A comprehensive review of European epidemiological studies on particulate matter exposure and health

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ABSTRACT

In 2006/2007 CONCAWE's Health Management Group (through H/STF-27) commissioned a literature survey and review with the primary aim of summarising the current state of science on particulate matter in ambient air and its possible effects on health. The survey and review were undertaken by the Department of Epidemiology, Mario Negri Institute, Milan, Italy[1], the International Agency for Research on Cancer, Lyon, France[2], the International Epidemiology Institute, Rockville, MD, USA[3] and the Institute of Medical Statistics and Biometry, University of Milan, Italy[4]. The authors of the study are Eva Negri[1], Silvano Gallus[1], Paolo Boffetta[2], Joseph K. McLaughlin[3] and Carlo La Vecchia[1,4]

The body of this report consists of a brief overview of the findings written by H/STF-27, followed by the detailed information in Appendix developed by the mentioned experts.

KEYWORDS

Air pollution, particulate matter, PM_{10}, $PM_{2.5}$, epidemiology, cardiovascular disease, cancer

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EUROPEAN EPIDEMIOLOGICAL STUDIES ON PARTICULATE MATTER EXPOSURE AND HEALTH: A COMPREHENSIVE REVIEW OF THE LITERATURE

SUMMARY

There are a limited number of papers on the long term effect of air pollution on morbidity and mortality in Europe, particularly with reference to small particles with aerodynamic diameters less than 2.5 microns ($PM_{2.5}$). Most information comes from US cohort studies, including the American Cancer Society Cancer Prevention Study II, the Harvard Six Cities Study, the Adventists' Health Study of Smog, and the Veterans' Cohort Mortality Study.

Ambient levels of several relevant pollutants are more variable within Europe than in the USA, and are in several areas comparably high. Selected European cohort studies, including the Netherlands Cohort Study on Diet and Cancer and the European Prospective Investigation on Cancer and Nutrition study found some association between indicators of air pollution such as PM_{10} or NO_2 and lung cancer risk, but the results were inconsistent and inadequate to address the health effects of exposure to $PM_{2.5}$.

In addition to the effect on mortality, there are open issues on the potential impact of air pollution on childhood asthma, allergy and airway disease. In consideration of the difficulties in estimating the prevalence of the conditions in various populations, these issues require additional focus.

In order to provide an indication on possible further analyses of existing European datasets, and on future new studies, a critical review of existing literature (with a focus on European data) was performed.

The project resulted in a detailed report (see **Appendix 1**) and in a paper published in the European Journal of Cancer Prevention [1].

1. INTRODUCTION

A comprehensive review of European epidemiological studies published between 1996 and 2006 was conducted.

A search string was defined to select relevant scientific literature. The results of these searches were screened by two independent reviewers and only original studies conducted in Europe with some direct measure of ambient particulate matter (PM) exposure were selected for this review. Studies investigating the effect of long-term exposure on cardiovascular disease (CVD) were included. Cancer studies that provided proxies of PM exposure (e.g. distance of the residence from a major road) were also included. Approximately 150 studies met the inclusion criteria.

2. EUROPEAN STUDIES ON SHORT-TERM PM EXPOSURE

The outcomes considered were mortality (total and by cause), hospital admissions for cardiovascular and respiratory diseases, and physician visits for respiratory diseases.

Several studies have investigated the association between day-to-day variations in PM concentrations and mortality or emergency hospital admissions. Many of these studies, however, had limitations, either because they were based on small populations or had problems in the statistical approach used, which in several instances tended to artefactually maximise the investigated association. Different and non-comparable measures of PM (PM with diameter <10 µm (PM_{10}), Black Smoke (BS), Total Suspended Particulate (TSP) etc.) were used in various studies.

Most of the European studies found a direct association between mortality and various indicators of PM levels. The multicentric APHEA2 study provided the best estimate of the relation between PM and day-to-day mortality in Europe.

The interpretation of studies on CVD admissions and PM exposure is complicated by the use of different lag times and the combination of emergency and elective hospital admissions (as well as other variations in the definition of outcome) in some of the studies. Despite these limitations, the evidence from European studies supports the hypothesis of an association between air pollution and hospital admissions for CVD. The results on respiratory admissions provided some support for an association between daily variations in air pollution and hospitalization for respiratory disease, although the specificity of the association with PM was not clarified.

Information on the separate effects of coarse, fine and ultrafine PM is limited. Given that more and more areas within Europe have, in recent years, started measuring fine and/or ultrafine PM, it is likely that in the next few years studies will investigate the effects of coarse, fine and ultrafine PM separately. Investigations aimed at separating the effects of PM of different diameters will have to deal with the thorny statistical and interpretational problems of the analysis of highly correlated variables, a problem which has also arisen in the investigation of several correlated pollutants, e.g. PM, NO_2, CO and SO_2.

Very few results are available from Central and Eastern European countries.

3. EUROPEAN STUDIES ON LONG-TERM PM EXPOSURE

Few European studies have investigated the long-term effects of PM exposure on health. Ecological studies are suggestive of a link and are generating hypotheses, but, given the potential biases inherent in their design, they cannot provide a solid base for inference.

Record linkage studies include a large number of cases, but the lack of individual variables, particularly smoking data, renders this type of study difficult to interpret.

Only a limited number of analytic studies have been conducted so far. Many of these were based on cohorts designed for other purposes but have exploited the availability of PM concentration data in the area under study. This has led to studies that were often based on small population size, often with exclusions of parts of the study population for which exposure data could not be retrieved or were not available.

In almost all long term studies conducted so far, the exposure to ambient PM has been estimated only on the base of the subjects' home address. No additional information was available on characteristics of the home (e.g. floor of residence) or of the subject's individual exposure pattern. Misclassification of exposure is likely to occur and to affect results.

Mortality was associated with various measures of long-term exposure to air pollution in cohort studies from the Netherlands, Germany and France, and in a record linkage study from Norway. The excesses were mainly attributed to cardiovascular and respiratory causes.

The evidence on long-term PM exposure and CVD morbidity is limited and difficult to interpret.

A few studies suggested associations between long-term PM exposure and asthma, lung function and various respiratory symptoms in children, although results were often not significant and not consistent. For adults, no clear evidence emerged for chronic bronchitis or asthma. Studies on air pollution and lung function, on the other hand, reported possible associations.

No clear indication of association emerged from the few studies investigating the relationship between long-term air pollution and lung or other cancers. Overall, the evidence is limited and inconsistent for this association. Limitations in the design of several studies conducted so far hinder any definite conclusion regarding cancer and long-term exposure to air pollution.

4. CONCLUSIONS

4.1. RECOMMENDATIONS FOR FUTURE RESEARCH ON HEALTH EFFECTS OF PM IN EUROPE

Previous studies on short-term effects of PM in Europe allow a general quantification of the risks. However, information on the possible confounding or modifying effect of covariables, and, in particular, data on course, fine and ultrafine particles are limited. Still, with the exception of Central and Eastern Europe where few data are available, further research on short-term effects of air pollution should not be given high priority.

Only a limited number of analytic studies have been conducted in Europe on long-term effects of air pollution, and these were mainly cohorts designed for different purposes. Their ability to provide valid results was limited by sub-optimal strategies for exposure assessment leading to misclassification, low statistical power, and heterogeneity of approaches. While it is possible that additional exposure data can be retrieved for these and other existing longitudinal studies, it is uncertain whether this approach would lead to major advances in our knowledge of health effects. In any case, priority should be given to the co-ordination and harmonization of exposure data in existing cohorts.

The establishment of new *ad hoc* studies represents the preferred strategy to provide new insights on long-term effects of air pollution. In areas where estimation of long-term PM exposure could be reconstructed, a case-control design should be considered. The design and implementation of new cohort studies would provide, in the long-term, the most reliable information, but would require great effort in terms of time and resources. Such new studies would rely on uniform methods to measure air pollutants, and be based on an increased number of new measuring stations. Participants should be periodically re-contacted and, in addition to information on possible outcomes, new exposure information based on a uniform methodology should be collected. Such new cohorts should give priority to the inclusion of populations from Central and Eastern Europe, and in particular, areas where air pollution might be higher and adverse health effects may be detected sooner than in less polluted areas of Europe.

5. GLOSSARY

ACS	American Cancer Society
ACS-CPS II	American Cancer Society – Cancer Prevention Study II
AHSMOG	Adventists Health Study of Smog
AIC	Akaike Information Criterion
AMI	Acute Myocardial Infarction
APHEA	Air Pollution and Heath: a European Approach
BMI	Body Mass Index
BS	Black Smoke
CI	Confidence Interval
CO	Carbon Oxide
COPD	Chronic Obstructive Pulmonary Disease
CV	Cardiovascular
CVD	Cardiovascular Disease
ECRHS I	European Community Respiratory Health Study I
EPA	Environmental Protection Agency (US)
EPIC	European Prospective Investigation on Cancer and Nutrition
FEF_{25-75}	Forced Expiratory Flow between 25th and 75th percent of the FVC
FEV_1	Forced Expiratory Volume in one second
FVC	Forced Vital Capacity
GAM	Generalized Additive Model
GLM	Generalized Linear Model
HEAPSS	Health Effects of Air Pollution among Susceptible Sub-population
HEI	Health Effects Institute
HR	Hazard Ratio
ICD	International Classification of Diseases
IHD	Ischemic Heart Disease

IQR	Inter-Quartile Range
Lag x	xth day Lag
Lag x-y	average x-y days Lag
LCL	Lower Confidence Limit
MC	Mass Concentration
MEF_{25-75}	Midexpiratory flow between 25 and 75th percent of the FVC
MeSH	Medical Subject Headings
NC	Number Concentration
NMMAPS	National Morbidity, Mortality and Air Pollution Study
NO	Nitrogen oxide
NO_2	Nitrogen dioxide
NO_3	Nitrate
NO_x	Oxides of nitrogen
NS	Not Significant
OLS	Ordinary Least Squares
OR	Odds Ratio
O_3	Ozone
PAARC	Pollution Atmosphérique et Affections Respiratoires
PM	Particulate Matter
PM_{10}	PM with diameter <10 µm
PM_x	PM less than x µm in aerodynamic diameter
PNC	Particle Number Concentration
RH	Relative humidity
RR	Relative Risk
SAPALDIA	Study on Air Pollution and Lung Diseases in Adults
SES	Socioeconomic status
SO_2	Sulphur dioxide

SO_4	Sulfate
TSP	Total Suspended Particles
UCL	Upper Confidence Limit

6. REFERENCES

1. Gallus, S. et al (2008) European studies on long-term exposure to ambient particulate matter and lung cancer. *European Journal of Cancer Prevention 17, 191-194*

APPENDIX 1 DETAILED REPORT

EUROPEAN EPIDEMIOLOGICAL STUDIES ON PARTICULATE MATTER EXPOSURE AND HEALTH: A COMPREHENSIVE REVIEW OF THE LITERATURE

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SUMMARY

The US Environmental Protection Agency (EPA) reviewed data from studies on particulate air pollution (particulate matter, PM) and health published between 1996 and 2002 (US EPA, 2004). Herein, we have conducted a comprehensive review of the European epidemiological studies published between 1996 and 2006.

By means of Medline literature searches, we identified a number of studies, which were then screened by two independent reviewers for inclusion. We selected original studies conducted in Europe with some direct measure of ambient particulate matter (PM) exposure. For studies investigating the effect of long-term exposure on cardiovascular disease (CVD) and cancer, we included also studies providing proxies of PM exposure (e.g. distance of the residence from a major road). Approximately, 150 studies met the inclusion criteria. Studies published before 1996, and included in the EPA report are presented in an appendix, but are not commented on in the text.

1) Studies on short-term PM exposure

The outcomes considered were mortality (total and by cause), hospital admissions for cardiovascular and respiratory diseases, and physician visits for respiratory diseases.

Several studies have investigated the association between day-to-day variations in PM concentrations and mortality or emergency hospital admissions. Many of these studies, however, had limitations, either because they were based on small populations or had problems in the statistical approach used, which in several instances tended to artefactually maximise the investigated association. Different and non-comparable measures of PM (PM with diameter <10 μm (PM_{10}), Black Smoke (BS), Total Suspended Particulate (TSP) etc.) were used in various studies.

Most of the European studies found a direct association between mortality and various indicators of PM levels. The multicentric APHEA2 study provided the best estimate of the relation between PM and day-to-day mortality in Europe. The APHEA2 study was based on a large population derived from several different areas in Europe, and the study data have been thoroughly re-analyzed to evaluate the influence of different statistical models, different time lags (up to 40 days), and the modification effects of some city characteristics, such as temperature or humidity, but also the percentage of people aged >65 years and of smokers. In the APHEA2 study, the estimated increase in total number of deaths associated with an increase of 50 $\mu g/m^3$ of PM_{10} (lag 0-1 days) ranged from 2.1% to 3.3%, according to the statistical model used. For an increase in BS of 50 $\mu g/m^3$ the estimated increase ranged from 1.4% to 2.8%. The associations of PM indicators with mortality approximately halved after adjustment for NO_2. Medium-term (40 days) analyses showed that the observed effect is likely not due to mortality displacement, i.e., a mere anticipation of time of deaths of a few days. On the contrary, medium-term effect estimates tended to be two times higher than short-term ones, indicating a possible underestimation of the global effect of PM when only a few days are considered. This problem appeared more pronounced for respiratory than for CVD deaths.

The interpretation of studies on CVD admissions and PM exposure is complicated by the use of different lag times and the combination of emergency and elective hospital admissions (as well as other variations in the definition of outcome) in some of the studies. Despite these limitations, the evidence from European studies supports the hypothesis of an association between air pollution and hospital

admissions for CVD. The results on respiratory admissions provided some support for an association between daily variations in air pollution and hospitalization for respiratory disease, although the specificity of the association with PM was not clarified.

Although age at death is, with sex, the only individual characteristic readily available from death certification data, the modifying effect of age on the relation between short-term PM exposure and mortality/morbidity has not been fully explored. The data from the APHEA2 study suggest that the effect of air pollution is greater at older ages.

Confounding by individual characteristics is not a major issue, since in time series comparisons are made from one day to another, using the same background populations. In the few studies that have analyzed data using a case-crossover design in addition to a time series approach, the results were comparable.

Limited or inadequate information is available in Europe on modification of the effects of air pollution exerted by individual variables (other than age and sex), e.g. socioeconomic status (SES), lifestyle habits (e.g. smoking), underlying medical conditions (e.g. COPD (chronic obstructive pulmonary disease), coronary disease, diabetes), occupational exposures, etc.

Information on the separate effects of coarse, fine and ultrafine PM is limited. Given that more and more areas within Europe have, in recent years, started measuring fine and/or ultrafine PM, it is likely that in the next several years studies will investigate the effects of coarse, fine and ultrafine PM separately. Investigations aimed at separating the effects of PM of different diameters will have to deal with the thorny statistical and interpretational problems of the analysis of highly correlated variables, a problem which has also arisen in the investigation of several correlated pollutants, e.g. PM, NO_2, CO and SO_2.

Presently, very few results are available from Central and Eastern European countries.

2) Studies on long-term exposure

Few European studies have investigated the long-term effects of PM exposure on health. Ecologic studies are suggestive and hypothesis generating, but, given the potential biases inherent in their design, they cannot provide a solid base for inference.

Record linkage studies include a large number of cases, but the lack of individual variables, particularly smoking data, renders this type of study difficult to interpret.

Only a limited number of analytic studies have been conducted so far. Many of these were based on cohorts designed for different purposes, which have exploited the availability of PM concentration data in the area under study. This has led to studies that were often based on small population size, often with exclusions of parts of the study population for which exposure data could not be retrieved or were not available.

In short-term time series, comparisons are ideally made between different days within individuals, and adjustment for day of week and holidays is often performed. In contrast, studies of long-term exposure are necessarily based on comparisons between individuals, and on cumulative exposure assessment. Misclassification of exposure is likely to occur and to affect results. In almost all studies conducted so

far, the exposure to ambient PM has been estimated only on the basis of the home address of the subjects. No additional information was available on characteristics of the home (e.g. type of dwelling) or of the subject's individual exposure pattern.

Mortality was associated with various measures of long-term exposure to air pollution in cohort studies from the Netherlands, Germany and France, and in a record linkage study from Norway. The excesses were mainly attributed to cardiovascular and respiratory causes.

The evidence on long-term PM exposure and CVD morbidity is scant and difficult to interpret.

A few studies suggested associations between long-term PM exposure and asthma, lung function and various respiratory symptoms in children, although results were often not significant and not consistent. For adults, no clear evidence emerged for chronic bronchitis or asthma. Studies on air pollution and lung function, on the other hand, reported positive results.

No clear indication of association emerged from the few studies investigating the relation between long-term air pollution and lung or other cancers. Overall, the evidence is scant and inconsistent for this association. Limitations in the design of several studies conducted so far hinder any definite conclusion regarding cancer and long-term exposure to air pollution.

3) Recommendations for future research on health effects of air pollution in Europe

Previous studies on short-term effects of air pollution in Europe allow a general quantification of the risks. However, information on the possible confounding or modifying effect of covariates, and mainly data on coarse, fine and ultrafine particles are limited. Still, with the exception of Central and Eastern Europe, where few data are available, further research on short-term effects of air pollution should not be given high priority.

Only a limited number of analytic studies have been conducted in Europe on long-term effects of air pollution, and these were mainly cohorts designed for different purposes. Their ability to provide valid results was limited by sub-optimal strategies for exposure assessment leading to misclassification, low statistical power, and heterogeneity of approaches. While it is possible that additional exposure data can be retrieved for these and other existing longitudinal studies, it is uncertain whether this approach would lead to major advances in knowledge of health effects. In any case, priority should be given to the co-ordination and harmonization of exposure data in existing cohorts.

The establishment of *ad hoc* studies represents the preferred strategy to provide new insights on long-term effects of air pollution. In areas where estimation of long-term PM exposure could be reconstructed, the case-control design should be considered. The design and implementation of new cohort studies would provide, in the long-term, the most reliable information, but would require great effort in terms of time and resources. Such new studies would rely on uniform methods to measure air pollutants, and be based on an increased number of new measuring stations. Participants should be periodically re-contacted and in addition to information on possible outcomes, new exposure information based on a uniform methodology should be collected. Such new cohorts should give priority to the inclusion of populations from Central and Eastern Europe, where air pollution is higher and adverse health effects may be detected sooner than in less polluted areas of Europe.

1. INTRODUCTION

Although most epidemiological research on health effects of air pollution has focused on short-term exposure, a few studies have considered long-term exposure. The US Environmental Protection Agency (EPA) reviewed data of studies on particulate air pollution (particulate matter, PM) and health published between 1996 and 2002 (US EPA, 2004).

There is relatively little published on the long-term effect of air pollution on morbidity and mortality in Europe, particularly with reference to small aerodynamic particles with diameters less than 2.5 microns ($PM_{2.5}$). Most information comes from US cohort studies, including the American Cancer Society - Cancer Prevention Study II (ACS-CPS II), the Harvard Six Cities Study, the Adventists Health Study of Smog (AHSMOG), and the Veterans' Cohort Mortality Study.

Ambient levels of several relevant pollutants are more variable within Europe than in the USA, and are, in several areas, comparably high. Selected European cohort studies, including the Netherlands Cohort Study on Diet and Cancer and the European Prospective Investigation on Cancer and Nutrition (EPIC) study found some association between indicators of air pollution such as PM_{10} or NO_2 and lung cancer risk, but the results were inconsistent and inadequate to address the health effects of exposure to $PM_{2.5}$.

In addition to the effect on mortality, there are open issues on the potential impact of air pollution on childhood asthma, allergy and airway disease. In consideration of the difficulties in estimating the prevalence of these conditions in various populations, these issues require additional focus.

In order to provide indication on possible further analyses of existing European datasets, and on future new studies, we performed a critical review of existing literature (with focus on European data). This leads to recommendations on the design of future epidemiological studies on health effects of air pollution in Europe.

We have therefore updated the literature from Europe up to 2006, and conducted a comprehensive review of the European epidemiological studies published between 1996 and 2006.

Most of the original studies considered the association between short-term exposure to ambient pollutants (including PM) and morbidity/mortality. Several components and measures of air pollution were analysed with reference to incidence or mortality from cardiovascular disease (CVD), hospital admissions for respiratory disease, incidence of asthma and other respiratory conditions, and decreased pulmonary function. However, the results were not consistent across studies, and precise quantification of risks remains unattainable.

Only a few studies provided data on long-term exposure to PM and morbidity/mortality in adults.

The main results of these studies are summarised in the present report.

2. METHODS

2.1. RETRIEVAL OF DATA

We retrieved from PubMed the abstracts of all the journal articles on European epidemiologic studies (96 papers) included in the EPA report. We identified the Medical Subject Headings (MeSH) terms common to all the 96 papers, and defined a search string to select the scientific literature for the period 2002-2006 as follows:

("air pollutants" [MeSH] OR "air pollution" [MeSH]) AND humans [MeSH] AND ("cardiovascular diseases" [MeSH] OR neoplasms [MeSH] OR "respiratory tract diseases" [MeSH] OR hospitalization [MeSH]).

Using PubMed, on November 1, 2006 we retrieved 3,168 papers, which were then included in an electronic database using Endnote (version 9).

On the basis of title, abstract (when available), and keywords (MeSH terms), two independent reviewers (Eva Negri and Silvano Gallus) independently classified all the 3,168 papers, in order to identify studies of high interest using a 1-5 score:

1. Paper not pertinent or of limited interest (eliminate)
2. Probably not pertinent or of limited interest (eliminate if the other reviewer also scores 1 or 2)
3. Not possible to evaluate on the basis of title/abstract/keywords only
4. Of high interest (important review or methodologic papers or original studies out of Europe)
5. Original study from Europe

From the first selection, 2,383 papers were eliminated (both reviewers' score <3).

Among the other 785 papers, approximately 100 papers were scored 5 by both reviewers. To these 785 papers we added 532 papers not yet "indexed for MEDLINE" ("in process", therefore without MeSH terms), using on November 25, 2006, the following search string:

(air [tiab] OR pollut* [tiab] OR "particulate matter" [tiab] OR ambient [tiab]) AND (particulate* [tiab] OR PM [tiab] OR PM10 [tiab] OR PM2.5 [tiab] OR PM5 [tiab]) NOT(medline[sb]).

On the basis of title, abstract (when available), and keywords (MeSH terms), Eva Negri and Silvano Gallus performed a second independent double classification of the 1,317 papers using a score from 1 to 10:

1. Paper of limited interest (eliminate)
2. Methodologic study of limited interest
3. Original study not conducted in Europe of limited interest
4. Review of limited interest
5. Not possible to evaluate on the basis of title/abstract/keywords, only
6. Original study not conducted in Europe of high interest
7. Methodologic study of high interest
8. Review of high interest
9. Original European study on co-pollutants only
10. Original European study on PM.

From the second selection we eliminated (both reviewers' score <5 OR (one reviewer's score=5 AND the other's <5) 738 papers. Among the other 579 papers, 144 were considered original European studies by both reviewers. Most of these studies evaluated the association with short-term exposure to ambient pollutants including PM.

Other searches targeting cancer were performed, using a specific search string on PubMed. Furthermore, all the publications from the most important international studies (e.g., APHEA and HEAPSS) were searched. Finally, reference lists of a number of published papers (original articles and reviews) were examined.

For all the 579 papers remaining in the database, the PDF of the original article was retrieved. All papers scored 9 or 10 by at least one reviewer were examined and classified according to outcome.

2.2. PRESENTATION OF FINDINGS

We used the tables on short-term PM exposure of the EPA 2004 report as basis (US EPA, 2004), and updated them with the new studies not included in the EPA 2004 report. From the original EPA tables we have abstracted only studies conducted in Europe. In the tables, the studies already present in the EPA 2004 report are shown on a grey background, while the new studies have a white background. The EPA 2004 report did not include tables summarizing findings from studies on long-term PM exposure and mortality, and CVD and cancer morbidity. We summarized papers published from 1996 also for these outcomes in a similar way.

The EPA 2004 report also included the re-analyses of some studies published in a HEI report (HEI, 2003). This report originated from the fact that problems were found in the statistical software S-Plus routine used in many studies to fit generalized additive models (GAM): the default convergence criteria used in the S-Plus GAM function resulted in biased estimates and under some circumstances the standard errors of the estimates were underestimated (Dominici *et al*, 2002). The authors were invited to reanalyze their data using more stringent convergence criteria. The corrected analyses were published in the HEI report and compared with the original ones. Fully parametric models (GLM with natural or penalized splines) were also explored as alternative ways of estimation in the re-analyses in the HEI report.

We have modified the order in which the studies appeared in the EPA tables, since we have grouped them in the following categories: 1) Large international multicity studies 2) Nationwide studies 3) Sub-national studies, grouped by country and geographic area (Northern, Central, Southern, Eastern Europe) 4) Studies on selected populations.

In the Appendix we reported the description of European epidemiologic studies published before 1996, and cited in the EPA 1997 report (US EPA, 1997)

2.3. STUDIES CONSIDERED

For the present revision of the literature we considered the following studies:

I. Studies on short-term PM exposure and mortality, including all the studies providing estimates for PM.

II. Studies on short-term PM exposure and CVD hospital admission including all the studies providing estimates for PM.

III. Studies on short-term PM exposure and respiratory hospital admission including all the studies providing estimates for PM.

IV. Studies on short-term PM exposure and respiratory medical visits including all the studies providing estimates for PM.

V. Studies on long-term PM exposure and mortality, including all the studies providing estimates for PM.

VI. Ecologic studies on long-term PM exposure and mortality, including all the studies providing estimates for PM.

VII. Studies on long-term PM exposure and CVD morbidity, including all the studies providing estimates for PM, or proxies of PM, as those studies having as outcome the distance between a major road and the residence.

VIII. Studies on long-term PM exposure and respiratory morbidity or symptoms, including all the studies providing estimates for PM.

IX. Studies on long-term PM exposure and cancer, including all the studies providing estimates for PM, other co-pollutants or proxies of PM, as those studies having as outcome the distance between a major road and the residence.

We have not considered studies on short-term PM exposure and pulmonary function tests or other symptoms in asthmatics or non-asthmatics.

2.4. KEY ABBREVIATIONS AND OTHER TERMS

AIC	Akaike Information Criterion
AMI	Acute Myocardial Infarction
APHEA	Air Pollution and Heath: a European Approach
BMI	Body Mass Index
BS	Black Smoke
CI	Confidence Interval
CO	Carbon Oxide
COPD	Chronic Obstructive Pulmonary Disease
CVD	Cardiovascular Disease
EPA	Environmental Protection Agency (US)
FEF_{25-75}	Forced Expiratory Flow between 25^{th} and 75^{th} percent of the FVC
FEV_1	Forced Expiratory Volume in one second
FVC	Forced Vital Capacity
GAM	Generalized Additive Model
GLM	Generalized Linear Model
HR	Hazard Ratio
ICD	International Classification of Diseases
IQR	Inter-Quartile Range

IHD	Ischemic Heart Disease
Lag x	x^{th} day Lag
Lag x-y	average x-y days Lag
LCL	Lower Confidence Limit
MEF_{25-75}	Midexpiratory flow between 25 and 75^{th} percent of the FVC
NO	Nitrogen oxide
NO_2	Nitrogen dioxide
NO_x	Oxides of nitrogen
NS	Not Significant
OLS	Ordinary Least Squares
OR	Odds Ratio
O_3	Ozone
RH	Relative humidity
PM	Particulate Matter
PM_x	PM less than x µm in aerodynamic diameter
PNC	Particle Number Concentration
RR	Relative Risk
SO_2	Sulphur dioxide
TSP	Total Suspended Particles
UCL	Upper Confidence Limit

3. SHORT-TERM PARTICULATE MATTER (PM) EXPOSURE AND MORTALITY

Table I (modified and updated from EPA 2004 Table 8A-1) presents the studies conducted in Europe that have considered the association between short term exposure to PM and mortality. The APHEA studies I and II were the only large international multicity studies on short-term effects of PM on mortality in Europe. For this reason, a brief description of the APHEA studies is given below, and particular prominence is given to the results of the APHEA2 study throughout this chapter.

3.1. THE APHEA STUDIES 1 AND 2

The APHEA1 study ended before the EPA 2004 report, and its main results were included there (Katsouyanni *et al*, 1997; Samoli *et al*, 2001; Samoli *et al*, 2003).

The APHEA1 study was conducted in 12 European cities over the period 1975-1992. However, BS indicators were available for 8 cities and PM_{10} for 6 cities only. In a first publication there was a significant heterogeneity between European areas, with a positive association between BS and PM_{10}, and total mortality in western European cities and no effect in central/eastern European ones (Katsouyanni *et al*, 1997). Two subsequent re-analyses of the data using different statistical models (GAM models with smoothing terms for seasonal trends and weather) considerably reduced heterogeneity between the two areas (Samoli *et al*, 2001; Samoli *et al*, 2003). In those re-analyses, BS and PM_{10} were positively associated to mortality overall and in the two areas separately, although the size of the effect depended on the statistical model used, and particularly on the method used to adjust for meteorological variables and other confounders.

Several publications concerning the APHEA2 study were already included in the EPA 2004 report (Touloumi *et al*, 1997; Katsouyanni *et al*, 2001; Katsouyanni *et al*, 2003; Zanobetti and Schwartz, 2003), and new publications have appeared thereafter (Aga *et al*, 2003; Zanobetti *et al*, 2003; Touloumi *et al*, 2005; Analitis *et al*, 2006). Moreover, we have added to **Table I** the data concerning a publication (Zanobetti *et al*, 2002) that should have been included in the EPA 2004 report, but was not listed there. In fact, in Table 8A-1 of the EPA 2004 report, the article by Zanobetti and Schwartz 2003, which was one of the re-analyses conducted within the HEI project, was indicated as “reanalysis of the above study”, but that study (Zanobetti *et al*, 2002) was missing from the table.

The APHEA2 study used data over the period 1990-1997 (most cities had data for at least 5 years) and included 29 European cities for a total population of over 43 million.

Data on BS were available for 14 cities, and PM_{10} data for 21 cities.

The estimated effects of BS and PM_{10} on total non accidental mortality, reanalyzed using more stringent convergence criteria, were presented in the HEI report (Katsouyanni *et al*, 2003). The APHEA2 study found a direct association between mortality and the average level of PM_{10} on the same day and on the day before. The total mortality excess risk per 50 $\mu g/m^3$ of PM_{10} varied between 2.1% (95% CI 1.2-3.0) and 3.3% (95% CI 2.7-3.9), according to the statistical model considered.

The new analyses of the APHEA2 study not included in the EPA 2004 report have concerned the comparison of short and medium-term effects of exposure to PM_{10} on mortality (Zanobetti *et al*, 2003), the effects of BS and PM_{10} exposure on cardiovascular and respiratory mortality (Analitis *et al*, 2006), the effect of PM on mortality in the elderly (Aga *et al*, 2003) and the effect of different modeling techniques of influenza epidemics on the association between PM_{10} and total and cardiovascular mortality (Touloumi *et al*, 2005).

3.2. LOCATION OF THE STUDIES

Besides the APHEA studies, which were based on several cities located throughout Europe, there were one nationwide study, conducted in the Netherlands (Hoek *et al*, 2000; Hoek *et al*, 2001; Hoek, 2003, Fisher, 2003 #726) and a number of studies conducted in one or more cities/areas, from the UK, Ireland, Finland, the Netherlands, Germany, the Czech Republic, France, Italy and Spain.

3.3. STUDY DESIGNS

Almost all studies were time series correlating daily mortality with particulate levels on one or more days. Only a study in the general population and a study in patients with COPD adopted a crossover design.

3.4. INDEX OF EXPOSURE TO PARTICULATE MATTER

Several different PM measures were used, including Total Suspended Particulate (TSP), Black Smoke (BS), PM_{10}, PM_{7}, PM_{13}, PM_{15}, $PM_{2.5}$, $PM_{2.5\text{-}10}$, Number Concentration (NC) and Mass Concentration (MC) of ultrafine (0.01-0.1 µm) and fine (0.1-2.5 µm) PM. A few studies also estimated associations with SO_4^{2-} and NO_3^-.

In the APHEA1 study the indicators of PM exposure used were BS, available for 8 cities, and PM_{10}, estimated for 6 cities and computed as follows: 0.55*TSP (3 cities), PM_{13} (2 cities) and PM_7 (1 city).

In the APHEA2 study data on BS were available for 14 cities, and PM_{10} was estimated for 21 cities as follows: measured directly as PM_{10} (11 cities), by regression to BS (2 cities) or TSP (2 cities), or as % of TSP (6 cities).

3.5. STATISTICAL MODELS USED

Different statistical models for time series analyses were used in various studies. The GAM has been the favored method in recent years. The HEI report (HEI, 2003) provides a comprehensive assessment of the impact of different statistic approaches, and in particular several ways of adjusting for time-related factors, such as long term trends in pollution levels and mortality.

The APHEA2 study has been analyzed using different statistical approaches, and was re-analyzed in the HEI report (Katsouyanni *et al*, 2003). Shortly, overall estimates were obtained using a two stage model. In the first stage an estimate of the association between either PM_{10} or BS was obtained for each city using the same statistical model. In the second stage city-specific effect estimates were regressed on city-specific covariates to obtain an overall estimate and to explore confounding, using both fixed and random effects models. The single city models

were adjusted for seasonality, long-term trends, temperature, humidity, influenza, day of the week, holidays and unusual events if necessary. The lag was set *a priori* to the average of days 0 and 1.

The results of the effects on daily total number of deaths of PM_{10} are reproduced below (Table 1 from Katsouyanni *et al*, 2003). As compared to the original estimates, based on the default convergence criteria, the use of more strict convergence criteria did not materially modify the estimated betas (-4%). The use of a parametric approach by means of natural splines led to increased standard errors and a 30-40% reduction in the estimated betas, and to a 10-15% reduction when penalized splines were used. Although the size of the effect was reduced using alternative statistical methods, this reanalysis confirmed the findings of the original investigation (Katsouyanni *et al*, 2001), i.e. that there is a positive association between daily number of deaths and PM_{10} levels.

Significant heterogeneity between cities was found for all models considered.

Table 1. PM_{10} ($\mu g/m^3$) Effects on Daily Total Number of Deaths: Results from GAM Using S-Plus Software Default Convergence Parameters (default), More Stringent Convergence Parameters (maximum number of iterations = 1000 and difference of two successive coefficients < 10^{-14}) (strict), Natural Splines[a] and Penalized Splines[a] for the APHEA2 Cities. All Models Adjusted for Seasonality, Long-Term Trends, Temperature, Humidity, Influenza, Day of the Week, Holidays, and Unusual Events if Necessary.

	Default		Strict		Natural Spline		Penalized Spline	
	β	SE	β	SE	β	SE	β	SE
City								
Athens	0.001534	0.000284	0.001473	0.000284	0.000914	0.000340	0.001311	0.000331
Barcelona	0.000928	0.000185	0.000856	0.000185	0.000274	0.000222	0.000575	0.000214
Basel	0.000412	0.000436	0.000407	0.000437	0.000288	0.000483	0.000462	0.000477
Birmingham	0.000282	0.000262	0.000289	0.000262	0.000233	0.000284	0.000305	0.000285
Budapest	0.000289	0.000462	0.000186	0.000461	−0.000734	0.000539	−0.000248	0.000520
Cracow	0.000135	0.000346	0.000118	0.000346	0.000245	0.000385	0.000155	0.000374
Erfurt	−0.000564	0.000394	−0.000570	0.000395	−0.000799	0.000431	−0.000465	0.000408
Geneva	−0.000103	0.000468	−0.000107	0.000469	−0.000284	0.000520	−0.000059	0.000512
Helsinki	0.000324	0.000427	0.000325	0.000427	0.000414	0.000446	0.000389	0.000442
London	0.000691	0.000175	0.000678	0.000175	0.000441	0.000197	0.000591	0.000197
Lyon	0.001353	0.000531	0.001356	0.000532	0.001362	0.000548	0.001554	0.000543
Madrid	0.000531	0.000238	0.000503	0.000237	0.000331	0.000270	0.000372	0.000269
Milano	0.001160	0.000189	0.001122	0.000188	0.000702	0.000239	0.000901	0.000228
Paris	0.000427	0.000230	0.000400	0.000229	0.000262	0.000273	0.000411	0.000277
Prague	0.000122	0.000183	0.000115	0.000183	0.000192	0.000198	0.000097	0.000201
Rome	0.001283	0.000270	0.001272	0.000270	0.001306	0.000302	0.001333	0.000301
Stockholm	0.000389	0.000863	0.000383	0.000863	0.000573	0.000887	0.000479	0.000883
Tel Aviv	0.000641	0.000259	0.000576	0.000258	0.000590	0.000282	0.000522	0.000276
Teplice	0.000641	0.000344	0.000639	0.000344	0.000758	0.000363	0.000876	0.000351
Torino	0.001046	0.000169	0.001006	0.000169	0.000568	0.000208	0.000938	0.000186
Zurich	0.000424	0.000370	0.000412	0.000370	0.000171	0.000399	0.000365	0.000388
Fixed Pooled Estimate								
	0.000682	0.000058	0.000654	0.000057	0.000420	0.000066	0.000573	0.000064
Random Pooled Estimate								
	0.000617	0.000106	0.000593	0.000103	0.000410	0.000091	0.000550	0.000097

[a] Using the same degree of freedom as were used in the original nonparametric city-specific model.

3.6. LAG TIME

The definition of the lag time, i.e. the time interval between exposure (as determined by ambient levels of particulate) and outcome, remains still a controversial issue.

On one hand, there is the need to investigate which is the “correct” time to be used in the model. Moreover, the interval between exposure and effect may differ according to cause of death considered, reflecting different mechanisms of action. Rossi and colleagues (Rossi *et al*, 1999) in their analysis of the effects of ambient TSP levels on mortality in Milan, Italy, focused on the difference in lag times on cause-specific mortality. They reported a significant association on the concurrent day for deaths from respiratory infection and from heart-failure, while an association with myocardial infarction and COPD were found for the means of 3 to 4 days prior to death. In the APHEA2 study, the extension of the lag time from 2 to 6 days led to an increase of 20-30% of the estimated effect for CVD deaths, while the increase was more marked (75-90%) for respiratory deaths (Analitis *et al*, 2006).

On the other hand, many investigators tried a number of different single day and cumulative day lag times, and chose to present the results with the strongest association. The authors generally did not apply statistical methods (e.g. to alter statistical significance levels according to the number of tests performed) to allow for the multiple testing. This is, from a statistical point of view, questionable.

The APHEA1 study was also affected by this problem, since the “best” individual day models (days 0, 1, 2, 3) and the “best” average of 2-4 consecutive days was selected for each centre (Katsouyanni *et al*, 1997). The lag time used was also allowed to vary across centres.

Conversely, in the APHEA2 study the lag time was set *a priori* to the average of days 0 and 1 (except for analyses on medium term and harvesting effects). Thus the results of the APHEA2 study are unaffected by the problem of multiple comparison due to the use of several different lag times.

A few studies presented a table showing how the estimated beta varies according to the chosen lag time.

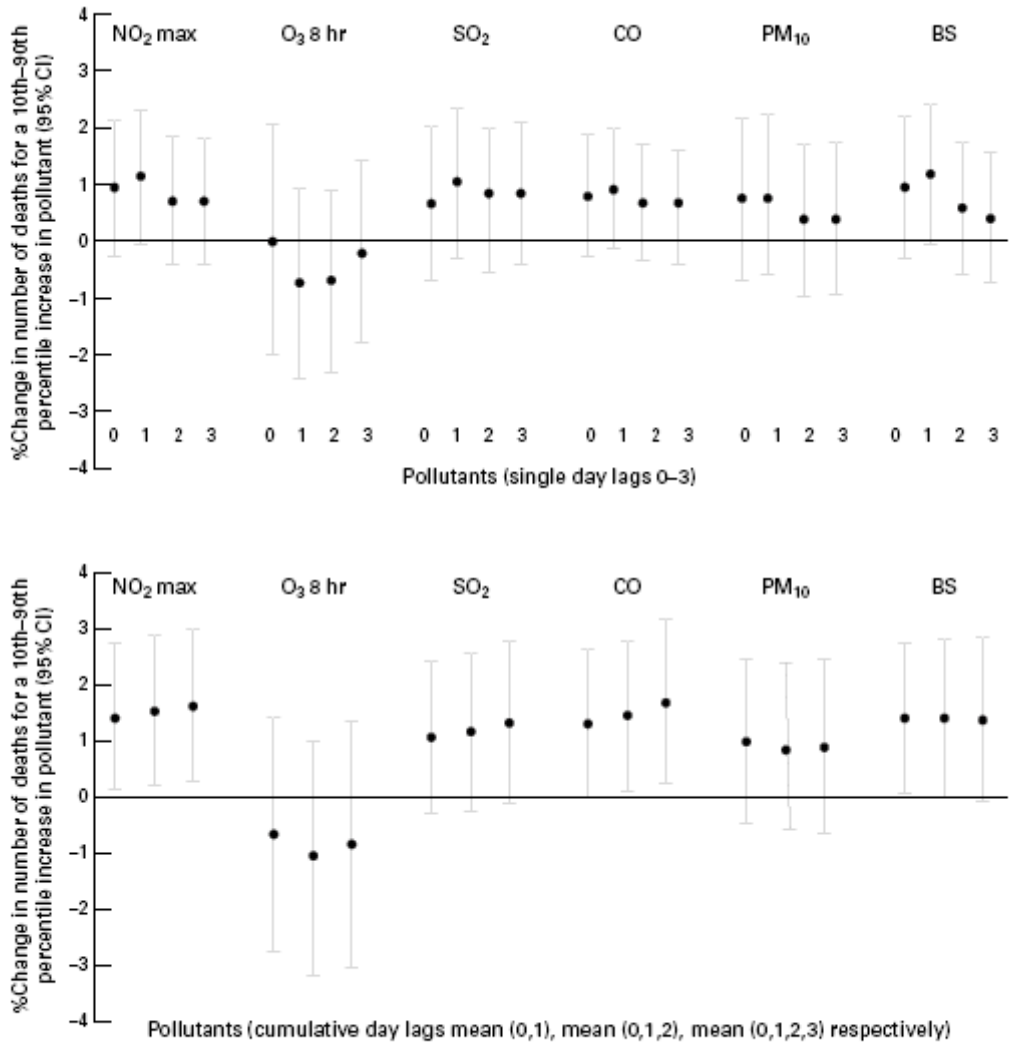


Figure 2 Percentage change in death count (95% CI) of mortality from all causes and all ages for an increase from the 10th to the 90th percentile across the range of each pollutant for all single lag (top panel) and cumulative lags (bottom panel) up to the third day.

For example, Figure 2 from Bremner (Bremner et al, 1999) above shows the estimated effects on total mortality of individual day lags 0, 1, 2 and 3 of cumulative lags mean 0-1, 0-2, and 0-3 for PM_{10} and BS (and gaseous pollutants). In this case, the estimated effects are all positive albeit non significant, although the point estimates varied. In other cases, however, the direction of the effect and the statistical significance vary according to the chosen lag (Ponka *et al*, 1998).

For the reasons explained above, we prioritize studies in which the lag time has been set *a priori* over those in which several lag times have been considered.

Most of the studies reported the association between daily deaths and pollution concentration on the same day or 1-2 days before. However, a few European studies investigated the medium-term effects of air pollution levels considering lag times up to 40 days (Zanobetti *et al*, 2002). The findings of these studies are reported in section 10 of the present chapter.

3.7. CO-POLLUTANTS

Many studies measured other pollutants besides PM. The ones reported in most studies were SO_2, NO_2, O_3 and CO. However, relatively few studies investigated the confounding effect of other pollutants on the relation between PM and mortality.

The APHEA1 study collected data on levels of SO_2, but they did not introduce SO_2 in the model because it was too strongly correlated to BS and PM_{10}.

The APHEA2 study measured SO_2, O_3 and NO_2, besides BS and PM_{10}, and presented two-pollutant models in Table 2 of the paper by Katsouyanni *et al*, 2001 (see below).

TABLE 2. Pooled* Estimates for the Increase in the Total Daily Number of Deaths Associated with PM_{10} and Black Smoke Increase of 10 gm/m^3 (Average of Lags 0 and 1) Adjusting Alternatively for Other Pollutants in Two Pollutant Models

Other Pollutant	PM_{10} Increase %				Black Smoke Increase %			
	FE Model		RE Model		FE Model		RE Model	
	%	95% CI	%	95% CI	%	95% CI	%	95% CI
None	0.68	0.6–0.8	0.62	0.4–0.8	0.51	0.4–0.6	0.58	0.3–0.8
SO_2	0.59	0.5–0.7	0.50	0.3–0.7	0.42	0.3–0.6	0.57	0.1–1.0
O_3	0.74	0.6–0.9	0.73	0.5–0.9	0.71	0.5–0.9	0.88	0.5–1.3
NO_2	0.35	0.2–0.5	0.41	0.2–0.7	0.26	0.1–0.4	0.26	0.0–0.6

FE = fixed effects; RE = random effects; PM_{10} = particulate matter less than 10 μm in aerodynamic diameter; SO_2 = sulfur dioxide; O_3 = ozone; NO_2 = nitrogen dioxide.
* The combined estimates were calculated using a multivariate second-stage regression program.

For both PM_{10} and BS, adjustment for O_3 resulted in an increase in the estimated coefficients, particularly for BS (+9% for PM_{10} and +40% for BS), adjustment for SO_2 resulted in a slight decrease of the association (-13% for PM_{10} and -18% for BS), while the association with mortality halved after adjustment for NO_2 (-49% for PM_{10} and -49% for BS). In all two-pollutant models, however, the associations between PM_{10} and BS with total mortality remained statistically significant.

Katsouyanni and colleagues (Katsouyanni *et al*, 2001) also fitted multivariate second stage regression models with the estimated effect parameters of PM and NO_2 for each city as dependent variables and average long-term NO_2 concentrations as a potential effect modifier. That analysis showed that, after adjustment for confounding of the daily fluctuations of NO_2 on the PM effect parameters, NO_2 continued to act as an effect modifier: the estimated increase in total daily mortality for an increase of 10 μg/m^3 of PM_{10} was 0.19% in a city with low average NO_2 concentration, and 0.80% in a city with high average NO_2 concentration. Corresponding estimates for BS were 0.26% and 0.73%. Also the ratio of PM_{10} to NO_2 was an effect modifier.

These estimates were affected by the problems due to the use of incorrect convergence criteria pointed out by Dominici and colleagues (Dominici *et al*, 2002). In the reanalysis presented in the HEI report (Katsouyanni *et al*, 2003), corresponding results were not shown. The authors however stated that exploration of the pattern of effect modification using parametric methods (natural and penalized splines) preserved exactly the same pattern of effect modification as the original analysis.

Hoek and colleagues (Hoek *et al*, 2000; Hoek, 2003), in their nationwide study in the Netherlands also extensively investigated the confounding effect of several

co-pollutants (O_3, SO_2, NO_2, CO) on the relation between total mortality and PM_{10} and BS levels. They also measured fine particle component sulfate (SO_4^{2-}) and nitrate (NO_3^-).

The Table 2 of the paper by Hoek (Hoek, 2003) below reproduces part of the results from the reanalysis in HEI report. We will comment on the results for the "GAM strict" model. For natural splines results were similar.

Table 2. Sensitivity of Total Mortality Associations with Air Pollution to Confounder Model Specification

	GAM Default		GAM Strict		Natural Spline		
Pollutant	RR	95% CI	RR	95% CI	RR	95% CI	*N*
PM_{10} lag1	1.018	1.003,1.034	1.019	1.003,1.034	1.018	1.002,1.035	1092
PM_{10} avg	1.023	1.004,1.041	1.023	1.005,1.041	1.019	0.998,1.040	1081
O_3 lag1	1.034	1.020,1.049	1.040	1.025,1.054	1.043	1.024,1.062	3196
O_3 avg	1.017	1.002,1.032	1.042	1.026,1.057	1.059	1.031,1.087	3191
BS lag1	1.020	1.010,1.030	1.019	1.010,1.029	1.019	1.009,1.030	3267
BS avg	1.028	1.017,1.038	1.026	1.015,1.036	1.022	1.009,1.035	3267
SO_2 lag1	1.027	1.017,1.037	1.026	1.016,1.036	1.023	1.012,1.034	3196
SO_2 avg	1.037	1.026,1.048	1.033	1.022,1.045	1.025	1.012,1.038	3191
NO_2 lag1	1.029	1.020,1.038	1.028	1.019,1.037	1.025	1.015,1.035	3184
NO_2 avg	1.031	1.023,1.040	1.027	1.018,1.035	1.020	1.009,1.031	3177
CO lag1	1.035	1.018,1.052	1.033	1.016,1.050	1.031	1.012,1.050	2158
CO avg	1.046	1.025,1.068	1.041	1.020,1.062	1.042	1.017,1.068	2153
SO_4^{2-} lag1	1.032	1.006,1.059	1.033	1.007,1.062	1.030	1.002,1.060	876
SO_4^{2-} avg	1.019	0.995,1.043	1.022	0.998,1.046	1.016	0.989,1.045	871
NO_3^- lag1	1.041	1.014,1.069	1.042	1.015,1.070	1.041	1.011,1.072	876
NO_3^- avg	1.029	1.005,1.053	1.030	1.006,1.054	1.024	0.996,1.053	871
Sec lag1	1.043	1.014,1.073	1.044	1.015,1.074	1.042	1.010,1.075	876
Sec avg	1.026	1.001,1.052	1.028	1.003,1.054	1.022	0.993,1.052	871

Note: The ranges for RR calculation were (weekly average in micrograms per cubic meter in parentheses) 100 (80) for PM_{10}; 50 (40) for BS and SO_2; 50 (30) for NO_2; 150 (120) for O_3; 1500 (1200) for CO; 25 (15) for sulfate and nitrate; 50 (30) for the sum of sulfate and nitrate. Sec = sum of sulfate and nitrate as an approximation of secondary aerosol; Avg = average of lag 0–6 days.

In the one pollutant models (lag 0-6 days) all pollutants considered were significantly and positively associated with mortality, with the exception of SO_4^{2-} for which the positive association was not significant. The point estimates were 1.023 for an increase of 100 µg/m^3 PM_{10}, 1.026 for 50 µg/m^3 of BS, 1.022 for 25 µg/m^3 of SO_4^{2-}, and 1.030 for 50 µg/m^3 of NO_3^-.

Table 5 from Hoek (Hoek, 2003) (see below) presents results for two pollutant models.

The RR for all 4 indicators of particulate increased after adjustment for O_3 or CO. Conversely, after adjusting for SO_2 or NO_2, the RR for PM_{10} was below 1, and that of BS was more than halved (1.012) and no longer statistically significant. Adjustment for SO_2 or NO_2 did not substantially change the estimated effects of SO_4^{2-} (1.019 and 1.022, respectively) and NO_3^- (1.027 and 1.029), although the standard error of the parameters increased with the introduction of the other pollutant.

It is also important to notice that the effect of SO_2 and NO_2 tended to remain positively and significantly associated with total mortality after adjustment for PM indicators.

Table 5. Sensitivity of Two Pollutant Models for Total Mortality

		GAM Default		GAM Strict		Spline		
Model	Pollutant[a]	RR	95% CI	RR	95% CI	RR	95% CI	*N*
$PM_{10}+O_3$	PM_{10}	1.025	1.007,1.043	1.026	1.007,1.044	1.021	1.001,1.042	1081
	O_3	1.045	1.018,1.074	1.050	1.022,1.079	1.048	1.014,1.083	1081
$PM_{10}+SO_2$	PM_{10}	0.983	0.960,1.006	0.987	0.964,1.011	0.986	0.959,1.014	1081
	SO_2	1.137	1.077,1.201	1.123	1.063,1.186	1.115	1.045,1.189	1081
$PM_{10}+NO_2$	PM_{10}	0.981	0.957,1.006	0.988	0.964,1.013	0.989	0.958,1.020	1081
	NO_2	1.052	1.028,1.076	1.044	1.020,1.068	1.037	1.007,1.067	1081
$PM_{10}+CO$	PM_{10}	1.038	1.005,1.072	1.044	1.011,1.079	1.056	1.015,1.099	1081
	CO	0.969	0.914,1.028	0.959	0.904,1.016	0.927	0.864,0.996	1081
$BS+O_3$	BS	1.037	1.026,1.048	1.034	1.023,1.045	1.029	1.016,1.043	3196
	O_3	1.041	1.026,1.056	1.046	1.031,1.061	1.048	1.029,1.067	3196
$BS+SO_2$	BS	1.013	0.999,1.028	1.012	0.998,1.026	1.014	0.995,1.034	3191
	SO_2	1.027	1.013,1.042	1.025	1.010,1.040	1.015	0.996,1.034	3191
$BS+NO_2$	BS	1.009	0.993,1.025	1.012	0.996,1.028	1.016	0.995,1.037	3177
	NO_2	1.026	1.014,1.038	1.019	1.007,1.032	1.010	0.993,1.027	3177
BS+CO	BS	1.048	1.015,1.081	1.050	1.018,1.084	1.062	1.021,1.104	2153
	CO	0.980	0.933,1.030	0.972	0.925,1.021	0.958	0.902,1.017	2153
$PM_{10}+BS$	PM_{10}	1.009	0.974,1.046	1.015	0.980,1.052	1.028	0.977,1.082	1081
	BS	1.017	0.977,1.059	1.010	0.970,1.052	0.988	0.928,1.051	1081
$SO_4^{2-}+PM_{10}$	SO_4^{2-}	1.029	0.997,1.062	1.029	0.997,1.062	1.028	0.994,1.064	876
	PM_{10}	1.005	0.981,1.031	1.007	0.983,1.033	1.003	0.974,1.033	876
$SO_4^{2-}+BS$	SO_4^{2-}	1.027	0.997,1.058	1.028	0.998,1.059	1.029	0.996,1.063	876
	BS	1.012	0.985,1.041	1.012	0.985,1.041	1.004	0.969,1.039	876
$SO_4^{2-}+O_3$	SO_4^{2-}	1.037	1.010,1.064	1.038	1.012,1.065	1.036	1.008,1.066	876
	O_3	1.070	1.038,1.104	1.075	1.043,1.108	1.076	1.035,1.118	876
$SO_4^{2-}+SO_2$	SO_4^{2-}	1.017	0.990,1.045	1.019	0.992,1.047	1.015	0.986,1.046	876
	SO_2	1.100	1.047,1.156	1.093	1.040,1.148	1.097	1.037,1.161	876
$SO_4^{2-}+NO_2$	SO_4^{2-}	1.019	0.991,1.048	1.022	0.994,1.051	1.019	0.989,1.051	876
	NO_2	1.027	1.008,1.047	1.023	1.004,1.043	1.020	0.997,1.044	876
$SO_4^{2-}+CO$	SO_4^{2-}	1.035	1.005,1.066	1.037	1.007,1.068	1.040	1.007,1.073	876
	CO	0.990	0.951,1.030	0.988	0.949,1.028	0.971	0.927,1.017	876
$NO_3^-+PM_{10}$	NO_3^-	1.040	1.007,1.074	1.040	1.007,1.074	1.042	1.007,1.078	876
	PM_{10}	1.002	0.977,1.027	1.004	0.979,1.029	0.998	0.970,1.027	876
NO_3^-+BS	NO_3^-	1.037	1.007,1.069	1.038	1.008,1.070	1.041	1.008,1.076	876
	BS	1.008	0.981,1.037	1.009	0.981,1.037	0.999	0.964,1.034	876
$NO_3^-+O_3$	NO_3^-	1.048	1.021,1.076	1.049	1.022,1.077	1.050	1.019,1.081	876
	O_3	1.074	1.041,1.107	1.078	1.046,1.111	1.080	1.039,1.123	876
$NO_3^-+SO_2$	NO_3^-	1.025	0.997,1.055	1.027	0.999,1.057	1.024	0.993,1.057	876
	SO_2	1.095	1.042,1.151	1.087	1.035,1.143	1.090	1.029,1.155	876
$NO_3^-+NO_2$	NO_3^-	1.026	0.995,1.058	1.029	0.999,1.061	1.030	0.996,1.065	876
	NO_2	1.023	1.003,1.045	1.019	0.999,1.040	1.016	0.991,1.041	876
NO_3^-+CO	NO_3^-	1.046	1.015,1.078	1.048	1.017,1.079	1.053	1.019,1.088	876
	CO	0.984	0.944,1.025	0.982	0.943,1.023	0.964	0.921,1.009	876

[a] Average of lag 0–6 days, except for ozone, nitrate, and sulfate (lag 1).

In conclusion, these data suggest that PM_{10} is not the only pollutant of concern, and the PM_{10}-effect should be carefully adjusted for co-pollutant effects.

3.8. CONFOUNDING/MODIFICATION EFFECT OF OTHER ENVIRONMENTAL VARIABLES

In most studies the authors adopted various methods to adjust for seasonality and long-term trends in air pollutants and daily mortality, while investigating the day to day association. Most studies also adjusted for meteorological variables like temperature at various lags and humidity. Other confounders often considered were day of the week, holydays and influenza epidemics.

One study conducted a sensitivity analysis examining the effect of different methods of modeling influenza epidemics on the estimated association between BS and total mortality in Barcelona, Spain (Tobias and Campbell, 1999). It found that the coefficient for BS decreased and became not statistically significant, when influenza was modeled by the daily number of cases, instead that by dummy variables identifying epidemic periods. Conversely, a reanalysis of the APHEA2 data controlling for influenzas by ten different methods found that the significant and positive association between PM_{10} and daily number of deaths remained and even increased after controlling for influenza, regardless of the method used for control (Touloumi *et al*, 2005).

In the APHEA2 study, the effect of PM was larger in warmer and drier cities, although temperature was a more important effect modifier than humidity (Katsouyanni *et al*, 2001). The HEI reanalysis (Katsouyanni *et al*, 2003) confirmed the same pattern of effect modification. When the authors investigated cause-specific mortality, average annual temperature and humidity were effect modifiers for CV death, but not for respiratory causes (Analitis *et al*, 2006)

In the Netherlands study, the effects of PM were stronger in summer than in winter (Hoek *et al*, 2000; Hoek, 2003). A stronger association in warmer periods was also reported in a few other studies (Anderson *et al*, 1996; Michelozzi *et al*, 1998; Anderson *et al*, 2001).

3.9. CAUSE-SPECIFIC MORTALITY

In the majority of studies, the endpoint considered was total non accidental mortality (ICD9 codes 1-799). A number of studies also considered CVD (ICD9 codes 390-459) and respiratory non cancer mortality (ICD9 codes 460-519) separately. In general, CVD deaths account for roughly half of total non accidental deaths, and often results for total and CVD mortality are similar. Conversely, respiratory mortality accounts for a much smaller proportion of total mortality. Thus, the results for respiratory mortality are much more affected by random variation, particularly in smaller studies.

Analitis and colleagues (Analitis *et al*, 2006) analyzed the effects of BS and PM_{10} separately for CVD and respiratory mortality in the APHEA2 study.

In Table 1 of their paper (below), they summarized the main results.

TABLE 1. Pooled Estimates for the Increase in the Daily Number of Cardiovascular (CVD) and Respiratory Deaths Associated With an Increase of 10 $\mu g/m^3$ in PM_{10} and Black Smoke (average of lags zero and one), Estimated With Penalized Splines, Using the Number of Degrees of Freedom (*df*) Chosen According to the Criterion of Minimization of the Partial Autocorrelation Function of the Residuals for Lags 3–30*

	PM_{10} Cause of Death		Black Smoke Cause of Death	
	CVD	Respiratory	CVD	Respiratory
Model	% Increase (95% CI)	% Increase (95% CI)	% Increase (95% CI)	% Increase (95% CI)
Fixed effects	0.64† (0.47 to 0.80)	0.58 (0.21 to 0.95)	0.57† (0.38 to 0.75)	0.50† (0.03 to 0.97)
Random effects	0.76 (0.47 to 1.05)	0.71 (0.22 to 1.20)	0.62 (0.35 to 0.90)	0.84 (0.11 to 1.57)

*Sensitivity analyses for the number of degrees of freedom as well as the use of alternative smoothers (natural splines and LOESS) can be seen in the online supplement Tables A3 and A4.
†Significant heterogeneity.

The results for the two causes were, in proportional terms, remarkably similar. For example, under the random effect model, the estimated % increase in daily number of deaths for an increase of 10 µg/m^3 of PM_{10} was 0.76% (0.47, 1.05) for CVD causes and 0.71% (0.22, 1.20) for respiratory causes. Corresponding values for BS were 0.62% and 0.84%. Estimates under the fixed effect model were lower, but still statistically significant for both causes of death. Their analysis suggested that the major impact of PM on CVD mortality occurs in the first two days (lags 0, 1), while the effects on respiratory mortality persist for several days.

Several other smaller studies considered CVD and respiratory mortality separately, but results were not always easy to interpret, given the smaller numbers of deaths, and hence the greater random variation in cause-specific mortality analyses. In the study based on 9 French cities (5 of which had data on BS) the excess RR (lag 0-1) associated with an increase of 50 µg/m^3 was 2.9% (1.3, 4.4) for total, 3.1% (0.5, 5.5) for CVD and 2.7% (-2.6, 8.3) for respiratory mortality (Le Tertre *et al*, 2002b).

In the Netherlands study, Hoek and colleagues (Hoek *et al*, 2001) analyzed associations with specific CVD causes of death. They found that deaths due to heart failure (ICD9 428), arrhythmia (ICD9 427), cerebrovascular causes (ICD9 430-436) and thrombocytic causes (ICD9 415.1, 433-4, 444, 452-3) were more strongly associated with PM (as well as with gaseous pollutants) than other CVD causes of death, including ischaemic heart diseases. This was confirmed in the HEI reanalysis (Hoek, 2003).

Cause-specific mortality was also considered in a study from Milan, Italy (Rossi *et al*, 1999). The authors found that respiratory infections and heart failure deaths were best predicted by TSP on the concurrent day, while, for deaths from myocardial infarction and COPD, lag 3-4 was the best predictor. The estimated RRs, however, were similar for heart failure (7% for 100 µg/m^3 TSP) and myocardial infarction (10%).

3.10. MORTALITY DISPLACEMENT AND MEDIUM-TERM EFFECTS OF PM

Although several time series found a direct relation between levels of PM and mortality, it has been questioned whether these excess deaths occur in those who would have died in a few days anyway (harvesting effect). If this is true, one would

expect an increase in mortality in the few days following a day with high levels of PM, followed by a decrease in the medium term. Zanobetti and colleagues (Zanobetti *et al*, 2002) analyzed the issue using the APHEA2 data. Due to time and resource constraints, it was decided *a priori* to limit the analysis of mortality displacement to the ten largest cities from different countries. Using the usual two stage methodology of the APHEA studies, different lag modes were fitted to the data. First a model for lag 0-1 was fitted, in order to estimate short-term effects. Then, different models for lag 0-40, measuring the cumulative PM_{10} exposure of the onset day and the previous 40 days, were fitted: an unconstrained distributed lag model, where one parameter for each day was used, and polynomial distributed lags of the third and fourth degree.

Estimated PM_{10} effect per 10 $\mu g/m^3$ are given below, for the original analysis (Zanobetti *et al*, 2002) and for the HEI reanalysis (Zanobetti and Schwartz, 2003) using more strict convergence criteria and penalized splines.

	Beta (SE)		
Lag, model	**Original GAM**	**Strict GAM**	**Penalized Splines**
0-1	0.70 (0.14)	0.67 (0.14)	0.57 (0.15)
0-40, unconstrained	1.61 (0.39)	Not given	Not given
0-40, cubic	1.57 (0.67)	Not given	Not given
0,40 4^{th} degree	1.61 (0.30)	1.45 (0.30)	1.08 (0.40)

Since the estimated effect of PM on mortality more than doubles when lag 0-40 days is used, instead of lag 0-1, the authors concluded that i) the effects observed in daily time series are not due primarily to short-term mortality displacement, and ii) the short-term risk assessment based on lag 0-1 associations likely underestimates the PM effect on mortality. The HEI reanalysis did confirm the same results, although all estimates were reduced for penalized splines. Similar results were reported in studies conducted in Milan, Italy (Zanobetti *et al*, 2000) and Dublin, Ireland (Goodman *et al*, 2004).

Zanobetti and colleagues (Zanobetti *et al*, 2000) also examined mortality displacement separately for cardiovascular and respiratory disease. In Table 2 of their paper (below), they found that the effect size more than doubled for CVD deaths, and increased 5-fold for respiratory deaths, when they used lag 0-40 instead than lag 0-1.

Table 2. Results for the combined estimated PM_{10} effect for the fourth degree and unrestricted models, with 40 days of delay using bootstrap methods.

	CVD		Respiratory disease	
	Percent	95% CI	Percent	95% CI
Mean lag 01	0.69	0.31–1.08	0.74	−0.17–1.66
Distributed lag				
Fourth degree	1.99	1.44–2.54	4.21	1.70–6.79
Unrestricted	1.97	1.38–2.55	4.20	1.08–7.42

Increases are for a 10 $\mu g/m^3$ increase in PM_{10}.

They also found a different pattern of mortality risk over time for CVD and respiratory deaths, with the elevation in risk of death after exposure declining more slowly over time for respiratory rather than CVD mortality.

3.11. ULTRAFINE, FINE AND COARSE PM

Only a few studies specifically considered fine or coarse PM separately.

Anderson and colleagues (Anderson *et al*, 2001) considered the association between PM_{10}, BS, $PM_{2.5}$, $PM_{2.5-10}$ and SO_4^{2-} on daily mortality in a study conducted between 1994-1996 in the west Midland conurbation of the UK. To compare estimates, they used as measurement unit for each pollutant the difference between the 10th and the 90th percentiles. The relative risk estimates at lag 0-1 were not significant for any of the PM indicators considered in the all season analysis (see Table 3 of their article below).

Table 3 Pollution and daily mortality for all causes, cardiovascular and respiratory causes (% change (95% CI) for pollution increment 10–90th percentile, mean lag 0+1 days)

Pollutant	*10–90th Percentile*	*All causes % (95% CI)*	*p Value*	*Interaction with season* p Value*	*Cardiovascular causes % (95% CI)*	*p Value*	*Interaction with season* p Value*	*Respiratory causes % (95% CI)*	*p Value*	*Interaction with season* p value*
PM_{10}	24.4	0.2 (−1.8 to 2.2)	0.9	0.007	1.0 (−1.9 to 4.0)	0.5	0.5	−1.4 (−6.0 to 3.5)	0.6	0.2
$PM_{2.5}$	17.7	0.6 (−1.5 to 2.7)	0.6	0.01	0.9 (−2.1 to 4.0)	0.6	0.7	−0.1 (−5.4 to 5.5)	0.98	0.1
$PM_{2.5-10}$	11.3	−0.6 (−4.2 to 2.3)	0.7	0.01	−0.8 (−4.8 to 3.5)	0.7	0.2	−7.6 (−13.9 to −0.9)	0.03	0.06
BS	16.7	0.6 (−1.5 to 2.7)	0.6	0.003	1.5 (−1.5 to 4.7)	0.3	0.5	0.1 (−4.8 to 5.2)	0.97	0.04
SO_4^{2-}	5.8	−0.4 (−2.3 to 1.5)	0.7	0.001	−1.3 (−4.0 to 1.5)	0.4	0.2	−1.8 (−6.4 to 3.0)	0.5	0.2
NO_2	25.5	1.4 (−0.4 to 3.2)	0.1	0.04	2.6 (−0.1 to 5.4)	0.06	0.6	2.8 (−1.6 to 7.5)	0.2	0.3
O_3	28.6	2.9 (−0.1 to 6.0)	0.05	0.01	0.9 (−3.4 to 5.4)	0.7	0.1	2.2 (−5.4 to 10.4)	0.6	0.1
SO_2	8.5	−0.2 (−2.1 to 1.8)	0.8	0.9	−0.2 (−3.0 to 2.6)	0.9	0.2	−1.9 (−6.3 to 2.7)	0.4	0.4
CO	1.0	0.8 (−0.6 to 2.2)	0.3	0.2	2.5 (0.4 to 4.6)	0.02	0.8	1.2 (−2.1 to 4.6)	0.5	0.3

*Significance of interaction term for warm (April–September) and cool (October–March) seasons.

The authors noted, however, that all measures of PM except $PM_{2.5-10}$ showed significant positive effects in the warm season (figure 1 below).

Although not significant, the estimates for coarse PM were not substantially different from those of other PM indicators, particularly for the warm season. Moreover, the correlation between PM_{10} and $PM_{2.5}$ was 0.92, thus the effects of the two measures were difficult to distinguish.

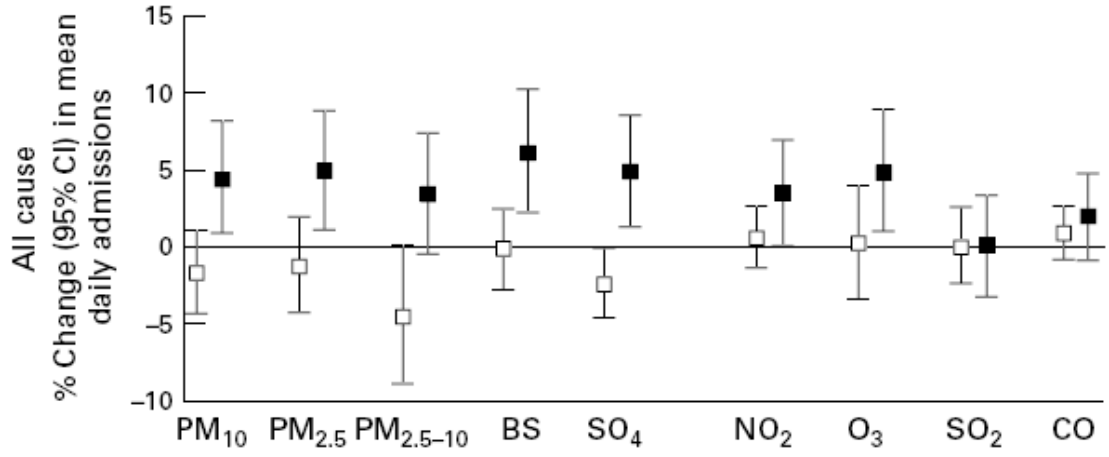


Figure 1 Cool (open square) and warm (black square) season estimates for effects of pollutants on daily mortality. Percentage change (95% CI) for a 10th–90th percentile change in pollutant.

A study from Erfurt, Germany, conducted between 1995 and 1997 assessed the association and role of particles of different size with respect to mortality in an urban setting (Wichmann *et al*, 2000). One specific aim was to compare the role of ultrafine (aerodynamic diameter <0.1 µm) and fine (0.1-2.5 µm) PM on mortality.

Number concentration (NC) was measured for each particle size range, while mass concentration (MC) was calculated for each particle size range from the NC assuming sphericity of particles and constant density.

In Table 18 of their report (see below) the authors show the estimated effect for the best fitting single day model and for polynomial distributed lag models over 5 or 6 days.

Table 18. Regression Results for Particle Number Concentration, Particle Mass Concentrations, and Gaseous Pollutants

	Interquartile Range (IQR)	Lag (Days)	TR	Relative Risk/IQR	CI	*P*
Particle Number Concentration (particles/cm^3): Best Single-Day Lag						
$NC_{0.01-0.03}$	5,177–14,065	4	log	1.048	1.000–1.099	0.05
$NC_{0.03-0.05}$	1,603–4,127	4	id[a]	1.031	0.998–1.066	0.07
$NC_{0.05-0.1}$	993–2,518	1	log	1.043	0.999–1.089	0.06
$NC_{0.01-0.1}$	8,042–20,732	4	log	1.046	0.997–1.097	0.07
$NC_{0.01-2.5}$	9,659–22,928	4	log	1.041	0.991–1.093	0.11
Particle Number Concentration (particles/cm^3): Polynomial Distributed Lag[d]						
$NC_{0.01-0.03}$		0–5	id	1.030	0.997–1.065	0.06
$NC_{0.03-0.05}$		0–4	id	1.038	1.000–1.077	0.05
$NC_{0.05-0.1}$		0–5	id	1.040	0.997–1.085	0.07
$NC_{0.01-0.1}$		0–4	id	1.041	1.001–1.082	0.04
$NC_{0.01-2.5}$		0–4	id	1.036	1.003–1.069	0.03
Particle Mass Concentration (μg/m^3): Best Single-Day Lag						
$MC_{0.1-0.5}$	9.8–25.2	0	id	1.026	0.995–1.058	0.10
$MC_{0.5-1.0}$	0.81–4.03	0	id	1.015	0.996–1.034	0.13
$MC_{1.0-2.5}$	0.56–1.55	3[b]	id	0.977	0.954–1.001	0.06
$MC_{0.01-1.0}$	11.3–31.0	0	id	1.028	0.996–1.060	0.09
$MC_{0.01-2.5}$	12.0–31.9	0	id	1.031	1.000–1.063	0.05
Particle Mass Concentration (μg/m^3): Polynomial Distributed Lag[d]						
$MC_{0.1-0.5}$		0–5	id	1.035	0.999–1.071	0.05
$MC_{0.5-1.0}$		0–5	id	1.028	1.004–1.052	0.02
$MC_{1.0-2.5}$		0–5	log	1.048	1.011–1.087	0.01
$MC_{0.01-1.0}$		0–5	id	1.040	1.002–1.080	0.04
$MC_{0.01-2.5}$		0–5	id	1.049	1.011–1.088	0.01
Other Particle Mass (μg/m^3): Best Single-Day Lag						
$PM_{2.5}$	13.0–31.5	3[c]	id	0.970	0.941–1.000	0.05
PM_{10}	19.9–47.6	0	id	1.035	1.001–1.069	0.04
TSP	28.8–61.9	1	log	1.023	0.981–1.067	0.28
Other Particle Mass (μg/m^3): Polynomial Distributed Lag[d]						
$PM_{2.5}$		0–1	id	1.022	0.988–1.058	0.20
PM_{10}		0–4	id	1.036	1.004–1.069	0.03
TSP		0–1	log	1.022	0.965–1.083	0.46
Gaseous Pollutants: Best Single-Day Lag						
SO_2 (μg/m^3)	5.5–19.8	0	log	1.060	1.011–1.112	0.02
NO_2 (μg/m^3)	26.0–46.0	4	id	1.029	0.992–1.067	0.12
CO (mg/m^3)	0.3–0.8	4	log	1.055	1.003–1.110	0.04
Gaseous Pollutants: Polynomial Distributed Lag[d]						
SO_2 (μg/m^3)		0–3	log	1.074	1.022–1.129	0.01
NO_2 (μg/m^3)		1–4	id	1.035	0.995–1.077	0.09
CO (mg/m^3)		1–4	log	1.076	1.017–1.138	0.02

[a] With log transformation fit was only slightly less well: lag = 4, TR = log, RR = 1.040, CI = 0.994–1.089, *P* = 0.09.

[b] The second best fit was lag = 0, TR = id, RR = 1.019, CI = 0.997–1.042, *P* = 0.1.

[c] The second best fit was lag = 0, TR = id, RR = 1.019, CI = 0.991–1.049, *P* = 0.19.

[d] The weights are given in Table 20.

The authors concluded that fine and ultrafine particles had direct effects on mortality which were comparable in strength, and the effect was stronger if the contributions of all size classes were added up, mainly for respiratory diseases, followed by CVD diseases. When they considered two-pollutant models, they concluded that “the

observed correlations of gaseous pollutants and mortality were explained by colinearity of the gases to particles rather than by an independent causal effect".

The authors also stated that there were indications from their data that the effects of fine particles occur more immediately (lag 0-1) and the effects of ultrafine particles more delayed (lag 4-5). The HEI Review Committee agreed with the authors' conclusion that fine and ultrafine particles were associated with mortality, but did not agree with the authors' suggestion of a different lag effect (immediate *vs* delayed) for the two particle size. The Committee also did not agree with the authors' interpretation that the association of SO_2 with mortality was an artifact due to confounding by PM.

The Committee also pointed out that the study had strengths like the use of a more precise PM metric, but also had concerns regarding the statistical analysis and interpretation, mainly linked to the problems of multiple comparisons, the sensitivity of the overall estimates to confounders like influenza, and to the definition of lag.

The HEI reanalysis using more strict convergence criteria for GAM and fully parametric methods (GLM) confirmed the major interpretations and conclusions of the original study (Stölzel *et al*, 2003).

An extension of the study to the period 1995-2001 currently published online ahead of print (Stolzel *et al*, 2006), found associations between ultrafine particles NC and total (RR=1.029, 95% CI 1.003, 1.055 for an increase of 9748 cm^{-3}) and cardio-respiratory (RR=1.031, 95% CI 1.003, 1.060) mortality. No association between fine particle MC and mortality was found.

Particle number concentration (PNC) - as a proxy for ultrafine particles - was also considered in a case-crossover study conducted between 1998 and 2000 in Rome on out-of-hospital coronary deaths (Forastiere *et al*, 2005). The study found a direct association between out-of-hospital fatalities and PNC, PM_{10} and CO. However, PNC were measured for the period April 2001-Jun 2002 and estimated retrospectively for the study period by means of a regression model with PNC as the dependent variable and other pollutants (PM_{10}, CO, NO_2 and O_3) and meteorological readings as explanatory variables. Moreover, given that the correlation between measured and estimated PNC was 0.90, and that between CO and PNC was 0.89, estimated PNCs were not a better proxy of "true" PNC than CO. Nevertheless, the same study was re-analyzed as a time series and yielded similar results (Stafoggia *et al*, 2005).

A study from the coal basin of the Czech Republic (Peters *et al*, 2000) found a significant association between PM_{10} and mortality only at lag 1 (RR=1.098, 95% CI 1.07, 1.197 for 100 $\mu g/m^3$ increase). For each given lag, estimates for a 100 $\mu g/m^3$ increase of $PM_{2.5}$ were lower than for a corresponding increase in PM_{10} (RR=1.059, 95% CI 0.980, 1.144 at lag 1).

3.12. SEX DIFFERENCES

Only a few studies considered sex differences in the association between PM and mortality. Although one study from Northern Bohemia, Czech Republic (Kotesovec et al, 2000), found different results in men and women (significant associations only for men below age 65 years, and for women only above age 65 years) these differences may be due to random variation in subgroup analysis. Another study

from Rome found similar associations between PM10 and fatal out-of-hospital coronary events for the two sexes (Forastiere et al, 2005).

3.13. AGE DIFFERENCES

In the APHEA2 study, the proportion of elderly in various cities was an effect modifier of the relation between PM_{10} and mortality, and the mortality excess risk for a 10 µg/m^3 increase in PM_{10} was 0.54% (0.38, 0.69) in a city at the 25th percentile of the distribution of proportion of elderly, and 0.76% (0.63, 0.90) in a city at the 75th percentile (Katsouyanni *et al*, 2001). Corresponding estimates for BS were 0.48% (0.34, 0.62) and 0.70% (0.51, 0.90).

When the analyses were carried out separately for CVD and respiratory mortality, the modifying effect was stronger for respiratory mortality (Analitis *et al*, 2006). For BS, the proportion of elderly explained less than 10% of the heterogeneity between cities for CVD mortality, while for respiratory mortality the effect at the 25th percentile was 0.44% (-0.01, 0.88) and at the 75th percentile was 1.57% (0.99, 2.16).

When analysis of the APHEA2 data was limited to the population aged 65 years or more (Aga *et al*, 2003) larger effects of PM_{10} and BS were found than in the all age analysis (see Table 1 from their article below).

Table 1.–Pooled estimates for the increase in the total daily number of deaths and deaths among the elderly associated with a 10 μg·m^{-3} increase in particles with a 50% cut-off aerodynamic diameter of 10 μm (PM10) and black smoke (BS) (average concentrations of lags 0 and 1)

Mortality	PM10	BS
Among ⩾65-yr-olds		
Fixed effects model	0.79 (0.66–0.92)	0.63 (0.49–0.78)
Random effects model	0.74 (0.52–0.95)	0.68 (0.43–0.92)
Total		
Fixed effects model	0.71 (0.60–0.83)	0.51 (0.39–0.64)
Random effects model	0.67 (0.47–0.87)	0.58 (0.32–0.84)

Data are presented as per cent increase (95% confidence interval).

The increases in estimates when analysis was restricted to the elderly population were around 10% for PM_{10} and around 20% for BS.

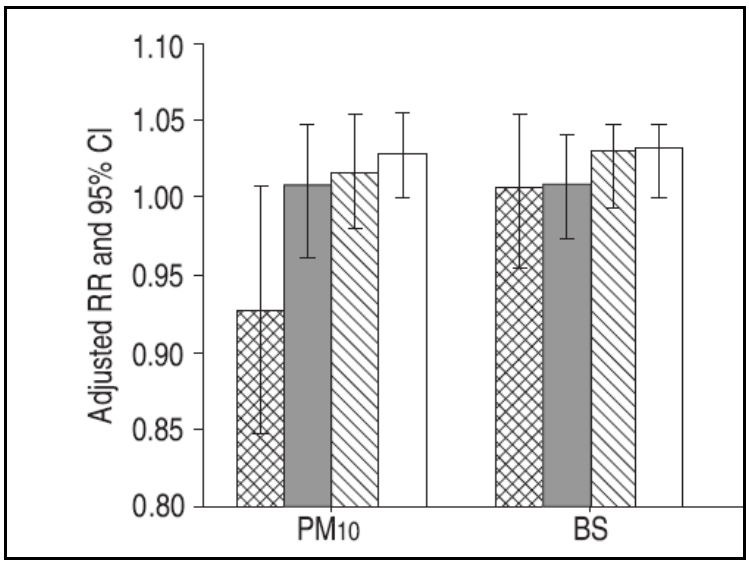
In the analysis restricted to the elderly, the same pattern of effect modification as in the overall analysis was reported, with larger PM effects in cities with higher NO_2 levels, higher temperature, lower humidity, higher age-standardized annual mortality rate, higher proportion of individuals ≥65 years and from Northwestern and Southern Europe.

An issue that still remains unclear is the quantification of the effect of PM on mortality in the population younger than 65 years. In the cities included in the

APHEA2 study the proportion of deaths occurring in the elderly ranged between 67% and 88% (Aga *et al*, 2003). Since the majority of deaths occurred in the elderly, mortality at all ages and in the elderly are highly correlated. Restricting mortality at younger ages may result in substantially different PM effect estimates, which however are clearly affected by larger random variation.

The APHEA2 analysis of the medium-term effects of PM (Zanobetti *et al*, 2003) found no association between PM_{10} and total mortality at age 15-64 years, but significant associations at ages 65-74 years and ≥75 years.

The association between PM_{10} and BS levels on the one hand and daily mortality on the other by age group was considered also in the Netherlands study (Fischer *et al*, 2003). Separate estimates were provided for the age groups <45, 45-64, 65-74 and ≥75 years for total mortality and for deaths due to CVD, COPD and pneumonia (see below figure 1 of Fisher et al., 2003). The RRs were calculated for a difference between the 1st and 99th percentiles (i.e., 80 μg/m^3 for PM_{10} and 40 μg/m^3 for BS).



From Fig 1 of Fischer et al., 2003. The successive age groups are <45, 45-64, 65-74 and ≥75 years.

When they analyzed specific causes of deaths, the pattern for CVD deaths was similar to overall mortality. Large random variation affected the estimates for COPD and pneumonia. However, for pneumonia, estimates appeared higher below age 65 years for PM_{10}, where the estimates in subsequent age categories were 1.43, 1.71*, 1.24 and 1.12* (the asterisk indicated that the CI does not include 1). No clear pattern across age groups for pneumonia mortality emerged for BS (RRs=0.74, 1.26, 0.95 and 1.12*, respectively).

The few smaller studies investigating the effect in different age groups were affected by substantial random variation, and yielded conflicting results: some found indications that the effect of PM was larger or limited to elderly people (Michelozzi *et al*, 1998; Goodman *et al*, 2004; Forastiere *et al*, 2005) some to younger people (Ponka *et al*, 1998; Bremner *et al*, 1999; Wichmann *et al*, 2000) and some did not find noticeable differences between age groups (Hoek *et al*, 1997; Prescott *et al*, 1998).

3.14. SOCIOECONOMIC DIFFERENCES

One case-crossover study investigated the effect of PM_{10} on daily mortality by socioeconomic status (SES) among residents in Rome aged over 35 years between 1998 and 2001 (Forastiere *et al*, 2005). For each death from natural causes, the day on which the death occurred was the "case" day, and the same days of the week within the same month were chosen as control days. Hospital discharge data for the 2 years before deaths were used to estimate history of selected diseases requiring hospitalization, including diabetes, hypertension, heart failure and COPD. As a surrogate for individual SES, two area-based indicators were used, i.e. the median *per capita* income and the average SES index of the census block of residence (Rome is divided in 5,736 census blocks, with an average of 480 inhabitants). The SES index was based on several characteristics of the census block, like educational level, occupational category, unemployment rate, family size, crowding and proportion of rented/owned dwellings. The two SES indexes were than divided in four groups by the 20th, 50th and 80th percentiles.

In the population of Rome the percentage of people living in areas with high levels of PM_{10}, CO, NO_x and benzene increased with increasing SES indicator, particularly for SES index: 9% of those with low SES, and 12%, 21% and 40% in those with mid-low, mid-high and high SES, respectively. This was due to the fact that people with high SES tended to live nearer to the more polluted city centre.

There was a monotonous inverse relation between both SES indicators and hospitalization rates for many chronic conditions - including malignant neoplasms, several cerebrovascular diseases, COPD and diabetes - two years to 29 days before deaths.

Figure 2 of the article presents the estimated % increase in daily mortality by SES:

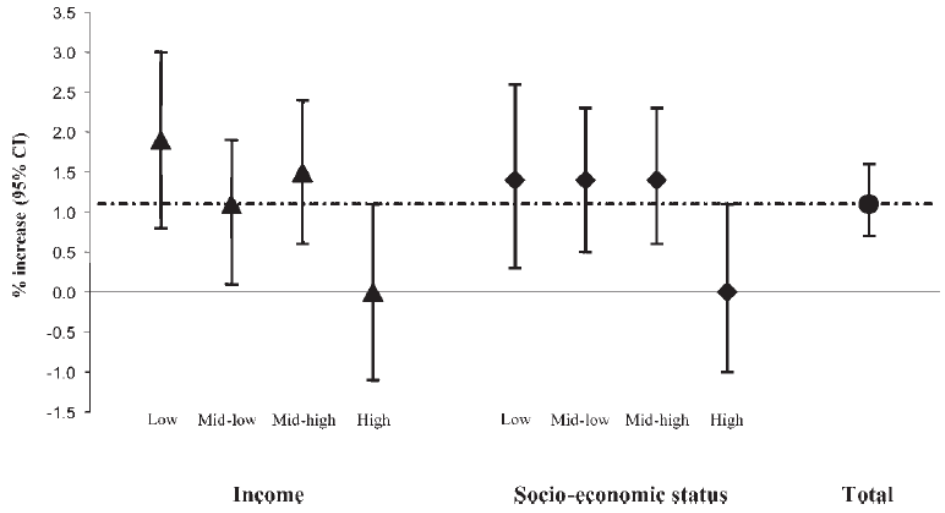


FIGURE 2. Effect of PM_{10} on natural mortality, by income and socioeconomic status[a], age 35+ years: percent increase in risk of dying[b] (and 95% confidence interval) per a 10 $\mu g/m^3$ increase in PM_{10} (Rome 1998–2001).

[a]Income and socioeconomic status are area-level indicators: they refer to the median distribution of values within the individual census-blocks of residence.

[b]Percent increase is calculated from odds ratio as: % = (OR − 1) × 100.

The effects of ambient PM_{10} on mortality were similar for the first three SES categories, but there was no association in the high SES category.

The authors concluded that the effect of PM was stronger in lower social classes. Given the observed pattern of exposure and of history of hospitalization for several severe conditions, they argued that the different effect of PM in SES groups was likely due to the differential burden of chronic health conditions conferring a greater susceptibility to lower SES groups.

However, as the authors pointed out, the monotonous increase in comorbidity across SES strata is not mirrored by a corresponding increase in PM effect, which appears, if anything, dichotomic.

3.15. STUDIES IN PATIENTS WITH SELECTED DISEASES (COPD)

Three articles (Garcia-Aymerich *et al*, 2000; Sunyer *et al*, 2000; Sunyer and Basagana, 2001) investigated the relation between ambient PM and mortality in a cohort of patients with COPD from Barcelona, Spain.

All patients aged 35 years or more attending the emergency room services in Barcelona for COPD between 1985 and 1989 were recruited (9,987 people).

In a time series analysis on the 3,245 patients who died in the period 1985-1889 (Garcia-Aymerich *et al*, 2000) the estimated percent increase in total mortality associated with an increase of 20 $\mu g/m^3$ in the patients in the cohort was 2.3% (-0.8, 15) and was, if anything, lower that the one estimated in the general population (5.6%, 95% CI 2.7, 8.7). Given the higher mortality rates in patients with COPD, in absolute terms, the effect may be higher than in the general population.

A case-crossover study (Sunyer *et al*, 2000) was conducted in patients from the cohort who died in the period 1990-1995 (2,305 patients). PM levels on the day of death were compared to those one week before and one week after. The estimated percent increase in mortality for an increase in BS of 20 $\mu g/m^3$ was 11.2% (1.7, 21.5) for all causes of deaths, 7.7% (1.3, 26.4) for CV mortality, and 18.2% (2.5, 36.5) for respiratory deaths.

When the same design was used to estimate PM_{10} effects (Sunyer and Basagana, 2001), the percent increase in total mortality for a 27 $\mu g/m^3$ (IQR) increase was 11.4% (0, 24). Although adjustment for other pollutants (NO_2, O_3, CO) resulted in larger SE of the parameters, the point estimates were not substantially modified and ranged from 10% to 13%.

However, it is important to notice that subjects with COPD are less likely to be exposed to outdoor air levels of pollutants because they spend more time indoors.

3.16. REGIONAL DIFFERENCES

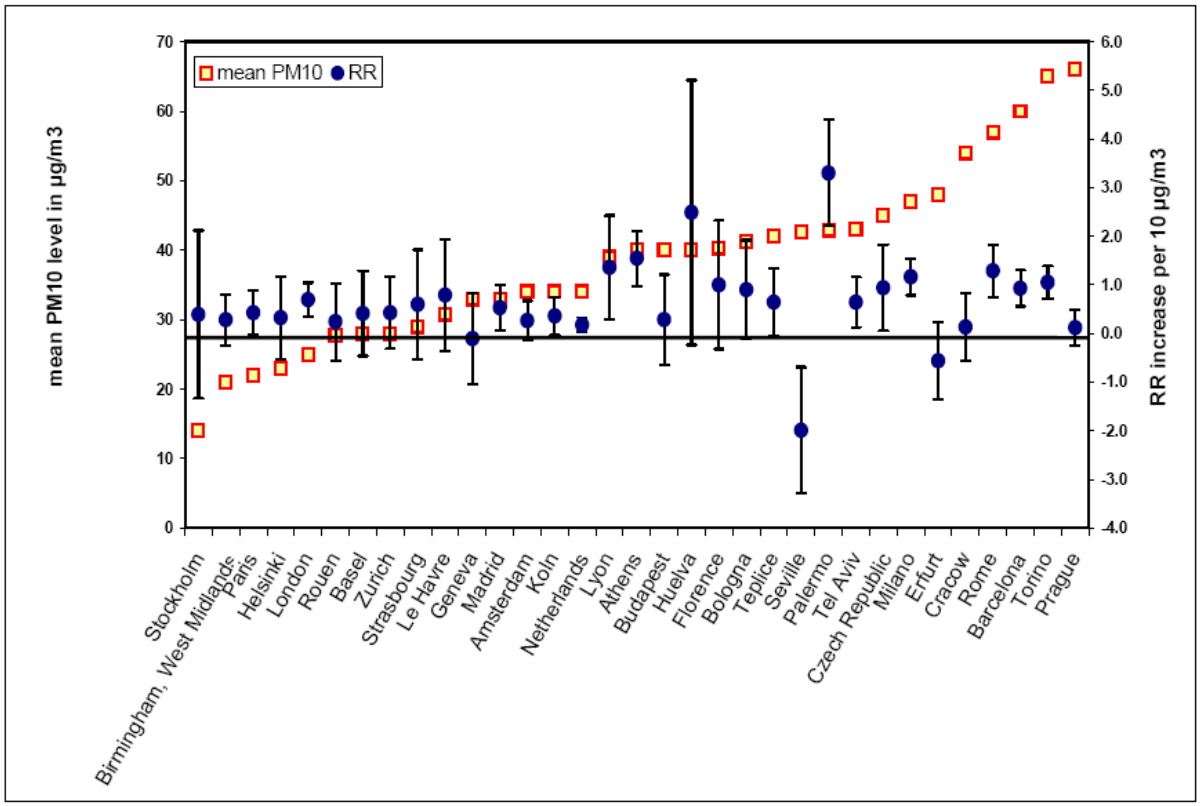
Regional differences were investigated within the APHEA Project in eight western and five central-eastern European countries, using different statistical models (Samoli *et al*, 2001). Using sinusoidal terms for seasonal control and polynomial terms for meterologic variables, the effects of air pollution on daily mortality were lower in central-eastern European cities (Katsouyanni *et al*, 1996; Katsouyanni *et al*, 1997). Data were re-analysed using generalized additive models (GAM), in order to

smooth differences in risk estimates across various countries. Thus, when excluding days with pollutant levels above 150 µg/m^3, an increase in BS by 50 ug/m^3 was associated with a 3.1% (2.6, 3.6) increase in mortality overall, a 3.1% (2.3, 3.9) increase in western countries, and a 2.9% (1.8, 4.1) increase in central-eastern countries (Samoli *et al*, 2001).

The APHEA2 study, including 29 European cities, has provided the best framework to investigate regional variation of PM effect in Europe. The median levels of PM_{10} concentration among the 21 cities providing data ranged between 14 to 166 ug/m^3. For BS median concentrations ranged between 9 and 64 ug/m^3 among the 14 cities providing data. The estimated increase in mortality for an increase of 10 µg/m^3 ranged from -0.6% to 1.5%, and there was significant heterogeneity between the single city estimates. Several city-specific factors acted as effect modifiers of the relation between PM_{10} and mortality, the effects being greater in cities with high average NO_2 levels, high mean temperature and low standardized mortality. Most of the heterogeneity between cities was explained by the inclusion of these three factors in the model (Katsouyanni *et al*, 2001).

3.17. THRESHOLDS AND DOSE-RISK RELATION

Combining estimates for cities included in the APHEA2 study and of a few other studies, Anderson and colleagues investigated the relation between mean PM_{10} concentration level and estimated short-term effect on total mortality (Ross Anderson et al, 2004) [Ross Anderson et al., 2004]. In Figure 1 of the report (shown below), the estimated PM_{10} effect on all-causes mortality is plotted against annual average levels of PM_{10} in individual European areas. No apparent relationship was evident, indicating that the relative risk does not depend on the average levels of PM_{10}, at least for a certain range of concentration.



As Brunekreef and Holgate pointed out, current knowledge, in particular from European studies, on short-term exposure to air pollution and mortality does not allow to understand whether thresholds concentrations exist below which air pollution has no effect on population health. In fact, most of the European studies analysing the association between air pollution levels and risk for health analyse time-series data. In these studies, total excess risks are usually estimated according to an increment of various measures of PM. This way of presentation of findings does not take into account the absolute pollution levels. In fact, in case of non-linearity, an increase from 100 to 110 µg/m^3 does not have the same population impact as an increase from 10 to 20 µg/m^3. This also demonstrates that time-series methodology is not suitable for detection of thresholds. (Brunekreef and Holgate, 2002).

In most studies, the statistical analysis took care of allowing a substantial variation in the possible shape of the confounders. For the PM effects however, generally linear, or in some cases log-linear, relationship with the dependent variable was assumed in the analysis. In the APHEA2 study, days with over 150 µg/m^3 were excluded because the investigators deemed that a linear relation may not hold at higher doses. In their analysis of the National Morbidity, Mortality and Air Pollution Study (NMMAPS), Dominici and colleagues found that the national average exposure-response curve was linear, although some modest departures from the linear model were observed in some regions (Dominici *et al*, 2003).

3.18. COMPARISON OF EUROPEAN WITH LEADING NORTH AMERICAN STUDIES

The two largest multicity studies from Europe (APHEA2) and the United States (National Morbidity Mortality Air Pollution Study, NMMAPS) have been reanalyzed using similar methodology within the HEI project (HEI, 2003).

The table below illustrates the estimated increase in total mortality from nonexternal causes in the two studies under different statistical models.

Estimated percent mortality change for an increase in daily PM_{10} of 10 µg/m^3 in Europe and the United States		
Model	**NMMAPS (lag 1)**	**APHEA2 (lag 0-1)**
GAM estimated with default S-Plus parameters	0.4 (0.3-0.6)	0.6 (0.4-0.8)
GAM with more stringent criteria for convergence	0.3 (0.2-0.8)	0.6 (0.4-0.8)
GLM with natural cubic splines	0.2 (0.1-0.3)	0.4 (0.2-0.6)

As can be seen, in both studies the estimated excess mortality changes according to the model used. In Europe, estimates tend however to be higher than in the Unites States. Some differences in the estimation process may explain, at least in part the differences obtained, including the different lag times used and the confounders included in the model). Differences in the quality of the air pollution measurements or in the pattern of exposure of the underlying population may also contribute to the discrepancies in results. Katsouyanni and colleagues (Katsouyanni *et al*, 2003), however, suggested that a possible explanation may be the difference in relative sources and contribution of PM_{10} in Europe and in the US. In particular diesel cars are rare in the US, while in many European cities they approach 50% of cars.

Since the APHEA2 study found that other city-specific characteristics acted as effect modifiers on the PM-mortality relation, it is also possible that differences in these factors between Europe and the US explain the different strength of the observed relation.

3.19. CONCLUSIONS

In spite of the many studies conducted in Europe, several uncertainties on the relation between ambient PM levels remain, even because of some still unresolved methodological issues.

Most of the European studies (**Table I**) found a direct association between mortality and various indicators of PM levels.

In the largest, multicity study (APHEA2) the estimated increase in total number of deaths associated with an increase of 50 µg/m^3 of PM_{10} (lag 0-1) ranged between 2.1% and 3.3% according to the statistical model used (Katsouyanni *et al*, 2003).

In the Netherlands study (Hoek, 2003), the corresponding estimates ranged between 0.9% and 1.2% according to statistical model and lag time (1 or 0-6) considered. For both studies, the 95% confidence intervals did not include unity.

For an increase in BS of 50 µg/m^3 the APHEA2 study's estimates ranged between 1.4% and 2.8% and in the Netherlands study's between 1.9% and 2.6%.

Medium-term (40 days) analyses have shown that the observed effect is likely not due to mortality displacement, i.e., a mere anticipation of time of deaths of a few days. On the contrary, medium-term effect estimates tended to be two times higher than short-term one, indicating a possible underestimation of the global effect of PM when only few days are considered. This problem may be more pronounced for respiratory deaths than for CVD ones.

Given the marked correlations between PM and gaseous pollutants, the reciprocal confounding effect is an important issue in the light of a causal interpretation of the observed association. Introduction of highly correlated variables in statistical regression models creates problems of instability and can seriously affect the estimates.

This may explain, at least in part, the inconsistencies observed between the major studies. In the APHEA2 study the effect of PM was only slightly reduced after adjustment for SO_2, but almost halved, remaining statistically significant, after adjustment for NO_2. In the Netherlands study, no association with PM_{10} was shown after adjustment for SO_2 or NO_2.

Besides the issue of confounding, other pollutants can also act as effect modifier on the relation between PM and mortality, as suggested by the APHEA2 study. This relation can be further modified by other meteorological variables, like temperature and humidity.

Individual variables - like age, general health status and SES - can also affect this relation.

Finally, the European studies aiming at separating the effects of fine (and ultrafine) and coarse PM are still too few and small-scaled to allow clear conclusions.

4. SHORT-TERM PM EXPOSURE AND CARDIOVASCULAR DISEASE (CVD) HOSPITAL ADMISSIONS

Table II (modified and updated from EPA 2004 Table 8B-1) presents European studies investigating the association between short-term ambient PM exposure and CVD hospital admissions. These include two international multicity studies, the APHEA2 (Le Tertre *et al*, 2002a) and the HEAPSS (von Klot *et al*, 2005; Lanki *et al*, 2006), two national multicity studies from France (Eilstein *et al*, 2004) and Italy (Biggeri *et al*, 2005) and a number of smaller studies from various countries.

4.1. THE APHEA2 STUDY

The APHEA2 study has been already discussed in the chapter on short term effects of PM on mortality. The analysis on CVD hospital admissions (Le Tertre *et al*, 2002a) was based on 8 cities/areas, i.e. Barcelona in Spain, Birmingham and London in the UK, Milan and Rome in Italy, Paris in France, Stockholm in Sweden and the whole of the Netherlands, for a total population close to 38 million.

The study period started between 1989 and 1994 and ended between 1994 and 1997, depending on the area. The number of days contributing to the analysis varied between city and PM exposure indicator, ranging between 930 and 2,904. Ambient PM exposure indicators used were BS, available for 5 cities, and PM_{10}, measured directly in 5 cities, as PM_{13} in Paris and as 0.75*TSP in Milan and Rome. Days with levels of PM exposure indicators above 150 $\mu g/m^3$ were excluded, because of the possible lack of linearity at higher doses.

Autoregressive Poisson models, adjusting for long-term trends, season, influenza and meteorology were used to estimate PM effects for each city. Pooled estimates were then obtained combining the city-specific effect estimates by means of fixed and random effect models. The lag was set *a priori* at 0-1.

Emergency admissions were used in all cities except Milan, Paris and Rome, where only general admission data were available. In order to exclude elective admissions, some diagnostic codes were excluded, based on the distinction between emergency and elective admissions in London for the period 1992-94. Causes with more than 70% of elective admissions were excluded, plus the code 414 (“other forms of ischemic heart disease”), for which 65% of admissions were elective. The outcomes considered were all cardiac causes (ICD9 390-429), ischemic heart disease (ICD9 410-413) and stroke (ICD9 430-438).

Table 5 Pooled percentage increases under fixed and random effect models for a 10 μg/m³ increase in pollutant levels

	PM_{10}		Black smoke	
	%	95% CI	%	95% CI
Cardiac				
Fixed	0.5	0.3 to 0.7	0.8	0.5 to 1.2
Random	0.5	0.2 to 0.8	1.1	0.4 to 1.8
Cardiac over 65 years				
Fixed	0.7	0.4 to 1.0	0.9	0.4 to 1.3
Random	0.7	0.4 to 1.0	1.3	0.4 to 2.2
IHD below 65 years				
Fixed	0.3	−0.1 to 0.6	0.1	−0.4 to 0.5
Random	0.3	−0.2 to 0.7	0.1	−0.4 to 0.5
IHD over 65 years				
Fixed	0.6	0.3 to 0.8	1.1	0.7 to 1.5
Random	0.8	0.3 to 1.2	1.1	0.6 to 1.6
Stroke over 65 years				
Fixed	0.0	−0.3 to 0.3	−0.1	−0.5 to 0.4
Random	0.0	−0.3 to 0.3	0.0	−0.7 to 0.6

Table 5 of the article (above) gives the pooled results for a 10 μg/m³ increase in PM_{10} or BS.

The percent increase of cardiac admissions for a 10 μg/m³ increase was 0.5% (0.3, 0.7) for PM_{10} and 0.8% (0.5, 1.2) for BS under the fixed effect model, and the estimates were higher when the analysis was limited to individuals above age 65 years. For IHD the estimates were 0.3% (-0.1, 0.6) below 65 years of age and 0.6% (0.3, 0.8) above age 65 years for PM_{10}; and 0.1% (-0.4, 0.5) below 65 years and 1.1% (0.7, 1.5) above age 65 years for BS. No effect of PM_{10} or BS was evident for stroke admissions. Estimates from random effect models were either similar or moderately higher.

The authors also fitted two pollutant-models (see Tables 6 and 7 of the article below):

Table 6 Pooled estimates for the increase in the total daily number of deaths associated with PM_{10} increase of 10 µg/m³ (average of lags 0 and 1) adjusting alternatively for other pollutants in two pollutant models

	PM_{10}	95% CI	$+SO_2$	95% CI	$+O_3$	95% CI	$+NO_2$	95% CI	+CO	95% CI	+BS	95% CI
Cardiac	0.5*	0.2 to 0.8	0.5*	−0.9 to 2.0	0.5*	0.2 to 0.9	−0.2†	−0.5 to 0.1	0.2*	−0.3 to 0.7	−0.2*	−1.2 to 0.8
Cardiac over 65 years	0.7†	0.4 to 1.0	0.9*	−1.1 to 3.0	0.7†	0.4 to 1.0	−0.2†	−0.5 to 0.2	0.5*	−0.6 to 1.6	0.1*	−0.4 to 0.7
IHD over 65 years	0.8*	0.3 to 1.2	1.3*	−1.8 to 4.4	0.9*	−0.1 to 1.9	0.3*	−1.1 to 1.7	0.5*	−0.7 to 1.7	0.2*	−0.9 to 1.4

*Random effect model. †Fixed effect model.

Table 7 Pooled estimates for the increase in the total daily number of deaths associated with black smoke (BS) increase of 10 µg/m³ (average of lags 0 and 1) adjusting alternatively for other pollutants in two pollutant models

	BS	95% CI	$+SO_2$	95% CI	$+O_3$	95% CI	$+NO_2$	95% CI	+CO	95% CI	$+PM_{10}$	95% CI
Cardiac	1.1*	0.4 to 1.8	0.6†	0.2 to 1.1	1.1*	0.4 to 1.7	0.7*	−1.0 to 2.4	1.2†	0.5 to 1.9	1.6*	−0.3 to 3.5
Cardiac over 65 years	1.3*	0.4 to 2.2	1.2*	−1.1 to 3.6	1.3*	−0.1 to 2.7	0.5*	−1.6 to 2.6	1.6†	0.7 to 2.4	1.5*	0.3 to 2.7
IHD over 65 years	1.1†	0.7 to 1.5	0.8†	0.3 to 1.4	1.1†	0.7 to 1.6	0.3†	−0.2 to 0.9	0.9†	0.3 to 1.5	0.8*	−1.1 to 2.7

*Random effect model. †Fixed effect model.

Although in the titles of Tables 6 and 7 the term "total daily number of deaths" appears, the results likely refer to hospital admissions, as written in the text (mortality data were not presented in this paper). The effects of PM_{10} on cardiac, cardiac over 65 years, and IHD over 65 years admissions decreased after adjustment for CO, and disappeared after adjustment for NO_2 or BS. Adjustment for NO_2 about halved the effects of BS, which became non significant. In contrast, the point estimates of the BS effects on cardiac emergency admissions became bigger after adjustment for CO or PM_{10}.

According to the authors, the stronger confounding of PM_{10} effect by NO_2 – a secondary pollutant mainly influenced by diesel and non-catalyzed gasoline fuelled engines – than by CO – a primary traffic pollutant representing mainly gasoline fuelled engines – suggests that diesel exhaust was primarily responsible. The authors also suggested that this conclusion was supported by the fact that BS, which is dominated by diesel particles, was little affected by confounding from CO or PM_{10}. This may be debatable, as BS may also reflect the contribution of other non traffic-related sources (coal, industrial, etc.).

4.2. THE HEAPSS STUDY

The Health Effects of Air Pollution among Susceptible Sub-population (HEAPSS) originally investigated the effect of traffic related air pollution on cardiac hospital readmissions in a cohort of subjects from five European cities who were admitted for first AMI (von Klot *et al*, 2005). In a subsequent analysis the group also investigated the association between air pollutants and hospitalization for first AMI, i.e., the event responsible for the inclusion into the HEAPSS cohort (Lanki *et al*, 2006). Thus, this second study is based on the general population, and not on a selected cohort.

4.2.1. Analysis on the general population

The HEAPSS study included five European cities, Augsburg in Germany, Barcelona in Spain, Helsinki in Finland, Rome in Italy and Stockholm in Sweden. For each city, the study period was within the range 1992 and 2000, and included at least three years.

PM was measured as PM_{10} and PNC. In Augsburg, PM_{10} was estimated as 0.83*TSP, and in Barcelona data were missing for two years and were estimated by linear prediction from TSP and BS. Monitoring of PNC started in 1999 in Augsburg, and in April 2001 in the other cities. Thus, during the study period no direct measurement of PNC was available. City-specific models for estimating PNC from other pollutants and meteorological variables were developed for the period when PNC was measured, and applied then retrospectively to predict daily PNC concentrations during the study period (Paatero *et al*, 2005). The correlation of measured and predicted half of PNC, using split-halves technique ranged between 0.72 and 0.89 in the five cities, and that of day-to-day differences in measured and predicted PNC between 0.61 and 0.88 (Paatero *et al*, 2005). Levels of NO_2, CO and O_3 were also recorded and analyzed.

The data on hospitalizations for first AMI were collected using AMI registers in Augsburg and Barcelona, and hospital discharge registers in the other three cities. The ager range was over 35 in all cities. Augsburg included patients up to 74 years, and Barcelona up to 79 years. In order to increase specificity of AMI diagnoses, hospitalizations shorter than 3 days were excluded. Elective hospitalizations were also excluded in Helsinki and Stockholm. To select first AMI only, the recorded patient history was used in AMI registers, and a record linkage with the hospital discharge data of the previous three years was used in the other three cities. The presence of codes indicating a previous infarction (ICD9 412) as secondary diagnosis was also a reason for exclusion.

City-specific models were fitted in the first stage. Poisson regression, adjusting for non-linear effects by means of penalized splines in GAM was used for the analysis. Time trend, apparent temperature, barometric pressure, day of the week, holiday, and population reduction in summer were considered as confounders. Lags 0, 1, 2 and 3 were considered and presented in the article. The estimates were then combined by means of either fixed or random effect models in case of heterogeneity between city-specific estimates.

Table 4 of the paper (below) shows the relative risk of hospitalization for a first AMI for a 10 $\mu g/m^3$ increase in PM_{10} and for a 10,000 particles/cm^3 in PNC.

Table 4 Pooled rate ratios (RRs) and 95 % confidence intervals (95% CIs) for the associations of daily air pollution levels with hospitalisation for first acute myocardial infarction

Pollutant	Lag	All five cities RR* (95% CI)	Three cities with HDR‡ RR* (95% CI)
CO	0	1.005 (1.000–1.010)	1.007 (1.001–1.012)
	1	1.002 (0.996–1.007)	1.002† (0.996–1.008)
	2	1.002 (0.997–1.007)	1.003 (0.998–1.009)
	3	0.998 (0.992–1.003)	1.004† (0.988–1.020)
NO_2	0	0.996 (0.988–1.005)	0.999 (0.989–1.008)
	1	0.998† (0.986–1.010)	0.998† (0.982–1.015)
	2	1.003 (0.994–1.011)	1.005 (0.996–1.015)
	3	1.001† (0.989–1.014)	1.005† (0.989–1.021)
PNC	0	1.005 (0.996–1.015)	1.013 (1.000–1.026)
	1	0.997† (0.982–1.012)	0.995† (0.953–1.039)
	2	0.999 (0.990–1.008)	1.001 (0.989–1.014)
	3	0.998† (0.979–1.017)	1.009† (0.974–1.046)
PM_{10}	0	1.003 (0.995–1.011)	1.003 (0.994–1.012)
	1	1.001† (0.990–1.011)	0.997 (0.988–1.006)
	2	1.002 (0.994–1.010)	1.003 (0.995–1.012)
	3	1.002† (0.991–1.013)	1.003† (0.986–1.020)
O_3	0	0.991 (0.979–1.003)	0.989 (0.976–1.003)
	1	0.992 (0.980–1.004)	0.991 (0.978–1.004)
	2	0.997 (0.985–1.010)	1.002 (0.988–1.015)
	3	1.002 (0.990–1.015)	1.002 (0.989–1.015)

*Rate ratios calculated for a change of 10 000 particles/cm^3 in PNC, 10 $\mu g/m^3$ in PM_{10}, 0.2 mg/m^3 in CO, 8 $\mu g/m^3$ in NO_2, and 15 $\mu g/m^3$ in O_3.
†City-specific results heterogeneous ($p<0.1$), random effects model used for pooling.
‡Hospital discharge register.
§Rate ratios for the 8 h O_3 during warm season (April–September).

PM_{10} was not associated with hospitalization for first AMI in all five cities, nor when the analysis was limited to the three cities using hospital discharge data to define the outcome. PNC was not associated in the overall analysis, but there was a 1.3% (0.0, 2.6) increase in hospitalization for first AMI at lag 0, albeit not at other lags, when the analysis was restricted to hospital discharge register data.

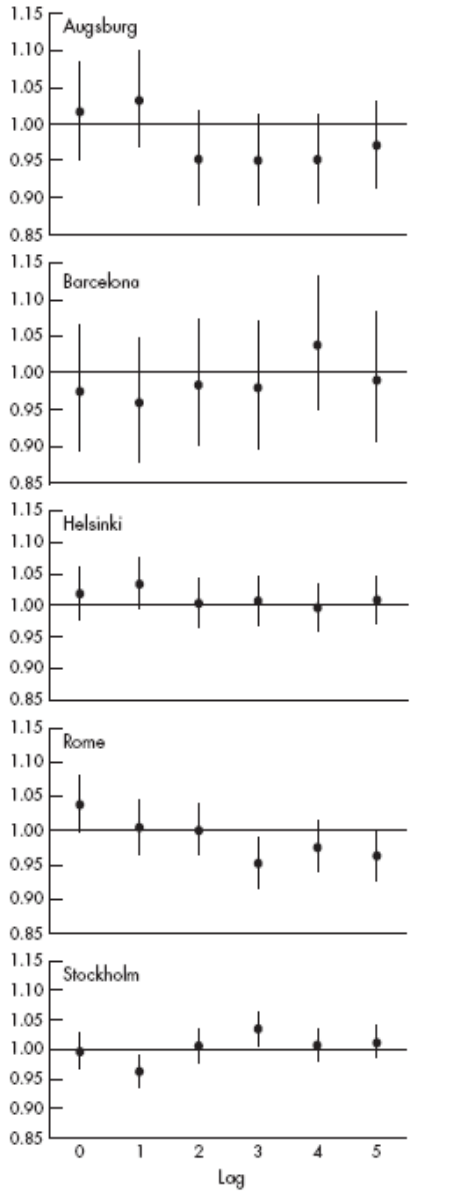


Figure 1 Rate ratios (RR; dots) and 95% confidence intervals (95% CI; vertical lines) based on single-day lag models with increasing lags for the association of particle number concentration (PNC) with hospitalisations for first acute myocardial infarction. RRs calculated for city-specific interquartile increases in PNC.

The authors excluded Augsburg and Barcelona since the upper limit on age in the inclusion criteria reduced the power in these two cities, and this could be the reason for the lack of association. However, including more cities should have, if anything, increased the power of the study. Consequently, even if nominally based on five cities, the main conclusions are based on analyses on three cities only. Figure 1 of the paper on the left gives the city specific associations. Although the authors claimed that there was no heterogeneity between the three cities (Helsinki, Rome, and Stockholm) at lag 0, there appeared to be an heterogeneity between Rome and Stockholm, since the point estimate of each of these cities was not included in the 95% CI of the estimate of the other. In fact, Rome and Stockholm are the only two

cities where some significant associations were observed. For Rome, a positive one at lag 0, and a strong inverse one at lag 3. For Stockholm, an inverse one at lag 1 and a positive one at lag 3.

The analysis was then conducted separately for fatal and non fatal AMI and for patients aged below and above 75 years, only for the three cities using hospital discharge data, and the results were presented in Table 5 of the article (see below).

Table 5 Pooled rate ratios (RRs) and 95 % confidence intervals (95% CIs) for the associations of daily air pollution levels with hospitalisation for first acute myocardial infarction *by age and fatality* in the three cities with hospital discharge registers

		Age <75		Age ≥75	
Pollutant	Lag	Non-fatal RR* (95 % CI)	Fatal RR (95 % CI)	Non-fatal RR (95 % CI)	Fatal RR (95 % CI)
CO	0	1.001 (0.995–1.008)	1.027 (1.006–1.048)	1.015 (1.004–1.026)	1.009 (0.992–1.026)
	1	1.000 (0.994–1.007)	1.021 (1.000–1.042)	1.006 (0.995–1.017)	1.001 (0.985–1.018)
	2	1.004 (0.998–1.011)	1.018 (0.997–1.039)	0.995 (0.983–1.006)	1.006 (0.990–1.023)
	3	0.999† (0.992–1.006)	1.015 (0.994–1.037)	0.998 (0.987–1.009)	1.000 (0.983–1.017)
NO_2	0	0.995 (0.982–1.008)	1.004 (0.971–1.039)	1.011 (0.993–1.029)	1.009 (0.984–1.034
	1	1.003† (0.979–1.028)	1.032 (0.998–1.066)	0.997 (0.979–1.015)	0.994 (0.969–1.019)
	2	1.015 (1.002–1.028)	1.021 (0.987–1.057)	0.995 (0.977–1.013)	0.997 (0.972–1.022
	3	1.009† (0.988–1.031)	1.019 (0.985–1.053)	1.010 (0.992–1.028)	0.985 (0.960–1.011)
PNC	0	1.001 (0.985–1.017)	1.050 (1.000–1.101)	1.032 (1.008–1.056)	1.016 (0.978–1.055
	1	0.999† (0.984–1.014)	1.058 (1.012–1.107)	1.009 (0.985–1.032)	1.001 (0.966–1.038)
	2	1.010 (0.996–1.025)	1.023 (0.977–1.071)	0.989 (0.966–1.013)	1.005 (0.969–1.041
	3	1.029† (0.976–1.084)	1.025 (0.979–1.073)	1.009† (0.969–1.051)	0.984 (0.948–1.021)
PM_{10}	0	0.997 (0.986–1.008)	1.031 (1.000–1.064)	1.012 (0.995–1.029)	1.009 (0.985–1.034
	1	0.997 (0.986–1.008)	1.026 (0.994–1.058)	1.000 (0.983–1.017)	0.998 (0.974–1.023
	2	1.005 (0.994–1.016)	0.999 (0.967–1.032)	0.999 (0.982–1.017	1.003 (0.978–1.028)
	3	0.994 (0.983–1.005)	1.022 (0.991–1.055)	1.001 (0.984–1.018)	1.018† (1.063–0.975)

*Rate ratios calculated for a change of 10 000 particles/cm^3 in PNC, 10 $\mu g/m^3$ in PM_{10}, 0.2 mg/m^3 in CO, and 8 $\mu g/m^3$ in NO_2.
†City-specific results heterogeneous ($p<0.1$), random effects model used for pooling.

No appreciable association emerged in this subgroup analysis for PM_{10}. Significant associations emerged for fatal AMI below age 75, and for non fatal AMI above age 75 years. Effects were more pronounced during the warm season. Two pollutant models were not performed.

Given the pattern of association with PNC (and CO), the authors concluded that their study supports the hypothesis that exposure to traffic related air pollution increases the risk of AMI, and that the most consistent associations were observed among fatal cases aged <75 years and in the warm season.

4.2.2. Analysis on survivors of first AMI

An article by von Klot and colleagues presented the results of the HEAPSS study for hospital readmission for cardiac causes after a first AMI (von Klot *et al*, 2005). The cohort of subjects on which this analysis was based included all subjects who had had a first non fatal AMI during the study period, i.e., all the subjects who had had an outcome in the analysis presented above (Lanki *et al*, 2006) and did not die within 28 days from the event. The enrollment period coincided with the one of the previous analysis, and the follow-up period was extended up to 2000-2001 for all centres. The cohort consisted of 22,006 subjects. Endpoints were defined as hospital readmission within the study area for 1) AMI, 2) angina pectoris and 3) cardiac causes, i.e., a combined endpoint including the previous two, heart failure and dysrhythmia. The start of the follow-up was the 29th day after the index event,

and the end of follow-up was either the endpoint of interest, death, migration out of study area, loss to follow-up or end of study period.

The levels of PM_{10} and PNC were defined as in Lanki et al (Lanki *et al*, 2006).

GAMs with penalized splines to control for confounders were used in city-specific models. The outcome was daily number of readmissions and the natural logarithm of the number of persons at risk each day was included as an offset. Pooled estimates were obtained by fixed or random effect models. Lag 0 was used for presenting results.

Table 3 of the article (below) presents the main results of their study.

PNC and PM_{10} were significantly associated with readmissions for cardiac causes. Point estimates for AMI only were higher than for cardiac causes, but not significant, because of smaller numbers of events resulting in wider CIs. Estimates for angina pectoris were above unity, but lower than for cardiac causes, and not significant.

TABLE 3. Pooled Results of Poisson Regressions of the Association of Hospital Readmissions and Same-Day Air Pollution Concentrations

		Hospital Readmissions, RR (95% CI)		
Pollutant	Unit	Myocardial Infarction	Angina Pectoris	Cardiac*
PNC	10 000/cm^3	1.039 (0.998–1.082)†	1.020 (0.992–1.048)	1.026 (1.005–1.048)
PM_{10}	10 μg/m^3	1.026 (0.995–1.058)	1.008 (0.986–1.032)	1.021 (1.004–1.039)
CO	0.2 mg/m^3 (0.172 ppm)	1.022 (0.998–1.047)	1.009 (0.992–1.026)	1.014 (1.001–1.026)
NO_2	8 μg/m^3 (4.16 ppb)	1.028 (0.997–1.060)	1.032 (1.006–1.058)	1.032 (1.014–1.051)
O_3‡	15 μg/m^3 (7.5 ppb)	1.000 (0.954–1.048)	1.044 (1.012–1.077)	1.026 (1.001–1.051)

*Hospital admissions for acute myocardial infarction, angina pectoris, dysrhythmia, or heart failure.
†Random-effects model.
‡Daily maximum 8-hour average.

In two-pollutant models, effects of PNC, CO and NO_2 were not affected by PM_{10} or O_3, while the association with PM_{10} was only slightly attenuated by traffic related pollutants.

4.3. NATIONAL MULTICITY STUDIES

Two multicity studies from France (Eilstein *et al*, 2004) and Italy (Biggeri *et al*, 2005) investigated the association between PM and hospital admissions for CVD.

The French study comprised nine cities, but the analysis on BS and CVD admissions was based on 5 cities, and that on PM_{10} and CVD admissions on 4. No significant associations were found for BS and PM_{10} at lags 0-1 and 0-5.

The Italian study was based on 8 cities. For two cities, PM_{10} was measured directly, while for the other six PM_{10} was estimated as a fraction of TSP. The pooled estimate of the percent change in number of admissions for cardiac causes (ICD9 390-429) for a 10 µg/m^3 increase in PM_{10} (lag 0-1) was 0.77% (0.40, 1.15) under the fixed

effect model and 0.82% (0.32, 1.32) under the random effect model. Results were similar to the random effect model when several Bayesian models were fitted.

4.4. STUDY DESIGN, STATISTICAL MODEL AND LAG TIME

As for mortality, almost all the studies were time series.

It is likely that some of the early studies (including the APHEA2 study) were affected by the statistical problems connected with the use of S-plus routines. However, in the case of mortality studies, the HEI reanalysis had shown that results changed only slightly by the use of more strict convergence criteria. Greater changes were observed by the use of different statistical models for the control of continuous confounders (HEI, 2003).

Some studies were also affected by multiple comparison problems due to the use of different lag times. The APHEA2 study defined lag time *a priori* while the HEAPSS study showed results for different lag times, and combined data across cities using the same lag time for each city. No evaluation of medium-term effects of PM on CVD hospital admissions was available.

4.5. INDEX OF EXPOSURE TO PM, FINE, ULTRAFINE AND COARSE PM AND CO-POLLUTANTS

The PM indexes used in the APHEA2 study were BS and PM_{10}, and PM_{10} and PNC in the HEAPSS study. In both studies, PM_{10} was not measured directly in all cities, but was estimated either from PM_{13} or TSP.

Within the APHEA2 study, the RR estimates for both PM_{10} and BS are given for an increase of 10 $\mu g/m^3$. The IQR however, was generally higher for PM_{10} (range 8.7-23.6 $\mu g/m^3$) than for BS (range 7.3-17.5 $\mu g/m^3$). However, when BS and PM_{10} were included together in a model, the effect of PM_{10} disappeared, while the effect of BS increased for cardiac causes overall, and was only slightly decreased for IHD.

In the HEAPSS study, no clear effect of PM_{10} was evident, except for certain subgroups. A problem in evaluating the results for PNC is the fact that PNC was estimated from regression on TSP or PM_{10} and other co-pollutants, rather than estimated directly. It is not clear how this may have affected the results. Overall, when all five cities were included, no clear effect emerged, while PNC was directly and significantly associated with AMI admissions when the analysis was restricted to the 3 cities that used hospital admission registers to ascertain the outcome, excluding the two cities where AMI registers were used. However, as previously pointed out, the results for PNC are not entirely convincing, given the exclusions *a posteriori*.

The conclusion of the HEAPSS study that AMI admissions are mostly related to traffic related air pollution are supported by a case-crossover study on non fatal AMI from Augsburg, Germany (Peters *et al*, 2004), that did not measure PM exposure, but found that transient exposure to traffic appeared to increase the risk of AMI.

In another article, the data from Rome included in the HEAPSS study were analyzed with a case-crossover design, confirming that in Rome PNC was associated with AMI risk at lag 0 (D'Ippoliti *et al*, 2003).

One study from the West Midlands conurbation of the UK (Anderson *et al*, 2001) examined the association between fine ($PM_{2.5}$) and coarse ($PM_{2.5-10}$) PM on CVD emergency admissions separately. For the cardiovascular causes considered - i.e. all cardiovascular (ICD9 390-459), cardiac (ICD9 390-429), IHD (ICD9 410-414) at age 65+ years and stroke (ICD9 430-438) at age 65+ years – no consistent associations emerged with either BS, PM_{10}, $PM_{2.5}$ or $PM_{2.5-10}$ (see Table 4 from the article, below).

Table 4 Pollution and daily admissions for cardiovascular diseases (% change (95% CI) for pollution increment from 10–90th percentile, mean lags 0+1)

Pollutant	*CVS all ages % change (95% CI)*	*p Value*	*Interaction with season p value*	*Cardiac all ages % change (95% CI)*	*p Value*	*Interaction with season p value*
PM_{10}	−0.6 (−2.5 to 1.3)	0.5	0.4	0.3 (−1.8 to 2.4)	0.8	0.2
$PM_{2.5}$	−0.5 (−2.6 to 1.6)	0.6	0.2	−0.4 (−2.8 to 2.2)	0.8	0.05
$PM_{2.5-10}$	−0.7 (−3.7 to 2.3)	0.2	0.4	−0.9 (−4.3 to 2.7)	0.6	0.4
BS	1.0 (−1.0 to 3.1)	0.3	0.3	1.7 (−0.6 to 3.9)	0.2	0.3
SO_4^{2-}	0.3 (−1.5 to 2.1)	0.7	0.03	0.9 (−1.2 to 2.9)	0.4	0.03
NO_2	0.3 (−1.4 to 2.1)	0.7	0.8	1.1 (−0.8 to 3.0)	0.3	0.5
O_3	0.1 (−2.7 to 3.0)	0.9	0.5	1.6 (−1.5 to 4.9)	0.3	0.3
SO_2	−0.4 (−2.2 to 1.5)	0.7	0.8	0.7 (−1.3 to 2.8)	0.5	0.7
CO	0.4 (−1.0 to 1.7)	0.6	0.9	0.9 (−0.6 to 2.4)	0.2	0.9

Pollutant	*IHD ⩾65 % change (95% CI)*	*p Value*	*Interaction with season p value*	*Stroke ⩾65 % change (95% CI)*	*p Value*	*Interaction with season p value*
PM_{10}	2.1 (−2.0 to 6.3)	0.3	0.1	−3.3 (−7.9 to 1.4)	0.2	0.8
$PM_{2.5}$	−0.3 (−4.5 to 4.2)	0.9	0.03	−1.6 (−6.6 to 3.6)	0.5	0.6
$PM_{2.5-10}$	1.1 (−4.1 to 6.6)	0.7	0.5	−8.2 (−13.9 to −2.2)	0.008	0.4
BS	2.0 (−2.3 to 6.4)	0.4	0.4	−2.7 (−7.6 to 2.4)	0.3	0.5
SO_4^{2-}	2.1 (−1.8 to 6.1)	0.3	0.3	2.0 (−2.5 to 6.7)	0.4	0.7
NO_2	2.3 (−1.4 to 6.2)	0.2	0.6	−0.8 (−5.0 to 3.6)	0.7	0.6
O_3	0.8 (−4.7 to 6.7)	0.8	0.04	−0.5 (−6.4 to 5.8)	0.9	0.1
SO_2	1.5 (−2.5 to 5.6)	0.5	0.7	−5.1 (−9.6 to −0.4)	0.03	0.9
CO	1.9 (−1.0 to 4.9)	0.2	0.3	−1.6 (−5.0 to 1.9)	0.4	0.2

The only significant finding was a strong negative association between $PM_{2.5-10}$ (and SO_2) and daily admissions for stroke at age 65+ years.

A small study from Trondheim, Norway, found no association between $PM_{2.5}$ and cardiovascular admissions (Mannsaker *et al*, 2004).

As concerns adjustment for other co-pollutants, the APHEA2 presented result for two–pollutant models, while the HEAPSS briefly discussed them in the discussion.

4.6. OUTCOME DEFINITION AND EFFECT FOR DIFFERENT CAUSES OF HOSPITAL ADMISSION AND AGE GROUPS

The main problem in the definition of outcomes was the difficulty to distinguish, in some studies, between emergency and elective admissions. In the APHEA2 study, emergency admissions were not available for three cities (Milan, Paris and Rome). The authors tried to exclude admission diagnosis where a high proportion (over 65-70%) were elective, based on data from London. It is difficult to estimate how this

may have affected the estimates. However, from the graphs presenting city-specific results, no difference was evident between these three cities and the others.

Within the range of CVD morbidity, different outcomes were considered in the various studies. The APHEA2 found associations with cardiac (ICD9 390-429) deaths overall, stronger over 65 years of age, and for IHD (ICD 410-413) over age 65 years. No clear association emerged for IHD below age 65 years, and for stroke over 65 years.

The outcome considered in the HEAPSS study was AMI (ICD 410). This outcome is overlapping with the IHD outcome considered in the APHEA2 study. To estimate comparability, in Italy in 1999 there were 89,079 hospital admissions for AMI, and 147,927 for the codes 411-413 [source Website of the Italian Ministry of Health, http://www.ministerosalute.it/programmazione/sdo/ric_informazioni/]. In contrast to the APHEA2 study, the HEAPSS study found the strongest associations for fatal AMI below age 65 years. This result should be interpreted with caution because apparent associations from subgroup analyses may arise by chance alone, given the multiple comparisons performed and the greater random variation due to the reduced sample size. Moreover, in the HEAPSS study the association with PNC in the older age group appeared, if anything, stronger for non-fatal events. These subgroup results are based on three cities only, since the other two cities were excluded because they had data on younger subjects only (even though those were the ones among whom the strongest relation was found in the other three cities).

The two multicity studies were based on partially overlapping populations, since three cities (Barcelona, Rome and Stockholm) were included in both projects.

As for mortality studies, there was some evidence from several studies that the effect of air pollution may be stronger in warmer or drier seasons/areas.

Finally, the HEAPSS study also analyzed the effects of PM on a susceptible population, i.e. survivors from a first AMI, and found stronger associations in this group than in the general population.

4.7. CONCLUSIONS

In the multicentric APHEA2 study, a significant increase in cardiac admission was reported for PM exposure, which might have resulted, in part, from confounding by NO_2, a marker of traffic pollution. Similar results were reached in the general-population analysis of hospitalization for myocardial infarction in the HEAPSS multicentric study. Results in survivors of a first myocardial infarction were stronger than those in the general population. A multicentric study from Italy found an association with PM exposure, while a similar French study reported no association.

The interpretation of studies on cardiac admissions and PM exposure is complicated by the use of different lag times and the combination of emergency and elective hospital admissions (as well as other aspects of the definition of outcome) in some of the studies. Despite these limitations, the evidence from European studies supports the hypothesis of an association between air pollution and hospital admissions for cardiovascular diseases.

5. SHORT-TERM PM EXPOSURE AND RESPIRATORY HOSPITAL ADMISSIONS

Table III (modified and updated from EPA 2004 Table 8B-2) presents European studies investigating the association between short-term ambient PM exposure and respiratory hospital admissions. These include two international multicity studies, the APHEA1 (Sunyer *et al*, 1997) and APHEA2 (Atkinson *et al*, 2001), two national multicity studies from France (Eilstein *et al*, 2004) and Italy (Biggeri *et al*, 2005), and a number of small studies from various countries. The two national multicity studies are the same already briefly discussed in the chapter on CV hospital admissions, since both outcomes were presented in the same article.

5.1. THE APHEA1 STUDY

An outline of the APHEA1 project has been already given in the chapter on mortality. One article investigated emergency admissions for asthma in Barcelona, Helsinki, London and Paris, i.e. the four cities participating to the APHEA project that collected data on asthma (Sunyer *et al*, 1997). Barcelona collected data on asthma emergency room visits in the age group 15-64 years, while London and Helsinki on daily asthma emergency admissions in children (0-14 years) and adults (15-64 years), and Paris on total asthma admissions in both age groups. Data for BS were not available for Helsinki. Thus, the analysis in children was limited to two cities (London and Paris), to which Barcelona was added for adults. The same two stage procedure (in the first stage an estimate of the association between either PM_{10} or BS was obtained for each city using the same statistical model; in the second stage city-specific effect estimates were regressed on city-specific covariates to obtain an overall estimate and to explore confounding, using both fixed and random effects models) was used as for the mortality analysis. Similarly, several one day and cumulative lags were fitted, and the best fitting one day and cumulative model was chosen for each centre. The study period was from 1986-87 to 1989-91, depending on city.

Table 2 of the paper (below) gives city specific and combined results for the age group 15-64 years.

Table 2 Adjusted† relative risk of asthma admissions for subjects aged 15–64 per 50 μg/m³ increase in air pollutants (and lag)[1,2]

Air pollutant	*Barcelona*	*Helsinki*	*London*	*Paris*	*Total (95% CI)*
Sulphur dioxide					
24 h average	0.968 (3)	1.365 (2)	0.968 (2)	1.012 (2)	0.997 (0.961 to 1.034)
Cumulative	0.999 (3)	1.647 (3)	0.971 (2)	1.007 (3)	1.003 (0.959 to 1.050)
Black smoke					
24 h average	1.036 (3)	–	1.035 (0)	1.012 (0)	1.021 (0.985 to 1.059)
Cumulative	1.027 (3)	–	1.026 (1)	1.032 (3)	1.030 (0.981 to 1.081)
Nitrogen dioxide					
Hourly maximum	1.023 (0)	1.065 (0)	1.008 (0)	1.017 (0)	1.012 (0.999 to 1.024)
24 h average	1.048 (0)	0.900 (1)	1.024 (0)	1.041 (1)	1.029 (1.003 to 1.055)*
Cumulative	1.087 (3)	0.905 (1)	1.025 (1)	1.078*(1)	1.038 (1.008 to 1.068)*
Ozone					
Hourly maximum	1.048*(0)	0.779 (0)	1.071*(1)	0.937 (1)	1.015 (0.955 to 1.078)
8 hour maximum	1.058 (0)	1.183 (2)	1.086*(1)	0.986 (1)	1.035 (0.937 to 1.144)

[1] Single day lag: effects may be on the same day (0) or lagged up to three days (3).
[2] Cumulative: effects of mean of same day and up to three previous days.
* $p < 0.025$.
† Adjusted for trend, seasonality, day of the week, temperature, humidity, and influenza epidemics.

The pooled percent daily increase for a 50 µg/m^3 increase in BS was 2.1% (-1.5, 5.9) for single day lags, and 3.0% (-1.9, 8.1) for cumulative lags. Single day lags used were 3 for Barcelona, and 0 for London and Paris. Cumulative lags combined were 0-3 for Barcelona and Paris, and 0-1 for London.

Table 3 of the paper (below) presents results for children.

Table 3 Adjusted† relative risk of asthma admissions under age 15 per 50 µg/m^3 increase in air pollutants (and lag)[1,2]

Air pollutant	*Helsinki*	*London*	*Paris*	*Total (95% CI)*
Sulphur dioxide				
24 h average	0.791 (0)	1.089**(1)	1.070**(2)	1.075 (1.026 to 1.126)*
Cumulative	0.709 (3)	1.113*(2)	1.022 (2)	1.061 (0.996 to 1.131)
Black smoke				
24 h average	–	1.031 (0)	1.030 (2)	1.030 (0.979 to 1.084)
Cumulative	–	1.046 (3)	1.046 (2)	1.046 (0.978 to 1.120)
Nitrogen dioxide				
Hourly maximum	0.958 (0)	1.011 (2)	1.008 (1)	1.011 (0.999 to 1.022)
24 h average	0.758 (0)	1.027**(2)	1.026 (2)	1.026 (1.006 to 1.049)**
Cumulative	0.903 (1)	1.034*(3)	1.062 (3)	1.037 (1.004 to 1.067)*
Ozone				
Hourly maximum	1.352 (1)	1.009 (1)	0.920 (2)	1.006 (0.976 to 1.037)
8 hour maximum	1.235 (1)	1.011 (2)	0.957 (1)	0.989 (0.941 to 1.038)

[1] Single day lag: effects may be on the same day (0) or lagged up to three days (3).
[2] Cumulative: effects of mean of same day and up to three previous days.
* $p < 0.05$; ** $p < 0.025$.
† Adjusted for trend, seasonality, day of the week, temperature, humidity, and influenza epidemics.

The pooled estimates under age 15 years were 3.0% (-2.1, 8.4) for single day lags, and 4.6% (-2.2, 12.0) for cumulative lags. Single day lags used were 0 for London and 2 for Paris, and cumulative ones 0-3 for London and 0-2 for Paris.

The reason given for the use of different lags in each city is that local factors like wind direction, size of the city or location of the monitoring sites vary between cities. It is however not clear why lags should differ between children and adults: in London the chosen cumulative lag was 0-1 for adults and 0-3 for children and in Paris the single day lag was 0 for adults and 2 for children. For adults, the pooled estimate using lag 0 in all cities was 2.0% (-1.7, 5.7), and 0.7% (-2.8, 4.5) for lag 1.

When two-pollutant models were considered (Table 4 of the paper, below), the effect of BS disappeared after adjustment for NO_2 or SO_2, while the effects of these two pollutants were still present after adjustment for BS.

Table 4 Two-pollutant models: adjusted† relative risk of asthma admissions per 50 μg/m³ increase in air pollutants (and lag)[1,2]

Age	*Air pollutants*	*Barcelona*	*London*	*Paris*	*Total (95% CI)*
15–64					
	24 h average				
	Nitrogen dioxide	1.039 (0)[1]	1.086*(0)	1.055*(1)	1.055 (1.005 to 1.109)*
	Black smoke	1.031 (0)	0.909*(0)	0.986 (1)	0.999 (0.952 to 1.049)
	Cumulative				
	Nitrogen dioxide	1.044 (3)[2]	1.104*(1)	1.112*(1)	1.088 (1.025 to 1.155)*
	Black smoke	1.076 (3)	0.881*(1)	0.965 (1)	0.991 (0.901 to 1.089)
<15					
	24 h average				
	Sulphur dioxide	–	1.090*(1)	1.094 (2)	1.092 (1.031 to 1.156)*
	Black smoke	–	0.978 (0)	0.972 (2)	0.974 (0.903 to 1.050)
	Nitrogen dioxide	–	1.065*(2)	0.975 (2)	1.036 (0.956 to 1.122)
	Black smoke	–	1.013 (0)	1.058 (2)	1.037 (0.965 to 1.063)
	Sulphur dioxide	–	1.063 (1)	1.092*(2)	1.075 (1.019 to 1.135)*
	Nitrogen dioxide	–	1.049*(2)	0.976 (2)	1.034 (0.988 to 1.082)

[1] Single day lag: effects may be on the same day (0) or lagged up to three days (3).
[2] Cumulative: effects of mean of same day and up to three previous days.
* $p < 0.05$.
† Adjusted for trend, seasonality, day of the week, temperature, humidity, influenza epidemics, and the other pollutant in the model.

5.2. THE APHEA2 STUDY

In the APHEA2 study, one article was dedicated to the association between PM_{10} and respiratory admissions (Atkinson *et al*, 2001). The methods, including the eight cities/areas included, the study period, PM_{10} estimation and the statistical model used were the same as for the CVD admission analysis (Le Tertre *et al*, 2002a).

Four different outcomes were considered, i.e., daily admissions for asthma (ICD9 493) at ages 0-14 and 15-64 years, COPD and asthma (ICD9 490-496) at age 65+ years, and all respiratory disease admissions (ICD9 460-519) at age 65+ years. The authors specify that, wherever possible, emergency admissions resulting in overnight hospital stay were specified, in order to exclude elective admissions and those resulting only in an emergency room visit. However, unlike for CVD admissions, no investigation of the proportion of elective admissions for specific admission diagnoses, and consequent exclusion of diagnoses with high prevalence of elective admissions, was performed.

In the following table (Table 3 of the article) the percent change in daily admissions associated with a 10 μg/m³ increase in PM_{10} or BS for each city is given, together with the pooled estimates. With few exceptions, the city-specific estimates were positive for all four endpoints, although only for a few of them the confidence interval did not include zero increase. For 5 of the 8 pooled results there was evidence of heterogeneity between cities.

For asthma in children the summary estimates were 1.2% (0.2, 2.3) for PM_{10} and 1.3% (0.3, 2.4) for BS, while for asthma in adults they were 1.1% (0.3, 1.8) for PM_{10} and 0.7% (-0.3, 1.8). Thus, for PM_{10} there was no evidence that children were

relatively more susceptible than adults to PM-induced asthma exacerbation. In the age group 65+ years, the pooled estimates for COPD plus asthma were 1.0% (0.4, 1.5) for PM_{10} and 0.2% (-1.3, 1.6) for BS. Corresponding estimates for all respiratory diseases were 0.9 % (0.6, 1.3) and 0.1% (-0.7, 0.9), respectively.

TABLE 3. SINGLE POLLUTANT MODEL RESULTS AND POOLED ESTIMATES FOR PARTICLE MEASURE*

Disease Group	City	Measure	Estimate (95% CI)	Measure	Estimate (95% CI)
Asthma, 0–14 yr	Barcelona	PM_{10}	2.7 (−4.9, 10.9)	BS	10.4 (0.4, 21.4)
	Birmingham	PM_{10}	2.8 (0.8, 4.8)	BS	2.0 (−1.9, 6.0)
	London	PM_{10}	0.6 (−0.8, 2.0)	BS	1.1 (−1.3, 3.6)
	Milan	TSP	3.0 (1.3, 4.8)	NA	
	Netherlands	PM_{10}	−0.9 (−2.1, 0.4)	BS	1.4 (−0.4, 3.3)
	Paris	PM_{13}	0.7 (−1.5, 3.0)	BS	0.9 (−0.8, 2.7)
	Rome	TSP	1.0 (−2.4, 4.6)	NA	
	Stockholm	PM_{10}	1.7 (−6.0, 10.2)	NA	
	Summary estimate	PM_{10} (RE)	1.2 (0.2, 2.3)	BS (FE)	1.3 (0.3, 2.4)
	Heterogeneity		$\chi^2 = 21.3$, df = 7		$\chi^2 = 3.5$, df = 4
Asthma, 15–64 yr	Barcelona	PM_{10}	0.4 (−3.5, 4.4)	BS	2.1 (−3.0, 7.5)
	Birmingham	PM_{10}	2.5 (0.1, 4.9)	BS	2.8 (−1.9, 7.7)
	London	PM_{10}	1.4 (−0.1, 3.0)	BS	1.8 (−0.9, 4.5)
	Milan	TSP	0.3 (−1.6, 2.3)	NA	
	Netherlands	PM_{10}	0.4 (−0.9, 1.8)	BS	−0.4 (−2.2. 1.5)
	Paris	PM_{13}	1.2 (−0.7, 3.2)	BS	0.8 (−0.7, 2.3)
	Rome	TSP	1.1 (−2.2, 4.4)	NA	
	Stockholm	PM_{10}	5.4 (−4.0, 15.7)	NA	
	Summary estimate	PM_{10} (FE)	1.1 (0.3, 1.8)	BS (FE)	0.7 (−0.3, 1.8)
	Heterogeneity		$\chi^2 = 3.6$, df = 7		$\chi^2 = 2.9$, df = 4
COPD + asthma, 65+ yr	Barcelona	PM_{10}	2.6 (1.0, 4.3)	BS	−2.1 (−4.3, 0.0)
	Birmingham	PM_{10}	0.5 (−1.4, 2.6)	BS	2.2 (−1.7, 6.2)
	London	PM_{10}	0.3 (−0.8, 1.5)	BS	0.4 (−1.6, 2.5)
	Milan	TSP	0.9 (0.0, 1.7)	NA	
	Netherlands	PM_{10}	1.1 (0.5, 1.7)	BS	0.7 (−0.2, 1.6)
	Paris	PM_{13}	−0.6 (−2.5, 1.3)	BS	0.2 (−1.3, 1.6)
	Rome	TSP	0.5 (−0.8, 1.9)	NA	
	Stockholm	PM_{10}	2.7 (−1.5, 7.1)	NA	
	Summary estimate	PM_{10} (RE)	1.0 (0.4, 1.5)	BS (RE)	0.2 (−0.7, 1.1)
	Heterogeneity		$\chi^2 = 9.2$, df = 7		$\chi^2 = 6.6$, df = 4
All respiratory, 65+ yr	Barcelona	PM_{10}	2.0 (0.8, 3.1)	BS	−0.7(−2.3, 0.9)
	Birmingham	PM_{10}	0.9 (−0.3, 2.2)	BS	2.9 (0.6, 5.4)
	London	PM_{10}	0.4 (−0.3, 1.2)	BS	−1.1 (−2.4, 0.3)
	Milan	TSP	0.8 (0.3, 1.3)	NA	
	Netherlands	PM_{10}	1.2 (0.7, 1.6)	BS	0.0 (−0.7, 0.7)
	Paris	PM_{13}	−0.1 (−1.3, 1.0)	BS	0.5 (−0.4, 1.4)
	Rome	TSP	0.5 (−0.4, 1.5)	NA	
	Stockholm	PM_{10}	1.7 (−1.2, 4.7)	NA	
	Summary estimate	PM_{10} (RE)	0.9 (0.6, 1.3)	BS (RE)	0.1 (−0.7, 0.9)
	Heterogeneity		$\chi^2 = 9.6$, df = 7		$\chi^2 = 10.3$, df = 4

Definition of abbreviations: BS = Black Smoke; COPD = chronic obstructive pulmonary disease; df = degrees of freedom; FE = fixed-effects estimates; NA = not available; PM_{10}, PM_{13} = particles with an aerodynamic diameter of less than 10 and 13 μm; RE = random-effects estimates; TSP = total suspended particles; χ^2 = chi-square test for heterogeneity.

* Table gives the associations as percentage change in mean number of admissions associated with 10 μg/m³ increases in particle measures. Only TSP measures were available in Milan and Rome. TSP estimates for Milan and Rome are scaled (PM_{10} = TSP/0.75) for inclusion in fixed (FE) and random-effects (RE) estimates. PM_{13} estimates for Paris are assumed to equate to PM_{10} measures. No BS measurements were available from Stockholm, Milan, or Rome.

Two-pollutant models were also fitted for PM_{10} (Table 4 of the paper, below).

TABLE 4. SUMMARY PM_{10} ESTIMATES FROM TWO-POLLUTANT MODELS*

Outcome	PM_{10} Only	+ NO_2	+ O_3	PM_{10} Only‡	+ SO_2	PM_{10} Only§	+ CO
Asthma, 0–14 yr	1.2 (0.2, 2.3)	0.1 (−0.8, 1.0)	1.3 (0.1, 2.5)†	1.3 (0.2, 2.5)	0.8 (−3.7, 5.6)†	1.5 (0.2, 2.7)	0.7 (−0.3, 1.7)†
Asthma, 15–64 yr	1.1 (0.3, 1.8)	0.4 (−0.5, 1.3)	1.1 (0.1, 2.1)†	1.1 (0.3, 1.9)	1.6 (0.6, 2.6)	1.0 (0.2, 1.9)	0.8 (0.2, 1.4)†
COPD + asthma, 65+ yr	1.0 (0.4, 1.5)	0.8 (−0.6, 2.1)†	0.4 (−1.5, 2.2)†	0.9 (0.5, 1.3)	1.3 (0.7, 1.8)	1.1 (0.7, 1.5)	1.0 (0.4, 1.5)†
All respiratory, 65+ yr	0.9 (0.6, 1.3)	0.7 (−0.3, 1.7)†	0.8 (0.2, 1.4)†	0.9 (0.6, 1.2)	1.1 (0.7, 1.4)	1.1 (0.8, 1.4)	1.0 (0.7, 1.3)

Definition of abbreviations: COPD = chronic obstructive pulmonary disease; PM_{10} = particles with an aerodynamic diameter of less than 10 μm.

* Table gives the percentage change in the mean daily number of admissions associated with 10 μg/m^3 increases in PM_{10}. The estimates are fixed or random-effect (†) estimates for all eight cities derived using a second-stage regression of results from city-specific two-pollutant models.

‡ Summary PM_{10} estimates derived from single-pollutant models excluding Barcelona (no SO_2 data available).

§ Summary PM_{10} estimates derived from single-pollutant models excluding Paris (no CO data available).

For asthma in children and adults, adjustment for NO_2 had the strongest effect on the PM_{10} estimates, which were substantially reduced. Ozone was the major confounder for COPD plus asthma in elderly people, while no substantial change in the point estimate for all respiratory diseases in the elderly was observed (although the inclusion in the model of correlated variables resulted in inflated standard errors of the estimates).

Finally the effect modification of several city-specific variables was considered. For asthma in children, humidity (inversely), smoking prevalence (inversely) and percent of population over 65 years (directly) reduced the heterogeneity χ^2 by over 40%. For the two endpoints considered for the elderly, higher mean ozone levels resulted in stronger PM effects.

5.3. NATIONAL MULTICITY STUDIES

In the same articles in which results for CVD admissions were presented, the French (Eilstein *et al*, 2004) and the Italian (Biggeri *et al*, 2005) studies investigated also the association between PM and hospital admissions for respiratory diseases.

The French study found a positive significant association between BS day to day variations and all respiratory admissions in the age group 0-14 years, and no effect at age 65+ years. The Italian study found a direct association between PM_{10} and respiratory admissions at all ages, with however large heterogeneity between cities.

5.4. FINE AND COARSE PM

The study from the West Midlands conurbation of the UK (Anderson *et al*, 2001) examined the association between fine ($PM_{2.5}$) and coarse PM ($PM_{2.5-10}$) with respiratory emergency admissions. The endpoints considered were daily emergency hospital admissions for respiratory causes (ICD9 460-519) at all ages and in the age groups 0-14, 15-64 and 65+ years, asthma in the age groups 0-14 and 15-64 years and COPD at ages 65+ years (Table 5 of the paper, below).

Table 5 Pollution and daily admissions for respiratory diseases (% change (95% CI) for pollution increment from 10–90th percentile, mean lag 0+1 days)

Pollutant	All ages % change (95% CI)	p Value	Interaction with season p value	Age 0–14 % change (95% CI)	p Value	Interaction with season p value
PM_{10}	1.5 (−0.7 to 3.6)	0.2	0.2	3.9 (0.6 to 7.4)	0.02	0.8
$PM_{2.5}$	1.2 (−0.9 to 3.4)	0.3	0.1	3.4 (−0.1 to 7.0)	0.05	0.6
$PM_{2.5-10}$	0.2 (−2.5 to 3.1)	0.9	0.5	4.4 (−0.3 to 9.4)	0.07	0.5
BS	2.1 (−0.1 to 4.2)	0.06	0.08	3.9 (0.7 to 7.3)	0.02	0.2
SO_4^{2-}	0.8 (−1.3 to 2.9)	0.4	0.08	1.5 (−1.7 to 4.9)	0.4	0.8
NO_2	1.7 (−0.2 to 3.7)	0.09	0.02	2.3 (−0.6 to 5.3)	0.1	0.6
O_3	−2.4 (−5.3 to 0.6)	0.1	0.1	−5.2 (−9.7 to −0.5)	0.03	0.9
SO_2	1.3 (−0.7 to 3.4)	0.2	0.5	4.6 (1.4 to 7.8)	0.004	0.1
CO	0.3 (−1.1 to 1.7)	0.7	0.6	1.5 (−0.6 to 3.6)	0.2	0.5

Pollutant	Age 15–64 % change (95% CI)	p Value	Interaction with season p value	Age ≥65 % change (95% CI)	p Value	Interaction with season p value
PM_{10}	0.1 (−4.0 to 4.4)	0.96	0.8	−1.1 (−4.3 to 2.1)	0.5	0.003
$PM_{2.5}$	−2.1 (−6.4 to 2.4)	0.4	0.3	−1.3 (−4.7 to 2.2)	0.5	0.0009
$PM_{2.5-10}$	−4.9 (−9.9 to 0.4)	0.07	0.5	−1.9 (−6.0 to 2.5)	0.4	0.007
BS	1.2 (−3.1 to 5.6)	0.6	0.6	−0.3 (−3.5 to 3.0)	0.9	0.01
SO_4^{2-}	0.5 (−3.4 to 4.7)	0.8	0.3	−1.3 (−4.4 to 2.0)	0.5	0.0005
NO_2	0.0 (−3.7 to 3.8)	0.997	0.7	1.0 (−1.8 to 3.9)	0.5	0.01
O_3	−2.8 (−7.7 to 2.4)	0.3	0.08	0.2 (−4.1 to 4.8)	0.9	0.4
SO_2	−0.9 (−4.8 to 3.3)	0.7	0.5	−2.0 (−4.9 to 1.1)	0.2	0.5
CO	−0.7 (−3.6 to 2.3)	0.7	0.1	0.0 (−2.1 to 2.1)	0.99	0.3

For all respiratory causes, significant positive associations were found in the age group 0-14 years for PM_{10} and BS, and borderline positive associations for $PM_{2.5}$ and $PM_{2.5-10}$, although the strongest positive association was found with SO_2.

Table 6 Pollution and daily admissions for asthma and COPD (% change (95% CI) for pollution increment from 10–90th percentile, mean lag 0+1 days)

Pollutant	Asthma age 0–14 % change (95% CI)	p Value	Interaction with season p value	Asthma age 15–64 % change (95% CI)	p Value	Interaction with season p value	COPD age ≥65 % change (95% CI)	p Value	Interaction with season p value
PM_{10}	8.3 (1.7 to 15.3)	0.01	0.03	−2.3 (−10.0 to 6.1)	0.6	0.9	−1.8 (−6.9 to 3.5)	0.5	0.3
$PM_{2.5}$	6.0 (−0.9 to 13.4)	0.09	0.03	−8.4 (−16.3 to 0.3)	0.06	0.9	−3.9 (−9.0 to 1.6)	0.2	0.3
$PM_{2.5-10}$	7.1 (−2.1 to 17.2)	0.1	0.4	−10.7 (−19.9 to −0.5)	0.04	0.3	−1.7 (−8.9 to 5.3)	0.6	0.8
BS	7.4 (0.7 to 14.5)	0.03	0.09	−2.8 (−10.7 to 5.8)	0.5	0.1	1.5 (−3.7 to 7.0)	0.6	0.1
SO_4^{2-}	2.1 (−3.9 to 8.6)	0.5	0.9	−4.2 (−11.7 to 3.9)	0.3	0.9	−0.3 (−5.3 to 4.9)	0.9	0.05
NO_2	4.0 (−2.0 to 10.2)	0.2	0.4	−3.3 (−10.4 to 4.4)	0.4	0.7	2.5 (−2.1 to 7.3)	0.3	0.2
O_3	−12.9 (−21.2 to −3.8)	0.007	0.02	−1.7 (−11.2 to 8.9)	0.8	0.9	0.2 (−7.0 to 8.0)	0.1	0.7
SO_2	10.9 (4.5 to 17.8)	0.0007	0.0006	2.4 (−5.5 to 10.9)	0.6	0.9	−4.2 (−8.9 to 0.8)	0.1	0.4
CO	3.9 (−0.5 to 8.5)	0.08	0.04	−4.9 (−10.6 to 1.1)	0.1	0.03	1.0 (−2.5 to 4.6)	0.6	0.7

For asthma in children, there were significant direct associations with PM_{10} and BS, while the association with $PM_{2.5}$ and $PM_{2.5-10}$ were not significant (Table 6 of the paper, above). The only other significant association was a negative one between asthma at 15-65 years and coarse PM.

5.5. CONCLUSIONS

In the multicentric European APHEA1 study, an association was reported between NO_2 and SO_2 exposure and respiratory hospital admissions. In the APHEA2 study several pollutants and respiratory diseases were considered, with positive associations detected for most pollutant-outcome combinations, albeit mostly not significant. Additional support for an association between air pollution, principally gaseous pollutants, and respiratory admissions is provided by a multicentric Italian study.

6. SHORT-TERM PM EXPOSURE AND OUTPATIENT VISITS

A few studies examined the relation between PM levels and outpatient visits in emergency department or at home, or dispensing of respiratory drugs. Most studies used as outcomes visits for respiratory diseases overall or asthma, although also allergic rhinitis and cardiovascular causes were considered in some studies. These studies are described in **Table IV** (modified and updated from EPA 2004 Table 8-B3).

7. ANALYTIC STUDIES ON LONG-TERM PM EXPOSURE AND MORTALITY

In 2003, at the time of the EPA report, only one cohort study from the Netherlands (Hoek *et al*, 2002) was available. In more recent years, other four studies from Sweden (Rosenlund *et al*, 2006), Norway (Naess *et al*, 2007), Germany (Gehring *et al*, 2006), and France (Filleul *et al*, 2005) have been published.

The description and results of each of these five studies are shown in **Table V**. In the following sections the methods and results of the four longitudinal studies are compared.

The Swedish study (Rosenlund *et al*, 2006) is a population based case-control study on first AMI. Since separate analyses have also been performed for fatal AMI, the study has been included also in this table. Its results, however, will be discussed in chapter VII, together with other studies investigating the association between long-term exposure to PM and CVD morbidity.

7.1. STUDY DESIGNS, SAMPLE SIZE, TIME FRAME AND POPULATION DEFINITION

The Norwegian study (Naess *et al*, 2007) is a record linkage study based on all inhabitants of Oslo (n=143,842) aged 51-90 years on January 1, 1992 and followed up until 1998.

The study from the Netherlands (Hoek *et al*, 2002) is a case-cohort study based on a random sample of 5,000 subjects selected from the over 120,000 participants to the Netherlands Cohort Study on Diet and Cancer aged 55-69 years in 1986, recruited from 204 of 714 municipalities with computerized population registries and covered by a cancer registry, who completed a self-administered questionnaire in 1986. Ninety percent of the sample (4,492 subjects) was successfully followed up until 1994.

The German study (Gehring *et al*, 2006), is based on about 4,800 women aged 50-59 years who participated to several cross-sectional surveys conducted in various towns of North Rhine Westphalia between 1985 and 1994 and followed up until 2002-2003. The overall response rate to the surveys was 70%, and data on follow-up and address were obtained for 97% of the sample.

The study from France (Filleul *et al*, 2005) is based on the PAARC (Pollution Atmosphérique et Affections Respiratoires) cohort study and includes 14,284 adults residing in 7 French cities, aged 25-59 years at enrollment in 1974 and followed up until 2001 for vital status. Cause of death was available until 1998 for 96% of the sample.

7.2. ASSESSMENT OF EXPOSURE TO PM AND CO-POLLUTANTS

For all the studies, exposure assessment was based solely on the home address, without considering other possible sources of exposure (other locations or occupation). The French study, however, excluded from the sample heads of households who were manual workers, to avoid confounding from other heavy

exposures. Occupation was controlled for in some studies (see section on statistical model and control of confounding).

Average ambient concentration at the home address over a period of several years was considered as indicator of exposure in all the studies. The follow-up studies evaluated exposure for 1-5 years around the baseline.

Several methods were used for estimating ambient PM concentrations based either on data from air monitor stations placed *ad hoc* (Filleul *et al*, 2005) or on air dispersion modeling systems (Hoek *et al*, 2002; Gehring *et al*, 2006; Naess *et al*, 2007), even corrected for distance to a major road (Hoek *et al*, 2002; Gehring *et al*, 2006).

Several PM indexes were used, including PM_{10}, $PM_{2.5}$, BS and TSP. Although other gaseous pollutants were measured in several studies, no mutual adjustments were performed.

7.3. STATISTICAL MODEL AND CONTROL OF CONFOUNDING

Cox proportional hazard models were used in the four longitudinal studies. In general, no other environmental variables were included. Sex and age were controlled for in all the studies. The record linkage study from Norway (Naess *et al*, 2007) recovered information on education and occupation (manual/non manual) from census data for 77% of the sample. Smoking and education/socioeconomic status were controlled for in most of the other studies, together with other potential confounders (physical activity, diabetes, body mass, diet, occupational exposure).

7.4. MAIN RESULTS

The hazard ratio (HR), as an estimate of RR, for deaths from all causes from the Norwegian record linkage study according to approximate quartiles of long-term $PM_{2.5}$ exposure are presented in Table 2 of the article (Naess *et al*, 2007) (below), separately by sex and age at enrollment (51-70 and 71-90 years).

Compared to those in the lowest exposure categories, the HRs were 0.96 (0.89, 1.04), 1.12 (1.03, 1.22) and 1.48 (1.36, 1.60) in subsequent quartiles of exposure for men aged 51-70 years. Corresponding estimates in older men were 0.99 (0.93, 1.06), 1.10 (1.03, 1.17) and 1.19 (1.12, 1.27). Estimates in women were very similar to those of men of the corresponding age group. Adjustment for education and occupational class did not materially modify the results.

TABLE 2. Hazard ratios with 95% confidence intervals for death (1992–1998) from all causes in the study population according to 4-year exposure to particulate matter less than 2.5 μm in aerodynamic diameter (μg/m³, quartiles) at participants' home addresses in 1992–1995, Oslo, Norway

	Crude		Adjusted*	
	HR†	95% CI†	HR	95% CI
Men				
Ages 51–70 years (n = 37,797)				
6.56–11.45	1.00		1.00	
11.46–14.25	0.96	0.89, 1.04	0.97	0.89, 1.06
14.26–18.43	1.12	1.03, 1.22	1.13	1.03, 1.23
18.44–22.34	1.48	1.36, 1.60	1.44	1.32, 1.58
p trend	<0.001		<0.001	
Ages 71–90 years (n = 19,072)				
6.56–11.45	1.00		1.00	
11.46–14.25	0.99	0.93, 1.06	0.99	0.93, 1.06
14.26–18.43	1.10	1.03, 1.17	1.04	0.97, 1.11
18.44–22.34	1.19	1.12, 1.27	1.18	1.10, 1.26
p trend	<0.001		<0.001	
Women				
Ages 51–70 years (n = 44,094)				
6.56–11.45	1.00		1.00	
11.46–14.25	0.96	0.87, 1.07	1.00	0.90, 1.11
14.26–18.43	1.08	0.98, 1.20	1.06	0.95, 1.18
18.44–22.34	1.44	1.30, 1.59	1.41	1.27, 1.57
p trend	<0.001		<0.001	
Ages 71–90 years (n = 38,014)				
6.56–11.45	1.00		1.00	
11.46–14.25	1.03	0.97, 1.09	1.03	0.97, 1.09
14.26–18.43	1.07	1.01, 1.12	1.05	0.99, 1.11
18.44–22.34	1.11	1.05, 1.16	1.11	1.05, 1.17
p trend	<0.001		<0.001	

* Adjusted for occupational class and length of education.
† HR, hazard ratio; CI, confidence interval.

Cause- and sex-specific HRs for PM_{10} and $PM_{2.5}$ (and NO_2) are presented in Table 3 of article for the age group 51-70 years and in Table 4 for the age group 71-90 years (Naess *et al*, 2007) (below).

TABLE 3. Hazard ratios with 95% confidence intervals for death (1992–1998) from cardiovascular causes (CVD†), COPD†, and lung cancer in men according to NO_2† PM_{10},† and $PM_{2.5}$† exposure (quartile increase) at participants' home addresses in 1992–1995‡ among men and women aged 51–70 years in Oslo, Norway

	Crude		Adjusted§	
	HR†	95% CI†	HR	95% CI
Men				
CVD (2,007 deaths)				
NO_2	1.08**	1.04, 1.13	1.08*	1.04, 1.13
PM_{10}	1.10**	1.06, 1.15	1.09**	1.04, 1.15
$PM_{2.5}$	1.11**	1.06, 1.16	1.10**	1.05, 1.16
COPD (233 deaths)				
NO_2	1.28**	1.13, 1.44	1.21*	1.05, 1.39
PM_{10}	1.33**	1.17, 1.50	1.29**	1.12, 1.48
$PM_{2.5}$	1.32**	1.17, 1.49	1.27**	1.11, 1.47
Lung cancer (449 deaths)				
NO_2	1.08	0.99, 1.18	1.07	0.97, 1.18
PM_{10}	1.07	0.98, 1.17	1.07	0.97, 1.18
$PM_{2.5}$	1.07	0.98, 1.17	1.07	0.97, 1.18
Women				
CVD (946 deaths)				
NO_2	1.11**	1.04, 1.18	1.07*	1.00, 1.14
PM_{10}	1.14**	1.07, 1.21	1.11*	1.04, 1.19
$PM_{2.5}$	1.16**	1.09, 1.24	1.14**	1.06, 1.21
COPD (203 deaths)				
NO_2	1.13*	1.00, 1.29	1.06	0.92, 1.21
PM_{10}	1.16*	1.02, 1.32	1.06	0.92, 1.22
$PM_{2.5}$	1.18*	1.03, 1.34	1.09	0.94, 1.25
Lung cancer (295 deaths)				
NO_2	1.19*	1.07, 1.33	1.23*	1.10, 1.38
PM_{10}	1.22**	1.10, 1.37	1.27**	1.13, 1.43
$PM_{2.5}$	1.23**	1.10, 1.37	1.27**	1.13, 1.43

* p for trend < 0.005; ** p for trend < 0.001.

† CVD, cardiovascular disease; COPD, chronic obstructive pulmonary disease; NO_2, nitrogen dioxide; PM_{10}, particulate matter less than 10 μm in aerodynamic diameter; $PM_{2.5}$, particulate matter less than 2.5 μm in aerodynamic diameter; HR, hazard ratio; CI, confidence interval.

‡ Average exposure values for the period 1992–1995 were assigned to all participants.

§ Adjusted for occupational class and length of education.

TABLE 4. Hazard ratios with 95% confidence intervals for death (1992–1998) from cardiovascular causes (CVD†), COPD,† and lung cancer in men according to NO_2,† PM_{10},† and $PM_{2.5}$† exposure (quartile increase) at participants' home addresses in 1992–1995‡ among men and women aged 71–90 years in Oslo, Norway

	Crude		Adjusted§	
	HR†	95% CI†	HR	95% CI
Men				
CVD (4,531 deaths)				
NO_2	1.04**	1.01, 1.07	1.02	0.99, 1.05
PM_{10}	1.05**	1.02, 1.08	1.04*	1.01, 1.08
$PM_{2.5}$	1.06**	1.03, 1.09	1.05*	1.01, 1.08
COPD (503 deaths)				
NO_2	1.08	0.99, 1.18	1.04	0.95, 1.14
PM_{10}	1.13*	1.04, 1.24	1.08	0.98, 1.18
$PM_{2.5}$	1.14*	1.04, 1.24	1.10*	1.00, 1.21
Lung cancer (424 deaths)				
NO_2	1.11*	1.01, 1.22	1.09	0.98, 1.20
PM_{10}	1.10*	1.00, 1.21	1.08	0.98, 1.20
$PM_{2.5}$	1.08	0.98, 1.19	1.07	0.97, 1.18
Women				
CVD (7,480 deaths)				
NO_2	1.01	0.99, 1.04	1.01	0.99, 1.04
PM_{10}	1.01	0.99, 1.04	1.01	0.99, 1.04
$PM_{2.5}$	1.02*	1.00, 1.05	1.03*	1.00, 1.05
COPD (516 deaths)				
NO_2	1.09	0.99, 1.18	1.07	0.97, 1.17
PM_{10}	1.11*	1.01, 1.21	1.08	0.98, 1.19
$PM_{2.5}$	1.09*	1.00, 1.18	1.05	0.96, 1.16
Lung cancer (285 deaths)				
NO_2	1.13*	1.01, 1.27	1.12	0.98, 1.27
PM_{10}	1.18*	1.04, 1.33	1.17*	1.03, 1.33
$PM_{2.5}$	1.16*	1.03, 1.31	1.16*	1.02, 1.32

* p for trend < 0.005; ** p for trend < 0.001.

† CVD, cardiovascular disease; COPD, chronic obstructive pulmonary disease; NO_2, nitrogen dioxide; PM_{10}, particulate matter less than 10 μm in aerodynamic diameter; $PM_{2.5}$, particulate matter less than 2.5 μm in aerodynamic diameter; HR, hazard ratio; CI, confidence interval.

‡ Average exposure values for the period 1992–1995 were assigned to all participants.

§ Adjusted for occupational class and length of education.

These results are difficult to interpret for two reasons. First, it is not clear what are the categories compared in the models. In the headings of the table the authors say "quartile increase". It is not clear whether this means that these are risks for an increase of exposure from one quartile (i.e. the exposure variable was entered as an ordered variable coded 1, 2, 3 or 4 according to the exposure quartile) or whether the forth and first quartiles were compared. In the first and more likely case, Table 2 points to a limitation of this analysis, since there was no increase in risk between the first two quartiles, and the biggest increase was observed between the third and fourth quartiles, particularly for younger subjects. In the second case, half of the

population (i.e. those in the second and third quartile) would not contribute to the HR estimates.

Moreover, division of the population in four subgroups according to age and sex renders the results difficult to interpret, in particular in the absence of clear justifications and formal tests of heterogeneity between subgroups.

Table 4 of the corresponding paper, below, shows the main results from the Netherlands study (Hoek *et al*, 2002) according to two different models. In the first model, average regional background concentration of BS and distance of the residence from a major road were entered separately, while in the second model these two were combined by adding a constant to BS exposure estimates for those living near a major road.

Model*	Variable	Cardiopulmonary	Non-cardiopulmonary, non-lung cancer	All-cause		
				Unadjusted (n=4466)	Adjusted† (n=3464)	Adjusted‡ (n=2788)
1	Black smoke (background)	1·34 (0·68–2·64)	1·15 (0·63–2·10)	1·37 (0·95–1·97)	1·17 (0·76–1·78)	1·04 (0·65–1·64)
	Major road	1·95 (1·09–3·51)	1·03 (0·54–1·96)	1·35 (0·93–1·95)	1·41 (0·94–2·12)	1·53 (1·01–2·33)
2	Black smoke (background and local)	1·71 (1·10–2·67)	1·09 (0·71–1·69)	1·37 (1·06–1·77)	1·32 (0·98–1·78)	1·31 (0·95–1·80)
3	Nitrogen dioxide (background)	1·54 (0·81–2·92)	1·07 (0·61–1·90)	1·37 (0·97–1·94)	1·24 (0·83–1·86)	1·09 (0·70–1·69)
	Major road	1·94 (1·08–3·48)	1·04 (0·54–1·97)	1·34 (0·93–1·95)	1·41 (0·94–2·11)	1·53 (1·01–2·32)
4	Nitrogen dioxide (background and local)	1·81 (0·98–3·34)	1·08 (0·63–1·85)	1·45 (1·05–2·01)	1·36 (0·93–1·98)	1·25 (0·83–1·89)

Values are relative risk (95% CI). Values are calculated for concentration changes from the 5th to the 95th percentile. For black smoke, this was rounded to 10 μg/m³, for NO_2 30 μg/m³. Adjusted for age, sex, education, Quetelet-index, occupation, active and passive cigarette smoking, and neighbourhood socioeconomic score.
*Models 1 and 3 contain the background concentration and an indicator variable for living near a major road. Models 2 and 4 contain an estimate of the home address concentration, by adding to this background concentration a quantitative estimate of living near a major road. Major road is an indicator variable (0/1, 1 indicating living near a major road). †Adjusted for confounders. ‡For individuals living 10 years or longer at their 1986 address, adjusted for above confounders.

Table 4: **Risk of cardiopulmonary, non-cardiopulmonary non-lung cancer, and all-cause mortality associated with long-term exposure to traffic related air pollution, NLCS subcohort 1986–94**

Subjects living near a major road had an increased risk of all cause mortality, particularly after adjustment for several confounders and in individuals who had lived 10 years or longer at their 1986 address (RR=1.53, 95% CI 1.01, 2.33). Most of the excess risk observed in total mortality appeared to be attributable to cardiopulmonary causes of death. Additional analyses of the Netherlands study have been reported in an abstract form (Beelen *et al*, 2007). Using a case-cohort approach, adjusted RRs for an increase of BS by 10 μg/m^3 were 1.03 (0.91, 1.17) for all causes except accidents and violence, 1.04 (0.90, 1.20) for cardiopulmonary, 1.16 (0.91, 1.48) for respiratory, 0.99 (0.80, 1.23) for lung cancer, and 1.03 (0.91, 1.16) for non-cardiopulmonary, non-lung cancer mortality. Corresponding RRs in the full cohort analyses, which included confounder information only on age, gender, active smoking and area-level socio-economic status, were 1.05 (1.00, 1.10) for all natural causes, 1.06 (0.98, 1.15) for cardiopulmonary, 1.22 (0.99, 1.49) for respiratory, 1.03 (0.88, 1.20) for lung cancer, and 1.00 (0.96, 1.11) for non-cardiopulmonary, non-lung cancer mortality (Beelen *et al*, 2007).

In the German study too, the effects of PM and traffic appeared stronger for - or limited to - cardiopulmonary mortality (Gehring *et al*, 2006). In that study, a similar approach to the Dutch study was used, i.e., background exposure and distance of the residence from a road with >10,000 cars/day were estimated independently. Background exposure was computed as average concentrations for the year of recruitment and for the four years preceding recruitment.

TABLE 4. Association of All-Cause, Cardiopulmonary, and Noncardiopulmonary Nonlung Cancer Mortality With an Interquartile Range* Increase in Air Pollution Concentrations and Distance of Home to Roads With >10,000 Cars/Day

	All Causes		Cardiopulmonary		Not Cardiopulmonary or Lung Cancer	
	Crude RR (95% CI)	Adjusted† RR (95% CI)	Crude RR (95% CI)	Adjusted† RR (95% CI)	Crude RR (95% CI)	Adjusted† RR (95% CI)
Distance to road						
≤50 meters vs >50 meters	1.33 (0.96–1.83)	1.29 (0.93–1.78)	1.66 (1.01–2.73)	1.70 (1.02–2.81)	1.26 (0.82–1.94)	1.21 (0.77–1.87)
1-yr average						
NO_2	1.26 (1.10–1.43)	1.17 (1.02–1.34)	1.69 (1.34–2.15)	1.57 (1.23–2.00)	1.04 (0.88–1.22)	0.99 (0.83–1.18)
PM_{10}‡	1.12 (0.97–1.28)	1.08 (0.94–1.25)	1.38 (1.09–1.74)	1.34 (1.06–1.71)	0.94 (0.78–1.12)	0.92 (0.76–1.10)
5-yr average						
NO_2	1.29 (1.11–1.50)	1.19 (1.02–1.39)	1.89 (1.41–2.52)	1.74 (1.29–2.33)	1.04 (0.88–1.24)	0.97 (0.80–1.18)
PM_{10}‡	1.20 (1.05–1.37)	1.13 (0.99–1.30)	1.66 (1.30–2.12)	1.59 (1.23–2.04)	0.95 (0.80–1.13)	0.91 (0.76–1.08)

*Interquartile ranges were calculated from 1-yr averages and rounded to 16 $\mu g/m^3$ for NO_2 and 7 $\mu g/m^3$ for PM_{10}.
†Adjusted for socioeconomic status and smoking.
‡Calculated as $PM_{10} = 0.71 \times TSP$.

The adjusted RRs for a 7 µg/m^3 increase in PM_{10} in the baseline year were 1.08 (0.94, 1.25) for all cause mortality, 1.34 (1.06, 1.71) for cardiopulmonary mortality and 0.92 (0.80, 1.10) for non cardiopulmonary non lung cancer mortality (see Table 4 of the corresponding paper, above). When exposure was measured for five years the RR for cardiopulmonary mortality increased to 1.59 (1.23, 2.04). Women living near a major road had a 70% (2, 181) increased risk of dying for cardiopulmonary causes. In the text the authors state that mutual adjustment of air pollution effects and proximity to roads did not change these estimates.

The French study (Filleul *et al*, 2005) estimated average exposure for the period 1974-76 (see Table 4 of the paper, below). When all 24 areas were included in the analysis, long-term exposure to BS or TSP did not affect the risk of mortality from all non-accidental causes, cardiopulmonary causes or lung cancer, all the RR ranging between 0.97 and 1.01.

Table 4 Adjusted* mortality rate ratios (and 95% confidence intervals) expressed for 10 µg/m^3 of air pollution

	24 areas		
	All non-accidental causes	Lung cancer	Cardiopulmonary disease
Sulphur dioxide	1.01 (0.99 to 1.03)	0.99 (0.92 to 1.07)	0.97 (0.92 to 1.02)
Acidimetric method	1.01 (0.99 to 1.02)	0.97 (0.92 to 1.02)	1.01 (0.98 to 1.04)
Total suspended partides	1.00 (0.99 to 1.01)	0.97 (0.94 to 1.01)	1.01 (0.99 to 1.03)
Black smoke	0.99 (0.98 to 1.01)	0.97 (0.93 to 1.01)	1.00 (0.97 to 1.02)
Nitrogen dioxide	0.96 (0.93 to 1.00)	0.97 (0.85 to 1.10)	1.01 (0.94 to 1.08)
Nitrogen oxide	0.99 (0.98 to 1.00)	0.97 (0.94 to 1.01)	1.00 (0.98 to 1.02)
	18 areas		
	All non-accidental causes	**Lung cancer**	**Cardiopulmonary disease**
Sulphur dioxide	1.01 (0.98 to 1.04)	1.00 (0.91 to 1.11)	0.95 (0.89 to 1.01)
Acidimetric method	1.00 (0.98 to 1.02)	0.95 (0.88 to 1.02)	1.01 (0.97 to 1.05)
Total suspended partides	**1.05 (1.02 to 1.08)**	1.00 (0.92 to 1.10)	**1.06 (1.01 to 1.12)**
Black smoke	**1.07 (1.03 to 1.10)**	1.03 (0.92 to 1.15)	1.05 (0.98 to 1.12)
Nitrogen dioxide	**1.14 (1.03 to 1.25)**	**1.48 (1.05 to 2.06)**	**1.27 (1.04 to 1.56)**
Nitrogen oxide	**1.11 (1.05 to 1.17)**	1.06 (0.87 to 1.29)	1.08 (0.96 to 1.22)

*Adjusted for age, smoking habits, body mass index, educational level, occupational exposure, and stratified by sex.

However, the authors repeated the analysis excluding subjects from six areas for which the ratio NO/NO_2 (measured in ppb) was more than 3. The reason for this exclusion was that NO is the principal component of the NO_x emissions by cars and the high NO/NO_2 ratio indicated that the monitoring station was close to a very busy roadside. Thus, the exposure measure was heavily influenced by local traffic and non representative of the mean exposure of the population of the entire area. When the analysis was restricted to 18 areas, the RR for a 10 $\mu g/m^3$ increase in TSP was 1.05 (1.02, 1.08) for total non-accidental mortality, 1.00 (0.92, 1.10) for lung cancer and 1.06 (1.01, 1.12) for all cardiopulmonary causes. Corresponding estimates for BS were 1.07 (1.03, 1.10), 1.03 (0.92, 1.15) and 1.05 (0.98, 1.12).

7.5. EFFECT MODIFICATION BY AGE, SEX, SOCIOECONOMIC STATUS OR OTHER VARIABLES

As we have already commented, the Norwegian study (Naess *et al*, 2007) shows all results separately for four subgroups defined by sex and age without however a formal evaluation of differences between subgroups. For total mortality, results appeared similar betweens sexes, and the associations with $PM_{2.5}$ were stronger in the younger age group, although, mainly based on models for NO_2, the authors argue for the opposite: The HRs for all cause mortality in the highest $PM_{2.5}$ exposure quartile were 1.44 (1.32, 1.58) in younger men and 1.18 (1.10, 1.26) in older men, 1.41 (1.27, 1.57) in younger women and 1.11 (1.05, 1.17) in older women.

The German study (Gehring *et al*, 2006) was based on women who were of similar age at recruitment, and thus could not investigate modification effects by age and sex. In the text the authors write that they “found modestly stronger NO_2 and PM_{10} effects on all-cause mortality for women with a low SES, for current smokers, and for nonsmokers exposed to environmental tobacco smoke”.

In the French study (Filleul *et al*, 2005), subgroup analyses by sex, smoking status, occupational exposure to dust, gases and fumes, education and age were shown in a graph (see Figure 2 of the paper, below). No clear differences were observed with age, sex, or smoking. The highest point estimates were observed in more educated or occupationally exposed subjects.

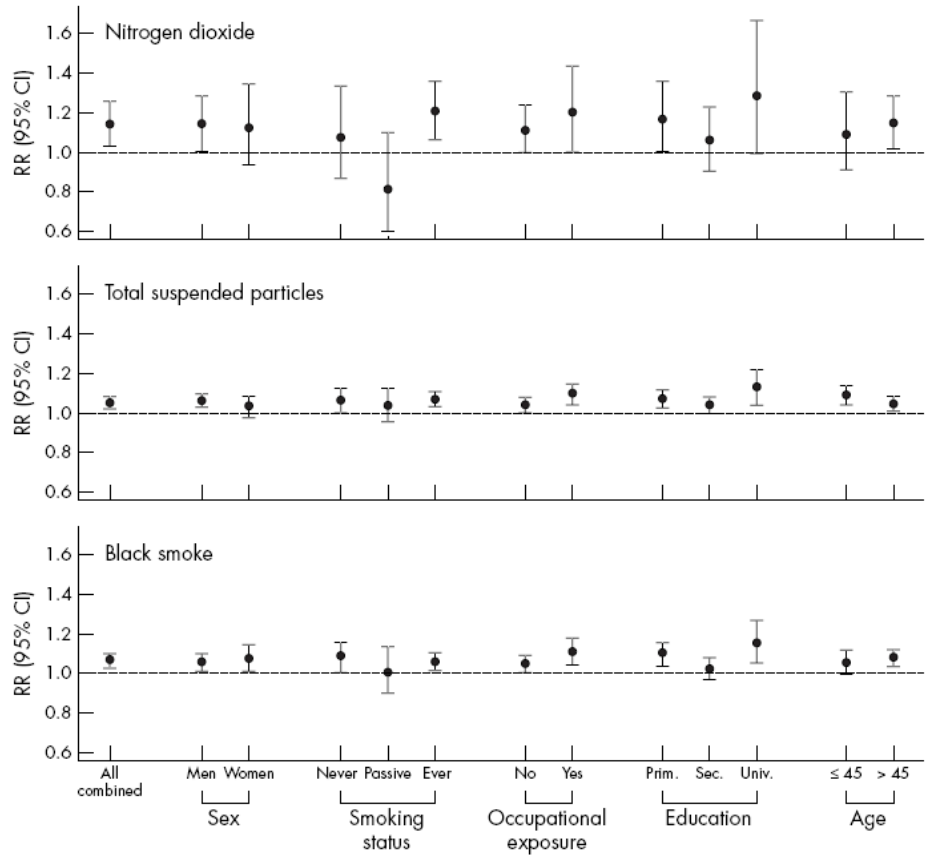


Figure 2 All-causes adjusted mortality rate ratios expressed for 10 μg/m^3 of air pollution after stratifying by sex, smoking habits, occupational exposure, educational level, and adjusting for all other risk factors; 18 areas with $NO/NO_2 < 3$ (in ppb).

7.6. COMPARISON OF EUROPEAN WITH LEADING NORTH AMERICAN STUDIES

European studies suggest that mortality from cardiopulmonary diseases is associated with long-term exposure to air pollution, but provide limited evidence that various measures of PM are related to total mortality. This is in apparent contrast with the leading North American studies, consistently providing direct associations between fine particles and total mortality. In the Harvard Six Cities study, 8,096 white participants from various cities of the USA were followed since the mid-1970 to 1998. The adjusted RRs for an increase of $PM_{2.5}$ of 10 μg/m^3 were 1.16 (1.07, 1.26) for total mortality, 1.28 (1.13, 1.44) for cardiovascular diseases, 1.08 (0.79, 1.49) for respiratory, 1.27 (0.96, 1.69) for lung cancer and 1.02 (0.90, 1.17) for other causes (Laden *et al*, 2006). In the ACS-CPS-II study, that linked air pollution data with the individual data of approximately 500,000 adults from the USA, followed from 1982 to the end of 1998 (Pope *et al*, 2002) (Pope *et al*, 2004), the adjusted RRs for an increase of $PM_{2.5}$ by 10 μg/m^3 were 1.06 (1.02, 1.11) for all-cause mortality, 1.12 (1.08, 1.15) for cardiovascular diseases plus diabetes, 0.92 (0.86, 0.98) for respiratory, 1.14 (1.04, 1.23) for lung cancer and 1.01 (0.95, 1.08) for all other causes. In that study, however, an interaction with education was evident. In fact, for subjects in the highest category of education (>high school), no association was found between increasing levels of $PM_{2.5}$ and total, cardiopulmonary and lung

cancer mortality. This is in contrast with the findings from the French study (Filleul *et al*, 2005), where the highest point estimates were observed in more educated subjects. Apart for chance and/or bias, at least part of the discrepancies could be explained by the different PM measure investigated. In fact, most European studies provided data on PM_{10} only, and not on finer PM.

7.7. CONCLUSIONS

In a Norwegian cohort study, a significant association was reported between PM exposure and mortality, although the interpretation of the results is not straightforward. Mortality was associated with various measures of air pollution in cohort studies from the Netherlands, Germany and France, and the excess risk in these studies was mainly attributed to cardiovascular and respiratory diseases.

8. ECOLOGIC STUDIES ON LONG-TERM PM EXPOSURE AND MORTALITY

One study compared mortality rates before and after the ban of coal sales in Dublin (Clancy *et al*, 2002). Given the deterioration of the air quality in the 1980s after a switch from oil to other fuels, mainly bituminous coal for domestic space and water heating, the Irish Government banned the marketing, sale and distribution of bituminous coals within the city of Dublin on September 1990. The Figure 1 of the paper, below, shows the consequent declines in BS and SO_2.

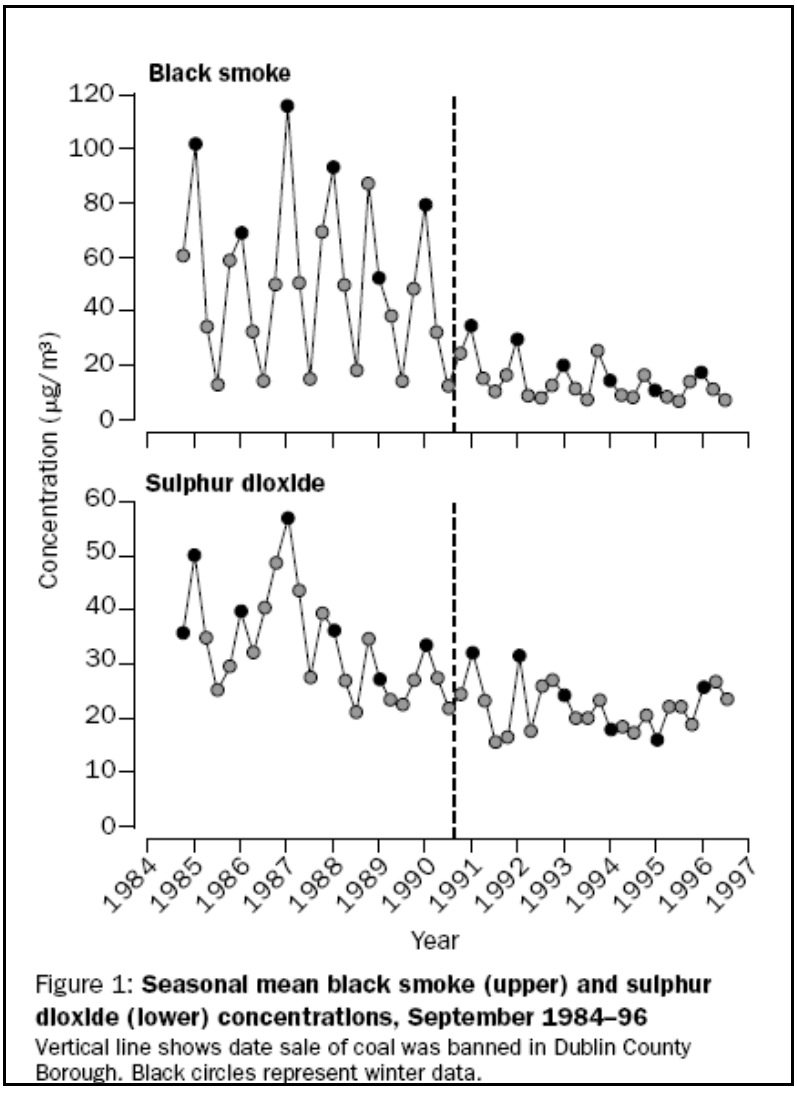


Figure 1: **Seasonal mean black smoke (upper) and sulphur dioxide (lower) concentrations, September 1984–96**
Vertical line shows date sale of coal was banned in Dublin County Borough. Black circles represent winter data.

Average BS concentrations declined by 35.6 µg/m^3 (70%) after the ban.

The authors compared age-adjusted death rates (directly standardized on the 1991 Irish census population) for the 72 months before (Sep 1984 to Aug 1990) and after (Sep 1990 to Aug 1996) the ban.

Table 2 of the paper, below, presents mortality rates for the two periods, overall and by season, for total non-accidental causes, and for cardiovascular, respiratory and other causes, separately.

	1984–90	1990–96	Change	p
Deaths per 1000 person-years				
Non-trauma				
Autumn	8·73	8·54	–0·19	<0·0001
Winter	11·03	9·88	–1·15	<0·0001
Spring	9·49	8·66	–0·83	<0·0001
Summer	8·40	7·56	–0·85	<0·0001
Total	9·41	8·65	–0·75	<0·0001
Cardiovascular				
Autumn	4·01	3·67	–0·34	<0·0001
Winter	5·18	4·47	–0·71	<0·0001
Spring	4·41	3·71	–0·69	<0·0001
Summer	3·89	3·29	–0·59	<0·0001
Total	4·37	3·78	–0·58	<0·0001
Respiratory				
Autumn	1·11	1·09	–0·02	0·51
Winter	2·00	1·55	–0·44	<0·0001
Spring	1·49	1·16	–0·33	<0·0001
Summer	0·93	0·83	–0·10	0·049
Total	1·38	1·16	–0·22	<0·0001
Other				
Autumn	3·61	3·78	0·17	0·0007
Winter	3·86	3·87	0·01	0·95
Spring	3·58	3·78	0·20	<0·0001
Summer	3·59	3·43	–0·16	0·0009
Total	3·66	3·71	0·05	0·031

Autumn=September–November; winter=December–February; spring=March–May; summer=June–August.

Table 2: **Age-standardised mortality rates for Dublin County Borough before (1984–90) and after (1990–96) ban of sale of coal, by season**

Significant decreases were observed for all non-accidental and cardiovascular mortality in all seasons, and the decreases were more marked in winter. Significant decreases were observed for respiratory mortality overall, in winter and spring, while no significant change was observed overall for other causes. The authors concluded that control of PM could substantially diminish daily death. However, it is worth noticing that, during the same period, mortality declined in several European countries. Thus, a causal link between the decline in mortality and the ban of coal sales is far from established. On the other hand, the authors interpreted the fact that the biggest declines were observed in winter, when the use of coal was highest, as suggestive of their hypothesis.

Two studies compared air pollution levels in 1,030 census enumeration districts in Sheffield, UK, to mortality and emergency hospital admission rates from coronary heart disease (Maheswaran *et al*, 2005b) and stroke (Maheswaran *et al*, 2005a). For each district a 5-year average PM_{10} concentration for the period 1994-1999 was computed. The districts were then divided according to quintiles of PM_{10} concentrations. The mean PM_{10} concentration in the highest quintile was 23.3 $\mu g/m^3$, and 16.0 $\mu g/m^3$ in the lowest one. Mortality and emergency hospitalization rates

were then computed for the districts' quintiles. For coronary heart disease, the rate ratios (adjusted for sex, age, deprivation and smoking prevalence) for the highest quintile compared to the lowest one were 1.08 (0.96, 1.20) for mortality and 1.01 (0.90, 1.14) for hospital admissions. Corresponding values for stroke were 1.33 (1.14, 1.56) and 1.13 (0.99, 1.29).

9. LONG-TERM PM EXPOSURE AND CARDIOVASCULAR MORBIDITY

Table VII summarizes results of studies on the effect of long-term exposure to PM and cardiovascular morbidity.

A population-based case-control study on 1,393 cases of first AMI and 1,870 population controls resident in Stockholm county, aged 45-70 years was conducted between 1992 and 1994 (Rosenlund *et al*, 2006). Response rates to the mailed questionnaire varied between 70-85% depending on sex and case-control status. For each subject, exposure to PM_{10} and $PM_{2.5}$ was reconstructed from 1960 to a year prior to enrollment (1992-1994), i.e., for over 20 years, using data on traffic around the home address only. Only data for long-term exposure to PM_{10} were used in the analysis, given the high correlation between PM_{10} and $PM_{2.5}$ (r=0.998).

Logistic regression models adjusted for the matching variables, i.e. age, sex and hospital catchment area, and smoking, physical inactivity, diabetes and SES were used to compute odds ratios (OR). Hypertension, body mass, job strain, diet, passive smoking, alcohol and coffee intake and occupational exposure to motor exhaust and other combustion products were also evaluated, but did not appear to confound the relation with PM.

Table 2 of the article (below) presents the main results of the study.

TABLE 2. Association of 30-Yr Average Exposure to Air Pollution From Traffic (NO_2, CO, and PM_{10}) and Heating (SO_2) With Myocardial Infarction

MI	No. of Cases	NO_2 From Traffic OR	NO_2 From Traffic (95% CI)	CO From Traffic OR	CO From Traffic (95% CI)	PM_{10} From Traffic* OR	PM_{10} From Traffic* (95% CI)	SO_2 From Heating OR	SO_2 From Heating (95% CI)
All cases	1357	0.99	(0.76–1.30)	1.04	(0.89–1.21)	1.00	(0.79–1.27)	1.03	(0.78–1.36)
Nonfatal cases†	1085	0.89	(0.67–1.19)	0.98	(0.82–1.16)	0.92	(0.71–1.19)	0.98	(0.73–1.32)
Fatal cases†	272	1.51	(0.96–2.37)	1.22	(0.98–1.52)	1.39	(0.94–2.07)	1.24	(0.77–2.02)
In-hospital death†	188	1.28	(0.75–2.17)	1.16	(0.89–1.51)	1.21	(0.75–1.94)	1.13	(0.64–1.99)
Out-of-hospital death†	84	2.17	(1.05–4.51)	1.36	(1.01–1.84)	1.84	(1.00–3.40)	1.54	(0.68–3.46)

*Assessed only for the year 2000, thus assuming constant levels during 1960 to 2000.

†All case series compared with a common control group in the same model using multinomial logistic regression. No. of controls = 1853. Values are calculated for a change in the air pollution level from the 5th to the 95th percentile, corresponding approximately to 30 $\mu g/m^3$ for NO_2, 300 $\mu g/m^3$ for CO, 5 $\mu g/m^3$ for PM_{10}, and 40 $\mu g/m^3$ for SO_2. All ORs and CIs adjusted for age, sex, hospital catchment area, smoking, diabetes, physical inactivity, and socioeconomic status (17 subjects dropped due to missing values on any of the covariates).

Overall, there was no association between PM_{10} and AMI (OR=1.00, 95% CI 0.79, 1.27). The point estimate was above unity for fatal cases (OR=1.39, 95% CI 0.94, 2.07) and below unity for non fatal cases (OR=0.92, 95% CI 0.71, 1.19) although none of these estimates was statistically significant. A borderline significant association was found when fatal cases were further restricted to those who died out of hospital (OR=1.84, 95% CI 1.00, 3.40). These were 84 out of 1,357 cases (6%). Although the authors interpret this finding as supportive of a possible association between air pollution exposure and mortality, random variation in small subgroups cannot be excluded.

Moreover, it is not clear how covariates were measured for fatal cases in general, and specifically in this group that died out of hospital. If proxy interviews were used for deceased cases, and direct interviews for controls, the effect of differential collection of covariates has to be considered.

The two ecologic studies from Sheffield, UK, discussed in the previous chapter found rate ratios of 1.01 (0.90, 1.14) for emergency hospital admissions for coronary heart disease and of 1.13 (0.99, 1.29) for emergency hospital admissions for stroke for subjects living in census enumeration districts with the highest levels of PM_{10} concentrations, as compared to the lowest ones.

Two studies investigated the association between long-term exposure to PM and prevalence of coronary or ischemic heart disease (Solomon *et al*, 2003; Hoffmann *et al*, 2006). Being based on prevalence data, these studies should be interpreted with caution.

A cross sectional postal survey on 1,166 women aged 45 years or more was conducted in 11 wards in the UK for which 30 years long concentration data on BS were available (Solomon *et al*, 2003). After adjustment for potential confounders, women living in areas with high BS concentrations did not report higher prevalence of ischaemic heart disease, as compared to women living in low BS areas (OR=1.00, 95% CI 0.7, 1.4).

Another study used baseline data from a newly started cohort study on 4,814 subjects aged 45-75 years from three large adjacent cities in the Rhein-Rhur region, Germany, to investigate the relation between background $PM_{2.5}$ exposure, residence close to a major road, and prevalence of coronary heart disease (Hoffmann *et al*, 2006). After adjustment for several potential confounders, the OR for those with high traffic exposure was 1.75 (1.16, 2.62), and for background $PM_{2.5}$ exposure 0.55 (0.14, 2.11), although the measurement unit for the latter OR is not given.

10. LONG-TERM PM EXPOSURE AND RESPIRATORY MORBIDITY OR SYMPTOMS

Many European studies have investigated the relation between PM and respiratory symptoms (**Table VIII**, modified and updated from EPA 2004 Table 8B8). The majority of these studies were on children, but some also in adults. Several different endpoints have been considered.

10.1. LONG-TERM PM EXPOSURE AND ASTHMA IN CHILDREN

A study from the Netherlands (Brauer *et al*, 2002) recruited about 4,000 children (during the seconds trimester of pregnancy) and evaluated the development of respiratory infections and asthmatic and allergic symptoms using questionnaires completed by the parents when the children were 2 years old. Outdoor concentrations of traffic-related $PM_{2.5}$ and soot at the home address of the children were estimated by means of a validated model. At two years of age, 176 children (5%) had developed physician-diagnosed asthma. After adjustment for several potential confounders, the OR for an increase equal to the IQR (3.2 $\mu g/m^3$ for $PM_{2.5}$ and $2x10^{-5}/m$ for soot, corresponding to 2.9 $\mu g/m^3$ of elemental carbon) were 1.12 (0.84, 1.50) for $PM_{2.5}$ and 1.12 (0.88, 1.43) for soot.

A cross-sectional survey conducted in France (Penard-Morand *et al*, 2005) on a random sample of 6,672 schoolchildren aged 9-11 years found an adjusted OR of asthma during the past year for an increment of PM_{10} by 10 $\mu g/m^3$ of 1.23 (0.77, 1.95), that was virtually unchanged after further adjustment for SO_2.

Among the 3,193 French children aged 5-9 years and included in the PAARC survey (Baldi *et al*, 1999), 195 (6%) were found to be asthmatic. The adjusted OR for an increase of 50 $\mu g/m^3$ in annual mean concentrations was 0.99 (0.81, 1.20) for TSP and 1.08 (0.85, 1.38) for BS.

10.2. LONG-TERM PM EXPOSURE AND LUNG FUNCTION IN CHILDREN

Spirometry was performed twice a year between 1994 and 1997 in 975 Austrian schoolchildren of grades 2-3 at baseline (Horak *et al*, 2002). After adjusting for potential confounders (sex, atopy, passive smoking, initial height, height difference, site, initial lung function) an increase of summer PM_{10} by 10 $\mu g/m^3$ was associated with a decrease in FEV_1 growth of 84 mL yr^{-1} and 329 mL s^{-1} yr^{-1} for MEF_{25-75}. No association was found for FVC or in winter (see Table 4 of the paper below).

Table 4. – Association of long-term seasonal mean concentration of air pollutants with growth in lung function: single-pollutant models

Model	Mean (range)	FVC dpd[#]		FEV1 dpd[¶]		MEF25–75 dpd[+]	
		β	p-value	β	p-value	β	p-value
PM_{10} $\mu g \cdot m^{-3}$							
Summer	17.4 (11.7–28.9)	0.001	0.938	-0.023	0.003	-0.090	0.000
Winter	21.0 (9.4–30.5)	0.008	0.042	0.001	0.885	-0.008	0.395
NO_2 ppb							
Summer	6.7 (1.1–15.0)	-0.000	0.992	-0.010	0.114	-0.041	0.008
Winter	11.5 (4.1–18.2)	-0.022	0.001	-0.026	0.000	-0.025	0.090
SO_2 $\mu g \cdot m^{-3}$							
Summer	6.9 (3.1–11.7)	0.009	0.336	0.005	0.576	0.015	0.483
Winter	16.8 (7.5–37.4)	0.006	0.009	0.005	0.013	0.003	0.637
O_3 ppb							
Summer	31.8 (18.7–49.3)	-0.015	0.001	-0.021	0.000	-0.013	0.217
Winter	19.8 (12.7–35.9)	-0.014	0.007	-0.020	0.000	-0.032	0.012

MEF25–75: midexpiratory flow between 25 and 75% of the forced vital capacity; PM10: particulate matter <10 μm in diameter; NO_2: nitrogen dioxide; SO_2: sulphur dioxide; O_3: ozone; FVC: forced vital capacity; FEV1: forced expiratory volume in one second. Model adjusted for sex, atopy, passive smoking, height 1994, height difference, site, lung function 1994. [#]: change in FVC $mL \cdot day^{-1}$; [¶]: change in FEV1 $mL \cdot day^{-1}$; [+]: change in MEF25–75 $mL \cdot s^{-1} \cdot day^{-1}$.

A study from the UK (Kulkarni *et al*, 2006) obtained airway macrophages and assessed the carbon content from 64 healthy children. PM_{10} concentrations near the home address, FEV_1 and FVC were also measured. They found that an increase of 1.0 $\mu g/m^3$ in modeled primary PM_{10} was associated with a 0.10 μm^2 (0.01, 0.18) increase in the carbon content of airway macrophages. Increased primary PM_{10} was inversely associated with the percentage of the predicted FEV_1 (P = 0.04) and the $FEF_{25–75}$ (P = 0.05). After adjusting for the carbon content of PM_{10}, the carbon content of airway macrophages remained inversely associated with the percentage of the predicted values of FEV_1, FVC, and $FEF_{25–75}$ (P = 0.02, P = 0.04, and P = 0.02, respectively), whereas PM_{10} was no longer significantly associated with lung function (Table 2 of the paper, below).

Table 2. Association between Lung Function and Carbon in Airway Macrophages from Healthy Children.*

Lung-Function Variable†	Linear Regression		Spearman's Rank Test	
	Coefficient (95% CI)‡	P Value	r	P Value
FEV_1 (N=64)				
% of predicted value	−17.0 (−28.4 to −5.6)	0.004	−0.30	0.02
z score	−2.0 (−3.1 to −0.9)	<0.001	−0.40	0.001
FVC (N=61)				
% of predicted value	−12.9 (−24.8 to −0.9)	0.03	−0.24	0.05
z score	−2.3 (−3.4 to −1.1)	<0.001	−0.46	<0.001
FEF_{25-75} (N=61)				
% of predicted value	−34.7 (−58.1 to −11.3)	0.004	−0.30	0.02
z score	−1.2 (−2.2 to −0.2)	0.01	−0.31	0.02
FEV_1:FVC (N=60)				
% of predicted value	−6.1 (−13.7 to 1.5)	0.11	−0.12	0.34
z score	−0.2 (−1.0 to 0.6)	0.58	−0.09	0.47
Post-bronchodilator FEV_1 (N=63)				
% of predicted value	−15.9 (−27.3 to −4.4)	0.007	−0.27	0.03
z score	−2.0 (−3.1 to −0.9)	0.001	−0.39	0.002

* Carbon in airway macrophages was defined as the median area (in square micrometers) occupied by carbon. CI denotes confidence interval, FEV_1 forced expiratory volume in one second, FVC forced vital capacity, and FEF_{25-75} forced expiratory flow between 25 and 75 percent of the FVC.
† Percentages of the predicted values for lung function were adjusted for height, weight, sex and race; z score was adjusted for height and weight but not race. FVC and FEF_{25-75} were not calculated for all children (see the Methods section). One child did not receive albuterol.
‡ The coefficient is of the change in lung function for each increase of 1.0 μm^2 in the carbon content of airway macrophages.

Finally, a study from eastern Germany (Frye *et al*, 2003) conducted three cross-sectional surveys of lung function in schoolchildren aged 11-14 between the early and late 1990s, and found that lung function of children has increased, while TSP and other pollutant levels had decreased during the study period.

10.3. LONG-TERM PM EXPOSURE AND RESPIRATORY SYMPTOMS IN CHILDREN

Two cohort studies investigated the issue.

The cohort of about 4,000 children from the Netherlands, that has been already discussed for asthma (Brauer *et al*, 2002), evaluated the development of respiratory infections and asthmatic and allergic symptom using questionnaires completed by the parents when the children were 2 years old.

TABLE 4. ASSOCIATION BETWEEN LONG-TERM EXPOSURE TO AIR POLLUTION AND INFECTIONS, ASTHMATIC AND ALLERGIC SYMPTOMS AT 2 YEARS OF AGE

	Unadjusted			Adjusted*		
	OR	95% CI	n	OR	95% CI	n
Wheeze						
$PM_{2.5}$	1.14	0.99–1.30	3,699	1.14	0.98–1.34	2,991
soot	1.11	0.99–1.24	3,699	1.11	0.97–1.26	2,991
NO_2	1.12	1.00–1.25	3,699	1.13	0.99–1.29	2,991
Doctor-diagnosed asthma						
$PM_{2.5}$	1.08	0.84–1.37	3,696	1.12	0.84–1.50	2,989
soot	1.07	0.87–1.31	3,696	1.12	0.88–1.43	2,989
NO_2	1.11	0.91–1.36	3,696	1.18	0.93–1.51	2,989
Dry cough at night						
$PM_{2.5}$	1.10	0.95–1.27	3,677	1.04	0.88–1.23	2,969
soot	1.08	0.95–1.21	3,677	1.02	0.88–1.17	2,969
NO_2	1.07	0.95–1.20	3,677	1.02	0.89–1.18	2,969
Doctor-diagnosed bronchitis						
$PM_{2.5}$	1.00	0.85–1.18	3,693	1.04	0.85–1.26	2,986
soot	0.98	0.85–1.12	3,693	0.99	0.84–1.17	2,986
NO_2	0.95	0.82–1.09	3,693	0.99	0.84–1.17	2,986
E,N,T infections						
$PM_{2.5}$	1.14	0.99–1.33	3,681	1.20	1.01–1.42	2,969
soot	1.12	0.99–1.27	3,681	1.15	1.00–1.33	2,969
NO_2	1.09	0.99–1.23	3,681	1.16	1.00–1.34	2,969
Doctor-diagnosed flu/serious colds						
$PM_{2.5}$	1.15	1.03–1.28	3,689	1.12	1.00–1.27	2,981
soot	1.13	1.03–1.23	3,689	1.09	0.98–1.21	2,981
NO_2	1.14	1.04–1.24	3,689	1.11	1.00–1.23	2,981
Itchy rash						
$PM_{2.5}$	1.07	0.95–1.20	3,707	1.01	0.88–1.16	2,995
soot	1.07	0.97–1.19	3,707	1.02	0.91–1.15	2,995
NO_2	1.06	0.96–1.17	3,707	1.02	0.91–1.15	2,995
Doctor-diagnosed eczema						
$PM_{2.5}$	1.02	0.90–1.16	3,677	0.95	0.83–1.10	2,970
soot	1.01	0.91–1.13	3,677	0.96	0.85–1.08	2,970
NO_2	1.00	0.90–1.11	3,677	0.96	0.85–1.08	2,970

Definition of abbreviations: CI = confidence interval; E, N, T = ear, nose, throat; NO_2 = nitrogen dioxide; OR = odds ratio; $PM_{2.5}$ = particulate matter less than 2.5 μm in aerodynamic diameter.

Crude and adjusted OR and 95% CI.

* OR and 95% CI adjusted for confounding factors in Table 3 and mothers' age but not for region. ORs are calculated for an interquartile range change in concentration.

Outdoor concentrations of traffic-related $PM_{2.5}$ and soot at the home address of the children were estimated by means of a validated model. Adjusted OR for the various symptoms and diseases were computed for an increase in exposure equal to the IQR i.e. 3.2 $\mu g/m^3$ for $PM_{2.5}$ and $2x10^{-5}/m$ for soot, corresponding to 2.9 $\mu g/m^3$ of elemental carbon. The results are presented in Table 4 of the article (above). Statistically significant increases in risk were found between $PM_{2.5}$ and ear, nose and throat infections (OR=1.20 95% CI 1.01, 1.42) and doctor-diagnosed flu/serious cold (OR=1.00, 1.27). For soot, the only significant association was with ear, nose and throat infections (OR=1.15 95% CI 1.00, 1.33).

A cohort of 4,400 children aged 1-5 years was recruited in Leichestershire, UK in 1998 (Pierse *et al*, 2006). Parents filled in a respiratory symptom questionnaire at baseline and again in 2001. Exposure to primary PM_{10} was calculated from the home address using a dispersion model based on estimated traffic emissions from traffic flow data. Adjusted OR for an increase in primary PM_{10} of 1 $\mu g/m^3$ were computed.

Table 2 Association between mean annual exposure of the home address to locally generated primary PM_{10} and prevalence of respiratory symptoms in young children

	Unadjusted			Adjusted*		
	OR†	95% CI	n‡	OR†	95% CI	n‡
Cough without a cold						
1998	1.22	1.10 to 1.36	2567	1.21	1.07 to 1.38	2164
2001	1.46	1.27 to 1.68	2301	1.56	1.32 to 1.84	1756
Night time cough						
1998	1.11	1.01 to 1.23	2579	1.06	0.94 to 1.19	2174
2001	1.25	1.09 to 1.43	2318	1.25	1.06 to 1.47	1771
Current wheeze						
1998	0.99	0.89 to 1.10	2584	0.99	0.88 to 1.12	2175
2001	1.09	0.93 to 1.30	2331	1.28	1.04 to 1.58	1774

OR, odds ratio; CI, confidence interval.
*Adjusted for confounding variables in table 1.
†Per $\mu g/m^3$ increase in locally generated primary PM_{10}.
‡Number of responses.

The prevalence of symptoms was first evaluated cross-sectionally in the two surveys (Table 2 of the paper, above). The authors then evaluated the OR of developing symptoms in the study period (Table 3 of the paper, below). The ORs were 1.62 (1.31, 2.00) for cough without a cold, 1.19 (0.96, 1.47) for night time cold, and 1.42 (1.02, 1.97) for wheeze.

Table 3 Association between exposure of the home address to locally generated primary PM_{10} and incident cough and wheeze (defined as not present in the 1998 survey and present in the 2001 survey versus no symptoms in both surveys)

	Unadjusted			Adjusted*		
	OR†	95% CI	n‡	OR†	95% CI	n‡
Cough without a cold	1.68	1.39 to 2.03	1479	1.62	1.31 to 2.00	1287
Night time cough	1.21	1.00 to 1.46	1382	1.19	0.96 to 1.47	1191
Wheeze	1.22	0.92 to 1.62	1533	1.42	1.02 to 1.97	1319

OR, odds ratio; CI, confidence interval.
*Adjusted for confounding variables in table 1.
†Per $\mu g/m^3$ increase in locally generated primary PM_{10}.
‡Number of responses.

A number of cross-sectional studies investigated the association between exposure to PM and prevalence of a number of respiratory symptoms. These studies are often difficult to interpret, given the unclear time relation between exposure and outcome and the high number of outcomes considered, and consequent problems related to multiple testing. Their results are summarized in **Table VIII**.

10.4. LONG-TERM PM EXPOSURE AND RESPIRATORY MORBIDITY OR SYMPTOMS IN ADULTS

A random sample of about 7,000 persons residing in 21 centres in 10 countries, who participated to the European Community Respiratory Health Study I (ECRHS I) in 1991-93, were re-interviewed in 2000-2002 to investigate the onset of symptoms for chronic bronchitis (response rate 65%). Table 4 (below) of the article presents the main findings.

Table 4 Multilevel model on chronic phlegm prevalence* at follow up (odds ratio, 95% confidence interval) by gender

	Males	Females
Individual level		
Age in years	0.97 (0.95–1.00)	1.00 (0.98–1.03)
Smoking status		
Non-smokers (ref)	1	1
With passive smoking	1.11 (0.52-2.36)	0.79 (0.41–1.54)
Ex-smokers	1.81 (1.13–2.91)	1.08 (0.68–1.71)
⩽ 10/day	2.21 (1.27–3.87)	1.81 (1.10–2.96)
10–20/day	2.56 (1.48–4.42)	3.14 (1.95–5.04)
> 20/day	4.86 (2.68–8.82)	4.81 (2.49–9.31)
Respiratory infections before age 5 (yes)	1.68 (1.05–2.71)	1.12 (0.76–1.66)
Rhinitis (yes)	1.78 (1.27–2.51)	2.00 (1.45–2.78)
Social class		
Professional and managerial (ref)	1	1
Other non-manual	1.58 (1.02–2.46)	1.46 (0.93–2.30)
Skilled manual	1.94 (1.20–3.14)	0.92 (0.30–2.86)
Semi/unskilled manual	2.52 (1.51–4.19)	2.13 (1.14–3.96)
Unclassified	1.47 (0.64–3.36)	1.79 (1.03–3.08)
Traffic		
None (ref)	1	1
Seldom	1.25 (0.82–1.93)	1.23 (0.77–1.96)
Frequent	1.26 (0.82–1.95)	1.46 (0.92–2.31)
Constant	0.88 (0.56–1.38)	1.86 (1.24–2.77)
Centre level†		
$PM_{2.5}$ in $\mu g/m^3$	0.97 (0.70–1.35)	0.99 (0.85–1.17)
Sulfur content in $\mu g/m^3$	1.00 (0.70–1.44)	1.00 (0.85–1.17)
Odds ratio between % chronic phlegm v response rate	0.88 (0.52–1.50)	1.46 (1.07–1.99)
Average educational level in years	1.01 (0.59–1.75)	0.98 (0.83–1.15)
% Smokers	0.36 (0.22–0.60)	4.44 (0.89–22.1)

*Each column is a multivariate model.
†The measure of association is the interval odds ratio; $PM_{2.5}$ was introduced in an alternative model instead of S content, but coefficients for individual level variables remain stable.

No association was found between centre level of $PM_{2.5}$ and chronic phlegm prevalence at follow up. The ORs were 0.97 (0.70, 1.35) for males and 0.99 (0.85, 1.17) for females, but the measurement unit was not given. A constant exposure to traffic was associated with prevalence of chronic phlegm in women (OR=1.86, 95% CI 1.24, 2.77), but not in men (OR=0.88, 95% CI 0.56, 1.38).

The PAARC study (Baldi *et al*, 1999) collected data also on 20,310 French adults aged 25-59 years, 1,261 (6%) of whom were found to be asthmatic. No association

was found between long-term exposure to TSP (OR for an increase of 50 $\mu g/m^3$=1.01, 95% CI 0.92, 1.11) or BS (OR=1.07, 95% CI 0.96, 1.20).

The SAPALDIA study (Zemp *et al*, 1999) is a cross-sectional investigation in a random sample of 9,651 Swiss adults aged 18-60 years. Asthma prevalence was inversely associated with TSP and PM_{10} in never smokers, while some respiratory symptoms showed a positive association with PM_{10}.

A cross-sectional postal survey on 1,166 women aged 45 years or more was conducted in 11 wards in the UK for which 30 years long concentration data on BS were available (Solomon *et al*, 2003). After adjustment for potential confounders, women living in areas with high BS concentrations reported lower prevalence of asthma, as compared to women living in low BS areas (OR=0.7, 95% CI 0.5, 1.0). Productive cough was not associated with BS (OR=1.0, 95% CI 0.7, 1.5).

Three studies investigated the relation between air pollution and lung function in adults. In the SAPALDIA study (Ackermann-Liebrich *et al*, 1997) significant inverse effects were found between PM_{10} and FVC and FEV_1 in the whole population and separately between never, ex and current smokers. The Health Survey for England (Wheeler and Ben-Shlomo, 2005), including 39,251 participants aged 16-79 years, found that low social class and poor air quality were independently associated with decreased lung function (FEV_1), but not asthma prevalence. For men, but not for women, the effects of air pollution on lung function appeared more marked in lower social classes. In a series of cross-sectional surveys on 4,757 women living in the Rhine-Ruhr Basin in Germany (Schikowski *et al*, 2005), a 7 $\mu g/m^3$ increase in PM_{10} was associated with a 5.1% (2.5, 7.7) decrease in FEV_1, a 3.7% (1.8, 5.5) decrease in FVC and an OR of 1.33 (1,03, 1.72) for COPD.

Finally, among the first 3,904 participants to the EPIC study residing in Athens, those living in the most polluted areas had a two-fold increase in prevalence of chronic bronchitis, emphysema or COPD (Karakatsani *et al*, 2003).

10.5. CONCLUSIONS

Three studies on PM exposure and asthma in children from the Netherlands and France reported weak, non-significant associations. Two studies on PM exposure and lung function in children from Austria and UK reported associations with some of the indicators of lung function, which were not confirmed by a further study from eastern Germany. Two cohort studies from the Netherlands and UK reported significant associations with various symptoms.

Studies in adults did not provide consistent evidence of an association between PM exposure and chronic bronchitis or asthma. Studies on air pollution and lung function, on the other hand, reported positive results.

11. LONG-TERM PM EXPOSURE AND CANCER

Table IX summarizes data on long-term PM exposure and cancer. Most studies considered lung cancer. Data for other neoplasms are sparse. A few studies considered exposure to traffic and childhood cancer, although the underlying etiologic hypothesis is in general connected to benzene, and not PM, exposure. They are listed in **Table IX**, but not discussed here.

11.1. ANALYTIC STUDIES ON LUNG CANCER

Three (Hoek *et al*, 2002; Filleul *et al*, 2005; Naess *et al*, 2007) of the four longitudinal studies that were discussed in the chapter on long-term exposure to PM and mortality (chapter V) also presented data on lung cancer mortality.

In the cohort study from the Netherlands (Hoek *et al*, 2002) 60 deaths from lung cancer were recorded. The adjusted relative risk for an increase of 10 $\mu g/m^3$ in BS was 1.06 (0.43, 2.63), and 1.25 (0.42, 3.72) for a 30 $\mu g/m^3$ increase in NO_2. The number of cases was too small to compute a risk for the indicator variable of living near a major road. Preliminary results of new analyses of the Netherlands study showed that the adjusted RRs for an increase of BS by 10 $\mu g/m^3$ was 0.99 (0.80, 1.23) in the case-cohort analysis, and 1.07 (0.96, 1.19) in the full cohort analysis, based on 1,935 lung cancer deaths (Beelen *et al*, 2007).

In the Norwegian record linkage study (Naess *et al*, 2007), risks were computed separately by sex and age group at baseline (51-70 and 71-90 years), for lung cancer too. For men, no significant excess was found, and the estimated RR for a "quartile increase" in PM_{10} was 1.07 (0.97, 1.18) in both age groups. Conversely, significantly increased risks were found for women in both age groups: 1.27 (1.13, 1.43) for younger and 1.17 (1.03, 1.33) for older women. Estimates for $PM_{2.5}$ were virtually identical to those for PM_{10}.

In the French PAARC study cohort (Filleul *et al*, 2005) 178 deaths from lung cancer were recorded, and the risk of lung cancer associated to an increase in exposure of 10 $\mu g/m^3$ of TSP was 0.97 (0.94, 1.01) when all 24 areas were considered, and 1.00 (0.92, 1.10) when the analysis was restricted to subjects living in the 18 areas with the ratio NO/NO_2 <3. Corresponding values for BS were 0.97 (0.93, 1.01) and 1.03 (0.92, 1.15). The only significant results for lung cancer was for NO_2, when the analysis was restricted to 18 areas (RR=1.48, 95% CI 1.05, 2.06).

A nested case-control study within EPIC (European Prospective Investigation on Cancer and Nutrition) cohort also investigated the association between long-term exposure to PM_{10} and the risk of lung cancer (Vineis *et al*, 2006). The over 500,000 healthy volunteers aged 35-74 of the EPIC cohort were recruited in 10 European countries between 1993 and 1998. Identification of cancer cases was mostly based on cancer registries during a median follow-up time of 7 years. A nested case-control study was conducted within the cohort. For each lung cancer case within selected areas, who was a non smoker or an ex smoker since more than 10 years, 3 controls were selected, matched on sex, age, smoking status, country of recruitment and follow-up time. Assessment of exposure to traffic-related air pollution was made for the period 1990-1999 using available data from monitoring stations from the various areas under study. Distance of the home from a major road was also computed. Given the different availability of exposure data from the various areas, analyses were based on different number of cases. Of the 271 cases

and 737 controls included in the study, data on PM_{10} exposure were available for 113 cases and 312 controls.

Table IV of the article (below) shows the results for pollutant concentrations. After adjustment for the matching variables, the OR was 0.91 (0.70, 1.18) for an increase in PM_{10} of 10 µg/m^3 and 0.98 (0.66, 1.45) for exposures over 27 µg/m^3, compared to less than 27 µg/m^3. The marked change observed when cotinine was added to the model was interpreted by the authors as an effect of random variation due to small numbers.

TABLE IV – ASSOCIATION BETWEEN LUNG CANCER AND AIR POLLUTANTS. ODDS RATIOS (OR) ARE FROM CONDITIONAL LOGISTIC REGRESSION FOR MATCHED PAIRS (3 CONTROLS PER CASE)

	Pollutant		SO_2
	NO_2	PM10	
No. Cases/controls with exposure assessment	122/352	113/312	135/397
Increments by 10 µg/m^3 OR (95% CI)	1.14 (0.78–1.67)	0.91 (0.70–1.18)	1.08 (0.89–1.30)
Analysis by tertiles:			
Reference category (lowest + intermediate tertiles)[1]			
OR	1.0	1.0	1.0
Exposure category (upper tertile)[1]			
Exposed cases	46	53	43
OR (95% CI)	1.30 (1.02–1.66)	0.98 (0.66–1.45)	1.01 (0.84–1.22)
OR (95% CI)[2]	1.56 (1.13–2.16)	1.05 (0.65–1.69)	1.15 (0.92–1.43)
OR (95% CI)[3]	1.62 (0.93–2.83)	2.85 (0.97–8.33)	1.15 (0.85–1.56)
OR (95% CI)[4]	1.37 (1.06–1.75)	1.02 (0.68–1.51)	1.00 (0.83–1.21)

Matching variables are gender, age (65 yrs), smoking habits (former or never smoker), time since recruitment and country.
[1]comparisons are ≥30 *vs* <30 µg/m^3 for NO_2, ≥27 *vs* <27 µg/m^3 for PM10, and ≥11 *vs* <11 µg/m^3 for SO_2 (see text).–[2]As in footnote 1 but additionally adjusted by BMI, education, intake of fruit and vegetables, intake of meat, intake of alcohol, physical activity.–[3]As in footnote 1 but additionally adjusted by cotinine.–[4]As in footnote 1 but additionally adjusted by occupational index (see text).

The OR was 1.38 (0.87, 2.19) for those living near a heavy traffic road.

A case-control study on lung cancer was conducted among men who died in Trieste, Italy, between 1979 and 1981 and between 1985 and 1986 (Barbone *et al*, 1995). Cases were 755 men who died of lung cancer, and controls 755 men who had died for other causes, non COPD nor various cancers of the upper aerodigestive tract, urinary tract, pancreas, liver or gastrointestinal system. Total daily deposition of particulate measured at the closest monitor station from the last subject's residence was used as measure of the subject's exposure. Compared to <0.18 g/m^2/day of deposition of particulate the OR was 1.1 (0.8, 1.5) for 0.18-0.30 and 1.4 (1.1, 1.8) for >0.30 g/m^2/day.

Table VIII/1 shows results of the various analytical studies.

Table VIII/1 Analytic studies investigating the relation between long-term PM exposure and lung cancer.

Study, design	Sex, age at recruitment	No. of cases	Risk indicator, measurement unit	Relative risk (95% CI)
Barbone et al., 1995, case-control, Italy	M	755	Particulate deposition 0.18-0.30 vs <0.18 g/m^2/day	1.1 (0.8-1.5)
			Particulate deposition >0.30 vs <0.18 g/m^2/day	1.4 (1.1-1.8)
Hoek et al., 2002, NLCS cohort, the Netherlands	MF, 55-69	60	BS, 10 µg/m^3	1.06 (0.43-2.63)
Beelen et al., 2007	MF, 55-69	1,935	BS, 10 µg/m^3	1.07 (0.96-1.19)
Filleul et al., 2005, PAARC cohort, France	MF, 25-59	178	TSP, 10 µg/m^3 (24 areas)	0.97 (0.94-1.01)
			TSP, 10 µg/m^3 (18 areas)	1.00 (0.92-1.10)
			BS, 10 µg/m^3 (24 areas)	0.97 (0.93-1.01)
			BS, 10 µg/m^3 (18 areas)	1.03 (0.92-1.15)
Vineis et al., 2006, case-control nested in the EPIC cohort, 7 European countries	MF, 35-74 Non- or ex-smokers	113	PM_{10}, 10 µg/m^3	0.91 (0.70-1.18)
			PM_{10} >27 vs <27 µg/m^3	0.98 (0.66-1.45)
Naess et al., 2007, cohort, Norway	M, 51-70	449	PM_{10}, quartile increase	1.07 (0.97-1.18)
			$PM_{2.5}$, quartile increase	1.07 (0.97-1.18)
	F, 51-70	295	PM_{10}, quartile increase	1.27 (1.13-1.43)
			$PM_{2.5}$, quartile increase	1.27 (1.13-1.43)
	M, 71-90	424	PM_{10}, quartile increase	1.08 (0.98-1.20)
			$PM_{2.5}$, quartile increase	1.07 (0.97-1.18)
	F, 71-90	285	PM_{10}, quartile increase	1.17 (1.03-1.33)
			$PM_{2.5}$, quartile increase	1.16 (1.02-1.32)

Three other studies on the association of air pollution and lung cancer did not directly measure the effect of PM. A case-control study from Poland (Jedrychowski *et al*, 1990) found ORs of 1.00 (0.75, 1.33) and 1.46 (1.06, 1.99) for subjects with intermediate and high exposure to air pollution, compared to those with low exposure, based on an index combining TSP and SO_2 levels. A case-control study from Sweden (Nyberg *et al*, 2000) did not find significant associations with NO_2 (OR=1.05, 95% CI 0.93, 1.18) or SO_2 (OR=1.00, 95% CI 0.96, 1.05). A cohort study from Norway (Nafstad *et al*, 2003) found a RR of 1.08 (1.02, 1.15) for a 10 µg/m^3 increase in exposure to NO_2. No association was found for SO_2 (OR=1.01, 95% CI 0.94, 1.08).

The evidence concerning the association between long-term PM exposure and lung cancer risk is still scanty. Some studies were based on small numbers of cases. The Norwegian linkage study (Naess *et al*, 2007) included a large number of cases, but

did not have information on possible confounding factors, particularly smoking. Moreover, an association was found only for women, but not for men, in the absence of a plausible explanation.

In general, the potential influence of residual confounding by smoking must always be taken into account when dealing with weak associations for lung cancer.

11.2. ECOLOGIC STUDIES ON LUNG AND OTHER CANCERS

A study (Nawrot *et al*, 2007) found a correlation of 0.57 (p=0.028) between age and smoking standardized lung cancer mortality rates in men and annual mean $PM_{2.5}$ concentrations in 15 European countries. No significant association was found in women (r=0.37, p=0.18).

No clear evidence for an association between residence along main roads and the incidence of cancer in adults was found in Amsterdam (Visser *et al*, 2004). Overall, cancer incidence in the area around Amsterdam Schipol Airport was similar to national incidence (Visser *et al*, 2005). A study from northern Italy (Parodi *et al*, 2005) investigated lung cancer incidence near a coke oven plant, finding no clear excess risk.

11.3. STUDIES ON AIR POLLUTION AND CANCER IN CHILDREN

A few studies evaluated the association between exposure to traffic and childhood cancer, yielding conflicting results (Raaschou-Nielsen *et al*, 2001; Crosignani *et al*, 2004; Knox, 2005; Knox, 2006). The main etiologic hypotheses, however, are related to exposure to benzene and polycyclic aromatic hydrocarbons, rather than to PM.

11.4. COMPARISON OF EUROPEAN WITH LEADING NORTH AMERICAN STUDIES

The findings of European studies on PM and lung cancer are not consistent, nor was a clear pattern of risk observed. More important, no clear association emerged in the major European cohort studies including measures of PM exposure. This is at apparent variance with findings from major US studies, which reported direct associations between fine particles and lung cancer mortality. In fact, the adjusted RRs for lung cancer mortality for an increase of $PM_{2.5}$ by 10 $\mu g/m^3$ were 1.27 (0.96, 1.69) in the Harvard Six Cities study (Laden *et al*, 2006), and 1.14 (1.04, 1.23) in the ACS study (Pope *et al*, 2002). In the ACS study, the association with $PM_{2.5}$ was limited to men, in agreement with the AHSMOG study, a cohort based on 6,338 nonsmoking white Californian adults and 36 incident lung cancer cases, which found that the RR for an IQR increase of mean concentrations of PM_{10} was 5.21 (1.94, 13.99) in men. The corresponding estimate for women was not significant and ranged between 1.0 and 1.2 (Beeson *et al*, 1998). This is in apparent contrast with the findings from the Norwegian record linkage study (Naess *et al*, 2007), where no significant excess risk was found for men, while there was a positive association in women.

However, most European studies provided data on PM_{10} only, and not on finer particulates. Other limitations of exposure measurement may account for at least part of these apparent discrepancies.

11.5. CONCLUSIONS

Five analytical epidemiological studies from Europe provided results on various measures of particulate matter (PM) and lung cancer. A case-control study from Trieste, Italy found that, compared to <0.18 g/m^2/day of deposition of particulates, the RR was 1.1 (0.8, 1.5) for 0.18-0.30 and 1.4 (1.1, 1.8) for >30 g/m^2/day. In a cohort study from the Netherlands the RR was 1.06 (0.43, 2.63) for an increase of 10 µg/m^3 in black smoke. In a French cohort study the RR of lung cancer associated with an increase in exposure of 10 µg/m^3 of total suspended particulate (TSP) was 0.97 (0.94, 1.01). In a nested case-control study within a multicentric European cohort the RR was 0.91 (0.70, 1.18) for an increase in PM_{10} of 10 µg/m^3 and 0.98 (0.66, 1.45) for exposures over 27 µg/m^3, compared to less than 27 µg/m^3. In a Norwegian record linkage study no significant excess risk was found for men, while there was an association in women. A few other studies considered indirect indicators of air pollution, and some ecological studies linked information on air pollution and cancer incidence or mortality. Although some of the latter studies reported positive associations, various limitations in their design hinder a causal inference.

12. DISCUSSION AND RECOMMENDATIONS FOR FUTURE STUDIES

12.1. STUDIES ON SHORT-TERM EXPOSURE

Given the availability in several areas of data on daily PM concentrations, and of mortality, and in some instances, hospital admissions, several studies have investigated the association between day-to-day variations in PM concentrations and mortality or emergency hospital admissions. Many of these studies, however, have limitations, either because they were based on small populations or had questionable statistical analysis, which in several instances tended to maximize the investigated association. The latter would affect results of a systematic reanalysis of published studies, and the computing of a pooled measure of association. The use of different measures of PM (PM_{10}, BS, TSP etc.) would further complicate the combination of results from various studies. A pooled re-analysis of various studies, based on the original data, and not on published material, would be more informative and valid, although it would require a great effort.

The APHEA2 study is the largest study on the relation between short-term PM exposure and mortality, and provides the best estimate of the relation between PM_{10} and day-to-day mortality in Europe. The data of the APHEA2 study were based on a large population from several different areas in Europe, and have been thoroughly re-analyzed to evaluate the influence of different statistical models, the medium-term effects of PM (up to 40 days), and the modification effects of some city characteristics, such as temperature or humidity, but also the percentage of people aged >65 years or of smokers.

Although age at death is, with sex, the only individual characteristic readily available from death certification data, the modifying effect of age on the relation between short-term PM exposure and mortality/morbidity has not been fully clarified. The data from the APHEA2 study suggest that the effect of air pollution is larger at older ages. Deaths in younger age groups are relatively rare, and even the largest study, i.e., the APHEA2, had problems with small numbers in some age categories. Only the combination of many datasets, either within Europe, or including studies from other areas of the world, would provide sufficient power to investigate the effects of air pollution in specific age groups, in particular when specific causes of death are investigated.

The issue of confounding by individual characteristics should not be a major issue, since, in time series data, comparisons are made from one day to another, using the same background populations. In the few studies that have analyzed data using a case-crossover design in addition to a time series approach, the results were comparable.

Scant or inadequate information is available in Europe on modification of the effects of air pollution exerted by individual variables (other than age and sex), e.g. socioeconomic status (SES), lifestyle habits (e.g. smoking), underlying medical conditions (e.g. COPD, coronary disease, diabetes), occupational exposures etc. In Rome a case-crossover design investigated the modification effect of SES using two area-based SES indicators, derived from census data (Forastiere *et al*, 2005). Although yielding interesting results, that analysis was based on small numbers and on a single population. That type of analysis was based on routinely collected data, and could, in principle, be extended to other datasets.

Information on the separate effects of coarse, fine and ultrafine PM is still limited. Given that more and more areas within Europe have, in recent years, started the measurement of fine and/or ultrafine PM, it is likely that in the next years several studies will investigate the effects of coarse, fine and ultrafine PM separately. This should be the case, for example, of the HEAPSS study. In the cities included in this study, PNC measurements have started in 2002. In a recent publication, PNC values for a previous period have been estimated retrospectively. New data from the HEAPSS study, from more recent periods and based on actual measurements of PNC, should be available in the next future. Investigations aimed at separating the effects of PM of different diameters will have to deal with the problem of the analysis of highly correlated variables, a problem which has also arisen in the investigation of several correlated pollutants, e.g. PM, NO_2, CO and SO_2.

As of now, very few results are available from central and eastern European countries.

12.2. STUDIES ON LONG-TERM EXPOSURE

Very few studies have investigated the long-term effects of PM exposure on health. Ecologic studies may be suggestive and hypothesis generating, but, given the potential biases inherent in their design, they cannot provide a solid base for inference.

Record linkage studies, such as the one recently published from Norway (Naess *et al*, 2007) may include a high number of cases, but the lack of individual variables, first of all smoking habit, renders this type of study difficult to interpret.

Only a limited number of analytic studies have been conducted so far. Many of these were based on cohorts designed for different purposes, which have exploited the availability of PM concentration data in the area under study. This has led to studies that were often based on small numbers, often with exclusions of parts of the study population for which exposure data could not be retrieved.

It is possible that for other longitudinal studies data on exposure could be retrieved and analyzed, but limited availability of reliable data on relevant exposures limits the usefulness of this approach. Thus, only the design of *ad hoc* studies could provide new insights on the issue.

A somewhat less attractive approach is the pooling of existing cohorts, given the heterogeneity of information on variables used to reconstruct air pollution exposure indicators and on potential confounders. Although technically feasible and relatively inexpensive, it is unclear whether this approach would provide more informative data on long-term effects of air pollution than traditional meta-analyses of already published data. Therefore, the establishment of new multicentric cohorts in Europe remains an appealing approach to investigate long-term effect of air pollution in this region.

In short-term time series, comparisons are ideally made between different days within individuals, and adjustment for day of week and holidays is often performed. In contrast, studies on long-term exposure are necessarily based on comparisons between individuals, and on cumulative exposure assessment. Misclassification of exposure is likely to occur and to affect results. To comment about the different models used for attributing exposure at a certain address is beyond the scope of this report. In almost all the studies conducted so far, the exposure to ambient PM

has been estimated only on the base of the subject's home address. No additional information was available on characteristics of the home (e.g. floor of residence) or of the subject's exposure pattern. Collecting and combining information on hours spent at home, at work, outdoors etc. during the day could improve individual estimates of long-term exposure. The collection of data on potential confounders specifically for the analysis of the association between PM exposure and mortality/morbidity would also provide important additional information.

12.3. RECOMMENDATIONS FOR FUTURE RESEARCH ON HEALTH EFFECTS OF AIR POLLUTION IN EUROPE

Previous studies on short-term effects of air pollution in Europe allow a general quantification of the risks. However, information on the possible confounding or modifying effect of covariates, and mainly data on course, fine and ultrafine particles is limited. Still, with the exception of Central and Eastern Europe, where few data are available, further research on short-term effects of air pollution should not be given high priority.

Only a limited number of analytic studies have been conducted in Europe on long-term effects of air pollution, and these were mainly cohorts designed for different purposes. Their ability to provide valid results was limited by sub-optimal strategies for exposure assessment leading to misclassification, low statistical power, and heterogeneity of approaches. While it is possible that additional exposure data can be retrieved for these and other existing longitudinal studies, it is uncertain whether this approach would lead to major advances. In any case, priority should be given to the co-ordination and harmonization of exposure data in existing cohorts.

The establishment of new studies represents the preferred strategy to provide new insights on long-term effects of air pollution. In areas where estimation of long-term PM exposure could be reconstructed, the case-control design should be considered. The design and implementation of new cohort studies would provide, in the long-term, the most reliable information, but would require great effort in terms of time and resources. Such new studies would rely on uniform methods to measure air pollutants, and be based on an increased number of new measuring stations. Participants should be periodically re-contacted and in addition to information on possible outcomes, new information on exposure based on uniform methodology should be collected. Such new cohorts should give priority to the inclusion of populations from Central and Eastern Europe, where air pollution is higher and adverse health effects may be detected sooner than in less polluted areas of Europe.

TABLE I - SHORT-TERM PARTICULATE MATTER EXPOSURE AND MORTALITY (Derived from EPA TABLE 8A-1).

Reference, Location, Years, PM Index, Mean or Median (µg/m^3).	Study Description. Modeling methods: lags, smoothing, co-pollutants and covariates.	Results and Comments.	PM Index, lag, percent excess risk% (95% LCL, UCL)
APHEA 1			
Katsouyanni et al. (1997) (Katsouyanni *et al*, 1997) 12 European cities (APHEA), 1975-1992 (study years different from city to city). Median BS levels ranged from 13 in London to 73 in Athens and Kracow.	Total daily deaths regressed on BS or SO_2 using Poisson GLM models, adjusting for seasonal cycles, day-of-week, influenza epidemic, holidays, temperature and humidity. Final analysis done with autoregressive Poisson models to allow for overdispersion and autocorrelation. Pollution effects examined at 0 through 3 day lags and multi-day averages thereof. When city-specific coefficients were tested to be homogeneous, overall estimates were obtained fixed effects models. When significant heterogeneity was present, source of heterogeneity sought by examining a predefined list of city-specific variables, including annual and seasonal means of pollution and weather variables, number of monitoring sites, correlation between measurements from different sites, age-standardized mortality, proportion of elderly people, smoking prevalence, and geographic difference (North-South, East-West). A random effects model was fit when heterogeneity could not be explained.	Substantial variation in pollution levels (winter mean SO_2 ranged from 30 to 330 µg/m^3), climate, and seasonal patterns were observed across cities. Significant heterogeneity was found for the effects of BS and SO_2, but only the separation between western and central-eastern European cities resulted in more homogeneous subgroups. Significant heterogeneity for SO_2 remained in western cities. Cumulative effects of prolonged (two to four days) exposure to air pollutants resulted in estimates comparable with the one day effects. The effects of both SO_2 and BS were stronger during the summer and were independent.	Total mortality excess deaths in single day for western European cities: BS (per 25 µg/m^3): 1.4% (1.0, 1.8) PM_{10} (per 50 µg/m^3): 2% (1, 3) In central/eastern European cities, BS (per 25 µg/m^3): 0.3% (0.05, 0.5).
Samoli et al. (2001) (Samoli *et al*, 2001) APHEA 1 cities (see Katsouyanni (1997) (Katsouyanni *et al*, 1997) At least five years between 1980-1992. The PM levels are the same as those in Katsouyanni et al. (1997) (Katsouyanni *et al*, 1997).	In order to further investigate the source of the regional heterogeneity of PM effects, and to examine the sensitivity of the RRs, the APHEA data were re-analyzed. Unlike previous model in which sinusoidal terms for seasonal control and polynomial terms for weather, the investigators this time used a GAM model with smoothing terms for seasonal trend and weather, which is more commonly used approach in recent years.	The estimated RRs for central-eastern cities were larger than those obtained from the previous model. Also, restricting the analysis to days with concentration < 150 µg/m^3 further reduced the differences between the western and central-eastern European cities. The authors concluded that part of the heterogeneity in the estimated air pollution effects between western and central eastern cities in previous publications was caused by the statistical approach and the data range.	Total mortality per 50 µg/m^3 of BS; GAM approach: all cities: 2.5% (2.1, 2.9) western cities: 3.1% (2.3, 3.8) central-eastern cities: 2.3% (1.7, 2.9) old method: all cities: 1.3% (0.9, 1.7) western cities: 2.9% (2.1, 3.7) central-eastern cities: 0.6% (0.1, 1.1).

Samoli et al. (2003) (Samoli *et al*, 2003) Re-analysis of above study.	Re-analysis of above study using stringent convergence criteria as well as natural splines.	BS risk estimates using GAM were reduced by ~ 10% when stringent convergence criteria were applied. Use of GLM/natural splines resulted in further and greater reductions.	Results corresponding to above using the GAM with stringent convergence criteria: all cities: 2.3% (1.9, 2.7) western cities: 2.7% (2.0, 3.4) central-eastern cities: 2.1% (1.5, 2.7). Corresponding GLM/natural splines results were: all cities: 1.2% (0.7, 1.7) western cities: 1.6% (0.8, 2.4) central-eastern cities: 1.0% (0.3, 1.7).
Zmirou et al. (1998) (Zmirou *et al*, 1998) 10 European cities (APHEA). 1977-1992 (study years different from city to city). Median BS levels ranged from 13 in London to 73 in Kracow.	Cardiovascular, respiratory, and digestive mortality series in 10 European cities analyzed to examine cause-specificity of air pollution. The mortality series were analyzed for associations with PM (BS, except TSP in Milan and Bratislava; PM_{13} in Lyon), NO_2, O_3, and SO_2. Poisson GLM models, lag/averaging of pollution, and computation of combined effects across the cities done in the same way as by Katsouyanni et al. (1997) (Katsouyanni *et al*, 1997), above.	The cardiovascular and respiratory mortality series were associated with BS and SO_2 in western European cities, but not in the five central European cities. NO_2 did not show consistent mortality associations. RRs for respiratory causes were at least equal to, or greater than those for cardiovascular causes. No pollutant exhibited any association with digestive mortality.	Pooled cardiovascular mortality percent excess deaths per 25 $\mu g/m^3$ increase in BS for western European cities: 1.0% (0.3, 1.7); for respiratory mortality, it was 2.0% (0.8, 3.2) in lag 0 (the lags apparently varied across cities).
APHEA 2			
Katsouyanni et al. (2001) (Katsouyanni *et al*, 2001) 29 European cities, 1990-1997 (variable from city to city). Median PM_{10} ranged from 14 (Stockholm) to 66 (Prague). Median BS ranged from 10 (Dublin) to 64 (Athens).	The 2nd phase of APHEA (APHEA 2) put emphasis on the effect modification by city-specific factors. The first stage of city specific regressions used GAM Poisson model. The second stage regression analysis was conducted to explain any heterogeneity of air pollution effects using city-specific variables. These city-specific variables included average air pollution levels, average temperature/humidity, age- standardize mortality rate, region indicators, etc.	The authors found several effect modifiers. The cities with higher NO_2 levels showed larger PM effects. The cities with warmer climate showed larger PM effects. The cities with low standardized mortality rate showed larger PM effects.	Total mortality excess risk per 50 $\mu g/m^3$ increase in PM_{10}: Fixed effects model: 3.5% (2.9, 4.1) Random effects model: 3.1% (2.1, 4.2).

Katsouyanni et al. (2003) (Katsouyanni *et al*, 2003) Re-analysis of above study.	Re-analysis of above study using stringent convergence criteria as well as natural splines and penalized splines.	The pooled estimate (random effects estimate) was reduced by 4% when stringent convergence criteria in GAM were used, by 34% when natural splines were used, and by 11% when penalized splines were used. The pattern of effect modification originally reported remained the same. The original findings were unchanged.	Total mortality excess risk per 50 µg/m^3 increase in PM_{10} using GAM (stringent convergence criteria): fixed effects: 3.3% (2.7, 3.9) random effects: 3.0% (2.0, 4.1) GLM/natural splines were fixed effects: 2.1% (1.5, 2.8) random effects: 2.1% (1.2, 3.0) Penalized splines fixed effects: 2.9% (2.3, 3.6) random effects: 2.8% (1.8, 3.8).
Touloumi et al. (1997) (Touloumi *et al*, 1997) 6 European cities (APHEA). 1977-1992 (study years different from city to city). Median BS levels ranged from 14.6 in London to 84.4 in Athens.	Results of the short-term effects of ambient NO_2 and/or O_3 on daily deaths from all causes (excluding accidents) were discussed to provide a basis for comparison with estimated SO_2 or BS effects in APHEA cities. Poisson GLM models, lag/averaging of pollution, and the computation of combined effects across the cities were done in the same way as done by Katsouyanni et al. (1997) (Katsouyanni *et al*, 1997).	Significant positive associations were found between daily deaths and both NO_2 and O_3. There was a tendency for larger effects of NO_2 in cities with higher levels of BS. When BS was included in the model, pooled estimate for O_3 effect was only slightly reduced, but coefficient for NO_2 was reduced by half. Authors speculated that short-term effects of NO_2 on mortality were confounded by other vehicle-derived pollutants.	NO_2 and/or O_3 estimates only.
Zanobetti et al., 2002 (Zanobetti *et al*, 2002) 1990-1996 (variable from city to city). 10 European cities (2/3 of population) from the APHEA 2 study. Mean PM_{10} ranged from 16 (Stockholm) to 76 (Prague).	Analysis of mortality displacement up to 40 days. In The first stage consisted of city specific regressions using GAM Poisson models with 4th degree polynomial distributed lag constraints with up to 40 days. In the second stage the city-specific estimates were combined using a random effect model.	The overall effect of PM_{10} for the 4th distributed lag model was higher (1.61% increase in daily deaths per 10 µg/m^3) than the model considering only lag 0-1 (0.70 %). The results were unchanged when an unconstrained distributed lag model was used. This suggests that the effect of PM on mortality is not due primarily to short-term mortality displacement.	For 4th degree polynomial distributed lag model, total mortality excess per 50 µg/m^3 increase was 8.1% (5.1, 11.0).

Zanobetti and Schwartz (2003) (Zanobetti and Schwartz, 2003) Re-analysis of the above study.	Re-analysis of above study using stringent convergence criteria as well as natural splines and penalized splines.	The pooled PM_{10} (lag 0-1) mortality risk estimate was reduced by 4% when stringent convergence criteria in GAM were used, by 18% when penalized splines were used. For the 4^{th} degree polynomial distributed lag model, corresponding reductions were 10% and 26%.	Combined total mortality excess risk per 50 $\mu g/m^3$ increase PM_{10} (lag 0-1) was 3.4% (2.0, 4.8) using GAM with stringent convergence criteria. For 4^{th} degree polynomial distributed lag model, it was 7.5% (4.4, 10.7). Corresponding reductions using penalized splines were 2.9% (1.4, 4.4) and 5.6% (1.5, 9.8), respectively.
Zanobetti et al., 2003 (Zanobetti *et al*, 2003) 10 cities of the APHEA 2 project, 1990-1996. PM_{10} means ranging between 15.5 (Stockholm) and 76.2 (Prague).	This study analysed the acute and medium-term (weeks to months) exposure effects of PM_{10} on cardiovascular and respiratory mortality, using a multi-city hierarchical modeling approach. A GAM Poisson regression was fitted and an unconstrained distributed lag and a 4^{th} degree polynomial distributed lag were used to model the effect of PM_{10} exposure on deaths up to 40 days after the exposure. The model was adjusted for weather, influenza epidemics, holidays, and day of the week.	This study confirmed that most of the effect on mortality of air pollution was not simply advanced by a few weeks and that effects persisted for more than 1 month after exposure. The effect size estimate for PM_{10} doubled when considering longer-term effects for all deaths and for cardiovascular deaths and became five times higher for respiratory deaths. The effects were similar when stratifying by age groups.	Considering PM_{10} the day of and day before the death, the percent increase mortality for an increment of 10 $\mu g/m^3$ of PM_{10} was 0.74% (-0.17, 1.66) for respiratory deaths and 0.69% (0.31, 1.08) for CVD deaths. Corresponding estimates in unrestricted distributed lag models, were 4.20% (1.08, 7.42) and 1.97% (1.38, 2.55), respectively.

Aga et al., 2003 (Aga *et al*, 2003) 28 European cities APHEA 2 project. Daily mean PM_{10} (21 cities) between 15 and 66 and BS (14 cities) between 10 and 64.	To study the effects of ambient particle concentrations (BS and PM_{10}) on total mortality among persons aged 65 years or more, a 2-stage analysis was applied, assessing city-specific effects first and then overall effects was used after adjustment for seasonality, long-term trends, temperature, humidity, influenza epidemics, other unusual events, day of the week, and holidays. Lag 0-1 was *a priori* chosen as exposure measure.	A significant association with total mortality was found for both PM_{10} and BS among the elderly, with relative risks comparable or slightly higher than those observed for total mortality and similar effect modification patterns.	Percent excess mortality for increase by 10 µg/m^3 of PM_{10} (lag 0-1) Total population Fixed effects: 0.71% (0.60, 0.83) Random effects: 0.67% (0.47, 0.87) Elderly (65+) Fixed effects: 0.79% (0.66, 0.92) Random effects: 0.74% (0.52, 0.95) Percent excess mortality for increase by 10 µg/m^3 of BS (lag 0-1) Total population Fixed effects: 0.51% (0.39, 0.64) Random effects: 0.58% (0.32, 0.84) Elderly (65+) Fixed effects: 0.63% (0.49, 0.78) Random effects: 0.68% (0.43, 0.92).
Analitis et al., 2006 (Analitis *et al*, 2006) 29 European cities APHEA2 project. Mean PM_{10} (21 cities) between 9 and 64 and BS (15 cities) between 14 and 166.	To study the effects of ambient particle concentrations (BS and PM_{10}) on cardiovascular and respiratory mortality, a 2-stage hierarchical modeling approach assessing city-specific effects first and then overall effects was used after adjustment for seasonality, long-term trends, temperature, humidity, influenza epidemics, other unusual events, day of the week, and holidays. Further adjustment for the daily levels of other pollutants was performed in 2-pollutant models.	A significant excess risk was found for both PM_{10} and BS. The greatest relative effect modification for PM_{10} on CVD mortality came from mean temperature and city-average NO_2 concentrations. Warmer towns with more NO_2 showed larger effects. There was less effect modification by NO_2 for BS than for PM_{10}, suggesting differential effects of traffic particles, for which PM_{10} is a less good indicator than BS.	An increment in PM_{10} of 10 µg/m^3 (lag 0-1) was associated with increases of 0.76% (0.47, 1.05) in CVD deaths and 0.58% (0.21, 0.95) in respiratory deaths. The same increment in BS was associated with increases of 0.62% (0.35, 0.90) and 0.84% (0.11, 1.57), respectively.

Touloumi et al 2005 (Touloumi *et al*, 2005) 7 European cities APHEA-2 project, 1990-1997. Median PM_{10} ranging between 13.7 and 40.2.	To investigate the effect of influenza epidemics on the association between PM_{10} and total and cardiovascular mortality, a GAM Poisson regression after adjustment for day of week and holidays was used. To control for influenza epidemics, 10 methods were compared.	The significant and direct association between PM_{10} and daily number of deaths remained and even increased after controlling for influenza, regardless of the method used for control. Simple methods, such as 1 or multiple indicators for influenza epidemics, are relatively easy and effective ways to control or to evaluate potential confounding effect of influenza epidemics. Respiratory mortality data may be used instead of influenza cases data if the latter are not available; respiratory mortality data may be more appropriate way to control when the outcome studied is a mortality outcome. None of the methods investigated in this study suggested appreciable confounding by influenza epidemics.	An increment by 10 $\mu g/m^3$ (lag 0-1) in PM_{10} concentrations was associated with a 0.48% (0.27, 0.70) increase in daily mortality without adjustment for influenza epidemics, and ranged between 0.45% (0.26, 0.69) to 0.67% (0.46, 0.89), after different adjustment for influenza epidemics. The corresponding figures for CVD mortality were 0.85% (0.53, 1.18) without the methods of control and from 0.86% (0.53, 1.19) to 1.06% (0.74, 1.39) with the methods of control.
National studies			
THE NETHERLANDS			
Hoek et al. (2000) (Hoek *et al*, 2000) The Netherlands, 1986-1994. PM_{10} median: 34 BS median: 10.	Total, cardiovascular, COPD, and pneumonia mortality series were regressed on PM_{10}, BS, sulfate, nitrate, O_3, SO_2, CO, adjusting for seasonal cycles, day of week, influenza, temperature, and humidity using Poisson GAM model. Deaths occurring inside and outside hospitals were also examined.	Particulate air pollution was less consistently associated with mortality than were the gaseous pollutants SO_2 and NO_2. Sulfate, nitrate, and BS were more consistently associated with total mortality than was PM_{10}. The RRs for all pollutants were larger in the summer months than in the winter months.	Mortality excess risk estimate per 50 $\mu g/m^3$ PM_{10} (lag 0-6): 1.2% (0.2, 2.2) for total mortality 0.9% (-0.8, 2.7) for CVD 5.9% (0.9, 11.2) for COPD 10.1% (3.6, 17.1) for pneumonia.
Hoek (2003) (Hoek, 2003) Re-analysis of the above study.	Re-analysis of above study using stringent convergence criteria and natural splines.	Very little change in PM risk coefficients (often slightly increased) whether GAM with stringent convergence criteria or GLM/natural splines were used.	Estimates per 50 $\mu g/m^3$ PM_{10} (lag 0-6) using GAM with stringent convergence criteria: Total mortality: 1.4% (0.3, 2.6) CVD: 0.9% (-0.8, 2.7) COPD: 6.1% (1.0, 11.4) Pneumonia: 10.3% (3.7, 17.2) Using GLM/natural splines were: Total mortality: 1.2% (-0.1, 2.5) CVD: 1.6% (-0.3, 3.5) COPD: 6.0% (0.4, 11.8) Pneumonia: 10.7% (3.5, 18.3).

Hoek et al. (2001) (Hoek *et al*, 2001) The Netherlands. 1986-1994. PM_{10} median: 34 BS median: 10.	This study of the whole population of the Netherlands, with its large sample size (mean daily total deaths ~ 330), allowed examination of specific cardiovascular cause of deaths. GAM Poisson regression models, adjusting for seasonal cycles, temperature, humidity, and day of week were used.	Deaths due to heart failure, arrhythmia, cerebrovascular causes, and thrombocytic causes were more strongly (~ 2.5 to 4 times larger relative risks) associated with air pollution than the overall CVD deaths or AMI and other IHD deaths.	For PM_{10} (lag 0-6), mortality per 50 µg/m^3 increase: Total CVD: 0.9% (-0.8, 2.7) AMI/IHD: 0.3% (-2.3, 3.0) Arrhythmia 2.5% (- 4.3, 9.9) Heart failure 2.2% (-2.5, 7.2) Cerebrovascular 1.9% (-1.8, 5.8) Thrombocytic: 0.6% (-6.8, 8.7). The excess risks for BS were larger and more significant than those for PM_{10}.
Hoek (2003) (Hoek, 2003) Re-analysis of the above study.	Re-analysis of above study using stringent convergence criteria and natural splines.	Very little change in PM risk coefficients (often slightly increased) whether GAM with stringent convergence criteria or GLM/natural splines were used.	For PM_{10} (lag 0-6), percent excess risk mortality per 50 µg/m^3 increase using GAM with stringent convergence criteria were: Total CVD: 0.9% (-0.8, 2.7), AMI/IHD: 0.4% (-2.2, 3.0), Arrhythmia: 2.7% (- 4.2, 10.1), Heart failure: 2.4% (-2.3, 7.4), Cerebrovascular: 2.0% (-1.7, 5.9), Thrombocytic: 0.7 %(-6.8, 8.8). The RRs for BS were larger and more significant than those for PM_{10}.

Fischer et al. (2003) (Fischer *et al*, 2003) The Netherlands. 1986-1994. PM_{10} median: 34 BS median: 10.	Age-specific analysis of the previous study. The relationship between daily (total and cause-specific) mortality and air pollution (PM_{10}, BS and other co-pollutants, including O_3, SO_2, CO and NO_2) was modelled using Poisson regression analysis. All pollution mortality associations were adjusted for long-term trends, seasonal trends, influenza epidemics, ambient temperature, ambient relative humidity, day of the week and holidays, using GAM models. The weekly average concentration for other pollutants (lag 0-6) was used for PM_{10} and BS.	PM_{10} slightly increased total mortality, and cardiovascular mortality in the elderly only (subjects aged 65 years or more). Both BS and PM_{10} significantly increased mortality for pneumonia in the elderly, only. Similar increased risks were shown for the other considered co-pollutants.	Percent excess total mortality risk per 100 µg/m^3 increase of PM_{10}: 2% (0, 3) Percent excess for 80 µg/m^3 increase of PM_{10} (99^{th}-1^{st} percentile): Cardiovascular mortality (years): <45: -9.4 (-27.2, 12.8) 45-64: 2.3 (-5.5, 10.6) 65-74: 0.2 (-5.5, 6.2) 75+: 1.6 (-1.9, 5.2) COPD mortality (years): <45: 15.3 (-41.3, 126.8) 45-64: 13.9 (-16.1, 54.1) 65-74: 16.6 (-0.9, 37.2) 75+: 6.6 (-3.5, 17.8) Pneumonia mortality (years): <45: 42.7 (-19.4, 152.5) 45-64: 71.2 (4.2, 181.5) 65-74: 24.0 (-12.1, 74.8) 75+: 12.3 (1.1, 24.7) Percent excess for 40 µg/m^3 increase of BS (99^{th}-1^{st} percentile): Cardiovascular mortality (years): <45: 5.7 (-6.4, 19.6) 45-64: 0.0 (-4.3, 4.6) 65-74: 4.0 (0.6, 7.5) 75+: 3.0 (1.0, 5.1) COPD mortality (years): <45: -12.8 (-40.1, 27.0) 45-64: 2.5 (-13.0, 20.9) 65-74: 20.4 (9.5, 32.4) 75+: 1.2 (-4.3, 7.0) Pneumonia mortality (years): <45:-25.9 (-48.1, 5.7) 45-64: 26.4 (-6.6, 71.1) 65-74: -4.9 (-23.3, 17.9) 75+: 12.3 (5.5, 19.6).

Subnational studies			
GREAT BRITAIN			
Bremner et al. (1999) (Bremner *et al*, 1999) London, UK, 1992-1994. BS mean: 13 PM_{10} mean: 29.	Total, cardiovascular, and respiratory (by age) mortality series were regressed on PM_{10}, BS, O_3, NO_2, CO, and SO_2, adjusting for seasonal cycles, day of week, influenza, holidays, temperature, humidity, and autocorrelation using Poisson GLM model.	All effect size estimates (except O_3) were positive for total deaths (though not significant for single lag models). The effects of O_3 found in 1987-1992 were not replicated, except in cardiovascular deaths. Multiple day averaging (e.g., 0-1, 0-2 days) tended to give more significant effect size estimates. The effect size for PM_{10} and BS were similar for the same distributional increment.	Percent excess risk 1.9% (0.0, 3.8) per 25 µg/m^3 BS at lag 1; 1.3% (-1.0, 3.6) per 50 µg/m^3 PM_{10} at lag 1 for total deaths. Respiratory deaths (lag 3): 4.9% (0.5, 9.4). CVD deaths (lag 1): 3.0% (0.3, 5.7).
Prescott et al. (1998) (Prescott *et al*, 1998) Edinburgh, UK, 1981-1995. PM_{10} mean: 21, by TEOM only for 1992-1995; BS mean: 8.7.	Both mortality (total, cardiovascular, and respiratory) and emergency hospital admissions (cardiovascular and respiratory), in two age groups (<65 and ≥ 65 years), were analyzed for their associations with PM_{10}, BS, SO_2, NO_2, O_3, and CO, using Poisson GLM regression adjusting for seasonal cycles, day-of-week, temperature, and wind speed.	Among all the pollutants, BS was most significantly associated with all cause, cardiovascular, and respiratory mortality series. In the subset in which PM_{10} data were available, the RR estimates for BS and PM_{10} for all cause elderly mortality were comparable. Other pollutants' mortality associations were generally inconsistent.	Percent excess risk 3.8% (1.3, 6.4) per 25 µg/m^3 increase in BS for all cause mortality in age 65+ group, lag 1-3.
Rooney et al. (1998) (Rooney *et al*, 1998) England and Wales, and Greater London, UK PM_{10} mean: 56 (during the worst heat wave); PM_{10} mean: 39 (July-August).	Excess deaths, by age, sex, and cause, during the 1995 heat wave were estimated by taking the difference between the deaths during heat wave and the 31-day moving averages (for 1995 and 1993-1994 separately). The pollution effects, additively for O_3, PM_{10}, and NO_2, were estimated based on the published season-specific coefficients from the 1987- 1992 study (Anderson et al., 1996) (Anderson *et al*, 1996).	Air pollution levels at all the locations rose during the heat wave. 8.9% and 16.1% excess deaths were estimated for England and Wales, and Greater London, respectively. Of these excess deaths, up to 62% and 38%, respectively for these locations, may be attributable to combined pollution effects.	2.6% increase for PM_{10} in Greater London during heat wave.
Wordley et al. (1997) (Wordley *et al*, 1997) Birmingham, UK, 1992-1994. PM_{10} mean: 26.	Mortality data were analyzed for COPD, pneumonia, all respiratory diseases, all circulatory diseases, and all causes. Mortality associations with PM_{10}, NO_2, SO_2, and O_3 were examined using OLS (with some health outcomes log- or square-root transformed), adjusting for day-of-week, month, linear trend, temperature and relative humidity. The study also analyzed hospital admission data.	Total, circulatory, and COPD deaths were significantly associated with 1-day lag PM_{10}. The gaseous pollutants "did not have significant associations independent from that of PM_{10}", and the results for gaseous pollutants were not presented. The impact of reducing PM_{10} to below 70 µg/m^3 was estimated to be "small" (0.2% for total deaths), but the PM_{10} level above 70 µg/m^3 occurred only once during the study period.	5.6% (0.5, 11.0) per 50 µg/m^3 PM_{10} at 1 d lag for total deaths. COPD (1 day lag) deaths: 27.6 (5.1, 54.9). Circulatory (1 day lag) deaths: 8.8 (1.9, 17.1).

Anderson et al. (1996) (Anderson *et al*, 1996) London, UK, 1987-1992. BS mean 15.	Total, cardiovascular, and respiratory mortality series were regressed on BS, O_3, NO_2, and SO_2, adjusting for seasonal cycles, day of week, influenza, holidays, temperature, humidity, and autocorrelation using Poisson GLM model.	Both O_3 (lag 0) and BS (lag 1) were significant predictors of total deaths. O_3 was also positively significantly associated with respiratory and cardiovascular deaths. The effect size estimates per the same distributional increment (10% to 90%) were larger for O_3 than for BS. These effects were larger in warm season. SO_2 and NO_2 were not consistently associated with mortality.	Percent excess mortality 2.8% (1.4, 4.3) per 25 µg/m^3 BS at 1-d lag for total deaths. CVD (1 d): 1.0% (-1.1, 3.1). Respiratory (1 d): 1.1% (-2.7, 5.0).
Anderson et al. (2001) (Anderson *et al*, 2001) The West Midlands conurbation, UK. 1994-1996. PM means: PM_{10}: 23, $PM_{2.5}$: 15, $PM_{10-2.5}$: 9, BS: 13.2.	Non-accidental cause, cardiovascular, and respiratory mortality (as well as hospital admissions) were analyzed for their associations with PM indices and gaseous pollutants using GAM Poisson models adjusting for seasonal cycles, day of week, and weather.	Daily non-accidental mortality was not associated with PM indices or gaseous pollutants in the all-year analysis. However, all the PM indices (except coarse particles) were positively and significantly associated with non-accidental mortality (age over 65) in the warm season. Of gaseous pollutants, NO_2 and O_3 were positively and significantly associated with non-accidental mortality in warm season. Two pollutant models were not considered because "so few associations were found".	Percent excess mortality for PM_{10}, $PM_{2.5}$, and $PM_{10-2.5}$ (lag 0-1) were: 0.2% (-1.8, 2.2) per 24.4 µg/m^3 PM_{10}, 0.6% (-1.5, 2.7) per 17.7 µg/m^3 $PM_{2.5}$, and -0.6% (-4.2, 2.3) per 11.3 µg/m^3 $PM_{10-2.5}$ in all-year analysis. The results for season specific analysis were given only as figures.
Keatinge and Donaldson (2001) (Keatinge andDonaldson, 2001) Greater London, England, 1976-1995. BS mean: 17.7.	The study examined potential confounding effects of atypical cold weather on air pollution/mortality relationships. First, air pollution variables (SO_2, CO and BS) were modeled as a function of lagged weather variables. These variables were deseasonalized by regressing on seine and cosine variables. Mortality regression (OLS) included various lagged and averaged weather and pollution variables. Analyses were conducted in the linear range of mortality/temperature relationship (15 to 0 degrees C).	Polluted days were found to be colder and less windy and rainy than usual. In the regression of mortality on the multiple-lagged temperature, wind, rain, humidity, sunshine, SO_2, CO, and BS, cold temperature was associated with mortality increase, but not SO_2 or CO. BS showed suggestive evidence, though not statistically significant, of association at lag 0 and lag 1.	Percent excess mortality 3% (NS) increase in daily mortality per 17.7 µg/m^3 of BS (lag 0 and 1).

Anderson et al. (1996) (Anderson *et al*, 1996) London, UK, 1987-1992. BS mean 15.	Total, cardiovascular, and respiratory mortality series were regressed on BS, O_3, NO_2, and SO_2, adjusting for seasonal cycles, day of week, influenza, holidays, temperature, humidity, and autocorrelation using Poisson GLM model.	Both O_3 (lag 0) and BS (lag 1) were significant predictors of total deaths. O_3 was also positively significantly associated with respiratory and cardiovascular deaths. The effect size estimates per the same distributional increment (10% to 90%) were larger for O_3 than for BS. These effects were larger in warm season. SO_2 and NO_2 were not consistently associated with mortality.	Percent excess mortality 2.8% (1.4, 4.3) per 25 µg/m^3 BS at 1-d lag for total deaths. CVD (1 d): 1.0% (-1.1, 3.1). Respiratory (1 d): 1.1% (-2.7, 5.0).
Anderson et al. (2001) (Anderson *et al*, 2001) The West Midlands conurbation, UK. 1994-1996. PM means: PM_{10}: 23, $PM_{2.5}$: 15, $PM_{10-2.5}$: 9, BS: 13.2.	Non-accidental cause, cardiovascular, and respiratory mortality (as well as hospital admissions) were analyzed for their associations with PM indices and gaseous pollutants using GAM Poisson models adjusting for seasonal cycles, day of week, and weather.	Daily non-accidental mortality was not associated with PM indices or gaseous pollutants in the all-year analysis. However, all the PM indices (except coarse particles) were positively and significantly associated with non-accidental mortality (age over 65) in the warm season. Of gaseous pollutants, NO_2 and O_3 were positively and significantly associated with non-accidental mortality in warm season. Two pollutant models were not considered because "so few associations were found".	Percent excess mortality for PM_{10}, $PM_{2.5}$, and $PM_{10-2.5}$ (lag 0-1) were: 0.2% (-1.8, 2.2) per 24.4 µg/m^3 PM_{10}, 0.6% (-1.5, 2.7) per 17.7 µg/m^3 $PM_{2.5}$, and -0.6% (-4.2, 2.3) per 11.3 µg/m^3 $PM_{10-2.5}$ in all-year analysis. The results for season specific analysis were given only as figures.
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Anderson et al. (1996) (Anderson *et al*, 1996) London, UK, 1987-1992. BS mean 15.	Total, cardiovascular, and respiratory mortality series were regressed on BS, O_3, NO_2, and SO_2, adjusting for seasonal cycles, day of week, influenza, holidays, temperature, humidity, and autocorrelation using Poisson GLM model.	Both O_3 (lag 0) and BS (lag 1) were significant predictors of total deaths. O_3 was also positively significantly associated with respiratory and cardiovascular deaths. The effect size estimates per the same distributional increment (10% to 90%) were larger for O_3 than for BS. These effects were larger in warm season. SO_2 and NO_2 were not consistently associated with mortality.	Percent excess mortality 2.8% (1.4, 4.3) per 25 µg/m^3 BS at 1-d lag for total deaths. CVD (1 d): 1.0% (-1.1, 3.1). Respiratory (1 d): 1.1% (-2.7, 5.0).
Anderson et al. (2001) (Anderson *et al*, 2001) The West Midlands conurbation, UK. 1994-1996. PM means: PM_{10}: 23, $PM_{2.5}$: 15, $PM_{10-2.5}$: 9, BS: 13.2.	Non-accidental cause, cardiovascular, and respiratory mortality (as well as hospital admissions) were analyzed for their associations with PM indices and gaseous pollutants using GAM Poisson models adjusting for seasonal cycles, day of week, and weather.	Daily non-accidental mortality was not associated with PM indices or gaseous pollutants in the all-year analysis. However, all the PM indices (except coarse particles) were positively and significantly associated with non-accidental mortality (age over 65) in the warm season. Of gaseous pollutants, NO_2 and O_3 were positively and significantly associated with non-accidental mortality in warm season. Two pollutant models were not considered because "so few associations were found".	Percent excess mortality for PM_{10}, $PM_{2.5}$, and $PM_{10-2.5}$ (lag 0-1) were: 0.2% (-1.8, 2.2) per 24.4 µg/m^3 PM_{10}, 0.6% (-1.5, 2.7) per 17.7 µg/m^3 $PM_{2.5}$, and -0.6% (-4.2, 2.3) per 11.3 µg/m^3 $PM_{10-2.5}$ in all-year analysis. The results for season specific analysis were given only as figures.
Keatinge and Donaldson (2001) (Keatinge andDonaldson, 2001) Greater London, England, 1976-1995. BS mean: 17.7.	The study examined potential confounding effects of atypical cold weather on air pollution/mortality relationships. First, air pollution variables (SO_2, CO and BS) were modeled as a function of lagged weather variables. These variables were deseasonalized by regressing on seine and cosine variables. Mortality regression (OLS) included various lagged and averaged weather and pollution variables. Analyses were conducted in the linear range of mortality/temperature relationship (15 to 0 degrees C).	Polluted days were found to be colder and less windy and rainy than usual. In the regression of mortality on the multiple-lagged temperature, wind, rain, humidity, sunshine, SO_2, CO, and BS, cold temperature was associated with mortality increase, but not SO_2 or CO. BS showed suggestive evidence, though not statistically significant, of association at lag 0 and lag 1.	Percent excess mortality 3% (NS) increase in daily mortality per 17.7 µg/m^3 of BS (lag 0 and 1).

Goodman et al., 2004 (Goodman *et al*, 2004); Dublin, Ireland, 1980-1996, BS mean 40.	This study analysed the acute and medium-term (weeks to months) exposure effects of BS and temperature on total and cause-specific mortality. In the analysis of the acute effects of exposure (3-day mean BS), GAM Poisson regression models for the log counts of daily age-standardized mortality rates were adjusted for meteorological measures, including temperature, humidity on the same and previous day, plus indicators for day of week and for respiratory epidemics. The cumulative effects of temperature and particulate air pollution over 40 days were analyzed simultaneously in a GAM model including distributed lag functions for minimum temperature and BS. Daily BS air pollution concentrations were measured at 6 residential monitoring stations.	The effects of particulate air pollution on mortality were strongest on the day of and the few days after exposure but extended out through about 40 days after exposure. This extended air pollution association was most marked for the elderly population groups and for respiratory causes of death. The extended follow-up effects were two to three times greater than the acute effects reported in other studies, and approached the effects reported in longer-term survival studies. The studies on the acute effects of air pollution could have underestimated the total effect of temperature and particulate air pollution on mortality.	For an increment of 10 µg/m^3 of BS, total mortality increased by 0.4% (0.3, 0.6) when only acute effects (3-day mean) were considered and by 1.1% (0.8, 1.3) when considering deaths in the 40 days after exposure. Corresponding estimates were 0.4% (0.2, 0.7) and 1.1% (0.7, 1.5) for CVD mortality, and 0.9% (0.5 to 1.2) and 3.6% (3.0, 4.3) for respiratory mortality.
FINLAND			
Pönkä et al. (1998) (Ponka *et al*, 1998) Helsinki, Finland, 1987-1993. TSP median: 64 PM_{10} median: 28.	Total and cardiovascular deaths, for age groups < 65 and 65 +, were related to PM_{10}, TSP, SO_2, NO_2, and O_3, using Poisson GLM model adjusting for temperature, relative humidity, day-of-week, temporal patterns, holiday and influenza epidemics.	No pollutant significantly associated with mortality from all cardiovascular or CVD causes in 65+ year age group. Only in age <65 year group, PM_{10} associated with total and CVD deaths with 4 and 5 d lags, respectively. The "significant" lags were rather "spiky". O_3 was also associated with CVD mortality <65 years group with inconsistent signs and late and spiky lags (negative on d 5 and positive on d 6).	18.8% (5.6, 33.2) per 50 µg/m^3 PM_{10} 4 day lag (other lags negative or zero).

Goodman et al., 2004 (Goodman *et al*, 2004); Dublin, Ireland, 1980-1996, BS mean 40.	This study analysed the acute and medium-term (weeks to months) exposure effects of BS and temperature on total and cause-specific mortality. In the analysis of the acute effects of exposure (3-day mean BS), GAM Poisson regression models for the log counts of daily age-standardized mortality rates were adjusted for meteorological measures, including temperature, humidity on the same and previous day, plus indicators for day of week and for respiratory epidemics. The cumulative effects of temperature and particulate air pollution over 40 days were analyzed simultaneously in a GAM model including distributed lag functions for minimum temperature and BS. Daily BS air pollution concentrations were measured at 6 residential monitoring stations.	The effects of particulate air pollution on mortality were strongest on the day of and the few days after exposure but extended out through about 40 days after exposure. This extended air pollution association was most marked for the elderly population groups and for respiratory causes of death. The extended follow-up effects were two to three times greater than the acute effects reported in other studies, and approached the effects reported in longer-term survival studies. The studies on the acute effects of air pollution could have underestimated the total effect of temperature and particulate air pollution on mortality.	For an increment of 10 µg/m^3 of BS, total mortality increased by 0.4% (0.3, 0.6) when only acute effects (3-day mean) were considered and by 1.1% (0.8, 1.3) when considering deaths in the 40 days after exposure. Corresponding estimates were 0.4% (0.2, 0.7) and 1.1% (0.7, 1.5) for CVD mortality, and 0.9% (0.5 to 1.2) and 3.6% (3.0, 4.3) for respiratory mortality.
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THE NETHERLANDS			
Roemer and Van Wijnen (2001). (Roemer andvan Wijnen, 2001) Amsterdam. 1987-1998. BS and PM_{10} means in "background": 10 and 39 BS mean in "traffic" area: 21. (No PM_{10} measurements available at traffic sites).	Daily deaths for those who lived along roads with more than 10,000 motor vehicle, as well as deaths for total population, were analyzed using data from background and traffic monitors. Poisson GAM model was used adjusting for season, day-of-week, and weather. BS, PM_{10}, SO_2, NO_2, CO, and O_3 were analyzed.	Correlations between the background monitors and traffic monitors were moderate for BS (r = 0.55) but higher for NO_2 (r = 0.79) and O_3 (r = 0.80). BS and NO_2 were associated with mortality in both total and traffic population. Estimated RR for traffic population using background sites was larger than the RR for total population using background sites. The RR for total population using traffic sites was smaller that RRs for total population using background sites. This is not surprising since the mean BS for traffic sites were larger than for background sites.	The excess risk per 100 µg/m^3 of BS (lag 1): Total population using background sites: 38.3% (15.3, 65.9) Traffic population using background sites: 88.7% (20.7, 194.9) Total population using traffic sites: 12.2% (2.3, 23.1). Results for traffic population using traffic sites not reported.
Hoek et al. (1997) (Hoek *et al*, 1997) Rotterdam, the Netherlands, 1983-1991. TSP median: 42, BS median: 13.	Total mortality (also by age group) was regressed on TSP, Fe (from TSP filter), BS, O_3, SO_2, CO, adjusting for seasonal cycles, day-of-week, influenza, temperature, and humidity using Poisson GAM model.	Daily deaths were most consistently associated with TSP. TSP and O_3 effects were "independent" of SO_2 and CO. Total iron (from TSP filter) was associated "less consistently" with mortality than TSP was. The estimated RRs for PM indices were higher in warm season than in cold season.	Percent excess mortality: 5.5% (1.1, 9.9) per 100 µg/m^3 TSP at lag 1.

GERMANY			
Wichmann et al., (2000) (Wichmann *et al*, 2000) Erfurt, Germany. 1995-1998. Number counts (NC) and mass concentrations (MC) of ultrafine particles using Spectrometryll Mobile Aerosol Spectrometry (MAS). MAS MC $PM_{2.5-0.01}$ (mean 25.8, median 18.8, IQR 19.9). Filter measurements of PM_{10} (mean 38.2, median 31.0, IQR 27.7) and $PM_{2.5}$ (mean 26.3, median 20.2, IQR 18.5). MAS $NC_{2.5-0.01}$ (mean 17,966 per cm^3, median 14,769, IQR 13,269).	Total non-accidental, cardiovascular, and respiratory deaths (mean 4.88, 2.87, 1.08 per day, respectively) were related to particle mass concentration and number counts in each size class, and to mass concentrations of gaseous co-pollutants NO_2, CO, SO_2, using GAM regression models adjusted for temporal trends, day of week, weekly national influenza rates, temperature and relative humidity. Data analyzed by season, age group, and cause of death separately. Single- day lags and polynomial distributed lag models (PDL) used. Particle indices and pollutants fitted using linear, log- transformed, and LOESS transformations. Two-pollutant models with a particle index and a gaseous pollutant were fitted. The "best" model was that having the highest t-statistic, since other criteria (e.g., log-likelihood for nested models) and AIC for non-nested models could not be applied due to different numbers of observations in each model. There should be little difference between these approaches and resulting differences in results should be small in practice. Sensitivity analyses included stratifying data by season, winter year, age, cause of death, or transformation of the pollution variable (none, logarithmic, non-parametric smooth).	Loss of statistical power by using a small city with a small number of deaths was offset by advantage of having good exposure representation from single monitoring site. Since ultrafine particles can coagulate into larger aggregates in a few hours, ultrafine particle size and numbers can increase into the fine particle category, resulting in some ambiguity. Significant associations were found between mortality and ultrafine particle NC, ultrafine particle MC, fine particle mass concentration, or SO_2 concentration. The correlation between $MC_{0.01-2.5}$ and $NC_{0.01-0.1}$ was only moderate, suggesting it may be possible to partially separate effects of ultrafine and fine particles. The most predictive single-day effects are either immediate (lag 0 or 1) or delayed (lag 4 or 5), but cumulative effects characterized by PDL are larger than single-day effects. The significance of SO_2 was robust, but hard to explain as a true causal factor since its concentrations were very low. Age was an important modifying factor, with larger effects at ages < 70 than > 70 years. Respiratory mortality had a higher RR than CVD mortality. A large number of models were fitted, with some significant findings of association between mortality and particle mass or number indices.	Total mortality excess deaths: Filter PM_{10} (lag 0-4): 6.6 (0.7, 12.8) per 50 µg/m^3. Filter $PM_{2.5}$ (lag 0-1): 3.0 (-1.7, 7.9). MC for $PM_{0.01-2.5}$ 6.2% (1.4, 11.2) for all year Winter: 9.2% (3.0, 15.7) Spring: 5.2% (-2.0, 12.8) Summer: -4.7% (-18.7, 11.7) Fall: 9.7% (1.9, 18.1) For ultrafine PM, $NC_{0.01-0.1}$ (lag 0-4): All Year: 8.2% (0.3, 16.9) Winter: 9.7% (0.3, 19.9) Spring: 10.5% (-1.4, 23.9) Summer: -13.9% (-29.8, 5.7) Fall: 12.0% (2.1, 22.7) Best single-day lag per 25 µg/m^3: $PM_{0.01-0.1}$: 3.6% (-0.4, 7.7) $PM_{0.01-2.5}$: 3.9% (0.0, 8.0) $PM_{2.5}$: -4.0% (-7.9, 0) PM_{10}: 6.4% (0.3, 12.9).

Stolzel et al. (2003) (Stölzel *et al*, 2003) Re-analysis of the above study.	Re-analysis of above study using GAM with stringent convergence criteria as well as GLM/natural splines. The polynomial distributed lag model was not re-analyzed.	Very little change in PM risk coefficients when GAM models with stringent convergence criteria were used. When GLM/natural splines were used, many of the coefficients for number concentrations slightly increased, but the coefficients for mass concentrations decreased slightly.	Best single-day lag using GAM (stringent) per 25 µg/m^3: $PM_{0.01-0.1}$: 3.6% (-0.4, 7.7) $PM_{0.01-2.5}$: 3.8% (-0.1, 7.8) $PM_{2.5}$: -4.0% (-7.8, -0.1) PM_{10}: 6.2% (0.1, 12.7) Best single-day lag using GLM/natural splines: $PM_{0.01-0.1}$: 3.1% (-1.6, 7.9) $PM_{0.01-2.5}$: 3.7% (-0.9, 8.4) $PM_{2.5}$: -3.4% (-7.9, 1.4) PM_{10}: 5.3% (-1.8, 12.9).
Stolzel et al., 2006 (Stolzel *et al*, 2006) Erfurt, Germany, 1995-2001.	To study the association between $PM_{0.01-0.1}$ and $PM_{0.1-2.5}$ and total and cardio-respiratory mortality Poisson GAM models adjusted for trend, seasonality, influenza epidemics, day of the week, and meteorology using smooth functions or indicator variables were used.	This study shows that ultrafine particles, representing fresh combustion particles, could be an important component of urban air pollution associated with health effects. In fact, statistically significant associations were found between elevated ultrafine particle number concentrations and total as well as cardio-respiratory mortality (lag 4). No association between fine particle MC and mortality was found.	The percent mortality excess risk (lag 4) for an increment of 9,748 no/cm^3 in $PM_{0.1-2.5}$, was 2.9% (0.3, 5.5) for total mortality, and 3.1% (0.3, 6.0) for cardio-respiratory mortality.
Rahlenbeck and Kahl (1996) (Rahlenbeck andKahl, 1996) East Berlin, 1981-1989. TSP (beta attenuation): 97.	Total mortality (as well as deviations from long-wave cycles) was regressed (OLS) on TSP and SO_2, adjusting for day of week, month, year, temperature, and relative humidity, using OLS, with options to log-transform pollution, and w/ and w/o days with pollution above 150 µg/m^3.	Both SP and SO_2 were significantly associated with total mortality with 2 day lag in single pollutant model. When both pollutants were included, their coefficients were reduced by 33% and 46% for TSP and SO_2, respectively.	6.1% per 100 µg/m^3 TSP at lag 2.

BAVARIA AND CZECH			
Peters et al. (2000) (Peters *et al*, 2000) A highly polluted coal basin area in the Czech Republic and a rural area in Germany, northeast Bavaria districts. 1982-1994. TSP mean: 121.1 and 51.6, respectively, for these two regions. PM_{10} and $PM_{2.5}$ were also measured in the coal basin during 1993-1994 (mean: 65.9 and 51.0, respectively).	Non-accidental total and cardiovascular deaths (mean: 18.2 and 12.0 per day, for the Czech and Bavaria areas, respectively). The APHEA approach (Poisson GLM model with sine/cosine, temperature as a quadratic function, relative humidity, influenza, day-of-week as covariates), as well as GLM with natural splines for temporal trends and weather terms were considered. Logarithm of TSP, SO_2, NO_2, O_3, and CO (and PM_{10} and $PM_{2.5}$ for 1993-1994) were examined at lags 0 through 3 days.	In the coal basin (i.e., the Czech Republic polluted area), on the average, 68% of the TSP was PM_{10}, and most of PM_{10} was $PM_{2.5}$ (75%). For the coal basin, associations were found between the logarithm of TSP and all-cause mortality at lag 1 or 2 days. SO_2 was also associated with all-cause mortality with slightly lower significance. PM_{10} and $PM_{2.5}$ were both associated with all-cause mortality in 1993-1994 with a lag of 1-day. NO_2, O_3 and CO were positively but more weakly associated with mortality than PM indices or SO_2. In the Bavarian region, neither TSP nor SO_2 was associated with mortality, but CO (at lag 1-day) and O_3 (at lag 0-day) were associated with all-cause mortality.	Total mortality excess deaths per 100 µg/m^3 increase in TSP for the Czech region: 3.8% (0.8, 6.9) at lag 2 for 1982-1994 period. For period 1993-1994, 9.5 % (1.2, 18.5) per 100 µg/m^3 increase in TSP at lag 1, and 4.8% (0.7, 9.0) per 50 µg/m^3 increase in PM_{10}; and 1.4 (-0.5, 3.4) per 25 µg/m^3 $PM_{2.5}$.
Kotšovec et al. (2000) (Kotesovec *et al*, 2000) Northern Bohemia, Czech Republic, 1982-1994. TSP mean: 121.3.	Total (excluding accidents and children younger than 1 year), cause specific (cardiovascular and cancer), age (65 and less vs. otherwise), and gender specific mortality series were examined for their associations with TSP and SO_2 using logistic model, adjusting for seasonal cycles, influenza epidemics, linear and quadratic temperature terms. Lags 0 through 6 days, as well as a 7 day mean values were examined.	For the total mortality, TSP, but not SO_2, was associated. Apparent differences in associations were found between men and women. For example, for age below 65 years, cardiovascular mortality was associated with TSP in men but not in women.	Total mortality percent excess deaths per 100 µg/m^3 increase in TSP at lag 2 was 3.4% (0.5, 6.4).
FRANCE			
Zeghnoun et al. (2001) (Zeghnoun *et al*, 2001) Rouen and Le Havre, France. 1990-1995. PM_{13} mean: 32.9 for Rouen, 36.4 for Le Havre. BS mean: 18.7 for Rouen, 16.3 for Le Havre.	Total, cardiovascular, and respiratory mortality series were regressed on BS, PM_{13}, SO_2, NO_2, and O_3 in 1- and 2-pollutant models using GAM Poisson models adjusting for seasonal trends, day of week, and weather.	In Rouen, O_3, SO_2, and NO_2 were each significantly associated with total, respiratory, and cardiovascular mortality, respectively. In Le Havre, SO_2 and PM_{13} were associated with cardiovascular mortality. However, the lack of statistical significance reported for most of these results may be in part due to the relatively small population size of these cities (430,000 and 260,000, respectively).	PM_{13} total mortality RRs per IQR were 0.5% (-1.1, 2.1) in Rouen (IQR=20.6, lag 1) and 1.9% (-0.8, 7.4) in Le Havre (IQR=23.9, 1-day lag). BS total mortality RRs per IQR were 0.5% (-1.8, 2.9) in Rouen (IQR=14.2, 1-day lag) and 0.3% (-1.6, 2.2) in Le Havre (IQR=11.5, lag 0-1).

Le Tertre et al., 2002 (Le Tertre *et al*, 2002b) Nine French Cities, 1990-1995. BS median ranging between 12.7-16.0 µg/m^3 (based on 5 cities, only).	This study examined the short-term effects of air pollution (BS, SO_2, NO_2, O_3) on mortality, using Poisson time-series regressions, controlling for trends in seasons, calendar effects, influenza epidemics, temperature, and humidity. Lag 0-1 was used for all the cities.	Significant and positive associations were found between total daily deaths and the four air pollution indicators considered. Similar results were obtained for cardiovascular mortality. Except for SO_2, positive but non significant associations were found with respiratory mortality. The results were consistent among all the cities considered.	A 50 µg/m^3 increase in BS (lag 0-1) was associated with 2.9% (1.3, 4.4) increase in total mortality, 3.1% (0.5, 5.5) in cardiovascular mortality, and 2.7% (-2.6, 8.3) in respiratory mortality. Corresponding estimates after exclusion of Paris were 4.6% (1.9, 7.4), 5.5% (0.9, 10.4) and 11.1% (1.3, 21.9), respectively.
Eilstein et al., 2004 (Eilstein *et al*, 2004) Nine French Cities, 1990-1997. Update of the above study. BS and PM_{10} level indicators not given. BS data were available for 6 cities and PM_{10} for 3 cities.	This study examined the short-term effects of air pollution (PM_{10}, BS, SO_2, NO_2, CO, O_3) on total, cardiovascular and respiratory mortality, using Poisson GAM, adjusting for trends in seasons, day of week, holidays, influenza epidemics, temperature, and humidity. Excess risks at lag 0-1 and lag 0-5 were shown.	Significant direct associations were found for all the air pollution indexes other than CO.	The percent excess risks for a 10 µg/m^3 increase in BS were 0.8 for total mortality, 0.5 for cardiovascular and 0.7 (non-significant, NS) for respiratory mortality at lag 0-1. Corresponding estimates at lag 0-5 were 1.2, 1.2 and 2.1, respectively. The percent excess risks for a 10 µg/m^3 increase in PM_{10} were 0.8 for total, 0.3 (NS) for cardiovascular and 0.6 (NS) for respiratory mortality at lag 0-1. Corresponding estimates at lag 0-5 were 1.0, 0.3 (NS) and 1.9, respectively.

ITALY			
Zanobetti et al. (2000) (Zanobetti *et al*, 2000) Milan, Italy. 1980-1989. TSP mean: 142.	The focus of this study was to quantify mortality displacement using what they termed "GAM distributed lag models" (smoothing term was fitted with penalized splines). Non-accidental total deaths were regressed on smooth function of TSP distributed over the same day and the previous 45 days using penalized splines for the smooth terms and seasonal cycles, temperature, humidity, day-of- week, holidays, and influenza epidemics. The mortality displacement was modelled as the initial positive increase, negative rebound (due to depletion), followed by another positive coefficient period, and the sum of the three phases were considered as the total cumulative effect.	TSP was positively associated with mortality up to 13 days, followed by nearly zero coefficients between 14 and 20 days, and then followed by smaller but positive coefficients up to the 45th day (maximum examined). The sum of these coefficients was over three times larger than that for the single-day estimate.	Total mortality percent increase estimates per IQR increase in TSP: 2.2% (1.4, 3.1) for single-day model; 6.7% (3.8, 9.6) for distributed lag model.
Rossi et al. (1999) (Rossi *et al*, 1999) Milan, Italy, 1980-1989 TSP (PM_{13} beta attenuation): 142.	Specific causes of death (respiratory, respiratory infections, COPD, circulatory, cardiac, heart failure, and AMI) were related to TSP, SO_2, and NO_2, adjusting for seasonal cycles, temperature, and humidity, using Poisson GAM model.	All three pollutants were associated with all cause mortality. Cause-specific analysis was conducted for TSP only. Respiratory infection and heart failure deaths were both associated with TSP on the concurrent day, whereas the associations for myocardial infarction and COPD deaths were found for the average of 3 to 4 day prior TSP.	3.3% (2.4, 4.3) per 100 µg/m^3 TSP at lag 0.
Michelozzi et al. (1998) (Michelozzi *et al*, 1998) Rome, Italy, 1992-1995. TSP (PM_{13} beta attenuation): 84.	Total mortality was related to PM_{13}, SO_2, NO_2, CO, and O_3, using Poisson GAM model, adjusting for seasonal cycles, temperature, humidity, day-of-week, and holiday. Analysis of mortality by place of residence, season, age, place of death (in or out of hospital), and cause was also conducted.	PM_{13} and NO_2 were most consistently associated with mortality. CO and O_3 coefficients were positive, SO_2 coefficients negative. RR estimates higher in the warmer season. RRs similar for in- and out-of hospital deaths.	1.9% (0.5, 3.4) per 50 µg/m^3 PM_{13} at lag 0.

Biggeri et al. (2005) (Biggeri *et al*, 2005) Eight cities of North, Centre and South of Italy 1990-1999. PM_{10} mean daily concentration: Turin, 91-94: 77.6 Turin, 95-98: 63.8 Milan, 90-94: 61.8 Milan, 95-97: 45.2 Verona, 95-99: 36.5 Ravenna, 91-95: 59.1 Bologna, 96-98: 41.2 Florence, 96-98: 40.3 Rome, 92-94: 69.7 Palermo, 97-99: 42.9.	Meta-analysis of short-term effects of air pollution on mortality (all causes, cardiovascular causes and respiratory causes) in eight Italian cities from 1990 to 1999. Daily concentrations of pollutants were collected. A generalized linear model adjusted for age, day of the week, holidays, influenza epidemics, meteorological variables, and seasonality pattern was fitted for PM_{10} and other co-pollutant (SO_2, NO_2, CO, and O_3). City-specific and fixed- and random-effects pooled estimates were shown. Lag 0-1 was used for mortality. Fixed- and random-effects models were shown.	A significant direct association was found between PM_{10} and total natural mortality. The effect of PM_{10} was greater during the warm season and for the elderly. A North-South gradient in risk was observed for total natural mortality. A significant association was also shown for cardiovascular and respiratory mortality. Similar increased risks were found for the other considered co-pollutants. The effects of PM_{10} showed the highest inter-city variability.	Percent excess mortality for 10 $\mu g/m^3$ change in PM_{10} (lag 0-1): All natural causes Fixed-effects: 0.85% (0.52, 1.18) Random-effects: 0.98% (0.35, 1.61) CVD causes Fixed-effects: 0.97% (0.45, 1.50) Random-effects: 1.21% (0.32, 2.10) Respiratory causes Fixed-effects: 1.74% (0.44, 3.05) Random-effects: 1.41% (-1.41, 4.32).
Stafoggia et al., 2005 (Stafoggia *et al*, 2005) Rome, Italy, 1998-2000 PM_{10} mean: 52.1; PNC mean 51,669 no/cm^3 In part, reanalysis of above study as time series.	This study examined the association between daily ambient air pollution levels (PNC, as a proxy of ultrafine particles, PM_{10}, CO, NO_2 and O_3) and the occurrence of fatal, out-of-hospital coronary events (5,144 subjects) and fatal hospitalised coronary events (1,411 subjects), using a GAM Poisson model adjusting for temporal trend, temperature, humidity, day of week, holidays, and population reduction in summer months. Lags 0, 1, 0-1 and 0-4 were considered.	Significant direct associations were found for PNC, PM_{10} and CO, and both out-of-hospital deaths and fatal coronary events. The associations were stronger in subjects older than 65 years.	Increase in risk of out-of-hospital coronary death associated with 29.7 $\mu g/m^3$ (IQR) PM_{10}: 7.0% (2.9, 11.2) at lag 0 6.4% (2.4, 10.6) at lag 1 8.1% (3.6, 12.9) at lag 0-1 9.6% (4.4, 15.2) at lag 0-4 Increase in risk for an increment in PNC of 28,001 no/cm^3 (IQR): 8.1% (3.0, 13.4) at lag 0 4.0% (-1.1, 9.3) at lag 1 7.8% (2.0, 14.0) at lag 0-1 8.3% (2.1, 14.9) at lag 0-4 The increases in risk of fatal coronary events at lag 0 were 5.0% (1.3, 8.9) for PM_{10} and 8.2% (3.6, 13.1) for PNC.

Forastiere et al., 2005 (Forastiere *et al*, 2005) Rome, Italy, 1998-2001, PM_{10} mean 51.0.	This study investigated whether social class is an effect modifier of the association between PM_{10} and daily mortality. Subjects included were 83,253 residents of Rome aged ≥35 years who died for natural causes between 1998 and 2001. A case-crossover design was used. Control days were selected using the time-stratified approach: all same days of the week within that month (of the same year) were chosen. Lag 0–1 was considered. Conditional logistic regression analysis was used after allowance for apparent temperature on the index day, and its difference from the average of the previous 3 days' values, influenza epidemics, holidays, and population reduction in summer months. As a surrogate for individual socioeconomic status (SES) two area-based indicators were used: income and SES of the population living in the same census block, as derived from the 2001 census.	A significant excess risk was found for PM_{10}. Subjects in the low, mid-low, mid-high categories of both income and socio-economic status showed an effect of PM_{10} very consistent with the overall estimate whereas those in the high category had effect estimates close to the null.	The increase in mortality associated with an increment of 10 µg/m^3 of PM_{10} (lag 0-1) was 1.1% (0.7, 1.6). There was a statistically significant effect modification of social class on a multiplicative scale. For the lowest and highest quintile of SES the increases were 1.9% and 0.0% for the highest quintile. Corresponding values for the lowest and highest quintiles of income were 1.4% and 0.1%.
Sansebastiano et al. (2003) (Sansebastiano *et al*, 2003) Parma, Italy, 1992-2001. mean daily concentration: PM_{10} (1998-2001: from 39,63 in 1998 to 57.68 in 2001; TSP: from 46.92 in 1996 to 62.39 in 1992.	This study examined the relationship between TSP and other co-pollutants (CO, NO_2, and SO_2), and general mortality in the city of Parma (population 170,000). The excess risk of hospital admission was not analysed for PM_{10} since information for PM_{10} was available for the period 1998-2001, only.	A direct association has been shown between TSP, SO_2 and general mortality.	Percent excess risk (95% CI) of total mortality for 1 µg/m^3 increment of TSP: 0.14% (0.08, 0.23).
SPAIN			
Tobias and Campbell (1999) (Tobias andCampbell, 1999) Barcelona, Spain. 1991-1995. BS (no data distribution was reported).	This study examined the sensitivity of estimated total mortality effects of BS to different approaches to modeling influenza epidemics: (1) with a single dummy variable; (2) with three dummy variables; (3) using daily number of cases of influenza. Poisson GLM regression used to model total daily mortality, adjusting for weather, long-term trend, and season, apparently following APHEA protocol.	Using the reported daily number of influenza cases resulted in a better fit (i.e., a lower AIC) than those using dummy variables. In the "better" model, the BS coefficient was about 10% smaller than those in the models with dummy influenza variables, but remained significant. Lags not reported.	Total mortality excess deaths per 25 µg/m^3 increase in BS: 1.37 (0.20, 2.56) for model using the daily case of influenza; 1.71 (0.53, 2.91) for model with three influenza dummy variables.

Alberdi Odriozola et al. (1998) (Alberdi Odriozola *et al*, 1998) Madrid, Spain, 1986-1992. TSP (beta attenuation): 47 for average of 2 stations.	Total, respiratory, and cardiovascular deaths were related to TSP and SO_2. Multivariate autoregressive integrated moving average models used to adjust for season, temperature, relative humidity, and influenza epidemics.	TSP (lag 1) and SO_2 (lag 3) were independently associated with mortality.	4.8% (1.8, 7.7) per 100 µg/m^3 TSP at lag 1.
Díaz et al. (1999) (Diaz *et al*, 1999) Madrid, Spain, 1990-1992. TSP (no data distribution was reported).	Non-accidental, respiratory, and cardiovascular deaths (mean = 62.4, 6.3, and 23.8 per day, respectively). Auto-Regressive Integrated Moving Average (ARIMA) models fit to both dependent and independent variables first to remove auto-correlation and seasonality (i.e., pre-whitening), followed by examining cross-correlation to find optimal lags. Multivariate OLS models thus included ARIMA components, seasonal cycles (sine/cosine), V-shaped temperature, and optimal lags found for pollution and weather variables. TSP, SO_2, NO_2, and O_3 were examined. Season-specific analyses were also conducted.	TSP was significantly associated with non-accidental mortality at lag 0 for year around and winter, but with a lag 1 in summer. A similar pattern was seen for circulatory deaths. For respiratory mortality, a significant association with TSP was found only in summer (lag 0). SO_2, NO_x, and NO_2 showed similar associations with non-accidental deaths at lag 0 day. O_3 associations with non-accidental mortality was U-shaped, with inconsistent lags (1, 4, and 10).	For non-accidental mortality, excess deaths was 7.4% (confidence bands not reported; $p < 0.05$) per 100 µg/m^3 TSP at lag 0.
Studies in subjects with COPD/asthma			
Garcia-Aymerich et al. (2000) (Garcia-Aymerich *et al*, 2000) Barcelona, Spain. 1985-1989. BS (no data distribution was reported).	Daily total (mean = 1.8/day), respiratory, and cardiovascular mortality counts of a cohort (9,987 subjects) with COPD or asthma were associated with BS (24-hr), SO_2 (24- hr and 1-hr max), NO_2 (24-hr and 1-hr max), O_3 (1-hr max), temperature, and relative humidity. Poisson GLM regression models using APHEA protocol were used. The resulting RRs were compared with those of the general population.	Daily mortality in COPD patients was associated with all six pollution indices. This association was stronger than in the general population only for daily 1-hr max of SO_2, daily 1-hr max and daily means of NO_2. BS and daily means of SO_2 showed similar or weaker associations for COPD patients than for the general population.	Total mortality percent increase per 25 µg/m^3 increase of BS at lag 0-3: 2.76% (1.31, 4.23) in general population, and 1.14% (-4.4, 6.98) in the COPD cohort.

Sunyer et al. (2000) (Sunyer *et al*, 2000) Barcelona, Spain. 1990-1995. BS means: 43.9 for case period, and 43.1 for control period.	Those over age 35 who sought emergency room services for COPD exacerbation during 1985-1989 and died during 1990-1995 were included in analysis. Total, respiratory, and cardiovascular deaths were analyzed using a conditional logistic regression analysis with a case-crossover design, adjusting for temperature, relative humidity, and influenza epidemics. Bi-directional control period at 7 days was used. Lag 0-2 was used for pollution exposure period. Data also stratified by potential effect modifiers (e.g., age, gender, severity and number of emergency room visits, etc.).	BS levels were associated with all cause deaths. The association was stronger for respiratory causes. Older women, patients admitted to intensive care units, and patients with a higher rate of emergency room visits were at greater risk of deaths associated with BS.	Percent increase per 25 μg/m^3 increase in 3-day average BS: 14.2% (1.6, 28.4) for all causes; 9.7% (-10.2, 34.1) for cardiovascular deaths; 23.2% (3.0, 47.4) for respiratory deaths.
Sunyer and Basagana (2001) (Sunyer and Basagana, 2001) Barcelona, Spain. 1990-1995. See Sunyer et al. (2000) (Sunyer *et al*, 2000) for PM levels.	The analysis assessed any "independent" particle effects, after controlling for gaseous pollutants, on a cohort of patients with COPD (see the summary description for Sunyer et al. (2000) (Sunyer *et al*, 2000) for analytical approach). PM_{10}, NO_2, O_3, and CO were analyzed.	PM_{10}, but not gaseous pollutants, was associated with mortality for all causes. In the two-pollutant models, the PM_{10}-mortality associations were not diminished, whereas those with gaseous pollutants were.	Percent excess risk for all cause mortality per 27 μg/m^3 (IQR) PM_{10} on the same-day was 11% (0, 24). In two pollutant models, the PM_{10} excess risks were 10.5%, 12.9%, and 10.8% with NO_2, O_3, and CO, respectively.

TABLE II – SHORT-TERM PARTICULATE MATTER EXPOSURE AND CARDIOVASCULAR HOSPITAL ADMISSIONS (Derived from EPA TABLE 8B-1).

Reference, Location, Years, PM Index, Mean or Median (μg/m^3).	Study Description. Modeling methods: lags, smoothing, co-pollutants and covariates.	Results and Comments.	PM Index, lag, percent excess risk% (95% LCL, UCL)
APHEA2			
Le Tertre et al. (2002a) (Le Tertre *et al*, 2002a) Eight-City - APHEA 2 Study mean (SD) PM_{10} Barcelona - 1/94-12/96 55.7 (18.4) Birmingham - 3/92-12/94 24.8 (13.1) London - 1/92-12/94 28.4 (12.3) Milan - No PM_{10} Netherlands - 1/92-9/95 39.5 (19.9) Paris - 1/92-9/96 PM_{13} - 22.7 (10.8) Rome - No PM_{10} Stockholm - 3/94-12/96 15.5 (7.2).	This study examined the association between PM_{10} and other co-pollutants, and hospital admissions for cardiac causes in eight European cities with a combined population of 38 million. Authors examined age factors and IHD and studies also stratified by age using autoregressive Poisson models controlled for long-term trends, season, influenza, epidemics, and meteorology, as well as confounding by other pollutants.	A significant effect of PM_{10} and BS on admissions for cardiac causes (all ages) and cardiac causes and IHD for people over 65 years was found. The impact of PM_{10} per unit of pollution was half that found in the United States. PM_{10} did not seem to be confounded by O_3 or SO_2. The effect was reduced when CO was incorporated in the regression model and eliminated when controlling for NO_2. There was little evidence of an impact of particles on hospital admissions for IHD for people below 65 years or stroke for people over 65 years. The authors state results were consistent with a role for traffic exhaust/diesel in Europe.	For a 10 μg/m^3 increase in PM_{10} Cardiac admissions/all ages 0.5% (0.2, 0.8) Cardiac admissions/over 65 years 0.7% (0.4, 1.0) IHD/over 65 years 0.8% (0.3, 1.2) For cardiac admissions for people over 65 years: All the city-specific estimates were positive with London, Milan, and Stockholm significant at the 5% level.

HEAPSS			
Lanki et al. (2006) (Lanki *et al*, 2006) HEAPSS Study: Five European cities, 1992-2000. PM_{10}; PNC ($1/cm^3$) median daily concentration: Augsburg, Germany, 95-99: 43.5; 12,400 Barcelona, Spain, 92-95: 57.4; 76,300 Helsinki, Finland, 93-99: 21.0; 13,600 Rome, Italy, 98-2000: 48.5; 46,000 Stockholm, Sweden, 94-99: 12.5; 11,800.	This study examined the association between measures of daily concentration of PM_{10}, PNC (as a proxy for ultrafine particles), other co-pollutants (CO, NO_2, O_3), and hospital admissions for first AMI in five European cities. AMI registers (Augsburg and Barcelona) or hospital discharge registers (HDR) (Helsinki, Rome and Stockholm) were used. During the study period no direct measurement of PNC was available. City-specific models for estimating PNC from other pollutants and meteorological variables were developed for the period when PNC was measured, and applied then retrospectively to predict daily PNC concentrations during the study period. GAM models were used after a stepwise selection of covariates. The starting model included time trend, apparent temperature, day of week, holiday, population reduction, temperature and barometric pressure. Lag 0, lag 1, lag 2 and lag 3 were considered.	During the study period, 26,854 individuals were hospitalised for AMI. The number of admissions was higher in the centres where HDRs were used compared with centres with AMI registers. When considering all five cities, the same day PNC and PM_{10} were not significantly associated to hospitalisation. Limiting analyses to cities with HDR, the same day PNC showed an excess risk of hospitalisation. No specific pattern of risk was seen considering lags 1-3. Similar associations as for PNC were found for CO, but no excess risk was found for NO_2 and O_3. In the 3 cities with HDR, the most consistent associations were shown among fatal cases aged <75 years. Effects of measures of concentration of PM were more pronounced for fatal cases aged <75 years.	Percent Excess Risk of hospitalisation for AMI (95% CI): Pooled effects (five cities) computed for 10 $\mu g/m^3$ change in PM_{10}: Lag 0: 0.3% (-0.5, 1.1) Lag 1: 0.1% (-1.0, 1.1) Lag 2: 0.2% (-0.6, 1.0) Lag 3: 0.2% (-0.9, 1.3) cities with HDR; lag 0: Overall: 0.3% (-0.6, 1.2) Non-fatal, Age <75: -0.3% (-1.4, 0.8) Fatal, Age <75: 3.1% (0.0, 6.4) Non-fatal, Age 75+: 1.2% (-0.5, 2.9) Fatal, Age 75+: 0.9% (-1.5, 3.4) Pooled effects (five cities) computed for 10,000/cm^3 change in PNC: Lag 0: 0.5% (-0.4, 1.5) Lag 1: -0.3% (-1.8, 1.2) Lag 2: -0.1% (-1.0, 0.8) Lag 3: -0.2% (-2.1, 1.7) cities with HDR; lag 0: Overall: 1.3% (0.0, 2.6) Non-fatal, Age <75: 0.1% (-2.5, 1.7) Fatal, Age <75: 5.0% (0.0, 10.1) Non-fatal, Age 75+: 3.2% (0.8, 5.6) Fatal, Age 75+: 1.6% (-2.2, 5.5).

von Klot. (2005) (von Klot *et al*, 2005) HEAPSS Study: Five European cities, 1992-2001. PM_{10}; PNC (1/cm^3) mean daily concentration: Augsburg, Germany, 95-2000: 44.7; 13,504 Barcelona, Spain, 92-2000: 52.2; 76,593 Helsinki, Finland, 93-2000: 25.3; 14,283 Rome, Italy, 98-2001: 51.1; 49,195 Stockholm, Sweden, 94-2000: 14.6; 12,553.	22,006 survivors of a first diagnosis of AMI were recruited in 5 European cities and followed for hospital readmissions. Daily concentration of PM_{10} and other co-pollutants (CO, NO_2, O_3) was measured and PNC was estimated as a proxy for ultrafine particles. Short-term effects of air pollution on hospital readmissions for AMI, angina pectoris, and cardiac causes (myocardial infarction, angina pectoris, dysrhythmia, or heart failure) were studied in city-specific Poisson regression analyses with subsequent pooling. Potential confounders were selected through penalized regression splines of trend (to control for long-term trends, seasonality, and changes in the baseline rate) and meteorology (daily temperature, relative humidity, air pressure, and the difference between current day temperature and the mean temperature of the previous 3 days), as well as indicators of day of week, vacation periods, or holidays. Trend and one temperature term remained in the model. Lag 0, 1, 2, 3 were considered. Given the results obtained, the effects of lag 0 air pollution concentrations were shown.	During follow-up, 6,655 cardiac readmissions were observed. Cardiac readmissions increased in association with same-day concentrations of PM_{10} and PNC. No associations were found considering lags 1-3. Effects of similar strength were observed for CO, NO_2 and O_3.	Pooled effects computed for 10 µg/m^3 change in PM_{10}: AMI: 2.6% (-0.5, 5.8) Angina pectoris: 0.8% (-1.4, 3.2) Cardiac readmission: 2.1% (0.4, 3.9) Pooled effects computed for 10,000/cm^3 change in PNC: AMI: 3.9% (-0.2, 8.2) Angina pectoris: 2.0% (-0.8, 4.8) Cardiac readmission: 2.6% (0.5, 4.8).

Subnational studies			
GREAT BRITAIN			
Atkinson et al. (1999b) (Atkinson *et al*, 1999b) Greater London, England 1992-1994. Pollutant: mean, median, 90-10 percentile range: PM_{10}: 28.5, 24.8, 30.7 BS: 12.7, 10.8, 16.1.	Daily emergency hospital admissions for total CVD (ICD9: 390-459), and IHD (ICD9: 410-414), for all ages, for persons less than 65, and for persons 65 and older. Mean daily admissions for CVD: 172.5 all ages, 54.5 <65, 117.8 ≥ 65; for IHD: 24.5 <65, 37.6 ≥ 65. Covariates: NO_2, O_3, SO_2, CO, temperature, relative humidity. Poisson regression using APHEA methodology; sine and cosine functions for seasonal control; day of week dummy variables. Lags 0-3, as well as corresponding multi-day averages ending on lag 0, were considered.	In single-pollutant models, both PM metrics showed positive associations with both CVD and IHD admissions across age groups. In Two- pollutant models, the BS effect, but not the PM_{10} effect, was robust. No quantitative results provided for two-pollutant models. This study does not support a PM_{10} effect independent of co-pollutants.	Effects computed for 50 µg/m^3 PM_{10} and 25 µg/m^3 BS PM_{10} (lag 0): All ages: CVD: 3.2% (0.9, 5.5) 0- 64 years: CVD: 5.6% (2.0, 9.4) IHD: 6.8% (1.3, 12.7) 65+ years: CVD: 2.5% (-0.2, 5.3) IHD: 5.0% (0.8, 9.3) BS (lag 0): All ages: CVD: 2.95% (1.00, 4.94) 0-64 years: CVD: 3.12% (0.05, 6.29) IHD: 2.78% (- 1.88, 7.63) 65+ years: CVD: 4.24% (1.89, 6.64) IHD (lag 3): 4.57% (0.86, 8.42).
Prescott et al. (1998) (Prescott *et al*, 1998) Edinburgh, Scotland 1981-1995 (BS and SO_2) 1992-1995 (PM_{10}, NO_2, O_3, CO) Means for long and short series: BS: 12.3, 8.7 PM_{10}: NA, 20.7.	Daily emergency hospital admissions for CVD (ICD9: 410-414, 426-429, 434-440) for persons less than 65 years and for persons 65 or older. Separate analyses presented for long (1981-1995) and short (1992-1995) series. Mean hospital admissions for long and short series: <65, 3.5, 3.4; 65+, 8.0, 8.7. Covariates: SO_2, NO_2, O_3, CO, wind speed, temperature, rainfall. PM_{10} measured by TEOM. Poisson log-linear regression; trend and seasons controlled by monthly dummy variables over entire series; day of week dummy variables; min daily temperature modeled using octile dummies. Pollutants expressed as cumulative lag 1-3 day moving avg.	In long series, neither BS nor NO_2 were associated with CVD admissions in either age group. In the short series, only 3-day moving average PM_{10} was positively and significantly associated with CVD admissions in single- pollutant models, and only for persons 65 or older. BS, SO_2, and CO also showed positive associations in this subset, but were not significant at the 0.05 level. The PM_{10} effect remained largely unchanged when all other pollutants were added to the model, however quantitative results were not given. Results appear to show an effect of PM_{10} independent of co-pollutants.	Percent Excess Risk (95% CI): Effects computed for 50 µg/m^3 change in PM_{10} and 25 µg/m^3 change in BS. Long series: BS, lag 1-3: <65: -0.5% (-5.4, 4.6) 65+: -0.5% (-3.8, 2.9) Short series: BS, lag 1-3: <65: -9.5% (-24.6, 8.0) 65+: 5.8% (-4.9, 17.8) PM_{10}, lag 1-3: <65: 2.0% (- 12.5, 19.0) 65+: 12.4% (4.6, 20.9).

Wong et al. (2002) (Wong *et al*, 2002) London, UK, 1992-1994. mean daily concentration of PM_{10}: 28.5.	The present study examined the relation between PM_{10} and other co-pollutants (NO_2, SO_2 and O_3), and daily admission for cardiac diseases (ICD9: 390-429) and IHD (ICD9: 410-414) in the city of London. The same analyses were performed for the city of Hong Kong (findings not shown in the present report). Poisson regression was used adjusting for non-parametric smooth functions of time, temperature, humidity, influenza epidemics, day of the week, holidays and seasons. An *a priori* lag 0-1 was used. Estimates for the best single day lag (0, 1, 2, 3) were also shown. The excess risks of hospitalisation were also shown after mutual adjustment for each single co-pollutant.	PM_{10} significantly increased the hospitalisation for cardiac diseases and IHD, particularly in cold seasons, even after further adjustment for O_3. When adjusting for NO_2 and SO_2, no excess admissions for cardiac diseases were found with PM_{10}. SO_2 and NO_2 increased and O_3 decreased cardiac hospital admission. Remarkably similar associations were found in Hong Kong.	Percent excess risk for an increment of PM_{10} by 10 µg/m^3: Cardiac diseases, all ages, lag 0-1: 0.8% (0.3, 1.4) Warm seasons: 0.1% (-0.7, 1.0) Cold seasons: 1.2% (0.5, 2.0) Adjusted for NO_2: 0.2% (-0.6, 1.0) Adjusted for O_3: 0.8% (0.3, 1.3) Adjusted for SO_2: -0.2% (-1.1, 0.4) IHD, all ages, lag 0-1: 0.9% (0.1, 1.6) Warm seasons: 0.1% (-1.1, 1.4) Cold seasons: 1.3% (0.3, 2.3)
Wordley et al. (1997) (Wordley *et al*, 1997) Birmingham, UK, 4/1/92-3/31/94. PM_{10} mean, min, max: 26, 3, 131.	Daily hospital admissions for IHD (ICD9: 410-429) for all ages. Mean hospitalizations: 25.6/day. Covariates: temperature and relative humidity. Linear regression was used after adjustment for day of week and monthly dummy variables, linear trend term. Lags of 0-3 considered, as well as the mean of lags 0-2.	No statistically significant effects were observed for PM_{10} on IHD admissions for any lag. Note that PM_{10} was associated with respiratory admissions and with cardiovascular mortality in the same study (results not shown here).	Percent change per 50 µg/m^3 change PM_{10} IHD admissions: lag 0: 1.4% (-4.4, 7.2) lag 1:-1.3% (-7.1, 4.4).

Anderson et al. (2001) (Anderson *et al*, 2001) West Midland, England (October 1994-December 1996) Population: 2.3 million PM_{10} mean: 23.3 $PM_{2.5}$ mean: 14.5 $PM_{10-2.5}$: 9.0.	Cardiovascular hospital admissions (ICD9: 390-459) related to PM_{10}, $PM_{2.5}$, $PM_{10-2.5}$, BS, sulfate, NO_2, O_3, SO_2, CO. GLM regression with quasi- likelihood approach, controlling for seasonal patterns, temperature, humidity, influenza episodes, day of the week. Adjusted for residual serial correlation and over-dispersion. Cardiac disease (ICD9: 390-429), IHD (considered for age ≥65 years, ICD9: 410-414) and stroke (considered for age ≥65 years ICD9: 430-438) were considered as subdiagnoses.	Hospital admissions (all ages) for CVD, cardiac disease and IHD were not associated with any considered pollutant. An inverse association between $PM_{10-2.5}$ and admission for stroke was found. The only significant seasonal interaction was for BS, which showed a positive association in the warm season.	CVD hospital admission; lag 0-1; PM_{10} Increment 10-90% (11.4-38.3 µg/m^3): All CVD: -0.6 (-2.5, 1.3) Cardiac: 0.3 (-1.8, 2.4) IHD: 2.1 (-2.0, 6.3) Stroke: -3.3 (-7.9, 1.4) $PM_{2.5}$ (6.0-25.8 µg/m^3) All CVD: -0.5 (-2.6, 1.6) Cardiac: -0.4 (-2.8, 2.2) IHD: -0.3 (-4.5, 4.2) Stroke: -1.6 (-6.6, 3.6) $PM_{10-2.5}$ (4.1-15.2 µg/m^3) All CVD: -0.7 (-3.7, 2.3) Cardiac: -0.9 (-4.3, 2.7) IHD: 1.1 (-4.1, 6.6) Stroke: -8.2 (-13.9, -2.2) BS (5.1-23.6 µg/m^3) All CVD: 1.0 (-1.0, 3.1) Cardiac: 1.7 (-0.6, 3.9) IHD: 2.0 (-2.3, 6.4) Stroke: -2.7 (-7.6, -2.4).
NORWAY			
Mannsaker (2004) (Mannsaker *et al*, 2004) Trondheim, Norway, 1993-2001. median daily concentration: PM_{10} 39.3; $PM_{2.5}$ 13.2.	This study compared the mean daily number of admissions for CVD to the St. Olav University hospital in the city of Trondheim, on days with relatively low and high levels of PM_{10}, $PM_{2,5}$, and other co-pollutants, including NO, NO_2, SO_2, O_3. A time series analysis was carried out to see how day-to-day variations in concentrations of air pollutants correlated with the number of admissions for cardiovascular disease.	Time series analysis did not show any statistically significant correlation between day-to-day variations in air pollution and hospital admissions for cardiovascular disease. The mean daily number of hospitalizations was found to be significantly higher on days with high levels of NO and NO_2, but not with other pollutants.	No risk shown.

GERMANY			
Wichmann et al (2004) (Wichmann, 2004) Rhine-Ruhr area, Germany, 1985, single episode. TSP during the episode in Rhine-Ruhr area: ~ 600.	In January 1985 an extended smog episode occurred in Central Europe together with very low temperatures. This paper reviews the health effects, including CVD admission, investigated during the smog period and a control period before and after the smog episode. The Rhine-Ruhr area (Western Germany) was affected for 5 days with maximum concentration of TSP of 600 µg/m^3 (24 h averages). In Augsburg (Southern Germany) the smog episode was less severe (100 µg/m^3 TSP, 24 h averages).	Rhine-Ruhr hospital admissions increased by 57% for cerebral circulation failure, by 30% for coronary insufficiency, by 19% for CVD, by 14% for heart insufficiency and by 10% for AMI.	No risk shown.
Peters et al (2004) (Peters *et al*, 2004) Augsburg, Germany, 1999-2001. No information on PM.	This is a case-crossover study in which 691 cases of non-fatal myocardial AMI were identified in the Augsburg Myocardial Infarction Registry in Augsburg, between February 1999 and July 2001. Cases provided information on factors that may have triggered the myocardial infarction. Data on subjects' activities during the four days preceding the onset of symptoms were collected with the use of patient diaries. Conditional logistic regression models were used to estimate the association between transient exposure to traffic and the risk of AMI. The "control period" of exposure was defined as an exposure to traffic by the same subject 24 to 71 hours before the hour of the onset of the AMI. Only subjects for whom there were discordant sets of data on exposure were included in the analyses.	An association was found between exposure to traffic and the onset of an AMI within one hour afterward (OR=2.92; 95% CI: 2.22-3.83). The time the subjects spent in cars, on public transportation, or on motorcycles or bicycles was consistently linked with an increased risk of AMI.	No data on PM

FRANCE			
Eilstein et al (2004) (Eilstein *et al*, 2004) Nine French cities, 1995-1999. No data distribution was reported.	This study examined the short term effects of PM_{10}, BS and other co-pollutants (CO, NO_2, SO_2, O_3) on mortality and hospitalisation for cardiovascular (and respiratory) disorders in nine French cities (Bordeaux, Le Havre, Lille, Lyon, Marseille, Paris, Rouen, Strasbourg and Toulouse) of the Surveillance Air et Sante program. The analysis assessed the city-specific and combined associations with various pollutants using Poisson GAM, after adjusting for trends in seasons, day of week, holidays, influenza epidemics, temperature and humidity. A combined RR was calculated for all the cities. Lag 0-1 and lag 0-5 were used.	Neither PM_{10} nor BS showed significant excess admission for CVD.	CVD admission, effects computed for 10 µg/m^3 change in exposition: Lag 0-1 PM_{10}; age 15-64: 0.0% NS PM_{10}; age 65+: 0.1% NS Lag 0-5 PM_{10}; age 15-64: 0.0% NS PM_{10}; age 65+: 0.7% NS Lag 0-1 BS; age 15-64: 0.4% NS BS; age 65+: 0.3% NS Lag 0-5 BS; age 15-64: 0.6% NS BS; age 65+: 0.3% NS
ITALY			
Biggeri et al. (2005) (Biggeri *et al*, 2005) Eight cities of North, Centre and South of Italy 1990-1999. PM_{10} mean daily concentration: Turin, 91-94: 77.6 Turin, 95-98: 63.8 Milan, 90-94: 61.8 Milan, 95-97: 45.2 Verona, 95-99: 36.5 Ravenna, 91-95: 59.1 Bologna, 96-98: 41.2 Florence, 96-98: 40.3 Rome, 92-94: 69.7 Palermo, 97-99: 42.9.	Meta-analysis of short-term effects of air pollution on mortality and hospital admission (cardiac causes – ICD9: 390-459-, and respiratory causes) in eight Italian cities from 1990 to 1999. Daily concentrations of pollutants were collected. A generalized linear model was used after adjustment for age, day of the week, holidays, influenza epidemics, meteorological variables, and seasonality pattern was fitted for PM_{10} and other co-pollutant (SO_2, NO_2, CO, and O_3). City-specific and fixed- and random-effects pooled estimates were shown. Lag 0-3 was used for hospital admission.	A significant direct association was found between PM_{10} and cardiac hospital admission. The other considered co-pollutants, with the exception of O_3, showed stronger associations. The excess risks were modified by deprivation score and by the NO_2/PM_{10} ratio.	Cardiac hospital admission, effects computed for 10 µg/m^3 change in PM_{10} (lag 0-3): Fixed-effects: 0.77% (0.40, 1.15) Random-effects: 0.82% (0.32, 1.32).

D'Ippoliti (2003) (D'Ippoliti *et al*, 2003) Rome, Italy, 1995-1997. TSP mean daily concentration from 5 monitors (SD): 66.9 (19.7).	A case-crossover analysis was conducted to evaluate the relation between TSP and other co-pollutants (SO_2, CO, NO_2) and hospital admission for a first episode of acute AMI (ICD9: 410). In the period of observation 6,531 subjects residing in Rome were hospitalized for AMI. A time-stratified case-crossover design was considered, using as control days the same day of the week as the myocardial infarction occurred, in other weeks of the month. ORs were derived by conditional logistic regression models after allowance for temperature and humidity. An *a priori* lag 0-2 was used. Estimates for lags 0, 1, 2, 3, and 4 were also shown.	Positive associations were found for total suspended particulate, NO_2 and CO. The strongest and most consistent effect was found for TSP, in particular during the warm season, among the elderly and among people with heart conduction disturbances.	Percent excess risk (95% CI) for an increment of TSP by 10 µg/m^3; Lag 0: 2.3 (0.4, 4.2) Lag 1: 1.5 (-0.4, 3.4) Lag 2: 1.7 (-0.1, 3.5) Lag 3: -0.9 (-2.6, 0.3 Lag 4: 0.1 (-1.3, 1.6) Lag 0-2: Overall: 2.8 (0.5, 5.2) Males: 2.3 (-0.5, 5.1) Females: 3.9 (0.0, 8.0) Age 18-64: 1.3 (-2.2, 4.8) Age 65-74: 3.2 (-1.0, 7.6) Age 75+: 4.6 (0.5, 8.9) Cold period: 1.8 (-1.1, 4.7) Warm period: 4.6 (0.8, 8.7).
Stafoggia et al. (2005) (Stafoggia *et al*, 2005) Rome, Italy, 1998-2000. PM_{10}; PNC (no/cm^3) mean daily concentration: 52.1; 51,669, respectively.	The study examined the relationship between PM_{10}, PNC and other co-pollutants (CO, NO_2, SO_2 and O_3) and coronary events for residents in Rome, considering both out-of-hospital deaths and hospitalisations. Generalised additive models adjusted by temporal trend, temperature, humidity, day of week, holidays, and population reduction in summer months were used. Lags 0, 1, 0-1 and 0-4 were considered.	A significant excess risk of hospital admission for coronary events was found with same-day PNC and CO. No association was found with same-day PM_{10}, NO_2, SO_2 and O_3. The associations with PNC and CO were stronger for elderly subjects.	Percent excess risk (95% CI) for an increment of PM_{10} by 29.7 µg/m^3 (IQR) Lag 0: 0.9 (-2.3, 4.2) Lag 1: -1.2 (-4.4, 2.2) Lag 0-1: 0.3 (-3.2, 4.0) Lag 0-4: -2.0 (-6.5, 2.6) Lag 0; age 35-65: -2.5 (-7.2, 2.4) Lag 0; age 65-74: 1.5 (-4.2, 7.6) Lag 0; age 75+: 3.2 (-2.4, 9.2) Percent excess risk (95% CI) for an increment of PNC by 28,001 no/cm^3 (IQR) Lag 0: 4.0 (0.1, 8.1) Lag 1: 0.4 (-3.5, 4.4) Lag 0-1: 2.8 (-1.6, 7.4) Lag 0-4: 0.2 (-4.7, 5.5) Lag 0; age 35-65: 2.4 (-3.5, 8.6) Lag 0; age 65-74: -0.2 (-6.9, 6.9) Lag 0; age 75+: 9.0 (2.2, 16.2).

SPAIN			
Díaz et al. (1999) (Diaz *et al*, 1999) Madrid, Spain, 1994-1996 TSP by beta attenuation. Summary statistics not given.	Daily emergency hospital admissions for all cardiovascular causes (ICD9: 390-459) for the Gregorio Maranon University Teaching Hospital. Mean admissions: 9.8/day. Covariates: SO_2, NO_2, O_3, temperature, pressure, relative humidity, excess sunlight. Box-Jenkins time-series methods were used to remove autocorrelations, followed by cross- correlation analysis; sine and cosine terms for seasonality; details unclear.	No significant effects of TSP on CVD reported.	No quantitative results presented for PM.
Llorca et al. (2005) (Llorca *et al*, 2005) Torrelavega, Spain, 1992-1995. No data distribution was reported.	This study analysed the relations between TSP and other co-pollutants (NO, NO_2, SO_2 and hydrogen sulfide), and emergency admissions for cardiac disease (ICD9: 390-459) in Torrelavega (60,000 inhabitants). RRs were estimated for each pollutant by Poisson regression adjusted for influenza, day of week, wind speed, wind and temperature. Lag 0 was apparently used.	A significant inverse association was found between TSP and admission for cardiac diseases; hydrogen sulfide decreased and NO_x increased the risk of cardiac admissions. After mutual adjustment for the other considered co-pollutants, no association emerged.	Percent excess risk for an increment of TSP by 10 µg/m^3. After adjustment for meteorological factors, day and influenza: -1.2 (-1.9, -0.5) After further adjustment for all the co-pollutants considered: 0.2 (-0.8, 1.2).

TABLE III – SHORT-TERM PARTICULATE MATTER EXPOSURE AND RESPIRATORY HOSPITAL ADMISSIONS (Derived from EPA TABLE 8B-2).

Reference, Location, Years, PM Index, Mean or Median (µg/m^3).	Study Description. Modeling methods: lags, smoothing, co-pollutants and covariates.	Results and Comments.	PM Index, lag, percent excess risk% (95% LCL, UCL)
APHEA 1			
Sunyer et al. (1997) (Sunyer *et al*, 1997) Barcelona (86 - 92) BS Median: 40 BS Range: 11-258 Helsinki (86 - 92) BS Median: - BS Range: - Paris (86 - 92) BS Median: 28 BS Range: 4-186 London (86 - 92) BS Median: 13 BS Range: 3-95.	This study examined the relation between BS, SO_2, NO_2, and O_3, and daily counts of hospital admissions for asthma and emergency visits in adults (ages 15-64 years: mean/day = 3.9 (B); 0.7 (H); 13.1 (L); 7.3 (P)) and children (ages < 15 years: mean/day = 0.9 (H); 19.8 (L); 4.6 (P)). Asthma (ICD9: 493) was studied in each city, but the outcome examined differed across cities: ED visits in Barcelona; emergency hospital asthma admissions in London and Helsinki, and total asthma admissions in Paris. Estimates from all cities obtained for entire period and also by warm or cold seasons, using time-series GLM regression, controlling for temperature and RH, viral epidemics, day of week effects, and seasonal and secular trends applied using the APHEA study approach.	Daily admissions for asthma in adults increased significantly with increasing ambient levels of NO_2, and positively (but non-significantly) with BS. The association between asthma admissions and pollution varied across cities, likely due to differing asthma outcomes considered. In children, daily admissions increased significantly with SO_2 and positively (but non-significantly) with BS and NO_2, though the latter only in cold seasons. No association was observed in children for O_3. Authors concluded that "In addition to particles, NO_2 and SO_2 (by themselves or as a constituent of a pollution mixture) may be important in asthma exacerbations".	Excess risk per 25 µg/m^3 BS (24 h Average) Asthma Admissions/Visits: <15 years.: London: 1.5% (lg 0d) Paris: 1.5% (lg 2d) Total: 1.5% (-1.1, 4.1) 15-64 years: Barcelona: 1.8% (lg 3d) London: 1.7% (lg 0d) Paris: 0.6% (lg 0d) Total: 1.0% (-0.8, 2.9) Two Pollutant (per 25 µg/m^3 BS) Asthma Admissions (24 h Avg) <15 years, (BS & NO_2): London: 0.6% (lg 0d) Paris: 2.9% (lg 2d) Total: 1.8% (-0.6, 4.3) <15 years, (BS & SO_2): London: -1.1% (lg 0d) Paris: -1.4% (lg 2d) Total: -1.3 (-5.0, 2.5) 15-64 years, (BS & NO_2): Barcelona: 1.5% (lg 0d) London: -4.7% (lg 0d) Paris: -0.7% (lg 1d) Total: -0.5% (-5.1, 4.4).

APHEA 2			
Atkinson et al. (2001) (Atkinson *et al*, 2001) Eight European cities Median/range Barcelona 1/94 - 12/96 PM_{10} 53.3 (17.1, 131.7) Birmingham 3/92 -12/94 PM_{10} 21.5 (6.5, 115) London 1/92 - 12/94 PM_{10} 24.9 (7.2, 80.4) Milan -No PM_{10} (TSP) Netherlands 1/92 - 9/95 PM_{10} 33.4 (11.3, 130.8) Paris 1/92 - 9/96 PM_{13} 20.1 (5.8, 80.9) Rome - No PM_{10} (TSP) Stockholm 3/94 - 12/96 PM_{10} 13.6 (4.3, 43.3).	As part of the APHEA 2 project, association between PM_{10} and daily counts of emergency hospital admissions for Asthma (0-14 and 15-64 years), COPD and all-respiratory disease (65+ years) regressed using GAM, controlling for environmental factors and temporal patterns.	This study reports that PM was associated with daily admissions for respiratory disease in a selection of European cities. Average daily ozone levels explained a large proportion of the between-city variability in the size of the particle effect estimates in the over 65 year age group. In children, the particle effects were confounded with NO_2 on a day-to-day basis.	For 10 µg/m^3 increase Asthma Admission Age 0-14 years: PM_{10} for cities ranged from -0.9% (-2.1, 0.4) to 2.8% (0.8, 4.8) with an overall effect estimate of 1.2% (0.2, 2.3) Asthma Admission Age 15-64 years: Overall PM 1.1% (0.3, 1.8) Admission of COPD and Asthma Age 65+ years: Overall PM 1.0% (0.4, 1.5) Admission All Respiratory Disease Age 65+ years: Overall PM 0.9% (0.6, 1.3).
Subnational studies			
GREAT BRITAIN			
Atkinson et al. (1999a) (Atkinson *et al*, 1999a) London (92 - 94) Population: 7.2 MM PM_{10} Mean: 28.5 10^{th}-90^{th} IQR: 15.8-46.5 BS mean: 12.7 10^{th}-90^{th} IQR: 5.5-21.6	All-age respiratory (mean=150.6/day), all-age asthma (38.7/day), COPD plus asthma in adults >64 years (22.9/day), and lower respiratory (64.1/day) in adults >64 years (16.7/day) hospital admissions in London hospitals were considered. Counts for ages 0-14, 15-64, and >64 years were also examined. Poisson GLM regression was used, controlling for season, day of week, meteorology, autocorrelation, overdispersion, and influenza epidemics.	Positive associations were found between respiratory- related emergency hospital admissions and PM_{10} and SO_2, but not for O_3 or BS. When SO_2 and PM_{10} were included simultaneously, size and significance of each was reduced. Authors concluded that SO_2 and PM_{10} are both indicators of the same pollutant mix in this city. SO_2 and PM_{10} analyses by temperature tertile suggest that warm season effects dominate. Overall, results consistent with earlier analyses for London, and comparable with those for North America and Europe.	PM_{10} (50 µg/m^3), no co-pollutant. All Respiratory Admissions: All age (lag 1d): 4.9% (CI: 1.8, 8.1) 0-14 (lag 1d): 8.1% (CI: 3.5, 12.9) 15-64 (lag 2d): 6.9% (CI: 2.1, 12.9) 65+ (lag 3d): 4.9% (CI: 0.8, 9.3) Asthma Admissions: All age (lag 3d): 3.4% (CI: -1.8, 8.9) 0-14 (lag 3d): 5.4% (CI: -1.2, 12.5) 15-64 (lag 3d): 9.4% (CI: 1.1, 18.5) 65+ (lag 0d): 12% (CI: -1.8, 27.7) COPD & Asthma Admissions (65+; lag 3): 8.6% (CI: 2.6, 15) Lower Respiratory Admissions (65+; lag 3d): 7.6% (CI: 0.9, 14.8).

Anderson et al. (1998) (Anderson *et al*, 1998) London, 1987-1992) Population: 7.2 MM BS daily mean: 14.6 BS 25-75th IQR: 24-38.	Poisson GLM log-linear regression was used to estimate the RR of London daily asthma hospital admissions associated with changes in O_3, SO_2, NO_2 and particles (BS) for all ages and for 0-14 years (mean=19.5/day), 15-64 years (mean=13.1/day) and 65 + years (mean =2.6/day). Analysis was controlled for time trends, seasonal factors, calendar effects, influenza epidemics, RH, temperature, and auto-correlation. Interactions with co-pollutants and aeroallergens were tested via 2 pollutant models and models with pollen counts (grass, oak and birch).	Daily hospital admissions for asthma were found to have associations with O_3, SO_2, NO_2, and BS, but there was lack of consistency across the age groups in the specific pollutant. BS association was strongest in the 65 + group, especially in winter. Pollens were not consistently associated with hospital admission for asthma, sometimes being positive, sometimes negative. Air pollution associations with hospital admissions were not explained by airborne pollens in simultaneous regressions, and there was no consistent pollen-pollutant interaction.	Asthma Admissions. BS=25 µg/m^3 BS Lag 0-3. All age: 5.98% (0.4, 11.9) <15: 2.2% (-4.6, 9.5) 15-64: 1.2% (-5.3, 8.1) 65+: 22.8% (6.1, 42.5) BS=50 µg/m^3, lag 2 & co-pollutant: Older Adult (>64 years.) Asthma Visits: BS alone: 14.6% (2.7, 27.8) & O_3: 20.0% (3.0, 39.8) & NO_2: 7.4% (-8.7, 26.5) SO_2: 11.8% (-2.2, 27.8).
Wong et al. (2002) (Wong *et al*, 2002) London, UK, 1992-1994. mean daily concentration: of PM_{10}: 28.5.	The present study examined the relation between PM_{10} and other co-pollutants (NO_2, SO_2 and O_3), and daily admission for asthma (ICD9: 493) for ages 15-64 years, and respiratory diseases (ICD9: 460-519) for ages 65+ years in the city of London. The same analyses were performed for the city of Hong Kong (findings not shown in the present report). Poisson regression was used controlling for non-parametric smooth functions of time, temperature, humidity, influenza epidemics, day of the week, holidays and seasons. An *a priori* average lag 0-1 was used. Estimates for the best single day lag (0, 1, 2, 3) were also shown. The excess risks of hospitalisation were also shown after mutual adjustment for each single co-pollutant.	No significant associations have been shown between PM_{10} and hospital admission for asthma (15-64 years) and respiratory diseases (age 65+), even after allowance for other co-pollutants, although excess risks were systematically over zero. In warm seasons, the direct association reached statistical significance. When considering the best single lag day, a significant association was found between PM_{10} and admission for both asthma and respiratory diseases. NO_2 increased the admission for asthma and O_3 the one of respiratory diseases.	Percent excess risk (95% CI) for an increment of PM_{10} by 10 µg/m^3; Respiratory diseases, age 65+, lag 0-1: 0.4% (-0.3, 1.2) Warm seasons: 1.8% (0.5, 3.1) Cold seasons: -0.5% (-1.5, 0.5) Adjusted for NO_2: 0.9% (-0.3, 2.0) Adjusted for O_3: 0.4% (-0.3, 1.2) Adjusted for SO_2: 0.7% (-0.5, 1.8) Lag 3 (best lag): 1.5% (0.8-2.2) Asthma, age 15-64, lag 0-1: 1.4% (-0.1, 3.0) Warm seasons: 0.6% (-1.9, 3.1) Cold seasons: 1.6% (-1.5, 0.5) Lag 2 (best lag): 2.2% (0.8-3.6).

Ponce de Leon et al. (1996) (Ponce de Leon *et al*, 1996) London, 4/1987-2/1992. Population: 7.3 million BS mean.:14.6 BS 5^{th}-95^{th} %=6 – 27.	Poisson GLM log-linear regression analysis of daily counts of hospital admissions (means/day: all ages=125.7; Ages 0-14=45.4; Ages 15-64=33.6; Ages 65+=46.7). Effects of trend, season and other cyclical factors, day of the week, holidays, influenza epidemic, temperature, humidity, and autocorrelation were addressed. However, temperature modeled as linear, with no RH interaction. Pollution variables were BS, SO_2, O_3, and NO_2, lagged 0-3 days.	O_3 associated with increase in daily hospital admission, especially in the "warm" season. However, U-shape of the O_3 dose-response suggests that linear temperature control was not adequate. Few significant associations were found with other pollutants, but these tended to be positive (especially in cold season, Oct-March, and for older individuals for BS).	Respiratory hospital admission (all ages); BS: 25 µg/m^3: Single Pollutant Models Oct-Mar; Lag 1: 0.2% (–1.9, 2.3) Apr-Sep; Lag 1: -2.7% (-6.0, 0.8) Respiratory hospital admissions (>65) Single Pollutant Models; BS: 25 µg/m^3 Oct-Mar; Lag 2: 1.2% (-2.1, 4.5) Apr-Sep; Lag 2:: 4.5% (-1.0, 10.4).
Wordley et al. (1997) (Wordley *et al*, 1997) Birmingham, UK, 4/1992 –3/1994. PM_{10} daily values: Mean: 25.6 range: 2.8, 130.9 PM_{10} 3 day mean: Mean: 25.5 range: 7.3, 104.7.	Relation between PM_{10} and total hospital admission for respiratory (mean = 21.8/day), asthma (mean=6.2/day), bronchitis (mean=2.4/day), pneumonia (mean=3.4/day), and COPD (mean=3.2/day) was analyzed, using log-linear regression after adjustment for day of week, month, linear trend, RH, and temperature (but not temperature-RH interaction).	PM_{10} positively associated with all hospital admissions for respiratory, asthma, bronchitis, pneumonia, and COPD. Pneumonia, all respiratory, and asthma hospital admissions also significantly positively associated with the mean of PM_{10} over the past three days, which gave 10 to 20% greater RR's per 10 µg/m^3, as expected given smaller day to day deviations. Other air pollutants were examined but not presented, as "these did not have a significant association with health outcomes independent from that of PM_{10}".	50 µg/m^3 in PM_{10} All Respiratory hospital admissions (all ages) Lag 0: 12.6% (5.7, 20) Asthma hospital admissions (all ages) Lag 2: 17.6% (3, 34.4) Bronchitis hospital admissions (all ages) Lag 0: 32.6% (4.4, 68.3) Pneumonia hospital admissions (all ages) Lag 3: 31.9% (15, 51.4) COPD hospital admissions (all ages) Lag 1: 11.5% (-3, 28.2).
McGregor et al. (1999) (McGregor *et al*, 1999) Birmingham, UK. Mean PM_{10}: 30.0.	A synoptic climatological approach used to investigate linkages between air mass types (weather situations), PM_{10}, and all respiratory hospital admissions (mean= 19.2/day) for the Birmingham area.	This study results show distinct differential responses of respiratory admission rates to the six winter air mass types. Two of three types of air masses associated with above-average admission rates also favor high PM_{10} levels. This is suggestive of possible linkage between weather, air quality, and health.	Estimates not reported

Anderson et al. (2001) (Anderson *et al*, 2001) West Midland, England (October 1994-December 1996) Population: 2.3 million PM_{10} mean: 23.3 $PM_{2.5}$ mean: 14.5 $PM_{10-2.5}$: 9.0.	Respiratory hospital admissions (mean: 66/day) related to PM_{10}, $PM_{2.5}$, $PM_{10-2.5}$, BS, sulfate, NO_2, O_3, SO_2, CO. GLM regression with quasi-likelihood approach, controlling for seasonal patterns, temp, humidity, influenza episodes, day of week. Adjusted for residual serial correlation and over-dispersion.	Respiratory admissions (all ages) were not associated with any pollutant. Analyses by age revealed some associations to PM_{10} and $PM_{2.5}$ and respiratory admissions in the 0-14 age group. There was a striking seasonal interaction in the cool season versus the warm season. $PM_{10-2.5}$ effects cannot be excluded. Two pollutant models examined particulate measures. $PM_{2.5}$ effects reduced by inclusion of black smoke.	Respiratory hospital admission (lag 0-1); PM_{10} increment 10-90% (11.4-38.3 µg/m^3): All ages: 1.5 (-0.7, 3.6) Ages 0-14: 3.9 (0.6, 7.4) Ages 15-64: 0.1 (-4.0, 4.4) Ages 65: -1.1 (-4.3, 2.1) $PM_{2.5}$ (6.0-25.8) All ages: 1.2 (-0.9, 3.4) Ages 0-14: 3.4 (-0.1, 7.0) Ages 15-64: -2.1 (-6.4, 2.4) Ages 65: -1.3 (-4.7, 2.2) $PM_{10-2.5}$ (4.1, 15.2) All ages: 0.2 (-2.5, 3.0) Ages 0-14: 4.4 (-0.3, 9.4) Ages 15-64: -4.9 (-9.9, 0.4) Ages 65: -1.9 (-6.0, 2.5) COPD (ICD9: 490-492, 494-496) PM_{10}: Age 65+: -1.8 (-6.9, 3.5) $PM_{2.5}$: Age 65+: -3.9 (-9.0, 1.6) $PM_{10-2.5}$: Age 65+: -1.7 (-8.9, 5.3) Asthma (ICD9: 493) (lag 0-1) PM_{10}; Ages 0-14: 8.3 (1.7, 15.3) PM_{10}; Ages 15-64: -2.3 (-10.0, 6.1) $PM_{2.5}$; Ages 0-14: 6.0 (-0.9, 13.4) $PM_{2.5}$;Ages 15-64: -8.4 (-16.4, 0.3) $PM_{10-2.5}$; Ages 0-14: 7.1 (-2.1, 17.2) $PM_{10-2.5}$; Ages 15-64: -10.7 (-19.9, -0.5)
Thompson et al. (2001) (Thompson *et al*, 2001) Belfast, Northern Ireland 1/1/93 – 12/31/95. PM_{10} mean (SD) May – October 24.9 (13.7) November – April 31.9 (24.3)	The rates of acute asthma admission to children's emergency was studied in relation to day-to-day fluctuation of PM_{10} and other pollutants using GLM Poisson regression.	A weak, but significant association between PM_{10} concentration and asthma emergency-department admissions was seen. After adjusting for multiple pollutants only the benzene level was independently associated with asthma emergency department admission. Benzene was highly correlated to PM_{10}, SO_2 and NO_2 levels.	—

Prescott et al. (1998) (Prescott *et al*, 1998) Edinburgh (10/1992-6/1995). Population: 0.45 MM PM_{10} mean.:20.7 PM_{10} min/max=5/72 PM_{10} 90^{th}-$10t^{h}$%: 20.	Poisson log-linear regression models used to investigate relation of daily hospital admissions with NO_2, O_3, CO, and PM_{10}. Adjustments were made for seasonal and day of week, daily temperature (using 8 dummy variables), and wind speed. Separate analyses for age<65 years (mean respiratory hospital admission: 3.4/day) and age >64 years (mean respiratory hospital admission: 8.7/day), and for subjects with multiple hospital admissions.	PM_{10} was consistently positively associated with Respiratory hospital admissions in both age groups, with the greatest effect size in those >64, especially among those with >4 hospital admissions during 1981-1995. Weak significances likely contributed to by low population size.	Single Pollutant Models PM_{10}: 50 µg/m^3, lag 1-3 Respiratory hospital admissions (age<65): 1.25% (-12.8, 17.5) Respiratory hospital admissions (age>64): 5.33% (-9.3, 22.3) Respiratory hospital admissions (age>64, >4 hospital admissions): 7.93% (-19.0, 43.7).
SWEDEN			
Hagen et al. (2000) (Hagen *et al*, 2000) Drammen, Sweden (11/1994-12/1997) Population: 110,000 PM_{10} mean: 16.8 PM_{10} IQR: 9.8-20.9.	Examined PM_{10}, SO_2, NO_2, VOC's, and O_3 associations with respiratory hospital admissions from one hospital (mean = 2.2/day). Used Poisson GAM controlling for temperature and RH (but not their interaction), long-wave and seasonality, day of week, holidays, and influenza epidemics.	As a single pollutant, the PM_{10} effect was of same order of magnitude as reported in other studies. The PM_{10} association decreased when other pollutants were added to the model. However, the VOC's showed the strongest associations.	Respiratory hospital admissions (all ages) for IQR=50 µg/m^3 -Single Pollutant Model: PM_{10} (lag 0): 18.3% (-4.2, 46) -Two Pollutant Model (with O_3): PM_{10} (lag 0): 18.3% (-4.2, 45.4) -Two Pollutant Model (with Benzene): PM_{10} (lag 0): 6.5% (-14 , 31.8).
NORWAY			
Oftedal et al. (2003) (Oftedal *et al*) Drammen, Norway, 1995-2000. Population: 110,000 PM_{10} mean (SD): total period: 16.6 (10.2). 1995-1997: 16.8 (10.2). 1998-2000: 16.5 (10.3).	This study examined the association between PM_{10}, and other co-pollutants (including SO_2, NO_2 and O_3) and respiratory hospital admissions in Drammen (mean = 2.3/day). Time-series analysis of counts was performed by means of GAM with log link and Poisson distribution, controlling for time trends. Lag 0 was apparently used.	PM_{10} did not significantly increase hospital admission for respiratory diseases. A direct association was found for NO_2 and SO_2. No association with O_3. Dividing the total study period into two 3-year periods, analyses for the second time period showed weaker association between these pollutants and the health outcome.	Percent excess risk of respiratory hospital admissions for 11.04 µg/m^3 (IQR): Single Pollutant Model; PM_{10} (lag 0) Total period: 2.1% (-1.0, 5.3) 1994-1997: 3.5% (-1.0, 8.3) 1998-2000: -0.8% (-5.2, 3.7) Two Pollutant Model (with benzene): 1.0% (-2.2, 4.3) Two Pollutant Model (with NO_2): -0.3% (-4.1, 3.7).

THE NETHERLANDS			
Schouten et al. (1996) (Schouten *et al*, 1996) Amsterdam/Rotterdam, 1977-1989. Amsterdam Pop.: 0.69 MM Rotterdam Pop.: 0.58 MM Amsterdam: BS mean.:11 BS 5th-95th%: 1 - 37 Rotterdam: BS mean.:26 BS 5^{th}-95^{th} %= 6-61.	Daily emergency hospital admission for respiratory diseases (ICD9: 460-519), COPD (490-492, 494, 496), and asthma (493). The mean HA/d (range) for these were: 6.70 (0-23), 1.74 (0-9) and 1.13 (0-7) respectively in Amsterdam and 4.79 (0-19), 1.57 (0-9), and 0.53 (0-5) in Rotterdam. Hospital admission associations with BS, O_3, NO_2, and SO_2 were analyzed, using autoregressive Poisson GLM regression allowing for overdispersion and controlling for season, day of week, meteorological factors, and influenza epidemics.	BS did not show any consistent effects in Amsterdam; but in Rotterdam BS was positively related to admissions. Most consistent BS associations in adults >64 years. in winter. Positive O_3 association in summer in people aged >64 in Amsterdam and Rotterdam. SO_2 and NO_2 did not show any clear effects. Results did not change in pollutant interaction analyses. The authors concluded that short-term air pollution-emergency admission association is not always consistent at these individual cities' relatively low counts of daily hospital admissions and low levels of air pollution. Analyses for all ages of all the Netherlands gave a strong BS-hospital admission association in winter.	Single Pollutant Models For BS=25 µg/m^3, lag 2; For all of the Netherlands: Respiratory hospital admissions (all ages): Winter: 2.0% (-1.5, 5.7) Summer: 2.4% (0.6, 4.3).
GERMANY			
Wichmann (2004) (Wichmann, 2004) Rhine-Ruhr area, Germany, 1985, single episode. TSP during the episode in Rhine-Ruhr area: ~ 600.	In January 1985 an extended smog episode occurred in Central Europe. This paper reviews the health effects, including respiratory admission, investigated during the smog period and a control period before and after the smog episode. The Rhine-Ruhr area (Western Germany) was affected for 5 days with maximum concentration of TSP of 600 µg/m^3 (24h averages). In Augsburg (Southern Germany) the smog episode was less severe (100 µg/m^3 TSP, 24 h averages).	Rhine-Ruhr hospital admissions increased by 39% for chronic bronchitis, by 7% (not significant) for respiratory diseases, and decreased by 14% for asthma (not significant).	No risk shown.

FRANCE			
Dab et al. (1996) (Dab *et al*, 1996) Paris, France (1987-1992) Population: 6.1 MM PM_{13} mean: 50.8 PM_{13} 5^{th}-95^{th} range: 19.0-137.3 BS mean: 31.9 BS 5^{th}-95^{th} Range:11.0-123.3.	Daily mortality and general admissions to Paris public hospitals for respiratory causes were considered (means: all respiratory=79/day, asthma=14/day, COPD=12/day). Time series analysis used linear regression model followed by a Poisson regression adjusted for epidemics of influenza A and B, temperature, RH, holidays, day of week, trend, long-wave variability, and nurses' strike. No two pollutant models considered.	For the all respiratory causes category, the authors found "the strongest association was observed with PM_{13}" for both hospital admissions and mortality, indicating a coherence of association across outcomes. Asthma was significantly correlated with NO_2 levels, but not PM_{13}.	For PM_{13}: 50 µg/m^3 ; BS: 25 µg/m^3; Respiratory admissions (all ages) PM_{13} Lag 0: 2.2% (0.2, 4.3) BS Lag 0: 1.0% (0.2, 1.8) COPD admissions (all ages) PM_{13} Lag 2: 2.3% (-6.7, 2.2) BS Lag 2: 1.1% (-2.9, 0.6) Asthma admissions (all ages): PM_{13} Lag 2: 1.3% (-4.6, 2.2) BS Lag 0: 1.2% (-0.5, 2.9)
Eilstein et al (2004) (Eilstein *et al*, 2004) Nine French cities, 1990-1997. No data distribution was reported.	This study examined the short-term effects of PM_{10}, BS and other co-pollutants (CO, NO_2, SO_2, O_3) on mortality and hospitalisation for cardiovascular or respiratory disorders in nine French cities (Bordeaux, Le Havre, Lille, Lyon, Marseille, Paris, Rouen, Strasbourg and Toulouse) of the Surveillance Air et Sante program. The analysis assessed the city-specific and combined associations with various pollutants using Poisson GAM, after adjustment for trends in seasons, day of week, holidays, influenza epidemics, temperature and humidity. A combined RR was calculated for all the cities. Lag 0-1 and Lag 0-5 were used.	At selected lags, some direct associations were found between both PM_{10} and BS, and admission for respiratory diseases, particularly in children aged 0-14 years. Stronger associations were found for SO_2, NO_2 and particularly for CO.	Effects computed for 10 µg/m^3 change in exposition: Lag 0-1 PM_{10}; age 15-64: 0.0 NS PM_{10}; age 65+: 0.8 NS Lag 0-5 PM_{10}; age 15-64: 1.7 $p<0.05$ PM_{10}; age 65+: 1.4 $p<0.05$ Lag 0-1 BS; age 15-64: 1.8 $p<0.05$ BS; age 65+: 0.0 NS Lag 0-5 BS; age 15-64: 4.7 $p<0.05$ BS; age 65+: 0.0 NS.

ITALY			
Biggeri et al. (2005) (Biggeri *et al*, 2005) Eight cities of North, Centre and South of Italy, 1990-1999. PM_{10} mean daily concentration: Turin, 91-94: 77.6 Turin, 95-98: 63.8 Milan, 90-94: 61.8 Milan, 95-97: 45.2 Verona, 95-99: 36.5 Ravenna, 91-95: 59.1 Bologna, 96-98: 41.2 Florence, 96-98: 40.3 Rome, 92-94: 69.7 Palermo, 97-99: 42.9.	Meta-analysis of short-term effects of air pollution on mortality (all causes, cardiovascular causes and respiratory causes) and hospital admission (cardiac causes, and respiratory causes – ICD9: 460-519) in eight Italian cities from 1990 to 1999. Daily concentrations of pollutants were collected. A generalized linear model adjusted for age, day of the week, holidays, influenza epidemics, meteorological variables, and seasonality pattern was fitted for PM_{10} and other co-pollutant (SO_2, NO_2, CO, and O_3). Lag 0-3 was used for hospital admission.	A significant direct association was found between PM_{10} and respiratory hospital admission. NO_2 and CO showed stronger associations.	Effects computed for 10 µg/m^3 change in PM_{10} (lag 0-3 avg.): Fixed-effects: 0.73% (0.27, 1.20) Random-effects: 0.91% (-0.04, 1.86).
Vigotti et al. (1996) (Vigotti *et al*, 1996) Milan, Ialy, 1980-1989 Population: 1.5 MM TSP mean: 139.0 TSP IQR: 82.0, 175.7.	Association between adult respiratory (15-64 years mean =11.3/day, and 65 + years mean =8.8/day) and air pollution evaluated, using the APHEA protocol. Poisson regression was used after adjustment for weather and long term trend, year, influenza epidemics, and season.	Increased risk of respiratory hospital admission was associated with both SO_2 and TSP. The relative risks were similar for both pollutants. There was no modification of the TSP effect by SO_2 level. There was a suggestion of a higher TSP effect on hospital admissions in the cool months.	Young Adult (15-64 years.) Respiratory admission per 100 µg/m^3 increase in TSP: Lag 2: 5% (CI: 0, 10) Older Adult (65+ years.) Respiratory admission per 100 µg/m^3 increase in TSP: Lag 1 ER: 5% (CI: -1, 10).
Fusco et al. (2001) (Fusco *et al*, 2001) Rome, Italy, 1995-1997. PM – suspended particles measured.	Daily counts of hospital admissions for total respiratory conditions, acute respiratory infection including pneumonia, COPD, and asthma was analyzed in relation to PM measures and gaseous pollutants using generalized additive GAM models controlling for mean temperature, influenza, epidermics, and other factors using spline smooths.	No effect was found for PM. Total respiratory admission were significantly associated with same-day level of NO_2 and CO. There was no indication that the effects of air pollution were present at lags >2 days. Among children, total respiratory and asthma admissions were strongly associated with NO_2 and CO. Multipollutant model analysis yielded weaker and more unstable results.	—

Sansebastiano et al. (2003) (Sansebastiano *et al*, 2003) Parma, Italy, 1992-2001. Mean daily concentration: PM_{10} (1998-2001): from 39,63 in 1998 to 57.68 in 2001; TSP: from 46.92 in 1996 to 62.39 in 1992.	This study examined the relationship between TSP and other co-pollutants (CO, NO_2, and SO_2), and daily hospital admission for specific respiratory diseases (including BPCO, polmonitis, pleuritis, asthma and respiratory symptoms) in the city of Parma (population 170,000). The excess risk of hospital admission was not analysed for PM_{10} since information for PM_{10} was available for the period 1998-2001, only.	A direct association has been shown between TSP, NO_2 and SO_2, and admission for selected respiratory diseases.	Effects computed for 1 µg/m^3 increment of TSP: 0.14% (0.04, 0.23).
Migliaretti et al. (2004) (Migliaretti andCavallo, 2004) Turin, Italy, 1/1997-12/1999. TSP levels for the period shown in one figure.	This study examined the relationship between TSP and NO_2, and hospitalisation for asthma (ICD9: 493) separately for children (<15 years) adults (15-64 years) and elderly (65+ years) in the city of Turin using a case-control design. Overall, 1,401 patients resident in Turin and admitted for asthma were defined as cases; 201,071 patients admitted for causes other than respiratory diseases or heart diseases were defined as controls. Percent excess risks were derived by multiple logistic regression models adjusted for sex, age, education, seasonality, temperature, humidity, solar radiation, day of week and holiday.	The number of emergency admissions for respiratory causes significantly rose with increased exposure to TSP and NO_2, particularly among young and elderly patients for both pollutants. After mutual adjustment for both pollutants, the associations became weaker and no more significant.	Effects computed for 10 µg/m^3 increment of TSP: Single-pollutant analysis: Total: 2.3% (1.1, 3.6) Age <15: 1.9% (0.4, 3.4) Age 15-64: 2.3% NS Age 65+: 8.3% (2.9, 13.7) Two-pollutants analysis Total: 0.9% NS Age <15: -0.1% NS Age 15-64: 1.2% NS Age 65+: 0.9% NS.
Migliaretti et al. (2005) (Migliaretti *et al*, 2005) Turin, Italy, 1/1997-12/1999. Same study as above, including adults. TSP levels for the period shown in one figure.	This study examined the relationship between TSP and NO_2, and hospitalisation for asthma (ICD9: 493) in children aged <15 years in the city of Turin using a case-control design. On the basis of the primary diagnosis, 1,060 pediatric patients resident in Turin and admitted for asthma were defined as cases; 25,523 age-matched patients admitted for causes other than respiratory diseases or heart diseases were defined as controls. Percent excess risks were derived by multiple logistic regression models after adjustment for 1) sex and age, and 2) after further allowance for seasonality, temperature, humidity, solar radiation, day of week and holiday. Lag 0-3 was apparently used.	The number of emergency admissions for respiratory causes significantly rose with increased exposure to TSP and NO_2. Considering the multivariate model, after mutual adjustment for both pollutants, no significant association was evident.	Effects computed for 10 µg/m^3 increment of TSP: Single-pollutant analysis: Age-sex adjusted model: Total: 2.8% (1.7, 4.0) Age <4: 2.3% (0.2, 3.4) Age 4-15: 3.1% (0.1, 4.8) Multivariate model: Total: 1.8% (0.3, 3.2) Age <4: 1.8% (0.0, 3.5) Age 4-15: 3.0% (0.1, 5.8) Two-pollutants analysis Age-sex adjusted model: Total: 1.4% (1.1, 4.0) Multivariate model: Total: 0.6% (-0.2, 3.0)

SPAIN			
Tenías et al (1998) (Tenias *et al*, 1998) Study Period.: 94 - 95 Valencia, Spain Hosp. Cachment Pop.:200,000 BS mean: 57.7 BS IQR: 25.6-47.7	Associations between adult (14+ years) emergency asthma emergency visits to one city hospital (mean =1.0/day) and BS, NO_2, O_3, SO_2 analyzed using GLM Poisson auto-regressive modeling, after adjustment for weather season and trends using the APHEA protocol.	Association with asthma was positive and more consistent for NO_2 and O_3 than for BS or SO_2. The study suggests that secondary oxidative-environment pollutants may be more asthma relevant than primary reduction-environment pollutants (e.g., carbonaceous particles). NO_2 had greatest effect on BS in co-pollutant models, but BS became significant once 1993 was added, showing power to be a limitation of this study.	Adult Asthma, BS: 25 µg/m^3; Lag 0: For 1993-1995: 10.6% (0.9, 21.1) For 1994-1995: 6.4% (-4.8, 18.8).
Galan et al (2003) (Galan *et al*, 2003) Madrid, Spain (1995-1998). Hospital Catchment Population:555,000 PM_{10} mean: 32.1.	This study shows the associations between emergency room admission for asthma to one city hospital (mean =3.3/day) in Madrid, and PM_{10} and other co-pollutants, including NO_2, O_3, and SO_2. Two analytical strategies were pursued: 1) autoregressive Poisson models and 2) GAM models. Both the models included terms for long-term trends, seasonality, day of week, holiday, temperature, humidity, influenza and acute respiratory infections. Further models included various pollens. Lag 0, 1, 2, 3, 4 were considered.	Relative risks of asthma emergency room admissions for a rise in pollutant levels were systematically, although not always significantly, over unity for PM_{10} and the other pollutants, for each lag used, also after further allowance for various different typers of pollen. The strongest associations were observed at 1 day lag for O_3 and 3 days lag for the remaining pollutants. Further adjustment for the different types of pollen did not sensibly modify the estimates. Slight differences were observed between the estimates obtained with parametric modelling and those obtained with GAM models.	Effects on admission for asthma computed for 10 µg/m^3 increment of PM_{10}: Lag 0: 1.1% (-2.0, 4.2) Lag 1: 0.6% (-2.4, 3.7) Lag 2: 0.8% (-2.2, 3.8) Lag 3: 3.9% (1.0, 6.8) Lag 4: 2.7% (-0.1, 5.6) After further adjustment for four types of pollen; Best lag (3): 4.5% (1.6, 7.4) GAM model; 5.8 (2.5, 9.1).
GREECE			
Kontos et al. (1999) (Kontos *et al*, 1999) Piraeus, Athens Greece, 1987-1992) BS mean:46.5 BS max:200.	Relation of respiratory hospital admission for children (0-14 years.) (mean = 4.3/day) to BS, SO_2, NO_2, and O_3 evaluated using a nonparametric stochastic dynamical system approach and frequency domain analyses. Long wave and effects of weather considered, but non-linearity and interactions of temperature and RH relation with HA's not addressed.	Pollution was found to explain significant portion of the HA variance. Of pollutants considered, BS was consistently among most strongly explanatory pollutants across various reported analyses.	Risks not reported

TABLE IV. ACUTE PARTICULATE MATTER EXPOSURE AND RESPIRATORY MEDICAL VISITS (Derived from EPA TABLE 8B-3).

Reference, Location, Years, PM Index, Mean or Median ($\mu g/m^3$).	Study Description. Modeling methods: lags, smoothing, co-pollutants and covariates.	Results and Comments.	PM Index, lag, percent excess risk% (95% LCL, UCL)
Subnational studies			
GREAT BRITAIN			
Atkinson et al. (1999b) (Atkinson *et al*, 1999b) London (92 - 94) Population: not reported PM_{10} Mean: 28.5 10th-90th IQR: 15.8-46.5 BS mean:12.7 10th-90th IQR: 5.5-21.6.	All-age respiratory (mean=90/day), asthma (25.9/day), and other respiratory (64.1/day) emergency doctor (ED) visits from 12 London hospitals were considered, but associated population size was not reported. Counts for ages 0-14, 15-64, and >64 were also examined. Poisson GLM regression was used, controlling for season, day of week, meteorology, autocorrelation, overdispersion, and influenza epidemics.	PM_{10} was positively associated, but not BS, for all- age/all-respiratory category. PM_{10} results were driven by significant children and young adult associations, while older adult visits had negative (but non-significant) PM_{10}-ED visit relationship. PM_{10} was positively associated for all ages, children, and young adults for asthma ED visits. However, PM_{10}-asthma relationship could not be separated from SO_2 in multi-pollutant regressions. Older adult ED visits most strongly associated with CO. No O_3-ED visits relationships was found (but no warm season analyses attempted).	PM_{10} (50 $\mu g/m^3$) No co-pollutant: All Respiratory ED visits All age (lag 1): 4.9% (1.3, 8.6) <15 (lag 2): 6.4% (1, 12.2) 15-64 (lag 1): 8.6% (3.4, 14) Asthma ED visits All age (lag 1): 8.9% (3, 15.2) <15 (lag 2): 12.3% (3.4, 22) 15-64 (lag 1): 13% (4.6, 22.1) PM_{10} (50 $\mu g/m^3$); lag 2 & co-pollutant; children's PM alone: 12.3% (3.4, 22) & NO_2: 7.8% (-1.2, 17.6) & O_3: 10.5% (1.6, 20.1) & SO_2: 8.1% (-1.1, 18.2) & CO: 12.1% (3.2, 21.7).
Hajat et al. (1999) (Hajat *et al*, 1999) London, England, 1992-1994. Population: 282,000 PM_{10} mean: 28.2 PM_{10} 10-90th%=16.3-46.4 BS mean: 10.1 BS 10t-90th%=4.5-15.9	This study examined associations of PM_{10}, BS, NO_2, O_3, SO_2, and CO, with primary care general practitioner asthma and other lower respiratory diseases (LRD) consultations. Asthma consultation means per day = 35.3 (all ages); 14.(0-14 years,); 17.7 (15-64 years.); 3.6 (>64 years.). LRD means = 155 (all ages); 39.7(0-14 years,); 73.8 (15-64 years.); 41.1 (>64 years.). Time-series analyses of daily numbers of consultations performed, controlling for time trends, season factors, day of week, influenza, weather, pollen levels, and serial correlation.	Positive associations, weakly significant and consistent across lags, observed between asthma consultations and NO_2 and CO in children, and with PM_{10} in adults, and between other LRD consultations and SO_2 in children. Authors concluded that there are associations between air pollution and daily concentrations for asthma and other lower respiratory disease in London. In adults, the authors concluded that the only consistent association was with PM_{10}. Across all of the various age, cause, and season categories considered, PM_{10} was the pollutant most coherent in giving positive pollutant RR estimates for both asthma and other LRD (11 of 12 categories positive) in single pollutant models considered.	Asthma Doctor's Visits 50 $\mu g/m^3$ PM_{10} -Year-round, Single Pollutant: All ages (lag 2): 5.4% (-0.6, 11.7) 0-14 (lag 1): 6.4% (-1.5, 14.6) 15-64 (lag 0): 9.2% (2.8, 15.9) >64 (lag 2): 11.7% (-1.8, 26.9) -Year-round, 2 Pollutant, Children (0-14): (lag 1) PM_{10}: W/ NO_2: 0.8% (-8.7, 11.4) W/ O_3: 5.5% (-2.1, 13.8) W/ SO_2: 3.2% (-6.4, 13.7) Other LRD; 50 $\mu g/m^3$ PM_{10} -Year-round, Single Pollutant: All ages (lag 2): 3.5% (0, 7.1) 0-14 (lag 1): 4.2% (-1.2, 9.9) 15-64 (lag 2): 3.7% (0.0, 7.6) >64yrs.(lag 2): 6.2% (0.5, 12.9).

Hajat et al. (2001) (Hajat *et al*, 2001) London,1992-1994. 44,406-49,596 registered patients <1 to 14 years. PM_{10} mean 28.5 (13.9)	Daily physician consultations (mean daily 4.8 for children; 15.3 for adults) for allergic rhinitis (ICD9: 477), SO_2, O_3, NO_2, CO, PM_{10}, and pollen using generalized additive models with nonparametric smoother.	SO_2 and O_3 show strong associations with the number of consultations for allergic rhinitis. Estimates largest for a lag of 3 or 4 days prior to consultations, with cumulative measures stronger than single day lags. Stronger effects were found for children than adults. The two- pollutant analysis of the children's model showed that PM_{10} and NO_2 associations disappeared once either SO_2 or O_3 was incorporated into the model.	PM_{10} - Increment (10-90%) (15.8-46.5) Age <1-14 years lag 3: 10.4 (2.0 to 19.4) Cum 0-3: 17.4 (6.8 to 29.0) Ages 15-64 years lag 2: 7.1 (2.6 to 11.7) Cum 0-6: 20.2 (14.1 to 26.6)

Hajat et al. (2002) (Hajat *et al*, 2002) London, 1992-1994. 268,718-295,740 registered patients. PM_{10} mean 28.5 (13.7). BS mean 12.7 (7.9).	This study examined the association between daily physician consultations (mean daily 4.8 for children; 15.3 for adults) for upper respiratory diseases, excluding allergic rhinitis (ICD9:460-463,, 465, 470-475), and PM_{10}, BS, SO_2, O_3, NO_2, CO, using GAMs with nonparametric smoothers to control for seasonal patterns. The models were further adjusted for day of the week, holiday, influenza, weather, pollen concentrations and serial correlation. Lag 0, lag1, lag2, lag3 were considered. The most significantly associated lag, regardless of whether the association was positive or negative, was shown.	Higher levels of SO_2 increased numbers of childhood consultation. Stronger associations were found with PM_{10} and BS in adults aged 15-64 and in adults aged 65 and over, also after further adjustment for other co-pollutants. In general, associations were strongest in elderly people, weakest in the children, and were largely found in the winter months for these two age groups, and in the summer months for adults aged 15-64. An apparent decrease in consultations was associated in colder months with O_3 for all ages and with BS in children.	PM_{10} - Increment (10-90%) (16-47 µg/m^3) All year: Age 0-14: 2.0% (-0.2, 4.2) adjustment NO_2: 2.0% (-0.2, 4.2) adjustment O_3: 1.8% (-0.4, 3.9) adjustment SO_2: 2.0% (-0.6, 4.6) Age 15-64: 5.7% (2.9, 8.6) adjustment NO_2: 2.8% (0.7, 4.9) adjustment O_3: 4.8% (2.6, 7.0) adjustment SO_2: 4.8% (2.2, 7.5) Age 65+: 10.2% (5.3, 15.3) adjustment NO_2: 4.6% (0.5, 8.8) adjustment O_3: 10.7% (5.7, 16.0) adjustment SO_2: 10.6% (4.5, 17.1) Warm season: Age 0-14: 1.1% (-2.4, 4.8) Age 15-64: 6.0% (2.7, 9.4) Age 65+: 0.1% (-7.7, 8.5) Cold season Age 0-14: 2.7% (-0.1, 5.5) Age 15-64: 3.6% (1.0, 6.4) Age 65+: 18.9% (11.7, 26.7) BS - Increment (10-90%) (6-22 µg/m^3) All year: Age 0-14: -2.4% (-4.4, -0.3) Age 15-64: 3.5% (0.6, 6.4) Age 65+: 8.8% (4.6, 13.3) Warm season: Age 0-14: 3.5% (0.3, 6.9) Age 15-64: 6.6% (3.6, 9.6) Age 65+: 2.8% (-3.9, 10.1) Cold season Age 0-14: -3.3% (-6.0, -0.6) Age 15-64: 1.5% (-0.9, 4.1) Age 65+: 9.9% (3.7, 16.3).

FRANCE			
Medina et al. (1997) (Medina *et al*, 1997) Greater Paris, 1991-1995 Population: 6.5 MM Mean PM_{13}: 25 PM_{13} min/max: 6/95 Mean BS: 21 BS min/max: 3/130.	This study evaluated short-term relationships between PM_{13} and BS concentrations and doctors' house calls (mean=8/day; 20% of city total) in Greater Paris. Poisson regression used, with non-parametric smoothing functions controlling for time trend, seasonal patterns, pollen counts, influenza epidemics, day of week, holidays, and weather.	A relationship between all age (0-64 years.) asthma house calls and PM_{13}, BS, SO_2, NO_2, and O_3 air pollution, especially for children aged 0-14 years (mean = 2/day). In two-pollutant models including BS with, successively, SO_2, NO_2, and O_3, only BS and O_3 effects remained stable. These results also indicate that air pollutant associations noted for hospital ED visits are also applicable to a wider population that visits their doctor.	Doctor's Asthma House Visits: 50 µg/m^3 13 PM Year-round, Single Pollutant: All ages (lag 2): 12.7% (4.1, 21.9) 0-14 (lag 0-3): 41.5% (20, 66.8) 15-64 (lag 2): 6.3% (-4.6, 18.5).
ITALY			
Vegni et al. (2005) (Vegni *et al*, 2005) Como, Italy 1995-1997. Population.= ~85,000 Mean TSP= 62.4 (28.6).	This study evaluated respiratory drug dispensing data as health indicators for the effects of TSP. Weekly air mean concentrations of TSP were modeled with: 1) weekly count of individuals having had at least one respiratory drug dispensed (cases) and 2) total weekly sum of daily defined doses (DDD) of respiratory drugs dispensed. A Poisson regression model adjusted for long-term trends, seasonal variations, holidays, and weather was used.	Significant direct associations between TSP and both cases and DDD were found. Authors concluded that both cases and DDD of dispensed respiratory drugs could be useful for epidemiological surveillance of air pollutant health effects.	Excess risk for a variation from 10th to 90th percentile of TSP (29-92 µg/m^3): Cases: 8.2% (0.2, 16.9) DDD: 13.7% (4.4, 23.8).
SPAIN			
Damiá et al. (1999) (de Diego Damia *et al*, 1999) Valencia, Spain, 3/1994-3/1995). BS mean: 101 BS range: 34-213.	Associations of BS and SO_2 with weekly total ED admissions for asthma patients aged > 12 years (mean = 10/week) at one hospital over one year assessed, using linear stepwise GLM regression. Season-specific analyses done for each of 4 seasons, but no other long-wave controls. Linear T, RH, BP, rain, and wind speed included as crude weather controls in ANOVA models.	Both BS and SO_2 correlated with ED admissions for asthma (SO_2: r=0.32; BS: r=0.35), but only BS significant in stepwise multiple regression. No linear relationship found with weather variables. Stratified ANOVA found strongest BS-ED association in the autumn and during above average temperatures. Uncontrolled autocorrelation (e.g., within-season) and weather effects likely remain in models.	Asthma ED Visits (all ages): BS: 40 µg/m^3 (single pollutant) BS as a lag 0 weekly average: 41.5% (39.1, 43.9).

GREECE			
Pantazopoulou et al. (1995) (Pantazopoulou *et al*, 1995) Athens, Greece, 1988. Winter (1/88-3/88,9/88-12/88) BS mean.:75 BS 5-95th %=26 - 161 Summer (3/22/88-3/88,9/21/88) BS mean.:55 BS 5-95th %=19 - 90	This study examined effects of air pollution on daily emergency outpatient visits and admissions for cardiac and respiratory causes. Air pollutants included: BS, CO, and NO_2. Multiple linear GLM regression models used, controlling for linear effects of temperature and RH, day of week, holidays, and dummy variables for month to crudely control for season, separately for winter and summer.	Daily number of emergency visits related positively with each air pollutant, but only reached nominal level of statistical significance for NO_2 in winter. However, the very limited time for each within-season analysis (6 mo.) undoubtably limited the power of this analysis to detect significant effects. Also, possible lagged pollution effects were apparently not investigated, which may have reduced effect estimates.	Single Pollutant Models For Winter (BS: 25 µg/m^3) Outpatient Hospital Visits: 1.1% (-0.7, 2.3) Respiratory hospital admissions: 4.3% (0.2, 8.3) For Summer (BS: 25 µg/m^3) Outpatient Hospital Visits 0.6% (-4.7, 6.0) Respiratory hospital admissions: 5.5% (-3.6, 14.7)
BOSNIA			
Hastings et al. (2002) (Hastings andJardine, 2002) Soldiers deployed to Bosnia 1997-1998. Mean PM_{10} maximum level: 92.9 Mean PM_{10} average level: 75.5.	This ecologic study was conducted to determine the relation between weekly levels of PM_{10} and weekly upper respiratory disease rates in soldiers deployed to Bosnia in 1997-1998. PM_{10} maximum level was defined as the highest PM_{10} level recorded at camp during a given week, PM_{10} average level was defined as the average of all readings taken at a camp during a given week.	When all camps were combined, there was a statistically significant association between the PM_{10} maximum level and upper respiratory tract rates based on Kruskal-Wallis and Mann-Whitney U tests (p=0.047), and the Pearson correlation was statistically significant (p=0.041). Although the relation was not statistically significant in analyses conducted on the individual camps, the average rate increased with each quartile of PM_{10} maximum exposure. There was no statistically significant association between PM_{10} average level and upper respiratory disease rates, although the average rate increased with each quartile of PM_{10} average exposure.	No risk shown
ISRAEL			
Garty et al. (1998) (Garty *et al*, 1998) Tel Aviv, Israel, 1993. PM_{10} mean: 45.	Seven day running mean of asthma ED visits by children (1-18 years) to a pediatric hospital modeled in relation to PM_{10} in Tel Aviv, Israel.	No PM_{10} associations found with ED visits. The ER visits–pollutant correlation increased significantly when the September peak was excluded. Use of a week-long average and associated uncontrolled long-wave fluctuations (with resultant autocorrelation) likely prevented meaningful analyses of short –term PM associations with ED visits.	No risks shown

TABLE V – LONG-TERM PARTICULATE MATTER EXPOSURE AND MORTALITY.

Reference, Location, Years, PM In dex, Mean or Median (µg/m^3).	Study Description. Met hods, co-p ollutants and covariates.	Results and Comments.	PM Index, RR (95% CI)
Subnational studies			
NORWAY			
Naess et al., 2007 (Naess *et al*, 2007) Cohort of all inhabitants of Oslo (143,842). Follow-up period: 1992-1998. $PM_{2.5}$ range: 6.56-22.34 PM_{10} range: 6.57-30.13	This study investigated the association between concentrations of PM_{10}, $PM_{2.5}$ and NO_2 in 1992-1995, and cause-specific mortality. The population included all inhabitants of Oslo Norway, aged 51–90 years on January 1992 with follow-up of deaths from 1992 to 1998. An air dispersion model was used to estimate levels of exposure in all 470 administrative neighbourhoods. Cox proportional hazards regression models were used after adjustment for age, education and occupational class. To model the relation between air pollutants and mortality, GAM models were used.	Some direct associations were observed between NO_2, PM_{10} and $PM_{2.5}$, and mortality for all causes, CVD, lung cancer, but mainly COPD. Increased risks for total mortality were stronger for subjects aged 51-70 years than in older subjects. Among the limitations of this study, there is an inadequate allowance for covariates, including smoking The three pollutants shared similar results, being their correlations high (between 0.88 and 0.95).	Occupational class and education adjusted HR for the 4th vs 1st quartile of exposure to $PM_{2.5}$: All cause mortality Men 51-70 years: 1.44 (1.32, 1.58) Women 51-70 years: 1.41 (1.27, 1.43) Men 71-90 years: 1.18 (1.10, 1.26) Women 71-90 years: 1.11 (1.05, 1.17) CVD (quartile increase of exposure) Men 51-70 years: 1.10 (1.05, 1.16) Women 51-70 years: 1.14 (1.06, 1.21) Men 71-90 years: 1.05 (1.01, 1.08) Women 71-90 years: 1.03 (1.00, 1.05) COPD (quartile increase of exposure) Men 51-70 years: 1.27 (1.11, 1.47) Women 51-70 years: 1.09 (0.94, 1.25) Men 71-90 years: 1.10 (1.00, 1.21) Women 71-90 years: 1.05 (0.96, 1.16)

			Lung cancer (quartile increase of exposure) Men 51-70 years: 1.07 (0.97, 1.18) Women 51-70 years: 1.27 (1.13, 1.43) Men 71-90 years: 1.07 (0.97, 1.18) Women 71-90 years: 1.16 (1.02, 1.32) Similar results were shown for PM_{10}.
SWEDEN			
Rosenlund et al. (2006) (Rosenlund *et al*, 2006) Stockolm, Sweden,1992-1994. Case-control study Subjects: 272 cases with fatal myocardial infarction and 1,870 hospital controls. 30 year residential PM_{10} exposure, median: 2.6 for cases (including non-fatal cases) and 2.4 for controls.	This case-control study examined the association between 30 year average exposure to PM_{10}, and other co-pollutants, including SO_2, NO_2 and CO, and first episode of fatal within 28 days (and non-fatal) myocardial infarction (MI). The annual mean level of PM_{10} was assessed only for the year 2000, thus assuming constant levels during the study period. The air pollution data for each year was linked to the history of residence of each subject for the corresponding year from 1960 to study inclusion. ORs were derived by multiple logistic regression models after adjustment for age, sex, hospital catchment area, smoking, physical activity, diabetes and socioeconomic status. Estimates for $PM_{2.5}$ were not shown, given the high correlation in this sample between $PM_{2.5}$ and PM_{10} (r=0.998).	PM_{10} was not significantly associated with risk of fatal MI. A borderline significant excess risk was found for "out of hospital death". Similar patterns of risk were found for NO_2, CO, and SO_2.	RR for an increment of 5 $\mu g/m^3$ (95^{th} – 5^{th} percentile) of PM_{10}. Mortality within 28 days from admission to hospital: Total deaths: 1.39 (0.94, 2.07) In-hospital deaths: 1.21 (0.75, 1.94) Out-of-hospital deaths: 1.84 (1.00, 3.0).

THE NETHERLANDS			
Hoek et al. (2002) (Hoek *et al*, 2002) The Netherlands, 1986-1994 Cohort study Subjects: 4,492 BS exposure, mean (SD): background 15.1 (2.5); background and local 15.5 (3.2).	This study examined the association between BS and NO_2 in a cohort of 4,492 residents in various areas of the Netherlands and cause-specific mortality. Long-term exposure to traffic-related BS and NO_2 was estimated for the 1986 home address. The association between exposure to air pollution and total, cardiopulmonary and non-cardiopulmonary, non-lung cancer mortality was assessed with Cox's proportional hazards models, after adjustment for age, sex, education, BMI, occupation, active and passive cigarette smoking, and neighbourhood socioeconomic score. Two models of exposure for every pollutant were used: 1) the background concentration was entered in the model with the indicator variable for living near a major road. 2) the sum of the background and the estimated contribution from living near a major road to air pollution concentrations. Too few people died from respiratory disorders and lung cancer to obtain stable estimates for the indicator variable for living near a major road.	Overall, 489 deaths occurred during th follow-up period. Cardiopulmonary mortality was significantly associated with living near a major road, less consistently with the estimated background concentration. Other causes of death, including lung cancer, were unrelated to air pollution.	RR for an increment of 10 (95^{th} – 5^{th} percentile) of BS. All cause mortality Background Unadjusted: 1.37 (0.95, 1.97) Adjusted: 1.17 (0.76, 1.78) Adjusted for individuals living 10 years or longer at their 1986 address: 1.04 (0.65, 1.64) Background and local All cause mortality Unadjusted: 1.37 (1.06, 1.77) Adjusted: 1.32 (0.98, 1.78) Adjusted for individuals living 10 years or longer at their 1986 address: 1.31 (0.95, 1.80) Cardiopulmonary Background: 1.34 (0.68, 2.64) Background and local 1.71 (1.10, 2.67) Non-cardiopulmonary non-lung cancer Background: 1.15 (0.63, 2.10) Background and local 1.09 (0.71, 1.69) Lung cancer Background and local: 1.06 (0.43, 2.63).

GERMANY			
Gehring et al. (2006) (Gehring *et al*, 2006) 7 cities of North Rhine-Westphalia, Germany Period of follow-up: from 1985 to 2002-2003. Subjects= 4,752 Mean TSP= 62.4 (28.6).	This study examined the association between long-term exposure to PM_{10}, calculated from TSP by using a 0.71 conversion factor, NO_2 and total, cardiopulmonary (ICD9: 400-440 and 460-519) and non-cardiopulmonary non-lung cancer mortality, in a cohort of approximately 4,800 German middle-age women. The limited number of deaths for lung cancer and pulmonary causes did not allow to obtain stable effect estimates, and corresponding RRs were not shown. RRs were estimated using Cox proportional hazard regression models after adjustment for socio-economic status and smoking. 1-year average daily concentration of PM_{10} for the year of the baseline examination, and 5-year average daily concentration of PM_{10} for the year of the baseline examination and the preceding 4 years were considered.	During 18 year follow-up, 399 women died. One-year average exposure to PM_{10} (computed by TSP) was associated to cardiopulmonary mortality, but not to all cause and non-cardiopulmonary non-lung cancer mortality. The pattern of risk was similar for 5-year average exposure to PM_{10}. Living within a 50-meter radius of a major road and NO_2 levels showed similar risks. Modestly stronger associations were found for women with a low socio-economic status, for current smokers and for non-smokers with exposure to environmental tobacco smoke (data not shown).	Mortality RR for an increment of 7 $\mu g/m^3$ of PM_{10} (corresponding to 10 $\mu g/m^3$ of TSP): 1-year average All causes: 1.08 (0.94-1.25) Cardiopulmonary: 1.34 (1.06-1.71) Non-cardiopulmonary non-lung cancer: 0.92 (0.76-1.10) 5-year average All causes: 1.13 (0.99-1.30) Cardiopulmonary: 1.59 (1.23-2.04) Non-cardiopulmonary non-lung cancer: 0.91 (0.76-1.08).

FRANCE			
Filleul et al. (2005) (Filleul *et al*, 2005) PAARC survey 24 areas of 7 French cities period of exposure measurement: 1974-1976 Subjects= 14,284 adults TSP min/max: 45/243 BS min/max: 18/152.	This study examined the long term effects of TSP, BS, SO_2, NO_2 and NO (daily assessed in 1974-1976) on mortality in the Pollution Atmospherique et Affections Respiratoires Chroniques (PAARC) survey, conducted in 24 areas of 7 French cities on 14,284 adults, followed for the period 1974-2001. RRs were estimated by Cox proportional hazard regression models, after adjustment for age, sex, smoking, BMI, education, and occupational exposure. Mortality for all non-accidental causes (ICD9 <800), cardiopulmonary disease (ICD9: 401-440 and 460-519) and lung cancer (ICD9: 162) were considered. The analyses were performed for all 24 areas and in a subgroup of 18 areas with a ratio of NO/ NO_2 <3 (with monitors potentially influenced by local traffic).	After approximately 25 years of follow-up, approximately 2,396 deaths from non-accidental causes, 546 from cardiopulmonary disease and 178 from lung cancer occurred. Considering all the 24 areas, no association was found between TSP, BS and the other considered co-pollutants, and mortality for all non-accidental causes, cardiopulmonary disease, or lung cancer. After exclusion of 6 areas influenced by local traffic, TSP showed a significant association with all non-accidental causes and cardiopulmonary disease mortality, and BS increased the risk of non-accidental causes mortality. NO_2 significantly increased the mortality for all non-accidental causes, cardiopulmonary disease and lung cancer. Authors concluded that urban air pollution assessed in the 1970s was associated with increased mortality over 25 years.	Mortality RR for an increment of 10 µg/m^3 of TSP: 24 areas: Non-accidental: 1.00 (0.99, 1.01) Cardiopulmonary: 1.01 (0.99, 1.03) Lung cancer: 0.97 (0.94, 1.01) 18 areas not influenced by local traffic: Non, accidental: 1.05 (1.02, 1.08) Cardiopulmonary: 1.06 (1.01, 1.12) Lung cancer: 1.00 (0.92, 1.10) Mortality RR for an increment of 10 µg/m^3 of BS: 24 areas: Non-accidental: 0.99 (0.98, 1.01) Cardiopulmonary: 1.00 (0.97, 1.02) Lung cancer: 0.97 (0.93, 1.01) 18 areas not influenced by local traffic: Non-accidental: 1.07 (1.03, 1.10) Cardiopulmonary:1.05 (0.98, 1.12) Lung cancer: 1.03 (0.92, 1.15).

TABLE VI - ECOLOGIC STUDIES ON LONG TERM PARTICULATE MATTER EXPOSURE AND MORTALITY.

Reference, Location, Years, PM In dex, Mean or Median (µg/m^3).	Study Description. Met hods, co-p ollutants and covariates.	Results and Comments.	PM Index, RR (95% CI)
Subnational studies			
GREAT BRITAIN			
Maheswaran et al. (2005b) (Maheswaran *et al*, 2005b) Sheffield, UK, 1994-1998 Population: 199,682 subjects aged ≥ 45 years. PM_{10}, median: 18.8.	To examine the relation between areas with different air pollution levels and coronary heart disease (ICD9: 410-414) mortality (and hospitalization), 5 year average of PM_{10}, NO_x and CO levels were interpolated to 1030 census enumeration districts, and linked to residence of each subject. Poisson regression models were used after adjustment for age, sex, deprivation and smoking prevalence. To adjust for smoking prevalence, survey data from a random sample of adults carried out in 2000 was used. Ward level smoking prevalence was attributed to all districts within each of the 29 wards in Sheffield. Analyses were rerun, substituting unsmoothed pollution variables with the 1km radius smoothed variables.	During the period 1994-1998, 6,857 deaths for coronary heart disease occurred. PM_{10} was significantly associated with mortality for coronary heart disease in the age-and-sex-adjusted model only. After further allowance for other covariates, no association was shown. A similar pattern of risk was found for CO. NO_x increased mortality for coronary hearth disease even after further allowance for smoking and deprivation.	RR for the highest vs the lowest quintile of exposure of PM_{10}. Mortality for coronary heart disease: Adjusted for sex and age: 1.30 (1.19, 1.43) Further adjusted for smoking and deprivation (not smoothed): 1.08 (0.96, 1.20) Further adjusted for smoking and deprivation (1km radius smoothed): 1.07 (0.96, 1.21).
Maheswaran et al. (2005a) (Maheswaran *et al*, 2005a) Sheffield, UK, Same study described above.	This study used the same data and methods described above to examine the association between PM_{10}, NO_x and CO, and stroke (ICD9: 430-438) mortality (and hospitalization).	During the period 1994-1998, 2,979 deaths for stroke occurred. PM_{10} was significantly associated with stroke mortality also after further allowance for other covariates, including smoking prevalence and deprivation. Similar patterns of risk were found for NO_x and CO.	RR for the highest vs the lowest quintile of exposure of PM_{10}. Stroke mortality: Adjusted for sex and age: 1.39 (1.23, 1.58) Further adjusted for smoking and deprivation (not smoothed): 1.33 (1.14, 1.56) Further adjusted for smoking and deprivation (1km radius smoothed): 1.24 (1.05, 1.47).

IRELAND			
Clancy et al. (2002) (Clancy *et al*, 2002) Dublin, Ireland, 1984-1996 Intervention study Subjects: 4,492; BS exposure, mean annual concentration ranged between 10 and 120 before the ban, and between 10 and 40 thereafter.	This study compared standardised non-trauma (ICD9 <800), respiratory (ICD9: 480-496 and 507), and cardiovascular (ICD9: 390-448) death rates 72 months before and after the ban of coal sales in Dublin (Aug 1990). The effect of the ban on age-standardised death rates was estimated with an interrupted time-series analysis, adjusting for weather, respiratory epidemics, and death rates in the rest of Ireland.	Average BS concentrations in Dublin declined by 35.6 µg/m^3 (70%) after the ban on coal sales. Adjusted non-trauma death rates decreased by 5·7% (95% CI: 4, 7), respiratory deaths by 15·5% (95% CI: 12, 19), and cardiovascular deaths by 10·3% (95% CI: 8, 13). Respiratory and cardiovascular standardised death rates fell coincident with the ban on coal sales.	No RR shown.

TABLE VII - LONG TERM PARTICULATE MATTER EXPOSURE AND CARDIOVASCULAR MORBIDITY.

Reference, Location, Years, PM In dex, Mean or Median (µg/m^3).	Study Description. Met hods, co-p ollutants and covariates.	Results and Comments.	PM Index, RR (95% CI)
Subnational studies			
GREAT BRITAIN			
Maheswaran et al. (2005b) (Maheswaran *et al*, 2005b) Sheffield, UK, 1994-1998. Population: 199,682 subjects aged ≥45 years. PM_{10}, median: 18.8.	To examine the relation between areas with different air pollution levels and coronary heart disease (ICD9: 410-414) hospitalization (and mortality), 5 year average of PM_{10}, NO_x and CO levels were interpolated to 1030 census enumeration districts, and linked to residence of each subject. Poisson regression models were used after adjustment for age, sex, deprivation and smoking prevalence. To adjust for smoking prevalence, survey data from a random sample of adults carried out in 2000 was used. Ward level smoking prevalence was attributed to all districts within each of the 29 wards in Sheffield. Analyses were rerun, substituting unsmoothed pollution variables with the 1km radius smoothed variables.	During the period 1994-1998, 11,407 admissions for coronary heart disease occurred. PM_{10} was associated with admission for coronary heart disease in the age-and-sex-adjusted model only. After further allowance for other covariates, no association was shown. A similar pattern of risk was found for CO and NO_x.	RR for the highest vs the lowest quintile of exposure of PM_{10}. Admission for coronary heart disease: Adjusted for sex and age: 1.36 (1.23, 1.50) Further adjusted for smoking and deprivation (not smoothed): 1.01 (0.90, 1.14) Further adjusted for smoking and deprivation (1km radius smoothed): 1.07 (0.95, 1.20).
Maheswaran et al. (2005a) (Maheswaran *et al*, 2005a) Sheffield, UK, Same study described above.	This study used the same data and methods described above to examine the association between PM_{10}, NO_x and CO, and stroke (ICD9: 430-438) hospitalization (and mortality).	During the period 1994-1998, 5,122 admissions for stroke occurred. PM_{10} was significantly associated with hospitalization for stroke in the age-and-sex-adjusted model. After further allowance for other covariates, a borderline significant association was shown. Similar patterns of risk were found for NO_x and CO.	RR for the highest vs the lowest quintile of exposure of PM_{10}. Admission for stroke: Adjusted for sex and age: 1.40 (1.26, 1.55) Further adjusted for smoking and deprivation (not smoothed): 1.13 (0.99, 1.29) Further adjusted for smoking and deprivation (1km radius smoothed): 1.15 (1.01, 1.31).

Solomon et al. (2003) (Solomon *et al*, 2003) 11 electoral wards of England and Wales, UK. 1,166 women Mean BS level, range across wards: 1966-1969: 40/180 1978-1981: 14/79 1994-1997: 4/14.	To explore the long-term influence of particulate air pollution on cardio-respirratory morbidity in the UK, a cross-sectional postal survey was conducted in 11 electoral wards of UK. Wards were classified in high (BS>120 µg/m^3 in 1966-1969) and low (BS<50 µg/m^3 in 1966-1969) pollution categories. Women from the two categories were compared in terms of self-reported history of ischaemic heart disease (and asthma and productive cough).	No excess risk of ischaemic heart disease was found in the areas with higher levels of BS.	RR for women living in the areas with higher BS levels: 1.0 (0.7, 1.4).
SWEDEN			
Rosenlund et al. (2006) (Rosenlund *et al*, 2006) Stockolm, Sweden, 1992-1994. Case-control study Subjects: 272 cases with fatal myocardial infarction and 1,870 hospital controls. 30 year residential PM_{10} exposure, median: 2.6 for cases (including non-fatal cases) and 2.4 for controls.	This case-control study examined the association between 30 year average exposure to PM_{10}, and other co-pollutants, including SO_2, NO_2 and CO, and first episode of non-fatal (and fatal) myocardial infarction (MI). The annual mean level of PM_{10} was assessed only for the year 2000, thus assuming constant levels during the study period. The air pollution data for each year was linked to the history of residence of each subject for the corresponding year from 1960 to study inclusion. ORs were derived by multiple logistic regression models after adjustment for age, sex, hospital catchment area, smoking, physical activity, diabetes and socioeconomic status. Estimates for $PM_{2.5}$ were not shown, given the high correlation in this sample between $PM_{2.5}$ and PM_{10} (r=0.998).	PM_{10} was not associated with nonfatal MI. Similar patterns of risk were found for NO_2, CO, and SO_2.	RR for an increment of 5 µg/m^3 (95^{th} – 5^{th} percentile) of PM_{10}. Hospital admission for non-fatal MI: 0.92 (0.71, 1.19).

GERMANY			
Hoffmann et al. (2006) (Hoffmann *et al*, 2006) Two cities of Germany (Essen and Mulheim), 2000-2003. Cohort study Subjects: 3,399 Mean (SD) $PM_{2.5}$: 23.3 (1.4) .	This study examined the relationship between the long-term residential exposure to traffic and self-reported history of coronary heart disease, using baseline data from the German Heinz Nixdorf RECALL study, a population-based cohort study. Long-term personal traffic and $PM_{2.5}$ exposures were assessed for each resident. $PM_{2.5}$ was assessed for the year 2002. ORs were derived by multivariable logistic regression models. For $PM_{2.5}$ four different models were considered: model 1: adjusted for traffic exposure; model 2: further adjusted for age and sex; model 3: further adjusted for education, diabetes, BMI, waist-to-hip ratio, smoking, environmental tobacco smoke, physical activity, city and area of residence; model 4: further adjusted for hypertension and lipids.	Overall, 242 subjects reported a history of coronary heart disease. No association was found with $PM_{2.5}$ exposure, but there was an excess risk in men only for residents living near major roads.	OR for $PM_{2.5}$ (increment apparently 1 $\mu g/m^3$): Model 1: 0.92 (0.36, 2.39) Model 2: 0.83 (0.31, 2.27) Model 3: 0.56 (0.16, 2.01) Model 4: 0.55 (0.14, 2.11).

TABLE VIII - LONG TERM PARTICULATE MATTER EXPOSURE AND RESPIRATORY MORBIDITY OR SYMPTOMS (Derived from EPA TABLE 8B-8).

Reference, Location, Years, PM In dex, Mean or Median (µg/m^3).	Study Description. Met hods, co-p ollutants and covariates.	Results and Comments.	PM Index, RR (95% CI)
ECRHS I study			
Sunyer et al. (2006) (Sunyer *et al*, 2006) 21 centres of 10 countries Follow-up period: 2000-2002. Population: 6,824 $PM_{2.5}$ mean 19.12 S mean 1167.07	This study examined the association between the prevalence and new onset of symptoms of chronic bronchitis and urban levels of $PM_{2.5}$, S, NO_2, in 6,824 subjects enrolled during 1991–93 in 21 centres of 10 European countries. Subjects were followed from 2000 to 2002. $PM_{2.5}$ and S were assessed at centre level with the same central monitoring site equipment, whereas NO_2 was measured during a 14 day period for 1,634 individuals of 16 centres at home (outdoor and indoor). Two definitions for symptoms of chronic bronchitis were considered: 1) productive chronic cough for chronic cough and chronic phlegm (more than three months each year, and 2) chronic phlegm alone. Results from the latter definition were shown. Hierarchical models were used. Confounding variables (including smoking, education, occupational groups, occupational exposures, respiratory infections during childhood, rhinitis, and asthma) were retained at individual level if $p < 0.10$ or the coefficient of the air pollution variable was modified by 10% or more. For $PM_{2.5}$, the association was measured with interval odds ratio (that is, covering 80% of the ORs).	Traffic intensity as well as home outdoor NO_2 were associated with (prevalence and new onset of= chronic phlegm, in women only. $PM_{2.5}$ and S content at centre level did not show any association with prevalence or new onset of chronic phlegm. Similar results were obtained with chronic productive cough.	Interval OR (95% CI)) for $PM_{2.5}$ in µg/m^3 Males: 0.97 (0.70, 1.35) Females: 0.99 (0.85, 1.17).

CESAR study			
Leonardi et al. (2000) (Leonardi *et al*, 2000) 17 cities of Central Europe Yearly average concentration (Nov. 1995 - Oct. 1996) across the 17 study areas varied from 41 to 96 for PM_{10}, from 29 to 67 for $PM_{2.5}$, and from 12 to 38 for $PM_{10-2.5}$.	Cross-sectional study collected blood and serum samples from 10-61 school children aged 9 to 11 in each community 11 April to 10 May 1996. Blood and serum samples examined for parameters in relation to PM. Final analysis group of 366 examined for peripheral lymphocyte type and total immunoglobulin classes. Association between PM and each log transformed biomarker studied by linear regression in two-stage model with adjustment for confounding factors (age, gender, number of smokers in house, laboratory, and recent respiratory illness). This survey was conducted within the frame work of the Central European study of Air Quality and Respiratory Health (CEASAR) study.	Number of lymphocytes (B, CD4+, CD8d, and NK) increased with increasing concentration of PM adjusted for confounders. The adjusted regression slopes are largest and statistically significant for $PM_{2.5}$ as compared to PM_{10}, but small and non statistically significant for $PM_{10-2.5}$. Positive relationship found between concentration of IgG in serum and $PM_{2.5}$ but not for PM_{10} or $PM_{10-2.5}$. Two other models produced similar outcomes: a multi-level linear regression model and an ordinal logistic regression model.	Adjusted Regression slope $PM_{2.5}$ CD4+ 80% (34, 143) p<0.001 Total IgG 24% (2, 52) p=0.034.
Subnational studies			
GREAT BRITAIN			
Solomon et al. (2003) (Solomon *et al*, 2003) 11 electoral wards of England and Wales, UK. 1,166 women Mean BS level, range across wards: 1966-1969: 40/180 1978-1981: 14/79 1994-1997: 4/14.	To explore the long-term influence of particulate air pollution on cardio-respiratory morbidity in the UK, a cross-sectional postal survey was conducted in 11 electoral wards of UK on 1,166 women. Wards were classified in high (BS>120 $\mu g/m^3$ in 1966-1969) and low (BS<50 $\mu g/m^3$ in 1966-1969) pollution categories. Women from the two categories were compared in terms of self-reported history of asthma and productive cough (and IHD).	The prevalence of asthma was lower in the areas with higher levels of BS. No excess risk of productive cough was found in the areas with higher levels of BS.	RR for women living in the areas with higher BS levels: Asthma: 0.7 (0.5, 1.0) Productive cough: 1.0 (0.7, 1.4).

Wheeler and Ben-Shlomo (2005) (Wheeler and Ben-Shlomo, 2005) Linkage analysis, England, 1995-1997. Mean (SD) PM_{10}: 23.95 (3.58); range: 17.87-41.37.	This study examined the relation between socioeconomic status and local air quality, and combined effects on respiratory health, Data on people taking part in the Health Surveys for England during 1995-1997 were attributed with a small area index of air pollution based on annual mean concentrations of PM_{10}, benzene, SO2 and NO_2. Regression models after adjustment for smoking status, passive smoking, BMI, rurality, previous asthma diagnosis and inhaler use were used to measure associations between social class, air quality, age-, sex- and height-standardized FEV1, and self reported asthma.	Urban lower social class households were more likely to be located in areas of poor air quality, but the association in rural areas was, if anything reversed. Low social class and poor air quality were independently associated with decreased lung function (FEV1), but not asthma prevalence, after adjustment for a number of potential confounders. Social class effects were not attenuated by adjustment for air quality. Authors concluded that the association between FEV1 and local air quality was of similar magnitude to that with social class, and the adverse effects of air pollution seemed to be greater in men in lower social classes.	No estimates for PM were provided.
Pierse et al. (2006) (Pierse *et al*, 2006) Cohort of 4,400 children from Leicester, UK. 1998-2001. Annual mean concentration of PM_{10} was 1.47 in 1998 and 1.33 in 2001.	This study examined he effect of primary PM_{10} (particles directly emitted from local sources) on prevalence and incidence of respiratory symptoms in a random sample cohort of 4,400 Leicestershire children aged 1–5 years surveyed in 1998 and again in 2001. Annual exposure to primary PM_{10} was calculated for the home address using the AIVIRO dispersion model and ORs were calculated for each $\mu g/m^3$ increase, after adjustment for age, sex, family history of asthma, coal heating in the home, household member's smoking status, and maternal and paternal education.	Exposure to primary PM_{10} was associated with the prevalence of cough without a cold in both 1998 and 2001, and with the prevalence of night time cough and current wheeze in 2001, only. An association between primary PM_{10} and incidence of cough without a cold and wheeze was also found.	Adjusted OR (95% CI) for an increment of 1 $\mu g/m^3$ Prevalence: Cough without a cold 1998: 1.21 (1.07, 1.38) 2001: 1.56 (1.32, 1.84) Night time cough 1998: 1.06 (0.94, 1.19) 2001: 1.25 (1.06, 1.47) Current wheeze 1998: 0.99 (0.88, 1.12) 2001: 1.28 (1.04, 1.58) Incidence (new onset symptoms, not present in 1998 survey and present in the 2001 survey versus no symptoms in both surveys) Cough without a cold 1.62 (1.31, 2.00) Night time cough 1.19 (0.96, 1.47) Current wheeze 1.42 (1.02, 1.97).

Kulkarni et al. (2006) (Kulkarni *et al*, 2006) Leicester, UK. Nov 2002 to Dec 2003. Annual mean level of PM_{10} was 1.21 (range: 0.10-2.71) in healthy children and 1.81 (range: 0.17-2.13) in asthmatic children.	This study examined the association between carbon content airway macrophages, as a marker of individual exposure to PM derived from fossil fuel, and lung function in 9 asthmatic and 64 healthy children from Leicester, UK. Airway macrophages were obtained from healthy children through sputum induction, and the area of airway macrophages occupied by carbon was measured. Lung function was measured with the use of spirometry. The exposure to PM_{10} was modeled at or near each child's home address. Linear regression was used to evaluate associations between carbon content of alveolar macrophages and variables that may affect individual exposure. Age, sex, race, weight, height, birth order, number of siblings, exercise measures and cotinine levels in saliva were considered as potential confounding variables.	An increase in PM_{10} was associated with a significant increase in the carbon content of airway macrophages. Carbon content was inversely associated with FEV_1, FVC and FEF_{25-75}. Increased primary PM_{10} was inversely associated with the percentage of the predicted FEV_1 (P = 0.04) and the $FEF_{25–75}$ (P = 0.05). In the multiple regression analysis, even after adjusting for the carbon content of airway macrophages, PM_{10} was no longer significantly associated with lung function, whereas the carbon content of airway macrophages remained inversely associated with the percentage of the predicted values of FEV_1, FVC, and $FEF_{25–75}$. The carbon content of airway macrophages was lower in children with asthma than in healthy children. Authors concluded that while there was a dose-dependent inverse association between the carbon content of airway macrophages and lung function in children, there was no evidence that reduced lung function itself caused an increase in carbon content.	Excess carbon content (μm^2) and lung function (%) associated with an increment of one $\mu g/m^3$ of PM_{10}. carbon content airway macrophages: 0.10 (0.01, 0.18) FEV_1 -4.3% (-8.5, -0.2) after allowance for carbon content: -2.9% (-6.9, 1.2) FVC -1.2% (-5.6, 3.2) after allowance for carbon content: 0.1% (-4.4, 4.6) FEV_1 -8.6% (-17.3, 0.1) after allowance for carbon content: -5.5% (-14.2, 3.1).

Burr et al. (2004) (Burr *et al*, 2004) Intervention study, North Wales, UK. mean concentration of PM_{10} Congested streets: 1996-1997: 35.2 1998-1999:27.2 Uncongested streets: 1996-1997: 11.6 1998-1999:8.2 $PM_{2.5}$ Congested streets: 1996-1997: 21.2 1998-1999:16.2 Uncongested streets: 1996-1997: 6.7 1998-1999: 4.9.	This study examined whether residents of congested streets had a higher prevalence of respiratory symptoms than residents of uncongested streets, and whether their respiratory health improves following a reduction in exposure to traffic related air pollutants, due to the construction of a "by-pass". A respiratory survey was conducted at baseline and again a year after the by-pass opened on 165 and 283 subjects in the congested and uncongested areas, respectively.	Initial concentrations of PM_{10} and $PM_{2.5}$ were substantially higher in the congested than in the uncongested streets. When the by-pass opened, the volume of heavy goods traffic fell by nearly 50%. PM_{10} decreased by 23% (8.0 mg/m^3) in the congested streets and by 29% (3.4 mg/m^3) in the uncongested streets, with similar proportionate falls in $PM_{2.5}$. The by-pass showed a tendency for most symptoms to improve in both areas. The improvement tended to be greater in the uncongested area for chest symptoms and for peak flow variability, and in the congested streets for rhinitis and rhinoconjunctivitis The by-pass reduced pollutant levels to a degree that probably alleviates rhinitis and rhinoconjunctivitis but has little effect on lower respiratory symptoms.	No estimates for PM_{10} nor for $PM_{2.5}$ were provided.
THE NETHERLANDS			
Brauer et al. (2002); (Brauer *et al*, 2002) Birth cohort of 3,934 children. $PM_{2.5}$ mean: 16.9 (range: 13.5-25.2).	This study examined the relationship between traffic-related air pollution and the predevelopment of asthmatic/allergic symptoms and respiratory infections (including wheezing, dry night-time cough, ear, nose, throat (E,N,T) infections, skin rash, and physician-diagnosed asthma, bronchitis, influenza, and eczema at 2 years of age) in a cohort of approximately 4,000 births. A validated model was used to assign outdoor concentrations of $PM_{2.5}$, NO_2 at the home of each subject of the cohort. The association between PM exposure and various outcomes was analyzed by multiple logistic regression after adjustment for various covariates, including sex, smoking and education of parents, family history of allergies, and mother's age.	Adjusted odds ratios for wheezing, physician-diagnosed asthma, E,N,T infections, and flu/serious colds indicated positive associations with air pollutants, some of which reached borderline statistical significance. No associations were observed for the other outcomes analyzed.	Adjusted OR (95% CI) for an IQR change in concentration of PM (i.e., 3.2µg/m^3) Wheeze: 1.14 (0.98, 1.34) Asthma: 1.12 (0.84, 1.50) Dry cough at night: 1.04 (0.88, 1.23) Bronchitis: 1.04 (0.85, 1.26) E,N,T infections: 1.20 (1.01, 1.42) Flu/serious colds: 1.12 (1.00, 1.27) Itchy rash: 1.01 (0.88, 1.16) Eczema: 0.95 (0.83, 1.10).

Brauer et al. (2006); (Brauer *et al*, 2006) Birth cohorts on 3,700 and 650 infants from the Netherlands and Munich (Germany), respectively. Period of recruitment: 1997-1998. $PM_{2.5}$ mean: The Netherlands: 16.9 Munich, Germany: 13.4.	This study analysed the association between $PM_{2.5}$ elemental carbon, and NO_2, and risk of otitis media in two birth cohorts of approximately 3,700 and 650 infants from the Netherlands and Germany, respectively. Air pollutants at home of children were measured at 40 individual sites in each country, and analyzed in relation to diagnosed history of otitis media (diagnosed by a physician)by parents of children in the first 2 years of life. ORs were derived by multiple logistic regression models after adjustment for potential confounding variables, including sex, parental atopy, maternal education and smoking, environmental tobacco smoke and presence of pet at home, and siblings.	Some significant direct associations were observed between various measures of air pollution and incidence of otitis media. Crude and adjusted ORs were systematically over unity for all the considered pollutants and in both the cohorts.	Adjusted OR for an increase in 3 $\mu g/m^3$ of $PM_{2.5}$: The Netherlands At 1 year of age: 1.13 (0.98, 1.32) At 2 years of age: 1.13 (1.00, 1.27) Munich, Germany At 1 year of age: 1.19 (0.73, 1.92) At 2 years of age: 1.24 (0.84, 1.83).
GERMANY			
Heinrich et al. (1999) (Heinrich *et al*, 1999) Bitterfeld, Zerbstand Hettstedt areas of former East Germany, During Sept. 1992 to July 1993 TSP ranged from 44 to 65; PM_{10} measured October 1993 - March 1994 ranged from 3 to 40; and BS ranged from 26 to 42. PM was measured with a Harvard impactor.	Parents of 2470 school children (5-14 year) completed respiratory health questionnaire. Children excluded from analysis if had lived < 2 years in their current home, yielding an analysis group of 2,335 children. Outcomes studied: physician diagnosis for asthma, bronchitis, symptom, bronchial reactivity, skin prick test, specific IgE. Multiple logistic regression analyses examined regional effects.	Controlling for medical, socio-demographic, and indoor factors, children in more polluted area had circa 50% increase for bronchitic symptoms and physician-diagnosed allergies compared to control area and circa twice the respiratory symptoms (wheeze, shortness of breath and cough). Pulmonary function tests suggested slightly increased airway reactivity to cold for children in polluted area.	No single pollutant could be separated out as being responsible for poor respiratory health.

Heinrich et al. (2000) (Heinrich *et al*, 2000) Three areas of former E. Germany Pollution measures: SO_2, TSP, and some limited PM_{10} data. TSP decreased from 65, 48, and 44 to 43, 39, and 36 in the three areas. PM was measured with a Harvard impactor.	Cross-sectional study of children (5-14 year). Survey conducted twice, in 1992-1993 and 1995-1996; 2,335 children surveyed in first round, and 2,536 in second round. Only 971 children appeared in both surveys. The frequency of bronchitis, otitis media, frequent colds, febrile infections studied. Because changes measured over time in same areas, covariate adjustments not necessary.	PM and SO_2 levels both decreased in the same areas; so results are confounded.	The prevalence of all respiratory symptoms decreased significantly in all three areas over time.
Heinrich et al. (2002) (Heinrich *et al*, 2002) Surveyed children aged 5-14 in 1992-3, 1995-6, 1998-9. Annual TSP levels ranged from 25-79. Small particles ($NC_{0.01-2.5}$ per $103cm^{-3}$) remained relatively constant.	A two-stage logistic regression model was used to analyze the data which adjusted for age, gender, educational level of parents, and indoor factors. The model included fixed area effects, random deviations, and errors from the adjustments. Parameters were estimated using GEE methods.	The study found bronchitis and frequency of colds were significantly related to TSP.	An increment of 50 $\mu g/m^3$ TSP was associated with an OR for bronchitis of 3.02 (1.72, 5.29) and an OR of 1.90 (1.17, 3.09) for frequency of colds.
Frye et al. (2003) (Frye *et al*, 2003) Surveyed children in 1992-3, 1995-6, 1998-9. Annual TSP levels ranged from 23-79.	This study examined the effects of improved air quality since 1990 in East Germany on lung function in children. Three consecutive cross-sectional surveys of schoolchildren aged 11–14 years from three communities in East Germany were performed during 1992-1999. Lung function tests were available from 2,493 children. Percent change of lung function parameters according to a decrease of TSP by 50 $\mu g/m^3$ were derived by linear regression models after adjustment for sex, height, season, lung function equipment, parental education, parental atopy and environmental tobacco smoke.	FVC and FEV_1 of the children increased from 1992–1993 to 1998–1999. Decrements of TSP (p=0.043) and SO2 (p = 0.029) were significantly associated with an improvement of FVC. Effects on FEV_1 were smaller and not statistically significant.	50 $\mu g/m^3$ decrease of TSP. Adjusted percent change (95% CI): FVC Total: 4.7% (0.2, 9.5) Boys: 3.7% (-1.2, 8.8) Girls: 5.9% (0.8, 11.1) FEV_1 Total: 2.9% (-1.4, 7.3) Boys: 1.7% (-2.9, 6.6) Girls: 4.1% (-0.7, 9.2).

Krämer et al. (1999) (Kramer *et al*, 1999) Six East and West Germany communities (Leipzig, Halle, Maddeburg, Altmark, Duisburg, Borken) Between 1991 and 1995 TSP levels in six communities ranged from 46 to 102. Each East Germany community had decrease in TSP between 1991 and 1995. TSP was measured using a low volume sampler.	The study assessed relationship between TSP and airway disease and allergies by parental questionnaires in yearly surveys of children (5-8 year) between February and May. The questions included pneumonia, bronchitis ever diagnosed by physician, number of colds, frequent cough, allergic symptoms. In all, 19,090 children participated. Average response was 87%. Analyses were conducted on 14,144 children for whom information on all covariates were available. Variables included gender; parent education, heating fuel, ETS. Logistic regression used to allow for time trends and SO_2 and TSP effects. Regression coefficients were converted to ORs.	TSP and SO_2 simultaneously included in the model. Bronchitis ever diagnosed showed a significant association. A decrease in raw percentage was seen between the start of the study and the end for bronchitis. Bronchitis seemed to be associated only with TSP in spite of huge differences in mean SO_2 levels.	Bronchitis ever diagnosed TSP per 50 µg/m^3 OR 1.63 (1.37, 1.93) Halle (East) Calendar Year; TSP (µg/m^3); Bronchitis 1991; 102; 60.5 1992; 73; 54.7 1993; 62; 49.6 1994; 52; 50.4 1995; 46; 51.9
Gehring et al. (2002) (Gehring *et al*, 2002) In Munich, Germany December 1997 - January 1999 Annual $PM_{2.5}$ levels determined by 40 sites and a GIS predictor for model. Mean $PM_{2.5}$ annual average of 13.4 with range of 11.90 to 21.90.	Effect of traffic-related air pollutants. $PM_{2.5}$ and NO_2 on respiratory health outcomes wheeze, cough, bronchitis, respiratory infections, and runny nose were evaluated using multiple logistic regression analyses of l,756 children during the first and second year of life adjusting for potential confounding factors.	There was some indication of an association between $PM_{2.5}$ and symptoms of cough but not other outcomes. In the second year of life most effects were attenuated.	OR (95% CI) for a change in $PM_{2.5}$ concentration of 1.5 µg/m^3 Wheeze Age of 1 year: 0.91 (0.76, 1.09) Age of 2 year: 0.96 (0.83, 1.12) Cough without infection Age of 1 year: 1.34 (1.11, 1.61) Dry cough at night Age of 1 year: 1.31 (1.07, 1.60) Age of 2 year: 1.20 (1.02, 1.42) Bronchitis Age of 1 year: 0.98 (0.80, 1.20) Age of 2 year: 0.92 (0.78, 1.09) Respiratory infections Age of 1 year: 1.04 (0.91, 1.19) Age of 2 year: 0.98 (0.80, 1.20) Sneezing Age of 1 year: 1.01 (0.85, 1.20) Age of 2 year: 0.96 (0.82, 1.12).

Schikowski et al. (2005) (Schikowski *et al*, 2005) Consecutive cross-sectional studies. Rhine-Rhur Basin, Germany 1985-1994. PM_{10} annual mean of 43 with range of 35 to 53 PM_{10} five year mean of 48 with range of 39 to 56.	This study examined the effect of long-term exposure to PM_{10} from industry and traffic and NO_2 on COPD, as defined by lung function, in 4,757 middle-aged women enrolled in consecutive cross sectional studies conducted between 1985 and 1994 in the Rhine-Ruhr Basin of Germany. NO_2 and PM_{10} exposure was assessed by measurements done in an 8 km grid, and traffic exposure by distance from the residential address to the nearest major road using GIS data. Lung function was determined and COPD was defined by using the GOLD criteria. Chronic respiratory symptoms and possible confounders were defined by questionnaire data. Linear and logistic regressions, including random effects were used after adjustment for age, socioeconomic status, smoking, environmental tobacco smoke, occupational exposure to temperature and dust, and heating with fossil fuels.	The prevalence of COPD (GOLD stages 1–4) was 4.5%. COPD and pulmonary function were strongest affected by PM_{10} and traffic related exposure. Women living less than 100 m from a busy road also had a significantly decreased lung function, and COPD was 1.79 times more likely than for those living farther away. Chronic symptoms as based on questionnaire information showed effects in the same direction, but less pronounced.	OR (95% CI) for 7 µg/m^3 increase in PM_{10} (IQR) Annual means Chronic bronchitis: 1.00 (0.85, 1.18) Chronic cough: 1.03 (0.87, 1.23) Frequent cough: 1.01 (0.93, 1.10) COPD: 1.37 (0.98, 1.92) FEV_1: 0.953 (0.916, 0.989) FVC: 0.966 (0.940, 0.992) Five year means Chronic bronchitis: 1.13 (0.95, 1.34) Chronic cough: 1.11 (0.93, 1.31) Frequent cough: 1.05 (0.94, 1.17) COPD: 1.33 (1.03, 1.72) FEV_1: 0.949 (0.923, 0.975) FVC: 0.963 (0.945, 0.982).
Polat et al. (2002) (Polat *et al*, 2002) 4 month cross-sectional survey in 4 locations (A, B1, B2, C) of 3 cities in Nordrhein-Westfalen, Germany Feb 2000 to May 2000. TSP mean (SD) Location A: 49.1 (23.9) Location B1: 78.5 (29.8) Location B2: 46.7 (19.3) Location C: 34.9 (12.6.).	At 4 locations, in 3 different cities of Nordrhein-Westfalen, TSP, O_3, NO_x and SO2 were derived from compliance measurements by governmental offices, and 884 subjects (501 mothers and 383 children, 6 ± 7 years old) were screened using nasal lavage. Authors studied a potential association between ambient exposure in the 4 locations and nasal inflammation in a 4-months cross-sectional survey.	No significant differences in total cell counts or percentage of neutrophils were found between mothers or children from the 4 different locations, despite small but significant differences in ambient exposure to TSP, SO_2, O_3, and NO_x during this period.	No estimates for TSP were provided.

Wolf (2002) (Wolf, 2002) 1,435 patients treated for rhinosinusitis in a hospital of Cologne, 1990-1999. Annual mean of TSP (1998): 39.	The study investigated the association between air pollution and chronic rhinosinusitis in Cologne, Germany. Addresses of 1,435 patients treated for chronic rhinosinusitis at the Otorhinolaryngology Department of the University Hospital of Cologne between 1990 and 1999 were assigned to one of the 85 city districts. TSP, SO_2 and NO_x were linked to these areas. A combined indicator of air quality was derived from the three considered measures. Regression analyses were computed adjusting for socioeconomic level of the 85 districts.	A weak but consistent relation between more polluted areas and the prevalence of chronic rhinosinusitis was found.	No estimates for TSP were provided.
FRANCE			
Baldi et al. (1999) (Baldi *et al*, 1999) 24 areas of seven French towns, 1974-1976. Pollutants: TSP, BS, and SO_2, NO4 3-year average TSP-mean annual values ranging between 45 and 243. TSP was measured by the gravimetric method.	Reanalysis of Pollution Atmospheric of Affection Respiratory Chroniques (PAARC) survey data to search for relationships between mean annual air pollutant levels and prevalence of asthma in 1291 adult (25-59 years) and 195 children (5-9 years) asthmatics. Random effects logistic regression model used and included age, smoking, and education level in the final model.	Only an association between SO_2 and asthma in adults observed. No other pollutant was associated. Nor was relationship with children seen. Meteorological variables and O_3 not evaluated.	For a 50 µg/m^3 increase in TSP Adult asthma prevalence OR 1.01 (0.92, 1.11)
Zeghnoun et al. (1999) (Zeghnoun *et al*, 1999) La Havre, France, 1993-1996. Daily mean BS levels measured in three stations ranged between 12 and 14.	Respiratory drug sales for mucolytic and anticough medications (most prescribed by a physician) were evaluated versus BS, SO_2, and NO_2 levels. An autoregressive Poisson regression model permitting overdispersion control was used in the analysis.	Respiratory drug sales associated with BS, NO_2, and SO_2 levels. Both an early response (0 to 3 day lag) and a longer one (lags of 6 and 9 days) were associated.	—

Penard-Morand et al. (2005); (Penard-Morand *et al*, 2005) ISAAC II Study, 6,672 schoolchildren from six French cities, Enrollment: March 1999-October 2000. Exposure: 1998-2000. 3-year-averaged concentration of PM_{10}, 22.	The present cross-sectional study analysed the associations between long-term exposure to background air pollution and atopic and respiratory outcomes in 6,672 schoolchildren aged 9–11 years recruited from 108 randomly schools in six French cities. Children underwent a clinical examination including a skin prick test (SPT) to common allergens, exercise-induced bronchial reactivity (EIB) and skin examination for flexural dermatitis. The prevalence of asthma, allergic rhinitis and atopic dermatitis was assessed by a standardized health questionnaire completed by the parents. Three-year-averaged concentrations of air pollutants (NO_2, SO_2, PM_{10} and O_3) were calculated at children' schools using measurements of background monitoring stations. ORs were derived by multiple logistic regression models after adjustment for age, sex, family history of allergy, passive smoking and parenteral education.	EIB, lifetime asthma and lifetime allergic rhinitis were directly associated to an increase in the exposure to SO_2, PM_{10} and O_3. Moreover, SPT positivity was associated with O_3. Associations with past year symptoms were consistent, even if not always statistically significant. Results persisted in long-term resident (current address for at least 8 years) children. Authors concluded that a moderate increase in long-term exposure to background ambient air pollution was associated with an increased prevalence of respiratory and atopic indicators in children.	OR (95% CI) for an increment of PM_{10} by 10 µg/m^3: During the clinical examination EIB: 1.43 (1.02, 2.01) Flexural dermatitis: 0.79 (0.59, 1.07) Past year Wheeze: 1.05 (0.72, 1.54) Asthma: 1.23 (0.77, 1.95) Rhinoconjunctivitis: 1.17 (0.86, 1.59) Atopic dermatitis: 1.28 (0.96, 1.71) Lifetime Asthma: 1.32 (0.96, 1.81) Allergic rhinitis: 1.32 (1.04, 1.68) Atopic dermatitis: 1.09 (0.88, 1.36) Atopy: 0.98 (0.80, 1.22) Pollen: 1.14 (0.85, 1.53) Indoor: 0.91 (0.72, 1.15) Moulds: 1.00 (0.53, 1.88).
SWITZERLAND			
Ackermann-Liebrich et al. (1997) (Ackermann-Liebrich *et al*, 1997) Eight Swiss regions Pollutants: SO_2, NO_2, TSP, O_3, and PM_{10}. PM was measured with a Harvard impactor. PM_{10} ranged from 10 to 53 with a mean of 37.	Long-term effects of air pollution studied in cross-sectional population-based sample of adults aged 18 to 60 years. Random sample of 2,500 adults in each region drawn from registries of local inhabitants. Natural logarithms of FVC and FEV_1 regressed against natural logarithms of height, weight, age, gender, atopic status, and pollutant variables.	Significant and consistent effects on FVC and FEV were found for PM_{10}, NO_2 and SO_2.	Estimated regression coefficient for PM_{10} versus FVC: - 0.035 (-0.041, -0.028). Corresponding value for FEV_1: -0.016 (-0.023, -0.01). Thus, 10 µg/m^3 PM_{10} increase estimated to lead to estimated 3.4 percent decrease in FVC and 1.6 percent decrease in FEV_1.

Braun-Fahrländer et al. (1997) (Braun-Fahrlander *et al*, 1997) 10 Swiss communities Pollutants: PM_{10}, NO_2, SO_2, and O_3. PM was measured with a Harvard impactor. PM_{10} ranged from 10 to 33.	Impacts of long-term air pollution exposure on respiratory symptoms and illnesses were evaluated in cross-sectional study of Swiss school children, (aged 6 to 15 years). Symptoms analyzed using a logistic regression model including covariates of family history of respiratory and allergic diseases, number of siblings, parental education, indoor fuels, passive smoking, and others.	Respiratory endpoints of chronic cough, bronchitis, wheeze and conjunctivitis symptoms were all related to the various pollutants. The colinearity of the pollutants including NO_2, SO_2, and O_3, prevented any causal separation.	PM_{10} Chronic cough OR 11.4 (2.8, 45.5) Bronchitis OR 23.2 (2.8, 45.5) Wheeze OR 1.41 (0.55, 3.58)
Bayer-Oglesby et al. (2005) (Bayer-Oglesby *et al*, 2005) 9,591 children from 9 Swiss communities, 1992-2001. PM_{10} ranged from 10 to 47.	The present cross-sectional study investigated whether a rather moderate decline of air pollution levels in the 1990s in Switzerland was associated with a reduction in respiratory symptoms and diseases in 9,591 school children of nine Swiss communities between 1992 and 2001. Parents of children completed identical questionnaires on health status and covariates. We assigned to each child an estimate of regional PM_{10} and determined change in PM_{10} since the first survey. ORs associated with a decline of 10 $\mu g/m^3$ in PM_{10} were derived after a priori adjustment for socioeconomic factors, health related factors, including family history of asthma, bronchitis and atopy, indoor factors, including smoking status of the mother, and avoidance behaviour with respect to allergies.	PM_{10} was directly associated with prevalence of chronic cough, bronchitis, common cold, nocturnal dry cough, and conjunctivitis symptoms. Changes in prevalence of sneezing during pollen season, asthma, and hay fever were not associated with PM_{10}.	Adjusted OR (95% CI) for a 10-$\mu g/m^3$ decline of PM_{10}: Chronic cough: 0.65 (0.54, 0.79) Bronchitis: 0.66 (0.55, 0.80) Common cold: 0.78 (0.68, 0.89) Nocturnal dry cough: 0.70 (0.60, 0.83) Conjunctivitis: 0.81 (0.70, 0.95) Wheeze: 0.8, NS Sneezing: 0.9, NS Asthma: 1.0, NS Hay fever: 1.0, NS.

Bayer-Oglesby et al. (2006) (Bayer-Oglesby *et al*, 2006) SAPALDIA cohort, Switzerland, 1991-2002. PM_{10} mean: 21.4.	This study examined the association between living near main streets and respiratory symptoms using the Swiss Cohort Study on Air Pollution and Lung Diseases in Adults (SAPALDIA) cohort. SAPALDIA 1 was conducted in 1991. In 2002 subjects were re-interviewed (SAPALDIA 2). The present analyses were based on a total of 12,999 observations from 8,555 subjects. Geographic information system data were used to assign individual traffic exposure estimates at each subject's residence. The generalized estimating equation regression models were derived after adjustment for various factors, including sex, age, education, active and passive smoking, occupational exposure, regional background PM_{10} (estimated by a dispersion model, using 44 monitoring sites in Switzerland in 2000)and health related factors,	Subjects living near busy streets reported more frequently respiratory symptoms. This leaves open the question whether the prevalence of bronchitis symptoms is due to "long-term effect" or reflects the acute effects of air pollution in longer periods.	No estimates for PM_{10}.
Zemp et al. (1999) (Zemp *et al*, 1999) 8 study sites in Switzerland. Pollutants: TSP, PM_{10}, SO_2, NO_2, and O_3. PM was measured with a Harvard impactor. PM_{10} ranged from 10 to 33 with a mean of 21.	Logistic regression analysis of associations between prevalences of respiratory symptoms in random sample of adults and air pollution. Regressions adjusted for age, BMI, gender, parental asthma, education, and foreign citizenship.	Chronic cough and chronic phlegm and breathlessness were related to TSP, PM_{10} and NO_2.	Chronic cough, chronic phlegm and breathlessness were related to PM_{10}, and TSP.
AUSTRIA			
Horak et al. (2002) (Horak *et al*, 2002) Frischer et al. (1999) (Frischer *et al*, 1999) Eight communities in lower Austria between 1994-1997. PM_{10} mean summer value of 17.36 and winter value of 21.03.	Lung function assessed in 975 schoolchildren in grade 2-3. A several step analysis included GEE and sensitivity analyses.	Concluded that long term exposure to PM_{10} had a significant negative effect on lung function with additional evidence for a further effect for O_3 and NO_2.	After adjusting for confounders an increase in PM_{10} by 10 µg/m^3 was associated with a decrease in FEV_1 growth at 84 mL/yr and 329 mL/s year for MEF_{25-75}.

GREECE			
Karakatsani et al. (2003) (Karakatsani *et al*, 2003) Nested case-control study of the EPIC study, Athens, Greece. BS for the most polluted area ranged from 34 to 79.	A case–control study nested in the EPIC cohort, undertaken in Athens, Greece, was conducted in order to examine the association between long-term exposure to ambient air pollution and the risk of chronic bronchitis, emphysema or COPD. Overall, 168 participants reporting a history of COPD symptomatology and 168 healthy controls individually matched for age and gender, were visited by a physician at their homes for conducting spirometry and a medical interview. Individualized personal exposure to air pollution was assessed on the basis of long-term residential and occupational subject history linked with geographical air pollution distribution.	Cases were more exposed to air pollution compared to controls, with ORs for subjects in the highest quartile of exposure *vs* all others included between 1.46 and 2.01. Authors concluded that long-term exposure to air pollution was an important factor in the development of chronic respiratory diseases.	No estimates on PM.
Sichletidis et al. (2005) (Sichletidis *et al*, 2005) 2000-2001. Children from five cities of Western Macedonia, Greece (three with information on TSP and PM_{10}). TSP mean: Ptolemaida: 132 Kozani: 88 Florina: 56 PM_{10} mean: Ptolemaida: 86.3 Kozani: 64.2 Florina: 58.3.	This study compares prevalence of rhinitis and bronchitis in 5 different cities of Western Macedonia characterized by different type and level of environmental pollution. During 2000 and 2001 3,559 children aged 9-12 years were enrolled in the study. Concentrations of TSP and PM_{10} were measured in 3 cities only.	Symptoms from the upper and lower respiratory system were more frequent in children living in more polluted areas.	No estimates for PM

POLAND			
Jedrychowski et al. (1999) (Jedrychowski *et al*, 1999) In Krakow, Poland in 1995 and 1997 Spacial distributions for BS and SO_2 derived from network of 17 air monitoring stations. BS 52.6 µg/m ± 53.98 in high area and 33.23 ± 35.99 in low area.	Effects on lung function growth studied in preadolescent children. Lung function growth rate measured by gain in FVC and FEV_1 and occurrence of slow lung function growth (SLFG) over the 2 year period defined as lowest quintile of the distribution of a given test in gender group. 1,129 children age 9 participated in first year and 1,001 in follow-up 2 years later. ATS standard questionnaire and PFT methods used. Initially univariate descriptive statistics of pulmonary function indices and SLFG were established, followed by multivariate linear regression analyses including gender, ETS, parental education, home heating system and mold. SO_2 was also analyzed.	Statistically significant negative association between air pollution level and lung function growth (FVC and FEV_1) over the follow up in both gender groups. SLFG was significantly higher in the more polluted areas only among boys. In girls there was consistency in the direction of the effect, but not stat. significant. Could not separate BS and SO_2 effects on lung function growth. Excluding asthma subjects sub-sample (size 917) provided similar results.	Boys SLFG (FVC) OR: 2.15 (1.25, 3.69) SLFG (FEV_1) OR: 1.90 (1.12, 3.25) Girls FVC OR: 1.50 (0.84, 2.68) FEV_1 OR: 1.39 (0.78, 2.44)
Jedrychowski and Flak (1998) (Jedrychowski andFlak, 1998) In Kracow Poland, in 1991-1995 Daily 24 h concentration of SPM (black smoke) measured at 17 air monitoring stations. High areas had 52.6 mean compared to low areas at 33.2.	Respiratory health survey of 1,129 school children (aged 9 year). Respiratory outcomes included chronic cough, chronic phlegm, wheezing, difficulty breathing and asthma. Multi-variable logistic regression used to calculate prevalence OR for symptoms adjusted for potential confounding.	The comparison of adjusted effect estimates revealed chronic phlegm as unique symptom related neither to allergy nor to indoor variable but was associated significantly with outdoor air pollution category (APL). No potential confounding variable had major effect.	It was not possible to assess separately the contribution of the different sources of air pollutants to the occurrence of respiratory symptoms. ETS and household heating (coal vs. gas vs. central heating) appeared to be of minimal importance.
BULGARIA			
Turnovska and Kostiranev (1999) (Turnovska T andKostianev S, 1999) Dimitrovgrad, Bulgaria, May 1996 TSP mean levels were 520 ± 161 in 1986 and 187 ± 9 in 1996. SO_2, H2S, and NO2 also measured.	Respiratory function of 97 schoolchildren (mean age 10.4 ± 0.6 year) measured in May 1996 as a sample of 12% of all four-graders in Dimitrovgrad. The obtained results were compared with reference values for Bulgarian children aged 7 to 14 year, calculated in the same laboratory in 1986. Variation analysis techniques were used to treat the data.	Vital capacity and FEV_1 were significantly lower (mean value. = 88.54% and 82.5% respectfully) comparing values between 1986 and 1996. TSP had decreased by 2.74 times to levels still higher than Bulgarian and WHO standards.	—

TABLE IX - LONG TERM PARTICULATE MATTER EXPOSURE AND CANCER.

Reference, Location, Years, PM In dex, Mean or Median (µg/m^3).	Study Description. Met hods, co-p ollutants and covariates.	Results and Comments.	PM Index, RR (95% CI)
EPIC			
Vineis et al., 2006 (Vineis *et al*, 2006); Vineis et al., 2007 (Vineis *et al*, 2007) Nested case-control study (271 cases, 737 matched controls) in the EPIC cohort; 10 countries. Recruitment period: 1993-1998 Median follow-up: 7 years. PM_{10} between 19.9 (Ile de France 1995-1999) and 73.4 (Turin 1990-1994).	In a nested case-control study of the European Prospective Study into Cancer and Nutrition (EPIC) cohort, based on more than 500,000 healthy volunteers aged 35-74 from 10 European countries, 271 ex-smoker (since at least 10 years) and never smoker cases with lung cancer occurred in a median follow-up of 7 years. Cases were compared with 737 controls frequency matched by age, smoking status, country and time between recruitment and diagnosis. In order to assess the exposure to traffic-related air pollution, the home address at the time of enrollment was considered. Both distances to a major street and annual average concentrations of PM_{10} (available for 113 cases and 312 controls) and other co-pollutants, including NO_2, O_3 and SO_2, were considered. ORs were derived by conditional logistic regression models after further adjustment for education, BMI, physical activity, energy intake, fruit, vegetables, meat and alcohol consumption. Further models include cotinine levels and occupational index.	No significant associations were found for increments by 10 µg/m^3 of PM_{10}, NO_2 (OR=1.14; 95% CI: 0.78-1.67) and SO_2. (OR=1.08; 95% CI: 0.89-1.30). Some excess risks were found when considering the third *vs* the other two tertiles of exposure to NO_2 (ORs ranged between 1.30 and 1.62 according to various models; PAR%=5%), but not to PM_{10} and SO_2. The OR of living nearby heavy traffic roads was 1.46 (95% CI: 0.89-2.40), corresponding to a PAR% of 7%.	Adjusted OR for increments of 10 µg/m^3 of PM_{10}: 0.91 (0.70, 1.18). OR for the upper *vs* the lowest and the intermediate tertiles (i.e., ≥27 vs <27 µg/m^3): Adjusted for matching variables: 0.98 (0.66, 1.45) Further adjusted model: 1.05 (0.65, 1.69) Further adjusted for cotinine: 2.85 (0.97, 8.33) Further adjusted for occupational index: 1.02 (0.68, 1.51).

EUROPEAN ECOLOGI C STUDY			
Nawrot et al., 2007 (Nawrot *et al*, 2007) Ecological study; 15 European countries. Annual mean $PM_{2.5}$; estimated for the year 2002) between 1 (Finland) and 22 (Belgium).	This ecological study analyzed the relation between age and smoking lung cancer rates in men across 15 European countries (obtained from the EUCAN database for the1998), and annual mean $PM_{2.5}$ concentrations estimated for the year 2002.	A significant correlation between countries'age and smoking standardized mortality rates for lung cancer in men and annual mean $PM_{2.5}$ was shown (Spearman correlation coefficient, r=0.57; p=0.03). No relation was evident for women (r=0.37; p=0.18). Authors concluded suggesting that some of the differences in lung cancer mortality in Europe could be explained by fine particulate air concentration.	RR for an increment of 5 $\mu g/m^3$ of $PM_{2.5}$ in men: 1.18 (1.04, 1.32).
Subnational studies			
GREAT BRITAIN			
Knox, 2005 (Knox, 2005) Population: All children dying for leukaemia or other cancers between 1955 and 1980 in Great Britain. Mean value of PM was not given.	In this study, birth and death addresses of children (aged < 16 years) dying from cancer between 1955 and 1980 in Great Britain were linked to emission hotspots for specific chemicals, including PM_{10}, CO, NO_x, obtained for the year 2001. Among children who moved house, distances from each address to the nearest hazard were compared. The aim of this study was to examine the excesses of close-to-hazard birth addresses compared with close to hazard death addresses, in order to understand whether prenatal or early postnatal exposure to oil combustion gases initiates cancers. Estimates of RR were based on birth/death ratios for children who moved houses within various distances. Atmospheric emissions hotspots were converted to coordinates. Distances to industrial sites, including bus station, railways, hospitals, incinerators, motorways were also considered.	There were excess RR within 1 km of hotspots for PM_{10}, CO, NO_x, and other oil based combustion gases (particularly 1,3-butadiene), and within 1.0 km of bus stations, hospitals, heavy transport centres, railways, and oil installations. The author concluded that childhood cancers were strongly determined by prenatal or early postnatal exposures to oil based combustion gases, especially from engine exhaust.	Among children who moved house, distances within 1 km from each address to the nearest emission of PM_{10} hotspot: Births= 1,420; Deaths=777 RR=1.83 (1.67, 2.00).

Knox, 2006 (Knox, 2006) Same study design as Knox, 2005 (Knox, 2005).	This is a re-analysis of the previous study for industrial sites and roads, considering more precise and adequate data on roads, rail and industrial sites.	Significant birth excesses were found within short distances of bus stations, railway stations, ferries, railways, and A, B class roads. As in the previous study, the author concluded that child cancer initiations were strongly determined by prenatal or early postnatal exposures to engine exhaust gases	No estimates for PM.
NORWAY			
Nafstad et al., 2003 (Nafstad *et al*, 2003); Nafstad et al., 2004 (Nafstad *et al*, 2004) Cohort of 16,209 men from Oslo, Norway, follow-up period: 1972/73 to 1998. No information on PM	This study examined the association between long term exposure to SO_2 and NO_x and lung cancer incidence in a cohort of Oslo men followed for 27 years. Cox proportional hazards regression after adjustment for smoking, education and age. An additional model included the two co-pollutants.	During the follow-up period, lung cancer occurred in 418 men. The adjusted RR for a 10 mg/m3 increase in average home address exposure between 1974 and 1978 was 1.08 (95% CI: 1.02-1.15) for NO_x and 1.01 (95% CI: 0.94-1.08) for SO_2.	No estimates for PM.
Naess et al., 2007 (Naess *et al*, 2007) Cohort of all inhabitants of Oslo (143,842). Follow-up period: 1992-1998. $PM_{2.5}$ range: 6.56-22.34 PM_{10} range: 6.57-30.13	This study investigated the association between concentrations of PM_{10}, $PM_{2.5}$ and NO_2 in 1992-1995, and cause-specific mortality, including lung cancer. The population included all inhabitants of Oslo Norway, aged 51–90 years on January 1992 with follow-up of deaths from 1992 to 1998. An air dispersion model was used to estimate levels of exposure in all 470 administrative neighbourhoods. Cox proportional hazards regression models were used after adjustment for age, education and occupational class. To model the relation between air pollutants and mortality, GAM models were used.	During follow-up, 1,453 lung cancer deaths occurred. Some direct associations were observed between PM and lung cancer mortality. The effects were small in the young age group (51-70 years) of men and moderate to large in the old age group (71-90 years). Women had particularly large effects in the young group. The three pollutants shared similar results, being their correlations high (between 0.88 and 0.95).	Occupational class and education adjusted HR for quartile increase of exposure: $PM_{2.5}$ Men 51-70 years: 1.07 (0.97-1.18) Women 51-70 years: 1.27 (1.13-1.43) Men 71-90 years: 1.07 (0.97-1.18) Women 71-90 years: 1.16 (1.02-1.32) PM_{10} Men 51-70 years: 1.07 (0.97-1.18) Women 51-70 years: 1.27 (1.13-1.43) Men 71-90 years: 1.08 (0.98-1.18) Women 71-90 years: 1.17 (1.03-1.33).

SWEDEN			
Nyberg et al. (2000) (Nyberg *et al*, 2000). Case-control study on 1,042 cases died for lung cancer and 2,364 controls died for other diseases in Stockholm. Study period 1985-1990. No information on PM.	This study examined the association between exposure to NO_x/NO_2 and SO_2 and lung cancer mortality in a case-control study based on 1,099 cases died for lung cancer and two companion groups (1,275 alive controls and 1,090 matched controls died for other diseases). Local air pollution levels were estimated using validated dispersion models. ORs were derived by logistic regression models after adjustment for age, smoking, exposure to occupational carcinogens and socioeconomic group (data obtained from each subject's next of kin).	NO_2 exposure over 30 years was not significantly associated to lung cancer mortality (OR for an increment by 10 µg/m^3 was 1.05 (95% CI: 0.93, 1.18). When considering NO_2 exposure 20 years previously, a borderline significant direct association was found with NO_2 (OR=1.10; 95% CI 0.97, 1.23) No association was observed with SO_2.	No estimates for PM.
DENMARK			
Raaschou-Nielsen et al. (2001) (Raaschou-Nielsen *et al*, 2001); Raaschou-Nielsen et al. (2002) (Raaschou-Nielsen *et al*, 2002). Case-control study on 1,989 children cases and 5,506 controls, Denmark, 1968-1991. No information on PM.	This study examined the association between traffic-related air pollution and the risk of cancer during childhood. During 1968-1991, the Danish Cancer Registry reported 1,989 children with a diagnosis of leukemia, cancer of the central nervous system, or malignant lymphoma. These children were compared with 5,506 control children randomly selected from the entire childhood population. The residential histories of the children were traced from 9 months before birth until the time of diagnosis of the cases and a similar period for the controls. For each of the 18,440 identified addresses, information on traffic and the configuration of streets and buildings was collected. Average concentrations of benzene and NO_2 (indicators of traffic-related air pollution) were calculated for the relevant period, and exposures to air pollution during pregnancy and during childhood were calculated separately.	The risks of leukemia, central nervous system tumors, and all selected cancers combined were not linked to exposure to benzene or NO_2. The risk of lymphomas increased by 25% (p for trend = 0.06) and 51% (p for trend = 0.05) for a doubling of the concentration of benzene and nitrogen dioxide, respectively, during the pregnancy. The association was restricted to Hodgkin's disease.	No estimates for PM.

THE NETHERLANDS			
Hoek et al. (2002) (Hoek *et al*, 2002) The Netherlands Cohort study 1986-1994 Subjects= 4,492; BS exposure, mean (SD): background 15.1 (2.5); background and local 15.5 (3.2).	This study examined the association between BS and NO_2 in a cohort of 4,492 residents in various areas of the Netherlands and cause-specific mortality, including lung cancer. Long-term exposure to traffic-related BS and NO_2 was estimated for the 1986 home address. Cox's proportional hazards models were used after adjustment for age, sex, education, BMI, occupation, active and passive cigarette smoking, and neighbourhood socioeconomic score. Two models of exposure for every pollutant were used: 1) the background concentration was entered in the model with the indicator variable for living near a major road. 2) the sum of the background and the estimated contribution from living near a major road to air pollution concentrations. Too few people died from lung cancer to obtain stable estimates for the indicator variable for living near a major road.	Overall, 60 lung cancer deaths occurred during the follow-up period. No significant association emerged between both BS and NO_2 and lung cancer mortality.	RR for an increment of 10 $\mu g/m^3$ (95^{th} – 5^{th} percentile) of BS. Background and local: 1.06 (0.43, 2.63).
Visser et al., 2004 (Visser *et al*, 2004) Ecologic study Amsterdam, 1989-1997; 27,157 cancer cases. No information on PM.	This study examined the association between residential traffic intensity, and cancer incidence in Amsterdam in 1989–1997. Daily traffic intensity data for individual addresses along the main roads were linked with the population-based regional cancer registry. SIR were derived by comparison between observed numbers of cancer for residents along main roads with expected numbers derived using the age group- and sex-specific cancer incidence in the population not residing along the main roads.	Analysing 27,157 cases, no clear evidence of an association between residence along main roads and the incidence of cancer in adults emerged (SIR=1.03; 95% CI: 1.00-1.07), although for subjects residents along the main roads an excess risk of hematological malignancies in females (SIR=1.23; 95% CI: 1.04-1.44) and children (SIR for acute lymphocytic leukaemia =2.5; 95% CI: 0.8-5.9) was found. Moreover, residential traffic intensity increased the risk of gastrointestinal cancer in males (SIR=1.16; 95CI: 1.04-1.28).	No estimates for PM.

Visser et al., 2005 (Visser *et al*, 2005) Ecologic study Schiphol, Amsterdam, 1988-2003; 13,207 cancer cases. PM_{10} (2002), mean: 40.	This study investigated the incidence of lung cancer between 1988 and 2003 for residents of the Amsterdam Airport Schiphol, where elevated concentrations of potential carcinogenic compounds, including benzene, PM_{10}, CO and SO_2, were observed. Cancer age-standardized incidence ratio (SIR) were computed using national incidence rates as a reference.	Analysing 13,207 cases, no clear evidence of an association between residence around Schiphol area and the incidence of cancer in adults emerged (SIR=1.02; 95% CI: 1.00, 1.03), a whereas statistically significantly increased incidence were found for hematological malignancies (SIR=1.12; 95%CI: 1.05, 1.19), the incidence of cancer of the respiratory system was statistically significantly decreased (SIR=0.94, 95% CI: 0.90, 0.99), because of to the low rate in males (SIR 0.89).	No estimates for PM.
FRANCE			
Filleul et al. (2005) (Filleul *et al*, 2005) PAARC survey 24 areas of 7 French cities period of exposure measurement: 1974-1976 Subjects= 14,284 adults TSP min/max: 45/243 BS min/max: 18/152.	This study examined the long term effects of TSP, BS, SO_2, NO_2 and NO (daily assessed in 1974-1976) on mortality, including lung cancer mortality in the Pollution Atmospherique et Affections Respiratoires Chroniques (PAARC) survey, conducted in 24 areas of 7 French cities on 14,284 adults, followed for the period 1974-2001. RRs were estimated by Cox proportional hazard regression models, after adjustment for age, sex, smoking, BMI, education, and occupational exposure. The analyses were performed for all 24 areas and in a subgroup of 18 areas with a ratio of NO/ NO_2 <3 (with monitors potentially influenced by local traffic).	After approximately 25 years of follow-up, 178 lung cancer deaths occurred. Considering all the 24 areas, and after exclusion of 6 areas influenced by local traffic, no association was found between TSP, BS and the other considered co-pollutants, and lung cancer mortality. NO_2 significantly increased the mortality for lung cancer.	Mortality RR for an increment of 10 µg/m^3 of TSP: 24 areas: 0.97 (0.94-1.01) 18 areas not influenced by local traffic: 1.00 (0.92-1.10) Mortality RR for an increment of 10 µg/m^3 of BS: 24 areas: 0.97 (0.93-1.01) 18 areas not influenced by local traffic: 1.03 (0.92-1.15).
ITALY			
Parodi et al. (2005) (Parodi *et al*, 2005). Cornigliano, a district of the Genoa municipality, northern Italy, 1986-1997. PM_{10}, annual mean between 57 and 79 before the coke oven closing (2001) and 43 in 2002.	This study investigated the incidence of lung cancer between 1986 and 1997 for residents of an area of northern Italy near a coke oven plant, where elevated concentrations of potential carcinogenic compounds, including benzene, PM_{10}, CO and SO_2, were observed around the coke oven. Age-standardized incidence ratios (SIR) between Cornigliano and two selected reference populations (Rivarolo and Genoa) were derived.	In Cornigliano, 158 lung cancer cases occurred in men, and 28 in women. Only a marginal excess risk of lung cancer was observed compared with two selected control populations while a gradient in the areas close to the plant emerged among females. Using Genoa as the reference population, the age-adjusted SIR for Cornigliano was 1.19 (95% CI: 1.01-1.38) in men, and 0.98 (95% CI: 0.65-1.41) in women.	No estimates for PM.

Barbone et al. (1995) (Barbone *et al*, 1995). Case-control study on 755 cases died for lung cancer and 755 matched controls died for other diseases in Trieste. Study period 1979-1981 and 1985-1986. Mean total particulate deposition between 0.210 (rural area) and 0.721 g/m^2/day (industrial area).	This study examined the association between particulate deposition and lung cancer mortality in a case-control study based on 755 cases died for lung cancer and 755 matched controls died for other diseases in Trieste from 1976 to 1981, and from 1985 to 1986. Air pollution at the residence of each subject was estimated from the average value of particulate deposition at the nearest of 28 monitoring stations. ORs were derived by logistic regression models after adjustment for age, smoking habit, exposure to occupational carcinogens and social class (data obtained from each subject's next of kin).	The risk of lung cancer increased with increasing level of air pollution for all types of lung cancer combined (p per trend=0.022), for small cell carcinoma (p=0.016) and for large cell carcinoma (p=0.049).	OR for total particulate deposition>0.298 vs <0.175 g/m^2/day: All lung cancers: 1.4 (1.1, 1.8) Squamous: 1.2 (0.8, 1.7) Small cell: 1.7 (1.1, 2.5) Large cell: 1.7 (0.9, 3.0) Adenocarcinoma: 1.3 (0.8, 2.0).
Crosignani et al. (2004) (Crosignani *et al*, 2004). Case-control study (120 cases with childhood leukaemia, and 480 controls), Varese, northern Italy, 1978-1997. No information on PM.	This study examined the effect of annual mean concentration of benzene on the risk of childhood leukemia, using a population-based case- control study in the Province of Varese, northern Italy. All 120 incident cases from 1978–97 were included in the study. Controls were 480 sex- and age-matched children sampled from the general population. The concentration of benzene was measured outside the home using a Gaussian diffusion model. ORs were derived by logistic regression conditioned by age and sex.	Compared to children whose homes was not exposed to road traffic emissions (<0.1 µg/m^3 of benzene annual average), the risk of childhood leukaemia was significantly higher for heavily exposed children (>10 µg/m^3), the RR being 3.91 (95% CI: 1.36, 11.27).	No estimates for PM.
POLAND			
Jedrychowski et al. (1990) (Jedrychowski *et al*, 1990) Case-control study on 1,099 cases died for lung cancer and 1,073 controls frequency matched by age and sex died for other diseases in Cracow. Study period 1980-1985. Mean TSP not provided.	This study examined the association between exposure to air pollution and lung cancer mortality in a case-control study based on 1,099 cases died for lung cancer and 1,073 matched controls died for other diseases in Cracow, Poland between 1980 and 1985. Air pollution at the residence of each subject was defined on the basis of the combined concentration of TSP and SO_2, determined by 20 monitoring stations for 8 years (1973-1980). ORs were derived by logistic regression models after adjustment for age, smoking habit, exposure to occupational carcinogens and education (data obtained from each subject's next of kin).	The risk of lung cancer increased with increasing level of air pollution in men (OR for the highest vs the lowest level of air pollution was 1.48; 95% CI 1.08, 2.01) but not in women (OR was 1.17; 95% CI 0.70, 1.96).	No estimates for TSP.

13. REFERENCES

1. Ackermann-Liebrich U, Leuenberger P, Schwartz J, Schindler C, Monn C, Bolognini G, Bongard JP, Brandli O, Domenighetti G, Elsasser S, Grize L, Karrer W, Keller R, Keller-Wossidlo H, Kunzli N, Martin BW, Medici TC, Perruchoud AP, Schoni MH, Tschopp JM, Villiger B, Wuthrich B, Zellweger JP, Zemp E (1997) Lung function and long term exposure to air pollutants in Switzerland. Study on Air Pollution and Lung Diseases in Adults (SAPALDIA) Team. *Am J Respir Crit Care Med* 155: 122-129.

2. Aga E, Samoli E, Touloumi G, Anderson HR, Cadum E, Forsberg B, Goodman P, Goren A, Kotesovec F, Kriz B, Macarol-Hiti M, Medina S, Paldy A, Schindler C, Sunyer J, Tittanen P, Wojtyniak B, Zmirou D, Schwartz J, Katsouyanni K (2003) Short-term effects of ambient particles on mortality in the elderly: results from 28 cities in the APHEA2 project. *Eur Respir J Suppl* 40: 28s-33s.

3. Alberdi Odriozola JC, Diaz Jimenez J, Montero Rubio JC, Miron Perez IJ, Pajares Ortiz MS, Ribera Rodrigues P (1998) Air pollution and mortality in Madrid, Spain: a time-series analysis. *Int Arch Occup Environ Health* 71: 543-549.

4. Analitis A, Katsouyanni K, Dimakopoulou K, Samoli E, Nikoloulopoulos AK, Petasakis Y, Touloumi G, Schwartz J, Anderson HR, Cambra K, Forastiere F, Zmirou D, Vonk JM, Clancy L, Kriz B, Bobvos J, Pekkanen J (2006) Short-term effects of ambient particles on cardiovascular and respiratory mortality. *Epidemiology* 17: 230-233.

5. Anderson HR, Bremner SA, Atkinson RW, Harrison RM, Walters S (2001) Particulate matter and daily mortality and hospital admissions in the west midlands conurbation of the United Kingdom: associations with fine and coarse particles, black smoke and sulphate. *Occup Environ Med* 58: 504-510.

6. Anderson HR, Ponce de Leon A, Bland JM, Bower JS, Emberlin J, Strachan DP (1998) Air pollution, pollens, and daily admissions for asthma in London 1987-92. *Thorax* 53: 842-848.

7. Anderson HR, Ponce de Leon A, Bland JM, Bower JS, Strachan DP (1996) Air pollution and daily mortality in London: 1987-92. *BMJ* 312: 665-669.

8. Atkinson RW, Anderson HR, Strachan DP, Bland JM, Bremner SA, Ponce de Leon A (1999a) Short-term associations between outdoor air pollution and visits to accident and emergency departments in London for respiratory complaints. *Eur Respir J* 13: 257-265.

9. Atkinson RW, Anderson HR, Sunyer J, Ayres J, Baccini M, Vonk JM, Boumghar A, Forastiere F, Forsberg B, Touloumi G, Schwartz J, Katsouyanni K (2001) Acute effects of particulate air pollution on respiratory admissions: results from APHEA 2 project. Air Pollution and Health: a European Approach. *Am J Respir Crit Care Med* 164: 1860-1866.

10. Atkinson RW, Bremner SA, Anderson HR, Strachan DP, Bland JM, de Leon AP (1999b) Short-term associations between emergency hospital admissions for respiratory and cardiovascular disease and outdoor air pollution in London. *Arch Environ Health* 54: 398-411.

11. Baldi I, Tessier JF, Kauffmann F, Jacqmin-Gadda H, Nejjari C, Salamon R (1999) Prevalence of asthma and mean levels of air pollution: results from the French PAARC survey. Pollution Atomospherique et Affections Respiratoires Chroniques. *Eur Respir J* 14: 132-138.

12. Barbone F, Bovenzi M, Cavallieri F, Stanta G (1995) Air pollution and lung cancer in Trieste, Italy. *Am J Epidemiol* 141: 1161-1169.

13. Bayer-Oglesby L, Grize L, Gassner M, Takken-Sahli K, Sennhauser FH, Neu U, Schindler C, Braun-Fahrlander C (2005) Decline of ambient air pollution levels and improved respiratory health in Swiss children. *Environ Health Perspect* 113: 1632-1637.

14. Bayer-Oglesby L, Schindler C, Hazenkamp-von Arx ME, Braun-Fahrlander C, Keidel D, Rapp R, Kunzli N, Braendli O, Burdet L, Sally Liu LJ, Leuenberger P, Ackermann-Liebrich U (2006) Living near main streets and respiratory symptoms in adults: the Swiss Cohort Study on Air Pollution and Lung Diseases in Adults. *Am J Epidemiol* 164: 1190-1198.

15. Beelen RMJ, Hoek G, Fischer PH, Van den Brandt PA, Bausch-Goldbohm RA, Schouten LJ, Brunekreef B (2007) Long-term effects of trarffic-related air pollution on mortality in a Dutch cohort study (NLCS-AIR Study). *Abstract - Health Effects Institute Annual Conference.* : Available online at: http://www.healtheffects.org/Pubs/AnnualConferenceProgram2007.pdf

16. Beeson WL, Abbey DE, Knutsen SF (1998) Long-term concentrations of ambient air pollutants and incident lung cancer in California adults: results from the AHSMOG study.Adventist Health Study on Smog. *Environ Health Perspect* 106: 813-823.

17. Biggeri A, Baccini M, Bellini P, Terracini B (2005) Meta-analysis of the Italian studies of short-term effects of air pollution (MISA), 1990-1999. *Int J Occup Environ Health* 11: 107-122.

18. Brauer M, Gehring U, Brunekreef B, de Jongste J, Gerritsen J, Rovers M, Wichmann HE, Wijga A, Heinrich J (2006) Traffic-related air pollution and otitis media. *Environ Health Perspect* 114: 1414-1418.

19. Brauer M, Hoek G, Van Vliet P, Meliefste K, Fischer PH, Wijga A, Koopman LP, Neijens HJ, Gerritsen J, Kerkhof M, Heinrich J, Bellander T, Brunekreef B (2002) Air pollution from traffic and the development of respiratory infections and asthmatic and allergic symptoms in children. *Am J Respir Crit Care Med* 166: 1092-1098.

20. Braun-Fahrlander C, Vuille JC, Sennhauser FH, Neu U, Kunzle T, Grize L, Gassner M, Minder C, Schindler C, Varonier HS, Wuthrich B (1997) Respiratory health and long-term exposure to air pollutants in Swiss schoolchildren. SCARPOL Team. Swiss Study on Childhood Allergy and Respiratory Symptoms with Respect to Air Pollution, Climate and Pollen. *Am J Respir Crit Care Med* 155: 1042-1049.

21. Bremner SA, Anderson HR, Atkinson RW, McMichael AJ, Strachan DP, Bland JM, Bower JS (1999) Short-term associations between outdoor air pollution and mortality in London 1992-4. *Occup Environ Med* 56: 237-244.

22. Brunekreef B, Holgate ST (2002) Air pollution and health. *Lancet* 360: 1233-1242.

23. Burr ML, Karani G, Davies B, Holmes BA, Williams KL (2004) Effects on respiratory health of a reduction in air pollution from vehicle exhaust emissions. *Occup Environ Med* 61: 212-218.

24. Clancy L, Goodman P, Sinclair H, Dockery DW (2002) Effect of air-pollution control on death rates in Dublin, Ireland: an intervention study. *Lancet* 360: 1210-1214.

25. Crosignani P, Tittarelli A, Borgini A, Codazzi T, Rovelli A, Porro E, Contiero P, Bianchi N, Tagliabue G, Fissi R, Rossitto F, Berrino F (2004) Childhood leukemia and road traffic: A population-based case-control study. *Int J Cancer* 108: 596-599.

26. D'Ippoliti D, Forastiere F, Ancona C, Agabiti N, Fusco D, Michelozzi P, Perucci CA (2003) Air pollution and myocardial infarction in Rome: a case-crossover analysis. *Epidemiology* 14: 528-535.

27. Dab W, Medina S, Quenel P, Le Moullec Y, Le Tertre A, Thelot B, Monteil C, Lameloise P, Pirard P, Momas I, Ferry R, Festy B (1996) Short term respiratory health effects of ambient air pollution: results of the APHEA project in Paris. *J Epidemiol Community Health* 50 Suppl 1: s42-46.

28. de Diego Damia A, Leon Fabregas M, Perpina Tordera M, Compte Torrero L (1999) Effects of air pollution and weather conditions on asthma exacerbation. *Respiration* 66: 52-58.

29. Diaz J, Garcia R, Ribera P, Alberdi JC, Hernandez E, Pajares MS, Otero A (1999) Modeling of air pollution and its relationship with mortality and morbidity in Madrid, Spain. *Int Arch Occup Environ Health* 72: 366-376.

30. Dominici F, McDermott A, Daniels M, Zeger SL, Samet JM (2003) Mortality among residents of 90 cities. In Revised analyses of time-series studies of air pollution and health. Special report. Revised analyses of the national morbidity. Mortality and air pollution study. Part II. Health Effects Institute: Boston, MA.

31. Dominici F, McDermott A, Zeger SL, Samet JM (2002) On the use of generalized additive models in time-series studies of air pollution and health. *Am J Epidemiol* 156: 193-203.

32. Eilstein D, Declercq C, Prouvost H, Pascal L, Nunes C, Filleul L, Cassadou S, Le Tertre A, Zeghnoun A, Medina S, Lefranc A, Saviuc P, Quenel P, Campagna D (2004) The impact of air pollution on health. The "Programme de Surveillance Air et Sante 9 villes" (Air and Health surveillance program in 9 cities). *Presse Med* 33: 1323-1327.

33. Filleul L, Rondeau V, Vandentorren S, Le Moual N, Cantagrel A, Annesi-Maesano I, Charpin D, Declercq C, Neukirch F, Paris C, Vervloet D, Brochard P, Tessier JF, Kauffmann F, Baldi I (2005) Twenty five year mortality and air pollution: results from the French PAARC survey. *Occup Environ Med* 62: 453-460.

34. Fischer P, Hoek G, Brunekreef B, Verhoeff A, van Wijnen J (2003) Air pollution and mortality in The Netherlands: are the elderly more at risk? *Eur Respir J Suppl* 40: 34s-38s.

35. Forastiere F, Stafoggia M, Picciotto S, Bellander T, D'Ippoliti D, Lanki T, von Klot S, Nyberg F, Paatero P, Peters A, Pekkanen J, Sunyer J, Perucci CA (2005) A case-

crossover analysis of out-of-hospital coronary deaths and air pollution in Rome, Italy. *Am J Respir Crit Care Med* 172: 1549-1555.

36. Frischer T, Studnicka M, Gartner C, Tauber E, Horak F, Veiter A, Spengler J, Kuhr J, Urbanek R (1999) Lung function growth and ambient ozone: a three-year population study in school children. *Am J Respir Crit Care Med* 160: 390-396.

37. Frye C, Hoelscher B, Cyrys J, Wjst M, Wichmann HE, Heinrich J (2003) Association of lung function with declining ambient air pollution. *Environ Health Perspect* 111: 383-387.

38. Fusco D, Forastiere F, Michelozzi P, Spadea T, Ostro B, Arca M, Perucci CA (2001) Air pollution and hospital admissions for respiratory conditions in Rome, Italy. *Eur Respir J* 17: 1143-1150.

39. Galan I, Tobias A, Banegas JR, Aranguez E (2003) Short-term effects of air pollution on daily asthma emergency room admissions. *Eur Respir J* 22: 802-808.

40. Garcia-Aymerich J, Tobias A, Anto JM, Sunyer J (2000) Air pollution and mortality in a cohort of patients with chronic obstructive pulmonary disease: a time series analysis. *J Epidemiol Community Health* 54: 73-74.

41. Garty BZ, Kosman E, Ganor E, Berger V, Garty L, Wietzen T, Waisman Y, Mimouni M, Waisel Y (1998) Emergency room visits of asthmatic children, relation to air pollution, weather, and airborne allergens. *Ann Allergy Asthma Immunol* 81: 563-570.

42. Gehring U, Cyrys J, Sedlmeir G, Brunekreef B, Bellander T, Fischer P, Bauer CP, Reinhardt D, Wichmann HE, Heinrich J (2002) Traffic-related air pollution and respiratory health during the first 2 yrs of life. *Eur Respir J* 19: 690-698.

43. Gehring U, Heinrich J, Kramer U, Grote V, Hochadel M, Sugiri D, Kraft M, Rauchfuss K, Eberwein HG, Wichmann HE (2006) Long-term exposure to ambient air pollution and cardiopulmonary mortality in women. *Epidemiology* 17: 545-551.

44. Goodman PG, Dockery DW, Clancy L (2004) Cause-specific mortality and the extended effects of particulate pollution and temperature exposure. *Environ Health Perspect* 112: 179-185.

45. Hagen JA, Nafstad P, Skrondal A, Bjorkly S, Magnus P (2000) Associations between outdoor air pollutants and hospitalization for respiratory diseases. *Epidemiology* 11: 136-140.

46. Hajat S, Anderson HR, Atkinson RW, Haines A (2002) Effects of air pollution on general practitioner consultations for upper respiratory diseases in London. *Occup Environ Med* 59: 294-299.

47. Hajat S, Haines A, Atkinson RW, Bremner SA, Anderson HR, Emberlin J (2001) Association between air pollution and daily consultations with general practitioners for allergic rhinitis in London, United Kingdom. *Am J Epidemiol* 153: 704-714.

48. Hajat S, Haines A, Goubet SA, Atkinson RW, Anderson HR (1999) Association of air pollution with daily GP consultations for asthma and other lower respiratory conditions in London. *Thorax* 54: 597-605.

49. Hastings DL, Jardine S (2002) The relationship between air particulate levels and upper respiratory disease in soldiers deployed to Bosnia (1997-1998). *Mil Med* 167: 296-303.

50. HEI (2003) *Revised analyses of time-series studies of air pollution and health. Special report.*

51. Heinrich J, Hoelscher B, Frye C, Meyer I, Pitz M, Cyrys J, Wjst M, Neas L, Wichmann HE (2002) Improved air quality in reunified Germany and decreases in respiratory symptoms. *Epidemiology* 13: 394-401.

52. Heinrich J, Hoelscher B, Wichmann HE (2000) Decline of ambient air pollution and respiratory symptoms in children. *Am J Respir Crit Care Med* 161: 1930-1936.

53. Heinrich J, Hoelscher B, Wjst M, Ritz B, Cyrys J, Wichmann H (1999) Respiratory diseases and allergies in two polluted areas in East Germany. *Environ Health Perspect* 107: 53-62.

54. Hoek G (2003) Daily mortality and air pollution in The Netherlands. In Revised analyses of time-series studies of air pollution and health. Special report pp. 133-142: Boston, MA.

55. Hoek G, Brunekreef B, Fischer P, van Wijnen J (2001) The association between air pollution and heart failure, arrhythmia, embolism, thrombosis, and other cardiovascular causes of death in a time series study. *Epidemiology* 12: 355-357.

56. Hoek G, Brunekreef B, Goldbohm S, Fischer P, van den Brandt PA (2002) Association between mortality and indicators of traffic-related air pollution in the Netherlands: a cohort study. *Lancet* 360: 1203-1209.

57. Hoek G, Brunekreef B, Verhoeff A, van Wijnen J, Fischer P (2000) Daily mortality and air pollution in The Netherlands. *J Air Waste Manag Assoc* 50: 1380-1389.

58. Hoek G, Schwartz JD, Groot B, Eilers P (1997) Effects of ambient particulate matter and ozone on daily mortality in Rotterdam, The Netherlands. *Arch Environ Health* 52: 455-463.

59. Hoffmann B, Moebus S, Stang A, Beck EM, Dragano N, Mohlenkamp S, Schmermund A, Memmesheimer M, Mann K, Erbel R, Jockel KH (2006) Residence close to high traffic and prevalence of coronary heart disease. *Eur Heart J* 27: 2696-2702.

60. Horak F, Jr., Studnicka M, Gartner C, Spengler JD, Tauber E, Urbanek R, Veiter A, Frischer T (2002) Particulate matter and lung function growth in children: a 3-yr follow-up study in Austrian schoolchildren. *Eur Respir J* 19: 838-845.

61. Jedrychowski W, Becher H, Wahrendorf J, Basa-Cierpialek Z (1990) A case-control study of lung cancer with special reference to the effect of air pollution in Poland. *J Epidemiol Community Health* 44: 114-120.

62. Jedrychowski W, Flak E (1998) Separate and combined effects of the outdoor and indoor air quality on chronic respiratory symptoms adjusted for allergy among preadolescent children. *Int J Occup Med Environ Health* 11: 19-35.

63. Jedrychowski W, Flak E, Mroz E (1999) The adverse effect of low levels of ambient air pollutants on lung function growth in preadolescent children. *Environ Health Perspect* 107: 669-674.

64. Karakatsani A, Andreadaki S, Katsouyanni K, Dimitroulis I, Trichopoulos D, Benetou V, Trichopoulou A (2003) Air pollution in relation to manifestations of chronic pulmonary disease: a nested case-control study in Athens, Greece. *Eur J Epidemiol* 18: 45-53.

65. Katsouyanni K, Schwartz J, Spix C, Touloumi G, Zmirou D, Zanobetti A, Wojtyniak B, Vonk JM, Tobias A, Ponka A, Medina S, Bacharova L, Anderson HR (1996) Short term effects of air pollution on health: a European approach using epidemiologic time series data: the APHEA protocol. *J Epidemiol Community Health* 50 Suppl 1: S12-18.

66. Katsouyanni K, Touloumi G, Samoli E, Gryparis A, Le Tertre A, Monopolis Y, Rossi G, Zmirou D, Ballester F, Boumghar A, Anderson HR, Wojtyniak B, Paldy A, Braunstein R, Pekkanen J, Schindler C, Schwartz J (2001) Confounding and effect modification in the short-term effects of ambient particles on total mortality: results from 29 European cities within the APHEA2 project. *Epidemiology* 12: 521-531.

67. Katsouyanni K, Touloumi G, Samoli E, Petasakis Y, Analitis A, Le Tertre A, Rossi G, Zmirou D, Ballester F, Boumghar A, Anderson HR, Wojtyniak B, Paldy A, Braunstein R, Pekkanen J, Schindler C, Schwartz J (2003) Sensitivity analysis of various models of short-term effects of ambient particles on total mortality in 29 cities in APHEA2. In Revised analyses of time-series studies of air pollution and health. Special report pp. 157-164. Health Effects Institute: Boston, MA.

68. Katsouyanni K, Touloumi G, Spix C, Schwartz J, Balducci F, Medina S, Rossi G, Wojtyniak B, Sunyer J, Bacharova L, Schouten JP, Ponka A, Anderson HR (1997) Short-term effects of ambient sulphur dioxide and particulate matter on mortality in 12 European cities: results from time series data from the APHEA project. Air Pollution and Health: a European Approach. *BMJ* 314: 1658-1663.

69. Keatinge WR, Donaldson GC (2001) Mortality related to cold and air pollution in London after allowance for effects of associated weather patterns. *Environ Res* 86: 209-216.

70. Knox EG (2005) Oil combustion and childhood cancers. *J Epidemiol Community Health* 59: 755-760.

71. Knox EG (2006) Roads, railways, and childhood cancers. *J Epidemiol Community Health* 60: 136-141.

72. Kontos AS, Fassois SD, Deli MF (1999) Short-term effects of air pollution on childhood respiratory illness in Piraeus, Greece, 1987-1992: nonparametric stochastic dynamic analysis. *Environ Res* 81: 275-296.

73. Kotesovec F, Skorkovsky J, Brynda J, Peters A, Heinrich J (2000) Daily mortality and air pollution in northern Bohemia: different effects for men and women. *Cent Eur J Public Health* 8: 120-127.

74. Kramer U, Behrendt H, Dolgner R, Ranft U, Ring J, Willer H, Schlipkoter HW (1999) Airway diseases and allergies in East and West German children during the first 5

years after reunification: time trends and the impact of sulphur dioxide and total suspended particles. *Int J Epidemiol* 28: 865-873.

75. Kulkarni N, Pierse N, Rushton L, Grigg J (2006) Carbon in airway macrophages and lung function in children. *N Engl J Med* 355: 21-30.

76. Laden F, Schwartz J, Speizer FE, Dockery DW (2006) Reduction in fine particulate air pollution and mortality: Extended follow-up of the Harvard Six Cities study. *Am J Respir Crit Care Med* 173: 667-672.

77. Lanki T, Pekkanen J, Aalto P, Elosua R, Berglind N, D'Ippoliti D, Kulmala M, Nyberg F, Peters A, Picciotto S, Salomaa V, Sunyer J, Tiittanen P, von Klot S, Forastiere F (2006) Associations of traffic-related air pollutants with hospitalisation for first acute myocardial infarction. The HEAPSS study. *Occup Environ Med* 63: 844-851.

78. Le Tertre A, Medina S, Samoli E, Forsberg B, Michelozzi P, Boumghar A, Vonk JM, Bellini A, Atkinson R, Ayres JG, Sunyer J, Schwartz J, Katsouyanni K (2002a) Short-term effects of particulate air pollution on cardiovascular diseases in eight European cities. *J Epidemiol Community Health* 56: 773-779.

79. Le Tertre A, Quenel P, Eilstein D, Medina S, Prouvost H, Pascal L, Boumghar A, Saviuc P, Zeghnoun A, Filleul L, Declercq C, Cassadou S, Le Goaster C (2002b) Short-term effects of air pollution on mortality in nine French cities: a quantitative summary. *Arch Environ Health* 57: 311-319.

80. Leonardi GS, Houthuijs D, Steerenberg PA, Fletcher T, Armstrong B, Antova T, Lochman I, Lochmanova A, Rudnai P, Erdei E, Musial J, Jazwiec-Kanyion B, Niciu EM, Durbaca S, Fabianova E, Koppova K, Lebret E, Brunekreef B, van Loveren H (2000) Immune biomarkers in relation to exposure to particulate matter: a cross-sectional survey in 17 cities of Central Europe. *Inhal Toxicol* 12 Suppl 4: 1-14.

81. Llorca J, Salas A, Prieto-Salceda D, Chinchon-Bengoechea V, Delgado-Rodriguez M (2005) Nitrogen dioxide increases cardiorespiratory admissions in Torrelavega (Spain). *J Environ Health* 68: 38867.

82. Maheswaran R, Haining RP, Brindley P, Law J, Pearson T, Fryers PR, Wise S, Campbell MJ (2005a) Outdoor air pollution and stroke in Sheffield, United Kingdom: a small-area level geographical study. *Stroke* 36: 239-243.

83. Maheswaran R, Haining RP, Brindley P, Law J, Pearson T, Fryers PR, Wise S, Campbell MJ (2005b) Outdoor air pollution, mortality, and hospital admissions from coronary heart disease in Sheffield, UK: a small-area level ecological study. *Eur Heart J* 26: 2543-2549.

84. Mannsaker B, Vikan T, Holme J (2004) Air pollution and cardiovascular disease in Trondheim. *Tidsskr Nor Laegeforen* 124: 1381-1383.

85. McGregor GR, Walters S, Wordley J (1999) Daily hospital respiratory admissions and winter air mass types, Birmingham, UK. *Int J Biometeorol* 43: 21-30.

86. Medina S, Le Tertre A, Quenel P, Le Moullec Y, Lameloise P, Guzzo JC, Festy B, Ferry R, Dab W (1997) Air pollution and doctors' house calls: results from the ERPURS system for monitoring the effects of air pollution on public health in Greater Paris, France, 1991-1995. Evaluation des Risques de la Pollution Urbaine pour la Sante. *Environ Res* 75: 73-84.

87. Michelozzi P, Forastiere F, Fusco D, Perucci CA, Ostro B, Ancona C, Pallotti G (1998) Air pollution and daily mortality in Rome, Italy. *Occup Environ Med* 55: 605-610.

88. Migliaretti G, Cadum E, Migliore E, Cavallo F (2005) Traffic air pollution and hospital admission for asthma: a case-control approach in a Turin (Italy) population. *Int Arch Occup Environ Health* 78: 164-169.

89. Migliaretti G, Cavallo F (2004) Urban air pollution and asthma in children. *Pediatr Pulmonol* 38: 198-203.

90. Naess O, Nafstad P, Aamodt G, Claussen B, Rosland P (2007) 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: 435-443.

91. Nafstad P, Haheim LL, Oftedal B, Gram F, Holme I, Hjermann I, Leren P (2003) Lung cancer and air pollution: a 27 year follow up of 16 209 Norwegian men. *Thorax* 58: 1071-1076.

92. Nafstad P, Haheim LL, Wisloff T, Gram F, Oftedal B, Holme I, Hjermann I, Leren P (2004) Urban air pollution and mortality in a cohort of Norwegian men. *Environ Health Perspect* 112: 610-615.

93. Nawrot TS, Nackaerts K, Hoet PH, Nemery B (2007) Lung cancer mortality and fine particulate air pollution in Europe. *Int J Cancer* 120: 1825-1826; author reply 1827.

94. Nyberg F, Gustavsson P, Jarup L, Bellander T, Berglind N, Jakobsson R, Pershagen G (2000) Urban air pollution and lung cancer in Stockholm. *Epidemiology* 11: 487-495.

95. Oftedal B, Nafstad P, Magnus P, Bjorkly S, Skrondal A (2003) Traffic related air pollution and acute hospital admission for respiratory diseases in Drammen, Norway 1995-2000. *Eur J Epidemiol* 18: 671-675.

96. Paatero P, Aalto P, Picciotto S, et a (2005) Estimating time series of aerosol particle number concentrations in the five HEAPSS cities on the basis of measured air pollution and meteorological variables. *Atmos Environ* 39: 2261-2273.

97. Pantazopoulou A, Katsouyanni K, Kourea-Kremastinou J, Trichopoulos D (1995) Short-term effects of air pollution on hospital emergency outpatient visits and admissions in the greater Athens, Greece area. *Environ Res* 69: 31-36.

98. Parodi S, Stagnaro E, Casella C, Puppo A, Daminelli E, Fontana V, Valerio F, Vercelli M (2005) Lung cancer in an urban area in Northern Italy near a coke oven plant. *Lung Cancer* 47: 155-164.

99. Penard-Morand C, Charpin D, Raherison C, Kopferschmitt C, Caillaud D, Lavaud F, Annesi-Maesano I (2005) Long-term exposure to background air pollution related to respiratory and allergic health in schoolchildren. *Clin Exp Allergy* 35: 1279-1287.

100. Peters A, Skorkovsky J, Kotesovec F, Brynda J, Spix C, Wichmann HE, Heinrich J (2000) Associations between mortality and air pollution in central Europe. *Environ Health Perspect* 108: 283-287.

101. Peters A, von Klot S, Heier M, Trentinaglia I, Hormann A, Wichmann HE, Lowel H (2004) Exposure to traffic and the onset of myocardial infarction. *N Engl J Med* 351: 1721-1730.

102. Pierse N, Rushton L, Harris RS, Kuehni CE, Silverman M, Grigg J (2006) Locally generated particulate pollution and respiratory symptoms in young children. *Thorax* 61: 216-220.

103. Polat D, Eberwein G, Becker A, Weishaupt C, Schins RP, Ranft U, Borm PJ (2002) Ambient exposure and nasal inflammation in adults and children--a preliminary analysis. *Int J Hyg Environ Health* 205: 229-234.

104. Ponce de Leon A, Anderson HR, Bland JM, Strachan DP, Bower J (1996) Effects of air pollution on daily hospital admissions for respiratory disease in London between 1987-88 and 1991-92. *J Epidemiol Community Health* 50 Suppl 1: s63-70.

105. Ponka A, Savela M, Virtanen M (1998) Mortality and air pollution in Helsinki. *Arch Environ Health* 53: 281-286.

106. Pope CA, 3rd, Burnett RT, Thun MJ, Calle EE, Krewski D, Ito K, Thurston GD (2002) Lung cancer, cardiopulmonary mortality, and long-term exposure to fine particulate air pollution. *JAMA* 287: 1132-1141.

107. Pope CA, 3rd, Burnett RT, Thurston GD, Thun MJ, Calle EE, Krewski D, Godleski JJ (2004) Cardiovascular mortality and long-term exposure to particulate air pollution: epidemiological evidence of general pathophysiological pathways of disease. *Circulation* 109: 71-77.

108. Prescott GJ, Cohen GR, Elton RA, Fowkes FG, Agius RM (1998) Urban air pollution and cardiopulmonary ill health: a 14.5 year time series study. *Occup Environ Med* 55: 697-704.

109. Raaschou-Nielsen O, Hertel O, Thomsen BL, Olsen JH (2001) Air pollution from traffic at the residence of children with cancer. *Am J Epidemiol* 153: 433-443.

110. Raaschou-Nielsen O, Hertel O, Thomsen BL, Olsen JH (2002) Traffic-related air pollution at the place of residence and risk of cancer among children. *Ugeskr Laeger* 164: 2283-2287.

111. Rahlenbeck SI, Kahl H (1996) Air population and mortality in East Berlin during the winters of 1981-1989. *Int J Epidemiol* 25: 1220-1226.

112. Roemer WH, van Wijnen JH (2001) Daily mortality and air pollution along busy streets in Amsterdam, 1987-1998. *Epidemiology* 12: 649-653.

113. Rooney C, McMichael AJ, Kovats RS, Coleman MP (1998) Excess mortality in England and Wales, and in Greater London, during the 1995 heatwave. *J Epidemiol Community Health* 52: 482-486.

114. Rosenlund M, Berglind N, Pershagen G, Hallqvist J, Jonson T, Bellander T (2006) Long-term exposure to urban air pollution and myocardial infarction. *Epidemiology* 17: 383-390.

115. Ross Anderson H, Atkinson R, Peacock J, Marston L, Konstantinou K (2004) *Meta-analysis of time-series studies ad panel studies of Particulate Matter (PM) and*

Ozone (O_3). Report of a WHO task group. World Health Organization: Denmark. Availabe online at: http://www.euro.who.int/document/e82792.pdf.

116. Rossi G, Vigotti MA, Zanobetti A, Repetto F, Gianelle V, Schwartz J (1999) Air pollution and cause-specific mortality in Milan, Italy, 1980-1989. *Arch Environ Health* 54: 158-164.

117. Samoli E, Schwartz J, Analitis A, Petasakis Y, Wojtyniak B, Touloumi G, Spix C, Balducci F, Medina S, Rossi G, Sunyer J, Anderson HR, Katsouyanni K (2003) Sensitivity analyses of regional differences in short-term effects of air pollution on daily mortality in APHEA cities. In Revised analyses of time-series studies of air pollution and health. Special report pp. 205-210. Health Effects Institute: Boston, MA.

118. Samoli E, Schwartz J, Wojtyniak B, Touloumi G, Spix C, Balducci F, Medina S, Rossi G, Sunyer J, Bacharova L, Anderson HR, Katsouyanni K (2001) Investigating regional differences in short-term effects of air pollution on daily mortality in the APHEA project: a sensitivity analysis for controlling long-term trends and seasonality. *Environ Health Perspect* 109: 349-353.

119. Sansebastiano G, Zoni R, Veronesi L, Stano MC, Tanzi ML, Caminiti C, Impallomeni M (2003) Air pollution and mortality and hospital admission for respiratory disease in Parma on 1992-2001 period. *Ann Ig* 15: 965-974.

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

121. Schouten JP, Vonk JM, de Graaf A (1996) Short term effects of air pollution on emergency hospital admissions for respiratory disease: results of the APHEA project in two major cities in The Netherlands, 1977-89. *J Epidemiol Community Health* 50 Suppl 1: s22-29.

122. Sichletidis L, Tsiotsios I, Gavriilidis A, Chloros D, Gioulekas D, Kottakis I, Pataka A (2005) The effects of environmental pollution on the respiratory system of children in western Macedonia, Greece. *J Investig Allergol Clin Immunol* 15: 117-123.

123. Solomon C, Poole J, Jarup L, Palmer K, Coggon D (2003) Cardio-respiratory morbidity and long-term exposure to particulate air pollution. *Int J Environ Health Res* 13: 327-335.

124. Stafoggia M, Picciotto S, Forastiere F, D'Ippoliti D, Cattani G, Marconi A, Perucci CA (2005) Air pollution and fatal and non fatal coronary events in Rome. *Epidemiol Prev* 29: 40-47.

125. Stolzel M, Breitner S, Cyrys J, Pitz M, Wolke G, Kreyling W, Heinrich J, Wichmann HE, Peters A (2006) Daily mortality and particulate matter in different size classes in Erfurt, Germany. *J Expo Sci Environ Epidemiol* (Epub ahead of print).

126. Stölzel M, Peters A, Wichmann H-E (2003) Daily mortality and fine and ultrafine particles in Erfurt, Germany. In Revised analyses of time-series studies of air pollution and health. Special report pp. 231-240. Health Effects Institute: Boston, MA.

127. Sunyer J, Basagana X (2001) Particles, and not gases, are associated with the risk of death in patients with chronic obstructive pulmonary disease. *Int J Epidemiol* 30: 1138-1140.

128. Sunyer J, Jarvis D, Gotschi T, Garcia-Esteban R, Jacquemin B, Aguilera I, Ackerman U, de Marco R, Forsberg B, Gislason T, Heinrich J, Norback D, Villani S, Kunzli N (2006) Chronic bronchitis and urban air pollution in an international study. *Occup Environ Med* 63: 836-843.

129. Sunyer J, Schwartz J, Tobias A, Macfarlane D, Garcia J, Anto JM (2000) Patients with chronic obstructive pulmonary disease are at increased risk of death associated with urban particle air pollution: a case-crossover analysis. *Am J Epidemiol* 151: 50-56.

130. Sunyer J, Spix C, Quenel P, Ponce-de-Leon A, Ponka A, Barumandzadeh T, Touloumi G, Bacharova L, Wojtyniak B, Vonk J, Bisanti L, Schwartz J, Katsouyanni K (1997) Urban air pollution and emergency admissions for asthma in four European cities: the APHEA Project. *Thorax* 52: 760-765.

131. Tenias JM, Ballester F, Rivera ML (1998) Association between hospital emergency visits for asthma and air pollution in Valencia, Spain. *Occup Environ Med* 55: 541-547.

132. Thompson AJ, Shields MD, Patterson CC (2001) Acute asthma exacerbations and air pollutants in children living in Belfast, Northern Ireland. *Arch Environ Health* 56: 234-241.

133. Tobias A, Campbell MJ (1999) Modelling influenza epidemics in the relation between black smoke and total mortality. A sensitivity analysis. *J Epidemiol Community Health* 53: 583-584.

134. Touloumi G, Katsouyanni K, Zmirou D, Schwartz J, Spix C, de Leon AP, Tobias A, Quennel P, Rabczenko D, Bacharova L, Bisanti L, Vonk JM, Ponka A (1997) Short-term effects of ambient oxidant exposure on mortality: a combined analysis within the APHEA project. Air Pollution and Health: a European Approach. *Am J Epidemiol* 146: 177-185.

135. Touloumi G, Samoli E, Quenel P, Paldy A, Anderson RH, Zmirou D, Galan I, Forsberg B, Schindler C, Schwartz J, Katsouyanni K (2005) Short-term effects of air pollution on total and cardiovascular mortality: the confounding effect of influenza epidemics. *Epidemiology* 16: 49-57.

136. Turnovska T, Kostianev S (1999) Effects of reduced air pollution on children's pulmonary function. *Cent Eur J Public Health* 7: 77-79.

137. US EPA (1997) *Air quality criteria for particulate matter*: Vol II. US Environmental Protection Agency, Research Triangle Park, NC. Document EPA/600/P-95/001cF. 3v.

138. US EPA (2004) *Air quality criteria for particulate matter*. Vol. II: Vol II. US Environmental Protection Agency, Research Triangle Park, NC. Document EPA/600/P-99/002aF.

139. Vegni FE, Castelli B, Auxilia F, Wilkinson P (2005) Air pollution and respiratory drug use in the city of Como, Italy. *Eur J Epidemiol* 20: 351-358.

140. Vigotti MA, Rossi G, Bisanti L, Zanobetti A, Schwartz J (1996) Short term effects of urban air pollution on respiratory health in Milan, Italy, 1980-89. *J Epidemiol Community Health* 50 Suppl 1: s71-75.

141. Vineis P, Hoek G, Krzyzanowski M, Vigna-Taglianti F, Veglia F, Airoldi L, Autrup H, Dunning A, Garte S, Hainaut P, Malaveille C, Matullo G, Overvad K, Raaschou-Nielsen O, Clavel-Chapelon F, Linseisen J, Boeing H, Trichopoulou A, Palli D, Peluso M, Krogh V, Tumino R, Panico S, Bueno-De-Mesquita HB, Peeters PH, Lund EE, Gonzalez CA, Martinez C, Dorronsoro M, Barricarte A, Cirera L, Quiros JR, Berglund G, Forsberg B, Day NE, Key TJ, Saracci R, Kaaks R, Riboli E (2006) Air pollution and risk of lung cancer in a prospective study in Europe. *Int J Cancer* 119: 169-174.

142. Vineis P, Hoek G, Krzyzanowski M, Vigna-Taglianti F, Veglia F, Airoldi L, Overvad K, Raaschou-Nielsen O, Clavel-Chapelon F, Linseisen J, Boeing H, Trichopoulou A, Palli D, Krogh V, Tumino R, Panico S, Bueno-De-Mesquita HB, Peeters PH, Lund EE, Agudo A, Martinez C, Dorronsoro M, Barricarte A, Cirera L, Quiros JR, Berglund G, Manjer J, Forsberg B, Day NE, Key TJ, Kaaks R, Saracci R, Riboli E (2007) Lung cancers attributable to environmental tobacco smoke and air pollution in non-smokers in different European countries: a prospective study. *Environ Health* 6: 7.

143. Visser O, van Wijnen JH, van Leeuwen FE (2004) Residential traffic density and cancer incidence in Amsterdam, 1989-1997. *Cancer Causes Control* 15: 331-339.

144. Visser O, van Wijnen JH, van Leeuwen FE (2005) Incidence of cancer in the area around Amsterdam Airport Schiphol in 1988-2003: a population-based ecological study. *BMC Public Health* 5: 127.

145. von Klot S, Peters A, Aalto P, Bellander T, Berglind N, D'Ippoliti D, Elosua R, Hormann A, Kulmala M, Lanki T, Lowel H, Pekkanen J, Picciotto S, Sunyer J, Forastiere F (2005) Ambient air pollution is associated with increased risk of hospital cardiac readmissions of myocardial infarction survivors in five European cities. *Circulation* 112: 3073-3079.

146. Wheeler BW, Ben-Shlomo Y (2005) 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* 59: 948-954.

147. Wichmann H-E, Spix C, Tuch T, Wolke G, Peters A, Heinrich J, Kreyling WG, Heyder J (2000) *Daily mortality and fine and ultrafine particles in Erfurt, Germany. Part I: role of particle number and particle mass. Research Report no. 98.* Health Effects Institute: Cambridge, MA.

148. Wichmann HE (2004) What can we learn today from the Central European smog episode of 1985 (and earlier episodes)? *Int J Hyg Environ Health* 207: 505-520.

149. Wolf C (2002) Urban air pollution and health: an ecological study of chronic rhinosinusitis in Cologne, Germany. *Health Place* 8: 129-139.

150. Wong CM, Atkinson RW, Anderson HR, Hedley AJ, Ma S, Chau PY, Lam TH (2002) A tale of two cities: effects of air pollution on hospital admissions in Hong Kong and London compared. *Environ Health Perspect* 110: 67-77.

151. Wordley J, Walters S, Ayres JG (1997) Short term variations in hospital admissions and mortality and particulate air pollution. *Occup Environ Med* 54: 108-116.

140. Vigotti MA, Rossi G, Bisanti L, Zanobetti A, Schwartz J (1996) Short term effects of urban air pollution on respiratory health in Milan, Italy, 1980-89. *J Epidemiol Community Health* 50 Suppl 1: s71-75.

141. Vineis P, Hoek G, Krzyzanowski M, Vigna-Taglianti F, Veglia F, Airoldi L, Autrup H, Dunning A, Garte S, Hainaut P, Malaveille C, Matullo G, Overvad K, Raaschou-Nielsen O, Clavel-Chapelon F, Linseisen J, Boeing H, Trichopoulou A, Palli D, Peluso M, Krogh V, Tumino R, Panico S, Bueno-De-Mesquita HB, Peeters PH, Lund EE, Gonzalez CA, Martinez C, Dorronsoro M, Barricarte A, Cirera L, Quiros JR, Berglund G, Forsberg B, Day NE, Key TJ, Saracci R, Kaaks R, Riboli E (2006) Air pollution and risk of lung cancer in a prospective study in Europe. *Int J Cancer* 119: 169-174.

142. Vineis P, Hoek G, Krzyzanowski M, Vigna-Taglianti F, Veglia F, Airoldi L, Overvad K, Raaschou-Nielsen O, Clavel-Chapelon F, Linseisen J, Boeing H, Trichopoulou A, Palli D, Krogh V, Tumino R, Panico S, Bueno-De-Mesquita HB, Peeters PH, Lund EE, Agudo A, Martinez C, Dorronsoro M, Barricarte A, Cirera L, Quiros JR, Berglund G, Manjer J, Forsberg B, Day NE, Key TJ, Kaaks R, Saracci R, Riboli E (2007) Lung cancers attributable to environmental tobacco smoke and air pollution in non-smokers in different European countries: a prospective study. *Environ Health* 6: 7.

143. Visser O, van Wijnen JH, van Leeuwen FE (2004) Residential traffic density and cancer incidence in Amsterdam, 1989-1997. *Cancer Causes Control* 15: 331-339.

144. Visser O, van Wijnen JH, van Leeuwen FE (2005) Incidence of cancer in the area around Amsterdam Airport Schiphol in 1988-2003: a population-based ecological study. *BMC Public Health* 5: 127.

145. von Klot S, Peters A, Aalto P, Bellander T, Berglind N, D'Ippoliti D, Elosua R, Hormann A, Kulmala M, Lanki T, Lowel H, Pekkanen J, Picciotto S, Sunyer J, Forastiere F (2005) Ambient air pollution is associated with increased risk of hospital cardiac readmissions of myocardial infarction survivors in five European cities. *Circulation* 112: 3073-3079.

146. Wheeler BW, Ben-Shlomo Y (2005) 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* 59: 948-954.

147. Wichmann H-E, Spix C, Tuch T, Wolke G, Peters A, Heinrich J, Kreyling WG, Heyder J (2000) *Daily mortality and fine and ultrafine particles in Erfurt, Germany. Part I: role of particle number and particle mass. Research Report no. 98.* Health Effects Institute: Cambridge, MA.

148. Wichmann HE (2004) What can we learn today from the Central European smog episode of 1985 (and earlier episodes)? *Int J Hyg Environ Health* 207: 505-520.

149. Wolf C (2002) Urban air pollution and health: an ecological study of chronic rhinosinusitis in Cologne, Germany. *Health Place* 8: 129-139.

150. Wong CM, Atkinson RW, Anderson HR, Hedley AJ, Ma S, Chau PY, Lam TH (2002) A tale of two cities: effects of air pollution on hospital admissions in Hong Kong and London compared. *Environ Health Perspect* 110: 67-77.

151. Wordley J, Walters S, Ayres JG (1997) Short term variations in hospital admissions and mortality and particulate air pollution. *Occup Environ Med* 54: 108-116.

152. Zanobetti A, Schwartz J (2003) Multicity assessment of mortality displacement within the APHEA2 project. In Revised analyses of time-series studies of air pollution and health. Special report pp. 249-254. Health Effects Institute: Boston, MA.

153. Zanobetti A, Schwartz J, Dockery DW (2000) Airborne particles are a risk factor for hospital admissions for heart and lung disease. *Environ Health Perspect* 108: 1071-1077.

154. Zanobetti A, Schwartz J, Samoli E, Gryparis A, Touloumi G, Atkinson R, Le Tertre A, Bobros J, Celko M, Goren A, Forsberg B, Michelozzi P, Rabczenko D, Aranguez Ruiz E, Katsouyanni K (2002) The temporal pattern of mortality responses to air pollution: a multicity assessment of mortality displacement. *Epidemiology* 13: 87-93.

155. Zanobetti A, Schwartz J, Samoli E, Gryparis A, Touloumi G, Peacock J, Anderson RH, Le Tertre A, Bobros J, Celko M, Goren A, Forsberg B, Michelozzi P, Rabczenko D, Hoyos SP, Wichmann HE, Katsouyanni K (2003) The temporal pattern of respiratory and heart disease mortality in response to air pollution. *Environ Health Perspect* 111: 1188-1193.

156. Zeghnoun A, Beaudeau P, Carrat F, Delmas V, Boudhabhay O, Gayon F, Guincetre D, Czernichow P (1999) Air pollution and respiratory drug sales in the City of Le Havre, France, 1993-1996. *Environ Res* 81: 224-230.

157. Zeghnoun A, Czernichow P, Beaudeau P, Hautemaniere A, Froment L, Le Tertre A, Quenel P (2001) Short-term effects of air pollution on mortality in the cities of Rouen and Le Havre, France, 1990-1995. *Arch Environ Health* 56: 327-335.

158. Zemp E, Elsasser S, Schindler C, Kunzli N, Perruchoud AP, Domenighetti G, Medici T, Ackermann-Liebrich U, Leuenberger P, Monn C, Bolognini G, Bongard JP, Brandli O, Karrer W, Keller R, Schoni MH, Tschopp JM, Villiger B, Zellweger JP (1999) Long-term ambient air pollution and respiratory symptoms in adults (SAPALDIA study). The SAPALDIA Team. *Am J Respir Crit Care Med* 159: 1257-1266.

159. Zmirou D, Schwartz J, Saez M, Zanobetti A, Wojtyniak B, Touloumi G, Spix C, Ponce de Leon A, Le Moullec Y, Bacharova L, Schouten J, Ponka A, Katsouyanni K (1998) Time-series analysis of air pollution and cause-specific mortality. *Epidemiology* 9: 495-503.

APPENDIX 1.1 - SHORT-TERM PARTICULATE MATTER (PM) AND MORTALITY (DERIVED FROM EPA 1997).

Reference, Location, Years, PM Index, Mean or Median (µg/m^3).	Study Description. Modeling methods: lags, smoothing, co-pollutants and covariates.	Results and Comments.
GREAT BRITAIN		
Thurston et al., (1989) (Thurston *et al*, 1989) BS mean: 90.1; 24-h avg. daily max: 709.	Daily total mortality analyzed for associations with BS, SO_2, and H_2SO_4 in London, England, during 1963 to 1972 winters. Mean daily temperature and RH also considered.	PM, SO_2, and H_2SO_4 all found to have statistical significant associations with mortality (0, 1 day lag). Temperature also correlated (negatively) with mortality, but with 2-day lag. Seasonality addressed by studying only winters and by applying high-pass filter to the series and analyzing residuals.
Ito et al., 1993 (Ito *et al*, 1993) BS mean: 90.1; range: 0-350.	Further analysis of London, England data (1965 to 1972) examined by Thurston et al. 1989 (Thurston *et al*, 1989). Spectral and advanced time series methods used, e.g. prewhitening and auto-regressive moving average methods. Variables considered included were BS, SO_2, H_2SO_4, temperature and RH.	Estimated pollution mean effect of 2 to 7% of all London winter deaths (mean = 281/day), but various pollutants' effects not separated. Independent model test on 1962 episode confirmed appropriateness of such methods. Long-wave addressed by considering winters only and by prewhitening the data.
GERMANY		
Spix et al. (1993) (Spix *et al*, 1993) TSP range: 10 to 650.	Daily total mortality in Erfurt, East Germany, during 1980 to 1989 (median = 6/day) related to SO_2, SP, T, RH, and precipitation. SP only measured in 1988-1989. Autoregresssive Poisson models used (due to low deaths/day) also included indicator variables for extreme temperature and adjustments for trend, season, and influenza epidemics.	Both SO_2 and SP found to be significantly associated with increased mortality. In a simultaneous regression, SP remained significant while SO_2 did not. Correlations of these coefficients not provided, however. Pollution effect size similar to that for meteorology.
FRANCE		
Derriennic et al. (1989) (Derriennic *et al*, 1989) mean TSP (OECD Method): Lyons, France: 87 (3 year) Marseilles, France: 126 (3 year).	Daily total, respiratory, and cardiac mortality for persons 65 years of age tested for associations with SO_2 and TSP during 1974 to 1976 in Lyons and Marseilles, France. Temperature also considered in analyses.	No significant mortality associations found with TSP, but SO_2 reported as associated with total elderly deaths in both cities. Seasonality addressed by analyzing deviations from 3-year average of 31-day running means of variables, but temperature lags not considered and probable seasonal differences in winter/summer temperature-mortality relationship not addressed.

GREECE		
Katsouyanni et al. 1990a (Katsouyanni *et al*, 1990a) BS.	Daily total mortality in Athens, Greece, and surrounding boroughs (1975 to 1987) related to BS, SO_2, NO_2, O3, and CO_2 using multiple regression.	During winter months 1983 to 1987, the daily number of deaths was positively and statistically significantly associated with all pollutants, but the association was strongest with BS.
Katsouyanni et al. 1990b (Katsouyanni *et al*, 1990b) BS annual mean range: 51.6 to 73.3; maximum daily value: 790.	For 1975 to 1982 in Athens, Greece 199 days with high SO_2 (>150 µg/m^3) each matched on temp., year, season, day of week, and holidays with two low SO_2 days. Mortality by-cause compared between groups by ANOVA by randomized blocks. BS correlated with SO_2 at r = 0.73, but not directly used in analysis.	Mortality was generally higher on high SO_2 days, with the difference being most pronounced for respiratory conditions. BS levels for each group not provided, and BS-SO_2 confounding not addressed, limiting interpretability of results.
Katsouyanni et al. 1993 (Katsouyanni *et al*, 1993) BS range: 50 to 250.	Daily total mortality in Athens, Greece, during July, 1987 (when a major heat wave occurred) compared to deaths in July for previous 6 yr. Variables considered included: BS, SO_2, temperature, discomfort index (DI). Effects of day-of-week, month, and long-term trends addressed via dummy variables in OLS regression models.	Mean daily temperature above 30 C found to be significantly associated with mortality. The main effects of all air pollutants were non-significant, but the interaction between high air pollution and temperature was significant for SO_2 and suggestive ($p < 0.20$) for O_3 and BS.
Touloumi et al. (1994) (Touloumi *et al*, 1994) BS mean: 83; range: 18 to 358.	Daily total mortality in Athens, Greece, during 1984-1988 (mean = 38/day) related to BS, SO_2, CO, T, and RH. Autoregressive OLS models employed also included indicator variables for season, day of week, and year.	BS, SO_2, and CO each individually significantly associated with increased mortality. The size of all coefficients declined in simultaneous regressions, with SO_2 still significant and BS approaching significance. CO was no longer significant, but highly correlated with BS (r = 0.74).

APPENDIX 1.2 - SHORT-TERM PARTICULATE MATTER (PM) AND RESPIRATORY MORBIDITY.

Reference, Location, Years, PM Index, Mean or Median (µg/m^3).	Study Description. Modeling methods: lags, smoothing, co-pollutants and covariates.	Results and Comments.
GERMANY		
Schwartz et al., 1991 (Schwartz *et al*, 1991) Study of acute respiratory illness in children in 5 German communities, 1983-1985. TSP medians 17 to 56.	This study examined the impact of short-term exposure to air pollution (TSP, SO2 and NO2) on respiratory illness in children. In 5 German cities daily counts of children's visits for croup symptoms and obstructive bronchitis were recorded. Data were collected for at least 2 years in each location. Autoregressive Poisson regression using GEE was used. To focus the analysis on short-term correlations and avoid seasonal confounding, biannual, annual (seasonal), and six shorter term cycles were controlled for in the regression models.	A total of 6,330 cases of croup and 4,755 cases of obstructive bronchitis were observed during the study. After controlling for short-term weather factors, TSP and NO2 were associated with croup cases. An increase in TSP levels from 10 to 70 µg/m^3 was associated with a 27% increase in cases of croup; the same increase in NO2 levels resulted in a 28% increase in cases. No pollutant was associated with daily cases of obstructive bronchitis.
SPAIN		
Sunyer et al. (1993) (Sunyer *et al*, 1993) Adults in Barcelona, Spain, 1985-1989. 15 monitoring stations measuring BS, mean: winter: 33% tile: 49; 67% tile = 77; summer: 33% tile =36; 67% tile = 55.	In order to examine the association between BS and SO_2 and the daily number of emergency room admission in Barcelona, Spain, for the period 198-1989, an autoregressive linear regression analysis (0-d lag best) after adjustment for temperature, day of week and year, was used.	An increase of 25 µg/m^3 in SO_2 (24-hour average) produced adjusted changes of 6% and 9% in emergency room admissions for chronic obstructive pulmonary disease during winter and summer, respectively. For BS, a similar change was found during winter (RR for 50 µg/m^3 increase was 1.15, 95% CI: 1.09-1.21), although the change was smaller in summer (RR for 50 µg/m^3 increase was 1.05, 95% CI: 0.98-1.12). The association of each pollutant with chronic obstructive pulmonary disease admissions remained significant after control for the other pollutant.

APPENDIX 1.3 - LONG-TERM PARTICULATE MATTER (PM) AND MORTALITY.

Reference, Location, Years, PM Index, Mean or Median (µg/m^3).	Study Description. Modeling methods: lags, smoothing, co-pollutants and covariates.	Results and Comments.
CZECH REPUBLIC		
Bobak & Leon, 1992 (Bobak andLeon, 1992) Ecologic study, Czech Republic, 1986-1988. PM10 mean: 68.5.	An ecological study of neonatal mortality (ages less than 1 month) and post-neonatal mortality (ages 1 to 12 months) and air pollution was conducted in the Czech Republic. Data on infant mortality and PM_{10}, SO_2 and NO_x were collected in the period 1986-88 for 46 of the 85 districts in the republic. RRs were derived by logistic regression models adjusted for district socioeconomic characteristics, such as income, car ownership, and abortion rate.	A weak positive association between neonatal mortality and quintile of PM_{10} and SO_2 was found. Stronger adjusted effects were seen for postneonatal mortality, with a consistent increase in risk for increasing quintiles of PM_{10} ($p < 0.001$). Weaker and less consistent evidence of a positive association with NO_x ($p = 0.061$) was observed. The strongest effects were seen for postneonatal respiratory mortality, which increased consistently with increasing quintiles of PM10 ($p = 0.013$). RRs for postneonatal respiratory mortality for the highest vs the lowest quintile were 2.41 (95% CI: 1.10-5.28) for PM_{10}, 3.91 (0.90-16.9) for SO_2, and 1.20 (0.37-3.91) for NO_x.

APPENDIX 1.4 - LONG-TERM PARTICULATE MATTER (PM) AND RESPIRATORY MORBIDITY.

Reference, Location, Years, PM Index, Mean or Median (µg/m^3).	Study Description. Modeling methods: lags, smoothing, co-pollutants and covariates.	Results and Comments.
GREAT BRITAIN		
Lunn et al., 1967 (Lunn *et al*, 1967) Sheffield, England.	A study analyzed the association between measures of PM and SO_2 and respiratory illnesses in 5- and 6-year old school children living in four areas of Sheffield, England.	Positive associations were found between air pollution concentrations and both upper and lower respiratory illness. Lower respiratory illness was 33 to 56% more frequent in the higher pollution areas than in the low-pollution area ($p < 0.005$). Also, decrements in lung function, measured by spirometry tests, were closely associated with respiratory disease symptom rates.
Lunn et al., 1970 (Lunn *et al*, 1970) England, 1963-1964.	A study conducted in England between 1963 and 1964 analyzed the association between BS and SO_2 and respiratory illnesses in 11-year-old children.	Results were similar to those found for the younger group. On the basis of the results reported, it appeared that increased frequency of lower respiratory symptoms and decreased lung function in children could occur with long-term exposures to annual BS levels in the range of 230 to 301 µg/m^3 and SO_2 levels of 181 to 275 µg/m^3. However, it was noted that these were only very approximate observed-effect levels because of uncertainties associated with estimating PM mass based on BS readings.
SWITZERLAND		
Ackermann-Liebrich et al. (1996) (Ackermann-Liebrich *et al*, 1997) eight different areas from Switzerland.	The aim of this study was to examine the effects of long term exposure to air pollutants on lung function in adults, taking advantage from a sample of 9,651 subjects aged 18 to 60 from eight different areas of Switzerland. FVC and FEV_1 were regressed against the natural logarithms of height, weight, age, age squared, gender, educational level, nationality, and work place exposure.	The results suggested that a 10 µg/m^3 increase in annual average PM_{10} was associated with a 3.4 percent decrease in FVC for healthy never smokers. Results were also consistent and significant for NO_2 and SO_2, but less for O_3.

ITALY		
Arossa et al. (1987) (Arossa *et al*, 1987) Turin, Italy, 1980-1983.	In this study, lung function of 1,880 school children was measured in Turin, Italy, during a time period when both TSP and SO_2 were being reduced. Three areas of Turin (central city, peripheral area, and suburban area) were studied during the winters of 1980 to 1981 and 1982 to 1983. Each child's respiratory health was assessed at the beginning and end of the study using a questionnaire which also obtained demographic information. Lung function measurements included FVC, FEV_1, FEF_{25-75}, and MEF_{50}. Daily SO_2 and TSP measurements were available from seven monitoring sites in the area. A GLM analysis adjusted for sex and anthropometric variables was used to estimate lung function values.	The pollution data confirmed that the large SO_2 differences across areas in 1980 to 1981 were reduced substantially by 1982 to 1983. The differences in TSP remained small but constant during the time period. Average slopes were significantly higher within the city of Turin when compared with the suburban area, suggesting to the authors that a decrease in pollution (primarily SO_2) resulted in an improvement of lung function.

APPENDIX 1.5 - LONG-TERM PARTICULATE MATTER (PM) AND LUNG CANCER.

Reference, Location, Years, PM Index, Mean or Median ($\mu g/m^3$).	Study Description. Modeling methods: lags, smoothing, co-pollutants and covariates.	Results and Comments.
Katsouyanni et al., 1991 (Katsouyanni *et al*, 1991).	A hospital-based case-control study was undertaken in Athens between 1987 and 1989 on 189 women with lung cancer and 89 female controls with fractures or other orthopedic conditions. Lifetime exposure to air pollution was assessed by linking blindly lifelong residential and employment addresses of all subjects with objectively estimated or presumed air pollution levels. RRs were derived by multiple logistic regression models adjusted for age.	Air pollution levels were associated with increased risk for lung cancer but the age-adjusted RR was small and not statistically significant. Whereas there was no effect of air pollution among non-smokers, an interaction with smoking duration has been shown. The interaction was almost exclusively accounted for by the non-adenocarcinoma lung cancers.

APPENDIX 1.6 - REFERENCES TO APPENDICES

1. Ackermann-Liebrich U, Leuenberger P, Schwartz J, Schindler C, Monn C, Bolognini G, Bongard JP, Brandli O, Domenighetti G, Elsasser S, Grize L, Karrer W, Keller R, Keller-Wossidlo H, Kunzli N, Martin BW, Medici TC, Perruchoud AP, Schoni MH, Tschopp JM, Villiger B, Wuthrich B, Zellweger JP, Zemp E (1997) Lung function and long term exposure to air pollutants in Switzerland. Study on Air Pollution and Lung Diseases in Adults (SAPALDIA) Team. *Am J Respir Crit Care Med* 155: 122-129.

2. Arossa W, Spinaci S, Bugiani M, Natale P, Bucca C, de Candussio G (1987) Changes in lung function of children after an air pollution decrease. *Arch Environ Health* 42: 170-174.

3. Bobak M, Leon DA (1992) Air pollution and infant mortality in the Czech Republic, 1986-88. *Lancet* 340: 1010-1014.

4. Derriennic F, Richardson S, Mollie A, Lellouch J (1989) Short-term effects of sulphur dioxide pollution on mortality in two French cities. *Int J Epidemiol* 18: 186-197.

5. Ito K, Thurston GD, Hayes C, Lippmann M (1993) Associations of London, England, daily mortality with particulate matter, sulfur dioxide, and acidic aerosol pollution. *Arch Environ Health* 48: 213-220.

6. Katsouyanni K, Hatzakis A, Kalandidi A, Trichopoulos D (1990a) Short-term effects of atmospheric pollution on mortality in Athens. *Arch Hellen Med* 7: 126-132.

7. Katsouyanni K, Karakatsani A, Messari I, Touloumi G, Hatzakis A, Kalandidi A, Trichopoulos D (1990b) Air pollution and cause specific mortality in Athens. *J Epidemiol Community Health* 44: 321-324.

8. Katsouyanni K, Pantazopoulou A, Touloumi G, Tselepidaki I, Moustris K, Asimakopoulos D, Poulopoulou G, Trichopoulos D (1993) Evidence for interaction between air pollution and high temperature in the causation of excess mortality. *Arch Environ Health* 48: 235-242.

9. Katsouyanni K, Trichopoulos D, Kalandidi A, Tomos P, Riboli E (1991) A case-control study of air pollution and tobacco smoking in lung cancer among women in Athens. *Prev Med* 20: 271-278.

10. Lunn JE, Knowelden J, Handyside AJ (1967) Patterns of respiratory illness in Sheffield infant schoolchildren. *Br J Prev Soc Med* 21: 7-16.

11. Lunn JE, Knowelden J, Roe JW (1970) Patterns of respiratory illness in Sheffield junior schoolchildren. A follow-up study. *Br J Prev Soc Med* 24: 223-228.

12. Schwartz J, Spix C, Wichmann HE, Malin E (1991) Air pollution and acute respiratory illness in five German communities. *Environ Res* 56: 1-14.

13. Spix C, Heinrich J, Dockery D, Schwartz J, Volksch G, Schwinkowski K, Collen C, Wichmann HE (1993) Air pollution and daily mortality in Erfurt, east Germany, 1980-1989. *Environ Health Perspect* 101: 518-526.

14. Sunyer J, Saez M, Murillo C, Castellsague J, Martinez F, Anto JM (1993) Air pollution and emergency room admissions for chronic obstructive pulmonary disease: a 5-year study. *Am J Epidemiol* 137: 701-705.

15. Thurston GD, Ito K, Lippmann M, Hayes C (1989) Reexamination of London, England, mortality in relation to exposure to acidic aerosols during 1963-1972 winters. *Environ Health Perspect* 79: 73-82.

16. Touloumi G, Pocock SJ, Katsouyanni K, Trichopoulos D (1994) Short-term effects of air pollution on daily mortality in Athens: a time-series analysis. *Int J Epidemiol* 23: 957-967.