | Children (1-16 y)                 | O <sub>3</sub>                  | Asthma EDV + HA              | RR = 0.48 95%CI: 0.44-0.86 per O <sub>3</sub> decrease of 27.9%       |
| Fischer et al., 2003 [16]       | Time-series                             | 1986-94          | Europe, Netherland        | Adults (< 65y)<br>Adults (65-74y) | O <sub>3</sub> (lag 1)          | COPD Mt                      | RR=2.137 95%CI: 1.26-3.63   |
|                                 |   |                  |                           |                                   | PM <sub>10</sub> (lag 0-6 days) | Pneumonia Mt                 | RR=1.597 95%CI: 1.16-2.19   |

EDV – emergency department visit, EDA – emergency department admission, HA – hospital admission, Mt – mortality, s – season, y – year, n.s. – not significant, ac.br- acute bronchitis

Table 2. Main results from selected long-term studies.

| Authors and year of publication | Study design                        | Year(s) of study | Site of study       | Population                 | Pollutant(s)                                | Health outcome       | Main results<br>(Odds Ratio or Hazard Ratio 95% Confidence Intervals) |
|---------------------------------|-------------------------------------|------------------|---------------------|----------------------------|---|----------------------|---|
| Schikowski et al., 2005 [30]    | Consecutive cross-sectional studies | 1985-94          | Europe, Germany     | Adults (women 55y)         | PM <sub>10</sub>                            | COPD                 | OR=1.33 95% CI: 1.03-1.72 per 7 µg/m <sup>3</sup> in 5y mean          |
|                                 |                                     |                  |                     |                            | Dist. HTRs <100m                            | COPD                 | OR=1.79 95% CI: 1.06-3.02   |
|                                 |                                     |                  |                     |                            | PM <sub>10</sub>                            | FEV1 decrease        | 5.1% 95% CI: 2.5%-7.7% per 7 µg/m <sup>3</sup> in 5y mean             |
|                                 |                                     |                  |                     |                            | Dist. HTRs <100m                            | Cough                | OR=1.24 95% CI: 1.03-1.49   |
| Cesaroni et al., 2011 [31]      | Cross-sectional                     | 1994-95          | Europe, Rome        | Adults (25-59y)            | SRT   | Asthma               | OR=1.46 95% CI: 1.05-2.03   |
|                                 |                                     |                  |                     |                            | SRT   | Rhinitis             | OR=1.30 95% CI: 1.05-1.62   |
|                                 |                                     |                  |                     |                            | Dist. from HTRs                             | Rhinitis             | OR=1.18 95% CI: 0.96-1.44   |
|                                 |                                     |                  |                     |                            | PME   | Rhinitis             | OR=1.37 95% CI: 1.14-1.64   |
| Ofstedal et al., 2009 [33]      | Cross-sectional (birth cohort)      | 2001-02          | Europe, Norway      | Children (9-10y)           | Dist. from HTRs                             | Asthma               | n.s.  |
|                                 |                                     |                  |                     |                            | TPM <sub>10</sub>                           | Asthma I             | HR=1.30 95% CI: 1.05-1.61 per 1 µg/m <sup>3</sup> change              |
| Kunzly et al., 2009 [13]        | Cohort                              | 1991-2002        | Europe              | Adults (16-60y)            | PM <sub>10</sub> (87ng/m <sup>3</sup> )     | Chr. phlegm          | OR=3.21 95% CI: 1.55-6.67   |
|                                 |                                     |                  |                     |                            | PM <sub>10-2.5</sub> (42ng/m <sup>3</sup> ) | Bronchitis           | OR=2.20 95% CI: 1.14-4.26   |
|                                 |                                     |                  |                     |                            | PM <sub>10-2.5</sub> (42ng/m <sup>3</sup> ) | Chr cough            | OR=1.46 95% CI: 1.12-1.90   |
|                                 |                                     |                  |                     |                            | PM <sub>10-2.5</sub> (42ng/m <sup>3</sup> ) | Chr. phlegm          | OR=2.83 95% CI: 1.93-4.16   |
|                                 |                                     |                  |                     |                            | TSP (263ng/m <sup>3</sup> )                 | Bronchitis           | OR=2.22 95% CI: 1.47-3.34   |
|                                 |                                     |                  |                     |                            | TSP (263ng/m <sup>3</sup> )                 | Chr. cough           | OR=1.35 95% CI: 1.02-1.79   |
| Zhang et al., 2002 [7]          | Cross-sectional                     | 1993-96          | China               | Children (5-12y)           | TSP (263ng/m <sup>3</sup> )                 | Chr. phlegm          | OR=2.52 95% CI: 1.97-3.21   |
|                                 |                                     |                  |                     |                            | PM <sub>10</sub> (87ng/m <sup>3</sup> )     | Asthma I             | OR=1.28 95% CI: 1.10-1.49 for increase in 3.2 µg/m <sup>3</sup>       |
|                                 |                                     |                  |                     |                            | PM <sub>2.5</sub>                           | Asthma P             | OR=1.26 95% CI: 1.04-1.51 for increase in 3.2 µg/m <sup>3</sup>       |
| Gehring et al., 2010 [19]       | Prospective birth cohort            | 1996-97          | Europe, Netherlands | Children (0-8y)            | PM <sub>2.5</sub>                           | Asthma               | RR=3.3 95% CI: 1.9-5.8  |
|                                 |                                     |                  |                     |                            | O <sub>3</sub> (high)                       | Asthma               | RR=2.0 95% CI: 1.1-3.6  |
| McConnell et al., 2002 [14]     | Cohort                              | 1993-98          | California, USA     | Young people (9-16y)       | PM <sub>10</sub> (high)                     | Pulmonary disease    | HR= 1.39 95% CI: 0.91-2.11 (8 km buffer)                              |
| Ostro et al., 2010 [9]          | Prospective cohort                  | 2002-07          | USA                 | Adults (female)            | PM <sub>2.5</sub>                           | Mt                   | HR=1.43 95% CI: 1.21-1.69 (30 km buffer)                              |
|                                 |                                     |                  |                     |                            | PM <sub>10</sub> (high)                     | COPD Mt              | RR=0.96 95% CI: 0.73-1.24 per 10 µg/m <sup>3</sup> increase           |
| Pope et al., 2004 [20]          | Cohort                              | 1982-88          | Colombia            | Adults ≥ 30y never smokers | PM <sub>2.5</sub>                           | Pneumonia Mt         | RR=1.02 95% CI: 1.02-1.41 for 10 µg/m <sup>3</sup> increase           |
|                                 |                                     |                  |                     |                            | PM <sub>10</sub> (high)                     | Other respir.dis. Mt | RR=0.74 95% CI: 0.56-0.97 for a 10 µg/m <sup>3</sup> increase         |

Table 2. Continued.

| Authors and year of publication | Study design                    | Year(s) of study | Site of study                        | Population      | Pollutant(s)     | Health outcome      | Main results<br>(Odds Ratio or Hazard Ratio 95% Confidence Intervals) |
|---------------------------------|---------------------------------|------------------|--------------------------------------|-----------------|------------------|---------------------|---|
| Naess et al., 2006 [8]          | Cohort follow-up                | 1992-98          | Europe                               | Adults (51-70y) | PM <sub>10</sub> | COPD, males         | HR=1.29 95%CI: 1.12-1.48  |
|                                 |                                 |                  |                                      |                 |                  | Lung cancer, female | HR=1.27 95%CI: 1.13-1.43  |
|                                 |                                 |                  |                                      |                 |                  | COPD, males         | HR=1.27 95%CI: 1.11-1.47  |
|                                 |                                 |                  |                                      |                 |                  | Lung cancer, female | HR=1.27 95%CI: 1.13-1.43  |
| Kunzly et al., 2000 [3]         | Meta-analytical effect estimate | 1996-98          | Europe, Austria, France, Switzerland | All ages        | PM <sub>10</sub> | Respiratory HA      | RR=1.013 95%CI: 1.001-1.025 increase for 10 µg/m <sup>3</sup>         |
|                                 |                                 |                  |                                      |                 |                  | Chr. bronchitis     | RR=1.098 95%CI: 1.009-1.194 increase for 10 µg/m <sup>3</sup>         |
|                                 |                                 |                  |                                      |                 |                  | Bronch. episodes    | RR=1.306 95%CI: 1.135-1.502 increase for 10 µg/m <sup>3</sup>         |
|                                 |                                 |                  |                                      |                 |                  | Asthma attacks      | RR=1.044 95%CI: 1.027-1.062 increase for 10 µg/m <sup>3</sup>         |
|                                 |                                 |                  |                                      | ≥ 15y           |                  | Asthma attacks      | RR=1.039 95%CI: 1.019-1.059 increase for 10 µg/m <sup>3</sup>         |

Mt – mortality, y – year, PME – PM emission, TRE – traffic-related exposure, PFD – pulmonary function decrease, TPM – traffic-related PM, TSP – total suspended particulates, HA – hospital admission, SRT – self-reported intense traffic, HTRS – high traffic roads, I – incidence, P – prevalence, n.s. – not significant

was found. Compared to the within-subject variability of FVC, this effect may be considered small, but Kunzli et al., using the impact of PM<sub>10</sub> on FVC as an example, translating the epidemiological findings into a clinically relevant context, demonstrated that clinically “small” effects of air pollution on FVC could have a large public health impact [29].

Long-term exposure to air pollution from PM<sub>10</sub> and NO<sub>2</sub> and living near major roads can increase the risk of developing COPD and can have a detrimental effect on lung function. In the cross-sectional study, Schikowski et al. [30] reported that the prevalence of COPD and pulmonary function were most strongly affected by PM<sub>10</sub> and traffic-related exposure. They found that women living less than 100 m from a busy road had significantly decreased lung function and COPD was 1.8 times more likely than for those living farther away. Cesaroni and coauthors [31] showed that area-based emissions of PM, among different indices of exposure to traffic-related air pollution, were consistently associated with an increased risk of rhinitis in adults, especially among non-smokers, while results for asthma were weak. There were no exposure indices associated with chronic bronchitis.

It was shown that traffic related pollution is associated with the onset of asthma in children [32, 33]. Its effect on adult onset asthma is poorly investigated. The cohort study of Kunzly and coauthors found associations between the 11-year change in outdoor traffic-related PM<sub>10</sub> and the incidence of asthma. The data suggest a role of traffic-related pollution in adult-onset asthma [13].

#### Morbidity in Children

The role of air pollution in the development of new onset asthma remains controversial, and the contribution of environmental risk factors to the pandemic remains unclear. Studies have demonstrated associations between short-term exposure and symptoms in children already diagnosed with asthma [2, 26]. However, it is less clear whether or not long-term exposure to air pollution causes asthma. Oftedal and coauthors [33] were not able to find positive associations between any long-term traffic-related exposures and onset of doctor-diagnosed asthma or current respiratory symptoms (wheeze, dry cough) in children. Zhang et al. [7] who examined respiratory health effects of long-term exposure to ambient air pollution in schoolchildren found positive associations between respiratory morbidity prevalence (wheeze, asthma, bronchitis, hospitalization, persistent cough, and phlegm) and outdoor levels of PM of all size fractions, but association appeared to be stronger for coarse particles (PM<sub>10-2.5</sub>).

In the study of Islam et al. [34], the effect of individual air pollutants on the association between lung function and asthma were evaluated. The protective effect of better lung function against new onset asthma was reduced in children exposed to higher levels of PM<sub>2.5</sub>. There were no substantial differences in the effect of lung function between “high” and “low” ozone communities.

An analysis from the California Children's Health Study [14] points to ozone as a cause in the development of asthma in young people who did not previously have the disease. The study found that children who were active in outdoor sports in areas with high ozone concentrations were more than three times as likely to develop asthma as those who did not engage in outdoor sports during the five-year follow-up study [14].

Although increasing evidence indicates that living near heavy traffic is associated with increased rates of asthma, some well designed studies have found only weak or no associations [33, 35]. Results of the McConnell et al. study [32] indicate that children exposed to higher levels of traffic-related air pollution at school and home are at increased risk of developing asthma, i.e. exposure at school and home both contribute to the risk of new-onset asthma.

The role of exposure to ambient air pollution in the development of childhood asthma, allergy, and related symptoms, however, remains less clear due in part to the limited number of prospective birth cohort studies. The prospective birth cohort study of Gehring et al. [19], found positive associations between traffic-related air pollution levels outside subjects' homes and the incidence and prevalence of asthma during the first 8 years of life. Results of this study provide evidence that air pollution exposure may contribute to the pathogenesis of asthma in children.

#### *Mortality*

Although much attention has been focused on the adverse health effects associated with daily exposure (short-term exposure) to air pollutants, researchers are reporting adverse health effects that are associated with long-term exposure, especially to  $PM_{10}$  and  $O_3$  [9, 36].

Several studies on long-term exposure to PM, indicate a direct association with mortality, particularly from cardiovascular and respiratory diseases [9, 20]. In most studies total mortality was directly associated with long-term exposure to fine and very fine PM. According to a systematic review of the relation between long-term exposure to ambient air pollution and chronic diseases, long-term exposure to  $PM_{2.5}$  increases the risk of nonaccidental mortality by 6% per a  $10 \mu g/m^3$  increase, independent of age, gender, and geographic region. Exposure to  $PM_{2.5}$  was also associated with an increased risk of mortality from lung cancer (range: 15% to 21% per a  $10 \mu g/m^3$  increase) [36]. A study by Naess et al. [8] investigated the concentration-response relation between PM pollutants ( $PM_{10}$  and  $PM_{2.5}$ ) and cause-specific mortality. A consistent effect on all causes of death was found for both sexes and age groups by all indicators of air pollution. In the cause-specific analyses, authors found an effect of all indicators for cardiovascular causes, lung cancer, and COPD. Results indicate that vulnerable persons with COPD and the elderly seem to be susceptible to air pollution at lower levels than the general population [8]. According to Pope et al. [20], long-term PM exposures were most strongly associated

with mortality attributable to ischemic heart disease, dysrhythmias, heart failure, and cardiac arrest, while mortality attributable to respiratory disease had relatively weak associations.

In the project of Kunzli et al. [3], the contribution of air pollution and traffic-related air pollution in Austria, France and Switzerland was estimated. A  $10 \mu g/m^3$  increase in PM was used to quantify the effects of air pollution. It was shown that air pollution causes 6% of total mortality or more than 40,000 attributable cases per year. About half of all mortality caused by air pollution was attributed to motorized traffic, accounting also for more than 25,000 new cases of chronic bronchitis (adults), more than 290,000 episodes of bronchitis (children), more than 0.5 million asthma attacks, and more than 16 million person-days of restricted activities. Although individual health risks of air pollution are relatively small, the public-health consequences are considerable. Traffic-related air pollution remains a key target for public health action all over the world.

The main characteristics and results of the selected above-mentioned long-term studies are presented in Table 2.

#### Conclusive Considerations and Research Gaps

Epidemiological studies of air pollution examine effects of air pollution in large human populations under real-world conditions. They look for associations between the exposure of interest (short- and long-term exposure) and health outcomes (acute or chronic). There is clear evidence of association between air pollution and respiratory morbidity and mortality. Although there has been progress in the investigation of the association between air pollution and health, a considerable need for further methodological improvement still exists.

The development of GIS techniques, intense ambient monitoring of air pollutants, air dispersion modeling, and land use regression modeling has improved the tools for better exposure assessment. Planning transportation and other urban development so as to limit population exposure to traffic exhaust, and more effective control of vehicular emissions, may result in substantial long-term public health benefits. Such insight eventually may direct the means for effective public health prevention and treatment of diseases associated with air pollution. The understanding of the extent to which air pollution affects human health requires an integrated approach to air pollution research, assembling a multidisciplinary team of investigators with various interfaces between: data management, exposure assessment, environmental and social epidemiology, biostatistics, health economics, and policy. Air quality standards and guidelines should be proposed to protect public health.

However, more research is needed to understand the role of air pollution on respiratory health, and to clarify the specific exposure indicator most sensitive in detecting a health effect.



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### References

- HILDEBRANDT K., RÜCKERL R., KOENIG W., SCHNEIDER A., PITZ M., HEINRICH J., MARDER V., FRAMPTON M., OBERDÖRSTER G., WICHMANN H.E., PETERS A. Short-term effects of air pollution: a panel study of blood markers in patients with chronic pulmonary disease. *Particle and Fibre Toxicology*. **6**, 25, **2009**.
- WEINMAYR G., ROMEO E., DE SARIO M., WEILAND S.K., FORASTIERE F. Short-Term Effects of PM<sub>10</sub> and NO<sub>2</sub> on Respiratory Health among Children with Asthma or Asthma-like Symptoms: A Systematic Review and Meta-Analysis. *Environ. Health Persp.* **118**, (4), 449, **2010**.
- KÜNZLI N., KAISER R., MEDINA S., STUDNICKA M., CHANEL O., FILLIGER P., HERRY M., HORAK F J.R., PUYBONNIEUX-TEXIER V., QUÉNEL P, SCHNEIDER J, SEETHALER R., VERGNAUD J.C, SOMMER H. Public-health impact of outdoor and traffic-related air pollution: a European assessment. *Lancet*. **356**, (9232), 795, **2000**.
- SICARD P., MANGIN A., HEBEL P., MALLEA P. Detection and estimation trends linked to air quality and mortality on French Riviera over the 1990-2005 period. *Sci. Total Environ.* **408**, 1943, **2010**.
- CAIRNCROSS E.K., JOHN J., ZUNCKEL M. A novel air pollution index based on the relative risk of daily mortality associated with short-term exposure to common air pollutants. *Atmos. Environ.* **41**, 8442, **2007**.
- VALAVANIDIS A., FIOTAKIS K., VLACHOGIANNI T. Airborne particulate matter and human health: Toxicological assessment and importance of size and composition of particles for oxidative damage and carcinogenic mechanisms. *J. Environ. Sci. Heal. C*, **26**, 339, **2008**.
- ZHANG J.J, HU W., WEI F., WU G., KORN L.R., CHAPMAN R.S. Children's respiratory morbidity prevalence in relation to air pollution in four Chinese cities. *Environ. Health Persp.* **110**, (9), 961, **2002**.
- NAESS Ø., NAFSTAD P., AAMODT G., CLAUSSEN B., ROSLAND P. Relation between concentration of air pollution and cause-specific mortality: four-year exposures to nitrogen dioxide and particulate matter pollutants in 470 neighborhoods in Oslo, Norway. *Am. J. Epidemiol.*, **165**, (4), 435, **2007**.
- OSTRO B., LIPSETT M., REYNOLDS P., GOLDBERG D., HERTZ A., GARCIA C., HENDERSON K.D., BERNSTEIN L. Long-Term Exposure to Constituents of Fine Particulate Air Pollution and Mortality: Results from the California Teachers Study. *Environ. Health Persp.* **118**, (3), 363, **2010**.
- BABIN S.M., BURKOM H.S., HOLTRY R.S., TABERNERO N.R., STOKES L.D., DAVIES- COLE J.O., DEHAAN K., LEE D.H. Pediatric patient asthma-related emergency department visits and admissions in Washington, DC, from 2001-2004, and associations with air quality, socio-economic status and age group. *Environ Health.* **6**, 9, **2007**.
- MEDINA-RAMON M., ZANOBBETTI A., SCHWARTZ J. The effect of ozone and PM<sub>10</sub> on hospital admissions for pneumonia and chronic obstructive pulmonary disease: a national multicity study. *Am. J. Epidemiol.* **163**, 579, **2006**.
- FRIEDMAN M.S., POWELL K.E, HUTWAGNER L., GRAHAM L.M., TEAGUE W.G. Impact of changes in transportation and commuting behaviors during the 1996 Summer Olympic Games in Atlanta on air quality and childhood asthma. *JAMA*. **285**, (7), 897, **2001**.
- KUNZLI N., BRIDEVAUX P.O., LIU L.J., GARCIA-ESTEBAN R., SCHINDLER C., GERBASE M.W., SUNYER J., KEIDEL D., ROCHAT T. Swiss Cohort Study on Air Pollution and Lung Diseases in Adults. *Thorax*. **64**, (8), 664, **2009**.
- MCCONNELL R., BERHANE K., GILLILAND F., LONDON S.J., ISLAM T., GAUDERMAN W.J., AVOL E., MARGOLIS H.G., PETERS J.M. Asthma in exercising children exposed to ozone: a cohort study. *Lancet*. **359**, (9304), 386, **2002**.
- STIEB D.M., SZYSZKOWICH M., ROWE B.H., LEECH J.A. Air pollution and emergency department visits for cardiac and respiratory conditions: multi-city time series analysis. *Environ Health.* **10**, 8, **2009**.
- FISCHER P., HOEK G., BRUNEKREEF B., VERHOEFF A., VAN WIJNEN J. Air pollution and mortality in The Netherlands: are the elderly more at risk? *Eur Respir J. Suppl.* **40**, 34s, **2003**.
- HALONEN J.I., LANKI T., YLI-TUOMI T., TIITTANEN P., KUMALA M., PEKKANEN J. Particulate air pollution and acute cardiorespiratory hospital admissions and mortality among elderly. *Epidemiology*. **20**, (1), 143, **2009**.
- YAMAZAKI S., SHIMA M., ANDO M., NITTA H. Modifying effect of age on the association between ambient ozone and nighttime primary care visits due to asthma attack. *J Epidemiol.* **19**, (3), 143, **2009**.
- GEHRING U., WIJGA A.H., BRAUER M., FISCHER P., DE JONGSTE J.C., KERKHOF M., OLDENWENING M., SMIT H.A., BRUNEKREEF B. Traffic-related Air Pollution and the Development of Asthma and Allergies during the First 8 Years of Life. *Am. J. Resp. Crit. Care*. **181**, 596, **2010**.
- POPE C.A. 3<sup>rd</sup>, BURNETT R.T., THURSTON G.D., THUN M.J., CALLE E.E., KREWSKI D., GODLESKI J.J. Cardiovascular mortality and long-term exposure to particulate air pollution: epidemiological evidence of general pathophysiological pathways of disease. *Circulation*. **109**, (1), 71, **2004**.
- BARNETT A.G., WILLIAMS G.M., SCHWARTZ J., NELLER A.H., BEST T.L., PETROESCHEVSKY A.L., SIMPSON R.W. Air pollution and child respiratory health: a case-crossover study in Australia and New Zealand. *Am. J. Resp. Crit. Care*. **171**, (11), 1272, **2005**.
- SAUERZAPF V., JONES A.P., CROSS J. Environmental factors and hospitalization for chronic obstructive pulmonary disease in a rural country of England. *J. Epidemiol. Commun. H.* **63**, (4), 324, **2009**.
- HALONEN J.I., LANKI T., TIITTANEN P., NIEMI J. V., LOH M., PEKKANEN J. Ozone and cause-specific cardiorespiratory morbidity and mortality. *J. Epidemiol. Commun. H.* [2009.087106](https://doi.org/10.1136/jech.2009.087106) published Online First: 23 October **2009**. doi: 10.1136/jech.2009.087106.
- KIECHL-KOHLENDORFER U., HORAK E., MUELLER W., STROBL R., HABERLAND C., FINK F.M., SCHWAIGER M., GUTENBERGER K.H., REICH H., MERANER D., KIECHL S. Living at high altitude and risk

- of hospitalisation for atopic asthma in children: results from a large prospective birth-cohort study. *Arch. Dis. Child.* **92**, (4), 339, **2007**.
25. MORTIMER K.M., TAGER I.B., DOCKERY D.W., NEAS L.M., REDLINE S. The effect of ozone on inner-city children with asthma: identification of susceptible subgroups. *Am. J. Resp. Crit. Care.* **162**, (5), 1838, **2000**.
26. MCCONNELL R., BERHANE K., MOLITOR J., GILLILAND F., KÜNZLI N., THORNE P.S., THOMAS D., GAUDERMAN W.J., AVOL E., LURMANN F., RAPPAPORT E., JERRETT M., PETERS J.M. Dog ownership enhances symptomatic responses to air pollution in children with asthma. *Environ Health Persp.* **114**, (12), 1910, **2006**.
27. RAGE E., JACQUEMIN B., NADIF R., ORYSZCZYN M.P., SIROUX V., AGUILERA I., KAUFFMANN F., KUNZLY N. Epidemiological study on the Genetics Environment of Asthma (EGEA). *Allergy.* **64**, (1), 40, **2008**.
28. LING S., VAN EEDEN S.F. Particulate matter air pollution exposure: role in the development and exacerbation of chronic obstructive pulmonary disease. *Int J Chron Obstruct Pulmon Dis.* **4**, 233, **2009**.
29. KÜNZLI N., ACKERMANN-LIEBRICH U., BRÄNDLI O., TSCHOPP J.M., SCHINDLER C., LEUENBERGER P. Clinically "small" effects of air pollution on FVC have a large public health impact. Swiss Study on Air Pollution and Lung Disease in Adults (SAPALDIA) -team. *Eur. Respir. J.* **15**, (1), 131, **2000**.
30. SCHIKOWSKI T., SUGIRI D., RANFT U., GEHRING U., HEINRICH J., WICHMANN H.E., KRÄMER U. Long-term air pollution exposure and living close to busy roads are associated with COPD in women. *Respir Res.* **6**, 152, **2005**.
31. CESARONI G., BADALONI C., PORTA D., FORASTIERE F., PERUCCI C.A. Comparison between various indices of exposure to traffic-related air pollution and their impact on respiratory health in adults. *Occup. Environ. Med.* **65**, (10), 683, **2008**.
32. MCCONNELL R., ISLAM T., SHANKARDASS K., JERRETT M., LURMANN F., GILLILAND F., GAUDERMAN J., AVOL E., KUENZLI N., YAO L., PETERS J., BERHANE K. Childhood Incident Asthma and Traffic-Related Air Pollution at Home and School. *Environ. Health Persp.* **118**, 1021, **2010**.
33. OFTEDAL B., NYSTAD W., BRUNEKREEF B., NAFSTAD P. Long-term traffic-related exposures and asthma onset in schoolchildren in Oslo, Norway. *Environ Health Persp.* **117**, (5), 839, **2009**.
34. ISLAM T., GAUDERMAN W., BERHANE K., MCCONNELL R., AVOL E., PETERS J.M., GILLILAND F.D. Relationship between air pollution, lung function and asthma in adolescents. *Thorax.* **62**, (11), 957, **2007**.
35. HEINRICH J., WICHMANN H.E. Traffic related pollutants in Europe and their effect on allergic disease. *Curr Opin Allergy Clin Immunol.* **4**, (5), 341, **2004**.
36. CHEN H., GOLDBERG M.S., VILLENEUVE P.J. A systematic review of the relation between long-term exposure to ambient air pollution and chronic diseases. *Rev. Environ. Health.* **23**, (4), 243, **2008**.