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Review of recent health effect studies with nitrogen dioxide

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Review of recent health effect studies with nitrogen dioxide

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ABSTRACT

This report focuses on published studies that have examined the epidemiologic associations of ambient air exposures to nitrogen dioxide and the occurrence of acute and chronic health effects in humans. All relevant studies published since the World Health Organization issued their Air Quality Review in 2005 were taken into consideration. Nearly a hundred of the 240 studies examined for preparation of this report dealt with the relationship between NO_2 exposures and acute respiratory disease or asthma exacerbation. This continues to be the heath outcome of greatest concern with NO_2 and will likely garner the most interest in future research programs.

Although a tremendous amount of new information has been gathered, there are still nagging issues that have not been sufficiently resolved to the extent needed to make definitive statements regarding causality and risk. Confounding and bias continue to plague many studies and the results from a limited number of new controlled human exposure studies suggest that NO_2 may not be responsible for the many of the reported associations that have been reported with asthmatics. Until improved statistical and monitoring methods are developed there will continue to be considerable doubt about the relevance of results from studies using single pollutant modelling and exposure estimates from fixed monitoring stations.

KEYWORDS

Nitrogen dioxide, morbidity, mortality, health effects, cardiovascular disease, respiratory disease, exposure misclassification, asthma, collinearity, grading, limit values, multi-pollutant models, variability

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SUMMARY

The following report critically examines and grades the quality of toxicology and epidemiology studies published since the World Health Organization published their review of nitrogen dioxide (NO_2) health studies in 2006. Over 240 epidemiology studies were identified in a literature review, then individually analysed and summarized to assess their relevance for making adjustments to prevailing ambient air guidance values. The legislative history of NO_2 in Europe is reviewed along with the emissions controls that are leading to the current downward trend in ambient air levels. Factors affecting the reliability and accuracy of studies showing a relationship between outside air NO_2 concentrations and morbidity and mortality estimates are reviewed in detail as they pertain to potential exposure misclassification, bias, confounding, imprecision, and inaccuracy. Interactions and effect modifications by age, sex, noise, weather conditions, seasons of the year, atmospheric chemistry, indoor sources, analytical methodologies, and pollutant collinearities are all explored in detail by examining the most recent recently published literature on these subjects.

Compliance with the annual EU limit values for NO_2 has been difficult to achieve for many Member States with approximately 30% of the monitoring zones found to be out of compliance in 2009. NO_2 ambient air levels are characterized by a high degree of spatial and temporal variability that needs to be captured in order to accurately estimate individual or population level exposures. Likewise, levels in ambient air show a strong positive correlation with a host of other pollutants including particulate matter, carbon monoxide, ultrafine particulates, and volatile organics that needs to be critically examined when evaluating the findings from an epidemiological investigation. This association has led most investigators to conclude that NO_2 acts as a proxy for other combustion-related products whose identity is yet to be positively identified. As such, only those studies that accounted for potential pollutant interactions through the use of a two- or multi-pollutant modelling approach were deemed worthy of serious consideration in this report. Likewise, preference was given to those studies that used advanced proximity or land use regression models to characterize the residential exposures. Many of the evaluated studies were judged to be insufficient or of low quality because of the bias introduced by the use of measurements from a limited number of central monitoring sites. This error is compounded by the fact that ambient air concentrations of NO_2 have been shown to be a poor surrogate for actual personal exposures, which may be elevated by indoor combustion sources such natural gas ranges and heating devices. A limited number of new toxicology studies were identified that focused on the generation of supportive mechanistic information using either human subjects or laboratory animals exposed under controlled conditions.

An evaluation of the strength and quality of new epidemiological evidence showing an association between NO_2 exposures and acute or chronic mortality, acute respiratory disease, acute cardiovascular disease, asthma, and birth-related deficits did not result in any fresh and compelling arguments to suggest that NO_2 limit values needed to be adjusted downwards, e.g., lowered. The results indicate that the following statement from the 2006 World Health Organization report is still valid:

> *"Nitrogen dioxide concentrations closely follow vehicle emissions in many situations, so nitrogen dioxide levels are generally a reasonable marker of exposure to traffic-related emissions. Health risks from nitrogen oxides may potentially result from nitrogen dioxide itself, correlated exhaust components such as ultrafine particles and hydrocarbons, or nitrogen dioxide chemistry products, including ozone and secondary particles"*

1. INTRODUCTION

Three overarching goals governed the preparation of this report. The first was to identify new policy-relevant research published since the World Health Organization released their last evaluation of nitrogen dioxide (NO_2) in 2006. The second was to critically evaluate the reliability of the results relative to acknowledged and well-vetted procedural guidelines. The final goal was to highlight and interpret the relevance of the compiled information vis-à-vis the establishment of new air quality guidelines. To accomplish these tasks a thorough search of published and unpublished air pollution literature was undertaken. Two approaches were utilized to identify NO_2-related research studies in animals and humans. First, assortments of authoritative technical reviews were examined for new NO_2-specific information. The focus of the approach was on studies published from 2005 until the end of 2012. The following reviews were examined: the USEPAs Integrated Science Assessment and associated Annexes, the state of California's Technical Support Document on the ambient air quality standard for NO_2, the St. George's University systematic review of short-term health associations prepared for UK Department of Health, the province of Alberta's Air Quality Guidelines, the USEPA's risk and exposure assessment supporting the 2010 NAAQS for NO_2, the New York State Energy Research and Development Authority's study of air contaminants and asthma, the Committee on the Medical Effects of Air Pollution (COMEAP) air pollution mortality report for the UK Dept. of Health, and the WHO's Review of Evidence on Health Aspects of Air Pollution – REVIHAAP project: final technical report (AE, 2007, Anderson *et al.*, 2007, ARB, 2007, COMEAP, 29 A.D., NYSDOH, 2006, USEPA, 2008a, USEPA, 2008b, WHO, 2013b). These expert reports were mined for all pertinent health related information that was either toxicological or epidemiological in nature. All studies regardless of their quality were initially reviewed and scored according to their adherence to a set of pre-developed acceptability criteria.

In addition to reviewing past reports, literature searches were performed using PubMed, Google Scholar, and the Web of Science (WOS) to identify epidemiology and toxicology studies published from 2005 through the year 2012. The key words used in these searches included the terms "nitrogen dioxide, air pollution, health effects or cardiovascular, respiratory, morbidity, mortality, hospitalization, or emergency room". A total of 524 papers were identified in PubMed and 478 from the WOS. These papers were then scanned and reduced in number to those that examined the association between airborne NO_2 levels and a particular health outcome. Likewise, studies such as reviews and conference proceedings that did not contain original peer-reviewed data were dropped from further consideration. Similar searches were performed for NO_2-related studies involving asthma, infants, children, lung function, and diabetes. The intent was to earmark those studies providing new information since the last WHO guidance issued in 2006. These keyword searches led to the identification of over 240 observational studies focusing on topics ranging from cardiovascular mortality to inflammatory disease, as well as a small number new toxicology studies. The epidemiology studies included new case-control, time-series, cohort, and panel studies that focused either on NO_2 alone or NO_2 in combination with other primary and secondary air pollutants.

An important goal of this review was to evaluate the strength of the evidence linking NO_2 exposures with morbidity or mortality estimates from individual studies. This task can be undertaken in a number of different ways ranging from the non-rigorous application of subjective criteria developed through personal experience, to the more robust application of a structured set of principles designed to gauge the strengths and weaknesses in a database. Whereas, the former approach may be appropriate for a hazard assessment that involves a paucity of information, most

experts now agree that a structured grading system can improve transparency and offer dramatic improvements in the quality of any recommendations. As such, several different grading systems were examined for use with the NO_2 dataset. Given the preponderance of new epidemiological evidence that exists for NO_2, a system was needed that could provide a rigorous approach for examining a diverse number of observational studies that spanned a range of procedural approaches, study populations, and outcome measures.

There has been a decided movement towards the use of grading schemes in the clinical sciences, where there has been a large demand for more objectivity when evaluating the evidence in support of alternative medical interventions. As a result, dozens of grading systems have been developed that are designed to examine both the quality of the research evidence and the strength of any resulting recommendations. Frameworks such as NICE (National Institute for Health and Clinical Excellence), SIGN (Scottish Intercollegiate Guideline Network), GRADE (Grading of Recommendations Assessment, Development and Evaluation) and CEBM (Centre for Evidence-Based Medicine, Oxford) were examined for use in this review (Garcia *et al.*, 2011). Overall, the GRADE system was judged to offer the greatest value because of its detailed structure, widespread use, and ease of implementation. This system was selected in preference to other more well-known grading systems such the ECETOC or IPCS frameworks for analysing human data since these systems are primarily based on a weight-of-evidence evaluation to establish causality rather than a more detailed appraisal of study quality (ECETOC, 2009, IPCS, 2008).

GRADE should not be confused with the Bradford-Hill criteria for establishing causality, although it does incorporate many of the same principles (Schunemann *et al.*, 2011). Likewise, since it was developed for use by clinicians performing systematic reviews of medical intervention studies, it is not perfectly adaptable for use in environmental epidemiology. A revised system termed GRADE PLUS is scheduled to published by the end of 2013 that will deal with some of the problems associated with the use of GRADE in the public health arena (Rehfuess and Akl, 2013, WHO, 2012). As devised, GRADE can be used to evaluate the quality of a descriptive study that is used to make scientific recommendation by assigning one of four rankings: high (++++), moderate (+++), low (++), and very low (+) (Balshem *et al.*, 2011). Randomized trials enter the process as high, while all observational designs (including quasi-experimental data) enter as low. These grades are then downgraded based on 5 factors (risk of bias, inconsistency, indirectness, imprecision, and publication bias) or increased based on three other criteria (size of the effect, evidence of a dose-response, and residual confounding) (see **Table 1**).

Table 1 Factors affecting the quality of evidence finding using the GRADE system

Lower Quality if				
Risk of Bias -1 Serious -2 Very serious	Inconsistency -1 Serious -2 Very serious	Indirectness -1 Serious -2 Very serious	Imprecision -1 Serious -2 Very serious	Publication bias -1 Likely -2 Very likely
Higher Quality if				
Large effect +1 Large +2 Very large	Dose response +1 Evidence of a gradient	All plausible residual confounding +1 Would reduce a demonstrated effect +1 Would suggest a spurious effect if no effect was observed		

Once released, GRADE PLUS will give more weight to quasi-experimental study designs, and will also take into account two other adjustment factors: i) effect consistency across varied settings and study designs, and ii) the availability of analogous evidence from studies focusing on other exposure sources such as indoor air pollution, wood smoke, or cigarette smoking (Bruce *et al.*, 2013). Of particular importance to the current evaluation, is the initial low quality ranking given to all observational studies relative to randomized controlled trials (RCT) that are the gold standard in most clinical interventions because of their ability to reduce bias through randomized assignment to an exposure or control group. Since RCT are not technically or economically feasible in studies of outdoor air pollution, a modified version of GRADE was adopted that has been developed by the American College of Physicians (Qaseem *et al.*, 2010).

Using this approach, studies are initially ranked according to their inherent ability to yield high quality information. As such, four study categories are defined with progressively lower reliability. This modified ranking scheme is more conservative that GRADE since it gives a higher initial score to observational studies. As such, many of the studies examined in this report were given an initial moderate quality score before being upgraded or downgraded according to the criteria in **Table 1**. One of the following four ratings is initially applied to a study, using the criteria described below, before evaluating its particular strengths and weaknesses:

- High – randomized controlled trials appropriately designed and with sufficient blinding.
- Moderate – weak randomized controlled trials, un-randomized controlled trials, as well as appropriately conducted time series, cohort, and case control studies
- Low – observational studies showing a small observed association, an absence of dose-response, or unacceptable confounding. Observational studies of particularly high quality may be listed as moderate quality
- Very low – studies which show unreasonable uncertainty, publication bias, or gross inconsistencies

The strength of the evidence from these studies may then be either increased or decreased according to the adjustment outlined in **Table 1**. A detailed description of the application of these adjustment factors is beyond the scope of this paper so readers are encouraged to examine the following publications for more detailed information (Balshem *et al.*, 2011, Guyatt *et al.*, 2011). It should be noted that the goal behind this grading approach is to assess the strengths and weaknesses of individual studies and to appraise whether the study is of sufficient quality to justify new regulatory interventions for NO_2. This approach is not without precedence; a similar grading scheme using the SIGN system was used by Latza *et al* to evaluate the quality of NO_2-related epidemiology studies conducted between 2002 and 2006 (Latza *et al.*, 2009). The SIGN system, however, is appreciably less rigorous than the GRADE system applied herein.

A final overall rating of high, moderate, low or insufficient is applied to each study using the following definitions:

1. High quality (⊕⊕⊕⊕) – very confident that the true effect lies close to that of the estimate of the effect
2. Moderate quality (⊕⊕⊕◯) – moderate confidence in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
3. Low quality (⊕⊕◯◯) – confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the true effect
4. Insufficient (⊕◯◯◯) – very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of the effect

A summarisation and evaluation of the individual studies identified in the literature search can be found in **Appendix I**. A more detailed analysis was performed on a select number of studies found to be of moderate, low, or insufficient quality to illustrate some of considerations that went into the ranking. This in depth analysis is presented in Appendix II. The summary evaluations are segregated by time course and or endpoint and include separate categorizations for hospital admissions and hospital emergency room visits. Each study was examined using a reporting checklist that examined the critical details such as the exposure methodology, number of patients, statistical modelling, bias, confounding, the expression of the results, and overall limitations (Vandenbroucke *et al.*, 2007). In addition, time-series studies were examined using the following set of additional criteria (NEPC, 2000):

- daily estimates of population exposure for at least five years at constant locations;
- sufficient fixed sites in the monitoring network to characterize the spatial distribution of air pollutants in the study region, i.e. sub regions within the airshed contain at least one monitoring site;
- sub-regional monitoring sites provide a measure of the distribution of population exposure not peak data;
- daily data from each sub-regional monitoring site available for at least 75 per cent of days; and
- air pollutants are not measured independently so that potential confounding can be assessed.

2. LEGISLATIVE HISTORY

There is no shortage of guidelines, standards, and limits restricting the airborne concentration of NO_2 throughout Europe. The European Commission (EC), World Health Organization (WHO), and United Nations Economic Commission (UNECE) have all published guideline values or recommendations that limit emissions or maximum attainable airborne concentrations of NO_2. There is a complex legislative history that goes along with the development of these limit and guideline values that continues to evolve to this day. An examination of NO_2 air quality values shows that the concentrations allowable in European cities are already amongst the lowest in the world (see **Table 2**).

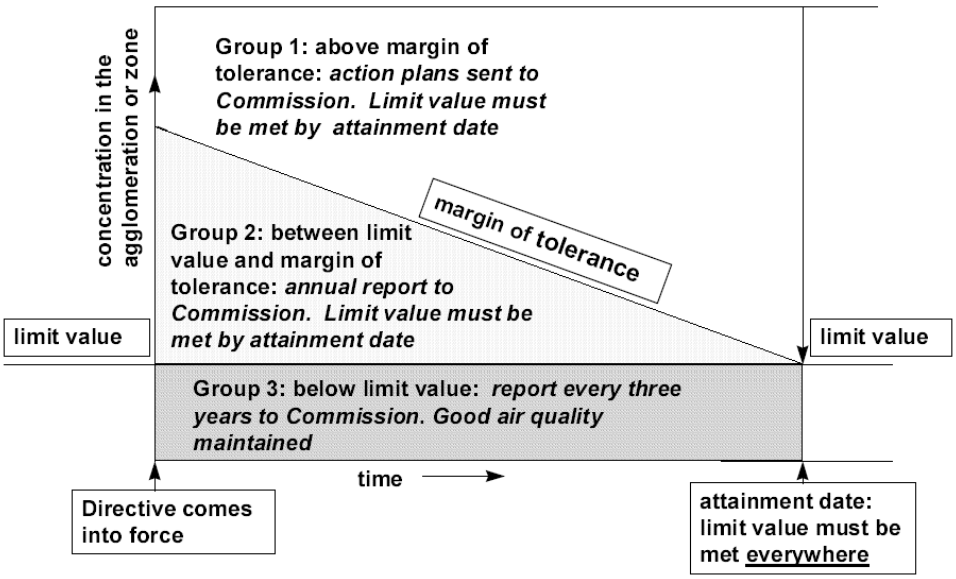
Table 2 Worldwide ambient air quality standards for nitrogen dioxide (Wood, 2012)

Country/Region	1-hr average (µg/m³/ppm)	24-hr average (µg/m³/ppm)	Annual (µg/m³/ppm)	Year
Canada	400/213	---	60/32	1999
Alberta	400/213	200/106	60/32	2007
United States	190/100	---	100/53	2010
New Zealand#	200/106#	---	---	2005
Australia	226/120	---	56/30	2009
European Union*	200/106	---	40/21	2006

* not to be exceeded more than 18 times per year
# not to be exceeded more than 9 times per year

The first Daughter Directive for the Air Quality Framework Directive of 1996 (99/30/EEC) created an hourly NO_2 limit value of 200 µg/m³ and an annual limit of 40 µg/m³ to protect human health in urban zones and 30 µg/m³ (as total nitrogen oxides or NO_x) to protect vegetation in regional areas of Europe (EC, 2000). By comparison, the annual ambient air quality standard for NO_2 in the US is appreciably higher at 100 µg/m³. The Directive specified that the hourly limit value should not be exceeded more than 18 times per year and that compliance was necessary by the year 2010. In addition, an alert threshold of 400 µg/m³ was established beyond which brief and transient exposures would cause an immediate adverse human health effect. To measure progress, a tolerance limit was placed on the annual and 1-hr limit values that progressively reduced the number of allowable exceedances from the year of initiation until the 2010 attainment date (see **Figure 1**). The tolerance limits allowed the European Commission to identify those zones with the worst air quality. Initial tolerance limits of 50% were allowed for NO_2, but yearly action plans were necessary from each Member State detailing how they intended to come into compliance as the Directive came into full force.

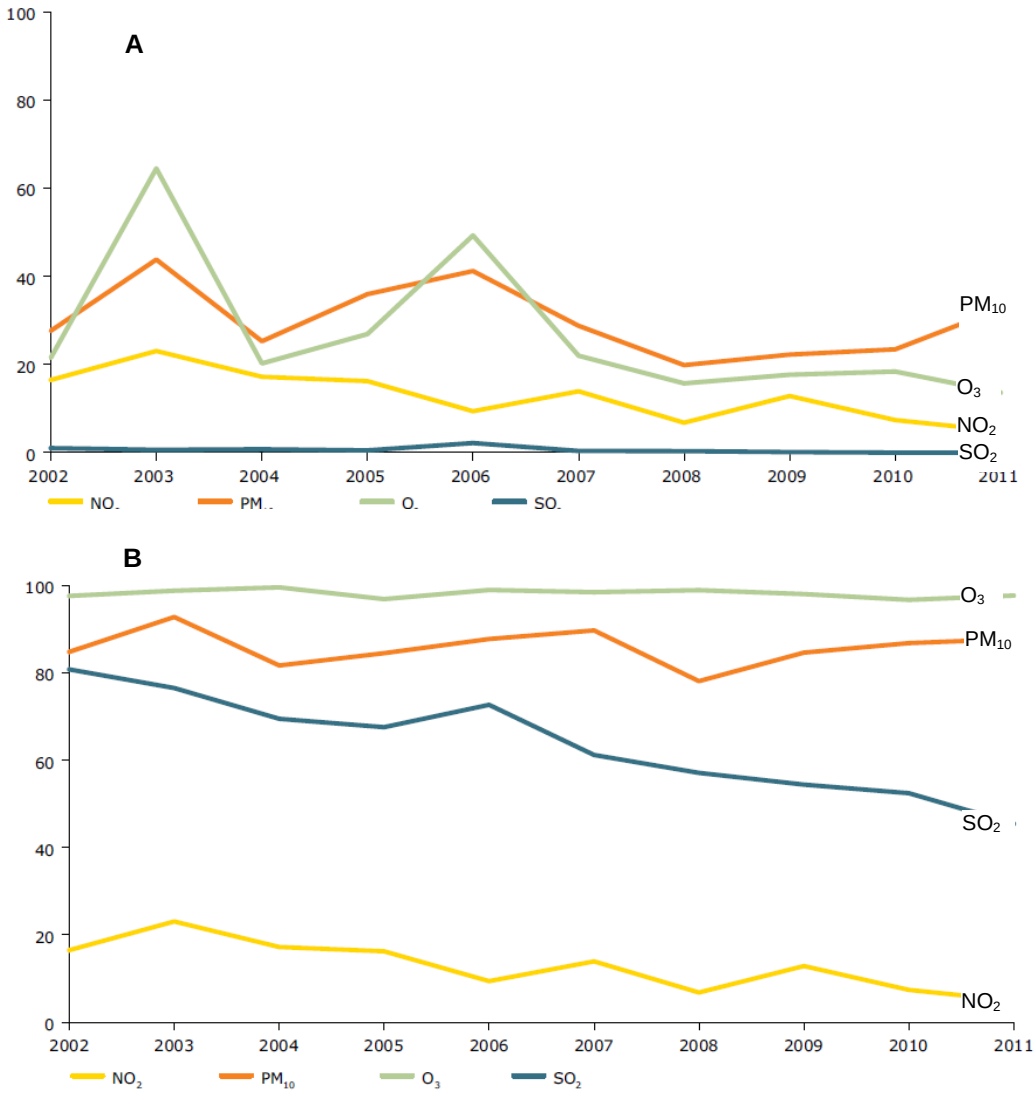
Figure 1 Achievement of limit values in the framework Directive through the passage of time (EC, 2000)



A new Air Quality Directive was issued in 2008 that merged the first three Daughter Directives and retained the limit values for NO_2, but allowed Member States to request a five year time extension for compliance (EC, 2008b). This action came in the face of a slow but steady downward trend in NO_2 concentrations throughout Europe (EEA, 2013). The most recent air quality information indicated that 43% of the monitoring sites showed a declining trend in NO_2 concentration; however, 42% of the monitoring stations located near high traffic areas exceeded the annual limit in 2011. The highest recorded annual NO_2 concentration was 103 µg/m^3. These data also revealed that 8% of the EU monitoring stations were in exceedance of the limit value for each of the preceding five years (2007-2011). The percentage of the population exposed to NO_2 at levels in excess of the annual limit values was shown to be approximately 5-13% (see **Figure 2**). These individuals were thought to reside in close proximity to high traffic areas rather than being strictly confined to busy urban environments.

The slow decline in air concentrations and persistent exceedances in some areas has been partially attributed to the widespread use of particulate filters and oxidation catalysts in new diesel-powered vehicles. Although these technologies remove a very high percentage of particulate matter (PM) from the exhaust stream, the improvements are accompanied by an increase in primary NO_2 emissions. It is worth noting, however, that the percentage of the population exposed to NO_2 levels in excess of the limit values continues to trend downwards, which points to the success of current emission control efforts and abatement technologies. It is anticipated that the progressive shift from two stroke to four stroke engines, the changing share of two-wheeled vehicles in passenger transport, the replacement of heavy duty trucks by light duty vehicles, and the changing ratio of vehicles used in freight transport versus personal travel will all help drive down the percentages down even further without the implementation any new regulatory initiatives.

Figure 2 Percentage of European urban population exposed to air pollutants exceeding EU (graph A) and WHO (graph B) air quality guidelines (EEA, 2013)



The new Air Quality Directive 28/50/EC was one of several recommendations that resulted from a critical evaluation included in the European Commission's 2005 Thematic Strategy on Air Pollution (TSAP) (EC, 2008b). Other suggestions included a revision of the National Emission Ceiling Directive (NECD), new on-road vehicle emission standards, emission reductions from international shipping, and new standards for small industrial combustion installations and non-road mobile machinery. These emission limits targeted total nitrogen oxides (NO_x) rather than NO_2 since NO_x incorporates the nitric oxide (NO) that is capable of being converted to secondary NO_2 following emission from a combustion source.

The overall goal of TSAP was to attain "levels of air quality that do not give rise to significant negative impacts on, and risk to human health and the environment" by the year 2020. Modelling estimates indicated that this could be accomplished through a 60% reduction in NO_x emissions. These initiatives were developed as part of the ECs 6th Environmental Action Programme (EAP), which was created to improve existing legislation over a ten-year period (2002-2012) by taking advantage of research and stakeholder input emerging from the CAFE (Clean Air for Europe) program (EC, 2002).

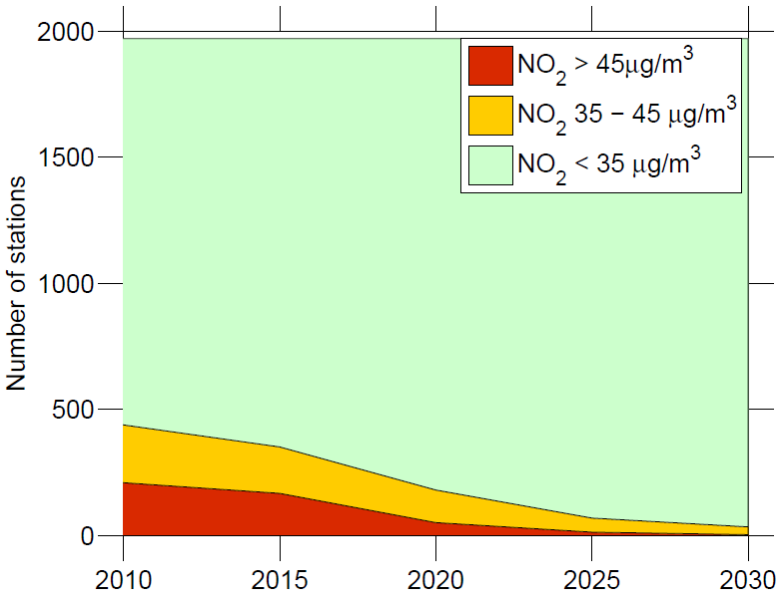
In 2011, the EC noted the need for a comprehensive review of the 6th EAP as well as the 2008 ambient air Quality Directive and embarked upon the creation of a 7th EAP that would last until the year 2020 (EC, 2013). A major goal of this initiative was to address the widespread exceedances of NO_2 as well as other pollutants and to address the failure of many Member States to meet their 2010 objectives as stipulated in the Air Quality Directive. In addition, the need for new NO_x emission control measures for on road vehicles, non-road transport, shipping, agriculture, small installations, and households was slated to be examined. The objective was to complete this review and update potential new control measures by the end of 2013, however at the time of this report the work had not been finalized. Considerable progress has been achieved, however, and detailed modelling of projected ambient air concentrations of NO_x for the year 2025 and beyond revealed that the existing annual limit value for NO_2 could be attained by 2025 if all existing emission control legislation were fully implemented and attained by the implementation dates specified in the regulation. The list below cites all existing EU legislation aimed at controlling NO_2 emissions from combustion sources (IIASA, 2013).

- Directive on Industrial Emissions for large combustion plants (derogations and opt-outs included according to information provided by national experts).
- BAT requirements for industrial processes according to the provisions of the Industrial Emissions directive.
- For light duty vehicles (692/2008/EC): All EURO standards, including adopted EURO 5 and EURO 6, becoming mandatory for all new registrations from 2011 and 2015 onwards, respectively (EC, 2008a) (see also comments below about the assumed implementation schedule of EURO 6).
- For heavy duty vehicles (595/2009/EC): All EURO standards, including adopted EURO 5 and EURO 6, becoming mandatory for all new registrations from 2009 and 2014 respectively (EC, 2009).
- For motorcycles and mopeds (2003/77/EC, 2005/30/EC, 2006/27/EC (EC, 2005, EC, 2006): All EURO standards for motorcycles and mopeds up to EURO 3, mandatory for all new registrations from 2007. Proposals for EURO 4/5/6 not yet legislated (EC, 2003, EC, 2005, EC, 2006).
- For non-road mobile machinery 2014 (2004/26/EC): All EU emission controls up to Stages IIIA, IIIB and IV, with introduction dates by 2006, 2011, and. Stage IIIB or higher standards do not apply to inland vessels IIIB, and railcars and locomotives are not subject to Stage IV controls (EC, 2004).
- MARPOL Annex VI revisions from MEPC57 regarding emission NO_x limit values for ships.
- National legislation and national practices (if stricter).

Assuming compliance with these restrictions, the number of air quality management zones in non-compliance within the 28 EU Member States was predicted to decline from 103/500 (20%) in 2010 to 13/500 (2.5%) in 2025. Non-compliance was predicted to be appreciably greater, however, if the new EURO 6 control standards

for NO_x emissions from light duty vehicles were not achieved and the emissions remained at EURO 5 levels. In this case, the number of zones in strong non-compliance would be about 9%, and approximately 18% of European population would be living in air quality management zones that did not achieve the NO_2 limit values. EURO 6 emission limits are slated to come into effect in September of 2014 and will require a 50% NO_x reduction compared to EURO 5 standards (Weiss *et al.*, 2012). The TSAP modelling exercise went on to project the number of roadside and background monitoring sites (1950 in total) that would be in non-compliance with three different annual limit values for NO_2 (Kiesewetter *et al.*, 2013). Interestingly, the bright line separations shown in **Figure 3** suggest that the EC may be contemplating a decrease in the annual limit for NO_2 from 40 µg/m^3 to 35 µg/m^3 in order to achieve the high attainment percentages that are predicted to occur at this value.

Figure 3 Predicted levels of NO_2 compliance for the 1,950 monitoring stations in the EU (Kiesewetter et al., 2013)



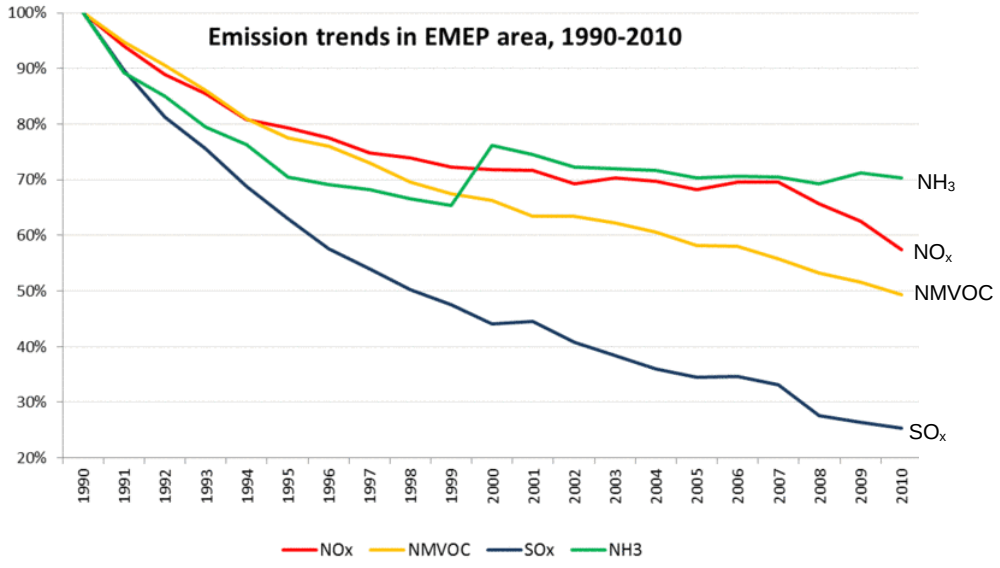
In addition to the legislative efforts within the EC on NO_2 and NO_x, guidance values are issued at regular intervals by the World Health Organization. Although the values have no legal standing, they are very influential and have long been used by the EU as a starting point for justifying any changes to their policy on limit values (WHO, 2006). As shown in **Table 3**, WHO issued their first guideline values in 1977 as a concentration range aimed at protecting against the short-term pulmonary effects seen in studies with mice (EHC, 1977). More recent evaluations have relied heavily on a plethora of epidemiology studies focusing on morbidity and mortality. The 2000 guidance limits of 200 µg/m^3 for 1-hr and 40 µg/m^3 annually have been in place for over a decade and they may be decreased based on recent technical reviews performed under the REVIHAAP and HRAPIE programs (WHO, 2013a, WHO, 2013b). Indications thus far suggest that modifications will be made to the annual limit; but questions remain whether these changes are warranted given the inability of the epidemiological studies to unequivocally show that morbidity and mortality associations are not the result of a surrogate effect, whereby NO_2 is simply serving as marker for another combustion-related pollutant that is the true causative agent.

Table 3 Guideline values for NO_2 issued by the World Health Organization

Year	1-hr value ($\mu g/m^3$)	24-hr value ($\mu g/m^3$)	Annual value ($\mu g/m^3$)	Reference
1977	190 -320	---	---	EHC, 1977
1987	400	150	---	WHO, 1987
2000	200	---	40	WHO, 2000
2005	200	---	40	WHO, 2006

A final piece of legislation that directly impacts the emission and transport of NO_x is the 1999 Gothenburg protocol administered by the United Nations Economic Commission for Europe (UNECE, 2007). The protocol is part of the 1979 Convention on Long-Range Transboundary Air Pollution (CLRTAP) that has been ratified by 31 European nations and the EU. The initial protocol went into force in 2005 and was slated to end by the year 2010. The treaty established emission limits for a wide range of mobile and stationary sources. The goal was to reduce the emissions of NO_x (expressed as NO_2 equivalents) in the EU by 49% by establishing emission ceilings for the individual Member States. A Cooperative Programme for the Monitoring and Evaluation of Long-range Transmission of Air Pollutants in Europe (EMEP) was established to track progress via the establishment a monitoring network and the creation of an inventory reporting protocol (UNECE, 1984). **Figure 4** shows the progress in emission reduction efforts in the EU based on a compilation of EMEP data (EMEP, 2013). In 2012, a revised Gothenburg protocol was adopted that set new emission reduction targets from a base year of 2005 (UNECE, 2012). The goal of this amendment was a further 42% reduction in NO_x emissions that needed to be achieved by 2020.

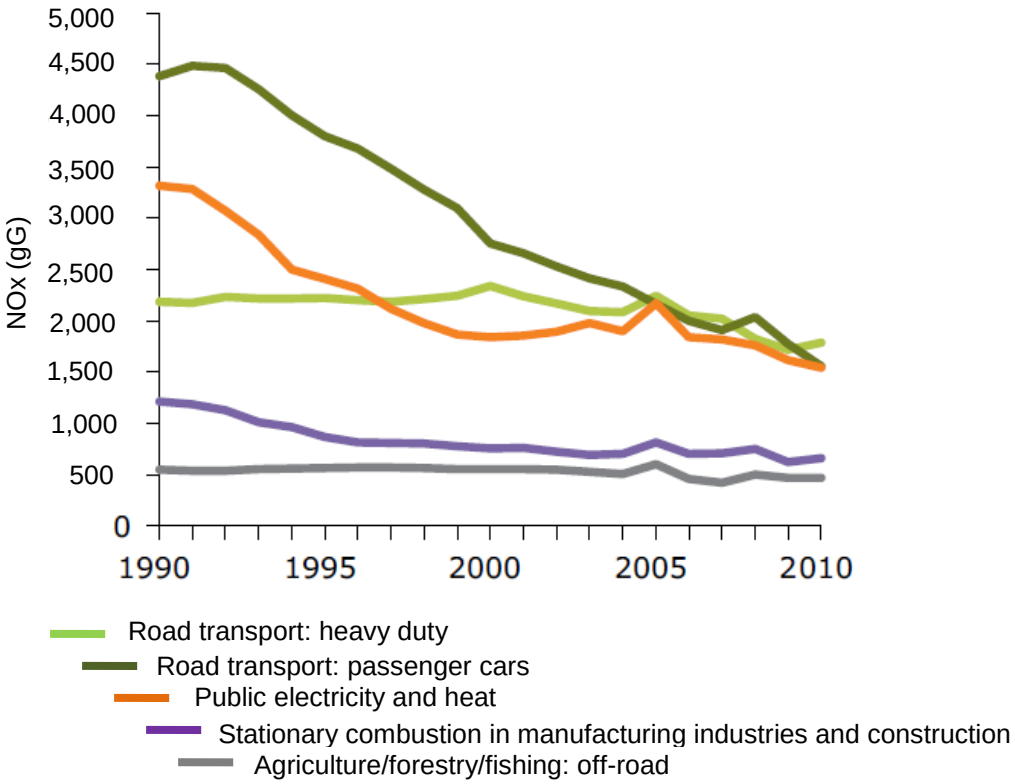
Figure 4 Twenty year emission reduction for NO_2 and other pollutants from EMEP monitoring (EMEP, 2013)



Although it is difficult to precisely measure the impact of each regulatory initiative on NO_2 air quality in Europe, the evidence from the previous Figures shows a decided overall improvement in ambient air quality. However, because pollutant reductions have not taken place at the desired pace at all locations, there has been a call for more stringent regulations with 2013 declared as the "Year of Air" in Europe (Morfeld *et al.*, 2013). The goal of this program is to strengthen and improve air quality initiatives such that all cities and regions in Europe are in attainment of all air quality objectives by the dates specified.

Given the economic conditions in Europe and the anticipated impact of new EURO 6 emission limits for automobiles, the EU may be needlessly implementing new legislation without fully evaluating the true cost-benefit. Source declines in NO_2 emissions such as those depicted in **Figure 5** are expected to continue in the absence of new legislation and the regulatory authorities need to allow full implementation of existing controls before hampering Member States with additional new requirements that will impose an even greater compliance burden (EEA, 2012). When local emission control measures are factored into the analysis there is a good probability that NO_2 limit values can be attained, even in those countries that have experienced the biggest attainment problems (Borrego *et al.*, 2012, Velders and Diederen, 2009).

Figure 5 NO_x emissions in the EU-27: trend in NO_x emissions from the five most important key categories, 1990–2010 (EEA, 2012)



3. ATMOSPHERIC CHEMISTRY

Perhaps unlike any other primary pollutant, NO_2 levels in ambient air are affected by a host of chemical, meteorological, and emissions-related factors that can have a decided influence on spatial and temporal concentration gradients. As such, an understanding of the factors impacting airborne concentrations is necessary to appreciate the multitude of extraneous conditions that can complicate any model-based predictions at a specific locale. The primary anthropogenic source of tropospheric NO_2 is fossil fuel combustion at point sources such as power plants and other area sources that are traffic-related. Background levels are derived from a variety of biogenic sources such as brush and forest fires, lightning strikes, volcanic eruptions, and bacterial soil release. NO_2 concentrations in urban or highly industrialized areas tend to exceed background concentrations at rural sites by many fold due to the source density.

Whereas, primary NO_2 is emitted directly from a combustion source, secondary NO_2 is formed in the atmosphere through the reaction of NO with any of several photochemical oxidants including hydroxy free radicals, alkylperoxy radicals, or ozone as depicted in the reactions shown below (Finlayson-Pitts and Pitts, 1999).

$$HO_2\cdot + NO \rightarrow OH\cdot + NO_2 \qquad (1)$$

$$RO_2\cdot + NO \rightarrow RO\cdot + NO_2 \qquad (2)$$

$$O_3 + NO \rightarrow NO_2 + O_2 \qquad (3)$$

The last reaction has particular significance since NO predominates over NO_2 in vehicle exhaust, but is rapidly transformed to NO_2 via reaction 3 as it diffuse away from the tailpipe. Together NO_2 and NO comprise total nitrogen oxides (NO_x) in the atmosphere and are often regulated as such due to their intimate interactions. Once formed, NO_2 can undergo reactions with other atmospheric constituents to form a variety of other oxidized nitrogen compounds including nitrogen pentoxide (N_2O_5), nitrous acid (HONO), nitric acid (HNO_3), peroxyacetyl nitrate (PAN), and nitrate radicals. The rate of these reactions is dictated by the availability of critical co-reactants such as water vapour, ozone, and hydroxyl radicals. During daylight hours, the concentration of NO and NO_2 are in equilibrium, with the overall NO_2/NO_x ratio dictated by sunlight intensity and the resulting rate of NO_2 to NO photolysis by the reactions depicted below.

$$OH\cdot + NO_2 \rightarrow HNO_3 \qquad (4)$$

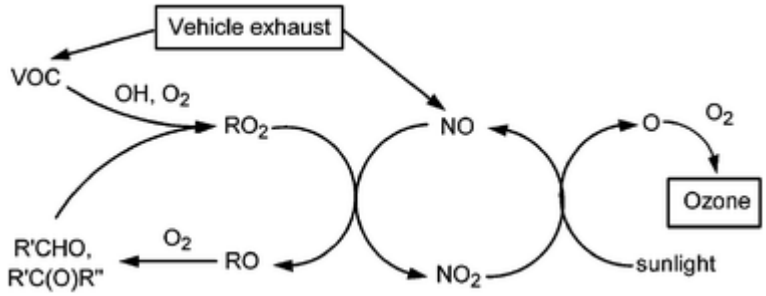
$$NO_2 + h\nu \rightarrow NO + O \qquad (5)$$

$$O + O_2 \xrightarrow{M} O_3 \qquad (6)$$

(M is an inert molecule that removes excess heat from the reaction)

The photooxidation of NO_2 by reaction 5 is the primary driver for ozone formation in NO_x-limited environments. Consequently, the NO_2 and O_3 levels in ambient air can be inversely correlated when found together in some environments. The inter-conversion of NO and NO_2 via reactions 3 and 5 can occur in the order of minutes, which complicates the unambiguous separation of NO_2 levels from those of NO. The atmospheric equilibrium that exists between NO_2, NO, and O_3 is often referred to as the ozone cycle (see **Figure 6**).

Figure 6 Involvement of NO and NO_2 in the ozone cycle



According to a recent survey, the ratio of background NO_2/NO_x in European cities generally ranges from 0.51 to 0.72 with appreciable city-to-city variation (Cyrys *et al.*, 2012). In contrast ratios of 0.03 to 0.20 were found to exist in six European countries over a five year period ending in 2000 (Grice *et al.*, 2009). These latter values are not appreciably different than the NO_2/NO_x ratios found in an Asian city (Seoul, Korea), which were found to range from 0.11 to 0.19 over a 14-year period from 1996-2009 (Shon *et al.*, 2011). The NO_2/NO_x ratios in Europe began to increase at a steady rate in the year 2000 and showed an estimated yearly increase of 19.6% over the next decade. The change is commonly attributed to the increased use of diesel-powered vehicles equipped with advanced after treatment devices that emitted higher amounts of NO_2. Similar time trends have been noted by other investigators, who noted that the higher levels, if accurate, would pose a challenge for meeting the emission limits specified under the NECD and Gothenburg Protocol (Beevers *et al.*, 2012). This shift in NO_2/NO_x ratios has caused NO_x levels to decline at faster rate than NO_2 levels near busy urban roadways (Hertel *et al.*, 2012); however this phenomenon has not been noted in all regions of Europe (Mavroidis and Ilia, 2012).

4. EXPOSURE COLLINEARITY

Numerous studies have shown that NO_2 concentrations in ambient air can be highly correlated with the emission of other traffic-related pollutants. In fact, NO_2 is often used as a proxy for traffic-related emissions since it cannot be unambiguously separated from many combustion products such as ultrafine particulates, carbon monoxide, or elemental carbon. Because community level exposures to common air pollutants occurs simultaneously, it is often difficult to identify a single component responsible for the pollution-related associations observed in human epidemiology studies. The problem stems in part from the use of area exposure measurements rather than personal monitoring, which leads to a loss in measurement heterogeneity and spatial resolution (Goldberg, 2007). The close interrelationships between the individual components in polluted ambient air have important implications for interpreting the results from epidemiology studies.

In many studies, particularly those using a single-pollutant model that do not adjust for co-linearity, NO_2 is often acting as a marker for other agents found in ambient air (Andersen *et al.*, 2012b, Weng *et al.*, 2008). Whereas, many standard setting bodies acknowledge that the effects associated with NO_2 may be due to other agents and that NO_2 may simply represent a marker for the true causative agent, it is reasoned that any regulation of the marker will lead to a reduction of the target substance by virtue of their co-linearity. This view ignores the fact that the true relationship between the marker (NO_2) and the actual causative agent may not vary in a proportional manner and that reductions in NO_2 levels may have less than the expected impact on levels of the target substance.

The difficulties associated separating the risks from NO_2 exposures with those from other co-pollutants is best demonstrated by examining the work by Eeftens *et al.* (Eeftens *et al.*, 2012). Their study, performed under the auspices of the ESCAPE program, compiled and compared exposure metrics for particulate matter and NO_2 in 20 locations throughout Europe. As shown in **Table 4**, the average correlations of $PM_{2.5}$, $PM_{2.5}$ absorbance, PM_{10} and PM_{coarse} (PM_{10}-$PM_{2.5}$) with NO_2 at all locations show r^2 (Pearson correlation squared) values ranging from 0.5 to 0.8, with the highest correlation observed for $PM_{2.5}$ absorbance. PM absorbance measurements are often used as surrogates for EC concentration because of the high observed correlations (r=0.94) seen in European locations (Cyrys *et al.*, 2012). Importantly, a study by Lewné *et al.* also observed a high correlation between NO_2 and PM absorbance (r^2=0.83) (Lewne *et al.*, 2004). The authors concluded that studies examining the relationship between long term average exposure concentration and a health outcome, the observed associations could be related to either NO_2 or PM.

Other studies have examined the relationship between NO_2 levels and UFP number concentration in Toronto, Canada. Using a fast mobility particle scanner capable of fractionating particle number (PN) sizes in 10-30 nm increments, Sabaliauskas *et al.* observed moderately high correlations ranging from 0.55 to 0.68 six particle sizes $PM_{20\text{-}30}$ trough $PM_{70\text{-}100}$ with highest correlation observed for particle number concentrations at $PM_{50\text{-}60}$ size range (Sabaliauskas *et al.*, 2012). Hagler *et al.* on the other hand, observed a somewhat lower correlation (r^2=0.34) for the relationship between NO_2 levels and ultrafine particulates, but in this study a less selective P-trak analyzer was used that operated at a size range of 20-1000 nm (Hagler *et al.*, 2009).

Table 4 Correlations (r^2) between NO_2 values and different PM-related metrics (Eeftens et al., 2012)

Location	$PM_{2.5}$	$PM_{2.5}$ absorbance	PM_{10}	PM_{coarse}
Mean 20 cities	0.51	0.80	0.61	0.50
Mean North	0.53	0.82	0.64	0.56
Mean West/Central	0.44	0.77	0.59	0.47
Mean South	0.50	0.80	0.64	0.52

* Note that values for the correlation coefficient (r) would be higher (an $r^2 = 0.50$ is equivalent to an r = 0.70).

Ambient measures of NO_2 are also highly correlated with CO levels due to their common source. Kim *et al.* compared and contrasted personal and ambient exposures air pollutants in small group of subjects residing in Toronto, Canada and reported a high correlation between CO and NO_2 for ambient, but not personal measurements (Kim *et al.*, 2006). This same study also noted moderately high correlations between $PM_{2.5}$ and NO_2 for both personal and ambient measurements. High correlations (r>0.70) between NO_2 and CO were also observed in a sampling program performed in Erfurt, Germany over a three year period (Cyrys *et al.*, 2003). This is an important consideration in studies examining the cardiovascular impact of NO_2 exposures because of carbon monoxide's well known cardiovascular impacts.

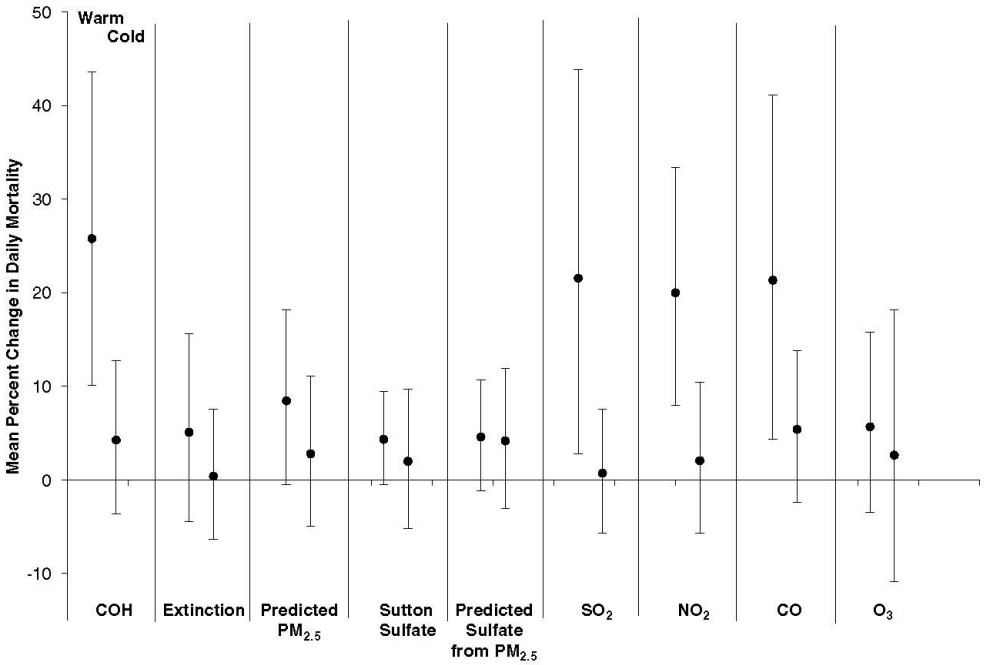
The problems of co-linearity are of such concern that some health impact assessments have not evaluated NO_2 over concerns that double counting of morbidity or mortality estimates may occur if NO_2 is examined along another co-varying pollutant such as PM (Pascal *et al.*, 2013). These authors acknowledged that the results from epidemiologic studies showing a link between NO_2 levels and various health effects, notably respiratory effects, could be due in part to other traffic-related pollutants such as ultrafine particles. It is therefore imperative that any analysis and evaluation of the results from an ecological or descriptive study considers the associations observed for all criteria and non-criteria pollutants in order to identify key interrelationships that may be masking the true causative agent.

Although methods such as principal component analysis, cluster analysis, and multi-pollutant modelling have been developed to identify those components of the mixture showing the strongest association with a particular health effect, these methods are not widely employed. In the absence of stratagems such as these, assessors are faced with the prospect of interpreting the information using a broad-based approach that examines the Spearman correlation coefficients for pair-wise exposure metric comparisons and the evaluating the strength of the associations for each individual pollutant in view of its plausibility as a likely causative agent. This approach is neither robust nor scientifically defensible when alternative methods are available.

These problem areas are demonstrated more fully in the example depicted in **Figure 7**, which describes the result from a mortality study of diabetics with underlying cardiovascular disease (Goldberg *et al.*, 2006). The results show strong seasonal differences with a statistically significant association for NO_2, as well as

CO, SO_2, and the coefficient of haze (COH) during the warm season. Since CO is also a traffic-related pollutant that often shows a high degree of correlation with NO_2 exposure measurements, it is difficult to make any conclusive statements about the relative impact of each pollutant (Jimenez *et al.*, 2012). The interpretation is further clouded by the fact that CO is better known for its cardiovascular effects than NO_2. In fact, ambient air concentrations of NO_2 often show a high degree of correlation with many outdoor air pollutants including $PM_{2.5}$, ultrafine particulates, and a variety of VOCs (see **Table 5**). Given these strong co-pollutant interactions and the potential for double counting, there is an abundant need for caution when interpreting the findings from epidemiology studies that rely on single-pollutant models. The alternative is multi-pollutant modelling that controls for the confounding effects of other pollutants using a multivariate model (Rushton, 2000). The preferred approach for assessing the impact that pollutant collinearity may have on predicted associations in observational studies is to consider whether any of the observed associations in single-pollutant models are robust to the inclusion of a second, third, or forth traffic-related pollutant using any of three regression techniques (Poisson, logistic or proportional hazards). Alternatively, some researchers have opted to investigate the impact of air pollutants as a mixture effect whereby all of the pollutants are examined as a whole using advanced statistical approaches (Billionnet *et al.*, 2012). This all-pollutant approach has been advocated for use by the National Research Council and is gaining momentum as epidemiologists come to recognize the flawed findings that come with an overreliance on single-pollutant models (Sacks *et al.*, 2012, Sun *et al.*, 2013).

Figure 7 Adjusted mean percentage change in daily mortality among subjects 65 years and over who were classified as having diabetes at the time of death, according to season*



* All pollutants were evaluated at the 3-day mean. The estimated mean percentage change in daily cause-specific mortality across the interquartile range is shown by the solid circles on the vertical lines (CI 95% confidence interval).

Table 5 Pearson correlations of NO_2 with traffic-related pollutants near a roadway (Beckerman et al., 2008)

Data set	NO_x	O_3	$PM_{2.5}$	UFPM	Benzene	Toluene	Ethyl-benzene	m/p-xylene	o-xylene	MTBE	n-hexane	THC
Pooled data	0.85**	-0.60**	0.70**	0.64**	0.85**	0.63**	0.51**	0.46*	0.51**	0.67**	0.52**	0.74**
Site controlled	0.83**	-0.79**	0.67**	0.71**	0.83**	0.61**	0.42*	0.36	0.42*	0.63**	0.82**	0.69**

Pooled – all data used
Site controlled – adjustment for site-specific characteristics
UFPM - ultrafine particulate matter
MTBE – methyl tertiary butyl ether
THC – total hydrocarbon
** Correlation is significant at the 0.01 level (two-tailed).
* Correlation is significant al the 0.05 level (two-tailed).

There is, however, a bias against the use of two-pollutant models since this approach will often lead to statistically insignificant results that are not readily accepted for publication (Anderson *et al.*, 2005). In some cases, authors will avoid describing the numerical results from two-pollutant modelling exercises if the results were not appreciably than those gathered with a single-pollutant model, yet these data could have a measurable impact on any subsequent meta-analyses that is performed. The use of two-pollutant models is of no value, however, if a study lacks adequate statistical power or is plagued by multiple comparisons that increase the likelihood of false positives (Pocock *et al.*, 2004). Although a systematic study of type I error prevalence in descriptive studies using NO_2 exposures has never been performed, there is a reasonable suspicion that the null hypothesis is being falsely rejected in a number of instances (Christley, 2010).

5. PERSONAL EXPOSURE

Spatial variability can dramatically affect NO_2 concentrations over small geographical domains and impact the sensitivity of any acute health effect determinations. The placement of centrally located monitoring sites is rarely optimized to capture the spatial variation that exists for traffic-related air pollutants such as NO_2 (Kanaroglou *et al.*, 2005). This trend is changing, however, and improvements in the algorithms used to position monitors within urban locales holds the promise of improving the reliability in exposure predictions by capturing the spatial variability at locations some distance away from major highways and thoroughfares (Kumar, 2009). Likewise, improvements in modelling techniques and the application of increasingly sophisticated approaches for reducing the bias between actual and estimated exposures hold promise for the future. Until then, however, spatial variability continues to be an area of concern for NO_2 determination that directly contributes to the exposure misclassification that can accompany health effect studies that do not correct for the disparity in some fashion.

Recent studies reveal that the spatial variability inherent in NO_2 exposure measurements may greatly diminish the reliability of central site monitoring data since the relationship between actual personal exposures and ambient measurements are poorly correlated under many circumstances (Meng *et al.*, 2012a, Meng *et al.*, 2012b). This calls into question the use of central site monitoring data as a basis for estimating personal NO_2 exposures and provides a reason to question the reliability of those ecological studies that do not correct for the measurement error. Although the consequence of this type of non-differential measurement error is conventionally believed to result in a bias towards the null (i.e. risk ratios = 1) due to the underestimation of variability and overestimation of actual personal exposure, the implications may not be that simple (Jurek *et al.*, 2005).

Two types of exposure misclassification can exist in observational studies; classical random error (i.e. non-differential) and Berkson error (differential) (Rhomberg *et al.*, 2011). Classical random error is thought to typify the exposure misclassification resulting from the use of non-spatially resolved ambient monitoring sites. Berkson error on the other hand, which biases results away from the null is only believed to exist when a portion of the true exposure has been measured (Sheppard *et al.*, 2012). Using outdoor measurements as metrics for true personal exposures can result in both types of errors, since underestimations of exposure will result in an overestimation of the true association. Moreover, it is incorrect to assume that non-differential exposure misclassification will always bias results towards the null, since simulations studies have shown that many conditions need to exist for this supposition to be correct. In reality, both non-differential (i.e. classical error) and differential (i.e. Berkson error) exposure misclassification occurs in most studies (Goldman *et al.*, 2011). An important consideration, however, is the true ability of outdoor measurements from ambient monitoring sites to actually represent personal exposures.

The relationship between indoor, outdoor and personal exposure measurements has been investigated in numerous studies and the results have not produced a consistent picture of the interrelationships that exist. For instance Lai *et al.* reported that indoor, outdoor, and personal exposures did not differ appreciably in a group of 50 volunteers from Oxford, England with reported average concentrations of 28.7, 26.9 and 26.9 $\mu g/m^3$, respectively (Lai *et al.*, 2004). Meanwhile, similar studies by Kornartit *et al.* showed significantly different indoor and outdoor concentrations of NO_2 during the winter months but not the summer period for 60 volunteers residing north of London, England (Kornartit *et al.*, 2010). The authors noted that personal

exposures were highly correlated with indoor levels and that the magnitude of the personal exposures was significantly influenced by the use gas stoves and cigarette smoking in the winter. The authors concluded that personal exposures to NO_2 were better correlated with indoor concentrations than outdoor concentrations. Valero *et al.* came to same conclusion and reported respective median personal, indoor, and outdoor concentrations of 40, 32, and 29 µg/m^3 in a large group of pregnant women (n=657) from Sabadell, Spain (Valero *et al.*, 2009). However, in this study environmental tobacco use had little impact on the findings. Gas stoves and water heaters were also shown to contribute to indoor exposures under some circumstances. A complete list of all the variables that can affect indoor exposure to NO_2 is listed in **Table 6** (WHO, 2010).

Table 6 Factors that influence indoor concentrations of nitrogen dioxide

Indoor sources
• Fuel-burning stoves (wood, kerosene, natural gas, propane, etc.)
• Fuel-burning heating systems (wood, oil, natural gas, etc.)
• Tobacco use
Source characteristics
• Flued/unflued sources
• Presence of pilot lights
Outdoor sources (via infiltration)
• Mobile sources (petrol- and diesel-powered vehicles)
• Stationary sources (industrial combustion)
Resident behaviour
• Stove usage (for fuel-burning appliances)
• Use of heating equipment (including cooking stoves)
Dwelling and indoor environment characteristics
• Dwelling size (where there are indoor sources)
• Air exchange rates
• Distance to roadway
• Surface characteristics
• Indoor humidity

No fewer than 15 studies have examined the associations between personal and ambient exposures using individually pooled, multiple longitudinal, or daily average measurements (Meng *et al.*, 2012a). In one example, statistically insignificant associations were found for personal and ambient exposures in subjects from three of the four cities examined. In many of the individuals, the correlation coefficients were negative (Sarnat *et al.*, 2006). Notably, the ambient NO_2 exposures in these studies were often more highly associated with personal $PM_{2.5}$ than NO_2 values, pointing to the very real possibility that NO_2 measurements may be serving as surrogate for other traffic-related pollutants (Kim *et al.*, 2006). This is evident in **Table 7**, which shows the correlations between personal and ambient measurements of NO_2 and $PM_{2.5}$.

Table 7 Summary of pollutant correlations for personal and fixed-site ambient measurements made at a central location (Kim et al., 2006)

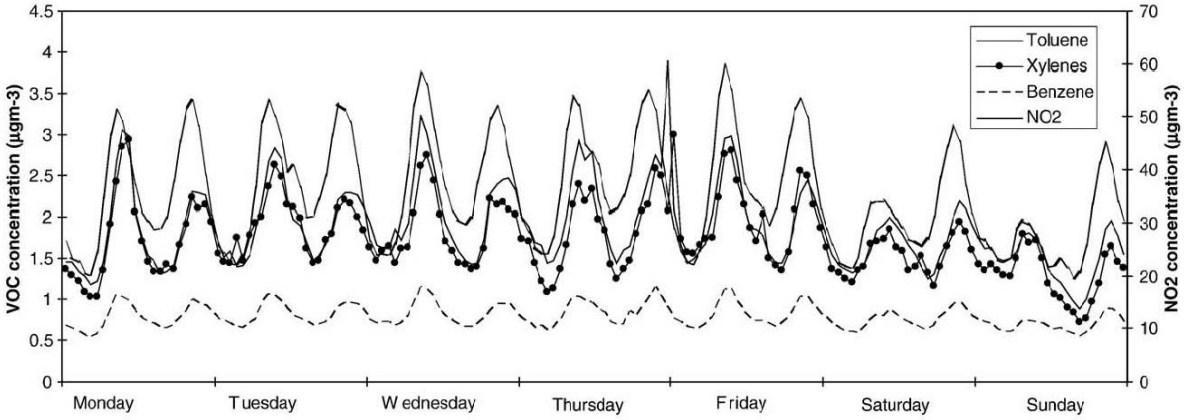
Statistic	Personal exposures			Ambient exposures		
	$PM_{2.5}$ NO_2	$PM_{2.5}$ CO	NO_2 CO	$PM_{2.5}$ NO_2	$PM_{2.5}$ CO	NO_2 CO
N	15	28	15	28	28	28
Mean	0.41	0.16	0.12	0.44	0.38	0.72
SD	0.28	0.42	0.42	0.35	0.32	0.22
Median	0.43	0.16	0.16	0.52	0.36	0.81
Min	-0.03	-0.84	-0.72	-0.53	-0.27	0.25
Max	0.78	0.93	0.63	1.00	1.00	1.00

Spearman's correlation coefficients were calculated for each subject.

Beckerman *et al.* observed moderate to high correlations between NO_2 measurements near a busy roadway and the concentration of other primary and secondary traffic-related pollutants (Beckerman *et al.*, 2008). The values shown in **Table 4** reveal statistically significant positive correlation coefficients ranging from 0.64 to 0.85 for NO, NO_x, $PM_{2.5}$ and UFPM. The negative relationship with ozone is presumably caused by the rapid atmospheric reaction between NO in the exhaust and ambient ozone to yield NO_2. Moderately high correlations were also observed for many of the VOCs in automobile exhaust and NO_2.

The relationship with ultrafine particulate matter was particularly interesting because the concentration fell off far more quickly than NO_2 as function of distance from the roadway. This finding indicates that NO_2 may not be a good surrogate for particulate matter in some circumstances because of the smaller gradient for NO_2 (2-fold) versus UFPM (26-fold). These studies have been replicated many times over past decade and they have repeatedly shown that NO_2 co-varies with a number of atmospheric contaminants. For instance, Parra *et al.* reported correlation coefficients for roadside NO_2 measurements that ranged from 0.57 to 0.66 for BTEX substances measured in northern Spain (Parra *et al.*, 2009). The diurnal variation for these substances was also closely aligned as shown in **Figure 8**. Daily maximum (8-10 AM) and minima (8-10 PM) corresponding with local traffic intensity.

Figure 8 Average weekly and diurnal cycles of benzene, toluene, xylenes and NO_2 at the urban air quality station for the period June 2006–June 2007 (Parra et al., 2009)



The most revealing results were obtained in a meta-analyses of studies where the daily average personal and ambient measurements were compared (Meng *et al.*, 2012a). The results from this type of analysis are directly relevant to panel and time-series investigations where the data from central monitoring site are often used as the surrogate for personal NO_2 exposures. After correction for publication bias correlation coefficients of 0.37, 0.16, and 0.45 were determined for pooled, longitudinal, and daily average comparisons. These weak, but statistically significant, correlations were found to be affected by a number of factors including study location, population characteristics, meteorological conditions, indoor sources, and co-pollutant concentrations. Stronger associations were generally observed in spring and fall rather than winter and spring when most households leave windows closed thereby decreasing the air exchange rate. The analysis also revealed a consistent positive association between personal measures of NO_2 exposure and personal O_3 and $PM_{2.5}$ levels. Together these data highlight the high degree of uncertainty that accompanies the use of ambient NO_2 measurements from central monitoring sites as a surrogate for personal exposure and also reinforce the likelihood that NO_2 exposures may be functioning as a proxy for another ambient air pollutant. This was the key conclusion of Van Roosbroeck *et al.* (2008) who noted than an adjustment for exposure misclassification through the use of personal rather than outdoor measurements of NO_2 resulted in effect estimates that 2-3 times higher for asthma–related symptom reporting (Van Roosbroeck *et al.*, 2007). The authors noted that actual personal exposures to NO_2, while lower than those assigned using outdoor monitoring station data, were capable of taking into consideration the true spatial variability of the NO_2 emanating from indoor sources.

Despite the higher effect estimates for the prevalence of respiratory symptoms in children using personal NO_2 exposures, the authors pointed out that the associations were not likely causal because of the strong correlation between NO_2 and other traffic-related pollutants. Others have noted that the use of land use regression models to improve the spatial resolution of NO_2 estimates from fixed monitoring sites did not appreciably improve the relationship between personal and outdoor annual NO_2 exposure measurements compared to the values obtained using inverse distance weighting of the ambient monitoring data (Nethery *et al.*, 2008). These authors found a poor relationship (r=0.05) between personal NO_2 exposure levels and those from fixed monitoring sites in a group of pregnant women from Vancouver, Canada, even after adjusted for home location using inverse distance weighting techniques. By taking into consideration time-activity patterns

and the amount of time spent indoors, personal measurements were shown to be lower (18.7 ppb) than those from fixed sites (19.6 ppb) but higher than those estimated using LUR techniques (17.4 ppb). The ambient monitoring data could not explain any of the between subject (spatial) variance and only a small portion of the within subject (temporal) variance. The strength of the association between personal and ambient NO_2 exposures has also been shown to be affected by seasonal influences, the degree of home ventilation, and gas stove usage (Brown *et al.*, 2009).

6. ALTERNATIVE EXPOSURE METRICS

Exposure measurements, perhaps more than any other determinant, are the single largest source of bias in many epidemiology studies focusing on air pollution. In the absence of personal monitoring data, investigators are often forced to use measurements from central monitoring sites, which are poorly related to personal exposure measurement (Bellander *et al.*, 2012, Steinle *et al.*, 2013). Since many epidemiological studies with NO_2 are ecological in nature, focusing on exposures at the population level rather than with the individual, the propensity for exposure misclassification is very high. In some cases, the measurements from monitoring sites are examined in finer detail to develop an exposure surrogate that is applicable to a particular residential location. However, even these measures fail to consider time-activity patterns, indoor sources of NO_2, and nearby traffic patterns (Baxter *et al.*, 2007, Devi *et al.*, 2013, Schweizer *et al.*, 2007). Despite the availability of statistical methods to correction for the bias caused by deviations between actual concentrations and estimated values, the techniques are rarely employed and the results from many observational studies are generally presented as raw uncorrected risk measures that may or may not be reflective of the actual circumstances in the population under study (Spiegelman, 2010).

Exposure misclassification of this sort occurs in nearly every epidemiology study and efforts to control for its impact have steadily improved over the last decade, but problems still remain with many investigators unwilling to invest the added effort needed to acquire validation data (Jurek *et al.*, 2006). Consequently, there is an often assumed non-differential bias towards the null in effect measures; however, quantitative determinations of the magnitude or impact of this misclassification are rarely provided so the actual impact is never known with any certainty (Goldman *et al.*, 2012, Greenland and Gustafson, 2006, Jurek *et al.*, 2005, Jurek *et al.*, 2008) . This has led to a false sense of security, with scientists and regulators comfortable in the belief that risk measures have been underestimated rather than over estimated and that any weakly significant statistical associations are at the lower limit for the observed risk.

In reality, non-differential and differential error often exist together in observational studies using ambient air measurements as surrogates for actual personal exposures. The magnitude of this error is impacted in part by the degree of coverage that exists for monitoring network and number of sites that were included in the exposure modelling. In many cases, morbidity or mortality estimates are based on measurements from just a few sites, which may cause considerable bias. This type bias was important factor that influenced how many studies were rated in this report. Under the GRADE scoring system, the exposure misclassification was deemed to be very serious if the number of monitoring sites was limited to 1 or 2, or if the sites were located in an areas that was not representative of the study population (see **Table 1**).

The methods used to gather estimates of personal exposure to NO_2 from area monitoring data have evolved considerably in the past decade. Techniques such as (i) proximity-based assessments based on distance from known sources, (ii) statistical interpolation using geographic information for distance adjustments from monitoring sites, iii) land use regression models that incorporate geographic information as well as traffic patterns into a mapping scheme to predict concentrations remote from a monitoring site, (iv) dispersion models that use local emissions data along with topographical an meteorological data to predict spatial and temporal patterns in exposure concentration, (v) Eularian grid models that include sophisticated meteorological, atmospheric chemistry, emission modules that

provide coarse spatial and fine temporal predictions, and (vi) hybrid models that integrate information from actual personal or regional exposure measurements along with secondary source emission profiles to validate the results using air shed models (Jerrett *et al.*, 2005). The characteristics of these models are described further in **Table 8**. It should be noted that each of these exposure estimation techniques has particular strengths and limitations, and that while a model may be suitable for use under a particular set of circumstances, the same method may produce ineffectual information in others.

Generally speaking, however, proximity modelling techniques yield the weakest results while hybrid models, given their use of validation routines, yield the strongest. Modelling techniques using traffic-related metrics such traffic volume, intensity, or roadway distance, while still employed to some degree, are not particularly informative for policy setting (Lipfert and Wyzga, 2008). In addition, these traffic-related metrics suffer because their relationship to actual pollutant exposure levels is open to question, especially for NO_2 where the use of traffic surrogates may introduce considerable error in the absence of validation studies (Baxter *et al.*, 2010, Boogaard *et al.*, 2011).

Table 8 Comparison of various urban exposure models according to various implementation criteria (Jerrett et al., 2005)

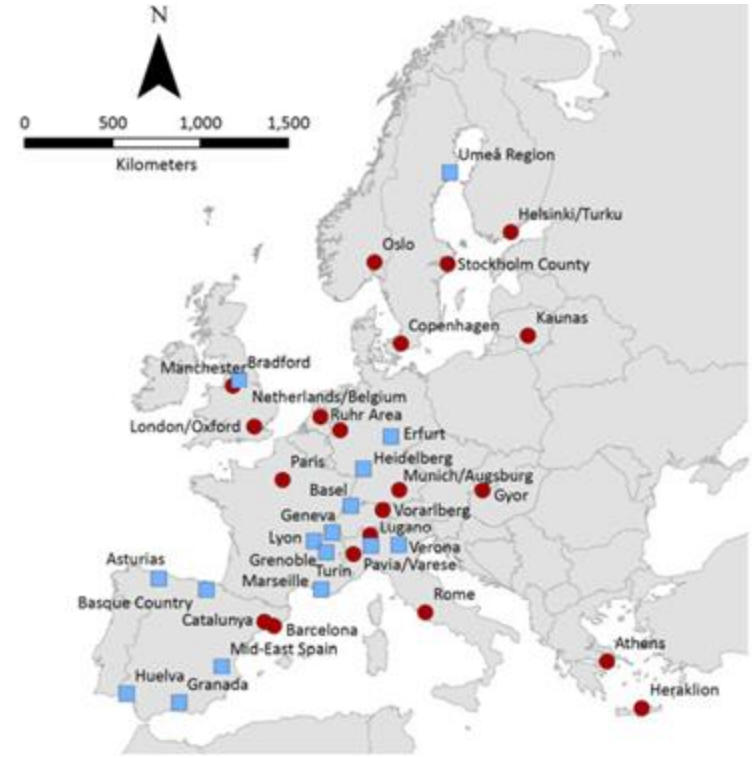
Model	Theory concept match	Limitations to health studies	Data requirements	Need for updated data	Software expertise	Overall implementation cost	Marginal benefit	Transferability
Proximity based	Low	Crude exposure estimates	Traffic volumes Distance from line source Questionnaire	Low	GIS Statistics	Equipment: low Software: low Personnel: medium	Base case	Low
Geostatistical	Medium	Depends on density of monitoring network	Monitoring measurements	Low	GIS Spatial statistics	Equipment: medium Software: medium Personnel: low	Transferability Error structure of estimate	Low
Land Use regression	Medium	Depends on density of observations	Traffic volumes Meteorology Monitoring measurements Land-use	Medium	GIS Statistics Monitor experts	Equipment: medium Software: medium Personnel: medium	Transferability Error structure of estimate	Medium
Dispersion	Medium	Extensive inputs Unrealistic assumptions about pollutant transport	Traffic volumes Point source emissions Meteorology Monitoring measurements Topography	Medium	GIS Statistics Monitor experts Dispersion software	Equipment: high Software: high Personnel: medium	Emphasis on process	High
Integrated meteorological emission	Medium	Coarse resolution	Traffic volumes Point source emissions Meteorology Monitoring measurements Topography	High	GIS Statistics Monitor experts	Equipment: high Software: high Personnel: high	Emphasis on process	Medium
Hybrid (personal monitoring & one of the preceding methods)	High	Small and biased sample Depends on combination	Questionnaire Personal monitoring data Other depending on combinations	Depends on combination	Personal monitor experts Survey design Depends on combination	Equipment: high Software: * Personnel: * * Depends on combination	Depends on combination	Low

Models are arranged in terms of increasing complexity with respect to the suitability, requirements, and the cost for their implementation. Each column corresponds to a different evaluation criterion; the first class of criteria concerns the matching of the method conceptualization to theory and the utility of the model/methods to respiratory studies.

Perhaps the greatest weakness in the approaches that incorporate some proximity consideration is the failure to consider the exposure variations caused by traffic intensity, indoor sources, or time activity patterns. This is a particularly important factor for NO_2 exposure assessment since concentration profiles display such a high degree of spatial and temporal variability within and between urban and rural locations. For instance, NO_2 exposures across eight regions of Switzerland for the years 1993 and 2003 were found to have a very high degree of spatio-temporal variability that could not be adequately described by any one exposure model (Liu *et al.*, 2012). Spatial variability accounted for 31-74% of the total variance in NO_2 measurements in 2003, whereas the range for 1993 the value was 8-65%. Of the six exposure models examined, including dispersion, GIS, and hybrid, no single approach worked well for all locations. Overall, however, hybrid models performed better on a national scale yielding correlation coefficients of approximately 0.8, but there were substantial differences between regions, with the Spearman correlation ranging from 0.28 to 0.68.

Similar findings have emerged from a recent comprehensive investigation of NO_2 levels across 36 regions (see **Figure 9**) of Europe undertaken as part of the ESCAPE (European Study of Cohorts for Air Pollution Effects) program (Cyrys *et al.*, 2012). Substantial spatial variability was seen to exist within the study area, with the average annual concentration of NO_2 ranging by as much as 54 $\mu g/m^3$ within an individual region. The greatest spatial variability was noted in the largest European cities such as London, Paris, and Barcelona. The spatial variance within each study area was considerably greater than between locations leading the authors to conclude that it was virtually impossible to characterize urban wide concentrations with just a single monitoring site and that epidemiology studies that assign an overall average exposure based on limited information from one or two monitoring locations would introduce considerable misclassification and random error that would bias the results. For this reason, exposure modelling using LUR or some other temporally and spatially robust method was deemed to be necessary.

Figure 9 European locations for the ESCAPE monitoring campaign (black dark circles mark the study areas where PM, NO_2, and NO_x were measured; blue squares show the areas where only NO_2 and NO_x were measured)



■ NO_x measurements
● PM and NO_x measurements

Because of their ability to take spatial variability into consideration, there has been a dramatic upswing in the use of LUR models. These models use the information from central monitoring sites along with measurements obtained during multiple sampling campaigns that take place over a period of 1-2 weeks. These data are then used together with a stochastic model that is built using predictor variables obtained from geographic information systems (GIS) maps (Hoek *et al.*, 2008). Once developed, the model can be applied to a large number of locations that have no monitoring sites to evaluate an air pollutants spatial variability. The list of potential predictor variables is very large and includes altitude, meteorology, land coverage, topography, population density, road density, road type, commercial land uses, and distance to local pollution sources.

Dozens of these models have been developed for predicting NO_2 exposures in different regions of Europe, the US, and Canada, however the models vary in quality and the degree of validation that has been performed. Correlations as high as 0.81 have been reported for the relationship between measured and predicted NO_2 levels in an urban environment (Su *et al.*, 2010). To achieve this degree of reliability however, their needs to be substantial validation using either a separate set of monitoring data that is distinct from the training set or the application of a “leave-one-out” cross-validation scheme.

Although LUR models are felt to perform well, it is essential that monitoring data is collected from a sufficient number of monitoring sites and that an adequate number of predictor variables are included in the model (Basagana *et al.*, 2013, Wang *et al.*, 2012). A minimum of 80 NO_2 monitoring locations is necessary to achieve reasonable estimates that are neither biased nor highly variable (Basagana *et al.*, 2012). The use of a small number of monitoring sites together with a large number of predictor variables has been shown to artificially increase the correlation coefficient between actual and predicted measurements. Johnson *et al.* noted that correlation coefficients could be inflated by 50% or more if an independent data set is not used for validation (Johnson *et al.*, 2010). Another drawback to the use of LUR models is their inability to account for temporal variably in NO_2 levels. Some have corrected for this problem by constructing separate models for discrete time periods lasting for just a year or two (Cesaroni *et al.*, 2012, Eeftens *et al.*, 2011).

Despite the propensity for error, LUR models continue to be developed for ever larger tracts of land. In fact, a LUR model was recently constructed for the entire United States using both ground satellite-based measurements of NO_2 (Novotny *et al.*, 2011). Improvements continue to be made in model-based estimates of NO_2 exposure with the application of new statistical procedures known as universal kriging for spatial interpolation across a surface map (Beelen *et al.*, 2009, Li *et al.*, 2012b, Mercer *et al.*, 2011). New hybrid models have also been examined that use air quality models together with LUR to increase the number of exposure sites that can be used in the training set (Molter *et al.*, 2010). The application of the newer approaches will reduce but entirely eliminate the potential for exposure misclassification that comes with the use central site monitoring data.

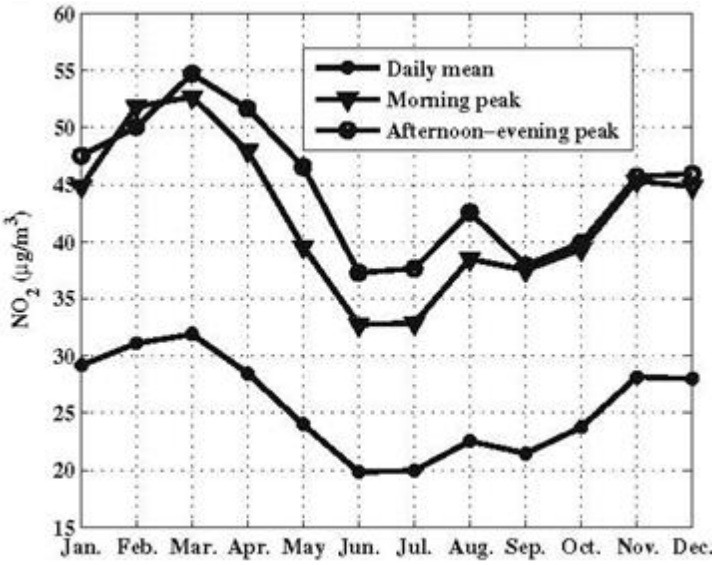
7. BIAS AND EFFECT MODIFICATION

The spatial variability of ambient NO_2 can be influenced by a number of factors, especially in urban environments where traffic patterns can vary considerably. Meteorological influences, such as wind direction, wind speed, temperature, solar radiation, and humidity can all impact regional and local levels (Ahmad *et al.*, 2011). Sorting out the contribution of these weather variables is not, however, entirely straightforward since the parameters are often correlated, which confounds any evaluation of their overall impact. Arain *et al.* examined spatial and temporal variation in NO_2 levels in the Toronto/Hamilton airshed and found that wind direction had a particularly strong influence on hourly NO_2 concentrations, with wind speed and temperature also impacting the results (Arain *et al.*, 2009). Strong seasonal patterns were also observed with higher mean concentrations observed in the winter months and higher individual hourly concentrations in the summer months. Concentrations tended to be higher in the morning and evening and lower in the afternoon and night.

Similar relationships were reported by Laurinaviciene for a large city in Lithuania with wind speed and rainfall negatively impacting NO_2 levels and temperature having no affect (Laurinaviciene, 2013). In this location, however, the highest levels were found in the spring and the lowest in the fall. These data demonstrate the influences of geography and metrology and underscore the importance of considering the high spatial variability that characterizes NO_2 levels in urban and suburban environments. Since central site monitors rarely capture this spatial variability, the information needs to carefully considered and supplemented with meteorological information whenever possible to ensure adequate representation.

Meteorological variability can also impact the temporal variability in NO_2 levels. This factor has become the subject of renewed interest in the past several years with many investigators examining the interactions between NO_2 levels and weather conditions. As shown in **Figure 10**, NO_2 levels in Europe show a clear diurnal trend in most cities that is intimately associated with local rush hour traffic (Bigi and Harrison, 2010). The levels on weekends are more uniform and do not peak in the same fashion as on weekdays. In addition, the NO_2 levels in winter are generally higher than in summer and the wintertime levels are often positively correlated with CO and NO. These seasonal and daily fluctuations in NO_2 concentration were observed in Puertollano, Spain by Saiz-Lopez *et al.* who found a mean value of 27.0 $\mu g/m^3$ in the winter and 15.5 $\mu g/m^3$ in the summer (Saiz-Lopez *et al.*, 2009). Seasonal relationships of this type were also observed in Windsor, Ontario by Wheeler *et al.*, who noted that NO_2 concentrations were well correlated ($r = 0.51$-0.84) with SO_2, benzene, and toluene levels in all four seasons (Wheeler *et al.*, 2008).

Figure 10 Durinal cycle of NO_2 concentrations for each season during 1999 to 2008. Seasonal cycle of daily mean, morning peak, afternoon–evening peak NO_2 concentrations in Gothenburg for 1999–2008 (Tang et al., 2011)



Wind speed and the vertical temperature profile can impact the NO_2 levels in urban environments and can account for up to 80% of the variability found during the afternoon driving peak (Tang *et al.*, 2011). Research has shown that weather conditions alone can account for a 2 μg/m^3 change in the annual average annual concentration of NO_2 and that a level of 38 μg/m^3 needs to be attained to ensure that meteorology will not have an impact on compliance (Velders and Diederen, 2009). Wind speed is known to be negatively correlated with NO_2 levels in urban environments such that the magnitude of any exceedances can be an indicator of local air stagnation (Ito *et al.*, 2007). Aside from the impact of ambient temperature as an effect modifier in time series studies, it can also impact the atmospheric chemistry of NO_2 by altering the rate photooxidation. This temperature effect is responsible, in part, for the seasonal differences noted above, with cold temperatures reducing the removal efficiency and effectively increasing the ambient air levels. In general, urban NO_2 levels can display a negative correlation with rainfall, ambient temperature, and wind speed, and a positive correlation with relative humidity (Ahmad *et al.*, 2011).

NO_2 concentrations generally show a similar seasonal profile regardless of location. There are also other factors that may obscure the true relationship between NO_2 and a health outcome of interest. Recent attention has focused on the interaction between noise and NO_2 exposures in urban environments where residences are located in close proximity to major roadways. Foraster *et al.* for instance found that annual average NO_2 measurements were well correlated with long-term measures of 24-hr weighted noise levels (r = 0.62) at residential locations in Girona, Spain (Foraster *et al.*, 2011). The study is important because transportation-related noise has been shown to be associated with cardiovascular effects much like NO_2 (Babisch, 2008). Others studies such as those Allen *et al.* and Davies *et al.* have yielded similar results using 5-min noise measurements and 2-week NO_2 levels (Allen *et al.*, 2009, Davies *et al.*, 2009). The correlation coefficients in these studies generally ranged from 0.41 to 0.62, but outliers did occur on some occasions.

Studies using estimated NO_2 concentrations from LUR models have yielded somewhat smaller correlation coefficients (r = 0.38), but the authors were quick to note that the results may have been impacted by the local road surface and building materials that may have attenuated the noise levels but not the NO_2 concentration (Gan *et al.*, 2011). The nature of the relationship is not a simple one, however, and may be modified by time of day, noise frequency, wind, and other variables. In the absence of information showing that NO_2 and noise act independently there is suggestive evidence of confounding based on the fact that exposures to these insults can co-vary. Given that both have been associated with conditions such as cardiovascular disease, the reliability past studies with NO_2 alone without noise adjustment can be called into question (Ross *et al.*, 2011). Confounding by noise is attracting considerable attention from leading investigators and will undoubtedly be examined in the coming years, until then however, there is good reason to believe that the proxy effect observed with NO_2 may be in part due to traffic-related noise exposures (Allen and Adar, 2011).

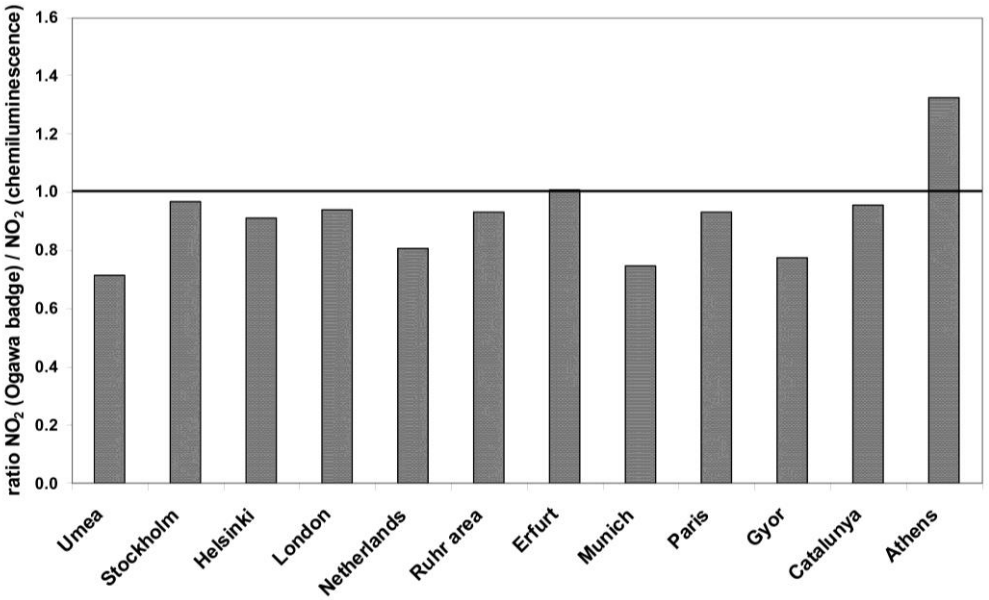
Another somewhat overlooked co-variate is socioeconomic status (SES). This is a critically important consideration in studies investigating the relation of NO_2 exposures with asthma or asthma-related symptoms. In a cohort of 5000-9000 individuals from the USA, Europe, Australia and New Zealand, a statistically significant association was observed in the prevalence and incidence of asthma without atopy and chronic bronchitis for those in the lowest education category but not for those in the lowest occupational class (Ellison-Loschmann *et al.*, 2007). Similarly, SES as measured by a deprivation index that included 19 demographic and socioeconomic indicators exhibited a positive and non-linear relation with NO_2 levels for individuals (n≈450,000) living in Strasbourg, France (Havard *et al.*, 2009). In this study, the most exposed individuals included those in the mid-level category rather than those in the lower SES strata. More attention has also been placed on psychological stress as a factor that may interact with traffic-related pollutants and affect the association with asthma onset or the symptoms of asthma (Chen et al., 2008, Shankardass et al., 2009). Clougherty *et al.*, in particular, only observed an association between NO_2 exposures and asthma when children were exposed to high levels of violence in the form of hitting, slapping, shooting, stabbing and hearing gunfire was considered (Clougherty *et al.*, 2009). These types of synergies and interactions point to the problems of establishing a causal link between NO_2 exposures and observationally-based changes in health risk. Certainly, the impact of these factors must be taken into consideration when evaluating the quality of an investigation using any grading system.

An often overlooked and rarely considered source of exposure misclassification bias in health effects studies concerns the chemical interference in the direct-reading NO_2 devices located in some but not all areas of Europe (Jurek *et al.*, 2006). Steinbacher *et al.* (2007) reported that NO_2 measurements based on chemiluminescence detectors using molybdenum-based thermal converters were capable of oxidizing PAN, HONO, HNO_3 and other organo-nitrates to NO_2. Collectively, these chemical interferents are referred to as NO_y compounds, and tend to be found at higher concentration in photochemically active air parcels such as those located close to urban centers. Measurement taken at three rural locations in Switzerland showed that only 70-83% of measured NO_2 could be attributed to actual NO_2 levels in ambient with the remainder due to other nitrogen oxides. The interference was more severe at high altitude locations (approx. 1000 m above sea level) where 43-76% of measured NO_2 was authentic. The degree of interference from secondary nitrogenous based compounds was appreciably worse in the winter and spring than in the summer and fall, which coincides with periods when NO_2 is at its seasonal high and low, respectively. Similar evaluations in urban settings in

Santiago, Chili and Mexico City have shown that molybdenum-based chemiluminescence measurements were 4-fold and 2-fold higher than those from a standardized reference method (Dunlea *et al.*, 2007, Villena *et al.*, 2012). Importantly, direct reading monitors relying on photolytic converters (i.e. luminal-based) for NO_2 oxidation are far less prone to this type of interference. Although molybdenum-based chemiluminescence techniques are commonplace at many European monitoring sites, some locations have installed the more robust photolytic-based systems (Lewne *et al.*, 2004). The use of non-standardized analytical methods with some monitors stations overestimating NO_2 concentrations can produce an appreciable measurement error that must be considered when evaluating the results from an epidemiology studies. The impact of this error cannot be over stated. Health effect studies relying on chemiluminescence-based measurements with molybdenum detectors will systematically overestimate NO_2 exposures by a variable degree leading to biased associations that are not representative of the actual condition.

Evidence for this bias was seen a recent study by Cyrys *et al.*, who compared NO_2 measurements made with Ogawa passive diffusion samplers with those from a chemiluminescence monitor at 12 locations throughout Europe (Cyrys *et al.*, 2012). As shown below in **Figure 11**, the ratio of the NO_2 values for the two measurement methods showed a persistent bias with passive diffusion badges yielding values that were 22-28% lower than the chemiluminescence measurements at four locations. Some locations showed ratios close to unity, which likely reflects the use of unbiased photolytic detectors in these monitoring stations.

Figure 11 Ratio of concentrations measured by Ogawa badge and chemiluminescence monitor co-located at routine monitoring sites for NO_2 (Cyrys et al., 2012)

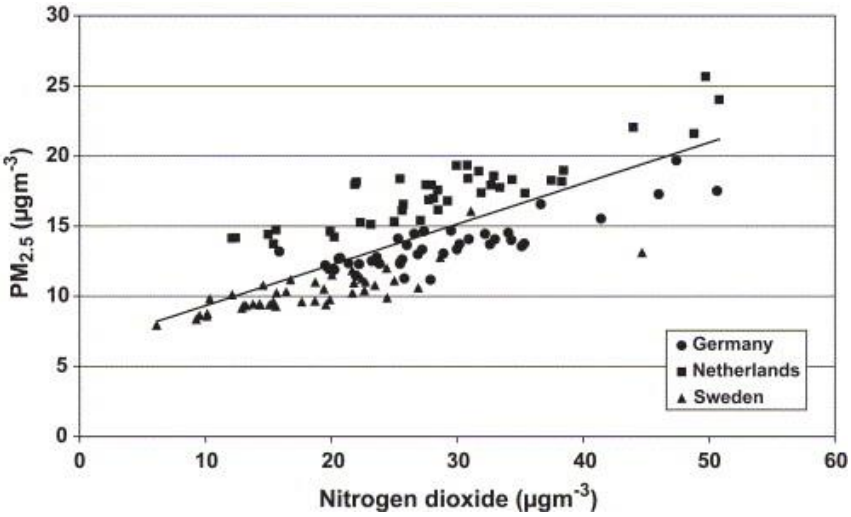


In many studies, particularly those centered in Europe, NO_2 is used as a surrogate for PM-related measurements that are not available with same degree of frequency or spatial intensity (Brunekreef, 2007). The justification for using NO_2 as a surrogate can be traced to studies such as those by Lewné *et al.*, where moderately high correlations (r^2=0.64-0.80) were found to exist between NO_2 and $PM_{2.5}$ levels in three areas of European (see **Figure 12**). The close relationships allowed the

authors to use NO_2 as metric for $PM_{2.5}$ based on the greater ease of measurement. The relationship between NO_2 and other tailpipe emissions have caused some investigators to state that NO_2 is merely an exposure proxy and that any associations with observed acute or chronic health effects may not be related to NO_2 exposures per se, but rather to another traffic-related pollutant (Andersen *et al.*, 2012a, Freire *et al.*, 2010, Jacquemin *et al.*, 2009, Jerrett *et al.*, 2008, Llop *et al.*, 2010, Weng *et al.*, 2008). The World Health Organization acknowledged this problem in their 2006 guidance on air pollutants, stating:

> "Nitrogen dioxide is itself toxic, and its concentrations are often strongly correlated with those of other toxic pollutants. As it is easier to measure, it is often used as a surrogate for the mixture as a whole. Achieving the guidelines for individual pollutants such as nitrogen dioxide may therefore bring benefits for public health that exceeds those anticipated based on estimates of the pollutant's specific toxicity." (WHO, 2006)

Figure 12 Nitrogen dioxide and $PM_{2.5}$ in all field sites in Germany, The Netherlands, and Sweden (Lewne et al., 2004)



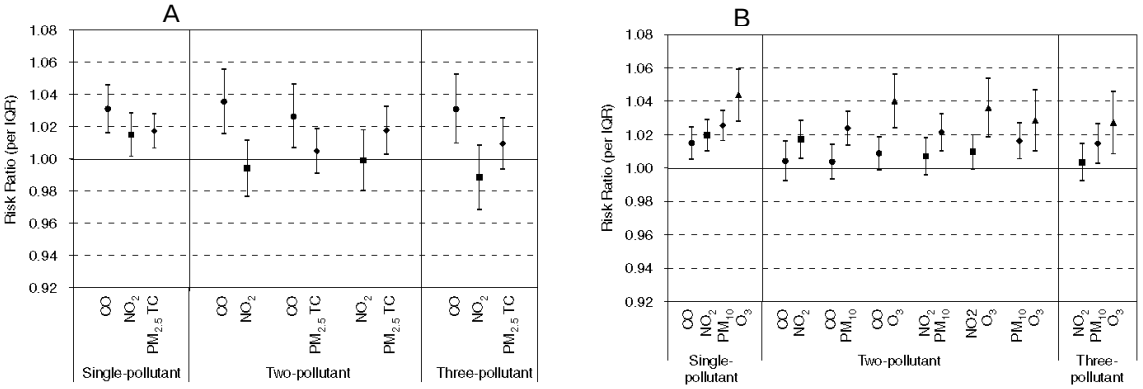
all countries: Y=0.29(±0.02)X+6.41(±0.59), r^2=0.60, N=122
Germany: Y=0.19X+8.15, r^2=0.71, N=40
Netherlands: Y=0.25X+10.39, r^2=0.80, N=40
Sweden: Y=0.17X+7.24, r^2=0.64, N=42

This statement assumes of course that there is a regular and predictable relationship between the NO_2 surrogate and the actual causative agent and that spatial and temporal change in the mixing ratios have no impact on the strength of the relationship. Issues such as pollutant co-linearity, confounding from mismeasured or unmeasured pollutants, antagonistic or synergist effects, and insufficient statistical power complicate any meaningful policy-related analysis of studies equating NO_2 exposure with a potential health outcome. Certainly, tools have been developed to help overcome these uncertainties, and they have helped improve the quality of the information. But many have begun to argue that the problems can only solved by moving away from a one pollutant model for regulating air pollutants to a "one-atmosphere" approach that includes an integrated assessment of the impacts of all pollutants. Whereas, there has been considerable movement in this direction by policy-makers and respected authorities, there are still considerable hurdles to overcome (Dominici *et al.*, 2010, Vedal and Kaufman,

2011). Until that time, other basic tools have come to be relied upon for improving the reliability of health effects studies. These include improved techniques for exposure assignment and the application multi-pollutant modelling techniques. Although these methods do not provide foolproof results, these methods are an improvement over past approaches relying on central site monitoring results or single-pollutant models that fail to consider possible interaction from co-varying pollutant concentrations.

Multi-pollutant models have the ability of factoring collinearity issues into consideration, and for identifying those pollutants showing the strongest relationship with a particular outcome. For instance, Tolbert *et al.* examined the association between emergency department visits for cardiovascular or respiratory illness and exposures to three pollutants both singly and in combination (Tolbert *et al.*, 2007). As shown in **Figure 13**, statistically significant associations were observed between three-day moving average air exposures and the risk ratios for cardiovascular and pulmonary ED visits using a single-pollutant model. When two-pollutant or three pollutant models were applied using NO_2, CO, $PM_{2.5}$ EC, O_3 or PM_{10} in some combination, the significant associations for NO_2 were no longer observed. Multi-pollutant modelling is necessary when individual pollutants are treated as independent risk factors but their exposure concentrations are strongly correlated, (Kim *et al.*, 2007). This is often the case with NO_2, whose airborne concentrations are often significantly correlated with other pollutants such as $PM_{2.5}$, UFP, and CO. In the above example, the results of multi-pollutant modelling showed that the strongest associations with cardiovascular visits occurred with CO, whereas the respiratory visits were associated with O_3. This example demonstrates the importance of multi-pollutant modelling for NO_2 and highlights the erroneous associations that may arise when single-pollutant models are relied upon as the primary basis for establishing an association. Still, multi-pollutant modelling is not a panacea, and assumptions regarding co-linearity between pollutants, non-differential seasonal effects, and the absence of appreciable interactions with other physical or environmental factors cannot be guaranteed.

Figure 13 Results of selected multi-pollutant models for combined cardiovascular (A) and respiratory (B) diseases group, 1998–2004, Study of Particles and Health in Atlanta (SOPHIA) (Tolbert et al., 2007)



CO, carbon monoxide;
IQR, inter-quartile range;
NO_2, nitrogen dioxide;
PM, particulate matter;
TC, total carbon.
Models shown include only days on which CO, NO_2, $PM_{2.5}$, and TC are all non-missing

Although providing a methodological improvement, multi-pollutant models are not able to rule out that the pollutant with the highest adjusted risk estimate may be acting as a surrogate for other unmeasured exposures that are the true causative agent. This was well demonstrated in a study by Brook *et al.*, who re-examined previous results of an association between NO_2 exposures and non-accidental mortality in 10 Canadian cities (Brook *et al.*, 2007, Burnett *et al.*, 2004). Although the original study indicated that an NO_2-associated increase in mortality that was unaffected by adjustments for O_3, CO, or SO_2 in a two-pollutant model, the authors re-examined their results and concluded that NO_2 could be acting as a surrogate for a specific $PM_{2.5}$ component or possibly even a VOC, PAH, or other oxidized nitrogen species. The authors based this opinion on the fact that high correlations were observed with a number of other traffic-related pollutants including VOCs and PAHs and that the strongest associations were observed in the summer months when photochemical reaction products are more frequently encountered in aged urban air masses.

These are preceding factors need to be considered when interpreting the results form observational studies, particularly time series studies examining the effects of short-term exposures. Whereas, some of the variables can bias the results downwards others are capable of working in the opposite direction. Regardless of the direction, however, the results are biased and do not provide an accurate and reliable representation of the relationship between exposure and effect.

8. EPIDEMIOLOGY SYNOPSIS

The following section summarizes the findings from NO_2-related epidemiology studies published since 2005. Pertinent Information regarding the conduct and findings from each study can be found in Appendix I. The studies have been segregated according exposure duration and endpoint with acute and chronic mortality studies separated from those looking at a particular outcome such as diabetes or asthma. The quality of each investigation was determined using the GRADE system described in Section I of this report. Most studies were assigned an initial designation of moderate quality then upgraded or downgraded according to the criteria described in **Table 1**. The same general criteria general were used to evaluate time-series, case-crossover, panel, case-control, and cohort studies. Preference was given to those studies that incorporated a multi-pollutant design, advanced exposure assessment methods, and a large study population.

8.1. ACUTE MORTALITY

The literature search identified a total of 25 new acute mortality studies that have been published since 2005. All but two of these studies were judged to be seriously flawed using the GRADE system and were assigned a quality rating of insufficient or low quality. The most common problems areas were exposure bias, small sample size, and the absence of any multi-pollutant modelling. Of the twenty-five papers examined, only one was found to be of moderate quality. The paper published by Park *et al.* was found to provide a robust assessment of the relationship between NO_2 exposure and acute mortality from non-accidental, cardiovascular, or respiratory causes (Gan *et al.*, 2011, Park *et al.*, 2011). This study found a significant association with a single-pollutant models that was rendered non-significant when two-pollutant modelling with performed with either $PM_{2.5}$ or CO. The confounding from CO on cardiovascular mortality was particularly strong.

Although there have been several recent meta-analyses that have pooled the results from past mortality studies with NO_2, nearly all of them have focused on the results from single-pollutant models. Lai *et al.* examined 26 studies performed in China are found significant pooled relative risk estimates for non-accidental, cardiovascular, and respiratory mortality following short-term exposure measurements (Lai *et al.*, 2013). The pooled relative risk for all-cause mortality was found to be 1.014 (95% CI 1.0106-1.0174) per 10 $\mu g/m^3$ increase in NO_2. Similar findings were reported by Shang *et al.* in their examination of acute mortality in 33 Chinese studies (Shang *et al.*, 2013). In this instance, the pooled respiratory risk was determined to be 1.62% (95% CI 1.32-1.92). Both of these studies employed random-effects models when tests for heterogeneity indicated a need to do so, but both suffered from a lag bias since the lag period was allowed to float across each study. Atkinson *et al.* pooled the results from 7 investigations of all-cause mortality conducted around the world and reported a relative risk of 0.98% (95% CI 0.54-1.42) for a 10 $\mu g/m^3$ increase in NO_2 (Atkinson *et al.*, 2011). Again, all of these evaluations used the results from single-pollutant models.

The only meta-analyses performed using the results from multi-pollutant models indicated that the mortality estimates associated with NO_2 exposure were robust to the incorporation of a second pollutant (Anderson *et al.*, 2007). This analysis was, however, restricted to 7 multi-city studies and did not examine the full range of multi-pollutant modelling results that were available. The preceding analysis provides a reasonable cause to believe that the observed associations with acute mortality using single-pollutant models are an artifact and should not be relied upon as the

sole basis for making any adjustments to NO_2 limit values. Until such time that co-pollutant interactions can be fully explored, there is a reasonable basis for believing that the associations with NO_2 exposure are specious and misleading.

8.2. CHRONIC MORTALITY

Eight studies were located that provided new information on the relationship between long-term NO_2 exposure and mortality from a variety of causes. These cohort studies and case-control studies were often underpowered and limited to a small number of cases. Only one of the studies was judged to be of moderate quality with the GRADE assessment (Gan *et al.*, 2011). The Gan *et al.* study is summarized in Appendix I and reviewed in detail in Appendix II. The study looked at the mortality of 450,000 individuals 45-85 years of age and employed LUR techniques for the exposure determination. Although statistically significant associations were observed using adjusted and unadjusted single-pollutant models, none were observed after controlling for the confounding effects from black carbon and $PM_{2.5}$ levels. The most serious limitation of this study was the failure to consider cigarette smoking, second-hand smoke, and ethanol consumption as confounding variables. These deficiencies were offset by the availability of concentration response functions, which helped to improve the overall reliability and led to the final assignment of a moderate quality rating. All of the remaining chronic mortality studies examined were judged to be insufficient or of low quality because of an exposure bias or a limited sample size.

Several very recently published meta-analyses are available that have examined the chronic mortality risks from NO_2. Hoek *et al.* reported that the relative risk for all-cause random effects mortality estimates from 15 studies was 5.5% (95% CI 3.1-8.0) per 10 µg/m^3 increase in NO_2 using a single-pollutant model (Hoek *et al.*, 2013). The analysis is notable since it only included studies that accounted for the spatial variability of NO_2, 6 of the 15 studies examined did not adjust for smoking status.

Another well conducted meta-analysis did not find any relationship between NO_2 exposure and chronic mortality using single or two-pollutant models that were applied to the 22 cohorts examined in the ESCAPE study (Beelen *et al.*, 2013). The results for the single-pollutant modelling are shown in **Table 9** and show that no meaningful associations were evident in a fully adjusted model (model 3) that considered smoking status. Taken together the results do not indicate that there is any relationship between NO_2 exposure and chronic mortality and that this is not a relevant endpoint for making any adjustments to the limit value.

Table 9 Results of random-effects meta-analyses for the association between natural cause mortality and exposure to air pollution and traffic intensity indicators (using main confounder models 1, 2, and 3)[#]

Metric	Number cohorts	Model 1*	Model 2*	Model 3*	p value for model 3	I^2 (p value)[†]
$PM_{2.5}$	19	1·18 (1·08–1·30)	1·09 (1·03–1·14)	1·07 (1·02–1·13)	0·02	0 (0·95)
$PM_{2.5\ absorbance}$	19	1·11 (1·04–1·18)	1·04 (0·99–1·09)	1·02 (0·97–1·07)	0·38	0 (0·99)
PM_{10}	19	1·12 (1·03–1·21)	1·05 (1·01–1·10)	1·04 (1·00–1·09)	0·08	0 (0·61)
PM_{coarse}	19	1·14 (1·03–1·26)	1·05 (0·99–1·12)	1·04 (0·98–1·10)	0·22	32·3 (0·09)
NO_2	22	1·06 (1·02–1·10)	1·02 (0·99–1·04)	1·01 (0·99–1·03)	0·18	0·7 (0·45)
NO_x	22	1·06 (1·03–1·09)	1·03 (1·00–1·05)	1·02 (1·00–1·04)	0·08	22·1 (0·17)
Traffic intensity on the nearest road	20	1·02 (1·00–1·03)	1·01 (0·99–1·02)	1·01 (1·00–1·03)	0·19	20·4 (0·20)
Traffic intensity on major roads within 100 m buffer	21	1·03 (1·00–1·07)	1·02 (0·98–1·05)	1·01 (0·98–1·05)	0·49	28·4 (0·11)

[#]Data are HR (95% CI), unless indicated otherwise. HRs are presented for the following increments: 5 $\mu g/m^3$ for $PM_{2.5}$, 10^{-5} m^{-1} for $PM_{2.5}$ absorbance, 10 $\mu g/m^3$ for PM_{10}, 5 $\mu g/m^3$ for PM_{coarse}, 10 $\mu g/m^3$ for NO_2, 20 $\mu g/m^3$ for NO_x, 5000 motor vehicles per day for the traffic intensity on the nearest road, and 4,000,000 motor vehicles x miles per day for the total traffic load on all major roads within a 100 m buffer. Only observations with complete information for model 3 variables were included in the analyses. The number of observations in particulate matter and NO_2 or NO_x analyses was the same for the different confounder models: 322,159 and 367,251, respectively.

*Model 1 was adjusted for sex and calendar time; model 2 was adjusted as in model 1, but also adjusted for smoking status, smoking intensity, smoking duration, environmental tobacco smoke, fruit intake, vegetables intake, alcohol consumption, body-mass index (BMI), educational level, occupational class, employment status, and marital status; and model 3 was adjusted as in model 2 but also adjusted for area-level socioeconomic status.

[†]I2 and Cochran's test for heterogeneity for model 3 of effect estimates between cohorts.

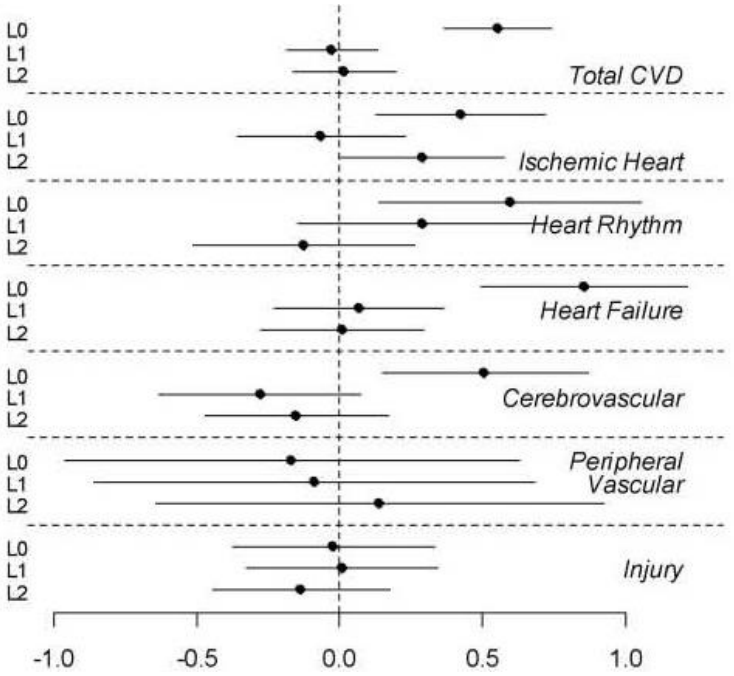
8.3. ACUTE CARDIOVASCULAR DISEASE

A total of 35 new studies were identified that explored relationships between short-term NO_2 exposure and hospital admissions or emergency room visits for a range of cardiovascular diseases including stroke, hypertension myocardial infarction, arrhythmia, ischemic heart disease, and congestive heart failure. The vast majority of these studies were downgraded one or two positions because of the potential for exposure bias or the imprecision arising from the small sample size. Of the studies examined, three were identified as being of moderately good quality using the GRADE system (Barnett et al., 2006, Chen et al., 2010, Kalantzi et al., 2011, Stieb et al., 2009). These studies all included a two-pollutant analysis and possessed a large sample size. Some studies were both downgraded and upgraded if concentration-response functions were provided. In addition several panel studies were examined that looked at changes in heart rate variability as a function of exposure. The study by Chen *et al.* found statistically significant associations between NO_2 and cardiovascular disease admissions in single and two-pollutant models after adjusting for PM_{10}. The associations were not robust to the incorporation of SO_2 in the model (see Appendix II). This study did suffer from a

failure to include CO in the analysis, which is highly correlated with NO_2 and a likely source of confounding. Similar results were obtained by Stieb *et al.*, who failed to observe any associations between NO_2 and emergency department visits for angina, myocardial infarction, heart failure, and dysrhythmia after applying a two-pollutant model that controlled for CO exposure. Barnett *et al.* conducted a multi-city investigation in Australia and New Zealand and failed to observe any significant association in the hospitalizations of adults (15-64 yrs age) or elderly (≥ 65 yrs of age) subjects for cardiovascular disease after adjusting for CO in a two-pollutant model. Taken together, these studies implicate CO as an important confounding factor that needs special consideration when evaluating the relationship between NO_2 exposure and cardiovascular disease.

The importance of CO as a co-variant is reinforced by studies that have examined its impact on admissions or visits for cardiovascular disease. The study by Bell *et al.* is particularly informative since it showed that hospitalizations for cardiovascular disease were positively associated with CO levels and that associations were not affected by the incorporation of NO_2 into the model (Bell *et al.*, 2009). The associations with ischemic heart disease, heart rhythm, heart failure, and cerebrovascular disease all remained statistically significant in the two-pollutant model (see **Figure 14**). In their examination of the risk of myocardial infarction from short-term exposures, Mustafic *et al.* noted that the pooled single-pollutant results from "good quality" studies was 1.022 (95% CI 1.009-1.034) per 1 mg/m^3 increase in CO and 1.007 (95% CI 1.002-1.012) for a 10 µg/m^3 increase in NO_2 (Mustafic *et al.*, 2012). Similarly, Shah *et al.* pooled the results from 35 studies and showed that a 10 ppb increase in NO_2 was associated with a population attributable risk of 1.67 (95% CI 1.23-2.11); whereas the results for a 1 ppm change in CO was 3.41 (95% CI 2.46-4.34) (Shah *et al.*, 2013). Future multi-pollutant studies will assuredly come to show that the cardiovascular effects being attributed to NO_2 are the result of surrogate effect with CO.

Figure 14 Percent increase in risk of cardiovascular and injury related hospital admissions for those aged ≥65 years for 92 US counties (1999–2005) (Bell et al., 2009)*



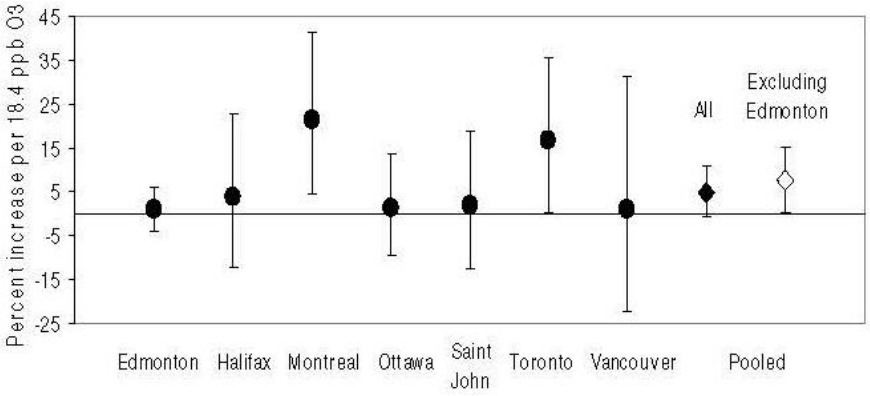
*risk per 1-ppm increase in the same-day1-hour daily maximum CO for multiple lag structures and causes of hospitalizations, with adjustment by NO_2 on lag day 0.

8.4. ACUTE RESPIRATORY DISEASE

There were 37 publications that examined the association of NO_2 exposure with some type of respiratory disease. The majority of these studies focused on asthma or the symptoms of asthma which is covered separately in the next section. Of the remaining studies, only three were judged to be of moderate quality (Son et al., 2010, Stieb et al., 2009, Zhao et al., 2008). Most studies were judged to insufficient or of low quality because moderate to severe exposure misclassifications, inconsistent findings, untenable lag structures, or imprecise methods. The study Son *et al.*, examined FVC and FEV_1 in adults and children using four different distance weighting techniques for exposure determination. NO_2 was not associated with a decline in FEV_1 in a single or two-pollutant model with O_3, but a significant association was observed with FVC using both a single and a two-pollutant model. The inclusion of O_3 had an appreciable impact on the strength of the association by reducing the percentage decrease in FVC from -3.72 (95% CI -4.33 - -2.54) to -1.74 (95% CI -2.97 - -0.51). The two-pollutant modelling was restricted to the exposure model that employed kriging for distance weighting and was not applied to pollutants other than O_3. Zhao *et al.* failed to observe an association between NO_2 and symptoms of allergies in school children after applying a hierarchical regression model that adjusted for multiple pollutants. Stieb *et al.* failed to see any associations with emergency department visits for asthma, COPD, and respiratory infections using a single-pollutant model. This study is notable since it pooled the findings from seven Canadian cites. Since no appreciable associations were observed in any of cities, two-pollutant modelling was not performed (see **Figure 15**). Importantly, the authors noted that O_3 produced the most consistent associations with the respiratory

conditions examined. This study stands in contrast to the results from past meta-analyses. Anderson *et al.* pooled 8 studies and reported that NO_2 was associated with a random effects risk estimate of 1.56% (95% CI 0.94-2.17) per 10 µg/m^3 increase using a random effects single-pollutant model that corrected for publication bias (Anderson *et al.*, 2007).

Figure 15 Percent increase in respiratory emergency department visits by center. (Point estimates and 95% confidence intervals are shown for chronic obstructive pulmonary disease



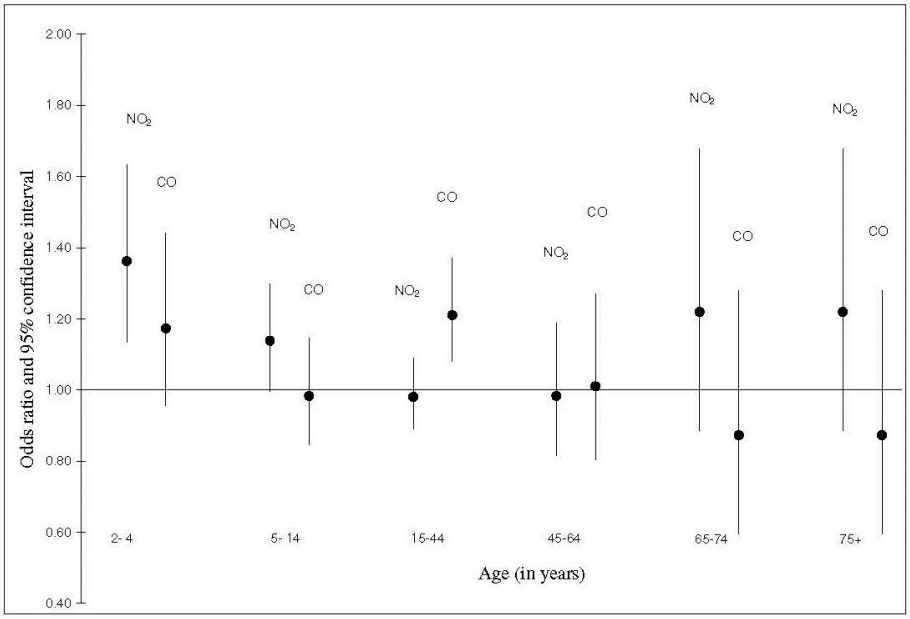
Although numerous studies have examined the relationship between NO_2 and emergency room visits or admission rates using two-pollutant models, many were seriously biased because they relied on just a single monitoring site to characterize the NO_2 exposure. It is difficult to predict whether NO_2 by itself is associated with conditions such chronic obstructive pulmonary disease, bronchitis, or pneumonia. Whereas, most government agencies have concluded that an association exists with respiratory conditions other than asthma, a meta-analysis has not been conducted that takes into consideration the confounding effects of O_3. This would certainly seem warranted given its role as an irritant gas. Until a clearer picture emerges, the available data does not unequivocally suggest that NO_2 is associated with the onset of respiratory disease.

8.5. ASTHMA

The literature search led to the review and summarisation fifty new studies focusing on asthma, which reinforces the public health importance this subject. Only two of these studies were found to be of moderate quality, with the remainder suffering from a host of problems that affected their reliability (Stieb *et al.*, 2009, Yang *et al.*, 2007). The Villeneuve *et al.* study was notable because it employed a two-pollutant model with CO that appreciably altered the relationship between NO_2 and asthma emergency department visits. Of the six age groups, examined, the odds ratio only remained significantly elevated in those 2-4 years old following adjustment for CO (see **Figure 16**). This study, however, was downgraded because of the modelling bias associated with the indiscriminate identification of the most relevant lag period. These findings also need to be balanced against those of Ko *et al.*, who noted a statistically significant association between NO_2 and hospitalizations for asthma in a three-pollutant model with O_3 and SO_2 but not in a two-pollutant model with O_3 alone. However, this study also displayed evidence of a modelling bias that was associated with the lag scheme judged to be the most appropriate. The results from the three pollutant modelling were not particularly striking and displayed a weak relative risk value of 1.014 (95% CI 1.003-1.025) per 10 µg/m^3 increase in NO_2. Lee

et al. used a five pollutant model with PM_{10}, $PM_{2.5}$, SO_2, and O_3 and found an increase in asthma admissions risk of 5.64% (95% CI 3.21-8.14) per 27.1 µg/m³ increase in NO_2. Yang *et al.* noted a statistically significant association between NO_2 and asthma hospital admissions in single- and two-pollutant models with PM_{10}, SO_2, CO, or O_3. The odds ratio for asthma admission per an interquartile NO_2 increase of 10.05 ppb (19.20 µg/m³) was 1.219 (95% CI 1.142-1.301) and 1.156 (95% CI 1.102-1.212) in a two-pollutant model with O_3 on warm and cold days, respectively.

Figure 16 Associations between asthma visits and levels of NO_2 and CO. (Villeneuve et al., 2007)*#



* Adjusted odds ratios obtained from a two-pollutant model in relation to an increase in the interquartile range of 5-day average concentration of NO_2 and CO, Edmonton, April 1 to September 30, 1992 to 2002
# Adjusted for relative humidity, temperature and daily number of emergency department visits for influenza

These findings using two-pollutant models are in general agreement with those from past meta-analyses. Weinmayr *et al.* pooled the results from 36 studies and reported a significant odds ratio of 1.031 (95% CI 1.001-1.062) for all asthma symptoms when all lag periods were examined in a single-pollutant model. The results became non-significant, however, when the lag period was restricted to the first two days (lag 01) (Weinmayr *et al.*, 2010). Anderson *et al.* restricted their meta-analyses to 13 cohort studies that examined asthma and wheeze symptom incidence and reported a random effects value of 1.15 (95% CI 1.06-1.26) for a 10 µg/m³ increase in NO_2 using a single-pollutant model unadjusted for publication bias (Anderson *et al.*, 2013a, Anderson *et al.*, 2013b). Similarly, Takenoue *et al.* found a random effect odds ratio of 1.135 (95% CI 1.031-1.251) for asthma development and 1.135 (95% CI 1.020-1.085) for wheeze symptoms after pooling the single-pollutant results from 12 studies with children 0-18 years of age (Takenoue *et al.*, 2012). Far weaker results were observed in a meta-analyses performed by Gasana *et al.*, who looked at the incidence and prevalence of asthma in children (Gasana *et al.*, 2012). This evaluation included both cohort and cross-sectional studies and yielded overall odds ratios of 1.05 (95% CI 1.00-1.11) and 1.14 (95% CI 1.06-1.24) for asthma prevalence and incidence, respectively. Despite these findings, however, an authoritative and thorough review of all the mechanistic and epidemiological

evidence indicated there was only limited evidence that air pollutants such as NO_2 play a role in asthma causation (Gowers *et al.*, 2012).

An often overlooked bias that is observed in many asthma-related time series studies is associated with the arbitrary selection of a lag period that produces the most significant outcome. It is common practice for investigators to examine a variety of lag structures within a particular study design, including single day, moving average, and distributed lag modelling schemes. When the results from a particular lag period are highlighted *a posteori* without taking into consideration the results from panel studies that have examined the development time for asthma symptoms, a modelling bias is introduced. Some investigators have taken note of this problem and offered reasonable solutions including the *a priori* selection of the most appropriate lag period based on fundamental knowledge of the disease process. The inconsistencies in lag-related results across studies have been noted in meta analyses that have compiled the results from studies with asthmatic children (Weinmayr *et al*., 2010). When the studies were compared using the lag period producing the greatest effect, then NO_2 was positively associated with asthma symptom development. In contrast, when the results were restricted to the findings from lag days 0 or 1, an association was not found. Those studies that fail to take into consideration the modelling bias that can result when subjectively emphasizing the results from a particular lag period without adequate justification need to be viewed with some suspicion.

Another major concern with many of the studies focusing on the asthma-NO_2 relationship is the unknown influence of indoor exposures. A recent simulation model estimated that wintertime hourly indoor air concentrations of NO_2 averaged 110 ppb (210 $\mu g/m^3$) in homes using natural gas ranges that were not properly exhausted with a venting hood (Logue *et al.*, 2013). The study went on to estimate that 55-70% of the homes with unvented natural gas ranges in Southern California routinely exceeded the NAAQS standard for NO_2. Since Lin *et al.* has shown in a 41-study meta-analyses that indoor NO_2 levels are significantly associated with asthma and wheeze in children, there is a distinct possibility that the studies focusing on outdoor NO_2 concentrations are being compromised by the indoor exposures (Lin *et al.*, 2013).

A recent European survey showed that 60-70% of the children live in homes that use gas ranges, so it is likely that the use of outdoor measurements to document personal exposure has been seriously underestimated in many asthma-related studies (Wong *et al.*, 2013). Consequently, it is difficult to justify making any changes to the ambient air quality standards on the basis of asthma risks until the relative importance of indoor and outdoor exposures is fully explored.

8.6. BIRTH OUTCOMES

A total of 26 new epidemiology studies were identified that focused on variety on birth-related conditions. The majority of these studies focused on birth weight in pre-term and full-term babies, but conditions such as infant mortality, fetal growth weight, stillbirths, cardiovascular malformations, motor function, and respiratory distress were also examined. Of the studies examined, none involved the use of two-pollutant models to evaluate co-pollutant confounding. As a result, no moderate quality studies were identified. Previous meta-analyses using single-pollutant results have been largely inconclusive. Shah *et al.* pooled the results from 16 studies using a random effects model and failed to find an association with three different birth outcomes: low birth weight, preterm birth, and small for gestational age (Shah and Balkhair, 2011). Hajat *et al.* combined the result from 10 English cities and failed to observe an association between NO_2 levels and infant mortality (Hajat *et al.*, 2007). Vrijheid *et al.*, on the other hand, pooled the results from 4 studies and looked at congenital malformations in infants (Vrijheid *et al.*, 2012). The authors noted an association with coarctation of the aorta and teratology of Fallot, but not ventricular septal defects, atrial septal defects, or cleft palate. Likewise Stieb *et al.* reported a statistically significant decrease in birth weight after pooling the results from 62 studies (Stieb *et al.*, 2012). The odds ratio for low birth weight following a full-term exposure to NO_2 was 1.05 (95% CI 1.00-1.09). No association was found between NO_2 exposure and preterm birth. Given the conflicting and mediocre nature of the available information, it is difficult to use the results from birth outcome studies as a basis for justifying any change to current limit values.

9. TOXICOLOGY STUDIES

Many of the most descriptive inhalation toxicology studies with NO_2 were conducted in the 70's through the 90's and lead to the identification of widely quoted LOAELs and NOAELs for a host of acute and chronic respiratory conditions (ARB, 2007). These studies have been reviewed and summarized in many past reports and are not re-examined herein. The focus of this section is on more recent investigations, particularly those that have taken place since 2005. Since these investigations tend to be more mechanistic in nature, their quality has not been examined in a fashion similar to the epidemiology studies. As a result, the human and animal studies described below are intended to give some sense of the areas of investigation that are garnering the most attention. Particular attention has been placed on those studies examining potential respiratory, inflammatory, or cardiovascular effects from NO_2 exposure. An important overarching impression that emerges from a comparison of recent human and animal studies is that humans do not appear to be as sensitive to the acute effects of NO_2 exposures as rats or mice. The reason for this difference may not be due to anatomical or physiological difference in the lung architecture since modelling studies have shown that the NO_2 concentration in the bronchi of humans is about 12-times higher than the rat, which suggest that tissue exposure and uptake is undoubtedly higher in humans (Tsujino *et al.*, 2005). To date, there has not been any systematic attempt to document the magnitude or nature of any species differences that may exist for NO_2 toxicity.

9.1. HUMAN STUDIES

Controlled human exposures to NO_2 have taken place in two forms: either as the pure gas or as a component of diesel exhaust. The diesel exhaust studies are complicated by the fact that the NO_2 in the exhaust stream is accompanied by host of particles and gases that may be contributing to the observed effect. This interference is reduced, however, when the studies have been performed with diesel exhaust that has been passed through a state-of-the-art particulate filter that is capable of removing a large percentage of the fine particulate matter. Several good reviews have been performed that summarize the available information on controlled human exposures to NO_2 at concentrations ranging from 0.1 -3.5 ppm (Hesterberg *et al.*, 2009). After reviewing more than 50 studies, Hesterberg *et al.* concluded that (i) healthy subjects exposed to NO_2 at concentrations less than1 ppm do not show pulmonary inflammation; (ii) there is no consistent evidence that NO_2 concentrations below 2 ppm increase susceptibility to viral infection; (iii) NO_2-induced lung inflammation is not expected at concentration less 0.6 ppm for asthmatics and individuals having chronic obstructive pulmonary disease (COPD); (iv) airway hyper-responsiveness (AHR) is not evident in asthmatic individuals who are challenged to a specific or nonspecific airway sensitizers (e.g., ragweed, methacholine) are not affected by NO_2 levels up to about 0.6 ppm, although some sensitive subsets may respond to levels as low as 0.2 ppm; and that changes in blood chemistry generally require NO_2 concentrations above 1–2 ppm.

A meta-analyses that critically evaluated the findings from 28 studies on AHR in asthmatic individuals found that NO_2 did not appreciably affect AHR at concentration s up to 0.6 ppm (Goodman *et al.*, 2009). Four metrics were used to judge if NO_2 had an effect on AHR; the 1 sec forced expiratory volume (FEV_1) , the fraction of subjects affected, the change in provocation dose needed, and the change in FEV_1 before and after an airway challenge.

Controlled human exposures to diesel exhaust indicate that NO_2 is not responsible for many of the observed vascular or pulmonary effects that have been observed. A double-blind, randomized, crossover study in 20 men with prior myocardial infarction found that a 1-hr exposure to dilute diesel exhaust containing approximately 1 ppm of NO_2 caused a greater increase of ischemic burden and a reduction in the release of endothelial plasminogen activator. The exposure did not, however, aggravate preexisting vasomotor dysfunction (Mills *et al.*, 2007). In subsequent studies by many of the same authors, a group of 16 healthy volunteers were exposed for 2 hours to dilute diesel exhaust, filtered diesel exhaust, or pure carbon nanoparticulates (Mills *et al.*, 2011). The NO_2 concentration in the dilute and filtered diesel exhaust was about 0.2 ppm. The diesel exhaust exposures caused an increase in systolic blood pressure and an attenuated vasodilatation from the infusion of bradykinin, acetylcholine, or sodium nitroprusside. The exposure to filtered diesel exhaust and carbon nanoparticulates had no effect on blood pressure or vasodilatation.

Similar results were obtained in a study by Lucking *et al.*, who used 18 male volunteers exposed for 1-hr to diesel exhaust or filtered diesel exhaust in a randomized, double blind, chamber study. The NO_2 levels during the exposure were about 0.7 ppm for the diesel exhaust and 3.4 ppm for the filtered diesel exhaust. Relative to the clean air exposures, the diesel exhaust caused a reduction in the vasodilatation from a group of four different vasodilators and an increase in ex-vivo thrombus formation. Exposure to filtered diesel exhaust caused an increase in vasodilatation with acetylcholine but not the other vasodilators. There was no change in ex-vivo thrombus formation or tissue plasminogen activator release compared to the clean air control, despite the nearly 5-fold increase in NO_2 levels for this exposure group. In a related experiment, mRNA from coronary endothelial arterial cells was harvested from the plasma of 7 male and female volunteers exposed to 100 $\mu g/m^3$ of diesel exhaust (4.7 ppm NO_2) or 0.5 ppm of pure NO_2 for 2 hrs under controlled conditions (Channell *et al.*, 2012). The expression of intracellular cell adhesion molecule (ICAM-1) and vascular cell adhesion molecule (VCAM-1) was increased in both the diesel exhaust and NO_2 treatment groups when plasma samples were collected either immediately after the exposure or at 24-hr post-exposure. In addition, the expression of interleukin -8 was also increased for those exposed to NO_2. These data indicate that both diesel exhaust and NO_2 are capable of activating proinflammatory factors in humans.

The impact of NO_2 on heart rate variability has also been investigated (Scaife *et al.*, 2012). In this study, 18 subjects with coronary heart disease and impaired left ventricular function were exposed to 0.4 ppm of NO_2 for 1-hr. Relative to the control group, there was no effect of NO_2 on heart rate, blood pressure, leukocyte coping capacity, or any measure of heart rate variability. The authors concluded that epidemiology studies showing an association with cardiac outcomes were likely due to a co-related pollutant rather than NO_2.

Huang *et al*. exposed a group of 23 male and female subjects 20-36 years old to 0.5 ppm NO_2 (955 $\mu g/m^3$) or a combination of NO_2 and 89.5 $\mu g/m^3$ of $PM_{2.5}$ concentrated ambient air particulates (CAPS) for 2-hr with intermittent exercise (Huang *et al.*, 2012). Control subjects were exposed to clean air for the same length of time. Acute cardiopulmonary measurements were performed 1-hr and 18-hrs post-exposure. Relative to controls, the test subjects receiving NO_2 alone caused a significant increase blood cholesterol and high density lipoproteins (HDL) at 18 hours, a decrease in high frequency measurements of heart rate variability at 1-hr and 18-hr, a decrease in the QT variability index at 1-hr, and an increase in lactate dehydrogenase (LDH) in bronchoalveolar lavage fluid (BAL) at 18 hours. Spirometry

measurements (FEV_1, FVC, and FEF_{25-75}) and diffusion capacity were unaffected as were differential cells counts in blood and BAL fluid. There was no effect of the exposure on many inflammatory markers such as blood C-reactive protein, plasminogen, fibrinogen, and von Willebrand's factor. Similarly, BAL measurements of interlukin-6 and α1-antitrypsin were not altered. Measurement of cardiac repolarization via various measures of the QT interval were largely unaffected by the NO_2 exposures. Relative to the exposures to NO_2 or CAPS alone, the combined exposure resulted in an increase in BAL α1-antitrypsin, the mean t-wave amplitude, and the low frequency component of the low frequency/high frequency (LF/HF) ratio measurements from the electrocardiogram; these changes indicted some interaction between the two-pollutants. These studies revealed that NO_2 was capable of causing some changes in markers of cardiovascular function in healthy human subjects.

There are several new studies suggesting that the cardiopulmonary effects observed in chamber studies with NO_2-containing diesel exhaust are being driven by the particle content and not by the NO_2 that is generated. Gong *et al*. exposed intermittently exercising elderly subjects with (18 volunteers) and without (6 volunteers) COPD to 0.4 ppm (764 µg/m^3) NO_2 for 2 hr under controlled conditions (Gong *et al.*, 2005). The healthy control subjects had an average age of 68 years, whereas the subjects with COPD were slightly older with an average age of 72 years. Combined exposures to NO_2 and CAPs (200 µg/m^3) were also performed. No effects were observed on most measures of symptom reporting and respiratory flow, and the differential cells counts were unaffected by either the single or combined exposures. Maximal mid-expiratory flow and oxygen saturation decrements were observed in the combined exposure but these effects were attributed to the CAPS. Langrish *et al.* exposed ten intermittently exercising healthy volunteers to 4 ppm NO_2 or clean filtered air for 1-hr and searched for changes in vasomotor or fibrinolytic function (Langrish *et al.*, 2010). The exposure did not affect resting forearm blood flow, lung function, or exhaled nitric oxide levels. Finally, Whitten *et al.*, found that the exposure of 15 house dust mite sensitive asthmatics to 0.4 ppm NO_2 for 3 hours with exercise did not show any change in the sputum concentration of five inflammatory biomarkers, the sputum cell distribution, or the FEV_1 value ether with or without an allergen challenge (Witten *et al.*, 2005). These three studies suggest that NO_2 is not primarily responsible for the respiratory and cardiovascular effects observed with diesel exhaust and reinforce the position that the associations observed in epidemiology studies with NO_2 may be artifactual in nature.

Several genotoxicity studies were identified using human cell lines. In one genotoxicity study, cultured nasal epithelial cells from 10 volunteers was used to evaluate the capacity of NO_2 to cause cytotoxicity, DNA damage (Comet assay), and chromosomal damage (micronucleus assay) (Koehler *et al.*, 2010). Following an exposure to 0.01, 0.1, 1, or 10 ppm NO_2 for 30 min, the cells showed an exposure-related increase in DNA fragmentation in the Comet assay, but no evidence of micronuclei formation, cell proliferation, necrosis, or apoptosis. In another study, human respiratory A549 cells were exposed to a 1/100 or 1/10 dilution of filtered (4.8 or 45.8 ppm NO_2), unfiltered (0.3 or 2.4 ppm NO_2), or supplemented (8.8 and 80.8 ppm NO_2) diesel exhaust for 60 min and examined for cell viability and gene expression (Tsukue *et al.*, 2010). The supplemented diesel exhaust containing the highest concentrations of particulate matter and NO_2 caused a significant increase in heme oxygenase-1 mRNA expression at the dilution rate of 1/100. Similar results were observed with both dilutions of the unfiltered diesel exhaust, which contained a high concentration of particulate matter and relatively low amount of NO_2. The supplemented exhaust containing a high concentration of NO_2 also affected cell viability to a considerable degree.

9.2. ANIMAL STUDIES

Campen *et al.* exposed apolipoprotein knockout mice ($Apo^{-/-}$) to NO_2 or vehicle exhaust for 6 hr/day for 7 days then looked at transcriptional changes in several markers of vascular activity (Campen *et al.*, 2010). Exposure concentrations of 0.2 or 2.0 ppm NO_2 failed to cause any alteration in mRNA transcript abundance for aortic geletinase, endothelian-1, matrix metalloproteinase-9, or the tissue inhibitor of metalloproteinase-9. There was, however, a concentration-related decrease in transcript abundance for heme oxygenase-1. Comparative studies with diesel or gasoline exhaust containing approximately 1.0 ppm NO_2 caused a significant up-regulation in several of the vascular markers. Karthikeyan *et al.*, recently investigated the effect of filtered and unfiltered diesel exhaust on cardiovascular function, inflammation, and oxidative stress in rats exposed 4 hrs/day for either 1 day or 3 days (Karthikeyan *et al.*, 2013). The concentration of NO_2 in the filtered exhaust was 4-times higher (16 ppm) than what was found in the unfiltered exhaust (4 ppm). Single exposures to unfiltered exhaust resulted in numerous biochemical, cytological, and transcriptional changes. Among these was an increase in neutrophil counts, total protein and BAL cytokines, as well as the level of growth-related oncogene/keratinocyte chemo-attractants, macrophage inflammatory protein-1α, and monocyte chemo-attractant protein-1 in lung lavage fluid. Gene expression of interleukin-6, prostaglandin-endoperoxide synthase 2, metallothionein 2A, tumor necrosis factor-α, inducible nitric oxide synthase, glutathione S-transferase A1, heme oxygenase-1, superoxide dismutase 2, endothelin-1 (ET-1), and endothelin-converting enzyme-1 in the lung were also affected. The changes in many of these endpoints were notably greater when the animals were treated with the filtered exhaust. The authors attributed the magnified inflammatory and oxidative stress response to the higher concentration of NO_2 in the filtered exhaust, although the role of ultrafine particulates could not be completely ruled out.

A chronic inhalation study using filtered diesel exhaust was recently published by HEI as part of their ACES (Advanced Collaborative Emissions Study) program (HEI, 2012). Rats and mice were exposed for up to a year (16 h/day, 5 days/wk) to particle free new technology diesel exhaust at NO_2 levels of 0.1, 0.8, and 4.2 ppm. All animals were evaluated for a host of clinical, physiological, and biochemical effects at regular intervals (1 and 3 months). The interim subchronic results have been released with the final 12-month bioassay results expected within the next year. An examination of over 100 biological response variables showed rats to be more sensitive than mice, with most effects confined to the highest exposure concentration. Although no statistically significant effects were noted at the low concentration, the mid level exposure produced increases in several markers of oxidative stress and pulmonary inflammation. This study is perhaps the most comprehensive toxicology study ever performed with the NO_2 in diesel exhaust. Approximately thirty separate plasma markers of inflammation or thrombosis were included in the study design. Small changes in respiratory function were noted at 3 months in rats, but of these, only a decrement in lung diffusion capacity persisted at 12 months. These results were consistent with histologic changes observed in the alveoli. Small changes in biochemical markers for oxidative stress were found in rat BAL fluid and lung tissue; however, overall though, these changes were small, and there was a lack of coherence among the endpoints. Genotoxicity studies were also undertaken in conjunction with the HEI ACES study. The results revealed that NO_2-containing diesel exhaust did not cause appreciable induction of micronuclei in rats or mice exposed for up to 3 months (16 h/day, 5 days/week) to NO_2 levels as high 4.2 ppm. In addition, the rats and mice showed no significant DNA strand breaks in the Comet assay, 8-hydroxy-deoxyguanosine adducts formation in an ELISA assay, or evidence of oxidative stress through lipid peroxidation. These results are

significant because elevated urinary 8-hydroxy-2'-deoxyguanosine levels have been associated with exposures to NO_2 (daily average 17.8 ppb) in humans who participated in the Veterans Normative Aging Study (Ren *et al.*, 2011). This study, however, was likely biased by an overreliance on monitoring data from a single urban site.

Other recently published animals studies of note include an examination of ischemic stroke in rats exposed 6 hr/day to 5 mg/m^3 of NO_2 for 2 or 3 months (Zhu *et al.*, 2012). This study recorded increases in blood viscosity, RBC aggregation index, RBC electrophoresis index, and RBC rigidity in the exposed animals, then proceeded to examine changes in a rat model for cerebral ischemic stroke. After inducing the ischemia by middle cerebral artery occlusion, the rats were exposed 6 hr/day for one week at an exposure concentration of 5 mg/m^3. The NO_2 exposures caused a time-dependent delay in the recovery from the surgical occlusion and exacerbated endothelial and inflammatory responses to the ischemia as seen by elevations in the expression of nitric oxide synthase, cyclooxygenase-1, and intercellular adhesion molecule. Ramos-Bonilla *et al.* examined electrocardiogram (ECG) responses in 180-day old mice exposed to a complex mixture of NO_2, PM, and CO at a low (8-35 ppm) or high (7.8-68.3) NO_2 concentration range (Ramos-Bonilla *et al.*, 2010). Whereas, NO_2 was significantly associated with declines in heart rate, CO was associated with declines in heart rate and heart rate variability. The nearly continuous exposure (23 hrs/day, 7days/week) of rats to 10 ppm NO_2 for 3, 7, 21 days revealed alveolar septal cell apoptosis by day 3 and airspace enlargement by day 7 (Fehrenbach *et al.*, 2007). The exposures also caused an increase in total surface volume, an increase in the absolute volume of the alveolar walls, and a reduction in the ratio of collagen to elastin after 21-days of exposure.

The allergic sensitization potential of NO_2 has been evaluated in rats exposed to diesel exhaust, carbon nanotubes, or the pure gas. Lung inflammation was investigated in ovalbumin sensitized mice exposed 3 days to about 5 or 25 ppm NO_2 for 4 hr/day (Alberg *et al.*, 2011). Prior to the exposures, the mice were treated intranasally with ovalbumin and/or diesel exhaust particulates (DEP). Measurement of total protein or tissue necrosis factor-α in BAL fluid, showed that the highest NO_2 exposures were capable of increasing the protein and cytokine levels both alone and in combination with DEP. When the animals were treated with ovalbumin 18 days following the exposure, DEP stimulated the production of allergen-specific IgE antibodies, but this change was not observed in the NO_2-exposed animals. The results indicated that combustion particles were more important in causing allergic sensitizations than NO_2.

In other studies, the interactions between carbon nanotubes and NO_2 exposure were examined in ovalbumin sensitized rats (Layachi *et al.*, 2012). The rats were exposed to 10 ppm NO_2 for 4 weeks at 6hr/day and 5 days/week. The carbon nanotubes were administered intranasally on days 0, 7, and 14. Airway responses to allergen challenge were measured together with histological changes, serum and BAL fluid cytokine content, and BAL cell counts. The NO_2 exposures significantly increased the cytokine markers of lung inflammation, but the change was not altered by the administration of carbon nanotubes. The combined exposure to NO_2 and nanotubes significantly reduced airway reactivity to allergen challenge. The results indicated that the proinflammatory effects of NO_2 could be immunologically modulated by the carbon nanotubes. Bevelander *et al.* exposed ovalbumin sensitized mice to 10 ppm NO_2 for 1-hr and examined the allergic response (Bevelander *et al.*, 2007). Relative to controls, the simultaneous exposure to ovalbumin aerosol and NO_2 resulted in an eosinophilic inflammation and mucus cell metaplasia, increased cytokine levels, and an increase in total protein and lactate

dehydrogenase activity in BAL fluid. These and other responses led the authors to conclude that NO_2 was capable promoting allergic sensitization to agents that were otherwise innocuous. Similar findings were reported by Kumae *et al.*, who found that rats continuously exposed from birth or the weanling period to 0.2, 0.5, or 2.0 ppm NO_2 had altered pulmonary immunity as evidenced by changes in the reactive oxygen generating capacity of the alveolar macrophages (Kumae and Arakawa, 2006).

The neurological hazard of NO_2 exposure were investigated in a recent study with rats exposed to 5, 10, or 20 mg/m^3 of NO_2 for one week at 6 hrs/day (Li *et al.*, 2012a). The exposures were shown to cause a decrease in brain-to-body weight ratio, mild brain pathology, an increase in neuronal apoptosis, altered antioxidant activity, an increase in oxidant-induced damage as measured by the formation of protein carbonyls, and an increase in oncogene expression. Whereas most of these adverse outcomes were observed at the two highest exposure concentrations, several were seen at all exposure levels. These concentration-related changes were seen to occur for neuronal apoptosis and for the expression of several oncogenes. Appreciable evidence of genotoxicity was also observed in rats exposed to 5, 10, or 20 mg/m^3 of NO_2 for a week at 6 hrs/day (Han *et al.*, 2013). DNA-protein cross-links and DNA strand breaks were detected in cells from the brain, lung, liver, spleen, kidney, or heart. DNA damage as measured using the Comet assay was observed at all exposure concentrations using lung, liver, and kidney cells.

10. CONCLUSIONS

A large number of new observational studies have been published on NO_2 since the WHO published their Air Quality Guidelines in 2005. Hardly a month goes by without the appearance of additional new peer-reviewed papers purporting to show that NO_2 is associated with an increase in morbidity or mortality as a result of ambient air exposures. A vast number of the studies recognize and acknowledge that NO_2 is likely serving as a surrogate for another pollutant which is acting as the true etiological agent for many of the health outcomes of interest. The primary concern surrounding NO_2 exposure has typically focused on asthmatics and its ability to directly affect pulmonary function in this group of individuals. Many of the epidemiology and controlled human exposure studies published up to 2005 were aimed at exploring the bronchitis and lung function decrements that accompanied exposures at low ambient air concentrations. In fact these issues, in large measure, formed the basis for the creation and continuation of the annual limit value of 40 $\mu g/m^3$ and the 1-hr short-term limit of 200 $\mu g/m^3$ set by the WHO.

Although asthma and respiratory morbidity continues to be topic of great interest for researchers and regulators; several new areas of concern have emerged that have been the target of intensive research. These include interest in the relationship between NO_2 exposure and acute and chronic mortality from non-accidental, respiratory, and cardiovascular causes. The chief limitation in many of the studies has been the overreliance on the results from single-pollutant rather than multi-pollutant models that are capable of considering the strong correlation of NO_2 ambient air levels with other pollutants such as PM and CO. There have also been confounding and exposure misclassification issues with many of the newer studies that have severely limited their overall utility in making any causality claims. Another topic of particular interest has been acute cardiovascular disease resulting in emergency room visits or hospital admissions. Stroke, hypertension, myocardial infarction, ischemic heart disease, and congestive heart failure have all been evaluated relative to ambient air levels of NO_2. For these health outcomes, however, it is extremely important to take CO levels into consideration since its role in cardiovascular damage is well established and ambient air levels of CO are often highly correlated with the NO_2 concentration. In many cases, the positive findings from past cardiovascular studies employed single pollutant models that failed to look at the confounding from CO collinearity. There have also been a notable number of new studies focusing on issues ranging from birth outcomes to diabetes. These studies have all been found to contain a variety of flaws ranging from small sample sizes and limited statistical power to the exposure misclassification resulting from an overreliance on fixed monitoring sites for exposure determinations.

Nearly a hundred of the 240 studies examined for preparation of this report dealt with the relationship between NO_2 exposures and acute respiratory disease or asthma exacerbation. This continues to be the heath outcome of greatest concern with NO_2 and will likely garner the most interest in future research programs. Although a tremendous amount of new information has been gathered, there are still nagging issues that have not been sufficiently resolved to the extent needed to make definitive statements regarding causality and risk. Confounding and bias continue to plague many studies and the results from a limited number of new controlled human exposure studies suggest that NO_2 may not be responsible for many of the reported associations that have been reported with asthmatics. Until improved statistical and monitoring methods are developed there will continue to be considerable doubt about the relevance of results from studies using single pollutant modelling and exposure estimates from fixed monitoring stations.

11. GLOSSARY

Acronym	Definition
ACES	Advanced Collaborative Emissions Study
BAL	Bronchoalveolar lavage fluid
BC	Black carbon
BS	Black smoke
BTEX	Benzene, toluene, ethylbenzene, and xylene
CAFE	Clean Air for Europe
CAPS	Concentrated ambient air particulates
CI	Confidence interval
CLRTAP	Convention on Long-Range Transboundary Air Pollution
CO	Carbon monoxide
COPD	Chronic obstructive pulmonary disease
DEP	Diesel exhaust particulates
EAP	Environmental Action Programme
EC	European Commission
EC	Elemental carbon
EMEP	European Monitoring and Evaluation Programme
ESCAPE	European Study of Cohorts for Air Pollution Effects
EU	European Union
FEV_1	Forced expiratory volume in 1 second
FVC	Forced vital capacity
GIS	Geographic information systems
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HNO_3	Nitric acid
HONO	Nitrous acid
HRAPIE	Health Risks of Air Pollution in Europe
IPCS	International Programme on Chemical Safety
IQR	Interquartile range
LOAEL	Lowest observed adverse effect level
LUR	Land use regression

Acronym	Definition
NAAQS	National Ambient Air Quality Standards
NECD	National Emission Ceiling Directive
NO	Nitric oxide
NO_2	Nitrogen dioxide
NOAEL	No observed adverse effect level
NO_x	Nitrogen oxides
O_3	Ozone
OC	Organic carbon
PAH	Polycyclic aromatic hydrocarbons
PAN	Peroxyacetyl nitrate
PM	Particulate matter
PM_{10}	Particulate matter less than 2.5 microns
$PM_{2.5}$	Particulate matter less than 2.5 microns
r^2	Coefficient of determination
RCT	Randomized controlled trials
REVIHAAP	Review of Evidence on Health Aspects of Air Pollution
SES	Socio-economic status
SO_2	Sulfur dioxide
THC	Total hydrocarbon
TSAP	Thematic Strategy on Air Pollution
TSP	Total suspended particulate
UFP	Ultrafine particulates
UFPM	Ultrafine particulate matter
UK	United Kingdom
UNECE	United Nations Economic Commission
USEPA	Unites States Environmental Protection Agency
VOC	Volatile organic compounds
WHO	World Health Organization
WOS	Web of Science

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APPENDIX I – STUDY SUMMARIES

Acute Mortality

author / location	exposure monitoring	NO_2 concentration	study type (duration)	endpoint	co-pollutants	participants	ratio or risk	confidence interval	results	GRADE quality of evidence
(Breitner *et al.*, 2009) Erfut, Germany	daily average from a single fixed monitoring site	daily mean concentration 24.9 µg/m³	time-series (11.5years)	total non-accidental mortality	association with PM_{10}, $PM_{2.5}$, UFP, CO, & NO_2	total of 17,713 deaths	no statistically significant increase in cumulative 6-day or 15 day (averaged and distributed lags periods) mean relative risk estimates per IQR for any of three measurement periods for different urban boundaries; the only exception to this finding was for the old city limits using a 15-day distributed lag period where the cumulative relative risk per IQR of 12.6 µg/m³ 15-day distributed lag - 1.027	no statistically significant increase in cumulative 6-day or 15 day (averaged and distributed lags periods) mean relative risk estimates per IQR for any of three measurement periods for different urban boundaries; the only exception to this finding was for the old city limits using a 15-day distributed lag period where the cumulative relative risk per IQR of 12.6 µg/m³ 15-day distributed lag - 1.000 - 1.055	slight statistical significance in single pollutant model using a cumulative 15-day distributed lag period for measurements over the entire analysis period in old city limit region; no statistical significance for cumulative 6-day lag averaged or distributed lag period in any city limit region or any measurement period	⊕○○○ (insufficient because of very serious risk of exposure bias)
(Brook *et al.*, 2007) 10 Canadian cities	hourly measurements from an unstated number of fixed monitoring sites	unstated daily 24-hr averages	time-series (20 years)	non-accidental mortality	association with PM_{10}, $PM_{10-2.5}$, SO_4, trace elements, NO & NO_2	total deaths or death rates not reported	relative risk per IQR of 10.29 ppb (19.65 µg/m³) in a pooled two-pollutant model for lag day 1 NO_2 only - 1.018 NO_2/NO - 1.022 $NO_2/PM_{2.5}$ - 1.016 $NO_2/PM_{10-2.5}$ - 1.017 NO_2/PM_{10} - 1.015 NO_2/SO_4 - 1.015	relative risk per IQR of 10.29 ppb (19.65 µg/m³) in a pooled two-pollutant model for lag day 1 NO_2 only - 1.007 - 1.028 NO_2/NO - 1.008 - 1.036 $NIO_2/PM_{2.5}$ - 1.003 - 1.029 $NO_2/PM_{10-2.5}$ - 1.006 - 1.028 NO_2/PM_{10} - 1.003 - 1.028 NO_2/SO_4 - 1.004 - 1.026	statistically significant association with non-accidental mortality in single and two-pollutant models with NO, $PM_{2.5}$, PM_{10}-2.5, sulfate, and 10 individual traffic-related trace elements on lag day 1; statistically significant association on lag days 0, 1, & 2 for summer and winter months with the exception of lag day 0 during the winter	⊕○○○ (insufficient because of very serious risk of reporting bias)

author / location	exposure monitoring	NO_2 concentration	study type (duration)	endpoint	co-pollutants	participants	ratio or risk	confidence interval	results	GRADE quality of evidence
(Cakmak *et al.*, 2011) Chile (four municipalities) Las Condes Santiago Pudahuel Cerrillos	daily mean from four centrally located fixed monitoring sites	daily mean (3 cities missing) Las Condes – 51 ppb (97.4 µg/m³) Santiago – 45.1 ppb (86.1 µg/m³) Pudahuel – 40.2 ppb (76.8 µg/m³) Cerrillos – 43.5 ppb (83.1 µg/m³)	time-series (120 months)	mortality among socially disadvantaged elderly	association with PM_{10}, $PM_{2.5}$, EC, OC, SO_2, CO, O_3, oxygenated VOCs, & NO_2	male & female (number not stated)	statistically significant increase in relative risk found in virtually every categorical comparison per unstated IQR increase using a single pollutant model partially adjusted relative risk per IQR (unstated) in single pollutant model overall - 1.086 highest age (>85 years) - 1.130 lowest education (primary school) - 1.100 lowest income (< $8,800/yr) - 1.096	statistically significant increase in relative risk found in virtually every categorical comparison per unstated IQR increase using a single pollutant model partially adjusted relative risk per IQR (unstated) in single pollutant model overall 1.076 - 1.096 highest age (>85 years) 1.112 - 1.147 lowest education (primary school) 1.076 - 1.124 lowest income (<$8,800/yr) 1.058 - 1.134	statistically significant association found for all 4 age groups, 4 of 5 education levels (those with university diploma not impacted),4 income categories, 3 employment categories, and male and female subgroups;	⊕○○○ (insufficient because of publication bias, limited sample size, and risk of exposure bias)
(Chen *et al.*, 2008b) Shanghai, China	mean daily concentration at six fixed monitoring locations	daily mean 66.6 µg/m³	time-series (48 months)	mortality rates all causes cardiovascular respiratory	differential effects of PM_{10}, SO_2, & NO_2	173,911 deaths	% change per 10 µg/m³ increment all cause - 0.73 cardiovascular - 0.95 respiratory - 0.62	% change per 10 µg/m³ increment all cause 0.14 - 1.32 cardiovascular 0.06 - 1.84 respiratory -0.92 - 2.16	increased total and cardiovascular mortality observed before and after adjustment for confounders (multipollutant model); increased risk only observed at concentrations greater than 50 µg/m³	⊕○○○ (insufficient because of single pollutant modelling and risk of exposure bias)

author / location	exposure monitoring	NO_2 concentration	study type (duration)	endpoint	co-pollutants	participants	ratio or risk	confidence interval	results	GRADE quality of evidence
(Chiusolo *et al.*, 2011) ten cities in Italy Bologna Cagliari Florence Mestre-Venice Milan Palermo Pisa Rome Taranto Turin	mean daily concentration from 1-5 fixed monitoring sites	ten cities in Italy Bologna - 52 µg/m³ Cagliari - 34 µg/m³ Florence - 46 µg/m³ Mestre-Venice - 38 µg/m³ Milan - 59 µg/m³ Palermo - 52 µg/m³ Pisa - 30 µg/m³ Rome - 62 µg/m³ Taranto - 26 µg/m³ Turin - 66 µg/m³	case-crossover (60 months)	acute mortality from natural causes, cardiac, cerebrovascular, and respiratory causes	association with PM_{10}, O_3, & NO_2	male & female 276,205 cases	pooled percent increase in mortality per 10 µg/m³ increase in two pollutant model with a lag of 0-5 days all seasons with PM_{10} natural - 1.95 cardiac - 2.58 respiratory - 3.39 summer season (Apr-Sept) with O_3 natural - 4.55 cardiac - 4.69 cerebrovascular - 7.26 respiratory - 10.07	percent increase in mortality per 10 µg/m³ increase in two pollutant model with a lag of 0-5 days all seasons with PM_{10} natural 0.50 - 3.43 cardiac 1.05 - 4.13 respiratory 0.77 - 6.08 summer season (Apr-Sept) with O_3 natural 3.32 - 5.79 cardiac 2.74 - 6.67 cerebrovascular 3.51 - 11.14 respiratory 3.69 - 16.83	statistically significant association with natural cardiac cerebrovascular and respiratory mortality for two pollutant model with O_3 in summer season but not winter, associations also observed for all seasons but not for cerebrovascular mortality; associations strongest for a 0-5 day lag period; stronger associations with natural mortality observed in males, older age groups and for those with specific chronic conditions and low SES status	⊕◯◯◯ (insufficient because of exposure bias and single pollutant modelling only)
(de Almeida *et al.*, 2011) Oporto, Portugal	daily mean concentration from three fixed monitoring locations	daily mean whole year – 44.6 µg/m³ summer season – 33.9 µg/m³	time-series (60 months)	cardiovascular, pulmonary and non-accidental mortality	association with PM_{10}, O_3, & NO_2	not stated	no significant increase in daily mortality for any of three mortality causes per 10 µg/m³ change using and adjusted single pollutant model	no significant increase in daily mortality for any of three cause per 10 µg/m³ change using and adjusted single pollutant model	no statistically significant association with cardiovascular, pulmonary and non-accidental mortality	⊕◯◯◯ (insufficient because of unknown number of cases and risk of exposure bias)

author / location	exposure monitoring	NO_2 concentration	study type (duration)	endpoint	co-pollutants	participants	ratio or risk	confidence interval	results	GRADE quality of evidence
(Fischer *et al.*, 2011) The Netherlands	daily average from 20 urban and rural fixed monitoring sites	daily mean concentration 30.8 µg/m³	time-series (15 years)	mortality from non-accidental, cardiovascular, respiratory, pneumonia, and chronic obstructive pulmonary diseases	association with PM_{10}, BS, O_3, & NO_2	mean daily mortality rates (pneumonia & COPD not provided) non-accidental - 362 cardiovascular - 133 respiratory - 36	percentage excess risk in mortality per IQR of 10 µg/m³ in a single pollutant model all cause lag 0 - 0.4 lag 1 - 0.6 lag 2 - 0.3 lag 0-6 - 1.0 cardiovascular lag 0 - 0.4 lag 1 - 0.4 lag 0-6 - 1.0 respiratory lag 1 - 0.6 lag 2 - 0.8 lag 3 - 0.7 lag 0-6 - 1.8 pneumonia lag 2 - 1.1 lag 3 - 1.1 lag 0-6 - 2.2 COPD lag 0-6 - 1.8	percentage excess risk in mortality per IQR of 10 µg/m³ in a single pollutant model all cause lag 0 0.2 - 0.5 lag 1 0.4 - 0.7 lag 2 0.1 - 0.4 lag 0-6 0.7 - 1.2 cardiovascular lag 0 0.2 - 0.7 lag 1 0.2 - 0.7 lag 0-6 0.6 - 1.4 respiratory lag 1 0.1 - 1.1 lag 2 0.3 - 1.2 lag 3 0.2 - 1.2 lag 0-6 0.9 - 2.7 pneumonia lag 2 0.4 - 1.8 lag 3 0.4 - 1.8 lag 0-6 0.9 - 3.6 COPD lag 0-6 0.6 - 3.0	statistically significant association with all five types of mortality measurements at various lag periods; statistically significant excess risk of COPD restricted to a single lag period; downward trend noted in excess risk estimates for pneumonia on lag day 1 when time period was segregated into 4 periods of 3-4 years (significant associations for first two periods of 1992-1994 and 1995-1998 and non-significant in the last two of 1999-2002 & 2003-2006; no trend noted for other causes of mortality	⊕⊕◯◯ (low quality because of bias from single pollutant model)
(Guo *et al.*, 2010a) Tianjin, China	mean daily concentration from an unstated number of fixed monitoring sites	daily mean 47 µg/m³	case-crossover (36 months)	cardiovascular mortality	association with PM_{10}, SO_2, & NO_2	male & female cases 32,387	relative risk percentage for mortality per 10 µg/m³ change in a single pollutant time-series model (lag day 0) 6 degrees of freedom - 1.0108 7 degrees of freedom - 1.0103	relative risk percentage for mortality per 10 µg/m³ change in a single pollutant time-series model (lag day 0) 6 degrees of freedom 1.0013 - 1.0204 7 degrees of freedom 1.0006 - 1.0200	statistically significant association with cardiovascular mortality in both the time-series and case-crossover studies at lag day however the results from time-series analysis were far more robust with less autocorrelation due to seasonal patterns; case -crossover results judged to be too crude for reliable results; statistically significant results were only observed when the degrees of freedom allowed in the time-series study were restricted to 6 or 7; the results were not significant when the DF was set at 8 or 9; DF less 6 produced unstable results that were not suitable for reporting	⊕◯◯◯ (insufficient because of small number of cases and risk of exposure bias)

author / location	exposure monitoring	NO_2 concentration	study type (duration)	endpoint	co-pollutants	participants	ratio or risk	confidence interval	results	GRADE quality of evidence
(Hu *et al.*, 2008) Sidney, Australia	daily averages from 13 fixed monitoring sites	daily mean concentration 0.87 pphm (8.7 ppb, 16.6 µg/m³)	time-series (10 years)	total mortality	association with PM_{10}, SO_2, CO, O_3, & NO_2	total deaths not reported but total daily rates averaged 63.36 per day	no significant change in percentage change in relative risk per 1 pphm (10 ppb, 19.1 µg/m³) in a model considering both NO_2 and maximum air temperature	no significant change in percentage change in relative risk per 1 pphm (10 ppb, 19.1 µg/m³) in a model considering both NO_2 and maximum air temperature	no statistically significant association with total mortality in model considering both NO_2 and temperature	⊕⊕◯◯ (low quality because of bias from single pollutant model)
(Kan *et al.*, 2008) Shanghai, China	daily average from six fixed monitoring locations	daily average warm season - 57.3 µg/m³ cool season - 76.0 µg/m³ entire period - 66.6 µg/m³	time-series (48 months)	all cause (non-accidental), respiratory, & cardiovascular mortality	association with PM_{10}, SO_2, O_3, & NO_2	male and female 173,911 deaths	percent increase per 10 µg/m³ increase for lag day 0-1 in a single pollutant model total mortality cool - 1.24 entire - 0.97 cardiovascular cool - 1.26 entire - 1.01 respiratory cool - 2.66 entire - 1.22 percent increase per 10 µg/m³ increase for entire population with lag day 0-1 in a single pollutant model female - 1.10 male - 0.88 age ≥ 65 yrs - 1.01	percent increase per 10 µg/m³ increase for lag day 0-1 in a single pollutant model total mortality cool 0.84 - 1.64 entire 0.66 - 1.26 cardiovascular cool 0.68 - 1.84 entire 0.55 - 1.47 respiratory cool 1.67 - 3.65 entire 0.42 - 2.01 percent increase per 10 µg/m³ increase for entire population with lag day 0-1 in a single pollutant model female 0.69 - 1.51 male 0.49 - 1.28 age ≥ 65 yrs 0.69 - 1.34	statistically significant association with total, cardiovascular, and respiratory mortality for the entire period and during the cool season (Oct-Mar) but not during the warm season (Apr-Sept) in a single pollutant model, statistically significant association with total mortality for males and females and those over 65 years of age but not younger age groups, statistically significant association with all three mortality groups for those with low education and for total and cardiovascular but not respiratory in those with a high education	⊕◯◯◯ (insufficient because of short duration and risk of exposure bias)
(Kan *et al.*, 2010) 4 Asian cities Bangkok, Thailand Hong Kong, China Shanghai, China Wuhan, China	daily mean from 6-10 fixed monitoring locations per city	daily mean values Bangkok – 44.7 µg/m³ Hong Kong - 58.7 µg/m³ Shanghai – 66.6 µg/m³ Wuhan – 51.8 µg/m³	time-series (48-84 months)	daily mortality (total, cardiovascular or respiratory)	association with PM_{10}, O_3, SO_2 & NO_2	male & female (daily mortality rate) 94.8-119.0 deaths/day	no excess risk form total, cardiovascular or respiratory mortality in a two pollutant model with SO_2 in either of four cities	no excess risk form total, cardiovascular or respiratory mortality in a two pollutant model with SO_2 in either of four cities	no statistically significant association with total, respiratory, or cardiovascular mortality in four cities using a two pollutant model with SO_2 and a 0-1 day lag period	⊕◯◯◯ (insufficient because of short duration and risk of exposure bias)

author / location	exposure monitoring	NO_2 concentration	study type (duration)	endpoint	co-pollutants	participants	ratio or risk	confidence interval	results	GRADE quality of evidence
(Lin *et al.*, 2008) Kaohsiung, Taiwan	mean daily concentration at an unnamed number of fixed monitoring locations	daily mean 29.0 ppb (55.4 µg/m³)	time-series (60 months)	total mortality and cardiovascular mortality	association with PM_{10}, O_3, SO_2, CO, & NO_2	male & female 7562 deaths	no significant change in relative risk using a single pollutant model	no significant change in relative risk using a single pollutant model	no statistically significant changes in total or cardiovascular mortality at any of three temperature quartiles of 19.7, 24.8, or 27.6 ˚C for any lag period using a multi-pollutant model; people aged 65 years or older also unaffected; associations observed for CO but co-variance with NO_2 not provided	⊕◯◯◯ (insufficient because of small number of cases and risk of exposure bias)
(Ou *et al.*, 2008) Hong Kong, China	daily mean concentration from eight fixed monitoring sites	daily mean 55.50 µg/m³	time-series (12 months)	mortality from natural causes	interaction study (type of housing, occupation, education, PM_{10} O_3, SO_2, & NO_2)	male & female 24,357 deaths	partly adjusted excess risk percentage per 10 µg/m³ increase in a stratified single pollutant model all age groups (≥ 30 years) primary education - 1.83 elderly (≥ 65 years) primary school - 1.80 adjusted excess risk percentage per 10 µg/m³ in an interaction model that considered SES along other covariates was significantly decreased (values not stated) when never employed cases were compared to blue-collar workers or white-collar were compared to blue collar	partly adjusted excess risk percentage per 10 µg/m³ increase in stratified single pollutant model all age groups (≥ 30 years) primary education 0.14 - 3.54 elderly (≥ 65 years) primary school 0.04 - 3.58 adjusted excess risk percentage per 10 µg/m³ in an interaction model that considered SES along other covariates was significantly decreased (values not stated) when never employed cases were compared to blue-collar workers or white-collar were compared to blue collar	statistically significant association with primary education in elderly and all age groups for those with a primary education but not those with no formal education or those with greater than a secondary education; statistically significant association with blue collar workers compared to never-employed workers or white-collar workers in both age groups; slight statistically significant association for those living in public versus private housing; age education, and occupations shown to be potential confounding variables	⊕◯◯◯ (insufficient because of short duration and risk of exposure bias)

author / location	exposure monitoring	NO_2 concentration	study type (duration)	endpoint	co-pollutants	participants	ratio or risk	confidence interval	results	GRADE quality of evidence
(Park *et al.*, 2011) Seoul, Korea	mean hourly concentrations for 27 fixed monitoring sites	daily mean concentration 36.0 ppb (68.8 µg/m³)	time-series (8.5 years)	non-accidental, cardiovascular & respiratory mortality	association with ambient temperature, PM_{10}, SO_2, CO, O_3, & NO_2	total mortality of 291,665 mean daily mortality rates non-accidental - 93.0 cardiovascular - 25.4 respiratory - 5.4	percent increase in mortality for those > 65 years of age for an IQR of 2 ppb (3.8 µg/m³) in a two pollutant model stratified by ambient temperature conditions using an average lag period of 0-1 days non-accidental (entire temperature range) NO_2 only - 0.28 NO_2/PM_{10} - 0.26 NO_2/SO_2 - 0.26 NO_2/CO - 0.25 NO_2/O_3 - 0.28 Non-accidental (< 25th percentile temp.) NO_2 only - 0.23 NO_2/PM_{10} - 0.26 non-accidental (50th-75th percentile temp) NO_2 only - 0.40 NO_2/PM_{10} - 0.36 NO_2/SO_2 - 0.41 NO_2/O_3 - 0.46 non-accidental (>75th percentile temp) NO_2 only - 0.49 NO_2/PM_{10} - 0.40 NO_2/O_3 - 0.46 cardiovascular (entire temperature range) NO_2 only - 0.24 NO_2/O_3 - 0.24	percent increase in mortality for those > 65 years of age for an IQR of 2 ppb (3.8 µg/m³) in a two pollutant model stratified by ambient temperature conditions using an average lag period of 0-1 days non-accidental (entire temperature range) NO_2 only 0.15 - 0.41 NO_2/PM_{10} 0.12 - 0.39 NO_2/SO_2 0.09- 0.43 NO_2/CO 0.02 - 0.47 NO_2/O_3 0.15 - 0.41 Non-accidental (< 25th percentile temp.) NO_2 only 0.00 - 0.46 NO_2/PM_{10} - 0.01 - 0.52 non-accidental (50th-75th percentile temp) NO_2 only 0.16 - 0.63 NO_2/PM_{10} 0.07 - 0.65 NO_2/SO_2 0.11 - 0.72 NO_2/O_3 0.14 - 0.78 non-accidental (>75th percentile temp) NO_2 only 0.23 - 0.74 NO_2/PM_{10} 0.07 - 0.73 NO_2/O_3 0.14 - 0.78 cardiovascular (entire temperature range) NO_2 only 0.01 - 0.47 NO_2/O_3 - 0.01- 0.46	statistically significant association with non-accidental mortality in a single pollutant model that considers all temperature ranges and the three temperature subgroups; associations in all but one comparison (all temperatures) were robust to the incorporation of PM_{10} or O_3 in a two-pollutant model, but were rendered non-significant after the incorporation of SO_2 or CO; no statistically significant associations for cardiovascular or respiratory mortality in any of the temperature subgroups for a single pollutant model; statistically significant association for cardiovascular mortality in the all temperature group was no longer significant following the incorporation of PM_{10}, O_3, or CO in a two-pollutant model; no statistically significant associations for non-accidental mortality in those > 75 years of age stratified into any temperature subgroup; CO produced the most predominate changes in at moderate temperatures and SO_2 at high temperatures	⊕⊕⊕◯ (moderate quality, no adjustment necessary)

author / location	exposure monitoring	NO_2 concentration	study type (duration)	endpoint	co-pollutants	participants	ratio or risk	confidence interval	results	GRADE quality of evidence
(Qian *et al.*, 2007) Wuhan, China	daily concentration from five fixed monitoring sites	average daily mean 51.8 µg/m³	tine series (4 years)	mortality from non-accidental, cardiovascular, respiratory, cardiac, stroke, & cardiopulmonary-related causes	association with PM_{10}, SO_2, O_3, & NO_2	total of 89,131 non-accidental deaths	percentage increase in mortality per 10 µg/m³ increase using two-pollutant for lag day 0 non-accidental NO_2 only - 1.43 NO_2/PM_{10} - 1.14 NO_2/SO_2 - 1.61 NO_2/O_3 - 1.41 cardiovascular NO_2 only - 1.65 NO_2/PM_{10} - 0.98 NO_2/SO_2 - 1.77 NO_2/O_3 - 1.71 stroke NO_2 only - 1.49 NO_2/SO_2 - 1.79 NO_2/O_3 - 1.58 cardiac NO_2 only - 1.77 NO_2/SO_2 - 1.59 NO_2/O_3 - 1.77 respiratory NO_2 only - 2.23 NO_2/SO_2 - 1.99 NO_2/O_3 - 2.09 cardiopulmonary NO_2 only - 1.60 NO_2/PM_{10} - 1.08 NO_2/SO_2 - 1.68 NO_2/O_3 - 1.56	percentage increase in mortality per 10 µg/m³ increase using two-pollutant for lag day 0 non-accidental NO_2 only 0.87 - 1.99 NO_2/PM_{10} 0.45 - 1.85 NO_2/SO_2 1.01 - 2.21 NO_2/O_3 0.84 - 1.99 cardiovascular NO_2 only 0.87 - 2.45 NO_2/PM_{10} 0.00 - 1.97 NO_2/SO_2 0.94 - 2.62 NO_2/O_3 0.90 - 2.53 stroke NO_2 only 0.56 - 2.43 NO_2/SO_2 0.81 - 2.79 NO_2/O_3 0.62 - 2.54 cardiac NO_2 only 0.44 - 3.12 NO_2/SO_2 0.18 - 3.02 NO_2/O_3 0.62 - 2.54 respiratory NO_2 only 0.52 - 3.96 NO_2/SO_2 0.16 - 3.86 NO_2/O_3 0.33 - 3.87 cardiopulmonary NO_2 only 0.85 - 2.35 NO_2/PM_{10} 0.14 - 2.02 NO_2/SO_2 0.88 - 2.49 NO_2/O_3 0.79 - 2.33	statistically significant association with all mortality causes in both single and two pollutant models with PM_{10}, SO_2, & O_3 on lag day 0, only exceptions two-pollutant modelling with PM_{10} where the results became non-significant for stroke cardiac, and reparatory mortality; the associations for all six mortality categories only applied to those greater than 65 years old with no statistically significant associations observed in younger age groups	⊕⊕◯◯ (low quality because of publication bias with no description of NO_2/CO results)

author / location	exposure monitoring	NO_2 concentration	study type (duration)	endpoint	co-pollutants	participants	ratio or risk	confidence interval	results	GRADE quality of evidence
(Qian *et al.*, 2010) Wuhan, China	mean daily concentration at five fixed monitoring locations	daily mean spring - 49.5 µg/m³ summer - 38.7 µg/m³ fall - 57.8 µg/m³ winter - 61.3 µg/m³	time-series (48 months)	mortality rates all causes cardiovascular stroke respiratory	seasonal activity	89,131 deaths	% change per 10 µg/m³ increment all cause spring - 2.68 winter - 3.28 cardiovascular spring - 2.97 winter - 3.74 stroke spring - 3.39 winter - 3.85 respiratory winter - 4.79	% change per 10 µg/m³ increment all cause spring 1.05 - 3.34 winter 2.36 - 4.21 cardiovascular spring 0.68 - 5.31 winter 2.50 - 5.00 stroke spring 0.66 - 6.19 winter 2.34 - 7.29 respiratory winter 2.34 - 7.29	increased mortality observed in the spring and winter months	⊕◯◯◯ (insufficient because of imprecision and risk of exposure bias)
(Sajani *et al.*, 2011) Six cites in Italy Piacenza Parma Reggio Emila Modena Bologna Ferrara	mean daily concentration from 2-22 monitoring sites analyzed using four approaches nearest background station average all stations within a city average for 3 cities (two macro groups) average for all six cities	daily average Piacenza - 32 µg/m³ Parma – 31 µg/m³ Reggio Emila – 40 µg/m³ Modena – 51 µg/m³ Bologna – 41 µg/m³ Ferrara – 37 µg/m³ all cities – 50 µg/m³	case-crossover (60 months)	acute daily mortality	association with PM_{10}, O_3, and NO_2	male & female 46,948 cases	no significant change in the percentage increase in mortality for any of the four exposure averaging approaches per 10 µg/m³ increase using a single pollutant model with a 1 day lag	no significant change in the percentage increase in mortality for any of the four exposure averaging approaches per 10 µg/m³ increase using a single pollutant model with a 1 day lag	no statistically significant association with acute mortality with any exposure measurement approach; greater associations observed with increasing data aggregation with mean values for all six cities showing a 435% increase over the associations observed using data from a single background monitoring location; progressively higher associations observed with increasing aggregation of monitoring data	⊕⊕◯◯ (low quality because of bias from single pollutant model)

author / location	exposure monitoring	NO_2 concentration	study type (duration)	endpoint	co-pollutants	participants	ratio or risk	confidence interval	results	GRADE quality of evidence
(Samoli *et al.*, 2006) 30 cities in Europe - Air Pollution and Health: A European Approach (APHEA2)	daily 1-hr maxima from an unstated number of fixed monitoring locations in each city	mean 1-hr maximum ranged from 46.2 µg/m³ (Wroclaw) to 154.8 µg/m³ (Milan)	time-series (8 years)	mortality from all, circulatory, & respiratory causes	association with BS, PM_{10}, SO_2, O_3, & NO_2	total deaths not reported but total daily rate averaged 6 (Erfut) to 342 (Netherlands) deaths per day	pooled fractional increase in mortality per 10 µg/m³ increase using two-pollutant random effects model total NO_2 only - 0.30 NO_2/BS - 0.33 NO_2/PM_{10} - 0.27 NO_2/SO_2 - 0.26 NO_2/O_3 - 0.33 cardiovascular NO_2 only - 0.40 NO_2/BS - 0.44 NO_2/PM_{10} - 0.35 NO_2/SO_2 - 0.33 NO_2/O_3 - 0.42 respiratory NO_2 only - 0.38 NO_2/PM_{10} - 0.37 NO_2/O_3 - 0.38	pooled fractional increase in mortality per 10 µg/m³ increase using two-pollutant random effects model total NO_2 only - 0.22 - 0.38 NO_2/BS - 0.23 - 0.42 NO_2/PM_{10} - 0.16 - 0.38 NO_2/SO_2 - 0.18 - 0.34 NO_2/O_3 - 0.22 - 0.43 cardiovascular NO_2 only - 0.29 - 0.52 NO_2/BS - 0.31 - 0.58 NO_2/PM_{10} - 0.21 - 0.50 NO_2/SO_2 - 0.20 - 0.47 NO_2/O_3 - 0.27 - 0.58 respiratory NO_2 only - 0.17 - 0.58 NO_2/PM_{10} - 0.08 - 0.67 NO_2/O_3 - 0.13 - 0.63	statistically significant association with total, respiratory and cardiovascular mortality in single and two-pollutant models with BS, PM_{10}, SO_2 and O_3, statistically significant association with respiratory mortality in single and two-pollutant model with BS, & O_3, but not with PM_{10} & SO_2; use of natural gas in the home acted as an effect modifier on cardiovascular mortality with the associations strengthening from 0.32 (CI 0.20 - 0.43) at the 25th percentile of use to 0.40 (CI 0.32 - 0.48) at the 75th percentile, but the prevalence of smoking had no impact ; PM 10 levels were also an effect modifier on respiratory mortality as was the proportion of elderly subjects , southern and western cites showed the strongest associations with none observed for eastern cities	⊕○○○ (insufficient because of very serious risk of exposure bias)
(Simpson *et al.*, 2005) 4 Australian cities Melbourne Perth Sydney Brisbane	daily 1-hr maxima from an unstated number of fixed monitoring locations in each city	mean 1-hr maximum Brisbane – 21.43 ppb (40.9 µg/m³) Sydney – 23.66 ppb (45.2 µg/m³) Melbourne – 23.65 ppb (45.2 µg/m³) Perth – 16.33 ppb (31.2 µg/m³)	time-series (4 year)	mortality from natural, circulatory, & respiratory causes	association with PM_{10}, $PM_{2.5}$, O_3, CO, & NO_2	total deaths not reported but rates (all causes) ranged from 16.03 (Brisbane) to 56.83 (Sydney)	relative risk per 1 ppb (1.91 µg/m³) increase for all cites using a pooled random effects model total mortality lag 1 - 1.0012 lag 2 - 1.0008 lag 3 - 1.0010 lag 0-1 - 1.0011 respiratory lag 1 - 1.0038 lag 2 - 1.0021 lag 0-1 - 1.0036 cardiovascular lag 1 - 1.0016 lag 2 - 1.0010 lag 3 - 1.0018 lag 0-1 - 1.0014	relative risk per 1 ppb (1.91 µg/m³) increase for all cites using a pooled random effects model total mortality lag 1 - 1.0006 - 1.0018 lag 2 - 1.0002 - 1.0014 lag 3 - 1.0004 - 1.0016 lag 0-1 - 1.0004 - 1.0019 respiratory lag 1 - 1.0017 - 1.0058 lag 2 - 1.0001 - 1.0042 lag 0-1 - 1.0011 - 1.0060 cardiovascular lag 1 - 1.0006 - 1.0025 lag 2 - 1.0001 - 1.0019 lag 3 - 1.0008 - 1.0027 lag 0-1 - 1.0003 - 1.0025	statistically significant association with total, respiratory and cardiovascular mortality on lag day 1, 2, 3 and 0-1 with the cardiovascular associations also noted in those > 65 years of age for some but not all lag periods; a two-pollutant model with PM 2.5 measured by light scattering (bsp) reduced but did not eliminate the association with total mortality (RR decreased from 1.0012 (CI 1.0004-1.0019) to 1.0010 (CI 1.0001 - 1.0019); no statistically significant associations observed when using GLM and natural splines	⊕○○○ (insufficient because of very serious risk of exposure bias)

author / location	exposure monitoring	NO_2 concentration	study type (duration)	endpoint	co-pollutants	participants	ratio or risk	confidence interval	results	GRADE quality of evidence
(Thach *et al.*, 2010) Hong Kong, China	daily averages from eight fixed monitoring sites	daily mean 58.7 µg/m³	time-series (84 months)	interaction with influenza and impact on mortality and hospitalizations for stroke, ischemic heart disease (IHD), lower respiratory infection, (LRI), acute respiratory disease (ARD), & chronic obstructive pulmonary disease (COPD)	association with PM0, SO_2, O_3, & NO_2	number of subjects not stated	unadjusted excess mortality risk per 10 µg/m³ increase in single pollutant model stroke - 1.13 IHD - 2.08 LRI - 1.75 COPD - 1.39 unadjusted excess hospitalization risk per 10 µg/m³ increase in single pollutant model IHD - 0.94 ARD - 1.22 COPD - 1.94	unadjusted excess mortality risk per 10 µg/m³ increase in single pollutant model stroke 0.19 - 2.08 IHD 1.10 - 3.07 LRI 0.74 - 2.77 COPD 0.18 - 2.61 unadjusted excess hospitalization risk per 10 µg/m³ increase in single pollutant model IHD 0.46 - 1.42 ARD 0.74 - 1.71 COPD 1.55 - 2.33	statistically significant association with mortality from stroke, IHD, LRI, & COPD, statistically significant association with hospitalizations from IHD, ARD, & COPD, no association in unadjusted risk from hospitalizations from stroke, adjustment for influenza epidemic periods or predominance caused greater than 0.1 % decrease in mortality from stroke, LRI, & COPD, adjustment for influenza intensity, epidemic periods, or predominance caused greater than 0.1 % decrease in hospitalizations from ARD,	⊕◯◯◯ (insufficient because of unknown number of cases and risk of exposure bias)
(Wong *et al.*, 2008a) Hong Kong, China	daily average from eight fixed monitoring locations	daily mean 58.7 µg/m³	time-series (84 months)	mortality from all non-accidental causes, circulatory causes, & respiratory causes	association with PM_{10}, SO_2, O_3, & NO_2	male & female 215,240 total deaths	adjusted percentage excess risk for all levels of social deprivation per 10 µg/m³ increase in a single pollutant model non-accidental day 0 - 0.75 day 1 - 0.79 day 3 - 0.37 cardiovascular day 0 - 1.17 day 1 - 1.08 respiratory day 1 - 0.88 day 1 - 0.90 day 2 - 0.92 day 3 - 0.75	adjusted percentage excess risk for all levels of social deprivation per 10 µg/m³ increase in a single pollutant model non-accidental day 0 0.45 - 1.06 day 1 0.49 - 1.10 day 3 0.07 - 0.67 cardiovascular day 0 0.61 - 1.73 day 1 0.53 - 1.64 respiratory day 1 0.19 - 1.58 day 1 0.22 - 1.60 day 2 0.25 - 1.60 day 3 0.08 - 1.42	statistically significant association with non-accidental, cardiovascular, and respiratory mortality on multiple lag days, statistically significant associations also apparent when stratified on the basis of social deprivation index (SDI) with cardiovascular and respiratory associations more prevalent in those with a middle or high SDI and all cause mortality evident in all three strata, no statistically significant associations for cardiovascular and respiratory for those in the low SDI group (high SES), no statistically significant associations on lag day 4	⊕⊕◯◯ (low quality because of bias from single pollutant model)
(Wong *et al.*, 2008b) four cities in Asia Bangkok Hong Kong Shanghai Wuhan	daily average from 6-10 fixed monitoring locations	daily mean Bangkok – 44.7 µg/m³ Hong Kong - 58.7 µg/m³ Shanghai – 66.6 µg/m³ Wuhan – 51.8 µg/m³	time-series (48 - 84 months)	mortality from natural, circulatory, & respiratory causes	association with PM_{10}, SO_2, O_3, & NO_2	mean daily all cause mortality deaths per day Bangkok - 94.8 Hong Kong - 84.2 Shanghai - 119.0 Wuhan - 61.0	pooled (random effects) excess percent risk per 10 µg/m³ increase in a single pollutant model for lag 0-1 day average all cause - 1.23 cardiovascular - 1.36 respiratory - 1.48	pooled (random effects) excess percent risk per 10 µg/m³ increase in a single pollutant model for lag 0-1 day average all cause - 0.84 - 1.62 cardiovascular - 0.89 - 1.82 respiratory - 0.68 - 2.28	statistically significant association with all mortality causes in pooled random effects model at an average lag period of 0-1 days; stratification by age revealed higher total death rates in two of the four cities for those greater than 65 years of age and even higher rates in those greater than 75;	⊕⊕◯◯ (low quality because of bias from single pollutant model)

author / location	exposure monitoring	NO_2 concentration	study type (duration)	endpoint	co-pollutants	participants	ratio or risk	confidence interval	results	GRADE quality of evidence
(Wong *et al.*, 2009) Hong Kong, China	daily average from eight fixed monitoring locations	daily mean 58.7 µg/m³	time-series (84 months)	hospitalization and mortality for acute respiratory (ARD), chronic obstructive pulmonary (COPD, and cardiovascular (CVD) disease	interaction study (influenza and PM_{10}, O_3, SO_2 & NO_2)	male & female (avg daily rates) mortality RD - 16.2 COPD - 5.9 CVD - 23.8 hospitalizations RD - 270.3 ARD - 104.9 COPD - 91.5 CVD - 203.5	excess risk for all subjects per 10 µg/m³ increase in single pollutant model baseline mortality RD - 1.24 CVD - 1.23 baseline hospitalizations RD - 0.85 COPD - 1.84 CVD - 0.98 excess risk for all subjects > 65 years of age per 10 µg/m³ increase in single pollutant model modifying effect hospitalizations COPD - 0.43	excess risk for all subjects per 10 µg/m³ increase in single pollutant model baseline mortality RD 0.27 - 2.22 CVD 0.41 - 2.06 baseline hospitalizations RD 0.51 - 1.18 COPD 1.32 - 2.35 CVD 0.63 - 1.33 excess risk for all subjects > 65 years of age per 10 µg/m³ increase in single pollutant model modifying effect hospitalizations COPD 0.05 - 0.81	statistically significant association with baseline mortality from respiratory and cardiovascular disease and baseline hospitalizations from respiratory, cardiopulmonary, and cardiovascular disease, statistically significant interaction with influenza for COPD-related hospitalizations in those > 65 years of age, no association for hospitalizations from acute respiratory disease, no statistically interactions with influenza for any mortality cause or any age-stratified group hospitalized for RD, ARD, or CVD	⊕◯◯◯ (insufficient because of bias from single pollutant model probability of type 1 error)
(Yorifuji *et al.*, 2011) Tokyo, Japan	mean daily concentration at four fixed monitoring locations	daily mean before and after enforcement 27.3 → 24.7 (ppb) 52.1 → 47.2 (µg/m³)	time-series (68 months)	mortality rates all causes circulatory disease ischemic heart disease arrhythmia cerebrovascular disease pulmonary disease pneumonia & influenza COPD & allied conditions other conditions	accountability study (impact of diesel emissions control)	371,921 deaths	adjusted rate ratios per IQR 10 ppb (19.1 µg/m³) on lag day 0 for a single pollutant model before enforcement all causes - 1.006 circulatory - 1.015 cerebrovascular - 1.020 after enforcement all cause - 0.999 circulatory - 1.003 cerebrovascular - 1.009	adjusted rate ratios per IQR 10 ppb (19.1 µg/m³) on lag day 0 for a single pollutant model before enforcement all causes 1.002 - 1.011 circulatory 1.006 - 1.024 cerebrovascular 1.020 - 1.034 after enforcement all cause 0.994 - 1.004 circulatory 0.993 - 1.014 cerebrovascular 0.993 - 1.025	NO_2 emission reductions reduced the rate ratios below the significance level, no significant difference when the entire study period examined	⊕◯◯◯ (insufficient because of single pollutant modelling and risk of exposure bias)

Chronic Mortality

author / location	exposure monitoring	NO_2 concentration	study type (duration)	endpoint	co-pollutants	participants	ratio or risk	confidence interval	results	GRADE quality of evidence
(Beelen *et al.*, 2008) The Netherlands	annual averages based on an independent evaluation of the contribution from regional, urban, and local sources, regional concentrations based on inverse distance weighting of the values from an unstated number of regional monitoring stations, the urban component used LUR together with urban monitoring and GIS variables, the local component used street level monitoring data along with measures of traffic intensity	5-year average (provided in companion paper) total - 39.2 µg/m³ regional - 30.2 µg/m³ urban - 6.5 µg/m³ local 2.5 µg/m³	prospective cohort and case control (120 months)	mortality from natural cause, cardiovascular, respiratory, lung cancer, and other	association with black smoke (BS), $PM_{2.5}$, SO_2, & NO_2	male & female 120,852 subjects	adjusted relative risk in full cohort per 30 µg/m³ in single pollutant model natural cause - 1.08 respiratory - 1.37	adjusted relative risk in full cohort per 30 µg/m³ in single pollutant model natural cause - 1.08 respiratory - 1.37	statistically significant association with natural cause and respiratory mortality for the full cohort, no statistically significant association with cardiovascular, lung cancer or other cause mortality; no statistically significant associations in the case control study	⊕⊕◯◯ (low quality because single pollutant modelling and no evaluation of indoor sources)
(Cao *et al.*, 2011) China	annual average from 103 monitoring stations in 31 cities	annual mean 50 µg/m³	cohort (9 years)	total mortality, cardiopulmonary disease, respiratory disease, & lung cancer	association with TSP, SO_2, & NOx	70,947 middle-aged men and women	% increase per 10 µg/m³ increment adjusted personal factors all cause - 1.5 cardiovascular - 2.3 adjusted personal factors & TSP all causes - 1.4	% increase per 10 µg/m³ increment adjusted personal factors all cause 0.4 - 2.5 cardiovascular 0.6 - 4.1 adjusted personal factors & TSP all causes 0.3 - 2.5	decreased mortality observed for cardiovascular, respiratory or lung cancer observed when model adjusted for personal factors and SO_2; all causes remained significantly increased when model adjusted for personal factors and TSP but increased decreased from 1.5 to 1.4%;	⊕⊕◯◯ (low quality because single pollutant modelling and no evaluation of SES or indoor sources)

author / location	exposure monitoring	NO_2 concentration	study type (duration)	endpoint	co-pollutants	participants	ratio or risk	confidence interval	results	GRADE quality of evidence
(Gan *et al.*, 2011) Vancouver, British Columbia	annual LUR residential exposures determined using 116 passive samplers at 25 locations together with predictor values for length of highways and roads, population density, and commercial land use; measurements from an unstated number of fixed monitoring sites was used to develop monthly adjustment factors that were assigned to specific geocodes	daily mean 29.2 µg/m³	cohort (108 months)	coronary heart disease hospitalization and mortality	association with black carbon (BC) $PM_{2.5}$, NO, & NO_2	male & female (45-85 years) 452,735 cases	relative risk per IQR of 8.4 µg/m³ hospitalization unadjusted single pollutant - 1.02 mortality unadjusted single pollutant - 1.19 adjusted single pollutant - 1.04	relative risk per IQR of 8.4 µg/m³ hospitalization unadjusted single pollutant 1.00 - 1.04 mortality unadjusted single pollutant 1.15 - 1.23 adjusted single pollutant 1.01 - 1.08	statistically significant association with hospitalization in an unadjusted single pollutant model, but not adjusted single pollutant model or multi-pollutant model; statistically significant association with mortality in an unadjusted and adjusted single pollutant model, but not an adjusted multi-pollutant model; statistically significant inverse association with hospitalizations when stratification by income in adjusted one and multi-pollutant model; statistically significant and income-related increase in the association with mortality for unadjusted, but not the adjusted or multi-pollutant model	⊕⊕⊕◯ (moderate quality, no adjustment necessary)

author / location	exposure monitoring	NO_2 concentration	study type (duration)	endpoint	co-pollutants	participants	ratio or risk	confidence interval	results	GRADE quality of evidence
(Hart *et al.*, 2011) continental United States	occupational exposures estimated using work description (8 categories), historical data, and employment history, ambient exposures using fixed monitoring data along with GIS information and proximity modelling at home address	average annual exposure 14.2 ppb (27.1 µg/m³)	cohort (9 years)	mortality of long haul truck drivers from all cause, cardiovascular disease, respiratory disease, lung cancer, and COPD	association with PM_{10}, $PM_{2.5}$, SO_2, & NO_2	males and females 53,814 subjects	percent increase in mortality per IQR of 8 ppb (15.3 µg/m³) in single and three-pollutant models (PM_{10}, SO_2, & NO_2) using all subjects and a group excluding long-haul truck drivers single pollutant (all subjects) all cause - 8.2 cardiovascular disease - 6.9 three pollutant (all subjects) all cause - 7.4 single pollutant (minus long haul) all cause - 14.9 cardiovascular disease - 10.9 respiratory disease - 20.1 three pollutant (minus long haul) all cause - 12.5	percent increase in mortality per IQR of 8 ppb (15.3 µg/m³) in single and three-pollutant models (PM_{10}, SO_2, & NO_2) using all subjects and a group excluding long-haul truck drivers single pollutant (all subjects) all cause 4.5 - 12.1 cardiovascular disease 0.6 - 13.6 three pollutant (all subjects) all cause 2.4 - 12.5 single pollutant (minus long haul) all cause 9.9 - 20.2 cardiovascular disease 2.7 - 19.8 respiratory disease 0.9 - 42.8 three pollutant (minus long haul) all cause 5.8 - 19.5	statistically significant increase in mortality of all truck drivers from all causes and cardiovascular disease but not from lung cancer, ischemic heart disease (IHD), or chronic obstructive pulmonary disease (COPD) in single pollutant model, statistically significant association in three pollutant model for all cause mortality but not lung cancer, cardiovascular disease, IHD, respiratory disease, or COPD, statistically significant association in a subgroup of drivers excluding long haul employees for all cause, cardiovascular, and respiratory disease a single pollutant model and for all cause mortality using a three pollutant model	⊕⊕◯◯ (low quality because of the failure to consider confounding from SES and smoking)
(Jerrett *et al.*, 2009) Toronto, Ontario	daily averages from LUR developed using passive samplers in two campaigns at 143 locations for two weeks and GIS information related to land use, traffic, geography, and population density	daily mean 22.9 µg/m³	prospective cohort (120 months)	mortality from all non-accidental causes, circulatory causes, respiratory causes, and all causes less circulatory, respiratory and lung cancer	association with $PM_{2.5}$, O_3, & NO_2	male & female 2,360 subjects 298 cases	partially and fully adjusted risk ratios for deaths due to circulatory-related disease per IQR of 4 ppb (7.6 µg/m³) in single pollutant model no adjustment - 1.52 partial adjustment - 1.45 full adjustment - 1.40	partially and fully adjusted risk ratios for deaths due to circulatory-related disease per IQR of 4 ppb (7.6 µg/m³) in single pollutant model no adjustment 1.19 - 1.95 partial adjustment 1.10 - 1.92 full adjustment 1.05 - 1.86	statistically significant association with death from circulatory-related disease in both unadjusted and adjusted model, no association with death from non-accidental causes, respiratory causes, or non-accidental causes less respiratory, circulatory, and lung cancer	⊕◯◯◯ (insufficient because of small number of cases and single pollutant measurements)

author / location	exposure monitoring	NO_2 concentration	study type (duration)	endpoint	co-pollutants	participants	ratio or risk	confidence interval	results	GRADE quality of evidence
(Lipfert *et al.*, 2009) USA	county wide means using emissions inventory & dispersion modelling	NOx subject-weighted annual mean all counties – 19.5 ppb (37.2 µg/m³) high traffic counties 31.0 ppb (59.2 µg/m³)	cohort (26 years)	total mortality	association with arsenic, benzene, chloride, diesel particulate matter, elemental carbon, formaldehyde, hydrochloric acid, mercury, manganese, nickel, lead, polycyclic organics, polypropylene, sulfate, traffic density, SO_2, & NOx	700, 000 hypertensive male military veterans	relative risk for cumulative mortality in single pollutant model for all 5 five measurement periods all subjects - 1.0764 high traffic density subjects - 1.1823 low traffic density subjects - 1.0292	relative risk for cumulative mortality in single pollutant model for all 5 five measurement periods all subjects 1.0612 - 1.0919 high traffic density subjects 1.1685 - 1.1963 low traffic density subjects 1.0115 - 1.0474	statistically significant association with mortality for the total cohort and when stratified by vehicle density level; statistically significant association also observed in a two pollutant model (pollutant and traffic density) for all measurement periods, but this association was not significant for the most recent measurement period of 1997 - 2001	⊕◯◯◯ (insufficient because of very serious bias from measuring NOx rather than NO_2)
(Maheswaran *et al.*, 2010) London, England	emission modelling from large and small sources for a single year validated against monitoring data from 56 fixed monitoring sites;	mean daily 41 µg/m³	cohort study (120 months)	mortality after stroke	association with PM_{10} and NO_2	male and female 3320 cohort 856 cases	adjusted hazard ratios for mortality per 10 µg/m³ increase complete dataset available (n=1787) - 1.41 augmented dataset using imputation (n=3320) - 1.28	adjusted hazard ratios for mortality per 10 µg/m³ increase complete dataset available (n=1787) 1.14 - 1.75 augmented dataset using imputation (n=3320) 1.11 - 1.48	statistically significant association in both unadjusted and adjusted hazard ratios; sensitivity analysis using the adjusted model revealed that nonsmokers, those less than 70 years old, those with hypertension, without diabetes, without CHD displayed statistically significant associations	⊕◯◯◯ (insufficient because of the small number of participants and exposure bias caused a single year of monitoring)

author / location	exposure monitoring	NO_2 concentration	study type (duration)	endpoint	co-pollutants	participants	ratio or risk	confidence interval	results	GRADE quality of evidence
(Rosenlund *et al.*, 2008) Rome, Italy	land use regression estimates based on three 1- week measurement periods at 61 sites; LUR used population density, altitude, and distance to roadways with benzene emission data serving as surrogate for some variables	not stated	cohort (36 month)	hospitalizations & mortality (in and outside hospital) amongst survivors of a cardiac event	association with NO_2	male & female 6513 survivors	adjusted relative risk per 10 µg/m³ increment total incidence - 1.03 cases fatal within 28 days - 1.07 outside hospital - 1.08	adjusted relative risk per 10 µg/m³ increment total incidence 1.00 - 1.07 cases fatal within 28 days 1.02 - 1.07 outside hospital 1.02 - 1.13	weak statistically significant association with the total incidence of fatal and nonfatal cardiac events as well as for cases that were fatal within 28 days; associations remained significant for deaths outside the hospital but not for deaths within the hospital; no significant associations with nonfatal hospitalizations	⊕◯◯◯ (insufficient because of the small number of cases and no evaluation of co-pollutants)
(Rosenlund *et al.*, 2009) Stockholm, Sweden	dispersion modelling using emissions database reconstructed at year intervals using historic information on traffic patterns and land use variations, limited validation with actual measurements	5-year median concentration 12.9 µg/m³ cases 11.8 µg/m³ controls	case control (12 years)	morbidity and mortality from myocardial infarction	association with PM_{10}, CO, & NO_2	males and females 15 - 79 years of age 24,347 cases 276,926 controls	adjusted odds ratio per 5-95% range of 31.6 µg/m³ for all subjects and those who did not relocate during the study period all subjects fatal cases - 1.23 out of hospital deaths -1.34 non-relocated subjects all cases - 1.11 fatal cases - 2.54 in hospital death - 2.39 out of hospital death - 2.62	adjusted odds ratio per 5-95% range of 31.6 µg/m³ for all subjects and those who did not relocate during the study period all subjects fatal cases 1.15 - 1.32 out of hospital deaths 1.23 - 1.46 non-relocated subjects all cases 1.01 - 1.23 fatal cases 1.96 - 3.29 in hospital death 1.55 - 3.68 out of hospital death 1.92 - 3.57	statistically significant association with fatal myocardial infarction (all cases) and out of hospital fatalities using a 5-year average exposure, statistically significant association with all case, fatal case, in-hospital deaths, and out of hospital deaths when the subjects were restricted to those that had not moved from the location, no statistically significant association with total nonfatal cases in either study population or with the all case group and the in hospital death group when all subjects were included in the analysis, no statistically significant differences when the results were stratified by sex, age, income, occupation, or marital status	⊕◯◯◯ (insufficient because of bias poorly validated exposure model and evidence of a publication bias)

Acute Emergency Department Visits

author / location	exposure monitoring	NO_2 concentration	study type (duration)	endpoint	co-pollutants	participants	ratio or risk	confidence interval	results	GRADE quality of evidence
(Chan *et al.*, 2008) Taipei, Taiwan	mean daily concentration at 16 fixed monitoring locations	daily mean high dust events – 34.9 ppb (66.7 µg/m³) low dust events – 29.4 ppb (56.2 µg/m³)	time-series (8 years)	emergency room visits for cardiovascular disease	interaction between Asian dust storms and PM_{10}, O_3, SO_2, & NO_2	male and female adults 5.7 - 7.2 cases per dust event	no significant change in odds ratio for cardiovascular disease (ischemic heart disease and cerebrovascular) emergency room visits per IQR 9.6 ppb (18.3 µg/m³)	no significant change in odds ratio for cardiovascular disease emergency room visits per IQR 9.6 ppb (18.3 µg/m³)	no statistically significant association with ischemic heart or cerebrovascular disease in a single pollutant model at lag periods ranging from day 0 to day 6	⊕⊕◯◯ (low quality because of bias from single pollutant model with not CO evaluation)
(Darrow *et al.*, 2011a) Atlanta, Georgia	mean hourly and daily concentrations at a single fixed monitoring location	1-hr max – 43 ppb (82.1 µg/m³) 24-hr avg – 22 ppb (42.0 µg/m³) 6-hr commute (0700-1000 & 1600-1900) – 21 ppb (40.1 µg/m³) 6-hr nighttime (2400-0600) – 25 ppb (47.8 µg/m³)	time-series (132 months)	emergency departments visits for respiratory problems (asthma, COPD, infection, & pneumonia)	association with $PM_{2.5}$, CO, O_3 & NO_2	male & female 1,068,525 cases	risk ratio per 10 ppb (19.1 µg/m³) increment (lag 1) 1-hr max NO_2 - 1.005 24-hr avg NO_2 - 1.009 6-hr commute NO_2 (0700-1000 & 1600-1900) - 1.006 6-hr nighttime NO_2 (2400-0600) - 1.007	risk ratio per 10 ppb (19.1 µg/m³) increment (lag 1) 1-hr max NO_2 1.003 - 1.007 24-hr avg NO_2 1.005 - 1.013 6-hr commute NO_2 (0700-1000 & 1600-1900) - 1.002 - 1.010 6-hr nighttime NO_2 (2400-0600) 1.005 - 1.009	significant associations with NO_2 using a single pollutant model and various metrics of exposure, but may be due to strong co-variance with O_3	⊕◯◯◯ (insufficient because of severe exposure bias)

author / location	exposure monitoring	NO_2 concentration	study type (duration)	endpoint	co-pollutants	participants	ratio or risk	confidence interval	results	GRADE quality of evidence
(Farhat *et al.*, 2005) Sao Paulo, Brazil	daily average from 6 urban fixed monitoring sites	daily mean concentration 125.3 µg/m³	time-series (1 year)	pediatric hospital and emergency room visits for lower respiratory disease (pneumonia, bronchopneumonia, asthma, & bronchiolitis)	association with PM_{10}, SO_2, O_3, CO, & NO_2	male & female children < 13 years of age 4534 admissions or visits	percentage increase in hospital and emergency room visits per IQR 65.0 µg/m³ increase using two-pollutant and multi-pollutant model for average lag day 0-3 total admission NO_2 only ≈ 18 (depicted graphically) NO_2/PM_{10} - 16.1 NO_2/SO_2 - 24.7 NO_2/O_3 - 16.1 NO_2/CO - 19.2 $NO_2/PM_{10},SO_2,O_3$,CO - 18.4 asthma and bronchiolitis NO_2 only ≈ 30 (depicted graphically) NO_2/PM_{10} - 47.7 NO_2/SO_2 - 33.1	percentage increase in hospital and emergency room visits per 65.0 µg/m³ increase using two-pollutant and multi-pollutant model for average lag day 0-3 total admission NO_2 only ≈ 13 -25 (depicted graphically) NO_2/PM_{10} 5.4 - 26.8 NO_2/SO_2 18.2 - 31.3 NO_2/O_3 9.5 - 22.7 NO_2/CO 11.8 - 26.6 $NO_2/PM_{10},SO_2,O_3$,CO 3.4 - 33.5 asthma and bronchiolitis NO_2 only ≈ 9 - 56 (depicted graphically) NO_2/PM_{10} 1.15 - 94.2 NO_2/SO_2 5.7 - 60.5	statistically significant association with total visits for all single, two pollutant and multi-pollutant models with a 0-4 day moving average lag period; statistically significant association with asthma and bronchiolitis visits for single and two-pollutant models with PM_{10} and SO_2, but not with two pollutant models with O_3 or CO or multi-pollutant models; no significant associations with visits for pneumonia or broncho-pneumonia;	⊕○○○ (insufficient because of imprecision from small number of cases and short duration)
(Goldman *et al.*, 2010) Atlanta, Georgia	1- hour maximum concentration from five central monitors with independent determination of measurement error (co-located instrument) and spatial variability (semivariogram)	mean 1-hr max urban – 38.1 ppb (72.8 µg/m³) rural – 7.74 ppb (14.8 µg/m³)	time-series (72 months)	impact of measurement error on relative risk for emergency department visits associated with cardiovascular disease (ischemic heart disease, dysrhythmia, congestive heart failure cerebrovascular disease)	association with PM_{10}, $PM_{2.5}$, CO, SO_2, O_3, NO, NOx, & NO_2 and $PM_{2.5}$ associated NO_3, SO_4, NH_4, EC, & OC	male & female 166,950 visits	risk ratio per ppm following error adjustment of the base case assessment measurement error - 1.0133 spatial error - 1.0046	confidence intervals not provided	factoring spatial variability into risk ratio resulted in a 43% reduction towards the null with the loss of significance association after the adjustment, factoring instrument precision into average risk ratios from a baseline assessment had little impact on the outcome	⊕○○○ (insufficient because of publication bias with no confidence intervals specified)

author / location	exposure monitoring	NO_2 concentration	study type (duration)	endpoint	co-pollutants	participants	ratio or risk	confidence interval	results	GRADE quality of evidence
(Guo *et al.*, 2009) Beijing, China	pooled mean daily concentration from eight fixed monitoring locations	daily mean 68.25 µg/m³	case-crossover (19 months)	cardiovascular disease (emergency room visits)	differential effects of $PM_{2.5}$, SO_2, & NO_2	male & female cases 8,377	unadjusted model only; lag day 0 - 1.005	unadjusted model only; lag day 0 1.001 - 1.024	odds ratios for NO_2 unaffected in unadjusted but not adjusted model; lag day 1,2,& 3 show no change in unadjusted model	⊕○○○ (insufficient because of bias from small number of cases, pooling of exposure data, and short duration)
(Guo *et al.*, 2010b) Beijing, China	mean daily concentration at eight fixed monitoring locations	daily mean 66.6 µg/m³	case-crossover (12 months)	emergency department visits for hypertension	association with PM_{10}, SO_2, & NO_2	male & female 1,491 cases	odds ratio per 10 µg/m³ increase on lag day 3 single pollutant model - 1.101 multi-pollutant (PM_{10}) - 1.114 multi-pollutant (SO_2) - 1.130 multi-pollutant (PM_{10} & SO_2) - 1.144	odds ratio per 10 µg/m³ increase on lag day 3 single pollutant model - 1.038 - 1.168 multi-pollutant (PM_{10}) - 1.037 - 1.195 multi-pollutant (SO_2) - 1.041 - 1.225 multi-pollutant (PM_{10} & SO_2) - 1.046 - 1.251	statistically significant association with emergency department visits for hypertension in a single pollutant model on lag days 0, 2, & 3; statistically significant association on lag days 2, 3, & 4 for a multi-pollutant model with SO_2 and on day 3 for a multi-pollutant model with PM_{10}; statistically significant association on lag days 3 & 4 for a multi-pollutant model with SO_2 and PM_{10}	⊕○○○ (insufficient because of small number of cases short duration)
(Halonen *et al.*, 2008) Helsinki, Sweden	daily average from a single monitoring site	daily mean concentration 28.2 µg/m³	time-series (7 years)	ED visits for asthma and COPD in three age groups	association with UFP (Aiken mode), UFP (accumulation mode), $PM_{2.5}$ $PM_{10-2.5}$ (coarse), CO & NO_2	males & females in three age groups children (< 15 years) - 4807 visits adults (14-64 years) - 6312 visits elderly (≥ 65 years) - 7239 visits	percent increase in asthma and COPD emergency room visits per IQR 14.2 µg/m³ for three age groups in a single pollutant model children lag day 3 - 4.53 lag day 4 - 10.9 lag day 5 - 9.36 adults lag day 5 - 3.7 elderly lag day 0 - 4.82	percent increase in asthma and COPD emergency room visits per IQR 14.2 µg/m³ for three age groups in a single pollutant model children lag day 3 0.19 - 9.05 lag day 4 6.38 - 15.5 lag day 5 4.95 - 14.0 adults lag day 5 0.15 - 7.37 elderly lag day 0 1.26 - 8.50	statistically significant association with ED visits for asthma and COPD in single pollutant model for children on lag days 3,4,&5, adults on lag day 5 and elderly on lag day 0; no associations on lag day 0 thru 2 for children, 0 thru 4 for adults or 1 thru 5 for elderly	⊕○○○ (insufficient because of severe exposure bias)

author / location	exposure monitoring	NO_2 concentration	study type (duration)	endpoint	co-pollutants	participants	ratio or risk	confidence interval	results	GRADE quality of evidence
(Ito *et al.*, 2007) New York, New York	daily average at 15 fixed monitoring sites	yearly average concentration all seasons – 31.1 ppb (59.4 µg/m³) warm season – 30.4 ppb (58.1 µg/m³) cold season - 31.8 ppb (60.7 µg/m³)	time-series (4 years)	emergency department visits for asthma	association with $PM_{2.5}$(FRM), $PM_{2.5}$ (TEOM), O_3, SO_2, CCO, & NO_2	unstated number of male and female of all ages	relative risk per 5-95% range of 29 ppb (55.4 µg/m³) in single and two pollutant models on avg lag 01 days during warm season (values estimated from graph) NO_2 only ≈ 1.30 $NO_2/PM_{2.5}$ ≈ 1.27 NO_2/O_3 ≈ 1.25 NO_2/CO ≈ 1.35 NO_2/SO_2 ≈ 1.32	relative risk per 5-95% range of 29 ppb (55.4 µg/m³) in single and two pollutant models on avg lag 01 days during warm season (values estimated from graph) NO_2 only ≈ 1.21 - 1.41 $NO_2/PM_{2.5}$ ≈ 1.18 - 1.40 NO_2/O_3 ≈ 1.15 - 1.36 NO_2/CO ≈ 1.24 - 1.48 NO_2/SO_2 ≈ 1.18 - 1.49	statistically significant association with asthma hospital admissions in both single and two pollutant models during warm season for average lag of 01 days, statistically significant association in single pollutant models for all year and warm season using alternative weather models, no significant associations for the cold season	⊕⊕○○ (low quality because unstated number of cases)
(Jalaludin *et al.*, 2006) Sydney, Australia	1-hr averages from 14 fixed monitoring sites	1-hr mean concentration 23.0 ppb (43.9 µg/m³)	time-series (5 years)	emergency department visits of elderly subjects for cardiovascular disease (cardiac disease, ischemic heart disease, & stroke)	association with nephelometric particulate matter (BSP) PM_{10}, $PM_{2.5}$, SO_2, O_3, CO, & NO_2	males and females ≥ 65 yrs of age daily rates of emergency department visits all cardiovascular disease types - 55.2 cardiac disease - 38.5 ischemic heart disease - 15.8 stroke - 11.3	percent change in total cardiovascular emergency department visits per IQR 9.3 ppb (17.8 µg/m³) in single and two-pollutant models on lag day 0 NO_2 only - 1.73 NO_2/PM_{10} ≈ 1.8 (depicted graphically) NO_2/O_3 ≈ 2.1 (depicted graphically) NO_2/SO_2 ≈ 1.5 (depicted graphically)	percent change in total cardiovascular emergency department visits per IQR 9.3 ppb (17.8 µg/m³) in single and two-pollutant models on lag day 0 NO_2 only 0.74 - 2.73 NO_2/PM_{10} ≈ 0.6 - 2.9 (depicted graphically) NO_2/O_3 ≈ 1.1 - 2.1 (depicted graphically) NO_2/SO_2 ≈ 0.3 - 2.7 (depicted graphically)	statistically significant association with cardiovascular ED visits on lag day 0 in single and two-pollutant models with PM_{10}, O_3, & SO_2 but with BSP or CO; statistically significant association with cardiac and ischemic heart disease on lag day 0 or 01 in single pollutant model but not for stroke: statistically significant association with all cardiovascular & cardiac ED visits on lag day 0 for cool but not warm periods, statistically significant association with stroke visits on lag day 2 in warm season, but no association in cool season; no statistically significant association for ischemic heart disease visits in two pollutant model with CO (data not presented)	⊕○○○ (insufficient because of publication bias with no confidence intervals provided and lag selection bias)

author / location	exposure monitoring	NO_2 concentration	study type (duration)	endpoint	co-pollutants	participants	ratio or risk	confidence interval	results	GRADE quality of evidence
(Jalaludin *et al.*, 2008) Sydney, Australia	1-hr measurements from 14 fixed monitoring sites	1-hr mean concentration 23.2 ppb (44.3 µg/m³)	case-crossover (5 years)	emergency department visits for asthma in children	association with PM_{10}, $PM_{2.5}$, SO_2, O_3, CO, & NO_2	male and female children aged 1-14 years 1826 visits	percent increase in ED visits for asthma in children of different age groups per IQR of 9.3 ppb (17.8 µg/m³) in single and two-pollutant models for lag day 0 1-14 years NO_2 only - 2.3 NO_2/PM_{10} - 1.0 $NO_2/PM_{2.5}$ - 1.1 NO_2/O_3 - 1.2 NO_2/CO - 1.8 NO_2/SO_2 - 1.0 1-4 years of age NO_2 only - 3.0 $NO_2/PM_{2.5}$ - 0.8 NO_2/O_3 - 1.6 NO_2/CO - 1.1 5-9 years of age NO_2/PM_{10} - 1.6 $NO_2/PM_{2.5}$ - 1.6 NO_2/O_3 - 1.9 NO_2/CO - 3.0 NO_2/SO_2 - 1.8 10-14 years of age NO_2/CO (lag day 2) - 3.5	percent increase in ED visits for asthma in children of different age groups per IQR of 9.3 ppb (17.8 µg/m³) in single and two-pollutant models for lag day 0 1-14 years NO_2 only 1.4 - 3.2 NO_2/PM_{10} 0.4 - 1.6 $NO_2/PM_{2.5}$ 0.6 - 1.6 NO_2/O_3 0.6 - 1.7 NO_2/CO 1.0 - 2.6 NO_2/SO_2 0.1 - 1.9 1-4 years of age NO_2 only 1.8 - 4.2 $NO_2/PM_{2.5}$ 0.1 - 1.5 NO_2/O_3 0.9 - 2.4 NO_2/CO 0.03 - 2.1 5-9 years of age NO_2/PM_{10} 0.4 - 2.8 $NO_2/PM_{2.5}$ 0.6 - 2.6 NO_2/O_3 0.6 - 3.2 NO_2/CO 1.3 - 4.6 NO_2/SO_2 0.04 - 3.6 10-14 years of age NO_2/CO (lag day 2) 1.4 - 5.7	statistically significant association with ED visits for asthma in single and two pollutant models for age group 1-14 years; statistically significant association in two pollutant models but not single pollutant model in age group 5-9 years; statistically significant association in single and two pollutant models for $PM_{2.5}$, O_3, & CO in age group 1-4 years; statistically significant association in two-pollutant model with CO in age group 10-14 years but only when lag day 2 was used in the comparison; statistically significant association in single pollutant model for warm but not cold months in age group 1-14 years	⊕○○○ (insufficient because of small number of cases and inconsistencies across age groups)

author / location	exposure monitoring	NO_2 concentration	study type (duration)	endpoint	co-pollutants	participants	ratio or risk	confidence interval	results	GRADE quality of evidence
(Leitte *et al.*, 2011) Beijing, China	mean daily concentration from eight fixed monitoring sites	daily mean 63 µg/m³	time-series (33 months)	emergency department visits for respiratory symptoms (acute infections, pneumonia, bronchitis, URT diseases, & chronic URT diseases)	association with PM_{10}, particle number concentration (PNC), particle surface concentration (PSAC), SO_2, & NO_2	male & female 15,981 cases	relative risk per 40 µg/m³ change in two-pollutant model with PM_{10} 3 day lag - 1.07 4 day lag - 1.07 5 day lag - 1.08	relative risk per 40 µg/m³ change in two-pollutant model with PM_{10} 3 day lag 1.01 - 1.13 4 day lag 1.01 - 1.14 5 day lag 1.01 - 1.15	statistically significant association with emergency room visits in two pollutant model on lag days 3, 4, & 5 but not lag days 0, 1, & 2; statistically significant association on lag day 3 using a cumulative effects model (6-day moving average) with a single pollutant; no associations on lag days 0, 1, 2, 3, or 4 with cumulative distribution model or on any lag day when using a single lag model or a polynomial distribution lag model	⊕⊕◯◯ (low quality because of imprecision with weak effects noted)
(Llorca *et al.*, 2005) Torrelavega, Spain	daily average from three fixed monitoring site	daily mean concentration 21.3 µg/m³	time-series (4 years)	total cardiorespiratory, cardiac, & respiratory emergency department visits	association with total suspended particulate (TSP), hydrogen sulfide (H2S), sulfur dioxide (SO_2), nitrogen oxide (NO), & NO_2	total admissions of 18,137 mean daily hospital admission rates cardiac - 7.61 respiratory - 4.93	relative risk per IQR 100 µg/m³ in single and multi-pollutant model with an unstated lag period total cardiopulmonary NO_2 only - 1.37 NO_2/TSP,H2S,SO_2,NO - 1.20 cardiac NO_2 only - 1.27 respiratory NO_2 only - 1.54 NO_2/TSP,H2S,SO_2,NO - 1.69	relative risk per IQR 100 µg/m³ in single and multi-pollutant model with an unstated lag period total cardiopulmonary NO_2 only 1.26 - 1.49 NO_2/TSP,H2S,SO_2,NO 1.05 - 1.39 cardiac NO_2 only 1.14 - 1.42 respiratory NO_2 only 1.34 - 1.76 NO_2/TSP,H2S,SO_2,NO 1.34 - 2.13	statistically significant association with hospital admissions for total cardiopulmonary, cardiac, & respiratory disease in single pollutant model with an unstated lag period; statistically significant association with admissions for total cardiopulmonary and respiratory causes in multi-pollutant models, but not for cardiac disease	⊕◯◯◯ (insufficient because of imprecision caused by no lag period, publication bias from poor method description)

author / location	exposure monitoring	NO_2 concentration	study type (duration)	endpoint	co-pollutants	participants	ratio or risk	confidence interval	results	GRADE quality of evidence
(Malinauskiene *et al.*, 2011) Kaunas, Lithuania	pooled monitoring data at 12 fixed monitoring sites	daily mean 25 µg/m³	case control (108 months)	myocardial infarction (emergency room visit)	association with indoor/outdoor NO_2 differences	women only cases 368 controls 725	no significant change in odds ratio	no significant change in odds ratio	odds ratios showed no associations with outdoor NO_2 exposures greater than 35 µg/m³	⊕○○○ (insufficient because of bias from small number of cases, pooling of exposure data, and short duration)
(Moura *et al.*, 2008) Rio de Janeiro, Brazil	hourly average at a single fixed monitoring site	daily mean 62.78 µg/m³	time-series (1 year)	emergency department visits for upper and lower respiratory symptoms	association with PM_{10}, O_3, CO, & NO_2	male and female children aged 1-12 years 45,595 visits	no significant change in relative risk for emergency department visits for respiratory symptoms	no significant change in relative risk for emergency department visits for respiratory symptoms	no significant change in relative risk for upper or lower respiratory symptoms at any lag period using a single pollutant model	⊕○○○ (insufficient because of severe exposure bias)
(Orazzo *et al.*, 2009) six Italian cities Ancona Bologna Florence Naples Padua Varese-Gallarate	daily means from an unstated number of fixed monitoring sites in each city	daily means Ancona - 42.5 µg/m³ Bologna - 64.8 µg/m³ Florence - 57.9 µg/m³ Naples - 78.6 µg/m³ Padua - 48.7 µg/m³ Varese-Gallarate - 40.8 µg/m³	case-crossover (60 months)	emergency department visits for wheeze or acute gastrointestinal disease	association with PM_{10}, O_3, CO, SO_2, & NO_2	male & female aged 0-2 yrs old 0.7-18.3 admissions/ day wheeze 0.4-8.0 admissions/ day GI disorders	no association for wheeze or GI admissions in adjusted single pollutant model for any lag period per IQRs ranging from 22.2-26.0 µg/m³	no association for wheeze or GI admissions in adjusted single pollutant model for any lag period per IQRs ranging from 22.2-26.0 µg/m³	no statistically significant association with wheeze or GI disorders on any lag day with single pollutant model	⊕○○○ (insufficient because of bias from the use of a unstated number of monitoring sites)

author / location	exposure monitoring	NO_2 concentration	study type (duration)	endpoint	co-pollutants	participants	ratio or risk	confidence interval	results	GRADE quality of evidence
(Peel *et al.*, 2005) Atlanta, GA	1-hr maximum from two fixed monitoring sites	1-hr maximum mean 45.9 ppb (87.7 µg/m³)	time-series (92 months)	emergency department visits of total respiratory, upper respiratory infection, asthma, pneumonia, & COPD	association with PM_{10}, total particle count (TPC), coarse PM, sulfate, acidity, OC, EC, oxy hydrocarbons, SO_2, O_3, CO, & NO_2	males and females (avg. ED visit rates) respiratory disease 172 visits/day URI 103 visits/day asthma 39.0 visits/day pneumonia 20.8 visits/day COPD 7.42 visits/day	risk ratio per 20 ppb (38.2 µg/m³) in a single pollutant model using two lag periods 0-2 day moving average lag upper respiratory infection - 1.027 COPD - 1.035 0-13 day distributed lag upper respiratory infection - 1.057 asthma - 1.047	risk ratio per 20 ppb (38.2 µg/m³) in a single pollutant model using two lag periods 0-2 day moving average lag upper respiratory infection 1.006 - 1.031 COPD 1.006 - 1.065 0-13 day distributed lag upper respiratory infection 1.029 - 1.085 asthma 1.011 - 1.085	statistically significant association with URI in single pollutant model at moving average lag 0-2 and distributed lag 0-13 days, statistically significant association with COPD at average lag asthma 0-2 days, at distributed lag 0-13 days, statistically significant association with all respiratory disease for moving average lag 0-2 days, no significant association pneumonia or COPD for either lag period or asthma with moving average lag 0-2 days, no attenuation of association in multi-pollutant models (data not shown), associations for asthma substantially stronger for infants (age 0-1 yrs) and children (age 2-18 yrs) than adults	⊕○○○ (insufficient because of publication bias and the bias using a very small number of monitoring sites)

author / location	exposure monitoring	NO_2 concentration	study type (duration)	endpoint	co-pollutants	participants	ratio or risk	confidence interval	results	GRADE quality of evidence
(Samoli *et al.*, 2011) Athens, Greece	1-hr maximum concentrations for 14 fixed monitoring locations	mean daily 1-hr maximum 84.8 µg/m³	time-series (60 months)	pediatric emergency admissions for asthma	association with PM_{10}, O_3, SO_2, & NO_2	male & female 3601 admissions	adjusted increase in asthma admissions per 10 µg/m³ increase (1-hr max) in single pollutant model for lag day 0 males (0-14 years) - 2.29 no significant increase in asthma admissions in adjusted single or two-pollutant model per 10 µg/m³ increase or IQR range (37.3 µg/m³) increase on lag day 0, 1, or 2	adjusted increase in asthma admissions per 10 µg/m³ increase (1-hr max) in single pollutant model for lag day 0 males (0-14 years) 0.13 - 4.50 no significant increase in asthma admissions in adjusted single or two-pollutant model per 10 µg/m³ increase or IQR range (37.3 µg/m³) increase on lag day 0, 1 or 2	statistically significant increase in asthma admissions for boys, but not girls, aged 0-14 years; no statistically significant associations for all children in two age groups (0-4 years and 5-14 years); no statistically significant association with asthma admissions for annual mean daily 1-hr maximum measurements (winter, spring, summer, or fall) using continuous or IQR values in a single pollutant model for lag day 0, 1, or 2; no statistically significant associations in a two-pollutant model with PM_{10}, SO_2, or O_3	⊕⊕◯◯ (low quality because of the small number of cases)
(Santos *et al.*, 2008) Sao Paulo, Brazil	mean daily concentration at seven fixed monitoring locations	daily mean 99.03 µg/m³	time-series (20 months)	emergency room visits for cardiac arrhythmia	association with PM_{10}, SO_2, O_3, CO, & NO_2	male and female adults 3251 admissions	percentage increase in ER visits per IQR of 49.5 µg/m³ in single pollutant model lag 0 ≈ 13 (depicted graphically)	percentage increase in ER visits per IQR of 49.5 µg/m³ in single pollutant model lag 0 ≈ 7 -18 (depicted graphically)	statistically significant association with emergency room visits for cardiac arrhythmia in a single pollutant model on lag day 0 only, no statistically significant associations in two pollutant model with CO or three pollutant model with PM_{10} and CO, quintile analysis suggests a threshold a threshold at a concentration range of 126.2 - 303.0 µg/m³	⊕◯◯◯ (insufficient because of publication bias and small number of cases)

author / location	exposure monitoring	NO_2 concentration	study type (duration)	endpoint	co-pollutants	participants	ratio or risk	confidence interval	results	GRADE quality of evidence
(Stieb *et al.*, 2009) Seven Canadian cities Montreal Ottawa Edmonton Saint John Halifax Toronto Vancouver	mean daily concentration from 1 to 14 fixed monitoring sites	hourly mean in ppb(µg/m³) Montreal – 19.4 (37.1 µg/m³) Ottawa – 18.8 (35.9 µg/m³) Edmonton – 21.9 (41.8 µg/m³) Saint John – 9.3 (17.8 µg/m³) Halifax – 17.5 (33.4 µg/m³) Toronto – 22.7 (43.4 µg/m³) Vancouver – 18.7 (35.7 µg/m³)	time-series (up to 120 months)	emergency department visits for cardiac (angina, myocardial infarction, heart failure, dysrhythmia) and respiratory (asthma, COPD, respiratory infections) conditions	association with PM_{10}, $PM_{2.5}$, SO_2, O_3, CO, & NO_2	male & female cardiac - 140.657 respiratory - 249,199 cases	pooled percent increase in cardiac visits per 18.4 ppb (35.1 µg/m³) in a single pollutant model for the summer season lag day 0 angina/infarction - 2.6 heart failure - 4.7 lag day 1 angina/infarction - 2.7	pooled percent increase in cardiac visits per 18.4 ppb (35.1 µg/m³) in a single pollutant model for the summer season lag day 0 angina/infarction 0.2 - 5.0 heart failure 1.2 - 8.4 lag day 1 angina/infarction 0.2 - 5.3	statistically significant association with angina/infarction and heart failure in a single pollutant model; no statistically significant associations for the winter season or for any respiratory conditions; no statistically significant association in a two pollutant model with CO	⊕⊕⊕○ (moderate quality, no adjustment necessary)
(Strickland *et al.*, 2010) Atlanta, Georgia	population weighted hourly maximum concentrations at an unstated number of fixed monitoring location	mean 1-hr maximum overall – 23.3 ppb (44.5 µg/m³) warm season – 22.0 (42.0 µg/m³) cold season – 24.5 (46.8 µg/m³)	case-crossover and time-series (12 years)	asthma emergency department visits by children aged 5-17 years	association with $PM_{2.5}$ mass, $PM_{2.5}$ sulfate, $PM_{2.5}$ EC, $PM_{2.5}$ OC, $PM_{2.5}$ soluble metals, PM_{10}, $PM_{10-2.5}$, SO_2, CO, O_3, & NO_2	male & female 91,387 cases	rate ratios for ER visits per 12.9 ppb (24.6 µg/m³) in adjusted model using 0-2 day lag overall - 1.036 warm season - 1.066 rate ratio for ER visits relative to the first NO_2 quintile (< 15.4 µg/m³) 3rd quintile 37.1 - <46 ppb (µg/m³) - 1.040 4th quintile 46 - <57.1 ppb (µg/m³) - 1.087 5th quintile 57.1 - ≤181 ppb (µg/m³) - 1.087	rate ratios for ER visits per 12.9 ppb (24.6 µg/m³) in adjusted model using 0-2 day lag overall 1.018 - 1.055 warm season 1.038 - 1.095 rate ratio for ER visits relative to the first NO_2 quintile (< 15.4 µg/m³) 3rd quintile 37.1 - <46 ppb (µg/m³) 1.000 - 1.081 4th quintile 46 - <57.1 ppb (µg/m³) 1.044 - 1.131 5th quintile 57.1 - ≤181 ppb (µg/m³) 1.036 - 1.140	statistically significant association in the overall model and the warm season using 0-2 day and 0-7 day moving average lag period; statistically significant association in single and two pollutant model with ozone; sensitivity analysis using time-series analysis with LOESS smoothing yielded similar results in a base model; no statistically significant association for the cold season either in the base model or by quintile	⊕⊕○○ (low quality because increased rating from dose response offset by the failure to describe the number of monitoring sites)

author / location	exposure monitoring	NO_2 concentration	study type (duration)	endpoint	co-pollutants	participants	ratio or risk	confidence interval	results	GRADE quality of evidence
(Strickland *et al.*, 2011) Atlanta, Georgia	1) one hour maximum from central monitor (six fixed monitoring sites) 2) unweighted average from monitoring sites 3) population-weighted average of spatially adjusted measurements from monitoring sites	1-hr maximum central monitor – 42.0 ppb (80.2 µg/m³) unweighted average - 27.7 ppb (52.9 µg/m³) population weighted average – 22.0 ppb (42.0 µg/m³)	time-series (144 months)	emergency department visits for pediatric asthma	association with PM_{10}, $PM_{2.5}$, CO, O_3, SO_2, & NO_2	male & female children (aged 5-17 years) 41,741 visits	rate ratio per 20 ppb (38.2 µg/m³) increase for 3-day average lag in single pollutant model (warm season only) central monitor - 1.052 unweighted - 1.079 pop. weighted - 1.105 rate ratio per IQR increase for 3-day average lag in single pollutant model central monitor (IQR 19.7 ppb, 37.6 µg/m³) - 1.051 unweighted (IQR 13.5 ppb, 25.8 µg/m³) - 1.053 pop. weighted (IQR 10.1 ppb, 19.3 µg/m³) - 1.052	rate ratio per 20 ppb (38.2 µg/m³) increase for 3-day average lag in single pollutant model (warm season only) central monitor 1.028 - 1.077 unweighted 1.044 - 1.1116 pop. weighted 1.060 - 1.15 rate ratio per IQR increase for 3-day average lag in single pollutant model central monitor (IQR 19.7 ppb, 37.6 µg/m³) 1.027 - 1.076 unweighted (IQR 13.5 ppb, 25.8 µg/m³) 1.029 - 1.077 pop. weighted (IQR 10.1 ppb, 19.3 µg/m³) 1.030 - 1.074	statistically significant association with emergency department visits by children with asthma using all three measures of hourly maximum NO_2 concentration; greater consistency when IQR is used to compare results across three measurement approaches	⊕⊕◯◯ (low quality because only single pollutant modelling)

author / location	exposure monitoring	NO_2 concentration	study type (duration)	endpoint	co-pollutants	participants	ratio or risk	confidence interval	results	GRADE quality of evidence
(Szyszkowicz and Rowe, 2010) Edmonton, Alberta	mean daily concentration at an unstated number of fixed monitoring locations	daily mean 21.9 ppb (41.8 µg/m³)	time-series (120 months)	emergency department visits for chest pain and weakness	association with PM_{10}, $PM_{2.5}$, SO_2, O_3, CO, & NO_2	male & female 68,714 chest pain cases 66,092 weakness cases	relative risk for chest pain per 12.8 ppb (24.4 µg/m³) change in a single pollutant model (lag day 0) all seasons, all patients - 2.6 all seasons, female patients - 3.3 all seasons, male patients - 2.4 warm seasons, all patients - 2.9 warm seasons, male patients - 3.8 cold seasons, all patients - 1.7 cold seasons, female patients - 2.8 relative risk for weakness per 12.8 ppb (24.4 µg/m³) change in a single pollutant model (lag day 2) all seasons, all patients - 2.1 all seasons, female patients - 2.1 all seasons, male patients - 2.4 cold seasons, all patients - 2.7 cold seasons, male patients - 3.4 cold seasons, female patients - 2.3	relative risk percentage for chest pain per 12.8 ppb (24.4 µg/m³) change in a single pollutant model (lag day 0) all seasons, all patients - 1.3 - 4.0 all seasons, female patients - 1.4 - 5.2 all seasons, male patients - 0.6 - 4.3 warm seasons, all patients - 0.0 - 5.8 warm seasons, male patients - 0.0 - 7.8 cold seasons, all patients - 0.1 - 3.4 cold seasons, female patients - 0.5 - 5.1 relative risk percentage for weakness per 12.8 ppb (24.4 µg/m³) change in a single pollutant model (lag day 2) all seasons, all patients - 0.7 - 3.6 all seasons, female patients - 0.2 - 4.0 all seasons, male patients - 0.5 - 4.4 cold seasons, all patients - 1.0 - 4.5 cold seasons, male patients - 1.0 - 5.9 cold seasons, female patients - 0.1 - 4.6	statistically significant association with admissions for chest pain in warm, cold, and both seasons for all patients but differential associations observed for men and women in warm and cold seasons; statistically significant associations observed for women but not men or all patients on lag day 1 (data not shown) as well as lag day 0; statistically significant associations for weakness on lag day 2 but not 0 or 1 for males, females and all patients; statistically significant association for weakness during cold but not warm seasons for males and females on lag day 2 only	⊕○○○ (insufficient because of bias from the use of a unstated number of monitoring sites and publication and imprecision with wide confidence intervals)

author / location	exposure monitoring	NO_2 concentration	study type (duration)	endpoint	co-pollutants	participants	ratio or risk	confidence interval	results	GRADE quality of evidence
(Szyszkowicz and Tremblay, 2011) Edmonton, Alberta	mean daily concentration at a single fixed monitoring locations	daily mean 21.9 ppb (41.8 µg/m³)	case-crossover (120 months)	emergency department visits for depression by adult females	association with control day separation, SO_2, CO & NO_2	female 15,556 cases	odds ratio per IQR of 12.8 ppb (24.5 µg/m³) in a two pollutant model for the stated number of days separating the case day from the control day linear spline (NO_2 + SO_2) 8 days - 1.057 all except day 6 - 1.047 linear spline (NO_2 + CO) 3 days - 1.070 4 days - 1.080 8 days - 1.099 all except day 6 - 1.090 natural spline (NO_2 + SO_2) all except day 6 - 1.046	odds ratio per IQR of 12.8 ppb (24.5 µg/m³) in a two pollutant model for the stated number of days separating the case day from the control day linear spline (NO_2 + SO_2) 8 days 1.000 - 1.117 all except day 6 1.002 - 1.094 linear spline (NO_2 + CO) 3 days 1.000 - 1.144 4 days 1.008 - 1.156 8 days 1.021 - 1.182 all except day 6 1.019 - 1.166 natural spline (NO_2 + SO_2) all except day 6 1.000 - 1.095	statistically significant association emergency department visits for depression in a single and two-pollutant model using different techniques for seasonal adjustment and different time intervals for the identification of control periods in the case-crossover design; single pollutant model yielded far more statistically significant results than the two pollutant model; linear adjustment for seasonality yielded more statistically significant results than the natural spline; statistically significant association were observed for some 20 year age groups depending on the control day interval that was selected	⊕◯◯◯ (insufficient because of severe exposure bias)

author / location	exposure monitoring	NO_2 concentration	study type (duration)	endpoint	co-pollutants	participants	ratio or risk	confidence interval	results	GRADE quality of evidence
(Szyszkowicz *et al.*, 2009a) Edmonton, Alberta Halifax, Nova Scotia Ottawa, Ontario Montreal, Quebec Toronto, Ontario Vancouver, British Columbia	mean daily concentration at an unstated number of fixed monitoring locations within six cities	daily mean (all cities) 20.2 ppb (38.6 µg/m³)	time-series (129 months)	emergency department visits for migraine or headache	association with PM_{10}, $PM_{2.5}$, SO_2, O_3, CO, & NO_2	male & female 64,839 migraine cases 68,498 headache cases	relative risk percentage for migraine per 20.2 ppb (38.6 µg/m³) change in a single pollutant model comparing unexposed and exposed groups (lag day 0) all seasons, all patients - 3.9 warm seasons, all patients - 6.9 all seasons, male patients - 4.1 warm seasons, male patients - 13.5 all seasons, female patients - 3.7 relative risk percentage for migraine per 20.2 ppb (38.6 µg/m³) change in a single pollutant model comparing unexposed and exposed groups (lag day 1) warm seasons, male patients - 7.2	relative risk percentage for migraine per 20.2 ppb (38.6 µg/m³) change in a single pollutant model comparing unexposed and exposed groups (lag day 0) all seasons, all patients 1.7 - 6.2 warm seasons, all patients 2.8 - 11.4 all seasons, male patients 0.7 - 7.6 warm seasons, male patients 6.7 - 20.7 all seasons, female patients 0.7 - 6.8 relative risk percentage for migraine per 20.2 ppb (38.6 µg/m³) change in a single pollutant model comparing unexposed and exposed groups (lag day 1) warm seasons, male patients 0.8 - 14.1	statistically significant association with headache but not migraine; associations generally occurred for a same day lag period for either the whole season or warm season analysis ; associations more common in comparisons with all patients or males only, rather than females only	⊕○○○ (insufficient because of bias from the use of a unstated number of monitoring sites)
(Szyszkowicz *et al.*, 2009b) Edmonton, Alberta Halifax, Nova Scotia Ottawa, Ontario Montreal, Quebec Toronto, Ontario Vancouver, British Columbia	mean daily concentration at an unstated number of fixed monitoring locations within six cities	daily mean (all cities) 20.1 ppb (38.4 µg/m³)	time-series (129 months)	emergency department visits for depression	association with PM_{10}, $PM_{2.5}$, SO_2, O_3, CO, & NO_2	male & female 27,047 visits	relative risk percentage per 20.1 ppb (38.4 µg/m³) change in a single pollutant model comparing unexposed and exposed groups (lag day 0) all seasons - 10.0 warm seasons - 20.0 cold seasons - 6.4	relative risk percentage per 20.1 ppb (38.4 µg/m³) change in a single pollutant model comparing unexposed and exposed groups (lag day 0) all seasons 6.6 - 13.6 warm seasons 13.3 - 27.2 cold seasons 2.1 - 10.8	statistically significant association with short-term exposures in all climatic seasons; associations with NO_2 parallel those observed with CO;	⊕⊕○○ (low quality because of bias from single pollutant model)

author / location	exposure monitoring	NO_2 concentration	study type (duration)	endpoint	co-pollutants	participants	ratio or risk	confidence interval	results	GRADE quality of evidence
(Szyszkowicz *et al.*, 2012) Edmonton, Canada	daily average concentration from three fixed monitoring sites	daily mean 21.9 ppb (41.8 µg/m³)	case-crossover (10 years)	emergency department visits for hypertension	association with PM_{10}, $PM_{2.5}$, CO, O_3, SO_2, & NO_2	males and females 5365 cases	odds ratio per IQR of 12.8 ppb (24.4 µg/m³) in single pollutant model using single and cumulative lag periods up to seven days lag day 3 - 1.06 lag day 02 - 1.08 lag day 03 - 1.07	odds ratio per IQR of 12.8 ppb (24.4 µg/m³) in single pollutant model using single and cumulative lag periods up to seven days lag day 3 1.00 - 1.12 lag day 02 1.01 - 1.15 lag day 03 1.00 - 1.14	statistically significant association with emergency dept visits for hypertension on lag day 3 and cumulative lags 02 and 03, no statistical significance on all the seven other single lag days and six other cumulative lag days	⊕⊕◯◯ (low quality because of using a single pollutant model only)
(Szyszkowicz, 2008a) Edmonton, Alberta	mean daily concentration at an unnamed number of fixed monitoring locations	daily mean 21.9 ppb (41.8 µg/m³)	time-series (120 months)	emergency department visits for asthma	association with PM_{10}, $PM_{2.5}$, O_3, SO_2, CO, & NO_2	male & female 62,563 visits	percent change in relative risk per IQR for lag day 2 (12.8 ppb; 24.5 µg/m³) age < 10 yrs total whole year - 5.3 male all year - 5.5 total warm season - 16.1 female warm season - 12.6 male warm season - 19.2 age ≥ 10 years female warm season - 6.2	percent change in relative risk per IQR for lag day 2 (12.8 ppb; 24.5 µg/m³) age < 10 yrs total whole year 2.2 - 8.5 male all year 1.8 - 9.2 total warm season 9.5 - 23.0 female warm season 2.8 - 23.3 male warm season 11.4 - 27.6 age ≥ 10 years female warm season 1.4 - 11.3	statistically significant associations in a single pollutant model at lag 2, but not lag day 0 or 1; associations more prominent in children than teenagers or adults; no statistically significant associations during winter months (Oct-Mar);	⊕◯◯◯ (insufficient because of exposure bias and single pollutant modelling only)

author / location	exposure monitoring	NO_2 concentration	study type (duration)	endpoint	co-pollutants	participants	ratio or risk	confidence interval	results	GRADE quality of evidence
(Szyszkowicz, 2008b) Edmonton, Alberta	mean daily concentration at three fixed monitoring locations	daily mean 21.9 ppb (41.8 µg/m³)	time-series (120 months)	short-term effect on emergency department visits for acute ischemic stroke	association with SO_2, O_3, CO & NO_2	male & female 10,881 visits	relative risk percentage per IQR 12.8 ppb (24.4 µg/m³) in a single pollutant model (lag day 0-2) group age 20-64 years all seasons & all genders - 6.3 all seasons & females - 12.4 cold seasons & females - 13.8 group age 65-100 years old warm season & all genders - 8.2	relative risk percentage per IQR 12.8 ppb (24.4 µg/m³) in a single pollutant model (lag day 0-2) group age 20-64 years all seasons & all genders 0.2 - 12.8 all seasons & females 2.9 - 22.7 cold seasons & females 2.1 - 26.7 group age 65-100 years old warm season & all genders 0.4 - 16.7	statistically significant association ED visits for ischemia in females but not males aged 20-64 years for all seasons and cold season but not the warm season; statistically significant association for males & females together aged 20-64 years for all seasons and the warm season but not the cold season; statistically significant association for elderly (aged 65-100 years) males and females during the warm season; no association for elderly males or elderly females for all seasons or the cold seasons	⊕○○○ (insufficient because of serious inconsistencies and the bias from the use of a single pollutant model)
(Tolbert *et al.*, 2007) Atlanta, Georgia	1-hr maximum for an unstated number of monitoring sites	average 1-hr maximum 43.2 ppb (82.5 µg/m³)	time-series (10 years)	cardiovascular & respiratory emergency department visits	association with PM_{10}, $PM_{10-2.5}$(course), $PM_{2.5}$, $PM_{2.5}$ sulfate, $PM_{2.5}$ EC, $PM_{2.5}$ OC, $PM_{2.5}$ TC, $PM_{2.5}$ soluble metals, oxygenated hydrocarbons, SO_2, CO, O_3, & NO_2	male and females 238,360 cardiovascular visits 1,072,429 respiratory visits	relative risk per IQR 23.0 ppb (43.9 µg/m³) in single and two-pollutant models with a 0-2 day average lag cardiovascular NO_2 only - 1.015 respiratory NO_2 only - 1.015 NO_2/CO ≈ 1.012 (depicted graphically)	relative risk per IQR 23.0 ppb (43.9 µg/m³) in single and two-pollutant models with a 0-2 day average lag cardiovascular NO_2 only 1.004 - 1.025 respiratory NO_2 only 1.004 - 1.025 NO_2/CO ≈ 1.008 - 1.029 (depicted graphically)	statistically significant association with emergency room visits for cardiovascular and respiratory diseases in a single pollutant model at an 0-1 lag period; statistically significant association for respiratory visits in a two pollutant model with CO; no association with respiratory visits in a two pollutant model with PM_{10} or O_3 and a three pollutant model PM_{10} & O_3; no association with cardiovascular visits in a two pollutant model with CO or $PM_{2.5}$ TC and a three pollutant model with $PM_{2.5}$ TC & CO;	⊕⊕○○ (low quality because of bias from the use of a unstated number of monitoring sites)

author / location	exposure monitoring	NO_2 concentration	study type (duration)	endpoint	co-pollutants	participants	ratio or risk	confidence interval	results	GRADE quality of evidence
(Tramuto *et al.*, 2011) Palermo, Italy	mean daily concentration at ten fixed monitoring locations	daily mean 41.5 µg/m³	case-crossover (48 months)	emergency department visits for respiratory symptoms (respiratory deficiency, emphysema, dyspnea, cough, asthma, pneumonia, bronchopathy, & obstructive pulmonary disease)	association with PM_{10}, O2, CO & NO_2	male & female 48,519 visits	adjusted odds ratio per 10 µg/m³ change in a single pollutant model (no lag) all seasons - 1.015 warm season - 1.043	adjusted odds ratio per 10 µg/m³ change in a single pollutant model (no lag) all seasons 1.004 - 1.026 warm season 1.021 - 1.065	statistically significant association with respiratory symptoms among all patients for all seasons, and the warm season but not the cold season in a single pollutant model with no lag; statistically significant associations observed for lag day 0 or 1 but 2, 3, 4, or 5 (values not presented); statistically significant association observed in some age groups (55-64, 65-74, 75-84 years old) for either all subjects, males only or females only (values not presented); associations in age stratified groups not uniformly distributed across age groups or gender type but the associations were restricted to all seasons or the warm seasons	⊕○○○ (insufficient because of publication bias with no lag period specified and very serious and the bias from the use of a single pollutant model
(Vencloviene *et al.*, 2011) Kaunas, Lithuania	mean daily concentration at three fixed monitoring locations	daily mean 34.6 µg/m³	case-crossover (36 months)	myocardial infarction & unstable angina pectoris (emergency room visit)	interaction study (NO_2 & geomagnetic activity)	male & female cases 6,594	IQR (19.05 µg/m³ NO_2) rate ratios NO_2 - 1.21 NO_2 & geomagnetic - 1.54	IQR (19.05 µg/m³ NO_2) rate ratios NO_2 0.96 - 1.53 NO_2 & geomagnetic 0.99 - 2.40	associations observed for patients < 65 years of age, but not with those >65 years old; risk of emergency hospitalization for those below 65 increased by 61% (for 19.1 µg/m³ increase) after extremely high or low geomagnetic activity	⊕○○○ (insufficient because of inconsistencies across age groups and bias from the small number of cases and short duration)

author / location	exposure monitoring	NO_2 concentration	study type (duration)	endpoint	co-pollutants	participants	ratio or risk	confidence interval	results	GRADE quality of evidence
(Villeneuve *et al.*, 2006) Edmonton, Alberta	daily average from three fixed monitoring sites	daily mean concentration 24.0 ppb (45.8 µg/m³)	case-crossover (11 years)	ED visits for acute ischemic, hemorrhagic, transient cerebral ischemic or other types of stroke in three elderly age groups	association with PM_{10}, $PM_{2.5}$, SO_2, O_3, CO, & NO_2	male and female adults ≥ 65 years of age 65 - < 75 yrs of age - 5435 visits 75 - < 85 yrs of age - 5129 visits > 85 yrs of age - 1858 visits	adjusted odds ratio for acute ischemic stroke per IQR of 13.5 ppb (25.8 µg/m³) in single pollutant model for the summer months 0 day lag - 1.17 1 day lag - 1.18 02 day lag - 1.26	adjusted odds ratio for acute ischemic stroke per IQR of 13.5 ppb (25.8 µg/m³) in single pollutant model for the summer months 0 day lag 1.05 - 1.31 1 day lag 1.05 - 1.32 02 day lag 1.09 - 1.46	statistically significant association with acute ischemic stroke(AIS) in single pollutant model during warm, but not cool, seasons using all three lag periods, stratification by sex showed a statistically significant association with AIS in females but not females > 65 years of age, no statistically significant associations with AIS in two-pollutant models with SO_2, CO, O_3, PM_{10}, or $PM_{2.5}$ for lag day O_2, no statistically significant association with hemorrhagic or transient cerebral ischemic stroke in warm or cold season or for male or female subgroups	⊕⊕◯◯ (low quality because of the small number of cases)

author / location	exposure monitoring	NO_2 concentration	study type (duration)	endpoint	co-pollutants	participants	ratio or risk	confidence interval	results	GRADE quality of evidence
(Villeneuve *et al.*, 2007) Edmonton, Alberta	daily average from three fixed monitoring sites	daily mean concentration summer – 17.5 ppb (33.4 µg/m³) winter – 28.5 ppb (54.4 µg/m³)	case-crossover (11 years)	ED visits for asthma and COPD in seven age groups	association with PM_{10}, $PM_{2.5}$, SO_2, O_3, CO, & NO_2	males & females in seven age groups (total 57,912 visits) 2 - 4 years - 7247 visits 5 -14 years - 13,145 visits 15 -24 years - 11,616 visits 25 - 44 years - 13,300 visits 45 - 64 years - 7899 visits 65 - 74 years - 2850 visits ≥ 75 years - 1855 visits	adjusted odds ratio for asthma ED visits in different age groups per IQR of 13. 5 ppb (25.8 µg/m³) for summer months (Apr-Sept) in a single pollution model 2 - ≥ 75 years lag 1 day - 1.07 lag 02 day - 1.09 lag 05 day - 1.14 2 - 4 years lag 1 day - 1.24 lag 02 day - 1.32 lag 05 day - 1.50 5 - 14 years lag 1 day - 1.08 lag 05 day - 1.13 15 - 44 years lag 02 day - 1.07 lag 05 day - 1.10 ≥ 75 years lag 02 day - 1.33 lag 05 day - 1.37	adjusted odds ratio for asthma ED visits in different age groups per IQR of 13. 5 ppb (25.8 µg/m³) for summer months (Apr-Sept) in a single pollution model 2 - ≥ 75 years lag 1 day 1.03 - 1.10 lag 02 day 1.04 - 1.13 lag 05 day 1.09 - 1.20 2 - 4 years lag 1 day 1.13 - 1.35 lag 02 day 1.18 - 1.48 lag 05 day 1.31 - 1.71 5 - 14 years lag 1 day 1.01 - 1.15 lag 05 day 1.02 - 1.24 15 - 44 years lag 02 day 1.00 - 1.14 lag 05 day 1.02 - 1.19 ≥ 75 years lag 02 day 1.03 - 1.70 lag 05 day 1.02 - 1.84	Statistically significant association with asthma ED visits in those aged 2 to ≥ 75 yrs of age for all lag periods except lag day 0 in a single pollutant model during summer months; statistically significant association in 4 of 6 age groups for at least two of the four lag periods investigated; no association in age groups in those aged 45- 64 and 65 -75; association generally confined to the summer months and all seasons with no statistically significant findings for the winter months (Oct - Mar); two pollutant modelling for the 05 day average lag revealed that the single pollutant results were not robust to CO for 5 of the 6 age groupings with the 2-4 year age group being the only population showing statistically significant results	⊕⊕◯◯ (low quality because of inconsistent seasonal findings)
(Wilhelm *et al.*, 2008) Los Angeles and San Diego counties, CA	annual averages from eight fixed monitoring sites	annual average 3 pphm (57.3 µg/m³)	cross-sectional (24 months)	asthma morbidity including symptom reporting (cough, wheeze, shortness of breath, chest tightness, or phlegm) or emergency department visits	association PM_{10}, $PM_{2.5}$, CO, O_3, & NO_2	male & female aged 0-17 yrs 617 children	no association for daily/weekly symptoms or ED visits in an adjusted single pollutant model per 1 pphm (19.1 µg/m³)	no association for daily/weekly symptoms or ED visits in an adjusted single pollutant model per 1 pphm (19.1 µg/m³)	no statistically significant association with symptom recording or emergency department visit in an adjusted single pollutant model	⊕◯◯◯ (insufficient because of short duration and the bias from using survey questionnaire)

author / location	exposure monitoring	NO_2 concentration	study type (duration)	endpoint	co-pollutants	participants	ratio or risk	confidence interval	results	GRADE quality of evidence
(Yamazaki *et al.*, 2009) Ichikawa, Japan	hourly mean concentration at a single monitoring site (grouped into 6-hr nighttime and 8-hr daytime metrics)	mean warm months (Apr-Sept) 16.9 ppb (32.3 µg/m³) mean cold months (Oct-Mar) 27.2 ppb (52.0 µg/m³)	case-crossover (12 months)	nighttime visits emergency clinic for asthma attack	association with $PM_{2.5}$, O_3 & NO_2	male & female 403 visits	odds ratio per 10 ppb (19.1 µg/m³) increment children 6-14 yrs (lag 6-12 hr) - 1.73 children 6-14 yrs (daytime NO_2) - 1.83	odds ratio per 10 ppb (19.1 µg/m³) increment children 6-14 yrs (lag 6-12 hr) 1.02 - 2.93 children 6-14 yrs (daytime NO_2) 1.05 - 3.20	weak association observed with adolescents, but not adults or young children using single pollutant model; no association using multipollutant model; associations found for warm but not cold months	⊕◯◯◯ (insufficient because of severe exposure bias)
(Zemek *et al.*, 2010) Edmonton, Alberta	seasonal averages from three fixed monitoring sites	seasonal average all months – 21.9 ppb (41.8 µg/m³) warm months – 16.5 ppb (31.5 µg/m³) cold months – 27.2 ppb (52.0 µg/m³)	case-crossover (120 months)	emergency department visits for otitis media	association with PM_{10}, $PM_{2.5}$, O_3, CO, SO_2, & NO_2	male and female children (1-3 yrs of age) 14,527 ED visits	odds ratio per IQR 12.8 ppb (24.4 µg/m³) for all patients in single pollutant model lag day 2 all months - 1.05 warm months - 1.10 cold months - 1.03 lag day 3 warm months - 1.08 odds ratio per IQR 12.8 ppb (24.4 µg/m³) for females lag day 2 all months - 1.06 warm months - 1.20 lag day 3 warm months - 1.14	odds ratio per IQR 12.8 ppb (24.4 µg/m³) for all patients in single pollutant model lag day 2 all months 1.01 - 1.08 warm months 1.02 - 1.19 cold months 1.00 - 1.07 lag day 3 warm months 1.00 -1.17 odds ratio per IQR 12.8 ppb (24.4 µg/m³) for females lag day 2 all months 1.01 - 1.11 warm months 1.06 - 1.34 lag day 3 warm months 1.02 - 1.29	statistically significant association in all patients and all seasons using a single pollutant model with a day lag, significant associations also observed for a 3 day lag in warm months, statistically significant association with females on lag day 2 for all months or warm months and with females on lag day 3 for warm months, no statistical y significant associations found for males in any season, negative associations observed in two-pollutant model with CO	⊕⊕◯◯ (low quality because of inconsistencies bias from single pollutant model)

Acute Hospital Admissions

author / location	exposure monitoring	NO_2 concentration	study type (duration)	endpoint	co-pollutants	participants	ratio or risk	confidence interval	results	GRADE quality of evidence
(Andersen *et al.*, 2007) Copenhagen, Denmark	daily average from a single fixed monitoring site	daily mean concentration 12 ppb (22.9 µg/m³)	time-series (6 years)	hospital admission of children (asthma) and the elderly (cardiovascular and respiratory disease)	association with PM_{10}, CO, & NO_2	male & female daily admissions cardiovascular (≥ 65 yrs) - 53 respiratory (≥ 65 yrs) - 21 asthma (5-18 yrs) - 3	adjusted relative risk for hospitalization per IQR 7 ppb (13.4 µg/m³) in single and two pollutant model respiratory lag 04 - 1.040 asthma lag 05 - 1.128	adjusted relative risk for hospitalization per IQR 7 ppb (13.4 µg/m³) ins ingle and two pollutant model respiratory lag 04 1.009 - 1.072 asthma lag 05 1.029 - 1.235	statistically significant association for respiratory disease (lag04) and asthma (lag05) admissions in a single pollutant model but not in a two pollutant model with PM_{10}; statistically significant association respiratory admission on lag days 2, 3, & 4 in single pollutant models and cardiovascular admission on lag day 3; no association with cardiovascular (lag03)admissions in single or two pollutant model with PM_{10}	⊕◯◯◯ (insufficient because of very serious risk of exposure bias)
(Andersen *et al.*, 2008) Copenhagen, Denmark	daily average from a single fixed monitoring site	daily mean concentration 11 ppb (21.0 µg/m³)	time-series (3.5 years)	hospital admission of children (asthma) and the elderly (cardiovascular and respiratory disease)	association with PM_{10}, $PM_{2.5}$, UFP (total number conc.), CO, O_3, & NO_2	male & female daily admissions cardiovascular (≥ 65 yrs) - 59 respiratory (≥ 65 yrs) - 22 asthma (5-18 yrs) - 3	adjusted relative risk for hospitalization per IQR 6 ppb (11.5 µg/m³) ins ingle and two pollutant model respiratory lag 04 - 1.06	adjusted relative risk for hospitalization per IQR 6 ppb (11.5 µg/m³) in single and two pollutant model respiratory lag 04 1.01 - 1.12	statistically significant association for respiratory disease admission in single pollutant model (lag04) but not in a two pollutant model with UFP (total number count); no association with cardiovascular (lag03) or asthma (lag05) admissions in single or two pollutant model with UFP (total number count)	⊕◯◯◯ (insufficient because of very serious risk of exposure bias)

author / location	exposure monitoring	NO_2 concentration	study type (duration)	endpoint	co-pollutants	participants	ratio or risk	confidence interval	results	GRADE quality of evidence
(Ballester *et al.*, 2006) 14 Spanish cities	daily average from an unstated number of fixed monitoring sites in each city	daily mean ranged from 23.1 µg/m³ in Castellon to 76.2 µg/m³ in Valencia	time-series (3-6 years)	hospital admissions for cardiovascular or heart disease	association with PM_{10}, TSP, BS, SO_2, O_3, CO, & NO_2	male & female daily mortality rates cardiovascular ranged from 4.4 (Oviedo) to 35.7 (Barcelona) heart disease ranged from 2.2 (Pamplona) to 20.7 (Barcelona)	pooled relative risk for combined cardiovascular and cardiac disease per 10 µg/m³ increase in a two pollutant model revealed that the association observed for NO_2 was not robust to either particulates (PM_{10}, TSP, or BS) or SO_2, but remained robust to CO (marginally) and O_3 (data presented graphically) pooled (fixed effect) percent increase in hospital admissions per IQR 10 µg/m³ in single and two pollutant model for average lag 01 cardiovascular disease NO_2 only ≈ 0.38 heart disease NO_2 only ≈ 0.86	pooled relative risk for combined cardiovascular and cardiac disease per 10 µg/m³ increase in a two pollutant model revealed that the association observed for NO_2 was not robust to either particulates (PM_{10}, TSP, or BS) or SO_2, but remained robust to CO (marginally) and O_3 (data presented graphically) pooled (fixed effect) percent increase in hospital admissions per IQR 10 µg/m³ in single and two pollutant model for average lag 01 cardiovascular disease NO_2 only 0.07 - 0.69 heart disease NO_2 only 0.44 - 1.28	statistically significant association with hospital admissions for cardiovascular and heart disease in a single pollutant model at avg lag 01 and in a two pollutant model (combined admissions) with CO and O_3, but not "particulates" or O_3	⊕⊕◯◯ (low quality because of bias from the use of an unstated number of monitoring sites)

author / location	exposure monitoring	NO_2 concentration	study type (duration)	endpoint	co-pollutants	participants	ratio or risk	confidence interval	results	GRADE quality of evidence
(Barnett *et al.*, 2005) Australia Brisbane Canberra Melbourne Perth Sydney New Zealand Christchurch Auckland	1-hr and 24-hr values from 0-9 fixed monitoring sites	daily averages Brisbane – 7.6 ppb (14.5 µg/m³) Canberra – 7.0 ppb (13.4 µg/m³) Melbourne - 11.7 ppb (22.4 µg/m³) Perth – 9.0 ppb (17.2 µg/m³) Sydney - 11.5 ppb (22.0 µg/m³) Christchurch - 7.1 ppb (13.6 µg/m³) Auckland - 10.2 ppb (19.5 µg/m³)	case-crossover (4 years)	hospital admissions of children for respiratory distress, asthma, and pneumonia plus acute bronchitis in three age groups	association with PM_{10}, $PM_{2.5}$, UFP, O_3, SO_2, & NO_2	male and female children ≤ 14 years of age dally admission rate ranges respiratory - 1.4 - 7.9 asthma – 0.9 - 2.2 pneumonia - 0.6 - 3.6	pooled percent increase in admission rate per IQR of 9.0 ppb (17.2 µg/m³) for 1-hr values and 5.1 ppb (9.7 µg/m³) for 24-hr measurements on lag days 01 single pollutant model-respiratory 1-4 yrs age (1-hr NO_2) - 2.8 5-14 yrs age (1-hr NO_2) - 4.7 5-14 yrs age (24-hr NO_2) - 5.8 single pollutant model - asthma 5-14 yrs age (24-hr NO_2) - 6.0 two pollutant model - respiratory 1-4 yrs age (1-hr NO_2) $NO_2/PM_{2.5}$ - 8.5 5-14 yrs age (24 hr NO_2) NO_2/PM_{10} - 6.4	pooled percent increase in admission rate per IQR of 9.0 ppb (17.2 µg/m³) for 1-hr values and 5.1 ppb (9.7 µg/m³) for 24-hr measurements on lag days 01 single pollutant model-respiratory 1-4 yrs age (1-hr NO_2) 0.7 - 4.9 5-14 yrs age (1-hr NO_2) 1.6 - 7.9 5-14 yrs age (24-hr NO_2) 1.7 - 10.1 single pollutant model - asthma 5-14 yrs age (24-hr NO_2) 0.2 - 12.1 two pollutant model - respiratory 1-4 yrs age (1-hr NO_2) $NO_2/PM_{2.5}$ 0.7 - 16.9 5-14 yrs age (24 hr NO_2) NO_2/PM_{10} 3.0 - 9.8	statistically significant association of 1-hr or 24 hr NO_2 exposures with hospital admissions in children pooled from 7 cites for respiratory effects (two age groups) and asthma (one age group) using a single pollutant model, statistically significant association with respiratory admissions in two pollutant model with PM_{10} (one age group or $PM_{2.5}$ (one age group), statistically significant association with 1-hr or 24-hr NO_2 levels and respiratory admission during cool season (one age group) or warm seasons (one age group), no statistically significant association with pneumonia in either of three age groups, no statistically significant association with any of three pulmonary conditions in children less than a year old	⊕⊕◯◯ (low quality because of imprecision caused by heterogeneity and/or inconsistency from multiple comparisons)

author / location	exposure monitoring	NO_2 concentration	study type (duration)	endpoint	co-pollutants	participants	ratio or risk	confidence interval	results	GRADE quality of evidence
(Chang *et al.*, 2005) Taipei, Taiwan	daily average from six fixed monitoring site	daily mean concentration 31.54 ppb (60.2 µg/m³)	case-crossover (5 years)	hospital admissions for cardiovascular disease	association with PM_{10}, SO_2, O_3, CO, & NO_2	total admissions of 74,509 mean daily hospital admission rates cardiovascular disease 40.80	odds ratio for cardiovascular disease admissions per IQR of 9.95 ppb (19.0 µg/m³) at two temperature limits in a two pollutant model at an average lag of 3 days (lag02) temp ≥ 20° C NO_2/PM_{10} - 1.194 NO_2/SO_2 - 1.279 NO_2/CO - 1.145 NO_2/O_3 - 1.165 temp < 20° C NO_2/SO_2 - 1.166 NO_2/CO - 1.126 NO_2/O_3 - 1.125	odds ratio for cardiovascular disease admissions per IQR of 9.95 ppb (19.0 µg/m³) at two temperature limits in a two pollutant model at an average lag of 3 days (lag02) temp ≥ 20° C NO_2/PM_{10} 1.159 - 1.230 NO_2/SO_2 1.244 - 1.315 NO_2/CO 1.106 - 1.186 NO_2/O_3 1.136 - 1.194 temp < 20° C NO_2/SO_2 1.095 - 1.241 NO_2/CO 1.046 - 1.213 NO_2/O_3 1.066 - 1.187	statistically significant association with hospital admissions for cardiovascular disease in a two pollutant model with PM_{10}, SO_2, CO and O_3 at high temperatures greater than or equal to 20°C; same significant associations at temperatures below 20° C for all co-pollutants except PM_{10}	⊕⊕◯◯ (low quality because of inconsistencies and potential modelling error stemming from the use of SAS)
(Chen *et al.*, 2010) Shanghai, China	daily average from six fixed monitoring sites	daily mean concentration 57 µg/m³	time-series (3 years)	total, cardiovascular & respiratory hospital admissions	association with PM_{10}, SO_2, & NO_2	total admissions of 1,702,180 mean daily hospital admission rates total – 1555 cardiovascular - 340 respiratory - 123	percent increase in admissions per IQR of 10 µg/m³ in single pollutant model total admissions lag day 4 - 0.97 lag day 5 - 0.99 cardiovascular lag day 4 - 1.23 lag day 5 - 0.80 lag days 06 - 1.54	percent increase in admissions per IQR of 10 µg/m³ in single pollutant model total admissions lag day 4 0.07 - 1.87 lag day 5 0.10 - 1.88 cardiovascular lag day 4 0.53 - 1.93 lag day 5 0.10 - 1.49 lag days 06 0.38 - 2.69	statistically significant association with total and cardiovascular admission rates on lag days 4 & 5 but not for the 4 shorter lag days using a single pollutant model, no associations with respiratory admission rates for any lag period; associations were confined to the cold season, with no significance in the warm season, two pollutant modelling with PM_{10} did not cause any change; however the significant associations for total and cardiovascular admissions on lag day 5 became non-significant after two-pollutant modelling with SO_2; J-shaped exposure response function observed	⊕⊕⊕◯ (moderate quality after decreasing for lag inconsistencies and increasing for the availability of dose response information)

author / location	exposure monitoring	NO_2 concentration	study type (duration)	endpoint	co-pollutants	participants	ratio or risk	confidence interval	results	GRADE quality of evidence
(Grineski *et al.*, 2010) Phoenix, Arizona	8-hr mean value from four fixed monitoring locations	8-hr average for evening hours (4 -11 PM) 46 ppb (87.9 µg/m³)	time-series (36 months)	hospitalization of children for asthma	interaction study (race, ethnicity, insurance type & NO_2)	male & female (14 years of age or younger) 16,413 admissions	relative risk for specific subgroup comparisons (condition/reference group) per 20 ppb (38.2 µg/m³) exceedance above seasonal mean lag day 1 no insurance/private insurance - 1.39 no insurance/Medicaid - 1.38 Hispanic no insurance/Hispanic private - 1.94 Hispanic no insurance/Hispanic Medicaid - 1.90 lag day 2 black private/white private - 1.27 black private/Hispanic private - 1.34 lag day 0 Hispanic no insurance/white no insurance - 2.06	relative risk for specific subgroup comparisons (condition/reference group) per 20 ppb (38.2 µg/m³) exceedance above seasonal mean lag day 1 no insurance/private insurance 1.07 - 1.81 no insurance/Medicaid 1.06 - 1.80 Hispanic no insurance/Hispanic private 1.26 - 2.99 Hispanic no insurance/Hispanic Medicaid 1.25 - 2.90 lag day 2 black private/white private 0.99 - 1.63 black private/Hispanic private 1.02 - 1.77 lag day 0 Hispanic no insurance/white no insurance 1.13 - 3.76	statistically significant association with those having no insurance together with exceedance of NO_2 levels relative to those with some type of insurance particularly for Hispanic populations; statistically significant association with blacks having private insurance compared to white or Hispanic with private insurance when the lag was 2 days	⊕⊕◯◯ (low quality because of the serious bias from not evaluating co-pollutants or their interactions)
(Hsieh *et al.*, 2010) Taipei, Taiwan	mean daily concentration at six fixed monitoring locations	daily mean 29.88 ppb (57.1 µg/m³)	case-crossover (132 months)	hospital admissions for myocardial infarction	association with PM_{10}, SO_2, O_3, CO, & NO_2	male & female 23,420 cases	odd ratio change per IQR of 10.44 ppb (19.9 µg/m³ NO_2 in two-pollutant model PM_{10} temp ≥ 23 ˚C - 1.12 temp < 23 ˚C - 1.11 SO_2 temp ≥ 23 ˚C - 1.16 temp < 23 ˚C - 1.18 CO temp ≥ 23 ˚C - 1.09 temp < 23 ˚C - 1.12 O_3 temp ≥ 23 ˚C - 1.09 temp < 23 ˚C - 1.18	odd ratio change per IQR of 10.44 ppb (19.9 µg/m³ NO_2 in two-pollutant model PM_{10} temp ≥ 23 ˚C 1.07 - 1.18 temp < 23 ˚C 1.06 - 1.16 SO_2 temp ≥ 23 ˚C 1.11 - 1.21 temp < 23 ˚C 1.13 - 1.24 CO temp ≥ 23 ˚C 1.03 - 1.15 temp < 23 ˚C - 1.05 - 1.20 O_3 temp ≥ 23 ˚C 1.05 - 1.14 temp < 23 ˚C 1.14 - 1.23	statistically significant associations for myocardial hospital admissions observed in both single pollutant models at both warm and cold temperatures, statistically significant associations in two-pollutant models with PM_{10}, SO_2, CO and O_3 at warm and cold temperatures	⊕⊕◯◯ (low quality because of inconsistencies and potential modelling error stemming from the use of SAS)

author / location	exposure monitoring	NO_2 concentration	study type (duration)	endpoint	co-pollutants	participants	ratio or risk	confidence interval	results	GRADE quality of evidence
(Kalantzi *et al.*, 2011) Magnesia, Greece	daily mean from three fixed monitoring sites	daily mean 30.12 µg/m³	time-series (84 months)	total hospitalizations and those for pulmonary (COPD, asthma, infections, & other) and cardiovascular (ischemic heart disease, heart failure, & other) diseases	association with PM_{10}, CO, SO_2, O_3, NO, NOx, & NO_2	male & female admissions rate respiratory - 2.94 /day cardiovascular - 4.88 /day	no change in risk coefficients in either a single or combined model	no change in risk coefficients in either a single or combined model	no statistically significant association with NO_2; statistically significant associations found for NOx and CO in a combined pollutant models	⊕⊕◯◯ (low quality because the focus on NOx and the exposure bias)
(Ko *et al.*, 2007) Hong Kong, China	daily average at 14 fixed monitoring sites	daily average all seasons – 53.2 µg/m³ cold season (< 20 °C) - 61.7 µg/m³ warm season (≥ 20 °C) - 50.0 µg/m³	time-series (6 years)	hospitalizations for asthma	association with PM_{10}, $PM_{2.5}$, O_3, SO_2, & NO_2	male & females of all ages 69,716 admissions	relative risk per 10 µg/m³ increase in single multi pollutant models for avg lag 04 days single pollutant 0-14 yrs age - 1.039 >14-65 yrs age - 1.018 > 65 yrs age - 1.023 multi-pollutant model NO_2/O_3,SO_2 - 1.014	relative risk per 10 µg/m³ increase in single multi pollutant models for avg lag 04 days single pollutant 0-14 yrs age 1.028 - 1.051 >14-65 yrs age 1.007 - 1.029 > 65 yrs age 1.014 - 1.033 multi-pollutant model NO_2/O_3,SO_2 1.003 - 1.025	statistically significant association with asthma hospitalization in all three age groups using single pollutant model and a cumulative lag of 04 days, statistically significant association for pooled population at all lag times, statistically significant association in three-pollutant model with O_3 and SO_2 but not in two-pollutant model with O_3 alone, higher risk noted for cold season relative to warm	⊕⊕⊕◯ (moderate quality, no adjustment necessary)
(Leitte *et al.*, 2009) Drobeta-Tunu Severin, Romania	pooled mean daily concentration from one fixed monitoring locations	daily mean 11.8 µg/m³	time-series (19 months)	hospital admissions for chronic obstructive pulmonary disease (COPD), asthma, chronic bronchitis	differential effects of TSP, SO_2, & NO_2	953 cases	odds ratio per 10 µg/m³ increment persistent cough using NO_2 outdoors at 1 year - 1.40	no effect on relative risk	no significant associations observed using a single pollutant model	⊕◯◯◯ (insufficient because of severe exposure bias and short duration)

author / location	exposure monitoring	NO_2 concentration	study type (duration)	endpoint	co-pollutants	participants	ratio or risk	confidence interval	results	GRADE quality of evidence
(Liao *et al.*, 2011) Taipei & Kaohsiung, Taiwan	mean daily concentration at nine fixed monitoring locations in two cities	daily mean Taipei - 25.40 ppb (48.5 µg/m³) Kaohsiung - 23.74 ppb (45.3 µg/m³)	time-series (96 months)	asthma hospital admissions rate	respiratory virus infections, PM_{10}, SO_2, O_3, CO & NO_2	male 3406 - 3608/100,000 female 3186 - 3506/100,00	no significant change in odds ratio	no significant change in odds ratio	no association with NO_2 exposure in single pollutant model	⊕◯◯◯ (insufficient because of imprecision from the atypical statistical analysis and use of a single pollutant model)
(Lee *et al.*, 2006) Hong Kong, China	daily average at 9-11 fixed monitoring sites	daily mean concentration 64.7 µg/m³	time-series (6 years)	hospital admissions for children with asthma	association with PM_{10}, $PM_{2.5}$, O_3, SO_2, & NO_2	male and female children ≤ 18 years of age total admissions - 879,384 asthma admissions - 26,663	percent increase in asthma admissions per IQR of 27.1 1 µg/m³ on lag day 3 in single and multi-pollutant models NO_2 only - 9.08 NO_2/PM_{10}/$PM_{2.5}$/SO_2/O_3 - 5.64	percent increase in asthma admissions per IQR of 27.1 1 µg/m³ on lag day 3 in single and multi-pollutant models NO_2 only 7.26 - 10.93 NO_2/PM_{10}/$PM_{2.5}$/SO_2/O_3 3.21 - 8.14	statistically significant association with asthma admissions in children for single and five-pollutant models on lag day 3, statistically significant association in single pollutant models on lag 0, 1, 2, 4, or 5 but percentage change appreciably lower	⊕⊕⊕◯ (moderate quality, no adjustment necessary)

author / location	exposure monitoring	NO_2 concentration	study type (duration)	endpoint	co-pollutants	participants	ratio or risk	confidence interval	results	GRADE quality of evidence
(Lee *et al.*, 2007) Kaohsiung, Taiwan	mean daily concentration at six fixed monitoring locations	daily mean 27.10 ppb (51.8 µg/m³)	case-crossover (9 year)	hospital admissions for congestive heart failure	association with PM_{10}, SO_2, O_3, CO, & NO_2	male and female adults 13,475 admissions	odds ratio per IQR 16.85 ppb (32.2 µg/m³ NO_2) in single and two pollutant models at 02 day lag single pollutant model temp > 25 ˚C - 1.20 temp < 25 ˚C - 1.89 two pollutant model NO_2/PM_{10} temp < 25 ˚C - 1.83 NO_2/SO_2 temp > 25 ˚C - 1.20 temp < 25 ˚C - 2.25 NO_2/CO temp < 25 ˚C - 2.01 NO_2/O_3 temp < 25 ˚C - 1.85	odds ratio per IQR 16.85 ppb (32.2 µg/m³ NO_2) in single and two pollutant models at 02 day lag single pollutant model temp > 25 ˚C 1.03 - 1.39 temp < 25 ˚C 1.65 - 2.16 two pollutant model NO_2/PM_{10} temp < 25 ˚C 1.52 - 2.19 NO_2/SO_2 temp > 25 ˚C 1.02 -1.41 temp < 25 ˚C 1.90 - 2.67 NO_2/CO temp < 25 ˚C 1.64 - 2.46 NO_2/O_3 temp < 25 ˚C 1.61 - 2.12	statistically significant association with admissions for congestive heart failure in warm and cold days using a single pollutant model with a lag of 02 days, statistically significant association with admissions using a two pollutant model with PM_{10}, SO_2, CO, or O_3 on cold days, no statistically significant association on warm days using a two pollutant model except for SO_2	⊕⊕◯◯ (low quality because of inconsistencies and potential modelling error stemming from the use of SAS)
(Luginaah *et al.*, 2005) Windsor, Ontario	daily average concentration from four fixed monitoring sites	daily mean 38.9 ppb (74.3 µg/m³)	time-series and case-crossover (6 years)	hospitalizations for respiratory problems	association with PM_{10}, SO_2, coefficient of haze (COH), total reduced sulfur (TRS) O_3, CO, & NO_2	males and females in three age groups (0 - ≥ 65 years of age) 4214 patients	risk ratio per an unstated IQR increase using case-crossover design with a single pollutant model and a lag period of 2 days females 0-14 years of age - 1.189	risk ratio per an unstated IQR increase using case-crossover design with a single pollutant model and a lag period of 2 days females 0-14 years of age 1.002 - 1.411	statistically significant association with hospitalization for respiratory illness in females aged 0-14 years in a single pollutant model on lag day 2 but not lag day 1 or 3, no statistically significant association in time-series studies for any age group, sex, or lag period, no statistically significant associations with males in any of four age groups for lag periods 1, 2, or 3 days using case-crossover design	⊕◯◯◯ (insufficient because of the small number of cases and no evaluation of co-pollutants)
(Rich *et al.*, 2010) New Jersey	daily average from nine fixed monitoring stations	not provided	case-crossover (36 months)	patient admissions for transmural myocardial infarctions	association with $PM_{2.5}$, O_3, SO_2, CO, & NO_2	male & female 5,864 patients	no statistically significant in relative risk per IQR of 16 ppb (30.6 µg/m³) in a single or two pollutant model with a lag of 0 days	no statistically significant in relative risk per IQR of 16 ppb (30.6 µg/m³) in a single or two pollutant model with a lag of 0 days	no statistically significant association with transmural infarctions on lag day 0 with single or two pollutant model with $PM_{2.5}$	⊕⊕◯◯ (low quality because small number of cases)

author / location	exposure monitoring	NO_2 concentration	study type (duration)	endpoint	co-pollutants	participants	ratio or risk	confidence interval	results	GRADE quality of evidence
(Rosenlund *et al.*, 2008) Rome, Italy	land use regression estimates based on three 1- week measurement periods at 61 sites; LUR used population density, altitude, and distance to roadways with benzene emission data serving as surrogate for some variables	not stated	cohort (36 month)	hospitalizations & mortality (in and outside hospital) amongst survivors of a cardiac event	association with NO_2	male & female 6513 survivors	adjusted relative risk per 10 µg/m³ increment total incidence - 1.03 cases fatal within 28 days - 1.07 outside hospital - 1.08	adjusted relative risk per 10 µg/m³ increment total incidence 1.00 - 1.07 cases fatal within 28 days 1.02 - 1.07 outside hospital 1.02 - 1.13	weak statistically significant association with the total incidence of fatal and nonfatal cardiac events as well as for cases that were fatal within 28 days; associations remained significant for deaths outside the hospital but not for deaths within the hospital; no significant associations with nonfatal hospitalizations	⊕◯◯◯ (insufficient because of the small number of cases and no evaluation of co-pollutants)
(Wellenius *et al.*, 2005) Pittsburgh, Pennsylvania	mean daily concentration at two fixed monitoring locations	daily mean 26.48 ppb (50.6 µg/m³)	case-crossover (13 years)	hospital admissions for congestive heart failure	association with PM_{10}, SO_2, O_3, CO, & NO_2	male and female adults ≥ 65 years of age 55,019 admissions	percentage increase in admissions per IQR of 11 ppb (21.0 µg/m³) in single and two pollutant models on lag day 0 NO_2 only - 4.22 NO_2/PM_{10} - 4.04 NO_2/O_3 - 3.73 NO_2/SO_2 - 3.79	percentage increase in admissions per IQR of 11 ppb (21.0 µg/m³) in single and two pollutant models on lag day 0 NO_2 only 2.61 - 5.85 NO_2/PM_{10} 1.83 - 6.31 NO_2/O_3 2.10 - 5.39 NO_2/SO_2 1.93 - 5.67	statistically significant increase in hospital admissions for congestive heart failure using single and two pollutant models for PM_{10}, O_3, and SO_2 on lag day 0, no statistically significant association in two pollutant mode with CO	⊕⊕◯◯ (low quality because of limited number of modelling sites)

author / location	exposure monitoring	NO_2 concentration	study type (duration)	endpoint	co-pollutants	participants	ratio or risk	confidence interval	results	GRADE quality of evidence
(Yang *et al.*, 2007) Taipei, Taiwan	mean daily concentration at six fixed monitoring locations	daily mean 30.77 ppb (58.8 µg/m³)	case-crossover (8 years)	hospital admissions for asthma	association with PM_{10}, O_3, SO_2, CO, & NO_2	male and female of all ages 25,602 admissions	odds ratio for asthma admission per IQR of 10.05 ppb (19.20 µg/m³) on warm and cold days for single and two pollutant models warm days (≥ 25 °C) NO_2 only - 1.178 NO_2/PM_{10} - 1.328 NO_2/SO_2 - 1.224 NO_2/O_3 - 1.219 cold days (< 25 °C) NO_2 only - 1.128 NO_2/PM_{10} - 1.144 NO_2/SO_2 - 1.219 NO_2/CO - 1.198 NO_2/O_3 - 1.156	odds ratio for asthma admission per IQR of 10.05 ppb (19.20 µg/m³) on warm and cold days for single and two pollutant models warm days (≥ 25 °C) NO_2 only 1.113 - 1.247 NO_2/PM_{10} 1.224 - 1.441 NO_2/SO_2 1.140 - 1.314 NO_2/O_3 1.142 - 1.301 cold days (< 25 °C) NO_2 only 1.076 - 1.182 NO_2/PM_{10} 1.077 - 1.215 NO_2/SO_2 1.150 -1.291 NO_2/CO 1.111 - 1.291 NO_2/O_3 1.102 - 1.212	statistically significant association with asthma hospital admissions in single and two pollutant models with PM_{10}, SO_2, CO, & O_3 on average lag days 02, no significant association in two pollutant model with CO on warm days	⊕⊕⊕◯ (moderate quality, no adjustment necessary)
(Yang *et al.*, 2005) Vancouver, British Columbia	daily average from 31 fixed monitoring sites	daily mean concentration 17.03 ppb (32.5 µg/m³)	time-series (5 years)	hospitalization of elderly patients for COPD	association with PM_{10}, SO_2, O_3, CO, & NO_2	male & female adults ≥ 65 years of age 6027 admissions	relative risk for COPD per IQR of 5.5 ppb (10.5 µg/m³) increase in two and multi-pollutant model for average lag day 0-6 NO_2 only - 1.11 NO_2/O_3 - 1.12 NO_2/SO_2 - 1.12	relative risk for COPD per IQR of 5.5 ppb (10.5 µg/m³) increase in two and multi-pollutant model for average lag day 0-6 NO_2 only 1.04 - 1.20 NO_2/O_3 1.04 - 1.20 NO_2/SO_2 1.02 - 1.24	statistically significant association with COPD hospitalization in single and two pollutant models with O_3 and SO_2 for average 7 day lag period, no association in two pollutant models with PM_{10} & CO; no association in multi-pollutant model with the 4 remaining co-pollutants	⊕⊕◯◯ (low quality because small number of cases)

Asthma

author / location	exposure monitoring	NO_2 concentration	study type (duration)	endpoint	co-pollutants	participants	ratio or risk	confidence interval	results	GRADE quality of evidence
(Akinbami *et al.*, 2010) USA	annual average in each metropolitan county based on values from an unstated number of fixed monitoring sites	quartiles for county wide annual mean 1st – 2.3 - < 11.8 ppb (4.4 - < 22.5 µg/m³) 2nd – 11.8 - < 21.3 ppb (22.5 - < 40.7 µg/m³) 3rd – 21.3 - < 30.8 ppb (40.7 - < 58.8 µg/m³) 4th – 30.8 - 40.2 ppb (58.8 - 76.8 µg/m³)	cross-sectional (48 months)	survey of current asthma and asthma attack in last year	association with PM_{10}, $PM_{2.5}$, O_3, SO_2 & NO_2	male & female 34,073 children aged 3-17 years	no change in odds ratio with crude or adjusted determinations of current asthma or asthma attack in single pollutant model with continuous or quartile comparison	no change in odds ratio with crude or adjusted determinations of current asthma or asthma attack in single pollutant model with continuous or quartile comparison	no statistically significant change in crude or adjusted odds ratio for current asthma or asthma attack using a single pollutant model; analysis as a continuous metric or by quintiles did not reveal any associations	⊕⊕◯◯ (low quality after decreasing for single pollutant model and cross-sectional design then increasing for the availability of dose response information)
(Andersen *et al.*, 2007) Copenhagen, Denmark	daily average from a single fixed monitoring site	daily mean concentration 12 ppb (22.9 µg/m³)	time-series (6 years)	hospital admission of children (asthma) and the elderly (cardiovascular and respiratory disease)	association with PM_{10}, CO, & NO_2	male & female daily admissions cardiovascular (≥ 65 yrs) - 53 respiratory (≥ 65 yrs) - 21 asthma (5-18 yrs) - 3	adjusted relative risk for hospitalization per IQR 7 ppb (13.4 µg/m³) in single and two pollutant model respiratory lag 04 - 1.040 asthma lag 05 - 1.128	adjusted relative risk for hospitalization per IQR 7 ppb (13.4 µg/m³) ins ingle and two pollutant model respiratory lag 04 1.009 - 1.072 asthma lag 05 1.029 - 1.235	statistically significant association for respiratory disease (lag04) and asthma (lag05) admissions in a single pollutant model but not in a two pollutant model with PM_{10}; statistically significant association respiratory admission on lag days 2, 3, & 4 in single pollutant models and cardiovascular admission on lag day 3; no association with cardiovascular (lag03)admissions in single or two pollutant model with PM_{10}	⊕◯◯◯ (insufficient because of very serious risk of exposure bias)

author / location	exposure monitoring	NO_2 concentration	study type (duration)	endpoint	co-pollutants	participants	ratio or risk	confidence interval	results	GRADE quality of evidence
(Andersen *et al.*, 2008) Copenhagen, Denmark	daily average from a single fixed monitoring site	daily mean concentration 11 ppb (21.0 µg/m³)	time-series (3.5 years)	hospital admission of children (asthma) and the elderly (cardiovascular and respiratory disease)	association with PM_{10}, $PM_{2.5}$, UFP (total number conc.), CO, O_3, & NO_2	male & female daily admissions cardiovascular (≥ 65 yrs) - 59 respiratory (≥ 65 yrs) - 22 asthma (5-18 yrs) - 3	adjusted relative risk for hospitalization per IQR 6 ppb (11.5 µg/m³) ins ingle and two pollutant model respiratory lag 04 - 1.06	adjusted relative risk for hospitalization per IQR 6 ppb (11.5 µg/m³) ins ingle and two pollutant model respiratory lag 04 1.01 - 1.12	statistically significant association for respiratory disease admission in single pollutant model (lag04) but not in a two pollutant model with UFP (total number count); no association with cardiovascular (lag03) or asthma (lag05) admissions in single or two pollutant model with UFP (total number count)	⊕◯◯◯ (insufficient because of very serious risk of exposure bias)
(Barnett *et al.*, 2005) Australia Brisbane Canberra Melbourne Perth Sydney New Zealand Christchurch Auckland	1-hr and 24-hr values from 0-9 fixed monitoring sites	daily averages Brisbane – 7.6 ppb (14.5 µg/m³) Canberra – 7.0 ppb (13.4 µg/m³) Melbourne - 11.7 ppb (22.4 µg/m³) Perth – 9.0 ppb (17.2 µg/m³) Sydney - 11.5 ppb (22.0 µg/m³) Christchurch - 7.1 ppb (13.6 µg/m³) Auckland - 10.2 ppb (19.5 µg/m³)	case-crossover (4 years)	hospital admissions of children for respiratory distress, asthma, and pneumonia plus acute bronchitis in three age groups	association with PM_{10}, $PM_{2.5}$, UFP, O_3, SO_2, & NO_2	male and female children ≤ 14 years of age dally admission rate ranges respiratory - 1.4 - 7.9 asthma – 0.9 - 2.2 pneumonia - 0.6 - 3.6	pooled percent increase in admission rate per IQR of 9.0 ppb (17.2 µg/m³) for 1-hr values and 5.1 ppb (9.7 µg/m³) for 24-hr measurements on lag days 01 single pollutant model-respiratory 1-4 yrs age (1-hr NO_2) - 2.8 5-14 yrs age (1-hr NO_2) - 4.7 5-14 yrs age (24-hr NO_2) - 5.8 single pollutant model - asthma 5-14 yrs age (24-hr NO_2) - 6.0 two pollutant model - respiratory 1-4 yrs age (1-hr NO_2) $NO_2/PM_{2.5}$ - 8.5 5-14 yrs age (24 hr NO_2) NO_2/PM_{10} - 6.4	pooled percent increase in admission rate per IQR of 9.0 ppb (17.2 µg/m³) for 1-hr values and 5.1 ppb (9.7 µg/m³) for 24-hr measurements on lag days 01 single pollutant model-respiratory 1-4 yrs age (1-hr NO_2) 0.7 - 4.9 5-14 yrs age (1-hr NO_2) 1.6 - 7.9 5-14 yrs age (24-hr NO_2) 1.7 - 10.1 single pollutant model - asthma 5-14 yrs age (24-hr NO_2) 0.2 - 12.1 two pollutant model - respiratory 1-4 yrs age (1-hr NO_2) $NO_2/PM_{2.5}$ 0.7 - 16.9 5-14 yrs age (24 hr NO_2) NO_2/PM_{10} 3.0 - 9.8	statistically significant association of 1-hr or 24 hr NO_2 exposures with hospital admissions in children pooled from 7 cites for respiratory effects (two age groups) and asthma (one age group) using a single pollutant model, statistically significant association with respiratory admissions in two pollutant model with PM_{10} (one age group or $PM_{2.5}$ (one age group), statistically significant association with 1-hr or 24-hr NO_2 levels and respiratory admission during cool season (one age group) or warm seasons (one age group), no statistically significant association with pneumonia in either of three age groups, no statistically significant association with any of three pulmonary conditions in children less than a year old	⊕⊕◯◯ (low quality because of imprecision caused by heterogeneity and/or inconsistency from multiple comparisons)

author / location	exposure monitoring	NO_2 concentration	study type (duration)	endpoint	co-pollutants	participants	ratio or risk	confidence interval	results	GRADE quality of evidence
(Castro-Giner *et al.*, 2009) 13 cities in Europe Union	daily averages from emission maps developed using profiles disaggregated according to population density then calibrating by distance weighting to concentrations at fixed monitoring sites, the spacial modelling final estimates used information from 13 monitoring sites in 6 countries	daily mean (range across cities) 12.2 - 47.4 µg/m³	case control (120 months)	prevalence of polymorphisms in oxidative stress genes in asthmatics; glutathione S-transferase (GSTM1, GSTT1, GSTP1), NADPH quinone oxidoreductase (NQO1), toll-like receptor (TLR4), tumor necrosis factor alpha (TNFA), adrenergic receptor beta2 (ADBR2)	association with NO_2 only	male and female 2,250 non-asthmatics 327 asthmatic	odds ratio for asthma development per 10 µg/m³ increase NQO1 variant C/C rs1800566 - 1.36 variant C/C rs2917666 - 1.54 TNFA variant C/C rs2844484 - 2.02	odds ratio for asthma development per 10 µg/m³ increase NQO1 variant C/C rs1800566 1.03 - 1.84 variant C/C rs2917666 1.10 - 2.24 TNFA variant C/C rs2844484 1.30 - 3.27	statistically significant association with the homozygous C/C variant for two out of three NQO1 polymorphisms and one out of three TNFA polymorphisms, statistically significant association with new onset asthma, no statistically significant association with existing asthma in all subjects, no statistically significant association with polymorphic forms and variants of GSTM1, GSTT1, GSTP1, TLR4, or ADRB2	⊕◯◯◯ (insufficient because of indirectness, small number of subjects and use of single pollutant)
(Chen *et al.*, 2008a) Vancouver, British Columbia	daily averages from a LUR model created using data from passive samplers placed at 116 locations for two 2-week periods and GIS information for primary and secondary roads population density, & commercial land use, temporal adjustments made use of information from 16 fixed monitoring sites	daily mean 16.5 ppb (31.5 µg/m³)	cross-sectional & prospective cohort (6 months)	immune (IL-4, IL-5, IL-13, IgE, & eosinophil count), clinical (peak expiratory flow rate (PEFR)), & symptom (cough, wheeze, shortness of breath, chest tightness) measures in asthmatic children	interaction study (chronic family stress and NO_2)	male & female children aged 9-18 yrs 71 asthmatics	outcome measures not provided	confidence intervals not provided	statistically significant interaction of family stress & NO_2 for IL-5, IgE, eosinophil count, child reported symptoms, parental reported symptoms, PEFR for those residing in areas with low but not high NO_2, no statistically significant association when chronic stress or NO_2 considered separately for any measurement, no statistically significant interaction for IL-4 & IL-13	⊕◯◯◯ (insufficient because of indirectness, small number of subjects, and publication bias)

author / location	exposure monitoring	NO_2 concentration	study type (duration)	endpoint	co-pollutants	participants	ratio or risk	confidence interval	results	GRADE quality of evidence
(Darrow *et al.*, 2011a) Atlanta, Georgia	mean hourly and daily concentrations at a single fixed monitoring location	1-hr max - 43 ppb (82.1 µg/m³) 24-hr avg - 22 ppb (42.0 µg/m³) 6-hr commute (0700-1000 & 1600-1900) - 21 ppb (40.1 µg/m³) 6-hr nighttime (2400-0600) - 25 ppb (47.8 µg/m³)	time-series (132 months)	emergency departments visits for respiratory problems (asthma, COPD, infection, & pneumonia)	association with $PM_{2.5}$, CO, O_3 & NO_2	male & female 1,068,525 cases	risk ratio per 10 ppb (19.1 µg/m³) increment (lag 1) 1-hr max NO_2 - 1.005 24-hr avg NO_2 - 1.009 6-hr commute NO_2 (0700-1000 & 1600-1900) - 1.006 6-hr nighttime NO_2 (2400-0600) - 1.007	risk ratio per 10 ppb (19.1 µg/m³) increment (lag 1) 1-hr max NO_2 1.003 - 1.007 24-hr avg NO_2 1.005 - 1.013 6-hr commute NO_2 (0700-1000 & 1600-1900) - 1.002 - 1.010 6-hr nighttime NO_2 (2400-0600) 1.005 - 1.009	significant associations with NO_2 using a single pollutant model and various metrics of exposure, but may be due to strong co-variance with O_3	⊕◯◯◯ (insufficient because of severe exposure bias)
(Delfino *et al.*, 2008) Riverside & Whittier, CA	daily averages from personal samplers worn 10 consecutive days and averages from two fixed centrally located monitors	daily average personal – 28.6 ppb (54.6 µg/m³) central site monitor – 25.0 ppb (47.6 µg/m³)	panel study (10 days)	respiratory function (FEV_1) in asthmatic children	association with $PM_{2.5}$, EC, OC, O_3, & NO_2	male & female aged 9-18 years 53 asthmatics	adjusted percent change in FEV1 for all subjects per personal IQR of 16.8 ppb (32.1 µg/m³) and central site IQR of 6.3 ppb (12.0 µg/m³) for in a single pollutant model on lag day 0 personal values - -1.217 central site - -0.408 adjusted percent change in FEV1 for those not using bronchodilator per personal IQR of 16.8 ppb (32.1 µg/m³) and central site IQR of 6.3 ppb (12.0 µg/m³) in a single pollutant model on lag day 0 personal - -1.443 central site - -0.555	adjusted percent change in FEV1 for all subjects per personal IQR of 16.8 ppb (32.1 µg/m³) and central site IQR of 6.3 ppb (12.0 µg/m³) for in a single pollutant model on lag day 0 personal values -1.958 - -0.476 central site - -0.768 - -0.047 adjusted percent change in FEV1 for those not using bronchodilator per personal IQR of 16.8 ppb (32.1 µg/m³) and central site IQR of 6.3 ppb (12.0 µg/m³) in a single pollutant model on lag day 0 personal -2.257 - -0.629 central site - -0.966 - -0.143	statistically significant association with FEV1 reduction on lag day 0 in a single pollutant model using either personal or central site values for all subjects and those not using bronchodilator medications, no association on lag day 1 for the entire cohort using either type of exposure measurement, statistically significant association in two-pollutant model with $PM_{2.5}$ on lag day 0-1 for all subjects and those not using bronchodilators, association observed with ambient values in all subjects no longer significant with two pollutant model incorporating personal NO_2 measurements, however the association with personal measurements still evident when ambient measurements considered in a two pollutant model,	⊕⊕◯◯ (low quality because of small number of cases)

author / location	exposure monitoring	NO_2 concentration	study type (duration)	endpoint	co-pollutants	participants	ratio or risk	confidence interval	results	GRADE quality of evidence
(Ebisu *et al.*, 2011) Hartford & New Haven counties, Connecticut	daily mean estimates using a GIS integrated traffic exposure model incorporating air dispersion, proximity considerations and annual average daily traffic patterns; model estimates verified using values from diffusion tubes positioned outside homes	not provided	cohort (36 months)	presence and severity of wheeze in infants during first year of life	association with NO_2 only	male & female 680 volunteers	no significant change in odds ratio using an adjusted single pollutant model over an IQR of 9.21 ppb (17.6 µg/m³)	no significant change in odds ratio using an adjusted single pollutant model over an IQR of 9.21 ppb (17.6 µg/m³)	no statistically significant association with wheeze using an adjusted single pollutant mode alone or in combination with urban land use factors such as the number of housing units or the percentage of impervious surfaces	⊕⊕◯◯ (low quality because of failure to consider co-pollutants such as O_3 and SO_2)
(Farhat *et al.*, 2005) Sao Paulo, Brazil	daily average from 6 urban fixed monitoring sites	daily mean concentration 125.3 µg/m³	time-series (1 year)	pediatric hospital and emergency room visits for lower respiratory disease (pneumonia, bronchopneumonia, asthma, & bronchiolitis)	association with PM_{10}, SO_2, O_3, CO, & NO_2	male & female children < 13 years of age 4534 admissions or visits	percentage increase in hospital and emergency room visits per IQR 65.0 µg/m³ increase using two-pollutant and multi-pollutant model for average lag day 0-3 total admission NO_2 only ≈ 18 (depicted graphically) NO_2/PM_{10} - 16.1 NO_2/SO_2 - 24.7 NO_2/O_3 - 16.1 NO_2/CO - 19.2 $NO_2/PM_{10},SO_2,O_3$,CO - 18.4 asthma and bronchiolitis NO_2 only ≈ 30 (depicted graphically) NO_2/PM_{10} - 47.7 NO_2/SO_2 - 33.1	percentage increase in hospital and emergency room visits per 65.0 µg/m³ increase using two-pollutant and multi-pollutant model for average lag day 0-3 total admission NO_2 only ≈ 13 -25 (depicted graphically) NO_2/PM_{10} 5.4 - 26.8 NO_2/SO_2 18.2 - 31.3 NO_2/O_3 9.5 - 22.7 NO_2/CO 11.8 - 26.6 $NO_2/PM_{10},SO_2,O_3$,CO 3.4 - 33.5 asthma and bronchiolitis NO_2 only ≈ 9 - 56 (depicted graphically) NO_2/PM_{10} 1.15 - 94.2 NO_2/SO_2 5.7 - 60.5	statistically significant association with total visits for all single, two pollutant and multi-pollutant models with a 0-4 day moving average lag period; statistically significant association with asthma and bronchiolitis visits for single and two-pollutant models with PM_{10} and SO_2, but not with two pollutant models with O_3 or CO or multi-pollutant models; no significant associations with visits for pneumonia or bronchopneumonia;	⊕◯◯◯ (insufficient because of imprecision from small number of cases and short duration)

author / location	exposure monitoring	NO_2 concentration	study type (duration)	endpoint	co-pollutants	participants	ratio or risk	confidence interval	results	GRADE quality of evidence
(Giovannini *et al.*, 2010) Milan, Italy	daily average at a single fixed monitoring site	monthly average range 27.5 - 86.7 µg/m³	time-series (1 year)	pediatric hospital admissions for all respiratory conditions, asthma, upper respiratory disease, and lower respiratory disease	association with PM_{10}, O_3, CO, & NO_2	male and female children ≤ 14 years of age monthly admission rate ranges all respiratory disease - 0.37 - 1.8 asthma - 0.03 - 0.23 upper respiratory - 0.11 - 0.60 lower respiratory - 0.16 - 0.95	adjusted rate ratio per IQR of 1 µg/m³ in single and multi-pollutant models all respiratory NO_2 only (0-6 day MWA) - 1.009 asthma NO_2 only (1 day lag) - 1.002 upper respiratory NO_2 only (1 day lag) - 1.003 lower respiratory NO_2 only (0-6 day MWA) - 1.005 NO_2/CO (0-6 day MWA) - 1.005	adjusted rate ratio per IQR of 1 µg/m³ in single and multi-pollutant models all respiratory NO_2 only (0-6 day MWA) 1.001 - 1.017 asthma NO_2 only (1 day lag) 1.000 - 1.004 upper respiratory NO_2 only (1 day lag) 1.000 - 1.006 lower respiratory NO_2 only (0-6 day MWA) 1.001 - 1.010 NO_2/CO (0-6 day MWA) 1.000 - 1.010	weak statistically significant association with hospital admissions for all respiratory conditions, asthma, upper and lower respiratory disease in single pollutant models, statistically significant association for lower respiratory disease in two pollutant model with CO, no significant associations for other conditions in multi-pollutant models with CO or PM_{10}	⊕◯◯◯ (insufficient because of severe exposure bias)

author / location	exposure monitoring	NO_2 concentration	study type (duration)	endpoint	co-pollutants	participants	ratio or risk	confidence interval	results	GRADE quality of evidence
(Grineski *et al.*, 2010) Phoenix, Arizona	8-hr mean value from four fixed monitoring locations	8-hr average for evening hours (4 -11 PM) 46 ppb (87.9 µg/m³)	time-series (36 months)	hospitalization of children for asthma	interaction study (race, ethnicity, insurance type & NO_2)	male & female (14 years of age or younger) 16,413 admissions	relative risk for specific subgroup comparisons (condition/reference group) per 20 ppb (38.2 µg/m³) exceedance above seasonal mean lag day 1 no insurance/private insurance - 1.39 no insurance/Medicaid - 1.38 Hispanic no insurance/Hispanic private - 1.94 Hispanic no insurance/Hispanic Medicaid - 1.90 lag day 2 black private/white private - 1.27 black private/Hispanic private - 1.34 lag day 0 Hispanic no insurance/white no insurance - 2.06	relative risk for specific subgroup comparisons (condition/reference group) per 20 ppb (38.2 µg/m³) exceedance above seasonal mean lag day 1 no insurance/private insurance 1.07 - 1.81 no insurance/Medicaid 1.06 - 1.80 Hispanic no insurance/Hispanic private 1.26 - 2.99 Hispanic no insurance/Hispanic Medicaid 1.25 - 2.90 lag day 2 black private/white private 0.99 - 1.63 black private/Hispanic private 1.02 - 1.77 lag day 0 Hispanic no insurance/white no insurance 1.13 - 3.76	statistically significant association with those having no insurance together with exceedance of NO_2 levels relative to those with some type of insurance particularly for Hispanic populations; statistically significant association with blacks having private insurance compared to white or Hispanic with private insurance when the lag was 2 days	⊕⊕◯◯ (low quality because of the bias from not evaluating co-pollutants or their interactions)
(Gul *et al.*, 2011) Eskisehir, Turkey	indoor/outdoor passive sampling at 3 school locations	outdoor school 1 - 24.82 µg/m³ school 2 - 15.29 µg/m³ school 3 - 14.93 µg/m³	cross sectional (1 month)	diagnosed pulmonary disease, wheezing, diagnosed asthma, chest tightness, diagnosed bronchitis, cough with phlegm, cough without infection, phlegm without infection	frequency of self-reported symptoms at three schools	male & female 667 high school students	odds ratio - industrial zone chronic pulmonary disease - 1.49 tightness in chest - 1.57 morning cough - 1.81	odds ratio - industrial zone chronic pulmonary disease 1.11 - 1.99 tightness in chest 1.22 - 2.02 morning cough 1.19 - 2.75	highest prevalence noted in the school located in an industrial zone where NO_2 and O_3 was highest	⊕◯◯◯ (insufficient because of bias from small sample size and short study duration)

author / location	exposure monitoring	NO_2 concentration	study type (duration)	endpoint	co-pollutants	participants	ratio or risk	confidence interval	results	GRADE quality of evidence
(Halonen *et al.*, 2008) Helsinki, Finland	daily average from a single monitoring site	daily mean concentration 28.2 µg/m³	time-series (7 years)	ED visits for asthma and COPD in three age groups	association with UFP (Aiken mode), UFP (accumulation mode), $PM_{2.5}$ $PM_{10-2.5}$ (coarse), CO & NO_2	males & females in three age groups children (< 15 years) - 4807 visits adults (14-64 years) - 6312 visits elderly (≥ 65 years of age) - 7239 visits	percent increase in asthma and COPD emergency room visits per IQR 14.2 µg/m³ for three age groups in a single pollutant model children lag day 3 - 4.53 lag day 4 - 10.9 lag day 5 - 9.36 adults lag day 5 - 3.7 elderly lag day 0 - 4.82	percent increase in asthma and COPD emergency room visits per IQR 14.2 µg/m³ for three age groups in a single pollutant model children lag day 3 0.19 - 9.05 lag day 4 6.38 - 15.5 lag day 5 4.95 - 14.0 adults lag day 5 0.15 - 7.37 elderly lag day 0 1.26 - 8.50	statistically significant association with ED visits for asthma and COPD in single pollutant model for children on lag days 3,4,&5, adults on lag day 5 and elderly on lag day 0; no associations on lag day 0 thru 2 for children, 0 thru 4 for adults or 1 thru 5 for elderly	⊕◯◯◯ (insufficient because of the exposure and modeling bias)
(Hansel *et al.*, 2008) Baltimore, MD	daily averages using indoor 72-hr passive area monitoring in the bedroom at 0, 3, & 6 months, outdoor monitoring using an unstated number of fixed monitoring sites	daily mean indoors overall mean – 30.0 ppb (57.3 µg/m³) w/o gas stoves – 16.8 ppb (32.1 µg/m³) w/ gas stoves – 33.1 ppb (63.2 µg/m³) outdoors spring – 30.7 ppb (58.6 µg/m³) summer – 15.9 ppb (30.4 µg/m³) fall – 30.8 ppb (58.8 µg/m³) winter – 41.4 ppb (79.1 µg/m³)	prospective cohort (6 months)	symptoms in asthmatic inner city children including wheeze, coughing, chest tightness causing nocturnal awakening (nocturnal), or reduced activity and appearance during the daytime or while running (running), coughing without a cold (cold), limited speech due to wheeze (speech)	association with indoor NO_2 only	male & female aged 2-6 yrs 150 asthmatics	fully adjusted incidence rate ratios per 20 ppb (38.2 µg/m³) indoor increase in a single pollutant model, symptoms affecting or occurring when speech - 1.17 running - 1.09 cold - 1.15 nocturnal awakening - 1.12	fully adjusted incidence rate ratios per 20 ppb (38.2 µg/m³) indoor increase in a single pollutant model, symptoms affecting or occurring when speech 1.08 - 1.27 running 1.01 - 1.17 cold 1.07 - 1.23 nocturnal awakening 1.04 - 1.19	statistically significant association with asthma symptoms appearing during while running or causing nocturnal awakening, coughing without a cold, or limited speech due to wheeze, no association with daytime symptoms reporting or reduced activity due symptom appearance, atopy and corticosteroid use did not affect the observed associations	⊕◯◯◯ (insufficient because of bias from small sample size, short study duration, and focus on a single pollutant)

author / location	exposure monitoring	NO_2 concentration	study type (duration)	endpoint	co-pollutants	participants	ratio or risk	confidence interval	results	GRADE quality of evidence
(Iskander *et al.*, 2012) Copenhagen, Denmark	daily averages at a single fixed monitoring site	daily mean 14.46 ppb (27.6 µg/m³)	case-crossover (92 months)	pediatric hospital admission for asthma	association with UFP, PM_{10}, $PM_{2.5}$, NOx, & NO_2	male and female children 0-18 years of age 8226 visits	odds ratio for asthma admission per IQR 8.62 ppb (16.5 µg/m³) in single and two pollutant models on lag day 04 single pollutant model all cases - 1.10 infants 0-1 yrs age - 1.10 preschool 2-5 yrs age - 1.10 school children 6-18 yrs age - 1.10 two pollutant model (all cases) NO_2/PM_{10} - 1.08 $NO_2/PM_{2.5}$ - 1.12 NO_2/UFP - 1.13	odds ratio for asthma admission per IQR 8.62 ppb (16.5 µg/m³) in single and two pollutant models on lag day 04 single pollutant model all cases 1.04 - 1.16 infants 0-1 yrs age 1.02 - 1.19 preschool 2-5 yrs age 1.02 - 1.19 school children 6-18 yrs age 1.02 - 1.20 two pollutant model (all cases) NO_2/PM_{10} 1.01 - 1.15 $NO_2/PM_{2.5}$ 1.05 - 1.19 NO_2/UFP 1.05 - 1.22	statistically significant association with hospital admissions for children in all three age groups using a single pollutant model and a moving average lag of 04 days, statistically significant association all boys but not all girls, statistically significant association in two-pollutant models with UFP, PM_{10}, and $PM_{2.5}$ but not with NOx	⊕◯◯◯ (insufficient because of severe exposure bias)
(Ito *et al.*, 2007) New York, New York	daily average at 15 fixed monitoring sites	yearly average concentration all seasons - 31.1 ppb (59.4 µg/m³) warm season - 30.4 ppb (58.1 µg/m³) cold season - 31.8 ppb (60.7 µg/m³)	time-series (4 years)	emergency department visits for asthma	association with $PM_{2.5}$ (FRM),$PM_{2.5}$ (TEOM), O_3, SO_2, CCO, & NO_2	unstated number of male and female of all ages	relative risk per 5-95% range of 29 ppb (55.4 µg/m³) in single and two pollutant models on avg lag 01 days during warm season (values estimated from graph) NO_2 only ≈ 1.30 $NO_2/PM_{2.5}$ ≈ 1.27 NO_2/O_3 ≈ 1.25 NO_2/CO ≈ 1.35 NO_2/SO_2 ≈ 1.32	relative risk per 5-95% range of 29 ppb (55.4 µg/m³) in single and two pollutant models on avg lag 01 days during warm season (values estimated from graph) NO_2 only ≈ 1.21 - 1.41 $NO_2/PM_{2.5}$ ≈ 1.18 - 1.40 NO_2/O_3 ≈ 1.15 - 1.36 NO_2/CO ≈ 1.24 - 1.48 NO_2/SO_2 ≈ 1.18 - 1.49	statistically significant association with asthma hospital admissions in both single and two pollutant models during warm season for average lag of 01 days, statistically significant association in single pollutant models for all year and warm season using alternative weather models, no significant associations for the cold season	⊕⊕◯◯ (low quality because unstated number of cases)

author / location	exposure monitoring	NO_2 concentration	study type (duration)	endpoint	co-pollutants	participants	ratio or risk	confidence interval	results	GRADE quality of evidence
(Jacquemin *et al.*, 2009) 17 cities within the European Union	daily averages from emission maps developed using emission profiles disaggregated according to population density then calibrating by distance weighting to concentrations at fixed monitoring sites, the spacial modelling final estimates used information from 714 monitoring sites in 15 countries	daily average mean - 27.7 µg/m³ range 12 - 57 µg/m³	cohort study (36 months)	self-reported asthma incidence and symptom reporting in non-asthmatics	NO_2 only	male & female 3999 cohort 186 cases	odds ratio per 10 µg/m³ increase asthma incidence (fully adjusted model) - 1.43 non-asthmatics symptoms (past 12 months) wheezing (12-mo) - 1.28 breathless with wheeze - 1.28 wheeze without cold symptoms - 1.42 awakened by chest tightness - 1.59 awakened by shortness of breath - 1.43	odds ratio per 10 µg/m³ increase asthma incidence (fully adjusted model) 1.02 - 2.01 non-asthmatics symptoms (past 12 months) wheezing (12-mo) - 1.00 - 1.62 breathless with wheeze - 1.00 - 1.62 wheeze without cold symptoms - 1.03 - 1.96 awakened by chest tightness - 1.22 - 2.07 awakened by shortness of breath - 1.02 - 1.99	weak but statistically significant association of NO_2 with asthma incidence and pulmonary symptoms in non-asthmatics	⊕◯◯◯ (insufficient because of the imprecision associated with self-reporting and the bias from examining only a single pollutant)

author / location	exposure monitoring	NO_2 concentration	study type (duration)	endpoint	co-pollutants	participants	ratio or risk	confidence interval	results	GRADE quality of evidence
(Jalaludin *et al.*, 2008) Sydney, Australia	1-hr measurements from 14 fixed monitoring sites	1-hr mean concentration 23.2 ppb (44.3 µg/m³)	case-crossover (5 years)	emergency department visits for asthma in children	association with PM_{10}, $PM_{2.5}$, SO_2, O_3, CO, & NO_2	male and female children aged 1-14 years 1826 visits	percent increase in ED visits for asthma in children of different age groups per IQR of 9.3 ppb (17.8 µg/m³) in single and two-pollutant models for lag day 0 1-14 years NO_2 only - 2.3 NO_2/PM_{10} - 1.0 $NO_2/PM_{2.5}$ - 1.1 NO_2/O_3 - 1.2 NO_2/CO - 1.8 NO_2/SO_2 - 1.0 1-4 years of age NO_2 only - 3.0 $NO_2/PM_{2.5}$ - 0.8 NO_2/O_3 - 1.6 NO_2/CO - 1.1 5-9 years of age NO_2/PM_{10} - 1.6 $NO_2/PM_{2.5}$ - 1.6 NO_2/O_3 - 1.9 NO_2/CO - 3.0 NO_2/SO_2 - 1.8 10-14 years of age NO_2/CO (lag day 2) - 3.5	percent increase in ED visits for asthma in children of different age groups per IQR of 9.3 ppb (17.8 µg/m³) in single and two-pollutant models for lag day 0 1-14 years NO_2 only 1.4 - 3.2 NO_2/PM_{10} 0.4 - 1.6 $NO_2/PM_{2.5}$ 0.6 - 1.6 NO_2/O_3 0.6 - 1.7 NO_2/CO 1.0 - 2.6 NO_2/SO_2 0.1 - 1.9 1-4 years of age NO_2 only 1.8 - 4.2 $NO_2/PM_{2.5}$ 0.1 - 1.5 NO_2/O_3 0.9 - 2.4 NO_2/CO 0.03 - 2.1 5-9 years of age NO_2/PM_{10} 0.4 - 2.8 $NO_2/PM_{2.5}$ 0.6 - 2.6 NO_2/O_3 0.6 - 3.2 NO_2/CO 1.3 - 4.6 NO_2/SO_2 0.04 - 3.6 10-14 years of age NO_2/CO (lag day 2) 1.4 - 5.7	statistically significant association with ED visits for asthma in single and two pollutant models for age group 1-14 years; statistically significant association in two pollutant models but not single pollutant model in age group 5-9 years; statistically significant association in single and two pollutant models for $PM_{2.5}$, O_3, & CO in age group 1-4 years; statistically significant association in two-pollutant model with CO in age group 10-14 years but only when lag day 2 was used in the comparison; statistically significant association in single pollutant model for warm but not cold months in age group 1-14 years	⊕◯◯◯ (insufficient because of small number of cases and inconsistencies across age groups)

author / location	exposure monitoring	NO_2 concentration	study type (duration)	endpoint	co-pollutants	participants	ratio or risk	confidence interval	results	GRADE quality of evidence
(Jerrett *et al.*, 2008) 11 town in Southern California	averages based on area monitors placed outside home for 2 weeks in mid-August and mid-November summer	4 week average 9.6 - 51.3 ppb (18.3 - 98.0 µg/m³) community range	prospective cohort (96 months)	asthma incidence in normal children	association with NO_2 only	male & female aged 10-18 yrs 217 children	adjusted hazard ratio for all communities per IQR of 6.2 ppb (11.8 µg/m³) in a single pollutant model controlling for relative humidity fall-winter - 1.29 summer - 1.27 annual - 1.29 adjusted hazard ratio for between community exposures per IQR of 6.2 ppb (11.8 µg/m³) in a single pollutant model controlling for relative humidity fall-winter - 1.28 summer - 1.32 annual - 1.28	adjusted hazard ratio for all communities per IQR of 6.2 ppb (11.8 µg/m³) in a single pollutant model controlling for relative humidity fall-winter 1.11 - 1.49 summer 1.03 - 1.57 annual 1.07 - 1.56 adjusted hazard ratio for between community exposures per IQR of 6.2 ppb (11.8 µg/m³) in a single pollutant model controlling for relative humidity fall-winter 1.09 - 1.51 summer 1.05 - 1.66 annual 1.05 - 1.57	statistically significant association with asthma incidence (30 cases) in a single pollutant model that incorporates and adjusts for relative humidity, no association when the humidity term is removed from the model; statistically significant association using community mean exposures but not when deviation across communities were considered; weakly significant association still apparent after adjusting for subjects with wheeze at the beginning of the study and those with early childhood chest illness	⊕◯◯◯ (insufficient because of the imprecision associated with the use of questionnaires and the bias from examining only a single pollutant)
(Kalantzi *et al.*, 2011) Magnesia, Greece	daily mean from three fixed monitoring sites	daily mean 30.12 µg/m³	time-series (84 months)	total hospitalizations and those for pulmonary (COPD, asthma, infections, & other) and cardiovascular (ischemic heart disease, heart failure, & other) diseases	association with PM_{10}, CO, SO_2, O_3, NO, NOx, & NO_2	male & female admissions rate respiratory - 2.94 /day cardiovascular - 4.88 /day	no change in risk coefficients in either a single or combined model	no change in risk coefficients in either a single or combined model	no statistically significant association with NO_2; statistically significant associations found for NOx and CO in a combined pollutant models	⊕⊕◯◯ (low quality because the focus on NOx and the exposure bias)

author / location	exposure monitoring	NO_2 concentration	study type (duration)	endpoint	co-pollutants	participants	ratio or risk	confidence interval	results	GRADE quality of evidence
(Ko *et al.*, 2007) Hong Kong, China	daily average at 14 fixed monitoring sites	daily average all seasons – 53.2 µg/m³ cold season (< 20 °C) - 61.7 µg/m³ warm season (≥ 20 °C) - 50.0 µg/m³	time-series (6 years)	hospitalizations for asthma	association with PM_{10}, $PM_{2.5}$, O_3, SO_2, & NO_2	male & females of all ages 69,716 admissions	relative risk per 10 µg/m³ increase in single multi pollutant models for avg lag 04 days single pollutant 0-14 yrs age - 1.039 >14-65 yrs age - 1.018 > 65 yrs age - 1.023 multi-pollutant model NO_2/O_3,SO_2 - 1.014	relative risk per 10 µg/m³ increase in single multi pollutant models for avg lag 04 days single pollutant 0-14 yrs age 1.028 - 1.051 >14-65 yrs age 1.007 - 1.029 > 65 yrs age 1.014 - 1.033 multi-pollutant model NO_2/O_3,SO_2 1.003 - 1.025	statistically significant association with asthma hospitalization in all three age groups using single pollutant model and a cumulative lag of 04 days, statistically significant association for pooled population at all lag times, statistically significant association in three-pollutant model with O_3 and SO_2 but not in two-pollutant with O_3 alone, higher risk noted for cold relative to warm season	⊕⊕◯◯ (low quality because of the lag-related modelling bias)
(Laurent *et al.*, 2008) Strasbourg, France	census block modelling of hourly measurements from an unknown number of monitoring sites	daily mean 36 µg/m³	case-crossover (72 months)	calls to physicians regarding asthma attack	association with socioeconomic status, PM_{10}, SO_2, O_3, & NO_2	male & female 4,677 calls	no significant change in odds ratio	no significant change in odds ratio	no association with socioeconomic status in any age group	⊕⊕◯◯ (low quality because of the bias from not evaluating co-pollutants interactions)
(Lee *et al.*, 2006) Hong Kong, China	daily average at 9-11 fixed monitoring sites	daily mean concentration 64.7 µg/m³	time-series (6 years)	hospital admissions for children with asthma	association with PM_{10}, $PM_{2.5}$, O_3, SO_2, & NO_2	male and female children ≤ 18 years of age total admissions - 879,384 asthma admissions - 26,663	percent increase in asthma admissions per IQR of 27.1 1 µg/m³ on lag day 3 in single and multi-pollutant models NO_2 only - 9.08 $NO_2/PM_{10}/PM_{2.5}/SO_2/O_3$ - 5.64	percent increase in asthma admissions per IQR of 27.1 1 µg/m³ on lag day 3 in single and multi-pollutant models NO_2 only 7.26 - 10.93 $NO_2/PM_{10}/PM_{2.5}/SO_2/O_3$ 3.21 - 8.14	statistically significant association with asthma admissions in children for single and five-pollutant models on lag day 3, statistically significant association in single pollutant models on lag 0, 1, 2, 4, or 5 but percentage change appreciably lower	⊕⊕◯◯ (low quality because of the lag-related modelling bias)

author / location	exposure monitoring	NO_2 concentration	study type (duration)	endpoint	co-pollutants	participants	ratio or risk	confidence interval	results	GRADE quality of evidence
(Leitte *et al.*, 2009) Drobeta-Tunu Severin, Romania	pooled mean daily concentration from one fixed monitoring locations	daily mean 11.8 µg/m³	time-series (19 months)	hospital admissions for chronic obstructive pulmonary disease (COPD), asthma, chronic bronchitis	differential effects of TSP, SO_2, & NO_2	953 cases	odds ratio per 10 µg/m³ increment persistent cough using NO_2 outdoors at 1 year - 1.40	no effect on relative risk	no significant associations observed using a single pollutant model	⊕○○○ (insufficient because of severe exposure bias and short duration)
(LI *et al.*, 2011) Detroit, MI	daily average from two fixed monitoring sites	daily mean 15.74 ppb (30.1 µg/m³)	time-series & case crossover with and without a (36 months)	emergency department visits and hospital admission for asthma	association with $PM_{2.5}$, O_3, SO_2, CO, & NO_2	male and female children 2-18 years of age – 7063 cases	risk ration per IQR 9.65 ppm (18.4 µg/m³) on lag day 5 time series – 1.038 case crossover – 1.039	risk ration per IQR 9.65 ppm (18.4 µg/m³) on lag day 5 time series – 1.005-1.072 case crossover – 1.010-1.070	statistically significant association on lag day 5 for both study designs when a threshold was assumed, but not when the threshold assumption was keep out; no statistically significant association on lag day 0, 1, 2, 3, 4, or moving average lag 01, 02, or 04 using a times series or case crossover study design	⊕⊕○○ (low quality because of the single pollutant modelling bias from not evaluating co-pollutants interactions)
(Liao *et al.*, 2011) Taipei & Kaohsiung, Taiwan	mean daily concentration at nine fixed monitoring locations in two cities	daily mean Taipei - 25.40 ppb (48.5 µg/m³) Kaohsiung - 23.74 ppb (45.3 µg/m³)	time-series (96 months)	asthma hospital admissions rate	respiratory virus infections, PM_{10}, SO_2, O_3, CO & NO_2	male 3406 - 3608/100,000 female 3186 - 3506/100,00	no significant change in odds ratio	no significant change in odds ratio	no association with NO_2 exposure in single pollutant model	⊕○○○ (insufficient because of imprecision from the atypical statistical analysis and use of a single pollutant model)

author / location	exposure monitoring	NO_2 concentration	study type (duration)	endpoint	co-pollutants	participants	ratio or risk	confidence interval	results	GRADE quality of evidence
(Liu *et al.*, 2009) Windsor, Ontario	daily means from two fixed monitoring sites	median value 1-day 19.8 ppb (37.8 µg/m³) 2-day - 18.3 ppb (35.0 µg/m³) 3-day - 18.3 ppb (35.0 µg/m³)	case-crossover (3 months)	pulmonary function (FVC, FEV_1, $FEF_{25-75\%}$), airway inflammation (exhaled nitric oxide, FENO) and oxidative stress (thiobarbituric reactive substances (TBARS), & 8-isoprostane) in asthmatics	association with $PM_{2.5}$, O_3, SO_2, & NO_2	male & female aged 9-14 yrs old 182 asthmatics	adjusted percent change in response per IQR of 6.8-9.8 ppb (13.0-18.7 µg/m³) in a single pollutant model $FEF_{25-75\%}$ 0 day -2.4 0-1 day -2.4 0-2 day -2.8 TBARS 0 day 21.2 0-2 day 32.9	adjusted percent change in response per IQR of 6.8-9.8 ppb (13.0-18.7 µg/m³) in a single pollutant model $FEF_{25-75\%}$ 0 day -4.3 - -0.4 0-1 day -4.3 - -0.3 0-2 day -5.0 - -0.5 TBARS 0 day 1.9 - 44.2 0-2 day 7.2 - 64.6	statistically significant association with FEF25-75% and TBARS for multiple lag periods in single and two-pollutant models, no statistically significant association with FEV_1, FENO, & 8-isoprostane for any lag period	⊕○○○ (insufficient because of exposure bias and short duration)
(Ma *et al.*, 2008) Yotsukaido City, Japan	outdoor concentrations at a single hospital site	outdoor mean 24-hr – 20.6 ppb (39.4 µg/m³) 12-hr night – 21.8 ppb (41.6 µg/m³) day – 19.3 ppb (36.9 µg/m³) 1-hr max night – 31.6 ppb (60.4 µg/m³) day – 31.5 ppb (60.2 µg/m³)	cohort (5 months)	peak expiratory flow & wheezing in asthmatics	association with $PM_{2.5}$ and NO_2	19 male and female children hospitalized with severe asthma	odds ratio per 10 ppb (19.1 µg/m³) increase NO_2 wheeze using 1-hr maximum NO_2 - 1.014	odds ratio per 10 ppb (19.1 µg/m³) increase NO_2 wheeze using 1-hr maximum NO_2 1.001 - 1.028	no associations using 12 and 24-hr values; no associations with peak expiratory flow; strong association with $PM_{2.5}$	⊕○○○ (insufficient because of imprecision from very small sample size and slight changes in risk)

author / location	exposure monitoring	NO_2 concentration	study type (duration)	endpoint	co-pollutants	participants	ratio or risk	confidence interval	results	GRADE quality of evidence
(Mann *et al.*, 2010) Fresno and Clovis, CA	daily means from an unstated number of fixed monitoring sites	daily mean 18. 6 ppb (35.5 µg/m³)	cohort (54 months)	wheeze in asthmatic children	association with $PM_{10-2.5}$, $PM_{2.5}$, EC, O_3, NO_3, & NO_2	male and female children aged 6-11 yrs 315 volunteers	adjusted odds ratio per 8.7 ppb (16.6 µg/m³) peak increase from day 0-1 for a 2-day lag (largest value for first 7 lag days) all children - 1.10 cat dander allergy - 1.27 fungi allergy - 1.23 boys mild asthma - 1.51	adjusted odds ratio per 8.7 ppb (16.6 µg/m³) peak increase from day 0-1 for a 2-day lag (largest value for first 7 lag days) all children 1.02 - 1.20 cat dander allergy 1.06 - 1.51 fungi allergy 1.10 - 1.39 boys mild asthma 1.23 - 1.85	statistically significant association for all asthmatic children on lag days 1, 2, 3, 6 & 7 and all but the first 2-14 moving average periods, statistically significant association on all but two lag days (10 & 11) & all moving average periods for children testing positive for mold allergy, statistically significant association on all but one lag day (7) & all moving average periods for children testing positive for cat dander, statistically significant association on all lag days & moving average periods for boys with intermittent allergy, no statistical significance for full group in two pollutant model the $PM_{2.5}$, statistical significance on slightly fewer lag days for cat dander sensitive, mold sensitive & boys with intermittent allergy using a two pollutant model with $PM_{2.5}$ or EC	⊕◯◯◯ (insufficient because of imprecision from small sample size and slight changes in risk and potential exposure bias)
(McConnell *et al.*, 2010) Southern California (13 communities)	annual average measurements from a single community monitoring site with spatial correction	annual average 20.4 ppb (39.0 µg/m³)	prospective cohort (36 months)	asthma (two physician-based diagnoses or one hospital visit) incidence in children	association with PM_{10}, $PM_{2.5}$, O_3, & NO_2	male and female aged 6 years or less 2497 children	hazard risk per 23.6 ppb (45.1 µg/m³) in a single pollutant model unadjusted - 2.17	hazard risk per 23.6 ppb (45.1 µg/m³) in a single pollutant model unadjusted 1.18 - 4.00	statistically significant association with new onset asthma in an unadjusted model, but no significance after adjusting for exposure to traffic-related pollution (NOx levels by dispersion modelling) at home and at school traffic	⊕◯◯◯ (insufficient because of severe exposure bias)

author / location	exposure monitoring	NO_2 concentration	study type (duration)	endpoint	co-pollutants	participants	ratio or risk	confidence interval	results	GRADE quality of evidence
(Morgenstern *et al.*, 2008) Munich, Germany	proximity modelling using the results from 40 fixed monitoring sites along with residential location relative to different types of roads, length of each road, land coverage, & population and household density	annual average 2-3 years of age – 34.7 µg/m³ 6 years of age – 34.6 µg/m³	cohort (unstated recruitment period)	physician diagnosed asthma or allergy (asthmatic/spastic/obstructive bronchitis, hay fever, eczema or parental symptom reporting (asthmatic/spastic/obstructive bronchitis, hay fever, eczema); allergic sensitization to inhalant, indoor, or outdoor allergens	association with $PM_{2.5}$ & NO_2	male & female cohort I – 1166 cases cohort II – 1900 cases	odds ratio per IQR of 6.4 µg/m³ in a single pollutant model doctor diagnosed eczema - 1.18	odds ratio per IQR of 6.4 µg/m³ in a single pollutant model doctor diagnosed eczema 1.00 - 1.39	statistically significant association with doctor diagnosed eczema but not asthmatic/spastic/obstructive bronchitis or hay fever; not statistically significant association with parental symptom reporting; no statistically significant association with allergic sensitization to any sources types(inhalants, indoor or outdoor allergens) at 6 years of age	⊕⊕◯◯ (low quality because of the bias from not evaluating co-pollutants interactions)
(Parker *et al.*, 2009) United States	annual averages for site specific monitors within 20 miles of residence weighted by inverse distance weighting	annual median 17.8 ppb (34.0 µg/m³)	cross-sectional study (84 months)	survey of childhood respiratory allergies and hay fever	association with PM_{10}, $PM_{2.5}$, O_3, SO_2, & NO_2	male and female 3-17 yrs of age 72,279 children	no association in crude or adjusted single or multi-pollutant model per 10 ppb (19.1 µg/m³)	no association in crude or adjusted single or multi-pollutant model per 10 ppb (19.1 µg/m³)	no statistically significant association with childhood asthma prevalence in crude or adjusted single or multi-pollutant models using IDW for monitors within a 20 mi or 5 mi radius	⊕⊕◯◯ (low quality because of inherent limitations of the cross sectional design)

author / location	exposure monitoring	NO_2 concentration	study type (duration)	endpoint	co-pollutants	participants	ratio or risk	confidence interval	results	GRADE quality of evidence
(Patel *et al.*, 2010) New York City	daily mean for two fixed monitoring sites located near each of five schools	levels not provided	cohort (1.5 months)	respiratory symptoms (wheeze, cough, shortness of breath, chest tightness, & use of asthma medications) in high school students	association with $PM_{2.5}$, BC, O_3, & NO_2	male & female teenagers 13-20 years of age 249 students	odds ratio per IQR of 16 ppb (30.6 µg/m³) for respiratory symptoms on different lag days wheeze 2-day lag - 1.15 3-day lag - 1.32 4-day lag - 1.57 5-day lag - 1.70 shortness of breath 0-day lag - 1.20 1-day lag - 1.15 2-day lag - 1.28 3-day lag - 1.32 4-day lag - 1.31 5-day lag - 1.35	odds ratio per IQR of 16 ppb (30.6 µg/m³) for respiratory symptoms on different lag days wheeze 2-day lag 1.00 - 1.33 3-day lag 1.11 - 1.56 4-day lag 1.29 - 1.91 5-day lag 1.36 - 2.13 shortness of breath 0-day lag 1.10 - 1.32 1-day lag 1.03 - 1.29 2-day lag 1.12 - 1.46 3-day lag 1.12 - 1.54 4-day lag 1.09 - 1.57 5-day lag 1.09 - 1.67	statistically significant association with shortness of breath for all lag periods and wheeze for 4 out of the six lag periods, no statistically significant positive association with cough, chest tightness, or asthma medication use, stratification by asthma status showed a statistically significant association with chest tightness only in asthmatic subjects	⊕◯◯◯ (insufficient because of bias caused by small number of cases, and short duration, with no two-pollutant modelling)
(Peel *et al.*, 2005) Atlanta, GA	1-hr maximum from two fixed monitoring sites	1-hr maximum mean 45.9 ppb (87.7 µg/m³)	time-series (92 months)	emergency department visits of total respiratory, upper respiratory infection, asthma, pneumonia, & COPD	association with PM_{10}, total particle count (TPC), coarse PM, sulfate, acidity, OC, EC, oxy hydrocarbons, SO_2, O_3, CO, & NO_2	males and females (avg. ED visit rates) respiratory disease 172 visits/day URI 103 visits/day asthma 39.0 visits/day pneumonia 20.8 visits/day COPD 7.42 visits/day	risk ratio per 20 ppb (38.2 µg/m³) in a single pollutant model using two lag periods 0-2 day moving average lag upper respiratory infection - 1.027 COPD - 1.035 0-13 day distributed lag upper respiratory infection - 1.057 asthma - 1.047	risk ratio per 20 ppb (38.2 µg/m³) in a single pollutant model using two lag periods 0-2 day moving average lag upper respiratory infection 1.006 - 1.031 COPD 1.006 - 1.065 0-13 day distributed lag upper respiratory infection 1.029 - 1.085 asthma 1.011 - 1.085	statistically significant association with URI in single pollutant model at moving average lag 0-2 and distributed lag 0-13 days, statistically significant association with COPD at average lag asthma 0-2 days, at distributed lag 0-13 days, statistically significant association with all respiratory disease for moving average lag 0-2 days, no significant association pneumonia or COPD for either lag period or asthma with moving average lag 0-2 days, no attenuation of association in multi-pollutant models (data not shown), associations for asthma substantially stronger for infants (age 0-1 yrs) and children (age 2-18 yrs) than adults	⊕◯◯◯ (insufficient because of publication bias and the bias using a very small number of monitoring sites)

author / location	exposure monitoring	NO_2 concentration	study type (duration)	endpoint	co-pollutants	participants	ratio or risk	confidence interval	results	GRADE quality of evidence
(Qian *et al.*, 2009) six US cities Boston, MA New York, NY Philadelphia, PA Denver, CO San Francisco, CA Madison, WI	daily averages centroid values from an unstated number of fixed monitoring sites	daily mean 23. 6 ppb (45.1 µg/m³)	cross sectional (23 months)	interaction with corticosteroid medication (triamcinolone, salmeterol, & placebo) and impact on exhaled nitric oxide in asthmatics	association with PM_{10}, SO_2, O_3, & NO_2	male & female 119 asthmatics	change exhaled conc. per 10 ppb (19.1 µg/m³) in single pollutant model total 0 day lag - 0.13 1 day lag - 0.08 0-3 day lag - 0.11 triamcinolone 0 day lag - 0.17 1 day lag - 0.09 0-3 day lag - 0.15 salmeterol 0 day lag - 0.11 1-day lag - 0.11 0-3 day lag - 0.15 change exhaled NO concentration per 10 ppb (19.1 µg/m³) in two pollutant with 0 day lag total O_3 - 0.11 SO_2 - 0.14 triamcinolone O_3 - 0.16 SO_2 - 0.18 placebo SO_2 - 0.13	change exhaled concentration per 10 ppb (19.1 µg/m³) in single pollutant model total 0 day lag 0.06 - 0.19 1 day lag 0.02 - 0.14 0-3 day lag 0.01 - 0.20 triamcinolone 0 day lag 0.06 - 0.27 1 day lag 0.00 - 0.18 0-3 day lag 0.01 - 0.30 salmeterol 0 day lag 0.01 - 0.22 1-day lag 0.01 - 0.21 0-3 day lag 0.00 - 0.30 change exhaled NO concentration per 10 ppb (19.1 µg/m³) in two pollutant model with 0 day lag total O_3 0.05 - 0.18 SO_2 0.06 - 0.22 triamcinolone O_3 0.06 - 0.26 SO_2 0.06 - 0.30 placebo SO_2 0.00 - 0.24	statistically significant interaction with all corticosteroid use and triamcinolone & salmeterol use on lag days 0, 1, & 0-3 in single pollutant model, no significant associations observed in lag day 2 or 3 with single pollutant model, statistically significant interaction total group and those using triamcinolone on lag day 0 using a two pollutant model with O_3 or SO_2, no association in two pollutant models with PM_{10}, no association with salmeterol in two pollutant model with PM_{10}, O_3, or SO_2	⊕◯◯◯ (insufficient because of bias caused by small number of cases, short duration, and unknown number of monitoring sites)

author / location	exposure monitoring	NO_2 concentration	study type (duration)	endpoint	co-pollutants	participants	ratio or risk	confidence interval	results	GRADE quality of evidence
(Rage *et al.*, 2009) Paris, Lyon, Marseille, Montpellier, & Ganogle, France	two approaches i) annual means from the monitoring site nearest the subject; ii) annual mean concentrations from a geostatistical model using monitoring data	annual mean monitoring method - 40.2 µg/m³ modelling method - 35.9 µg/m³	case control and family study combination (12 months)	asthma severity based on symptom questionnaire and treatment needs	association with SO_2, O_3, & NO_2	male & female 328 cases	no significant change in odds ratio	no significant change in odds ratio	no association in single or multi-pollutant model using either measure of exposure	⊕⊕◯◯ (low quality because of the indirectness from using medical questionnaire)
(Sahsuvaroglu *et al.*, 2009) Hamilton, Ontario	two approaches i) passive monitoring at 107 locations for two-week period with stochastic interpolation (kriging) ii) land use regression estimates based on traffic density, open land use, industrial land use, highway presence near industrial core, distance to lake, relative wind direction and background NO_2 concentrations from 107 passive dosimetry readings	mean kriging technique – 15.36 ppb (29.3 µg/m³) LUR technique – 14.84 ppb (28.3 µg/m³)	cross sectional (24 months)	asthma prevalence in 1467 grade 1 (6-7 yrs) & grade 8 (13-14 yrs) school children with and without hay fever or wheeze	association with PM_{10}, SO_2, O_3, & NO_2	male and female 1467 asthma cases	adjusted odds ratio for asthma without hay fever per 1 ppb (1.9 µg/m³) in multi-pollutant model both age groups NO_2/SO_2 - 1.162 NO_2/O_3 - 1.171 older girls (grade 8) NO_2/SO_2 - 1.289 NO_2/PM_{10} - 1.287 NO_2/O_3 - 1.304	adjusted odds ratio for asthma without hay fever per 1 ppb (1.9 µg/m³) in multi-pollutant model both age groups NO_2/SO_2 1.000 - 1.350 NO_2/O_3 1.004 - 1.3666 older girls (grade 8) NO_2/SO_2 1.017 - 1.634 NO_2/PM_{10} 1.0008 - 1.643 NO_2/O_3 1.025 - 1.658	statistically significant association for girls (all ages and grade 8) for asthma without hay in adjusted multi-pollutant model; statistically significant associations also observed for asthma without wheeze; statistically significant associations observed for all and older girls with asthma without hay fever using an unadjusted single pollutant model but not when the model was partially adjusted for individual confounders	⊕⊕◯◯ (low quality because of the indirectness from using medical questionnaire)

author / location	exposure monitoring	NO_2 concentration	study type (duration)	endpoint	co-pollutants	participants	ratio or risk	confidence interval	results	GRADE quality of evidence
(Samoli *et al.*, 2011) Athens, Greece	1-hr maximum concentrations for 14 fixed monitoring locations	mean daily 1-hr maximum 84.8 µg/m³	time-series (60 months)	pediatric emergency admissions for asthma	association with PM_{10}, O_3, SO_2, & NO_2	male & female 3601 admissions	adjusted increase in asthma admissions per 10 µg/m³ increase (1-hr max) in single pollutant model for lag day 0 males (0-14 years) - 2.29 no significant increase in asthma admissions in adjusted single or two-pollutant model per 10 µg/m³ increase or IQR range (37.3 µg/m³) increase on lag day 0, 1, or 2	adjusted increase in asthma admissions per 10 µg/m³ increase (1-hr max) in single pollutant model for lag day 0 males (0-14 years) 0.13 - 4.50 no significant increase in asthma admissions in adjusted single or two-pollutant model per 10 µg/m³ increase or IQR range (37.3 µg/m³) increase on lag day 0, 1 or 2	statistically significant increase in asthma admissions for boys, but not girls, aged 0-14 years; no statistically significant associations for all children in two age groups (0-4 years and 5-14 years); no statistically significant association with asthma admissions for annual mean daily 1-hr maximum measurements (winter, spring, summer, or fall) using continuous or IQR values in a single pollutant model for lag day 0, 1, or 2; no statistically significant associations in a two-pollutant model with PM_{10}, SO_2, or O_3	⊕⊕◯◯ (low quality because of the small number of cases)
(Sinclair *et al.*, 2010) Atlanta, Georgia	hourly maximum concentrations at a single fixed monitoring location	mean 25 month period – 49.8 ppb (95.1 µg/m³) 28 month period – 41.7 ppb (79.7 µg/m³)	time-series (25 - 28 month)	acute outpatient visits for adult asthma, child asthma, upper respiratory tract infection, & lower respiratory tract infection	association with $PM_{2.5}$ mass, $PM_{2.5}$ sulfate, $PM_{2.5}$ EC, $PM_{2.5}$ OC, PM_{10}, $PM_{10\text{-}2.5}$, PM, SO_2, CO, O_3, oxygenated VOCs	male & female child asthma - 28,487 cases adult asthma - 19,085 cases LRT infection - 17,373 cases URT infection - 425,808 cases	relative risk per 17.88 ppb (34.2 µg/m³) increment (lag 6-8) LRT infection 28 month - 1.062	relative risk per 17.88 ppb (34.2 µg/m³) increment (lag 6-8) LRT infection 28 month 1.005 - 1.123	no association at any lag with adult or child asthma; no association with warm or cold seasons; negative association with URT infection in 25 month study at a lag 6-8 days; positive association with LRT infection in 28 day study at a lag of 6-days	⊕◯◯◯ (insufficient because of severe exposure bias)

author / location	exposure monitoring	NO_2 concentration	study type (duration)	endpoint	co-pollutants	participants	ratio or risk	confidence interval	results	GRADE quality of evidence
(Stieb *et al.*, 2009) Seven Canadian cities Montreal Ottawa Edmonton Saint John Halifax Toronto Vancouver	mean daily concentration from 1 to 14 fixed monitoring sites	hourly mean Montreal – 19.4 ppb (37.1 µg/m³) Ottawa – 18.8 (35.9 µg/m³) Edmonton – 21.9 (41.8 µg/m³) Saint John – 9.3 (17.8 µg/m³) Halifax - 17.5 ppb (33.4 µg/m³) Toronto - 22.7 ppb (43.4 µg/m³) Vancouver - 18.7 ppb (35.7 µg/m³)	time-series (up to 120 months)	emergency department visits for cardiac (angina, myocardial infarction, heart failure, dysrhythmia) and respiratory (asthma, COPD, respiratory infections) conditions	association with PM_{10}, $PM_{2.5}$, SO_2, O_3, CO, & NO_2	male & female cardiac - 140.657 respiratory - 249,199 cases	pooled percent increase in cardiac visits per 18.4 ppb (35.1 µg/m³) in a single pollutant model for the summer season lag day 0 angina/infarction - 2.6 heart failure - 4.7 lag day 1 angina/infarction - 2.7	pooled percent increase in cardiac visits per 18.4 ppb (35.1 µg/m³) in a single pollutant model for the summer season lag day 0 angina/infarction 0.2 - 5.0 heart failure 1.2 - 8.4 lag day 1 angina/infarction 0.2 - 5.3	statistically significant association with angina/infarction and heart failure in a single pollutant model; no statistically significant associations for the winter season or for any respiratory conditions; no statistically significant association in a two pollutant model with CO	⊕⊕⊕◯ (moderate quality, no adjustment necessary)
(Strickland *et al.*, 2010) Atlanta, Georgia	population weighted hourly maximum concentrations at an unstated number of fixed monitoring location	mean 1-hr maximum overall - 23.3 ppb (44.5 µg/m³) warm season - 22.0 (42.0 µg/m³) cold season - 24.5 (46.8 µg/m³)	case-crossover and time-series (12 years)	asthma emergency department visits by children aged 5-17 years	association with $PM_{2.5}$ mass, $PM_{2.5}$ sulfate, $PM_{2.5}$ EC, $PM_{2.5}$ OC, $PM_{2.5}$ soluble metals, PM_{10}, $PM_{10\text{-}2.5}$, SO_2, CO, O_3, & NO_2	male & female 91,387 cases	rate ratios for ER visits per 12.9 ppb (24.6 µg/m³) in adjusted model using 0-2 day lag overall - 1.036 warm season - 1.066 rate ratio for ER visits relative to the first NO_2 quintile (< 15.4 µg/m³) 3rd quintile 37.1 - <46 ppb (µg/m³) - 1.040 4th quintile 46 - <57.1 ppb (µg/m³) - 1.087 5th quintile 57.1 - ≤181 ppb (µg/m³) - 1.087	rate ratios for ER visits per 12.9 ppb (24.6 µg/m³) in adjusted model using 0-2 day lag overall 1.018 - 1.055 warm season 1.038 - 1.095 rate ratio for ER visits relative to the first NO_2 quintile (< 15.4 µg/m³) 3rd quintile 37.1 - <46 ppb (µg/m³) 1.000 - 1.081 4th quintile 46 - <57.1 ppb (µg/m³) 1.044 - 1.131 5th quintile 57.1 - ≤181 ppb (µg/m³) 1.036 - 1.140	statistically significant association in the overall model and the warm season using 0-2 day and 0-7 day moving average lag period; statistically significant association in single and two pollutant model with ozone; sensitivity analysis using time-series analysis with LOESS smoothing yielded similar results in a base model; no statistically significant association for the cold season either in the base model or by quintile	⊕⊕◯◯ (low quality because increased rating from dose response offset by the modelling bias and the failure to describe the number of monitoring sites)

author / location	exposure monitoring	NO_2 concentration	study type (duration)	endpoint	co-pollutants	participants	ratio or risk	confidence interval	results	GRADE quality of evidence
(Strickland *et al.*, 2011) Atlanta, Georgia	1) one hour maximum from central monitor (six fixed monitoring sites) 2) unweighted average from monitoring sites 3) population-weighted average of spatially adjusted measurements from monitoring sites	1-hr maximum central monitor - 42.0 ppb (80.2 µg/m³) unweighted average - 27.7 ppb (52.9 µg/m³) population weighted average - 22.0 ppb (42.0 µg/m³)	time-series (144 months)	emergency department visits for pediatric asthma	association with PM_{10}, $PM_{2.5}$, CO, O_3, SO_2, & NO_2	male & female children (aged 5-17 years) 41,741 visits	rate ratio per 20 ppb (38.2 µg/m³) increase for 3-day average lag in single pollutant model (warm season only) central monitor - 1.052 unweighted - 1.079 pop. weighted - 1.105 rate ratio per IQR increase for 3-day average lag in single pollutant model central monitor (IQR 19.7 ppb, 37.6 µg/m³) - 1.051 unweighted (IQR 13.5 ppb, 25.8 µg/m³) - 1.053 pop. weighted (IQR 10.1 ppb, 19.3 µg/m³) - 1.052	rate ratio per 20 ppb (38.2 µg/m³) increase for 3-day average lag in single pollutant model (warm season only) central monitor 1.028 - 1.077 unweighted 1.044 - 1.1116 pop. weighted 1.060 - 1.152 rate ratio per IQR increase for 3-day average lag in single pollutant model central monitor (IQR 19.7 ppb, 37.6 µg/m³) 1.027 - 1.076 unweighted (IQR 13.5 ppb, 25.8 µg/m³) 1.029 - 1.077 pop. weighted (IQR 10.1 ppb, 19.3 µg/m³) 1.030 - 1.074	statistically significant association with emergency department visits by children with asthma using all three measures of hourly maximum NO_2 concentration; greater consistency when IQR is used to compare results across three measurement approaches	⊕⊕◯◯ (low quality because only single pollutant modelling)
(Szyszkowicz, 2008a) Edmonton, Alberta	mean daily concentration at an unnamed number of fixed monitoring locations	daily mean 21.9 ppb (41.8 µg/m³)	time-series (120 months)	emergency department visits for asthma	association with PM_{10}, $PM_{2.5}$, O_3, SO_2, CO, & NO_2	male & female 62,563 visits	percent change in relative risk per IQR for lag day 2 (12.8 ppb; 24.5 µg/m³) age < 10 yrs total whole year - 5.3 male all year - 5.5 total warm season - 16.1 female warm season - 12.6 male warm season - 19.2 age ≥ 10 years female warm season - 6.2	percent change in relative risk per IQR for lag day 2 (12.8 ppb; 24.5 µg/m³) age < 10 yrs total whole year 2.2 - 8.5 male all year 1.8 - 9.2 total warm season 9.5 - 23.0 female warm season 2.8 - 23.3 male warm season 11.4 - 27.6 age ≥ 10 years female warm season 1.4 - 11.3	statistically significant associations in a single pollutant model at lag 2, but not lag day 0 or 1; associations more prominent in children than teenagers or adults; no statistically significant associations during winter months (Oct-Mar);	⊕◯◯◯ (insufficient because of exposure bias and single pollutant modelling only)

author / location	exposure monitoring	NO_2 concentration	study type (duration)	endpoint	co-pollutants	participants	ratio or risk	confidence interval	results	GRADE quality of evidence
(Tramuto *et al.*, 2011) Palermo, Italy	mean daily concentration at ten fixed monitoring locations	daily mean 41.5 µg/m³	case-crossover (48 months)	emergency department visits for respiratory symptoms (respiratory deficiency, emphysema, dyspnea, cough, asthma, pneumonia, bronchopathy, & obstructive pulmonary disease)	association with PM_{10}, O2, CO & NO_2	male & female 48,519 visits	adjusted odds ratio per 10 µg/m³ change in a single pollutant model (no lag) all seasons - 1.015 warm season - 1.043	adjusted odds ratio per 10 µg/m³ change in a single pollutant model (no lag) all seasons 1.004 - 1.026 warm season 1.021 - 1.065	statistically significant association with respiratory symptoms among all patients for all seasons, and the warm season but not the cold season in a single pollutant model with no lag; statistically significant associations observed for lag day 0 or 1 but 2, 3, 4, or 5 (values not presented); statistically significant association observed in some age groups (55-64, 65-74, 75-84 years old) for either all subjects, males only or females only (values not presented); associations in age stratified groups not uniformly distributed across age groups or gender type but the associations were restricted to all seasons or the warm seasons	⊕◯◯◯ (insufficient because of publication bias with no lag period specified and very serious and the bias from the use of a single pollutant model

author / location	exposure monitoring	NO_2 concentration	study type (duration)	endpoint	co-pollutants	participants	ratio or risk	confidence interval	results	GRADE quality of evidence
(Villeneuve *et al.*, 2007) Edmonton, Alberta	daily average from three fixed monitoring sites	daily mean concentration summer – 17.5 ppb (33.4 µg/m³) winter – 28.5 ppb (54.4 µg/m³)	case-crossover (11 years)	ED visits for asthma and COPD in seven age groups	association with PM_{10}, $PM_{2.5}$, SO_2, O_3, CO, & NO_2	males & females in seven age groups (total 57,912 visits) 2 - 4 years - 7247 visits 5 -14 years - 13,145 visits 15 -24 years - 11,616 visits 25 - 44 years - 13,300 visits 45 - 64 years - 7899 visits 65 - 74 years - 2850 visits ≥ 75 years - 1855 visits	adjusted odds ratio for asthma ED visits in different age groups per IQR of 13. 5 ppb (25.8 µg/m³) for summer months (Apr-Sept) in a single pollution model 2 - ≥ 75 years lag 1 day - 1.07 lag 02 day - 1.09 lag 05 day - 1.14 2 - 4 years lag 1 day - 1.24 lag 02 day - 1.32 lag 05 day - 1.50 5 - 14 years lag 1 day - 1.08 lag 05 day - 1.13 15 - 44 years lag 02 day - 1.07 lag 05 day - 1.10 ≥ 75 years lag 02 day - 1.33 lag 05 day - 1.37	adjusted odds ratio for asthma ED visits in different age groups per IQR of 13. 5 ppb (25.8 µg/m³) for summer months (Apr-Sept) in a single pollution model 2 - ≥ 75 years lag 1 day 1.03 - 1.10 lag 02 day 1.04 - 1.13 lag 05 day 1.09 - 1.20 2 - 4 years lag 1 day 1.13 - 1.35 lag 02 day 1.18 - 1.48 lag 05 day 1.31 - 1.71 5 - 14 years lag 1 day 1.01 - 1.15 lag 05 day 1.02 - 1.24 15 - 44 years lag 02 day 1.00 - 1.14 lag 05 day 1.02 - 1.19 ≥ 75 years lag 02 day 1.03 - 1.70 lag 05 day 1.02 - 1.84	Statistically significant association with asthma ED visits in those aged 2 to ≥ 75 yrs of age for all lag periods except lag day 0 in a single pollutant model during summer months; statistically significant association in 4 of 6 age groups for at least two of the four lag periods investigated; no association in age groups in those aged 45- 64 and 65 -75; association generally confined to the summer months and all seasons with no statistically significant findings for the winter months (Oct - Mar); two pollutant modelling for the 05 day average lag revealed that the single pollutant results were not robust to CO for 5 of the 6 age groupings with the 2-4 year age group being the only population showing statistically significant results	⊕⊕◯◯ (low quality because of the lag-related modelling bias)

author / location	exposure monitoring	NO_2 concentration	study type (duration)	endpoint	co-pollutants	participants	ratio or risk	confidence interval	results	GRADE quality of evidence
(Wallace *et al.*, 2010) Hamilton, Ontario	daytime and nighttime (12-hr) mean levels based on hourly measurements from three fixed monitoring locations	12-hr median stable daytime normal day - 18.1 ppb (34.6 µg/m³) inversion day - 20.0 ppb (38.2 µg/m³) exacerbated daytime normal day - 19.1 ppb (36.5 µg/m³) inversion day - 32.1 ppb (61.3 µg/m³)	time-series (36 months)	sputum cell counts (neutrophils, eosinophils, macrophages, & lymphocytes) in asthmatics visiting a clinic	association with $PM_{2.5}$, O_3, CO & NO_2 during normal and boundary layer inversion days	male & female 485 stable asthmatics 189 exacerbated asthmatics	no associations with neutrophil percentages in stable asthmatics for inversion days, normal days, or total days per IQR of 9 ppb (17.2 µg/m³); no association with macrophage percentages in exacerbated asthmatics for total days per IQR of 18.7 ppb (35.7 µg/m³)	no associations with neutrophil percentages in stable asthmatics for inversion days, normal days, or total days per IQR of 9 ppb (17.2 µg/m³); no association with macrophage percentages in exacerbated asthmatics for total days per IQR of 18.7 ppb (35.7 µg/m³)	no statistically significant association with neutrophils in stable asthmatics or macrophages in exacerbated asthmatics for total days; no association with neutrophils in stable asthmatics for inversion or non-inversion; a seasonal relationship was observed between monthly NO_2 levels total sputum cell counts	⊕⊕◯◯ (low quality because of indirect measurements)
(Wilhelm *et al.*, 2008) Los Angeles and San Diego counties, CA	annual averages from eight fixed monitoring sites	annual average 3 pphm (57.3 µg/m³)	cross-sectional (24 months)	asthma morbidity including symptom reporting (cough, wheeze, shortness of breath, chest tightness, or phlegm) or emergency department visits	association with PM_{10}, $PM_{2.5}$, CO, O_3, & NO_2	male & female aged 0-17 yrs 617 children	no association for daily/weekly symptoms or ED visits in an adjusted single pollutant model per 1 pphm (19.1 µg/m³)	no association for daily/weekly symptoms or ED visits in an adjusted single pollutant model per 1 pphm (19.1 µg/m³)	no statistically significant association with symptom recording or emergency department visit in an adjusted single pollutant model	⊕◯◯◯ (insufficient because of short duration and the bias from using survey questionnaire)
(Wiwatanadate and Liwsrisakun, 2011) Chiang Mai, Thailand	mean daily concentration at a single fixed monitoring locations	daily mean 17.24 ppb (32.9 µg/m³)	time-series (10 months)	peak expiratory flow rates and unspecified symptoms in young and old asthmatics	association with $PM_{2.5}$, PM_{10}, CO, O_3, SO_2, & NO_2	male & female 121 cases	no significant change in odds ratio for multi-pollutant model	no significant change in odds ratio for multi-pollutant model	statistically significant positive changes in morning PERF using a single pollutant, but not a multipollutant model; no statistically significant associations with symptom reporting on any lag day	⊕◯◯◯ (insufficient because of very serious risk of exposure bias)

author / location	exposure monitoring	NO_2 concentration	study type (duration)	endpoint	co-pollutants	participants	ratio or risk	confidence interval	results	GRADE quality of evidence
(Wiwatanadate and Trakultivakorn, 2010) Chiang Mai, Thailand	mean daily concentration at a single fixed monitoring locations	17.24 ppb (32.9 µg/m³) mean	case-crossover (10 months)	peak expiratory flow rates in young asthmatics	association with $PM_{2.5}$, PM_{10}, CO, O_3, & NO_2	male & female 31 asthmatics	no significant change PEFR volume using single pollutant model	no significant change PEFR volume using single pollutant model	no statistically significant associations in morning, evening, daily average, or daily change PEFR measurements at any lag time;	⊕◯◯◯ (insufficient because of very serious risk of exposure bias)
(Yamazaki *et al.*, 2009) Ichikawa, Japan	hourly mean concentration at a single monitoring site (grouped into 6-hr nighttime and 8-hr daytime metrics)	mean warm months (Apr-Sept) 16.9 ppb (32.3 µg/m³) mean cold months (Oct-Mar) 27.2 ppb (52.0 µg/m³)	case-crossover (12 months)	nighttime visits emergency clinic for asthma attack	association with $PM_{2.5}$, O_3 & NO_2	male & female 403 visits	odds ratio per 10 ppb (19.1 µg/m³) increment children 6-14 yrs (lag 6-12 hr) - 1.73 children 6-14 yrs (daytime NO_2) - 1.83	odds ratio per 10 ppb (19.1 µg/m³) increment children 6-14 yrs (lag 6-12 hr) 1.02 - 2.93 children 6-14 yrs (daytime NO_2) 1.05 - 3.20	weak association observed with adolescents, but not adults or young children using single pollutant model; no association using multipollutant model; associations found for warm but not cold months	⊕◯◯◯ (insufficient because of severe exposure bias)
(Yamazaki *et al.*, 2011) Yotsukaido City, Japan	hourly average at a single fixed monitoring site	hourly average morning (7-8 AM) - 25.0 ppb (47.8 µg/m³) noon (12-1 PM) – 22.2 ppb (42.4 µg/m³) evening (6-7 PM) – 32.6 ppb (62.3 µg/m³) night (12-1 AM) – 8.3 ppb (54.1 µg/m³)	panel study (3 months)	peak expiratory flow (PEF) in severely asthmatic children	association with $PM_{2.5}$. photochemical oxidants, & NO_2	17 male and female asthmatic children aged 8-15 years	no tabular presentation of the findings graphical depiction of declines in PEF per 10 ppb (19.1 µg/m³) indicate declines in single and three-pollutant (NO_2/oxidants/PM_{10}) models, single pollutant associations tended to occur when PEF measurements were recorded in the evening between 8 PM - 11 AM (8-23 hr lag) - 17 out 24 hourly determinations three pollutant associations tended to occur when PEF measurements were recorded in the evening between 11 PM - 2 AM (15-20 hr lag) - 4 out of 24 hourly determinations	no tabular presentation of the findings, confidence intervals much wider for three pollutant modelling than for single pollutant	statistically significant associations with PEF in severely asthmatic children when measurements were recorded at hourly intervals in the morning (10 of 24 sessions) and evening (17 of 24 sessions) using a single pollutant model, statistically significant associations with PEF in the morning (4 of 24 sessions) and evening (4 of 24 sessions) using a three pollutant model	⊕◯◯◯ (insufficient because of severe exposure bias)

author / location	exposure monitoring	NO_2 concentration	study type (duration)	endpoint	co-pollutants	participants	ratio or risk	confidence interval	results	GRADE quality of evidence
(Yang *et al.*, 2007) Taipei, Taiwan	mean daily concentration at six fixed monitoring locations	daily mean 30.77 ppb (58.8 µg/m³)	case-crossover (8 years)	hospital admissions for asthma	association with PM_{10}, O_3, SO_2, CO, & NO_2	male and female of all ages 25,602 admissions	odds ratio for asthma admission per IQR of 10.05 ppb (19.20 µg/m³) on warm and cold days for single and two pollutant models warm days (≥ 25 °C) NO_2 only - 1.178 NO_2/PM_{10} - 1.328 NO_2/SO_2 - 1.224 NO_2/O_3 - 1.219 cold days (< 25 °C) NO_2 only - 1.128 NO_2/PM_{10} - 1.144 NO_2/SO_2 - 1.219 NO_2/CO - 1.198 NO_2/O_3 - 1.156	odds ratio for asthma admission per IQR of 10.05 ppb (19.20 µg/m³) on warm and cold days for single and two pollutant models warm days (≥ 25 °C) NO_2 only 1.113 - 1.247 NO_2/PM_{10} 1.224 - 1.441 NO_2/SO_2 1.140 - 1.314 NO_2/O_3 1.142 - 1.301 cold days (< 25 °C) NO_2 only 1.076 - 1.182 NO_2/PM_{10} 1.077 - 1.215 NO_2/SO_2 1.150 -1.291 NO_2/CO 1.111 - 1.291 NO_2/O_3 1.102 - 1.212	statistically significant association with asthma hospital admissions in single and two pollutant models with PM_{10}, SO_2, CO, & O_3 on average lag days 02, no significant association in two pollutant model with CO on warm days	⊕⊕⊕◯ (moderate quality, no adjustment necessary)

Acute Cardiovascular

author / location	exposure monitoring	NO_2 concentration	study type (duration)	endpoint	co-pollutants	participants	ratio or risk	confidence interval	results	GRADE quality of evidence
(Andersen *et al.*, 2007) Copenhagen, Denmark	daily average from a single fixed monitoring site	daily mean concentration 12 ppb (22.9 µg/m³)	time-series (6 years)	hospital admission of children (asthma) and the elderly (cardiovascular and respiratory disease)	association with PM_{10}, CO, & NO_2	male & female daily admissions cardiovascular (≥ 65 yrs) - 53 respiratory (≥ 65 yrs) - 21 asthma (5-18 yrs) - 3	adjusted relative risk for hospitalization per IQR 7 ppb (13.4 µg/m³) in single and two pollutant model respiratory lag 04 - 1.040 asthma lag 05 - 1.128	adjusted relative risk for hospitalization per IQR 7 ppb (13.4 µg/m³) ins ingle and two pollutant model respiratory lag 04 1.009 - 1.072 asthma lag 05 1.029 - 1.235	statistically significant association for respiratory disease (lag04) and asthma (lag05) admissions in a single pollutant model but not in a two pollutant model with PM_{10}; statistically significant association respiratory admission on lag days 2, 3, & 4 in single pollutant models and cardiovascular admission on lag day 3; no association with cardiovascular (lag03)admissions in single or two pollutant model with PM_{10}	⊕◯◯◯ (insufficient because of very serious risk of exposure bias)
(Andersen *et al.*, 2008) Copenhagen, Denmark	daily average from a single fixed monitoring site	daily mean concentration 11 ppb (21.0 µg/m³)	time-series (3.5 years)	hospital admission of children (asthma) and the elderly (cardiovascular and respiratory disease)	association with PM_{10}, $PM_{2.5}$, UFP (total number conc.), CO, O_3, & NO_2	male & female daily admissions cardiovascular (≥ 65 yrs) - 59 respiratory (≥ 65 yrs) - 22 asthma (5-18 yrs) - 3	adjusted relative risk for hospitalization per IQR 6 ppb (11.5 µg/m³) ins ingle and two pollutant model respiratory lag 04 - 1.06	adjusted relative risk for hospitalization per IQR 6 ppb (11.5 µg/m³) ins ingle and two pollutant model respiratory lag 04 1.01 - 1.12	statistically significant association for respiratory disease admission in single pollutant model (lag04) but not in a two pollutant model with UFP (total number count); no association with cardiovascular (lag03) or asthma (lag05) admissions in single or two pollutant model with UFP (total number count)	⊕◯◯◯ (insufficient because of very serious risk of exposure bias)

author / location	exposure monitoring	NO_2 concentration	study type (duration)	endpoint	co-pollutants	participants	ratio or risk	confidence interval	results	GRADE quality of evidence
(Baja *et al.*, 2010) Boston, MA	hourly means from six fixed monitoring sites	hourly mean during ECG - 21 ppb (40.1 µg/m³) 10-hr before ECG - 19 ppb (36.3 µg/m³)	panel study (60 months)	impact on heart rate QTc interval in susceptible populations (diabetes, obesity, smokers, polymorphic for oxidative stress genes that included 2 GST, 5 SNPs (single nucleotide polymorphisms), & a microsatellite repeat polymorphisms)	association with BC, $PM_{2.5}$, O_3, CO, SO_2, & NO_2	adult males only 2,280 volunteers	adjusted percent standard deviation change in QTc per IQR 13 ppb (24.8 µg/m³) in a 4-hr single pollutant lag model diabetics - 24.02 obese - 20.92 never smokers - 16.14	adjusted percent standard deviation change in QTc per IQR 13 ppb (24.8 µg/m³) in a 4-hr single pollutant lag model diabetics 6.67 - 41.37 obese 2.90 - 38.95 never smokers 0.27 - 32.02	statistically significant association with diabetics, obese individuals, & never smokers in an adjusted single pollutant 4-hr lag model but not in a distributed lag model that considered cumulative 10 hr exposures, no association in the total population or non-diabetics, non-obese, or smokers, no association with total genetic susceptibility score that considered genotypes for 5 enzyme polymorphisms	⊕⊕◯◯ (low quality because of indirect measurements)
(Ballester *et al.*, 2006) 14 Spanish cities	daily average from an unstated number of fixed monitoring sites in each city	daily mean ranged from 23.1 µg/m³ in Castellon to 76.2 µg/m³ in Valencia	time-series (3-6 years)	hospital admissions for cardiovascular or heart disease	association with PM_{10}, TSP, BS, SO_2, O_3, CO, & NO_2	male & female daily mortality rates cardiovascular ranged from 4.4 (Oviedo) to 35.7 (Barcelona) heart disease ranged from 2.2 (Pamplona) to 20.7 (Barcelona)	pooled relative risk for combined cardiovascular and cardiac disease per 10 µg/m³ increase in a two pollutant model revealed that the association observed for NO_2 was not robust to either particulates (PM_{10}, TSP, or BS) or SO_2, but remained robust to CO (marginally) and O_3 (data presented graphically) pooled (fixed effect) percent increase in hospital admissions per IQR 10 µg/m³ in single and two pollutant model for average lag 01 cardiovascular disease NO_2 only ≈ 0.38 heart disease NO_2 only ≈ 0.86	pooled relative risk for combined cardiovascular and cardiac disease per 10 µg/m³ increase in a two pollutant model revealed that the association observed for NO_2 was not robust to either particulates (PM_{10}, TSP, or BS) or SO_2, but remained robust to CO (marginally) and O_3 (data presented graphically) pooled (fixed effect) percent increase in hospital admissions per IQR 10 µg/m³ in single and two pollutant model for average lag 01 cardiovascular disease NO_2 only 0.07 - 0.69 heart disease NO_2 only 0.44 - 1.28	statistically significant association with hospital admissions for cardiovascular and heart disease in a single pollutant model at avg lag 01 and in a two pollutant model (combined admissions) with CO and O_3, but not "particulates" or O_3	⊕⊕◯◯ (low quality because of bias from the use of an unstated number of monitoring sites)

author / location	exposure monitoring	NO_2 concentration	study type (duration)	endpoint	co-pollutants	participants	ratio or risk	confidence interval	results	GRADE quality of evidence
(Barnett *et al.*, 2006) seven cities in Australia and New Zealand	daily average measurements from 1 to 13 fixed monitoring sites in each city	daily mean ranged from 7.0 ppb (13.4 µg/m³) in Canberra to 11.7 ppb (22.34 µg/m³) in Melbourne	case-crossover (5 years)	hospitalization of adults (15-64 yrs age) elderly (≥ 65 yrs of age) subjects for cardiovascular disease (arrhythmia, cardiac disease, cardiac failure, ischemic heart disease, & myocardial infarction)	association with PM_{10}, $PM_{2.5}$, O_3, CO, & NO_2	total deaths not reported but total daily cardiovascular hospitalization rates averaged from 7.7 (Melbourne) to 17.6 (Canberra) for adults and 15.5 (Sydney) to 26.6 (Christchurch) for the elderly	pooled (random effects) percent increases in cardiac hospitalizations per IQR 5.1 ppb (9.7 µg/m³) increase in single and two-pollutant models for a lag of 01 days adults (15-64 yrs) NO_2 only - 2.2 elderly (≥ 65 yrs old) NO_2 only - 3.4	pooled (random effects) percent increases in cardiac hospitalizations per IQR 5.1 ppb (9.7 µg/m³) increase in single and two-pollutant models for a lag of 01 days adults (15-64 yrs) NO_2 only - 0.9 - 3.4 elderly (≥ 65 yrs old) NO_2 only 1.9 - 4.9	statistically significant association with cardiac admissions in all seven cities using single pollutant model and an average lag of 01 days, statistically significant association after pooling the results from all cites using a random effects model, the 15-64 year age group showed statistically significant associations for two (arrhythmia and cardiac disease) of the five conditions whereas the over 65 age group showed significant associations for four (cardiac disease, cardiac failure, ischemic heart disease, & myocardial infarction) of the five disease states, no significant associations observed using the pooled results for total cardiovascular admissions using a two pollutant model with CO for either the 15-64 year age group or the over 65 age group	⊕⊕⊕◯ (moderate quality, no adjustment necessary)
(Chan *et al.*, 2008) Taipei, Taiwan	mean daily concentration at 16 fixed monitoring locations	daily mean high dust events – 34.9 ppb (66.7 µg/m³) low dust events – 29.4 ppb (56.2 µg/m³)	time-series (8 years)	emergency room visits for cardiovascular disease	interaction between Asian dust storms and PM_{10}, O_3, SO_2, & NO_2	male and female adults 5.7 - 7.2 cases per dust event	no significant change in odds ratio for cardiovascular disease (ischemic heart disease and cerebrovascular) emergency room visits per IQR 9.6 ppb (18.3 µg/m³)	no significant change in odds ratio for cardiovascular disease emergency room visits per IQR 9.6 ppb (18.3 µg/m³)	no statistically significant association with ischemic heart or cerebrovascular disease in a single pollutant model at lag periods ranging from day 0 to day 6	⊕⊕◯◯ (low quality because of bias from single pollutant model with no CO evaluation)

author / location	exposure monitoring	NO_2 concentration	study type (duration)	endpoint	co-pollutants	participants	ratio or risk	confidence interval	results	GRADE quality of evidence
(Chang *et al.*, 2005) Taipei, Taiwan	daily average from six fixed monitoring site	daily mean concentration 31.54 ppb (60.2 µg/m³)	case-crossover (5 years)	hospital admissions for cardiovascular disease	association with PM_{10}, SO_2, O_3, CO, & NO_2	total admissions of 74,509 mean daily hospital admission rates cardiovascular disease 40.80	odds ratio for cardiovascular disease admissions per IQR of 9.95 ppb (19.0 µg/m³) at two temperature limits in a two pollutant model at an average lag of 3 days (lag02) temp ≥ 20° C NO_2/PM_{10} - 1.194 NO_2/SO_2 - 1.279 NO_2/CO - 1.145 NO_2/O_3 - 1.165 temp < 20° C NO_2/SO_2 - 1.166 NO_2/CO - 1.126 NO_2/O_3 - 1.125	odds ratio for cardiovascular disease admissions per IQR of 9.95 ppb (19.0 µg/m³) at two temperature limits in a two pollutant model at an average lag of 3 days (lag02) temp ≥ 20° C NO_2/PM_{10} 1.159 - 1.230 NO_2/SO_2 1.244 - 1.315 NO_2/CO 1.106 - 1.186 NO_2/O_3 1.136 - 1.194 temp < 20° C NO_2/SO_2 1.095 - 1.241 NO_2/CO 1.046 - 1.213 NO_2/O_3 1.066 - 1.187	statistically significant association with hospital admissions for cardiovascular disease in a two pollutant model with PM_{10}, SO_2, CO and O_3 at high temperatures greater than or equal to 20°C; same significant associations at temperatures below 20° C for all co-pollutants except PM_{10}	⊕⊕◯◯ (low quality because of inconsistencies and potential modelling error stemming from the use of SAS)
(Chen *et al.*, 2010) Shanghai, China	daily average from six fixed monitoring sites	daily mean concentration 57 µg/m³	time-series (3 years)	total, cardiovascular & respiratory hospital admissions	association with PM_{10}, SO_2, & NO_2	total admissions of 1,702,180 mean daily hospital admission rates total - 1555 cardiovascular - 340 respiratory - 123	percent increase in admissions per IQR of 10 µg/m³ in single pollutant model total admissions lag day 4 - 0.97 lag day 5 - 0.99 cardiovascular lag day 4 - 1.23 lag day 5 - 0.80 lag days 06 - 1.54	percent increase in admissions per IQR of 10 µg/m³ in single pollutant model total admissions lag day 4 0.07 - 1.87 lag day 5 0.10 - 1.88 cardiovascular lag day 4 0.53 - 1.93 lag day 5 0.10 - 1.49 lag days 06 0.38 - 2.69	statistically significant association with total and cardiovascular admission rates on lag days 4 & 5 but not for the 4 shorter lag days using a single pollutant model, no associations with respiratory admission rates for any lag period; associations were confined to the cold season, with no significance in the warm season, two pollutant modelling with PM_{10} did not cause any change; however the significant associations for total and cardiovascular admissions on lag day 5 became non-significant after two-pollutant modelling with SO_2; J-shaped exposure response function observed	⊕⊕⊕◯ (moderate quality after decreasing for lag inconsistencies and increasing for the availability of dose response information)

author / location	exposure monitoring	NO_2 concentration	study type (duration)	endpoint	co-pollutants	participants	ratio or risk	confidence interval	results	GRADE quality of evidence
(Chuang *et al.*, 2011) Taipei, Taiwan	annual average from 72 fixed monitoring sites	annual mean concentration 24.53 ppb (46.8 µg/m³)	panel study (1 year)	biochemical and physiological measurements on volunteers including systolic BP, diastolic BP, total cholesterol, triglycerides, HDL cholesterol, fasting glucose, hemoglobin, interleukin 6, & neutrophils	association with PM_{10}, $PM_{2.5}$, SO_2, O_3, CO, & NO_2	male and female adults aged 54 - 90 years 1023 subjects	percent increase in biomarkers per IQR 12.83 ppb (24.5 µg/m³) systolic BP - 14.40 diastolic BP - 12.43 total cholesterol - 39.31 fasting glucose - 17.03 hemoglobin - 1.08 interleukin 6 - 0.32 neutrophils - 9.54	percent increase in biomarkers per IQR 12.83 ppb (24.5 µg/m³) systolic BP 10-98 - 17.82 diastolic BP 10.63 - 14.23 total cholesterol 32.38 - 46.24 fasting glucose 10.37 - 23.69 hemoglobin 0.84 - 1.33 interleukin 6 0.06 - 0.59 neutrophils 7.88 - 11.21	statistically significant association with 7 of nine biochemical or physiological biomarkers in a single pollutant model using a lag period of 1 year, no statistically significant association in two pollutant models with PM_{10}, $PM_{2.5}$, O_3, SO_2, and CO	⊕⊕◯◯ (low quality because of indirect measurements)
(Dietrich *et al.*, 2008) Switzerland	annual means using GIS information together with dispersion model information that was partially validated using outdoor measurements for an unstated number of subjects, daily values derived from an unstated number of fixed monitoring sites	daily mean (annual unavailable) men - 25.4 µg/m³ women - 24.5 µg/m³	panel study (36 months)	heart rate variability (standard deviation of normal to normal heart beat intervals (SDNN), total power (TP), high frequency (HF), low frequency (LF) & LF:HF ratio) using 24-hr electrocardiograms	association with outdoor NO_2 only	male & female > 50 yrs of age 683 men 725 women	adjusted percentage decline in women per 10 µg/m³ increase in annual exposure 24-hr values SDNN - -3 night time values LF - -6 LF:RF - -5 24-hr values (stay at home women) SDNN - -3 TP - -9	adjusted percentage decline in women per 10 µg/m³ increase in annual exposure 24-hr values SDNN -4 - -1 night time values LF -11 - -1 LF:RF -9 - 0 24-hr values (stay at home women) SDNN -6 - -0.4 TP -15 - -3	statistically significant association with a single measure of heart variability (SDNN) in women monitored for 24 hrs and two measures (LF & LF:HF ratio) in women examined during the night time, stratification by time spent at home showed a statistically significant association in 24-hr SSDNN and TP for those spending a larger percentage of time at home, no statistically significant association for HRV for any group of males, statistically significant association with SDNN in those reporting previous cardiovascular disease but not when the effect was stratified by sex	⊕⊕◯◯ (low quality because of indirect measurements)
(Goldberg *et al.*, 2008) Montreal, Quebec	pooled mean daily concentration from nine fixed monitoring locations	not provided	panel study design (2 months)	oxygen saturation & pulse rate in patients with congestive heart failure	differential effects of $PM_{2.5}$, SO_2, O_3, CO & NO_2	male and female 31 subjects	IQR (16.0 µg/m³ NO_2) mean difference pulse rate lag day 1 - 1.21	IQR (16.0 µg/m³ NO_2) mean differences pulse rate lag day 1 0.008 - 0.742	mean difference change only observed in the unadjusted model for lag day 1; no change for lag 0 or the 3-day lag mean; the effects were removed in the adjusted model	⊕⊕◯◯ (low quality because of indirect measurements)

author / location	exposure monitoring	NO_2 concentration	study type (duration)	endpoint	co-pollutants	participants	ratio or risk	confidence interval	results	GRADE quality of evidence
(Goldman *et al.*, 2010) Atlanta, Georgia	1- hour maximum concentration from five central monitors with independent determination of measurement error (co-located instrument) and spatial variability (semivariogram)	mean 1-hr max urban – 38.1 ppb (72.8 µg/m³) rural – 7.74 ppb (14.8 µg/m³)	time-series (72 months)	impact of measurement error on relative risk for emergency department visits associated with cardiovascular disease (Ischemic heart disease, dysrhythmia, congestive heart failure cerebrovascular disease)	association with PM_{10}, $PM_{2.5}$, CO, SO_2, O_3, NO, NOx, & NO_2 and $PM_{2.5}$ associated NO_3, SO_4, NH_4, EC, & OC	male & female 166,950 visits	risk ratio per ppm following error adjustment of the base case assessment measurement error - 1.0133 spatial error - 1.0046	confidence intervals not provided	factoring spatial variability into risk ratio resulted in a 43% reduction towards the null with the loss of significance association after the adjustment, factoring instrument precision into average risk ratios from a baseline assessment had little impact on the outcome	⊕○○○ (insufficient because of publication bias with no confidence intervals specified)
(Guo *et al.*, 2009) Beijing, China	pooled mean daily concentration from eight fixed monitoring locations	daily mean 68.25 µg/m³	case-crossover (19 months)	cardiovascular disease (emergency room visits)	differential effects of $PM_{2.5}$, SO_2, & NO_2	male & female cases 8,377	unadjusted model only; lag day 0 - 1.005	unadjusted model only; lag day 0 1.001 - 1.024	odds ratios for NO_2 unaffected in unadjusted but not adjusted model; lag day 1,2,& 3 show no change in unadjusted model	⊕○○○ (insufficient because of bias from small number of cases, pooling of exposure data, and short duration)
(Guo *et al.*, 2010b) Beijing, China	mean daily concentration at eight fixed monitoring locations	daily mean 66.6 µg/m³	case-crossover (12 months)	emergency department visits for hypertension	association with PM_{10}, SO_2, & NO_2	male & female 1,491 cases	odds ratio per 10 µg/m³ increase on lag day 3 single pollutant model - 1.101 multi-pollutant (PM_{10}) - 1.114 multi-pollutant (SO_2) - 1.130 multi-pollutant (PM_{10} & SO_2) - 1.144	odds ratio per 10 µg/m³ increase on lag day 3 single pollutant model - 1.038 - 1.168 multi-pollutant (PM_{10}) - 1.037 - 1.195 multi-pollutant (SO_2) - 1.041 - 1.225 multi-pollutant (PM_{10} & SO_2) - 1.046 - 1.251	statistically significant association with emergency department visits for hypertension in a single pollutant model on lag days 0, 2, & 3; statistically significant association on lag days 2, 3, & 4 for a multi-pollutant model with SO_2 and on day 3 for a multi-pollutant model with PM_{10}; statistically significant association on lag days 3 & 4 for a multi-pollutant model with SO_2 and PM_{10}	⊕○○○ (insufficient because of small number of cases short duration)

author / location	exposure monitoring	NO_2 concentration	study type (duration)	endpoint	co-pollutants	participants	ratio or risk	confidence interval	results	GRADE quality of evidence
(Hsieh *et al.*, 2010) Taipei, Taiwan	mean daily concentration at six fixed monitoring locations	daily mean 29.88 ppb (57.1 µg/m³)	case-crossover (132 months)	hospital admissions for myocardial infarction	association with PM_{10}, SO_2, O_3, CO, & NO_2	male & female 23,420 cases	odd ratio change per IQR of 10.44 ppb (19.9 µg/m³ NO_2 in two-pollutant model PM_{10} temp ≥ 23 ˚C - 1.12 temp < 23 ˚C - 1.11 SO_2 temp ≥ 23 ˚C - 1.16 temp < 23 ˚C - 1.18 CO temp ≥ 23 ˚C - 1.09 temp < 23 ˚C - 1.12 O_3 temp ≥ 23 ˚C - 1.09 temp < 23 ˚C - 1.18	odd ratio change per IQR of 10.44 ppb (19.9 µg/m³ NO_2 in two-pollutant model PM_{10} temp ≥ 23 ˚C 1.07 - 1.18 temp < 23 ˚C 1.06 - 1.16 SO_2 temp ≥ 23 ˚C 1.11 - 1.21 temp < 23 ˚C 1.13 - 1.24 CO temp ≥ 23 ˚C 1.03 - 1.15 temp < 23 ˚C - 1.05 - 1.20 O_3 temp ≥ 23 ˚C 1.05 - 1.14 temp < 23 ˚C 1.14 - 1.23	statistically significant associations for myocardial hospital admissions observed in both single pollutant models at both warm and cold temperatures, statistically significant associations in two-pollutant models with PM_{10}, SO_2, CO and O_3 at warm and cold temperatures	⊕⊕◯◯ (low quality because of inconsistencies and potential modelling error stemming from the use of SAS)
(Jalaludin *et al.*, 2006) Sydney, Australia	1-hr averages from 14 fixed monitoring sites	1-hr mean concentration 23.0 ppb (43.9 µg/m³)	time-series (5 years)	emergency department visits of elderly subjects for cardiovascular disease (cardiac disease, ischemic heart disease, & stroke)	association with nephelometric particulate matter (BSP) PM_{10}, $PM_{2.5}$, SO_2, O_3, CO, & NO_2	males and females ≥ 65 yrs of age daily rates of emergency department visits all cardiovascular disease types - 55.2 cardiac disease - 38.5 ischemic heart disease - 15.8 stroke - 11.3	percent change in total cardiovascular emergency department visits per IQR 9.3 ppb (17.8 µg/m³) in single and two-pollutant models on lag day 0 NO_2 only - 1.73 NO_2/PM_{10} ≈ 1.8 (depicted graphically) NO_2/O_3 ≈ 2.1 (depicted graphically) NO_2/SO_2 ≈ 1.5 (depicted graphically)	percent change in total cardiovascular emergency department visits per IQR 9.3 ppb (17.8 µg/m³) in single and two-pollutant models on lag day 0 NO_2 only 0.74 - 2.73 NO_2/PM_{10} ≈ 0.6 - 2.9 (depicted graphically) NO_2/O_3 ≈ 1.1 - 2.1 (depicted graphically) NO_2/SO_2 ≈ 0.3 - 2.7 (depicted graphically)	statistically significant association with cardiovascular ED visits on lag day 0 in single and two-pollutant models with PM_{10}, O_3, & SO_2 but with BSP or CO; statistically significant association with cardiac and ischemic heart disease on lag day 0 or 01 in single pollutant model but not for stroke: statistically significant association with all cardiovascular & cardiac ED visits on lag day 0 for cool but not warm periods, statistically significant association with stroke visits on lag day 2 in warm season, but no association in cool season; no statistically significant association for ischemic heart disease visits in two pollutant model with CO (data not presented)	⊕◯◯◯ (insufficient because of publication bias with no confidence intervals provided and lag selection bias)

author / location	exposure monitoring	NO_2 concentration	study type (duration)	endpoint	co-pollutants	participants	ratio or risk	confidence interval	results	GRADE quality of evidence
(Kalantzi *et al.*, 2011) Magnesia, Greece	daily mean from three fixed monitoring sites	daily mean 30.12 µg/m³	time-series (84 months)	total hosp. and those for pulmonary (COPD, asthma, infections, & other) and cardiovascular (ischemic heart disease, heart failure, & other) diseases	association with PM_{10}, CO, SO_2, O_3, NO, NOx, & NO_2	male & female admissions rate respiratory - 2.94 /day cardiovascular - 4.88 /day	no change in risk coefficients in either a single or combined model	no change in risk coefficients in either a single or combined model	no statistically significant association with NO_2; statistically significant associations found for NOx and CO in a combined pollutant models	⊕⊕◯◯ (low quality because the focus on NOx and the exposure bias)
(Lee *et al.*, 2007) Kaohsiung, Taiwan	mean daily concentration at six fixed monitoring locations	daily mean 27.10 ppb (51.8 µg/m³)	case-crossover (9 year)	hospital admissions for congestive heart failure	association with PM_{10}, SO_2, O_3, CO, & NO_2	male and female adults 13,475 admissions	odds ratio per IQR 16.85 ppb (32.2 µg/m³ NO_2) in single and two pollutant models at 02 day lag single pollutant model temp > 25 ˚C - 1.20 temp < 25 ˚C - 1.89 two pollutant model NO_2/PM_{10} temp < 25 ˚C - 1.83 NO_2/SO_2 temp > 25 ˚C - 1.20 temp < 25 ˚C - 2.25 NO_2/CO temp < 25 ˚C - 2.01 NO_2/O_3 temp < 25 ˚C - 1.85	odds ratio per IQR 16.85 ppb (32.2 µg/m³ NO_2) in single and two pollutant models at 02 day lag single pollutant model temp > 25 ˚C 1.03 - 1.39 temp < 25 ˚C 1.65 - 2.16 two pollutant model NO_2/PM_{10} temp < 25 ˚C 1.52 - 2.19 NO_2/SO_2 temp > 25 ˚C 1.02 -1.41 temp < 25 ˚C 1.90 - 2.67 NO_2/CO temp < 25 ˚C 1.64 - 2.46 NO_2/O_3 temp < 25 ˚C 1.61 - 2.12	statistically significant association with admissions for congestive heart failure in warm and cold days using a single pollutant model with a lag of 02 days, statistically significant association with admissions using a two pollutant model with PM_{10}, SO_2, CO, or O_3 on cold days, no statistically significant association on warm days using a two pollutant model except for SO_2	⊕⊕◯◯ (low quality because of inconsistencies and potential modelling error stemming from the use of SAS)

author / location	exposure monitoring	NO_2 concentration	study type (duration)	endpoint	co-pollutants	participants	ratio or risk	confidence interval	results	GRADE quality of evidence
(Llorca *et al.*, 2005) Torrelavega, Spain	daily average from three fixed monitoring site	daily mean concentration 21.3 µg/m³	time-series (4 years)	total cardiorespiratory, cardiac, & respiratory emergency department visits	association with total suspended particulate (TSP), hydrogen sulfide (H2S), sulfur dioxide (SO_2), nitrogen oxide (NO), & NO_2	total admissions of 18,137 mean daily hospital admission rates cardiac - 7.61 respiratory - 4.93	relative risk per IQR 100 µg/m³ in single and multi-pollutant model with an unstated lag period total cardiopulmonary NO_2 only - 1.37 NO_2/TSP,H2S,SO_2,NO - 1.20 cardiac NO_2 only - 1.27 respiratory NO_2 only - 1.54 NO_2/TSP,H2S,SO_2,NO - 1.69	relative risk per IQR 100 µg/m³ in single and multi-pollutant model with an unstated lag period total cardiopulmonary NO_2 only 1.26 - 1.49 NO_2/TSP,H2S,SO_2,NO 1.05 - 1.39 cardiac NO_2 only 1.14 - 1.42 respiratory NO_2 only 1.34 - 1.76 NO_2/TSP,H2S,SO_2,NO 1.34 - 2.13	statistically significant association with hospital admissions for total cardiopulmonary, cardiac, & respiratory disease in single pollutant model with an unstated lag period; statistically significant association with admissions for total cardiopulmonary and respiratory causes in multi-pollutant models, but not for cardiac disease	⊕○○○ (insufficient because of imprecision caused by no lag period, publication bias from poor method description)
(Malinauskiene *et al.*, 2011) Kaunas, Lithuania	pooled monitoring data at 12 fixed monitoring sites	daily mean 25 µg/m³	case control (108 months)	myocardial infarction (emergency room visit)	association with indoor/outdoor NO_2 differences	women only cases 368 controls 725	no significant change in odds ratio	no significant change in odds ratio	odds ratios showed no associations with outdoor NO_2 exposures greater than 35 µg/m³	⊕○○○ (insufficient because of bias from small number of cases, pooling of exposure data, and short duration)
(Min *et al.*, 2008) Taein Island, Japan	mean daily concentration at an unknown number of fixed monitoring locations	daily mean 24 ppb (45.8 µg/m³)	cross-sectional study (12 months)	heart rate variability using heart rate in the N-N interval, low frequency heart rate modulation, & high frequency heart rate modulation	association with PM_{10}, SO_2, & NO_2	male & female 1349 subjects	percentage change in heart rate variability per ISD 17 ppb; 32.5 µg/m³ 0-6hr lag low frequency -7.32 0-9 hr lag heart rate -3.31 low frequency -10.40 0-12 hr lag low frequency -10.44	percentage change in heart rate variability per ISD 17 ppb; 32.5 µg/m³ 0-6hr lag low frequency -14.32 - 0.26 0-9 hr lag heart rate -7.06 - 0.60 low frequency -18.26 - -1.79 0-12 hr lag low frequency -19.19 - -0.75	statistically significant declines in low frequency heart rate modulation at three short lag periods, but not at longer time periods in a single pollutant model; similar results in a multi-pollutant model;	⊕○○○ (insufficient because of potential exposure measurement bias and short duration)

author / location	exposure monitoring	NO_2 concentration	study type (duration)	endpoint	co-pollutants	participants	ratio or risk	confidence interval	results	GRADE quality of evidence
(Santos *et al.*, 2008) Sao Paulo, Brazil	mean daily concentration at seven fixed monitoring locations	daily mean 99.03 µg/m³	time-series (20 months)	emergency room visits for cardiac arrhythmia	association with PM_{10}, SO_2, O_3, CO, & NO_2	male and female adults 3251 admissions	percentage increase in ER visits per IQR of 49.5 µg/m³ in single pollutant model lag 0 ≈ 13 (depicted graphically)	percentage increase in ER visits per IQR of 49.5 µg/m³ in single pollutant model lag 0 ≈ 7 -18 (depicted graphically)	statistically significant association with emergency room visits for cardiac arrhythmia in a single pollutant model on lag day 0 only, no statistically significant associations in two pollutant model with CO or three pollutant model with PM_{10} and CO, quintile analysis suggests a threshold a threshold at a concentration range of 126.2 - 303.0 µg/m³	⊕◯◯◯ (insufficient because of publication bias and small number of cases)

author / location	exposure monitoring	NO_2 concentration	study type (duration)	endpoint	co-pollutants	participants	ratio or risk	confidence interval	results	GRADE quality of evidence
(Stieb *et al.*, 2009) Seven Canadian cities Montreal Ottawa Edmonton Saint John Halifax Toronto Vancouver	mean daily concentration from 1 to 14 fixed monitoring sites	hourly mean Montreal – 19.4 ppb (37.1 µg/m³) Ottawa – 18.8 (35.9 µg/m³) Edmonton – 21.9 (41.8 µg/m³) Saint John – 9.3 (17.8 µg/m³) Halifax – 17.5 ppb (33.4 µg/m³) Toronto – 22.7 ppb (43.4 µg/m³) Vancouver – 18.7 ppb (35.7 µg/m³)	time-series (up to 120 months)	emergency department visits for cardiac (angina, myocardial infarction, heart failure, dysrhythmia) and respiratory (asthma, COPD, respiratory infections) conditions	association with PM_{10}, $PM_{2.5}$, SO_2, O_3, CO, & NO_2	male & female cardiac - 140.657 respiratory - 249,199 cases	pooled percent increase in cardiac visits per 18.4 ppb (35.1 µg/m³) in a single pollutant model for the summer season lag day 0 angina/infarction - 2.6 heart failure - 4.7 lag day 1 angina/infarction - 2.7	pooled percent increase in cardiac visits per 18.4 ppb (35.1 µg/m³) in a single pollutant model for the summer season lag day 0 angina/infarction 0.2 - 5.0 heart failure 1.2 - 8.4 lag day 1 angina/infarction 0.2 - 5.3	statistically significant association with angina/infarction and heart failure in a single pollutant model; no statistically significant associations for the winter season or for any respiratory conditions; no statistically significant association in a two pollutant model with CO	⊕⊕⊕◯ (moderate quality, no adjustment necessary)

author / location	exposure monitoring	NO_2 concentration	study type (duration)	endpoint	co-pollutants	participants	ratio or risk	confidence interval	results	GRADE quality of evidence
(Szyszkowicz and Rowe, 2010) Edmonton, Alberta	mean daily concentration at an unstated number of fixed monitoring locations	daily mean 21.9 ppb (41.8 µg/m³)	time-series (120 months)	emergency department visits for chest pain and weakness	association with PM_{10}, $PM_{2.5}$, SO_2, O_3, CO, & NO_2	male & female 68,714 chest pain cases 66,092 weakness cases	relative risk percentage for chest pain per 12.8 ppb (24.4 µg/m³) change in a single pollutant model (lag day 0) all seasons, all patients - 2.6 all seasons, female patients - 3.3 all seasons, male patients - 2.4 warm seasons, all patients - 2.9 warm seasons, male patients - 3.8 cold seasons, all patients - 1.7 cold seasons, female patients - 2.8 relative risk percentage for weakness per 12.8 ppb (24.4 µg/m³) change in a single pollutant model (lag day 2) all seasons, all patients - 2.1 all seasons, female patients - 2.1 all seasons, male patients - 2.4 cold seasons, all patients - 2.7 cold seasons, male patients - 3.4 cold seasons, female patients - 2.3	relative risk percentage for chest pain per 12.8 ppb (24.4 µg/m³) change in a single pollutant model (lag day 0) all seasons, all patients - 1.3 - 4.0 all seasons, female patients - 1.4 - 5.2 all seasons, male patients - 0.6 - 4.3 warm seasons, all patients - 0.0 - 5.8 warm seasons, male patients - 0.0 - 7.8 cold seasons, all patients - 0.1 - 3.4 cold seasons, female patients - 0.5 - 5.1 relative risk percentage for weakness per 12.8 ppb (24.4 µg/m³) change in a single pollutant model (lag day 2) all seasons, all patients - 0.7 - 3.6 all seasons, female patients - 0.2 - 4.0 all seasons, male patients - 0.5 - 4.4 cold seasons, all patients - 1.0 - 4.5 cold seasons, male patients - 1.0 - 5.9 cold seasons, female patients - 0.1 - 4.6	statistically significant association with admissions for chest pain in warm, cold, and both seasons for all patients but differential associations observed for men and women in warm and cold seasons; statistically significant associations observed for women but not men or all patients on lag day 1 (data not shown) as well as lag day 0; statistically significant associations for weakness on lag day 2 but not 0 or 1 for males, females and all patients; statistically significant association for weakness during cold but not warm seasons for males and females on lag day 2 only	⊕◯◯◯ (insufficient because of bias from the use of a unstated number of monitoring sites and publication and imprecision with wide confidence intervals)

author / location	exposure monitoring	NO_2 concentration	study type (duration)	endpoint	co-pollutants	participants	ratio or risk	confidence interval	results	GRADE quality of evidence
(Szyszkowicz *et al.*, 2012) Edmonton, Canada	daily average concentration from three fixed monitoring sites	daily mean 21.9 ppb (41.8 µg/m³)	case-crossover (10 years)	emergency department visits for hypertension	association with PM_{10}, $PM_{2.5}$, CO, O_3, SO_2, & NO_2	males and females 5365 cases	odds ratio per IQR of 12.8 ppb (24.4 µg/m³) in single pollutant model using single and cumulative lag periods up to seven days lag day 3 - 1.06 lag day 02 - 1.08 lag day 03 - 1.07	odds ratio per IQR of 12.8 ppb (24.4 µg/m³) in single pollutant model using single and cumulative lag periods up to seven days lag day 3 1.00 - 1.12 lag day 02 1.01 - 1.15 lag day 03 1.00 - 1.14	statistically significant association with emergency dept visits for hypertension on lag day 3 and cumulative lags 02 and 03, no statistical significance on all the seven other single lag days and six other cumulative lag days	⊕⊕◯◯ (low quality because of using a single pollutant model only)
(Szyszkowicz, 2008b) Edmonton, Alberta	mean daily concentration at three fixed monitoring locations	daily mean 21.9 ppb (41.8 µg/m³)	time-series (120 months)	short-term effect on emergency department visits for acute ischemic stroke	association with SO_2, O_3, CO & NO_2	male & female 10,881 visits	relative risk percentage per IQR 12.8 ppb (24.4 µg/m³) in a single pollutant model (lag day 0-2) group age 20-64 years all seasons & all genders - 6.3 all seasons & females - 12.4 cold seasons & females - 13.8 group age 65-100 years old warm season & all genders - 8.2	relative risk percentage per IQR 12.8 ppb (24.4 µg/m³) in a single pollutant model (lag day 0-2) group age 20-64 years all seasons & all genders 0.2 - 12.8 all seasons & females 2.9 - 22.7 cold seasons & females 2.1 - 26.7 group age 65-100 years old warm season & all genders 0.4 - 16.7	statistically significant association ED visits for ischemia in females but not males aged 20-64 years for all seasons and cold season but not the warm season; statistically significant association for males & females together aged 20-64 years for all seasons and the warm season but not the cold season; statistically significant association for elderly (aged 65-100 years) males and females during the warm season; no association for elderly males or elderly females for all seasons or the cold seasons	⊕◯◯◯ (insufficient because of serious inconsistencies and the bias from the use of a single pollutant model)

author / location	exposure monitoring	NO_2 concentration	study type (duration)	endpoint	co-pollutants	participants	ratio or risk	confidence interval	results	GRADE quality of evidence
(Thach *et al.*, 2010) Hong Kong, China	daily averages from eight fixed monitoring sites	daily mean 58.7 µg/m³	time-series (84 months)	interaction with influenza and impact on mortality and hospitalizations for stroke, ischemic heart disease (IHD), lower respiratory infection, (LRI), acute respiratory disease (ARD), & chronic obstructive pulmonary disease (COPD)	association with PM_{10}, SO_2, O_3, & NO_2	number of subjects not stated	unadjusted excess mortality risk per 10 µg/m³ increase in single pollutant model stroke - 1.13 IHD - 2.08 LRI - 1.75 COPD - 1.39 unadjusted excess hospitalization risk per 10 µg/m³ increase in single pollutant model IHD - 0.94 ARD - 1.22 COPD - 1.94	unadjusted excess mortality risk per 10 µg/m³ increase in single pollutant model stroke 0.19 - 2.08 IHD 1.10 - 3.07 LRI 0.74 - 2.77 COPD 0.18 - 2.61 unadjusted excess hospitalization risk per 10 µg/m³ increase in single pollutant model IHD 0.46 - 1.42 ARD 0.74 - 1.71 COPD 1.55 - 2.33	statistically significant association with mortality from stroke, IHD, LRI, & COPD, statistically significant association with hospitalizations from IHD, ARD, & COPD, no association in unadjusted risk from hospitalizations from stroke, adjustment for influenza epidemic periods or predominance caused greater than 0.1 % decrease in mortality from stroke, LRI, & COPD, adjustment for influenza intensity, epidemic periods, or predominance caused greater than 0.1 % decrease in hospitalizations from ARD,	⊕◯◯◯ (insufficient because of unknown number of cases and risk of exposure bias)
(Tolbert *et al.*, 2007) Atlanta, Georgia	1-hr maximum for an unstated number of monitoring sites	average 1-hr maximum 43.2 ppb (82.5 µg/m³)	time-series (10 years)	cardiovascular & respiratory emergency department visits	association with PM_{10}, $PM_{10-2.5}$(course), $PM_{2.5}$, $PM_{2.5}$ sulfate, $PM_{2.5}$ EC, $PM_{2.5}$ OC, $PM_{2.5}$ TC, $PM_{2.5}$ soluble metals, oxygenated hydrocarbons, SO_2, CO, O_3, & NO_2	male and females 238,360 cardiovascular visits 1,072,429 respiratory visits	relative risk per IQR 23.0 ppb (43.9 µg/m³) in single and two-pollutant models with a 0-2 day average lag cardiovascular NO_2 only - 1.015 respiratory NO_2 only - 1.015 NO_2/CO ≈ 1.012 (depicted graphically)	relative risk per IQR 23.0 ppb (43.9 µg/m³) in single and two-pollutant models with a 0-2 day average lag cardiovascular NO_2 only 1.004 - 1.025 respiratory NO_2 only 1.004 - 1.025 NO_2/CO ≈ 1.008 - 1.029 (depicted graphically)	statistically significant association with emergency room visits for cardiovascular and respiratory diseases in a single pollutant model at an 0-1 lag period; statistically significant association for respiratory visits in a two pollutant model with CO; no association with respiratory visits in a two pollutant model with PM_{10} or O_3 and a three pollutant model PM_{10} & O_3; no association with cardiovascular visits in a two pollutant model with CO or $PM_{2.5}$ TC and a three pollutant model with $PM_{2.5}$ TC & CO;	⊕⊕◯◯ (low quality because of bias from the use of a unstated number of monitoring sites)

author / location	exposure monitoring	NO_2 concentration	study type (duration)	endpoint	co-pollutants	participants	ratio or risk	confidence interval	results	GRADE quality of evidence
(Vencloviene *et al.*, 2011) Kaunas, Lithuania	mean daily concentration at three fixed monitoring locations	daily mean 34.6 µg/m³	case-crossover (36 months)	myocardial infarction & unstable angina pectoris (emergency room visit)	interaction study (NO_2 & geomagnetic activity)	male & female cases 6,594	IQR (19.05 µg/m³ NO_2) rate ratios NO_2 - 1.21 NO_2 & geomagnetic - 1.54	IQR (19.05 µg/m³ NO_2) rate ratios NO_2 0.96 - 1.53 NO_2 & geomagnetic 0.99 - 2.40	associations observed for patients < 65 years of age, but not with those >65 years old; risk of emergency hospitalization for those below 65 increased by 61% (for 19.1 µg/m³ increase) after extremely high or low geomagnetic activity	⊕◯◯◯ (insufficient because of inconsistencies across age groups and bias from the small number of cases and short duration)
(Villeneuve *et al.*, 2006) Edmonton, Alberta	daily average from three fixed monitoring sites	daily mean concentration 24.0 ppb (45.8 µg/m³)	case-crossover (11 years)	ED visits for acute ischemic, hemorrhagic, transient cerebral ischemic or other types of stroke in three elderly age groups	association with PM_{10}, $PM_{2.5}$, SO_2, O_3, CO, & NO_2	male and female adults ≥ 65 years of age 65 - < 75 yrs of age - 5435 visits 75 - < 85 yrs of age - 5129 visits > 85 yrs of age - 1858 visits	adjusted odds ratio for acute ischemic stroke per IQR of 13.5 ppb (25.8 µg/m³) in single pollutant model for the summer months 0 day lag - 1.17 1 day lag - 1.18 02 day lag - 1.26	adjusted odds ratio for acute ischemic stroke per IQR of 13.5 ppb (25.8 µg/m³) in single pollutant model for the summer months 0 day lag 1.05 - 1.31 1 day lag 1.05 - 1.32 02 day lag 1.09 - 1.46	statistically significant association with acute ischemic stroke(AIS) in single pollutant model during warm, but not cool, seasons using all three lag periods, stratification by sex showed a statistically significant association with AIS in females but not females > 65 years of age, no statistically significant associations with AIS in two-pollutant models with SO_2, CO, O_3, PM_{10}, or $PM_{2.5}$ for lag day O2, no significant association with hemorrhagic or transient cerebral ischemic stroke in warm or cold season or for male or female subgroups	⊕⊕◯◯ (low quality because of the small number of cases)
(Wellenius *et al.*, 2005) Pittsburgh, Pennsylvania	mean daily concentration at two fixed monitoring locations	daily mean 26.48 ppb (50.6 µg/m³)	case-crossover (13 years)	hospital admissions for congestive heart failure	association with PM_{10}, SO_2, O_3, CO, & NO_2	male and female adults ≥ 65 years of age 55,019 admissions	percentage increase in admissions per IQR of 11 ppb (21.0 µg/m³) in single and two pollutant models on lag day 0 NO_2 only - 4.22 NO_2/PM_{10} - 4.04 NO_2/O_3 - 3.73 NO_2/SO_2 - 3.79	percentage increase in admissions per IQR of 11 ppb (21.0 µg/m³) in single and two pollutant models on lag day 0 NO_2 only 2.61 - 5.85 NO_2/PM_{10} 1.83 - 6.31 NO_2/O_3 2.10 - 5.39 NO_2/SO_2 1.93 - 5.67	statistically significant increase in hospital admissions for congestive heart failure using single and two pollutant models for PM_{10}, O_3, and SO_2 on lag day 0, no statistically significant association in two pollutant mode with CO	⊕⊕◯◯ (low quality because of limited number of modelling sites)

author / location	exposure monitoring	NO_2 concentration	study type (duration)	endpoint	co-pollutants	participants	ratio or risk	confidence interval	results	GRADE quality of evidence
(Wong *et al.*, 2009) Hong Kong, China	daily average from eight fixed monitoring locations	daily mean 58.7 µg/m³	time-series (84 months)	hospitalization and mortality for acute respiratory (ARD), chronic obstructive pulmonary (COPD, and cardiovascular (CVD) disease	interaction study (influenza and PM_{10}, O_3, SO_2 & NO_2)	male & female (avg daily rates) mortality RD - 16.2 COPD - 5.9 CVD - 23.8 hospitalizations RD - 270.3 ARD - 104.9 COPD - 91.5 CVD - 203.5	excess risk for all subjects per 10 µg/m³ increase in single pollutant model baseline mortality RD - 1.24 CVD - 1.23 baseline hospitalizations RD - 0.85 COPD - 1.84 CVD - 0.98 excess risk for all subjects > 65 years of age per 10 µg/m³ increase in single pollutant model modifying effect hospitalizations COPD - 0.43	excess risk for all subjects per 10 µg/m³ increase in single pollutant model baseline mortality RD 0.27 - 2.22 CVD 0.41 - 2.06 baseline hospitalizations RD 0.51 - 1.18 COPD 1.32 - 2.35 CVD 0.63 - 1.33 excess risk for all subjects > 65 years of age per 10 µg/m³ increase in single pollutant model modifying effect hospitalizations COPD 0.05 - 0.81	statistically significant association with baseline mortality from respiratory and cardiovascular disease and baseline hospitalizations from respiratory, cardiopulmonary, and cardiovascular disease, statistically significant interaction with influenza for COPD-related hospitalizations in those > 65 years of age, no association for hospitalizations from acute respiratory disease, no statistically interactions with influenza for any mortality cause or any age-stratified group hospitalized for RD, ARD, or CVD	⊕⊕◯◯ (low quality because of bias from using single pollutant models only)
(Yamazaki *et al.*, 2011) 13 cites in Japan	hourly measurements from a single fixed monitoring site in each city	daily mean ranged from 14. 8 ppb (28.3 µg/m³; Sendai) to 36.9 ppb (70.5 µg/m³; Yokohama)	case-crossover (5 years)	mortality from intracerebral hemorrhage (ICH) and ischemic stroke (IS)	association with PM_7, photochemical oxidants & NO_2	total of 17,354 deaths for ICH and 46,370 for IS	no significant change in odds ratio per 10 ppb (1.91 µg/m³) in a pooled multi-pollutant model that included daily average PM7, total oxidants, temperature and humidity	no significant change in odds ratio per 10 ppb (1.91 µg/m³) in a pooled multi-pollutant model that included daily average PM7, total oxidants, temperature and humidity	no statistically significant association for either ICH or IS mortality in a multi-pollutant model at any lag period for either the warm or cold months; no statistically significant associations for either 1-hr or 24-hr measures of NO_2 concentration	⊕◯◯◯ (insufficient because of severe exposure bias)
(Yang, 2008) Taipei, Taiwan	mean daily concentration at six fixed monitoring locations	daily mean 30.59 ppb (58.4 µg/m³)	case-crossover (108 months)	hospitalization for congestive heart failure	association with PM_{10}, O_3, CO, SO_2, & NO_2	male & female 24,240 cases	IQR (10.04 ppb; 19.2 µg/m³ NO_2) odds ratio (two-pollutant model) PM_{10} temp ≥ 20 ˚C - 1.17 SO_2 temp ≥ 20 ˚C - 1.32 CO temp ≥ 20 ˚C - 1.18 O_3 temp ≥ 20 ˚C - 1.15	IQR (10.04 ppb; 19.2 µg/m³ NO_2) odds ratio (two-pollutant model) PM_{10} temp ≥ 20 ˚C 1.11 - 1.24 SO_2 temp ≥ 20 ˚C - 1.25 - 1.39 CO temp ≥ 20 ˚C - 1.10 - 1.26 O_3 temp ≥ 20 ˚C - 1.10 - 1.20	significant associations observed in both single and two-pollutant models for warm days, no associations observed on cold days	⊕⊕◯◯ (low quality because of inconsistencies and potential modelling error stemming from the use of SAS)

author / location	exposure monitoring	NO_2 concentration	study type (duration)	endpoint	co-pollutants	participants	ratio or risk	confidence interval	results	GRADE quality of evidence
(Zanobetti *et al.*, 2010)	30-min averages from five fixed monitoring sites	mean value (30 min, 2-hr, 72-hr, & 120 hr) 30 min – 21 ppb (40.1 µg/m³)	time-series (30 months)	heart rate variability (standard deviation of normal to normal heart beat intervals (SDNN), root mean square successive difference (RMSSD), and high frequency (HF)) in discharged patients with coronary artery disease	association with $PM_{2.5}$, BC, O_3, & NO_2	male & female 46 patients	percent change in response per IQR of 13.4 µg/m³ at a lag of 72 hr in a two pollutant model RMSSD BC co-pollutant 2.27 HF $PM_{2.5}$ co-pollutant -7.63	percent change in response per IQR of 13.4 µg/m³ at a lag of 72 hr in a two pollutant model RMSSD BC co-pollutant 0.00 - 4.59 HF $PM_{2.5}$ co-pollutant -13.44 - -1.44	statistically significant negative association with HF in a single pollutant model at all lag times and negative association with RMSSD at the 120 hr lag time, statistically significant positive association with RMSSD at 72 hr lag time in a two pollutant model with BC and a negative association with HF in a two pollutant model with $PM_{2.5}$, no association for RMSSD in two pollutant model with $PM_{2.5}$ or for HF in two pollutant model with BC	⊕⊕◯◯ (low quality because of indirect measurements)

Acute Respiratory

author / location	exposure monitoring	NO_2 concentration	study type (duration)	endpoint	co-pollutants	participants	ratio or risk	confidence interval	results	GRADE quality of evidence
(Andersen *et al.*, 2007) Copenhagen, Denmark	daily average from a single fixed monitoring site	daily mean concentration 12 ppb (22.9 µg/m³)	time-series (6 years)	hospital admission of children (asthma) and the elderly (cardiovascular and respiratory disease)	association with PM_{10}, CO, & NO_2	male & female daily admissions cardiovascular (≥ 65 yrs) - 53 respiratory (≥ 65 yrs) - 21 asthma (5-18 yrs) - 3	adjusted relative risk for hospitalization per IQR 7 ppb (13.4 µg/m³) in single and two pollutant model respiratory lag 04 - 1.040 asthma lag 05 - 1.128	adjusted relative risk for hospitalization per IQR 7 ppb (13.4 µg/m³) ins ingle and two pollutant model respiratory lag 04 1.009 - 1.072 asthma lag 05 1.029 - 1.235	statistically significant association for respiratory disease (lag04) and asthma (lag05) admissions in a single pollutant model but not in a two pollutant model with PM_{10}; statistically significant association respiratory admission on lag days 2, 3, & 4 in single pollutant models and cardiovascular admission on lag day 3; no association with cardiovascular (lag03)admissions in single or two pollutant model with PM_{10}	⊕◯◯◯ (insufficient because of very serious risk of exposure bias)
(Andersen *et al.*, 2008) Copenhagen, Denmark	daily average from a single fixed monitoring site	daily mean concentration 11 ppb (21.0 µg/m³)	time-series (3.5 years)	hospital admission of children (asthma) and the elderly (cardiovascular and respiratory disease)	association with PM_{10}, $PM_{2.5}$, UFP (total number conc.), CO, O_3, & NO_2	male & female daily admissions cardiovascular (≥ 65 yrs) - 59 respiratory (≥ 65 yrs) - 22 asthma (5-18 yrs) - 3	adjusted relative risk for hospitalization per IQR 6 ppb (11.5 µg/m³) ins ingle and two pollutant model respiratory lag 04 - 1.06	adjusted relative risk for hospitalization per IQR 6 ppb (11.5 µg/m³) ins ingle and two pollutant model respiratory lag 04 1.01 - 1.12	statistically significant association for respiratory disease admission in single pollutant model (lag04) but not in a two pollutant model with UFP (total number count); no association with cardiovascular (lag03) or asthma (lag05) admissions in single or two pollutant model with UFP (total number count)	⊕◯◯◯ (insufficient because of very serious risk of exposure bias)

author / location	exposure monitoring	NO_2 concentration	study type (duration)	endpoint	co-pollutants	participants	ratio or risk	confidence interval	results	GRADE quality of evidence
(Barnett *et al.*, 2005) Australia Brisbane Canberra Melbourne Perth Sydney New Zealand Christchurch Auckland	1-hr and 24-hr values from 0-9 fixed monitoring sites	daily averages in ppb (µg/m³) Brisbane – 7.6 (14.5 µg/m³) Canberra – 7.0 (13.4 µg/m³) Melbourne - 11.7 (22.4 µg/m³) Perth – 9.0 (17.2 µg/m³) Sydney – 11.5 (22.0 µg/m³) Christchurch – 7.1 (13.6 µg/m³) Auckland – 10.2 (19.5 µg/m³)	case-crossover (4 years)	hospital admissions of children for respiratory distress, asthma, and pneumonia plus acute bronchitis in three age groups	association with PM_{10}, $PM_{2.5}$, UFP, O_3, SO_2, & NO_2	male and female children ≤ 14 years of age dally admission rate ranges respiratory - 1.4 - 7.9 asthma – 0.9 - 2.2 pneumonia - 0.6 - 3.6	pooled percent increase in admission rate per IQR of 9.0 ppb (17.2 µg/m³) for 1-hr values and 5.1 ppb (9.7 µg/m³) for 24-hr measurements on lag days 01 single pollutant model-respiratory 1-4 yrs age (1-hr NO_2) - 2.8 5-14 yrs age (1-hr NO_2) - 4.7 5-14 yrs age (24-hr NO_2) - 5.8 single pollutant model - asthma 5-14 yrs age (24-hr NO_2) - 6.0 two pollutant model - respiratory 1-4 yrs age (1-hr NO_2) $NO_2/PM_{2.5}$ - 8.5 5-14 yrs age (24 hr NO_2) NO_2/PM_{10} - 6.4	pooled percent increase in admission rate per IQR of 9.0 ppb (17.2 µg/m³) for 1-hr values and 5.1 ppb (9.7 µg/m³) for 24-hr measurements on lag days 01 single pollutant model-respiratory 1-4 yrs age (1-hr NO_2) 0.7 - 4.9 5-14 yrs age (1-hr NO_2) 1.6 - 7.9 5-14 yrs age (24-hr NO_2) 1.7 - 10.1 single pollutant model - asthma 5-14 yrs age (24-hr NO_2) 0.2 - 12.1 two pollutant model - respiratory 1-4 yrs age (1-hr NO_2) $NO_2/PM_{2.5}$ 0.7 - 16.9 5-14 yrs age (24 hr NO_2) NO_2/PM_{10} 3.0 - 9.8	statistically significant association of 1-hr or 24 hr NO_2 exposures with hospital admissions in children pooled from 7 cites for respiratory effects (two age groups) and asthma (one age group) using a single pollutant model, statistically significant association with respiratory admissions in two pollutant model with PM_{10} (one age group or $PM_{2.5}$ (one age group), statistically significant association with 1-hr or 24-hr NO_2 levels and respiratory admission during cool season (one age group) or warm seasons (one age group), no statistically significant association with pneumonia in either of three age groups, no statistically significant association with any of three pulmonary conditions in children less than a year old	⊕⊕◯◯ (low quality because of imprecision caused by heterogeneity and/or inconsistency from multiple comparisons)

author / location	exposure monitoring	NO_2 concentration	study type (duration)	endpoint	co-pollutants	participants	ratio or risk	confidence interval	results	GRADE quality of evidence
(Chen *et al.*, 2010) Shanghai, China	daily average from six fixed monitoring sites	daily mean concentration 57 µg/m³	time-series (3 years)	total, cardiovascular & respiratory hospital admissions	association with PM_{10}, SO_2, & NO_2	total admissions of 1,702,180 mean daily hospital admission rates total - 1555 cardiovascular - 340 respiratory - 123	percent increase in admissions per IQR of 10 µg/m³ in single pollutant model total admissions lag day 4 - 0.97 lag day 5 - 0.99 cardiovascular lag day 4 - 1.23 lag day 5 - 0.80 lag days 06 - 1.54	percent increase in admissions per IQR of 10 µg/m³ in single pollutant model total admissions lag day 4 0.07 - 1.87 lag day 5 0.10 - 1.88 cardiovascular lag day 4 0.53 - 1.93 lag day 5 0.10 - 1.49 lag days 06 0.38 - 2.69	statistically significant association with total and cardiovascular admission rates on lag days 4 & 5 but not for the 4 shorter lag days using a single pollutant model, no associations with respiratory admission rates for any lag period; associations were confined to the cold season, with no significance in the warm season, two pollutant modelling with PM_{10} did not cause any change; however the significant associations for total and cardiovascular admissions on lag day 5 became non-significant after two-pollutant modelling with SO_2; J-shaped exposure response function observed	⊕⊕◯◯ (low quality because only a single pollutant model was applied)
(Dales *et al.*, 2008) Windsor, Ontario	long-term annual exposures using LUR estimates generated from 50 sites taken each season for a 2-week period together with GIS information regarding population and swelling counts, industrial point source, & road networks, short-term daily exposures determined from two stationary fixed monitoring sites	annual mean 13.58 ppb (25.9 µg/m³)	cross-sectional (15 years)	respiratory function (FEV, FVC, & expired nitric oxide) in children	association with PM_{10}, $PM_{2.5}$, BS, SO_2, & NO_2	male & female aged 9-11 years 2,328 children	no association in adjusted single pollutant model per 1 µg/m³ increase	no association in adjusted single pollutant model per 1 µg/m³ increase	no statistically significant association with respiratory function in school children	⊕⊕◯◯ (low quality because only a single pollutant model was applied)

author / location	exposure monitoring	NO_2 concentration	study type (duration)	endpoint	co-pollutants	participants	ratio or risk	confidence interval	results	GRADE quality of evidence
(Darrow *et al.*, 2011a) Atlanta, Georgia	mean hourly and daily concentrations at a single fixed monitoring location	1-hr max - 43 ppb (82.1 µg/m³) 24-hr avg - 22 ppb (42.0 µg/m³) 6-hr commute (0700-1000 & 1600-1900) - 21 ppb (40.1 µg/m³) 6-hr nighttime (2400-0600) - 25 ppb (47.8 µg/m³)	time-series (132 months)	emergency departments visits for respiratory problems (asthma, COPD, infection, & pneumonia)	association with $PM_{2.5}$, CO, O_3 & NO_2	male & female 1,068,525 cases	risk ratio per 10 ppb (19.1 µg/m³) increment (lag 1) 1-hr max NO_2 - 1.005 24-hr avg NO_2 - 1.009 6-hr commute NO_2 (0700-1000 & 1600-1900) - 1.006 6-hr nighttime NO_2 (2400-0600) - 1.007	risk ratio per 10 ppb (19.1 µg/m³) increment (lag 1) 1-hr max NO_2 1.003 - 1.007 24-hr avg NO_2 1.005 - 1.013 6-hr commute NO_2 (0700-1000 & 1600-1900) - 1.002 - 1.010 6-hr nighttime NO_2 (2400-0600) 1.005 - 1.009	significant associations with NO_2 using a single pollutant model and various metrics of exposure, but may be due to strong co-variance with O_3	⊕◯◯◯ (insufficient because of severe exposure bias)
(Delfino *et al.*, 2006) Riverside & Whittier, CA	daily averages from personal samplers worn 10 consecutive days and averages from two fixed centrally located monitors	daily average Riverside personal – 24.26 ppb (46.3 µg/m³) ambient – 27.18 ppb (51.9 µg/m³) Whittier personal – 30.89 ppb (59.0 µg/m³) ambient – 28.07 ppb (53.6 µg/m³)	panel study (5 months)	measurement fractional concentration of nitric oxide in exhaled air (FE_{NO})	association with PM_{10}, $PM_{2.5}$, EC, OC, CO, O_3, & NO_2	male & female aged 9-18 years 45 asthmatics	adjusted concentration change in FENO exhalation per personal IQR of 17.0 ppb (32.5 µg/m³) and central site IQR of 12.0 ppb (22.9 µg/m³) for in a single and two pollutant models single pollutant model personal exposures 01 avg lag - 1.63 ambient exposures lag day 1 - 0.72 01 avg lag - 1.36 two pollutant model (01 avg lag) personal exposures NO_2/OC ≈ 0.75 (depicted graphically) ambient exposures $NO_2/PM_{2.5}$ ≈ 0.85 (depicted graphically)	adjusted concentration change in FENO exhalation per personal IQR of 17.0 ppb (32.5 µg/m³) and central site IQR of 12.0 ppb (22.9 µg/m³) for in a single and two pollutant models single pollutant model personal exposures 01 avg lag 0.43 - 2.83 ambient exposures lag day 1 0.08 - 1.36 01 avg lag 0.39 - 2.33 two pollutant model (01 avg lag) personal exposures NO_2/OC ≈ 0.15 - 1.35 (depicted graphically) ambient exposures $NO_2/PM_{2.5}$ ≈ 0.30 - 1.65 (depicted graphically)	statistically significant association with nitric oxide levels in expired air using a single pollutant model and personal measurements and a moving average lag of 01 days or ambient measurements and a lag of 1 day or a moving average of 01 days, statistically significant association with a two pollutant model (01 day average lag) and OC with personal exposures and with $PM_{2.5}$ using ambient measurements, no statistically significant association in two pollutant models with $PM_{2.5}$ and EC for personal exposures and EC and OC for ambient exposures, statistically significant association (01 avg lag) in those taking anti-inflammatory medications or inhaled corticosteroids but not in those who did not use medications	⊕⊕◯◯ (low quality because of small sample size)

author / location	exposure monitoring	NO_2 concentration	study type (duration)	endpoint	co-pollutants	participants	ratio or risk	confidence interval	results	GRADE quality of evidence
(Eckel *et al.*, 2011) Southern California (12 communities)	five metrics applied but only one used for assessment: dispersion modelling with 2 weeks of sampling at 942 locations	daily mean 19.4 ppb (37.1 µg/m³)	cohort study (24 months)	fractional concentration of nitric oxide (Fe_{NO}) in exhaled air in children	association with NO, NOx & NO_2	male and female children (7-11 years) 2143 subjects	no statistically significant change in percentage exhaled FeNO per 10 ppb (19.1 µg/m³) in an adjusted single pollutant model	no statistically significant change in percentage exhaled FeNO per 10 ppb (19.1 µg/m³) in an adjusted single pollutant model	no statistically significant association with predicted NO_2 values in either asthmatic or non-asthmatic children;	⊕⊕◯◯ (low quality because of indirect measurements)
(Farhat *et al.*, 2005) Sao Paulo, Brazil	daily average from 6 urban fixed monitoring sites	daily mean concentration 125.3 µg/m³	time-series (1 year)	pediatric hospital and emergency room visits for lower respiratory disease (pneumonia, bronchopneumonia, asthma, & bronchiolitis)	association with PM_{10}, SO_2, O_3, CO, & NO_2	male & female children < 13 years of age 4534 admissions or visits	percentage increase in hospital and emergency room visits per IQR 65.0 µg/m³ increase using two-pollutant and multi-pollutant model for average lag day 0-3 total admission NO_2 only ≈ 18 (depicted graphically) NO_2/PM_{10} - 16.1 NO_2/SO_2 - 24.7 NO_2/O_3 - 16.1 NO_2/CO - 19.2 $NO_2/PM_{10},SO_2,O_3$,CO - 18.4 asthma and bronchiolitis NO_2 only ≈ 30 (depicted graphically) NO_2/PM_{10} - 47.7 NO_2/SO_2 - 33.1	percentage increase in hospital and emergency room visits per 65.0 µg/m³ increase using two-pollutant and multi-pollutant model for average lag day 0-3 total admission NO_2 only ≈ 13 -25 (depicted graphically) NO_2/PM_{10} 5.4 - 26.8 NO_2/SO_2 18.2 - 31.3 NO_2/O_3 9.5 - 22.7 NO_2/CO 11.8 - 26.6 $NO_2/PM_{10},SO_2,O_3$,CO 3.4 - 33.5 asthma and bronchiolitis NO_2 only ≈ 9 - 56 (depicted graphically) NO_2/PM_{10} 1.15 - 94.2 NO_2/SO_2 5.7 - 60.5	statistically significant association with total visits for all single, two pollutant and multi-pollutant models with a 0-4 day moving average lag period; statistically significant association with asthma and bronchiolitis visits for single and two-pollutant models with PM_{10} and SO_2, but not with two pollutant models with O_3 or CO or multi-pollutant models; no significant associations with visits for pneumonia or broncho-pneumonia;	⊕◯◯◯ (insufficient because of imprecision from small number of cases and short duration)

author / location	exposure monitoring	NO_2 concentration	study type (duration)	endpoint	co-pollutants	participants	ratio or risk	confidence interval	results	GRADE quality of evidence
(Giovannini *et al.*, 2010) Milan, Italy	daily average at a single fixed monitoring site	monthly average range 27.5 - 86.7 µg/m³	time-series (1 year)	pediatric hospital admissions for all respiratory conditions, asthma, upper respiratory disease, and lower respiratory disease	association with PM_{10}, O_3, CO, & NO_2	male and female children ≤ 14 years of age monthly admission rate ranges all respiratory disease - 0.37 - 1.8 asthma - 0.03 - 0.23 upper respiratory - 0.11 - 0.60 lower respiratory - 0.16 - 0.95	adjusted rate ratio per IQR of 1 µg/m³ in single and multi-pollutant models all respiratory NO_2 only (0-6 day MWA) - 1.009 asthma NO_2 only (1 day lag) – 1.002 upper respiratory NO_2 only (1 day lag) – 1.003 lower respiratory NO_2 only (0-6 day MWA) - 1.005 NO_2/CO (0-6 day MWA) - 1.005	adjusted rate ratio per IQR of 1 µg/m³ in single and multi-pollutant models all respiratory NO_2 only (0-6 day MWA) 1.001 - 1.017 asthma NO_2 only (1 day lag) 1.000 - 1.004 upper respiratory NO_2 only (1 day lag) 1.000 - 1.006 lower respiratory NO_2 only (0-6 day MWA) 1.001 - 1.010 NO_2/CO (0-6 day MWA) 1.000 - 1.010	weak statistically significant association with hospital admissions for all respiratory conditions, asthma, upper and lower respiratory disease in single pollutant models, statistically significant association for lower respiratory disease in two pollutant model with CO, no significant associations for other conditions in multi-pollutant models with CO or PM_{10}	⊕◯◯◯ (insufficient because of severe exposure bias)
(Halonen *et al.*, 2008) Helsinki, Sweden	daily average from a single monitoring site	daily mean concentration 28.2 µg/m³	time-series (7 years)	ED visits for asthma and COPD in three age groups	association with UFP (Aiken mode), UFP (accumulation mode), $PM_{2.5}$ $PM_{10-2.5}$ (coarse), CO & NO_2	males & females in three age groups children (< 15 years) - 4807 visits adults (14-64 years) - 6312 visits elderly (≥ 65 years of age) - 7239 visits	percent increase in asthma and COPD emergency room visits per IQR 14.2 µg/m³ for three age groups in a single pollutant model children lag day 3 - 4.53 lag day 4 - 10.9 lag day 5 - 9.36 adults lag day 5 - 3.7 elderly lag day 0 - 4.82	percent increase in asthma and COPD emergency room visits per IQR 14.2 µg/m³ for three age groups in a single pollutant model children lag day 3 0.19 - 9.05 lag day 4 6.38 - 15.5 lag day 5 4.95 - 14.0 adults lag day 5 0.15 - 7.37 elderly lag day 0 1.26 - 8.50	statistically significant association with ED visits for asthma and COPD in single pollutant model for children on lag days 3,4,&5, adults on lag day 5 and elderly on lag day 0; no associations on lag day 0 thru 2 for children, 0 thru 4 for adults or 1 thru 5 for elderly	⊕◯◯◯ (insufficient because of severe exposure bias)

author / location	exposure monitoring	NO_2 concentration	study type (duration)	endpoint	co-pollutants	participants	ratio or risk	confidence interval	results	GRADE quality of evidence
(Kalantzi *et al.*, 2011) Magnesia, Greece	daily mean from three fixed monitoring sites	daily mean 30.12 µg/m³	time-series (84 months)	total hospitalizations and those for pulmonary (COPD, asthma, infections, & other) and cardiovascular (ischemic heart disease, heart failure, & other) diseases	association with PM_{10}, CO, SO_2, O_3, NO, NOx, & NO_2	male & female admissions rate respiratory - 2.94 /day cardiovascular - 4.88 /day	no change in risk coefficients in either a single or combined model	no change in risk coefficients in either a single or combined model	no statistically significant association with NOx; statistically significant associations found for NOx and CO in a combined pollutant models	⊕⊕◯◯ (low quality because the focus on NOx and the exposure bias)
(Lee *et al.*, 2011) Taiwan	annual mean concentration at 14 fixed monitoring locations	mean 3-year period - 18.13 ppb (34.6 µg/m³) 3-month period - 13.21 ppb (25.2 µg/m³)	self-controlled case series (36 months)	pulmonary function test (PFT), maximal mid-expiratory flow (MMEF), 1 second forced expiratory volume (FEV1), & peak expiratory flow	association with PM_{10}, $PM_{2.5}$, O_3, SO_2, NOx, NO, & NO_2	male & female school children 3957 volunteers	volume decrement (ml) per IQR (8.86 ppb; 16.9 µg/m³ for 3-year) FVC -94.5 FEV1 -83.2 MMEF -110.1 volume decrement (ml) per IQR (7.91 ppb; 15.1 µg/m³ for 3-month) FEV1 -73.8 MMEF -126.6 PEFR -227.7	volume decrement (ml) per IQR (8.86 ppb; 16.9 µg/m³ for 3-year) FVC -166.6 - -2.3 FEV1 -144.7 - -21.6 MMEF -216 - -4.3 volume decrement (ml) per IQR (7.91 ppb; 15.1 µg/m³ for 3-month) FEV1 -138.2 - -9.5 MMEF -224.7 - -28.5 PEFR -443.3 - -12.0	statistically significant pulmonary function decrements for 3-year and 3-month exposure time frames; effects more severe in boys than girls; effects also observed with NOx & NO in variable fashion, FEV1 & MMEF most severely affected; effects associated with CO but not related to PM_{10}, $PM_{2.5}$, or SO_2	⊕⊕◯◯ (low quality because only a single pollutant model was applied)
(Leitte *et al.*, 2009) Drobeta-Tunu Severin, Romania	pooled mean daily concentration from one fixed monitoring locations	daily mean 11.8 µg/m³	time series (19 months)	chronic obstructive pulmonary disease (COPD), asthma, chronic bronchitis	differential effects of TSP, SO_2, & NO_2	953 cases	odds ratio per 10 µg/m³ increment persistent cough using NO_2 outdoors at 1 year - 1.40	no effect on relative risk	no significant associations observed using a single pollutant model	⊕◯◯◯ (insufficient because of severe exposure bias)

author / location	exposure monitoring	NO_2 concentration	study type (duration)	endpoint	co-pollutants	participants	ratio or risk	confidence interval	results	GRADE quality of evidence
(Leitte *et al.*, 2011) Beijing, China	mean daily concentration from eight fixed monitoring sites	daily mean 63 µg/m³	time-series (33 months)	emergency department visits for respiratory symptoms (acute infections, pneumonia, bronchitis, URT diseases, & chronic URT diseases)	association with PM_{10}, particle number concentration (PNC), particle surface concentration (PSAC), SO_2, & NO_2	male & female 15,981 cases	relative risk per 40 µg/m³ change in two-pollutant model with PM_{10} 3 day lag - 1.07 4 day lag - 1.07 5 day lag - 1.08	relative risk per 40 µg/m³ change in two-pollutant model with PM_{10} 3 day lag 1.01 - 1.13 4 day lag 1.01 - 1.14 5 day lag 1.01 - 1.15	statistically significant association with emergency room visits in two pollutant model on lag days 3, 4, & 5 but not lag days 0, 1, & 2; statistically significant association on lag day 3 using a cumulative effects model (6-day moving average) with a single pollutant; no associations on lag days 0, 1, 2, 3, or 4 with cumulative distribution model or on any lag day when using a single lag model or a polynomial distribution lag model	⊕⊕◯◯ (low quality because of imprecision with weak effects noted)
(Llorca *et al.*, 2005) Torrelavega, Spain	daily average from three fixed monitoring site	daily mean concentration 21.3 µg/m³	time-series (4 years)	total cardiorespiratory, cardiac, & respiratory emergency department visits	association with total suspended particulate (TSP), hydrogen sulfide (H2S), sulfur dioxide (SO_2), nitrogen oxide (NO), & NO_2	total admissions of 18,137 mean daily hospital admission rates cardiac - 7.61 respiratory - 4.93	relative risk per IQR 100 µg/m³ in single and multi-pollutant model with an unstated lag period total cardiopulmonary NO_2 only - 1.37 NO_2/TSP,H2S,SO_2,NO - 1.20 cardiac NO_2 only - 1.27 respiratory NO_2 only - 1.54 NO_2/TSP,H2S,SO_2,NO - 1.69	relative risk per IQR 100 µg/m³ in single and multi-pollutant model with an unstated lag period total cardiopulmonary NO_2 only 1.26 - 1.49 NO_2/TSP,H2S,SO_2,NO 1.05 - 1.39 cardiac NO_2 only 1.14 - 1.42 respiratory NO_2 only 1.34 - 1.76 NO_2/TSP,H2S,SO_2,NO 1.34 - 2.13	statistically significant association with hospital admissions for total cardiopulmonary, cardiac, & respiratory disease in single pollutant model with an unstated lag period; statistically significant association with admissions for total cardiopulmonary and respiratory causes in multi-pollutant models, but not for cardiac disease	⊕◯◯◯ (insufficient because of imprecision caused by no lag period, publication bias from poor method description)

author / location	exposure monitoring	NO_2 concentration	study type (duration)	endpoint	co-pollutants	participants	ratio or risk	confidence interval	results	GRADE quality of evidence
(Marks *et al.*, 2010) New South Wales, Australia	geometric mean of passive dosimetry measurements in 22 schools on 2 days/week for 6 weeks	classroom mean concentration (6-hr period) overall – 23.5 ppb (44.9 µg/m³) flued heater – 17.5 ppb (33.4 µg/m³) unflued heater – 31.6 (60.4 µg/m³)	double blind randomized crossover (1.5 months)	lung function (PEF, FEV1 & exhaled NO) and respiratory symptoms (cough, wheeze, sore teeth, stomach ache, bronchodilators use) in school children residing in classrooms with flued or unflued gas heaters (blinded operation)	association with formaldehyde & NO_2	male and female school children (mean age 10.6 yrs) 400 volunteers	morning FEV1 (L) differential unflued-flued all days - no statistically sig diff days > 30 % heater use - 0.030 evening PEF (L/min) differential unflued-flued all days - no statistically sig diff days > 30 % heater use - 5.185 all days (asthma subgroup) - 7.130 days > 30 % heater use (asthma subgroup) - no statistically sig diff unadjusted odds ratio evening cough all days - 1.161 morning wheeze all days - 1.381 all days (adjusted for home NO_2 sources) - 1.603 all days (atopic subgroup) - 1.849 days > 30 % heater use (atopic subgroup) - 7.721 evening wheeze days > 30 % heater use (atopic subgroup) - 3.968 stomach ache all days (atopic subgroup) - 1.627 bronchodilator use all days (atopic subgroup) - 1.868	morning FEV1 (L) differential unflued-flued all days - no statistically sig diff days > 30 % heater use 0.003 - 0.057 evening PEF (L/min) differential unflued-flued all days - no statistically sig diff days > 30 % heater use 1.032 - 9.338 all days (asthma subgp) 0.578 - 13.682 days > 30 % heater use (asthma subgp) - no statistically sig diff unadjusted odds ratio evening cough all days 1.008 - 1.336 morning wheeze all days - 1.041 - 1.832 all days (adjusted for home NO_2 sources) 1.171 - 2.194 all days (atopic subgp) 1.258 - 2.718 days > 30 % heater use (atopic subgp) 1.551- 38.434 evening wheeze days > 30 % heater use (atopic subgp) 1.369 - 11.502 stomach ache all days (atopic subgp) 1.064 - 2.488 bronchodilator use all days (atopic subgp) 1.075 - 3.247	statistically significant increase in FEV1 following unflued heater use for mornings but not evenings and only when examining those schools where heater use was > 30% (all asthma subgroups unaffected), statistically significant increase PEF following unflued heater use for evenings but not mornings and only when examining those school where heater use was > 30%, the asthma subgroup was also significantly increased but only the entire sample and not those restricted to high heater use; statistically significant association with reported evening cough and morning wheeze for all days but not the restricted sample with high heater use, no association with evening cough or morning wheeze, significant association observed for morning wheeze in both categories of heater use, associations also found for evening wheeze in high heater usage group, numerous associations observed in the atopic subgroup	⊕◯◯◯ (insufficient because of the bias from the small number of cases and relatively short duration)

author / location	exposure monitoring	NO_2 concentration	study type (duration)	endpoint	co-pollutants	participants	ratio or risk	confidence interval	results	GRADE quality of evidence
(Min *et al.*, 2008) Taein Island, Japan	mean daily concentration at an unknown number of fixed monitoring locations	daily mean 24 ppb (45.8 µg/m³)	cross-sectional study (12 months)	heart rate variability using heart rate in the N-N interval, low frequency heart rate modulation, & high frequency heart rate modulation	association with PM_{10}, SO_2, & NO_2	male & female 1349 subjects	percentage change in heart rate variability per ISD 17 ppb; 32.5 µg/m³ 0-6hr lag low frequency -7.32 0-9 hr lag heart rate -3.31 low frequency -10.40 0-12 hr lag low frequency -10.44	percentage change in heart rate variability per ISD 17 ppb; 32.5 µg/m³ 0-6hr lag low frequency -14.32 - 0.26 0-9 hr lag heart rate -7.06 - 0.60 low frequency -18.26 - -1.79 0-12 hr lag low frequency -19.19 - -0.75	statistically significant declines in low frequency heart rate modulation at three short lag periods, but not at longer time periods in a single pollutant model; similar results in a multi-pollutant model;	⊕○○○ (insufficient because of potential exposure measurement bias and short duration)
(Mortimer *et al.*, 2008) Fresno, California	daily averages determined by inverse distance weighting of the results from 1-3 fixed monitoring sites	not provided	cohort (144 months)	peak expiratory flow (PEF), forced vital capacity (FVC), 1 second forced expiratory volume (FEV1), forced expiratory flow at 25% (FEV25) and 75% (FEV75) of vital capacity, forced expiratory flow (FEF25-75) between 25% and 75% , Ratios of FEV25-75/FVC and FEV1/FEV	association with PM_{10}, O_3, CO, & NO_2	male and female aged 6-11 years 232 children	the best model for i) FVC included daily maximum NO_2 exposures during the 2nd trimester and black race considerations (effect size per IQR = -7.1%) ii) FEV1 included NO_2 exposures from 6 AM - 6 PM during the 2nd trimester (effect size per IQR = -1.2%)	confidence intervals not provided	prenatal exposures during the 2nd trimester had a significant impact on FVC and FEV1 values in young adolescents; the remaining 6 metrics were impacted to greater degree by CO or PM 10 exposures; high correlation between NO_2 and CO (r=0.7)	⊕○○○ (insufficient because imprecision and small number of cases)
(Moura *et al.*, 2008) Rio de Janeiro, Brazil	hourly average at a single fixed monitoring site	daily mean 62.78 µg/m³	time-series (1 year)	emergency department visits for upper and lower respiratory symptoms	association with PM_{10}, O_3, CO, & NO_2	male and female children aged 1-12 years 45,595 visits	no significant change in relative risk for emergency department visits for respiratory symptoms	no significant change in relative risk for emergency department visits for respiratory symptoms	no significant change in relative risk for upper or lower respiratory symptoms at any lag period using a single pollutant model	⊕○○○ (insufficient because of severe exposure bias)

author / location	exposure monitoring	NO_2 concentration	study type (duration)	endpoint	co-pollutants	participants	ratio or risk	confidence interval	results	GRADE quality of evidence
(Nordling *et al.*, 2008) Sweden (4 municipalities)	dispersion model using emissions, meteorology, topography; validation using background concentrations at 16 fixed monitoring locations	annual mean (first year) 23.1 µg/m³	cohort (48 month)	respiratory symptoms (wheeze and allergic rhinitis), peak expiratory flow, serum IgE antibodies	association with outdoor PM_{10} and NO_2, and indoor SO_2	male and females (2 months of age) 3515 infant volunteers	adjusted odds ratio per 44 µg/m³ (5-95% range) increment persistent wheeze - 1.60 allergic sensitization from pollen - 1.67	adjusted odds ratio per 44 µg/m³ (5-95% range) increment persistent wheeze 1.09 - 2.36 allergic sensitization from pollen 1.10 - 2.53	statistically significant association with persistent wheeze that was associated with girls but not boys, no association with transient or late onset wheeze; no association peak expiratory flow rate decrements in either sex for the first year of life; significant association with sensitization to pollen allergens but not to food or pet allergens	⊕◯◯◯ (insufficient because imprecision from using a questionnaire and inconsistencies in the results)
(Oftedal *et al.*, 2008) Oslo, Norway	hourly levels from a dispersion model using emissions, meteorology, topography, and background concentrations at an unnamed number of fixed monitoring locations	mean levels first year - 39.1 µg/m³ lifetime - 29.0 µg/m³	self-controlled case series (12 months)	peak expiratory flow (PEF), forced vital capacity (FVC), 1 second forced expiratory volume (FEV1), forced expiratory flow (FEF) at 25% and 50% of FVC	association with PM_{10}, $PM_{2.5}$, & NO_2	male & female children aged 9-10 years old 2307 volunteers	flow rate decrement (ml/sec) per IQR of 27.4 µg/m³ for first year of life PEF -84.4 FEF(25%) -85.5 FEF(50%) -54.4 flow rate decrement (ml/sec) per IQR of 19.7 µg/m³ for lifetime exposure PEF -79.2 FEF(25%) -73.9	flow rate decrement (ml/sec) per IQR of 27.4 µg/m³ for first year of life PEF -134.8 - -33.9 FEF(25%) -142.2 - -28.8 FEF(50%) -103.7 - -5.1 flow rate decrement (ml/sec) per IQR of 19.7 µg/m³ for lifetime exposure PEF -127.9 - -30.5 FEF(25%) -128.7 - -19.1	statistically significant pulmonary function decrements for 1-year and lifetime exposure time frames; effects more severe in girls than in boys; effects also observed with PM_{10} and $PM_{2.5}$, FEV1 & FVC volumes changes not statistically significant	⊕⊕◯◯ (low quality because only a single pollutant model was applied)
(Orazzo *et al.*, 2009) six Italian cities Ancona Bologna Florence Naples Padua Varese-Gallarate	daily means from an unstated number of fixed monitoring sites in each city	daily means Ancona – 42.5 µg/m³ Bologna – 64.8 µg/m³ Florence – 57.9 µg/m³ Naples – 78.6 µg/m³ Padua – 48.7 µg/m³ Varese-Gallarate – 40.8 µg/m³	case-crossover (60 months)	emergency department visits for wheeze or acute gastrointestinal disease	association with PM_{10}, O_3, CO, SO_2, & NO_2	male & female aged 0-2 yrs old 0.7-18.3 admissions/day wheeze 0.4-8.0 admissions/day GI disorders	no association for wheeze or GI admissions in adjusted single pollutant model for any lag period per IQRs ranging from 22.2-26.0 µg/m³	no association for wheeze or GI admissions in adjusted single pollutant model for any lag period per IQRs ranging from 22.2-26.0 µg/m³	no statistically significant association with wheeze or GI disorders on any lag day with single pollutant model	⊕◯◯◯ (insufficient because of bias from the use of a unstated number of monitoring sites)

author / location	exposure monitoring	NO_2 concentration	study type (duration)	endpoint	co-pollutants	participants	ratio or risk	confidence interval	results	GRADE quality of evidence
(Parker *et al.*, 2009) United States	annual averages for site specific monitors within 20 miles of residence weighted by inverse distance weighting	annual median 17.8 ppb (34.0 µg/m³)	cross-sectional study (84 months)	survey of childhood respiratory allergies and hay fever	association with PM_{10}, $PM_{2.5}$, O_3, SO_2, & NO_2	male and female 3-17 yrs of age 72,279 children	no association in crude or adjusted single or multi-pollutant model per 10 ppb (19.1 µg/m³)	no association in crude or adjusted single or multi-pollutant model per 10 ppb (19.1 µg/m³)	no statistically significant association with childhood asthma prevalence in crude or adjusted single or multi-pollutant models using IDW for monitors within a 20 mi or 5 mi radius	⊕⊕◯◯ (low quality because of inherent limitations of the cross sectional design)
(Patel *et al.*, 2010) New York City	daily mean for two fixed monitoring sites located near each of five schools	levels not provided	cohort (1.5 months)	respiratory symptoms (wheeze, cough, shortness of breath, chest tightness, & use of asthma medications) in high school students	association with $PM_{2.5}$, BC, O_3, & NO_2	male & female teenagers 13-20 years of age 249 students	odds ratio per IQR of 16 ppb (30.6 µg/m³) for respiratory symptoms on different lag days wheeze 2-day lag - 1.15 3-day lag - 1.32 4-day lag - 1.57 5-day lag - 1.70 shortness of breath 0-day lag - 1.20 1-day lag - 1.15 2-day lag - 1.28 3-day lag - 1.32 4-day lag - 1.31 5-day lag - 1.35	odds ratio per IQR of 16 ppb (30.6 µg/m³) for respiratory symptoms on different lag days wheeze 2-day lag 1.00 - 1.33 3-day lag 1.11 - 1.56 4-day lag 1.29 - 1.91 5-day lag 1.36 - 2.13 shortness of breath 0-day lag 1.10 - 1.32 1-day lag 1.03 - 1.29 2-day lag 1.12 - 1.46 3-day lag 1.12 - 1.54 4-day lag 1.09 - 1.57 5-day lag 1.09 - 1.67	statistically significant association with shortness of breath for all lag periods and wheeze for 4 out of the six lag periods, no statistically significant positive association with cough, chest tightness, or asthma medication use, stratification by asthma status showed a statistically significant association with chest tightness only in asthmatic subjects	⊕◯◯◯ (insufficient because of bias caused by small number of cases, and short duration, with no two-pollutant modelling)
(Sinclair *et al.*, 2010) Atlanta, Georgia	hourly maximum concentrations at a single fixed monitoring location	mean 25 month period – 49.8 ppb (95.1 µg/m³) 28 month period – 41.7 ppb (79.7 µg/m³)	time-series (25 - 28 month)	acute outpatient visits for adult asthma, child asthma, upper respiratory tract infection, & lower respiratory tract infection	association with $PM_{2.5}$ mass, $PM_{2.5}$ sulfate, $PM_{2.5}$ EC, $PM_{2.5}$ OC, PM_{10}, $PM_{10-2.5}$, PM, SO_2, CO, O_3, oxygenated VOCs	male & female child asthma - 28,487 cases adult asthma - 19,085 cases LRT infection - 17,373 cases URT infection - 425,808 cases	relative risk per 17.88 ppb (34.2 µg/m³) increment (lag 6-8) LRT infection 28 month - 1.062	relative risk per 17.88 ppb (34.2 µg/m³) increment (lag 6-8) LRT infection 28 month 1.005 - 1.123	no association at any lag with adult or child asthma; no association with warm or cold seasons; negative association with URT infection in 25 month study at a lag 6-8 days; positive association with LRT infection in 28 day study at a lag of 6-days	⊕◯◯◯ (insufficient because of severe exposure bias)

author / location	exposure monitoring	NO_2 concentration	study type (duration)	endpoint	co-pollutants	participants	ratio or risk	confidence interval	results	GRADE quality of evidence
(Son *et al.*, 2010) Ulsan, Korea	daily mean concentration computed by four different methods using data from 13 fixed monitoring locations	daily mean average across monitors - 21.39 ppb (40.8 µg/m³) nearest monitor - 19.75 ppb (37.7 µg/m³) inverse distance weighting - 21.10 ppb (40.3 µg/m³) kriging extrapolation - 21.41 (40.9 µg/m³)	cohort (60 months)	forced vital capacity (FVC) and 1 second forced expiratory volume (FEV_1) in normal children and adults	association with PM_{10}, O_3, SO_2, CO, & NO_2	male & female 2102	percentage change in FVC per 10 ppb (19.1 µg/m³) change - single pollutant model lag 0-2 average across monitors – -3.97 nearest monitor – -3.46 inverse distance weighting - -3.44 kriging extrapolation – -3.72	percentage change in FVC per 10 ppb (19.1 µg/m³) change - single pollutant model lag 0-2 average across monitors - 5.16 - -2.79 nearest monitor -4.41 - -2.50 inverse distance weighting - 4.54 - -2.34 kriging extrapolation -4.90 - -2.54	statistically significant decline in FEV for all four measurement methods with the largest effect noted using the average value for all monitors; associations remained significant for all six lag periods investigated; no association with FEV1 using any measurement method; FVC results using the kriging extrapolation procedure remained significant in a two-pollutant model with O_3 but the change was reduced appreciably	⊕⊕⊕○ (moderate quality, no adjustment necessary)
(Stieb *et al.*, 2009) Seven Canadian cities Montreal Ottawa Edmonton Saint John Halifax Toronto Vancouver	mean daily concentration from 1 to 14 fixed monitoring sites	hourly mean in ppb (µg/m³) Montreal – 19.4 (37.1 µg/m³) Ottawa – 18.8 (35.9 µg/m³) Edmonton – 21.9 (41.8 µg/m³) Saint John – 9.3 (17.8 µg/m³) Halifax – 17.5 (33.4 µg/m³) Toronto – 22.7 (43.4 µg/m³) Vancouver – 18.7 (35.7 µg/m³)	time-series (up to 120 months)	emergency department visits for cardiac (angina, myocardial infarction, heart failure, dysrhythmia) and respiratory (asthma, COPD, respiratory infections) conditions	association with PM_{10}, $PM_{2.5}$, SO_2, O_3, CO, & NO_2	male & female cardiac - 140.657 respiratory - 249,199 cases	pooled percent increase in cardiac visits per 18.4 ppb (35.1 µg/m³) in a single pollutant model for the summer season lag day 0 angina/infarction - 2.6 heart failure - 4.7 lag day 1 angina/infarction - 2.7	pooled percent increase in cardiac visits per 18.4 ppb (35.1 µg/m³) in a single pollutant model for the summer season lag day 0 angina/infarction 0.2 - 5.0 heart failure 1.2 - 8.4 lag day 1 angina/infarction 0.2 - 5.3	statistically significant association with angina/infarction and heart failure in a single pollutant model; no statistically significant associations for the winter season or for any respiratory conditions; no statistically significant association in a two pollutant model with CO	⊕⊕⊕○ (moderate quality, no adjustment necessary)

author / location	exposure monitoring	NO_2 concentration	study type (duration)	endpoint	co-pollutants	participants	ratio or risk	confidence interval	results	GRADE quality of evidence
(Thach *et al.*, 2010) Hong Kong, China	daily averages from eight fixed monitoring sites	daily mean 58.7 µg/m³	time-series (84 months)	interaction with influenza and impact on mortality and hospitalizations for stroke, ischemic heart disease (IHD), lower respiratory infection, (LRI), acute respiratory disease (ARD), & chronic obstructive pulmonary disease (COPD)	association with PM0, SO_2, O_3, & NO_2	number of subjects not stated	unadjusted excess mortality risk per 10 µg/m³ increase in single pollutant model stroke - 1.13 IHD - 2.08 LRI - 1.75 COPD - 1.39 unadjusted excess hospitalization risk per 10 µg/m³ increase in single pollutant model IHD - 0.94 ARD - 1.22 COPD - 1.94	unadjusted excess mortality risk per 10 µg/m³ increase in single pollutant model stroke 0.19 - 2.08 IHD 1.10 - 3.07 LRI 0.74 - 2.77 COPD 0.18 - 2.61 unadjusted excess hospitalization risk per 10 µg/m³ increase in single pollutant model IHD 0.46 - 1.42 ARD 0.74 - 1.71 COPD 1.55 - 2.33	statistically significant association with mortality from stroke, IHD, LRI, & COPD, statistically significant association with hospitalizations from IHD, ARD, & COPD, no association in unadjusted risk from hospitalizations from stroke, adjustment for influenza epidemic periods or predominance caused greater than 0.1 % decrease in mortality from stroke, LRI, & COPD, adjustment for influenza intensity, epidemic periods, or predominance caused greater than 0.1 % decrease in hospitalizations from ARD,	⊕◯◯◯ (insufficient because of unknown number of cases and risk of exposure bias)
(Tolbert *et al.*, 2007) Atlanta, Georgia	1-hr maximum for an unstated number of monitoring sites	average 1-hr maximum 43.2 ppb (82.5 µg/m³)	time-series (10 years)	cardiovascular & respiratory emergency department visits	association with PM_{10}, $PM_{10-2.5}$(course), $PM_{2.5}$, $PM_{2.5}$ sulfate, $PM_{2.5}$ EC, $PM_{2.5}$ OC, $PM_{2.5}$ TC, $PM_{2.5}$ soluble metals, oxygenated hydrocarbons, SO_2, CO, O_3, & NO_2	male and females 238,360 cardiovascular visits 1,072,429 respiratory visits	relative risk per IQR 23.0 ppb (43.9 µg/m³) in single and two-pollutant models with a 0-2 day average lag cardiovascular NO_2 only - 1.015 respiratory NO_2 only - 1.015 NO_2/CO ≈ 1.012 (depicted graphically)	relative risk per IQR 23.0 ppb (43.9 µg/m³) in single and two-pollutant models with a 0-2 day average lag cardiovascular NO_2 only 1.004 - 1.025 respiratory NO_2 only 1.004 - 1.025 NO_2/CO ≈ 1.008 - 1.029 (depicted graphically)	statistically significant association with emergency room visits for cardiovascular and respiratory diseases in a single pollutant model at an 0-1 lag period; statistically significant association for respiratory visits in a two pollutant model with CO; no association with respiratory visits in a two pollutant model with PM_{10} or O_3 and a three pollutant model PM_{10} & O_3; no association with cardiovascular visits in a two pollutant model with CO or $PM_{2.5}$ TC and a three pollutant model with $PM_{2.5}$ TC & CO;	⊕⊕◯◯ (low quality because of bias from the use of a unstated number of monitoring sites)

author / location	exposure monitoring	NO_2 concentration	study type (duration)	endpoint	co-pollutants	participants	ratio or risk	confidence interval	results	GRADE quality of evidence
(Tramuto *et al.*, 2011) Palermo, Italy	mean daily concentration at ten fixed monitoring locations	daily mean 41.5 µg/m³	case-crossover (48 months)	emergency department visits for respiratory symptoms (respiratory deficiency, emphysema, dyspnea, cough, asthma, pneumonia, bronchopathy, & obstructive pulmonary disease)	association with PM_{10}, O2, CO & NO_2	male & female 48,519 visits	adjusted odds ratio per 10 µg/m³ change in a single pollutant model (no lag) all seasons - 1.015 warm season - 1.043	adjusted odds ratio per 10 µg/m³ change in a single pollutant model (no lag) all seasons 1.004 - 1.026 warm season 1.021 - 1.065	statistically significant association with respiratory symptoms among all patients for all seasons, and the warm season but not the cold season in a single pollutant model with no lag; statistically significant associations observed for lag day 0 or 1 but 2, 3, 4, or 5 (values not presented); statistically significant association observed in some age groups (55-64, 65-74, 75-84 years old) for either all subjects, males only or females only (values not presented); associations in age stratified groups not uniformly distributed across age groups or gender type but the associations were restricted to all seasons or the warm seasons	⊕◯◯◯ (insufficient because of publication bias with no lag period specified and very serious and the bias from the use of a single pollutant model
(Van Roosbroeck *et al.*, 2008) Netherlands	annual average outdoor concentration at 24 schools (surrogate exposure) and personal monitoring at 3 of the 24 schools using diffusion tubes (real exposure used for adjustment)	annual mean outdoor - 37.4 µg/m³ personal - 23.7 µg/m³	cohort (14 months)	respiratory symptoms (wheeze and phlegm), conjunctivitis, and serum IgE antibodies	association with soot and NO_2 when using personal rather than outdoor data	male & female schoolchildren 2083 volunteers	adjusted prevalence rate per 17.6 µg/m³ increment (prevalence ratio = rate original study with outdoor measurements/rate in new study with indoor measurements) conjunctivitis - 6.60 phlegm - 3.82 elevated IgE - 4.20	adjusted prevalence rate per 17.6 µg/m³ increment (prevalence ratio = rate original study with outdoor measurements/rate in new study with indoor measurements) conjunctivitis 1.33 - 32.77 phlegm 1.03 - 14.21 elevated IgE 1.54 - 11.48	appreciable increase in prevalence ratios for conjunctivitis, phlegm, and immunoglobulin E levels when indoor corrected outdoor exposures are used for the assessment; unadjusted (no indoor correction) also showed a statistically significant association for the same three outcomes; no statistically significant associations of wheeze with unadjusted or adjusted prevalence ratios	⊕⊕◯◯ (low quality because of indirect measurements)

author / location	exposure monitoring	NO_2 concentration	study type (duration)	endpoint	co-pollutants	participants	ratio or risk	confidence interval	results	GRADE quality of evidence
(Villeneuve *et al.*, 2007) Edmonton, Alberta	daily average from three fixed monitoring sites	daily mean concentration summer – 17.5 ppb (33.4 µg/m³) winter – 28.5 ppb (54.4 µg/m³)	case-crossover (11 years)	ED visits for asthma and COPD in seven age groups	association with PM_{10}, $PM_{2.5}$, SO_2, O_3, CO, & NO_2	males & females in seven age groups (total 57,912 visits) 2 - 4 years - 7247 visits 5 -14 years - 13,145 visits 15 -24 years - 11,616 visits 25 - 44 years - 13,300 visits 45 - 64 years - 7899 visits 65 - 74 years - 2850 visits ≥ 75 years - 1855 visits	adjusted odds ratio for asthma ED visits in different age groups per IQR of 13. 5 ppb (25.8 µg/m³) for summer months (Apr-Sept) in a single pollution model 2 - ≥ 75 years lag 1 day - 1.07 lag 02 day - 1.09 lag 05 day - 1.14 2 - 4 years lag 1 day - 1.24 lag 02 day - 1.32 lag 05 day - 1.50 5 - 14 years lag 1 day - 1.08 lag 05 day - 1.13 15 - 44 years lag 02 day - 1.07 lag 05 day - 1.10 ≥ 75 years lag 02 day - 1.33 lag 05 day - 1.37	adjusted odds ratio for asthma ED visits in different age groups per IQR of 13. 5 ppb (25.8 µg/m³) for summer months (Apr-Sept) in a single pollution model 2 - ≥ 75 years lag 1 day 1.03 - 1.10 lag 02 day 1.04 - 1.13 lag 05 day 1.09 - 1.20 2 - 4 years lag 1 day 1.13 - 1.35 lag 02 day 1.18 - 1.48 lag 05 day 1.31 - 1.71 5 - 14 years lag 1 day 1.01 - 1.15 lag 05 day 1.02 - 1.24 15 - 44 years lag 02 day 1.00 - 1.14 lag 05 day 1.02 - 1.19 ≥ 75 years lag 02 day 1.03 - 1.70 lag 05 day 1.02 - 1.84	Statistically significant association with asthma ED visits in those aged 2 to ≥ 75 yrs of age for all lag periods except lag day 0 in a single pollutant model during summer months; statistically significant association in 4 of 6 age groups for at least two of the four lag periods investigated; no association in age groups in those aged 45- 64 and 65 -75; association generally confined to the summer months and all seasons with no statistically significant findings for the winter months (Oct - Mar); two pollutant modelling for the 05 day average lag revealed that the single pollutant results were not robust to CO for 5 of the 6 age groupings with the 2-4 year age group being the only population showing statistically significant results	⊕⊕⊕◯ (moderate quality, no adjustment necessary)

author / location	exposure monitoring	NO_2 concentration	study type (duration)	endpoint	co-pollutants	participants	ratio or risk	confidence interval	results	GRADE quality of evidence
(Weichenthal *et al.*, 2011) Ottawa, Ontario	hourly averages from a single fixed monitoring site	daily means high traffic route - 4.8 ppb (9.2 µg/m³) low traffic route - 4.6 ppb (8.8 µg/m³)	case crossover (2.5 months)	pulmonary function (FENO, FEV1, FVC, & FEF25-75%) and cardiovascular function (heart rate (HR), low frequency power (LF), high frequency power (HF), LF:HF ratio, SDNN, RMSSD, & percentage of normal to normal intervals differing by > 50 msec (pNN50)) in cyclists riding indoors and outdoors	association with $PM_{2.5}$, UFP, BC, O_3, SO_2, CO, total VOCs, & NO_2	male and female 42 volunteers	adjusted change in response per IQR of 4 ppb (7.6 µg/m³) in single pollutant model FEV1 2-hr lag - 121 3-hr lag - 129 LF:RF ratio 2-hr lag - 1.4 3-hr lag - 1.7 SDNN 2-hr lag - -10	adjusted change in response per IQR of 4 ppb (7.6 µg/m³) in single pollutant model FEV1 2-hr lag 27 - 216 3-hr lag 23 - 234 LF:RF ratio 2-hr lag 0.35 - 2.5 3-hr lag 0.56 - 2.9 SDNN 2-hr lag -20 - -0.34	statistically significant association with a several cardiovascular and respiratory measures on 2 of 4 lag days in a single or two-pollutant model, no statistically significant association with 3 of 4 respiratory parameters or 4 of 6 cardiovascular parameters	⊕○○○ (insufficient because of severe exposure bias)
(Wong *et al.*, 2009) Hong Kong, China	daily average from eight fixed monitoring locations	daily mean 58.7 µg/m³	time-series (84 months)	hospitalization and mortality for acute respiratory (ARD), chronic obstructive pulmonary (COPD, and cardiovascular (CVD) disease	interaction study (influenza and PM_{10}, O_3, SO_2 & NO_2)	male & female (avg daily rates) mortality RD - 16.2 COPD - 5.9 CVD - 23.8 hospitalizations RD - 270.3 ARD - 104.9 COPD - 91.5 CVD - 203.5	excess risk for all subjects per 10 µg/m³ increase in single pollutant model baseline mortality RD - 1.24 CVD - 1.23 baseline hospitalizations RD - 0.85 COPD - 1.84 CVD - 0.98 excess risk for all subjects > 65 years of age per 10 µg/m³ increase in single pollutant model modifying effect hospitalizations COPD - 0.43	excess risk for all subjects per 10 µg/m³ increase in single pollutant model baseline mortality RD 0.27 - 2.22 CVD 0.41 - 2.06 baseline hospitalizations RD 0.51 - 1.18 COPD 1.32 - 2.35 CVD 0.63 - 1.33 excess risk for all subjects > 65 years of age per 10 µg/m³ increase in single pollutant model modifying effect hospitalizations COPD 0.05 - 0.81	statistically significant association with baseline mortality from respiratory and cardiovascular disease and baseline hospitalizations from respiratory, cardiopulmonary, and cardiovascular disease, statistically significant interaction with influenza for COPD-related hospitalizations in those > 65 years of age, no association for hospitalizations from acute respiratory disease, no statistically interactions with influenza for any mortality cause or any age-stratified group hospitalized for RD, ARD, or CVD	⊕○○○ (insufficient because of bias from single pollutant model probability of type 1 error)

author / location	exposure monitoring	NO_2 concentration	study type (duration)	endpoint	co-pollutants	participants	ratio or risk	confidence interval	results	GRADE quality of evidence
(Wood *et al.*, 2010) United Kingdom	annual mean from a geographical database built using emissions reporting from industrial sources and dispersion modelling together with regression analysis	annual mean 24.20 µg/m³	cohort (120 months)	carbon monoxide transfer coefficient (KOC) and 1 second forced expiratory volume (FEV_1) in adults with chronic obstructive pulmonary disease with α-1-antitrypsin deficiency	association with PM_{10}, O_3, SO_2 & NO_2	male & female 401 cases	no change in FEV1 volume or KCO diffusion rate per 1 µg/m³ increase in NO_2 exposure	no change in FEV1 volume or KCO diffusion rate per 1 µg/m³ increase in NO_2 exposure	no statistically significant association with changes in FEV1 or KCO diffusion rate in COPD adults with at least one follow-up evaluation of lung function; a subgroup with four follow-up evaluations was similarly unaffected; ozone was the most significant predictor of any decline	⊕○○○ (insufficient because of bias from single pollutant model and the small number of cases)
(Yang *et al.*, 2005) Vancouver, British Columbia	daily average from 31 fixed monitoring sites	daily mean concentration 17.03 ppb (32.5 µg/m³)	time-series (5 years)	hospitalization of elderly patients for COPD	association with PM_{10}, SO_2, O_3, CO, & NO_2	male & female adults ≥ 65 years of age 6027 admissions	relative risk for COPD per IQR of 5.5 ppb (10.5 µg/m³) increase in two and multi-pollutant model for average lag day 0-6 NO_2 only - 1.11 NO_2/O_3 - 1.12 NO_2/SO_2 - 1.12	relative risk for COPD per IQR of 5.5 ppb (10.5 µg/m³) increase in two and multi-pollutant model for average lag day 0-6 NO_2 only 1.04 - 1.20 NO_2/O_3 1.04 - 1.20 NO_2/SO_2 1.02 - 1.24	statistically significant association with COPD hospitalization in single and two pollutant models with O_3 and SO_2 for average 7 day lag period, no association in two pollutant models with PM_{10} & CO; no association in multi-pollutant model with the 4 remaining co-pollutants	⊕⊕○○ (low quality because small number of cases)
(Zhao *et al.*, 2008) Taiyuan, China	weekly averages using indoor (classroom) and outdoor diffusion samplers placed at 10 schools	daily mean indoors – 39.4 µg/m³ outdoors – 52.3 µg/m³	cross-sectional (4 months)	conditions or symptoms (wheeze, daytime breathlessness, nighttime breathlessness, pet or pollen allergy, respiratory infection) in school children	association with indoor and outdoor formaldehyde, SO_2, O_3, & NO_2	male & female aged 11-15 years 1,933 school children	adjusted odds ratio per 10 µg/m³ increase for nocturnal breathlessness in single pollutant model multiple regression - 1.45 hierarchical regression - 1.45	adjusted odds ratio per 10 µg/m³ increase for nocturnal breathlessness in single pollutant model multiple regression 1.00 - 2.45 hierarchical regression 1.00 - 2.08	weak statistically significant association with nocturnal breathlessness in single pollutant model using multiple regression or hierarchical regressions, no statistically significant association with wheeze, daytime breathlessness, pet or pollen allergy, or respiratory infection, no association using hierarchical regression model that nests the data for school, classroom, individual and also adjusts for multiple pollutants	⊕⊕⊕○ (moderate quality, no adjustment necessary)

Birth Outcomes

author / location	exposure monitoring	NO_2 concentration	study type (duration)	endpoint	co-pollutants	participants	ratio or risk	confidence interval	results	GRADE quality of evidence
(Aguilera *et al.*, 2009) Barcelona, Spain	trimester means using a LUR model constructed using personal measurements made during four 1-week campaigns at 57 locations as well as land coverage, topography,, population density, roads, & distance to local pollution sources, & altitude, temporal adjustments made using the results from only a single fixed monitoring site	trimester mean entire pregnancy - 32.17 µg/m³ 1st trimester – 32.66 µg/m³ 2nd trimester – 31.86 µg/m³ 3rd trimester – 32.67 µg/m³	cohort (24 months)	term birth weight and gestational age considering time-activity patterns	association with BTEX & NO_2	male & female 570 births	simultaneously adjusted decrease in birth weight (g) per IQR of 12 µg/m³ in women who spend < 2 hr/day in nonresidential outdoor environments 2nd trimester -74.7	simultaneously adjusted decrease in birth weight (g) per IQR of 12 µg/m³ in women who spend < 2 hr/day in nonresidential outdoor environments 2nd trimester -140.4 - -9.0	statistically significant association during 2nd trimester for women who spend < 2hr/day in outdoor environments, no association for all women or women who spend ≥ 15 hr/day at home, no association in crude estimates or when adjustments are made per trimester rather all trimesters simultaneously	⊕○○○ (insufficient because of bias from small sample size and failure to consider co-pollutants such as O_3 and SO_2)

author / location	exposure monitoring	NO_2 concentration	study type (duration)	endpoint	co-pollutants	participants	ratio or risk	confidence interval	results	GRADE quality of evidence
(Aguilera *et al.*, 2010) Catalonia, Spain	annual averages from land use regression model using GIS data such as vehicle density, distance to main road, land use, & altitude; validation using measurements from 93 locations; temporal changes considered using the measurements form 7 fixed monitoring locations	mean levels week 1-12 - 32.45 µg/m³ week 12-20 - 31.68 µg/m³ week 20-32 - 32.13 µg/m³	cohort (36 months)	fetal growth (femur length, head circumference, abdominal circumference, biparietal diameter, & estimated weight) by ultrasound	association with BTEX (benzene, toluene, ethylbenzene, & xylenes) & NO_2	male & female 562 infants	adjusted mean percent change in SD scores per IQR (12.19 µg/m³) exposure change during weeks 1-12 of pregnancy head circumference week 20 - -7.02 week 32 - -5.41 weeks 12-20 - -6.24 abdominal circumference week 32 - -5.25 weeks 20-32 - -4.86 biparietal diameter weeks 20-32 - -5.37 estimated fetal weight week 32 - -5.05 week 20-32 - -4.78	adjusted mean percent change in SD scores per IQR (12.19 µg/m³) exposure change during weeks 1-12 of pregnancy head circumference week 20 -12.78 - -1.12 week 32 -10.24 - -0.5 weeks 12-20 -11.94 - -0.4 abdominal circumference week 32 -10.16 - -0.26 weeks 20-32 -9.62 - -0.02 biparietal diameter weeks 20-32 -10.65 - -0.01 estimated fetal weight week 32 -9.81 - -0.22 week 20-32 -9.47 - -0.02	statistically significant association found for ultrasound measurements from some measurement times for women who spent less than 2 hrs/day in nonresidential outdoor environments, no associations found for women who spend ≥ 15hrs/day at home; no association in full cohort when exposures measured for weeks 1-12, 12-20, or 20-32	⊕○○○ (insufficient because of bias from small sample size and failure to consider co-pollutants such as O_3 and SO_2)
(Ballester *et al.*, 2010) Valencia, Spain	annual averages from land use regression model using GIS data such as vehicle density, distance to main road, land use, & altitude; validation using measurements from 93 locations; temporal changes considered using the measurements form 7 fixed monitoring locations	daily mean entire pregnancy - 36.9 µg/m³ 1st trimester – 37.9 µg/m³ 2nd trimester – 35.9 µg/m³ 3rd trimester – 37.0 µg/m³	cohort (32 months)	infant birth weight, length, & head circumference	association with NO_2 only	male & female 785 births	adjusted odds ratio per 10 µg/m³ for weight at a small gestational age 2nd trimester - 1.369	adjusted odds ratio per 10 µg/m³ for weight at a small gestational age 2nd trimester 1.013 - 1.849	statistically significant decrease in SGA weight during second trimester but not the first or third trimester using an adjusted model; a statistically significant reduction in birth weight for exposures during the first trimester that were greater than 40 µg/m³; no associations for length or head circumference or when an unadjusted model was employed	⊕⊕○○ (low quality because of failure to consider co-pollutants such as O_3 and SO_2)

author / location	exposure monitoring	NO_2 concentration	study type (duration)	endpoint	co-pollutants	participants	ratio or risk	confidence interval	results	GRADE quality of evidence
(Brauer *et al.*, 2008) Vancouver, British Columbia	mean during entire pregnancy using three techniques i) nearest of 22 fixed monitoring sites using assigned postal codes ii) inverse distance weighting (IDW) using three nearest fixed monitoring values iii) land use regression (LUR) using 116 passive monitors deployed for 14 days along with GIS variables for primary and secondary road density & commercial land use and fixed monitoring data for temporal adjustments	mean during pregnancy nearest - 34.4 µg/m³ IDW - 32.5 µg/m³ LUR - 31.6 µg/m³	cohort (48 months)	preterm births, term low birth weight (LBW), and small for gestational age (SGA)	association with PM_{10}, $PM_{2.5}$, BC, O_3, SO_2, CO, NO, & NO_2	male & female 70,249 births	adjusted odds ratio per 10 µg/m³ increase in single pollutant model SGA IDW - 1.14 LBW IDW - 1.11	adjusted odds ratio per 10 µg/m³ increase in single pollutant model SGA IDW 1.09 - 1.1 LBW IDW 1.01 - 1.23	statistically significant association with LBW and SGA with crude and adjusted model using IDW measurements but not LUR estimates, no statistically significant association for preterm births using crude or adjusted odds ratios	⊕⊕◯◯ (low quality because of bias from single pollutant model reliance)
(Dadvand *et al.*, 2011) Northeast England	weekly average measurements at five fixed monitoring locations during weeks 3-8 of pregnancy	weekly mean cases - 32.31 µg/m³ controls 32.27 µg/m³	case control (120 months)	congenital heart disease in infants (congenital malformations of cardiac chamber, cardiac septa, pulmonary and tricuspid valves, aortic and mitral valves, arteries and veins; as well as atrial septal defects coarctation of aorta, pulmonary valve stenosis, ventricular septal defect, and teratology of fallot)	association with PM_{10}, CO, O_3, SO_2, NO, & NO_2	male & female cases 2140 controls 14,256	no significant change in odds ratio for any of the ten measures of congenital heart disease for each 1 µg/m³ increase using an adjusted single pollutant model	no significant change in odds ratio for any of the ten measures of congenital heart disease for each 1 µg/m³ increase using an adjusted single pollutant model	no statistically significant association for the pooled heart disease incidence or specific heart disease estimates using an adjusted single pollutant model	⊕⊕◯◯ (low quality because of failure to consider co-pollutants)

author / location	exposure monitoring	NO_2 concentration	study type (duration)	endpoint	co-pollutants	participants	ratio or risk	confidence interval	results	GRADE quality of evidence
(Dales *et al.*, 2006) 11 Canadian cities	daily average from an unstated number of fixed monitoring sites in each city	daily mean ranged from 9.2 ppb (17.6 µg/m³) in Saint John to 25.6 ppb (48.9 µg/m³) in Calgary	time series (15 years)	hospitalization of neonates for respiratory disease (asphyxia, respiratory failure, dyspnea respiratory distress syndrome, unspecified birth asphyxia, other respiratory problems, & pneumonia)	association with PM_{10}, SO_2, O_3, CO, & NO_2	male & female infants neonates from birth to 27 days of age 9542 patients	pooled (random and fixed effects) percent increase in neonatal respiratory hospitalization per IQR of 10 ppb (19.1 µg/m³) in single and multi-pollutant model on lag day 1 NO_2 only - 2.94 NO_2/CO, O_3, & SO_2 - 2.85 NO_2/PM_{10}, CO, O_3, & SO_2 - 2.48	pooled (random and fixed effects) percent increase in neonatal respiratory hospitalization per IQR of 10 ppb (19.1 µg/m³) in single and multi-pollutant model on lag day 1 NO_2 only 1.93 - 3.95 NO_2/CO, O_3, & SO_2 1.68 - 4.02 NO_2/PM_{10}, CO, O_3, & SO_2 1.18 - 3.80	statistically significant association for neonatal respiratory hospitalization in single and multi-pollutant models; slight attenuation of association when using multi-pollutant model with PM_{10}	⊕⊕○○ (low quality because of bias from single pollutant model reliance)
(Darrow *et al.*, 2009) Atlanta, Georgia	mean daily concentration within 4 miles of four fixed monitoring locations	1-hr maximum 1-week mean 23.5 ppb (44.9 µg/m³) 4-week mean 23.4 ppb (44.7 µg/m³) 6-week mean 23.6 ppb (45.1 µg/m³)	time series (120 months)	preterm births (before week 37)	association with $PM_{2.5}$, PM_{10}, CO, O_3, SO_2, & NO_2	male & female 15,946 cases	risk ratio per 5 ppb (9.6 µg/m³) IQR (lag 6 week) 1-hr max NO_2 - 1.06	risk ratio per 5 ppb (9.6 µg/m³) IQR (lag 6 week) 1-hr max NO_2 1.02 - 1.09	statistically significant increase in pre-term infants with a six week lag period; no associations for a 1 or 4-week lag; no associations for infants born throughout the 5 county monitoring area without sorting for proximity to a monitoring site	⊕⊕○○ (low quality because of bias from single pollutant model reliance)
(Darrow *et al.*, 2011b) Atlanta, Georgia	population weighted spacial averages for census tracts using information from 6 fixed monitoring sites	1-hr maximum concentration 1st month gestation - 23.6 ppb (45.1 µg/m³) 3rd trimester - 23.8 ppb (45.5 µg/m³)	cohort study (120 months)	birth weight in full-term infants	association with PM_{10}, PM_{10}-2.5 (course), $PM_{2.5}$, $PM_{2.5}$ sulfate, $PM_{2.5}$ nitrate, $PM_{2.5}$ EC, $PM_{2.5}$ OC, $PM_{2.5}$ soluble metals, SO_2, CO, O_3, & NO_2	male & female 406,627 births	mean change in birth weight per 5 ppb (9.6 µg/m³) change in a single pollutant model 3rd trimester - -4.5	mean change in birth weight per 5 ppb (9.6 µg/m³) change in a single pollutant model for the five county area 3rd trimester -8.5 - -0.6	statistically significant association with decrease birth weights for exposures during the 3rd trimester but not for exposures during the 1st month of gestation, statistically significant association observed for the 8th and 9th months but not earlier months; no statistically significant associations births in areas that were close (<4 miles) to a monitoring station; no effect modification according to ethnicity	⊕⊕○○ (low quality because of bias from single pollutant model reliance)

author / location	exposure monitoring	NO_2 concentration	study type (duration)	endpoint	co-pollutants	participants	ratio or risk	confidence interval	results	GRADE quality of evidence
(Ebisu *et al.*, 2011) Hartford & New Haven counties, Connecticut	daily mean estimates using a GIS integrated traffic exposure model incorporating air dispersion, proximity considerations and annual average daily traffic patterns; model estimates verified using values from diffusion tubes positioned outside homes	not provided	cohort (36 months)	presence and severity of wheeze in infants during first year of life	association with NO_2 only	male & female 680 volunteers	no significant change in odds ratio using an adjusted single pollutant model over an IQR of 9.21 ppb (17.6 µg/m³)	no significant change in odds ratio using an adjusted single pollutant model over an IQR of 9.21 ppb (17.6 µg/m³)	no statistically significant association with wheeze using an adjusted single pollutant mode alone or in combination with urban land use factors such as the number of housing units or the percentage of impervious surfaces	⊕⊕◯◯ (low quality because of failure to consider co-pollutants such as O_3 and SO_2)
(Esplugues *et al.*, 2011) Valencia, Spain	land use regression of the monitoring data from 93 locations (during pregnancy); passive monitoring at homes postnatally	outdoor prenatal - 39.1 µg/m³ postnatal - 27.4 µg/m³	cohort (20 months)	lower respiratory tract infections during first year of life (bronchitis, bronchiolitis, pneumonia, wheezing, persistent cough)	NO_2 only	male & female 352 children	odds ratio per 10 µg/m³ increment persistent cough using outdoor NO_2 at 1 year - 1.40	odds ratio per 10 µg/m³ increment persistent cough using outdoor NO_2 at 1 year 1.02 - 1.92	a slight but non-significant increase in cough using outdoor NO_2 concentration at 1 year; no other associations observed during or after pregnancy using the adjusted model	⊕◯◯◯ (insufficient because of bias from single pollutant approach and the small number of cases)
(Estarlich *et al.*, 2011) four cities in Spain Asturias Gipuzkoa Sabadell Valencia	individual residential exposures determined using 67-93 passive sampling for one week periods together with land use regression estimates based distance to road, urban land coverage, agricultural/forest land coverage road type, distance to industry 1-7 fixed monitoring readings	daily mean 29.2 µg/m³	cohort study (64 months)	infant birth weight, length, & head circumference	association with benzene & NO_2	male & female 2337 cases	absolute length change per 10 µg/m³ increase in residential exposure using adjusted two-pollutant model all women -0.16 home time ≥ 15hr/day -0.23	absolute length change per 10 µg/m³ increase in residential exposure using adjusted two-pollutant model all women -0.29 - -0.03 home time ≥ 15hr/day -0.39 - -0.07	statistically significant association with infant length decline, but not weight or head circumference in adjusted one- and two-pollutant models; statistically significant association observed for all monitoring periods (first, second, third trimesters and total pregnancy);	⊕⊕◯◯ (low quality because of failure to consider co-pollutants such as O_3 and SO_2)

author / location	exposure monitoring	NO_2 concentration	study type (duration)	endpoint	co-pollutants	participants	ratio or risk	confidence interval	results	GRADE quality of evidence
(Freire *et al.*, 2010) Granada, Spain	annual mean from outdoor measurements at each residence (two 7-day periods) together with LUR	mean 20.75 µg/m³ (measured) 20.88 µg/m³ (LUR predicted)	cohort (12 months)	child cognitive development based on perceptual, verbal, quantitative, memory, motor, executive function, memory span, verbal memory, working memory, gross motor, & free motor scores	association with NO_2	210 children	decrement in gross motor function relative to first NO_2 tertile (< 15.4 µg/m³) 2nd tertile (15.40-24.75 µg/m³) -8.31 3rd tertile (> 24.75 µg/m³) -8.61	decrement in gross motor function relative to first NO_2 tertile (< 15.4 µg/m³) 2nd tertile (15.40-24.75 µg/m³) -17.69 - 1.09 3rd tertile (> 24.75 µg/m³) -18.96 - 1.74	negative trends but no statistically significant associations with any measure of cognitive function except gross motor control in a fully adjusted model when NO_2 exposure tertiles compared	⊕⊕○○ (low quality because of failure to consider co-pollutants such as O_3 and SO_2)
(Gehring *et al.*, 2011) Netherlands	temporally adjusted land use regression estimates based on traffic, road, and population density along with daily concentration at 40 pre-selected selected monitoring sites and 23 fixed monitoring sites for validation	daily mean entire pregnancy – 30.4 µg/m³ 1st trimester – 31.5 µg/m³ last month before birth - 28.9 µg/m³	cohort (24 months)	pre-term and term birth weight	association with $PM_{2.5}$, soot, & NO_2	male & female 3853 births	fully adjusted mean difference in term birth weight (g) per IQR of 14.4 µg/m³ 1st trimester exposure - 34.3	fully adjusted mean difference in term birth weight (g) per IQR of 14.4 µg/m³ 1st trimester exposure 9.7 - 58.8	statistically significant increase in term birth weight relative to exposures during the first trimester of pregnancy using a fully adjusted model; crude model and partially adjusted model showed no change; no associations in term birth weights using measurements for the full pregnancy or for the final month; no statistically significant change in odds ratio for pre-term birth weight using any measure of exposure; no effect on odds ratio for pre-term births	⊕○○○ (insufficient because of very serious imprecision as seen by wide confidence intervals)

author / location	exposure monitoring	NO_2 concentration	study type (duration)	endpoint	co-pollutants	participants	ratio or risk	confidence interval	results	GRADE quality of evidence
(Hansen *et al.*, 2008) Brisbane, Australia	seasonal averages using data from 17 fixed monitoring sites	daily mean in ppb (µg/m³) all – 9.8 (18.7 µg/m³) summer – 6.3 (12.0 µg/m³) fall – 10.0 (19.1 µg/m³) winter – 13.2 (25.2 µg/m³) spring – 9.4 (18.0 µg/m³)	cross-sectional (124 months)	ultrasonic measures of fetal growth (biparietal diameter (BPD), femur length (FL), abdominal circumference (AC), & head circumference (HC) during gestational weeks13-26	association with PM_{10}, SO_2, O_3, & NO_2	male & female fetuses 14,734 pregnancies	no association in crude or adjusted single pollutant model per 5 ppb (9.6 µg/m³)	no association in crude or adjusted single pollutant model per 5 ppb (9.6 µg/m³)	no statistically significant association with ultrasonic measure of fetal growth for women within 2 km of a monitoring site	⊕⊕◯◯ (low quality because of bias from single pollutant model reliance)
(Hwang *et al.*, 2011) Taiwan	geocoding and inverse distance weighting of mean daily concentration from 72 fixed monitoring sites	daily mean 21.7 ppb (41.4 µg/m³)	case control (84 months)	stillbirths	association with PM_{10}, SO_2, O_3, CO, & NO_2	male & female 9325 cases 93,250 controls	no effect on odds ratio over an IQR of 10 ppb (19.1 µg/m³) for any trimester in an adjusted single or multi-pollutant model	no effect on odds ratio over an IQR of 10 ppb (19.1 µg/m³) for any trimester in an adjusted single or multi-pollutant model	no statistically significant association with exposure during any trimester for preterm births (<37 weeks), term births (≥37 weeks), or all births using an adjusted single pollutant or three pollutant model	⊕⊕⊕◯ (moderate quality, no adjustment necessary)
(Kashima *et al.*, 2011) Shizuoka, Japan	temporally adjusted land use regression estimates based on roadway number and density, traffic counts, and housing density along with the annual concentrations from 14 fixed monitoring location for validation	quintile ranges during 9 months of pregnancy 1st - ≤ 24.9 µg/m³ 2nd - 24.9 - 27.6 µg/m³ 3rd - 27.6 - 29.7 µg/m³ 4th - 29.7 - 31.9 µg/m³ 5th - > 31.9 µg/m³	cross-sectional study (12 months)	birth weight including term low birth weight (LBW), and small for gestational age (SGA)	association with NO_2 only	male & female 14,204 single births	no significant change in any of three birth weight categories per quintile range or continuous (10 µg/m³) increase using a crude or adjusted model	no significant change in any of three birth weight categories per quintile range or continuous (10 µg/m³) increase using a crude or adjusted model	no statistically significant association with mean birth weight, term low birth weights (LBW), or small birth weight for gestational age (SGA) using any measure of continuous or quintile exposure; findings were replicated in crude, partially adjusted, and fully adjusted models	⊕⊕◯◯ (low quality because of failure to consider co-pollutants such as O_3 and SO_2)

author / location	exposure monitoring	NO_2 concentration	study type (duration)	endpoint	co-pollutants	participants	ratio or risk	confidence interval	results	GRADE quality of evidence
(Lepeule *et al.*, 2010) Poitiers and Nancy, France	trimester means using two methods i) nearest of nine air quality monitoring stations (AQMS) ii) temporally adjusted geostatistical model that using diffusive monitoring measurements from 159 locations over a 14-day period together with fixed monitoring data that was smoothed using kriging techniques then temporally adjusted	trimester mean both locations nearest AQMS 1st trimester – 28.8 µg/m³ 2nd trimester – 29.0 µg/m³ 3rd trimester – 28.6 µg/m³ TAG model 1st trimester – 23.7 µg/m³ 2nd trimester – 24.1 µg/m³ 3rd trimester – 23.3 µg/m³	prospective cohort (40 months)	infant birth weight	association with NO_2 only	male & female 776 births	no significant change in mean differences for any trimester using either the AQMS or TAG exposure methods	no significant change in mean differences for any trimester using either the AQMS or TAG exposure methods	no statistically significant association with infant birth weight using either of two exposure models examined both spatially and temporally for each trimester	⊕⊕◯◯ (low quality because of failure to consider co-pollutants such as O_3 and SO_2)
(Llop *et al.*, 2010) Valencia, Spain	land use regression estimates based on traffic information, topography, and kriging-based land use information along with measurements from 4 weekly sampling periods at 91 sites using diffusion samplers	daily mean during pregnancy – 36.9 µg/m³	cohort (36 months)	preterm births	association with benzene and NO_2	male & female 738 births	adjusted odds ratio per 1 µg/m³ increment in single pollutant model at concentrations greater than 46.2 µg/m³ 2nd trimester - 1.11 3rd trimester - 1.10 entire pregnancy - 1.29	adjusted odds ratio per 1 µg/m³ increment in single pollutant model at concentrations greater than 46.2 µg/m³ 2nd trimester 1.03 - 1.21 3rd trimester 1.00 - 1.21 entire pregnancy 1.13 - 1.46	statistically significant association with preterm births at concentrations greater than 46.2 µg/m³ using measurements throughout pregnancy or during the 2nd and 3rd trimester, no associations found with measurements from the 1st trimester or when the concentrations were less than 46.2 µg/m³	⊕⊕◯◯ (low quality because of failure to consider co-pollutants such as O_3 and SO_2)

author / location	exposure monitoring	NO_2 concentration	study type (duration)	endpoint	co-pollutants	participants	ratio or risk	confidence interval	results	GRADE quality of evidence
(Madsen *et al.*, 2010) Oslo, Norway	daily mean exposures using measurements from a single fixed monitoring location or the estimates from a dispersion model that considered emission, meteorology, topography and background concentration	daily mean dispersion model – 29.8 µg/m³ monitoring station – 35.6 µg/m³	cohort (48 months)	mass in term birth weight, low birth weight (LBW), & small for gestational age (SGA) babies	association with PM_{10}, $PM_{2.5}$, & NO_2	male & female 25,229 births	crude birth weight relative to first NO_2 quartile (conc. ≤ 20.3 µg/m³) in single pollutant model using dispersion data 4th quartile (> 38.0 µg/m³) - -29.7	crude birth weight relative to first NO_2 quartile (conc. ≤ 20.3 µg/m³) in single pollutant model using dispersion data 4th quartile (> 38.0 µg/m³) -46.9 - -12.5	statistically significant decrease in term birth weight fin the 4th exposure quartile for the dispersion model estimates of exposure; no statistically significant changes following adjustment for confounders; no statistically significant decreases in LBW and SGA babies using an adjusted model with dispersion estimates or monitoring data	⊕⊕◯◯ (low quality because of bias from single pollutant model reliance)
(Morello-Frosch *et al.*, 2010) California	mean weakly concentration within 10 km of the nearest monitoring location for unstated number of fixed monitoring sites throughout the state	mean for full pregnancy period 24.2 ppb (46.2 µg/m³)	cohort (120 months)	birth weight in full-term births	association with course PM, PM_{10}, $PM_{2.5}$, SO_2, O_3, CO, & NO_2	male & female 3,545,177 births	odds ratio per 10 µg/m³ for birth weight < 2500 g at specific distances from monitoring site 3 km - 1.03 5 km - 1.04 10 km - 1.03	odds ratio per 10 µg/m³ for birth weight < 2500 g at specific distances from monitoring site 3 km 1.01 - 1.05 5 km 1.03 - 1.05 10 km 1.02 - 1.04	slight statistically significant increase in odds ratio for low birth weight (<2500 g) at distances of 3, 5, & 10 km from the monitoring site; associations stronger in neighborhoods with a high poverty level; stratification against other race and ethnicity showed no change; multi-pollutant modelling had no dramatic impact on the associations; associations observed using exposure measurements for the first & third trimester and the full term, but not the second trimester-	⊕⊕◯◯ (low quality because of the bias that comes with the failure to consider confounding from alcohol and tobacco use)

author / location	exposure monitoring	NO_2 concentration	study type (duration)	endpoint	co-pollutants	participants	ratio or risk	confidence interval	results	GRADE quality of evidence
(Peel *et al.*, 2011) Atlanta, Georgia	1-hr maximum concentration at a single fixed monitoring site	mean 1-hr maximum 41.7 ppb (79.6 µg/m³)	time series (53 months)	apnea and bradycardia in high risk infants	association with PM_{10}, $PM_{10-2.5}$ (course), $PM_{2.5}$, $PM_{2.5}$ sulfate, $PM_{2.5}$ EC, $PM_{2.5}$ OC, $PM_{2.5}$ soluble metals, oxygenated hydrocarbons, SO_2, CO, O_3, & NO_2	male and female 2358 apnea cases 3875 bradycardia cases	odds ratio per 20 ppb (38.2 µg/m³) for lag day 0-1 bradycardia - 1.025	odds ratio per 20 ppb (38.2 µg/m³) for lag day 0-1 bradycardia 1.000 - 1.050	statistically significant association with bradycardia but not apnea in a single pollutant model only; no statistically significant associations with a multi-pollutant model with ozone; no statistically significant associations when the dependant variables were stratified by gestational age or birth weight	⊕○○○ (insufficient because of very serious risk of exposure bias)
(Rich *et al.*, 2009) New Jersey	mean daily concentration at 11 fixed monitoring locations (closest monitoring site assigned to each residence)	very small gestational age (VSGS) group mean in ppb (µg/m³) 1st trimester – 26.3 (50.2 µg/m³) 2nd trimester – 26.4 (50.4 µg/m³) 3rd trimester – 26.4 (50.4 µg/m³)	cohort (60 months)	gestational age development based on fetal birthrate relative to control	association with $PM_{2.5}$, SO_2, CO, & NO_2	male and female 16,340 (SGA births) 4683 (VSGA births)	percentage change in risk per IQR of 10 ppb (19.1 µg/m³) - two pollutant model 1st trimester - 8.9 2nd trimester - 9.7 3rd trimester - 8.6	percentage change in risk per IQR of 10 ppb (19.1 µg/m³) - two pollutant model 1st trimester 1.6 - 16.7 2nd trimester 2.9 - 17.0. 3rd trimester 2.1 - 15.5	statistically significant associations in one and two ($PM_{2.5}$ & NO_2) pollutant model for infants with very small gestational age during all three trimesters; infants of small gestational age unaffected; temperature, calendar month, and year of birth had little impact on results; higher associations observed for Hispanic women than white or African American.	⊕⊕○○ (low quality because of serious imprecision as evidenced by wide confidence intervals)
(Son *et al.*, 2008) Seoul, Korea	pooled mean daily concentration from 27 fixed monitoring locations	daily mean 35.6 ppb (68.0 µg/m³)	time series (60 months)	postnatal mortality in first born infants	differential effects of PM_{10}, SO_2, O_3, CO & NO_2	9,137 deaths	no significant change in relative risk	no significant change in relative risk	no significant associations observed using either a time series or case crossover design	⊕⊕○○ (low quality because of bias from single pollutant model reliance)

author / location	exposure monitoring	NO_2 concentration	study type (duration)	endpoint	co-pollutants	participants	ratio or risk	confidence interval	results	GRADE quality of evidence
(Strickland *et al.*, 2009) Atlanta, Georgia	weighted mean daily concentration during weeks 3-7 of gestation from a single centrally located fixed monitoring site	daily mean by conception year in ppb (µg/m³) 1986-1991 – 28.0 (53.5 µg/m³) 1992-1997 – 24.3 (46.4 µg/m³) 1998-2003 – 22.5 (43.0 µg/m³)	retrospective cohort (18 years)	cardiovascular malformations (12 types) in infants	association with PM_{10}, SO_2, O_3, CO, & NO_2	male & female 3,338 cases	risk ratios for cardiovascular malformations per 5.7 ppb (10.9 µg/m³) IQR using less stringent control for seasonal & temporal variation patent ductus arteriosus - 1.40	risk ratios for cardiovascular malformations per 5.7 ppb (10.9 µg/m³) IQR using less stringent control for seasonal & temporal variation patent ductus arteriosus 1.07 - 1.83	no statistically significant association with any of 12 different cardiovascular malformation in infants using reaching at least 20 weeks gestation; statistically significant association with patent ductus arteriosus observed when seasonal and temporal variations were relaxed; a sensitivity analysis restricting the number of gestations, number of malformations, weighting of pollution metrics, or duration of pollution monitoring failed to show any associations	⊕◯◯◯ (insufficient because of very serious risk of exposure bias)
(Wilhelm *et al.*, 2011) Los Angeles County, California	1) annual averages from land use regression model using traffic counts, roadway lengths, distance to truck routes, land use characteristics, soil brightness & measurements from 181 locations for validation 2) daily means from four fixed monitoring sites	mean during pregnancy in ppb (µg/m³) LUR (no seasonal adjustment) – 25.2 (48.1 µg/m³) LUR (seasonal adjustment) – 26.7 (51.0 µg/m³) monitoring – 29.3 (56.0 µg/m³)	case control (22 months)	pre-term births (< 37 weeks gestational age)	association with source attributed $PM_{2.5}$, EC & OC ($PM_{2.5}$ & PM_{10}), naphthalene, benzo(a)pyrene, benzo(g,h,i)-perylene, total PAHs, benzene, vanadium, TSP, NO, NOx, O_3, CO & NO_2	male & female 10,265 cases 102,650 controls	adjusted odds ratio per IQR of 4.2 ppb (8.0 µg/m³) for entire pregnancy in single pollutant model LUR unadjusted - 1.04	adjusted odds ratio per IQR of 4.2 ppb (8.0 µg/m³) for entire pregnancy in single pollutant model LUR unadjusted 1.02 - 1.07	small statistically significant association with pre-term birth using a crude or adjusted single pollutant model with land use estimates not seasonally adjusted; no associations when using NO_2 concentrations from seasonally adjusted LUR or monitoring data; statistically significant association observed with last month of exposure (values not shown); no association	⊕⊕◯◯ (low quality because of bias from single pollutant model reliance)

author / location	exposure monitoring	NO_2 concentration	study type (duration)	endpoint	co-pollutants	participants	ratio or risk	confidence interval	results	GRADE quality of evidence
(Wu *et al.*, 2011) Los Angeles and Orange Counties, California	daily mean concentration by three methods 1. values from 17-19 fixed monitoring locations 2. land use regression estimates using values from passive diffusion samplers at 1161 sites along with traffic, highway, and land use information 3. land use regression estimates using temporally and seasonally adjusted values from an unstated number of fixed monitoring locations	daily mean measured value in ppb (µg/m³) 24.9 (47.6 µg/m³) unadjusted LUR - 22.4 (42.8 µg/m³) adjusted LUR – 28.0 (53.5 µg/m³)	cohort (120 months)	adverse pregnancy outcome (preeclampsia, preterm births less than 37 weeks, preterm births less than 30 weeks)	association with PM_{10}, $PM_{2.5}$, CO, O_3, NO, NOx, & NO_2	male and female births 81,186 births	adjusted odds ratio per IQR of 11.7 ppb (22.4 µg/m³) measured 4.3 ppb (8.2 µg/m³) unadjusted LUR 5.1 ppb (9.7 µg/m³) adjusted LUR preeclampsia unadjusted LUR (LA county) - 1.16 adjusted LUR (LA county) - 1.12 pre-term (< 37 weeks) measured values (orange cty) - 1.13 unadjusted LUR (LA county) - 1.07 pre-term (<30 weeks) measured values (LA county) - 1.46 measured values (orange cty) - 1.43 unadjusted LUR (LA county) - 1.42	adjusted odds ratio per IQR of 11.7 ppb (22.4 µg/m³) measured 4.3 ppb (8.2 µg/m³) unadjusted LUR 5.1 ppb (9.7 µg/m³) adjusted LUR preeclampsia unadjusted LUR (LA county) 1.07 - 1.26 adjusted LUR (LA county) 1.02 - 1.23 pre-term (< 37 weeks) measured values (orange cty) 1.02 - 1.25 unadjusted LUR (LA county) 1.02 - 1.13 pre-term (<30 weeks) measured values (LA county) 1.11 - 1.92 measured values (orange cty) 1.02 - 2.01 unadjusted LUR (LA county) 1.24 - 1.62	statistically significant association with preeclampsia and pre-term births mostly using unadjusted LUR estimates of exposure for Los Angeles county; associations observed with pre-term births were significant with both and unadjusted LUR estimates; no associations observed after seasonal adjustment of LUR estimates	⊕⊕◯◯ (low quality because of imprecision resulting from the limited treatment of confounders)

Cancer

author / location	exposure monitoring	NO_2 concentration	study type (duration)	endpoint	co-pollutants	participants	ratio or risk	confidence interval	results	GRADE quality of evidence
(Amigou *et al.*, 2011) France	three metrics employed but one only involved categorical exposure estimates using a multiple determinant model with road traffic and emissions data	three categories based on overall distribution <50th percentile - 12.2 µg/m³ 50-75th percentile - 12.2 - 16.1 µg/m³ ≥75th percentile - 16.2 µg/m³	case control study (24 months)	childhood acute lymphoblastic leukemia (ALL), acute myeloblastic leukemia (AML), & acute non-lymphoblastic leukemia (ANLL)	association with benzene & NO_2	male & female children (<15 years) 763 cases 1681 controls	odds ratio relative to low exposure group (conc. <12.2 µg/m³) intermediate exposure (12.2 - 16.1 µg/m³) all AL - 1.3 ALL - 1.3 high exposure (≥16.2 µg/m³) all AL - 1.2 ALL - 1.2 ANLL - 1.5	odds ratio relative to low exposure group (conc. <12.2 µg/m³) intermediate exposure (12.2 - 16.1 µg/m³) all AL 1.0 - 1.6 ALL 1.0 - 1.6 high exposure (≥16.2 µg/m³) all AL 1.0 - 1.5 ALL 1.0 - 1.5 ANLL 1.0 - 2.4	statistically significant association with all acute leukemia's (AL), acute lymphoblastic leukemia (ALL), and acute non-lymphoblastic leukemia (ANLL) at the medium and high exposures relative to the low exposure group; significant associations also observed using qualitative indicators for road proximity or traffic density; stratification by residence location (urban or rural) revealed statistically significant associations for urban residents at intermediate but not the high exposure level; stratification by relocation (no moves last two years) revealed stronger associations at the intermediate and high exposure levels	⊕⊕○○ (low quality because of failure to consider co-pollutants)
(Crouse *et al.*, 2010) Montreal, Quebec	annual mean value using an LUR model developed using passive diffusion measurements from 133 locations during a 1-year campaign together with land use and traffic related variables, resulting exposure map used together with historical data from 9-10 fixed monitoring sites and inverse distance weighting to assess temporal variability	annual average 2006 - 11.3 ppb (21.6 µg/m³) 1996 - 12. 7 ppb (24.3 µg/m³) 1985 - 15.8 ppb (30.2 µg/m³) mean 1985 & 1996 - 14.3 ppb (27.3 µg/m³)	case control (24 months)	post-menopausal breast cancer (histologically confirmed)	association with NO_2 only	female 383 cases 416 controls	fully adjusted odds ratio per 5 ppb (9.6 µg/m³) increase in single pollutant year 1996 - 1.31	fully adjusted odds ratio per 5 ppb (9.6 µg/m³) increase in single pollutant year 1996 1.00 - 1.71	statistically significant association with breast cancer for a single year using LUR back extrapolations based on predicted NO_2 concentrations for the year 2006; no statistically significant associations when actual NO_2 measurements are used for the LUR back extrapolations	⊕○○○ (insufficient because of bias from single pollutant model and the small number of cases)

author / location	exposure monitoring	NO_2 concentration	study type (duration)	endpoint	co-pollutants	participants	ratio or risk	confidence interval	results	GRADE quality of evidence
(Weng *et al.*, 2008) Taiwan	mean daily concentration at 64 fixed monitoring locations	tertile median 1st tertile - 17.08 ppb; 32.6 µg/m³) 2nd tertile - 24.09 ppb; 46.0 µg/m³) 3rd tertile - 29.13 ppb; 55.6 µg/m³)	case control (132 months)	childhood leukemia	association with NO_2	male & female 308 cases 308 controls	odds ratio relative to first NO_2 tertile (conc. ≤ 20.9 ppb; 39.9 µg/m³) 2nd tertile (20.99-24.09 ppb) - 1.70 3rd tertile (26.33-44.85 ppb) - 2.29	odds ratio relative to first NO_2 tertile (conc. ≤ 20.9 ppb; 39.3 µg/m³) 2nd tertile (20.99-24.09 ppb) 1.12 - 2.58 3rd tertile (26.33-44.85 ppb) 1.44 - 3.64	significant association in an adjusted single pollutant model using NO_2 as a surrogate for traffic-related air pollution	⊕○○○ (insufficient because of bias from single pollutant model and the small number of cases)
Beelan *et al.*, 2008 Netherlands	sum of regional, urban, and local concentration at home location using land use regression for estimating urban concentration and proximity to monitoring sites for regional concentration; local concentrations were estimated from traffic patterns and highway locations	daily mean - 36.9 µg/m³	cohort study (135.6 months)	lung cancer	association with $PM_{2.5}$, black smoke, SO_2, & NO_2	male & female 114,378 cohort 2,183 cases	no significant change in relative risk using a partially adjusted or fully adjusted model	no significant change in relative risk using a partially adjusted or fully adjusted model	no statistically significant associations found before or after complete adjustment for potential confounders	⊕⊕⊕○ (moderate quality, no adjustment necessary)

Diabetes

author / location	exposure monitoring	NO_2 concentration	study type (duration)	endpoint	co-pollutants	participants	ratio or risk	confidence interval	results	GRADE quality of evidence
(Brook *et al.*, 2008) Hamilton & Toronto, Ontario	passive samplers at 193 urban locations used to develop land use regression (LUR) model	Hamilton male – 15.2 ppb (29.0 µg/m³) female – 15.3 ppb (29.2 µg/m³) Toronto male – 23.0 ppb (43.9 µg/m³) female – 2.9 ppb (43.7 µg/m³)	case control (96 months)	diabetes (visits to disease clinics)	measurement of disease prevalence	men cases 622 controls 2830 female cases 630 controls 3552	odds ratio per 1 ppb increment (women only) Hamilton - 1.029 Toronto - 1.055	odds ratio per 1 ppb increment (women only) Hamilton 0.98 - 1.08 Toronto 0.999 - 1.11	odds ratio increase observed with women, but not men living in Hamilton and Toronto; 17% increase in odds over the interquartile range of 4 ppb NO_2	⊕⊕○○ (low quality because of inconsistency with no effect modification from smoking)
(Dijkema *et al.*, 2011) Westfriesland, the Netherlands	land use regression estimates based on traffic, road location, and residential land use, and background NO_2 concentrations along with daily concentration by passive sampling at urban and rural sites for validation	daily mean 1st quartile 8.8 - 14.2 µg/m³ 2nd quartile 14.2-15.2 µg/m³ 3rd quartile 5.2-16.5 µg/m³ 4th quartile 16.5-36.0 µg/m³	cross-sectional (36 months)	diagnosed type II diabetes in adults aged 50-75 years old	association with NO_2 only	male & female 8,018 participants	no change in odds ratios for top three exposure quartile (14.2-15.2, 15.2-16.5, 16.5-36.0 µg/m³) relative to the first quartile (8.8-14.2 µg/m³) in either a crude or adjusted model; females but not males showed an association with exposure at the 3rd quartile only	no change in odds ratios for top three exposure quartile (14.2-15.2, 15.2-16.5, 16.5-36.0 µg/m³) relative to the first quartile (8.8-14.2 µg/m³) in either a crude or adjusted model for either males or females	no statistically significant association with type II diabetes in males with a crude or adjusted model for any quartile of exposure; statistically significant association was observed in females and the group diagnosed during the study design for the third but not the fourth exposure quartile using an adjusted model (values not provided);	⊕⊕○○ (low quality because of bias from single pollutant model reliance)

author / location	exposure monitoring	NO_2 concentration	study type (duration)	endpoint	co-pollutants	participants	ratio or risk	confidence interval	results	GRADE quality of evidence
(Kramer *et al.*, 2010) North-Rhine, West Germany	five year average determined by three methods i) nearest fixed monitor ii) emissions inventory data together with an unstated air pollution model iii) LUR based on 1-year of monitoring data at 40 locations using 14 days of sampling in each season and unstated GIS and traffic-related variables	five year average monitoring data - 41.7 µg/m³ emission inventory - given as emission rate per unit surface area LUR - 34.5 µg/m³	cross-sectional (192 months)	incidence type II diabetes in subjects with normal and abnormal inflammatory C3c (compliment factor C3 cleavage product) levels	association with PM_{10}, soot, & NO_2	adult females only 1,775 non-diabetics	adjusted hazard ratio for entire cohort per IQR (24.9 µg/m³, 19 tons/yr/km2, & 15 µg/m³) in single pollutant model monitoring stations - 1.34 emission inventory - 1.15 LUR - 1.42 adjusted hazard ratio for cohort members with C3c levels > mean per IQR (19 tons/yr/km2, & 15 µg/m³) in single pollutant model emission inventory - 1.24 LUR - 1.31	adjusted hazard ratio for entire cohort per IQR (24.9 µg/m³, 19 tons/yr/km2, & 15 µg/m³) in single pollutant model monitoring stations 1.02 - 1.76 emission inventory 1.04 - 1.27 LUR 1.16 - 1.73 adjusted hazard ratio for cohort members with C3c levels > mean per IQR (19 tons/yr/km2, & 15 µg/m³) in single pollutant model emission inventory 1.08 - 1.41 LUR 1.01 - 1.70	statistically significant association of diabetes incidence with NO_2 in an adjusted but not an unadjusted model, statistically significant association in adjusted model for those individuals with a C3c level greater than the mean but not those with values less than the mean	⊕⊕◯◯ (low quality because of bias from single pollutant model reliance)

Inflammation

author / location	exposure monitoring	NO_2 concentration	study type (duration)	endpoint	co-pollutants	participants	ratio or risk	confidence interval	results	GRADE quality of evidence
(Chuang *et al.*, 2011) Taipei, Taiwan	annual average from 72 fixed monitoring sites	annual mean concentration 24.53 ppb (46.8 µg/m³)	panel study (1 year)	biochemical and physiological measurements on volunteers including systolic BP, diastolic BP, total cholesterol, triglycerides, HDL cholesterol, fasting glucose, hemoglobin, interleukin 6, & neutrophils	association with PM_{10}, $PM_{2.5}$, SO_2, O_3, CO, & NO_2	male and female adults aged 54 - 90 years 1023 subjects	percent increase in biomarkers per IQR 12.83 ppb (24.5 µg/m³) systolic BP - 14.40 diastolic BP - 12.43 total cholesterol - 39.31 fasting glucose - 17.03 hemoglobin - 1.08 interleukin 6 - 0.32 neutrophils - 9.54	percent increase in biomarkers per IQR 12.83 ppb (24.5 µg/m³) systolic BP 10-98 - 17.82 diastolic BP 10.63 - 14.23 total cholesterol 32.38 - 46.24 fasting glucose 10.37 - 23.69 hemoglobin 0.84 - 1.33 interleukin 6 0.06 - 0.59 neutrophils 7.88 - 11.21	statistically significant association with 7 of nine biochemical or physiological biomarkers in a single pollutant model using a lag period of 1 year, no statistically significant association in two pollutant models with PM_{10}, $PM_{2.5}$, O_3, SO_2, and CO	⊕⊕⊕○ (moderate quality, no adjustment necessary)
(Delfino *et al.*, 2006) Riverside & Whittier, CA	daily averages from personal samplers worn 10 consecutive days and averages from two fixed centrally located monitors	daily average in ppb (µg/m³) Riverside personal – 24.26 (46.3 µg/m³) ambient – 27.18 (51.9 µg/m³) Whittier personal – 30.89 (59.0 µg/m³) ambient – 28.07 (53.6 µg/m³)	panel study (5 months)	measurement fractional concentration of nitric oxide in exhaled air (FE_{NO})	association with PM_{10}, $PM_{2.5}$, EC, OC, CO, O_3, & NO_2	male & female aged 9-18 years 45 asthmatics	adjusted concentration change in FENO exhalation per personal IQR of 17.0 ppb (32.5 µg/m³) and central site IQR of 12.0 ppb (22.9 µg/m³) for in a single and two pollutant models single pollutant model personal exposures 01 avg lag - 1.63 ambient exposures lag day 1 - 0.72 01 avg lag - 1.36 two pollutant model (01 avg lag) personal exposures NO_2/OC ≈ 0.75 (depicted graphically) ambient exposures $NO_2/PM_{2.5}$ ≈ 0.85 (depicted graphically)	adjusted concentration change in FENO exhalation per personal IQR of 17.0 ppb (32.5 µg/m³) and central site IQR of 12.0 ppb (22.9 µg/m³) for in a single and two pollutant models single pollutant model personal exposures 01 avg lag 0.43 - 2.83 ambient exposures lag day 1 0.08 - 1.36 01 avg lag 0.39 - 2.33 two pollutant model (01 avg lag) personal exposures NO_2/OC ≈ 0.15 - 1.35 (depicted graphically) ambient exposures $NO_2/PM_{2.5}$ ≈ 0.30 - 1.65 (depicted graphically)	statistically significant association with nitric oxide levels in expired air using a single pollutant model and personal measurements and a moving average lag of 01 days or ambient measurements and a lag of 1 day or a moving average of 01 days, statistically significant association with a two pollutant model (01 day average lag) and OC with personal exposures and with $PM_{2.5}$ using ambient measurements, no statistically significant association in two pollutant models with $PM_{2.5}$ and EC for personal exposures and EC and OC for ambient exposures, statistically significant association (01 avg lag) in those taking anti-inflammatory medications or inhaled corticosteroids but not in those who did not use medications	⊕⊕○○ (low quality because of small sample size)

author / location	exposure monitoring	NO_2 concentration	study type (duration)	endpoint	co-pollutants	participants	ratio or risk	confidence interval	results	GRADE quality of evidence
(Rudez *et al.*, 2009) Rotterdam, The Netherlands	hourly averages form a single fixed monitoring site	median value during study period 37 µg/m³	time series (24 months)	effects on biomarkers of homeostasis and inflammation (platelet aggregation, thrombin, fibrinogen, & C-reactive protein)	association with PM_{10}, O_3, CO, NO, & NO_2	adult male and female 40 volunteers	percent change in response per IQR of 21 µg/m³ at various lag times in a single pollutant model platelet aggregation maximum response 48-72 hr - 5.6 late response 48-72 hr - 8.9 0-96 hr - 16.1 thrombin endogenous potential 24-48 hr - 3.5 peak response 24-48 hr - 8.0 lag time 24-48 hr - -3.1 48-72 hr - -2.5	percent change in response per IQR of 21 µg/m³ at various lag times in a single pollutant model platelet aggregation maximum response 48-72 hr 1.5 - 9.7 late response 48-72 hr 2.6 - 15.2 0-96 hr 5.0 - 27.2 thrombin endogenous potential 24-48 hr 0.2 - 6.8 peak response 24-48 hr 2.4 - 13.6 lag time 24-48 hr -5.1 - -1.0 48-72 hr -4.3 - -0.6	statistically significant association with platelet aggregation and thrombin generation parameters for 1-2 "indirect" lag times in a single pollutant model, no association with inflammatory biomarkers (fibrinogen or c-reactive protein) at any lag time	⊕○○○ (insufficient because of very serious risk of exposure bias)

author / location	exposure monitoring	NO_2 concentration	study type (duration)	endpoint	co-pollutants	participants	ratio or risk	confidence interval	results	GRADE quality of evidence
(Steinvil *et al.*, 2008) Tel-Aviv, Israel	daily mean concentration from three fixed monitoring locations	daily mean 19.5 ppb (37.2 µg/m³)	panel study (48 months)	short-term effect on inflammatory biomarkers (C-reactive protein, fibrinogen, white blood cell count)	association with PM_{10}, O_3, SO_2, CO, & NO_2	male & female 3659 volunteers	serum fibrinogen concentration (mg/dL) change per IQR of 12.7 ppb (24.3 µg/m³) in multi-pollutant models two pollutant (men lag day 4) NO_2/PM_{10} - -8.3 NO_2/SO_2 - -10.9 NO_2/O_3 - -15.6 NO_2/CO - -10.9 three pollutant model (men lag day 4) $NO_2/PM_{10}/SO_2$ - -9.3 $NO_2/SO_2/O_3$ - -16.7 NO_2/SO_2/CO - -11.9 four pollutant model (men lag day 4) $NO_2/PM_{10}/SO_2/O_3$ - -14.2 $NO_2/PM_{10}/SO_2$/CO - -9.7 two pollutant model (women lag day 0) NO_2/O_3 - -7.9	serum fibrinogen concentration (mg/dL) change per IQR of 12.7 ppb (24.3 µg/m³) in multi-pollutant models two pollutant (men lag day 4) NO_2/PM_{10} -12.4 - -4.2 NO_2/SO_2 -16.4 - -5.4 NO_2/O_3 -21.7 - -9.6 NO_2/CO -18.0 - -3.8 three pollutant model (men lag day 4) $NO_2/PM_{10}/SO_2$ -15.1 - -3.5 $NO_2/SO_2/O_3$ -23.8 - -9.6 NO_2/SO_2/CO -19.5 - -4.2 four pollutant model (men lag day 4) $NO_2/PM_{10}/SO_2/O_3$ -21.7 - -6.7 $NO_2/PM_{10}/SO_2$/CO -17.7 - -1.8 two pollutant model (women lag day 0) NO_2/O_3 -15.3 - -0.5	statistically significant decrease in fibrinogen in males using a single pollutant (all lag times) or multipollutant model (4 day lag time); statistically significant increase in white blood cell count in males using a single pollutant model with a lag of 6 or 7 days; statistically significant decrease in fibrinogen levels for women in single pollutant model on lag day 0 or lag days 0-6; no statistically significant association in women at any lag time for WBC or CRP or with men for CRP; no link established between short-term exposure and an increase in inflammatory markers	⊕⊕⊕○ (moderate quality, no adjustment necessary)
(Thompson *et al.*, 2010) Toronto, Ontario	hourly measurements from a single fixed monitoring site	seasonal average spring – 24.98 ppb (47.7 µg/m³) summer – 20.83 ppb (39.8 µg/m³) autumn – 22.61 ppb (43.2 µg/m³) winter – 26.78 ppb (51.2 µg/m³)	panel study (48 months)	blood levels of inflammatory biomarkers (interleukin 6 & fibrinogen)	association with $PM_{2.5}$, SO_2, O_3, CO, & NO_2	male and female 45 adult volunteers	no significant change in mean percentages	no significant change in mean percentages	no statistically significant association with blood interleukin-6 or fibrinogen on any lag day	⊕○○○ (insufficient because of very serious risk of exposure bias)

Sensory Effects

author / location	exposure monitoring	NO_2 concentration	study type (duration)	endpoint	co-pollutants	participants	ratio or risk	confidence interval	results	GRADE quality of evidence
(Nikolic *et al.*, 2010) Nis, Serbia	mean daily concentration from two fixed monitoring sites at each of two schools	daily mean school 1 – 62 µg/m³ school 2 – 25 µg/m³	retrospective (120 months)	skin changes and atopic dermatitis	association with black smoke, SO_2 & NO_2	male & female schoolchildren (11-14 years of age) 215 exposed 139 unexposed	odds ratio for exposure to all three pollutants signs atopic dermatitis - 4.93 symptoms dryness - 1.75 itching - 1.70 rash - 3.18 prickling - 2.13	odds ratio for exposure to all three pollutants signs atopic dermatitis 2.40 - 10.37 symptoms dryness 1.04 - 2.97 itching - 1.03 - 2.79 rash 1.29 - 8.18 prickling 1.02 - 4.52	statistically significant association of soot, SO_2, & NO_2 with increased frequently of atopic dermatitis and symptom incidence for dryness, itching, rash, & prickling; roughness and erythema symptoms unaffected;	⊕○○○ (insufficient because imprecision with the impact of NO_2 merged with all other pollutants)
(Novaes *et al.*, 2010) Sao Paulo, Brazil	mean daily exposure from continuous personal monitoring using passive dosimeters	not stated	cross-sectional (longitudinal panel) study (7 days)	ocular disease symptom index (ODSI) questionnaire, tear film break-up (TBUT), vital staining, biomicroscopy, Schirmer test	association with NO_2 only	male & female 55 volunteers	exposure related increase in OSDI score across the 4 quartiles (< 20, 20-26, 26-35, & >35 µg/m³); statistically significant increase in the frequency of symptom reporting for ocular irritation 1st quartile (<20 µg/m³) - 5 2nd quartile (20 - 26 µg/m³) - 9 3rd quartile (26 - 35 µg/m³) - 10 4th quartile (>35 µg/m³) - 13	NA	statistically significant increase in exposure-response for the OSDI score from the questionnaire; statistically significant increase in the reporting frequency for ocular irritation but not heaviness/fatigue, itching, or dry eyes; statistically significant negative association with TBUT but not Schirmer I values statistically significant increase in meibomitis by biomicroscopy	⊕○○○ (insufficient because biased data reporting and small number of cases)

author / location	exposure monitoring	NO_2 concentration	study type (duration)	endpoint	co-pollutants	participants	ratio or risk	confidence interval	results	GRADE quality of evidence
(Zemek *et al.*, 2010) Edmonton, Alberta	seasonal averages from three fixed monitoring sites	seasonal average in ppb (µg/m³) all months – 21.9 (41.8 µg/m³) warm months – 16.5 (31.5 µg/m³) cold months – 27.2 (52.0 µg/m³)	case-crossover (120 months)	emergency department visits for otitis media	association with PM_{10}, $PM_{2.5}$, O_3, CO, SO_2, & NO_2	male and female children (1-3 yrs of age) 14,527 ED visits	odds ratio per IQR 12.8 ppb (24.4 µg/m³) for all patients in single pollutant model lag day 2 all months - 1.05 warm months - 1.10 cold months - 1.03 lag day 3 warm months - 1.08 odds ratio per IQR 12.8 ppb (24.4 µg/m³) for females lag day 2 all months - 1.06 warm months - 1.20 lag day 3 warm months - 1.14	odds ratio per IQR 12.8 ppb (24.4 µg/m³) for all patients in single pollutant model lag day 2 all months 1.01 - 1.08 warm months 1.02 - 1.19 cold months 1.00 - 1.07 lag day 3 warm months 1.00 -1.17 odds ratio per IQR 12.8 ppb (24.4 µg/m³) for females lag day 2 all months 1.01 - 1.11 warm months 1.06 - 1.34 lag day 3 warm months 1.02 - 1.29	statistically significant association in all patients and all seasons using a single pollutant model with a day lag, significant associations also observed for a 3 day lag in warm months, statistically significant association with females on lag day 2 for all months or warm months and with females on lag day 3 for warm months, no statistical y significant associations found for males in any season, negative associations observed in two-pollutant model with CO	⊕⊕◯◯ (low quality because of inconsistencies bias from single pollutant model)

APPENDIX II – DETAILED ANALYSIS OF SELECTED STUDIES

Acute and Chronic Mortality

1. **Samoli, E., Aga, E., Touloumi, G., Nislotis, K., Forsberg, B., Lefranc, A., Pekkanen, J., Wojtyniak, B., Schindler, C., Niciu, E., Brunstein, R., Fikfak, M. D., Schwartz, J., and Katsouyanni, K. 2006. Short-term effects of nitrogen dioxide on mortality: An analysis within the APHEA project. *European Respiratory Journal* 27:1129-1137.**

Rating
Insufficient (⊕○○○)

Description
This multi-city examined the short-term effects of BS, PM_{10}, SO_2, O_3, and NO_2 on all cause, circulatory, and respiratory mortality for 30 European cities. The paper described the results for the APHEA 2 (Air Pollution and Health: A European Approach program and relied on daily 1-hr maxima NO_2 values from an unstated number of fixed monitoring sites within in each city. A population-based time series model was employed that is not likely to be confounded by factors such as diet, smoking or SES since they do not co-vary with NO_2 levels over the short time periods being examined. A hierarchical Poisson model was employed with the first stage that focused on within-city associations. Distributed lag periods of 0 to 5 days were examined. The second stage relied on a fixed effects weighted regression analysis of the pooled city-specific estimates. A random effects model was also employed because appreciable heterogeneity was observed. The effect estimates focused on the mean for lag days 0 and 1. The maximum hourly NO_2 concentrations over a 24-hr period ranged 46. 2 µg/m³ in Wroclaw to 154.8 µg/m³ in Milan (see **Table 1**). The average daily mortality rate ranged from 6 in Erfut to 342 in the Netherlands. Confounding for weather related variables (temperature and relative humidity), influenza epidemics, holidays, and day of week effects were controlled for using smoothing splines. Two-pollutant models were examined that recorded the pooled fractional increase in mortality per 10 µg/m³ increase.

Results
A slight statistically significant association with total, respiratory and cardiovascular mortality in single and two-pollutant models with BS, PM_{10}, SO_2 and O_3 that ranged from about 0.25 – 0.45% (see **Table 2**). A statistically significant association was observed with respiratory mortality in single and two-pollutant model with BS, & O_3, but not with PM_{10} & SO_2. The use of natural gas in the home acted as an effect modifier on cardiovascular mortality with the associations strengthening from 0.32 (CI 0.20 - 0.43) at the 25th percentile of use to 0.40 (CI 0.32 - 0.48) at the 75th percentile. The prevalence of smoking affected total and cardiovascular mortality with stronger associations observed for NO_2 when the prevalence was lower had no impact; PM 10 levels were also an effect modifier on respiratory mortality as was the proportion of elderly subjects. Southern and western cites showed the strongest associations, but none were observed for eastern cities.

Table 1. City descriptive data on the study period, population, exposure nitrogen dioxide (NO_2) and outcome (daily number of deaths).

City	Study period (month/year)	Population x 1000	Mean number deaths/day			NO_2 1 h (mg/m^3)
			Total	CVD	Respiratory	
Athens	01/1992–12/1996	3073	73	36	5	129.9 (84.3–187.0)
Barcelona	01/1991–12/1996	1644	40	16	4	91.1 (63.2–124.7)
Basel	01/1990–12/1995	360	9	4	1	65.9 (44.2–92.1)
Bilbao	04/1992–03/1996	667	15	5	1	78.7 (58.1–101.6)
Birmingham	01/1992–12/1996	2300	61	28	9	74.5 (49.3–99.5)
Budapest	01/1992–12/1995	1931	80	40	3	131.9 (88.0–185.6)
Bucharest	01/1992–12/1996	2100	71	38	4	50.5 (31.4–85.5)
Cracow	01/1990–12/1996	746	18	10	0	79.4 (37.7–132.0)
Erfurt	01/1991–12/1995	216	6	---	---	76.0 (36.0–119.0)
Geneva	01/1990–12/1995	317	6	2	0	79.2 (54.1–111.4)
Helsinki	01/1993–12/1996	828	18	9	2	62.4 (40.4–87.0)
Ljubljana	01/1992–12/1996	322	7	3	0	80.0 (47.5–115.0)
Lodz	01/1990–12/1996	828	30	17	1	66.4 (40.1–96.4)
London	01/1992–12/1996	6905	169	71	29	94.8 (67.1–128.5)
Lyon	01/1993–12/1997	416	9	3	1	107.2 (75.1–143.2)
Madrid	01/1992–12/1995	3012	61	22	6	122.9 (83.7–174.7)
Marseille	01/1990–12/1995	855	22	8	2	119.6 (80.9–163.1)
Milan	01/1990–12/1996	1343	29	11	2	154.8 (104.7–217.8)
The Netherlands	01/1990–09/1995	15400	342	140	29	53.1 (32.8–74.9)
Paris	01/1991–12/1996	6700	124	38	9	84.0 (55.1–118.5)
Poznan	01/1990–12/1996	582	17	9	1	81.1 (45.1–119.7)
Prague	02/1992–12/1996	1213	38	22	1	60.7 (37.7–86.5)
Rome	01/1992–12/1996	2775	56	23	3	147.6 (111.6–189.2)

City	Study period (month/year)	Population x 1000	Mean number deaths/day			NO_2 1 h (mg/m^3)
			Total	CVD	Respiratory	
Stockholm	01/1990–12/1996	1126	30	15	3	47.6 (31.2–64.2)
Tel Aviv	01/1991–12/1996	1141	27	12	2	139.7 (57.5–254.9)
Teplice	01/1990–12/1997	625	18	10	1	59.7 (40.9–81.7)
Torino	01/1990–12/1996	926	21	9	1	132.4 (78.2–199.6)
Valencia	01/1994–12/1996	753	16	6	2	116.5 (60.8–170.3)
Wroclaw	01/1990–12/1996	643	15	9	1	46.2 (29.5–63.7)
Zurich	01/1990–12/1995	540	13	6	1	70.2 (46.9–97.4)

Table 2. Pooled estimates for the increase in mortality associated with an increase of 10 μg/m^3 in nitrogen dioxide (NO_2; average of lags 0 and 1 of the 1-h maxima of NO_2), adjusting alternatively for the other pollutants (average of lags 0 and 1).

Other pollutant	Total mortality		CVD mortality		Respiratory mortality	
	Fixed effects	Random effects	Fixed effects	Random effects	Fixed effects	Random effects
None	0.30 (0.25–0.35)	0.30 (0.22–0.38)	0.41 (0.34–0.49)	0.40 (0.29–0.52)	0.34 (0.17–0.51)	0.38 (0.17–0.58)
BS	0.33 (0.23–0.42)	0.33 (0.23–0.42)	0.44 (0.31–0.58)	0.44 (0.31–0.58)	0.28 (-0.02–0.58)	0.26 (-0.12–0.65)
PM_{10}	0.27 (0.20–0.34)	0.27 (0.16–0.38)	0.35 (0.24–0.45)	0.35 (0.21–0.50)	0.37 (0.13–0.61)	0.37 (0.08–0.67)
SO_2	0.26 (0.20–0.33)	0.26 (0.18–0.34)	0.37 (0.27–0.46)	0.33 (0.20–0.47)	0.16 (-0.06–0.39)	0.19 (-0.07–0.45)
O_3 8-h	0.34 (0.27–0.40)	0.33 (0.22–0.43)	0.45 (0.36–0.54)	0.42 (0.27–0.58)	0.34 (0.14–0.53)	0.38 (0.13–0.63)

Data are presented as % increase (95% confidence interval). CVD: cardiovascular disease; BS: black smoke; PM_{10}: particle matter with a 50% cut-off aerodynamic diameter of 10 mm; SO_2: sulphur dioxide; O_3 8-h: maximum daily 8-h O_3 concentration

Critique

Several notable problems exist with the APEA2 analysis. The most severe is the failure to consider the confounding from CO exposures despite the fact this pollutant was routinely evaluated as part of the 30-city program (Samoli *et al.*, 2007). More importantly, APHEA2 documented that CO was associated with short-term increases in total and cardiovascular mortality that remained significant in two-pollutant models with BS or NO_2. The results also stand in contrast to those from the multi-city NMAPS in the US, where a consistent association with mortality was not observed for NO_2 (Samet *et al.*, 2000). The paradoxical effect observed for smoking status (i.e. stronger NO_2 associations with lower smoking prevalence) was is attributed to a harvesting or a mortality

displacement effect. This explanation does not, however, fully explain the observation since smoking is not a likely confounder in a time-series study since its impacts are more long-term. In addition, the extremely high levels of NO in cigarette smoke (300 – 500 ppm; 368- 613 mg/m^3) would suggest that the opposite relationship should have been observed (Cueto and Pryor, 1994). The findings suggest that NO_2 is acting as surrogate for another agent.

There was poor documentation of the location and number of fixed monitoring sites within individual cities, and no indication of spatial fluctuations that were observed. This is an important consideration since the location and density of monitoring sites can cause a spatial misalignment and bias the results in time series studies. This is an especially important consideration for a pollutant such as NO_2 which can show a high degree of spatial heterogeneity due to the influence of roadway emissions and traffic density (Sarnat *et al.*, 2010). Another factor of concern with this study is the fact that there was no measurement of important co-pollutant such as $PM_{2.5}$ and UFP that may have modified the magnitude of the mortality associations observed with NO_2. Non-uniform distribution of effect modifiers across each city may have also biasing the findings.

2. **Wong, C. M., Vichit-Vadakan, N., Kan, H. D., and Qian, Z. M. 2008b. Public health and air pollution in Asia (PAPA): A multicity study of short-term effects of air pollution on mortality. *Environmental Health Perspectives* 116:1195-1202.**

Rating
Low quality (⊕⊕◯◯)

Description
This time series study examined the association of daily average PM_{10}, O_3, SO_2, NO_2 concentrations with mortality from natural, circulatory, & respiratory causes in four cities as part of the Public Health and AI Pollution in Asia (PAPA) study. Measurements were taken from 6-10 fixed monitoring locations in Bangkok, Hong Kong, Shanghai, and Wuhan. Daily average NO_2 levels ranged from 44.7 µg/m³ in Bangkok to 66.6 µg/m³ in Shanghai. The mean number of deaths per day was 94.8 for Bangkok, 84.2 for Hong Kong, 119.0 for Shanghai, and 61.0 for Wuhan. Confounding from temperature, humidity, day of week, holidays, influenza, and extreme weather was considered. A single-pollutant generalized linear model was applied using natural smoothing splines and lag periods of 0 days and an average lag period of 0-1 and 0-4 days. Pooled and single city test results were presented but pooling was confined to a random effects model due to the high heterogeneity observed. Pooling was performed for all four cities and for the 3 Chinese cities.

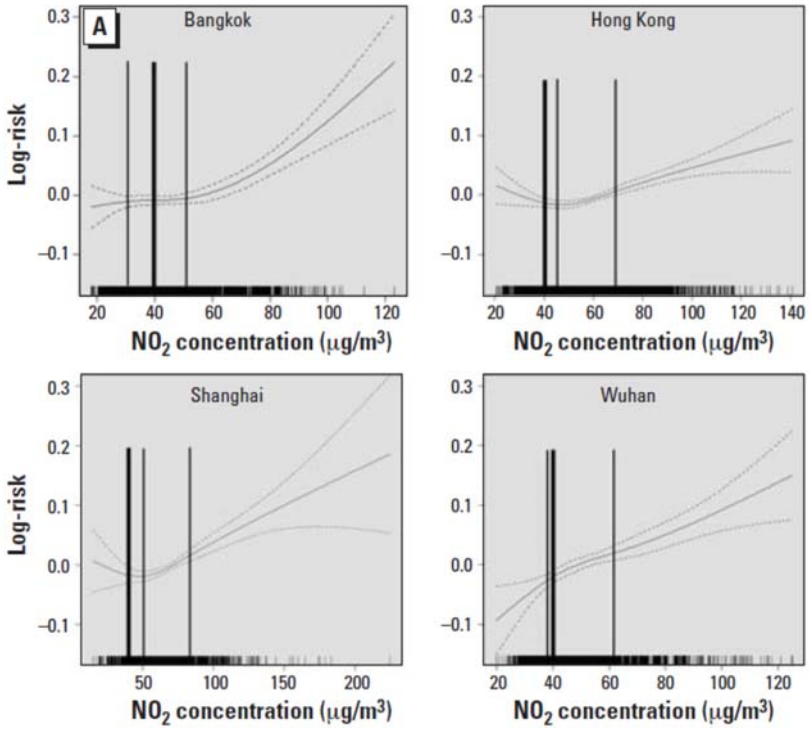
Results
The average lag period of 01 days yield the highest excess risk estimates for 3 of 4 cities. The risks tended to be greater with older age groups. The percentage of excess risk from NO_2 ranged from 0.90 to 1.97 in the four cities and was statistically significant. Appreciable heterogeneity was observed for NO_2 on all cause mortality. A comparison of the excess risk for the pooled 4-city and 3-city results did not reveal any appreciable differences (see **Table 3**). Stratification by age revealed higher total death rates in two of the four cities for those greater than 65 years of age, with even higher rates observed in those greater than 75 years. Concentration response functions for all cause mortality were best described by the linear models shown in **Figure 1**. Visible inspection of the response curves suggests that is no appreciable increase in all cause at concentrations below the WHO annual limit of 40 µg/m³ for 3 of the 4 cities examined. The lag patterns showing maximum excess risk were noted to be appreciably longer (04 day average) for Bangkok than the other three cities. Two-pollutant modelling with PM_{10}, O_3 and SO_2 revealed substantial impact of PM_{10} on all cause and cardiovascular mortality in Bangkok, but not the remaining three cities. The excess risk per 10 µg/m³ increase in NO_2 became statistically insignificant for a lag of 01 days.

Table 3. Excess risk (ER%) of mortality (95% CI) for a 10 μg/m^3 increase in the average concentration of lag 0–1 days for all ages using combined random effects for either three or 4 cites.

Condition	Pollutant	Random effects (4 cities)		Random effects (3 Chinese cities)	
		ER%	95% CI	ER%	95% CI
All natural causes	NO_2	1.23	0.84 to 1.62*	1.19	0.71 to 1.66*
	SO_2	1.00	0.75 to 1.24	0.98	0.74 to 1.23
	PM_{10}	0.55	0.26 to 0.85#	0.37	0.21 to 0.54
	O_3	0.38	0.23 to 0.53	0.31	0.13 to 0.48
Cardiovascular	NO_2	1.36	0.89 to 1.82	1.32	0.79 to 1.86
	SO_2	1.09	0.71 to 1.47	1.09	0.72 to 1.47
	PM_{10}	0.58	0.22 to 0.93**	0.44	0.19 to 0.68
	O_3	0.37	0.01 to 0.73	0.29	–0.09 to 0.68
Respiratory	NO_2	1.48	0.68 to 2.28	1.63	0.62 to 2.64*
	SO_2	1.47	0.85 to 2.08	1.46	0.84 to 2.08
	PM_{10}	0.62	0.22 to 1.02	0.60	0.16 to 1.04
	O_3	0.34	–0.07 to 0.75	0.23	–0.22 to 0.68

p-Values (homogeneity test): *0.01 < p ≤ 0.05; **0.001 < p ≤ 0.01; and #p ≤ 0.001

Figure 1. Concentration-response curves for all natural-cause mortality at all ages in all four cities for the average concentration of lag 0–1 days for NO_2. The thin vertical lines represent the IQR of pollutant concentrations. The thick lines represent the WHO guidelines of 40 µg/m^3 for 1-year averaging time.



Critique

The two-pollutant modelling did not include pollutants that traditionally co-vary with NO_2 such as CO and $PM_{2.5}$, so the interpretation of findings is severely hampered. In addition, highly variable relationships were observed in degree of correlation between NO_2 and some of the other pollutant measurements in the four cites. The Spearman's correlation coefficient for NOs and SO_2 ranged from 0.27 to 0.76 and demonstrates the appreciable heterogeneity. This extended to the effect estimates as well with relative risk associated with all cause mortality from NO_2 being appreciable greater in Bangkok and Wuhan; yet there was a limited attempt at identifying the effect modifiers that could be at play. Perhaps the most serious problem with this study stems from monitoring station locations in each city. In Hong Kong and Shanghai the monitors were located close to major roadways, whereas in Wuhan and Bangkok the monitors were at background locations. As such, the results are not directly comparable and an exposure misclassification bias was knowingly applied due to the spatial misalignment. There was also no consideration of known effect modifiers such as gas appliance usage, air conditioner use, or distance to roadways. Subsequent studies also implicated very high ambient temperature in Wuhan as partly responsible for increased risk estimates in this city (HEI, 2010).

3. **Gan, W. Q., Koehoorn, M., Davies, H. W., Demers, P. A., Tamburic, L., and Brauer, M. 2011. Long-term exposure to traffic-related air pollution and the risk of coronary heart disease hospitalization and mortality. *Environmental Health Perspectives* 119:501-507.**

Rating
Moderate quality (⊕⊕⊕○)

Description
This cohort study was performed in Vancouver, British Columbia and employed land use regression techniques to define the spatial variability of black carbon (BC), $PM_{2.5}$, NO, and NO concentrations within the city. The LUR model relied on length of highways and roads, population density, and commercial land use as predictor variables and the measurements from 116 passive samplers at 25 locations and an unstated number of fixed monitoring sites to estimate monthly residential exposures. A Cox proportional hazards model was used to determined coronary heart disease hospitalization and mortality in 452,735 males and females 45-85 years of age. The daily mean concentration of NO_2 was 29.2 µg/m³. Confounding from age, sex, preexisting co-morbidity (diabetes, COPD, & hypertensive heart disease), and SES was considered.

Results
A statistically significant association was observed between NO_2 levels and hospitalization using an unadjusted single-pollutant model, but not with an adjusted model or with multi-pollutant models (see **Table 14**). Statistically significant associations were also found with mortality in an unadjusted and adjusted single-pollutant model, but not with an adjusted multi-pollutant model. A significant inverse association was found to exist with hospitalizations when the results were stratified by income in adjusted single-pollutant and multi-pollutant models. Income stratification also revealed a significant inverse association with mortality using an unadjusted, but not an adjusted single or multi-pollutant model. The relative risk per IQR NO_2 increase of 8.4 µg/m³ was 1.02 (95% CI, 1.00 - 1.04) for cardiovascular hospitalization and 1.19 (95% CI, 1.15 - 1.23) for mortality using an unadjusted single-pollutant model. A response trend was not observed when the models were fully adjusted for potential confounders (see **Figure 7**).

Table 14. RRs (95% CIs) of CHD hospitalization and mortality for an IQR elevation in average concentrations of traffic-related air pollutants.

Model	BC (0.94 × 10–5/m)[a]	$PM_{2.5}$ (1.58 µg/m³)[a]	NO_2 (8.4 µg/m³)[a]	NO (13.2 µg/m³)[a]
Hospitalization				
Model 1: unadjusted single pollutant	1.04 (1.03–1.06)	1.03 (1.01–1.05)	1.02 (1.00–1.04)	0.99 (0.97–1.02)
Model 2: + sex, age, comorbidity, SES	1.01 (1.00–1.03)	1.00 (0.98–1.02)	0.97 (0.95–0.99)	0.96 (0.94–0.98)
Model 3: + two other pollutants[b]	1.03 (1.01–1.05)	1.02 (1.00–1.05)	0.96 (0.94–0.98)	0.95 (0.92–0.97)
Mortality				
Model 1: unadjusted single pollutant	1.14 (1.11–1.17)	1.13 (1.09–1.16)	1.19 (1.15–1.23)	1.13 (1.09–1.17)
Model 2: + sex, age, comorbidity, SES	1.06 (1.03–1.09)	1.01 (0.98–1.05)	1.04 (1.01–1.08)	1.06 (1.02–1.10)
Model 3: + two other pollutants[b]	1.06 (1.03–1.09)	1.00 (0.96–1.03)	1.03 (0.99–1.07)	1.03 (0.99–1.08)

[a] IQR.

[b] Additionally adjusted for $PM_{2.5}$ and NO_2 for black carbon, black carbon and NO_2 for $PM_{2.5}$, black carbon and $PM_{2.5}$ for NO_2 and NO.

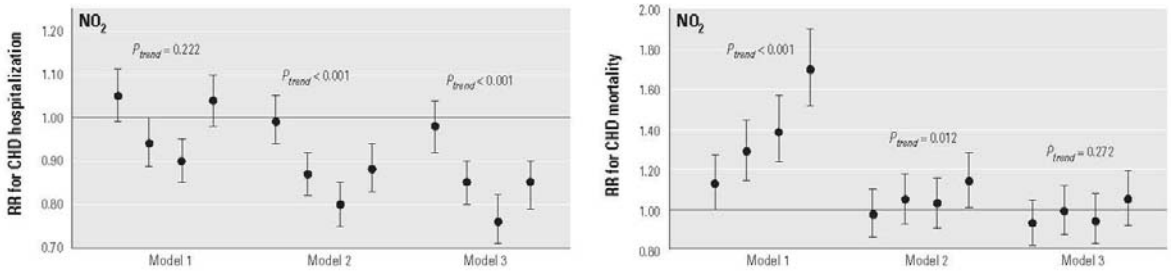


Figure 7. RRs and 95% CIs of coronary heart disease (CHD) hospitalization (*A*) and mortality (*B*) for quintiles of NO_2. Quintile 1 (lowest) was the reference category. From left to right, each error bar represents RR and 95% CI of CHD hospitalization (*A*) or mortality (*B*) for quintiles 2–5, respectively, compared with quintile 1. p_{trend} indicates linear trend across quintile groups. Model 1, bivariable analysis; model 2, adjusted for age, sex, preexisting co-morbidity, and neighborhood SES; model 3, additionally adjusted for co-pollutants (black carbon and $PM_{2.5}$ for NO_2).

Critique

Perhaps the most important limitation of this study is the failure to consider cigarette smoking, second hand smoke, and ethanol consumption as confounding variables. It was also noted that the only measure of socioeconomic status was total income. Some bias may have also been introduced by the death registries rather than original medical records to identify cases of coronary heart disease. These deficiencies are partly offset by the availability of concentration response functions, which helped to improve the overall reliability of this study.

Acute Hospitalization

1. **Wellenius, G. A., Bateson, T. F., Mittleman, M. A., and Schwartz, J. 2005. Particulate air pollution and the rate of hospitalization for congestive heart failure among Medicare beneficiaries in Pittsburgh, Pennsylvania. *American Journal of Epidemiology* 161:1030-1036.**

Rating
Insufficient (⊕◯◯◯)

Description
This case-crossover study was conducted over a 13-year period and focused on hospital admissions for congestive heart failure in relation to PM_{10}, SO_2, O_3, CO, and NO_2 in Pittsburgh, Pennsylvania. Mean daily concentrations of NO_2 were determined at two fixed monitoring locations and yielded a value of 26.48 ppb (50.6 µg/m³). The study population was limited to male and female adults greater than or equal to 65 years of age. A total of 55,019 admissions were identified using ICD-9 coding. Temperature, barometric pressure, and day of week confounding were addressed using conditional logistic regression with linear smoothing splines.
Lag periods of 0, 1, and 2 days were examined as well as a moving average lag of 01 days. Effect modification by age, sex, and co-diagnosis of atrial fibrillation was also investigated, but the results were not presented for NO_2.

Results
NO_2 levels were highly correlated with PM_{10} (r=0.64) and CO (r=0.70). A statistically significant increase in the percentage of hospital admissions for congestive heart failure was found in single-pollutant models and two-pollutant models for PM_{10}, O_3, and SO_2 on lag day 0 (see **Table 21**). There was no statistically significant association in a two-pollutant model with CO. The percentage increase in admissions per interquartile increase of 11 ppb (21.0 µg/m³) NO_2 in a single-pollutant models on lag day 0 was 4.22% (2.61 - 5.85%, 95% CI).

Table 21. Percent increase (and 95% confidence interval) in the rate of hospital admission for congestive heart failure associated with an interquartile-range increase in pollutant levels in single-pollutant and two-pollutant models, Allegheny County, Pennsylvania, 1987–1999.

Pollutant (IQR)	Single Pollutant		Adjusted for PM_{10}		Adjusted for CO		Adjusted for NO_2		Adjusted for O_3		Adjusted for SO_2	
	% increase	95% CI	% increase	95% CI	% increase	95% CI	% increase	95% CI	% increase	95% CI	% increase	95% CI
PM_{10} (24 µg/m³)	3.07	1.59-4.57	NA	---	-1.10	-3.02-0.86	0.52	-1.46-2.53	2.80	1.29-4.33	2.18	0.37-4.02
CO (0.55 ppm)	4.55	3.33-5.79	5.18	3.49-6.89	NA	---	4.84	3.06-6.66	4.35	3.08-5.64	4.51	3.15-5.90
NO_2 (11 ppb)	4.22	2.61-5.85	4.05	1.83-6.31	-0.37	-2.59-1.89	NA	---	3.73	2.10-5.39	3.79	1.93-5.67
O_3 (17 ppb)	-1.60	-3.77-0.61	-1.96	-4.14-0.27	0.13	-2.12-2.44	-1.19	-3.38-1.06	NA	---	-1.41	-3.58-0.81
SO_2 (11 ppb)	2.36	1.05-3.69	1.35	-0.27-2.99	0.10	-1.35-1.57	0.68	-0.82-2.21	2.02	0.68-3.37	NA	---

Models controlling for barometric pressure and apparent temperature.
IQR, interquartile range; PM_{10}, particulate matter with an aerodynamic diameter of <10 lm; CI, confidence interval; NA, not applicable.

Critique

This study examined a large number of patients in a single northeastern city in the US. There were no $PM_{2.5}$ measurements and no information on chronic risk factors, personal exposure levels or the degree of exposure misclassification that resulted from the use of two monitoring sites. The probability of exposure misclassification is very high given the known discrepancy between ambient and personal measures of NO_2 exposure (Williams *et al.*, 2012b). This fact is reinforced by a study showing that the indoor contribution to NO_2 personal exposures can as high as 78% of the total exposure depending on the type ventilation, cooking stove, and heating system (Piechocki-Minguy *et al.*, 2006). These same studies also showed that personal exposures during summer weekends were appreciably lower (17 µg/m³) than during winter weekends (38 µg/m³). Despite these sources of error, however, this study is notable because it documented the expected amelioration of admission rates for congestive heart failure when CO was included in two-pollutant models with NO_2. The results point to the importance of considering CO exposures when investigating the association of NO_2 exposures with any type of cardiovascular disease.

2. **Chang, C. C., Tsai, S. S., Ho, S. C., and Yang, C. Y. 2005. Air pollution and hospital admissions for cardiovascular disease in Taipei, Taiwan. *Environmental Research* 98:114-119.**

Rating
Low quality (⊕⊕◯◯)

Description
The authors of this study looked at the association of hospital admissions for cardiovascular disease with the levels of PM_{10}, SO_2, O_3, CO, and NO_2 in Taipei, Taiwan. Single and two-pollutant modelling was performed using conditional logistic regression and an unstated smoothing algorithm. The daily mean concentration of NO_2 was determined to be 31.54 ppb (60.2 µg/m³) from six fixed monitoring site. A case crossover design was employed in the analysis of 74,509 total admissions with a mean daily hospital admission rate 40.8 for cardiovascular disease. Temperature, humidity, and day of week effects were controlled for in a bidirectional time stratified manner. A cumulative lag of 02 days was applied and effect modification by daily temperatures greater than or less than 20 °C was examined.

Results
A statistically significant association was found to exist for NO_2 exposure and hospital admissions for cardiovascular disease in a single-pollutant model when the temperatures were greater than or equal to 20 °C, but not when the temperatures were less than 20°C. Similar results were obtained in two-pollutant models with either PM_{10}, SO_2, CO or O_3 when the temperatures were greater than or equal to 20 °C (see **Table 17**). Two-pollutant modelling at cold temperatures also yielded statistically significant increase in the odds ratio for all co-pollutants except PM_{10}. The odds ratio for cardiovascular disease admissions per interquartile NO_2 increase of 9.95 ppb (19.0 µg/m³) in the two-pollutant models at temperatures ≥20 °C ranged from 1.145 for CO to 1.279 with SO_2. The odds ratio results for colder temperatures were only modestly lower than the values at temperatures ≥20 °C.

Table 17. ORs (95% CI) of cardiovascular disease admissions for each interquartile range change in two-pollutant model system.

Condition	Adjusted for PM_{10}		Adjusted for SO_2		Adjusted for NO_2		Adjusted for CO		Adjusted for O_3	
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
PM_{10}										
≥20 °C	—	—	1.131*	1.103–1.161	0.977	0.950–1.006	1.025	0.999–1.052	1.064*	1.039–1.090
<20 °C	—	—	1.235*	1.184–1.288	1.148*	1.103–1.194	1.165*	1.121–1.212	1.142*	1.105–1.180
SO_2										
≥20 °C	0.897*	0.868–0.926	—	—	0.826*	0.798–0.854	0.903*	0.876–0.931	0.953*	0.926–0.981
<20 °C	0.824*	0.771–0.880	—	—	0.922*	0.865–0.984	0.960	0.901–1.022	1.014	0.963–1.067
NO_2										
≥20 °C	1.194*	1.159–1.230	1.279*	1.244–1.315	—	—	1.145*	1.106–1.186	1.165*	1.136–1.194
<20 °C	0.986	0.928-1.048	1.166*	1.095–1.241	—	—	1.126*	1.046–1.213	1.125*	1.066–1.187
CO										
≥20 °C	1.171*	1.132–1.211	1.232*	1.194–1.272	1.048*	1.003–1.095	—	—	1.196*	1.161–1.232
<20 °C	0.946	0.892–1.003	1.098*	1.034–1.165	0.983	0.914–1.058	—	—	1.092*	1.031–1.157
O_3										
≥20 °C	1.066*	1.038–1.094	1.097*	1.070–1.125	1.033*	1.006–1.060	1.099*	1.072–1.127	—	—
<20 °C	0.980	0.924–1.039	0.986	0.929–1.046	1.038	0.974–1.106	1.042	0.971–1.117	—	—

*P<0.05.
Calculated for an interquartile range increase of PM_{10} (24.51 mg/m^3), SO_2 (2.75 ppb), NO_2 (9.95 ppb), CO (0.49 ppm), and O_3 (9.95 ppb). Adjusted for temperature and humidity.

Critique

This investigation is seriously hampered by the inverse relationship that is observed in two-pollutant models with SO_2. The results suggest that a systemic bias or misclassification error may be impacting the results and affecting the veracity of the observations. The significant associations with NO_2 levels in two-pollutant models were also observed on warm and cold days, which is inconsistent with the known seasonal differences that have been observed in many other studies. The failure of CO to modify the associations with NO_2 levels is also at odds with studies by Chan *et al.*, which also took place in Taipei, Taiwan (Chan *et al.*, 2006). In these studies, NO_2 was not related to cardiovascular hospital admissions in single-pollutant models and that CO was no longer related after adjustment in two or three pollutant models following adjustment with $PM_{2.5}$ or PM_{10} and O_3. The reason for these discrepancies may lie with the SAS software used to conduct the conditional logistic regression. A recent investigation found that when SAS is used in a case crossover investigation, there can be a 22%-39% bias away from the null if the fitting parameters aren't carefully selected (Wang *et al.*, 2011). Given these facts, the results from this study should not be given tremendous weight.

3. **Chen, R. J., Chu, C., Tan, J. G., Cao, J. S., Song, W. M., Xu, X. H., Jiang, C., Ma, W. J., Yang, C. X., Chen, B. H., Gui, Y. H., and Kan, H. D. (2010). Ambient air pollution and hospital admission in Shanghai, China. *Journal of Hazardous Materials* 181(1-3), 234-240.**

Rating
Moderate quality (⊕⊕⊕○)

Description
The methods used in this study were similar to preceding mortality study by Chen *et al.* (2008). A time-series investigation was performed for a 3-year period (2005-2007) using hospital admission records maintained by the Shanghai Health Insurance Systems which covers the health plans for 95% of population. The analysis examined total, cardiovascular, and respiratory hospital admissions relative to airborne concentrations of PM_{10}, SO_2, and NO_2 in Shanghai, China. A total of 1,702,180 hospital admissions were examined showing an average daily rate of 340 for cardiovascular disease and 123 for respiratory disease. Exposures were assessed from six fixed monitoring stations situated at background sites located away from traffic, buildings, factories, and other combustion sources. The mean daily exposure concentration over the study period was 57 $\mu g/m^3$ for NO_2. Linear Poisson models were used to analyze the data with day of week, humidity, and temperature used to control for seasonal effects. Single (L0 to L6) and multi-day (L01 to L06) lag periods were examined as were possible seasonal effects (warm and cold).

Results
NO_2 levels were highly correlated with PM_{10} (r=0.70) and SO_2 (r=0.76) concentrations. Statistically significant associations were observed in a single-pollutant model for cardiovascular admissions at lag days 4, 5, and 6. Total hospital admissions were associated with NO_2 exposures on lag day 4 and 5. Respiratory admissions were not associated with NO_2 exposures for any lag interval. The percentage increase remained statistically significant for the cool but not the warm season following stratification. The associations with total and cardiovascular admissions became insignificant when a two-pollutant model with SO_2 was examined for lag day 5 (see **Table 22**). The associations remained significant, however, when a two-pollutant model with PM_{10} was examined, with a 10 $\mu g/m^3$ increase in NO_2 resulting in increases of 1.27 (CI 0.07-1.50) and 0.71 (CI 0.00-1.41) percent in total and cardiovascular mortality, respectively. The authors noted a J-shaped concentration response curve that was much more pronounced with the cardiovascular admissions (see **Figure 8**) than the total hospital admissions.

Table 22. Percent increase of hospital admission from all and cardiovascular causes associated with 10 μg/m^3 increase of pollutant concentrations with single and multiple pollutant models.

Pollutant	Model	Total Admission	Cardiovascular
PM_{10}	Without adjustment	0.18 (−0.15, 0.52	0.23 (−0.03, 0.48)
	Adjusted for SO_2	−0.11 (−0.62, 0.39)	−0.04 (−0.43, 0.36)
	Adjusted for NO_2	−0.14 (−0.63, 0.34)	0.04 (−0.33, 0.42)
SO_2	Without adjustment	0.63 (0.03, 1.23)*	0.65 (0.19, 1.12)*
	Adjusted for PM_{10}	0.79 (0.07, 1.50)*	0.70 (0.05, 1.35)*
	Adjusted for NO_2	0.24 (−0.65, 1.13)	0.50 (−0.19, 1.20)
NO_2	Without adjustment	0.99 (0.10, 1.88)*	0.80 (0.10, 1.49)*
	Adjusted for PM_{10}	1.27 (0.17, 2.37)*	0.71 (0.00, 1.41)*
	Adjusted for SO_2	0.74 (−0.59, 2.07)	0.28 (−0.76, 1.32)

[a] Single-day lag 5 was used.
* $p < 0.05$.

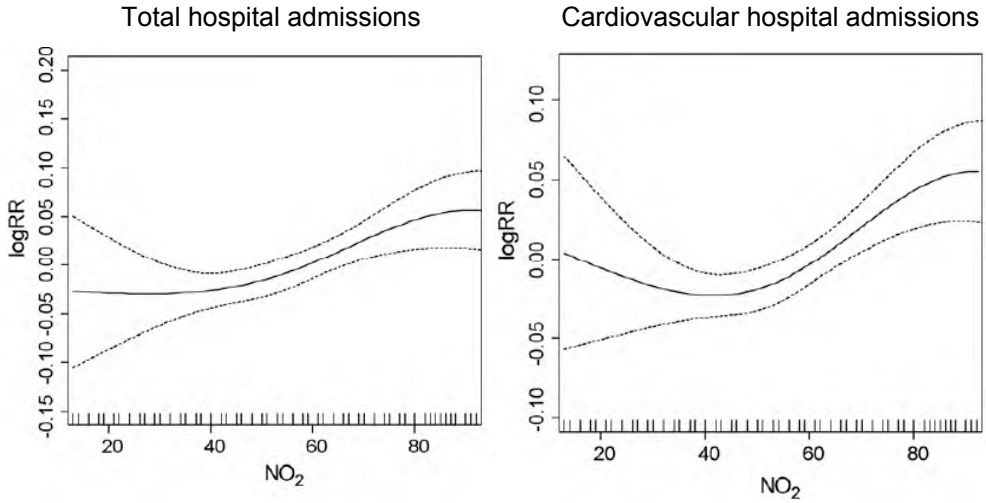


Figure 8. Smoothing plots of NO_2 against hospital admission (df=3). X-axis is the pollutant concentration (μg/m^3) (single day lag, L5). The solid lines indicate the estimated mean percentage of change in daily hospital admission, and the dotted lines represent twice the standard error.

Critique

This study suffers from many of the same problems that plagued the earlier mortality study by the same group of authors. Notably, this included the severe exposure misclassification that results from the use background measurements as a surrogate for personal NO_2 exposures. This approach can result in a nearly 2-fold underestimation of the actual exposure due to the large

spatial differences in exposure concentration between residential locations where traffic dominates and background locations (Boogaard *et al.*, 2011). In addition, the authors failed to consider the impact PAHS, UFPs, or $PM_{2.5}$ exposures, which are often highly correlated with NO_2 measurements. There are also striking inconsistencies in the data with the earlier mortality showing no impact of SO_2 in a two-pollutant model and the later hospital admission study showing just the opposite. Although, this discrepancy could simply be due to mechanistic differences for acute and chronic impacts, a more likely explanation is that NO_2 is simply acting as a proxy for another unknown substance that is serving as the true causative agent (Brook *et al.*, 2007); a fact that the authors acknowledged as a possibility when interpreting the implications of their findings.

Emergency Room Visits

1. **Guo, Y. M., Tong, S. L., Li, S. S., Barnett, A. G., Yu, W. W., Zhang, Y. S., and Pan, X. C. 2010. Gaseous air pollution and emergency hospital visits for hypertension in Beijing, China: a time-stratified case-crossover study. *Environmental Health* 9:1-7.**

Rating
Insufficient (⊕○○○)

Description
This study used a multi-pollutant modelling approach to investigate the relationship between PM_{10}, SO_2, and NO_2 concentration and emergency department visits for hypertension in Beijing, China. The mean daily concentration at eight fixed monitoring locations was 66.6 µg/m³. Cases and controls were matched by day of week. A total of 1,491 cases were examined using a time stratified case-crossover design that controlled for temperature and relative humidity using polynomial smoothing. A polynomial distributed lag model was in place for 0, 1, 2, 3, 4, and 5 days.

Results
A moderate statistically significant association was observed between NO_2 and emergency department visits for hypertension in single-pollutant models on lag days 0, 2, and 3 (see **Figure 10**). A significant increase in the odds ratio was seen for lag days 2, 3, and 4 in a two-pollutant model with SO_2 and on day 3 for a two-pollutant model with PM_{10}. Multi-pollutant model with SO_2 and PM_{10} was also statistically significant on lag days 3 and 4. The greatest increase was generally observed on lag day 3 where the odds ratio was as high as 1.114. NO_2 levels were highly correlated with SO_2 (r=0.65) and PM_{10} (r=0.64).

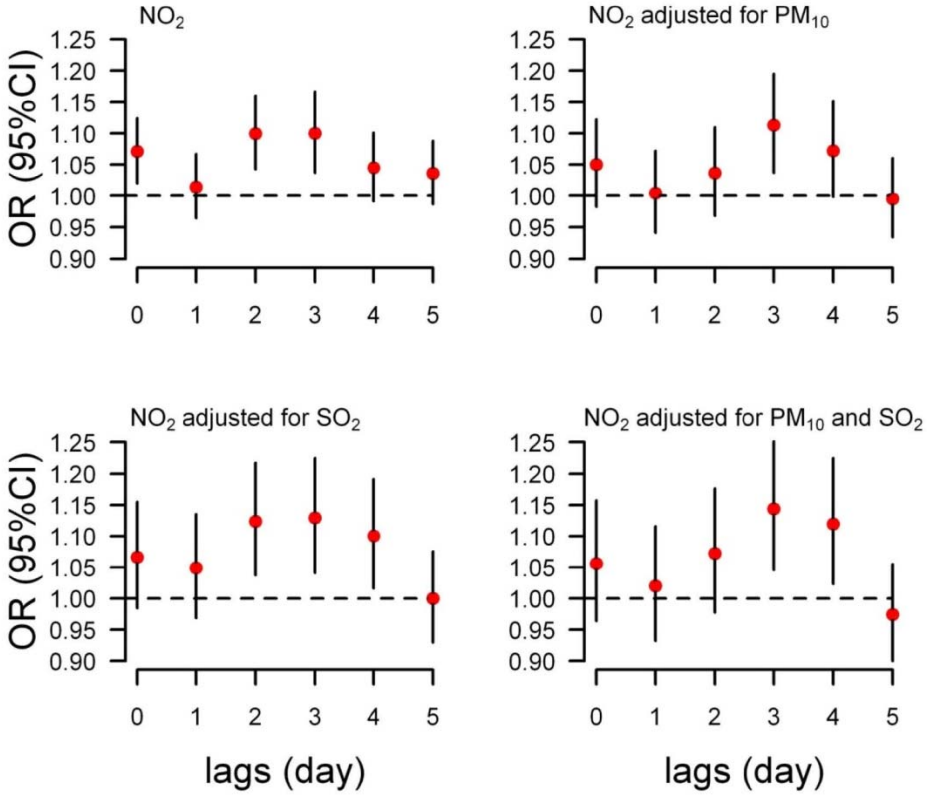


Figure 10. The association between a 10 μg/m^3 increase in NO_2 and daily emergency hospital visits for hypertension at lag days 0 to 5 in single-pollutant and multiple pollutants models (time-stratified case-crossover controlling temperature and relative humidity).

Critique

This study examined a small number of cases over a limited duration which severely limited its statistical power. Indoor and personal exposures were not evaluated and there was no stratification by age or sex. More importantly, however, the results are not consistent with those from other studies which have failed to show a consistent relationship between NO_2 exposure and blood pressure (Choi *et al.*, 2007, Santos *et al.*, 2005). In fact some studies, though cross-sectional in nature, have found an inverse relationship between NO_2 and blood pressure (Sorensen *et al.*, 2012). Confounding from ambient noise is a likely reason for the discrepancies, since new research has shown that railway noise is associated with an increase in systolic and diastolic blood pressure even after adjustment for NO_2 exposures (Dratva *et al.*, 2012).

2. **Leitte, A. M., Schlink, U., Herbarth, O., Wiedensohler, A., Pan, X. C., Hu, M., Richter, M., Wehner, B., Tuch, T., Wu, Z. J., Yang, M. J., Liu, L. Q., Breitner, S., Cyrys, J., Peters, A., Wichmann, H. E., and Franck, U. 2011. Size-segregated particle number concentrations and respiratory emergency room visits in Beijing, China.** ***Environmental Health Perspectives*** **119:508-513.**

Rating
Low quality (⊕⊕◯◯)

Description
This study centered on the relationship between emergency department visits for respiratory symptoms (acute infections, pneumonia, bronchitis, URT diseases, and chronic URT diseases) and ambient levels of PM_{10}, particle number concentration (PNC), particle surface concentration (PSC), SO_2, and NO_2 using single and two-pollutant models. A mean daily concentration of 63 µg/m^3 NO_2 was measured at 8 fixed monitoring sites in Beijing, China. The time analysis considered potential confounding from temperature, relative humidity, air pressure, holidays, calendar time, and day of week. A total of 15,981 cases were identified using ICD-10 criteria. A general additivity model (GAM) with Poisson regression was applied using an unstated type of smoothing spline. Distributed lag models for 0, 1, 2, 3, 4, and 5 days were examined along with single day lag models (0 through 7 days) and cumulative lag models with a moving average of 05 days. A sensitivity analysis was performed to ensure that the appropriate degree of smoothness (i.e. degrees of freedom) was applied to the time varying meteorological parameters.

Results
A weak, but statistically significant association was observed for emergency room visits in a two-pollutant model with PM_{10} on lag days 3, 4, and 5 but not lag days 0, 1, and 2 (see **Table 23**). Single-pollutant modelling revealed a statistically significant association on lag day 3 using a cumulative effects model (6-day moving average). No significant associations were observed on lag days 0, 1, 2, 3, or 4 with cumulative lag model or on any lag day when using a single lag model or a polynomial distributed lag model. The relative risk per 40 µg/m³ change of NO_2 in two-pollutant model with PM_{10} increased slightly after the adjustment, moving from 1.06 (1.00 - 1.12, 95% CI) to 1.073 (1.01 - 1.15, 95% CI) using a 5-day moving average lag period. Two-pollutant modelling of PNC and PSC while controlling for NO_2 generally yielded non-significant associations

Table 23. Overview of risk ratios (95% CIs) between respiratory ERV and an IQR increment of air pollutant while controlling for NO_2 or PM_{10}.

Pollutant	Time delay (days)	IQR	While controlling for NO_2	While controlling for PM_{10}
NO_2	3	40	—	1.07 (1.01–1.13)*
	4	40	—	1.07 (1.01–1.14)*
	5	40	—	1.08 (1.01–1.15)*
PNC50–100	2	3,600	1.06 (0.99–1.14)	1.07 (1.00–1.15)*
	3	3,600	1.06 (0.98–1.16)	1.08 (1.00–1.17)*
PNC100–300	2	4,400	1.08 (1.00–1.17)	1.10 (1.02–1.19)*
	3	4,400	1.06 (0.97–1.16)	1.11 (1.02–1.21)*
PSC50–100	2	60	1.06 (0.99–1.14)	1.07 (1.01–1.15)*
	3	60	1.07 (0.98–1.16)	1.09 (1.01–1.17)*
PSC100–300	2	440	1.07 (0.99–1.16)	1.10 (1.02–1.19)*
	3	440	1.05 (0.95–1.15)	1.10 (1.01–1.20)*

Units for IQR: NO_2 (μg/m^3); PNCx (1/cm^3); PSCx (μm^2/cm^3).
*p < 0.05 (p-values for the null hypothesis that the corresponding parameter is zero).

Critique

There was no two-pollutant modelling with PNC or PSC despite the fact that the correlation coefficients were generally greater than 0.50. Although the conduct of this study this was generally quite good with a reasonable number of cases examined, there were some unusual inconsistencies that cause some concern. First, there is a high probability that the GAM model was used with non-parametric smoothers that are known to affect the convergence and cause an overestimation of the relative risk. It has been shown that the use of non-GAM models or GAM models with parametric smoothers leads to more robust analysis using times series data (Stieb *et al.*, 2003). There was an unusually low correlation coefficient with UFP (r=0.06) that is difficult to rationalize in view of the high coefficients observed with PNC over discrete size ranges. Since these measurements occurred at only a single monitoring site the potential for exposure misclassification is very great. This calls into question the two-pollutant modelling results for PNC and PSC. Secondly, the failure to observe any significant associations in single-pollutant NO_2 models that utilized a polynomial distributed lag model is inconsistent with other studies that have shown higher risk ratios for respiratory emergency department visits with distributed rather cumulative lag models (Peel *et al.*, 2005). Finally, when study showed very weakly significant associations following adjustment with PM_{10} that suggest that $PM_{2.5}$ or CO could be more important co-variants.

3. **Stieb, D. M., Szyszkowicz, M., Rowe, B. H., and Leech, J. A. 2009. Air pollution and emergency department visits for cardiac and respiratory conditions: a multi-city time-series analysis. *Environmental Health* 8:1-13.**

Rating
Moderate quality (⊕⊕⊕○)

Description
This time series investigation took place in seven Canadian cities: Montreal, Ottawa, Edmonton, Saint John, Halifax, Toronto, and Vancouver. The association of emergency department visits for cardiac (angina, myocardial infarction, heart failure, and dysrhythmia) and respiratory (asthma, COPD, and respiratory infections) conditions with PM_{10}, $PM_{2.5}$, SO_2, O_3, CO, and NO_2 was examined. The 1-hr concentrations of NO_2 from 1 to 14 fixed monitoring sites were either averaged to obtain either a daily or a 3-hr value. The average daily NO_2 concentrations ranged from 9.3 ppb (17.8 µg/m³) in Saint John to 22.7 ppb (43.4 µg/m³) in Toronto. A total of 140.657 cardiac cases were identified along with 249,199 respiratory cases using ICD-9 or ICD-10 criteria. A general linear model was used together with Poisson regression and natural smoothing splines to adjust for the effects of holidays, daily temperature, relative humidity, and day of week. Two types of lag structures were employed: within day and between day. The within day examined eight day 3-hr averages (e.g. 12 AM-3 AM). The risk estimates were presented as a pooled data set for the entire year and during the warm and cold seasons.

Results
NO_2 was highly correlated with PM_{10} and CO in most cities with coefficients ranging from 0.59 to 0.83. A slight statistically significant association was observed for NO_2 exposures and angina/infarction and heart failure in a single-pollutant model using a lag period of either 0 or 1 day with the pooled data set (see **Table 25**). Individual city results for heart failure and angina/myocardial infarction are depicted in **Figures 13** and **14**. The associations with angina/myocardial infarction were approximately 50% higher in the warm season than the whole year. No associations were observed between NO_2 and any cardiac or respiratory condition for the winter season. These relationships were paralleled by a similar set of findings with CO. No statistically significant associations were seen for any respiratory conditions. In fact statistically significant negative associations were observed for COPD on lag days 1 and 2. There was no statistically significant association with angina/myocardial infarction when two-pollutant modelling was conducted with CO. The pooled percent increase in angina/infarction decreased from 2.7 (0.2-3.3, 95% CI) in single-pollutant model to 1.18% (-2.64-5.15, 95% CI) in the two-pollutant model. There was no evidence of a consistent associations between any pollutant and cardiac or respiratory visits on sub-daily time scales.

Table 25. Percent increase in cardiac or respiratory ER visits (95% confidence interval) for a 18.4 ppb (35.1 µg/m³) change in NO_2 concentration for three lag periods.

Lag	Angina/Myocardial Infarction	Heart Failure	Dysrhythmia	Asthma	COPD	Respiratory Infection
0	2.6 (0.2, 5.0)	4.7 (1.2, 8.4)	-1.3 (-4.1, 1.5)	-0.4 (-4.4, 3.9)	0.1 (-5.6, 6.2)	-0.9 (-2.9, 1.1)
1	2.7 (0.2, 5.3)	2.8 (-1.3, 7.1)	-0.9 (-3.8, 2.1)	-1.2 (-4.6, 2.3)	-3.4 (-6.6, -0.1)	0.7 (-3.7, 5.3)
2	0.7 (-1.6, 3.1)	1.9 (-3.1, 7.1)	0.3 (-2.6, 3.3)	0.0 (-2.4, 2.5)	-4.8 (-11.5, 2.5)	0.6 (-1.4, 2.6)

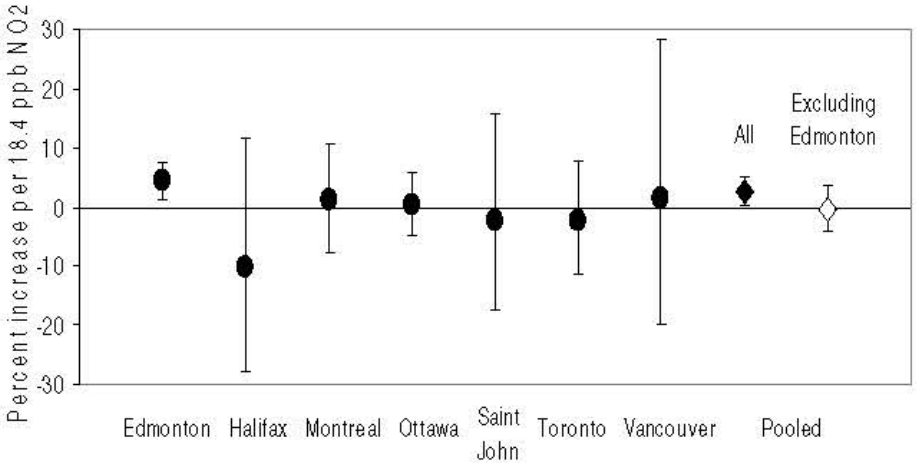


Figure 13. Percent increase in emergency department visits for angina/myocardial infarction by center. Point estimates and 95% confidence intervals are shown for NO_2.

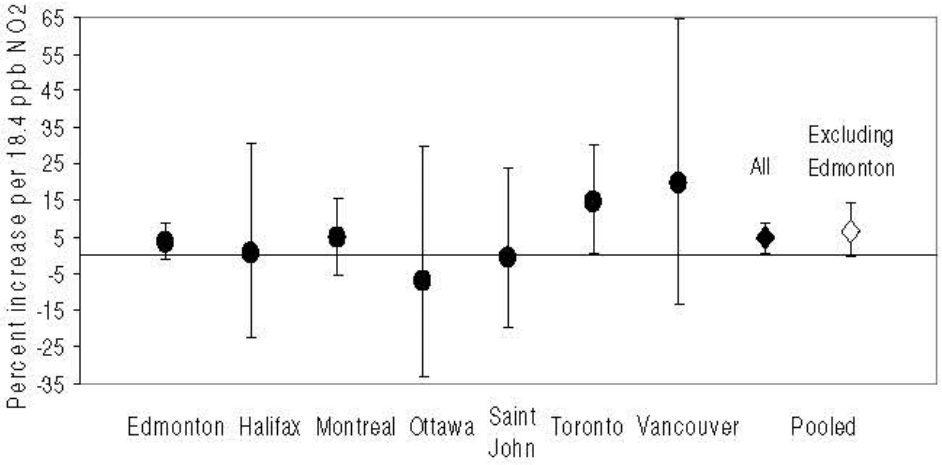


Figure 14. Percent increase in emergency department visits for heart failure by center. Point estimates and 95% confidence intervals are shown for NO_2.

Critique

This investigation was also well conducted and included a very large number of cases. Although the observed associations with ER visits for angina/myocardial infarction were shown to be confounded by CO exposures, two-pollutant modelling was not performed with the remaining pollutants: PM_{10}, $PM_{2.5}$, SO_2 and O_3. Given the reliance on only a single monitoring site in some cities there was a high likelihood of exposure misclassification because of the wide within-in city spatial variability that is known to exist for NO_2 (Cyrys *et al.*, 2012, Eeftens *et al.*, 2012). Although this type of exposure measurement error is frequently ignored when interpreting the results from time series studies, it is important that the impact be considered in careful and meaningful way (Jurek *et al.*, 2006). The results from large scale studies such as one described here await the development of improved hybrid models that will substantially reduce within Berkson-type error that arises when the results from a single monitoring station are used to represent an entire population (Baxter *et al.*, 2013). Despite these problems, however, the results from the current study are considered to be highly relevant since they demonstrate surrogate effects that can occur with NO_2 and the importance on controlling for CO confounding.

Asthma

1. **Jalaludin, B., Khalaj, B., Sheppeard, V., and Morgan, G. 2008. Air pollution and ED visits for asthma in Australian children: a case-crossover analysis. *International Archives of Occupational and Environmental Health* 81:967-974.**

Rating
Insufficient (⊕○○○)

Description
This case-crossover analysis occurred over a 5 year period and examined emergency department visits for asthma in children 1-14 years of age as a function of airborne PM_{10}, $PM_{2.5}$, SO_2, O_3, CO, and NO_2 levels. Average 1-hr measurements of NO_2 from 14 fixed monitoring sites in Sydney, Australia yielded a value of 23.2 ppb (44.3 µg/m³). The number of cases was limited to 1826 visits when classified according to ICD 9 criteria. Temperature, relative humidity, and holiday effects were handled using conditional logistic regression and time stratification. Lag periods of 0, 1, 2, and 3 days were applied as well as a cumulative lag of 01 days. Single and two-pollutant models were applied and the results were stratified by age group. Seasonal effect modification was examined for the warm (Nov-Apr) and cool (May-Oct) periods.

Results
Statistically significant association with ED visits for asthma in single-pollutant models for age group 1-14 years on lag day 0, 1, 3 and 01. The percentage increases also observed in children 1-4 years of age on lag 0, 1, and 01 days, but no significant increases were observed in those 5-9 or 10-14 years of age. The percentage increase in ED visits for asthma in children of different age groups was reported per interquartile range of 9.3 ppb (17.8 µg/m³) in single and two-pollutant models. Two-pollutant modelling was confined to the lag periods showing the strongest associations (lag day 0 for NO_2). Statistically significant changes were also observed in two-pollutant models that used all 5 co-pollutants with the age groups of 1-4 years and 1-14 years, but not the remaining two age groups. The strength of the associations was considerably reduced, however with values in the 1-14 year group declining from 2.3 % (1.4 - 3.2, 95% CI) in the single-pollutant model to 1.3 to 1.9 in the two-pollutant modelling (see **Table 29**). The two-pollutant modelling did not apply the same lag period for each pollutant, but instead utilized the lag period showing the strongest association. A statistically significant association was seen in single-pollutant models for warm but not cold months in age group 1-4 years and 1-14 years, but not in the remaining age groups.

Table 29. Percentage change in emergency department visits for asthma for interquartile increase in air pollutants, two-pollutant models, 1997–2001, Sydney, Australia.

1–4 years	**PM_{10} L0**	**$PM_{2.5}$ L0**	**O_3 1-h L1**	**NO_2 1-h L0**	**CO L0**	**SO_2 L0**
PM_{10} L0	1.4 (0.7, 2.1)	–	0.6 (¡0.3, 1.5)	0.7 (¡0.1, 1.5)	0.9 (0.1, 1.7)	1.1 (0.3, 1.9)
$PM_{2.5}$ L0	–	1.3 (0.7, 2.0)	0.7 (0.1, 1.4)	0.8 (0.1, 1.5)	1.0 (0.3, 1.7)	1.1 (0.5, 1.8)
O_3 L1	1.8 (1.0, 2.6)	1.7 (0.9, 2.5)	2.0 (1.3, 2.7)	1.6 (0.9, 2.4)	1.9 (1.2, 2.6)	1.9 (1.2, 2.6)
NO_2 L0	2.5 (1.2, 3.8)	2.3 (1.0, 3.6)	2.1 (0.9, 3.4)	3.0 (1.8, 4.2)	2.4 (1.1, 3.7)	2.6 (1.4, 3.9)
CO L0	1.4 (0.4, 2.5)	1.3 (0.3, 2.3)	1.7 (0.8, 2.6)	1.1 (0.03, 2.1)	1.9 (1.0, 2.9)	1.6 (0.7, 2.6)
SO_2 L0	1.3 (0.2, 2.5)	1.3 (0.2, 2.4)	1.3 (0.2, 2.4)	1.0 (-0.1, 2.2)	1.4 (0.3, 2.5)	1.8 (0.8, 2.9)
5–9 years	**PM_{10} L0**	**$PM_{2.5}$ L0**	**O_3 1-h L0**	**NO_2 1-h L0**	**CO L0**	**SO_2 L0**
PM_{10} L0	1.6 (0.5, 2.7)	–	1.1 (-0.1, 2.3)	1.6 (0.4, 2.8)	0.9 (-0.3, 2.1)	1.3 (0.2, 2.5)
$PM_{2.5}$ L0	–	1.5 (0.6, 2.4)	1.2 (0.2, 2.1)	1.6 (0.6, 2.6)	1.0 (0.01, 2.0)	1.3 (0.4, 2.3)
O_3 L0	1.4 (0.1, 2.8)	1.3 (-0.03, 2.7)	1.9 (0.7, 3.2)	1.9 (0.6, 3.2)	2.0 (0.8, 3.3)	1.7 (0.4, 3.0)
NO_2 L0	0.01 (-1.9, 2.0)	¡0.2 (-2.2, 1.8)	0.3 (-1.5, 2.2)	1.1 (-0.7, 2.9)	-0.5 (-2.5, 1.5)	0.4 (-1.5, 2.4)
CO L0	2.3 (0.7, 3.9)	2.1 (0.5, 3.7)	2.9 (1.4, 4.4)	3.0 (1.3, 4.6)	2.8 (1.3, 4.3)	2.5 (1.0, 4.1)
SO_2 L0	1.3 (-0.4, 3.1)	1.3 (-0.5, 3.0)	1.4 (-0.3, 3.1)	1.8 (0.04, 3.6)	1.3 (-0.5, 3.0)	1.9 (0.3, 3.6)
10–14 years	**PM_{10} L3**	**$PM_{2.5}$ L0**	**O_3 1-h L3**	**NO_2 1-h L2**	**CO L2**	**SO_2 L3**
PM_{10} L3	1.3 (¡0.2, 2.8)	–	1.0 (¡0.6, 2.7)	1.1 (¡0.5, 2.7)	0.7 (¡0.8, 2.3)	1.9 (0.3, 3.6)
$PM_{2.5}$ L0	–	1.2 (0.01, 2.5)	1.1 (¡0.1, 2.3)	1.1 (¡0.1, 2.4)	0.9 (¡0.3, 2.2)	1.2 (0.02, 2.5)
O_3 L3	0.6 (¡0.9, 2.1)	0.9 (¡0.5, 2.2)	1.0 (¡0.3, 2.3)	0.8 (¡0.6, 2.2)	0.8 (¡0.5, 2.2)	1.4 (-0.1, 2.9)
NO_2 L2	0.8 (¡1.1, 2.8)	1.0 (¡0.8, 2.9)	0.9 (¡1.1, 2.8)	1.2 (¡0.6, 3.1)	¡0.9 (¡3.1, 1.3)	1.6 (-0.3, 3.5)
CO L2	2.8 (1.1, 4.6)	2.8 (1.1, 4.6)	3.0 (1.3, 4.7)	3.5 (1.4, 5.7)	3.0 (1.3, 4.8)	3.2 (1.5, 5.0)
SO_2 L3	-1.7 (-3.7, 0.4)	-0.4 (-2.3, 1.4)	-1.4 (-3.4, 0.7)	-1.0 (-3.0, 0.9)	-1.2 (¡3.0, 0.7)	-0.6 (-2.4, 1.3)
1–14 years	**PM_{10} L0**	**$PM_{2.5}$ L0**	**O_3 1-h L1**	**NO_2 1-h L0**	**CO L0**	**SO_2 L0**
PM_{10} L0	1.4 (0.8, 2.0)	–	0.9 (0.3, 1.5)	1.0 (0.4, 1.6)	0.9 (0.3, 1.5)	1.2 (0.6, 1.8)
$PM_{2.5}$ L0	–	1.4 (0.9, 1.8)	1.0 (0.5, 1.5)	1.1 (0.6, 1.6)	0.9 (0.4, 1.5)	1.2 (0.7, 1.7)
O_3 L1	1.1 (0.5, 1.7)	1.0 (0.4, 1.6)	1.5 (0.9, 2.0)	1.2 (0.6, 1.7)	1.4 (0.8, 1.9)	1.3 (0.8, 1.9)
NO_2 L0	1.6 (0.6, 2.6)	1.4 (0.4, 2.4)	1.6 (0.6, 2.6)	2.3 (1.4, 3.2)	1.3 (0.3, 2.3)	1.9 (0.9, 2.9)
CO L0	1.8 (1.0, 2.6)	1.6 (0.8, 2.4)	2.1 (1.3, 2.8)	1.8 (1.0, 2.6)	2.2 (1.5, 3.0)	2.0 (1.3, 2.8)
SO_2 L0	1.0 (0.2, 1.9)	1.0 (0.1, 1.8)	1.2 (0.3, 2.0)	1.0 (0.1, 1.9)	1.0 (0.2, 1.9)	1.6 (0.7, 2.4)

Odds ratios in bold are for single pollutant models

Critique

The study examined a very small number of cases and likely lacked enough statistical power to reliable establish the relationship between asthma ED visits and NO_2 exposure. Studies using a much large sample size from an Atlanta hospital and a longer sampling duration failed to observe an increase in asthma admissions for children 5-17 years of age using two-pollutant models with O_3 (Strickland *et al.*, 2010). Likewise similar findings were obtained in an asthma study from Greece where the association with asthma ED visits using a single pollutant model with NO_2, were not evident in a two-pollutant with O_3, PM_{10}, or SO_2 in children 0-14 years of age (Samoli *et al.*, 2011). These inconsistencies in two-pollutant modelling results suggest that the current study suffered from some methodological deficiencies that impacted the results. There was also a high probability of lag selection bias in the two-pollutant modelling that was by the preferential use of lag periods showing the strongest impact with each pollutant (Andersen *et al.*, 2008). Together these factors considerably weaken the value of this study.

2. **Samoli, E., Nastos, P. T., Paliatsos, A. G., Katsouyanni, K., and Priftis, K. N. 2011. Acute effects of air pollution on pediatric asthma exacerbation: Evidence of association and effect modification. *Environmental Research* 111:418-424.**

Rating
Low quality (⊕⊕◯◯)

Description
The preceding study looked at emergency pediatric hospital admissions for asthma in relation to PM_{10}, O_3, SO_2, and NO_2 levels in Athens, Greece. Daily 1-hr maximum concentrations of NO_2 were measured at 14 fixed monitoring locations and yielded an average value of 84.8 µg/m³. The study included 3601 admissions identified by ICD-9 criteria that were restricted to males and females aged 0-14 years. Air temperature, relative humidity, day of week, holidays, and influenza outbreaks were adjusted for using Poisson regression with unstated model and cubic splines for smoothing. The lag periods were limited to 0, 1, and 2 days. Effect modification by age and sex was examined.

Results
A statistically significant increase in asthma admissions was observed for boys, but not girls, aged 0-14 years in a single-pollutant model with NO_2 (see **Table 30**). No statistically significant associations for all children in the 0-4 years age group or the 5-14 years group. The associations were also not significant asthma admissions and mean daily 1-hr maximum measurements during the winter, spring, summer, or fall per 10 µg/m³ increase or interquartile increase of 37.3 µg/m³ in a single-pollutant model that considered a lag period of 0, 1, or 2 days. Two-pollutant models of NO_2 and PM_{10}, SO_2, or O_3 did not reveal any significant associations per 10 µg/m³ increase in 1-hr maximum value for same day lag period (see **Table 31**).

Table 30. Percent increase (and 95% CI) in daily asthma admissions stratified by sex and age group in Athens, Greece over the period 2001–2004, for10 mg/m^3 increase in the levels of the corresponding pollutant on the same day (lag 0).

Pollutant	All ages (males)	All ages (females)	All (0–4 years)	All (5–14 years)
PM_{10}	3.9 (0.98 - 6.91)	- 0.05 (- 3.74 - 3.79)	1.87 (-0.92 - 4.74)	3.14 (- 0.75 - 7.18)
SO_2	8.97 (2.67 - 15.65)	1.09 (- 5.93 - 8.63)	5.71 (0.10 - 11.64)	6.49 (- 2.16 - 15.91)
NO_2	2.29 (0.13 - 4.50)	- 0.91 (- 3.46 - 1.71)	1.55 (- 0.46 - 3.60)	0.30 (- 2.60 - 3.29)
O_3	- 1.13 (- 5.41 - 3.33)	- 6.62 (-11.47 - - 1.51)	- 2.37 (- 6.33 - 1.77)	- 5.93 (- 11.23- -0.31)
O_3 Summer	10.32 (- 2.85 - 25.27)	8.25 (- 7.41 - 26.56)	5.35 (- 5.97 - 18.03)	21.25 (2.32 - 43.68)

Table 31. Percent increase (and 95% CI) in daily asthma admissions for ages 0-14 years in Athens, Greece over the period 2001–2004 for 10 mg/m^3 increase in the levels of the corresponding pollutant on the same day (lag 0), as estimated from two-pollutant models

Pollutant	Annual	+ PM_{10}	+SO_2	+NO_2	+O_3
PM_{10}	2.54 (0.06 - 5.08)		1.72 (- 0.92 - 4.44)	2.28 (- 0.36 - 4.99)	2.28 (- 0.21 - 4.84)
SO_2	5.98 (0.88 - 11.33)	4.76 (- 0.57 - 10.38)		7.60 (0.41 - 15.30)	5.97 (0.87 - 11.32)
NO_2	1.10 (- 0.68, 2.91)	0.54 (- 1.33 - 2.45)	- 0.78 (- 3.22 - 1.73)		1.30 (- 0.49 - 3.13)
O_3	-3.07 (- 6.55 - 0.53)	-2.66 (- 6.16 - 0.98)	- 3.21 (- 6.67 - 0.37)	-3.37 (- 6.86 - 0.24)	
O_3 summer	9.30 (- 1.07 - 20.76)	8.35 (- 2.08 - 19.90)	7.94 (- 3.19 - 20.34)	6.35 (- 4.89 - 18.93)	

Critique

Given the relatively small number of admissions, the statistical power with this study is limited. The number of lag periods selected for use was also truncated and restricted to single lag periods. This is not a likely source of concern, however, since most examination of asthma hospitalizations and single-pollutant NO_2 exposures have shown that lag days 0 and 1 yield the strongest associations (Jalaludin *et al.*, 2008, Pereira *et al.*, 2010, Yamazaki *et al.*, 2009). The study also benefitted from the adequate treatment of effect modification by age and sex. The authors correctly noted that NO_2 was likely a proxy indicator for other traffic-related pollutants. The study would have benefited greatly from the inclusion of $PM_{2.5}$ and CO in the analysis.

3. **Ko, F. W. S., Tam, W., Wong, T. W., Lai, C. K. W., Wong, G. W. K., Leung, T. F., Ng, S. S. S., and Hui, D. S. C. 2007. Effects of air pollution on asthma hospitalization rates in different age groups in Hong Kong. *Clinical and Experimental Allergy* 37:1312-1319.**

Rating
Moderate quality (⊕⊕⊕○)

Description
This retrospective time series study focused on hospitalizations for asthma in relation to $PM_{2.5}$, O_3, SO_2, and NO_2 in Hong Kong, China. The authors accumulated hourly NO_2 data from 14 fixed monitoring and computed daily averages, which resulted in values of 53.2 µg/m³ for the entire year, 61.7 µg/m³ for the cold season (< 20 °C), and 50.0 µg/m³ for the warm season (≥ 20 °C). A total of 69,716 admissions were documented and coded using ICD-9 criteria. Male and females of all ages were included in the analysis. Confounding from temperature, humidity, day of week, and holidays was handled using a generalized additivity model with Poisson regression and an unstated type of smoothing spline. Multiple lag structures were evaluated including single day lags of 0, 1, 2, 3, 4, and 5 days and cumulative lags 01, 02, 03, 04, and 05 days. Effect modification from season and age were also examined along with the impact of co-varying pollutants in two- and three-pollutant models were applied to those pollutants showing a correlation coefficient greater than 0.7.

Results
A statistically significant association was found for asthma hospitalization and NO_2 exposure in all three age groups using a single-pollutant model and a cumulative 5 day (days 04) lag period (see **Table 27**). A statistically significant association was also noted for the entire population at all lag times. A significant association occurred in a three pollutant model with O_3 and SO_2 but not with a two-pollutant model with O_3 (see **Table 28**). The greatest relative risk per 10 µg/m³ increase in NO_2 was 1.039 (1.028 - 1.051, 95% CI) for those 0-14 years of age using a single-pollutant model and 5-day cumulative lag period.

Table 27. Relative risk and 95% confidence intervals for pollutants per 10 mg/m^3 increase in concentration for hospitalization due to acute exacerbation of asthma in different age groups

Pollutant	Best lag period	0-14 yrs	Best lag period	>14-65 yrs	Best lag period	>65 yrs
NO_2	Lag 0–4	1.039 (1.028–1.051)	Lag 0–4	1.018 (1.007–1.029)	Lag 0–4	1.023 (1.014–1.033)
O_3 (8 h)	Lag 0–5	1.039 (1.030–1.048)	Lag 0–5	1.041 (1.032–1.050)	Lag 0–4	1.023 (1.015–1.030)
PM_{10}	Lag 0–5	1.023 (1.015–1.031)	Lag 0–5	1.014 (1.006–1.022)	Lag 0–4	1.015 (1.009–1.022)
$PM_{2.5}$	Lag 0–4	1.024 (1.013–1.034)	Lag 0–5	1.018 (1.008–1.029)	Lag 0–4	1.021 (1.012–1.030)
SO_2	---	NS	Lag 0–3	1.018 (1.001–1.035)	---	NS

Best lag day was chosen by the air pollutant concentration that yielded the highest $\chi 2$ score.
NS, no significant association between asthma admissions and every 10 mg/m^3 increase in the concentration of the pollutant.

Table 28. Relative risk and 95% confidence intervals for the pollutants per 10 mg/m^3 increase in the concentration for hospitalizations due to asthma in two and three pollutant models that adjusted for $PM_{2.5}$ and PM_{10}.

Model	NO_2 (lag 0–4)	O_3 (8 h) (lag 0–5)	SO_2 (lag 0)
Three pollutant model	1.014 (1.003–1.025)*	1.029 (1.029–1.036)*	0.988 (0.975–1.001)
Two pollutant model	1.006 (0.998–1.015)	1.031 (1.025–1.038)*	

*P < 0.05.

Critique

This study indicates that O_3 levels show a stronger relationship with asthma admissions than NO_2. Other studies suggest, however, that NO_2 interacts strongly with weather variables such as wind speed and airborne dust concentration may be important effect modifiers that need to be considered (Grineski *et al.*, 2011). In addition, evidence points to import influences of pollen levels, the use of rescue medications, and socioeconomic status as important effect modifiers that may affect the magnitude of the association between NO_2 levels and asthma hospitalization (DellaValle *et al.*, 2012, Grineski *et al.*, 2010). Finally, there is abundant evidence from other studies that adjustment for other pollutions using two-pollutant models decreases the association between NO_2 levels and asthma hospitalization, rendering the relationship insignificant (Iskander *et al.*, 2012, Samoli *et al.*, 2011, Ueda *et al.*, 2010). It is important to note, however, that this study did not consider influenza, pneumonia, or alloallergens levels as possible confounders. Another reason behind the inconsistent observations from this study and the findings of others may be due to the relatively high ambient air concentrations of NO_2 that were observed.

Birth Outcomes

1. **Bell, M. L., Ebisu, K., and Belanger, K. Ambient air pollution and low birth weight in Connecticut and Massachusetts. *Environmental Health Perspectives* 115(7), 1118-1124. 2007.**

Rating
Insufficient (⊕○○○)

Description
This retrospective cohort study examined low birth weight (LBW) over a 4-year period (1999-2002) maintained by National Center for Health Statistics. A total of 358,504 live births in the states of Massachusetts and Connecticut were identified in 15 counties and paired with information on birth location by county, prenatal care, age, race, marital status , education, alcohol and tobacco use during pregnancy, birth order, gestational age, infant birth weight, and infant sex. Exposures to NO_2, PM_{10}, $PM_{2.5}$, SO_2, and CO were measured at the county level using monitoring data from one or more fixed monitoring sites. Births were excluded if monitoring information was not available for ≥ 75 % of weeks for the individual trimesters. The average daily exposure to NO_2 during the gestational period was 17.4 ppb (33.2 μg/m^3). Logistic models were used to compare infants with normal and low (< 2500 g) birth weight following adjustment for marital status, tobacco and alcohol use during pregnancy, education, age, and race. A select group of covariates that included temperature by trimester, type of delivery, child's sex, use of prenatal care, birth order, gestational length, and year of birth were investigated for inclusion in the model. An interaction model was used to investigate the influence of race on the observed associations.

Results
LBW comprised 4.0% of the births examined, with somewhat smaller percentages in males than females. NO_2 concentrations were moderately correlated with $PM_{2.5}$ (r=0.64) and PM_{10} (r=0.55) levels. LBW was significantly associated with female sex short gestational period, maternal tobacco use, low maternal education, prenatal care late in pregnancy, first in birth order, unmarried marital status, and young or old maternal age. Alcohol use was not significantly associated with LBW. Following adjustment for these covariates, an odds ratio of 1.027 (CI 1.002-1.051) was observed for an IQR of 4.8 ppb (9.2 μg/m^3) in a single-pollutant model (see **Table 37**). Adjustment for CO and SO_2 in a two-pollutant model did not substantially alter the association of NO_2 exposure with declines in absolute birth weight with the values remaining near 7-10 g (see **Figure 23**). The strongest associations with NO_2 exposures were observed for the 1st trimester of pregnancy. Race was not found to be an important effect modifier with no statistical difference in the regression coefficients for infants from black or white mothers.

Table 37. Change in birth weight per IQR increase in pollution for the gestational period (95% confidence interval).

Pollutant	Difference in birth weight (g)	Odds ratio for low birth weight (< 2,500 g)
NO_2	–8.9 (–10.8 to –7.0)*	1.027 (1.002 to 1.051)**
CO	–16.2 (–19.7 to –12.6)*	1.028 (0.983 to 1.074)
SO_2	–0.9 (–4.4 to 2.6)	1.003 (0.961 to 1.046)
PM_{10}	–8.2 (–11.1 to –5.3)*	1.027 (0.991 to 1.064)
$PM_{2.5}$	–14.7 (–17.1 to –12.3)*	1.054 (1.022 to 1.087)**

*p < 0.001; **p < 0.05.

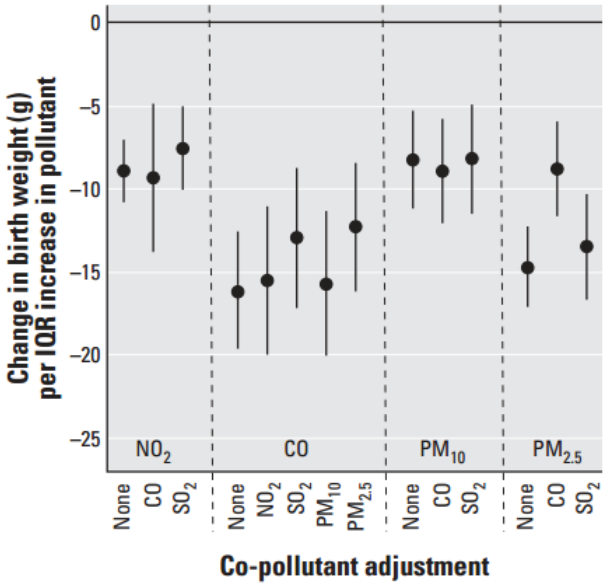


Figure 23. Change in birth weight per IQR increase in gestational exposure to pollutant, for single and two-pollutant linear models. The point reflects the central estimate; the vertical line represents the 95% confidence interval.

Critique

Use of ambient fixed monitoring measurements as a surrogate for personal exposures NO_2 exposures has been shown to bias the associative relationships by failing to adequately account for spatial variability. Although hierarchical methods are available to correct for the spatial misalignment and misclassification error caused by the use measurements from fixed sites, these were not applied. Research has shown that the failure to correct for this error in multi-pollutant models can bias results towards or away from the null, depending on the degree of measurement error for each pollutant (Zeger *et al.*, 2000, Zeka and Schwartz, 2004). Another serious problem with this study is the long distances that may separate the monitoring location from the individual's residence. Studies have shown that this is an important consideration for NO_2 that may introduce

considerable error when the distances are great (Monn, 2001, Stroh *et al.*, 2012) . Since some of the counties in this were located in rural environments that occupied many square miles of area, the failure to include some proximity weighting into the exposure assessment introduced some severe bias in the estimates. It was also noted that the multi-pollutant modelling conducted in this study was not performed correctly, focusing on the co-pollutants with low rather high correlation coefficients. The measures with the highest correlations with NO_2 levels, PM_{10} and $PM_{2.5}$, were not examined in a two-pollutant model using Poisson log linear model (Kim *et al.*, 2007). Finally, the failure to show that race was an effect modifier suggests that this study was underpowered, since racial disparity is hallmark finding in many studies on low birth weight (Collins and David, 2009).

2. **Ballester, F., Estarlich, M., Iniguez, C., Llop, S., Ramon, R., Esplugues, A., Lacasana, M., and Rebagliato, M. 2010. Air pollution exposure during pregnancy and reduced birth size: a prospective birth cohort study in Valencia, Spain. *Environmental Health* 9:1-11.**

Rating
Low quality (⊕⊕○○)

Description
This time series investigation focused on hospital admissions for cardiovascular or heart disease in 14 Spanish cities. Associations with PM_{10}, TSP, BS, SO_2, O_3, CO, and NO_2 were measured at an unstated number of fixed monitoring sites in each city. Daily mean concentrations of NO_2 ranged from 23.1 µg/m³ in Castellon to 76.2 µg/m³ in Valencia. Procedures were used to ensure the completeness of the measurement data set, the imputation of missing values, and the representativeness of the urban monitoring sites. Admission rates for cardiovascular disease ranged from 4.4 per day ranged in Oviedo to 35.7 in Barcelona; whereas the rates for heart disease ranged from 2.2 in Pamplona to 20.7 in Barcelona. Non-parametric LOESS smoothing splines were used with a generalized additivity model and Poisson regression to adjust for temperature, barometric pressure, humidity, influenza, and day of week effects. Lag periods of 0, 1, 2, and 3 days were applied along with average lags of 01 and 23 days. Only the pooled effects were described using a fixed effect meta-analyses that considered the degree of heterogeneity in the NO_2 results. The results were presented for both single and two-pollutant models.

Results
A statistically significant association was seen with hospital admissions for cardiovascular and heart disease in a single-pollutant model at an average lag of 01 days. Two-pollutant models considered the combined admissions for both disease types and found weakly significant associations using CO and O_3, but not with “particulates” or SO_2 (see **Figure 21**). The strength of the associations in two-pollutant models was considerably weakened for all co-pollutants except O_3. The definition of "particulates" for the two-pollutant modelling with NO_2 was not specified and may have constituted PM_{10}, TSP, or BS. The pooled relative risk for combined cardiovascular and cardiac disease per 10 µg/m³ increase in the single-pollutant model at a lag of lag 01was approximately 0.38 for cardiovascular disease and 0.86 for heart disease.

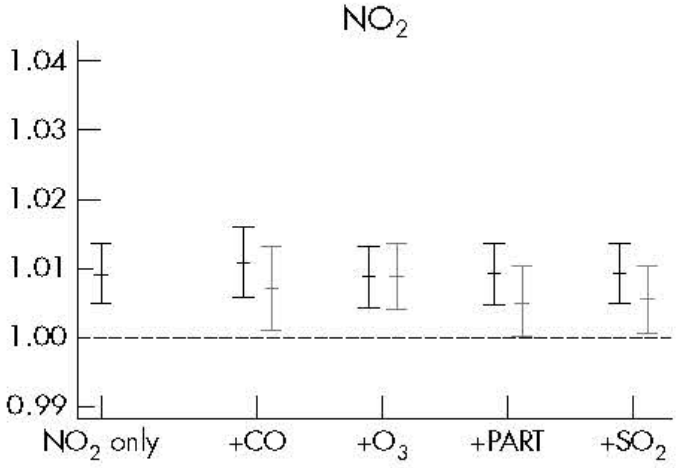


Figure 21. Combined estimates of the association between hospital admissions for heart diseases and air pollutants. The effects are expressed as relative risk (and 95% confidence interval) of hospital admissions for a 10 mg/m^3 (1 mg for CO) increase in air pollutant level using two-pollutant models.

Critique

The analysis revealed that the association observed for NO_2 in a single-pollutant model was not robust to the two-pollutant inclusion of either particulates (PM_{10}, TSP, or BS) or SO_2, but remained somewhat robust to CO and O_3 when both types of cardiovascular disease were combined. These associations were observed using a fixed effect model that was justified on the basis of heterogeneity tests that were acknowledged to have weak statistical power especially when the sample sizes are small (Ioannidis *et al.*, 2007). The observed weak association may have been an artifact that arose from the use of a fixed-effect rather than random-effect model for the multi-city analysis. Given the large number of cities examined and the failure to describe the number of monitoring sites in each city, the lack of heterogeneity is very surprising and at odds with the results from other studies. At a minimum both random- and fixed-effects models should have been applied to improve overall confidence in the findings.

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