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THE EFFECTS OF AIR POLLUTION ON THE RESPIRATORY AND CARDIOVASCULAR SYSTEM: A SYSTEMATIC REVIEW

UTICAJ AEROZAGAĐENJA NA RESPIRATORNI I KARDIOVASKULARNI SISTEM: SISTEMATSKI PREGLED LITERATURE

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Key words

Air pollution; chronic respiratory diseases; cardiovascular diseases; morbidity; mortality; particulate matter (PM_{10} and $PM_{2.5}$); ozone; statistical methods.

Ključne reči

Aerozagađenje; hronične respiratorne bolesti; kardiovaskularne bolesti; morbiditet; mortalitet; respirabilne čestice (PM_{10} and $PM_{2.5}$); ozon; statističke metode.

Abstract

Increasingly science is providing evidence linking the disease burden of people with exposure to air pollution. Epidemiological studies have shown a significant increase in the hospital admission rates and mortality in patients with chronic respiratory and cardiovascular diseases in relation to moderate increases in atmospheric pollution. We performed a systematic review of literature published between January 2000 and June 2010 that focused on the short and long-term effects of outdoor air pollution, in particular, particulate matter (PM_{10} and $PM_{2.5}$) and ozone, on respiratory and cardiovascular health outcomes, as well as systematic review of statistical methods used in epidemiological studies on health effects and air pollution.

INTRODUCTION

Epidemiological studies continue to associate air pollution with increases in human morbidity and mortality. Increasing evidence suggests that short-term or long-term exposure to ambient air pollution may adversely affect respiratory [1,2] and cardiovascular system [3,4].

Particulate matter (PM), with a diameter of 10μm or less ($PM_{10-2.5}$), and smaller size fraction particles ($PM_{2.5}$) has been widely associated with adverse effects on mortality and exacerbation of chronic respiratory diseases [5,6]. The long-term health effects of exposure to PM are associated with shortening of life expectancy, increased rates of bronchitis, asthma [7], chronic obstructive pulmonary disease (COPD) and lung cancer [8]. Respiratory morbidity, including asthma and COPD, also has been linked with the short-term changes in O_3 levels in several studies [9].

Many epidemiological studies in the last few decades reported acute associations between elevated air pollution levels and increased death [3,10] and hospitalization rates due to cardiovascular diseases [4,11], although several studies have not shown such an association [12-14].

The consistent findings suggest direct associations between both short- and long-term exposure to PM and coronary heart disease (CHD) incident. However, biological mechanisms underlying the association between PM and CHD remain to be elucidated [15].

Identifying the independent effects of a specific pollutant requires careful adjustment for simultaneous exposure to a complex mixture of co pollutants. Extensive covariate adjustment is required to control for confounding factors (e.g., age effects, weather variables, and seasonality). In addition, exposure measurement error can potentially lead to bias in estimates of the health effects of air pollution.

Because much of modern air pollution epidemiology is oriented toward the analysis and evaluation of complex data about the health effects of air pollution, advanced statistical methods have figured prominently in epidemiologic applications; such methods include generalized regression models for count and binary time-series (GAMs), and hierarchical models [16].

METHOD

Data source

We performed a systematic review of literature published between January 2000 and June 2010 that focused on the short and long-term effects of outdoor air pollution (in particular PM and Ozone), on respiratory and cardiovascular health outcomes, as well as systematic review of statistical methods used in studies on health effects and air pollution. Publications were identified through the MEDLINE electronic database searched via PubMed, using topic-related search terms, either alone or in combination, both for the exposure and for the health outcomes.

Literature search strategy

The search strings for respiratory search consisted of next key words: ("Ozone" or "Particulate Matter") and ("Pulmonary Disease" or "Respiratory Disease" or "Asthma") and ("Incidence" or "Prevalence" or "Morbidity" or "Mortality"). For the cardiovascular search the same search strategy was applied with the "Cardiovascular disease" as search term instead of respiratory terms. For the review of statistical methods used in literature following search strategy was used: ("particulate matter" or ozone or "air pollution") and ("pulmonary disease" or asthma or cardiovascular or "population health" or "general health") and (incidence or prevalence or mortality) and (statistic*[ti] or analy*[ti] or model*[ti])

The search was restricted to humans and to articles published in English.

Data processing and quality assessment

The first selection in data processing was based on title and abstract. Data presented only in abstracts were not included. 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 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 researcher can conclude from the title and abstract that they are presented in the full text paper.

3. Marginal relevant papers - data about incidence, prevalence or mortality are not presented in the abstract, and researcher can conclude from the title and abstract that they are probably not presented either in the full text paper.

Only extremely relevant papers were recommended for further reading. The full text papers were rated for quality of research as high, medium or low quality papers. The quality assessment was based on following criteria: clearly stated aims, appropriate methods used, context of the study well constituted, clearly described, valid and reliable results, clearly described analysis, possible influences of the outcome considered, conclusion linked to the aim, analysis and interpretation of results of the study and limitations of research identified.

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

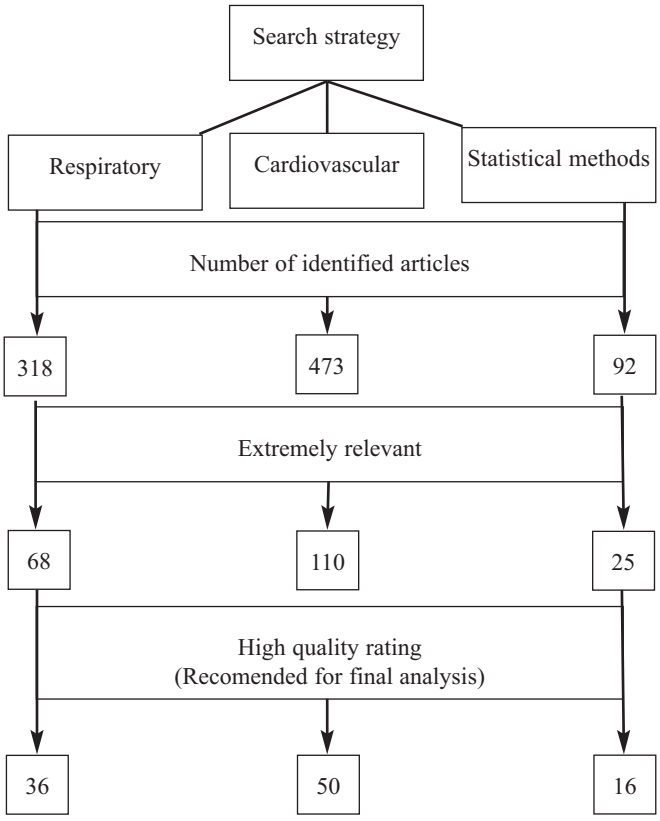

Figure 1. Search strategy for systematic review of air pollution adverse effects on the respiratory and cardiovascular system

RESULTS

Air pollution and chronic respiratory diseases

There is evidence that various components of ambient air pollution produce significant effect within the respiratory system. 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 [17,18]. Monitoring data reveals that urban populations are more likely to be exposed to elevated levels of these pollutants. Fischer et al. [19] found that the elderly are at higher risk for acute mortality effects of air pollution compared to younger age groups. Statistically significant associations were found for O_3 (total and COPD mortality), PM_{10} (pneumonia), NO_2 (pneumonia) and CO (pneumonia). Children are uniquely predisposed to the potential harmful effects of PM and O_3 [2,20].

Exposure to ambient air pollution can exacerbate existing 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 goal of the meta-analysis of the Weinmayr et al. [2] was to quantify the short-term effects of PM_{10} and NO_2 on respiratory health of asthmatic children. They found a clear

evidence of effects of PM_{10} on the occurrence of asthma symptom episodes, and to a lesser extent on cough and Peak Expiratory Flow (PEF).

In the study of Islam et al. [7] effect of individual air pollutants on the association between lung function and asthma were evaluated. Protective effect of better lung function against new onset asthma was reduced in children exposed to higher levels of $PM_{2.5}$. There were no substantial differences in the effect of lung function between "high" and "low" ozone communities.

The role of air pollution in the development of new onset asthma remains controversial, and the contribution of this environmental risk factor to the pandemic remains unclear. 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 [21,22].

McConnell and coauthors [23] showed that children exposed to higher levels of traffic-related air pollution at school and home are at increased risk of developing asthma.

In the project of Kunzli et al. [24] 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 risk of air pollution is relatively small, the public-health consequences are considerable.

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 a chronic low-grade exposure to ambient PM can cause the development and progression of COPD [25]. Vulnerable group (COPD) and the elderly persons seem to be susceptible to air pollution at lower levels than the general population. Study of Naess et al. [8] investigated the concentration-response relation between PM pollutants (PM_{10} and $PM_{2.5}$) and cause-specific mortality. 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 chronic obstructive pulmonary disease [8].

Outdoor air quality is associated with respiratory morbidity and mortality. Less is known of the relationship of indoor air quality to respiratory health. Osman et al. [5] investigated the association of health status with indoor air quality in homes, among patients with COPD. Small size of particles was significantly associated with increased symptom burden. Higher levels of small size fraction of particles are associated with worse health status of patients with severe COPD.

Lung function and exacerbations of COPD have been associated with short-term exposure to air pollution. Medina-Ramon et al [17] 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 [17].

Epidemiological studies have repeatedly established adverse health effects due to long- term exposure to ambient pollution. Long-term exposure to air pollution from PM_{10} and NO_2 and living near a major road can increase the risk of developing COPD and can have a detrimental effect on lung function. In the cross-sectional study Schikowski et al. [26] reported that the prevalence of COPD and pulmonary function were strongest affected by PM_{10} and traffic related exposure. They found that women living less than 100 m from a busy road had a significantly decreased lung function and COPD was 1.8 times more likely than for those living farther away. Zhang et al. [27] who examined respiratory health effects of long-term exposure to ambient air pollution found positive associations between morbidity prevalence (wheeze, asthma, bronchitis, hospitalization, and persistent cough) and outdoor levels of PM of all size fractions, but association appeared to be stronger for coarse particles ($PM_{10-2.5}$).

Air pollution and cardiovascular diseases

Most studies investigate short term effects of air pollution on hospital admissions for cardiovascular diseases [4,28] or mortality [29,30]. The latency period between air pollution increases and related cardiovascular health effects in most studies falls in the 1-3 days interval range [29,13] or within a few weeks [15,31].

High concentrations of particulate air pollution have been associated with higher rates of hospital admissions and daily deaths in many industrialized countries, like the USA [32], France, Switzerland and Austria [4]. In developing countries, daily PM_{10} concentration was positively associated with hospital visits for CVD among elderly (>65years) [33].

Particles in the $PM_{2.5}$ size, which are more likely to result from combustion processes, can reach the smaller airways and alveoli. Bell et al. [34] found statistically significant evidence that $PM_{2.5}$ RR for cardiovascular hospitalization is higher in counties and seasons with higher elemental carbon, nickel, or vanadium $PM_{2.5}$ content. An adverse relationship between exposures to ambient $PM_{2.5}$ is confirmed in other studies, as well [35,36].

The health effects associated with ambient exposure to the particles in the size range of greater than 2.5 μm and 10 μm or less in diameter ($PM_{10-2.5}$; coarse particles) could differ from those of $PM_{2.5}$ according to the sites of deposition preferentially in the upper and larger airways. Peng et al. [28] estimated a 0.36% increase in CVD hospital admissions per 10-μg/m3 increase in $PM_{10-2.5}$.

Among a frail population, individuals diagnosed with myocardial infarction or diabetes were at greatest risk of death associated with high concentrations of PM_{10}. These results suggest that their susceptibility may derive from prior vascular damage to the heart [37]. The risk of CVD mortality associated with $PM_{2.5}$ is higher than what was observed for PM_{10} [38].

For cardiovascular deaths, immediate exposure (same-day or day before the event) contributed more consistently to the deaths [10,31]. A 10-μg/m3 increase in the 2-day mean of

PM_{10} was associated with a 0.7% (95% CI: 0.3, 1.1) increase in deaths [5]. A short-term effect of air pollution on health was observed in twenty-nine European cities. However, there was regional heterogeneity: the increase was 0.54% in northwestern cities, 1.25% in southern cities, and 0.25% in central-eastern cities [39]. In a large multicenter study in the USA, the estimated increase in the relative rate of death from cardiovascular mortality associated with PM_{10} was 0.31% [40].

Although the air pollution mainly affects the people in the developed counties, fossil fuel combustion emissions and traffic-related air pollution remain key targets for public health in developping countries. However, only a few studies concerning outdoor air pollution and cardiovascular deaths have been conducted in these countries [38].

Relatively few studies have investigated the relationship of mortality with $PM_{2.5}$ particles. There is evidence of significant association of $PM_{2.5}$ with daily CVD mortality [41].

The adverse response to pollution persists to a month or longer after exposure for CVD mortality. The effects of long term exposure to particulate mater (PM_{10}, $PM_{2.5}$) were investigated in only few studies, however, the results are controversial [13,15].

A meta-analysis of 144 effect estimates from 39 time-series studies provided strong evidence of a short-term association between ozone and cardiovascular and respiratory mortality, the elderly, and current day ozone exposure. It was found that a 10-ppb increase in ozone in the few previous days is associated with a 0.85% increase in CVD mortality (95% CI-0.66 to 2.39) [42]. The magnitude of ozone-cardiovascular mortality association varied across different regions in the USA [43] and in the European cities [44].

Review of statistical methods

In this article we also review statistical contributions to the analyses of air pollution and health outcomes, and discuss how different statistical methods have provided a clearer understanding of the extent to which air pollution affects human health [45-50].

Statistical methods applied to analyse short term effects of ambient air pollution

- Poisson regression models for time-series analyses of air pollution and health;

It is a widely used approach for time-series analyses of air pollution and health.

- Sensitivity of Generalized Additive Models (GAM) applied to time-series data;

Implementing GAMs to analyze time-series data of air pollution and health outcomes could overestimate the air pollution effects. The investigators conduct new analyses of their data by applying [1] the gam function of S-Plus with appropriate programming changes, and [2] other methods that would estimate standard errors more accurately. These new analyses of time-series studies highlighted a second important epidemiologic and statistical issue known as confounding bias.

- Combining information in multi-site time-series studies - hierarchical models;

Hierarchical models have provided an appropriate approach for summarizing and integrating the findings of research studies in a particular geographical area.

- Generalized Additive Model (GAM) for spatial air pollution data;

The GAM has become a standard tool for epidemiologic analysis exploring the effect of air pollution on population health. Later, the use of the GAM has been extended from time-series data to spatial data.

- Polled cross-sectional time series analysis with corrected fixed regression models;

Very few studies have tried to assess the advantage of using a pooled ecological design that increases statistical power.

- Case-crossover design in studying the acute health effect of air pollution;

By design, this can avoid some common concerns about the time-series approach, which was most frequently used to assess the short term effects of air-pollution.

- Linkage analysis of two different preexisting sources of valuable data;

The analysis is concerned not simply with the association between air quality and respiratory health, but explicitly with associations between socioeconomic status and air pollution exposure, and their combined health effects.

- Trajectory cluster analysis for exposure assessment;

The trajectory clustering approach does not focus on individual composition of particles, but on the flow of air masses.

- Factor analysis of household factors;

In a factor analysis, inter-correlated variables are combined into a smaller number of new variables (factors).

- Life-table model for fine particles-sensitivity analysis.

The effect of uncertainty was studied by conducting a comprehensive sensitivity analysis of a life-table model.

Statistical methods applied to analyse long term exposure to ambient air pollution:

- Cox proportional hazard model;

Research might consider short-term fluctuations as well as individualized estimates of long-term exposures to ambient particles in assessing the health impact of environmental exposures. For these studies, Cox regression analyses would be the method of choice.

- Statistical modelling integrating random effects and nonparametric spatial smoothing into the Cox proportional hazards model.

The spatially adjusted risk estimates are subject to somewhat greater uncertainty than the original risk estimates as a consequence of the presence of significant spatial autocorrelation in the study data.

CONCLUSION

There is a clear evidence of association between air pollution and respiratory and cardiovascular morbidity and mortality. Many epidemiological studies have shown statistically significant associations of short- or long-term effects of air pollution on hospital admissions for cardiopulmonary diseases and cardiovascular and respiratory mortality. However, more research is needed to understand the role of air pollution on respiratory and cardiovascular health, and to clarify the specific exposure indicator most sensitive in detecting a health effect.

Although progress has been made in investigating the association between air pollution and health, important

questions still need to be addressed and considerable need remains for further data collection and methods development.

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 [16]. Research in this field would be greatly enhanced by this systematic integration of research efforts from the aforementioned fields to establish a system for monitoring pollutant concentrations, their sources, and health effects, and also to evaluate the role of new regulations in improving health status in populations by curtailing air pollution.

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Apstrakt

Naučne činjenice o povezanosti između izloženosti aerozagađenju i bolesti kod ljudi su u porastu. Epidemiološke studije su pokazale da sa umerenim porastom aerozagađenja značajno rastu stope prijema u bolnicu zbog hroničnih respiratornih i kardiovaskularnih bolesti, kao i stope mortaliteta od ovih bolesti. Sistematski pregled literature, publikovane od januara 2000. do juna 2010. godine, bio je fokusiran na kratkotrajne i dugotrajne efekte aerozagađenja, posebno na uticaj respirabilnih čestica (PM_{10} and $PM_{2.5}$) i ozona, na respiratorne i kardiovaskularne zdravstvene ishode. Takođe je urađen i sistematski pregled korišćenih statističkih metoda u epidemiološkim studijama kojima se ispituje uticaj aerozagađenja na zdravlje ljudi.

REFERENCES:

1. Hildebrandt K, Rückerl R, Koenig W, Schneider A, Pitz M, Heinrich J et al. Short-term effects of air pollution: a panel study of blood markers in patients with chronic pulmonary disease. Particle and Fibre Toxicology. 2009; 6: 25.

2. Weinmayr G, Romeo E, De Sario M, Weiland SK and Forastiere F. Short-Term Effects of PM10 and NO2 on Respiratory Health among Children with Asthma or Asthma-like Symptoms: A Systematic Review and Meta-Analysis. Environmental Health Perspectives. 2010; 118, 4: 449-457.

3. Gouveia N, Fletcher T. Time series analysis of air pollution and mortality: effects by cause, age and socioeconomic status. J Epidemiol Community Health. 2000; 54: 750-5.

4. Kunzli N, Kaiser R, Medina S, Studnicka M, Chanel O, Filliger P, et al. Public-health impact of outdoor and traffic-related air pollution: a European assessment. Lancet. 2000; 356: 795-801.

5. Osman LM, Douglas JG, Garden C, Reglitz K, Lyon J, Gordon S et al. Indoor air quality in homes of patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med.2007; 176, 5: 465-72.

6. Ostro B, Lipsett M, Reynolds P, Goldberg D, Hertz A, Garcia C et al. Long-Term Exposure to Constituents of Fine Particulate Air Pollution and Mortality: Results from the California Teachers Study. Environmental Health Perspectives. 2010; 118, 3: 363-369.

7. Islam T, Gauderman WJ, Berhane K, McConnell R, Avol E, Peters JM et al. Relationship between air pollution, lung function and asthma in adolescents. Thorax 2007; 62, 11: 957-63.

8. 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. 2007; 165, 4: 435-43.

9. Babin SM, Burkom HS, Holtry RS, Tabernero NR, Stokes LD, Davies-Cole JO et al. 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. 2007; 6: 9.

10. Braga AL, Zanobetti A, Schwartz J. The lag structure between particulate air pollution and respiratory and cardiovascular deaths in 10 US cities. J Occup Environ Med. 2000; 143: 927-33.

11. Le Tertre A, Quenel P, Eilstein D, Medina S, Prouvost H, Pascal L, et al. Short-term effects of air pollution on mortality in nine French cities: a quantitative summary. Arch Environ Healt. 2002; 57: 311-9.

12. Franklin M, Zeka A, Schwartz J. Association between PM2.5 and all-cause and specific-cause mortality in 27 US communities. J Expo Sci Environ Epidemiol. 2007; 17, 3: 279-87.

13. Hanigan IC, Johnston FH, Morgan GG. Vegetation fire smoke, indigenous status and cardio-respiratory hospital admissions in Darwin, Australia, 1996-2005: a time-series study. Environ Health. 2008; 7: 42.

14. Cho YS, Lee JT, Jung CH, Chun YS, Kim YS. Relationship between particulate matter measured by optical particle counter and mortality in Seoul, Korea, during 2001. J Environ Health. 2008; 71: 37-43.

15. Miller KA, Siscovick DS, Sheppard L, Shepherd K, Sullivan JH, Anderson GL, et al. Long-term exposure to air pollution and incidence of cardiovascular events in women. N Engl J Med. 2007; 356: 447-58.

16. Dominici F. Time-Series Analysis of Air Pollution and Mortality: A Statistical Review. Research Report 123. December 2004. Health Effects Institute, Boston MA.

17. Medina-Ramón M, Zanobetti A, Schwartz J. The Effect of Ozone and PM10 on Hospital Admissions for Pneumonia and Chronic Obstructive Pulmonary Disease: A National Multicity Study. American Journal of Epidemiology. 2006; 163: 579-588.

18. Stieb DM, Szyszkowich M, Rowe BH, Leech JA. Air pollution and emergency department visits for cardiac and respiratory conditions: multi-city time series analysis. Environ Health. 2009; 10: 8-25.

19. 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.2003; Suppl.40: 34s-38s.

20. Graham LM. All I need is the air that I breath: outdoor air quality and asthma. Paediatr Respir Rev. 2004; 5 Suppl A: S59-64.

21. Heinrich J and Wichmann HE. Traffic related pollutants in Europe and their effect on allergic disease. Curr Opin Allergy Clin Immunol. 2004; 4, 5: 341-8.

22. Oftedal B, Nystad W, Brunekreef B, Nafstad P. 2009. Long-term traffic-related exposures and asthma onset in schoolchildren in Oslo, Norway. Environ Health Perspect. 2009; 117, 5: 839-844.

23. McConnell R, Islam T, Shankardass K, Jerrett M, Lurmann F, Gilliland F et al. Childhood Incident Asthma and Traffic-Related Air Pollution at Home and School.Environmental Health Perspectives. 2010; 118: 1021-1026.

24. Künzli N, Kaiser R, Medina S, Studnicka M, Chanel O, Filliger P et al. Public-health impact of outdoor and traffic-related air pollution: a European assessment. Lancet. 2000; 356, 9232: 795-801.

25. Ling S, van Eeden SF. Particulate matter air pollution exposure: role in the development and exacerbation of chronic obstructive pulmonary disease. Int J Chron Obstruct Pulmon Dis. 2009; 4: 233-43.

26. Schikowski T, Sugiri D, Ranft U, Gehring U, Heinrich J, Wichmann HE et al. Long-term air pollution exposure and living close to busy roads are associated with COPD in women. Respir Res. 2005; 6: 152.

27. Zhang JJ, Hu W, Wei F, Wu G, Korn LR, Chapman RS. Children's respiratory morbidity prevalence in relation to air pollution in four Chinese cities. Environ Health Perspect. 2002; 110, 9: 961-7.

28. Peng RD, Chang HH, Bell ML, McDermott A, Zeger SL, Samet JM, et al. Coarse particulate matter air pollution and hospital admissions for cardiovascular and respiratory diseases among Medicare patients. JAMA. 2008; 299: 2172-9.

29. Ballester F, Saez M, Perez-Hoyos S, Iniguez C, Gandarillas A, Tobias A, et al. The EMECAM project: a multicentre study on air pollution and mortality in Spain: combined results for particulates and for sulfur dioxide. Occup Environ Med. 2002; 59: 300-8.

30. Samet, JM, Dominici F, Curriero FC, Coursac I., Zeger SL. Fine particulate air pollution and mortality in 20 U.S. cities, 1987-1994. N Engl J Med. 2000; 343: 1742-9.

31. Kim H, Kim Y, Hong YC. The lag-effect pattern in the relationship of particulate air pollution to daily mortality in Seoul, Korea. Int J Biometeorol. 2003; 48: 25-30.

32. Dominici F, Zanobetti A, Zeger SL, Schwartz J, Samet JM. Hierarchical bivariate time series models: a combined analysis of the effects of particulate matter on morbidity and mortality. Biostatistics. 2004; 5: 341-60.

33. Buadong D, Jinsart W, Funatagawa I, Karita K, Yano E. Association between PM10 and O3 levels and hospital visits for cardiovascular diseases in Bangkok, Thailand. J Epidemiol. 2009; 19: 182-8.

34. Bell ML, Ebisu K, Peng RD, Samet JM, Dominici F. Hospital admissions and chemical composition of fine particle air pollution.Am J Respir Crit Care Med. 2009; 179: 1115-20.

35. Haley VB, Talbot TO, Felton HD.Surveillance of the short-term impact of fine particle air pollution on cardiovascular disease hospitalizations in New York State. Environ Health. 2009; 8: 42.

36. Dominici F, Peng RD, Bell ML, Pham L, McDermott A, Zeger SL, Samet JM. Fine particulate air pollution and hospital admission for cardiovascular and respiratory diseases. JAMA. 2006; 295: 1127-34.

37. Bateson TF, Schwartz J. Who is sensitive to the effects of particulate air pollution on mortality? A case-crossover analysis of effect modifiers. Epidemiology. 2004; 15:143-9.

38. Zanobetti A, Schwartz J. The effect of fine and coarse particulate air pollution on mortality: a national analysis. Environ Health Perspect. 2009; 117, 6: 898-903.

39. Analitis A, Katsouyanni K, Dimakopoulou K, Samoli E, Nikoloulopoulos AK, Petasakis Y, et al. Short-term effects of ambient particles on cardiovascular and respiratory mortality. Epidemiology. 2006; 17: 230-3.

40. Dominici F, McDermott A, Zeger SL, Samet JM. National maps of the effects of particulate matter on mortality: exploring geographical variation. Environ Health Perspect. 2003; 11: 39-44.

41. Ostro B, Broadwin R, Green S, Feng WY, Lipsett M. Fine particulate air pollution and mortality in nine California counties: results from CALFINE. Environ Health Perspect. 2006; 114: 29-33.

42. Bell M, Dominici F, Samet JM. A meta-analysis of time-series studies of ozone and mortality with comparison to the national morbidity, mortality, and air pollution study. Epidemiology. 2005; 16: 436-45.

43. Ren C, Williams GM, Mengersen K, Morawska L, Tong S. Temperature enhanced effects of ozone on cardiovascular mortality in 95 large US communities, 1987-2000: Assessment using the NMMAPS data. Arch Environ Occup Health. 2009; 64: 177-84.

44. Samoli E, Zanobetti A, Schwartz J, Atkinson R, LeTertre A, Schindler C, et al. The temporal pattern of mortality responses to ambient ozone in the APHEA project. Epidemiol Community Health. 2009; 63: 960-6.

45. Peters A, von Klot S, Berglind N, Hörmann A, Löwel H, Nyberg F, Pekkanen J,Perucci CA, Stafoggia M, Sunyer J, Tiittanen P, Forastiere F. Comparison of different methods in analyzing short-term air pollution effects in a cohort study of susceptible individuals. Epidemiol Perspect Innov. 2006; 3: 10.

46. Dominici F, Zanobetti A, Zeger SL, Schwartz J, Samet JM. Hierarchical bivariate time series models: a combined analysis of the effects of particulate matter on morbidity and mortality. Biostatistics. 2004; 5, 3: 341-60.

47. Ramsay TO, Burnett RT, Krewski D. The effect of concurvity in generalized additive models linking mortality to ambient particulate matter. Epidemiology. 2003; 14, 1: 18-23.

48. Arah OA, Westert GP, Delnoij DM, Klazinga NS. Health system outcomes and determinants amenable to public health in industrialized countries: a pooled, cross-sectional time series analysis. BMC Public Health. 2005; 2, 5:81.

49. Wheeler BW, Ben-Shlomo Y. Environmental equity, air quality, socioeconomic status, and respiratory health: a linkage analysis of routine data from the Health Survey for England. J Epidemiol Community Health. 2005; 59, 11:948-54.

50. Tainio M, Tuomisto JT, Hänninen O, Ruuskanen J, Jantunen MJ, Pekkanen J. Parameter and model uncertainty in a life-table model for fine particles (PM2.5): a statistical modeling study. Environ Health. 2007; 23, 6:24.

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