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Review of recent health effect studies with sulphur dioxide

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Review of recent health effect studies with sulphur dioxide

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ABSTRACT

This report focuses on published toxicology and epidemiology studies that have examined the relationship between sulphur dioxide exposures and the occurrence of acute and chronic health effects in laboratory animals and humans. All relevant studies published since the World Health Organization issued their Air Quality Review in 2005 were taken into consideration. A total of 225 environmental epidemiology and toxicology studies were individually examined and summarized in the course of preparing this report. Whereas an appreciable number of new morbidity and mortality investigations have been conducted on both acute and chronic health outcomes, the focus of most studies continues to be on the relationship between SO_2 exposures and respiratory disease and asthma exacerbation. In addition, there has been a large increase in the number observational focusing on associations between SO_2 exposure and variety of birth outcomes such low body weight, malformations, and infant mortality.

Although a tremendous amount of new information has been published there are many problems with a majority of the observational studies including a heavy overreliance on concentration measurements from central monitoring sites as a surrogate for personal exposures. Despite the existence of studies showing that there is no relationship between these measures and personal SO_2 exposures, central monitoring site measurements continue to be used unabated. In addition, most of the studies have been performed used a single pollutant modelling approach that did not take into consideration the correlations between ambient SO_2 levels and the concentrations of other pollutants such as PM_{10} and $PM_{2.5}$. Those studies that have incorporated a multi-pollutant design have generally shown that and observed health associations emerging from a single pollutant model are not robust to the inclusion of a correlated co-pollutant. As a result, a majority of the epidemiological studies conducted with SO_2 suffer from a very high degree of exposure misclassification that renders them unusable for a hazard or risk determination. Given these circumstances, there is no good justification for making any adjustment to current limit values.

KEYWORDS

Sulphur dioxide, morbidity, mortality, health effects, cardiovascular disease, respiratory disease, exposure asthma, collinearity, limit values, multi-pollutant models, confounding, misclassification, central site monitoring

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This report is available as an Adobe pdf file on the Concawe website (www.concawe.org).

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SUMMARY

The following report critically examines those toxicology and epidemiology studies published since the 2006 World Health Organization's review of sulphur dioxide (SO_2) health hazards. Over 175 epidemiology and 50 toxicology-related studies were identified from a literature review. The observational studies were individually summarized and graded to assess their relevance for making adjustments to prevailing ambient air guidance values. The toxicology studies were primarily mechanistic in nature and did not include any new human inhalation studies that substantially added to the body of accumulated knowledge on the health effects of SO_2. The report also summarizes the legislative history of SO_2 in Europe and examines those exposure-related factors and considerations that can affect the interpretation of findings from observational studies. These include topics such as indoor air sources, spatial heterogeneity, collinearity concerns, personal exposure, misclassification bias, and measurement errors. The atmospheric chemistry and fate of SO_2 from natural and anthropogenic sources has also been examined in light of the ability of sulfate aerosols to mitigate global warming by reflecting incoming solar radiation back into space.

Unlike the situation in Asia where the declines in ambient SO_2 levels have been modest at best, the situation in Europe and North America has been dramatically different. Many regions of Europe have seen an 80% reduction in SO_2 since 1990 and these reductions are likely to continue as newer emission reduction efforts come in full force. In fact, it is highly likely that the levels of SO_2 in some European cities will begin to approach background amounts, which will impact the conduct of future epidemiology studies that rely on ambient monitoring data as the sole source of exposure information. Consequently, it is highly likely that researchers in China and India will begin to assume a preeminent role in designing, performing, and interpreting new investigations into the health hazards of SO_2.

Since anthropogenic SO_2 is largely emitted by power plants and other industrial operations that act as fixed point sources, ambient levels are characterized by a high degree of spatial and temporal variability. Although methods such as land use regression and inverse distance weight are available to partially compensate for the differences in SO_2 between an individual's residence and the location of the fixed monitoring station, these methods have rarely been employed. As a result, many of the observational studies on SO_2 suffer from a high degree of exposure misclassification. In addition, a large percentage of the reviewed studies relied on the use of single pollutant models that did take into consideration the pollutant collinearity that often exists between SO_2 and $PM_{2.5}$, PM_{10}, or NO_2.

These problems, however, are dwarfed by a much larger issue that calls into question the reliability of each and every observational study that uses the measurements from central sites. This critical defect is the result of information showing that personal SO_2 exposures are unrelated to the levels found at fixed monitoring stations. More importantly, studies have convincingly shown that SO_2 measurements taken at monitoring stations are a far better proxy for personal $PM_{2.5}$ exposures than personal SO_2 levels. The importance of these findings cannot be overstated, since they call into question the results from many studies, particularly those that do not take $PM_{2.5}$ or PM_{10} confounding into consideration. Since the majority of SO_2 studies incorporate a single pollutant design, these results are of little or no value in a risk determination. When a two-pollutant design has been applied, the health outcomes and relative risks attributed to SO_2 were often reduced to an insignificant level. Although PM_{10} has been the co-pollutant most often

responsible for any observed two pollutant interaction, nitrogen dioxide (NO_2) and $PM_{2.5}$ have also occasionally been implicated as confounders. Still, multi-pollutant modeling is not a panacea, and assumptions regarding collinearities between pollutants, non-differential seasonal effects, and the deleterious influence of interactions with other physical or environmental factors cannot be guaranteed. Although providing a methodological improvement, multi-pollutant models are not able to rule out that the pollutant with the highest adjusted risk estimate may simply be acting as a surrogate for another unmeasured substance.

An evaluation of the strength and quality of available new evidence showing an association between SO_2 exposures and acute or chronic mortality, acute respiratory disease, acute cardiovascular disease, asthma, and birth-related deficits did not provide any compelling new arguments to suggest that an adjustment is necessary in the guidance values for SO_2. Similarly, there have not been any substantive new controlled human exposure studies suggesting that SO_2 is capable of causing health effects at concentrations that are below current standards. There are, however, new human studies showing that SO_2 is not a pulmonary or sensory irritant in humans at commonly encountered concentrations. Likewise, new information has emerged to show that endogenously produced SO_2 has an important role in maintaining cardiovascular function. This has obvious implications for those who believe that an exposure threshold does not exist in the concentration response curve for SO_2. In summary, there has not been any compelling new evidence to suggest that the health hazards of SO_2 are any more serious than previously believed. Consequently, there is no legitimate basis for making an adjustment to airborne limit values based on the existence of new health concerns.

1. BACKGROUND

In many ways, this report is a companion to the nitrogen dioxide (NO_2) review issued in 2014. Although the approach taken to address many of the most pertinent issues regarding human exposure and risk are similar, the confounding factors affecting these determinations are substantially different for the two gases. As was the case for NO_2, the primary goal behind this report is the identification and evaluation of new policy-relevant health research published since the World Health Organization's last evaluation of SO_2 in 2006. The evaluation also examines whether there is a need to change the airborne limit values for SO_2 within the European Union. Heuristically, this is not a particularly difficult determination since airborne levels of SO_2 have been steadily declining in Europe and elsewhere since the early 90's, and the reductions are likely to continue as new emission restrictions come into full force (Henschel *et al.*, 2013, le Tertre *et al.*, 2014). Since these rapid year-to-year changes provide genuine exposure relief, reviews and summaries of potential health risks at a particular exposure concentration do not serve any real purpose other than to document the most recent findings for a particular hazard. This is because the ambient air levels of today are not reflective of those that may exist in the future. Although the rapid decline of urban SO_2 levels may be sufficient to mitigate any hazards that are perceived to exist, it is still instructive to examine the strength of the evidence in support of a change in the airborne limits. Consequently, a thorough literature search was performed to identify new published and unpublished information dealing with SO_2 exposures, hazards, and risks.

The SO_2 literature search was performed using both direct and indirect methods. The indirect approach relied on an examination of authoritative technical reviews published since 2005 to identify new policy-relevant research in humans and laboratory animals. This included reports such as the U.S. EPA's Integrated Science Assessment for SO_2, COMEAP's (Committee on the Medical Effects of Air Pollution) air pollution mortality report for the UK Dept. of Health, and WHO's Review of Evidence on Health Aspects of Air Pollution (REVIHAAP) project (COMEAP, 2009, USEPA, 2008, WHO, 2013b). In addition, the St. George's University systematic review of short-term health associations prepared for UK Department of Health was also consulted (Anderson *et al*., 2007). These expert reports were mined for all pertinent SO_2-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, human panel, and animal toxicology studies published from 2005 through the year 2015 (Falagas *et al.*, 2008). The following key words were used in a variety of search term combinations to identify the most relevant papers for inclusion this review: sulfur dioxide, air pollution, health effects or cardiovascular, respiratory, morbidity, mortality, hospitalization, emergency room and toxicity. Alternatively, the words "sulphur dioxide" were used in the search to accommodate worldwide differences in spelling. A total of 567 papers were identified in PubMed and 534 from the WOS. Google Scholar on the other hand flagged a total 1660 original publications that contained any or all of the key words cited above. The abstracts from these papers were then scanned for relevance in order to reduce the search to those studies that examined the association between airborne SO_2 levels and a particular health outcome. In additions, studies were earmarked if they reported on

the *in vivo* or *in vitro* health effects of SO_2 in human panel or laboratory animal experiments. Reviews and conference proceedings that did not contain original peer-reviewed data were dropped from further consideration. Similar searches were performed for SO_2-related studies involving asthma, infants, children, lung function, birth defects, and inflammation. The intent was to highlight those studies providing new information since the last WHO guidance issued in 2006. This process led to the identification of over 175 observational studies focusing on topics ranging from cardiovascular mortality to inflammatory disease, as well as an appreciable number of new toxicology studies. The epidemiology studies included new case-control, time-series, cohort, and panel studies that focused either on SO_2 alone or SO_2 in combination with other primary or secondary air pollutants.

The grading system used to evaluate the strength and weaknesses of the individual studies was similar to the method employed in the NO_2 health effects review. The GRADE (Grading of Recommendations Assessment, Development and Evaluation) approach was selected because it provided a structured set of principles that could be applied to a range of procedural approaches, study populations, and outcome measures (Garcia *et al.*, 2011). The GRADE system also offered 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 as the ECETOC or IPCS frameworks for analyzing human data because these latter 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). In addition, the validity of this approach was recently bolstered when the U.S. National Toxicology Program's Office of Health Assessment and Translation (OHAT) formally recommended the GRADE approach as the preferred method for evaluating the strength and weaknesses of individual studies used to develop its health hazard evaluations (NTP, 2015).

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 was set to be released by the end of 2013, but has not yet been published. GRADE PLUS 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 a 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**). The application of these scoring criteria needs to take place in strictly objective manner that takes into consideration the overriding strengths and weaknesses of a particular study. This was a somewhat difficult exercise in the case of SO_2, because of evidence showing that ambient measures of SO_2 exposure are a particularly poor surrogate for personal exposures. Since the vast majority of epidemiology studies focusing on SO_2 use measurements form central monitoring sites, the problem of exposure misclassification is a rampant and persistent problem that taints the findings from a majority of these investigations. Although this deficiency would automatically downgrade the results from many if not all of the identified studies summarized in this report, this approach seemed to

negate and obviate the positive characteristics incorporated into some of the study designs. As a result, GRADE downgrading due to exposure misclassification was applied in a judicious manner that targeted those studies where the likelihood of exposure error was particularly egregious.

Table 1 Factors affecting the quality of evidence finding using GRADE

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		

As noted, GRADE PLUS will provide a strong alternative to the GRADE system for evaluating individual health hazard studies. Once released, GRADE PLUS will give more weight to quasi-experimental study designs, and will also take into account two other adjustment factors: i) the consistency of effect 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), which are the gold standard in most clinical arenas because of their ability to reduce bias through randomized assignment to an exposure or a 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 than 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:

a) High – randomized controlled trials appropriately designed and with sufficient blinding.
b) Moderate – weak randomized controlled trials, un-randomized controlled trials, as well as well conducted time-series, cohort, and case control studies
c) 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
d) Very low – studies which show unreasonable uncertainty, publication bias, or 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.

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 (⊕⊕⊕◯) – moderately 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

Examples of the evaluation process for individual SO_2 studies in each of the rating categories can be found in **Appendix A**. 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. The summary analysis of the individual studies identified from the literature search is presented in **Appendix B**. 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 modeling, 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

Virtually every country in the industrialized world has established air quality values for SO_2. These limits span a range of allowable concentrations and averaging times that are a function of the health or environmental effects deemed to be the most critical. These standards and guidance values fall into two categories, primary standards aimed at preventing adverse health effects in human populations and secondary standards aimed at protecting human welfare, which includes soil, water, vegetation, visibility, and climate. A recent review of national air quality standards and guidelines found that 76 out of 192 UN member countries have promulgated mandatory or voluntary 24-hour limit values for SO_2 (Vahlsing and Smith, 2012). The average daily concentration limit for these countries was 182 µg/m^3 (95% CI 158-205 µg/m^3). **Figure 1** provides a worldwide map of national ambient air quality standards for SO_2. In many cases, these country-wide limit values are based on evaluations performed by other authoritative bodies such as the European Commission (EC), the World Health Organization (WHO), or US Environmental Protection Agency (USEPA). **Table 2** compares and contrasts the standards issued by a small percentage of the countries that openly listed their values on-line or provided a response to a mailed survey questionnaire. Of the 24 countries that responded to the questionnaire, 91% indicated that they intended to use WHO air quality guidelines to update their air quality standards for SO_2. The current WHO air quality guideline values for SO_2 have been set at 500 µg/m^3 for a 10-minute measurement period and 20 µg/m^3 for a 24-hour interval.

Figure 1 Countries with established mandatory or voluntary 24-hour ambient air quality standards (AAQS) for SO_2 (Vahlsing and Smith, 2012)

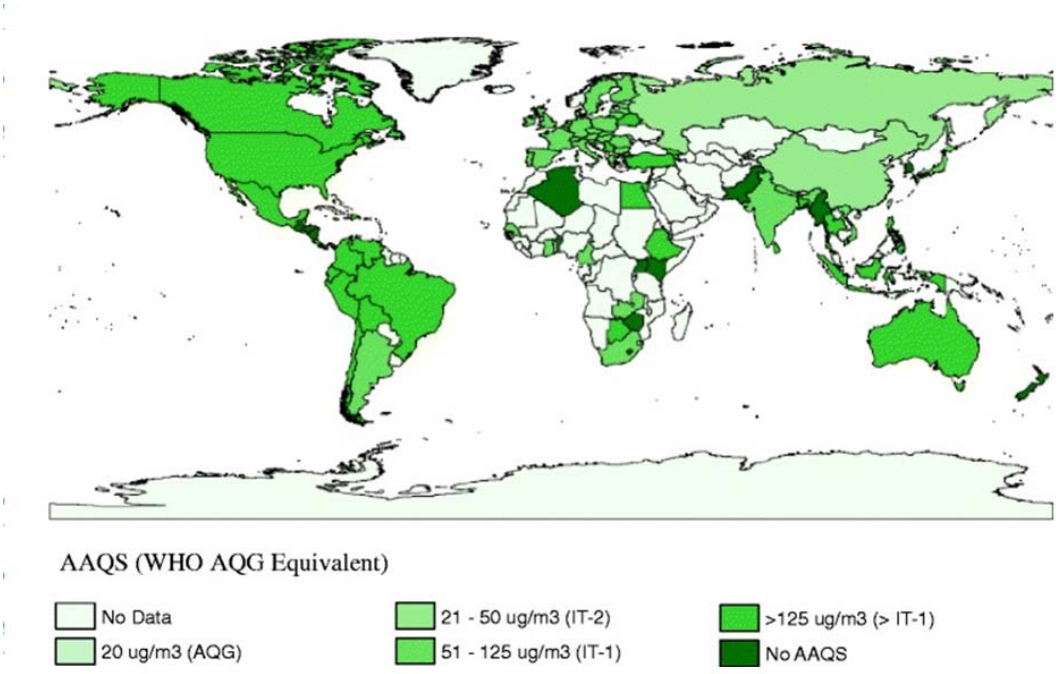


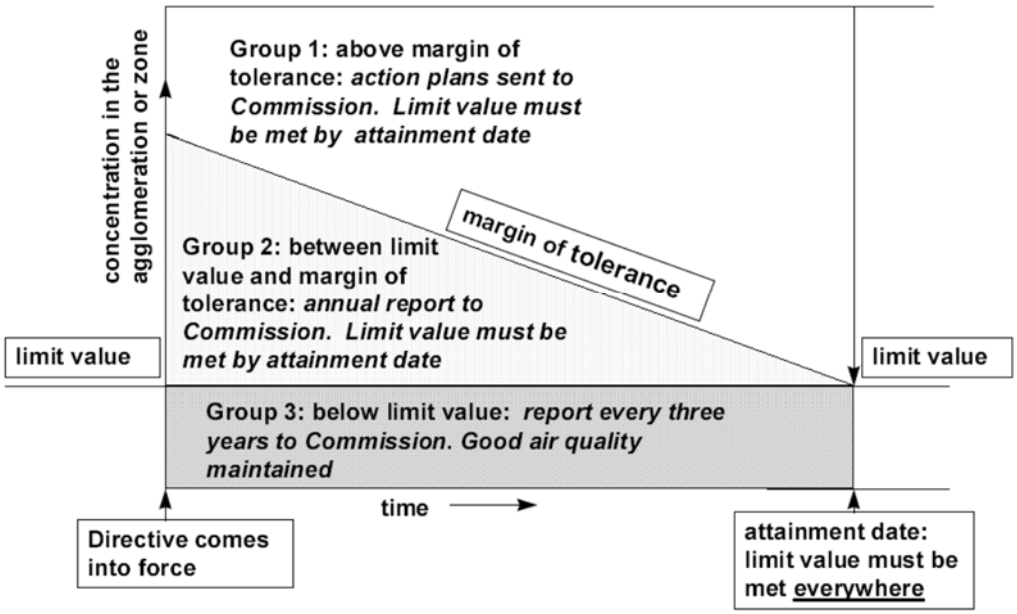
Table 2 Worldwide ambient air quality standards for SO_2 (Vahlsing and Smith, 2012, Wood, 2012)

Country/Region	1-hr average (µg/m³/ppb)	24-hr average (µg/m³/ppb)	Annual (µg/m³/ppb)	Year
Canada#	838/315	279/105	56/21	1998
China‡	500/191	150/57	60/23	2010
Japan	/100	/40	---	1973
United States	200/75	---	---	2010
India	---	80/30	50/19	2008
Australia	532/200	213/80	53/20	1998
European Union	350/134*	125/48†	20/8	2005

maximum acceptable level
‡ Grade II standard applicable to residential, mixed commercial, cultural, industrial, and rural areas
* not to be exceeded more than 24 times per year
† not to be exceeded more than 3 times per year

The EU began issuing air quality limit values for SO_2 in 1980 with the publication of Council Directive 80/779/EEC (EC, 1980). This directive established annual and 30-minute limit values of 140 and 400 µg/m³, respectively. These values were revised downward when the First Daughter Directive for the Air Quality Framework Directive was released in 1999 (99/30/EEC) (EC, 1999b). The new hourly SO_2 limit value of 350 µg/m³ and daily limit of 125 µg/m³ were aimed at protecting human health in urban zones; whereas the annual limit of 20 µg/m³ was directed at sensitive ecosystems within Europe (EC, 2000). The Directive specified that compliance was necessary by the year 2010 and that the hourly and daily limit values should not be exceeded more than 24 and 3 times per year, respectively. In addition, an alert threshold of 500 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 2**). The tolerance limits allowed the European Commission to identify those zones with the worst air quality. Initial tolerance limits of 50% were allowed for SO_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. A new Air Quality Directive was issued in 2008 that merged the first three Daughter Directives and retained the limit values for SO_2, but allowed Member states to request a five year time extension for compliance (EC, 2008b).

Figure 2 Achievement of limit values in the framework Directive through the passage of time (EC, 2000)

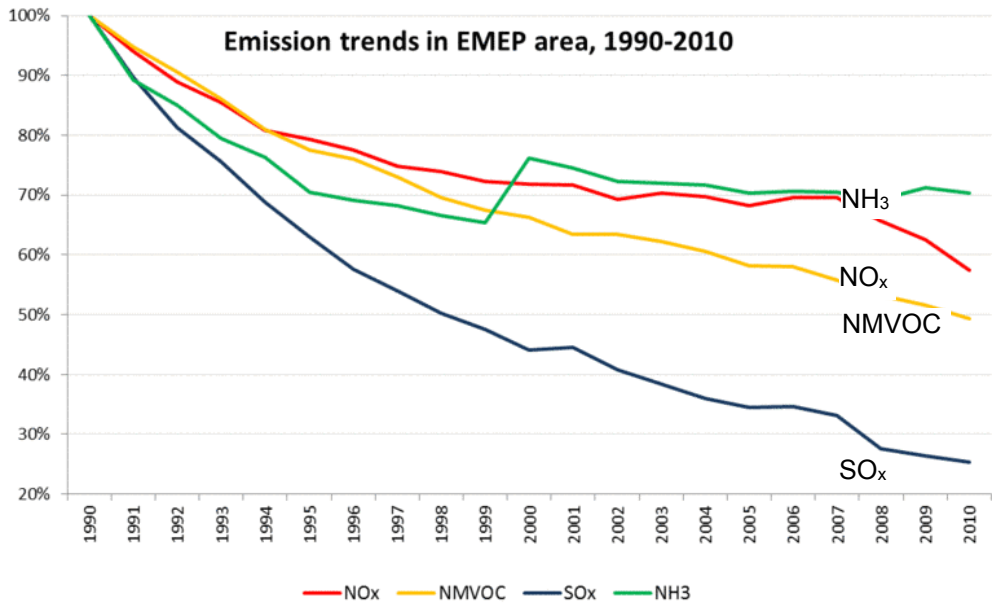


There is a complex legislative history that goes along with the development of the EU limit values which includes the creation of policies that restricted combustion-related emissions. Several different emission limits have been issued that restrict the release of SO_2 during the combustion of fuels from both area and stationary sources. These include the Integrated Pollution Prevention and Control Directive (2008/1/EC) which limits industrial emissions and requires the use of the best available technology to desulphurize the solid and liquid fuels used in combustion processes (EC, 2008a). Similarly, the National Emission Ceiling (NEC) Directive (2001/81/EC) established SO_2 emission limits for each member country that had to be attained by the year 2010 (EC, 2001). The first NEC directive was responsible for reducing SO_2 emissions to a level that was nearly 50% below the aggregate ceiling of 8297 kilotons/year. A new NEC directive was expected in 2013 as part of the Clean Air Programme for Europe but has been delayed because of a lingering debate over the emission targets. The revision is expected to establish more stringent reductions that could reduce SO_2 emissions another 81% (based on 2005 levels) to 1530 kilotons/year by the year 2030. Finally, a pair of Fuel Quality Directives (1998/70/EC and 1999/32/EC) have been issued that initially limited the sulphur content of petrol to 150 mg/kg, diesel fuel to 350 mg/kg, and marine gas oil to 0.2% (EC, 1998, EC, 1999a). Two other directives were subsequently passed in 2003 that initially restricted the sulphur content to 50 mg/kg for petrol, diesel fuel, and gas oils; but these were modified again in 2009 to create the current limit of 10 mg/kg for these fuels (EC, 2003, EC, 2009).

A final piece of legislation that directly impacted the emission and transport of SO_x (i.e. SO_2 and SO_3) is the 1999 Gothenburg protocol administered by the United Nations Economic Commission for Europe (UNECE, 2007). The protocol was part of the 1979 Convention on Long-Range Transboundary Air Pollution (CLRTAP) that has been ratified by 47 European nations, Canada, the United States, 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 sulphur from stationary sources. The goal was to reduce SO_x emissions by 63% by restricting the sulphur content of gas oil fuels used by power plants and other power generating facilities to 0.2 % by July 2000 and 0.1% by January 2008. In Europe, a Cooperative Programme for the Monitoring and Evaluation of Long-range Transmission of Air Pollutants (EMEP) was established to track progress via the establishment a monitoring network and the creation of an inventory reporting protocol (UNECE, 1984). As of 2010, an 82% decline SO_x emissions was achieved in the European Union (EEA, 2013). These achievements are depicted in **Figure 3**, which clearly shows the notable reductions in SO_x especially in relation to the more modest declines in other targeted pollutants.

Figure 3 Twenty year emission reduction for SO_X and other pollutants from EMEP monitoring (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 59% reduction in SO_2 emissions by 2020. The European Union is also in the process of amending the Emission Ceiling Directive and mandating a further 81% reduction in SO_2 emission limits by 2030 (EPRS, 2015). The net effect of these new pieces of legislation is the assurance that even greater reductions in ambient SO_2 levels will be seen in the future and the very real possibility that these changes will outpace any benefits that can realized from further in the limit values.

Taken together, the passage of the preceding legislation has had a large impact on airborne levels of SO_2 throughout Europe with a majority of the 28 Member countries witnessing declines of more than 70% from 1990-2011 (Guerreiro *et al.*, 2014, Vestreng *et al.*, 2009). As shown in **Figure 4**, this has resulted in an overall 74% decline of SO_x emissions from the 33 European Environment Agency Member

countries (Iceland, Liechtenstein, Norway, Switzerland and Turkey are not members of the EU) (EEA, 2014). All 28 EU member countries met their 2010 emission ceiling objectives for SO_2 in large part because of substantial emission declines in the energy production and industrial energy use sectors, which saw SO_2 reductions of 76% and 72%, respectively (see **Figure 5**). The emission reductions resulted in airborne levels that were below EU limit values levels so European residents were not exposed to SO_2 in excess of this standard in 2011; however 46% of the population was exposed to SO_2 levels that were in excess of the WHO daily air quality guideline value of 20 µg/m^3.

Figure 4 Sulphur dioxide emission trends in Europe from 1990-2011 (EMEP, 2013)

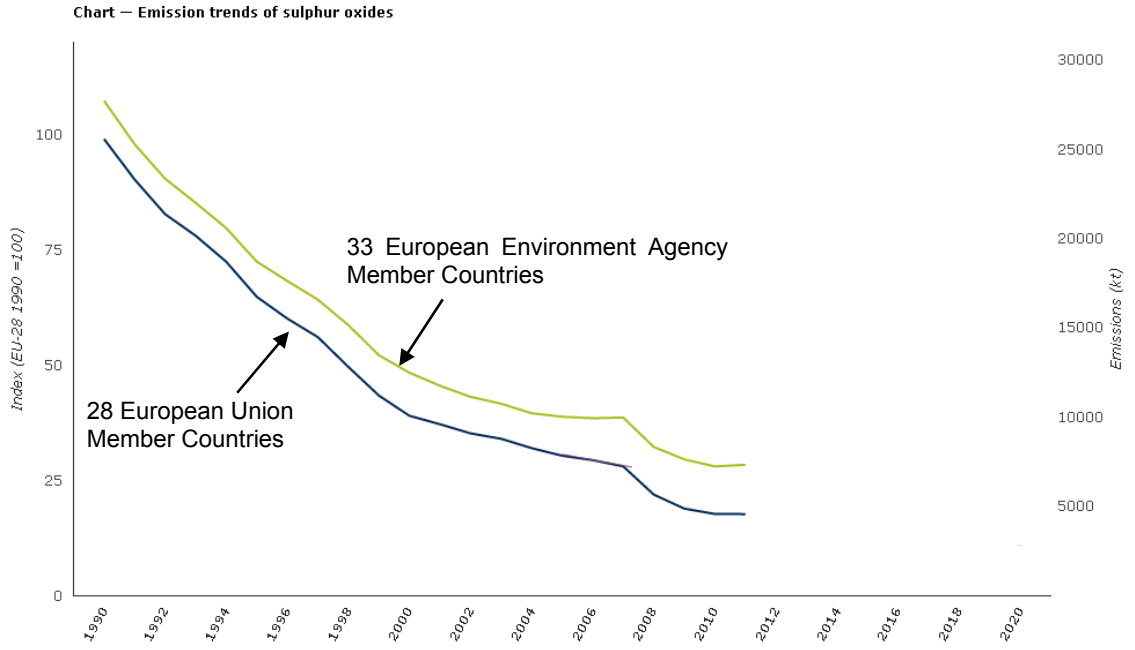
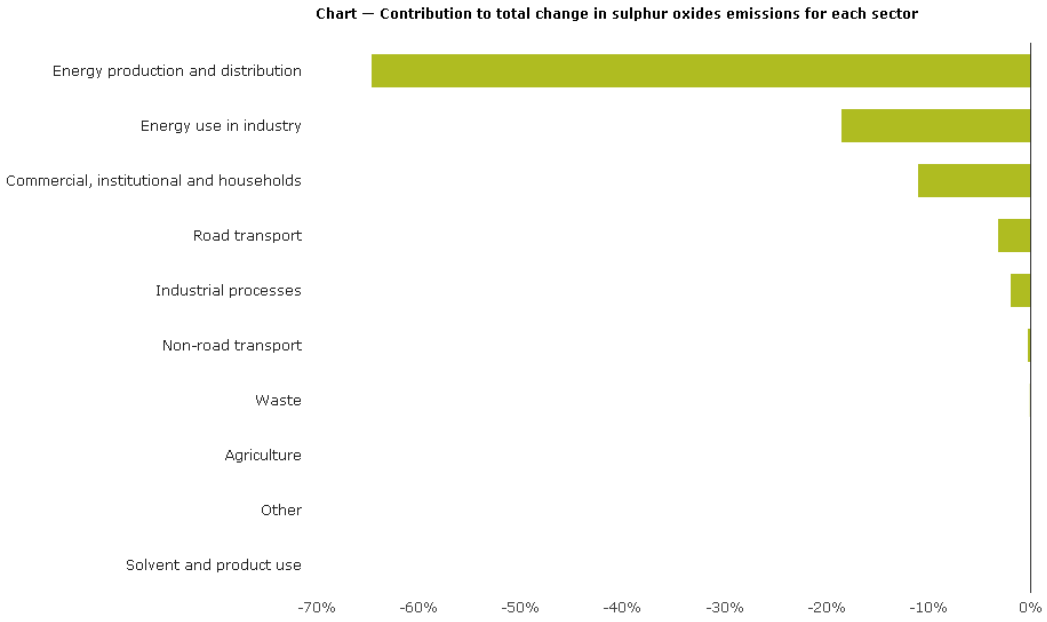


Figure 5 Sector contributions to the 1990-2011 emissions decline of SOx in Europe (EEA, 2014)



The declines in European SO_2 emissions mirror those from other regions of the world. In fact, modeling studies have shown that many countries, including the United States, Canada, Russia, Korea, and Latin America have experienced notable declines in the release of anthropogenic SO_2 for the period from 2000 to 2010 (Klimont et al., 2013, Ray and Kim, 2014). These same models also predict that in the absence of new legislation, global emissions of SO_2 will decline up to 10% more by 2030 (Amann *et al.*, 2013). This number would be much higher if greater strides could be made in India and China where SO_2 emissions have either risen steadily or fluctuated based on the trade-offs between economic growth and environmental policy (Lu *et al.*, 2011). India is perhaps the most intractable case since it has seen a large increase in energy consumption with no new initiatives to constrain emissions. However, the total SO_2 emissions of 32,673 tons from China were more than 5 times higher than those from India in 2005 (Smith *et al.*, 2011). In fact, China alone accounted for about 28% of the total global anthropogenic emissions of SO_2 in 2005, but these levels have been declining in recent years with decreasing residential coal use and the passage of legislation that requires power plant flue gas desulphurization (Su *et al.*, 2011).

The declines in SO_2 emissions in many regions of the world are reflected in the documented downward trends in ambient air concentration. For instance, South Korean cities have witnessed a 3-5 fold reduction in SO_2 for period from 1989-2010 (Ray and Kim, 2014). Interestingly, SO_2 in these Korean cities still show a high degree of correlation with ambient air levels of total suspended particulates and carbon monoxide (CO). In Taiwan, yearly SO_2 reductions of 0.51 ppb (1.36 $\mu g/m^3$) have been reported for the years 1994 to 2003 (Chang and Lee, 2007). Reductions of similar magnitude have also been seen in Finland, where the annual average rate of decline was about 2.2% from 1994 to 2007 (Anttila and Tuovinen, 2010). In many areas of Finland, the ambient air concentration of SO_2 was approaching background

levels. Similar changes have reported in the United Kingdom, where SO_2 levels have declined by an average of 4.3% to 8.4% per year depending on the location of the monitoring site (Jones and Harrison, 2011). The ambient concentrations of SO_2 in industrial and rural regions of Portugal declined by 60% for the period from 1999 to 2002 (Pereira *et al*., 2007). These results are not atypical and are reflective of the conditions that prevail in many urban cites outside of Asia. The time may soon arrive when it will be difficult to conduct an observational study using central site monitoring data since in many areas outside Asia the ambient SO_2 levels are approaching the limit of quantitation for the analytical methods employed. This fact alone, calls into question the need to further regulate ambient SO_2 levels given the immense progress that continues to be made.

Air pollution guidance values are currently issued at regular intervals by the WHO and although the values have no legal standing, the values are very influential within EU government circles; often serve as a starting point for justifying a change to official policy on air limit values (WHO, 2006). As shown in **Table 3**, WHO issued their first SO_2 guideline values in 1979 as a concentration range aimed at protecting against respiratory symptoms and illness in adults and children (EHC, 1979). More recent evaluations have relied heavily on the plethora of epidemiology studies that have been performed. The 2005 guidance limits of 500 µg/m^3 for 10-min and 20 µg/m^3 for 24-hr have been in place for over a decade and there is some pressure to revise the 10-min value downward based on recent technical reviews performed under the REVIHAAP program (WHO, 2013a, WHO, 2013b). Indications thus far suggest that modifications may be made; but questions remain whether these changes are warranted given that ambient levels of SO_2 are a poor surrogate for personal exposure and the apparent weaknesses of the panel studies being used to justify any adjustment (Johns *et al.*, 2010, Sarnat *et al.*, 2007a). The inability of epidemiological studies to unequivocally show that the morbidity and mortality associations observed in single pollutant studies are robust to the inclusion of other pollutants such as PM_{10} suggest that SO_2 may be acting as a surrogate or marker for another combustion-related pollutant that is the true causative agent.

Table 3 Guideline values for SO_2 issued by the World Health Organization

Year	10-min value (µg/m^3)	24-hr value (µg/m^3)	annual value (µg/m^3)	Reference
1979	---	100 - 150	40 - 60	EHC, 1979
1987	---	125	50	WHO, 1987
2000	500	125	50	WHO, 2000
2005	500	20	---	WHO, 2006

3. ATMOSPHERIC CHEMISTRY

Sulfur dioxide is a primary air pollutant that is directly emitted from any combustion source using a fossil fuel, such as coal, petroleum, or natural gas, as an energy supply. Of available sources, the release of SO_2 and SO_3 from coal-fired power plants has attracted the most attention (Stevens *et al.*, 2012). Coal burning is the single largest man-made source of SO_2, accounting for about 50% of the annual global emissions, with oil burning accounting for an additional 25 to 30%. Other industrial sources include petroleum refining, metal smelting, and sulphuric acid production. Importantly, regulations restricting the sulphur content of automotive and marine fuels have minimized the impact of these two combustion sources on tropospheric SO_2 (Smith *et al.*, 2011, Tan *et al.*, 2009, Tao *et al.*, 2013). Primary biogenic sources of SO_2 include sporadic volcanic eruptions, biomass burning, and the release from high sulphur containing soils. Although volcanic eruptions are relatively rare, these are capable of releasing large amounts of SO_2 depending upon the stage of the eruption, with greater amounts often released during the early explosive stage when extensive degassing occurs (Mori and Kato, 2013). The global emissions of SO_2 from volcanic sources was estimated to be 26.7×10^6 tons/yr in 2005 (Diehl *et al.*, 2012). By comparison, the total anthropogenic release of SO_2 in China has been estimated to be 3.05×10^7 tons for the year 2005 (Su *et al.*, 2011). These amounts are far greater than those found in a recent inventory of SO_2 release from all types of agricultural and incidental biomass burning in China. For these events, an average yearly SO_2 release of 49,000 tons/yr was estimated to take place during a period lasting from 2000-2006 (Song *et al.*, 2009).

Although soil is typically a sink for atmospheric SO_2, certain types of acidic soils near costal waterways can act as an important regional source (Kinsela *et al.*, 2011). This source of SO_2 appears to originate from the bisulfite that is generated as water evaporates from the soil (Macdonald *et al.*, 2004). Air temperature is another important factor with daytime SO_2 fluxes from acidic soil being up to 16.5-fold higher than nighttimes emissions (Kinsela *et al.*, 2011). Other secondary sources of biogenic SO_2 have also been shown to exist that are associated with the atmospheric photo-transformation of precursor substances such as dimethyl sulfide (DMS), which is released into the atmosphere naturally from oceans through the action of phytoplankton (Gray *et al.*, 2011). Once released, DMS reacts rapidly with available hydroxyl radicals to produce SO_2 at an 85% yield (De Bruyn *et al.*, 2006). Measurements made with airplane flights over the Pacific Ocean have shown that DMS leads to the formation of SO_2 that is subsequently oxidized to sulfate aerosol (57%) or removed by dry deposition (27%) (Faloona *et al.*, 2009). As a result, DMS is an important source of SO_2 and accounts for 25% of the sulfate aerosols formed globally (Kloster *et al.*, 2006). The oxidation of natural and anthropogenic SO_2 leads to the formation of sulphuric acid that may have some effect on local and regional climate through the formation of cloud condensation nuclei (Woodhouse *et al.*, 2013). The release of SO_2 of all of these natural sources contributes to the background levels of SO_2 that are detected at remote locations.

The atmospheric chemistry of SO_2 has been extensively studied since the early 1970's and has been mapped out in great detail because of its role in acid rain formation and the biogeochemical sulphur cycle. Following release into the atmosphere, several different physical or chemical processes can occur depending on local weather conditions and chemical oxidant availability. The chemical processes include i) aqueous phase reactions; ii) gaseous phase reactions; and iii) heterogenous reactions on the surface of particles. The physical processes include

dissolution in rainwater or cloud droplets followed by wet deposition. Alternatively, dry deposition can occur through the direct adsorption of gaseous SO_2 onto vegetation and soil (Baumgardner *et al.*, 2002). All of these processes occur at a relatively rapid rate, which results in an SO_2 tropospheric lifetime ranging from 19 hours in the summer to 58 hours in the winter, which partly reflect differences in atmospheric oxidant level and moisture content for each of these seasons (Lee *et al.*, 2011a).

The gas phase reactions of SO_2 lead to the formation of sulphuric acid and sulfate aerosols as shown below in reactions 1 thru 4. The resulting ammonium sulfate can either lead to the formation of secondary aerosols that can be wet deposited during precipitation events or act as condensation nuclei leading to cloud formation. The initial gas phase reaction proceeds as shown in reaction 1 and involves any of several atmospheric oxidants including hydroxyl radical ($^{\bullet}HO$), hydrogen peroxide (H_2O_2), ozone (O_3), methylhydroperoxide (CH_4O_2), and peoxyacetic acid (CH_3CO_3H). Since the levels of these oxidants tends to be higher in the summer than in the winter, SO_2 is scavenged from the air more efficiently during the summer months leading to lower tropospheric concentrations at this time of the year. The hydroxysulfonyl radical ($HOSO_2^{\bullet}$) resulting from reaction 1 reacts with molecular oxygen under dry conditions to yield sulphur trioxide (SO_3) and hydroperoxyl radical ($HO_2^{\bullet}$) according to reaction 2. Sulphur trioxide together with SO_2 constitute the primary sulphur oxides (SO_x) released during fossil fuel combustion, but it does not have a long half life in moist air where it reacts quickly with water vapor to form sulphuric acid (Hewitt, 2001). Because of its low vapor pressure, sulphuric acid condenses onto aerosol particles or cloud droplets where it quickly dissociates to form sulfate aerosols. Once formed, the sulfate is free to react with atmospheric ammonia to yield ammonium sulfate aerosols via reaction 4.

$$SO_2 + HO^{\bullet} \longrightarrow HOSO_2^{\bullet} \qquad (1)$$

$$HOSO_2^{\bullet} + O_2 \longrightarrow SO_3 + HO_2^{\bullet} \qquad (2)$$

$$SO_3 + H_2O \longrightarrow H_2SO_4 \text{ (mist)} \qquad (3)$$

$$H_2SO_4 + 2NH_3 \longrightarrow (NH_4)_2SO_4 \qquad (4)$$

Another scheme for the gas phase reaction of SO_2 involves its direct photooxidation following activation by ultraviolet light. This pathway is shown is reaction 5 and is relatively slow compared to the other oxidation reactions shown above, but it may lead to appreciable amounts of sulphuric acid on bright sunny days with low photochemical oxidant levels.

$$2SO_2 + O_2 \xrightarrow{\lambda} 2SO_3 \qquad (5)$$

Aqueous phase reactions of sulphur dioxide are quite common and frequently occur in the water droplets found within clouds (Harris *et al.*, 2012). These reactions are faster than those in the gas phase and are responsible for the vast majority of sulfate formation in ambient air. The aqueous phase reactions are affected by the pH of the cloud water, which typically is less than 5. Under these conditions, the initial reaction involves the dissolution of SO_2 in the liquid droplet with the formation of sulphurous acid (H_2SO_3) that dissociates into bisulfite (HSO_3^-) and a hydrogen ion as shown in reaction 6. The resulting bisulfite reacts with hydrogen peroxide (H_2O_2) which is the primary oxidant in cloud water droplets under acidic conditions (Yang *et*

al., 2011). If the rain water is basic, the reaction proceeds through the action of dissolved ozone (O_3) rather than hydrogen peroxide.

$$SO_2 + H_2O \longrightarrow H_2SO_3 \longrightarrow HSO_3^- + H^+ \quad (6)$$

$$HSO_3^- + H_2O_2 + H^+ \longrightarrow SO_4^{2-} + 2H^+ + H_2O \quad (7)$$

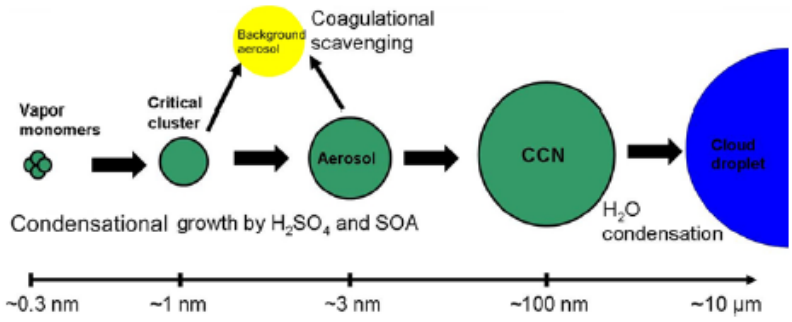
Heterogenous reactions also take place after SO_2 has adsorbed onto a mineral dust particle. Although the reaction scheme is similar to gas and aqueous phase reactions with ultimate formation of sulfate aerosols, the mechanism has been shown to differ with the intermediate formation of sulfite as shown in reaction 8. The final production of sulfate proceeds as shown in reaction 9 and involves the action of dissolved ozone or a similar oxidant (Li *et al.*, 2006). Although the rate limiting step in this reaction scheme is the relatively slow reaction of SO_2 with water, the entire process can still take place at a relatively rapid rate with an atmospheric half-life as short as 1-2 hour in a dust storm where there is an abundant source of particulate matter (Ullerstam *et al.*, 2002). The sulfate aerosols formed in these reactions often leads to the reduced visibility that accompanies haze formation (Wang *et al.*, 2012b).

$$SO_2 + H_2O \longrightarrow SO_3^{2-} + 2H^+ \quad (8)$$

$$O_3^{2-} + O_3 \longrightarrow SO_4^{2-} + O_2 \quad (9)$$

All three reaction sequences (gas phase, aqueous phase, and solid phase) lead to the formation sulphuric acid and/or sulfate aerosols that may be removed by wet deposition. Alternatively, the sulphuric acid may coagulate on preexisting particles or self-condense to form new particles through a nucleation reaction that is highly dependent on weather conditions and atmospheric concentrations (Bzdek *et al.*, 2012). As shown in **Figure 6**, the sulphuric acid clusters may then form sulfate aerosols that can serve as condensation nuclei (CCN) for cloud formation and growth (Westervelt *et al.*, 2013). These processes are important because aerosols and clouds can impact climate and radiative forcing both directly and indirectly by scattering incoming solar radiation back into space. This results in a net cooling effect that can partly offset the changes caused by greenhouse gasses.

Figure 6 Pathway for particle growth and the formation of cloud condensation nuclei (CCN) and cloud water droplets from sulphuric acid mist and secondary organic aerosols (SOA) (Westervelt et al., 2013)

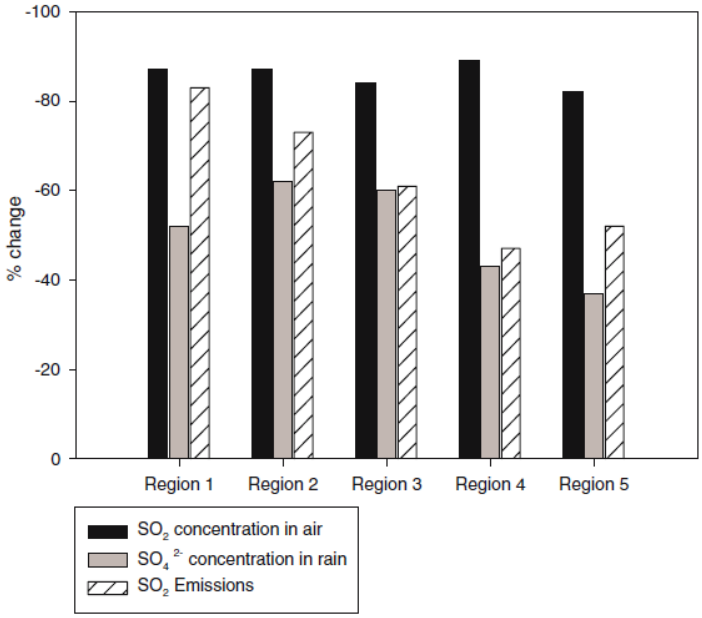


In Europe, the radiative forcing by sulfate aerosols peaked in the 1980s and has been on the decline ever since due to policies and regulations that have restricted

SO_2 emissions (Marmer *et al.*, 2007). In fact, recent modeling indicates that relative to 2005, current and planned SO_2 reduction policies will result in an additional 30% decline in radiative forcing by sulfate by 2030 (Pere *et al.*, 2012). These findings are not surprising given the large percentage of sulfate aerosols formed from the gas phase (36%) and aqueous phase (64%) reactions of SO_2 (Chin *et al.*, 2000). Overall, the urban conversion ratio for sulfate formation from ambient SO_2 has been shown to average 7.6% and 16.8% for the winter and summer seasons, respectively (Khoder, 2002).

A disproportionate change in the wet deposition of sulfate and dry deposition of SO_2 has also been shown to be taking place in Europe that has been difficult to attribute to any single atmospheric condition. As seen in **Figure 7**, despite continuously declining atmospheric levels of SO_2 in the five regions of Europe, the loss of sulfate via wet deposition has not kept pace with the SO_2 concentration declines, which have exceeded sulfate wet deposition losses by 10-30% over a twenty year period beginning in 1980 (Fowler et al., 2007). The dramatic decline in European SO_2 levels has not affected the inter-annual, seasonal, weekly or diurnal concentration patterns. For instance, an examination of the hourly SO_2 levels in six European cities in 2009 have shown that compared to 1993 there was still an early morning peak of SO_2 during the weekdays and higher weekday than weekend levels (Henschel et al., 2013). The cause of the disproportionality between SO_2 concentration reductions and SO_2 emission changes and sulfate rainwater concentrations is not known with any certainty, but it may be related to perturbations in oxidant availability that are associated with co-reductions in ammonia emissions (Banzhaf et al., 2013).

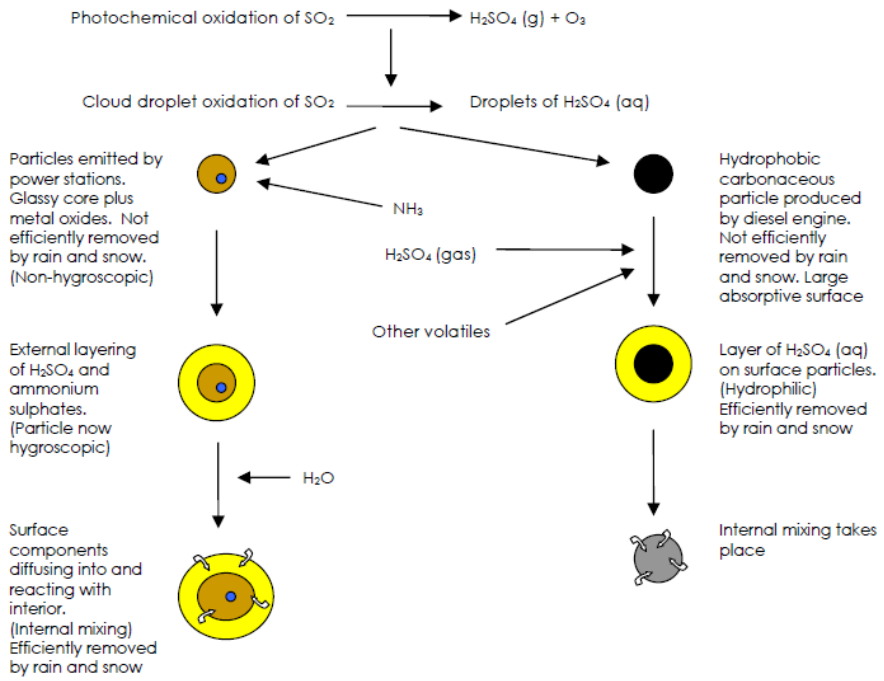
Figure 7 Changes in the ambient air levels and emission of SO_2 and rainwater sulfate in five regions of Europe for the period 1980-2000 (Fowler et al., 2007)



Although many of the reaction schemes depicted above lead to the formation of sulphuric acid and the subsequent dissociation and release sulfate aerosols, the

fate of these aerosols is a function of local atmospheric conditions and the type of particulates providing an adsorptive surface. The left side of **Figure 8** depicts the interaction of SO_2 with the carbonaceous particulates from diesel exhaust, whereas the scheme on the right shows the adsorption onto the hydrophobic particulates from a power plant plume. In both cases, the adsorption of H_2SO_4 leads to the formation of a hydrophilic particulate that can be scavenged and removed by wet deposition; however, the physical and chemical properties of each particulate type are quite different, so the propensity for wet deposition following absorption is not the same for both pathways.

Figure 8 Pathways to particulate sulfate aerosol following the oxidation of ambient SO_2 (COMEAP, 2009)



4. EXPOSURE DETERMINATION

4.1. SPATIAL HETEROGENEITY

Epidemiology studies with SO_2 have traditionally relied on measurements from central monitoring sites as a surrogate for personal exposures. These measurements are, however, notoriously unreliable and often provide an underestimate or overestimate of the actual exposure levels because of the spatial variability that SO_2 and other primary pollutants exhibit in urban locations where nearby emission sources, local terrain, and weather conditions can change dramatically over a small geographical domain (Goldman *et al.*, 2011a, Wade *et al.*, 2006, Wheeler *et al.*, 2008). An examination of monitor-to-monitor correlations for SO_2 levels in the city of New York showed relatively poor correlation and low precision suggesting that the simple reliance on the values from monitoring stations could bias risk determinations especially in short-term time-series studies (Ito *et al.*, 2007). An evaluation of SO_2 variability in Rio de Janeiro found that local source emission, air temperature, and humidity all contribute to the spatial changes observed across the city (Zeri *et al.,* 2011). Likewise, a study of spatial variability in Sarnia, Ontario found that industrial land use within 1600 m and roadway proximity within 100 m were major determinants of the SO_2 concentration at a particular urban location (Atari *et al*., 2008). Uncertainties in the SO_2 exposure measurements used in observation studies are due in part to the placement of centrally located monitoring sites, which is generally dictated by regulatory factors rather than a desire to understand local variability in ambient air levels (Ibarra-Berastegi *et al.*, 2009, Matte *et al.*, 2013). In addition to these spatial concerns, there are seasonal variations in SO_2 levels that need to be captured in order to accurately assess exposures for long term studies that may take place over a period of years. Since ambient levels of SO_2 are generally higher during the winter months in the northern hemisphere due to the increased use of fossil fuels and lower atmospheric oxidant levels, any determination of annual exposure levels needs to consider seasonal fluctuations (Chen *et al.*, 2001). Those studies that estimate annual average exposures based on a limited number of measurements during a single season will contain an inherent positive or negative bias depending on which season was chosen to calculate the average concentration.

4.2. EXPOSURE BIAS

The spatial variability inherent in SO_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. This calls into question the use of central site monitoring data as a basis for estimating personal SO_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). In fact, some have argued that the likelihood of a statistical false positive in a hypothesis driven observational study is far more probable than a non-differential error with a bias toward the null (Burstyn *et al*., 2014).

Two types of exposure misclassification can exist in observational studies; classical random error (i.e. non-differential) and Berkson error (i.e. 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*., 2011b, Strickland *et al*., 2015). An important consideration, however, is the true ability of outdoor measurements from ambient monitoring sites to actually represent personal exposures.

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 (Steinle *et al*., 2013). Since many epidemiological studies with SO_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 (Butland *et al*., 2013). 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 and indoor sources of SO_2. 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 (Lash *et al*., 2014, Spiegelman, 2010, Zeka and Schwartz, 2004).

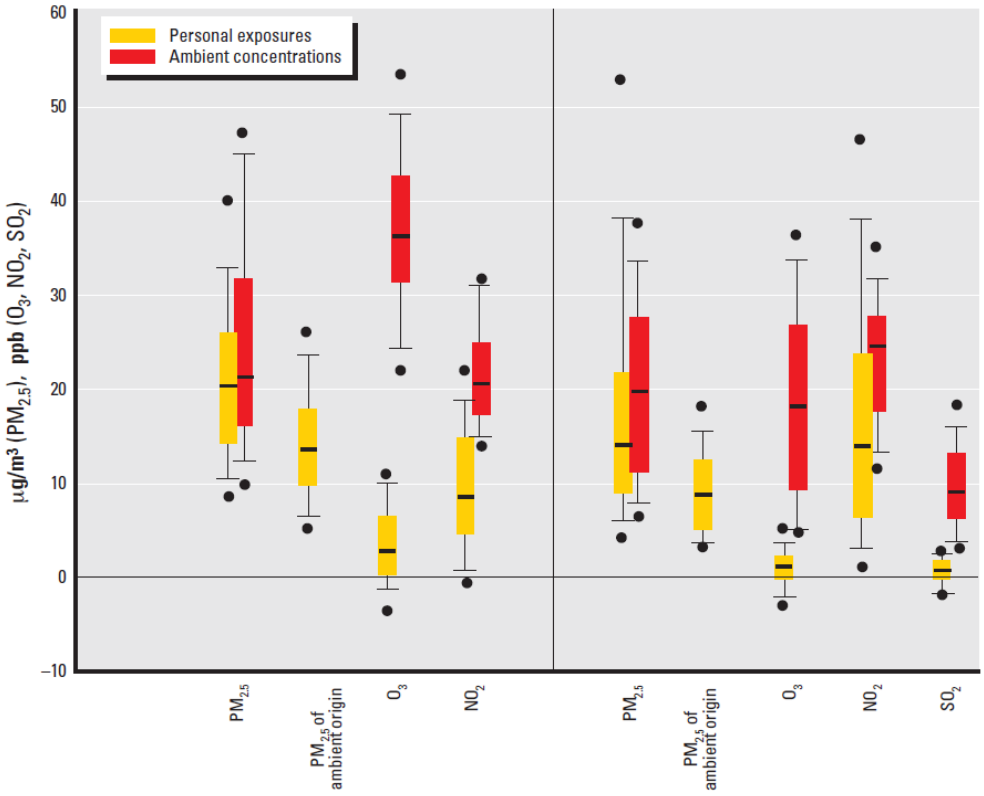
Exposure misclassification occurs in nearly every epidemiology study and efforts to control for its impact have steadily improved over the last decade, but problems still remain with many investigators unwilling to invest the added effort needed to acquire validation data (Jurek *et al*., 2006). Consequently, there is an often assumed non-differential bias towards the null in the 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 the monitoring network and the number of sites that were included in the exposure modeling. 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 an important factor that influenced how many of the studies were ultimately rated for 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 locations, or if the sites were situated in an area that was not representative of the study population (see **Table 1**).

4.3. PERSONAL EXPOSURES

The optimal approach to eliminating the exposure uncertainties associated with central monitoring site measurements is the collection of personal exposure data. A survey of the literature revealed that a sizable number of studies have documented personal exposure levels of SO_2 in members of the general public. These studies indicate that personal exposures to SO_2 are far lower than outdoor air concentration measurements taken at a central monitoring site. The first study to intensively examine the bias caused by the use of exposure estimates from central monitoring sites was performed in Boston in 1988 (Brauer *et al.*, 1989). Collection of multiple personal 24-hr SO_2 exposure measurements from two volunteers yielded an average value of about 1 ppb (2.7 $\mu g/m^3$), which was approximately 5-times lower than the 24-hr measurements from a central monitoring site. Indoor measurements of SO_2 were only slightly higher than the personal exposure measurements, which is consistent with the high percentage of time the individuals spend indoors. Although the outdoor home concentration of SO_2 was lower than the values obtained from the central monitoring site, this differential was attributed to the shorter sampling duration (daylight hours only) for outdoor home measurements relative to the central site. A 1999 wintertime study in the city of Baltimore found that the 24-hr integrated personal exposure levels of SO_2 over a 12 day period yielded an undetectable amounts of SO_2 (max. 1.5 ppb) whereas the ambient air levels at a single monitoring site averaged 8.9 ppb (23.7 $\mu g/m^3$) (Sarnat *et al.*, 2000). The authors noted that 70% of the personal samples were below the detection limit of 6.5 ppb (17.3 $\mu g/m^3$). These studies were confirmed and expanded upon in a subsequent study in the same city (Sarnat *et al.*, 2001). The results from this study are depicted in **Figure 9** and show that personal 12-hr time-weighted average exposures to SO_2 averaged about 1 ppb (2.7 $\mu g/m^3$) versus an average value of about 9 ppb (23.9 $\mu g/m^3$) at a nearby monitoring station. In fact, the study found a significant negative association between wintertime personal SO_2 levels in 45 individuals and the local ambient air concentration. Surprisingly, there was a good correlation between personal $PM_{2.5}$ measurements and ambient SO_2 levels. This relationship raises the specter that SO_2 is merely serving as a surrogate for personal $PM_{2.5}$ in those studies investigating its association with acute and chronic health effects.

Figure 9 Distribution (5th, 10th, 25th median, 75th, 90th and 95th percentiles) of personal exposure measurements and ambient air measurements for summer and winter seasons in Baltimore 1998-1999 (Sarnat et al., 2001)



Studies showing low personal exposures to SO_2 in Baltimore have been duplicated in other U.S. cites. A monitoring program conducted in Boston using 43 children and adults found that over 95% of the personal 24-hr SO_2 exposure measurements were below detection limits of 3.2 and 2.3 ppb (8.5 and 6.1 µg/m^3) during the winter and summer, respectively (Sarnat *et al.*, 2005). The mean personal exposure level in the remaining samples was less than 1.9 ppb (5.1 µg/m^3), whereas the comparable outdoor levels ranged from 2.8 to 10.7 ppb (7.4 to 28.5 µg/m^3). As such, there was no correlation between the personal SO_2 exposure concentrations and ambient outdoor levels. As in the earlier study, outdoor SO_2 levels correlated well with personal exposures to $PM_{2.5}$ during the summer, but not the winter, seasons. Another sampling program was performed in Steubenville, Ohio over a 23 week period using 15 volunteers who were personally monitored for SO_2 levels over a 24-hr period during the summer and fall seasons (Sarnat *et al.*, 2006). Personal exposures to SO_2 averaged 1.5 ppb and 0.7 ppb (4.0 and 1.9 µg/m^3) during the summer and fall seasons, respectively; whereas the levels at a nearby outdoor monitoring location were 2.7 ppb and 5.5 ppb (7.2 and 14.6 µg/m^3). The authors reported that the number of personal samples below the limit of detection was 53.5% and 36.1% for the summer and fall seasons, respectively. Unlike the previous studies, a significant relationship was observed between personal SO_2 levels and ambient outdoor measurements but only for the fall season. In addition, a weak but significant association was observed between ambient SO_2 level and personal $PM_{2.5}$ exposures, as was noted in other studies from this series. As before, the authors

reiterated their belief that ambient outdoor SO_2 measurements were not suitable for use as proxies of personal exposure especially in short-term time-series studies.

The reliability of using single day SO_2 measurements to estimate personal exposures was investigated in 50 individuals residing in Yeochun, Korea (Lee *et al.*, 2004). The results showed that 31% of individual SO_2 measurements were misclassified as being high or low when relying on personal exposure measurements collected on a single day rather than a much longer 2-week time frame. Although these data indicate that temporal variability may lead to misclassification of SO_2 personal exposures, they do not provide any insight on the spatial variability that is known to exist. Taken together, these studies of personal SO_2 exposures indicate that the levels are far lower than those measured at central monitoring sites and that the monitoring site values are poor surrogates of the actual exposures taking place during a 24-hr period.

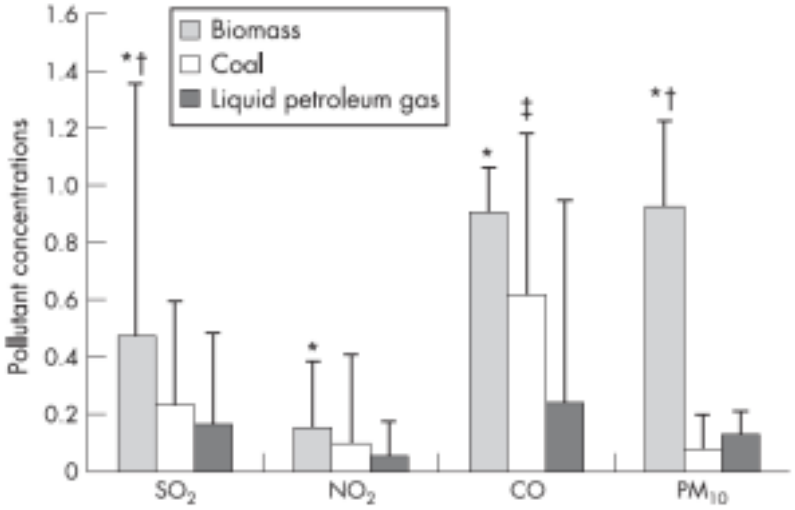
Ordinarily, the overestimates of personal exposure afforded by the use of monitoring site measurements would result in a non-differential error and an underestimate of risk in an observational study. However, with SO_2 the circumstances are far more complex since the magnitude of the ambient and personal exposures are often close to the limit of quantitation for many analytical methods. It is highly unlikely that these low level personal exposures to SO_2 can account for the associations that are often observed in time-series and cohort studies, so alternative explanation must be entertained (Sarnat *et al.*, 2007b). The most probable reason for any observed relationships between ambient SO_2 levels and a targeted health effect is more likely to be related to the collinearity of SO_2 with another unknown or unmeasured contaminants found in the ambient air. This possibility has been acknowledged in the 12-city APHEA mortality study where the authors recognized that the excess mortality associated with ambient measurements of SO_2 was likely the result of a surrogate effect (Katsouyanni *et al.*, 1997). In the face of this possibility, it is necessary to take a very skeptical view of those studies purporting to show an association between ambient SO_2 levels and a particular health effect. In all likelihood, these studies are suffering from a serious exposure bias that fails to consider the extremely low personal SO_2 exposure concentrations that most individuals from the western world experience on a routine basis.

4.4. INDOOR EXPOSURES

A conspicuous problem with many epidemiology studies focusing on the acute health effects of SO_2 is the failure to consider indoor air levels. Time activity evaluations have shown that Europeans spend a high percentage of their time indoors at home, so it is important to account for any indoor/outdoor concentration differences that may exist. Measurements across seven regions of Europe have shown that the time spent indoors can range from 56 to 66% and that factors such as gender and work status are important determinants of the regional variability found to exist (Schweizer et al., 2007). This is a particularly important exposure determinant for SO_2 because indoor levels of SO_2 can vary dramatically depending upon the type of fuel used for heating and cooking. Although indoor levels of SO_2 in Europe and North America are generally lower than outdoor levels by at least a factor of two, these differences are not universally observed in all regions of the world (Andersen, 1972, Kindzierski and Sembaluk, 2001, Spengler *et al.*, 1979). The use of some solid and liquid fuels that have high sulphur content can release a substantial amount of SO_2 into the air and result in indoor/outdoor SO_2 ratios that are substantially greater than 1. Under these conditions, the SO_2 exposure measurements form central monitoring sites will yield an underestimation of the true

exposure and an overestimation of the association with the particular health effect being examined. Of particular concern are studies originating from China and India where the indoor use of fuels such biomass materials (wood charcoal, crop residues, and animal dung), coal, and kerosene can lead to high indoor air levels of SO_2. For example, as summarized in **Figure 10**, a study performed in an urban and rural province of China found that indoor air levels of SO_2 in the kitchen of non-smoking homes using either biomass briquettes or coal as a cooking fuel were appreciably higher than those homes that used liquefied petroleum gas (LPG) (Liu et al., 2007b). In fact, regardless of the fuel type, the average levels in the kitchen often exceeded 500 $\mu g/m^3$, which was generally about ten-fold higher than the levels found outside. The findings from this study were confirmed in others which found that the concentration of SO_2 in the kitchens of homes that used biomass briquettes or low grade coal ranged as high as 780 and 800 $\mu g/m^3$, respectively (Isobe *et al.*, 2005). The levels of SO_2 in the major living quarters of homes using biomass briquettes or coal are typically higher in the winter months when these fuels are used for both heating and cooking (Jin *et al.*, 2005). These studies are important because they indicate the need to control for indoor fuel type when investigating the association of SO_2 with a particular health effect. Since potential confounding from indoor air sources of SO_2 is rarely if ever consider, those studies originating in developing countries where solid fuel use is common must be viewed with a high degree of suspicion (Heltberg, 2004).

Figure 10 SO_2 levels inside the kitchens of residents from two regions of China that used biomass briquettes, coal, or LPG as a cooking fuel (Liu et al., 2007b)



The other major contributor to indoor air levels of SO_2 is a reliance on kerosene. The use of kerosene for cooking and lighting is widespread in Africa, Asia, and Latin America with 500 million households still using this fuel source as the primary source of illumination (Mills, 2005). The indoor emission of SO_2 from the use of kerosene cooking devices has been well studied and the resulting indoor air levels are comparable to those seen following the use of cattle dung, wood or coal (Raiyani *et al.*, 1993). Indoor SO_2 measurements made in households using kerosene heaters, fireplaces, wood stoves, or gas space heaters found that the kerosene heaters could result in over a 30-fold increase in indoor air levels (see

Table 5) (Triche *et al.*, 2005). The use of kerosene heaters in these homes resulted in indoor SO_2 levels that were approximately 2-fold higher than the annual average concentrations measured at monitoring locations for Eastern United States during the same time frame (Kelly *et al.*, 2002). Other studies performed in Chilean homes have confirmed these findings and shown that the use of kerosene heaters resulted in indoor air SO_2 levels of 14.36 µg/m^3 (Ruiz *et al.*, 2010). By comparison, the use of LPG or compressed natural gas as a fuel source did not appreciably affect the indoor air concentration. Likewise, cigarette smoking does not appear to alter indoor SO_2 levels based on studies performed under semi-controlled conditions (Halios *et al.*, 2005). Surprisingly, the indoor/outdoor SO_2 ratio in homes located near an oil sand extraction and production facility in Alberta, Canada were not appreciably different from other urban or rural homes (Assimakopoulos *et al.*, 2008, Kindzierski and Ranganathan, 2006). The failure of SO_2 to accumulate in homes is surely associated with its rapid conversion to sulfate in air and the ability of some home furnishings to act as a sink for any SO_2 that may infiltrate the home (Ashmore and Dimitroulopoulou, 2009). These loss mechanisms are borne out by studies showing that i) 75% of the sulfate found indoors is the result of SO_2 oxidation and ii) cotton and wool fabrics as well as leather upholstery and emulsion-based paints are all good scavengers of indoor SO_2 (Leaderer *et al.*, 1999, Spedding, 1977).

Table 4 Median indoor air level of SO_2 in homes using any of four sources of heat during the winter of 1994-1995 in the Eastern United States (Triche et al., 2005)

Conditions	Median indoor air SO_2 levels (µg/m^3)			
	kerosene heater	fireplace	gas space heater	wood stove
no use	0.53	0.80	0.80	0.80
use	17.02	1.06	1.72	0.80
conc. ratio	32.7	1.3	2.2	0.0

Spatial variability can dramatically affect SO_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 SO_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 modeling 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 that can directly impact the exposure misclassification that affects the reliability of many health effect studies with SO_2.

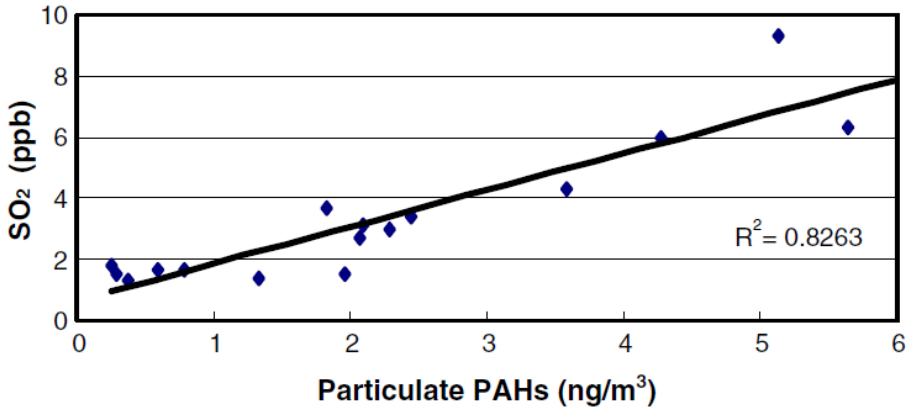
4.5. COLLINEARITY

A described above, a serious concern with studies purporting to show a change in relative health risk in relation to ambient exposure levels is the possibility that SO_2 is

merely serving as surrogate for another unidentified or unmeasured chemical. Whereas, the use of two-pollutant models can help to identify if this type of interaction is taking place, investigators often overlook or abandon this approach in favor of using a simpler single pollutant design. Although many authorities acknowledge that there may be proxy effects with SO_2, it is reasoned that any regulation of SO_2 will lead to a reduction of the target substance by virtue of their collinearity. This view, however, ignores the fact that the true relationship between the marker and the actual causative agent may not vary in a proportional manner at all exposure concentrations, and that reductions in SO_2 levels may have less than the expected impact on levels of the true causative agent.

There have been many instances where authors have been concerned that an observed relationship with SO_2 may actually be related to a secondary substance that varied in a collinear fashion. This concern is reasonable since studies have shown a particularly strong correlation between SO_2 and particulate levels. Of particular interest is recent research examining the relationship between ambient SO_2 and particulate PAHs, which has yielded some useful insight into the nature of the proxy effect with SO_2. The most compelling work was performed in Hiroshima, Japan and showed that a particularly high correlation existed between ambient SO_2 and total particulate PAHs (Tham *et al.*, 2008a). As shown in **Figure 11**, the coefficient of determination for the regression line shows that ambient PAH levels could explain 82% of the variance in simultaneously collected SO_2 measurements. When the PAHs were speciated, statistically significant Pearson correlations greater than 0.56 were observed for 10 the 13 PAHs examined, with the highest correlation of 0.92 observed for benzo(a)pyrene.

Figure 11 Correlation in urban SO_2 levels with ambient particulate PAHs (Tham et al., 2008a)



These findings were duplicated in a subsequent study performed in the same city (Tham *et al.*, 2008b). In this instance, a Pearson correlation coefficient of 0.88 was found between the particle-bound PAHs and ambient SO_2 levels suggesting that the two substances had a common emission source and dispersal pattern. This relationship, however, did not extend to the lower molecular weight PAHs found in the gas phase (Tsapakis and Stephanou, 2005). The sum total of 24 particulate bound PAHs detected in urban air samples collected in Heraklion, Greece were significantly correlated with winter time levels of SO_2 (r=0.65), but a similar relationship was not observed with the total of all gas phase PAHs (r=−0.34). The correlations were attributed to the co-release of particulate PAHs and SO_2 from

domestic central heating units during the winter. Strong wintertime associations of SO_2 with PAHs were also observed in a study performed at five locations in Greece and England where stronger correlations were observed during the winter season (r=0.24−0.48) than the summer season (r=0.05−0.37) (Vardoulakis and Kassomenos, 2008). In other studies from Kozani, Greece, the correlation of SO_2 with 16 particle bound PAHs was found to be stronger for fine $PM_{2.5}$ particulates (r=0.62) than for coarse PM_{10} particulates (r=0.40) (Evagelopoulos *et al.*, 2010). These results were consistent with the analytical results from a study performed in Athens, Greece where ambient SO_2 levels were more strongly correlated with $PM_{2.5}$ bound three and four ring semi-volatile PAHs (r=0.28) than non-volatile five or six ring PAHs (r=0.19) (Gini *et al.*, 2013). These results demonstrate the strong collinear relationship between outdoor SO_2 and particle bound PAHs and the very real possibility that health-related associations attributed to SO_2 may be in fact related to a polyaromatic substance that has adsorbed unto the surface of particulates in the atmosphere.

It is not unreasonable to assume that many of the SO_2-related associations observed in observational studies may be indicative of a proxy effect because SO_2 is so often correlated with the levels of other substances, particularly particulates (Chen et al., 2012a, Lee et al., 2000, Milutinovic et al., 2009). Noting a correlation coefficient of 0.74 between outdoor SO_2 and PM_{10} levels, Pereira *et al.* cited the possibility that the associations with intrauterine mortality may have been due to some other substance (Pereira *et al.*, 1998). In their examination of acute asthma exacerbations, Chew *et al.* found that ambient SO_2 and total suspended particulates (TSP) levels both showed significant associations with emergency room visits; however the statistically significant relationship between SO_2 and TSP (r=0.17) limited concluding statements regarding their relative importance (Chew *et al.*, 1999). An examination of the relationship between SO_2 levels and daily mortality in four Asian cities found that SO_2 was associated total, cardiovascular, and respiratory mortality; however there was a moderate to strong correlation (r=0.24−0.76) with both NO_2 and PM_{10} in all four of these cities (Kan *et al.*, 2010). Two pollutant modeling using SO_2 and either NO_2 or PM_{10} eliminated or attenuated the SO_2-related associations. A particularly insightful study of the association between ambient SO_2 and emergency room visits for cardiovascular disease in seven European cities found that the statistically significant relationship observed in a single pollutant model with SO_2 was entirely eliminated following a two-pollutant adjustment for CO, NO_2, PM_{10} or black smoke levels (Sunyer *et al.*, 2003b). The investigators noted that their findings were consistent with 10 of 13 other studies which found that and a two-pollutant adjustment for particulate levels eliminated any association observed with SO_2 using a single pollutant model.

Perhaps the single most important example of the confounding effect of co-pollutant exposures on the observed health-related associations with SO_2 exposures emerged from the APHEA 2 (Air Pollution and Health: A European Approach) study (Sunyer *et al.*, 2003a). This study examined hospital admissions for asthma, chronic obstructive pulmonary disease (COPD) and all respiratory diseases in 7 European cites. The authors found that a significant association existed between SO_2 levels and asthma in children aged 0-14 years, but the inclusion of CO (r=0.53) or PM_{10} (r=0.64) into the model resulted in non-significant associations with SO_2. This study reinforces the importance of viewing any reported association of SO_2 with an acute or chronic health effect with measured suspicion; especially when there has not been adequate control of the confounding influences from pollutants that vary collinearly with the SO_2 found in the ambient air.

The problems of collinearity are of such concern that epidemiologic studies suggesting a link between SO_2 levels and a particular health effect need to be very carefully examined to ensure that the possible influences of PM_{10} and $PM_{2.5}$ have been addressed. It is, therefore, imperative that any analysis and evaluation of the results from an observational study considers the associations observed for all criteria and non-criteria pollutants in order to identify key interrelationships that may be accentuating or masking the true nature of the observed relationships. Although methods such as principal component analysis, cluster analysis, and multi-pollutant modeling 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 will sometimes interpret their findings using a broad-based approach that examines the Spearman correlation coefficients for pair-wise exposure metric comparisons followed by an evaluation of the strength of any observed association in light of the correlation magnitudes that exist. This approach, however, is neither robust nor scientifically defensible when alternative methods are available that are more robust.

Given the 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 modeling that controls for the confounding effects of other pollutants using a multivariate model (Rushton, 2000). The preferred approach for assessing the impact of pollutant collinearity 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).

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 modeling exercises if the results were not appreciably greater 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 SO_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).

4.6. INSTRUMENT ERROR

The exposure misclassification caused by an overreliance on measurements form central monitoring sites is compounded by the fact that the analytical methods used to measure SO_2 have been shown to give biased determinations especially at the lower end of the concentration range. Until 2012, the European Monitoring and Evaluation Programme (EMEP) used three different methods to detect ambient

levels SO_2. Two involved periodic measurements using solutions of hydrogen peroxide (H_2O_2) or potassium tetrachloromecurate (TCM) to trap the SO_2 as a sulfite complex that then reacted with p-rosaniline to form a stable dye that could be measured colorimetrically. A third method employed a pulsed ultraviolet fluorescence (UVF) analyzer to measure SO_2 levels on a continuous basis. EMEP has performed a series of field investigations over the years to investigate the performance of SO_2 monitoring methods relative to a reference method that could be set up to run in parallel with the particular method being evaluated at a selected monitoring station. The results from these studies revealed that all of the methods suffered from some degree of interference especially at ambient air levels near the limit of detection (Aas and Semb, 2001). The wet chemistry method using an H_2O_2 solution as an adsorbent showed the worst performance with the degree of positive bias dependant on the site being evaluated. On average, an error of 16% was observed for this method, but for some locations the H_2O_2-based method yielded results that were very poorly correlated with the reference method throughout the operable concentration range (Aas *et al.*, 2007). The TCM adsorbent was only modestly better, but the results varied depending on the amount of time taken to deliver the liquid samples to the laboratory for analysis. In general, however, the TCM method gave results that were biased low relative to the reference method. In some cases, the TCM method yielded SO_2 values that were judged to be completely unreliable. The cause seemed to be related to the non-specific adsorption of secondary oxidants such as ozone that interfered with dye formation.

Since 2012, the wet chemistry methods described above for ambient air SO_2 have been largely replaced by automated continuous measurements that use pulsed UVF for quantitation. Yet, even this state-of-the-art approach has been shown to give imperfect results. When the reference method was taken to five monitoring sites that used the UVF approach, four of the five sites showed an average positive bias of 18%, which was felt to be caused by interference from nitric oxide in the ambient air. In addition, frequent maintenance and recalibration was needed to obtain reliable results with the UVF method. A positive bias was also observed in two of five monitoring sites in Finland that used the UVF technique (Leppanen *et al.*, 2005). In these instances, an average bias of 8% and 12% was observed, with the most reliable results coming from a site that was frequently visited for maintenance and calibration. The preceding information has important implication for the exposure misclassification and error that can accompany studies using measurements form central monitoring sites. For those epidemiology studies performed in Europe before about 2010, there is a high likelihood that methodological errors have contributed to the exposure misclassification caused by the use central monitoring site measurements. This is especially true if the measurements yielded values that were at or near the limit of quantitation.

4.7. PROXIMITY DETERMINATIONS

The exposure misclassification caused by the use measurements from fixed monitoring sites can be partially corrected through the application of a proximity adjustment. Several different methods are available for making this correction, but these have not been widely used in past observational studies with SO_2. For example, Son *et al*. used measurements of exposure from central monitoring sites in conjunction with several different methods for spatial interpolation to investigate the association of ambient SO_2 levels with measures of lung function (Son *et al.*, 2010). The authors examined the relative accuracy of using three different approaches for correcting the SO_2 concentrations for the distance from the residential location to the monitoring site. A comparison of inverse distance weighting, ordinary kriging,

and use of the nearest monitor value rather than an average from all monitors revealed that the most accurate results were obtained using the kriging approach. This method provides weighted estimates of exposure that take into consideration and corrects for the autocorrelation that may exist when nearby monitors are located close together. All of these methods rely of geocoding of residential addresses to provide an accurate estimate of the distance between the monitoring site and the residential location. As a result, the exposure estimates are obtained for an individual rather than a sample population so these methods are all well suited for use in cohort studies rather than those with an ecological design.

Since the collection of personal exposure data is cost prohibitive in epidemiology studies where hundreds if not thousands of individuals are examined, researchers seeking more robust approaches need to adopt more refined modeling techniques. **Table 4** provides a list of these alternative exposure modeling techniques. Unfortunately, however, these methods have been rarely applied in epidemiology studies with SO_2, so many of the studies published since 2005 are still constrained by the exposure misclassification that comes with the use of estimates from central monitoring sites. There has been some trend towards the use of more modern methods such as land use regression (LUR), but unlike their rapid adoption for use in NO_2-related health effects studies, LUR has been slow to arrive for SO_2. Exposure misclassification due to spatial variability can be dramatically reduced but not entirely eliminated through the use of use land use regression (LUR) models that use geocoding and spatial mapping techniques to account for the differences at each residential locale (Amini *et al.*, 2014). This method, however, does not account for the temporal changes in ambient air levels that may occur over time. As a result, LUR models are better suited for use in short term time-series studies rather than chronic cohort studies, which require the time consuming re-construction and re-validation of the model for each of the time periods being examined (Gulliver *et al.*, 2011). Because of the expertise required to construct LUR models, they have not been widely used to reduce exposure bias in SO_2 observational studies. This will undoubtedly change as more and more researchers come to recognize the value of using LUR to account for spatial heterogeneity in SO_2 exposure levels in complex urban settings (Clougherty *et al.*, 2013).

Table 5 Comparative analysis 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 Emissions from point sources 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 Emissions from point sources Meteorology Monitoring measurements Topography	High	GIS Statistics Monitor experts	Equipment: high Software: high Personnel: high	Emphasis on Process	Medium

Model	Theory concept match	Limitations to health studies	Data requirements	Need for updated data	Software expertise	Overall implementation cost	Marginal benefit	Transferability
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.

Land use regression models and other more advanced exposure modeling techniques are not, however, a panacea. Many problems still remain with the use of measurements from central monitoring sites. For instance, when using LUR methods 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.*, 2012a). A minimum of 80 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. Some have noted that correlation coefficients can be inflated by 50% or more if an independent data set is not used for validation (Johnson *et al.*, 2010). As noted earlier, another drawback to the use of LUR models is their inability to account for temporal variably, which some have corrected for by constructing separate models for discrete time periods lasting up to several years (Cesaroni *et al.*, 2012, Eeftens *et al.*, 2011).

5. EPIDEMIOLOGY SYNOPSIS

The following section summarizes the findings from the detailed examination of SO_2-related epidemiology studies published since 2005. Pertinent Information regarding the conduct and findings from each study can be found in **Appendix B**. **Appendix A**, in contrast, provides contains detailed summaries for a sample of studies rated as moderate quality, low quality, or inadequate. The studies in both Appendices have been segregated according to exposure duration and endpoint with acute and chronic mortality studies separated from those looking at a particular outcome such as asthma or birth defects. The quality of each investigation was determined using the GRADE system as described in the Introduction. 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, human panel, case-control, and cohort studies. Preference was given to those studies that incorporated a multi-pollutant design, advanced exposure assessment methodologies, a large study population or a multi-city appraoch, and an evaluation of the covariance between SO_2 and PM_{10}/$PM_{2.5}$.

5.1. ACUTE MORTALITY

The literature search identified a total of 28 new acute mortality studies that had been published since 2005. All but two of these studies were judged to be insufficient or of low quality using the GRADE system. The most common problems were the severe exposure bias associated with a reliance on measurements from a limited number of monitoring stations to describe the exposures, the small number of cases examined, and the absence of any multi-pollutant modeling to account for the covariance with other combustion-related pollutants such as PM_{10} and $PM_{2.5}$. The two studies of moderate quality were notable because they included two-pollutant modeling, possessed a large sample size, and evaluated the degree of collinearity with particulates. Importantly, these two studies were not downgraded for the exposure misclassification resulting from the unsubstantiated use of central site monitoring measurements as a proxy for personal exposures since this was a serious problem for all of the observational studies examined. In fact, it could be argued that every observational study using measurements from fixed sites are inherently flawed and unsuitable for use in a hazard determination.

The two “moderate quality” acute mortality studies with SO_2 have some properties in common. The paper published by Park *et al.* contained a robust assessment of the relationship between SO_2 exposure and acute mortality from non-accidental, cardiovascular, or respiratory causes stratified by ambient temperature (Park *et al.*, 2011). A significant association was observed with non-accidental mortality using a single-pollutant model, but it was not robust to the inclusion of PM_{10}, NO_2, or CO at either of three temperature tertiles. Likewise, single pollutant modeling of cardiovascular and respiratory mortality revealed significant associations at the highest ambient temperature tertile, but this was rendered insignificant using a two-pollutant model with PM_{10}. In contrast, the study by Guo *et al.* focused on all cause mortality in a retrospective time-series study. The authors found that the statistically significant associations found with a single pollutant model were not robust to the inclusion of PM_{10}, $PM_{2.5}$, or NO2 in two or three pollutant models (Guo *et al.*, 2013). The Spearman correlation coefficients between SO_2 and $PM_{2.5}$, PM_{10}, and NO_2 were 0.32, 0.44, and 0.60, respectively. These studies demonstrate the importance of using a multi-pollutant modeling approach when investigating the relationship of

ambient SO_2 levels with acute mortality when the evidence suggests a moderate to high degree of collinearity.

Although there have been several recent meta-analyses that have pooled the results from past mortality studies with SO_2, both failed to consider the quality of the evidence as a prerequisite for inclusion in the analysis. Meta analyses are essentially mathematical exercises aimed at improving statistical power by combining the result from individual studies. Ideally, the studies selected for analysis have undergone some degree of pre-screening to isolate those which fail to meet minimum quality standards. This is rarely the case in the air pollution arena, however, and oftentimes all available single pollutant and multi-pollutant studies are incorporated into the same meta analysis regardless of the bias and confounding that may exist. In the case of SO_2, two meta analyses have been published which combined the results from available acute mortality studies. Shang *et al.* examined 13 non-accidental mortality studies, 12 respiratory mortality studies, and 17 cardiovascular mortality studies performed in China and published from 2003 to 2012 (Shang *et al.*, 2013). The authors found statistically significant pooled relative risk estimates of 0.81, 1.18, and 0.85% for non-accidental, cardiovascular, and respiratory mortality, respectively. Time-series and case-crossover studies were both included and a random-effects model was adopted when tests for heterogeneity indicated a high degree of variance. Aside from the selection bias associated with the inadequate quality determination, the Shang *et al*. meta analysis suffered from a lag bias. This occurred because the authors did not fix the lag period across all of the studies, but instead selected the findings showing the most significant risk regardless of the lag period. This approach distorts the analysis and increases the likelihood that a significant association will be observed.

Atkinson *et al.* pooled the results from 15 all cause, 7 respiratory, 9 cardiovascular, and 4 chronic obstructive pulmonary disease (COPD) mortality studies conducted throughout Asia and reported the random effects modeling results per a 10 $\mu g/m^3$ increase in SO_2 (Atkinson *et al.*, 2011). The evaluation used the results from single-pollutant models and the lag period was allowed to fluctuate across the individual studies in order to capture the value that was the most statistically significant. The results of the meta analysis demonstrated that a statistically significant association existed between SO_2 ambient air levels and all four mortality causes. A meta analysis using the results from multi-pollutant models indicated that the mortality estimates associated with SO_2 exposure were not robust to the incorporation of a second pollutant (Anderson *et al.*, 2007). Although this analysis was restricted to 5 multi-city studies and did not examine the full range of multi-pollutant modelling possibilities, the results indicated that a surrogate effect is probable, with SO_2 acting as a marker for another chemical agent. The present literature review of acute mortality studies with SO_2 found a very high percentage of single-pollutant modelling studies that did not provide sufficient grounds for making any adjustments to SO_2 limit values. Those studies that did incorporate a multi-pollutant design often failed to show a relationship between SO_2 and any type of acute mortality. Until such time that personal exposure relationships and co-pollutant interactions can be fully explored, any and all single pollutant mortality results should be viewed with suspicion.

5.2. CHRONIC MORTALITY

A total of six studies were identified that focused on the relationship between long-term SO_2 exposure and chronic mortality from any of several causes. The majority of these cohort and case-control studies were found to be inadequate or of low

quality because they failed to consider two or three-pollutant interactions. Of the two studies that incorporated a two-pollutant design, one was judged to be of moderate quality using the GRADE criteria (Hart *et al.*, 2011). The study by Hart *et al*. examined chronic mortality in truck drivers from all causes, lung cancer, respiratory disease, cardiovascular disease, and COPD. A total of 53,814 subjects located throughout the U.S. were included in the cohort. Occupational exposure information together with residentially geocoded ambient air measurements were used to determine overall exposure to SO_2. Although statistically significant associations were observed using single-pollutant models, none were found after including PM_{10} and NO_2 measurements into a three-pollutant model. The most serious limitation of this study was the failure to consider cigarette smoking, second-hand smoke, or preexisting comorbidities as potential confounders. These deficiencies were offset by the multi-pollutant modeling that was performed and the inclusion of an extended set of mortality causes that included lung cancer mortality. These considerations helped improve the overall reliability of the study 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 the overreliance on the results from single pollutant models.

Although there have not been any recent pooled estimates of the association between SO_2 exposures and chronic mortality, several ancillary studies support the absence of any association with chronic mortality causes. For instance, Eitan *et al.* constructed spatial maps of cancer incidence rates around Haifa, Israel and failed to note any relationship with the spatial patterns of SO_2 over the same area (Eitan *et al.*, 2010). Likewise, a well conducted single pollutant study (NLCS-AIR Study) performed in The Netherlands failed to show any association between SO_2 levels and natural cause, cardiovascular, respiratory, lung cancer, or other causes of mortality (Beelen *et al.*, 2008b). The results from this study are provided in **Table 6** for both the case control group and the cohort. The study is noteworthy because of the exemplary control of potential confounders such as smoking, socioeconomic status, alcohol use and occupational exposure. Further supporting evidence of the absence of an association between chronic SO_2 exposure and lung cancer comes from an extension of the NLCS-AIR Study that included an additional number of cases in the analysis (Beelen *et al.*, 2008a). As before there was no statistically significant association between lung cancer risk and a 20 $\mu g/m^3$ increase in SO_2 levels. A very recent meta analyses of the pooled relationship between SO_2 levels and lung cancer indicted that a small but significant association existed when the results from 5 studies were combined using a fixed effects model that assumed no heterogeneity (odds ratio 1.03%, 95% CI 1.02-1.05) (Chen *et al.*, 2015). This evaluation, however, did not consider the negative results from either of the published NLCS-AIR studies or the results from the two-pollutant study published by Hart *et al.* (Hart et al., 2011).

Table 6 Adjusted risk ratios and 95% confidence intervals for the association of air pollutants with different cause specific mortalities for a full cohort and case control study performed in The Netherlands (Beelen et al., 2008b)[a]

Mortality	BS (10 µg/m^3)		$PM_{2.5}$ (10 µg/m^3)		NO_2 (30 µg/m^3)		SO_2 (20 µg/m^3)	
	Full cohort	Case control	Full cohort	Case control	Full cohort	Case control	Full cohort	Case control
Natural cause	1.05 (1.00–1.11)	0.97 (0.83–1.13)	1.06 (0.97–1.16)	0.86 (0.66–1.13)	1.08 (1.00–1.16)	0.87 (0.69–1.10)	0.97 (0.90–1.05)	0.91 (0.71–1.16)
Cardiovascular	1.04 (0.95–1.13)	0.98 (0.81–1.18)	1.04 (0.90–1.21)	0.83 (0.60–1.15)	1.07 (0.94–1.21)	0.88 (0.66–1.17)	0.94 (0.82–1.06)	0.88 (0.65–1.18)
Respiratory	1.22 (0.99–1.50)	1.29 (0.91–1.83)	1.07 (0.75–1.52)	1.02 (0.56–1.88)	1.37 (1.00–1.87)	1.26 (0.74–2.15)	0.88 (0.64–1.22)	0.88 (0.51–1.50)
Lung cancer	1.03 (0.88–1.20)	1.03 (0.77–1.38)	1.06 (0.82–1.38)	0.87 (0.52–1.47)	0.91 (0.72–1.15)	0.80 (0.52–1.23)	1.00 (0.79–1.26)	0.99 (0.62–1.58)
Other	1.04 (0.97–1.12)	0.91 (0.78–1.07)	1.08 (0.96–1.23)	0.85 (0.65–1.12)	1.09 (0.98–1.21)	0.83 (0.66–1.06)	1.00 (0.90–1.12)	0.93 (0.72–1.19)

[a] Full cohort analyses adjusted for age, sex, smoking status, and area level indicators of socioeconomic status. Case–cohort analyses adjusted for age, sex, BMI, active smoking, passive smoking, education, occupational exposure, marital status, alcohol use, vegetable intake, fruit intake, energy intake, fatty acids intake, folate intake, fish consumption, and area-level indicators of socioeconomic status. BS, $PM_{2.5}$, and NO_2 are quantitative overall concentrations. SO_2 is background concentration (including traffic intensity on nearest road in model). The number of person-years in full cohort analyses is 984,589, and the number of person-years in case–cohort analyses is 28,522.

Although some studies have suggested that an association exists between SO_2 levels and some mortality causes, the overall evidence indicates that chronic exposures are not associated with chronic mortality from lung cancer or any of the other commonly investigated causes.

5.3. ACUTE CARDIOVASCULAR DISEASE

A total of 36 new studies were found that explored the relationship between short-term SO_2 exposure and a range of cardiovascular events that included emergency room visits, hospital admissions, changes in blood coagulation parameters or inflammatory biomarkers, heart rate variability, and myocardial infarction. Emergency department (ED) visits and hospitalizations were generally related to conditions such as stroke, hypertension myocardial infarction, dysrhythmia, ischemic heart disease, and congestive heart failure. All of the cardiovascular studies were downgraded one or two positions because of severe exposure bias or the failure to apply a two-pollutant modeling design that examined potential confounding from co-varying pollutants such as PM_{10} and $PM_{2.5}$. Most of the studies relied heavily on measurements collected at a limited number of fixed monitoring sites in order to obtain a pooled average exposure value or a nearest site value as a surrogate for personal SO_2 exposures.

Although none of the studies was given a grade of moderately good using the GRADE system, two stood out from the others because of their multi-city design or their use of geocoding techniques to account for the spatial variability of SO_2. The time-series study by Stieb *et al.* examined pooled ED visits in seven Canadian cities using a range of within-day or between-day lag periods for the summer and winter seasons (Stieb *et al.*, 2009). Although a significant association was observed for angina/myocardial infarction ED visits during the summer season on lag day 2 using

a single pollutant model, SO_2 was not associated with ED visits for heart failure or dysrhythmia during the summer or winter seasons. In addition, there was no association with angina/myocardial infarction when the statistical analysis was not individually optimized for each of the seven cities before the results were pooled. This deficiency and the failure to perform two-pollutant modeling despite the high Person correlations ($r>0.5$) between SO_2 and PM_{10} or $PM_{2.5}$ in four of the seven cites, necessitated a quality downgrade despite the multi-city design. The final low quality rating for this study is consistent with the author's failure to highlight and stress the associations that were observed between SO_2 exposures and ED visits for angina/myocardial infarction were possibly the result of a surrogate effect.

A second cohort study, ultimately judged to be of low quality, was performed by Rosenlund *et al.* and focused on myocardial infarction with fatal and non-fatal outcomes (Rosenlund *et al.*, 2006). The study is important because it was the only investigation that employed advanced dispersion modeling and residential geo-coding techniques to determine the SO_2 exposures resulting from the of use of home heating fuels. The exposure modeling allowed the calculation of 30-year average exposure levels at each residential location. In addition, confounding from socioeconomic status, ethanol consumption, and smoking status were taken into consideration. The results did not show any association with myocardial infarctions that were segregated into non-fatal cases, fatal cases, in-hospital fatal cases, or out-of-hospital fatal cases. Although this was a well conceived and conducted cohort study with an adequate number of participants, the study suffered from several deficiencies, including the failure to evaluate the exposure contribution from background levels of SO_2 in ambient air that were the result of releases from nearby emission sources.

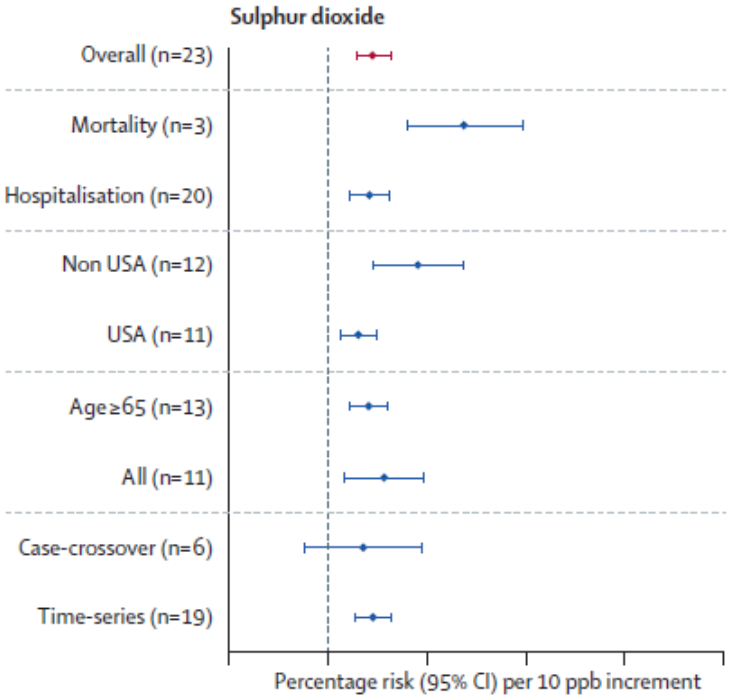
The two studies described above are representative of a fundamental shift that is taking place in the design and conduct of environmental epidemiology studies. There is slow but steady movement away from simply using central monitoring site data as a surrogate for personal exposure and a rejection of single pollutant modeling in favor of the more robust findings using a multi-pollutant approach. The problem is that both of these methodological improvements are needed to produce an acceptable study, but oftentimes only one of these improvements has been adopted. A case in point is a recently conducted time-series study by Xie *et al.*, who reported that SO_2 measurements were not related to ED visits for any of five types of coronary heart disease using either single or two pollutant models that included NO_2 or PM_{10} (Xie *et al.*, 2014). The study included a description of the concentration response relationship and a stratification of the results by season, age, sex. Yet, the entire analysis was built off of the results obtained from a single monitoring site. Consequently, there is a very good chance that the results suffer from a high degree of exposure misclassification. Once proximity determinations and geocoding principles are more widely incorporated into the experimental designs of acute and chronic investigations, there will be a decided uptick in the value of any reported associations.

A relatively large number of meta analyses have been performed using the compiled results from previous case-crossover and time-series studies focusing on the relationship between SO_2 and cardiovascular disease. A hallmark of these evaluations has been the high heterogeneity across studies, which is often attributed to differences in the study populations from the various studies. Many of these meta analyses have detected a publication bias showing a preference for studies that found a positive association with a cardiovascular outcome. The meta analyses performed with SO_2 are also notable because they generally took a very

comprehensive and all-inclusive view of the literature that failed to restrict inclusion to those studies meeting a strict set of quality criteria. Given the large number of statistically significant positive associations that have been observed in single pollutant models with SO_2, it is not surprising that many of the meta analyses have concluded that SO_2 exposures are related to cardiovascular diseases such as stoke or myocardial infarction. For example, a recent meta analysis performed by Shah *et al.* found that SO_2 exposures were significantly associated with stroke mortality and hospital admissions (Shah *et al.*, 2015). This investigation excluded those studies that showed a high risk of case selection bias, exposure assessment bias, or residual confounding. Exposure assessment bias was, however, assessed solely on the basis of the frequency of data collection from central monitoring sites. Those studies that included daily measurements were considered to be at a low risk of bias, whereas the intermittent collection of measurements was felt to provide a biased exposure estimate. Based on these criteria none of the 47 studies published from 1997 to 2013 were excluded from the meta analysis on the basis of exposure bias. Not surprisingly, SO_2 was found to be associated with an increase relative risk of stroke admissions, stroke mortality, and stoke incidence in those greater than 65 years of age per 10 $\mu g/m^3$ change in concentration.

A slightly more judicious meta analysis was performed by Yang *et al.* following the compilation of 22 case-crossover and time-series studies (Yang *et al.*, 2014). In this instance, SO_2 was associated with an increased risk of stoke morality or hospitalization, but only when the studies performed in Asia were compiled (2.13, 95% CI 1.20-3.17). Studies from Europe and North America failed to show a statistically significant increase in relative risk for stroke (0.75, 95% CI -0.15-1.65). In another meta analysis performed by Musafic *et al.*, an overall relative risk of 1.010 (95% CI 1.003-1.017) was calculated for myocardial infarction using the results from 14 studies published from 1997 to 2011 (Mustafic *et al.*, 2012). In this instance, the quality of SO_2 measurements from central monitoring sites was judged on basis of measurement frequency and the number of missing data points. The meta analysis performed by Teng *et al.* examined seven studies published between 2000 and 2013 that focused on the association between SO_2 and out-of-hospital cardiac arrests. The literature search failed to find a single study that yielded a statistically significant positive association for any lag period (Teng *et al.*, 2014). In contrast, Shah *et al.* looked at 23 short-term studies that evaluated the relationship between SO_2 and the mortality and hospitalizations from decompensated heart failure (Shah *et al.*, 2013). As shown in **Figure 12**, all but one of the evaluations indicated a statistically significant positive association with SO_2 levels. The only exception was for the 6 case-crossover studies, which yielded a relative risk percentage that was not statistically significant per 10 ppb (26.6 $\mu g/m^3$) increment in SO_2.

Figure 12 Meta analyses of the percent risk of heart failure in studies where SO_2 exposure levels were determined using measurements from fixed monitoring sites (Shah et al., 2013)



Although these meta analyses provide a useful compilation of available acute cardiovascular studies published from the early 90's, they all suffer serious shortcomings. The most notable of these are the failure to consider spatial heterogeneity and collinearity as important sources of confounding. This is partially attributable to the fact that few if any of the compiled studies have incorporated a two pollutant design or a geo-statistical model that compensated for the distance between a subject's residence and the fixed monitoring site. As such, the findings from meta analyses that have compiled and summarized the results from single pollutant studies should be viewed with considerable suspicion and doubt as to their veracity.

5.4. ACUTE RESPIRATORY DISEASE

The literature review yielded a total of 30 studies focusing on the association of SO_2 exposures with respiratory function or some type of acute respiratory disease such as COPD, bronchitis, or pulmonary infection. Many of these studies included asthma or the symptoms of asthma as a respiratory outcome. Since this topic has attracted a considerable amount of attention by regulators, asthma studies are summarized separately in the next section. Of the respiratory studies examined, three were judged to be of moderate quality based on their admirable attempts to control for exposure misclassification or collinearity concerns. The vast majority of the evaluated studies included a single pollutant design or simple exposure averaging techniques from a limited number of monitoring sites to examine the risks associated with ambient air levels of SO_2. As a result, these studies were given a a low or insufficient quality rating and the findings were deemed to be too heavily compromised to be of value in a hazard determination. The study by Parker *et al.*,

examined respiratory allergy and hay fever in a group of over 40,000 U.S. children aged 3-17 years old (Parker *et al.*, 2009). Inverse distance weighting was used to adjust the measurements collected at monitoring sites located within 20 miles of the each child's residence. This cross-sectional study did not reveal any significant increase in the odds ratio for hay fever or allergies using partially or fully-adjusted single or two pollutant models with PM_{10}, $PM_{2.5}$, O_3, or NO_2. Surprisingly, the authors did not find that ambient SO_2 levels were correlated with PM_{10} or $PM_{2.5}$ to any substantial degree.

Although the study by Ko *et al.* did not include any geocoding techniques to reduce the spatial variability from SO_2 measurements taken from central monitoring sites, it contained a particularly robust assessment of the interactions taking place between the pollutants (Ko *et al.*, 2007a). The authors examined the risk of hospitalization from chronic obstructive pulmonary disease in a group of nearly 120,000 adults using single, three-pollutant (SO_2, $PM_{2.5}$, & O_3), and four-pollutant (SO_2, $PM_{2.5}$, O_3, & NO_2) time series models. SO_2 was weakly associated with COPD hospitalization in a single pollutant model (1.007, 95% CI 1.001-1.014) on lag day 0, but not on any of the other 11 lag periods examined. Although weak statistically significant changes in relative risk were observed in the three- and four-pollutant models (1.008, 95% CI 1.001-1.015), stronger relationships were observed with $PM_{2.5}$ and O_3 indicating that these two pollutants contributed more to the overall risk of COPD hospitalization than SO_2 (see **Table 7**).

Table 7 Relative risk (95% CI) of COPD hospitalization in three and four-pollutant models per 10 µg/m^3 increase in SO_2 on lag day 0 (Ko et al., 2007a)

Model	NO_2 (lag 0–3)	O_3 (lag 0–5)	SO_2 (lag 0)	$PM_{2.5}$ (lag 0–5)
4 pollutant	0.993 (0.985 to 1.001)	1.029 (1.022 to 1.036)*†	1.008 (1.001 to 1.015)*	1.014 (1.007 to 1.022)*
3 pollutant	---------	1.029 (1.022 to 1.034)*†	1.008 (1.001 to 1.015)*	11.011 (1.004 to 1.017)

* $p<0.05$.
† Pollutant with the highest Chi square score

Farhat *et al.* examined emergency room visits and hospitalizations for pneumonia, bronchopneumonia, asthma, and bronchiolitis in a group of children from Sao Paulo, Brazil that were less than 13 years of age (Farhat *et al.*, 2005). Although statistically significant associations were observed in hospital admissions using single pollutant models, these were not evident in two-pollutant models with SO_2 and either PM_{10}, O_3, or CO, or in five-pollutant models that included SO_2, PM_{10}, O_3, NO_2 and CO. Likewise, total emergency department visits for respiratory disease were significantly associated with SO_2 in single and some two-pollutant time-series models, but not in the five pollutant model. These results are not surprising given the high observed correlations between ambient SO_2 levels and PM_{10} (r=0.69), NO_2 (r=0.66) and CO (r=0.49). These results are consistent with studies focusing on pulmonary function, which failed to show a relationship between ambient SO_2 and lung function. For instance, a single pollutant study by Dales *et al.* did not reveal an association between SO_2 levels estimated at the place of residence using a land use regression model and respiratory function in children 9-11 years of age (Dales *et al.*, 2008). Measurements of exhaled nitric oxide, forced vital capacity (FVC), and forced expired volume in 1 second (FEV_1) were not statistically elevated relative to

SO_2 exposure in this cross-sectional study. Taken together, these studies failed to yield any compelling evidence to suggest that SO_2 was intimately linked with the development or exacerbation of respiratory disease in adults or children.

In contrast to the large number of meta analyses focusing on cardiovascular disease, there have been relatively few dealing with respiratory outcomes, and these were often restricted in their scope and experimental design. For instance, Lai *et al.* compiled studies performed in Chinese cites and reported statistically significant associations of SO_2 with emergency room admissions for respiratory disease, but not regular hospital admissions or emergency room visits (Lai *et al.*, 2013). The analysis, however, was limited to just one or two single pollutant studies and the results were inconsistent. Atkinson *et al.* examined the evidence from six studies that evaluated hospital admissions for respiratory disease and failed to find an association with SO_2 exposures when the results were pooled using a random or fixed-effects model (Atkinson *et al.*, 2012). Another regionally restricted meta analysis was performed by Biggeri *et al.*, who examined the evidence from eight Italian cities (Biggeri *et al.*, 2005). Using various methods to pool the findings from the individual studies, the authors obtained mixed results with the fixed effect models yielding significant associations between SO_2 and hospital admissions for respiratory disease and the random effects models showing no associations with admissions. Meanwhile, three of four Bayesian hierarchical models showed no association. A subsequent, follow-up study that included a total of 15 Italian cites failed to find an increase in hospital admissions as a function of SO_2 exposures, which led the authors to conclude that SO_2 played a minor role in eliciting short-term respiratory health effects (Bellini *et al.*, 2007). A major consideration in this and other recently conducted short-term studies was the low levels of SO_2 that were encountered in many urban areas outside of Asia. In fact, in some studies the measurements were at or below the limit of quantitation, which severely limited statistical strength and the ability to detect any relationships that may have existed.

5.5. ASTHMA

Predictably, there have been a large number of case-crossover and time-series studies focusing on the relationship between ambient SO_2 levels and asthma outcomes. Although a total of 42 studies were identified and reviewed for this report, only five were judged to be of moderate quality with the remainder being unsuitable for risk characterization. The single greatest problem with the vast majority of these poorly designed studies was the over reliance on single pollutant modeling results to render some judgment on the nature of the relationship between ambient SO_2 and asthma. These studies were also characterized by their heavy reliance on central monitoring site measurements that were not spatially adjusted for the distance between the monitoring site or the subject's residence. This was not the case, however, in the moderate quality study performed by Portnov *et al.*, who examined the impact of SO_2 on the prevalence of asthma in nearly 4000 Israeli children 6-15 years of age (Portnov *et al.*, 2012). Exposure misclassification was minimized in this study by using residential geocoding used along with kriging and inverse distance weighting to improve spatial resolution of the SO_2 values from 14 monitoring sites. Although the analysis showed that SO_2 was associated with asthma prevalence in a single pollutant model, this relationship was not significant when PM_{10} was introduced into a two-pollutant model.

Similarly, residential proximity adjustments were also performed in a study conducted by Chan *et al.*, who investigated the relationship between SO_2 and outpatient visits or emergency room visits for asthma in groups of children and

adults residing in 12 different districts with Taipei, Taiwan (Chan *et al.*, 2009). This study is rather unique since it employed a single-pollutant and a four-pollutant design that included SO_2 along with PM_{10}, O_3, and NO_2. This approach was justified based on the high correlations between SO_2 and the other pollutants (r=0.31-0.63). The results showed that outpatient visits for asthma were associated ambient SO_2 levels in both the single- and four-pollutant models on lag days 0 and 1, but the same relationships did not exist for asthma-related emergency room visits. In this instance, a positive relationship was only observed on lag day 2 using a single pollutant model. Although the authors did not provide a cogent explanation for this discrepancy between visits and hospitalizations, it may have been due to a difference in the availability of outpatient clinics and hospital emergency rooms for the study population, or a difference in pollutant interactions in different areas of the city. The authors were correct to note that the relationship with asthma patient visits was, in general, weaker for SO_2 than PM_{10} and NO_2, which suggests that SO_2 levels were not as important a contributing factor.

Although the study by Yang *et al.* did not incorporate a residential proximity adjustment for the SO_2 results from fixed monitoring sites, the study is notable for its consideration of two-pollutant interactions and stratification of the results according to ambient temperature (Yang *et al.*, 2007). The study tracked asthma hospital admissions in children and adults residing in Taipei, Taiwan and found that a significant association existed on warm summer days with a temperature ≥ 25 °C using a single pollutant model. This relationship was not apparent, however, using a two pollutant model with either PM_{10}, O_3, NO_2, or CO, regardless of the ambient temperature. In fact, a negative relationship was observed with asthma hospital admissions on cold days when two-pollutants were included in the model. These findings are consistent with those of Farhat *et al.*, who failed to find that SO_2 measurements from fixed sites in Sao Paulo, Brazil were associated with hospital admissions for asthma or bronchiolitis exacerbations in a group of children less than 13 years old (Farhat *et al.*, 2005). This study demonstrated that the associations observed with single-pollutant models failed to be replicated with a two-pollutant model that included PM_{10}, NO_2, or O_3, or in five-pollutant models that included SO_2, PM_{10}, O_3, NO_2 and CO. As was noted in study by Yang *et al.*, several of the two- and five-pollutant comparisons in the Farhat *et al.* study yielded a negative association with asthma hospitalization.

Perhaps the most revealing moderate quality study was performed by Schildcrout *et al.*, who examined asthma exacerbations in a group of 990 children 5-13 years of age residing in one of seven cities in North America (Schildcrout *et al.*, 2006). Asthma symptom incidence and inhaler usage were recorded in a diary that was maintained by each child. SO_2 exposures were based on the unadjusted measurements from 2-9 central monitoring sites located in each of the targeted cities. Weak, but statistically significant, associations were observed with asthma symptom occurrence but not inhaler usage when single pollutant models were applied using a 3 day moving sum of SO_2 levels (1.04, 95% CI 1.00-1.08). These associations were not observed, however, following the application of a two-pollutant model that included both SO_2 and PM_{10}. This study is important because it reinforces the problems of pollutant collinearity and demonstrates the need to incorporate PM_{10} or $PM_{2.5}$ measurements into any consideration of the relationship between SO_2 levels and asthma outcomes. When examined broadly, the five studies of moderate quality indicate that asthma prevalence or intensification cannot be reasonably attributed to SO_2 levels in the ambient air and that the results obtained with a single pollutant analysis are likely to be confounded by the presence of other co-pollutants. It is therefore argued that any evaluation of the findings from

observation studies needs to be restricted to those investigations that adequately consider the potential confounding from co-pollutants that can be emitted from the same sources as SO_2.

Several groups of authors have attempted to pool the results from past studies by examining the relationship between asthma occurrence or treatment and SO_2 exposure magnitude. These studies, however, are generally tainted by their use of crude exclusion criteria that do not take into consideration the well documented correlation between SO_2 levels and other pollutants such PM_{10} and $PM_{2.5}$. For example Gasana *et al.*, pooled the results for 5-6 studies that examined the prevalence and/or incidence of asthma or wheeze in children (Gasana *et al.*, 2012). Using a random effects model, the meta analyses revealed a weak statistically significant odds ratio risk for SO_2 and wheeze (1.04, 95% CI 1.01-1.07) but not asthma (1.02, 95% CI 0.96-1.08). The authors did not offer an explanation for the discrepancy, but did note that the study may have suffered from a lack of precision because the studies used different metrics to describe the spatial or temporal change in SO_2 concentration. Anderson *et al.* did not find a significant association with lifetime asthma prevalence or wheeze prevalence when the results from 5-6 cross sectional studies were pooled in either a fixed or random effects model (Anderson *et al.*, 2013b). This analysis was then extended to cohort studies that followed the incidence of asthma or wheeze over a longer time period; but the authors could only locate a single study which precluded a detailed evaluation (Anderson *et al.*, 2013a). Although there is some disagreement across these studies, a preponderance of the evidence from expertly designed and implemented observational studies indicates that ambient levels of SO_2 are not definitively associated with the occurrence or exacerbation of asthma in humans.

A major overriding issue with many of these studies is, however, the fact that ambient levels are poor surrogate of personal SO_2 exposures and a good surrogate for personal PM exposures (Sarnat *et al.*, 2006). The exposure misclassification resulting from the spurious assumption that ambient measurements provide a reasonable approximation of personal exposure is likely to be very large. Although, rarely discussed in the epidemiology literature, it is imperative that this fact be recognized when evaluating the relevance and reliability of the results from any observational study that relies on measurements from central monitoring sites as a proxy for the exposure concentrations that individuals actually experience while at home or at work.

5.6. BIRTH OUTCOMES

A surprising number of new epidemiology studies have been devoted to investigating the relationship between ambient SO_2 and a variety of birth-related conditions ranging from hypertensive disorders and malformations to low birth weights and infant mortality. Of the 25 studies published since 2005, a precious few accounted for co-pollutant interactions using a multi-pollutant approach. Of those that did, most failed to account for the spatial variability of SO_2 by adjusting for the distance between a monitoring site and a residential location. Regardless, three studies were given a somewhat tenuous moderate quality designation because of their multi-city design or large sample size. The remaining studies were assigned a rating of insufficient or low quality, often because they failed to investigate confounding from correlated co-pollutants. The study by Woodruff *et al.* is notable for its sheer size. Infant mortality was examined using information on 3.5 million births from 96 counties throughout the U.S. (Woodruff *et al.*, 2008). This case control study found that there was no significant increase in the odds ratio for SO_2-

related mortality from all causes, respiratory, sudden infant death, and other causes using a single-pollutant model. Similar results were obtained when respiratory and sudden infant death mortality was examined in four pollutant models that included SO_2, PM_{10}, O_3, and CO or SO_2, $PM_{2.5}$, O_3, and CO. These results are consistent with a cohort study that examined intrauterine fetal growth restriction as a function of ambient SO_2 levels in three Canadian cities (Liu *et al*., 2007a). In this study, SO_2 was not associated with decreases in fetal weight during any month or trimester of pregnancy using a single pollutant model. Two pollutant modeling was not performed with SO_2 because there was no indication of a positive association in any of the single pollutant comparisons. The results from this study and others suggest that SO_2 does not have any detrimental impact on intrauterine fetal growth that could result in stillbirths or neonatal death.

In a separate study, Dales *et al.* evaluated infant hospitalization for respiratory disease in a time-series study involving nearly 10,000 patients from 11 Canadian cities (Dales *et al.*, 2006). Single- and multi-pollutant models that included SO_2, PM_{10}, CO, O_3, and NO_2 both yielded statistically significant increases in the percentage of hospitalizations from asphyxia, respiratory failure, dyspnea, respiratory distress syndrome, unspecified birth asphyxia, and pneumonia. The authors noted that the Pearson correlation between ambient SO_2 levels and PM_{10} was highly variable (r=-0.09-0.61) across the eleven cities. There was no stratification of the findings across the different types of respiratory disease, infant sex, or individual cities which allowed the relative importance of each factor to be independently evaluated. Although this study was judged to be of moderate quality based on its multi-pollutant modeling and multi-city pooling, it was deficient in its heavy reliance on 24-hour averages of the SO_2 concentrations from an unstated number of monitoring stations within each city. Consequently, the results from this study need to be viewed with some suspicion since the results may represent a statistical artifact that is the result of using biased measurements or a poorly vetted method for pooling the results from each city.

There have been several recent attempts to compile the information from all available studies on the relationship between ambient SO_2 and any of a variety of birth outcomes. Shah *et al.* performed a systematic review of studies evaluating low birth weights or pre-term births. Candidate studies were initially screened for inclusion based on set of established criteria that included selection bias, exposure misclassification, confounder adjustment and other factors (Shah and Balkhair, 2011). Eleven of the nineteen single-pollutant studies focusing on low birth weight did not show a relationship with SO_2 levels, whereas 4 of the five studies looking at pre-term births showed an association. Based on this analysis, the authors concluded that SO_2 levels were associated with an increased percentage of pre-term births. Alternatively, Vrijheid *et al.* pooled the results from four single-pollutant studies that focused on congenital malformations in infants (Vrijheid *et al.*, 2012). The meta analysis showed an association with coarctation of the aorta and teratology of Fallot, but not ventricular septal defects or atrial septal defects. In another examination of congenital malformations in neonates, Chen *et al*. pooled the results from a separate group of 4-5 studies and did not detect an statistically significant association between SO_2 levels and coarctation of the aorta, teratology of Fallot, ventricular septal defects, or atrial septal defects (Chen *et al.*, 2014). The discrepancies between the studies by Chen *et al*. and Vrijheid *et al*. were attributed to differences in the handling of the exposure measurements as a categorical or continuous variable. Given the conflicting and less than optimal nature of the available information on birth outcomes, it is difficult to justify the use of the meta analysis results as a basis for classifying the neonatal hazards of SO_2.

6. TOXICOLOGY STUDIES

Many of the most informative inhalation toxicology studies with SO_2 were conducted prior to 2005. These studies included controlled inhalation exposure studies using human volunteers and a range of laboratory animal studies focusing on effects such as pulmonary inflammation, airway hyper-responsiveness, allergic sensitization, cardiovascular and hematological effects as well as studies on reproductive and developmental changes, hepatotoxicity, neurotoxicity, and carcinogenicity. The studies published before 2005, have all been well described and summarized in government reports on the hazards of SO_2 exposures. The most recent Integrated Science Assessment released by the USEPA is a useful source of information on early animal toxicology (USEPA, 2008). Another useful source of background information on early controlled human exposure studies can be found in a pair of publications issued by Johns *et al.* (Johns *et al.*, 2010, Johns and Linn, 2011). In many cases, these early toxicological studies have provided the theoretical foundation for new areas of inquiry that have been the subject of more recent investigations. The reader is directed to these early studies to learn more about the range of adverse health effects that SO_2 has been shown to elicit under laboratory conditions.

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 graded or scored since the results do not carry the same weight as human observational studies, which can provide evidence that is directly applicable to a hazard determination. Instead, a general overview is provided of these studies in order to convey some insight into the research questions and areas of inquiry that are garnering the most interest. Particular attention has been placed on those studies focusing on the respiratory, inflammatory, or cardiovascular responses that accompany *in vivo* and *in vitro* SO_2 exposures in laboratory animals and controlled whole body inhalation exposures in human volunteers.

6.1. HUMAN STUDIES

Recent human volunteer studies with SO_2 have generally been restricted to health surveys following an environmental or occupational exposure or end-point measurements following a controlled exposure in an environmental chamber. The health surveys have targeted occupationally exposed workers, emergency response personnel, and individuals residing near an active volcano. In general, the exposure concentrations experienced by these individuals have been far greater than ambient air quality standards issued in North America or Europe, so the findings are of little assistance in evaluating the need for more restrictive control limits. The results are of value, however, for examining the spectrum of health outcomes that accompany excessively high levels that can occur in specific microenvironments. Only two controlled laboratory studies have been performed in recent years. In the first study, heart rate variability and circulating biomarkers of inflammation were determined in 20 healthy volunteers and 20 with stable angina *(Routledge et al*., 2006). Both groups were exposed to 200 ppb (532 $\mu g/m^3$) of SO_2 for 4 hours with intermittent electrocardiogram (ECG), blood coagulation and hematologic measurements before, during, and after the exposure. Compared to a clean air exposure, SO_2 caused a decrease in a heart rate variability marker for vagal control in the healthy subjects but not in those with stable angina. Blood cell count, platelet aggregation, or fibrinogen measurements were not affected by the SO_2 exposures in either test

group. Separately, the sensory and pulmonary irritancy of SO_2 was examined in a group of 16 male and female volunteers exposed to 0.5, 1, or 2 ppm (1.3, 2.7, or 5.3 $\mu g/m^3$) SO_2 for 4 hours (van Thriel *et al.*, 2010). Eye blink frequency, nasal airflow, and lung function were not affected at any of the three exposure concentrations. The test subjects did report weak to moderate odor annoyance at all exposure concentrations.The authors concluded that the evidence was not sufficient to warrant a change in occupational exposure limits.

The results obtained in laboratory studies are somewhat at odds with the results from field investigations. Granslo *et al.* performed a cross-sectional study of 75 workers who were employed in a harbor where an oil tank explosion occurred (Granslo *et al.*, 2014). The estimated levels of SO_2 levels near the explosion site were 0.6-1.5 mg/m^3. Compared to controls, the exposed men had increased odds ratio for subjectively determined upper airway irritation and dyspnea upon exertion 18 to 22 months after the event. There were, however, no changes in pulmonary function tests. Similar results were obtained in a retrospective survey of soldiers who extinguished a sulfur plant fire in Iraq that resulted in airborne SO_2 levels as high as 283 mg/m^3 (Baird *et al.*, 2012). In this case, there was no clinical evidence of respiratory disease in the cohort of 6532 firefighters and support personnel, but there was an increase in self-reported symptoms and medical problems (cough, runny nose, and difficulty breathing) relative to a control population. This was also the case with 896 workers temporarily placed on the volcanically active island of Miyakejima, Japan for a period of 1-15 days. The workers were subdivided into very low, low, middle, and high exposure groups according to the prevailing wind direction for the volcanic plume. The group in the high exposure group experienced an increased incidence of respiratory symptoms such a cough, scratchy or sore throat, and breathlessness as a results of hourly maximum SO_2 exposures of 2.0 ppm (5.3 mg/m^3) or greater (Ishigami *et al.*, 2008). Similar results, were obtained in a 2-year follow-up study with residents who returned to the island with a higher prevalence of cough and phlegm reported in the absence of a notable decline in lung function for those exposed to an average of 31 ppb (82.5 $\mu g/m^3$) of SO_2 (Iwasawa *et al.*, 2009).

A small but diverse array of occupational and environmental field studies has been performed with SO_2. Using nitrate and nitrite levels in expired breath condensate (EBC) as a measure of exhaled nitric oxide production, Yildirim *et al*. examined the effect of occupational SO_2 exposures on pulmonary inflammation in a group of 56 smoking and non-smoking seasonal employees working in apricot sulfurization chambers (Yildirim *et al.*, 2012). The volunteers were exposed to SO_2 for about an hour when the chambers were opened, vented, and reloaded with crates of apricots. The SO_2 exposure concentrations in the vicinity of the sulfurization chambers were previously determined to range from 106.6-721.0 ppm (284-1918 mg/m^3) (Koksal *et al.*, 2003). The exposures resulted in a significant decrease in pulmonary function (FEV_1 and $FEV_{25\%-75\%}$) and an increase in nitrite but not nitrate in the EBC. The authors concluded that nitrative stress may have played a role in the bronchoconstriction and acute airway response observed in these workers. In a separate, but related, study with apricot workers, SO_2 exposures in the same concentration range were shown to affect forced vital capacity (FVC), forced expiratory flow in 1 second (FEV_1) and mid-expiratory flow ($FEV_{25\%-75\%}$) that could be alleviated through the administration of a bronchodilator (ipratropium bromide) prior to the SO_2 exposure (Yildirim *et al.*, 2005). The authors also showed that repeated exposure to SO_2 during the apricot harvesting season did not significantly affect the results from pulmonary function, skin prick or broncho-provocation tests relative to a control group (Ermis *et al.*, 2010). These findings contrast with those

from a sulphite pulp mill, where 4112 workers who reported being exposed to SO_2 were found to have a higher incidence of adult onset asthma than a control group with no exposures (Andersson *et al.*, 2013).

Several studies have focused on the health status of individual residing in the vicinity of a volcanic plume that contained particularly high concentrations of SO_2. The average 2-hr personal exposure of 10 volcanologists working near a New Zealand fumarole was 24 ppm (63.8 mg/m^3) (Durand *et al.*, 2005). Lower, but still substantial, hourly episodic exposures as high as 453 ppb (1205 µg/m^3), were experienced by 19 villagers living near Hawaii's Kilauea volcano (Chow *et al.*, 2010). Measurements of heart rate variability in these test subjects did not show any relationship with the SO_2 exposures. By comparison, the hourly maximum SO_2 exposures for residents living downwind of a large Taiwanese petrochemical complex ranged from 103.8-335.6 ppb (276.1-892.7 µg/m^3) (Shie *et al.*, 2013)

Several studies have been published in recent years that have examined the *in vitro* effects of SO_2 metabolic products on cultured tissues. Following inhalation, SO_2 is rapidly converted to sulfurous acid, which then dissociates into sulfite and bisulfite derivatives. *In vitro* genotoxicity and toxicogenomic studies with SO_2 are therefore often aimed at studying these two breakdown products. The treatment of cultured human bronchial epithelial cells with 0.001, 0.01, 0.1, 1.0 and 2.0 mM of sulfite or bisulfite resulted in an over expression of mRNA and protein for two proto-oncogenes c-fos and c-jun and the tumor suppressor gene c-myc at all exposure concentrations (Qin and Meng, 2009). There was also and under expression of the p53 tumor suppressor gene and H-ras proto-oncogene at the two highest treatment levels. The authors postulated that these changes could play a role in SO_2-induced lung cancer, which some epidemiology studies have shown to occur at a higher incidence rate in female non-smokers (Tseng *et al.*, 2012). In other studies, the effects of SO_2 on epidermal growth factor (EGF), epidermal growth factor receptor (EGFR), intercellular adhesion molecule-1 (ICAM-1), and cyclooxygenase-2 (COX-2) mRNA and protein levels was studied in cultured bronchial epithelium treated with 0.001, 0.01, 0.1, and 1.0 mM of sulfite or bisulfite (Li *et al.*, 2007). All four of these asthma-related genes were inductively expressed by the SO_2 products at the two highest treatment levels and the activation remained for 24 hours post-exposure for some genes.

The genotoxicity of SO_2 gas has also been examined using culture human lymphocytes (Uren *et al.*, 2014). The treatment of cells with 0.1, 0.5, or 1.0 ppm (0.3, 1.3, or 2.7 µg/m^3) of SO_2 resulted in a higher frequency of sister chromatid exchange and micronucleus formation at the two highest exposure levels and a decrease in the mitotic and replication index at all levels. The results showed that SO_2 was a potent genotoxin in this cell type. The *in vitro* cytotoxicity of SO_2 was also investigated in several different types of human alveolar epithelial cell lines (Bakand *et al.*, 2007). Test atmospheres were created dynamically using a metered device and dilution apparatus that resulted in levels of 10, 20, 40, 80, and 200 ppm (26.6, 53.2, 106.4, 212.8, and 532.0 mg/m^3). An assessment of cell viability using measurements of MTS conversion, neutral red uptake, and ATP content revealed a concentration-related decline using all three assays. The 50% inhibitory concentration (IC_{50}) was greatest for the ATP assay, which gave a value of 48±2.83 ppm (127.7±7.53 mg/m^3) for the SO_2 exposures.

6.2. ANIMAL STUDIES

The majority of recently published laboratory animal studies have examined the role of SO_2 exposures on respiratory inflammation responses; however there have also been a sizable number of studies that have looked at cardiovascular and genetic interactions. Each of these target systems are examined separately in the subsections that follow. Studies involving the *in vitro* exposure of tissue cultures and *in vivo* exposure of whole animals have also been examined.

6.2.1. Respiratory studies

A recent review by Reno *et al.* provides a good summary of past and present mechanistic studies examining airway sensitivity and biochemical responses in asthmatic laboratory animals exposed to SO_2 (Reno *et al.*, 2015). This information is further supplemented by the summaries that follow, which in some cases overlaps with the studies highlighted in the Reno *et al.* report. Inhalation exposures to SO_2 were used to investigate the creation of an animal model for COPD using Sprague-Dawley rats (Wagner *et al.*, 2006). Following continuous treatment for 3 days or 20-25 days at SO_2 exposure concentrations of 5, 10, 20, 40, or 80 ppm (13.3, 26.6, 53.2, 106.4, or 212.8 mg/m^3), pulmonary histology revealed a dose-related increase in edema formation and inflammatory cell infiltration in the animals exposed for 3 hours. In those exposed for nearly a month, the edematous tissue was replaced by fibrous tissue. Basal and acetylcholine stimulated secretory activity was most prominent in those animals exposed to 20 ppm of SO_2. The hypersecretion was associated with glandular hypertrophy and metaplasia rather than hyperplasia. Following the exposure of rats to 100, 200, or 400 ppm (266, 532, or 1064 mg/m^3) SO_2 for up to 4 weeks at 5 day/week and 5 hr/day, ultra-structural changes were observed in the lung parenchyma (Abdalla, 2015). These included a loss of cilia, vacuolation, pyknosis, goblet cell hyperplasia and the development of a stratified squamous metaplasia after 2-7 days of exposure at 200 ppm. Exposure to 40 ppm (106.4 mg/m^3) of SO_2 for 6 weeks at 4 hr/day did not result in any ultra-structural changes, but a single 40 ppm SO_2 exposure accompanied by a carbon dust exposure of 740 mg/m^3 resulted in a neutrophilic response that was attributed to adsorption and subsequent slow desorption of SO_2 from the particulate surface. Similar changes were observed in mice exposed to 28 or 56 mg/m^3 for 7 days at 4 hr/day (Meng and Liu, 2007). Electron microscopy showed that the type II alveolar cells were altered with vacuolation of eosinophilic multi-lamellar infiltrates, a decrease in microvilli content, mitochondrial pyknosis, and nuclear and chromatin alterations. In addition, distinct cellular lesions were also observed in the liver, cerebral cortex, myocardium, kidney, and testes.

Several studies have examined steps in the causal pathway that results in the development of asthma like symptoms following SO_2 exposures. In one study, using ovalbumin sensitized rats responsive to an allergic challenge, the animals were exposed to 2 ppm (5.6 mg/m^3) of SO_2 for 4 weeks at 4 hr/day and evaluated for changes in airway function or architecture (Song *et al.*, 2012). The treatment resulted in a significant increase in airway resistance, impedance and intrapleural pressure as well as an increase in interleukin-4 in serum and bronchoalveolar lavage fluid (BALF). The contractility and stiffness of airway smooth muscle cells was also increased in the sensitized rats relative to treated control animals, which led the authors to postulate that SO_2 may selectively exacerbate airway hyper-responsiveness in asthmatics alone. Li *et al.* exposed ovalbumin-sensitized rats to 5.6 mg/m^3 of SO_2 for 7 days at 1 hr/day and then measured mRNA an protein levels in lung tissue, inflammatory markers in BALF, and histopathologic lesions in the

respiratory tract (Li *et al.*, 2014). The exposures in sensitized rats resulted in an up-regulation and activation of nuclear factor kappa (NF-κB), which regulated the immune response to an allergic challenge. In addition, tissue necrosis factor (TNF-α) and IL-6 levels were elevated in the BALF of treated animals relative to ovalbumin-treated controls. Severe inflammatory cell infiltration, prominent mucus secretion, and thickened epithelial cell layers were noted in the lungs of the treated animals. In related experiments, Li *et al.* also noted that three genes were up regulated in the lungs of rats treated with 5.6 mg/m^3 of SO_2 for 7 days at 1 hr/day (Li *et al.*, 2008). The mRNA and protein levels EGF, EGFR, and COX-2 were elevated in the lung tissue of the treated animals, suggesting that these genes played a role in eliciting the pathological response.

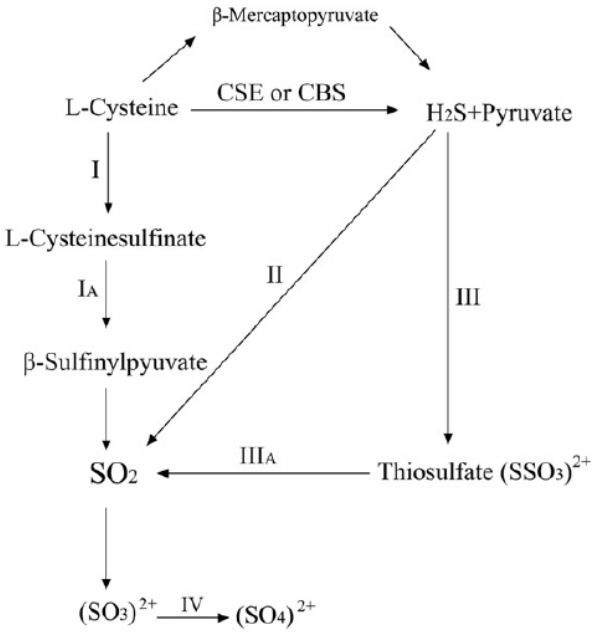
The exposure of rats to SO_2 has been shown to lessen the allergic response to a chemical agent known to cause a hypersensitivity reaction (Arts *et al.*, 2010). Exposure of female rats to 300 ppm (798 mg/m^3) SO_2 for 1 or 10 days at 2.4 hr/day reduced the laryngeal ulceration, goblet-cell hyperplasia, and pulmonary inflammation from a challenge dose of trimellitic anhydride, a known respiratory sensitizer. The mechanism was felt to involve the SO_2-induced replacement of sensitive respiratory epithelium by less reactive squamous epithelium. The exposure of mice to 50 ppm (133 mg/m^3) of SO_2 for 3 days at 1 hr/day resulted in neutrophilic inflammation and epithelial sloughing along with an elevation of endothelin-1, a profibrotic mediator, in the BALF (Cai *et al.*, 2008). This was indicative of chronic allergic airway inflammation (CAAI) in these animals. Ovalbumin treatment for 5 or 9 weeks resulted in subepithelial fibrosis (SEF) and an increase in hydroxyproline levels in the lung and transforming growth factor-β1 levels in the BALF. The study showed that CAAI and SEF developed in parallel through an over expression of the two profibrotic mediators. Ovalbumin sensitized rats were used as a model to study the biological correlates of the airway hyper-responsiveness that accompanies the asthma related symptoms observed following SO_2 exposure (Song *et al.*, 2012).

The ability of SO_2 exposure to promote a cough reflex was investigated in guinea pigs exposed to 1000 ppm for 4 days at 3 hrs/day (Mcleod *et al.*, 2007). The pulmonary inflammation produced by the SO_2 exposure was capable of activating the capsaicin-sensitive TRPV1 vanilloid receptor that was one of the pathways responsible for the cough reflex. The resulting inflammatory change was associated with an increase in the capsaicin-induced cough response that could be attenuated by corticosteroid treatment. The neutrophilic inflammation was accompanied by cellular extravasations and goblet cell metaplasia. Treatment of male rats with 14.11, 28.36, or 56.25 mg/m^3 of SO_2 for 7 days at 6 hrs/day was shown to affect mRNA levels and cytochrome P450 activity in lung and liver (Qin and Meng, 2006a). Lung microsomal CYP2B1/2 enzymatic activity and mRNA levels were reduced in the lungs and liver at the two highest exposure concentrations. The activity of CYP2E1 activity was also affected but only in the lung tissue. The adverse effects of SO_2 was investigated in spontaneously hypertensive rats receiving a 250 or 350 ppm (665 or 931 mg/m^3) exposure for 4 days at 5 hr/day (Kodavanti *et al.*, 2006). The treatment resulted in a concentration-related increase in the total number of cells and neutrophilic inflammation in the BALF of the hypertensive rats relative to normo-tensive rats. Increased mucin production was also observed along with a predominant up-regulation of inflammatory modulation and oxidative response genes.

6.2.2. Cardiovascular studies

Sulfur dioxide can be produced endogenously and has a role as an antioxidant, anti-inflammatory, anti-hypertensive, and anti-atherogen (Wang *et al.*, 2014). Circulating levels of SO_2 have been shown to help regulate many cardiovascular functions including vascular tone, calcium channel vitality, cardiac function, and lipid metabolism (Wang *et al.*, 2011c). Endogenous SO_2 is produced from sulfur-containing amino acids such as cysteine and from hydrogen sulfide via the pathways shown in **Figure 13**. Circulating levels in rat plasma were found to be 15.54 µmol/L with the stomach and aorta containing the highest levels amongst the tissues examined (Du *et al.*, 2008). In fact, the wide tissue distribution of SO_2 and two important activating enzymes, cysteine dioxygenase and aspartate aminotransferase, has provided support for the belief that SO_2 possesses some unique signaling and transmitter properties (Luo *et al.*, 2011). The vasorelaxant effects of SO_2 have been attributed to the parent chemical rather than the sulfite and bisulfite breakdown products (Meng *et al.*, 2009). However, studies conducted *in vivo* found that the administration of sulfite/bisulfite was capable of improving the vasorelaxation in spontaneously hypertensive rats (Lu *et al.*, 2012). Intraperitoneal treatment of the rats with daily dosages of 0.54 mmol/kg resulted in decreased blood pressure presumably by promoting the generation nitric oxide (NO), which is a known vasorelaxant. These results were supported by other *in vitro* studies showing that SO_2 dissolved in saline was capable of inducing NO formation in isolated aortic slices (Li *et al.*, 2010). The incubation of the slices with of 30, 300, and 1500 µM SO_2 potentiated the activity endothelial nitric oxide synthase and up-regulated the gene responsible for the expression of this enzyme.

Figure 13 Metabolism of SO_2 in mammals (Wang et al., 2011c)



I Cysteine dioxygenase
IA Aspartate aminotransferase
II Nicotinamide-adenine dinucleotide phosphate oxidase
III Sulfide oxidase
IIIA Thiosulfate sulfurtransferase or thiosulfate reductase
IV Sulfite oxidase

In fact, some believe that the modulation of cardiovascular function by SO_2 can provide the basis for new treatments of cardiovascular disease (Liu *et al.*, 2010). The anti-atherogenic effects of SO_2 have been demonstrated in atherosclerotic rats fed a high cholesterol diet for 8 weeks (Li *et al.*, 2011). The animals subsequently treated intraperitoneally with a daily dose of 0.54 mmol/kg sulfite and bisulfite displayed smaller atherosclerotic lesions than the untreated control animals. In addition, the sulfite/bisulfite treatment reduced the levels high-density lipoprotein, cholesterol and triglyceride suggesting that the anti-atherogenic activity was associated with a reduction in plasma lipids. The myocardial injury that accompanied cardiovascular trauma and the pulmonary vascular restructuring that was seen with pulmonary hypertension were also lessened in rats following a similar treatments with these SO_2 derivatives (Chen *et al.*, 2012b, Sun *et al.*, 2010). The intraperitoneal treatment of rats with 85 mg/kg sulfite/bisulfite solution for 7 days resulted in improved cardiac function and myocardial structure and a down-regulation of the genes associated with the endoplasmic stress caused by the isoproterenol pre-treatment. Further studies with 1-10 µmol/kg of the sulfite/bisulfite derivative of SO_2 was shown to reduce the myocardial apoptosis and biochemical changes that accompanied an ischemia/reperfusion injury (Wang *et al.*, 2011b). The daily intraperitoneal administration of a 0.54 mmol/kg dose of a sulfite/bisulfite derivative of SO_2 for 8 weeks was found to alleviate systolic pulmonary pressure in a rat model of pulmonary hypertension (Luo *et al.*, 2013). The protective effect was attributed to increased mRNA and protein expression and augmented production of H_2S, which has direct effect on the regulation of pulmonary hypertension.

Aside from the beneficial physiological effects of endogenous SO_2, other studies have focused on the adverse changes that accompanied the inhalation of exogenous SO_2. A comparative simulation study of SO_2 absorption in rats, dogs, and humans found no appreciable differences in the pulmonary absorption pattern with all three species predicted to retain over 96 % in the upper airways (Tsujino *et al.*, 2005). Using a rat model of ischemic stroke using middle cerebral artery occlusion (MCAO), SO_2 exposures of 7 mg/m^3 for 7 days at 6 hr/day were capable of causing a cortical increase in mRNA and protein levels for endothelian-1 (ET-1) inducible nitric oxide synthase (iNOS), intracellular adhesion molecule 1 (ICAM-1), and COX-2 genes relative to sham control animals (Sang *et al.*, 2010). The same responses were also observed in normal rats exposed to 7, 14, and 28 mg/m^3 of SO_2, but the changes were not as great as those observed in the MCAO animals treated at the lowest exposure concentration. Pre-treatment of mice for 4 days with salicylic acid or vitamin C protected against the oxidative stress caused by a 56 mg/m^3 SO_2 exposure for 10 days at 4 hr/day (Zhao *et al.*, 2008a). The two anti-oxidants were effective in reducing the elevations of thiobarbituric acid reactive substance (TBARS), an indicator of oxidative stress. In addition, superoxide dismutase (SOD), peroxidase (POD), and catalase (CAT) activity was significantly elevated in liver and brain tissue relative to controls.

6.2.3. Genomic studies

The regulatory effects of SO_2 on gene expression have been examined in a variety of rat and mouse tissues. For example, the exposure of rats to 14, 28, or 56 mg/m^3 SO_2 for 7 days at 6 hr/day induced protein oxidation, apoptosis, and the formation of DNA-protein crosslinks in the hippocampus of these animals (Sang *et al.*, 2009). The DNA-protein crosslinks were significantly elevated at the two highest exposure concentration and were believed to be the result of the hydroxyl radicals formed following the peroxidase catalyzed creation of sulfite radicals ($^{\bullet}SO_3^-$) from bisulfite.

Protein oxidation and DNA-crosslinks were also observed in the lungs, livers, and hearts of mice exposed to 14, 28, or 56 mg/m^3 of SO_2 for 7 days at 6 hr/day (Xie *et al.*, 2007). The responses were concentration-related and appeared in both male and female mice with the greatest changes observed in the lung and the least in the heart. Single strand DNA breaks were observed in the lymphocytes harvested from mice treated with 14, 28, 56, and 112 mg/m^3 of SO_2 for 7 days at 6 hr/day (Meng *et al.*, 2005). The concentration-related increase in DNA damage was also observed in cells taken from the brain, liver, lung, spleen, kidney, intestine, testes.

Further, SO_2 exposures of same magnitude and duration were capable of up-regulating the nuclear factor kappa (NF-κB) and cyclooxygenase-2 activity in the rat hippocampus. This activity was thought to be responsible for the formation of prostaglandin E_2 that was postulated to be a factor in the neuronal damage caused by SO_2. Using the same SO_2 exposure paradigm of 14, 28, and 56 mg/m^3 for 7 days at 6 hr/day, Yun *et al.* showed that the treatment affected mRNA and protein levels of TNF-α, IL-1β, iNOS, ICAM-1, and the ratio of two apoptotic genes bax and bcl-2 in rat heart and lung tissue (Yun *et al.*, 2011). These changes were associated with inflammatory cell infiltrations in these tissues. In a final set of experiments, the inhalation exposure of rats at the same three exposure concentrations resulted in an increased expression of p53, c-fos, c-jun, bax, and bcl-2 genes in the hippocampus (Yun *et al.*, 2010). Changes in the transcription and translation of these apoptosis-related genes were felt to be mediated by the sulfite/bisulfite derivatives that are generated. Not all proto-oncogenes are up-regulated by SO_2 exposures. The protein and mRNA levels in the lungs of rats exposed to 14, 28, or 56 mg/m^3 of SO_2 for 7 days at 6 hr/day were increased for the proto-oncogenes c-jun, c-myc, Ki-ras, and p53, whereas the levels were decreased for the tumor suppressor genes Rb and p16 (Bai and Meng, 2010). Similar results were obtained with the apoptosis promoter genes p53 and bax which were up-regulated while the apoptotic suppressor gene bcl-2 was down-regulated in the rat lung and liver (Bai and Meng, 2005a, Bai and Meng, 2005b). The exposure of rats to 56 mg/m^3 of SO_2 for 7 days at 6 hr/day also caused a significant decline in the mRNA levels and associated enzymatic activities for CYP1A1 and CYP1A2 in lung tissue (Qin and Meng, 2006b).

The preceding studies demonstrate that SO_2 possess both advantageous physiological properties and adverse toxicological properties. As such, the dose response relationships for any adverse effect would be expected to show a threshold concentration at or near a level that did not overload the biochemical processes that control SO_2 formation and fate *in vivo*.

7. CONCLUSIONS

A detailed review and examination of the results from over 175 observational epidemiology studies and 50 toxicology studies did not yield any compelling evidence to suggest that current guidance values for limiting ambient air exposures to SO_2 are not protective of human health. In fact, there are very serious concerns with the findings from many of the epidemiology studies using measurements from central monitoring site as a surrogate for personal exposure. Comparisons of personal exposure to SO_2 with the results from monitoring stations clearly show that the two are unrelated and that ambient air levels of SO_2 are instead a good measure of personal $PM_{2.5}$ exposure. This relationship indicates that any health outcome attributed to SO_2 may in fact be due to particulate matter or substance adsorbed to particulate matter. In addition, Studies incorporating a multi-pollutant design that includes PM_{10} and/or $PM_{2.5}$ have, in many cases, shown that these two co-pollutants vary in a collinear fashion in the atmosphere. Consequently, those studies that fail to use a multi-pollutant model to explore possible associations between atmospheric levels of SO_2 and a targeted health concern should be viewed with suspicion because of the serious exposure misclassification that may exist.

Toxicology studies published since 2005 have largely focused on the genetic and metabolic mechanisms responsible for the adverse effects seen in rats and mice exposed to high concentrations of SO_2. In addition, there have been a relatively large number of new studies that have shown that endogenously produced SO_2 acts as a transmitter responsible for maintaining cardiovascular homeostasis. There have been few new controlled human exposure studies with SO_2 and those that exist have either involved exposures at high concentrations or explored the ocular and pulmonary irritancy of SO_2 in an occupational setting.

Although a wide variety of new outcomes such as diabetes, hypertension, depression, and arthritis have been investigated to a some degree in new observational studies, the focus of most investigations continues to be on more traditional morbidity and mortality outcomes. Acute and chronic mortality continue to generate a considerable amount of interest by researchers but the results from these studies have largely been negative. Although asthma and its related symptoms continue to garner considerable interest, there have not been any studies in laboratory animals or humans suggesting that there are new SO_2-related health concerns for people who suffer from this condition. Likewise, well conducted investigations focusing on respiratory and cardiovascular disease have not yielded new information to suggest that members of the general public are at a greater risk than once believed. The area of environmental research that seems to have shown the highest level of interest in recent years is the association between ambient SO_2 levels and any of a variety of adverse birth-related outcomes included congenital malformations, neonatal death, and low birth weights. New observational studies in this area, although largely negative, have suffered from wide range of methodological problems, not the least of which is the exposure misclassification that has biased the outcome estimates in an unpredictable fashion.

Although a tremendous amount of new information has been gathered on SO_2, there are still a number of perennial issues that have not been sufficiently resolved to the extent needed to make definitive statements about the inherent hazards and risks of SO_2 exposures. Confounding and bias continue to plague many observational studies to the point that they all need to be regarded with a high level of distrust. Complicating matters, SO_2 levels in Europe and North America have declined

precipitously since 1990 and have shown no sign of levelling off. Consequently, the levels in many regions of Europe are approaching background, raising the possibility that future observational studies with SO_2 will need to take place in those countries that are still having a problem with emissions control. Until such time that confidence can be restored in the findings from observational studies, the results from previously conducted controlled human exposure studies will need to serve as the primary basis for assessing hazards and regulating exposures.

8. GLOSSARY

Acronym	Definition
AAQS	Ambient air quality standards
APHEA	Air Pollution and Health: A European Approach
BALF	Bronchoalveolar lavage fluid
BMI	Basel metabolic index
CAAI	Chronic allergic airway inflammation
CAT	Catalase
CH_3CO_3H	peoxyacetic acid
CH_4O_2	methylhydroperoxide
CLRTAP	Convention on Long-Range Transboundary Air Pollution
CCN	Condensation nuclei
CO	Carbon monoxide
COMEAP	Committee on the Medical Effects of Air Pollution
COPD	Chronic obstructive pulmonary disease
COX-2	Cyclooxygenase-2
CYP2E1	Cytochrome P450 2E1
DMS	Dimethyl sulfide
EBC	Expired breath condensate
EC	European Commission
ECETOC	European Centre for Ecotoxicology and Toxicology of Chemicals
ECG	Electrocardiogram
ED	Emergency department
EEA	European Environment Agency
EGF	Epidermal growth factor
EGFR	Epidermal growth factor receptor
EMEP	European Monitoring and Evaluation Programme
ET-1	Endothelian-1
FVC	Forced vital capacity
GRADE	Grading of Recommendations Assessment, Development and Evaluation
H_2O_2	Hydrogen peroxide
H_2SO_3	Sulphurous acid
HO	Hydroxyl radical
HO_2	Hydroperoxyl radical
$HOSO_2$	Hydroxysulfonyl radical
HSO_3	Bisulfite
ICAM-1	Intercellular adhesion molecule-1
iNOS	Inducible nitric oxide synthase
LPG	Liquefied petroleum gas
LUR	Land use regression
MCAO	Middle cerebral artery occlusion
NEC	National Emission Ceiling
NO	Nitric oxide
NO_2	Nitrogen dioxide
O_3	Ozone
OHAT	U.S. National Toxicology Program's Office of Health Assessment and Translation
PAH	Polycyclic aromatic hydrocarbons
PM	Particulate matter

Acronym	Definition
$PM_{2.5}$	Particulate matter with diameter of 2.5 micrometres or less
PM_{10}	Particulate matter with diameter of 10 micrometres or less
POD	Peroxidase
REVIHAAP	Review of Evidence on Health Aspects of Air Pollution
SEF	Subepithelial fibrosis
SO_2	Sulphur dioxide
SO_3	Sulphur trioxide
$^{\bullet}SO_3$	Sulfite radicals
SO_x	Sulphur oxide
SOA	Secondary organic aerosols
SOD	Superoxide dismutase
TBARS	Thiobarbituric acid reactive substance
TCM	potassium tetrachloromecurate
TNF	Tissue necrosis factor
TSP	Total suspended particulates
UNECE	United Nations Economic Commission for Europe
USEPA	US Environmental Protection Agency
UVF	Ultraviolet fluorescence
WHO	World Health Organization
WOS	Web of Science

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APPENDIX I - DETAILED ANALYSIS OF SELECTED STUDIES

Acute Mortality

1. **Park, A. K., Hong, Y. C., and Kim, H. 2011. Effect of changes in season and temperature on mortality associated with air pollution in Seoul, Korea. *Journal of Epidemiology and Community Health* 65:368-375.**

Rating
Moderate quality (⊕⊕⊕○)

Description
This time-series evaluation of acute non-accidental, cardiovascular & respiratory mortality took place in Seoul, Korea over a period of nearly nine years. Mean hourly concentrations were collected from 27 fixed monitoring sites and yielded an overall daily mean concentration of 5.2 ppb (13.8 µg/m³) that ranged from a low of 1.8 ppb (4.8 µg/m³) to a high of 19.6 ppb (52.1 µg/m³). Poisson regression with natural cubic splines was employed using a 2-day moving average lag period of 0-1 days. A total mortality of 291,665 was observed over the observation period with mean daily mortality rates of 93 deaths/day for non-accidental, 25.4 deaths/day for cardiovascular and 5.4 deaths/day for respiratory. Associations with ambient temperature, PM_{10}, NO_2, CO, O_3, and SO_2 were investigated. Confounding from temperature, relative humidity, influenza epidemics, holidays, and day of week effects was considered.

Results
The results for SO_2 were expressed as the percent increase in relative risk for those > 65 years of age for an interquartile range (IQR) of 0.5 ppb (1.3 µg/m³) in single and two-pollutant models stratified by ambient temperature ranges of <25th percentile (<8.2 °C), 25-50th percentile (8.2 – 19.1 °C), 50-75th percentile (19.1 – 26.2 °C)and ≥75th percentile (≥26.2 °C). The greatest seasonal associations were observed with SO_2 during the springtime. The highest associations in single-pollutant models with SO_2 exposure were observed for non-accidental and cardiovascular mortality at two of the four temperature ranges for those of all ages and those > 65 years of age (see **Figure 14**). The associations with respiratory mortality were either insignificant or barely significant. Two-pollutant modeling with PM_{10} did not affect the degree of association with SO_2, but the incorporation of NO_2 and CO decidedly affected the results for non-accidental mortality in those greater than 65 years of age by appreciably reducing the percentage increase from SO_2 at all temperatures except the highest days that were ≥26.2 °C (see **Table 8**). Surprisingly, the significant associations observed for respiratory and cardiovascular mortality when the temperatures were ≥26.2 °C were rendered insignificant when PM_{10} was incorporated into a two-pollutant model. The association of ambient SO2 levels with respiratory mortality was also attenuated by the incorporation of NO_2, CO and O_3 into a two pollutant model. An important aspect of this study was the impact of temperature alone on non-accidental and cardiovascular mortality. As shown in **Figure 15**, temperatures ≥26.2 °C were associated with a higher risk relative independent of the SO_2 and O_3 levels. This raises the possibility that the non-accidental mortality risks being attributed to SO_2 on hot days are in reality related to the temperature change alone.

Figure 14 Mean percentage change in relative risk for non-accidental mortality stratified by temperature and age group.

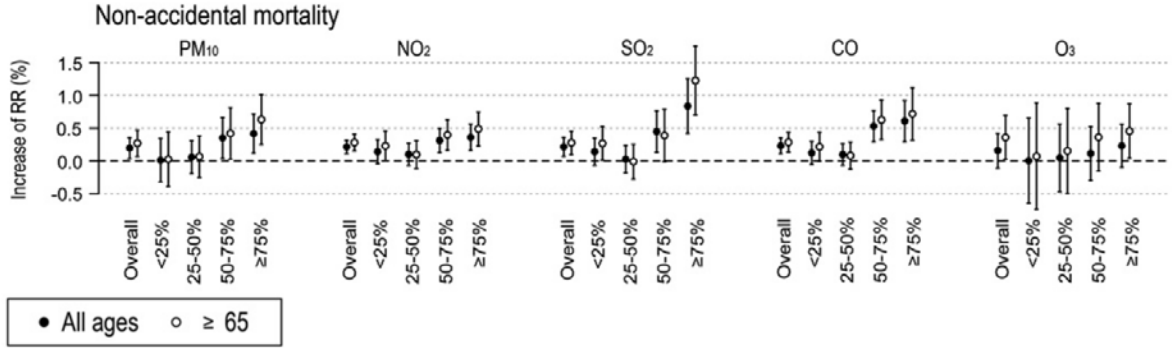


Figure 15 Mean percent change in relative risk of mortality stratified by maximum ambient temperature in a model that adjusted for SO_2 and O_3 levels.

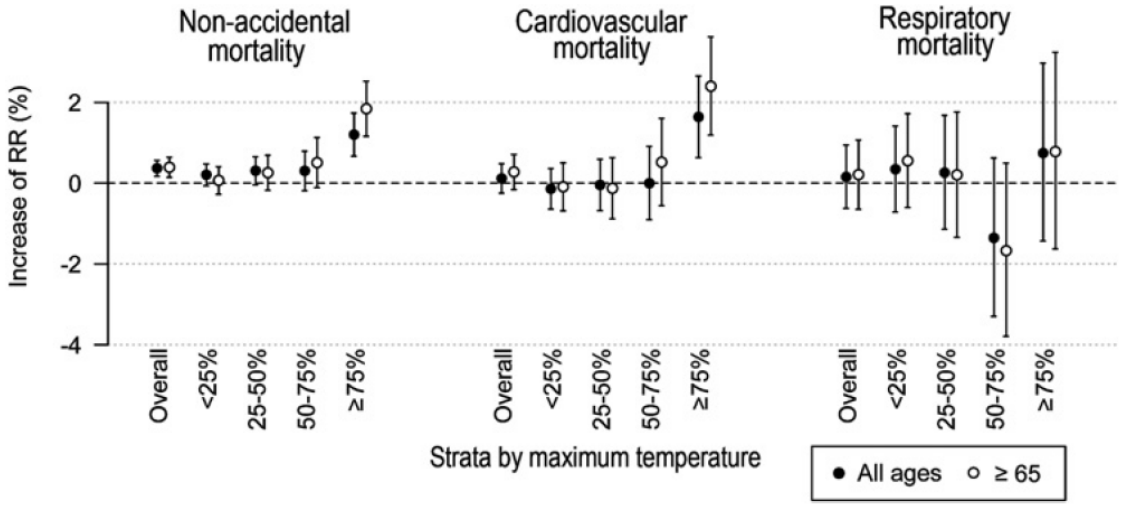


Table 8 Mean percentage change air pollution effects (95% CI) in older people (>65 years) with adjustment for other pollutants in the two-pollutant model in Seouk, Korea (1 June 1999 to 31 December 2007)

Pollutant	Mortality	Strata by temperature	No co-pollutant	Co-pollutant				
				PM_{10}	NO_2	SO_2	CO	O_3
PM_{10}	Non-accidental	Whole year	0.27 (0.07 to 0.47)*		0.08 (-0.14 to 0.31)	0.14 (-0.10 to 0.37)	0.07 (-0.17 to 0.30)	0.26 (0.05 to 0.46)*
		50-75%	0.42 (0.03 to 0.81)*		0.13 (-0.35 to 0.61)	0.33 (-0.18 to 0.83)	_0.09 (-0.58 to 0.40)	0.46 (0.06 to 0.87)*
		≥75%	0.63 (0.25 to 1.01)*		0.32 (-0.17 to 0.80)	0.07 (-0.41 to 0.56)	0.24 (-0.32 to 0.81)	0.59 (0.13 to 1.04)*
	Cardiovascular	≥75%	0.73 (0.06 to 1.40)*		0.78 (-0.07 to 1.64)	0.25 (-0.60 to 1.12)	0.69 (-0.31 to 1.70)	0.90 (0.11 to 1.71)*
	Respiratory	≥75%	1.40 (0.05 to 2.77)*		1.16 (-0.56 to 2.92)	0.91 (-0.83 to 2.67)	0.68 (-1.30 to 2.70)	1.23 (-0.38 to 2.88)
NO_2	Non-accidental	Whole year	0.28 (0.15 to 0.41)*	0.26 (0.12 to 0.39)*		0.26 (0.09 to 0.43)*	0.25 (0.02 to 0.47)*	0.28 (0.15 to 0.41)*
		<25%	0.23 (0.00 to 0.46)	0.26 (0.01 to 0.52)*		0.11 (-0.21 to 0.43)	0.15 (-0.28 to 0.58)	0.21 (-0.07 to 0.49)
		50-75%	0.40 (0.16 to 0.63)*	0.36 (0.07 to 0.65)*		0.41 (0.11 to 0.72)*	0.12 (-0.21 to 0.46)	0.40 (0.16 to 0.63)*
		≥75%	0.49 (0.23 to 0.74)*	0.40 (0.07 to 0.73)*		0.11 (-0.25 to 0.47)	0.28 (-0.10 to 0.67)	0.46 (0.14 to 0.78)*
	Cardiovascular	Whole year	0.24 (0.01 to 0.47)*	0.20 (-0.03 to 0.44)		0.20 (-0.10 to 0.50)	0.08 (-0.31 to 0.47)	0.24 (0.01 to 0.46)*
		50-75%	0.41 (0.00 to 0.82)	0.49 (-0.01 to 1.00)		0.38 (-0.15 to 0.91)	0.03 (-0.56 to 0.62)	0.41 (-0.01 to 0.82)
		≥75%	0.79 (-0.14 to 1.72)	0.36 (-0.80 to 1.55)		0.20 (-1.10 to 1.51)	0.04 (-1.32 to 1.42)	0.64 (-0.50 to 1.79)
	Respiratory	Whole year	0.28 (0.10 to 0.45)*	0.23 (0.04 to 0.42)*	0.04 (-0.20 to 0.27)		0.09 (-0.15 to 0.33)	0.27 (0.09 to 0.45)*
		<25%	0.27 (0.01 to 0.52)*	0.37 (0.06 to 0.68)*	0.18 (-0.17 to 0.54)		0.20 (-0.18 to 0.57)	0.24 (-0.02 to 0.51)
		50-75%	0.39 (-0.01 to 0.79)	0.20 (-0.31 to 0.72)	_0.06 (-0.57 to 0.47)		_0.14 (-0.64 to 0.35)	0.40 (-0.02 to 0.83)
		≥75%	1.22 (0.70 to 1.75)*	1.26 (0.57 to 1.95)*	1.09 (0.36 to 1.83)*		1.02 (0.35 to 1.69)*	1.23 (0.63 to 1.84)*
SO_2	Non-accidental	Whole year	0.24 (0.01 to 0.47)*	0.20 (-0.03 to 0.44)		0.20 (-0.10 to 0.50)	0.08 (-0.31 to 0.47)	0.24 (0.01 to 0.46)*
		<25%	0.23 (0.00 to 0.46)	0.26 (0.01 to 0.52)*		0.11 (-0.21 to 0.43)	0.15 (-0.28 to 0.58)	0.21 (-0.07 to 0.49)
		50-75%	0.40 (0.16 to 0.63)*	0.36 (0.07 to 0.65)*		0.41 (0.11 to 0.72)*	0.12 (-0.21 to 0.46)	0.40 (0.16 to 0.63)*
		≥75%	0.49 (0.23 to 0.74)*	0.40 (0.07 to 0.73)*		0.11 (-0.25 to 0.47)	0.28 (-0.10 to 0.67)	0.46 (0.14 to 0.78)*
	Cardiovascular	Whole year	0.24 (0.01 to 0.47)*	0.20 (-0.03 to 0.44)		0.20 (-0.10 to 0.50)	0.08 (-0.31 to 0.47)	0.24 (0.01 to 0.46)*
		50-75%	0.41 (0.00 to 0.82)	0.49 (-0.01 to 1.00)		0.38 (-0.15 to 0.91)	0.03 (-0.56 to 0.62)	0.41 (-0.01 to 0.82)
		≥75%	0.79 (-0.14 to 1.72)	0.36 (-0.80 to 1.55)		0.20 (-1.10 to 1.51)	0.04 (-1.32 to 1.42)	0.64 (-0.50 to 1.79)
	Respiratory	Whole year	0.28 (0.10 to 0.45)*	0.23 (0.04 to 0.42)*	0.04 (-0.20 to 0.27)		0.09 (-0.15 to 0.33)	0.27 (0.09 to 0.45)*
		<25%	0.27 (0.01 to 0.52)*	0.37 (0.06 to 0.68)*	0.18 (-0.17 to 0.54)		0.20 (-0.18 to 0.57)	0.24 (-0.02 to 0.51)
		50-75%	0.39 (-0.01 to 0.79)	0.20 (-0.31 to 0.72)	_0.06 (-0.57 to 0.47)		_0.14 (-0.64 to 0.35)	0.40 (-0.02 to 0.83)
		≥75%	1.22 (0.70 to 1.75)*	1.26 (0.57 to 1.95)*	1.09 (0.36 to 1.83)*		1.02 (0.35 to 1.69)*	1.23 (0.63 to 1.84)*
CO	Non-accidental	Whole year	0.28 (0.13 to 0.44)*	0.25 (0.09 to 0.41)*	0.05 (-0.21 to 0.31)	0.23 (0.03,0.44)*		0.28 (0.13 to 0.44)*
		<25%	0.21 (-0.01 to 0.44)	0.30 (0.03 to 0.58)*	0.08 (-0.33 to 0.50)	0.09 (-0.23 to 0.42)		0.18 (-0.07 to 0.44)
		50-75%	0.63 (0.33 to 0.93)*	0.67 (0.30 to 1.05)*	0.48 (0.04 to 0.92)*	0.68 (0.31 to 1.05)*		0.63 (0.33 to 0.94)*
		≥75%	0.72 (0.32 to 1.12)*	0.63 (0.03 to 1.23)*	0.38 (-0.21 to 0.98)	0.22 (-0.29 to 0.74)		0.66 (0.20 to 1.12)*
	Cardiovascular	Whole year	0.31 (0.04 to 0.57)*	0.26 (-0.03 to 0.55)	0.23 (-0.22 to 0.69)	0.29 (-0.07 to 0.65)		0.31 (0.04 to 0.57)*
		50-75%	0.69 (0.16 to 1.23)*	0.86 (0.19 to 1.53)*	0.67 (-0.11 to 1.45)	0.72 (0.06 to 1.38)*		0.68 (0.15 to 1.22)*
	Respiratory	≥75%	1.57 (0.14 to 3.01)*	1.13 (-0.97 to 3.27)	1.51 (-0.60 to 3.67)	1.10 (-0.72 to 2.95)		1.42 (-0.21 to 3.08)

Pollutant	Mortality	Strata by temperature	No co-pollutant	Co-pollutant				
				PM_{10}	NO_2	SO_2	CO	O_3
O_3	Non-accidental	Apr-Sept	0.36 (0.03 to 0.69)*	0.28 (-0.06 to 0.63)	0.19 (-0.16 to 0.54)	0.21 (0.14 to 0.57)	0.11 (-0.25 to 0.46)	
		≥75%	0.45 (0.04 to 0.87)*	0.29 (-0.23 to 0.81)	0.17 (-0.39 to 0.74)	0.09 (-0.39 to 0.57)	0.20 (-0.29 to 0.69)	
	Respiratory	Apr-Sept	1.00 (-0.19 to 2.20)	1.11 (-0.12 to 2.35)	0.93 (-0.31 to 2.19)	0.96 (-0.30 to 2.23)	0.67 (-0.59 to 1.95)	
		<25%	2.46 (-0.34 to 5.34)	2.64 (-0.18 to 5.53)	2.57 (-0.24 to 5.46)	2.72 (-0.26 to 5.79)	2.26 (-0.54 to 5.15)	

*Significance values $p<0.05$.

Critique

The most serious drawback of this study is its ecological design which all but ensures that some exposure misclassification has occurred. The nature of the error caused by this misclassification is difficult to predict, however, given the complex multivariate design. In all likelihood both types of error (classical and Berksonian) probably exist to differing degrees (Sheppard *et al.*, 2012). Whereas, the classical error causes a bias towards the null, the Berksonian error causes inaccurate confidence interval estimates, but no bias (Zeger *et al.*, 2000). In addition to these problems, it is difficult to making any definitive statements regarding SO_2 involvement with mortality at high ambient temperatures since hot days alone were shown to be associated with increased non-accidental and cardiovascular mortality. In addition, the cardiovascular and respiratory mortality associations observed on hot days with those >65 years of age were not robust to the inclusion of PM_{10} into the model, which is consistent with the fact that ambient SO2 levels are a good proxy for personal particulate matter exposures especially during the summer season (Sarnat *et al.*, 2005). These findings are important because they demonstrate the importance of considering co-pollutant effects and confounding that can arise from an over reliance on the results from single pollutant models. Finally, the importance of elevated ambient temperatures as an effect modifier needs to be considered since they may be causing mortality displacement whereby the pool of individuals in very poor health and at a high risk of death are the only individuals affected (Basu, 2009). In other words, the observed interactions between air pollution and temperature may simply reflect a harvesting phenomenon that is primary attributable to the elevated temperatures (Kolb *et al.*, 2007).

2. **Chen, R. J., Huang, W., Wong, C. M., Wang, Z., Thach, T.Q., Chen, B., and Kan, H. 2012. Short-term exposure to sulfur dioxide and daily mortality in 17 Chinese cities: The China air pollution and health effects study (CAPES). Environmental Research 118:101-106.**

Rating
Low quality (⊕⊕◯◯)

Description
A two stage Bayesian hierarchical model was used to examine the association between PM_{10}, SO_2, and NO_2 and mortality from total, circulatory, & respiratory causes in 17 Chinese cities as part of the CAPES (Chinese Air Pollution and Health Effects Study) evaluation. Daily average exposure concentration of NO_2 were collected from 2-13 fixed monitoring units located at background sites within each city and indicated an mean concentration ranging from 16 µg/m³ in Fuzou to 66 µg/m³ in Lanzhou. The time series investigation took place over a 2-7 year period beginning in 1996. Mortality information were collected from death certificates and coded according to the International Classification of Disease (ICD-10). Total deaths were not reported but average daily rates ranged from 11 in Tianjin to 119 in Shanghai. Confounding from temperature, humidity, and day of week effects were considered. The first modeling stage included the use of generalized linear models and Poisson regression for individual cities followed by the application of Bayesian hierarchical statistical models for the pooled data. Lag periods of 0, 1, 2, 3, and 4 days were applied along with a average lag period of 01days. Single and two-pollutant models were examined.

Results
The pooled percentage increase in mortality per 10 µg/m³ increase in SO_2 using single and two-pollutant for average day lag 01 are shown in **Table 9**. The significant associations observed in single pollutant models were robust to the incorporation of PM_{10} but not NO_2. The ambient air levels of SO_2 were highly correlated with PM_{10} (r=0.49) and NO_2 (r=0.65). A statistically significant association was observed in single-pollutant models for total, cardiovascular, and respiratory mortality at daily lag periods of 0, 1, 2, 3, and 4 days and 2-day average lag (01). Stronger associations were observed for those greater than 65 years of age, female gender, and low socioeconomic status. Appreciable heterogeneity was observed for all cause mortality associations in the 17 cities that was attributed to the characteristics of the study sites, including such factors as weather patterns, topography, underlying susceptibility of the population (due to or reflected by socioeconomic status, age structure, and smoking prevalence), air pollution levels. The strongest associations with all three mortality types were observed for the average lag periods of 01 days.

Table 9 Pooled estimates (mean and 95% CI) for the increase in mortality associated with an increase of 10 µg/m³ in SO_2 (average of lags 0 and 1 of the 24-h average concentrations) in the CAPES cities

Model type	Co-pollutant	Total mortality		Cardiovascular mortality		respiratory mortality	
		% Increase	95% CI	% Increase	95% CI	% Increase	95% CI
Single-pollutant	–	0.75	0.47 – 1.02	0.83	0.47 – 1.19	1.25	0.78 – 1.73
Multi-pollutant	+ PM_{10}	0.42	0.17 – 0.67	0.38	0.03 – 0.73	0.77	0.34 – 1.20
Multi-pollutant	+NO_2	0.16	-0.06 – 0.38	0.18	00.18 – 0.54	0.44	-0.01 – 0.90

Critique
This study suffers from many of same problems observed with other studies with SO_2. The severe exposure misclassification arising out of the use of measurements from background monitoring sites as a proxy for personal exposures is noteworthy. This calls the results into question and suggests that the exposures may well have been unrepresentative of the levels at an individual's residence. The study also failed to factor in the impact of influenza outbreaks and holidays into the time series analysis. Furthermore, the focus on just a few contaminants overlooked the distinct possibility that interactions could be occurring with $PM_{2.5}$, CO, O_3, UFP, and PAHs. This may explain the statistically significant heterogeneity observed across the different cities examined in this study, since the correlations with the true causal agent would be expected to differ depending on environmental factors at each location. This study also failed to investigate probable sources for the significant inter-city heterogeneity that was observed. This is a particularly serious oversight since China has the highest prevalence of tobacco use in the world and this secondary source of pollutant exposure could be distorting the findings (Giovino *et al.*, 2013). Finally the lag structure observed in this study suggests that mortality displacement effects may be occurring that is primarily affecting the pool of frail individuals who are close to death.

3. **Cakmak, S., Dales, R. E., Rubio, M. A., and Vidal, C. B. 2011. The risk of dying on days of higher air pollution among the socially disadvantaged elderly. Environmental Research 111:388-393.**

Rating
Insufficient (⊕◯◯◯)

Description
This time series investigation focused on the mortality among socially disadvantaged elderly living in seven municipalities within Chili. Total mortality rates were determined for PM_{10}, $PM_{2.5}$, EC, OC, NO_2, CO, O_3, oxygenated VOCs, and SO_2 using information from a single fixed monitoring site located in each city. Daily SO_2 averages were as follows for the seven cities: Independencia 14.5 (38.6 µg/m³), La Florida 12.6 (33.5 µg/m³), Las Condes 8.5 ppb (22.5 µg/m³), Santiago 12.5 ppb (33.3 µg/m³), Pudahuel 9.3 ppb (24.7 µg/m³), Cerrillos 13.2 ppb (35.1 µg/m³), and El Bosque 13.3(35.1 µg/m³). The interquartile range was provided for the the individual cites ICD-9 criteria were used judge the cause of death and the rates ranged from 7.29 to 15.6 deaths/day in the seven cities. Poisson distributions were applied using natural alpine smoothing along with unstated modeling algorithm. Weather variables such as temperature, humidity, barometric pressure, humidex, and day of week were taken into consideration. Effect modification by age gender, education, income, and occupation were examined. The analysis was confined to single-pollutant models with the distributed lag period constrained to 7 days. A random effects model was used to pool the results from the individual cities.

Results
Statistically significant increases in relative risk found in virtually every categorical comparison per unstated IQR increase using a single-pollutant model. Some of the most salient relative risk estimates were observed in the three stratified age groups greater than 65 years of age. There were no distinct differences in the risk ratios for males and females, those with the lowest or highest level of education, those with a high (>$13,395/yr) or low (<$8,800/yr) income level, or those who employed or unemployed. The overall association of SO_2 with mortality in all individuals in a single-pollutant model was 1.089 (95% CI 1.064 - 1.114).

Table 10 Spearman correlations between air pollutants for seven urban centers in Chile from January 1997 to December 2007. The minimum and maximum urban center-specific correlations are presented

Pollutant	O_3 (ppb)	NO_2 (ppb)	SO_2 (ppb)	PM_{10} (µg/m3)	$PM_{2.5}$ (µg/m3)	EC (µg/m3)	OC (µg/m3)
CO (ppm)	- 0.49: - 0.3	0.79:0.85	0.34:0.71	0.63:0.83	0.75:0.9	0.73:0.86	0.66:0.76
O_3 (ppb)	1:01	- 0.4: - 0.25	- 0.045:0.097	- 0.18:0.091	- 0.32: - 0.16	- 0.35: - 0.29	- 0.43: - 0.34
NO_2 (ppb)			0.3:0.63	0.63:0.77	0.73:0.82	0.63:0.8	0.64:0.64
SO_2 (ppb)				0.44:0.72	0.39:0.67	0.3:0.69	0.34:0.48
PM_{10} (µg/m3)					0.86:0.9	0.53:0.77	0.52:0.72
$PM_{2.5}$ (µg/m3)						0.67:0.84	0.64:0.83
EC (µg/m3)							0.31:0.65

Critique
This was a very poorly conducted study for many reasons including the noticeable lack of methodological detail. Two-pollutant modeling was not performed with co-pollutants despite the high correlations that were observed (see **Table 10**) . As shown, a high degree of correlation observed between SO_2 and CO, NO2, PM_{10}, $PM_{2.5}$, EC, and OC. In addition, many of the experimental details were not described including the modeling details and an interquartile range was not provided for the pooled analysis. Exposure misclassification was highly likely given the application of monitoring data from a single site over a wide spatial domain. The magnitude of the observed associations was not affected by any of the co-variates that were examined, whic raise considerable suspicions about the conduct and interpretation of the findings from this study. The absence of a sensitivity analysis to assess the reliability of the modeling approach should have been performed to ensure that the underlying assumptions were robust (Bhaskaran *et al.*, 2013).

Acute Hospitalization

1. **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. 2007b. 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
A retrospective time series study was conducted over a period of 6 years using pollutant measurements collected at 14 fixed monitoring sites located in Hong Kong, China. A total of 69,716 men and women of all ages were surveyed to determine the rate of hospitalization for asthma relative to airborne levels of $PM_{2.5}$, PM_{10}, NO_2, O_3, and SO_2. The daily average concentration of SO_2 18.8 µg/m³ for the entire year, 18.0 µg/m³ for the cold season (<20 °C), and 19.1 µg/m³ for the warm season (≥20 °C). A large number of lag periods were examined that included single lags of 0, 1, 2, 3, 4, and 5 days and cumulative lag periods 0-1, 0-2, 0-3, 0-4, and 0-5 days. A generalized additivity model was applied using Poisson regression to control for temperature, humidity, day of week, and holidays.

Results
An association with asthma hospitalization was not observed with all subjects at any of the eleven lag periods examined with a single pollutant model. Following stratification, a statistically significant association was observed with asthma hospitalization in one of three age groups (>14-65 years of age) using a single pollutant model and a cumulative lag of 0-3 days (see **Table 11**). An association with hospitalization was not seen in the 0-14 yrs age group or the >65 year age group per 10 µg/m³ increase using a single pollutant model. In addition, **Table 12** shows that there was no statistically significant association using a three-pollutant model with O_3 and NO_2 on lag day 0. The levels of SO_2 were found to be highly correlated with NO_2 (r=0.57), $PM_{2.5}$ (r=0.48), and PM_{10} (r=0.44).

Table 11 Relative risk and 95% confidence intervals for pollutants per 10 µg/m³ increase in concentration using a single pollutant model for hospitalization due to acute exacerbation of asthma in different age groups

Pollutant	Age group		Age group		Age group	
	best lag (days)	0–14 years	best lag (days)	>14-65 years	best lag (days)	>65 years
NO_2	0–4	1.039 (1.028–1.051)	0–4	1.018 (1.007–1.029)	0–4	1.023 (1.014–1.033)
O_3 (8 hrs)	0–5	1.039 (1.030–1.048)	0–5	1.041 (1.032–1.050)	0–4	1.023 (1.015–1.030)
PM_{10}	0–5	1.023 (1.015–1.031)	0–5	1.014 (1.006–1.022)	0–4	1.015 (1.009–1.022)
$PM_{2.5}$	0–4	1.024 (1.013–1.034)		1.018 (1.008–1.029)	0–4	1.021 (1.012–1.030)
SO_2	---	not significant	0–3	1.018 (1.001–1.035)	---	not significant

Table 12 Relative risk and 95% confidence intervals for the pollutants per 10 µg/m³ increase in the concentration for hospitalizations due to asthma (multi-pollutant model)

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

* Statistically significant (P<0.05).

Critique

Although generally well conducted, this study did suffer from a number of minor deficiencies that may have impacted the outcome. The most notable of these limitations include the failure to perform any geo-coding or distance weighting to account for the differences in airborne levels of SO_2 between the monitoring site location and a subject's residence. The analysis also failed to take into consideration the impact of influenza outbreaks, which have been shown to impact asthma hospitalization rates (O'Riordan *et al*., 2010). Finally, the strength of the study would have been increased if CO measurements were included in the analysis.

2. **Lee, I. M., Tsai, S. S., Ho, C. K., Chiu, H. F., and Yang, C. 2007. Air pollution and hospital admissions for congestive heart failure in a tropical city: Kaohsiung, Taiwan. Inhalation Toxicology 19:899-904.**

Rating
Low quality (⊕⊕◯◯)

Description
This case crossover analysis examined hospital admissions for congestive heart failure in relation to airborne levels of PM_{10}, nO_2, O_3, CO, and sO_2 in Kaohsiung, Taiwan. The mean daily SO_2 concentration at six fixed monitoring locations was found to be 9.32 ppb (24.8 µg/m³). A total of 13,475 admissions were examined over a 6 year period using ICD-9 coding. Confounding from temperature, humidity, and day of week effects were handled using conditional logistic regression and an unstated type of smoothing spline. A cumulative average lag period of 0-2 days was applied. The effect modification by daily temperatures greater than or less than 20 °C was examined in both single and two-pollutant models.

Results
A statistically significant association was shown to exist for SO_2 exposures and admissions for congestive heart failure on cold days using a single-pollutant model with a cumulative lag of 0-2 days. The odds ratio per interquartile SO_2 increase of 5.53 ppb (14.7 µg/m³) in a single-pollutant model were 1.15 (95% CI 1.03 - 1.29) on the cold (<25 ˚C) days. A significant association was also found in two-pollutant models with O3 on cold days. No significant associations were found to exist with PM_{10}, NO_2, or CO on warm or cold days. Of the pollutants examined, the highest odds ratios were generally observed for NO_2 in both single and two-pollutant models.

Table 13 ORs (95% CI) of CHF admissions for each interquartile range change in two-pollutant models.†

	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}										
>25 °C	—	—	1.25*	1.08–1.45	1.23*	1.02–1.50	1.15	0.98–1.35	1.00	0.83–1.20
<25 °C	—	—	1.48*	1.30–1.68	1.05	0.89–1.23	1.2*9	1.11–1.51	1.46*	1.28–1.67
SO_2										
>25 °C	1.02	0.95–1.09	—	—	1.00	0.92–1.08	0.96	0.88–1.04	1.07	0.99–1.15
<25 °C	1.01	0.90–1.14	—	—	0.78*	0.67–0.89	1.00	0.88–1.13	1.16*	1.04–1.31
NO_2										
>25 °C	1.03	0.85–1.26	1.20*	1.02–1.41	—	—	0.95	0.77–1.17	1.05	0.90–1.24
<25 °C	1.83*	1.52–2.19	2.25*	1.90–2.67	—	—	2.01*	1.64–2.46	1.85*	1.61–2.12
CO										
>25 °C	1.15*	1.04–1.27	1.23*	1.11–1.36	1.22*	1.08–1.39	—	—	1.17*	1.07–1.28
<25 °C	1.21*	1.06–1.38	1.39*	1.24–1.55	0.94	0.81–1.10	—	—	1.36*	1.22–1.51
O_3										
>25 °C	1.25*	1.12–1.39	1.27*	1.16–1.38	1.24*	1.13–1.36	1.24*	1.13–1.35	—	—
<25 °C	1.04	0.90–1.20	1.26*	1.10–1.43	1.13	0.99–1.29	1.16*	1.02–1.33	—	—

† Calculated for an interquartile range increases of PM_{10} (62.53 $\mu g/m^3$), SO_2 (5.53 ppb), NO_2 (16.85 ppb), CO (0.31 ppm), and O_3 (20.18 ppb).
* $p < 0.05$

Critique

This is one of many case-crossover studies performed by a group of investigators at Kaohsiung University. This is generally a well conducted study that included a sufficiently large number of cases and a multi-pollutant design. The researchers, however, used SAS software for their statistical analysis; however, a recent investigation found that SAS may cause a 22%-39% bias away from the null if used improperly (Wang et al., 2011a). The problem lies in the selection of the curve fitting parameters, but this information was omitted from the materials and methods section of the paper. Consequently, it is impossible to say whether the study results are biased, but the possibility exists despite the failure to observe statistically significant odds ratios for SO_2. For these and other reasons related to the disparity in temperature-related associations, the results from this and other studies by this group should be discounted.

3. **Rich, D. Q., Kipen, H. M., Zhang, J. F., Kamat, L., Wilson, A. C., and Kostis, J. B. 2010. Triggering of transmural infarctions, but not nontransmural infarctions, by ambient fine particles. Environmental Health Perspectives 118:1229-1234.**

Rating
Insufficient (⊕◯◯◯)

Description
A case crossover study was performed to determine the relationship between patient admissions for transmural myocardial infarction and exposure to $PM_{2.5}$, O_3, NO_2, CO, and SO_2 in the state of New Jersey. Daily average SO_2 levels were determined at nine fixed monitoring stations; however the average concentrations were not provided. A total of 5864 myocardial infarction cases in male and female patients greater than 18 years of age were identified using ICD-9 criteria. Time stratified conditional logistic regression with natural spline smoothing was used to adjust for the effects of ambient temperature, dew point, and day of week. A single lag period of 0 days was examined. Effect modification was performed for COPD status, diabetes status, age, sex, race, and season was determined for $PM_{2.5}$ but not SO_2.

Results
SO_2 levels were highly correlated with NO_2 (r=0.56), CO (r=0.42), and $PM_{2.5}$ (r=0.44). As shown in **Table 14**, no statistically significant increases in relative risk were found between SO_2 and transmural infarctions on lag day 0 in either single or two-pollutant model with $PM_{2.5}$ for and interquartile increase of 4.1 ppb (10.9 µg/m³).

Table 14 Risk of transmural infarction (and 95% CI) associated with each IQR increase in mean pollutant concentration in the previous 24 hr.†

Pollutant	Model type	No. of infarctions	OR (95% CI)
$PM_{2.5}$	Single pollutant	1,262	1.10 (1.00–1.21)
NO_2	Single pollutant		1.11 (0.97–1.25)
$PM_{2.5}$	Two pollutant		1.08 (0.96–1.22)
NO_2	Two pollutant		1.04 (0.88–1.22)
$PM_{2.5}$	Single pollutant	1,183	1.08 (0.98–1.19)
CO	Single pollutant		1.02 (0.93–1.12)
$PM_{2.5}$	Two pollutant		1.10 (0.98–1.22)
CO	Two pollutant		0.97 (0.87–1.08)
$PM_{2.5}$	Single pollutant	1,238	1.08 (0.98–1.18)
SO_2	Single pollutant		1.02 (0.93–1.11)
$PM_{2.5}$	Two pollutant		1.10 (0.98–1.24)
SO_2	Two pollutant		0.96 (0.86–1.08)

Pollutant	Model type	No. of infarctions	OR (95% CI)
$PM_{2.5}$	**Single pollutant**		**1.08 (0.97–1.21)**
O_3	**Single pollutant**		**0.95 (0.81–1.12)**
$PM_{2.5}$	**Two pollutant**	**1,003**	**1.08 (0.97–1.21)**
O_3	**Two pollutant**		**0.95 (0.81–1.11)**

† IQR = 10.8 µg/m3 for $PM_{2.5}$, 16 ppb for NO_2, 0.35 ppm for CO, 4.1 ppb for SO_2, and 18 ppb for O_3.

Critique

The primary focus of this study was on $PM_{2.5}$ with few descriptive details provided for SO_2. The study results are not particularly compelling given the limited number of lag days, the failure to describe the monitoring results, the high probability of case and exposure misclassification with an overreliance on administrative coding of cases, the inability to consider those who died before admission, and an overreliance on admission time rather than pain onset to gauge pollutant impact.

Acute Emergency Department Visits

1. **Farhat, S. C. L., Paulo, R. L. P., Shimoda, T. M., Conceicao, G. M. S., Lin, C. A., Braga, A. L. F., Warth, M. P. N., and Saldiva, P. H. N. 2005. Effect of air pollution on pediatric respiratory emergency room visits and hospital admissions. Brazilian Journal of Medical and Biological Research 38:227-235.**

Rating
Moderate quality (⊕⊕⊕◯)

Description
Single, two-pollutant, and multi-pollutant models were used to examine the relationship between PM_{10}, NO_2, O_3, CO, and SO_2 levels and pediatric hospital and emergency room visits for lower respiratory disease (pneumonia, bronchopneumonia, asthma, and bronchiolitis) in Sao Paulo, Brazil. Daily measurements from 6 urban fixed monitoring sites showed very high concentrations of SO_2 in ambient air that averaged 23.7 ± 10.0 µg/m³ over 396 days. The minimum concentration of SO_2 observed during this period was 3.4 µg/m³ and the maximum was 75.2 µg/m³. A total of 4534 hospital admissions or visits were recorded for male and female children less than 13 years of age. A generalized additivity model with Poisson regression and non-parametric LOESS smoothing was used to correct for temperature, humidity, and day of week effects. Moving average lag periods ranging from 0-1 to 0-7 days were examined and the highest risk changes were greatest for a 5-day lag period of 0-4 days. The multi-pollutant models considered the effect of the remaining four pollutants.

Results
The wide interquartile range indicates a broad distribution in NO_2 exposure levels.
Airborne concentrations of SO_2 were strongly correlated with the remaining 4 pollutants with coefficients ranging from 0.69 for PM_{10} to 0.28 for O_3. A moderate statistically significant association was shown to exist with hospital admissions and visits for lower respiratory diseases as well as pneumonia or bronchopneumonia using a single pollutant model with a moving average lag of 0-4 days. Statistically significant associations were also observed with lower respiratory admissions and visits using a two pollutant model with CO and with pneumonia or bronchopneumonia using two-pollutant models with O_3 and CO. No statistically significant positive associations were observed for lower respiratory tract or pneumonia or bronchopneumonia ED visits or admissions using a two-pollutant model with PM_{10}, NO_2, or with the multi-pollutant models (see Tables 15 and 16). A significant negative association was observed for lower respiratory tract disease and SO_2 using a multi-pollutant model. Significant associations were not seen for asthma and bronchiolitis hospital admissions and visits susingsingle-, two-, or multi-pollutant models.

Table 15 Increases of lower respiratory tract disease emergency room visits due to interquartile range increases in 5-day moving average of PM_{10}, 4-day moving average of NO_2, 5-day moving average of SO_2, 4-day moving average of O_3, and 2-day moving average of CO in a multi-pollutant and co-pollutant models.†

	Co-pollutant model					Multi-pollutant model
	PM_{10}	**NO_2**	**SO_2**	**O_3**	**CO**	
PM_{10}	-	**2.1 (-7.1 - 11.3)**	**16.5* (10.5 - 22.6)**	**10.1* (5.0 - 15.2)**	**14.1* (8.1 - 20.2)**	**5.2 (-4.6 - 15.1)**
NO_2	**16.1* (5.4 - 26.8)**	-	**24.7* (18.2 - 31.3)**	**16.1* (9.5 - 22.7)**	**19.2* (11.8 - 26.6)**	**18.4* (3.4 - 33.5)**
SO_2	**-3.44 (-10.8 - 3.62)**	**-7.0* (-13.8 - -0.15)**	-	**4.47 (-1.6 - 10.5)**	**8.2* (1.87 - 14.5)**	**-7.9* (-0.6 - -15.3)**
O_3	**7.7* (0.7 - 14.7)**	**3.0 (-4.0 - 10.0)**	**12.0* (5.6 - 18.4)**	-	**13.1* (7.0 - 19.2)**	**2.6 (-5.4 - 10.6)**
CO	**-0.1 (-5.6 - 5.3)**	**-1.2 (-6.7 - 4.2)**	**3.7 (-1.0 - 8.4)**	**4.8* (0.5 - 9.1)**	-	**-0.64 (-6.9 - 5.6)**

† Data are reported as percent increase and 95% confidence interval. PM_{10} = particulate matter with aerodynamic diameter smaller than 10 µm. *P < 0.05 (likelihood-ratio test: full model *vs* reduced model).

Table 16 Increases of pneumonia or bronchopneumonia hospital admissions due to interquartile range increases in 2-day moving average of PM_{10}, 2-day moving average of NO_2, 2-day moving average of SO_2, 3-day moving average of O_3, and 2-day moving average of CO in a multi-pollutant and co-pollutant models.†

	Co-pollutant model					Multi-pollutant model
	PM_{10}	**NO_2**	**SO_2**	**O_3**	**CO**	
PM_{10}	-	14.8 (-3.8 - 33.4)	14.8 (-0.3 - 30.0)	16.2* (1.0 - 31.3)	17.6* (0.4 - 34.8)	5.23 (-16.2 - 26.6)
NO_2	8.11 (-11.4 - 27.6)	-	13.1 (-3.4 - 29.7)	12.4 (-5.6 - 30.4)	14.6 (-4.9 - 34.1)	1.8 (-23.9 - 27.6)
SO_2	13.3 (-5.7 - 32.3)	16.5 (-1.6 - 34.6)	-	18.4* (0.5 - 36.2)	18.4* (0.5 - 36.2)	13.3 (-5.9 - 32.6)
O_3	10.9 (-10.4 - 32.2)	12.6 (-88.7 - 33.9)	16.0 (-4.2 - 36.1)	-	19.4* (0.4 - 38.4)	12.0 (-11.7 - 35.7)
CO	4.4 (-7.9 - 16.7)	4.4 (-88.7 - 17.5)	7.8 (-2.5 - 18.2)	9.6 (-0.5 - 19.7)	-	5.1 (-9.6 - 19.7)

† Data are reported as percent increase and 95% confidence interval. PM_{10} = particulate matter with aerodynamic diameter smaller than 10 µm. *P < 0.05 (likelihood-ratio test: full model *vs* reduced model).

Critique
This study examined the associations with both hospitals admissions and visits and included a somewhat limited number of total cases. In addition, the distribution of SO_2 concentrations was quite high with the yearly mean of 23.7 µg/m³ exceeded the WHO daily limit of 20 µg/m³. There was no examination of effect modifiers such as sex, age, or season. Very suspicious and highly implausible protective effects were observed for SO_2 when it was included in a co-pollutant model with NO_2 and in a multi-pollutant model, which raises some doubt about the veracity of the measurements (see **Table 15** and **16**). In addition, the results from this study cannot be compared with others since the emergency room visits and admissions were combined. The author's of this study were not able to definitively ascribe the increase in hospital visits to any single-pollutant because of the ecological design and the significant associations observed with all five pollutants under some circumstances but not others.

2. **Strickland, M. J., Darrow, L. A., Klein, M., Flanders, W. D., Sarnat, J. A., Waller, L. A., Sarnat, S. E., Mulholland, J. A., and Tolbert, P. E. 2010. Short-term associations between ambient air pollutants and pediatric asthma emergency department visits. American Journal of Respiratory and Critical Care Medicine 182:307-316.**

Rating
Low quality (⊕⊕◯◯)

Description
This study used both case crossover and time-series designs to evaluate asthma emergency department visits by children with an age of 5-17 years in Atlanta, Georgia. 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}, $PM_{10\text{-}2.5}$, NO_2, CO, O_3, and SO_2 were examined. Population weighted hourly maximum concentrations were determined at an unstated number of fixed monitoring locations. Mean 1-hr maximum SO_2 levels 10.8 ppb (28.7 µg/m³) were found for the entire year, 9.6 ppb (25.5 µg/m³) for the warm season, and 12.0 ppb (31.9 µg/m³) for the cold season. The study examined a large number of cases (91,387 visits) that were coded using ICD-9 criteria. Confounding from ambient temperature, dew point, upper respiratory infections, pollen levels, day of season were accomplished using Poisson regression and generalized linear (GLM) and generalized additivity (GAM) models for the case-crossover and time series analysis, respectively. A moving average lag period of 0-2 days was examined as were single day lag periods ranging from 0 to 7 days.

Results
The case-crossover analysis using the GLM model showed a statistically significant association between SO_2 levels and asthma visits for the entire year and the warm season using a 3-day moving average lag period and an interquartile increase of 11.5 ppb (30.6 µg/m³) in a single-pollutant model. The rate ratios for asthma ER visits during the warm season was 1.030 (95% CI 1.002-1.058) versus 1.001 (95% CI 0.978-1.025). Similar significant associations ere observed for all eight of the single day lag periods examined (see **Figure 16**). An appreciably higher risk ratio of 1.033 (95% CI 1.006-1.062) was observed when the respiratory infections were not controlled for in the model. The GLM and GAM results were also found to be highly sensitive to the manner in which the year, month and day interactions were described within the models. No statistically significant association for the cold season either using the GLM model. As shown in **Table 17**, a comparison of the risk ratios by quintile showed statistically significant association at the third and fourth quintile, but not the second and fifth. The strongest associations were generally observed for O_3 in single and two-pollutant models. SO_2 levels were modestly correlated with NO_2 (r=0.37) and uncorrelated with PM_{10} (r=0.15).

Figure 16 Rate ratio and 95% confidence interval for SO_2 correspond to an interquartile range increase in the cumulative ambient pollutant concentration during the 8-day period of interest (lags 0–7).

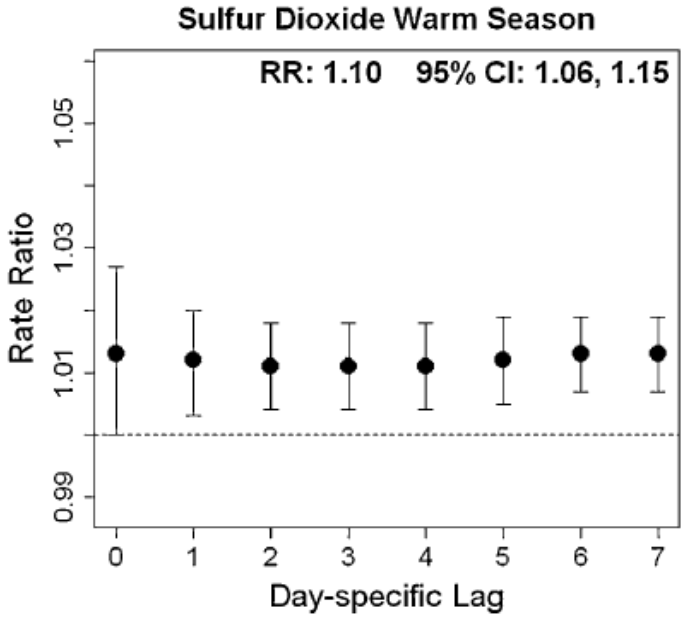


Table 17 Rate ratios and 95% confidence intervals for quintiles of three-day moving average population weighted ambient air pollutant concentrations.†

	Warm Season risk ratio (95% CI)*	**Cold Season risk ratio (95% CI)***
Ozone (ppb)		
Q2 (26.3 to <38.7)	**1.002 (0.953–1.054)**	**1.039 (0.998–1.081)**
Q3 (38.7 to <51.5)	**1.016 (0.961–1.074)**	**1.097 (1.037–1.161)**
Q4 (51.5 to <67)	**1.061 (0.999–1.127)**	**1.151 (1.065–1.243)**
Q5 (67 to ≤147.5)	**1.111 (1.038–1.189)**	**1.150 (1.013–1.306)**
Nitrogen dioxide (ppb)		
Q2 (28 to <37.1)	**1.033 (0.999–1.069)**	**0.996 (0.964–1.030)**
Q3 (37.1 to <46)	**1.040 (1.000–1.081)**	**0.984 (0.950–1.020)**
Q4 (46 to <57.1)	**1.087 (1.044–1.131)**	**1.024 (0.985–1.064)**
Q5 (57.1 to ≤181)	**1.087 (1.036–1.140)**	**1.014 (0.973–1.056)**

	Warm Season risk ratio (95% CI)*	Cold Season risk ratio (95% CI)*
Carbon monoxide (ppm)		
Q2 (0.70 to <1.01)	1.019 (0.986–1.054)	1.010 (0.977–1.045)
Q3 (1.01 to <1.05)	1.046 (1.008–1.086)	1.040 (1.005–1.076)
Q4 (1.05 to <2.30)	1.097 (1.049–1.147)	1.005 (0.969–1.042)
Q5 (2.30 to ≤.70)	1.112 (1.054–1.174)	1.021 (0.981–1.064)
Sulfur dioxide (ppb)		
Q2 (3.1 to <7)	1.021 (0.988–1.055)	0.968 (0.935–1.002)
Q3 (7 to <13)	1.041 (1.007–1.077)	0.998 (0.964–1.034)
Q4 (13 to <24.2)	1.048 (1.010–1.087)	0.982 (0.947–1.017)
Q5 (24.2 to <149)	1.008 (0.967–1.051)	0.987 (0.949–1.026)
PM_{10} (mg/m^3)		
Q2 (16 to <21.9)	1.014 (0.968–1.061)	1.008 (0.978–1.038)
Q3 (21.9 to <28	1.029 (0.981–1.080)	0.996 (0.963–1.030)
Q4 (28 to <36)	1.027 (0.979–1.078)	1.017 (0.977–1.059)
Q5 (36 to ≤98.4)	1.059 (1.006–1.116)	1.047 (0.991–1.106)
$PM_{10-2.5}$ (mg/m^3)		
Q2 (5 to <7.1)	0.975 (0.924–1.028)	0.972 (0.930–1.012)
Q3 (7.1 to <9.3)	0.986 (0.934–1.040)	1.006 (0.960–1.054)
Q4 (9.3 to <12.3)	0.964 (0.909–1.022)	1.045 (0.996–1.097)
Q5 (12.3 to ≤50.4)	1.005 (0.942–1.072)	1.075 (1.015–1.139)
$PM_{2.5}$ (mg/m^3)		
Q2 (10 to <13.7)	0.993 (0.943–1.047)	0.985 (0.952–1.019)
Q3 (13.7 to <17.6)	1.008 (0.956–1.062)	0.979 (0.943–1.017)
Q4 (17.6 to <23.8)	1.018 (0.966–1.073)	1.006 (0.960–1.049)
Q5 (23.8 to ≤65.8)	1.052 (0.995–1.112)	1.050 (0.997–1.106)

* Relative to the first quintile (concentrations less than the lower bound of the second quintile).
† Measurements available January 1993 to December 2004.
‡ Measurements available August 1998 to December 2004.
x Measurements available August 1998 to December 2004.

Critique
This is a very large study that included a sophisticated sensitivity analysis to examine potential misclassification bias. A good effort was made to control for the spatial variability of the SO_2 measurements by incorporating a population weighting scheme that reduces overall bias (Ivy *et al.*, 2008); however two-pollutant modeling was restricted to looking at interactions involving O_3 and five of the other pollutants with exception of SO_2. In addition, the number of monitoring sites included in the analysis was not stated and may have been unacceptably small. There results obtained for all eight lag days showed little variation and are suspiciously consistent. Overall, the study was nicely conceived and executed and there are only a few areas where some issues arise about its overall relevance. SO_2 levels were similar for both the warm and cold season, yet the statistically significant associations were only observed for the warm season. The explanation provided for this phenomenon included greater sensitivity, more time outdoors, reduced competition from viral outbreaks, and differing dose response functions; however none of these suppositions were systematically evaluated.

3. **Orazzo, F., Nespoli, L., Ito, K., Tassinari, D., Giardina, D., Funis, M., Cecchi, A., Trapani, C., Forgeschi, G., Vignini, M., Nosetti, L., Pigna, S., and Zanobetti, A. 2009. Air pollution, aeroallergens, and emergency room visits for acute respiratory diseases and gastroenteric disorders among young children in six Italian cities. Environmental Health Perspectives 117:1780-1785.**

Rating
Insufficient (⊕◯◯◯)

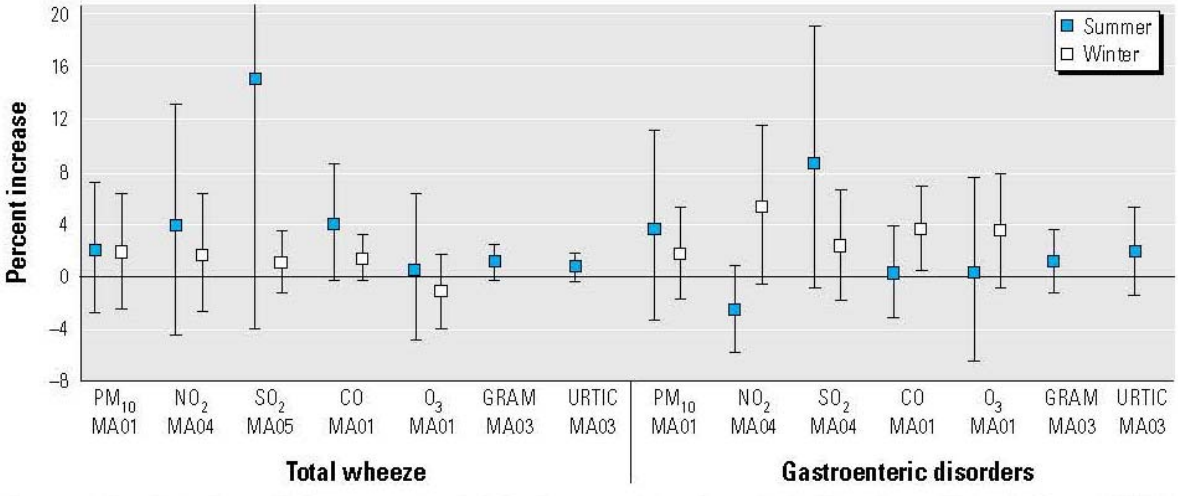
Description
This study focused on the relationship between emergency department visits for wheeze or acute gastrointestinal disease in children 0-2 years old and exposure to PM_{10}, O_3, CO, SO_2, NO_2, and two alloallergens (Graminaceae and Urticaceae) in six Italian cities. The daily mean concentration of SO_2 in Ancona, Bologna, Florence, Naples, Padua, and Varese-Gallarate ranged from 1.3 µg/m^3 in Varese-Gallarate to 2.6 µg/m³ in Naples. A case-crossover design was employed using conditional logistic regression and natural cubic splines to smooth for temperature and humidity. Control days were matched on the same day of the week in the same month and year using a time-stratified approach. The city specific effects were combined using a random effects meta-analyses. Admission rates ranged from 0.7-18.3 per day for wheeze and 0.4-8.0 per day for GI disorders. Moving average lag periods 0-1, 0-2, 0-3, 0-4, 0-5, and 0-6 days were employed.

Results
In the pooled analysis, there was a statistically significant association for wheeze admissions using an adjusted single-pollutant model with moving average lag periods of 0-3, 0-4, 0-5, or 0-6 days as shown in **Table 18**. There was also a significant association with admissions for gastrointestinal disorders for a lag period of 0-5 and 0-6 days. Stratification by season did not reveal and significant associations for summer (Apr-Sept) or winter (Oct-Mar) (see **Figure 17**).

Table 18 Pooled percentage increase (95% CI) in risk of wheeze or gastroenteric disorders for an interquartile (IQR) increase in air pollution across the six cities.

Pollutant	Percent (95% CI)	IQR	p-Value for homogeneity
Wheeze ED visits			
SO2 lag 0–1	0.1 (–1.4 to 1.6)	8.7	0.85
SO2 lag 0–2	0.9 (–0.7 to 2.5)	8.5	0.90
SO2 lag 0–3	1.7 (0.0 to 3.4)	8.3	0.82
SO2 lag 0–4	2.1 (0.4 to 3.9)	8.2	0.54
SO2 lag 0–5	2.8 (0.9 to 4.6)	8.1	0.52
SO2 lag 0–6	3.4 (1.5 to 5.3)	8.0	0.61
Gastrointestinal disorder ED visits			
SO2 lag 0–1	–0.1 (–2.5 to 2.3)	8.7	0.78
SO2 lag 0–2	0.2 (–2.3 to 2.8)	8.5	0.84
SO2 lag 0–3	1.0 (–1.6 to 3.7)	8.3	0.50
SO2 lag 0–4	4.1 (–0.5 to 9.0)	8.2	0.16
SO2 lag 0–5	7.0 (0.1 to 14.3)	8.1	0.06
SO2 lag 0–6	8.5 (0.6 to 16.9)	8.0	0.04

Figure 17 Combined results by season for total wheeze and gastroenteric disorders. Alloallergen abbreviations: GRAM (Graminaceae); URTIC (Urticaceae). Results are expressed as percent increase (95% CI) in risk of wheeze and gastroenteric disorders for an IQR increase in air pollution. The results by season for selected moving averages (MA) are presented for lag days 1, 3, 4, and 5.



Critique
In addition to the exposure misclassification that likely occurred in this study, it also possessed limited statistical power due to the low rates for the emergency department visits. Another factor that may have limited the statistical power of this study is the difference in exposure levels between the case days and the control days. If this difference is small then the study will not be able to detect any differences in the risk (Kunzli and Schindler, 2005). In addition, studies suggest that case crossover analyses that use a bidirectional design for the control period are more robust than those using the time stratified approach employed in this study (Carracedo-Martinez *et al.*, 2010). Further the lag periods showing statistical significance are unusually long.

Asthma

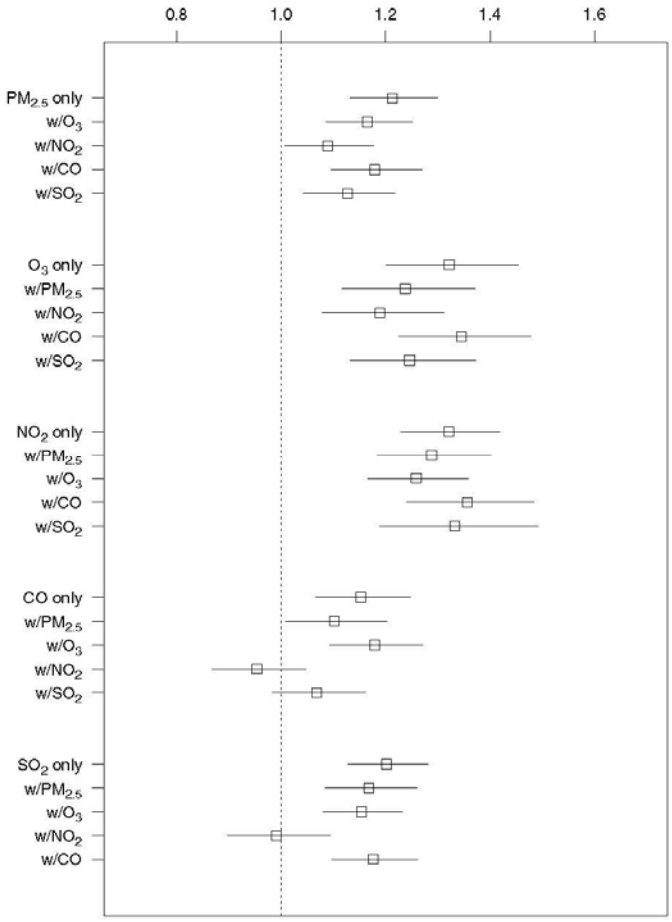
1. **Ito, K., Thurston, G. D., and Silverman, R. A. 2007. Characterization of PM2.5, gaseous pollutants, and meteorological interactions in the context of time-series health effects models. Journal of Exposure Science and Environmental Epidemiology 17:S45-S60.**

Rating
Moderate quality (⊕⊕⊕◯)

Description
This time series investigation examined emergency department visits for asthma in relation to $PM_{2.5}$ (FRM method), $PM_{2.5}$ (TEOM method), O_3, NO_2, CO, and SO_2 exposures in New York City. The primary purpose behind of the study was to examine the confounding caused by multi-collinearity among pollutants and weather variables, so several different weather models of increasing complexity were constructed and evaluated. Daily average SO_2 concentrations were determined at 19 fixed monitoring sites which yielded values of 7.7 ppb (20.7 µg/m³) for all seasons, 5.4 ppb (14.4 µg/m³) for the warm season, and 10.2 ppb (27.1 µg/m³) for the cold season. Few details were provided on the number, age, or coding scheme used to identify the asthmatics evaluated in this study. Temperature, barometric pressure, wind speed, and day of week effects were adjusted for using a Poisson generalized linear model with natural spline smoothing. A single average lag period of 0-1 days was examined.

Results
Statistically significant associations were observed for asthma hospital admissions in both single and two-pollutant models during the entire year, the warm season, and the cold season, using a lag of 01 days. A statistically significant association was also in single-pollutant models for the entire year and the warm season using alternative weather models that applied the smoothing splines in differing manners. Two-pollutant modeling with $PM_{2.5}$, O_3, and CO also resulted in statistically significant increases for asthma ED visits, but the results were not significant in a two pollutant model with NO_2. Monitor to monitor comparison showed that the SO2 measurements at individual sites were poorly correlated indicated high spatial heterogeneity.

Figure 15 Relative risks per 5th to 95th percentile of air pollutants for asthma emergency department (ED) visits in single- and two-pollutant models using weather model C, NYC during warm season (April through August), 1999–2002.



Critique

The primary purpose of this study was to examine issues of confounding as they related to ecologic error (i.e. spatial/temporal uniformity of temporal fluctuations of air pollution), the type of lag structure used for temporal correlation between air pollutants and weather variables, and the impact of multi-collinearily on model-based risk associations. Because of the experimental nature of this study important attributes of the epidemiological portion of the study were not presented. As such, a major portion of the discussion was devoted to examining the issues of confounding and collinearity in terms of which pollutants were impacted to the greatest degree. The authors noted that NO_2 showed the lowest concurvity and smallest ecologic error of the pollutants examined, which influenced the two-pollutant findings with SO_2. The failure to describe key factors behind the selection of the study population such as the number cases and coding criteria somewhat detracted from the overall quality 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, NO_2, and SO_2 levels in Athens, Greece. Daily 1-hr maximum concentrations of SO_2 were measured at 14 fixed monitoring locations and yielded an average value of 16.8 μg/m³. The study included 3601 admissions of males and females aged 0-14 years, who were identified by ICD-9 criteria. Air temperature, relative humidity, day of week, holidays, and influenza outbreaks were adjusted for using Poisson regression 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 of all ages, but not girls on lag day 0 using a single pollutant model. In addition, associations were seen in all children aged 0-4 years, but not in those aged 5-14 years (see **Table 19**). No significant increase in asthma admissions in adjusted single pollutant model per 10 μg/m³ increase on lag day 1and 2. The all age group associations were observed in the winter and spring months but not the summer and winter. Statistically significant associations were found for all children in two pollutant models with NO_2 and O_3 but not PM_{10} on lag day 0 (see **Table 20**).

Table 19 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).

	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 20 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/m3 increase in the levels of the corresponding pollutant on the same day (lag 0), as estimated from two-pollutant models

	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 examinations of asthma emergency room visits have shown that lag days 0 and 1 yield the strongest associations. The study also benefitted from the adequate treatment of effect modification by age, sex, and season. The study quality would have increased if $PM_{2.5}$ and CO were included in the analysis. In addition, the wide confidence intervals indicate that study lacked statistical power, which was likely due to the limited number of cases examined.

3. **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}, $PM_{2.5}$, NO_2, O_3, CO, and SO_2 levels. Average 1-hr measurements of SO_2 from 14 fixed monitoring sites in Sydney, Australia yielded an average value of 1.07 ppb (2.85 µg/m³) for all seasons. 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 0-1 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 cumulative lag 0-1. Significant increases also observed stratified age groups of 1-4 years and 5-9 years for the cumulative 0-1 day lag period. A significant association was not observed in those 10-14 years of age for any of the lag periods. The percentage increase in ED visits for asthma in children of different age groups was reported per interquartile range of 0.8 ppb (2.13 µg/m³) in single and two-pollutant models. Statistically significant changes were also observed in two-pollutant models that used PM_{10}, $PM_{2.5}$, O_3, NO_2, or CO with the age groups of 1-4 years, 5-9 years, and 1-14 years, but not the 10-14 yea age groups. The strength of the associations was considerably reduced, however with values in the 1-14 year group declining from 1.6 (95% CI 0.7 – 2.4) in the single-pollutant model to about 1.0 (95% CI 0.1-1.8 for $PM_{2.5}$) in the two-pollutant modeling (see **Table 21**). The two-pollutant modeling did not apply the same lag period for each pollutant, but instead utilized the lag period showing the strongest association (lag day 0 for SO_2). A statistically significant association was seen in single-pollutant models for the cool but not warm months in the 1-14 year age group, but not in the remaining three age groups.

Table 21 Percentage change in emergency department visits for asthma for interquartile increase in air pollutants two-pollutant models for lag periods of 0, 1, 2, or 3 days.

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 reliably determine the relationship between asthma ED visits and SO_2 exposure. The results are also surprising in light of the very SO_2 exposures that were documented. In a study using a much large sample size, asthma ED visits using a single pollutant model with SO_2 were not evident in a two-pollutant with PM_{10} in children 0-14 years of age (Samoli *et al.*, 2011). These inconsistencies in two-pollutant modeling results suggest that the current study suffered from some methodological deficiencies that impacted the results. There was also a high probability of a lag selection bias in the two-pollutant modeling that was by caused the preferential use of lag periods showing the strongest impact with each pollutant (Andersen *et al*., 2008). There were also likely false positives resulting from the large number comparisons that were performed. The authors also acknowledged a likely misclassification bias. Together these factors considerably weaken the value of this study.

APPENDIX II – STUDY SUMMARIES
Acute Mortality

author	location	exposure monitoring	SO_2 concentration	study type (duration)	endpoint	co-pollutants	participants	ratio or risk	confidence interval	results	GRADE evidence quality
(Cakmak et al., 2011)	Chili (seven municipalities) Independencia La Florida Las Condes Santiago Pudahuel Cerrillos El Bosque	daily mean from centrally located fixed monitoring site located in each of seven cities	daily mean Independencia - 14.5 (38.6 µg/m³) La Florida - 12.6 (33.5 µg/m³) Las Condes - 8.5 ppb (22.5 µg/m³) Santiago - 12.5 ppb (33.3 µg/m³) Pudahuel - 9.3 ppb (24.7 µg/m³) Cerrillos - 13.2 ppb (35.1 µg/m³) El Bosque - 13.3(35.1 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)	pooled random effects risk ration per IQR increase (unstated size) using a single pollutant model overall - 1.089 age < 64 yrs - 1.053 65 - 74 years - 1.116 75 - 84 years - 1.129 >85 years) - 1.089 sex male - 1.086 female - 1.095 education no primary school - 1.093 primary school - 1.075 high school - 1.081 some college - 1.077 college degree - 1.066 income < $8,800/yr - 1.073 $8800 - 10651 - 1.076 > $10651 - 13395 - 1.086 > $13395 - 1.066 employment unemployed - 1.079 blue-collar - 1.078 white collar - 1.062	pooled random effects risk ration per IQR increase (unstated size) using a single pollutant model overall - 1.064 - 1.114 age < 64 yrs - 1.029 - 1.077 65 - 74 years - 1.086 - 1.146 75 - 84 years - 1.082 - 1.178 >85 years) - 1.047 - 1.133 sex male - 1.063 - 1.110 female - 1.066 - 1.124 education no primary school - 1.078 - 1.108 primary school - 1.068 - 1.081 high school - 1.065 - 1.097 some college - 1.040 - 1.113 college degree - 1.046 - 1.087 income < $8,800/yr - 1.057 - 1.088 $8800 - 10651 - 1.070 - 1.082 > $10651 - 13395 - 1.079 - 1.093 > $13395 - 1.056 - 1.077 employment unemployed - 1.056 - 1.103 blue-collar - 1.050 - 1.107 white collar - 1.030 - 1.095	statistically significant association found overall in all age groups, education levels, income categories, employment categories, sexes;	⊕○○○ (insufficient because of publication bias, unknown sample size, and exposure misclassification)

author	location	exposure monitoring	SO_2 concentration	study type (duration)	endpoint	co-pollutants	participants	ratio or risk	confidence interval	results	GRADE evidence quality
(Chen et al., 2008)	Shanghai, China	mean daily concentration at six fixed monitoring locations	daily mean 44.7 µg/m³	time-series (48 months)	daily mortality rates all causes cardiovascular respiratory	differential effects of PM_{10}, SO_2, & NO_2	173,911 deaths	percent change mortality per 10 µg/m³ increment using single and multipollutant models total mortality single pollutant - 0.95 multipollutant (SO_2/PM_{10}) - 0.80 cardiovascular single pollutant - 0.91 multipollutant (SO_2/PM_{10}) - 0.69 respiratory single pollutant - 1.37 multipollutant (SO_2/PM_{10}) - 1.45	percent change mortality per 10 µg/m³ increment using single and multipollutant models total mortality single pollutant - 0.62 - 1.28 multipollutant (SO_2/PM_{10}) - 0.37 - 1.24 cardiovascular single pollutant - 0.42 - 1.41 multipollutant (SO_2/PM_{10}) - 0.04 - 1.34 respiratory single pollutant - 0.51 - 2.23 multipollutant (SO_2/PM_{10}) - 0.32 - 2.59	increased total and cardiovascular mortality observed with single multipollutant models with PM 10, but not in multipollutant models with NO_2 alone or NO_2 & PM_{10} together	⊕○○○ (insufficient because of single pollutant modeling and high probability of exposure misclassification)

author	location	exposure monitoring	SO_2 concentration	study type (duration)	endpoint	co-pollutants	participants	ratio or risk	confidence interval	results	GRADE evidence quality
(Chen et al., 2012a)	17 Chinese cities - Chinese Air Pollution and Health Effects Study (CAPES)	daily averages from 2-13 fixed monitoring units located in background sites within each city	daily mean Anshan - 59 µg/m³ Beijing - 41 µg/m³ Fuzhou - 16 µg/m³ Guangzhou - 50 µg/m³ Hangzhou - 51 µg/m³ Hong Kong - 18 µg/m³ Lanzhou - 66 µg/m³ Nanjing - 48 µg/m³ Shanghai - 45 µg/m³ Shenyang - 55 µg/m³ Suzhou - 45 µg/m³ Taiyuan - 77 µg/m³ Tangshan - 84 µg/m³ Tianjin - 67 µg/m³ Urumqi - 100 µg/m³ Wuhan - 52 µg/m³ Xi'an - 48 µg/m³	time-series (2 years)	mortality from total, circulatory, & respiratory causes	association with PM_{10}, SO_2, & NO_2	males and females aged 0 to > 65 years of age non-accidental - 11-119 deaths/day/city cardiovascular - 6-54 deaths/day/city respiratory - 1-16 deaths/day/city	pooled 17 city percentage increase in mortality per 10 µg/m³ increase using single and two-pollutant models for an average 2 day lag (0-1) total all cause SO_2 only - 0.75 male - 0.60 female - 0.88 ≥ 65 years - 0.88 low education - 0.60 SO_2/PM_{10} - 0.42 cardiovascular SO_2 only - 0.83 SO_2/PM_{10} - 0.38 respiratory SO_2 only - 1.25 SO_2/PM_{10} - 0.77	pooled 17 city percentage increase in mortality per 10 µg/m³ increase using single and two-pollutant models for an average 2 day lag (0-1) total all cause SO_2 only - 0.47 - 1.02 male - 0.22 - 0.98 female - 0.43 - 1.33 ≥ 65 years - 0.42 - 1.34 low education - 0.95 - 1.66 SO_2/PM_{10} - 0.17 - 0.67 cardiovascular SO_2 only - 0.47 - 1.19 SO_2/PM_{10} - 0.0.3 - 0.73 respiratory SO_2 only - 0.78 - 1.73 SO_2/PM_{10} - 0.34 - 1.20	statistically significant association with total, cardiovascular, and respiratory mortality in single pollutant models on lag days 0, 1, 2, 3, 4 and moving average lag periods of 2, 4, and 8 days with no associations on lag days 5, 6, or 7; stratification revealed a statistically significant association with total mortality in both males and females, those ≥ 65 years old, and those with a low education using a single pollutant model and a 2 day average lag; no associations for total mortality in those 5-64 years of age or those with a high education in the single pollutant model; statistically significant association with total, cardiovascular, and respiratory mortality in two pollutant models with PM_{10} but not NO_2 using a 2 day average lag	⊕⊕○○ (low quality because collinearity from $PM_{2.5}$ not evaluated)

author	location	exposure monitoring	SO_2 concentration	study type (duration)	endpoint	co-pollutants	participants	ratio or risk	confidence interval	results	GRADE evidence quality
(Chen et al., 2013)	8 cities in China	daily averages from 2-12 fixed monitoring units located in background sites within each city	daily mean Beijing - 41 µg/m³ Fuzhou - 16 µg/m³ Guangzhou - 50 µg/m³ Hong Kong - 18 µg/m³ Shanghai - 45 µg/m³ Shenyang - 55 µg/m³ Suzhou - 45 µg/m³ Tangshan - 84 µg/m³	time-series (12 years)	stroke mortality	association with PM_{10}, SO_2, & NO_2	males and females 4-26 deaths/day	pooled percent increase in stroke mortality per 10 µg/m³ increase using a 2 day (0-1) moving average lag SO_2 only - 0.88 SO_2/PM_{10} - 0.54	pooled percent increase in stroke mortality per 10 µg/m³ increase using a 2 day (0-1) moving average lag SO_2 only - 0.54 - 1.22 SO_2/PM_{10} - 0.06 - 1.01	statistically significant association with stroke in single pollutant model on lag days 0 and 1 and moving averages for 2 and 5 days but not on lag days 2,3, and 4; statistically significant association with stroke mortality in single pollutant and a two pollutant model with PM_{10} but not with NO_2 using 2 day moving average lag; associations observed with stoke in 7 of the 8 cites examined	⊕⊕◯◯ (low quality because collinearity from $PM_{2.5}$ not evaluated)
(Filleul et al., 2006)	Le Havre, France	source indicator values used to improve the assignment of exposures using the values form 5 fixed monitoring stations that varied the relative weighted mean contribution from the urban and industrial stations	daily mean from five stations Industrial stations Neiges - 33.09 µg/m³ Gonfreville - 38.24 µg/m³ Rogerville - 43.98 µg/m³ Urban stations Caucriauville - 39.53 µg/m³ Air normand - 26.96 µg/m³	time-series (4 years)	mortality from non-accidental, circulatory, and respiratory causes	black smoke and SO_2	male and female averages non-accidental - 6 deaths/day cardiovascular - 2 deaths/day respiratory - <1 death/day	no excess risk of mortality from any cause per 10 µg/m³ increase using a single pollutant model and a cumulative 6 day lag regardless of the type of proximity exposure indicator applied	no excess risk of mortality from any cause per 10 µg/m³ increase using a single pollutant model and a cumulative 6 day lag regardless of the type of proximity exposure indicator applied	no statistically significant association with non-accidental, cardiovascular, or respiratory mortality using a single pollutant model and a 6 day (0-5) distributed lag model; no associations observed after weighting the exposure according to the percentage contribution from urban and industrial monitoring stations	⊕⊕◯◯ (low quality because collinearity from PM_{10} & $PM_{2.5}$ not evaluated)

author	location	exposure monitoring	SO_2 concentration	study type (duration)	endpoint	co-pollutants	participants	ratio or risk	confidence interval	results	GRADE evidence quality
(Goldberg et al., 2006)	Montreal, Quebec	mean daily concentration from thirteen fixed monitoring sites	mean daily concentration 17.8 µg/m³	time-series (10 years)	total and diabetes-induced mortality	association with PM_{10}, $PM_{2.5}$, TSP, sulfate, O_3, SO_2, & NO_2	males and females ≥ 65 years of age 133,904 total deaths 3653 diabetic deaths	mean percent change in mortality per IQR of 11.50 µg/m³ in single pollutant model for subjects ≥ 65 years of age diabetes mortality lag 1 day - 5.95 lag 02 days - 10.00	mean percent change in mortality per IQR of 11.50 µg/m³ in single pollutant model for subjects ≥ 65 years of age diabetes mortality lag 1 day 0.85 - 11.30 lag 02 days 3.18 - 17.27	statistically significant association with diabetes-related mortality in single pollutant model on lag day 1 or 02 (3-day) but not on lag day 0 for those ≥ 65 years of age, statistically significant association with diabetes-related deaths in cold but not warm seasons on lag 02 days, statistically significant association in non-accidental death amongst those with diabetes with or cardiovascular disease for the warm but not the cold season, but no association in ether season for those with coronary artery disease , no statistically significant association in those with diabetes without overlying cancer, congestive heart failure, or atherosclerosis for either season on lag day 02 or in those with chronic coronary artery disease before death	⊕○○○ (insufficient because of problems with mortality coding and no two-pollutant modeling)
(Guo et al., 2010a)	Tianjin, China	mean daily concentration from an unstated number of fixed monitoring sites in six different districts around the city	daily mean 68 µg/m³	time-series and case-crossover (36 months)	cardiovascular mortality	association with PM_{10}, SO_2, & NO_2	male & female cases 32,387	no significant association with cardiovascular mortality in either the case-crossover (risk ratio) or time-series (odds ratio) analysis per 10 µg/m³ change using a single pollutant model on lag day 0	no significant association with cardiovascular mortality in either the case-crossover (risk ratio) or time-series (odds ratio) analysis per 10 µg/m³ change using a single pollutant model on lag day 0	no statistically significant association with cardiovascular mortality in either the time-series and case-crossover studies at lag day 0; the results from the 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; the two modeling approaches were evaluated when the degrees of freedom allowed in the time-series study were allowed to range from 6 to 9 and the strata length in case-crossover study were allowed to range from 14 to 28 months	⊕○○○ (insufficient because of number of sites not stated and no two-pollutant modeling)

author	location	exposure monitoring	SO_2 concentration	study type (duration)	endpoint	co-pollutants	participants	ratio or risk	confidence interval	results	GRADE evidence quality
(Guo et al., 2013)	Beijing, China	daily averages from eight fixed monitoring sites	daily mean 48.6 µg/m³	time-series (5 years)	all cause mortality	association with $PM_{2.5}$, PM_{10}, SO_2, & NO_2	males and females ≤65 years of age and > 65 years of age mean rate 44.1 deaths/day	increase in the percentage of deaths from all causes per IQR increase of 49 µg/m³ using a 2 day (0-1) moving average lag single pollutant model - 1.8	increase in the percentage of deaths from all causes per IQR increase of 49 µg/m³ using a 2 day (0-1) moving average lag single pollutant model - 0.4 - 3.2	statistically significant association with all cause mortality in single pollutant model but not with a two pollutant model with $PM_{2.5}$, PM_{10}, or NO_2 or a three pollutant model with $PM_{2.5}/NO_2$ or PM_{10}/NO_2 using a 2 day moving average lag; significant association in those aged > 65 years but not in those ≤65 years using a single pollutant model; no association in male or female mortality following stratification by sex in a single pollutant model	⊕⊕⊕○ moderate quality, but no proximity modeling)

author	location	exposure monitoring	SO_2 concentration	study type (duration)	endpoint	co-pollutants	participants	ratio or risk	confidence interval	results	GRADE evidence quality
(Guo et al., 2014b)	18 provinces in Thailand	daily averages from an unstated number of fixed monitoring studies in each province	daily average conc. Ayutthaya - 2.7 ppb (7.2 µg/m³) Bangkok - 5.7 ppb (15.2 µg/m³) Chachoengsao - 2.5 ppb (6.6 µg/m³) Chiang mai - 1.6 ppb (4.3 µg/m³) Chon buri -3.9 ppb (10.4 µg/m³) Khon kaen - 2.7 ppb (7.2 µg/m³) Lampang - 1.1 ppb (2.9 µg/m³) Nakhon sawan - 1.9 ppb (5.1 µg/m³) Nakhon ratchasima - 2.3 ppb (6.1 µg/m³) Nonthaburi - 4.9 ppb (13.0 µg/m³) Pathum thani - 4.7 ppb (12.5 µg/m³) Ratchaburi - 3.7 ppb (9.8 µg/m³) Rayong - 4.2 ppb (11.2 µg/m³) Samutprakan- 6.5 ppb (17.3 µg/m³) Samut sakhon - 13.9 ppb (37.0 µg/m³) Saraburi - 3.0 ppb (8.0 µg/m³) Songkhla - 2.3 ppb (6.1 µg/m³) Surat thani - 2.3 ppb (6.1 µg/m³)	case-crossover (10 year)	non-accidental, cardiovascular and respiratory mortality	association with PM_{10}, SO_2, and O_3	males and females non-accidental 4-66 deaths/day cardiovascular - 1-14 deaths/day respiratory - 1-8 deaths/day	pooled percentage change in mortality per 1 ppb (2.7 µg/m³) increase using a 4 day (0-3) moving average lag non-accidental mortality single pollutant all seasons - 0.34 summer - 0.32 winter - 0.57 multi-pollutant SO_2/PM_{10} - 0.21 SO_2/O_3 - 0.31 $SO_2/PM_{10}/O_3$ - 0.23 cardiovascular mortality single pollutant summer - 0.71	pooled percentage change in mortality per 1 ppb (2.7 µg/m³) increase using a 4 day (0-3) moving average lag non-accidental mortality single pollutant all seasons - 0.17 - 0.50 summer - 0.02 - 0.62 winter - 0.31 - 0.84 multi-pollutant SO_2/PM_{10} - 0.08 - 0.41 SO_2/O_3 - 0.31 - 0.14 - 0.47 $SO_2/PM_{10}/O_3$ - 0.06 - 0.40 cardiovascular mortality single pollutant summer - 0.01 - 1.40	statistically significant association with non-accidental mortality in pooled single pollutant models with eight of the eleven lag periods and during all seasons and the summer and winter seasons but not the rainy season using a 4 day lag; significant association with cardiovascular mortality during the summer season using a single pollutant model and 4 day lag; , significant association with non-accidental mortality in pooled two and three pollutant models with PM_{10} and O_3 and a moving average lag of 4 days (0-3); no association with respiratory mortality using single or multi-pollutant models; no association with cardiovascular mortality in multi-pollutant models or during the rainy or winter season using single pollutant models	⊕⊕◯◯ (low quality because collinearity from $PM_{2.5}$ not evaluated)

author	location	exposure monitoring	SO_2 concentration	study type (duration)	endpoint	co-pollutants	participants	ratio or risk	confidence interval	results	GRADE evidence quality
(Hu et al., 2008)	Sidney, Australia	daily averages from 13 fixed monitoring sites	daily mean concentration 0.1 pphm (0.001 ppb, 0.003 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	relative risk for all cause mortality per 1 pphm (0.01 ppb, 0.03 µg/m³) in a model considering an air temperature increase of 1 ˚C SO_2 alone - 22.3	relative risk for all cause mortality per 1 pphm (0.01 ppb, 0.03 µg/m³) in a model considering an air temperature increase of 1 ˚C SO_2 alone - 6.4 - 40.5	statistically significant association with total mortality in an unusual single pollutant model that considered the interaction between very low concentrations of SO_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 - 39.4 µg/m³ cool season - 50.1 µg/m³ entire period - 44.7 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 - 1.10 entire - 0.95 cardiovascular cool - 1.02 entire - 0.91 respiratory cool - 2.47 entire - 1.37 percent increase per 10 µg/m³ increase for entire population with lag day 0-1 in a single pollutant model female - 1.06 male - 0.85 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 0.66 - 1.53 entire 0.62 - 1.28 cardiovascular cool 0.40 - 1.65 entire 0.42 - 1.41 respiratory cool 1.41 - 3.54 entire 0.51 - 2.23 percent increase per 10 µg/m³ increase for entire population with lag day 0-1 in a single pollutant model female 0.62 - 1.51 male 0.43 - 1.28 age ≥ 65 yrs 0.65 - 1.36	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 mortality but not cardiovascular or respiratory mortality in those with a high education	⊕◯◯◯ (insufficient because of short duration and high likelihood of exposure misclassification)

author	location	exposure monitoring	SO_2 concentration	study type (duration)	endpoint	co-pollutants	participants	ratio or risk	confidence interval	results	GRADE evidence quality
(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 - 13.2 µg/m³ Hong Kong - 17.8 µg/m³ Shanghai - 44.7 µg/m³ Wuhan - 39.2 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	excess risk in mortality using for individual cities and pooled (random effects) grouping per 10 µg/m³ change using a single pollutant model and a 2 day moving average lag period Bangkok total - 1.61 Hong Kong total - 0.87 cardiovascular - 1.19 respiratory - 1.28 Shanghai total - 0.95 cardiovascular - 0.91 respiratory - 1.37 Wuhan total - 1.19 cardiovascular - 1.47 respiratory - 2.11 Pooled (4 city) total - 1.00 cardiovascular - 1.09 respiratory - 1.47	excess risk in mortality using for individual cities and pooled (random effects) grouping per 10 µg/m³ change using a single pollutant model and a 2 day moving average lag period Bangkok total - 0.08 - 3.16 Hong Kong total - 0.38 - 1.36 cardiovascular - 0.29 - 2.10 respiratory - 0.19 - 2.39 Shanghai total - 0.62 - 1.28 cardiovascular - 0.42 - 1.41 respiratory - 0.51 - 2.23 Wuhan total - 0.65 - 1.74 cardiovascular - 0.70 - 2.25 respiratory - 0.60 - 3.65 Pooled (4 city) total - 0.75 - 1.24 cardiovascular - 0.71 - 1.47 respiratory - 0.85 - 2.08	significant associations with all cause mortality in all four cities and the pooled analysis using a single pollutant model and a 01 day moving lag; significant associations with cardiovascular and respiratory mortality in 3 of 4 cites and the pooled analysis using a single pollutant model; significant associations using single pollutant model using same day (0) lag in 3 of 4 cities and in the pooled estimate as well as a 5 day (04 lag) lag 1 of 4 cites and the pooled estimate; two pollutant modeling with O_3 using the 2 day lag yielded significant associations with total, cardiovascular, and respiratory mortality in 3 of the 4 cities; two pollutant modeling with PM_{10} was associated with total mortality in 2 cities and respiratory mortality in 1 city; no associations found with using pollutant modeling with NO_2	⊕⊕◯◯ (low quality because collinearity from $PM_{2.5}$ not evaluated)

author	location	exposure monitoring	SO_2 concentration	study type (duration)	endpoint	co-pollutants	participants	ratio or risk	confidence interval	results	GRADE evidence quality
(Kowalska et al., 2010)	Katowice, Poland	daily averages from 11 fixed monitoring sites	daily average 35.2 µg/m³	time-series (2 years)	all cause mortality	association with PM_{10}, SO_2, and NOx	males and females average rate - 52.7 deaths/day	regression coefficient for total daily mortality per 10 µg/m³ increase using a single pollutant model same day lag - 0.0007 3-day average lag - 0.0012 5-day average lag - 0.0013 7-day average lag - 0.0014 14-day average lag - 0.0016 30-day average lag - 0.0020 40-day average lag - 0.0022 50-day average lag - 0.0019 60-day average lag - 0.0015	regression coefficient for total daily mortality per 10 µg/m³ increase using a single pollutant model same day lag - 0.0001 - 0.0012 3-day average lag - 0.0005 - 0.0019 5-day average lag - 0.0005 - 0.0020 7-day average lag - 0.0005 - 0.0022 14-day average lag - 0.0005 - 0.0026 30-day average lag - 0.0006 - 0.0034 40-day average lag - 0.0006 - 0.0037 50-day average lag - 0.0004 - 0.0035 60-day average lag - 0.0001 - 0.0030	statistically significant association with all cause and cardiorespiratory mortality at all 9 lag periods using a single pollutant model, significant association with all cause and cardiorespiratory mortality in those >65 years of age following stratification by age	⊕○○○ (insufficient because of poor methodological description and lack of two-pollutant modeling)
(Lin and Liao, 2009)	Kaohsiung, Taiwan	mean daily concentration at single fixed monitoring location	daily mean 9.0 ppb (23.9 µg/m³)	time-series (5 years)	total mortality and cardiovascular mortality	association with PM_{10}, O_3, SO_2, CO, & NO_2	male & female 4324 males 3238 females	no increase in relative risk for total mortality or cardiovascular mortality at any lag period for those of all ages or > 65 years using a multi-pollutant model and an IQR increase of 6.1 ppb (16.2 µg/m³) in ether of three temperature quartiles (19.7 ˚C, 24.8 ˚C, or 27.6 ˚C)	no increase in relative risk for total mortality or cardiovascular mortality at any lag period for those of all ages or > 65 years using a multi-pollutant model and an IQR increase of 6.1 ppb (16.2 µg/m³) in ether of three temperature quartiles (19.7 ˚C, 24.8 ˚C, or 27.6 ˚C)	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 (SO_2/PM_{10}/O_3/CO/NO_2); all individuals and those aged 65 years or older unaffected	⊕○○○ (insufficient because of high likelihood of exposure misclassification)

author	location	exposure monitoring	SO_2 concentration	study type (duration)	endpoint	co-pollutants	participants	ratio or risk	confidence interval	results	GRADE evidence quality
(Lopez-Villarrubia et al., 2012)	two cities in Canary Islands Las Palmas Santa Cruz	daily average concentration from three fixed monitoring sites	daily mean concentration Las Palmas - 8.1 µg/m³ Santa Cruz - 14.1 µg/m³	time-series (5 years)	mortality from all causes, respiratory disease, & heart disease	association with PM_{10}, $PM_{2.5}$, SO_2, O_3, CO, & NO_2	males and females adults death rates ranged from 0.4 -7.4 deaths/day	percent increase in mortality per 10 µg/m³ increase in either city on various lag periods (graphical interpolation) Las Palmas (total mortality) lag day 0 - 6 Las Palmas (heart disease) lag day 0 - 11 lag day 5 - 14 distributed 6 day lag - 18.5 Santa Cruz (total mortality) lag day 2 - 3 Santa Cruz (respiratory) lag day 3 - 5 lag day 4 - 6 distributed 6 day lag - 12.5	percent increase in mortality per 10 µg/m³ increase in either city on various lag periods (graphical interpolation) Las Palmas (total mortality) lag day 0 - 2 -13 Las Palmas (heart disease) lag day 0 - 1 - 24 lag day 5 - 3 -24 distributed 6 day lag - 2.1 - 37.4 Santa Cruz (total mortality) lag day 2 - 0 -5 Santa Cruz (respiratory) lag day 3 - 0 -11 lag day 4 - 0 - 12 distributed 6 day lag - 1.1 - 12.2	statistically significant association in Las Palmas for total mortality on lag day 0, respiratory mortality and cardiovascular mortality on lag 0 and the 6 day distributed lag; no association with respiratory mortality in in Las Palmas, significant association Santa Cruz for total mortality on lag day 2 and respiratory mortality on lag day 3, 4, and the distributed 6 day lag, disease, or heart disease mortality for Las Palmas or Santa Cruz in a single pollutant model at lag 01 day or distributed lag 05 days, no statistically significant associations in two pollutant models with unknown co-pollutants; no association with cardiovascular mortality in in Santa Cruz,	⊕○○○ (insufficient because of publication bias and high likelihood of type 1 error resulting from the multiple comparisons)
(Lyons et al., 2014)	Dublin, Ireland	daily averages from 3 fixed monitoring sites	daily median quintile 1 - 0.87 µg/m³ quintile 2 - 1.59 µg/m³ quintile 3 - 2.52 µg/m³ quintile 4 - 4.11 µg/m³ quintile 5 - 7.23 µg/m³	prospective cohort (10 years)	acute in-hospital mortality over a 30-day period	association with PM_{10}, SO_2, and NOx	males and females 55,596 admissions	odds ratio for any cause mortality relative to the first exposure quintile per IQR increase using a single pollutant model with admission day exposure estimates quintile 3 (IQR 0.57 µg/m³)- 1.43 quintile 4 (IQR 1.17 µg/m³) - 1.54 quintile 5 (IQR 4.52 µg/m³) - 1.58	odds ratio for any cause mortality relative to the first exposure quintile per IQR increase using a single pollutant model with admission day exposure estimates quintile 3 (IQR 0.57 µg/m³)- 1.26 - 1.62 quintile 4 (IQR 1.17 µg/m³) - 1.36 - 1.75 quintile 5 (IQR 4.52 µg/m³) - 1.39 - 1.80	statisitcally significant association with all cause 30-day in-hospital mortalityon admission day exposure quintiles 3, 4, and 5 using a single pollitant model	⊕○○○ (insufficient because of the lack of two-pollutant modeling and the high likelihood of exposure misclassification)

author	location	exposure monitoring	SO_2 concentration	study type (duration)	endpoint	co-pollutants	participants	ratio or risk	confidence interval	results	GRADE evidence quality
(Meng et al., 2013)	four cities in China Beijing Shanghai Guangshou Hong Kong	daily averages from 7-8 fixed monitoring sites in each city	daily mean Beijing - 41.4 µg/m³ Shanghai - 44.7 µg/m³ Guangshou - 50.1 µg/m³ Hong Kong - 17.8 µg/m³	time-series (12 years)	COPD-related mortality	association with PM_{10}, SO_2, & NO_2	males and females ≤65 years of age and > 65 years of age mean rate 5.6 to 12.2 deaths/day	pooled (random effects) percentage increase in COPD mortality per 10 µg/m³ increase using a 2 day (0-1) moving average lag single pollutant model - 1.38 two pollutant model (PM_{10}) - 0.72	pooled (random effects) percentage increase in COPD mortality per 10 µg/m³ increase using a 2 day (0-1) moving average lag single pollutant model - 0.92 - 1.85 two pollutant model (PM_{10}) - 0.11 - 1.33	statistically significant association with pooled four city COPD mortality in single pollutant model and two pollutant model with PM_{10} but not with a two pollutant model with NO_2 using a 2 day moving average lag; significant association in 2 of the four cities using a single pollutant model and one four cities using a two pollutant model with PM_{10}; associations found lag days 0, 1, 2, and 7 and all three moving average lags of 2, 5, and 8 days	⊕⊕◯◯ (low quality because collinearity from $PM_{2.5}$ not evaluated)
(Milojevic et al., 2014)	England and Wales	daily averages from the nearest of 71 fixed monitoring sites	daily median 3.1 µg/m³	case-crossover(7 years)	hospital admissions and mortality for cardiovascular disease, myocardial infarction, stroke, ischemic heart disease chronic ischemic heart disease, arrhythmias, atrial fibrillation, pulmonary embolism, heart failure, and atrioventricular conduction disorder	association with $PM_{2.5}$, PM_{10}, SO_2, O_3, CO, & NO_2	males and females 380,743 admissions	percent increase in admissions for myocardial infarctions without an elevation in ST segment (non-STEMI) in the EEG per 10.4 µg/m³ increase using a single pollutant model and a 0-4 day distributed lag non-STEMI - 2.3	percent increase in admissions for myocardial infarctions without an elevation in ST segment (non-STEMI) in the EEG per 10.4 µg/m³ increase using a single pollutant model and a 0-4 day distributed lag non-STEMI - 0.0 - 4.7	statistically significant increase non-STEMI myocardial infarction admissions in single pollutant model using a 5 day distributed lag period, no association with all myocardial infarctions or STEMI-related myocardial infarction admissions in a single pollutant model; no statistically significant positive increase in risk for admission or mortality from cardiovascular disease, myocardial infarction, stroke, ischemic heart disease chronic ischemic heart disease, arrhythmias, atrial fibrillation, pulmonary embolism, heart failure, or atrioventricular conduction disorder	⊕◯◯◯ (insufficient because of the lack of two-pollutant modeling and the high likelihood of exposure misclassification)

author	location	exposure monitoring	SO_2 concentration	study type (duration)	endpoint	co-pollutants	participants	ratio or risk	confidence interval	results	GRADE evidence quality
Moolgavkar et al., 2013)	85 cities in the United States	average daily level from an unstated number of monitoring sites	daily mean not provided	time-series (14 years)	total non-accidental and non-suicidal mortality	association with PM_{10}, SO_2, O_3, CO, & NO_2	not provided	mean percent increase in total mortality per 10 ppb (26.6 µg/m³) increase on lag day 0 single pollutant - 1.46 three pollutant (SO_2/CO/NO_2) - 0.82	mean percent increase in total mortality per 10 ppb (26.6 µg/m³) increase on lag day 0 single pollutant - 1.07 - 1.74 three pollutant (SO_2/CO/NO_2) -0.48 - 1.15	statistically significant association with mortality in a sub sampling of 4 of the 85 cites with available information using a single or three pollutant model on lag day 0; statistically significant association using both 50 or 100 degrees of freedom to track temporal changes in weather using a single pollutant model	⊕⊕◯◯ (low quality because number of monitoring sites not stated and collinearity from $PM_{2.5}$ not evaluated)
(Ou et al., 2008)	Hong Kong, China	daily mean concentration from eight fixed monitoring sites	daily mean 13.26 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 & females greater than 30 years of age 24,357 deaths	partly adjusted excess risk in two age groups per 10 µg/m³ increase in a stratified SES consing a single pollutant model at one of 4 the lag days (unstated) type of housing all ages (≥ 30 years) public rental - 2.53 occupation all ages blue collar - 3.73 elderly (≥ 65 years) blue collar - 4.36 education all ages no education - 3.33 elderly (≥ 65 years) no education - 3.74 primary education - 1.83	partly adjusted excess risk in two age groups per 10 µg/m³ increase in a stratified SES conditions using a single pollutant model at one of 4 the lag days (unstated) type of housing all ages (≥ 30 years) public rental - 0.12 - 5.00 occupation all ages blue collar - 1.69 - 5.81 elderly (≥ 65 years) blue collar - 1.94 - 6.83 education all ages no education - 0.50 - 6.24 elderly (≥ 65 years) no education - 0.79 - 6.78 primary education - 1.83	statistically significant association with the use public rental housing, blue collar occupation, and the lack of a formal education in all combined age groups (≥ 30 years) using a single pollutant model ; significant association with a blue collar occupation and the lack of a formal education in the elderly age group (≥ 65 years), no association the use of private housing, white collar or never employed work status, or a primary or secondary education in the combined age groups; no association the use of public rental or private housing, white collar or never employed worker status, or a primary or secondary education in the elderly age group	⊕◯◯◯ (insufficient because no two-pollutant modeling and no consideration of collinearity from $PM_{2.5}$)

author	location	exposure monitoring	SO_2 concentration	study type (duration)	endpoint	co-pollutants	participants	ratio or risk	confidence interval	results	GRADE evidence quality
(Park et al., 2011)	Seoul, Korea	mean hourly concentration from 27 fixed monitoring sites	daily mean concentration 5.2 ppb (13.8 µg/m³)	time-series (107 months)	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 0.5 ppb (1.3 µg/m³) in single and two pollutant models stratified by ambient temperature conditions using an average lag period of 0-1 days non-accidental (entire temperature range) SO_2 only - 0.28 SO_2/PM_{10} - 0.23 SO_2/O_3 - 0.27 non-accidental (< 25th percentile temp.) SO_2 only - 0.27 SO_2/PM_{10} - 0.37 non-accidental (>75th the percentile temp) SO_2 only - 1.22 SO_2/PM_{10} - 1.26 SO_2/NO_2 - 1.09 SO_2/CO - 1.02 SO_2/O_3 - 1.23 cardiovascular (>75th the percentile temp) SO_2 only - 1.23 SO_2/NO_2 - 1.66 SO_2/CO - 1.21 SO_2/O_3 - 1.41 respiratory (>75th the percentile temp) SO_2 only - 1.89	percent increase in mortality for those > 65 years of age for an IQR of 0.5 ppb (1.3 µg/m³) in single and two pollutant models stratified by ambient temperature conditions using an average lag period of 0-1 days non-accidental (entire temperature range) SO_2 only - 0.10 - 0.45 SO_2/PM_{10} - 0.04 - 0.42 SO_2/O_3 - 0.09 - 0.45 non-accidental (< 25th percentile temp.) SO_2 only - 0.01 - 0.52 SO_2/PM_{10} - 0.06 - 0.68 non-accidental (>75th the percentile temp) SO_2 only - 0.70 - 1.75 SO_2/PM_{10} - 0.57 - 1.95 SO_2/NO_2 - 0.36 - 1.83 SO_2/CO - 0.35 - 1.69 SO_2/O_3 - 0.63 - 1.84 cardiovascular (>75th the percentile temp) SO_2 only - 0.31 - 2.17 SO_2/NO_2 - 0.35 - 2.98 SO_2/CO - 0.02 - 2.41 SO_2/O_3 - 0.35 - 2.49 respiratory (>75th the percentile temp) SO_2 only - 0.04 - 3.78	statistically significant association with non-accidental mortality in a single pollutant model at 3 of the 4 temperature ranges in a single pollutant model with a moving lag period of 2 days (0-1); no association with non-accidental mortality at the 50-75 the percentile of the temperature distribution in either single or two-pollutant modeling; significant association with cardiovascular and respiratory mortality at the 75th temperature percentile, but not at other temperatures using a single pollutant model; associations with non-accidental mortality 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 NO_2 or CO at temperatures <25th percentile; associations with non-accidental mortality at the 75th temperature percentile were robust to the incorporation of PM_{10}, O_3, NO_2, or CO in two-pollutant models but were rendered non-significant after the incorporation of at temperatures <25th percentile; associations with cardiovascular mortality at the 75th were robust to the incorporation of O_3, NO_2, and CO but not PM_{10} in two pollutant models; associations with respiratory mortality at the 75th were not robust to the incorporation of PM_{10}, O_3, NO_2, or CO in two pollutant models	⊕⊕⊕○ moderate quality, but no evaluation of $PM_{2.5}$ collinearity)

author	location	exposure monitoring	SO_2 concentration	study type (duration)	endpoint	co-pollutants	participants	ratio or risk	confidence interval	results	GRADE evidence quality
(Qian et al., 2007)	Wuhan, China	daily concentration from five fixed monitoring sites	average daily mean 44.1 µg/m³	time-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 deaths over study 89,131 non-accidental 40,623 cardiovascular 25,557 stroke 12,166 cardiac 10,287 respiratory 50,910 cardiopulmonary	no increase in the daily mortality percentage for non-accidental, cardiovascular, stroke , cardiac, respiratory, or cardiopulmonary mortality in those <65 or ≥ 65 years of age per 10 µg/m³ increase using a single pollutant model on lag day 0 thru 3	no increase in the daily mortality percentage for non-accidental, cardiovascular, stroke , cardiac, respiratory, or cardiopulmonary mortality per 10 µg/m³ increase using a single pollutant model on lag days 0 thru 3	no statistically significant association with any cause of mortality in single pollutant models on lag day 0, 1, 2, or 3; no association with any of the six mortality causes in those less than 65 years of age or those greater than or equal to 65 years of age; two pollutant modeling apparently performed but the results not provided	⊕⊕○○ (low quality because of no evaluation of $PM_{2.5}$ collinearity and publication bias)
(Qian et al., 2010)	Wuhan, China	mean daily concentration at four fixed monitoring locations	daily mean spring - 34.5 µg/m³ summer - 24.6 µg/m³ fall - 39.5 µg/m³ winter - 58.4 µg/m³	time-series (48 months)	mortality from all causes, cardiovascular, stroke, and respiratory disease	association with PM_{10}, SO_2, & NO_2	males and females all causes - 89,131 deaths cardiovascular - 40623 deaths stroke - 25,557 deaths respiratory - 10,287 deaths	percent change in mortality per 10 µg/m³ increment in single pollutant model with a 2 day (0-1) average lag all cause spring - 1.70 winter - 2.15 cardiovascular spring - 2.07 winter - 2.58 stroke winter - 2.31 respiratory winter - 3.05	percent change in mortality per 10 µg/m³ increment in single pollutant model with a 2 day (0-1) average lag all cause spring - 0.42 - 3.00 winter - 1.46 - 2.84 cardiovascular spring - 0.31 - 3.97 winter - 1.63 - 3.54 stroke winter - 1.18 - 3.46 respiratory winter - 1.24 - 4.88	statistically significant increase in all cause and cardiovascular mortality in spring and winter but not summer and fall using a single pollutant model with a average 2 day (0-1) lag; significant association with stroke and respiratory mortality in the winter but not the spring, summer or fall months using a single pollutant model; significant association with all cause and cardiovascular mortality in two pollutant models with PM_{10} or NO_2 in the summer and winter but not the summer or fall; significant association with stroke and cardiovascular mortality in two pollutant models with PM_{10} but not NO_2 in the winter but not the spring, summer or fall	⊕○○○ (insufficient because no evaluation of $PM_{2.5}$ collinearity and the probable exposure misclassification)

author	location	exposure monitoring	SO_2 concentration	study type (duration)	endpoint	co-pollutants	participants	ratio or risk	confidence interval	results	GRADE evidence quality
Sacks et al., 2012	Philadelphia, PA	1-hr maximum from a single fixed monitoring site	avg 1-hr maximum 8.4 ppb (22.3 µg/m³)	time-series (52 months)	total cardiovascular mortality	association with $PM_{2.5}$, SO_2, O_3, CO, NO_2, & nine trace elements	male and female of all ages 17,968 deaths	percentage increase in cardiovascular mortality per IQR of 7.8 ppb (20.7 µg/m³) in different models from previous studies on lag day 0-1 in a single pollutant model APHEA2 - 5.3 California - 4.7 Canada - 4.7 Harvard - 4.1	percentage increase in cardiovascular mortality per IQR of 7.8 ppb (20.7 µg/m³) in different models from previous studies on lag day 0-1 in a single pollutant model APHEA2 - 1.6 - 9.1 California - 1.1 - 8.5 Canada - 1.0 - 8.6 Harvard - 0.4 - 7.9	statistically significant association with cardiovascular mortality using 4 time-series models developed for the multi-city studies performed in Europe (APHEA2), California, Canada, and Harvard using a single pollutant model and a 2 day average lag period (0-1); no association with time-series models developed for the HARVARD AT study or the NMAPS study using a single pollutant model	⊕○○○ (insufficient because of high likelihood of exposure misclassification)
(Vanos et al., 2014)	12 Canadian cities	daily averages from an unstated number of fixed monitoring sites	daily averages dry moderate - 3.32 ppb (8.83 µg/m³) dry tropical - 4.63 ppb (12.32 µg/m³) moist moderate - 3.02 ppb (8.03 µg/m³) moist tropical - 3.22 ppb (8.57 µg/m³) moist tropical plus - 3.47 ppb (9.23 µg/m³)	time-series (28 years)	interaction of five weather patterns (dry moderate, dry tropical, moist moderate, moist tropical, and moist tropical plus) on overall non-accidental mortality	association with $PM_{2.5}$, SO_2, O_3, and NO_2	average male and female mortality rate per 100,000 dry moderate - 1.68 cases dry tropical - 1.75 cases moist moderate - 1.67 cases moist tropical - 1.75 cases moist tropical plus - 1.92 cases	pooled (random effects) relative risk of mortality per an unstated increase in single pollutant model dry moderate - 1.059 dry tropical - 1.272 moist moderate - 1.041 moist tropical - 1.077 moist tropical plus - 1.117	pooled (random effects) relative risk of mortality per increase in single pollutant model dry moderate - 1.042 - 1.076 dry tropical - 1.057 - 1.531 moist moderate - 1.027 - 1.055 moist tropical - 1.041 - 1.114 moist tropical plus - 1.018 - 1.225	statistically significant association with non-accidental mortality for all five types of seasonal conditions using the pooled analysis of the results for all 12 cites in a single pollutant model; statistically significant association observed in dry moderate periods using a two pollutant model with either $PM_{2.5}$, O_3, or NO_2 (data presented graphically); significant association observed in dry moderate and moist moderate weather conditions using a two pollutant model with either $PM_{2.5}$, and NO_2 but not O3 (data presented graphically); association observed in dry tropical weather conditions using a two pollutant model with NO_2 and O_3 but not $PM_{2.5}$ (data presented graphically);	⊕⊕○○ (low quality because number of monitoring sites not stated and collinearity from PM_{10} not evaluated)

author	location	exposure monitoring	SO_2 concentration	study type (duration)	endpoint	co-pollutants	participants	ratio or risk	confidence interval	results	GRADE evidence quality
(Wong et al., 2008a)	Hong Kong, China	daily average from eight fixed monitoring locations	daily mean 17.8 µg/m³	time-series (84 months)	mortality from all non-accidental causes, circulatory causes, & respiratory causes as a function of social deprivation index (low, middle, high) that considered employment status, income, education, household occupancy, marital status, home ownership)	association PM_{10}, SO_2, O_3, & NO_2	male & female 215,240 total deaths	adjusted percentage of excess risk for mortality at 3 different levels of social deprivation (low, middle, and high) per 10 µg/m³ increase in a single pollutant model on five different lag days non-accidental middle SDI (lag day 0) - 0.76 middle SDI (lag day 1) - 0.62 high SDI (lag day 1) - 1.44 all SDI classes (lag day 0) - 0.68 all SDI classes (lag day 1) - 0.62 cardiovascular high SDI (lag day 0) - 1.85 high SDI (lag day 1) - 2.88 all SDI classes (lag day 0) - 1.03 all SDI classes (lag day 1) - 0.93 respiratory all SDI classes (lag day 0) - 1.02 all SDI classes (lag day 1) - 0.99	adjusted percentage of excess risk for mortality at 3 different levels of social deprivation (low, middle, and high) per 10 µg/m³ increase in a single pollutant model on five different lag days non-accidental middle SDI (lag day 0) - 0.14 - 1.38 middle SDI (lag day 1) - 0.02 - 1.23 high SDI (lag day 1) - 0.60 - 2.29 all SDI classes (lag day 0) - 0.24 - 1.12 all SDI classes (lag day 1) - 0.19 - 1.06 cardiovascular high SDI (lag day 0) - 0.28 - 3.44 high SDI (lag day 1) - 1.35 - 4.43 all SDI classes (lag day 0) - 0.21 - 1.85 all SDI classes (lag day 1) - 0.13 - 1.74 respiratory all SDI classes (lag day 0) - 0.04 - 2.01 all SDI classes (lag day 1) - 0.03 - 1.96	statistically significant association with non-accidental, cardiovascular, and respiratory mortality for all subjects on lag day 0 or 1 in a single pollutant model; significant association with non-accidental mortality for those with a middle social deprivation index (SDI) on lag days 0 or 1 and those with a high SDI on lag day 1 but not on other longer lag days; association with cardiovascular mortality those with a high SDI on lag days 0 or 1 but not on other longer lag days; no association with respiratory mortality for those with a low, middle, or high SDI on any lag day; no statistically significant associations on lag day 4; no association with non-accidental, cardiovascular, and respiratory mortality for those with a low SDI on any of five lag days	⊕⊕◯◯ (low quality because of bias from single pollutant model and the failure to consider $PM_{2.5}$ collinearity)

author	location	exposure monitoring	SO_2 concentration	study type (duration)	endpoint	co-pollutants	participants	ratio or risk	confidence interval	results	GRADE evidence quality
(Wong et al., 2008b)	four cities in Asia Bangkok Hong Kong Shanghai Wuhan	daily average from 6-10 fixed monitoring locations	daily mean Bangkok - 13.2 µg/m³ Hong Kong - 17.8 µg/m³ Shanghai - 44.7 µg/m³ Wuhan - 39.2 µg/m³	time-series (48 - 84 months)	mortality from natural, circulatory, & respiratory causes	association 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	4 city pooled (random effects) excess percent risk of mortality per 10 µg/m³ increase in a single pollutant model for a 2 day (0-1) average all cause - 1.00 cardiovascular - 1.09 respiratory - 1.47	4 city pooled (random effects) excess percent risk of mortality per 10 µg/m³ increase in a single pollutant model for a 2 day (0-1) average all cause - 0.75 - 1.24 cardiovascular - 0.71 - 1.47 respiratory - 0.85 - 2.08	statistically significant association with all mortality causes in 4-city pooled random effects model at an average lag period of 2 days using a single pollutant model; significant association found for all cause, cardiovascular, and respiratory mortality in all cities except Bangkok where only the non-accidental mortality was significant; stratification by age revealed associations with all three mortality categories for those of all ages, > 65 years of age, or those ≥ 75 years of age	⊕⊕◯◯ (low quality because of publication bias and the failure to consider $PM_{2.5}$ collinearity)
(Wong et al., 2009)	Hong Kong, China	daily average from eight fixed monitoring locations	daily mean 17.8 µg/m³	time-series (84 months)	impact of influenza on hospitalizations and mortality for respiratory disease (RD), acute respiratory (ARD), chronic obstructive pulmonary disease (COPD), and cardiovascular disease (CVD)	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 respiratory hospitalizations or mortality per 10 µg/m³ increase in single pollutant model with a 2 day (0-1) average lag baseline (no influenza) mortality CVD (all subjects) - 1.64 baseline (no influenza) hospitalizations CVD (all subjects) - 1.10 CVD (> 65 years) - 1.50 adjusted (influenza) hospitalizations ARD (all subjects) - 0.86	excess risk for respiratory hospitalizations or mortality per 10 µg/m³ increase in single pollutant model with a 2 day (0-1) average lag baseline (no influenza) mortality CVD (all subjects)- 0.27 - 3.02 baseline (no influenza) hospitalizations CVD (all subjects) - 0.52 - 1.69 CVD (> 65 years) - 0.83 - 2.17 adjusted (influenza) hospitalizations ARD (all subjects) - 0.20 - 1.53	statistically significant association with baseline (no influenza) mortality from cardiovascular disease but not respiratory disease or COPD in a single pollutant model with a 2 day (0-1) average lag; no association with total respiratory disease or COPD mortality in the adjusted or baseline influenza models; significant association with adjusted (10% influenza rate) and baseline hospitalizations for CVD disease in single pollutant model for both the all age group and those > 65 years of age; significant association with adjusted but not baseline hospitalizations for acute respiratory disease in single pollutant model that considered all age groups; no association with hospitalizations for all respiratory disease or COPD in either the adjusted or baseline model for either age comparison groups	⊕⊕◯◯ (low quality because of publication bias and the failure to consider $PM_{2.5}$ collinearity)

Chronic Mortality

author	location	exposure monitoring	SO_2 concentration	study type (duration)	endpoint	co-pollutants	participants	ratio or risk	confidence interval	results	GRADE quality of evidence
(Beelen et al., 2008b)	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	10-year average background - 13.7 µg/m³	prospective cohort and case control (120 months)	mortality from natural cause, cardiovascular, respiratory, lung cancer, and other causes	association black smoke (BS), $PM_{2.5}$, SO_2, & NO_2	male & female 120,852 subjects	no significant change in relative risk using a partially adjusted (cohort) or fully adjusted (case cohort) model	no significant change in relative risk using a partially adjusted (cohort) or fully adjusted (case cohort) model	no statistically significant association with natural cause mortality or deaths from cardiovascular, respiratory, lung cancer and other causes using the full cohort or the case cohort that fully accounted for potential confounders	⊕⊕◯◯ (low quality because single pollutant modeling and high collinearity with other pollutants)

author	location	exposure monitoring	SO_2 concentration	study type (duration)	endpoint	co-pollutants	participants	ratio or risk	confidence interval	results	GRADE quality of evidence
(Berglind et al., 2009)	Augsburg, Germany Barcelona, Spain Helsinki, Finland Rome, Italy Stockholm, Sweden	daily average concentration in five European cites using an unstated number of fixed monitoring locations	daily median concentration Augsburg - 4.22 µg/m³ Barcelona - 11.00 µg/m³ Helsinki - 3.13 µg/m³ Rome - 3.98 µg/m³ Stockholm - 2.61 µg/m³	cohort study (up to 240 months)	mortality amongst survivors of myocardial infarction	association with PM_{10}, CO, O_3, SO_2, & NO_2	male & female 25,006 cohort 8,555 cases	pooled random effects change in the percentage of non-traumatic deaths per 2 µg/m³ change using a single pollutant model day lag 0 to 14 - 8.06	pooled random effects change in the percentage of non-traumatic deaths per 2 µg/m³ change using a single pollutant model day lag 0 to 14 - 4.38 - 11.90	statistically significant association with daily non-traumatic deaths with a 15 day lag period but not a 2-day or 5 day lag period when measurements pooled for 4 of the five cites examined; no association with deaths due to cardiovascular disease; statistical association with the group aged 35-65 yrs, but not in those 65-74, > 75 years, no association with groups followed up for a year longer or a year less	⊕⊕◯◯ (low quality because single pollutant modeling and high collinearity with other pollutants)
(Cao et al., 2011)	China	annual average from 103 monitoring stations in 31 cities, monitoring data linked to a ZIP code that defined a residential location within 15 km of the site	annual average 73 µg/m³	cohort (10 years)	total mortality, cardiopulmonary disease, respiratory disease, & lung cancer	association with TSP, SO_2, & NOx	70,947 middle-aged men and women	percent increase per 10 µg/m³ increment single pollutant model adjusted for covariates all cause - 1.8 cardiovascular - 3.2 respiratory - 3.2 lung cancer - 4.2 Adjusted multipollutant model (TSP) all cause - 1.8 cardiovascular - 3.1 respiratory - 3.2 lung cancer - 4.1 Adjusted multipollutant model (NO_2) all cause - 1.8 cardiovascular - 3.1 respiratory - 3.1 lung cancer - 4.1 all causes - 1.4	percent increase per 10 µg/m³ increment single pollutant model adjusted for covariates all cause - 1.3 - 2.3 cardiovascular - 2.3 - 4.0 respiratory - 1.8 - 4.7 lung cancer - 2.3 - 6.2 Adjusted multipollutant model (TSP) all cause - 1.3 - 2.3 cardiovascular - 2.2 - 4.0 respiratory - 1.7 - 4.7 lung cancer - 2.1 - 6.1 Adjusted multipollutant model (NO_2) all cause - 1.3 - 2.3 cardiovascular - 2.2 - 4.0 respiratory - 1.6 - 4.6 lung cancer - 2.1 - 6.1 all causes - 1.4	statistically significant decrease in mortality in single and multipollutant models (TSP and NO_2) for all cause, cardiovascular, respiratory and lung cancer observed when model adjusted for covariates including smoking status, and smoking frequency	⊕⊕◯◯ (low quality because of the failure to consider PM_{10} and $PM_{2.5}$ collinearity)

author	location	exposure monitoring	SO_2 concentration	study type (duration)	endpoint	co-pollutants	participants	ratio or risk	confidence interval	results	GRADE quality of evidence
(Dong et al., 2012)	Shenyang, China	mean daily concentration from fixed monitoring sites located in five provincial regions	annual mean 63 µg/m³	retrospective cohort (12 years)	total respiratory mortality from respiratory disease, lung cancer, emphysema, & respiratory failure	association with PM_{10}, SO_2, & NO_2	males and females 35 - 103 yrs old	no association using mortality hazard ratio per 10 µg/m³ increase in single pollutant model	no association using mortality hazard ratio per 10 µg/m³ increase in single pollutant model	no statistically significant association with respiratory disease in a single pollutant model; strong effect modification by smoking, basal metabolic index, and exercise	⊕⊕◯◯ (low quality because single pollutant modeling and the failure to consider $PM_{2.5}$ collinearity)
(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 modeling at home address	average annual exposure 4.8 ppb (12.8 µg/m³)	cohort study (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 4 ppb (10.6 µg/m³) in single and three-pollutant models with PM_{10} and NO_2 using all subjects and a group excluding long-haul truck drivers single pollutant (all cause mortality) all subjects - 6.9 subgroup without long haul - 10.6 single pollutant (respiratory mortality) subgroup without long haul - 9.2	percent increase in mortality per IQR of 4 ppb (10.6 µg/m³) in single and three-pollutant models with PM_{10} and NO_2 using all subjects and a group excluding long-haul truck drivers single pollutant (all cause mortality) all subjects - 2.3 - 11.6 subgroup without long haul -4.6 16.9 single pollutant (respiratory mortality) subgroup without long haul - 2.0 - 53.5	statistically significant increase in mortality of all truck drivers from all cause mortality but not cardiovascular disease, lung cancer, ischemic heart disease (IHD), or chronic obstructive pulmonary disease (COPD) in single pollutant model, statistically significant association in a subgroup of drivers excluding long haul employees for all cause and respiratory disease mortality using a single pollutant model; no statistically significant association for any cause of death for the main cohort or the sub-group using a three pollutant model with PM_{10} and NO_2	⊕⊕⊕◯ (moderate quality no adjustment necessary but no evaluation smoking)

author	location	exposure monitoring	SO_2 concentration	study type (duration)	endpoint	co-pollutants	participants	ratio or risk	confidence interval	results	GRADE quality of evidence
(Katanoda et al., 2011)	three prefectures in Japan Miyagi Aichi Osaka	mean annual concentration at 1-2 fixed monitoring sites within each of 6 locations for three prefectures	10 year average concentration 1974-1983 Miyagi Wakuya/Tajiri - 2.4 ppb (6.4 µg/m³) Sendai - 12.0 ppb (31.9 µg/m³) Aichi Inuyama - 9.5 ppb (25.3 µg/m³) Nagoya - 10.4 ppb (27.7 µg/m³) Osaka Nose/Kanan/Kumatori - 13.5 ppb (35.9 µg/m³) Osaka - 19.0 ppb (50.4 µg/m³)	cohort (10 year)	mortality from respiratory disease and lung cancer	association with suspended particulate matter (SPM), $PM_{2.5}$, SO_2, and NO_2	males and females 63,520 participants 6687 deaths	adjusted hazard ratio per IQR 10 ppb (26.6 µg/m³) in single pollutant model for all six locations fully adjusted respiratory disease - 1.43 partially adjusted (age & sex) lung cancer - 1.36 respiratory disease - 1.38	adjusted hazard ratio per IQR 10 ppb (26.6 µg/m³) in single pollutant model for all six locations fully adjusted respiratory disease 1.33 - 1.54 partially adjusted (age & sex) lung cancer - 1.20 - 1.54 respiratory disease - 1.23 - 1.55	statistically significant association with respiratory disease but not lung cancer in a single pollutant model fully adjusted for all potential confounders, significant association with lung cancer in a partially adjusted (no consideration of parents smoking habits, vegetable consumption, occupation, or type of health insurance); statistically significant association with lung cancer in male current smokers and respiratory disease in male current and female never smokers; statistically significant association with lung cancer in those with a history of respiratory disease; no statistically significant association with lung cancer in male former smokers or female never smokers	⊕⊕◯◯ (low quality because single pollutant modeling and the failure to consider PM_{10} collinearity)

Acute Emergency Department Visits

author	location	exposure monitoring	SO_2 concentration	study type (duration)	endpoint	co-pollutants	participants	ratio or risk	confidence interval	results	GRADE quality of evidence
(Brook and Kousha, 2015)	Calgary and Edmonton, Canada	daily averages from an unstated number of fixed monitoring sites	daily medians Calgary - 1.0 ppb (2.6 µg/m³) Edmonton - 0.9 ppb (2.4 µg/m³)	case-crossover (2 years)	emergency department visits for hypertension	association with $PM_{2.5}$, SO_2, O_3, and NO_2	males and females aged 0 to 100 6532 visits	pooled (fixed effects) odds ratio for hypertension stratified by sex and season per IQR increase of 0.78 ppb (2.07 µg/m³) in a single pollutant model on various lag days males (cold season) lag day 6 - 1.074 females (cold season) lag day 4 - 1.108 lag day 5 - 1.077 lag day 8 - 1068 females (warm season) lag day 2 - 1.080 lag day 8 - 1.052	pooled (fixed effects) odds ratio for hypertension stratified by sex and season per IQR increase of 0.78 ppb (2.07 µg/m³) in a single pollutant model on various lag days males (cold season) lag day 6 - 1.000 - 1.048 females (cold season) lag day 4 - 1.040 - 1.177 lag day 5 - 1.009 - 1.144 lag day 8 - 1005 - 1.131 females (warm season) lag day 2 - 1.022 - 1.138 lag day 8 - 1.000 - 1.110	statistically significant association with ED visits for hypertension in males during the cold season on lag day 6 but not lag days 0, 1, 2, 3, 4, 5, 7, or 8 using a single pollutant model; significant association in females in cold season on lag days 4, 5, and 8 but not the remaining 6 lag days; significant association in females during warm season on lag days 2 and 8 but not the remaining 7 lag days; no association with males during the warm season on any lag day	⊕○○○ (insufficient because of high likelihood of exposure misclassification and the failure to consider PM_{10} in two pollutant models)

author	location	exposure monitoring	SO_2 concentration	study type (duration)	endpoint	co-pollutants	participants	ratio or risk	confidence interval	results	GRADE quality of evidence
(Chan et al., 2009)	12 districts in Taipei, Taiwan	mean daily concentration from 11 fixed monitoring locations that were assigned district level geostatistical spatial levels using ordinary kriging	3 year average levels Beitou - 1.59 ppb (4.23 µg/m³) Da-an - 3.26 ppb (8.67 µg/m³) Datong - 3.43 ppb (9.12 µg/m³) Jhongiheng - 2.92 ppb (7.77 µg/m³) Jhongshan - 3.13 ppb (8.33 µg/m³) Nangang - 3.61 ppb (9.60 µg/m³) Neihu - 2.61 ppb (6.94 µg/m³) Shihlin - 1.88 ppb (5.00 µg/m³) Sinyi - 3.80 ppb (10.11 µg/m³) Songshan - 3.33 ppb (8.86 µg/m³) Wanhua - 2.97 ppb (7.90 µg/m³) Wunshan - 2.96 ppb (7.87 µg/m³)	time-series (3 years)	outpatient and emergency room visits for asthma	association with PM_{10}, O_3, SO_2, & NO_2	male and female adults aged 0 to >66 years outpatient - 724,075 visits emergency room - 34,274 visits	percentage increase in vests per 10% increase in concentration in single and four pollutant (SO_2/PM_{10}/O_3/NO_2) models on lag day 0 Outpatients (age 0 -15 yrs) single pollutant - 0.28 four pollutant - 0.12 Outpatients (age 16 - 65 yrs) single pollutant - 0.51 four pollutant - 0.20 Outpatients (age > 65 yrs) single pollutant -0.36 four pollutant - 0.33 Outpatients (age all ages) single pollutant - 0.44 four pollutant - 0.27	percentage increase in vests per 10% increase in concentration in single and four pollutant (SO_2/PM_{10}/O_3/NO_2) models on lag day 0 Outpatients (age 0 -15 yrs) single pollutant - 0.08 - 0.47 four pollutant - 0.20 - 0.44 Outpatients (age 16 -65 yrs) single pollutant - 0.36 - 0.66 four pollutant - 0.04 - 0.36 Outpatients (age > 65 yrs) single pollutant -0.23 - 0.49 four pollutant - 0.19 - 0.47 Outpatients (age all ages) single pollutant - 0.31 - 0.57 four pollutant - 0.12 - 0.41	statistically significant positive association with outpatient visits for asthma in all patents and each of three age groups using single and four pollutant (SO_2/PM_{10}/O_3/NO_2) models on lag day 0; no association or negative association (single pollutant model in > 65 yr age group) with emergency room visits for all patents and each of three age groups using single pollutant and four pollutant models on lag day 0; significant association with all age outpatient room visits on lag days 0, 1, and 2 and emergency room visits on lag day 2 using a single pollutant model, significant association with all age outpatient visits on lag days 0 and 1 but not lag day 2 using four pollutant model, no association with all age emergency room visits on any lag day using four pollutant model	⊕⊕⊕○ moderate quality, but no evaluation of $PM_{2.5}$)

author	location	exposure monitoring	SO_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 thirteen urban fixed monitoring sites	daily mean concentration 23.7 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 43,635 visits	percentage increase in hospital and emergency room visits per IQR 12.5 µg/m³ increase using one pollutant ,two-pollutant and multi-pollutant models for 5 day moving average lag respiratory disease admissions SO_2 only ≈ 10 (depicted graphically) SO_2/CO - 8.2 pneumonia and bronchopneumonia SO_2 only ≈ 20 (depicted graphically) SO_2/O_3 - 18.4 SO_2/CO - 18.4	percentage increase in hospital and emergency room visits per IQR 12.5 µg/m³ increase using one pollutant ,two-pollutant and multi-pollutant models for 5 day moving average lag respiratory disease admissions SO_2 only ≈ 5 - 17 (depicted graphically) SO_2/CO - 1.87 - 14.5 pneumonia and bronchopneumonia SO_2 only ≈ 4 - 38 (depicted graphically) SO_2/O_3 - 0.5 - 36.2 SO_2/CO - 0.5 - 36.2	statistically significant positive association with the percentage increase in respiratory-related and pneumonia/bronchopneumonia-related emergency room visits for single pollutant models and two pollutant models with CO (respiratory) and O_3 or CO (pneumonia/bronchopneumonia) using a 0-4 day moving average lag period; no statistically significant association with asthma and bronchiolitis visits for single, two-pollutant or multipollutant models under any conditions models; no significant associations with respiratory disease ER visits with two pollutant models with PM_{10}, NO_2, or O_3; no associations with pneumonia/bronchopneumonia using two pollutant models with PM_{10} or NO_2; no positive associations with any condition using multi-pollutant model with PM_{10}, NO_2, O_3, CO; statistically significant negative associations seen for respiratory disease visits in two pollutant model with PM_{10} and with the multi-pollutant model	⊕⊕⊕○ (moderate quality, but no evaluation of $PM_{2.5}$)

author	location	exposure monitoring	SO_2 concentration	study type (duration)	endpoint	co-pollutants	participants	ratio or risk	confidence interval	results	GRADE quality of evidence
(Filho et al., 2008)	Sao Paulo, Brazil	daily average from thirteen fixed monitoring sites	daily average 13.8 µg/m³	time-series (31 months)	emergency room visits for cardiovascular disease (ischemic heart disease and hypertension) in type 2 diabetics and non-diabetics	association with PM_{10}, SO_2, O_3, CO, & NO_2	males and females (daily rates) diabetics - 0.6 visits/day non-diabetics - 16.8 visits/day	percent increase in cardiovascular ER visits per IQR 8.0 µg/m³ for diabetics and non-diabetics in single pollutant model at various lag periods (data depicted graphically) diabetics lag day 0 ≈ 20 avg lag 01 ≈ 25 avg lag 02 ≈ 25 non-diabetics lag day 0 ≈ 7 avg lag 01 ≈ 7 avg lag 02 ≈ 6 avg lag 03 ≈ 7	percent increase in cardiovascular ER visits per IQR 8.0 µg/m³ for diabetics and non-diabetics in single pollutant model at various lag periods (data depicted graphically) diabetics lag day 0 ≈ 4 - 37 avg lag 01 ≈ 5 - 44 avg lag 02 ≈ 2 - 47 non-diabetics lag day 0 ≈ 3 - 11 avg lag 01 ≈ 3 - 10 avg lag 02 ≈ 2 - 10 avg lag 03 ≈ 2 - 11	statistically significant association with cardiovascular emergency room visits for diabetics on lag day 0, 01, and 02 and non-diabetics on lag day 0, 01, 02 and 03, no statistically significant association on lag day 2 & cumulative lag 03 for diabetics and lag day 1 and cumulative lag 01 for non-diabetics	⊕○○○ (insufficient because no two-pollutant modeling and the failure to consider PM_{10} in two pollutant models)
(Goldman et al., 2010)	Atlanta, Georgia	1- hour maximum concentration from four central monitors with independent determination of measurement error (co-located instrument) and spatial variability (semi-variograms)	mean 1-hr max urban 11.4 ppb (30.3 µg/m³) rural 6.32 ppb (16.8 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, SO4, NH4, EC, & OC	male & female 166,950 visits	risk ratio for cardiovascular emergency department visits per 1 ppm (2.66 mg/m³) increase following spatial error adjustment of the base case assessment 1-hour max SO_2 - 1.0045	risk ratio for cardiovascular emergency department visits per 1 ppm (2.66 mg/m³) increase following spatial error adjustment of the base case assessment 1-hour max SO_2 - 1.0023 - 1.0065	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 and absence of two pollutant modeling)

author	location	exposure monitoring	SO_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 49.32 µg/m³	case-crossover (19 months)	emergency room visits for cardiovascular disease	differential effects of $PM_{2.5}$, SO_2, & NO_2	male & female cases 8,377	odds ratio for hospitalization per 10 µg/m³ increase using single and two pollutant models single pollutant lag day 0 - 1.014 lag day 1 - 1.012 lag day 2 - 1.011	odds ratio for hospitalization per 10 µg/m³ increase using single and two pollutant models single pollutant lag day 0 - 1.004 - 1.024 lag day 1 - 1.003 - 1.022 lag day 2 - 1.002 - 1.021	statistically significant association with cardiovascular emergency room visits using a single pollutant model with a lag of 0, 1, or days, but not on lag day 3; no associations with ER visits using two pollutant models with $PM_{2.5}$ or NO_2 on lag day 0	⊕○○○ (insufficient because of exposure misclassification 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 47.3 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 using a single pollutant SO_2 only - 1.037	odds ratio per 10 µg/m³ increase on lag day 3 using a single pollutant SO_2 only - 1.004 - 1.071	statistically significant association with emergency department visits for hypertension in a single pollutant model on lag days 0 and 2 but not lag days 1, 3, 4, or 5; no statistically significant association in multi-pollutant models with PM_{10}, NO_2, or PM_{10}/NO_2 together on lag day 0	⊕⊕○○ (low quality because of exposure misclassification)
(Guo et al., 2014a)	Shanghai, China	daily averages from an unstated number of fixed monitoring studies	daily average concentration 30 µg/m³	time-series (2 years)	outpatient visits for acute bronchitis	association with PM_{10}, SO_2, & NO_2	males and females 58,740 hospital visits	percent increase in hospital visits for acute bronchitis per 10 µg/m³ increase using a 7 day (0-6) moving average lag single pollutant males - 9.90 females - 12.05 age group (5 -65 yrs) - 12.66 age group (>66 yrs) - 7.82 cool season - 6.56 warm season - 17.19 multi-pollutant SO_2/PM_{10} - 10.24 SO_2/NO_2 - 9.50 $SO_2/PM_{10}/NO_2$ - 12.47	percent increase in hospital visits for acute bronchitis per 10 µg/m³ increase using a 7 day (0-6) moving average lag single pollutant males - 9.33 - 10.47 females - 11.58 - 12.53 age group (5 -65 yrs) - 12.22 - 13.09 age group (>66 yrs) - 7.15 - 8.49 cool season - 6.13 - 6.98 warm season - 16.36 - 18.02 multi-pollutant SO_2/PM_{10} - 9.82 - 10.66 SO_2/NO_2 - 9.06 - 9.95 $SO_2/PM_{10}/NO_2$ - 11.57 - 13.36	statistically significant association with acute bronchitis hospital visits at all 13 single and moving average lag times in a single pollutant model; statistically significant association in both sexes, seasons and age groups using a single pollutant model and a 7 day moving average lag; significant association in two and three pollutant models with PM_{10} and NO_2 using a 7 day moving avg. lag	⊕○○○ (insufficient because of the number of monitoring sites not stated and the failure to consider $PM_{2.5}$ in two pollutant models)

author	location	exposure monitoring	SO_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, NY	daily averages from 19 fixed monitoring sites	daily average all year -7.8 ppb (20.7 µg/m³) warm months - 5.4 ppb (14.4 µg/m³) cold months - 10.2 ppb (27.1 µg/m³)	time-series (4 years)	emergency department visits for asthma	association with $PM_{2.5}$, PM_{10}, SO_2, O_3, CO, & NO_2	unstated number of males and females aged 2 to 45 years	relative risk for asthma ED visits per 5th-95th percentile increase using a single and two pollutant model with a 2 day average lag and a weather model that considers only temperature change (graphical data presentation) single pollutant all year (14 ppb rise) - 1.08 cold months (15 ppb rise) - 1.08 warm months (7 ppb rise) - 1.15 two pollutant warm months (7 ppb rise) $SO_2/PM_{2.5}$ - 1.17 SO_2/O_3 - 1.15 SO_2/CO - 1.16	relative risk for asthma ED visits per 5th-95th percentile increase using a single and two pollutant model with a 2 day average lag and a weather model that considers only temperature change (graphical data presentation) single pollutant all year (14 ppb rise) - 1.03 - 1.16 cold months (15 ppb rise) - 1.03 - 1.16 warm months (7 ppb rise) - 1.08 - 1,26 two pollutant warm months (7 ppb rise) $SO_2/PM_{2.5}$ - 1.09 - 1.27 SO_2/O_3 - 1.08 - 1.26 SO_2/CO - 1.10 - 1.28	statistically significant association with ED visits for asthma during the entire season, warm months, and cold months using a single pollutant model with a 2 day average lag that incorporates a weather model that considers temperature only; statistically significant associations with asthma visits for all three seasonal stratifications using a single pollutant model that incorporates alternative weather model that consider both temperature and dew point; significant association with asthma visits during the warm season using a two pollutant model with PM2.5, O_3, and CO but not NO_2 and a 2 day average lag with the temperature only weather model	⊕⊕⊕◯ moderate quality, but high probability of exposure misclassification)

author	location	exposure monitoring	SO_2 concentration	study type (duration)	endpoint	co-pollutants	participants	ratio or risk	confidence interval	results	GRADE quality of evidence
(Jalaludin et al., 2006)	Sydney, Australia	daily averages from 14 fixed monitoring sites	daily mean concentration 1.07 ppb (2.85 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 2.2 ppb (5.9 µg/m³) in single and two-pollutant models cardiovascular total (lag day 0) SO_2 only - 1.33 SO_2/O_3 ≈ 2.1 (depicted graphically) cardiac disease (lag day 0) SO_2 only - 1.62 ischemic heart disease (lag day 2) SO_2 only - 1.97	percent change in total cardiovascular emergency department visits per IQR 2.2 ppb (5.9 µg/m³) in single and two-pollutant models cardiovascular total (lag day 0) SO_2 only - 0.24 - 2.43 SO_2/O_3 ≈ 0.04 - 2.7 (depicted graphically) cardiac disease (lag day 0) SO_2 only - 0.33 -2.93 ischemic heart disease (lag day 2) SO_2 only - 0.07 - 3.91	statistically significant association with total cardiovascular ED visits on lag day 0 in single and two-pollutant models with O3, but not with PM_{10}, PM2.5, CO, or NO_2; statistically significant association with cardiac disease on lag day 0 and ischemic heart disease on lag day 2 in single pollutant model but not for stroke on any lag day: statistically significant positive association with all total cardiovascular, cardiac disease, and ischemic heart disease ED visits on lag day 0 for cool period but not warm periods, no statistically significant association with stroke visits for either season	⊕○○○ (insufficient because of publication, selection, and lag bias)

author	location	exposure monitoring	SO_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	daily averages from 14 fixed monitoring sites	daily mean concentration all season - 1.07 ppb (2.85 µg/m³) cool period - 1.1 ppb (2.93 µg/m³) warm period - 1.03 (2.74 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 0.8 ppb (2.13 µg/m³) in single and two-pollutant models for lag day 0, 1, 2, or 3 1-4 years of age SO_2 only - 1.8 SO_2/PM_{10} - 1.1 $SO_2/PM_{2.5}$ - 1.1 SO_2/O_3 - 1.9 SO_2/NO_2 - 2.6 SO_2/CO - 1.6 5-9 years of age SO_2 only - 1.9 SO_2/PM_{10} - 1.3 $SO_2/PM_{2.5}$ - 1.3 SO_2/O_3 - 1.7 SO_2/CO - 2.5 10-14 years of age SO_2/PM_{10} - 1.9 $SO_2/PM_{2.5}$ - 1.2 SO_2/CO - 3.2 1-14 years SO_2 only - 1.6 SO_2/PM_{10} - 1.2 $SO_2/PM_{2.5}$ - 1.2 SO_2/O_3 - 1.3 SO_2/NO_2 - 1.9 SO_2/CO - 2.0	percent increase in ED visits for asthma in children of different age groups per IQR of 0.8 ppb (2.13 µg/m³) in single and two-pollutant models for lag day 0, 1, 2, or 3 1-4 years of age SO_2 only - 0.8 - 2.9 SO_2/PM_{10} - 0.3 - 1.9 $SO_2/PM_{2.5}$ - 0.5 - 1.8 SO_2/O_3 - 1.2 - 2.6 SO_2/NO_2 - 1.4 - 3.9 SO_2/CO - 0.7 - 2.6 5-9 years of age SO_2 only - 0.3 - 3.6 SO_2/PM_{10} - 0.2 - 2.5 $SO_2/PM_{2.5}$ - 0.4 - 2.3 SO_2/O_3 - 0.4 - 3.0 SO_2/CO - 1.0 - 4.1 10-14 years of age SO_2/PM_{10} - 0.3 - 3.6 $SO_2/PM_{2.5}$ - 0.02 - 2.5 SO_2/CO - 1.5 - 5.0 1-14 years SO_2 only - 0.7 - 2.4 SO_2/PM_{10} - 0.6 - 1.8 $SO_2/PM_{2.5}$ - 0.7 - 1.7 SO_2/O_3 - 0.8 - 1.9 SO_2/NO_2 - 0.9 - 2.9 SO_2/CO - 1.3 - 2.8	statistically significant association with ED visits for asthma in single and all two pollutant models for age group 1-14 years and age group 1-4 years on lag day 0; statistically significant association in single and many two pollutant models for age group 5-9 years on lag day 0 (SO_2/NO2 was the only exception); no association with age group 10-14 years using single pollutant model but two pollutant models for with PM_{10}, $PM_{2.5}$, & CO yielded positive associations if lag days 2 and 3 were used in the co-pollutant model; no statistically significant associations in single pollutant model for warm or cold months in any age group except 1-14 years where a positive association was found in cool but not warm months	⊕○○○ (insufficient because of small number of cases and consistencies across models and age groups)

author	location	exposure monitoring	SO_2 concentration	study type (duration)	endpoint	co-pollutants	participants	ratio or risk	confidence interval	results	GRADE quality of evidence
(Karr et al., 2009)	British Columbia	levels at the most proximal (within 10 km) of 14 fixed monitoring sites	lifetime exposure 5.6 µg/m³	case control (4 years)	outpatient or hospitalization for bronchiolitis in children	association with $PM_{2.5}$, PM_{10}, SO_2, O_3, CO, NO, NO_2, wood smoke, and black carbon	males and females 2 - 12 months of age 1465 cases 57,127 controls	adjusted odds ratio for bronchiolitis hospitalization per IQR increase of 3.2 µg/m³ in as single pollutant model using different exposure metrics lifetime exposure - 1.04 previous month exposure - 1.03	adjusted odds ratio for bronchiolitis hospitalization per IQR increase of 3.2 µg/m³ in as single pollutant model using different exposure metrics lifetime exposure - 1.01 - 1.06 previous month exposure - 1.01 - 1.05	statistically significant association with infant bronchiolitis hospitalization using and adjusted single pollutant model based on lifetime exposures or the previous month exposure, stratification showed significant association for the fourth quartile of lifetime exposures but not the second or third using a single pollutant model; no associations observed using crude single pollutant models for any exposure metric	⊕○○○ (insufficient because no two-pollutant modeling and high likelihood of exposure misclassification)
(Kim et al., 2007b)	Seoul, Korea	daily averages from 27 fixed monitoring sites located within 5 regions of the city (25 districts)	mean concentration 4.7 µg/m³	case-crossover (1 year)	interaction socioeconomic position (SEP) measured using income levels with hospital visits for asthma	association with PM_{10}, SO_2, O_3, CO, & NO_2	males and females aged 9 to > 70 years 92,535 cases	change in relative risk for ED asthma vests per 3.3 0 µg/m³ increase using a single pollutant model and a day 3 lag value for individuals in 5 different income quintiles quintile 1 (highest SEP) - 1.03 quintile 2 (high SEP) - 1.04 quintile 4 (low SEP) - 1.04	change in relative risk for ED asthma vests per 3.3 0 µg/m³ increase using a single pollutant model and a day 3 lag value for individuals in 5 different income quintiles quintile 1 (highest SEP)- 1.01 - 1.06 quintile 2 (high SEP)- 1.02 - 1.07 quintile 4 (low SEP)- 1.01 - 1.07	statistically significant association for asthma ED visits for those individuals in the two highest income quintiles and those in the second lowest quintile using a single pollutant model on lag day 3; significant associations also observed when socioeconomic position (i.e. income) was assigned to the urban region of residence rather than the individual; significant associations with asthma visits for all individuals on lag days 3 and 4 but not lag days 0, 1, 2, or the 3 day moving average lag	⊕○○○ (insufficient because no two-pollutant modeling and inconsistent results)

author	location	exposure monitoring	SO_2 concentration	study type (duration)	endpoint	co-pollutants	participants	ratio or risk	confidence interval	results	GRADE quality of evidence
(Kim et al., 2012)	Seoul, Korea	averages from the nearest fixed monitor but the distance and number of monitors was not stated	daily averages spring - 6.9 ppb (18.420.7 µg/m³) summer - 4.9 ppb (13.0 µg/m³) fall - 6.5 ppb (17.3 µg/m³) winter - 8.8 ppb (23.4 µg/m³)	case-crossover (5 years)	hospital visits for refractory asthma exacerbations	association with PM_{10}, SO_2, CO, O_3, & NO_2	males and females aged 19 to 87 years 39 non-smoking subjects 43 smoking subjects	adjusted odds ratio for asthma exacerbations for those sensitive and insensitive to dust mite allergens during the winter season per 1 ppb (2.6 µg/m³) increase in as single and multi-pollutant models for the winter months single pollutant - non-smoking subjects lag day 1 - 1.147 lag day 2 - 1.140 multi-pollutant (SO_2/PM_{10}/O_3/CO/NO_2) - non-smoking subjects lag day 1 - 1.197 lag day 2 - 1.164 multi-pollutant (SO_2/PM_{10}/O_3/CO/NO_2) - all subjects lag day 2 - 1.114	adjusted odds ratio for asthma exacerbations for those sensitive and insensitive to dust mite allergens during the winter season per 1 ppb (2.6 µg/m³) increase in as single and multi-pollutant models for the winter months single pollutant - non-smoking subjects lag day 1 - 1.019 - 1.292 lag day 2 - 1.024 - 1.268 multi-pollutant (SO_2/PM_{10}/O_3/CO/NO_2) - non-smoking subjects lag day 1 - 1.033 - 1.387 lag day 2 - 1.030 - 1.316 multi-pollutant (SO_2/PM_{10}/O_3/CO/NO_2) - all subjects lag day 2 - 1.028 - 1.208	statistically significant association with asthma exacerbations in all patients during the winter months using a single pollutant model with a 1 or day lag but not with a lag of 0 or 3 days; statistically significant association during the winter months for nonsmokers using a multipollutant model with PM_{10}, O_3, CO, and NO_2 on lag days 1 and 2 but not days 0 or 3; significant association with all patients using a multi-pollutant model on lag day 2 but not days 0, 1, or 3; significant associations for those not sensitive to dust mite allergens using a multi-pollutant model on lag day 1 and 2 but not days 0, or 3; no association with all patients or non-smokers for the spring, summer, or fall seasons using single and multi-pollutant models, no association with non-smokers using single and multi-pollutant models for any season or any lag day, no association with those sensitive to dust mite allergens using single and multi-pollutant models for any season or any lag day	⊕○○○ (insufficient because of small sample size and he failure to state the number of monitoring sites)

author	location	exposure monitoring	SO_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 8 fixed monitoring sites	daily mean 87 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	no increase in relative risk for respiratory emergency room visits per 100 µg/m³ increment using a single pollutant model using same day or a 5 day moving average lag	no increase in relative risk for respiratory emergency room visits per 100 µg/m³ increment using a single pollutant model using same day or a 5 day moving average lag	no significant associations with respiratory emergency room visits using a single pollutant model with a short or a long lag period	⊕○○○ (insufficient because no two-pollutant and high likelihood of exposure misclassification)
(Llorca et al., 2005)	Torrelavega, Spain	daily average from three fixed monitoring site	daily mean concentration 13.3 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	no increase in relative risk for cardiopulmonary, cardiac, or respiratory admissions per 100 µg/m³ change using single and multi-pollutant model with an unstated lag period	no increase in relative risk for cardiopulmonary, cardiac, or respiratory admissions per 100 µg/m³ change using single and multi-pollutant model with an unstated lag period	no statistically significant association with hospital admissions for total cardiopulmonary, cardiac, or respiratory disease in single pollutant or multi-pollutant (SO_2/TSP/H2S/NO_2/NO) models at an unstated lag period	⊕○○○ (insufficient because of publication bias, exposure misclassification, and poor method description)
(Orazzo et al., 2009)	six Italian cities Ancona Bologna Florence Naples Padua Varese-Gallarate	daily means from at least one fixed monitoring site in each city	daily means Ancona - 2.1 µg/m³ Bologna - 1.4 µg/m³ Florence - 1.5 µg/m³ Naples - 2.6 µg/m³ Padua - 1.9 µg/m³ Varese-Gallarate - 1.3 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	adjusted percent increase in for wheeze or GI disorder risk in a random effect pooled city analysis using single pollutant model for specific moving average lag periods and IQRs wheeze lag 0-3 (IQR 8.3 µg/m³) - 1.7 lag 0-4 (IQR 8.2 µg/m³) - 2.1 lag 0-5 (IQR 8.1 µg/m³) - 2.8 lag 0-3 (IQR 8.0 µg/m³) - 3.4 GI disorders lag 0-4 (IQR 8.1 µg/m³) - 7.0 lag 0-5 (IQR 8.03 µg/m³) - 8.5	adjusted percent increase in for wheeze or GI disorder risk in a random effect pooled city analysis using single pollutant model for specific moving average lag periods and IQRs wheeze lag 0-3 (IQR 8.3 µg/m³) - 0.0 - 3.4 lag 0-4 (IQR 8.2 µg/m³) - 0.4 - 3.9 lag 0-5 (IQR 8.1 µg/m³) - 0.9 - 4.6 lag 0-3 (IQR 8.0 µg/m³) - 1.5 - 4.3 GI disorders lag 0-4 (IQR 8.1 µg/m³) - 0.1 - 14.3 lag 0-5 (IQR 8.03 µg/m³) - 0.6 16.9	statistically significant association with wheeze at moving average lag periods of 0-3, 0-4, 0-5, and 0-6 days but not 0-1 or 0-2 days; statistically significant association with GI disorders at moving average periods of 0-5 and 0-6 days but not 0-1, 0-2, 0-3, or 0-4 days; no associations with wheeze or GI disorders when the results were stratified by season using a moving average lag of 0-5or 0-4 days, respectively	⊕○○○ (insufficient because of exposure bias and the absence of two-pollutant modeling)

author	location	exposure monitoring	SO_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 16.5 ppb (43.9 µg/m³)	time-series (92 months)	emergency department visits for total respiratory disease, 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 (53.2 µg/m³) in a single pollutant model using either of two lag periods 0-13 day distributed lag upper respiratory infection - 1.062 COPD - 1.116 0-2 day moving average lag (ARIES monitoring site) all respiratory disease - 1.020	risk ratio per 20 ppb (53.2 µg/m³) in a single pollutant model using either of two lag periods 0-13 day distributed lag upper respiratory infection - 1.031 - 1.095 COPD - 1.024 - 1.217 0-2 day moving average lag (ARIES monitoring site) all respiratory disease - 1.001 - 1.038	statistically significant association with emergency department visits for upper respiratory tract infections and chronic obstructive pulmonary disease in a single pollutant model using a 14 day distributed lag (0-13), no statistically significant associations for any disease state using a 3 day (0-2) moving average lag; statistically significant association with all respiratory disease with the ARIES monitoring data but not measurements from the AQS site using a single pollutant model and a 3-day moving average lag; no association of 1-hour maximum SO_2 with ED visits for all respiratory disease, URI, asthma, pneumonia, or COPD in a single pollutant model using a 3 day moving average lag (0-2)	⊕○○○ (insufficient because of the small number of monitoring sites and the lack of two-pollutant modeling)

author	location	exposure monitoring	SO_2 concentration	study type (duration)	endpoint	co-pollutants	participants	ratio or risk	confidence interval	results	GRADE quality of evidence
(Peel et al., 2007)	Atlanta, GA	1-hr maximum concentration at a single fixed monitoring site	1-hr maximum average 16.5 ppb (43.9 µg/m³)	case-crossover (92 months)	emergency room visits for all cardiovascular disease, congestive heart failure, ischemic heart disease, dysrhythmia, & cerebrovascular disease segregated according to underlying co morbid conditions such as hypertension, diabetes, and COPD	association with PM_{10}, SO_2, O_3, CO, & NO_2	males and females (avg. ED visit rates) all cardiovascular disease - 103,551 visits congestive heart failure - 20,073 visits ischemic heart disease - 32,731 visits dysrhythmia - 27,342 visits cerebrovascular disease - 23,411 visits	no increase in odds ratio for any cardiovascular disease in those with or without overlying hypertension, diabetes, or COPD per 20 ppb (53.2 µg/m³) increase in a single pollutant model for 3 a day moving average lag period (0-2)	no increase in odds ratio for any cardiovascular disease in those with or without overlying hypertension, diabetes, or COPD per 20 ppb (53.2 µg/m³) increase in a single pollutant model for 3 a day moving average lag period (0-2)	no statistically significant association with cardiovascular disease, ischemic heart disease, cerebrovascular disease, dysrhythmia or congestive failure in those with or without hypertension, diabetes, or COPD using a single pollutant model on a 3 day average lag period, no statistically significant association with all cardiovascular disease, ischemic heart disease, dysrhythmia, peripheral vascular disease, or congestive heart failure using a time-series or case-crossover study design	⊕○○○ (insufficient because of the high likelihood of exposure misclassification and the lack of two-pollutant modeling)
(Santos et al., 2008)	Sao Paulo, Brazil	mean daily concentration at seven fixed monitoring locations	daily mean 15.05 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	no increase in percentage of arrhythmia emergency room visits per IQR of 9.3 µg/m³ in single pollutant model on lag day 0, 1, 2, 3, 4, 5, or 6	no increase in percentage of arrhythmia emergency room visits per IQR of 9.3 µg/m³ in single pollutant model on lag day 0, 1, 2, 3, 4, 5, or 6	no statistically significant association with emergency room visits for cardiac arrhythmia in a single pollutant model on any of 7 lag days	⊕○○○ (insufficient because of the small number of cases and the absence of two-pollutant modeling)

author	location	exposure monitoring	SO_2 concentration	study type (duration)	endpoint	co-pollutants	participants	ratio or risk	confidence interval	results	GRADE quality of evidence
(Sinclair et al., 2010)	Atlanta, Georgia	hourly maximum concentration at a single fixed monitoring location	average 1-hr daily maximum 25 month period warm months - 15.92 ppb (42.3 µg/m³) cold months - 24.31 ppb (64.7 µg/m³) 28 month period warm months - 13.82 ppb (36.8 µg/m³) cold months - 22.60 ppb (60.1 µg/m³)	time-series (25 month and 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 for respiratory tract infections over a 25 or 28 day period per 16.47 ppb (43.8 µg/m³) change in a single pollutant model at various lag times 25 month period LRT infection (lag 0-2 days) - 1.055 28 month period URT infection (lag 6-8 days) - 1.033	relative risk for respiratory tract infections over a 25 or 28 day period per 16.47 ppb (43.8 µg/m³) change in a single pollutant model at various lag times 25 month period LRT infection (lag 0-2 days) - 1.005 - 1.108 28 month period URT infection (lag 6-8 days) - 1.015 - 1.051	statistically significant association with outpatient visits for lower respiratory tract infection in the 25 month study in a single pollutant model at the 0-2 day lag period but not at the other 2 longer lag periods; statistically significant association with visits for upper respiratory tract infection in the 28 month study in a single pollutant model at the 6-8 day lag period but not at the other 2 shorter lag periods; statistically significant negative association for LRI in the 28 month study at a lag time of 0-2 days; no association with adult or childhood asthma regardless of study duration or lag; no association with visits for childhood asthma in either warm or cold seasons using single pollutant model	⊕○○○ (insufficient because of the high likelihood of exposure misclassification and the lack of two-pollutant modeling)

author	location	exposure monitoring	SO_2 concentration	study type (duration)	endpoint	co-pollutants	participants	ratio or risk	confidence interval	results	GRADE quality of evidence
(Smargiassi et al., 2009)	Montreal, Canada	residential daily average and peak levels as well as 5 day averages using AERMOD dispersion modeling of the stack emissions from a local oil refinery	modeled concentration daily mean - 3.0 ppb (8.0 µg/m³) daily peak - 17.5 ppb (46.6 µg/m³) 5-day average - 3.0 ppb (8.0 µg/m³)	case-crossover (9 years)	hospitalization or emergency department visit for asthma	association with SO_2 only	male and female children 2 - 4 years of age 263 hospitalizations 1579 ED visits	adjusted odds ratio for asthma hospitalizations per IQR increase using a single pollutant model with various lag days hospital admissions daily mean (lag 0, IQR 4.3 ppb) - 1.14 daily peak (lag 0, IQR 31.2 ppb) - 1.42 ED visits daily peak (lag 0, IQR 31.2 ppb) - 1.10 daily mean (lag 1, IQR 4.3 ppb) - 1.05	adjusted odds ratio for asthma hospitalizations per IQR increase using a single pollutant model with various lag days hospital admissions daily mean (lag 0, IQR 4.3 ppb) - 1.00 - 1.30 daily peak (lag 0, IQR 31.2 ppb) - 1.10 - 1.82 ED visits daily peak (lag 0, IQR 31.2 ppb) - 1.00 - 1.22 daily mean (lag 1, IQR 4.3 ppb) - 1.00 - 1.12	statistically significant association with adjusted asthma hospital admissions using daily mean and daily peak levels on lag day 0 but not on lag day 1 or the 5-day average lag using a single pollutant model; significant association with asthma emergency department visits using daily peak on lag day 0 and daily mean on lag day 1; significant associations in crude admissions and ED visits for mean and peak exposures on lag day 0; no associations in crude hospital admissions or ED visits on mean or peak daily lag 1 or 5 day average models; associations restricted to those living to the east and southwest of the source and not those living	⊕○○○ (insufficient because of the small number of cases and the absence of two-pollutant modeling)

author	location	exposure monitoring	SO_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 11 fixed monitoring sites	hourly mean Montreal - 4.8 ppb (12.8 µg/m³) Ottawa - 3.9 (10.4 µg/m³) Edmonton - 2.6 (6.9 µg/m³) Saint John - 7.7 (20.5 µg/m³) Halifax - 10.0 ppb (26.6 µg/m³) Toronto - 4.2 ppb (11.2 µg/m³) Vancouver - 2.6 ppb (6.9 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 (fixed and random effects) percent increase in emergency department visits per 5.1 ppb (13.6 µg/m³) in a single pollutant model for the summer season angina/infarction lag day 1 - 2.1	pooled (fixed and random effects) percent increase in emergency department visits per 5.1 ppb (13.6 µg/m³) in a single pollutant model for the summer season angina/infarction lag day 1 - 0.2 - 4.0	statistically significant association with ED visits for angina/infarction in a single pollutant model on lag day 2; no statistically significant associations ED visits for all other cardiac and respiratory conditions in a single pollutant model at any of three daily lag periods or any of six within day 3 hour lag periods; no associations with visits for any condition during the winter months	⊕⊕◯◯ (low quality because of absence of methodological details and the lack of two-pollutant models)

author	location	exposure monitoring	SO_2 concentration	study type (duration)	endpoint	co-pollutants	participants	ratio or risk	confidence interval	results	GRADE quality of evidence
(Strickland et al., 2010)	Atlanta, Georgia	population weighted hourly maximum concentration at an unstated number of fixed monitoring location	mean 1-hr maximum overall - 10.8 ppb (28.7 µg/m³) warm season - 9.6 (25.5 µg/m³) cold season - 12.0 (31.9 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 for asthma per 11.5 ppb (30.6 µg/m³) in adjusted single pollutant model using a 3 day (0-2) moving average lag warm season - 1.030 rate ratio for ER visits relative to the first SO_2 exposure quintile (< 3.1 ppb) 3rd quintile (7.0 - <13 ppb) - 1.041 4th quintile (13 - <24.2 ppb) - 1.048	rate ratios for ER visits for asthma per 11.5 ppb (30.6 µg/m³) in adjusted single pollutant model using a 3 day (0-2) moving average lag warm season - 1.002 - 1.058 rate ratio for ER visits relative to the first SO_2 exposure quintile (< 3.1 ppb) 3rd quintile (7.0 - <13 ppb) - 1.007 - 1.077 4th quintile (13 - <24.2 ppb) - 1.010 - 1.087	statistically significant association in the overall base model in the warm season but not for all seasons or the cold season using a single pollutant model and a distributed lag periods of 1, 2, 3, 4, 5, 6, 7, and 8 days2 day moving average lag period; statistically significant association in single pollutant base model at the 3rd and 4th exposure quintiles but not at the 1st or 5th exposure quintiles where the exposures or lower (3.1 - <7 ppb) and higher (57.1 - ≤181 ppb); sensitivity analysis showed that alternative time-series and case-crossover models that used alternative approaches to control for weather interactions did not yield statistically significant increases in asthma visits	⊕○○○ (insufficient because of the number of monitoring sites not stated and no two pollutant modeling)

author	location	exposure monitoring	SO_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	three methods employed involving i) one hour maximum from a central monitor (five fixed monitoring sites available), ii) unweighted average from all monitoring sites, and iii) population-weighted average of spatially adjusted measurements from monitoring sites using inverse distance squaring	1-hr maximum central monitor - 13.9 ppb (37.0 µg/m³) unweighted average - 10.2 ppb (27.1 µg/m³) population weighted average - 9.6 ppb (25.5 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	change in rate ratio per 20 ppb (53.2 µg/m³) increase for a 3-day moving average lag in single pollutant model (warm season only) unweighted - 1.062 pop. weighted - 1.053	change in rate ratio per 20 ppb (53.2 µg/m³) increase for a 3-day moving average lag in single pollutant model (warm season only) unweighted - 1.014 - 1.111 pop. weighted - 1.0004 - 1.104	statistically significant association with emergency department visits by children with asthma using exposure unweighted and population weighted exposure measurement from central sites using a single pollutant model and a 3 day moving average lag; no associations observed for asthma visits using a exposure values from central site monitors	⊕⊕◯◯ (low quality because only single pollutant modeling only)
(Szyszkowicz M, 2011)	Edmonton, Alberta	mean daily concentration at an unstated number of fixed monitoring locations	daily mean 2.6 ppb (6.9 µg/m³)	case-crossover (120 months)	emergency department visits for clinical depression	association with control day separation, SO_2, CO & NO_2	female 15,556 cases	change in odds ratio for depression ED visits per an unstated IQR increase using a single pollutant model lag day 0 all seasons, female patients - 3.0 warm seasons, female patients - 4.5 lag day 2 all seasons, female patients - 3.5 warm season, female patients - 3.8	change in odds ratio for depression ED visits per an unstated IQR increase using a single pollutant model lag day 0 all seasons, female patients - 0.2 - 5.8 warm seasons, female patients - 0.1 - 9.1 lag day 2 all seasons, female patients - 0.7 - 6.3 warm season, female patients - 0.1 - 7.7	statistically significant association emergency department visits for depression in females for both seasons and the warm season using a single pollutant model on lag days o and 2 but not on lag day 1; no association with males or all patients for any lag period or any seasonal stratification	⊕◯◯◯ (insufficient because of the unstated number of monitoring sites and failure to perform two-pollutant modeling)

author	location	exposure monitoring	SO_2 concentration	study type (duration)	endpoint	co-pollutants	participants	ratio or risk	confidence interval	results	GRADE quality of evidence
(Szyszkowic M, 2008a)	Edmonton, Alberta	mean daily concentration at an unnamed number of fixed monitoring locations	daily mean 2.6 ppb (6.9 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 from 0 to 80 years of age 62,563 visits	no change in relative risk percentage for asthma ED visits for males or females in either age group per 2. 3 ppb (6.1 µg/m³) IQR increase using a single pollutant model and a 0, 1, or 2 day lag period	no change in relative risk percentage for asthma ED visits for males or females in either age group per 2. 3 ppb (6.1 µg/m³) IQR increase using a single pollutant model and a 0, 1, or 2 day lag period	no statistically significant associations asthma ED visits in a single pollutant model at lag day o, 1, or 2 with a single pollutant model; no associations with asthma visits following stratification by sex (male and female or age group (< 10 yrs or ≥ 10 yrs), or season (all season, warm, and cold)	⊕○○○ (insufficient because of the unstated number of monitoring sites and failure to perform two-pollutant modeling)
(Szyszkowic M et al., 2009b)	7 Canadian cities Edmonton, Alberta Halifax, Nova Scotia Ottawa, Ontario Montreal, Quebec Toronto, Ontario Sunnybrook, Ontario Vancouver, British Columbia	mean daily concentration at an unstated number of fixed monitoring locations within seven cities	daily mean concentration Edmonton - 2.6 ppb (6.9 µg/m³) Halifax - 10.0 ppb (26.6 µg/m³) Ottawa - 4.8 ppb (12.8 µg/m³) Montreal - 3.9 ppb (10.4 µg/m³) Toronto - 4.2 ppb (11.2 µg/m³) Sunnybrook - 4.5 ppb (12.0 µg/m³) Vancouver - 2.5 ppb (6.6 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	pooled and adjusted percentage relative risk for depression ED visits per 4.6 ppb (12.2 µg/m³) change in a single pollutant model on lag day 0 warm season (Apr - Sept) - 5.9	pooled and adjusted percentage relative risk for depression ED visits per 4.6 ppb (12.2 µg/m³) change in a single pollutant model on lag day 0 warm season (Apr - Sept) - 1.1 - 11.0	statistically significant association depression ED vests in warm summer months using a single pollutant model on lag day 0, no association observed for all seasons and the cold months	⊕⊕○○ (low quality because of bias from single pollutant model)

author	location	exposure monitoring	SO_2 concentration	study type (duration)	endpoint	co-pollutants	participants	ratio or risk	confidence interval	results	GRADE quality of evidence
(Szyszkowicz M et al., 2009a)	6 Canadian cities Edmonton, Alberta Halifax, Nova Scotia Ottawa, Ontario Toronto, Ontario Sunnybrook, Ontario Vancouver, British Columbia	mean daily concentration at an unstated number of fixed monitoring locations within six cities	daily mean concentration Edmonton - 2.6 ppb (6.9 µg/m³) Halifax - 10.0 ppb (26.6 µg/m³) Ottawa - 3.9 ppb (10.4 µg/m³) Toronto - 4.2 ppb (11.2 µg/m³) Sunnybrook - 4.5 ppb (12.0 µg/m³) Vancouver - 2.5 ppb (6.6 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	pooled percentage increase in relative risk for migraine ED visits per 2.3 ppb (6.1 µg/m³) change using a single pollutant model on lag day 0 warm seasons, female patients - 4.0	pooled percentage increase in relative risk for migraine ED visits per 2.3 ppb (6.1 µg/m³) change using a single pollutant model on lag day 0 warm seasons, female patients - 0.8 - 7.3	statistically significant association with ED visits for migraine in females during the warm season using a single pollutant model with the same day lag; no associations with visits for migraine in males or for males or females in all seasons combined or for the cold season for lag days 1 & 2; no association ED visits for headache following stratification by sex or season for any lag	⊕⊕◯◯ (low quality because of bias from single pollutant model)

author	location	exposure monitoring	SO_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 2.6 ppb (6.9 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 emergency department visits per unstated IQR increase in a single pollutant model chest pain (lag day 0) all seasons, all patients - 1.1 all seasons, female patients - 2.0 weakness (lag day 0) all seasons, female patients - 2.4 cold season, female patients - 2.4 all seasons, all patients - 1.6 cold season, all patients - 1.6 weakness (lag day 2) cold season, male patients - 2.2 cold season, all patients - 1.5	relative risk percentage for emergency department visits per unstated IQR increase in a single pollutant model chest pain (lag day 0) all seasons, all patients - 2.6 all seasons, female patients - 3.3 weakness (lag day 0) all seasons, female patients - 0.9 - 3.9 cold seasons, female patients - 0.5 - 4.5 all seasons, all patients - 0.4 - 2.7 cold seasons, all patients - 0.1 - 3.1 weakness (lag day 2) cold season, male patients - 0.1 - 4.4 cold seasons, all patients - 0.0 - 3.1	statistically significant association with emergency department visits for chest pain in both seasons for all patients and female but not males in single pollutant model on lag day 0, no association with chest pain visits for males or females during the summer or winter months on lag days 1 or 2; statistically significant associations with ED visits for weakness in both seasons and the cold season for all patients and female patients but not males using a single pollutant model on lag day 0; statistically significant associations with visits for weakness in the cold season for all patients and males on lag day 2 but not lag day 1; no association with weakness in females in any season or for any lag period	⊕○○○ (insufficient because of bias from the use of a unstated number of monitoring sites and methodological imprecision)

author	location	exposure monitoring	SO_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 2.6 ppb (6.9 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	change in relative risk percentage for ED visits for ischemic stroke per IQR 2.3 ppb (6.1 µg/m³) in a single pollutant model group age 20-64 years cold seasons & females (lag day 1) - 6.0 group age 65-100 years old cold season & all sexes (lag day 1) - 4.4 all seasons & females (lag day 1) - 4.6 warm seasons & males (lag day 0) - 9.1	change in relative risk percentage for ED visits for ischemic stroke per IQR 2.3 ppb (6.1 µg/m³) in a single pollutant model group age 20-64 years cold seasons & females (lag day 1) - 0.5 - 11.8 group age 65-100 years old cold season & all sexes (lag day 1) - 0.4 - 8.6 all seasons & females (lag day 1) - 0.4 - 9.0 warm seasons & males (lag day 0) - 2.2 - 16.4	statistically significant association ED visits for ischemia in females but not males aged 20-64 years for the cold season but not all seasons or the warm season in a single pollutant model on lag day 1; statistically significant association for males and females aged 65- 100 years old during the cold season on lag day 1 and males during the warm season on lag day 0; significant association for all season females on lag day 1 but not other seasons or lag days; no association in all season or cold season for males on lag days 1 and 2; no association warm or cold season for females on lag days 0 or 2	⊕○○○ (insufficient because of the exposure misclassification and the failure to perform two-pollutant modeling)
(Szyszkowicz et al., 2012b)	Edmonton, Canada	daily average concentration from three fixed monitoring sites	daily mean 2.6 ppb (6.9 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	increased odds ratio for hypertension ED visits per IQR of 2.3 ppb (6.1 µg/m³) in single pollutant model using single or cumulative 3-day lag periods up to seven days lag day 3 - 1.04	increased odds ratio for hypertension ED visits per IQR of 2.3 ppb (6.1 µg/m³) in single pollutant model using single or cumulative 3-day lag periods up to seven days lag day 3 - 1.00 - 1.08	statistically significant association with emergency dept visits for hypertension using a single pollutant model on lag day 3, no statistical significance on the other seven single lag days all eight 3-day cumulative lag periods	⊕○○○ (insufficient because of the exposure misclassification and the failure to perform two-pollutant modeling)

author	location	exposure monitoring	SO_2 concentration	study type (duration)	endpoint	co-pollutants	participants	ratio or risk	confidence interval	results	GRADE quality of evidence
(Szyszkowicz et al., 2012a)	Vancouver, Canada	daily averages from 4 to 11 fixed monitoring stations over the course of the study	daily average 2.5 ppb (6.6 µg/m³)	case-crossover (51 months)	emergency department visits for stroke or seizure	association with $PM_{2.5}$, PM_{10}, SO_2, O_3, CO, & NO_2	males and females aged 0 to 85 years stroke - 1002 cases seizure - 2120 cases	odds ratio for stoke or seizure ED visits per IQR increase of 1.9 ppb (5.1 µg/m³) in single and two pollutant models at various lag periods stroke (single pollutant) all subjects (lag day 3) - 1.12 female subjects (lag day 0) - 1.17 seizure (single pollutant) female subjects (lag day 1) - 1.15 female subjects (lag day 2) - 1.18 stroke (multi pollutant; lag day 3) all subjects (SO_2/O_3) - 1.16 all subjects (SO_2/CO) - 1.11 all subjects ($SO_2/CO/O_3$) - 1.11	odds ratio for stoke or seizure ED visits per IQR increase of 1.9 ppb (5.1 µg/m³) in single and two pollutant models at various lag periods stroke (single pollutant) all subjects (lag day 3) - 1.02 -1.23 female subjects (lag day 0) - 1.01 - 1.33 seizure (single pollutant) female subjects (lag day 1) - 1.02 - 1.28 female subjects (lag day 2) - 1.05 - 1.32 stroke (multi pollutant; lag day 3) all subjects (SO_2/O_3) - 1.05 - 1.29 all subjects (SO_2/CO) - 1.00 - 1.24 all subjects ($SO_2/CO/O_3$) - 1.00 - 1.24	statistically significant association with ED visits for stroke in all patients on lag day 3 and females on lag day 0 but not in any of other 7 lag periods examined using a single pollutant model, no significant associations with ED visits for stroke in males on any of eight lag days using a single pollutant model; association with ED visits for seizure with females on lag days 1 and 2 but not other lag periods using a single pollutant model; no significant associations with ED visits for seizure in all patients or males on any of eight lag days using a single pollutant model; significant association with visits for stroke in all patients using a two pollutant model with O_3 and CO and a three pollutant model with O_3 and CO together using a 3 day lag	⊕○○○ (insufficient because of the small number of cases and publication bias)
(Tolbert et al., 2007)	Atlanta, Georgia	1-hr maximum for an unstated number of monitoring sites	average 1-hr maximum 14.9 ppb (39.6 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	no change relative risk for emergency department visits for cardiovascular or respiratory disease per IQR 16 ppb (42.6 µg/m³) in single pollutant models with a 3 day (0-2) moving average lag	no change relative risk for emergency department visits for cardiovascular or respiratory disease per IQR 16 ppb (42.6 µg/m³) in single pollutant models with a 3 day (0-2) moving average lag	no statistically significant association with emergency room visits for cardiovascular or respiratory diseases in a single pollutant model at an 0-1 moving average lag period	⊕○○○ (insufficient because of bias from the use of a unstated number of monitoring sites and publication bias)

author	location	exposure monitoring	SO_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 all season - 2.6 (6.9 µg/m³) summer - 2.1 ppb (5.6 µg/m³) winter - 3.1 ppb (8.2 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 ED visits for cardiovascular events per IQR of 3.0 ppb (8.0 µg/m³) in single pollutant model for those aged 65 years or older on lag day 0 stroke summer - 1.11 cerebral ischemia all season - 1.06 summer - 1.11	adjusted odds ratio for ED visits for cardiovascular events per IQR of 3.0 ppb (8.0 µg/m³) in single pollutant model for those aged 65 years or older on lag day 0 stroke summer - 1.0 - 1.22 cerebral ischemia all season - 1.00 - 1.12 summer - 1.02 - 1.22	weak statistically significant association with emergency department visits for acute ischemic stroke in those ≥ 65 yrs using single pollutant model during warm, but not cool or all seasons using a same day lag but not with a day 1 lag or a 3 day moving average lag; weak significant association with ED visits for transient cerebral ischemia for those ≥ 65 yrs during all seasons and the warm months using a single pollutant model and a same day lag but not lags of 1 day or 3 day average lag; no association with visits for hemorrhagic stroke in those ≥ 65 yrs for any of the three lag periods; no associations with ED visits for any of the three cardiovascular conditions in warm or cold seasons following stratification by sex	⊕◯◯◯ (insufficient because of the exposure misclassification and the failure to perform two-pollutant modeling)

author	location	exposure monitoring	SO_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 - 2.0 ppb (5.3 µg/m³) winter - 3.0 ppb (8.0 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	no positive change in adjusted odds ratio for asthma ED visits any of seven different age groups per IQR of 3.0 ppb (8.0 µg/m³) for all seasons, summer months (Apr-Sept), or winter months (Oct - Mar) in a single pollution model for any of four lag periods	no positive change in adjusted odds ratio for asthma ED visits with any of seven different age groups per IQR of 3.0 ppb (8.0 µg/m³) for all seasons, summer months (Apr-Sept), or winter months (Oct - Mar) in a single pollution model for any of four lag periods	no statistically significant positive association with all season asthma ED visits in those aged 2 to ≥ 75 yrs of age or any of seven age stratified subgroups (2 - 4, 5 -14, 15 -24, 25 - 44 , 45 - 64, 65 - 74, or ≥ 75 years) for any of four lag periods; no associations following warm (Apr - Sept) or cold (Oct - Mar) season stratification; statistically significant negative associations seen for asthma visits in those 2 to ≥ 75 yrs of age in single pollutant model at all four lag periods for all seasons and the winter season	⊕○○○ (insufficient because of the exposure misclassification and the failure to perform two-pollutant modeling)
(Zemek et al., 2010)	Edmonton, Alberta	seasonal averages from three fixed monitoring sites	seasonal average all months - 2.6 ppb (6.9 µg/m³) warm months - 2.1 ppb (5.6 µg/m³) cold months - 3.1 ppb (8.2 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	no positive change in odds ratio for otitis media hospital visits per IQR of 2.3 ppb (6.1 µg/m³) for all patients, males or females for all, warm, or cold months in single pollutant model on lag days 0, 1, 2, 3, or 4	no positive change in odds ratio for otitis media hospital visits per IQR of 2.3 ppb (6.1 µg/m³) for all patients, males or females for all, warm, or cold months in single pollutant model on lag days 0, 1, 2, 3, or 4	no statistically significant positive association visits for otitis media in all patients, males or females or for all, warm, or cold months using a single pollutant model with any of five lag days, significant negative association seem in male patients during cold months using a single pollutant model with a 4 day lag	⊕○○○ (insufficient because of the exposure misclassification and the failure to perform two-pollutant modeling)

Acute Hospital Admissions

author	location	exposure monitoring	SO_2 concentration	study type (duration)	endpoint	co-pollutants	participants	ratio or risk	confidence interval	results	GRADE quality of evidence
(Atkinson et al., 2015)	England	annual averages using dispersion models created with emission profiles for road transport and power generation then validated against monitoring site measurement	annual mean concentration 3.9 µg/m³	cohort (5 years)	chronic obstructive pulmonary disease (COPD) diagnosis from a general practitioner (GP) or on hospital admission	association with $PM_{2.5}$, PM_{10}, SO_2, O_3, & NO_2	males and females aged 40 - 89 years GP diagnosis - 16,034 cases hospital diagnosis - 2910 cases	fully adjusted change in hazards ratio for COPD diagnosis per IQR increase of 2.2 µg/m³ using a single or two pollutant model single pollutant GP diagnosis - 1.07 two pollutant SO_2/PM_{10} - 1.09 SO_2/O_3 - 1.06 SO_2/NO_2 - 1.07	fully adjusted change in hazards ratio for COPD diagnosis per IQR increase of 2.2 µg/m³ using a single or two pollutant model single pollutant GP diagnosis - 1.03 - 1.11 two pollutant SO_2/PM_{10} - 1.05 - 1.14 SO_2/O_3 - 1.01 - 1.11 SO_2/NO_2 - 1.03 - 1.12	statistically significant association with COPD diagnosed by their general practitioner using partially and fully adjusted a single or two pollutant model with PM_{10} O_3, & NO_2; statistically significant association with COPD diagnosed at the hospital using partially but not a fully adjusted a single pollutant model, no association with COPD in fully adjusted two pollutant models for those diagnosed at the hospital	⊕⊕◯◯ (low quality because of the small number of cases and use a single year of exposure measurement data)

author	location	exposure monitoring	SO_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 Barcelona - 15.5 µg/m³ Bolbao - 18.6 µg/m³ Cartegena - 27.1 µg/m³ Casellon - 7.7 µg/m³ Gijon - 29.4 µg/m³ Granada - 19.1 µg/m³ Huelva - 11.9 µg/m³ Madrid - 21.8 µg/m³ Ovieda - 40.9 µg/m³ Pamplona - 7.6 µg/m³ Seville - 9.6 µg/m³ Valcencia 16.6 µg/m³ Vigo - 9.3 µg/m³ Zaragoza - 9.3 µg/m³	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 reveled that the association observed in a single pollutant model for SO_2 was not robust to the inclusion of either CO or NO_2, but remained significant with both O_3 and particulates (PM_{10}, TSP, or BS) (data presented graphically) pooled (fixed effect) percent increase in cardiovascular hospital admissions per IQR 10 µg/m³ in single and two pollutant model for average lag 01 cardiovascular disease SO_2 only ≈ 1.018 SO_2/O_3 only ≈ 1.018 SO_2/particulate ≈ 1.010	pooled relative risk for combined cardiovascular and cardiac disease per 10 µg/m³ increase in a two pollutant model reveled that the association observed in a single pollutant model for SO_2 was not robust to the inclusion of either CO or NO_2, but remained significant with both O_3 and particulates (PM_{10}, TSP, or BS) (data presented graphically) pooled (fixed effect) percent increase in cardiovascular hospital admissions per IQR 10 µg/m³ in single and two pollutant model for average lag 01 cardiovascular disease SO_2 only ≈ 1.006 -1.030 SO_2/O_3 only ≈ 1.007 - 1.035 SO_2/particulate ≈ 1.005 - 1.030	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 ; statistically significant association with cardiovascular disease admissions on lag day 0 but not day 1, 2, or 3; statistically significant association with heart disease admissions on lag days 0 and 1 but not days 2 & 3;	⊕⊕◯◯ (low quality because of bias from the use of an unstated number of monitoring sites and poor description of methodological approach)

author	location	exposure monitoring	SO_2 concentration	study type (duration)	endpoint	co-pollutants	participants	ratio or risk	confidence interval	results	GRADE quality of evidence
(Barnett et al., 2005)	3-4 cities in Australia and New Zealand	1-hr and 24-hr values from 1-4 fixed monitoring sites	1 hour mean Brisbane - 7.6 ppb (20.2 µg/m³) Christchurch - 10.1 ppb (26.9 µg/m³) Sydney - 3.7 ppb (9.8 µg/m³) 24 hour mean Auckland - 4.3 ppb (11.4 µg/m³) Brisbane - 1.8 ppb (4.8 µg/m³) Christchurch - 2.8 ppb (7.4 µg/m³) Sydney - 0.9 ppb (2.4 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 5.4 ppb (14.4 µg/m³) for 1-hr values on lag days 01 single pollutant model (1-hr SO_2 only) pneumonia and bronchitis 1 -4 yrs age - 6.9 respiratory 0 yrs age - 3.2 1 -4 yrs age - 2.7	pooled percent increase in admission rate per IQR of 5.4 ppb (14.4 µg/m³) for 1-hr values on lag days 01 single pollutant model (1-hr SO_2 only) pneumonia and bronchitis 1 -4 yrs age 2.3 - 11.7 respiratory 0 yrs age 0.3 - 6.3 1 -4 yrs age 0.6 - 4.8	statistically significant association of 1-hr SO_2 exposures with hospital admissions in children pooled from 3.4 cites for pneumonia and bronchitis (one age group) and respiratory effects (two age groups) using a single pollutant model, no statistically significant association with pneumonia & bronchitis, respiratory, or asthma admissions using a two pollutant model with PM_{10}, no statistically significant association with 24-hr SO_2 levels for of three pulmonary conditions	⊕⊕◯◯ (low quality because of exposure misclassification and imprecision caused by exposure heterogeneity)
(Bell et al., 2008)	Taipei, Taiwan	daily average concentration from thirteen fixed monitoring sites	daily mean concentration 4.7 ppb (12.5 µg/m³)	time-series (8 years)	hospital admissions for ischemic heart disease, cerebrovascular disease, asthma, & pneumonia	interaction of sandstorms with PM_{10}, $PM_{2.5}$, SO_2, O_3, CO, & NO_2 associations	males and females IHD - 6909 admissions CVD - 11,466 admits pneumonia - 10,996 admits asthma - 10,231 admits	no significant percent change in admissions on any lag day per 5 ppb (13.3 µg/m³) in single pollutant model using single and cumulative daily lag periods	no significant percent change in admissions on any lag day per 5 ppb (13.3 µg/m³) in single pollutant model using single and cumulative daily lag periods	no statistically significant association with ischemic heart disease, cerebrovascular disease, asthma, or pneumonia using single pollutant model on lag day 0, 1, 2, 3 or cumulative lag period 03	⊕⊕◯◯ (low quality because of exposure misclassification and imprecision caused by exposure heterogeneity)

author	location	exposure monitoring	SO_2 concentration	study type (duration)	endpoint	co-pollutants	participants	ratio or risk	confidence interval	results	GRADE quality of evidence
(Cai et al., 2014)	Shanghai, China	daily average from six fixed monitoring sites	daily average concentration 45 µg/m³	time-series (7 years)	hospitalization for asthma	association with PM_{10}, SO_2, NO_2, and black carbon	males and females 18 to ≥ 65 years old 15,678 admissions	percent increase in asthma hospital admissions per IQR increase of 36 µg/m³ using single and two pollutant models with a 2 day (0-1) moving average lag single pollutant cool season - 5.55 females - 5.78 males - 7.11 < 65 years age - 7.35 two pollutant SO_2 only - 6.41 SO_2/PM_{10} - 15.06	percent increase in asthma hospital admissions per IQR increase of 36 µg/m³ using single and two pollutant models with a 2 day (0-1) moving average lag single pollutant cool season - 0.42 - 10.68 females - 0.44 - 11.12 males - 1.47 - 12.75 < 65 years age - 2.45 - 12.24 two pollutant SO_2 only - 2.32 - 10.49 SO_2/PM_{10} - 6.13 - 24.00	statistically significant association with asthma hospitalization in all subjects using a single day lag of 0 and 1 and 2 day average lag of 0-1 but not on single day lag days of 2, 3, 4, or 5 using a single pollutant model; significant association in males and females for all seasons using a single pollutant model with a 2 day average lag; significant association in cool but not the warms season and in those < 65 years of age but not those ≥ 65 years of age using a single pollutant model; association in two pollutant model with PM_{10} but not NO_2	⊕⊕◯◯ (low quality because of the imprecision and poor statistical power and the failure to consider $PM_{2.5}$ collinearity)

author	location	exposure monitoring	SO_2 concentration	study type (duration)	endpoint	co-pollutants	participants	ratio or risk	confidence interval	results	GRADE quality of evidence
(Cakmak et al., 2006b)	10 Canadian cites	1 hour maximum levels from an unstated number of fixed monitoring stations in each city	hour maximum average Calgary - 3.5 ppb (9.3 µg/m³) Edmonton - 2.8 ppb (7.4 µg/m³) Halifax - 10.2 ppb (27.1 µg/m³) London - 3.3 ppb (8.8 µg/m³) Ottawa - 3.5 ppb (9.3 µg/m³) Saint John - 7.4 ppb (19.7 µg/m³) Toronto - 4.5 ppb (12.0 µg/m³) Vancouver - 3.9 ppb (10.4 µg/m³) Windsor - 7.7 ppb (20.5 µg/m³) Winnipeg - 8.0 ppb (21.3 µg/m³)	time-series (8 years)	hospital admissions for cardiac disease (congestive heart failure, ischemic heart disease, and dysrhythmia)	association with SO_2, O_3, CO, & NO_2	males and females admission rates ranged from 1.9-48 patients/day for the 10 cities	pooled (random effects) percent increase in cardiac disease hospitalizations per 4.6 ppb (12.2 µg/m³) increase using a single or two pollutant model single pollutant model with different lag times for each city males - 1.1 2nd education quartile - 2.9 2nd income quartile - 1.6 4th income quartile - 1.5	pooled (random effects) percent increase in cardiac disease hospitalizations per 4.6 ppb (12.2 µg/m³) increase using a single or two pollutant model single pollutant model with different lag times for each city males - 0.3 - 1.9 2nd education quartile - 0.1 - 5.7 2nd income quartile - 0.5 - 2.7 4th income quartile - 0.2 - 2.8	no statistically significant associations with cardiac disease admissions using a single or a multi-pollutant model; statistically significant association with hospitalizations for cardiac disease males but not females using a single pollutant multi-city model; significant association with e 2nd lowest SES quartile but the lowest or the two highest quartiles using a single pollutant model; associations with the 2nd ($21,309-$28,161) and 4th (>$35,905) income quartiles but not the 1st (<$21,309) or the 4th ($28,161-$35,905) quartiles	⊕⊕○○ (low quality because of lag selection bias and the failure to evaluate PM_{10} and $PM_{2.5}$ collinearities)
(Chang et al., 2005)	Taipei, Taiwan	daily average from six fixed monitoring site	daily mean concentration 4.32 ppb (11.5 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 2.75 ppb (7.31 µg/m³) at two temperature limits in a two pollutant model at an average lag of 3 days (lag02) temp ≥ 20° C SO_2/PM_{10} - 0.897 SO_2/NO_2 - 0.862 SO_2/CO - 0.903 SO_2/O_3 - 0.953 temp < 20° C SO_2/PM_{10} - 0.824 SO_2/NO_2 - 0.922	odds ratio for cardiovascular disease admissions per IQR of 2.75 ppb (7.31 µg/m³) at two temperature limits in a two pollutant model at an average lag of 3 days (lag02) temp ≥ 20° C SO_2/PM_{10} - 0.868 - 0.926 SO_2/NO_2 - 0.798 - 0.854 SO_2/CO - 0.876 - 0.931 SO_2/O_3 - 0.926 - 0.981 temp < 20° C SO_2/PM_{10} - 0.771 - 0.880 SO_2/NO_2 - 0.865 - 0.984	statistically significant negative association with hospital admissions for cardiovascular disease in a two pollutant model with PM_{10}, NO_2, CO and O_3 at high temperatures greater than or equal to 20 °C and with PM_{10} and NO_2 at temperatures < 20 °C; no significant associations at temperatures < 20° C for CO and O_3 co-pollutants	⊕○○○ (insufficient because of negative associations and the failure to evaluate $PM_{2.5}$ interactions)

author	location	exposure monitoring	SO_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 56 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 5 - 0.63 cardiovascular lag day 4 - 0.64 lag day 5 - 0.65	percent increase in admissions per IQR of 10 µg/m³ in single pollutant model total admissions lag day 5 - 0.03 - 1.23 cardiovascular lag day 4 - 0.17 - 1.11 lag day 5 - 0.19 - 1.12	statistically significant association with total and cardiovascular admission rates on lag days 4 & 5 but not for the shorter lags 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; the significant associations for total and cardiovascular admissions on lag day 5 became non-significant after two-pollutant modeling with NO_2, but remained significant in two pollutant modeling with PM_{10}	⊕⊕○○ (low quality because of the failure to consider $PM_{2.5}$ interactions and lag period inconsistencies)
(Cheng et al., 2009)	Kaohsiung, Taiwan	mean daily concentration at six fixed monitoring locations	daily mean 9.33 ppb (24.82 µg/m³)	case-crossover (132 months)	hospitalization for myocardial infarction	association with PM_{10}, SO_2, O_3, CO, & NO_2	male & female cases 9,349	odds ratio per IQR of 5.16 ppb (13.72 µg/m³) in single and two-pollutant model single pollutant temp < 25 ˚C - 1.09 two pollutant (SO_2/O_3) temp ≥ 25 ˚C - 1.05 temp < 25 ˚C - 1.09	odds ratio per IQR of 5.16 ppb (13.72 µg/m³) in single and two-pollutant model single pollutant temp < 25 ˚C - 1.01 - 1.19 two pollutant (SO_2/O_3) temp ≥ 25 ˚C - 1.00 - 1.11 temp < 25 ˚C - 1.01 - 1.19	statistically significant associations observed in single pollutant model at ambient temperatures < 25 ˚C and in a two-pollutant model with O_3 at temperatures < 25 ˚C and ≥ 25 ˚C; not significant associations in two pollutant models with PM_{10}, NO_2, or CO	⊕⊕○○ (low quality because no evaluation of $PM_{2.5}$ interactions)
(Corea et al., 2012)	Mantua, Italy	daily averages from 7 fixed monitoring sites	daily average exposures not stated	case-crossover (3 years)	hospitalization for cerebrovascular disease (transient ischemic attack and stroke)	association with PM_{10}, SO_2, O_3, CO, NO, NO_2, and benzene	males and females 781 cases	no change is odds ration for any cerebrovascular even or ischemic stroke in men or women per an unstated increase in SO_2 using a single pollutant model with an unstated lag period	no change is odds ration for any cerebrovascular even or ischemic stroke in men or women per an unstated increase in SO_2 using a single pollutant model with an unstated lag period	no statistically significant association with cerebrovascular disease or stroke hospital admissions in single pollutant model; no significant association found with 6 different stroke subtypes	⊕○○○ (insufficient because of poor methodological description and absence of two-pollutant modeling)

author	location	exposure monitoring	SO_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 Calgary - 3.6 ppb (9.6 µg/m³) Edmonton - 2.7 ppb (7.2 µg/m³) Halifax - 10.1 ppb (26.9 µg/m³) Hamilton - 8.2 ppb (21.8 µg/m³) London - 3.7 ppb (9.8 µg/m³) Ottawa - 3.9 ppb (10.4 µg/m³) Saint John - 8.3 ppb (22.1 µg/m³) Toronto - 4.5 ppb (12.0 µg/m³) Vancouver - 4.6 ppb (12.2 µg/m³) Windsor - 7.6 ppb (20.1 µg/m³) Winnipeg - 1.2 ppb (3.2 µg/m³)	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 3.8 ppb (10.1 µg/m³) in single and multi-pollutant model on lag day 2 SO_2 only - 2.06 SO_2/CO, O_3, & NO_2 - 1.66 SO_2/PM_{10}, CO, O_3, & NO_2 - 1.41	pooled (random and fixed effects) percent increase in neonatal respiratory hospitalization per IQR of 3.8 ppb (10.1 µg/m³) in single and multi-pollutant model on lag day 2 SO_2 only - 1.04 - 3.08 SO_2/CO, O_3, & NO_2 - 0.63 - 2.69 SO_2/PM_{10}, CO, O_3, & NO_2 - 0.35 - 2.47	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}	⊕⊕⊕○ moderate quality, but no evaluation of $PM_{2.5}$)

author	location	exposure monitoring	SO_2 concentration	study type (duration)	endpoint	co-pollutants	participants	ratio or risk	confidence interval	results	GRADE quality of evidence
(Dales et al., 2009)	Santiago, Chile	daily averages from seven fixed monitoring sites	daily concentration 9.32 ppb (24.79 µg/m³)	time-series (5 years)	hospitalization for headaches categorized as i) not otherwise specified, ii) migraine, and iii) specified cause (tension, cluster, vascular, post-traumatic, & drug-related)	association with $PM_{2.5}$, PM_{10}, SO_2, O_3, CO, & NO_2	males and females not otherwise specified - 1.168 cases/day migraine - 0.744 cases/day specified cause - 0.561 cases/day	pooled relative risk of headache hospitalization per IQR increase of 6.20 ppb (16.49 µg/m³) using a single pollutant model with 2 different lag periods not otherwise specified lag day 1 - 1.094 distributed lag 0-5 days - 1.108 migraine lag day 1 - 1.104 distributed lag 0-5 days - 1.133 specified cause lag day 1 -1.113 distributed lag 0-5 days - 1.125	pooled relative risk of headache hospitalization per IQR increase of 6.20 ppb (16.49 µg/m³) using a single pollutant model with 2 different lag periods not otherwise specified lag day 1 - 1.033 - 1.158 distributed lag 0-5 days - 1.014 - 1.202 migraine lag day 1 - 1.040 - 1.172 distributed lag 0-5 days - 1.049 - 1.217 specified cause lag day 1 -1.020 - 1.215 distributed lag 0-5 days - 1.017 - 1.233	statistically significant association with hospitalization for 3 types of headache (cause not specified, migraine, and specified cause) using a single pollutant model with either a single day or distributed 6 day lag period; significant association observed for caused not specified and migraine headaches using two pollutant models with either $PM_{2.5}$, PM_{10}, O3, and CO but not NO_2; significant association observed headaches with specified causes using two pollutant models with O3 & NO_2 but not $PM_{2.5}$, PM_{10}, or CO; stratification by age showed association for those ≤ 64 years of age, > 64 years of age for cause not specified and migraine headaches; stratification by sex found associations in males for cause not specified headache and females for migraine headache; stratification by season showed no association; stratification by age, sex or season showed no association with headaches with a specified cause	⊕⊕◯◯ (low quality because of the sex-related inconsistencies and the likelihood of case misidentification)

author	location	exposure monitoring	SO_2 concentration	study type (duration)	endpoint	co-pollutants	participants	ratio or risk	confidence interval	results	GRADE quality of evidence
(Fung et al., 2006)	Windsor, Ontario	daily mean of the highest value from four fixed monitoring sites	daily mean of the highest hourly concentration 27.5 ppb (73.2 µg/m³)	time-series (68 months)	hospitalizations for cardiovascular disease (congestive heart disease, ischemic heart disease, & dysrhythmia)	association with PM_{10}, SO_2, coefficient of haze (COH), total reduced sulfur (TRS) O_3, CO, & NO_2	males and females < 65 years - 3273 patients ≥ 65 years - 8359 patients	percent change in risk estimates for cardiovascular admissions per IQR of 19.3 ppb (51.3 µg/m³) with individuals ≥ 65 years of age using a single pollutant models on different lag days lag day 0 - 2.6 lag day 01 - 4.0 lag day 02 - 5.6	percent change in risk estimates for cardiovascular admissions per IQR of 19.3 ppb (51.3 µg/m³) with individuals ≥ 65 years of age using a single pollutant models on different lag days lag day 0 - 0.0 - 5.3 lag day 01 - 0.6 - 7.6 lag day 02 - 1.5 - 9.9	statistically significant association with cardiovascular admissions in those ≥ 65 years of age using a single pollutant model with all three lag periods day 0, day 01, & day 02); no association with those in the < 65 age group for any lag period; lag day 0, 1, or 2, associations remained significant with multi-pollutant model with PM_{10} but the relative risk values were not provided	⊕○○○ (insufficient because of the failure to examine PM2.5 interactions and the absence of two-pollutant modeling)
(Hosseinpoor et al., 2005)	Tehran, Iran	daily average concentration from a single fixed monitoring sites	daily mean 73.74 µg/m³	time-series (5 year)	hospital admissions for angina pectoris	association with PM_{10}, SO_2, O_3, CO, & NO_2	males and female hospitalization rate 23.48 admissions/day	no relationship with angina admissions per 10 µg/m³ increase using single pollutant model on lad day 1	no relationship with angina admissions per 10 µg/m³ increase using single pollutant model on lad day 1	no statistically significant association with angina admissions in single pollutant model on lag day 1	⊕○○○ (insufficient because of the failure to examine $PM_{2.5}$ interactions and the exposure misclassification)
(Hsieh et al., 2010)	Taipei, Taiwan	mean daily concentration at six fixed monitoring locations	daily mean 4.36 ppb (11.60 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	no positive relationships with myocardial infarction admissions in single or two pollutant models with PM_{10}, NO_2, O_3, or CO with an IQR increase of 2.69 ppb (7.16 µg/m³ NO_2) at temperatures ≥ 23 ˚C or < 23 ˚C on lag day 0 plus the previous two days; some negative associations observed with two-pollutant models	no positive relationships with myocardial infarction admissions in single or two pollutant models with PM_{10}, NO_2, O_3, or CO with an IQR increase of 2.69 ppb (7.16 µg/m³ NO_2) at temperatures ≥ 23 ˚C or < 23 ˚C; some negative associations observed with two-pollutant models	no statistically significant positive change in the odds ratio for myocardial infarction in either of two temperature groups (≥ 23 ˚C or < 23 ˚C) using single or two -pollutant models with PM_{10}, NO_2, O_3, or CO; statistically significant negative associations observed with two-pollutant modeling using PM_{10}, NO_2, or CO	⊕○○○ (insufficient because of the failure to examine $PM_{2.5}$ interactions and imprecision indicated by the negative associations)

author	location	exposure monitoring	SO_2 concentration	study type (duration)	endpoint	co-pollutants	participants	ratio or risk	confidence interval	results	GRADE quality of evidence
(Ito et al., 2011)	five boroughs of New York City, New York	mean daily concentration at an unstated number of fixed monitoring locations within five boroughs	daily mean 7.4 ppb (19.7 µg/m³)	time-series (84 months)	cardiovascular hospitalization (hypertensive disease, myocardial infarction, ischemic heart disease, dysrhythmia, heart failure, & stroke) and mortality	association with $PM_{2.5}$, $PM_{2.5}$ trace metals, SO_2, CO, & NO_2	male & female > 40 years of age CVD mortality - 59.8 cases/day CVD hospitalizations - 281.3 cases/day	percent excess risk for hospitalization per IQR of 6.6 ppb (17.6 µg/m³) in a single pollutant model (values estimated from graph) all year - ≈ 2.3 warm season - ≈ 2.4 cold season - ≈ 2.2	percent excess risk for hospitalization per IQR of 6.6 ppb (17.6 µg/m³) in a single pollutant model (values estimated from graph) all year ≈ 1.8 - 2.8 warm season ≈ 1.6 - 3.2 cold season - ≈ 1.1 - 3.3	statistically significant association for hospitalization on lag day 0, but not lag day 1, 2, or 3, for all seasons, warm season, & cold season in single pollutant model; negative association observed for same day (0 lag) cardiovascular mortality but not on lag days 1, 2, and 3	⊕○○○ (insufficient because the number of monitoring sites not stated and the failure to evaluate PM_{10} interactions)
(Karr et al., 2009)	British Columbia	levels at the most proximal (within 10 km) of 14 fixed monitoring sites	lifetime exposure 5.6 µg/m³	case control (4 years)	outpatient or hospitalization for bronchiolitis in children	association with $PM_{2.5}$, PM_{10}, SO_2, O_3, CO, NO, NO_2, wood smoke, and black carbon	males and females 2 - 12 months of age 1465 cases 57,127 controls	adjusted odds ratio for bronchiolitis hospitalization per IQR increase of 3.2 µg/m³ in as single pollutant model using different exposure metrics lifetime exposure - 1.04 previous month exposure - 1.03	adjusted odds ratio for bronchiolitis hospitalization per IQR increase of 3.2 µg/m³ in as single pollutant model using different exposure metrics lifetime exposure - 1.01 - 1.06 previous month exposure - 1.01 - 1.05	statistically significant association with infant bronchiolitis hospitalization using and adjusted single pollutant model based on lifetime exposures or the previous month exposure, stratification showed significant association for the fourth quartile of lifetime exposures but not the second or third using a single pollutant model; no associations observed using crude single pollutant models for any exposure metric	⊕○○○ (insufficient because the high likelihood of exposure misclassification and absence of two-pollutant modeling)

author	location	exposure monitoring	SO_2 concentration	study type (duration)	endpoint	co-pollutants	participants	ratio or risk	confidence interval	results	GRADE quality of evidence
(Ko et al., 2007b)	Hong Kong, China	daily average at 14 fixed monitoring sites	daily average all seasons - 18.8 µg/m³ cold season (< 20 °C) - 18.0 µg/m³ warm season (≥ 20 °C) - 19.1 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 03 days single pollutant >14-65 yrs age - 1.018	relative risk per 10 µg/m³ increase in single multi pollutant models for avg lag 03 days single pollutant >14-65 yrs age - 1.001 - 1.035	statistically significant association with asthma hospitalization in one of three age groups (>14 - 65 years of age) using a single pollutant model and a cumulative lag of 03 days, no association with asthma in the 0-14 yrs age group or the > 65 yrs age group; no statistically significant association for all ages at any of the 11 lag times examined, no significant association in multi--pollutant model with O_3 and NO_2	⊕⊕⊕◯ moderate quality, no adjustment necessary)
(Ko et al., 2007a)	Hong Kong, China	daily average concentration from fourteen fixed monitoring sites	daily mean 15 µg/m³	time-series (5 years)	hospital admissions for chronic obstructive pulmonary disease (COPD)	association with PM_{10}, $PM_{2.5}$, O_3, SO_2, & NO_2	males and females 119,225 admissions	relative risk of COPD admissions per 10 µg/m³ increase in single pollutant and multi-pollutant models for a single lag period single pollutant - 1.007 three pollutant (SO_2/$PM_{2.5}$/O_3) - 1.008 four pollutant (SO_2/$PM_{2.5}$/O_3/NO_2) - 1.008	relative risk of COPD admissions per 10 µg/m³ increase in single pollutant and multi-pollutant models for a single lag period single pollutant - 1.001 - 1.014 three pollutant (SO_2/$PM_{2.5}$/O_3) - 1.001 - 1.015 four pollutant (SO_2/$PM_{2.5}$/O_3/NO_2) - 1.001 - 1.015	statistically significant association with hospitalizations for COPD in single pollutant model for a single same day lag period (0 days), no association for any of the remaining ten lag periods examined; slight statistically significant association in three pollutant model with $PM_{2.5}$ and O_3 or a four pollutant model with $PM_{2.5}$, O_3, & NO_2 for a days 0 lag period; statistically significant association in cold but not warm season in single pollutant model	⊕⊕⊕◯ moderate quality, but very weak associations)

author	location	exposure monitoring	SO_2 concentration	study type (duration)	endpoint	co-pollutants	participants	ratio or risk	confidence interval	results	GRADE quality of evidence
(Lee et al., 2006)	Hong Kong, China	daily average at 9-11 fixed monitoring sites	daily mean concentration 17.7 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 11.1 µg/m³ in single pollutant model single pollutant lag day 4 - 1.40 lag day 5 - 1.46	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 positive association with asthma admissions in children for single pollutant models on lag day 4 and 5, statistically significant negative association in single pollutant models on lag days 0 and 1; no associations with single pollutant modeling on day 3 or for with five - pollutant modeling on day 5 that included SO_2/PM_{10}/$PM_{2.5}$/NO_2/O_3	⊕⊕⊕○ moderate quality, no adjustment necessary, but unusually long lag periods)
(Lee et al., 2007a)	Kaohsiung, Taiwan	mean daily concentration at six fixed monitoring locations	daily mean 9.32 ppb (24.79 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 5.53 ppb (14.71 µg/m³) in single and two pollutant models at 02 day lag single pollutant model temp < 25 ˚C - 1.15 two pollutant model (SO_2/O_3) temp < 25 ˚C - 1.16	odds ratio per IQR 5.53 ppb (14.71 µg/m³) in single and two pollutant models at 02 day lag single pollutant model temp < 25 ˚C - 1.03 - 1.29 two pollutant model (SO_2/O_3) temp < 25 ˚C - 1.04 - 1.31	statistically significant association with admissions for congestive heart failure on cold but not warm says using a single pollutant model with a lag of 02 days, statistically significant association with admissions using a two pollutant model with O_3 on cold days but not warm days, no statistically significant association on warm or cold days using a two pollutant models with PM_{10}, NO_2, or CO	⊕⊕○○ (low quality because of the failure to evaluate $PM_{2.5}$ interactions)
(Lee et al., 2007b)	Busan, Korea	average daily level from eight monitoring sites	daily average concentration 6.6 ppb (17.6 µg/m³)	time-series (3 months)	hospital admissions for asthma	association with PM_{10}, SO_2, O_3, CO, & NO_2	males and females children < 15 years of age mean admission rate 4.9 cases/day	relative risk increase for asthma admissions per 22.82 µg/m³ increase in a single pollutant model using an unstated lag period single pollutant - 1.34	relative risk increase for asthma admissions per 22.82 µg/m³ increase in a single pollutant model using an unstated lag period single pollutant - 1.06 - 1.68	statistically significant association with asthma admission in a single pollutant model for an unstated lag day	⊕⊕○○ (low quality because of the lag selection bias and the failure to evaluate $PM_{2.5}$ interactions)

author	location	exposure monitoring	SO_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 location	daily mean 4.68 µg/m³	time-series (19 months)	hospital admissions for chronic obstructive pulmonary disease (COPD), asthma, chronic bronchitis	differential effects of humidity, TSP, SO_2, & NO_2	males and females hospitalizations 953 admissions	increase in relative risk per 1 µg/m³ increment using a single pollutant model with various lag times and exposure data handling lag day 2 (graphically interpolated) raw actual values - 1.06 raw + interpolated values - 1.15 lag day 7 raw + interpolated values - 1.07	increase in relative risk per 1 µg/m³ increment using a single pollutant model with various lag times and exposure data handling lag day 2 (graphically interpolated) raw actual values - 1.01 - 1.10 raw + interpolated values - 1.06 - 1.26 lag day 7 raw + interpolated values - 1.01 - 1.18	statistically significant associations with chronic bronchitis in single pollutant model on lag days 2 and 7 using original and interpolated exposure values used to account for missing data, stated significant associations observed with chronic bronchitis using a three pollutant model (SO_2/TSP/NO_2) on lag day 2 but the results not shown; no associations with chronic bronchitis; no statistically significant associations observed total respiratory admissions, COPD, or asthma using a single or multi-pollutant model on any lag day	⊕○○○ (insufficient because the high likelihood of exposure misclassification and the absence of two-pollutant modeling)

author	location	exposure monitoring	SO_2 concentration	study type (duration)	endpoint	co-pollutants	participants	ratio or risk	confidence interval	results	GRADE quality of evidence
(Luginaah et al., 2005)	Windsor, Ontario	daily average concentration from four fixed monitoring sites	daily mean 25.5 ppb (73.2 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 - 1.111	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 1.011 - 1.221	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 (all ages, 0-14 years, 15-64 years, or ≥ 65 years), 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 the failure to include PM2.5 in the analysis and the absence of two-pollutant modeling)

author	location	exposure monitoring	SO_2 concentration	study type (duration)	endpoint	co-pollutants	participants	ratio or risk	confidence interval	results	GRADE quality of evidence
(Milojevic et al., 2014)	England and Wales	daily averages from the nearest of 71 fixed monitoring sites	daily median 3.1 µg/m³	case-crossover (7 years)	hospital admissions and mortality for cardiovascular disease, myocardial infarction, stroke, ischemic heart disease chronic ischemic heart disease, arrhythmias, atrial fibrillation, pulmonary embolism, heart failure, and atrioventricular conduction disorder	association with $PM_{2.5}$, PM_{10}, SO_2, O_3, CO, & NO_2	males and females 380,743 admissions	percent increase in admissions for myocardial infarctions without an elevation in ST segment (non-STEMI) in the EEG per 10.4 µg/m³ increase using a single pollutant model and a 0-4 day distributed lag non-STEMI - 2.3	percent increase in admissions for myocardial infarctions without an elevation in ST segment (non-STEMI) in the EEG per 10.4 µg/m³ increase using a single pollutant model and a 0-4 day distributed lag non-STEMI - 0.0 - 4.7	statistically significant increase non-STEMI myocardial infarction admissions in single pollutant model using a 5 day distributed lag period, no association with all myocardial infarctions or STEMI-related myocardial infarction admissions in a single pollutant model; no statistically significant positive increase in risk for admission or mortality from cardiovascular disease, myocardial infarction, stroke, ischemic heart disease chronic ischemic heart disease, arrhythmias, atrial fibrillation, pulmonary embolism, heart failure, or atrioventricular conduction disorder	⊕○○○ (insufficient because the high likelihood of exposure misclassification and absence of two-pollutant modeling)
(Rich et al., 2010)	New Jersey	daily average from fourteen 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 increase in relative risk per IQR increase of 4.1 ppb (10.9 µg/m³) in a single or two pollutant model with a lag of 0 days	no increase in relative risk per IQR increase of 4.1 ppb (10.9 µg/m³) in a single or two pollutant model with a lag of 0 days	no statistically significant association with hospital admissions for transmural infarctions on lag day 0 with single or two pollutant model with $PM_{2.5}$	⊕○○○ (insufficient because the failure to include PM_{10} in the analysis)

author	location	exposure monitoring	SO_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 concentration for 14 fixed monitoring locations	daily average 16.8 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 for males and females 0-14 years of age per 10 µg/m³ increase (1-hr max) in single and two pollutant model for lag day 0 SO_2 only (annual)- 5.98 SO_2 only (winter)- 7.25 SO_2 only (spring)- 11.06 SO_2/NO_2 (annual) - 7.60 SO_2/O_3 (annual) - 5.97	adjusted increase in asthma admissions for males and females 0-14 years of age per 10 µg/m³ increase (1-hr max) in single and two pollutant model for lag day 0 SO_2 only (annual)- 0.88 - 11.33 SO_2 only (winter)- 0.27 - 17.70 SO_2 only (spring)- 1.85 - 21.10 SO_2/NO_2 (annual) -0.41 - 15.30 SO_2/O_3 (annual) - 0.87 - 11.32	statistically significant increase in asthma admissions for children aged 0-14 years in single pollutant model on lag day 0 for all seasons, winter, and spring but not for summer or fall ; statistically significant associations for all children i0-14 years in two pollutant model with NO_2 and O_3 but not for PM_{10} on lag day 0; significant association for all age males but not females and those aged 0-4 years but not those 5-14 years using a single pollutant model and day 0 lag; no significant increase in asthma admissions in adjusted single pollutant model per 10 µg/m³ increase on lag day 1 and 2 or distributed lag days 0-2	⊕⊕◯◯ (low quality because no evaluation of $PM_{2.5}$ interactions and wide confidence intervals indicating a lack of sensitivity)

author	location	exposure monitoring	SO_2 concentration	study type (duration)	endpoint	co-pollutants	participants	ratio or risk	confidence interval	results	GRADE quality of evidence
(Smargiassi et al., 2009)	Montreal, Canada	residential daily average and peak levels as well as 5 day averages using AERMOD dispersion modeling of the stack emissions from a local oil refinery	modeled concentration daily mean - 3.0 ppb (8.0 µg/m³) daily peak - 17.5 ppb (46.6 µg/m³) 5-day average - 3.0 ppb (8.0 µg/m³)	case-crossover (9 years)	hospitalization or emergency department visit for asthma	association with SO_2 only	male and female children 2 - 4 years of age 263 hospitalizations 1579 ED visits	adjusted odds ratio for asthma hospitalizations per IQR increase using a single pollutant model with various lag days hospital admissions daily mean (lag 0, IQR 4.3 ppb) - 1.14 daily peak (lag 0, IQR 31.2 ppb) - 1.42 ED visits daily peak (lag 0, IQR 31.2 ppb) - 1.10 daily mean (lag 1, IQR 4.3 ppb) - 1.05	adjusted odds ratio for asthma hospitalizations per IQR increase using a single pollutant model with various lag days hospital admissions daily mean (lag 0, IQR 4.3 ppb) - 1.00 - 1.30 daily peak (lag 0, IQR 31.2 ppb) - 1.10 - 1.82 ED visits daily peak (lag 0, IQR 31.2 ppb) - 1.00 - 1.22 daily mean (lag 1, IQR 4.3 ppb) - 1.00 - 1.12	statistically significant association with adjusted asthma hospital admissions using daily mean and daily peak levels on lag day 0 but not on lag day 1 or the 5-day average lag using a single pollutant model; significant association with asthma emergency department visits using daily peak on lag day 0 and daily mean on lag day 1; significant associations in crude admissions and ED visits for mean and peak exposures on lag day 0; no associations in crude hospital admissions or ED visits on mean or peak daily lag 1 or 5 day average models; associations restricted to those living to the east and southwest of the source and not those living	⊕○○○ (insufficient because of the small number of cases and the absence of two-pollutant modeling)
(Spiezia et al., 2014)	Padua, Italy	monthly average form the nearest of two fixed monitoring sites	monthly exposure average not stated	case control (5 years)	hospital admission for thromboembolism	association with PM_{10}, SO_2, O_3, CO, NOx, benzene, benzo(a)pyrene, cadmium, nickel, lead, and arsenic	males and female > 18 years of age 17 cases 24 controls	no change in unadjusted or adjusted odds ratio for pulmonary embolism hospitalization per 2nd tertile increase of 2.01 µg/m³ using a single pollutant model	no change in unadjusted or adjusted odds ratio for pulmonary embolism hospitalization per 2nd tertile increase of 2.01 µg/m³ using a single pollutant model	no statistically significant association with admissions for pulmonary embolism in an unadjusted or adjusted single pollutant model	⊕○○○ (insufficient because the exposure misclassification and absence of two pollutant modeling)

author	location	exposure monitoring	SO_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 17.8 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	male and female daily means mortality stroke - 8.9 cases cardiac heart disease - 12.0 cases LRI - 9.3 cases COPD - 5.9 cases hospitalizations stroke - 47.1 cases IHD - 46.1 cases LRI - 104.9 cases COPD - 91.5 cases	influenza epidemic adjusted excess risk per 10 µg/m³ increase in single pollutant model on lag days 0-1 cardiovascular mortality cardiac hear disease - 2.70 LRI - 2.11 cardiovascular hospitalization IHD - 1.01 COPD - 0.62 cardiorespiratory mortality all cause - 0.90 cardiovascular - 1.23 respiratory - 1.26 cardiorespiratory hospitalization cardiovascular - 0.98	influenza epidemic adjusted excess risk per 10 µg/m³ increase in single pollutant model on lag days 0-1 cardiovascular mortality cardiac hear disease - 1.21 - 4.22 LRI - 0.60 - 3.63 cardiovascular hospitalization IHD - 0.28 - 1.74 COPD - 0.02 - 1.22 cardiorespiratory mortality all cause - 0.39 - 1.41 cardiovascular - 0.26 - 2.20 respiratory - 0.15 - 2.39 cardiorespiratory hospitalization cardiovascular - 0.57 - 1.38	statistically significant association with cardiovascular mortality from cardiac heart disease and lower respiratory infection but not stroke or COPD in an influenza unadjusted and adjusted single pollutant model after a 2 day (0-1) lag period; significant association with cardiovascular hospitalization for ischemic heard disease and COPD but not LRI or stoke in an influenza adjusted and unadjusted single pollutant model; association with all cause, cardiovascular and respiratory mortality and cardiovascular hospitalization in an influenza adjusted model; no association in influenza unadjusted or adjusted risk from hospitalizations from respiratory, acute respiratory disease or asthma	⊕○○○ (insufficient because the failure to include $PM_{2.5}$ in the analysis and the absence of two-pollutant modeling

author	location	exposure monitoring	SO_2 concentration	study type (duration)	endpoint	co-pollutants	participants	ratio or risk	confidence interval	results	GRADE quality of evidence
(Tsai et al., 2006b)	Kaohsiung, Taiwan	daily average from six monitoring stations	daily mean concentration 9.49 ppb (25.24 µg/m³)	case-crossover (8 years)	asthma hospital admissions	association with PM_{10}, SO_2, O_3, CO, & NO_2	male and female 17,682 admissions	increase odds ratio per IQR of 5.79 ppb (15.40 µg/m³) in single and two-pollutant model using a cumulative 2 day lag single pollutant temp < 25 ˚C - 1.187 two pollutant (SO_2/CO) temp < 25 ˚C - 1.036	increase odds ratio per IQR of 5.79 ppb (15.40 µg/m³) in single and two-pollutant model using a cumulative 2 day lag single pollutant temp < 25 ˚C - 1.073 - 1.314 two pollutant (SO_2/CO) temp < 25 ˚C - 1.027 - 1.046	statistically significant positive association with asthma admission at temperatures below 25 ˚C using single pollutant model and a 2 day cumulative lag period; no associations using single pollutant model at temperatures ≥ 25 ˚C; significant positive association with admissions using a two pollutant model with CO at cold but not warm temperature greater than or equal to 25 ˚C; no positive associations at any temperature using two pollutant models with either PM_{10}, O_3, or NO_2; negative associations observed in two pollutant modeling with CO (≥ 25 ˚C) and NO_2 (< 25 ˚C)	⊕⊕◯◯ (low quality because no evaluation of $PM_{2.5}$ interactions)

author	location	exposure monitoring	SO_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 17.8 µg/m³	time-series (84 months)	impact of influenza on hospitalizations and mortality for respiratory disease (RD), acute respiratory (ARD), chronic obstructive pulmonary disease (COPD), and cardiovascular disease (CVD)	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 respiratory hospitalizations or mortality per 10 µg/m³ increase in single pollutant model with a 2 day (0-1) average lag baseline (no influenza) mortality CVD (all subjects) - 1.64 baseline (no influenza) hospitalizations CVD (all subjects) - 1.10 CVD (> 65 years) - 1.50 adjusted (influenza) hospitalizations ARD (all subjects) - 0.86	excess risk for respiratory hospitalizations or mortality per 10 µg/m³ increase in single pollutant model with a 2 day (0-1) average lag baseline (no influenza) mortality CVD (all subjects)- 0.27 - 3.02 baseline (no influenza) hospitalizations CVD (all subjects) - 0.52 - 1.69 CVD (> 65 years) - 0.83 - 2.17 adjusted (influenza) hospitalizations ARD (all subjects) - 0.20 - 1.53	statistically significant association with baseline (no influenza) mortality from cardiovascular disease but not respiratory disease or COPD in a single pollutant model with a 2 day (0-1) average lag; no association with total respiratory disease or COPD mortality in the adjusted or baseline influenza models; significant association with adjusted (10% influenza rate) and baseline hospitalizations for CVD disease in single pollutant model for both the all age group and those > 65 years of age; significant association with adjusted but not baseline hospitalizations for acute respiratory disease in single pollutant model that considered all age groups; no association with hospitalizations for all respiratory disease or COPD in either the adjusted or baseline model for either age comparison groups	⊕⊕◯◯ (low quality because of publication bias and the failure to consider $PM_{2.5}$ collinearity)

author	location	exposure monitoring	SO_2 concentration	study type (duration)	endpoint	co-pollutants	participants	ratio or risk	confidence interval	results	GRADE quality of evidence
(Yang et al., 2005)	Vancouver, British Columbia	daily average from five fixed monitoring sites	daily mean concentration 3.79 ppb (10.03 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 hospitalization per IQR of 2.8 ppb (7.4 µg/m³) increase in single and two-pollutant models for a moving average lag of up to 7 days single pollutant (6 day average lag) SO_2 only - 1.06 two pollutant (7 day average lag) SO_2/O_3 - 1.07	relative risk for COPD hospitalization per IQR of 2.8 ppb (7.4 µg/m³) increase in single and two-pollutant models for a moving average lag of up to 7 days single pollutant (6 day average lag) SO_2 only - 1.00 - 1.13 two pollutant (7 day average lag) SO_2/O_3 - 1.00 - 1.14	statistically significant association with COPD hospitalization in single pollutant model using a 6 day moving average lag but no average lags of 1, 2, 3, 4, 5, or 7days; significant association in a two pollutant model with O_3 but no association with PM_{10}, CO, or NO_2 for an 7 day average lag period; no association in pollutant models with PM_{10} & CO; no association in multi-pollutant model that included PM_{10}, CO, or NO_2 and O_3	⊕⊕○○ (low quality because no evaluation of $PM_{2.5}$ interactions)
(Yang et al., 2007)	Taipei, Taiwan	mean daily concentration at six fixed monitoring locations	daily mean 3.90 ppb (10.4 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 2.79 ppb (7.42 µg/m³) on warm days (≥ 25 °C) using a single pollutant model with a 3 day cumulative lag SO_2 only - 1.074	odds ratio for asthma admission per IQR of 2.79 ppb (7.42 µg/m³) on warm days (≥ 25 °C) using a single pollutant model with a 3 day cumulative lag SO_2 only - 1.113 - 1.247	statistically significant association with asthma hospital admissions on warm (≥ 25 °C) but not cold (< 25 °C) days using a single pollutant model with a 3 day cumulative lag; no positive associations observed in two pollutant models with PM_{10}, NO_2, CO, or O_3 on either warm or cold days with the 0-2 average lag, significant negative association seen with a two pollutant model with CO on cold days	⊕⊕⊕○ (moderate quality, no adjustment necessary but no $PM_{2.5}$)

author	location	exposure monitoring	SO_2 concentration	study type (duration)	endpoint	co-pollutants	participants	ratio or risk	confidence interval	results	GRADE quality of evidence
(Yang, 2008)	Taipei, Taiwan	mean daily concentration at six fixed monitoring locations	daily mean 4.27 ppb (11.36 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	no change odds ratio for CHF hospital admissions per IQR increase of 2.74 ppb (7.29 µg/m³) on warm or cold says using single or two-pollutant model with a cumulative 3 day lag	no change odds ratio for CHF hospital admissions per IQR increase of 2.74 ppb (7.29 µg/m³) on warm or cold days using single or two-pollutant model with a cumulative 3 day lag	no statistically significant positive associations for congestive heart failure hospital admissions on warm (≥ 20 ˚C) or cold (< 20 ˚C) days using a single pollutant model or a two-pollutant model with PM_{10}, NO_2, CO, or O_3 and a 3 day cumulative lag period; significant negative associations seen in all two-pollutant models on warm days	⊕⊕◯◯ (low quality because no evaluation of $PM_{2.5}$ interactions)

Asthma

author	location	exposure monitoring	SO_2 concentration	study type (duration)	endpoint	co-pollutants	participants	ratio or risk	confidence interval	results	GRADE quality of evidence
(Akinbami et al., 2010)	metropolitan areas of the United States	annual average in each metropolitan county based Aerometric information Retrieval System (AIRS) values from an unstated number of fixed monitoring sites	quartiles for country wide annual mean 1st - 0.1 - < 4.2 ppb (0.2 - < 11.2 µg/m³) 2nd - 4.2 - < 8.3 ppb (11.2 - < 22.1 µg/m³) 3rd - 8.3 - < 12.5 ppb (22.1 - < 33.3 µg/m³) 4th - 12.5 - 16.6 ppb (33.3 - 44.2 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 following adjustment with covariates using a single pollutant model with continuous or quartile comparison ; unadjusted odds ratio per 1 ppb (2.66 µg/m³) increase in SO_2 current asthma - 1.06 asthma attack - 1.07	no change in odds ratio following adjustment with covariates using a single pollutant model with continuous or quartile comparison ; unadjusted confidence interval per 1 ppb (2.66 µg/m³) increase in SO_2 current asthma 1.03 - 1.09 asthma attack - 1.03 - 1.10	no statistically significant change in 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 ; unadjusted model revealed associations for both end points	⊕⊕◯◯ (low quality because of cross-sectional design and the failure to include two-pollutant modeling)
(Amster et al., 2014)	Hadera, Israel	spatially assigned residential values from 20 fixed monitoring sites using ordinary kriging techniques	daily average all sources (power plant and background) 2.52 ppb (6.70 µg/m³)	cross sectional study (8 years)	respiratory symptoms (COPD, asthma, shortness of breath, chronic cough, chronic phlegm, nocturnal dyspnea) in those living near a power plant	association with SO_2 & NOx	males and females 18 to 75 years old 2244 participants	unadjusted and adjusted odds ratio increase for respiratory disease symptoms per 1 ppb (2.66 µg/m³) in single and two pollutant model with NOx asthma single pollutant model unadjusted - 1.90 adjusted - 1.89 asthma two pollutant model adjusted -1.85 shortness of breath single pollutant model unadjusted - 1.68 adjusted - 1.90 shortness of breath two pollutant model adjusted -1.89	unadjusted and adjusted odds ratio increase for respiratory disease symptoms per 1 ppb (2.66 µg/m³) in single and two pollutant model with NOx asthma single pollutant model unadjusted - 1.10 - 3.27 adjusted - 1.10 - 3.25 asthma two pollutant model adjusted -1.05 - 3.27 shortness of breath single pollutant model unadjusted - 1.49 - 1.94 adjusted - 1.10 - 3.27 shortness of breath two pollutant model adjusted -1.10 - 3.25	statistically significant association with reports of asthma and shortness of breath symptoms with adjusted and unadjusted single pollutant model and adjusted two pollutant model with NOx; no association with COPD, chronic cough, chronic phlegm, or nocturnal dyspnea in single or two pollutant models, no association with any of the 6 types of respiratory conditions when the SO_2 power plant exposures were evaluated independent of background by either of two techniques	⊕◯◯◯ (insufficient because the failure to include PM_{10} in the analysis and the absence of two-pollutant modeling)

author	location	exposure monitoring	SO_2 concentration	study type (duration)	endpoint	co-pollutants	participants	ratio or risk	confidence interval	results	GRADE quality of evidence
(Arnedo-Pena et al., 2009)	7 cities in Spain	annual averages from an unstated number of fixed monitoring sites	pooled annual average level 12.4 µg/m³	cross sectional (1 year)	prevalence of asthma symptoms (rhinitis, rhino conjunctivitis, wheezing, severe asthma, nocturnal dry cough, and atopic eczema)	association with $PM_{2.5}$, PM_{10}, SO_2, O_3, CO, & NO_2	male and female schoolchildren aged 6 and 7 years 10,249 males 10,631 females	pooled adjusted odds ratio for asthma symptoms relative to the first exposure tertile using a single pollutant model rhinitis 2nd tertile (26-74%) - 1.40 3rd tertile ((≥75%) - 1.56 rhino conjunctivitis 2nd tertile (26-74%) - 1.49 3rd tertile ((≥75%) - 1.70 severe asthma 2nd tertile (26-74%) - 1.29 3rd tertile ((≥75%) - 1.32 nocturnal dry cough 2nd tertile (26-74%) - 1.50 3rd tertile ((≥75%) - 1.17	pooled adjusted odds ratio for asthma symptoms relative to the first exposure tertile using a single pollutant model rhinitis 2nd tertile (26-74%) - 1.26 - 1.56 3rd tertile ((≥75%) - 1.39 - 1.75 rhino conjunctivitis 2nd tertile (26-74%) - 1.29 - 1.73 3rd tertile ((≥75%) - 1.45 - 2.00 severe asthma 2nd tertile (26-74%) - 1.02 - 1.63 3rd tertile ((≥75%) - 1.01 - 1.73 nocturnal dry cough 2nd tertile (26-74%) - 1.12 - 2.00 3rd tertile ((≥75%) - 1.02 - 1.33	statistically significant increase in the prevalence of rhinitis, rhino conjunctivitis, severe asthma, and nocturnal dry cough symptoms in asthmatic children at the two highest exposure tertiles using a single pollutant model; no association with wheezing or atopic eczema symptoms at the two highest exposure tertiles	⊕○○○ (insufficient because the failure to include two-pollutant modeling and the cross-sectional design)

author	location	exposure monitoring	SO_2 concentration	study type (duration)	endpoint	co-pollutants	participants	ratio or risk	confidence interval	results	GRADE quality of evidence
(Barnett et al., 2005)	3-4 cities in Australia and New Zealand	1-hr and 24-hr values from 1-4 fixed monitoring sites	1 hour mean Brisbane - 7.6 ppb (20.2 µg/m³) Christchurch - 10.1 ppb (26.9 µg/m³) Sydney - 3.7 ppb (9.8 µg/m³) 24 hour mean Auckland - 4.3 ppb (11.4 µg/m³) Brisbane - 1.8 ppb (4.8 µg/m³) Christchurch - 2.8 ppb (7.4 µg/m³) Sydney - 0.9 ppb (2.4 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 5.4 ppb (14.4 µg/m³) for 1-hr values on lag days 01 single pollutant model (1-hr SO_2 only) pneumonia and bronchitis 1 -4 yrs age - 6.9 respiratory 0 yrs age - 3.2 1 -4 yrs age - 2.7	pooled percent increase in admission rate per IQR of 5.4 ppb (14.4 µg/m³) for 1-hr values on lag days 01 single pollutant model (1-hr SO_2 only) pneumonia and bronchitis 1 -4 yrs age 2.3 - 11.7 respiratory 0 yrs age 0.3 - 6.3 1 -4 yrs age 0.6 - 4.8	statistically significant association of 1-hr SO_2 exposures with hospital admissions in children pooled from 3.4 cites for pneumonia and bronchitis (one age group) and respiratory effects (two age groups) using a single pollutant model, no statistically significant association with pneumonia & bronchitis, respiratory, or asthma admissions using a two pollutant model with PM_{10}, no statistically significant association with 24-hr SO_2 levels for of three pulmonary conditions	⊕⊕◯◯ (low quality because of exposure misclassification and imprecision caused by exposure heterogeneity)

author	location	exposure monitoring	SO_2 concentration	study type (duration)	endpoint	co-pollutants	participants	ratio or risk	confidence interval	results	GRADE quality of evidence
(Burra et al., 2009)	Toronto, Canada	daily averages from six fixed monitoring stations	daily average level 9.7 ppb (25.8 µg/m³)	time-series (10 years)	physician visits for asthma	association with $PM_{2.5}$, SO_2, O_3, & NO_2	male and females visitation rate per 100,000 children (1-17 yrs) - 1.27 - 5.96 adults (18-64 yrs) - 0.87 - 5.31	adjusted risk ratios for asthma visits per IQR increase of 7 ppb (18.6 µg/m³) for different income levels and lag periods using a single pollutant model males aged 1-17 yrs low income 1 day lag - 1.022 2 day lag -1.017 3 day lag - 1.012 4 day lag - 1.006 males aged 1-17 yrs high income 1 day lag - 1.017 2 day lag - 1.015 3 day lag - 1.012 females aged 1-17 yrs low income 1 day lag - 1.021 2 day lag - 1.021 3 day lag - 1.017 4 day lag - 1.011 females aged 1-17 yrs high income 1 day lag - 1.015 2 day lag - 1.017 3 day lag - 1.009 (data for age group 18-64 years not shown)	adjusted risk ratios for asthma visits per IQR increase of 7 ppb (18.6 µg/m³) for different income levels and lag periods using a single pollutant model males aged 1-17 yrs low income 1 day lag - 1.018 - 1.025 2 day lag -1.013 - 1.021 3 day lag - 1.007 - 1.017 4 day lag - 1.000 - 1.012 males aged 1-17 yrs high income 1 day lag - 1.013 - 1.021 2 day lag - 1.010 - 1.018 3 day lag - 1.006 - 1.018 females aged 1-17 yrs low income 1 day lag - 1.017 - 1.025 2 day lag - 1.016 - 1.027 3 day lag - 1.011 - 1.024 4 day lag - 1.004 - 1.018 females aged 1-17 yrs high income 1 day lag - 1.010 - 1.019 2 day lag - 1.011 - 1.024 3 day lag - 1.002 - 1.016 (data for age group 18-64 years not shown)	statistically significant association with physician visits for asthma in males and females aged 1-17 years at the lowest income levels at cumulative lag periods of 1, 2, 3, or 4 days but not 5 days using a single pollutant model; statistically significant association with physician visits for asthma in males and females aged 1-17 years at the highest income level at cumulative lag periods of 1, 2, or 3 days but not 4 or 5 days; significant association with physician visits for asthma in males and females aged 18-64 years at the lowest income level at cumulative lag periods of 1, 2, or 3 days but not 4 or 5 days; significant association with physician visits for asthma in males and females aged 18-64 years at the highest income level at cumulative lag periods of 1 and 2 days but not 3, 4, or 5 days	⊕○○○ (insufficient because the failure to include PM_{10} and two-pollutant modeling in the analysis)

author	location	exposure monitoring	SO_2 concentration	study type (duration)	endpoint	co-pollutants	participants	ratio or risk	confidence interval	results	GRADE quality of evidence
(Cai et al., 2014)	Shanghai, China	daily average from six fixed monitoring sites	daily average concentration 45 µg/m³	time-series (7 years)	hospitalization for asthma	association with PM_{10}, SO_2, NO_2, and black carbon	males and females 18 to ≥ 65 years old 15,678 admissions	percent increase in asthma hospital admissions per IQR increase of 36 µg/m³ using single and two pollutant models with a 2 day (0-1) moving average lag single pollutant cool season - 5.55 females - 5.78 males - 7.11 < 65 years age - 7.35 two pollutant SO_2 only - 6.41 SO_2/PM_{10} - 15.06	percent increase in asthma hospital admissions per IQR increase of 36 µg/m³ using single and two pollutant models with a 2 day (0-1) moving average lag single pollutant cool season - 0.42 - 10.68 females - 0.44 - 11.12 males - 1.47 - 12.75 < 65 years age - 2.45 - 12.24 two pollutant SO_2 only - 2.32 - 10.49 SO_2/PM_{10} - 6.13 - 24.00	statistically significant association with asthma hospitalization in all subjects using a single day lag of 0 and 1 and 2 day average lag of 0-1 but not on single day lag days of 2, 3, 4, or 5 using a single pollutant model; significant association in males and females for all seasons using a single pollutant model with a 2 day average lag; significant association in cool but not the warms season and in those < 65 years of age but not those ≥ 65 years of age using a single pollutant model; association in two pollutant model with PM_{10} but not NO_2	⊕⊕◯◯ (low quality because of the imprecision and poor statistical power and the failure to consider $PM_{2.5}$ collinearity)
(Canova et al., 2010)	Padua, Italy	daily averages from four fixed monitoring sites	daily mean concentration 3.57 ppb (9.50 µg/m³)	time-series (2 years)	peak expiratory flow (PEF), forced expiratory volume in 1 second (FEV_1), forced vital capacity (FVC) in asthmatics	association with PM_{10}, SO_2, CO & NO_2	asthmatics aged 15-44 years 19 cases	no change in the absolute percentage increase in morning or evening FEV1, PEF, or FEV per 10 µg/m³ change in a single pollutant model on lag days 0, 1, 2, or 3 and cumulative lag 0-1 or 0-3	no change in the absolute percentage increase in morning or evening FEV1, PEF, or FEV per 10 µg/m³ change in a single pollutant model on lag days 0, 1, 2, or 3 and cumulative lag 0-1 or 0-3	no statistically significant association with any of four pulmonary function measurements in a single pollutant model with used six different lag periods	⊕◯◯◯ (insufficient because the small sample size and lack of statistical power as indicated by the wide confidence intervals)

author	location	exposure monitoring	SO_2 concentration	study type (duration)	endpoint	co-pollutants	participants	ratio or risk	confidence interval	results	GRADE quality of evidence
(Chan et al., 2009)	12 districts in Taipei, Taiwan	mean daily concentration from 11 fixed monitoring locations that were assigned district level geostatistical spatial levels using ordinary kriging	3 year average levels Beitou - 1.59 ppb (4.23 µg/m³) Da-an - 3.26 ppb (8.67 µg/m³) Datong - 3.43 ppb (9.12 µg/m³) Jhongiheng - 2.92 ppb (7.77 µg/m³) Jhongshan - 3.13 ppb (8.33 µg/m³) Nangang - 3.61 ppb (9.60 µg/m³) Neihu - 2.61 ppb (6.94 µg/m³) Shihlin - 1.88 ppb (5.00 µg/m³) Sinyi - 3.80 ppb (10.11 µg/m³) Songshan - 3.33 ppb (8.86 µg/m³) Wanhua - 2.97 ppb (7.90 µg/m³) Wunshan - 2.96 ppb (7.87 µg/m³)	time-series (3 years)	outpatient and emergency room visits for asthma	association with PM_{10}, O_3, SO_2, & NO_2	male and female adults aged 0 to >66 years outpatient - 724,075 visits emergency room - 34,274 visits	percentage increase in vests per 10% increase in concentration in single and four pollutant (SO_2/PM_{10}/O_3/NO_2) models on lag day 0 Outpatients (age 0 -15 yrs) single pollutant - 0.28 four pollutant - 0.12 Outpatients (age 16 - 65 yrs) single pollutant - 0.51 four pollutant - 0.20 Outpatients (age > 65 yrs) single pollutant -0.36 four pollutant - 0.33 Outpatients (age all ages) single pollutant - 0.44 four pollutant - 0.27	percentage increase in vests per 10% increase in concentration in single and four pollutant (SO_2/PM_{10}/O_3/NO_2) models on lag day 0 Outpatients (age 0 -15 yrs) single pollutant - 0.08 - 0.47 four pollutant - 0.20 - 0.44 Outpatients (age 16 -65 yrs) single pollutant - 0.36 - 0.66 four pollutant - 0.04 - 0.36 Outpatients (age > 65 yrs) single pollutant -0.23 - 0.49 four pollutant - 0.19 - 0.47 Outpatients (age all ages) single pollutant - 0.31 - 0.57 four pollutant - 0.12 - 0.41	statistically significant positive association with outpatient visits for asthma in all patents and each of three age groups using single pollutant and four pollutant (SO_2/PM_{10}/O_3/NO_2) models on lag day 0; no association or negative association (single pollutant model in > 65 yr age group) with emergency room visits for all patents and each of three age groups using single pollutant and four pollutant models on lag day 0; significant association with all age outpatient room visits on lag days 0, 1, and 2 and emergency room visits on lag day 2 using a single pollutant model, significant association with all age outpatient visits on lag days 0 and 1 but not lag day 2 using four pollutant model, no association with all age emergency room visits on any lag day using four pollutant model	⊕⊕⊕◯ (moderate quality no adjustment necessary but no evaluation of $PM_{2.5}$)

author	location	exposure monitoring	SO_2 concentration	study type (duration)	endpoint	co-pollutants	participants	ratio or risk	confidence interval	results	GRADE quality of evidence
(Clark et al., 2010)	southwestern British Columbia	averages by inverse distance weighting of daily measurement from 22 fixed monitoring sites to postal code assignments of location or LUR modeling	daily average in utero period - 5.25 µg/m³ first year of life - 5.37 µg/m³	nested case control (36 - 59 months)	asthma (two physician-based diagnoses or one hospital visit) incidence in children	association with PM_{10}, $PM_{2.5}$, wood smoke, BC, O_3, SO_2, CO, NO, & NO_2	male and female 3,482 cases 11,110 controls	adjusted odds ratio per 1 µg/m³ exposure interval increase in single pollutant model in utero period - 1.03 first-year period - 1.03	adjusted odds ratio per 1 µg/m³ exposure interval increase in single pollutant model in utero period - 1.02 - .05 first-year period - 1.02 - 1.05	significant association with asthma diagnosis for in utero and first-year exposures using inverse distance weighting of monitoring data in a single pollutant model; no consistent trend in odds ratios across exposure quartiles with positive and negative associations seen when the exposures were expressed for the period and the first year of life	⊕⊕◯◯ (low quality because of the reliance on single pollutant modeling only)
(Deger et al., 2012)	Montreal, Canada	annual residential and school averages estimated using AERMOD dispersion modeling along with the stack emissions from local oil refineries	annual average active asthma - 4.75 µg/m³ poor asthma control - 5.37 µg/m³	cross sectional (4 months)	active asthma and poor asthma control based on questionnaire responses	association with SO_2 only	male and female children aged 6 months to `12 years active asthma - 142 cases poor asthma control - 51 cases	prevalence ratio for poor asthma control per IQR increase of 4.7 µg/m³ in a single pollutant model crude - 1.45 adjusted - 1.39	prevalence ratio for poor asthma control per IQR increase of 4.7 µg/m³ in a single pollutant model crude - 1.03 - 2.03 adjusted - 1.00 - 1.94	statistically significant association with crude and adjusted prevalence of poor asthma control using a single pollutant model, no association with active asthma in crude or adjusted single pollutant models	⊕◯◯◯ (insufficient because the failure to include two-pollutant modeling and the cross-sectional design)

author	location	exposure monitoring	SO_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 thirteen urban fixed monitoring sites	daily mean concentration 23.7 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 43,635 visits	percentage increase in hospital and emergency room visits per IQR 12.5 µg/m³ increase using one pollutant ,two-pollutant and multi-pollutant models for 5 day moving average lag respiratory disease admissions SO_2 only ≈ 10 (depicted graphically) SO_2/CO - 8.2 pneumonia and bronchopneumonia SO_2 only ≈ 20 (depicted graphically) SO_2/O_3 - 18.4 SO_2/CO - 18.4	percentage increase in hospital and emergency room visits per IQR 12.5 µg/m³ increase using one pollutant ,two-pollutant and multi-pollutant models for 5 day moving average lag respiratory disease admissions SO_2 only ≈ 5 - 17 (depicted graphically) SO_2/CO - 1.87 - 14.5 pneumonia and bronchopneumonia SO_2 only ≈ 4 - 38 (depicted graphically) SO_2/O_3 - 0.5 - 36.2 SO_2/CO - 0.5 - 36.2	statistically significant positive association with the percentage increase in respiratory-related and pneumonia/bronchopneumonia-related emergency room visits for single pollutant models and two pollutant models with CO (respiratory) and O_3 or CO (pneumonia/bronchopneumonia) using a 0-4 day moving average lag period; no statistically significant association with asthma and bronchiolitis visits for single, two-pollutant or multipollutant models under any conditions models; no significant associations with respiratory disease ER visits with two pollutant models with PM_{10}, NO_2, or O_3; no associations with pneumonia/bronchopneumonia using two pollutant models with PM_{10} or NO_2; no positive associations with any condition using multi-pollutant model with PM_{10}, NO_2, O_3, CO; statistically significant negative associations seen for respiratory disease visits in two pollutant model with PM_{10} and with the multi-pollutant model	⊕⊕⊕◯ (moderate quality, but no evaluation of $PM_{2.5}$)

author	location	exposure monitoring	SO_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, NY	daily averages from 19 fixed monitoring sites	daily average all year -7.8 ppb (20.7 µg/m³) warm months - 5.4 ppb (14.4 µg/m³) cold months - 10.2 ppb (27.1 µg/m³)	time-series (4 years)	emergency department visits for asthma	association with $PM_{2.5}$, PM_{10}, SO_2, O_3, CO, & NO_2	unstated number of males and females aged 2 to 45 years	relative risk for asthma ED visits per 5th-95th percentile increase using a single and two pollutant model with a 2 day average lag and a weather model that considers only temperature change (graphical data presentation) single pollutant all year (14 ppb rise) - 1.08 cold months (15 ppb rise) - 1.08 warm months (7 ppb rise) - 1.15 two pollutant warm months (7 ppb rise) $SO_2/PM_{2.5}$ - 1.17 SO_2/O_3 - 1.15 SO_2/CO - 1.16	relative risk for asthma ED visits per 5th-95th percentile increase using a single and two pollutant model with a 2 day average lag and a weather model that considers only temperature change (graphical data presentation) single pollutant all year (14 ppb rise) - 1.03 - 1.16 cold months (15 ppb rise) - 1.03 - 1.16 warm months (7 ppb rise) - 1.08 - 1,26 two pollutant warm months (7 ppb rise) $SO_2/PM_{2.5}$ - 1.09 - 1.27 SO_2/O_3 - 1.08 - 1.26 SO_2/CO - 1.10 - 1.28	statistically significant association with ED visits for asthma during the entire season, warm months, and cold months using a single pollutant model with a 2 day average lag that incorporates a weather model that considers temperature only; statistically significant associations with asthma visits for all three seasonal stratifications using a single pollutant model that incorporates alternative weather model that consider both temperature and dew point; significant association with asthma visits during the warm season using a two pollutant model with $PM_{2.5}$, O_3, and CO but not NO_2 and a 2 day average lag with the temperature only weather model	⊕○○○ (insufficient because no two-pollutant modeling and inconsistent results)

author	location	exposure monitoring	SO_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	daily averages from 14 fixed monitoring sites	daily mean concentration all season - 1.07 ppb (2.85 µg/m³) cool period - 1.1 ppb (2.93 µg/m³) warm period - 1.03 (2.74 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 kids of different age per IQR of 0.8 ppb (2.13 µg/m³) in single and two-pollutant models for lag day 0 thru 3 1-4 years of age SO_2 only - 1.8 SO_2/PM_{10} - 1.1 $SO_2/PM_{2.5}$ - 1.1 SO_2/O_3 - 1.9 SO_2/NO_2 - 2.6 SO_2/CO - 1.6 5-9 years of age SO_2 only - 1.9 SO_2/PM_{10} - 1.3 $SO_2/PM_{2.5}$ - 1.3 SO_2/O_3 - 1.7 SO_2/CO - 2.5 10-14 years of age SO_2/PM_{10} - 1.9 $SO_2/PM_{2.5}$ - 1.2 SO_2/CO - 3.2 1-14 years of age SO_2 only - 1.6 SO_2/PM_{10} - 1.2 $SO_2/PM_{2.5}$ - 1.2 SO_2/O_3 - 1.3 SO_2/NO_2 - 1.9 SO_2/CO - 2.0	percent increase in ED visits for asthma in children of different age groups per IQR of 0.8 ppb (2.13 µg/m³) in single and two-pollutant models for lag day 0, 1, 2, or 3 1-4 years of age SO_2 only - 0.8 - 2.9 SO_2/PM_{10} - 0.3 - 1.9 $SO_2/PM_{2.5}$ - 0.5 - 1.8 SO_2/O_3 - 1.2 - 2.6 SO_2/NO_2 - 1.4 - 3.9 SO_2/CO - 0.7 - 2.6 5-9 years of age SO_2 only - 0.3 - 3.6 SO_2/PM_{10} - 0.2 - 2.5 $SO_2/PM_{2.5}$ - 0.4 - 2.3 SO_2/O_3 - 0.4 - 3.0 SO_2/CO - 1.0 - 4.1 10-14 years of age SO_2/PM_{10} - 0.3 - 3.6 $SO_2/PM_{2.5}$ - 0.02 - 2.5 SO_2/CO - 1.5 - 5.0 1-14 years of age SO_2 only - 0.7 - 2.4 SO_2/PM_{10} - 0.6 - 1.8 $SO_2/PM_{2.5}$ - 0.7 - 1.7 SO_2/O_3 - 0.8 - 1.9 SO_2/NO_2 - 0.9 - 2.9 SO_2/CO - 1.3 - 2.8	statistically significant association with ED visits for asthma in single and all two pollutant models for age group 1-14 years and age group 1-4 years on lag day 0; statistically significant association in single and many two pollutant models for age group 5-9 years on lag day 0 (SO_2/NO2 was the only exception); no association with age group 10-14 years using single pollutant model but two pollutant models for with PM_{10}, $PM_{2.5}$, & CO yielded positive associations if lag days 2 and 3 were used in the co-pollutant model; no statistically significant associations in single pollutant model for warm or cold months in any age group except 1-14 years where a positive association was found in cool but not warm months	⊕○○○ (insufficient because of small sample size and the failure to state the number of monitoring sites)

author	location	exposure monitoring	SO_2 concentration	study type (duration)	endpoint	co-pollutants	participants	ratio or risk	confidence interval	results	GRADE quality of evidence
(Kim et al., 2007b)	Seoul, Korea	daily averages from 27 fixed monitoring sites located within 5 regions of the city (25 districts)	mean concentration 4.7 µg/m³	case-crossover (1 year)	interaction socioeconomic position (SEP) measured using income levels with hospital visits for asthma	association with PM_{10}, SO_2, O_3, CO, & NO_2	males and females aged 9 to > 70 years 92,535 cases	change in relative risk for ED asthma vests per 3.3 0 µg/m³ increase using a single pollutant model and a day 3 lag value for individuals in 5 different income quintiles quintile 1 (highest SEP) - 1.03 quintile 2 (high SEP) - 1.04 quintile 4 (low SEP) - 1.04	change in relative risk for ED asthma vests per 3.3 0 µg/m³ increase using a single pollutant model and a day 3 lag value for individuals in 5 different income quintiles quintile 1 (highest SEP)- 1.01 - 1.06 quintile 2 (high SEP)- 1.02 - 1.07 quintile 4 (low SEP)- 1.01 - 1.07	statistically significant association for asthma ED visits for those individuals in the two highest income quintiles and those in the second lowest quintile using a single pollutant model on lag day 3; significant associations also observed when socioeconomic position (i.e. income) was assigned to the urban region of residence rather than the individual; significant associations with asthma visits for all individuals on lag days 3 and 4 but not lag days 0, 1, 2, or the 3 day moving average lag	⊕○○○ (insufficient because no two-pollutant modeling and inconsistent results)

author	location	exposure monitoring	SO_2 concentration	study type (duration)	endpoint	co-pollutants	participants	ratio or risk	confidence interval	results	GRADE quality of evidence
(Kim et al., 2012)	Seoul, Korea	averages from the nearest fixed monitor but the distance and number of monitors was not stated	daily averages spring - 6.9 ppb (18.420.7 µg/m³) summer - 4.9 ppb (13.0 µg/m³) fall - 6.5 ppb (17.3 µg/m³) winter - 8.8 ppb (23.4 µg/m³)	case-crossover (5 years)	hospital visits for refractory asthma exacerbations	association with PM_{10}, SO_2, CO, O_3, & NO_2	males and females aged 19 to 87 years 39 non-smoking subjects 43 smoking subjects	adjusted odds ratio for asthma exacerbations for those sensitive and insensitive to dust mite allergens during the winter season per 1 ppb (2.6 µg/m³) increase in as single and multi-pollutant models for the winter months single pollutant - non-smoking subjects lag day 1 - 1.147 lag day 2 - 1.140 multi-pollutant (SO_2/PM_{10}/O_3/CO/NO_2) - non-smoking subjects lag day 1 - 1.197 lag day 2 - 1.164 multi-pollutant (SO_2/PM_{10}/O_3/CO/NO_2) - all subjects lag day 2 - 1.114	adjusted odds ratio for asthma exacerbations for those sensitive and insensitive to dust mite allergens during the winter season per 1 ppb (2.6 µg/m³) increase in as single and multi-pollutant models for the winter months single pollutant - non-smoking subjects lag day 1 - 1.019 - 1.292 lag day 2 - 1.024 - 1.268 multi-pollutant (SO_2/PM_{10}/O_3/CO/NO_2) - non-smoking subjects lag day 1 - 1.033 - 1.387 lag day 2 - 1.030 - 1.316 multi-pollutant (SO_2/PM_{10}/O_3/CO/NO_2) - all subjects lag day 2 - 1.028 - 1.208	statistically significant association with asthma exacerbations in all patients during the winter months using a single pollutant model with a 1 or day lag but not with a lag of 0 or 3 days; statistically significant association during the winter months for nonsmokers using a multipollutant model with PM_{10}, O_3, CO, and NO_2 on lag days 1 and 2 but not days 0 or 3; significant association with all patients using a multi-pollutant model on lag day 2 but not days 0, 1, or 3; significant associations for those not sensitive to dust mite allergens using a multi-pollutant model on lag day 1 and 2 but not days 0, or 3; no association with all patients or non-smokers for the spring, summer, or fall seasons using single and multi-pollutant models, no association with non-smokers using single and multi-pollutant models for any season or any lag day, no association with those sensitive to dust mite allergens using single and multi-pollutant models for any season or any lag day	⊕○○○ (insufficient because of small sample size and the failure to state the number of monitoring sites)

author	location	exposure monitoring	SO_2 concentration	study type (duration)	endpoint	co-pollutants	participants	ratio or risk	confidence interval	results	GRADE quality of evidence
(Ko et al., 2007b)	Hong Kong, China	daily average at 14 fixed monitoring sites	daily average all seasons - 18.8 µg/m³ cold season (< 20 °C) - 18.0 µg/m³ warm season (≥ 20 °C) - 19.1 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 03 days single pollutant >14-65 yrs age - 1.018	relative risk per 10 µg/m³ increase in single multi pollutant models for avg lag 03 days single pollutant >14-65 yrs age - 1.001 - 1.035	statistically significant association with asthma hospitalization in one of three age groups (>14 - 65 years of age) using a single pollutant model and a cumulative lag of 03 days, no association with asthma in the 0-14 yrs age group or the > 65 yrs age group; no statistically significant association for all ages at any of the 11 lag times examined, no significant association in multi--pollutant model with O_3 and NO_2	⊕○○○ (insufficient because no two-pollutant modeling and inconsistent results)
(Laurent et al., 2008)	Strasbourg, France	averages from geographical census block deterministic modeling of hourly measurements from an unknown number of monitoring sites along with meteorological data and emissions inventories	daily mean 8.9 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 for any of three age groups using a single pollutant model and lag period of 0, 0-1, 0-2, 0-3, or 0-4 days	no significant change in odds ratio for any of three age groups using a single pollutant model and lag period of 0, 0-1, 0-2, 0-3, or 0-4 days	no statistically y significant change in the odds ratio for emergency asthma calls using a single pollutant model and a 2 day lag period with 4 age groups of 0 - >64 years, 0 - 19 years, 20 - 64 years, or > 64 years; no associations after stratification by socioeconomic deprivation	⊕○○○ (insufficient because of small sample size and the failure to state the number of monitoring sites)

author	location	exposure monitoring	SO_2 concentration	study type (duration)	endpoint	co-pollutants	participants	ratio or risk	confidence interval	results	GRADE quality of evidence
(Lee et al., 2006)	Hong Kong, China	daily average at 9-11 fixed monitoring sites	daily mean concentration 17.7 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 11.1 µg/m³ in single pollutant model single pollutant lag day 4 - 1.40 lag day 5 - 1.46	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 positive association with asthma admissions in children for single pollutant models on lag day 4 and 5, statistically significant negative association in single pollutant models on lag days 0 and 1; no associations with single pollutant modeling on day 3 or for with five - pollutant modeling on day 5 that included SO_2/PM_{10}/$PM_{2.5}$/NO_2/O_3	⊕○○○ (insufficient because no two-pollutant modeling and inconsistent results)
(Lee et al., 2007b)	Busan, Korea	average daily level from eight monitoring sites	daily average concentration 6.6 ppb (17.6 µg/m³)	time-series (3 months)	hospital admissions for asthma	association with PM_{10}, SO_2, O_3, CO, & NO_2	males and females children < 15 years of age mean admission rate 4.9 cases/day	relative risk increase for asthma admissions per 22.82 µg/m³ increase in a single pollutant model using an unstated lag period single pollutant - 1.34	relative risk increase for asthma admissions per 22.82 µg/m³ increase in a single pollutant model using an unstated lag period single pollutant - 1.06 - 1.68	statistically significant association with asthma admission in a single pollutant model for an unstated lag day	⊕○○○ (insufficient because of small sample size and the failure to state the number of monitoring sites)

author	location	exposure monitoring	SO_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 location	daily mean 4.68 µg/m³	time-series (19 months)	hospital admissions for chronic obstructive pulmonary disease (COPD), asthma, chronic bronchitis	differential effects of humidity, TSP, SO_2, & NO_2	males and females hospitalizations 953 admissions	increase in relative risk per 1 µg/m³ increment using a single pollutant model with various lag times and exposure data handling lag day 2 (graphically interpolated) raw actual values - 1.06 raw + interpolated values - 1.15 lag day 7 raw + interpolated values - 1.07	increase in relative risk per 1 µg/m³ increment using a single pollutant model with various lag times and exposure data handling lag day 2 (graphically interpolated) raw actual values - 1.01 - 1.10 raw + interpolated values - 1.06 - 1.26 lag day 7 raw + interpolated values - 1.01 - 1.18	statistically significant associations with chronic bronchitis in single pollutant model on lag days 2 and 7 using original and interpolated exposure values used to account for missing data, stated significant associations observed with chronic bronchitis using a three pollutant model (SO_2/TSP/NO_2) on lag day 2 but the results not shown; no associations with chronic bronchitis; no statistically significant associations observed total respiratory admissions, COPD, or asthma using a single or multi-pollutant model on any lag day	⊕○○○ (insufficient because the high likelihood of exposure misclassification and the absence of two-pollutant modeling)

author	location	exposure monitoring	SO_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 - 4.5 ppb (12.0 µg/m³) 2-day - 5.0 ppb (13.3 µg/m³) 3-day - 5.6 ppb (14.9 µg/m³)	case-crossover (3 months)	pulmonary function (FEV_1, $FEF_{25-75\%}$), airway inflammation (exhaled nitric oxide, FENO) and oxidative stress (thiobarbituric reactive substances (TBARS), & 8-isoprostane exhalation 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 respiratory response per IQR increase using a single pollutant model at various lag times TBARS 0 day lag (IQR 6.5 ppb; 17.3 µg/m³) - 17.4 2 day lag (IQR 5.6 ppb; 14.9 µg/m³) - 35.1 3 day lag (IQR 5.4 ppb; 14.4 µg/m³) - 61.8 8-isoprostane exhalation 0 day lag (IQR 6.5 ppb; 17.3 µg/m³) - 14.1	adjusted percent change in respiratory response per IQR increase using a single pollutant model at various lag times TBARS 0 day lag (IQR 6.5 ppb; 17.3 µg/m³) - 0.3 - 37.4 2 day lag (IQR 5.6 ppb; 14.9 µg/m³) - 9.5 - 66.8 3 day lag (IQR 5.4 ppb; 14.4 µg/m³) - 24. 9 - 109 8-Isoprostane exhalation 0 day lag (IQR 6.5 ppb; 17.3 µg/m³) - 2.5 - 26.9	statistically significant association with TBARS measurements for same day lag periods and periods of 2 and 3 days in single pollutant models, no statistically significant association with TBARS in single pollutant model on lag day 1; no statistically significant association with FEV_1, $FEF_{25-75}\%$, and FE_{NO} for any of the 4 lag periods examined; statistically significant association with TBARS change in two pollutant model with O_3 using a 3 day lag; no statistically significant associations with FEV_1, $FEF_{25-75}\%$, FENO, or TBARS on any lag day in two pollutant models with either $PM_{2.5}$ or NO_2	⊕○○○ (insufficient because of the high probability of exposure misclassification and the failure to consider PM_{10} levels)
(Nishimura et al., 2013)	5 locations in Puerto Rico and United States	annual average using inverse distance weighting from the nearest four monitoring sites within 50 km (total numbers not stated)	annual average Chicago - 5.1 ppb (13.6 µg/m³) Houston - 3.6 ppb (9.6 µg/m³) New York - 11.7 ppb (31.1 µg/m³) Puerto Rico - 4.1 ppb (10.9 µg/m³) San Francisco - 1.6 ppb (4.3 µg/m³) All - 4.0 ppb (10.6 µg/m³)	case control (6 years)	childhood asthma diagnosis in Latino and African Americans	association with $PM_{2.5}$, PM_{10}, SO_2, O_3, & NO_2	male and female 8-21 years of age 2291 cases 2029 controls	no change in pooled (random effects) odds ratio per 5 ppb (13.3 µg/m³) increase in exposure during the first year or the first 3-years of life using a single pollutant model	no change in pooled (random effects) odds ratio per 5 ppb (13.3 µg/m³) increase in exposure during the first year or the first 3-years of life using a single pollutant model	statistically significant associations with asthma diagnosis in minority children using exposures from the first year or the first 3 years of life in a single pollutant model; significant associations observed in one of five location specific analyses for exposures measured during the first year (Puerto Rico) or the first 3 years (Houston)	⊕⊕○○ (low quality because of the reliance on single pollutant modeling alone)

author	location	exposure monitoring	SO_2 concentration	study type (duration)	endpoint	co-pollutants	participants	ratio or risk	confidence interval	results	GRADE quality of evidence
(O'Connor et al., 2008)	5 communities in the United States	daily average from the nearest monitoring site within a reasonable distance (avg. 2.3 km)	pooled average concentration (graphical representation) 1 day avg. ≈ 5 ppb (13.3 µg/m³) 5 day avg. ≈ 5 ppb (13.3 µg/m³)	time-series (4 years)	peak expiratory flow rate spirometry (FEV_1 and PEFR) measurements and symptom (wheeze-cough, night time asthma, slow play, and missed school) recording in minority children with asthma	association with $PM_{2.5}$, SO_2, CO, O_3, & NO_2	males and females 5 to 12 years of age 937 cases	pooled mean percentage change in pulmonary function measurements per 12.4 ppb (33.0 µg/m³)increase in single pollutant model using a 5 day moving average lag FEV_1 - -1.60 PEFR - -2.14	pooled mean percentage change in pulmonary function measurements per 12.4 ppb (33.0 µg/m³)increase in single pollutant model using a 5 day moving average lag FEV1 - -2.54 - -0.67 PEFR - -3.08 - -1.19	statistically significant association with FEV_1 and PFER pulmonary function decrements in asthmatic children using a single pollutant model; no significant association with wheeze-cough, night time asthma, slow play, or missed school using a single pollutant model	⊕○○○ (insufficient because of potential recall bias and the failure to consider PM_{10} levels)
(Parker et al., 2009)	United States	annual averages for site specific monitors within 20 miles of residence weighted by inverse distance weighting	annual median 3.9 ppb (10.4 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 42,791 children	no change in odds ratio for allergy and hay fever reporting in partial or fully adjusted single or multi-pollutant models per 3 ppb (8.0 µg/m³) increase	no change in odds ratio for allergy and hay fever reporting in partial or fully adjusted single or multi-pollutant models per 3 ppb (8.0 µg/m³) increase	no statistically significant association with childhood allergy and hay fever prevalence in partial or fully adjusted single or multi-pollutant (PM_{10}, $PM_{2.5}$, O_3, & NO) models using IDW for monitors within a 20 mi or 5 mi radius; statistically significant association observed in unadjusted single pollutant models	⊕⊕○○ (low quality because of inherent limitations of the cross sectional design)

author	location	exposure monitoring	SO_2 concentration	study type (duration)	endpoint	co-pollutants	participants	ratio or risk	confidence interval	results	GRADE quality of evidence
(Penard-Morand et al., 2010)	6 cities in France	annual average based on dispersion modeling that used local street level emission estimates and regional background levels that considered background concentrations of air pollutants, traffic density, proportion of main vehicle classes, average speed, percentage of gridlocks, direction and slope of the street, number of traffic lines, geometry of the buildings, quality of the roads surface, wind speed and direction, and precipitation	annual average level Bordeax - 8.5 µg/m³ Clermont-Ferrand - 4.8 µg/m³ Creteil - 8.8 µg/m³ Marseille - 13.2 µg/m³ Reims - 4.1 µg/m³ Strasbourg - 10.6 µg/m³	cross sectional (20 months)	prevalence of asthma and allergy conditions including exercised induced asthma, asthma in the last year, lifetime asthma, sensitization to pollens, rhino conjunctivitis in last year, lifetime allergic rhinitis, eczema in last year, and lifetime eczema,	association with benzene, VOC, PM_{10}, SO_2, CO, NOx & NO_2	male and female school aged children with varying degree of home residency home residence for ≥ 3 years - 4907 subjects home residence for ≥ 8 years - 2834 subjects home residence since birth - 2213 subjects	adjusted odds ratio for asthma and allergy health outcomes per IQR increase of 5 µg/m³ in a single pollutant model for those living in the same residence for ≥ 3 years exercised induced asthma - 1.27 asthma in last year - 1.29 lifetime asthma - 1.26	adjusted odds ratio for asthma and allergy health outcomes per IQR increase of 5 µg/m³ in a single pollutant model for those living in the same residence for ≥ 3 years exercised induced asthma - 1.11 - 1.53 asthma in last year - 1.03 - 1.71 lifetime asthma - 1.11 - 1.42	statistically significant association with exercised induces asthma, asthma in last year and lifetime asthma in a single pollutant model when examining children who resided in the same residence for ≥ 3 years ; significant association with lifetime asthma for those children who resided at the same residence for ≥ 3 years or ≥ 8 years but not for those who resided at the same residence since birth, no association with sensitization to pollens, rhino conjunctivitis in last year, lifetime allergic rhinitis, eczema in last year, and lifetime eczema for those who resided in the same residence for ≥ 3 years	⊕○○○ (insufficient because the failure to include two-pollutant modeling and the cross-sectional design)

author	location	exposure monitoring	SO_2 concentration	study type (duration)	endpoint	co-pollutants	participants	ratio or risk	confidence interval	results	GRADE quality of evidence
(Portnov et al., 2012)	7 cities in Israel	residential geocoding used along with kriging and inverse distance weighting to improve spatial resolution of the values from 14 monitoring sites	daily mean Qiryat Tivon - 8.5 ppb (22.6 µg/m³) Nesher - 6.2 ppb (16.5 µg/m³) Haifa - 5.4 ppb (14.4 µg/m³) Qiryat Ata - 3.6 ppb (9.6 µg/m³) Qiryat Motzkin - 6.1 ppb (16.2 µg/m³) Qiryat Bialik - 6.7 ppb (17.8 µg/m³) Qiryat Yam - 5.0 ppb (13.3 µg/m³)	cross sectional study (1 year)	prevalence of childhood asthma	association with PM_{10} and SO_2	males and females aged 6 - 15 years 3922 cases	pooled change in odds ratio for asthma prevalence in single pollutant model SO_2 only - 1.104	pooled change in odds ratio for asthma prevalence in single pollutant model SO_2 only - 1.012 - 1.204	statistically significant association with asthma prevalence in a polled city analysis using a single pollutant model and kriging for exposure proximity determination, no association observed in a two-pollutant model with PM_{10} using kriging or in a single pollutant model using inverse distance weighting for spatial resolution of exposures, design does not guarantee that exposure preceded response	⊕⊕⊕○ (moderate quality, but no evaluation of $PM_{2.5}$)
(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 5.3 ppb (14.1 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	no change exhaled nitric oxide concentration for those using triamcinolone or salmeterol corticosteroid or a placebo per 10 ppb (26.6 µg/m³) increase in single or two pollutant model during any of 5 lag periods	no change exhaled nitric oxide concentration for those using triamcinolone or salmeterol corticosteroid or a placebo per 10 ppb (26.6 µg/m³) increase in single or two pollutant model during any of 5 lag periods	no statistically significant interaction of placebo, total corticosteroid, triamcinolone, or salmeterol use on nitric oxide exhalation in single pollutant model on lag days 0, 1, 2, 3, or cumulative 4 day lag (0-3) or two pollutant models with PM_{10}, O_3, or NO_2 on lag day 0	⊕○○○ (insufficient because of bias caused by small number of cases, short duration, and unknown number of monitoring sites)

author	location	exposure monitoring	SO_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 methods used i) annual means from one of 69 monitoring site nearest the subject residence; ii) annual mean concentrations from a geostatistical model (kriging or inverse distance weighting) used residential proximity determination	annual mean monitoring method - 21.3 µg/m³ modeling method - 9.9 µg/m³	case control study (12 months)	asthma severity based on symptom questionnaire and treatment needs	association with SO_2, O_3, & NO_2	male & female 328 cases	crude and adjusted odds ratio for asthma severity score in single and three pollutant model per IQR increase of 8.2 µg/m³ using the GIS based exposure results single pollutant crude - 1.81 adjusted - 1.70 three pollutant model (SO_2/O_3/NO_2) adjusted - 2.27	crude and adjusted odds ratio for asthma severity score in single and three pollutant model per IQR increase of 8.2 µg/m³ using the GIS based exposure results single pollutant crude - 1.33 - 2.46 adjusted - 1.19 - 2.44 three pollutant model (SO_2/O_3/NO_2) adjusted - 1.39 - 3.70	statistically significant association for asthma severity (four class system) in adjusted single and thee-pollutant model when using geo-coded residential exposure measurements but not when the value from the closest monitor was used; no significant associations using an alternative asthma severity scoring system (five class system) using adjusted single or three-pollutant model	⊕⊕○○ (low quality because of the indirectness from using medical questionnaire)
(Sahsuvaroglu et al., 2009)	Hamilton, Ontario	geostatistical approximation of to the postal code of the residential address using Theissen polygons and the measurements from 7 - 9 fixed monitoring sites	mean daily level al subjects -5.81 ppb (15.45 µg/m³) boys - 5.88 ppb (15.64 µg/m³) girls - 5.74 ppb (15.27 µg/m³)	cross sectional (24 months)	non-allergic asthma prevalence in 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	unadjusted regression coefficient between exposure and asthma without hay fever per 1 ppb (2.66 µg/m³) in a single pollutant model in those aged 6-7 years old boys and girls - 1.294	unadjusted regression coefficient between exposure and asthma without hay fever per 1 ppb (2.66 µg/m³) in a single pollutant model in those aged 6-7 years old boys and girls - 1.019 - 1.643	statistically significant association with asthma prevalence in boys and girls aged 6- 7 years but not older children (aged 13-14 years) using a unadjusted single pollutant model; no association with asthma in unadjusted or adjusted single pollutant model following stratification by sex or age	⊕⊕○○ (low quality because of the indirectness from using medical questionnaire)

author	location	exposure monitoring	SO_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	daily average 16.8 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 for males and females 0-14 years of age per 10 µg/m³ increase (1-hr max) in single and two pollutant model for lag day 0 SO_2 only (annual)- 5.98 SO_2 only (winter)- 7.25 SO_2 only (spring)- 11.06 SO_2/NO_2 (annual) - 7.60 SO_2/O_3 (annual) - 5.97	adjusted increase in asthma admissions for males and females 0-14 years of age per 10 µg/m³ increase (1-hr max) in single and two pollutant model for lag day 0 SO_2 only (annual)- 0.88 - 11.33 SO_2 only (winter)- 0.27 - 17.70 SO_2 only (spring)- 1.85 - 21.10 SO_2/NO_2 (annual) -0.41 - 15.30 SO_2/O_3 (annual) - 0.87 - 11.32	statistically significant increase in asthma admissions for children aged 0-14 years in single pollutant model on lag day 0 for all seasons, winter, and spring but not for summer or fall ; statistically significant associations for all children i0-14 years in two pollutant model with NO_2 and O_3 but not for PM_{10} on lag day 0; significant association for all age males but not females and those aged 0-4 years but not those 5-14 years using a single pollutant model and day 0 lag; no significant increase in asthma admissions in adjusted single pollutant model per 10 µg/m³ increase on lag day 1 and 2 or distributed lag days 0-2	⊕⊕◯◯ (low quality because no evaluation of $PM_{2.5}$ interactions and wide confidence intervals indicating a lack of sensitivity)

author	location	exposure monitoring	SO_2 concentration	study type (duration)	endpoint	co-pollutants	participants	ratio or risk	confidence interval	results	GRADE quality of evidence
(Schildcrout et al., 2006)	7 cities in the North America	daily averages from 2 to 9 central site monitoring stations in each city	daily average concentration Baltimore - 6.7 ppb (25.24 µg/m³) Boston - 5.8 ppb (25.24 µg/m³) Denver - 4.4 ppb (25.24 µg/m³) San Diego - 2.2 ppb (25.24 µg/m³) Seattle - 6.0 ppb (25.24 µg/m³) St. Louis - 7.4 ppb (25.24 µg/m³) Toronto - 2.5 ppb (25.24 µg/m³)	time-series (22 months)	asthma symptoms (type not specified) and inhaler use	association with PM_{10}, SO_2, O_3, CO, & NO_2	male and female asthmatic children 5-13 years of age 990 cases	change in odds ratio for asthma symptom prevalence or inhaler use per 100 ppb (26.6 µg/m³) increase in single or two pollutant models at various lag periods single pollutant (asthma symptoms) 3 day moving lag - 1.04 two pollutant (asthma symptoms) 2 day lag (SO_2/CO) - 1.10 3 day moving lag (SO_2/CO) - 1.05 2 day lag (SO_2/NO_2) - 1.09 3 day moving lag (SO_2/NO_2) - 1.04 two pollutant (inhaler use) 2 day lag (SO_2/CO) - 1.08 3 day moving lag (SO_2/CO) - 1.04 2 day lag (SO_2/NO_2) - 1.06	change in odds ratio for asthma symptom prevalence or inhaler use per 100 ppb (26.6 µg/m³) increase in single or two pollutant models at various lag periods single pollutant (asthma symptoms) 3 day moving lag - 1.00 - 1.08 two pollutant (asthma symptoms) 2 day lag (SO_2/CO) - 1.02 - 1.18 3 day moving lag (SO_2/CO) - 1.00 - 1.09 2 day lag (SO_2/NO_2) - 1.01 - 1.17 3 day moving lag (SO_2/NO_2) - 1.01 - 1.090 two pollutant (inhaler use) 2 day lag (SO_2/CO) - 1.03 - 1.13 3 day moving lag (SO_2/CO) - 1.00 - 1.08 2 day lag (SO_2/NO_2) - 1.01 - 1.11	weak statistically significant association with asthma symptoms in single pollutant model on 3 day moving sum lag period but not on lag days 0, 1, or 2; no associations with rescue inhaler use with single pollutant model on any lag day; significant association with asthma symptom in two pollutant model with CO on lag day 2 and the 3 day moving sum lag, but not on lag days 0 or 1; significant association with inhaler use in two pollutant model with NO_2 on lag day 2 and the 3 day moving sum lag, but not on lag days 0 or 1; no associations in two pollutant models with PM_{10} at any lag period	⊕⊕⊕◯ moderate quality,

author	location	exposure monitoring	SO_2 concentration	study type (duration)	endpoint	co-pollutants	participants	ratio or risk	confidence interval	results	GRADE quality of evidence
(Sinclair et al., 2010)	Atlanta, Georgia	hourly maximum concentrations at a single fixed monitoring location	average 1-hr daily maximum 25 month period warm months - 15.92 ppb (42.3 µg/m³) cold months - 24.31 ppb (64.7 µg/m³) 28 month period warm months - 13.82 ppb (36.8 µg/m³) cold months - 22.60 ppb (60.1 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 for respiratory tract infections over a 25 or 28 day period per 16.47 ppb (43.8 µg/m³) change in a single pollutant model at various lag times 25 month period LRT infection (lag 0-2 days) - 1.055 28 month period URT infection (lag 6-8 days) - 1.033	relative risk for respiratory tract infections over a 25 or 28 day period per 16.47 ppb (43.8 µg/m³) change in a single pollutant model at various lag times 25 month period LRT infection (lag 0-2 days) - 1.005 - 1.108 28 month period URT infection (lag 6-8 days) - 1.015 - 1.051	statistically significant association with outpatient visits for lower respiratory tract infection in the 25 month study in a single pollutant model at the 0-2 day lag period but not at the other 2 longer lag periods; statistically significant association with visits for upper respiratory tract infection in the 28 month study in a single pollutant model at the 6-8 day lag period but not at the other 2 shorter lag periods; statistically significant negative association for LRI in the 28 month study at a lag time of 0-2 days; no association with adult or childhood asthma regardless of study duration or lag; no association with visits for childhood asthma in either warm or cold seasons using single pollutant model	⊕○○○ (insufficient because of severe exposure bias)

author	location	exposure monitoring	SO_2 concentration	study type (duration)	endpoint	co-pollutants	participants	ratio or risk	confidence interval	results	GRADE quality of evidence
(Smargiassi et al., 2009)	Montreal, Canada	residential daily average and peak levels as well as 5 day averages using AERMOD dispersion modeling of the stack emissions from a local oil refinery	modeled concentration daily mean - 3.0 ppb (8.0 µg/m³) daily peak - 17.5 ppb (46.6 µg/m³) 5-day average - 3.0 ppb (8.0 µg/m³)	case-crossover (9 years)	hospitalization or emergency department visit for asthma	association with SO_2 only	male and female children 2 - 4 years of age 263 hospitalizations 1579 ED visits	adjusted odds ratio for asthma hospitalizations per IQR increase using a single pollutant model with various lag days hospital admissions daily mean (lag 0, IQR 4.3 ppb) - 1.14 daily peak (lag 0, IQR 31.2 ppb) - 1.42 ED visits daily peak (lag 0, IQR 31.2 ppb) - 1.10 daily mean (lag 1, IQR 4.3 ppb) - 1.05	adjusted odds ratio for asthma hospitalizations per IQR increase using a single pollutant model with various lag days hospital admissions daily mean (lag 0, IQR 4.3 ppb) - 1.00 - 1.30 daily peak (lag 0, IQR 31.2 ppb) - 1.10 - 1.82 ED visits daily peak (lag 0, IQR 31.2 ppb) - 1.00 - 1.22 daily mean (lag 1, IQR 4.3 ppb) - 1.00 - 1.12	statistically significant association with adjusted asthma hospital admissions using daily mean and daily peak levels on lag day 0 but not on lag day 1 or the 5-day average lag using a single pollutant model; significant association with asthma emergency department visits using daily peak on lag day 0 and daily mean on lag day 1; significant associations in crude admissions and ED visits for mean and peak exposures on lag day 0; no associations in crude hospital admissions or ED visits on mean or peak daily lag 1 or 5 day average models; associations restricted to those living to the east and southwest of the source and not those living	⊕○○○ (insufficient because of the small number of cases and the absence of two-pollutant modeling)

author	location	exposure monitoring	SO_2 concentration	study type (duration)	endpoint	co-pollutants	participants	ratio or risk	confidence interval	results	GRADE quality of evidence
(Strickland et al., 2010)	Atlanta, Georgia	population weighted hourly maximum concentrations at an unstated number of fixed monitoring location	mean 1-hr maximum overall - 10.8 ppb (28.7 µg/m³) warm season - 9.6 (25.5 µg/m³) cold season - 12.0 (31.9 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 for asthma per 11.5 ppb (30.6 µg/m³) in adjusted single pollutant model using a 3 day (0-2) moving average lag warm season - 1.030 rate ratio for ER visits relative to the first SO_2 exposure quintile (< 3.1 ppb) 3rd quintile (7.0 - <13 ppb) - 1.041 4th quintile (13 - <24.2 ppb) - 1.048	rate ratios for ER visits for asthma per 11.5 ppb (30.6 µg/m³) in adjusted single pollutant model using a 3 day (0-2) moving average lag warm season - 1.002 - 1.058 rate ratio for ER visits relative to the first SO_2 exposure quintile (< 3.1 ppb) 3rd quintile (7.0 - <13 ppb) - 1.007 - 1.077 4th quintile (13 - <24.2 ppb) - 1.010 - 1.087	statistically significant association in the overall base model in the warm season but not for all seasons or the cold season using a single pollutant model and a distributed lag periods of 1, 2, 3, 4, 5, 6, 7, and 8 days2 day moving average lag period; statistically significant association in single pollutant base model at the 3rd and 4th exposure quintiles but not at the 1st or 5th exposure quintiles where the exposures or lower (3.1 - <7 ppb) and higher (57.1 - ≤181 ppb); sensitivity analysis showed that alternative time-series and case-crossover models that used alternative approaches to control for weather interactions did not yield statistically significant increases in asthma visits	⊕○○○ (insufficient because of the number of monitoring sites not stated and no two pollutant modeling)

author	location	exposure monitoring	SO_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	three methods employed involving i) one hour maximum from a central monitor (five fixed monitoring sites available), ii) unweighted average from all monitoring sites, and iii) population-weighted average of spatially adjusted measurements from monitoring sites using inverse distance squaring	1-hr maximum central monitor - 13.9 ppb (37.0 µg/m³) unweighted average - 10.2 ppb (27.1 µg/m³) population weighted average - 9.6 ppb (25.5 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	change in rate ratio per 20 ppb (53.2 µg/m³) increase for a 3-day moving average lag in single pollutant model (warm season only) unweighted - 1.062 pop. weighted - 1.053	change in rate ratio per 20 ppb (53.2 µg/m³) increase for a 3-day moving average lag in single pollutant model (warm season only) unweighted - 1.014 - 1.111 pop. weighted - 1.0004 - 1.104	statistically significant association with emergency department visits by children with asthma using exposure unweighted and population weighted exposure measurement from central sites using a single pollutant model and a 3 day moving average lag; no associations observed for asthma visits using a exposure values from central site monitors	⊕⊕◯◯ (low quality because only single pollutant modeling only)
(Szyszkowicz, 2008a)	Edmonton, Alberta	mean daily concentration at an unnamed number of fixed monitoring locations	daily mean 2.6 ppb (6.9 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 from 0 to 80 years of age 62,563 visits	no change in relative risk percentage for asthma ED visits for males or females in either age group per 2. 3 ppb (6.1 µg/m³) IQR increase using a single pollutant model and a 0, 1, or 2 day lag period	no change in relative risk percentage for asthma ED visits for males or females in either age group per 2. 3 ppb (6.1 µg/m³) IQR increase using a single pollutant model and a 0, 1, or 2 day lag period	no statistically significant associations asthma ED visits in a single pollutant model at lag day o, 1, or 2 with a single pollutant model; no associations with asthma visits following stratification by sex (male and female or age group (< 10 yrs or ≥ 10 yrs), or season (all season, warm, and cold)	⊕◯◯◯ (insufficient because of the unstated number of monitoring sites and failure to perform two-pollutant modeling)

author	location	exposure monitoring	SO_2 concentration	study type (duration)	endpoint	co-pollutants	participants	ratio or risk	confidence interval	results	GRADE quality of evidence
(Tsai et al., 2006b)	Kaohsiung, Taiwan	daily average from six monitoring stations	daily mean concentration 9.49 ppb (25.24 µg/m³)	case-crossover (8 years)	asthma hospital admissions	association with PM_{10}, SO_2, O_3, CO, & NO_2	male and female 17,682 admissions	increase odds ratio per IQR of 5.79 ppb (15.40 µg/m³) in single and two-pollutant model using a cumulative 2 day lag single pollutant temp < 25 ˚C - 1.187 two pollutant (SO_2/CO) temp < 25 ˚C - 1.036	increase odds ratio per IQR of 5.79 ppb (15.40 µg/m³) in single and two-pollutant model using a cumulative 2 day lag single pollutant temp < 25 ˚C - 1.073 - 1.314 two pollutant (SO_2/CO) temp < 25 ˚C - 1.027 - 1.046	statistically significant positive association with asthma admission at temperatures below 25 ˚C using single pollutant model and a 2 day cumulative lag period; no associations using single pollutant model at temperatures ≥ 25 ˚C; significant positive association with admissions using a two pollutant model with CO at cold but not warm temperature greater than or equal to 25 ˚C; no positive associations at any temperature using two pollutant models with either PM_{10}, O_3, or NO_2; negative associations observed in two pollutant modeling with CO (≥ 25 ˚C) and NO_2 (< 25 ˚C)	⊕⊕◯◯ (low quality because no evaluation of $PM_{2.5}$ interactions)

author	location	exposure monitoring	SO_2 concentration	study type (duration)	endpoint	co-pollutants	participants	ratio or risk	confidence interval	results	GRADE quality of evidence
(Wiwatanadate and Liwsrisakun, 2011)	Chiang Mai, Thailand	mean daily concentration at a single fixed monitoring locations	daily mean 1.73 ppb (4.60 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	adjusted percentage change in peak expiratory flow rates in asthmatic children per 1 ppb (2.67 µg/m³) change in exposures using a single pollutant or two pollutant model on lag day 4 single pollutant model evening PEFR - -2.12 average PEFR - -1.75 daily change PEFR - 0.73 two-pollutant model (SO_2/O_3) average PEFR - -1.60	adjusted percentage change in peak expiratory flow rates in asthmatic children per 1 ppb (2.67 µg/m³) change in exposures using a single pollutant or two pollutant model on lag day 4 single pollutant model evening PEFR - -3.83 - -0.41 average PEFR - -3.22 - -0.28 daily change PEFR - -1.33 - -0.12 two-pollutant model (SO_2/O_3) average PEFR - -3.10 - -0.11	statistically significant negative association with measurements of the evening, average, daily change peak expiratory flow rate in asthmatic children using a single pollutant model and two pollutant model (SO_2/O_3) on lag day 4 but not the remaining six lag periods; no association seen with morning PEFR measurements on any lag day using a single pollutant model; no statistically significant associations with symptom reporting on any lag day	⊕○○○ (insufficient because of very serious risk of exposure bias)
(Yang et al., 2007)	Taipei, Taiwan	mean daily concentration at six fixed monitoring locations	daily mean 3.90 ppb (10.4 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 2.79 ppb (7.42 µg/m³) on warm days (≥ 25 °C) using a single pollutant model with a 3 day cumulative lag SO_2 only - 1.074	odds ratio for asthma admission per IQR of 2.79 ppb (7.42 µg/m³) on warm days (≥ 25 °C) using a single pollutant model with a 3 day cumulative lag SO_2 only - 1.113 - 1.247	statistically significant association with asthma hospital admissions on warm (≥ 25 °C) but not cold (< 25 °C) days using a single pollutant model with a 3 day cumulative lag; no positive associations observed in two pollutant models with PM_{10}, NO_2, CO, or O_3 on either warm or cold days with the 0-2 average lag, significant negative association seen with a two pollutant model with CO on cold days	⊕⊕⊕○ (moderate quality, no adjustment necessary but no $PM_{2.5}$)

author	location	exposure monitoring	SO_2 concentration	study type (duration)	endpoint	co-pollutants	participants	ratio or risk	confidence interval	results	GRADE quality of evidence
(Zhao et al., 2008b)	Taiyuan, China	weekly averages using indoor (classroom) and outdoor diffusion samplers placed at 10 schools	daily mean indoor schools - 264.8 µg/m³ outdoor schools - 712.8 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	odds ratio for asthmatic symptoms per 1 µg/m³ increase for nocturnal breathlessness in single pollutant model unadjusted multiple regression - indoor levels wheeze or whistling- 1.18 nocturnal breathlessness - 1.28 unadjusted hierarchical regression - indoor levels nocturnal breathlessness - 1.27 adjusted hierarchical regression - indoor levels wheeze or whistling- 1.55	odds ratio for asthmatic symptoms per 1 µg/m³ increase for nocturnal breathlessness in single pollutant model unadjusted multiple regression - indoor levels wheeze or whistling- 1.03 - 1.35 nocturnal breathlessness - 1.02 - 1.59 unadjusted hierarchical regression - indoor levels nocturnal breathlessness - 1.02 - 1.59 adjusted hierarchical regression - indoor levels wheeze or whistling- 1.06 - 2.27	statistically significant association with wheeze and nocturnal breathlessness in an unadjusted single pollutant model using indoor exposure measures and a multiple regression model; significant association with nocturnal breathlessness using an unadjusted single pollutant model, indoor levels and a hierarchical regression model, significant association with wheeze using a fully adjusted single pollutant model with indoor levels and a hierarchical regression model, no statistically significant association with cumulative asthma, daytime breathlessness, pet or pollen allergy, or respiratory infection using indoor or outdoor exposure levels and either regression model; no association with any symptom using outdoor levels and either the unadjusted multiple regression model or the unadjusted or adjusted hierarchical regression model	⊕○○○ (insufficient because the failure to include $PM_{2.5}$ and PM_{10} and the use of a cross-sectional design)

Acute Cardiovascular

author	location	exposure monitoring	SO_2 concentration	study type (duration)	endpoint	co-pollutants	participants	ratio or risk	confidence interval	results	GRADE quality of evidence
(Baccarelli et al., 2007)	Lombardia, Italy	hourly measurement averages from 53 fixed monitoring sites	hourly median autumn (Sept-Nov) - 6.0 µg/m³ winter (Dec-Feb) - 9.6 µg/m³ spring (Mar-May) - 4.7 µg/m³ summer (Jun-Aug) - 3.6 µg/m³	time-series (11 years)	blood coagulation (prothrombin time, activated partial thromboplastin time, fibrinogen, functional antithrombin, functional C protein, protein C antigen, functional protein S, or free protein S) parameters	association with SO_2, CO, O_3, & NO_2	males and females from 11 to 84 years of age 490 males 728 females	no change in any coagulation parameter using a single pollutant model with a lag of 0 hours or a moving average lag of 7 or 30 days	no change in any coagulation parameter using a single pollutant model with a lag of 0 hours or a moving average lag of 7 or 30 days	no statistically significant association with a change in prothrombin time, activated partial thromboplastin time, fibrinogen, functional antithrombin, functional C protein, protein C antigen, functional protein S, or free protein S using a single pollutant model at any lag time	⊕○○○ (insufficient because the failure to include $PM_{2.5}$ and PM_{10} and the use of single pollutant models only)
Baja (Baja et al., 2010)	Boston, MA	hourly means from six fixed monitoring sites	hourly mean during ECG - 5.2 ppb (13.8 µg/m³) 10-hr before ECG - 4.2 ppb (11.2 µg/m³)	longitudinal 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	no prolongation of the adjusted mean change in heart rate interval for diabetics, obese individuals, or never smokers per IQR 3 ppb (8.0 µg/m³) in a 4-hr single pollutant lag model	no prolongation of the adjusted mean change in heart rate interval for diabetics, obese individuals, or never smokers per IQR 3 ppb (8.0 µg/m³) in a 4-hr single pollutant lag model	no statistically significant association with diabetics, obese individuals, & never smokers in an adjusted single pollutant 4-hr lag model or 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 a total genetic susceptibility score that considered genotypes for 5 enzyme polymorphisms	⊕⊕○○ (low quality because no evaluation of PM_{10} interactions)

author	location	exposure monitoring	SO_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 Barcelona - 15.5 µg/m³ Bolbao - 18.6 µg/m³ Cartegena - 27.1 µg/m³ Casellon - 7.7 µg/m³ Gijon - 29.4 µg/m³ Granada - 19.1 µg/m³ Huelva - 11.9 µg/m³ Madrid - 21.8 µg/m³ Ovieda - 40.9 µg/m³ Pamplona - 7.6 µg/m³ Seville - 9.6 µg/m³ Valcencia 16.6 µg/m³ Vigo - 9.3 µg/m³ Zaragoza - 9.3 µg/m³	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 reveled that the association observed in a single pollutant model for SO_2 was not robust to the inclusion of either CO or NO_2, but remained significant with both O_3 and particulates (PM_{10}, TSP, or BS) (data presented graphically) pooled (fixed effect) percent increase in cardiovascular hospital admissions per IQR 10 µg/m³ in single and two pollutant model for average lag 01 cardiovascular disease SO_2 only ≈ 1.018 SO_2/O_3 only ≈ 1.018 SO_2/particulate ≈ 1.010	pooled relative risk for combined cardiovascular and cardiac disease per 10 µg/m³ increase in a two pollutant model reveled that the association observed in a single pollutant model for SO_2 was not robust to the inclusion of either CO or NO_2, but remained significant with both O_3 and particulates (PM_{10}, TSP, or BS) (data presented graphically) pooled (fixed effect) percent increase in cardiovascular hospital admissions per IQR 10 µg/m³ in single and two pollutant model for average lag 01 cardiovascular disease SO_2 only ≈ 1.006 -1.030 SO_2/O_3 only ≈ 1.007 - 1.035 SO_2/particulate ≈ 1.005 - 1.030	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 ; statistically significant association with cardiovascular disease admissions on lag day 0 but not day 1, 2, or 3; statistically significant association with heart disease admissions on lag days 0 and 1 but not days 2 & 3;	⊕⊕◯◯ (low quality because of bias from the use of an unstated number of monitoring sites and poor description of methodological approach)

author	location	exposure monitoring	SO_2 concentration	study type (duration)	endpoint	co-pollutants	participants	ratio or risk	confidence interval	results	GRADE quality of evidence
(Berglind et al., 2009)	Augsburg, Germany Barcelona, Spain Helsinki, Finland Rome, Italy Stockholm, Sweden	daily average concentration in five European cites using an unstated number of fixed monitoring locations	daily median concentration Augsburg - 4.22 µg/m³ Barcelona - 11.00 µg/m³ Helsinki - 3.13 µg/m³ Rome - 3.98 µg/m³ Stockholm - 2.61 µg/m³	cohort study (up to 240 months)	mortality amongst survivors of myocardial infarction	association with PM_{10}, CO, O_3, SO_2, & NO_2	male & female 25,006 cohort 8,555 cases	pooled random effects change in the percentage of non-traumatic deaths per 2 µg/m³ change using a single pollutant model day lag 0 to 14 - 8.06	pooled random effects change in the percentage of non-traumatic deaths per 2 µg/m³ change using a single pollutant model day lag 0 to 14 4.38 - 11.90	statistically significant association with daily non-traumatic deaths with a 15 day lag period but not a 2-day or 5 day lag period when measurements pooled for 4 of the five cites examined; no association with deaths due to cardiovascular disease; statistical association with the group aged 35-65 yrs, but not in those 65-74, > 75 years, no association with groups followed up for a year longer or a year less	⊕⊕◯◯ (low quality because single pollutant modeling and high collinearity with other pollutants)
(Bruske et al., 2011)	Augsburg, Germany	daily concentration at a single fixed monitoring site	daily mean 3.0 µg/m³	cohort study (10 months)	phospholipase A_2 in myocardial infarction survivors	association with PM_{10}, $PM_{2.5}$, particle number concentration (PNC), SO_2, O_3, CO, NO, & NO_2	male and female 200 cases	no significant percentage change in plasma phospholipase A2 per 1.2 µg/m³ SO_2 increase in a single pollutant model unadjusted for confounders	no significant percentage change in plasma phospholipase A_2 per 1.2 µg/m³ SO_2 increase in a single pollutant model unadjusted for confounders	no statistically significant association on any lag day using an unadjusted single pollutant model; no statistically significant associations using a distributed lag model	⊕⊕◯◯ (low quality because single pollutant modeling and high collinearity with other pollutants)

author	location	exposure monitoring	SO_2 concentration	study type (duration)	endpoint	co-pollutants	participants	ratio or risk	confidence interval	results	GRADE quality of evidence
(Cakmak et al., 2006a)	10 Canadian cites	1 hour maximum levels from an unstated number of fixed monitoring stations in each city	hour maximum average Calgary - 3.5 ppb (9.3 µg/m³) Edmonton - 2.8 ppb (7.4 µg/m³) Halifax - 10.2 ppb (27.1 µg/m³) London - 3.3 ppb (8.8 µg/m³) Ottawa - 3.5 ppb (9.3 µg/m³) Saint John - 7.4 ppb (19.7 µg/m³) Toronto - 4.5 ppb (12.0 µg/m³) Vancouver - 3.9 ppb (10.4 µg/m³) Windsor - 7.7 ppb (20.5 µg/m³) Winnipeg - 8.0 ppb (21.3 µg/m³)	time-series (8 years)	hospital admissions for cardiac disease (congestive heart failure, ischemic heart disease, and dysrhythmia)	association with SO_2, O_3, CO, & NO_2	males and females admission rates ranged from 1.9-48 patients/day for the 10 cities	pooled (random effects) percent increase in cardiac disease hospitalizations per 4.6 ppb (12.2 µg/m³) increase using a single or two pollutant model single pollutant model with different lag times for each city males - 1.1 2nd education quartile - 2.9 2nd income quartile - 1.6 4th income quartile - 1.5	pooled (random effects) percent increase in cardiac disease hospitalizations per 4.6 ppb (12.2 µg/m³) increase using a single or two pollutant model single pollutant model with different lag times for each city males - 0.3 - 1.9 2nd education quartile - 0.1 - 5.7 2nd income quartile - 0.5 - 2.7 4th income quartile - 0.2 - 2.8	no statistically significant associations with cardiac disease admissions using a single or a multi-pollutant model; statistically significant association with hospitalizations for cardiac disease males but not females using a single pollutant multi-city model; significant association with e 2nd lowest SES quartile but the lowest or the two highest quartiles using a single pollutant model; associations with the 2nd ($21,309-$28,161) and 4th (>$35,905) income quartiles but not the 1st (<$21,309) or the 4th ($28,161-$35,905) quartiles	⊕⊕◯◯ (low quality because of lag selection bias and the failure to evaluate PM_{10} and $PM_{2.5}$ collinearities)
(Chang et al., 2005)	Taipei, Taiwan	daily average from six fixed monitoring site	daily mean concentration 4.32 ppb (11.5 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 2.75 ppb (7.31 µg/m³) at two temperature limits in a two pollutant model at an average lag of 3 days (lag02) temp ≥ 20° C SO_2/PM_{10} - 0.897 SO_2/NO_2 - 0.862 SO_2/CO - 0.903 SO_2/O_3 - 0.953 temp < 20° C SO_2/PM_{10} - 0.824 SO_2/NO_2 - 0.922	odds ratio for cardiovascular disease admissions per IQR of 2.75 ppb (7.31 µg/m³) at two temperature limits in a two pollutant model at an average lag of 3 days (lag02) temp ≥ 20° C SO_2/PM_{10} - 0.868 - 0.926 SO_2/NO_2 - 0.798 - 0.854 SO_2/CO - 0.876 - 0.931 SO_2/O_3 - 0.926 - 0.981 temp < 20° C SO_2/PM_{10} - 0.771 - 0.880 SO_2/NO_2 - 0.865 - 0.984	statistically significant negative association with hospital admissions for cardiovascular disease in a two pollutant model with PM_{10}, NO_2, CO and O_3 at high temperatures greater than or equal to 20 °C and with PM_{10} and NO_2 at temperatures < 20 °C; no significant associations at temperatures < 20° C for CO and O_3 co-pollutants	⊕◯◯◯ (insufficient because of negative associations and the failure to evaluate $PM_{2.5}$ interactions)

author	location	exposure monitoring	SO_2 concentration	study type (duration)	endpoint	co-pollutants	participants	ratio or risk	confidence interval	results	GRADE quality of evidence
(Cheng et al., 2009)	Kaohsiung, Taiwan	mean daily concentration at six fixed monitoring locations	daily mean 9.33 ppb (24.82 µg/m³)	case-crossover (132 months)	hospitalization for myocardial infarction	association with PM_{10}, SO_2, O_3, CO, & NO_2	male & female cases 9.349	odds ratio per IQR of 5.16 ppb (13.72 µg/m³) in single and two-pollutant model single pollutant temp < 25 ˚C - 1.09 two pollutant (SO_2/O_3) temp ≥ 25 ˚C - 1.05 temp < 25 ˚C - 1.09	odds ratio per IQR of 5.16 ppb (13.72 µg/m³) in single and two-pollutant model single pollutant temp < 25 ˚C - 1.01 - 1.19 two pollutant (SO_2/O_3) temp ≥ 25 ˚C - 1.00 - 1.11 temp < 25 ˚C - 1.01 - 1.19	statistically significant associations observed in single pollutant model at ambient temperatures < 25 ˚C and in a two-pollutant model with O_3 at temperatures < 25 ˚C and ≥ 25 ˚C; not significant associations in two pollutant models with PM_{10}, NO_2, or CO	⊕⊕○○ (low quality because no evaluation of $PM_{2.5}$ interactions)
(Filho et al., 2008)	Sao Paulo, Brazil	daily average from thirteen fixed monitoring sites	daily average 13.8 µg/m³	time-series (31 months)	emergency room visits for cardiovascular disease (ischemic heart disease and hypertension) in type 2 diabetics and non-diabetics	association with PM_{10}, SO_2, O_3, CO, & NO_2	males and females (daily rates) diabetics - 0.6 visits/day non-diabetics - 16.8 visits/day	percent increase in cardiovascular ER visits per IQR 8.0 µg/m³ for diabetics and non-diabetics in single pollutant model at various lag periods (data depicted graphically) diabetics lag day 0 ≈ 20 avg lag 01 ≈ 25 avg lag 02 ≈ 25 non-diabetics lag day 0 ≈ 7 avg lag 01 ≈ 7 avg lag 02 ≈ 6 avg lag 03 ≈ 7	percent increase in cardiovascular ER visits per IQR 8.0 µg/m³ for diabetics and non-diabetics in single pollutant model at various lag periods (data depicted graphically) diabetics lag day 0 ≈ 4 - 37 avg lag 01 ≈ 5 - 44 avg lag 02 ≈ 2 - 47 non-diabetics lag day 0 ≈ 3 - 11 avg lag 01 ≈ 3 - 10 avg lag 02 ≈ 2 - 10 avg lag 03 ≈ 2 - 11	statistically significant association with cardiovascular emergency room visits for diabetics on lag day 0, 01, and 02 and non-diabetics on lag day 0, 01, 02 and 03, no statistically significant association on lag day 2 & cumulative lag 03 for diabetics and lag day 1 and cumulative lag 01 for non-diabetics	⊕○○○ (insufficient because no two-pollutant modeling and the failure to consider PM_{10} in two pollutant models)

author	location	exposure monitoring	SO_2 concentration	study type (duration)	endpoint	co-pollutants	participants	ratio or risk	confidence interval	results	GRADE quality of evidence
(Fung et al., 2006)	Windsor, Ontario	daily mean of the highest value from four fixed monitoring sites	daily mean of the highest hourly concentration 27.5 ppb (73.2 µg/m³)	time-series (68 months)	hospitalizations for cardiovascular disease (congestive heart disease, ischemic heart disease, & dysrhythmia)	association with PM_{10}, SO_2, coefficient of haze (COH), total reduced sulfur (TRS) O_3, CO, & NO_2	males and females < 65 years - 3273 patients ≥ 65 years - 8359 patients	percent change in risk estimates for cardiovascular admissions per IQR of 19.3 ppb (51.3 µg/m³) with individuals ≥ 65 years of age using a single pollutant models on different lag days lag day 0 - 2.6 lag day 01 - 4.0 lag day 02 - 5.6	percent change in risk estimates for cardiovascular admissions per IQR of 19.3 ppb (51.3 µg/m³) with individuals ≥ 65 years of age using a single pollutant models on different lag days lag day 0 - 0.0 - 5.3 lag day 01 - 0.6 - 7.6 lag day 02 - 1.5 - 9.9	statistically significant association with cardiovascular admissions in those ≥ 65 years of age using a single pollutant model with all three lag periods day 0, day 01, & day 02); no association with those in the < 65 age group for any lag period; lag day 0, 1, or 2, associations remained significant with multi-pollutant model with PM_{10} but the relative risk values were not provided	⊕○○○ (insufficient because of the failure to examine PM2.5 interactions and the absence of two-pollutant modeling)
(Goldberg et al., 2008)	Montreal, Quebec	pooled mean daily concentration from three fixed monitoring locations	daily mean 11.8 µg/m³	repeated measures 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	unadjusted and adjusted associations with the mean differences per IQR increase of 8.6 µg/m³ using a single pollutant model oxygen saturation unadjusted lag day 1 - -0.129 adjusted lag day 1 - -0.191 unadjusted lag day 02 - -0.125 pulse rate unadjusted lag day 1 - 0.449 adjusted lag day 1 - 0.393 unadjusted lag day 02 - 0.548	unadjusted and adjusted associations with the mean differences per IQR increase of 8.6 µg/m³ using a single pollutant model oxygen saturation unadjusted lag day 1 - -0.198 - -0.060 adjusted lag day 1 - -0.163 - -0.019 unadjusted lag day 02 - -0.225 - -0.024 pulse rate unadjusted lag day 1 - 0.128 - 0.770 adjusted lag day 1 - 0.056 - 0.730 unadjusted lag day 02 - 0.063 - 1.032	statistically significant negative association with blood oxygen saturation on lag day mean difference change only observed in the unadjusted model for lag day 1 using an adjusted model; statistically significant positive association with pulse rate on lag day 1 using an adjusted model; no associations on lag days 0 or the 02 using the adjusted model	⊕○○○ (insufficient because of the failure to examine PM_{10} interactions and the small sample size)

author	location	exposure monitoring	SO_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 four central monitors with independent determination of measurement error (co-located instrument) and spatial variability (semi-variograms)	mean 1-hr max urban 11.4 ppb (30.3 µg/m³) rural 6.32 ppb (16.8 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, SO4, NH4, EC, & OC	male & female 166,950 visits	risk ratio for cardiovascular emergency department visits per 1 ppm (2.66 mg/m³) increase following spatial error adjustment of the base case assessment 1-hour max SO_2 - 1.0045	risk ratio for cardiovascular emergency department visits per 1 ppm (2.66 mg/m³) increase following spatial error adjustment of the base case assessment 1-hour max SO_2 - 1.0023 - 1.0065	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 and absence of two pollutant modeling)
(Guo et al., 2009)	Beijing, China	pooled mean daily concentration from eight fixed monitoring locations	daily mean 49.32 µg/m³	case-crossover (19 months)	emergency room visits for cardiovascular disease	differential effects of $PM_{2.5}$, SO_2, & NO_2	male & female cases 8,377	odds ratio for hospitalization per 10 µg/m³ increase using single and two pollutant models single pollutant lag day 0 - 1.014 lag day 1 - 1.012 lag day 2 - 1.011	odds ratio for hospitalization per 10 µg/m³ increase using single and two pollutant models single pollutant lag day 0 - 1.004 - 1.024 lag day 1 - 1.003 - 1.022 lag day 2 - 1.002 - 1.021	statistically significant association with cardiovascular emergency room visits using a single pollutant model with a lag of 0, 1, or days, but not on lag day 3; no associations with ER visits using two pollutant models with $PM_{2.5}$ or NO_2 on lag day 0	⊕○○○ (insufficient because of exposure misclassification bias from small number of cases, pooling of exposure data, and short duration)

author	location	exposure monitoring	SO_2 concentration	study type (duration)	endpoint	co-pollutants	participants	ratio or risk	confidence interval	results	GRADE quality of evidence
(Guo et al., 2010a)	Tianjin, China	mean daily concentration from an unstated number of fixed monitoring sites in six different districts around the city	daily mean 68 µg/m³	time-series and case-crossover (36 months)	cardiovascular mortality	association with PM_{10}, SO_2, & NO_2	male & female cases 32,387	no significant association with cardiovascular mortality in either the case-crossover (risk ratio) or time-series (odds ratio) analysis per 10 µg/m³ change using a single pollutant model on lag day 0	no significant association with cardiovascular mortality in either the case-crossover (risk ratio) or time-series (odds ratio) analysis per 10 µg/m³ change using a single pollutant model on lag day 0	no statistically significant association with cardiovascular mortality in either the time-series and case-crossover studies at lag day 0; the results from the 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; the two modeling approaches were evaluated when the degrees of freedom allowed in the time-series study were allowed to range from 6 to 9 and the strata length in case-crossover study were allowed to range from 14 to 28 months	⊕○○○ (insufficient because of number of sites not stated and no two-pollutant modeling)
(Hosseinpoor et al., 2005)	Tehran, Iran	daily average concentration from a single fixed monitoring sites	daily mean 73.74 µg/m³	time-series (5 year)	hospital admissions for angina pectoris	association with PM_{10}, SO_2, O_3, CO, & NO_2	males and female hospitalization rate 23.48 admissions/day	no relationship with angina admissions per 10 µg/m³ increase using single pollutant model on lad day 1	no relationship with angina admissions per 10 µg/m³ increase using single pollutant model on lad day 1	no statistically significant association with angina admissions in single pollutant model on lag day 1	⊕○○○ (insufficient because of the failure to examine $PM_{2.5}$ interactions and the exposure misclassification)

author	location	exposure monitoring	SO_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 4.36 ppb (11.60 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	no positive relationships with myocardial infarction admissions in single or two pollutant models with PM_{10}, NO_2, O_3, or CO with an IQR increase of 2.69 ppb (7.16 µg/m³ NO_2) at temperatures ≥ 23 ˚C or < 23 ˚C on lag day 0 plus the previous two days; some negative associations observed with two-pollutant models	no positive relationships with myocardial infarction admissions in single or two pollutant models with PM_{10}, NO_2, O_3, or CO with an IQR increase of 2.69 ppb (7.16 µg/m³ NO_2) at temperatures ≥ 23 ˚C or < 23 ˚C; some negative associations observed with two-pollutant models	no statistically significant positive change in the odds ratio for myocardial infarction in either of two temperature groups (≥ 23 ˚C or < 23 ˚C) using single or two -pollutant models with PM_{10}, NO_2, O_3, or CO; statistically significant negative associations observed with two-pollutant modeling using PM_{10}, NO_2, or CO	⊕○○○ (insufficient because of the failure to examine $PM_{2.5}$ interactions and imprecision indicated by the negative associations)
(Ito et al., 2011)	five boroughs of New York City, New York	mean daily concentration at an unstated number of fixed monitoring locations within five boroughs	daily mean 7.4 ppb (19.7 µg/m³)	time-series (84 months)	cardiovascular hospitalization (hypertensive disease, myocardial infarction, ischemic heart disease, dysrhythmia, heart failure, & stroke) and mortality	association with $PM_{2\cdot5}$, $PM_{2\cdot5}$ trace metals, SO_2, CO, & NO_2	male & female > 40 years of age CVD mortality - 59.8 cases/day CVD hospitalizations - 281.3 cases/day	percent excess risk for hospitalization per IQR of 6.6 ppb (17.6 µg/m³) in a single pollutant model (values estimated from graph) all year - ≈ 2.3 warm season - ≈ 2.4 cold season - ≈ 2.2	percent excess risk for hospitalization per IQR of 6.6 ppb (17.6 µg/m³) in a single pollutant model (values estimated from graph) all year ≈ 1.8 - 2.8 warm season ≈ 1.6 - 3.2 cold season - ≈ 1.1 - 3.3	statistically significant association for hospitalization on lag day 0, but not lag day 1, 2, or 3, for all seasons, warm season, & cold season in single pollutant model; negative association observed for same day (0 lag) cardiovascular mortality but not on lag days 1, 2, and 3	⊕○○○ (insufficient because the number of monitoring sites not stated and the failure to evaluate PM_{10} interactions)

author	location	exposure monitoring	SO_2 concentration	study type (duration)	endpoint	co-pollutants	participants	ratio or risk	confidence interval	results	GRADE quality of evidence
(Jalaludin et al., 2006)	Sydney, Australia	daily averages from 14 fixed monitoring sites	daily mean concentration 1.07 ppb (2.85 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 2.2 ppb (5.9 µg/m³) in single and two-pollutant models cardiovascular total (lag day 0) SO_2 only - 1.33 SO_2/O_3 ≈ 2.1 (depicted graphically) cardiac disease (lag day 0) SO_2 only - 1.62 ischemic heart disease (lag day 2) SO_2 only - 1.97	percent change in total cardiovascular emergency department visits per IQR 2.2 ppb (5.9 µg/m³) in single and two-pollutant models cardiovascular total (lag day 0) SO_2 only - 0.24 - 2.43 SO_2/O_3 ≈ 0.04 - 2.7 (depicted graphically) cardiac disease (lag day 0) SO_2 only - 0.33 -2.93 ischemic heart disease (lag day 2) SO_2 only - 0.07 - 3.91	statistically significant association with total cardiovascular ED visits on lag day 0 in single and two-pollutant models with O3, but not with PM_{10}, PM2.5, CO, or NO_2; statistically significant association with cardiac disease on lag day 0 and ischemic heart disease on lag day 2 in single pollutant model but not for stroke on any lag day: statistically significant positive association with all total cardiovascular, cardiac disease, and ischemic heart disease ED visits on lag day 0 for cool period but not warm periods, no statistically significant association with stroke visits for either season	⊕○○○ (insufficient because of publication, selection, and lag bias)
(Lee et al., 2007a)	Kaohsiung, Taiwan	mean daily concentration at six fixed monitoring locations	daily mean 9.32 ppb (24.79 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 5.53 ppb (14.71 µg/m³) in single and two pollutant models at 02 day lag single pollutant model temp < 25 ˚C - 1.15 two pollutant model (SO_2/O_3) temp < 25 ˚C - 1.16	odds ratio per IQR 5.53 ppb (14.71 µg/m³) in single and two pollutant models at 02 day lag single pollutant model temp < 25 ˚C - 1.03 - 1.29 two pollutant model (SO_2/O_3) temp < 25 ˚C - 1.04 - 1.31	statistically significant association with admissions for congestive heart failure on cold but not warm says using a single pollutant model with a lag of 02 days, statistically significant association with admissions using a two pollutant model with O_3 on cold days but not warm days, no statistically significant association on warm or cold days using a two pollutant models with PM_{10}, NO_2, or CO	⊕⊕○○ (low quality because of the failure to evaluate $PM_{2.5}$ interactions)

author	location	exposure monitoring	SO_2 concentration	study type (duration)	endpoint	co-pollutants	participants	ratio or risk	confidence interval	results	GRADE quality of evidence
(Milojevic et al., 2014)	England and Wales	daily averages from the nearest of 71 fixed monitoring sites	daily median 3.1 µg/m³	case-crossover (7 years)	hospital admissions and mortality for cardiovascular disease, myocardial infarction, stroke, ischemic heart disease chronic ischemic heart disease, arrhythmias, atrial fibrillation, pulmonary embolism, heart failure, and atrioventricular conduction disorder	association with $PM_{2.5}$, PM_{10}, SO_2, O_3, CO, & NO_2	males and females 380,743 admissions	percent increase in admissions for myocardial infarctions without an elevation in ST segment (non-STEMI) in the EEG per 10.4 µg/m³ increase using a single pollutant model and a 0-4 day distributed lag non-STEMI - 2.3	percent increase in admissions for myocardial infarctions without an elevation in ST segment (non-STEMI) in the EEG per 10.4 µg/m³ increase using a single pollutant model and a 0-4 day distributed lag non-STEMI - 0.0 - 4.7	statistically significant increase non-STEMI myocardial infarction admissions in single pollutant model using a 5 day distributed lag period, no association with all myocardial infarctions or STEMI-related myocardial infarction admissions in a single pollutant model; no statistically significant positive increase in risk for admission or mortality from cardiovascular disease, myocardial infarction, stroke, ischemic heart disease chronic ischemic heart disease, arrhythmias, atrial fibrillation, pulmonary embolism, heart failure, or atrioventricular conduction disorder	⊕○○○ (insufficient because the high likelihood of exposure misclassification and absence of two-pollutant modeling)

author	location	exposure monitoring	SO_2 concentration	study type (duration)	endpoint	co-pollutants	participants	ratio or risk	confidence interval	results	GRADE quality of evidence
(Min et al., 2008b)	Tae-in, Korea	hourly average from a single fixed monitoring site	daily mean 6 ppb (16 µg/m³)	cross-sectional study (1 year)	heart rate variability using heart rate in the N-N interval (SDDN), low frequency heart rate modulation (LF), & high frequency heart rate modulation (HF)	association with PM_{10}, SO_2, & NO_2	male & female 1349 subjects	percentage change in heart rate variability per 7 ppb (18.6 µg/m³) change in single pollutant model at various lag times; 0-6 hr lag N-N intervals (SDDN) -3.71 low frequency modulation -6.90 0-9 hr lag N-N intervals (SDDN) -5.49 low frequency modulation -11.60 0-12 hr lag N-N intervals (SDDN) -6.95 low frequency modulation -16.21 0-24 hr lag N-N intervals (SDDN) -5.40 low frequency modulation -16.19	percentage change in heart rate variability per 7 ppb (18.6 µg/m³) change in single pollutant model at various lag times; 0-6 hr lag N-N intervals (SDDN) -6.90 - -0.42 low frequency modulation -13.89 - -0.66 0-9 hr lag N-N intervals (SDDN) -9.83 - -0.94 low frequency modulation -20.74 - -1.42 0-12 hr lag N-N intervals (SDDN) -11.91 - -1.72 low frequency modulation -26.19 - -4.87 0-24 hr lag N-N intervals (SDDN) -10.55 - -0.05 low frequency modulation -26.39 - -4.58	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 the exposure misclassification from the use of a single site and the failure to examine $PM_{2.5}$ interactions)

author	location	exposure monitoring	SO_2 concentration	study type (duration)	endpoint	co-pollutants	participants	ratio or risk	confidence interval	results	GRADE quality of evidence
(Rich et al., 2005)	Boston, MA	hourly and daily average from six fixed monitoring sites	mean concentration hourly - 4.3 ppb (11.4 µg/m³) daily - 4.8 ppb (12.8 µg/m³)	case-crossover (4.5 years)	ventricular arrhythmias (tachycardia or fibrillation) in patients with a cardiac pacemaker	association with $PM_{2.5}$, BC, SO_2, O_3, CO, & NO_2	males and females 203 patients	increase in odds ratio for ventricular arrhythmia for those with a recent event per IQR of 0.51 ppb (1.36 µg/m³) in a single pollutant model and moving average lag period of 0-23 hours recent event - 1.20	increase in odds ratio for ventricular arrhythmia for those with a recent event per IQR of 0.51 ppb (1.36 µg/m³) in a single pollutant model and moving average lag period of 0-23 hours recent event - 1.01 - 1.44	statistically significant association on odds ratio for ventricular arrhythmia in those having a recent event (within 72 hrs) but not in those with no recent event using a single pollutant model and a 24 hour moving average lag period; no increase in odds ratio per IQR of 0.49-0.56 ppb (1.30-1.49 µg/m³) in single pollutant model and moving lag periods of 0-2, 0-6, 0-23, or 0-47 hours; two pollutant modeling apparently performed but the results not provided	⊕○○○ (insufficient because of publication bias, small number of cases, and the failure to examine PM_{10} interactions)
(Rich et al., 2010)	New Jersey	daily average from fourteen 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 increase in relative risk per IQR increase of 4.1 ppb (10.9 µg/m³) in a single or two pollutant model with a lag of 0 days	no increase in relative risk per IQR increase of 4.1 ppb (10.9 µg/m³) in a single or two pollutant model with a lag of 0 days	no statistically significant association with hospital admissions for transmural infarctions on lag day 0 with single or two pollutant model with $PM_{2.5}$	⊕○○○ (insufficient because the failure to include PM_{10} in the analysis)

author	location	exposure monitoring	SO_2 concentration	study type (duration)	endpoint	co-pollutants	participants	ratio or risk	confidence interval	results	GRADE quality of evidence
(Rosenlund et al., 2006)	Stockholm, Sweden	determination of geo-coded residential levels using dispersion model that included emission estimates of oil consumption for home heating and sulfur content then linear back extrapolation of levels to earlier periods of life	30 year median concentration cases - 25.5 µg/m³ controls - 24.6 µg/m³	case control (30 years)	myocardial infarction (all cases, fatal, non-fatal, in-hospital, and out-of-hospital)	association with PM_{10}, SO_2, CO & NO_2	males and females 1397 cases 1870 controls	no change in adjusted odds ratio for all cases, fatal, non-fatal, in-hospital, or out-of-hospital myocardial infarction per 40 µg/m³ (5-95% range) increment using a single pollutant model for indoor exposures	no change in adjusted odds ratio for all cases, fatal, non-fatal, in-hospital, or out-of-hospital myocardial infarction per 40 µg/m³ (5-95% range) increment using a single pollutant model for indoor exposures	no statistically significant association with fatal or non-fatal myocardial infarction occurring either inside or outside the hospital	⊕○○○ (insufficient because of failure to perform two-pollutant modeling and the failure to examine $PM_{2.5}$ interactions)
(Santos et al., 2008)	Sao Paulo, Brazil	mean daily concentration at seven fixed monitoring locations	daily mean 15.05 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	no increase in percentage of arrhythmia emergency room visits per IQR of 9.3 µg/m³ in single pollutant model on lag day 0, 1, 2, 3, 4, 5, or 6	no increase in percentage of arrhythmia emergency room visits per IQR of 9.3 µg/m³ in single pollutant model on lag day 0, 1, 2, 3, 4, 5, or 6	no statistically significant association with emergency room visits for cardiac arrhythmia in a single pollutant model on any of 7 lag days	⊕○○○ (insufficient because of the small number of cases and the absence of two-pollutant modeling)

author	location	exposure monitoring	SO_2 concentration	study type (duration)	endpoint	co-pollutants	participants	ratio or risk	confidence interval	results	GRADE quality of evidence
(Schwartz et al., 2005)	Cambridge, MA	daily measurement from a single fixed site	daily mean concentration 20 ppb (53.2 µg/m³)	panel study (28 weeks)	heart rate variability including standard deviation of normal to normal heart beat intervals (SDNN), percentage of normal to normal intervals differing by > 50 msec (pNN50), root mean square between successive RR intervals (rMSSD), and high frequency to low frequency ratio (LFHFR) using 30-min electrocardiograms	association with $PM_{2.5}$, BC, secondary sulfate particles, O_3, CO, SO_2, & NO_2	males and females aged 61-89 years 28 subjects	no association with the percentage change in any of the four heart rate measurements per IQR of 0.523 ppm (1.39 mg/m³) in single pollutant model at a lag of 0-1 or 0-24 hours	no association with the percentage change in any of the four heart rate measurements per IQR of 0.523 ppm (1.39 mg/m³) in single pollutant model at a lag of 0-1 or 0-24 hours	no statistically significant association with any measure of heart rate variability in elderly subjects	⊕○○○ (insufficient because of the exposure misclassification from the use of a single site and the failure to examine PM_{10} interactions)
(Silverman et al., 2010)	New York, New York	pooled mean daily concentration from 15 fixed monitoring locations	daily mean annual - 6.3 ppb (16.8 µg/m³) warm season - 4.2 ppb (11.2 µg/m³) cold season - 9.3 ppb (24.7 µg/m³)	time-series and case-crossover (60 months)	cardiac arrest (out of hospital)	differential effects of $PM_{2.5}$, SO_2, O_3, CO & NO_2	males and females in three age groups 8,216 cases	no change in annual, warm season, or cold season relative risk for cardiac arrest for an IQR increase of 6 ppb (16.0 µg/m³) in a single pollutant model a 2 day average lag	no change in annual, warm season, or cold season relative risk for cardiac arrest for an IQR increase of 6 ppb (16.0 µg/m³) in a single pollutant model a 2 day average lag	no significant associations for yearly, cold season, or warm season cardiac arrests using a single pollutant model with a time-series design	⊕○○○ (insufficient because of single pollutant modeling and no examination of PM_{10})

author	location	exposure monitoring	SO_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 2.8 ppb (7.4 µg/m³)	time-series (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	absolute change serum biomarkers per IQR of 1.6 ppb (4.3 µg/m³) in multi-pollutant models serum fibrinogen concentration (mg/dL) men single pollutant lag day 4 - -5.5 lag day 5 - -3.9 lag day 0-6 avg - -7.1 men two pollutant model SO_2/O_3 lag day 4 - -5.1 white blood cell count men single pollutant lag day 6 - -115 lag day 7 - -151	absolute change serum biomarkers per IQR of 1.6 ppb (4.3 µg/m³) in multi-pollutant models serum fibrinogen concentration (mg/dL) men single pollutant lag day 4 - -9.1 - -2.0 lag day 5 - -7.4 - -0.5 lag day 0-6 avg - -12.3 - -2.0 men two pollutant model SO_2/O_3 lag day 4 - -9.5 - -0.7 white blood cell count men single pollutant lag day 6 - -222 - -8 lag day 7 - -258 - -45	statistically significant decrease in fibrinogen in males using a single pollutant model with a lag of 4 or 5 days or average one week lag but no association with the remaining lag periods; significant association with decreased white blood cell count with males in a single pollutant model on lag days 6 and 7 but not with the remaining 7 lag periods; no association with any biomarker changes in females using single or multi-pollutant models for any lag period; significant decrease in fibrinogen in males using a two pollutant model with O_3 but not with PM_{10},, NO_2, or CO on lag day 4; no association with decreased fibrinogen using three or four pollutant models with PM_{10},, NO_2, O_3, or CO on lag day 4	⊕⊕◯◯ (low quality because of the failure to examine $PM_{2.5}$ interactions)

author	location	exposure monitoring	SO_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 11 fixed monitoring sites	hourly mean Montreal - 4.8 ppb (12.8 µg/m³) Ottawa - 3.9 (10.4 µg/m³) Edmonton - 2.6 (6.9 µg/m³) Saint John - 7.7 (20.5 µg/m³) Halifax - 10.0 ppb (26.6 µg/m³) Toronto - 4.2 ppb (11.2 µg/m³) Vancouver - 2.6 ppb (6.9 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 (fixed and random effects) percent increase in emergency department visits per 5.1 ppb (13.6 µg/m³) in a single pollutant model for the summer season angina/infarction lag day 1 - 2.1	pooled (fixed and random effects) percent increase in emergency department visits per 5.1 ppb (13.6 µg/m³) in a single pollutant model for the summer season angina/infarction lag day 1 - 0.2 - 4.0	statistically significant association with ED visits for angina/infarction in a single pollutant model on lag day 2; no statistically significant associations ED visits for all other cardiac and respiratory conditions in a single pollutant model at any of three daily lag periods or any of six within day 3 hour lag periods; no associations with visits for any condition during the winter months	⊕⊕◯◯ (low quality because of methodological details and the lack of two-pollutant models)

author	location	exposure monitoring	SO_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 2.6 ppb (6.9 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 emergency department visits per unstated IQR increase in a single pollutant model chest pain (lag day 0) all seasons, all patients - 1.1 all seasons, female patients - 2.0 weakness (lag day 0) all seasons, female patients - 2.4 cold season, female patients - 2.4 all seasons, all patients - 1.6 cold season, all patients - 1.6 weakness (lag day 2) cold season, male patients - 2.2 cold season, all patients - 1.5	relative risk percentage for emergency department visits per unstated IQR increase in a single pollutant model chest pain (lag day 0) all seasons, all patients - 2.6 all seasons, female patients - 3.3 weakness (lag day 0) all seasons, female patients - 0.9 - 3.9 cold seasons, female patients - 0.5 - 4.5 all seasons, all patients - 0.4 - 2.7 cold seasons, all patients - 0.1 - 3.1 weakness (lag day 2) cold season, male patients - 0.1 - 4.4 cold seasons, all patients - 0.0 - 3.1	statistically significant association with emergency department visits for chest pain in both seasons for all patients and female but not males in single pollutant model on lag day 0, no association with chest pain visits for males or females during the summer or winter months on lag days 1 or 2; statistically significant associations with ED visits for weakness in both seasons and the cold season for all patients and female patients but not males using a single pollutant model on lag day 0; statistically significant associations with visits for weakness in the cold season for all patients and males on lag day 2 but not lag day 1; no association with weakness in females in any season or for any lag period	⊕○○○ (insufficient because of bias from the use of a unstated number of monitoring sites and methodological imprecision)

author	location	exposure monitoring	SO_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 2.6 ppb (6.9 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	change in relative risk percentage for ED visits for ischemic stroke per IQR 2.3 ppb (6.1 µg/m³) in a single pollutant model group age 20-64 years cold seasons & females (lag day 1) - 6.0 group age 65-100 years old cold season & all sexes (lag day 1) - 4.4 all seasons & females (lag day 1) - 4.6 warm seasons & males (lag day 0) - 9.1	change in relative risk percentage for ED visits for ischemic stroke per IQR 2.3 ppb (6.1 µg/m³) in a single pollutant model group age 20-64 years cold seasons & females (lag day 1) - 0.5 - 11.8 group age 65-100 years old cold season & all sexes (lag day 1) - 0.4 - 8.6 all seasons & females (lag day 1) - 0.4 - 9.0 warm seasons & males (lag day 0) - 2.2 - 16.4	statistically significant association ED visits for ischemia in females but not males aged 20-64 years for the cold season but not all seasons or the warm season in a single pollutant model on lag day 1; statistically significant association for males and females aged 65- 100 years old during the cold season on lag day 1 and males during the warm season on lag day 0; significant association for all season females on lag day 1 but not other seasons or lag days; no association in all season or cold season for males on lag days 1 and 2; no association warm or cold season for females on lag days 0 or 2	⊕○○○ (insufficient because of the exposure misclassification and the failure to perform two-pollutant modeling)
(Tolbert et al., 2007)	Atlanta, Georgia	1-hr maximum for an unstated number of monitoring sites	average 1-hr maximum 14.9 ppb (39.6 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	no change relative risk for emergency department visits for cardiovascular or respiratory disease per IQR 16 ppb (42.6 µg/m³) in single pollutant models with a 3 day (0-2) moving average lag	no change relative risk for emergency department visits for cardiovascular or respiratory disease per IQR 16 ppb (42.6 µg/m³) in single pollutant models with a 3 day (0-2) moving average lag	no statistically significant association with emergency room visits for cardiovascular or respiratory diseases in a single pollutant model at an 0-1 moving average lag period	⊕○○○ (insufficient because of bias from the use of a unstated number of monitoring sites and publication bias)

author	location	exposure monitoring	SO_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 all season - 2.6 (6.9 µg/m³) summer - 2.1 ppb (5.6 µg/m³) winter - 3.1 ppb (8.2 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 ED visits for cardiovascular events per IQR of 3.0 ppb (8.0 µg/m³) in single pollutant model for those aged 65 years or older on lag day 0 stroke summer - 1.11 cerebral ischemia all season - 1.06 summer - 1.11	adjusted odds ratio for ED visits for cardiovascular events per IQR of 3.0 ppb (8.0 µg/m³) in single pollutant model for those aged 65 years or older on lag day 0 stroke summer - 1.0 - 1.22 cerebral ischemia all season - 1.00 - 1.12 summer - 1.02 - 1.22	weak statistically significant association with emergency department visits for acute ischemic stroke in those ≥ 65 yrs using single pollutant model during warm, but not cool or all seasons using a same day lag but not with a day 1 lag or a 3 day moving average lag; weak significant association with ED visits for transient cerebral ischemia for those ≥ 65 yrs during all seasons and the warm months using a single pollutant model and a same day lag but not lags of 1 day or 3 day average lag; no association with visits for hemorrhagic stroke in those ≥ 65 yrs for any of the three lag periods; no associations with ED visits for any of the three cardiovascular conditions in warm or cold seasons following stratification by sex	⊕◯◯◯ (insufficient because of the exposure misclassification and the failure to perform two-pollutant modeling)

author	location	exposure monitoring	SO_2 concentration	study type (duration)	endpoint	co-pollutants	participants	ratio or risk	confidence interval	results	GRADE quality of evidence
(Yang, 2008)	Taipei, Taiwan	mean daily concentration at six fixed monitoring locations	daily mean 4.27 ppb (11.36 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	no change odds ratio for CHF hospital admissions per IQR increase of 2.74 ppb (7.29 µg/m³) on warm or cold says using single or two-pollutant model with a cumulative 3 day lag	no change odds ratio for CHF hospital admissions per IQR increase of 2.74 ppb (7.29 µg/m³) on warm or cold says using single or two-pollutant model with a cumulative 3 day lag	no statistically significant positive associations for congestive heart failure hospital admissions on warm (≥ 20 ˚C) or cold (< 20 ˚C) days using a single pollutant model or a two-pollutant model with PM_{10}, NO_2, CO, or O_3 and a 3 day cumulative lag period; significant negative associations seen in all two-pollutant models on warm days	⊕⊕◯◯ (low quality because no evaluation of $PM_{2.5}$ interactions)

Acute Respiratory

author	location	exposure monitoring	SO_2 concentration	study type (duration)	endpoint	co-pollutants	participants	ratio or risk	confidence interval	results	GRADE quality of evidence
(Amster et al., 2014)	Hadera, Israel	spatially assigned residential values from 20 fixed monitoring sites using ordinary kriging techniques	daily average all sources (power plant and background) 2.52 ppb (6.70 µg/m³)	cross sectional study (8 years)	respiratory symptoms (COPD, asthma, shortness of breath, chronic cough, chronic phlegm, nocturnal dyspnea) in those living near a power plant	association with SO_2 & NOx	males and females 18 to 75 years old 2244 participants	unadjusted and adjusted odds ratio increase for respiratory disease symptoms per 1 ppb (2.66 µg/m³) in single and two pollutant model with NOx asthma single pollutant model unadjusted - 1.90 adjusted - 1.89 asthma two pollutant model adjusted -1.85 shortness of breath single pollutant model unadjusted - 1.68 adjusted - 1.90 shortness of breath two pollutant model adjusted -1.89	unadjusted and adjusted odds ratio increase for respiratory disease symptoms per 1 ppb (2.66 µg/m³) in single and two pollutant model with NOx asthma single pollutant model unadjusted - 1.10 - 3.27 adjusted - 1.10 - 3.25 asthma two pollutant model adjusted -1.05 - 3.27 shortness of breath single pollutant model unadjusted - 1.49 - 1.94 adjusted - 1.10 - 3.27 shortness of breath two pollutant model adjusted -1.10 - 3.25	statistically significant association with reports of asthma and shortness of breath symptoms with adjusted and unadjusted single pollutant model and adjusted two pollutant model with NOx; no association with COPD, chronic cough, chronic phlegm, or nocturnal dyspnea in single or two pollutant models, no association with any of the 6 types of respiratory conditions when the SO_2 power plant exposures were evaluated independent of background by either of two techniques	⊕○○○ (insufficient because of the recall bias associated with questionnaire use and the failure to examine PM_{10} and $PM_{2.5}$ interactions)
(Atkinson et al., 2015)	England	annual averages using dispersion models created with emission profiles for road transport and power generation then validated against monitoring site measurements	annual mean concentration 3.9 µg/m³	cohort (5 years)	chronic obstructive pulmonary disease (COPD) diagnosis from a general practitioner (GP) or on hospital admission	association with $PM_{2.5}$, PM_{10}, SO_2, O_3, & NO_2	males and females aged 40 - 89 years GP diagnosis - 16,034 cases hospital diagnosis - 2910 cases	fully adjusted change in hazards ratio for COPD diagnosis per IQR increase of 2.2 µg/m³ using a single or two pollutant model single pollutant GP diagnosis - 1.07 two pollutant SO_2/PM_{10} - 1.09 SO_2/O_3 - 1.06 SO_2/NO_2 - 1.07	fully adjusted change in hazards ratio for COPD diagnosis per IQR increase of 2.2 µg/m³ using a single or two pollutant model single pollutant GP diagnosis - 1.03 - 1.11 two pollutant SO_2/PM_{10} - 1.05 - 1.14 SO_2/O_3 - 1.01 - 1.11 SO_2/NO_2 - 1.03 - 1.12	statistically significant association with COPD diagnosed by their general practitioner using partially and fully adjusted a single or two pollutant model with PM_{10} O_3, & NO_2; statistically significant association with COPD diagnosed at the hospital using partially but not a fully adjusted a single pollutant model, no association with COPD in fully adjusted two pollutant models for those diagnosed at the hospital	⊕⊕○○ (low quality because of the small number of cases and use a single year of exposure measurement data)

author	location	exposure monitoring	SO_2 concentration	study type (duration)	endpoint	co-pollutants	participants	ratio or risk	confidence interval	results	GRADE quality of evidence
(Canova et al., 2010)	Padua, Italy	daily averages from four fixed monitoring sites	daily mean concentration 3.57 ppb (9.50 µg/m³)	time-series (2 years)	peak expiratory flow (PEF), forced expiratory volume in 1 second (FEV_1), forced vital capacity (FVC) in asthmatics	association with PM_{10}, SO_2, CO & NO_2	asthmatics aged 15-44 years 19 cases	no change in the absolute percentage increase in morning or evening FEV1, PEF, or FEV per 10 µg/m³ change in a single pollutant model on lag days 0, 1, 2, or 3 and cumulative lag 0-1 or 0-3	no change in the absolute percentage increase in morning or evening FEV1, PEF, or FEV per 10 µg/m³ change in a single pollutant model on lag days 0, 1, 2, or 3 and cumulative lag 0-1 or 0-3	no statistically significant association with any of four pulmonary function measurements in a single pollutant model with used six different lag periods	⊕○○○ (insufficient because the small sample size and lack of statistical power as indicated by the wide confidence intervals)
(Chang et al., 2012)	Taipei, Taiwan	6-day average from five fixed monitoring sites	6-day average 2.6 ppb (6.92 µg/m³) day 0 mean 4.6 - 10.0 ppb (12.2 - 26.6 µg/m³) peak 5.9 - 35.2 ppb (15.7 - 93.6 µg/m³) day 1 mean 1.8 - 5.4 ppb (4.8 - 14.4 µg/m³) peak 3.8 - 22.8 ppb (10.1 - 60.6 µg/m³) day 2 mean 1.9 - 5.6 ppb (5.1 - 14,9 µg/m³) peak 5.7 - 23.1 ppb (15.2 - 61.4 µg/m³)	panel study (6 months)	forced expiratory volume 1 sec (FEV_1) and forced vital capacity (FVC) in children	association with PM_{10}, O_3, SO_2, CO, & NO_2	male and female schoolchildren 2919 volunteers	fractional decrease in air volume per 1 ppb (2.66 µg/m³) increase in single pollutant model using daytime average and daytime peak concentrations daytime average FVC lag day 1 -12.9 FEV_1 lag day 1 -11.73 daytime peak FVC lag day 1 -8.96 FEV_1 lag day 1 -8.48	fractional decrease in air volume per 1 ppb (2.66 µg/m³) increase in single pollutant model using daytime average and daytime peak concentrations daytime average FVC lag day 1 -20.7 - -5.09 FEV_1 lag day 1 -19.3 - -4.16 daytime peak FVC lag day 1 -13.5 - -4.40 FEV_1 lag day 1 -12.9 - -4.06	statistically significant association with decrements in FVC and FEV_1 on lag day 1 but not lag day 0 or 2 using daytime average and daytime peak exposure measurements in a single pollutant model	⊕○○○ (insufficient because of the failure to perform two-pollutant modeling and the absence of $PM_{2.5}$ measurements)

author	location	exposure monitoring	SO_2 concentration	study type (duration)	endpoint	co-pollutants	participants	ratio or risk	confidence interval	results	GRADE quality of evidence
(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 dwelling counts, industrial point source, & road networks, short-term daily exposures determined from two stationary fixed monitoring sites; estimated exposures determined by combining TWAs at school and at home	annual mean 5.39 ppb (14.34 µg/m³)	cross-sectional (12 months)	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 with lung function measurements in adjusted single pollutant model per 1 µg/m³ increase	no association with lung function measurements in adjusted single pollutant model per 1 µg/m³ increase	no statistically significant association with forced expired volume (1 sec) forced vital capacity, or expired nitric oxide in school children using a single pollutant model	⊕⊕◯◯ (low quality because of the failure to perform multi-pollutant modeling)

author	location	exposure monitoring	SO_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 thirteen urban fixed monitoring sites	daily mean concentration 23.7 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 43,635 visits	percentage increase in hospital and emergency room visits per IQR 12.5 µg/m³ increase using one pollutant ,two-pollutant and multi-pollutant models for 5 day moving average lag respiratory disease admissions SO_2 only ≈ 10 (depicted graphically) SO_2/CO - 8.2 pneumonia and bronchopneumonia SO_2 only ≈ 20 (depicted graphically) SO_2/O_3 - 18.4 SO_2/CO - 18.4	percentage increase in hospital and emergency room visits per IQR 12.5 µg/m³ increase using one pollutant ,two-pollutant and multi-pollutant models for 5 day moving average lag respiratory disease admissions SO_2 only ≈ 5 - 17 (depicted graphically) SO_2/CO - 1.87 - 14.5 pneumonia and bronchopneumonia SO_2 only ≈ 4 - 38 (depicted graphically) SO_2/O_3 - 0.5 - 36.2 SO_2/CO - 0.5 - 36.2	statistically significant positive association with the percentage increase in respiratory-related and pneumonia/bronchopneumonia-related emergency room visits for single pollutant models and two pollutant models with CO (respiratory) and O_3 or CO (pneumonia/bronchopneumonia) using a 0-4 day moving average lag period; no statistically significant association with asthma and bronchiolitis visits for single, two-pollutant or multipollutant models under any conditions models; no significant associations with respiratory disease ER visits with two pollutant models with PM_{10}, NO_2, or O_3; no associations with pneumonia/bronchopneumonia using two pollutant models with PM_{10} or NO_2; no positive associations with any condition using multi-pollutant model with PM_{10}, NO_2, O_3, CO; statistically significant negative associations seen for respiratory disease visits in two pollutant model with PM_{10} and with the multi-pollutant model	⊕⊕⊕◯ (moderate quality no adjustments necessary, but no evaluation of $PM_{2.5}$)

author	location	exposure monitoring	SO_2 concentration	study type (duration)	endpoint	co-pollutants	participants	ratio or risk	confidence interval	results	GRADE quality of evidence
(Guo et al., 2014a)	Shanghai, China	daily averages from an unstated number of fixed monitoring studies	daily average concentration 30 µg/m³	time-series (2 years)	outpatient visits for acute bronchitis	association with PM_{10}, SO_2, & NO_2	males and females 58,740 hospital visits	percent increase in hospital visits for acute bronchitis per 10 µg/m³ increase using a 7 day (0-6) moving average lag single pollutant males - 9.90 females - 12.05 age (5 -65 yrs) - 12.66 age (>66 yrs) - 7.82 cool season - 6.56 warm season - 17.19 multi-pollutant SO_2/PM_{10} - 10.24 SO_2/NO_2 - 9.50 $SO_2/PM_{10}/NO_2$ - 12.47	percent increase in hospital visits for acute bronchitis per 10 µg/m³ increase using a 7 day (0-6) moving average lag single pollutant males - 9.33 - 10.47 females - 11.58 - 12.53 age (5 -65 yrs) - 12.22 - 13.09 age (>66 yrs) - 7.15 - 8.49 cool season - 6.13 - 6.98 warm season - 16.36 - 18.02 multi-pollutant SO_2/PM_{10} - 9.82 - 10.66 SO_2/NO_2 - 9.06 - 9.95 $SO_2/PM_{10}/NO_2$ - 11.57 - 13.36	statistically significant association with acute bronchitis hospital visits at all 13 single and moving average lag times in a single pollutant model; statistically significant association in both sexes, seasons and age groups using a single pollutant model and a 7 day moving average lag; significant association in two and three pollutant models with PM_{10} and NO_2 using a 7 day moving average lag	⊕○○○ (insufficient because of the number of monitoring sites not stated and the failure to consider $PM_{2.5}$ in two pollutant models)
(Karr et al., 2009)	British Columbia	levels at the most proximal (within 10 km) of 14 fixed monitoring sites	lifetime exposure 5.6 µg/m³	case control (4 years)	outpatient or hospitalization for bronchiolitis in children	association with $PM_{2.5}$, PM_{10}, SO_2, O_3, CO, NO, NO_2, wood smoke, and black carbon	males and females 2 - 12 months of age 1465 cases 57,127 controls	adjusted odds ratio for bronchiolitis hospitalization per IQR increase of 3.2 µg/m³ in as single pollutant model using different exposure metrics lifetime exposure - 1.04 previous month exposure - 1.03	adjusted odds ratio for bronchiolitis hospitalization per IQR increase of 3.2 µg/m³ in as single pollutant model using different exposure metrics lifetime exposure - 1.01 - 1.06 previous month exposure - 1.01 - 1.05	statistically significant association with infant bronchiolitis hospitalization using and adjusted single pollutant model based on lifetime exposures or the previous month exposure, stratification showed significant association for the fourth quartile of lifetime exposures but not the second or third using a single pollutant model; no associations observed using crude single pollutant models for any exposure metric	⊕○○○ (insufficient because no two-pollutant modeling and high likelihood of exposure misclassification)

author	location	exposure monitoring	SO_2 concentration	study type (duration)	endpoint	co-pollutants	participants	ratio or risk	confidence interval	results	GRADE quality of evidence
(Ko et al., 2007a)	Hong Kong, China	daily average concentration from fourteen fixed monitoring sites	daily mean 15 µg/m³	time-series (5 years)	hospital admissions for chronic obstructive pulmonary disease (COPD)	association with PM_{10}, $PM_{2.5}$, O_3, SO_2, & NO_2	males and females 119,225 admissions	relative risk of COPD admissions per 10 µg/m³ increase in single pollutant and multi-pollutant models for a single lag period single pollutant - 1.007 three pollutant (SO_2/$PM_{2.5}$/O_3) - 1.008 four pollutant (SO_2/$PM_{2.5}$/O_3/NO_2) - 1.008	relative risk of COPD admissions per 10 µg/m³ increase in single pollutant and multi-pollutant models for a single lag period single pollutant - 1.001 - 1.014 three pollutant (SO_2/$PM_{2.5}$/O_3) - 1.001 - 1.015 four pollutant (SO_2/$PM_{2.5}$/O_3/NO_2) - 1.001 - 1.015	statistically significant association with hospitalizations for COPD in single pollutant model for a single same day lag period (0 days), no association for any of the remaining ten lag periods examined; slight statistically significant association in three pollutant model with $PM_{2.5}$ and O_3 or a four pollutant model with $PM_{2.5}$, O_3, & NO_2 for a days 0 lag period; statistically significant association in cold but not warm season in single pollutant model	⊕⊕⊕◯ (moderate quality, but very weak associations)
(Lee et al., 2011b)	Taiwan	annual mean concentration at 14 fixed monitoring locations	mean 3-year period - 4.68 ppb (12.45 µg/m³) 3-month period - 3.90 ppb (10.37 µg/m³)	self-controlled case series (36 months)	pulmonary function test (PFT), maximal mid-expiratory flow (MMEF), 1 second forced expiratory volume (FEV_1), & peak expiratory flow	association with PM_{10}, $PM_{2.5}$, O_3, SO_2, NOx, NO, & NO_2	male & female school children 3957 volunteers	no association with the percent change in pulmonary function indices for either acute (3 month) IQR increase of 1.68 ppb (4.47 µg/m³) or a chronic (3 year) IQR increase of 2.30 ppb (6.12 µg/m³) using a single pollutant model	no association with the percent change in pulmonary function indices for either acute (3 month) IQR increase of 1.68 ppb (4.47 µg/m³) or a chronic (3 year) IQR increase of 2.30 ppb (6.12 µg/m³) using a single pollutant model	no statistically significant pulmonary function decrements for 3-year and 3-month exposure time frames for changes in pulmonary function test (PFT), maximal mid-expiratory flow (MMEF), 1 second forced expiratory volume (FEV_1), & peak expiratory flow	⊕⊕◯◯ (low quality because of the failure to perform multi-pollutant modeling)
(Lee et al., 2014)	Taipei, Taiwan	annual average from the nearest of 25 fixed monitoring stations	annual average 3.7 ppb (9.8 µg/m³)	cohort (3 years)	osteoporosis in elderly subjects with chronic obstructive pulmonary disease (COPD)	association with PM_{10}, SO_2, O_3, CO, & NO_2	males and females aged 65 to 87 years old 70 subjects	no change in odds ratio for osteoporosis in COPD patients per 1 ppb (2.6 µg/m³) increase using a single pollutant model	no change in odds ratio for osteoporosis in COPD patients per 1 ppb (2.6 µg/m³) increase using a single pollutant model	no statistically significant association with osteoporosis in subjects with COPD using a single pollutant model	⊕◯◯◯ (insufficient because the small sample size and the failure to perform multi-pollutant modeling)

author	location	exposure monitoring	SO_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 location	daily mean 4.68 µg/m³	time-series (19 months)	hospital admissions for chronic obstructive pulmonary disease (COPD), asthma, chronic bronchitis	differential effects of humidity, TSP, SO_2, & NO_2	males and females hospitalizations 953 admissions	increase in relative risk per 1 µg/m³ increment using a single pollutant model with various lag times and exposure data handling lag day 2 (graphically interpolated) raw actual values - 1.06 raw + interpolated values - 1.15 lag day 7 raw + interpolated values - 1.07	increase in relative risk per 1 µg/m³ increment using a single pollutant model with various lag times and exposure data handling lag day 2 (graphically interpolated) raw actual values - 1.01 - 1.10 raw + interpolated values - 1.06 - 1.26 lag day 7 raw + interpolated values - 1.01 - 1.18	statistically significant associations with chronic bronchitis in single pollutant model on lag days 2 and 7 using original and interpolated exposure values used to account for missing data, stated significant associations observed with chronic bronchitis using a three pollutant model (SO_2/TSP/NO_2) on lag day 2 but the results not shown; no associations with chronic bronchitis; no statistically significant associations observed total respiratory admissions, COPD, or asthma using a single or multi-pollutant model on any lag day	⊕○○○ (insufficient because the high likelihood of exposure misclassification and the absence of two-pollutant modeling)
(Leitte et al., 2011)	Beijing, China	mean daily concentration from 8 fixed monitoring sites	daily mean 87 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	no increase in relative risk for respiratory emergency room visits per 100 µg/m³ increment using a single pollutant model using same day or a 5 day moving average lag	no increase in relative risk for respiratory emergency room visits per 100 µg/m³ increment using a single pollutant model using same day or a 5 day moving average lag	no significant associations with respiratory emergency room visits using a single pollutant model with a short or a long lag period	⊕○○○ (insufficient because no two-pollutant and high likelihood of exposure misclassification)

author	location	exposure monitoring	SO_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 - 4.5 ppb (12.0 µg/m³) 2-day - 5.0 ppb (13.3 µg/m³) 3-day - 5.6 ppb (14.9 µg/m³)	case-crossover (3 months)	pulmonary function (FEV_1, $FEF_{25-75\%}$), airway inflammation (exhaled nitric oxide, FENO) and oxidative stress (thiobarbituric reactive substances (TBARS), & 8-isoprostane exhalation 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 respiratory response per IQR increase using a single pollutant model at various lag times TBARS 0 day lag (IQR 6.5 ppb; 17.3 µg/m³) - 17.4 2 day lag (IQR 5.6 ppb; 14.9 µg/m³) - 35.1 3 day lag (IQR 5.4 ppb; 14.4 µg/m³) - 61.8 8-isoprostane exhalation 0 day lag (IQR 6.5 ppb; 17.3 µg/m³) - 14.1	adjusted percent change in respiratory response per IQR increase using a single pollutant model at various lag times TBARS 0 day lag (IQR 6.5 ppb; 17.3 µg/m³) - 0.3 - 37.4 2 day lag (IQR 5.6 ppb; 14.9 µg/m³) - 9.5 - 66.8 3 day lag (IQR 5.4 ppb; 14.4 µg/m³) - 24. 9 - 109 8-Isoprostane exhalation 0 day lag (IQR 6.5 ppb; 17.3 µg/m³) - 2.5 - 26.9	statistically significant association with TBARS measurements for same day lag periods and periods of 2 and 3 days in single pollutant models, no statistically significant association with TBARS in single pollutant model on lag day 1; no statistically significant association with FEV_1, $FEF_{25-75}\%$, and FE_{NO} for any of the 4 lag periods examined; statistically significant association with TBARS change in two pollutant model with O_3 using a 3 day lag; no statistically significant associations with FEV_1, $FEF_{25-75}\%$, FENO, or TBARS on any lag day in two pollutant models with either $PM_{2.5}$ or NO_2	⊕○○○ (insufficient because of the high probability of exposure misclassification and the failure to consider PM_{10} levels)

author	location	exposure monitoring	SO_2 concentration	study type (duration)	endpoint	co-pollutants	participants	ratio or risk	confidence interval	results	GRADE quality of evidence
(Luginaah et al., 2005)	Windsor, Ontario	daily average concentration from four fixed monitoring sites	daily mean 25.5 ppb (73.2 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 - 1.111	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 1.011 - 1.221	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 (all ages, 0-14 years, 15-64 years, or ≥ 65 years), 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 the failure to include PM2.5 in the analysis and the absence of two-pollutant modeling)
(Min et al., 2008a)	Tae-in, Korea	hourly average from a single fixed monitoring site	daily mean 6 ppb (16 µg/m³)	cross sectional (1 year)	forced expiratory volume 1 sec (FEV_1) and forced vital capacity (FVC) in children	association with PM_{10}, SO_2, & NO_2	male and female children 9-19 years of age 181 subjects	no significant change in FEV_1 or FVC per an unstated exposure change in single or two pollutant models for any lag period	no significant change in FEV_1 or FVC per an unstated exposure change in single or two pollutant models for any lag period	no statistically significant association with lung function (FEV_1 and FVC) change in children	⊕○○○ (insufficient because the high likelihood of exposure misclassification and the absence of $PM_{2.5}$ measurements)

author	location	exposure monitoring	SO_2 concentration	study type (duration)	endpoint	co-pollutants	participants	ratio or risk	confidence interval	results	GRADE quality of evidence
(Moon et al., 2009)	4 cities in Korea	daily averages from an unspecified number of monitoring stations located near schools	daily averages Seoul - not stated Incheon - not stated Busan - not stated Jeju - not stated	time-series (40 days)	lower respiratory, upper respiratory, and irritation symptoms from a questionnaire	association with PM_{10}, SO_2, O_3, CO, & NO_2	male and female school children of an unspecified age 1050 participants	odds ratio increase in lower respiratory (LRS), upper respiratory (URS), and irritation (IS) symptoms per IQR increase in single pollutant model at the most sensitive lag period all cities (IQR 2.96 ppb; 7.87 µg/m³) URS (lag 0 days) - 1.032 Seoul (IQR 2.17 ppb; 5.77 µg/m³) IS (lag moving 3 days) - 1.086 Incheon (IQR 2.90 ppb; 7.71 µg/m³) URS (lag 0 days) - 1.062 IS (lag moving 3 days) - 1.096 Busan (IQR 5.80 ppb; 15.43 µg/m³) URS (lag 1 days) - 1.122	odds ratio increase in lower respiratory (LRS), upper respiratory (URS), and irritation (IS) symptoms per IQR increase in single pollutant model at the most sensitive lag period all cities (IQR 2.96 ppb; 7.87 µg/m³) URS (lag 0 days) - 1.010 - 1.054 Seoul (IQR 2.17 ppb; 5.77 µg/m³) IS (lag moving 3 days) - 1.012 - 1.166 Incheon (IQR 2.90 ppb; 7.71 µg/m³) URS (lag 0 days) - 1.001 - 1.127 IS (lag moving 3 days) - 1.024 - 1.172 Busan (IQR 5.80 ppb; 15.43 µg/m³) URS (lag 1 days) - 1.070 - 1.177	statistically significant positive association in pooled all city analysis with URS but not LRS or IS using a single pollution model on lag day 0; significant positive association in Seoul for IS but not LRS or URS using a single pollution model using a moving average lag of 0-2 days; significant positive association in Inchon for URS (lag day 0) and IS (moving average lag 0-2 days) but not or LRS using a single pollution model; significant positive association in Busan with URS but not LRS or IS using a single pollution model on lag day 0; significant negative associations observed in the city of Jeju for LRS and URS and no association for with IS	⊕○○○ (insufficient because of the recall bias associated with questionnaire use and the failure to examine $PM_{2.5}$ interactions)

author	location	exposure monitoring	SO_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)	determination of home levels using local dispersion model that included emission estimates of oil consumption for home heating and sulfur content then linear back extrapolation of levels to earlier periods of life	source specific increase in annual mean concentration first year of life - 2.5 µg/m³	prospective cohort (48 month)	respiratory symptoms for wheeze (transient, late onset, or persistent), peak expiratory flow (PEF), and serum IgE antibodies for any food, any inhalant, pollens, or furred pets	association with outdoor PM_{10} and NO_2, and indoor SO_2	male and females (2 mo of age) 3515 infant volunteers	no change in adjusted odds ratio for transient, late onset, or persistent wheeze, PEF, or IgE antibodies to any food, any inhalant, pollens or furred pets per 3 µg/m³ (5-95% range) increment using a single pollutant model for indoor exposures	no change in adjusted odds ratio for transient, late onset, or persistent wheeze, PEF, or IgE antibodies to any food, any inhalant, pollens or furred pets per 3 µg/m³ (5-95% range) increment using a single pollutant model for indoor exposures	no statistically significant association of indoor levels with transient, late onset, or persistent wheeze in boys or girls up to four years of age in a single pollutant model; no association of indoor levels with peak expiratory flow in boys or girls; no association with IgE antibodies in both sexes to any food, any inhalant, pollen (birch, timothy, or mugwort, or furred (cats, horse, or dogs)	⊕◯◯◯ (insufficient because of the exposure misclassification and the failure to examine $PM_{2.5}$ interactions in a two pollutant model)
(O'Connor et al., 2008)	5 communities in the United States	daily average from the nearest monitoring site within a reasonable distance (avg. 2.3 km)	pooled average concentration (graphical representation) 1 day avg. ≈ 5 ppb (13.3 µg/m³) 5 day avg. ≈ 5 ppb (13.3 µg/m³)	time-series (4 years)	peak expiratory flow rate spirometry (FEV_1 and PEFR) measurements and symptom (wheeze-cough, night time asthma, slow play, and missed school) recording in minority children with asthma	association with $PM_{2.5}$, SO_2, CO, O_3, & NO_2	males and females 5 to 12 years of age 937 cases	pooled mean percentage change in pulmonary function measurements per 12.4 ppb (33.0 µg/m³)increase in single pollutant model using a 5 day moving average lag FEV_1 - -1.60 PEFR - -2.14	pooled mean percentage change in pulmonary function measurements per 12.4 ppb (33.0 µg/m³)increase in single pollutant model using a 5 day moving average lag FEV1 - -2.54 - -0.67 PEFR - -3.08 - -1.19	statistically significant association with FEV_1 and PFER pulmonary function decrements in asthmatic children using a single pollutant model; no significant association with wheeze-cough, night time asthma, slow play, or missed school using a single pollutant model	⊕◯◯◯ (insufficient because of potential recall bias and the failure to consider PM_{10} levels)

author	location	exposure monitoring	SO_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 3.9 ppb (10.4 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 42,791 children	no change in odds ratio for allergy and hay fever reporting in partial or fully adjusted single or multi-pollutant models per 3 ppb (8.0 µg/m³) increase	no change in odds ratio for allergy and hay fever reporting in partial or fully adjusted single or multi-pollutant models per 3 ppb (8.0 µg/m³) increase	no statistically significant association with childhood allergy and hay fever prevalence in partial or fully adjusted single or multi-pollutant (PM_{10}, $PM_{2.5}$, O_3, & NO) models using IDW for monitors within a 20 mi or 5 mi radius; statistically significant association observed in unadjusted single pollutant models	⊕⊕⊕◯ (moderate quality, no adjustment necessary)
(Peacock et al., 2011)	London England	measurements from a single air pollution monitoring station	monthly mean level all seasons - 7.5 ppb (20.0 µg/m³) autumn and winter - 9.8 ppb (26.1 µg/m³) spring and summer - 5.5 ppb (14.6 µg/m³)	time-series (2 years)	peak expiratory flow (PEF), forced expiratory volume in 1 second (FEV_1), forced vital capacity (FVC), respiratory symptoms (dyspnea, sputum changes, nasal discharge, wheeze, and upper respiratory symptoms), and PEF/COPD exacerbations	association with black smoke, PM_{10}, SO_2, O_3, & NO_2	COPD patients 31 males	no change in odds ratio for PEF, FEV1, FVC, dyspnea, sputum changes, nasal discharge, wheeze, and upper respiratory symptoms, or COPD exacerbations using a single pollutant model on lag day 1	no change in odds ratio for PEF, FEV1, FVC, dyspnea, sputum changes, nasal discharge, wheeze, and upper respiratory symptoms, or COPD exacerbations using a single pollutant model on lag day 1	no statistically significant association with decrements in peak expiratory flow, forced expiratory volume in 1 second, forced vital capacity, respiratory symptoms such as dyspnea, sputum changes, nasal discharge, wheeze, and upper respiratory symptoms, or COPD exacerbations and PEF deficiencies requiring evaluation at a clinic using a single pollutant model on lag day 1; two pollutant modeling apparently performed but the results no displayed because of the negative results	⊕◯◯◯ (insufficient because the high likelihood of exposure misclassification and the small number of cases)

author	location	exposure monitoring	SO_2 concentration	study type (duration)	endpoint	co-pollutants	participants	ratio or risk	confidence interval	results	GRADE quality of evidence
(Sinclair et al., 2010)	Atlanta, Georgia	hourly maximum concentrations at a single fixed monitoring location	average 1-hr daily maximum 25 month period warm months - 15.92 ppb (42.3 µg/m³) cold months - 24.31 ppb (64.7 µg/m³) 28 month period warm months - 13.82 ppb (36.8 µg/m³) cold months - 22.60 ppb (60.1 µg/m³)	time-series (25 month and 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 for respiratory tract infections over a 25 or 28 day period per 16.47 ppb (43.8 µg/m³) change in a single pollutant model at various lag times 25 month period LRT infection (lag 0-2 days) - 1.055 28 month period URT infection (lag 6-8 days) - 1.033	relative risk for respiratory tract infections over a 25 or 28 day period per 16.47 ppb (43.8 µg/m³) change in a single pollutant model at various lag times 25 month period LRT infection (lag 0-2 days) - 1.005 - 1.108 28 month period URT infection (lag 6-8 days) - 1.015 - 1.051	statistically significant association with outpatient visits for lower respiratory tract infection in the 25 month study in a single pollutant model at the 0-2 day lag period but not at the other 2 longer lag periods; statistically significant association with visits for upper respiratory tract infection in the 28 month study in a single pollutant model at the 6-8 day lag period but not at the other 2 shorter lag periods; statistically significant negative association for LRI in the 28 month study at a lag time of 0-2 days; no association with adult or childhood asthma regardless of study duration or lag; no association with visits for childhood asthma in either warm or cold seasons using single pollutant model	⊕○○○ (insufficient because of the high likelihood of exposure misclassification and the lack of two-pollutant modeling)

author	location	exposure monitoring	SO_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 including i) monitor average, ii) nearest monitor, iii) inverse distance weighting, and iv) kriging using the data from 13 fixed monitoring locations	daily mean average across monitors - 8.60 ppb (22.88 µg/m³) nearest monitor - 7.25 ppb (19.28 µg/m³) inverse distance weighting - 8.35 ppb (22.21 µg/m³) kriging extrapolation - 8.29 (22.05 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 subjects	percentage change in pulmonary function per 5.2 ppb (13.83 µg/m³) changes FVC single pollutant model (lag 0-2 days) average across monitors - -3.68 nearest monitor - -2.96 inverse distance weighting - -2.80 kriging extrapolation - -3.27 FVC two pollutant (SO_2/CO) model (lag 0-2 days) kriging extrapolation - -4.56 FEV_1 two pollutant (SO_2/CO) model (day 2 lag) kriging extrapolation - -0.63	percentage change in pulmonary function per 5.2 ppb (13.83 µg/m³) changes FVC single pollutant model (lag 0-2 days) average across monitors -4.81 - -2.55 nearest monitor -3.89 - -2.03 inverse distance weighting -3.74 - -1.85 kriging extrapolation - 4.33 - -2.21 FVC two pollutant (SO_2/CO) model (lag 0-2 days) kriging extrapolation - -5.85 - -3.27 FEV_1 two pollutant (SO_2/CO) model (day 2 lag) kriging extrapolation - -1.25 - -0.02	statistically significant decline in FVC for all four exposure measurement methods using a single pollutant model and all six lag periods with the largest effect noted using the average value for all monitors; statistically significant increase in FEV1 for all four exposure methods at a lag period of 1 day or an average lag of 0-1 days using a single pollutant model; significant associations with FVC and FEV_1 using a two pollutant model and the kriging exposure method with CO but not O_3 with average lag of 0-2 days or a single day lag on day 2, respectively	⊕⊕◯◯ (low quality because of the failure to examine $PM_{2.5}$ interactions)

author	location	exposure monitoring	SO_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 17.8 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	male and female daily means mortality stroke - 8.9 cases cardiac heart disease - 12.0 cases LRI - 9.3 cases COPD - 5.9 cases hospitalizations stroke - 47.1 cases IHD - 46.1 cases LRI - 104.9 cases COPD - 91.5 cases	influenza epidemic adjusted excess risk per 10 µg/m³ increase in single pollutant model on lag days 0-1 cardiovascular mortality cardiac hear disease - 2.70 LRI - 2.11 cardiovascular hospitalization IHD - 1.01 COPD - 0.62 cardiorespiratory mortality all cause - 0.90 cardiovascular - 1.23 respiratory - 1.26 cardiorespiratory hospitalization cardiovascular - 0.98	influenza epidemic adjusted excess risk per 10 µg/m³ increase in single pollutant model on lag days 0-1 cardiovascular mortality cardiac hear disease - 1.21 - 4.22 LRI - 0.60 - 3.63 cardiovascular hospitalization IHD - 0.28 - 1.74 COPD - 0.02 - 1.22 cardiorespiratory mortality all cause - 0.39 - 1.41 cardiovascular - 0.26 - 2.20 respiratory - 0.15 - 2.39 cardiorespiratory hospitalization cardiovascular - 0.57 - 1.38	statistically significant association with cardiovascular mortality from cardiac heart disease and lower respiratory infection but not stroke or COPD in an influenza unadjusted and adjusted single pollutant model after a 2 day (0-1) lag period; significant association with cardiovascular hospitalization for ischemic heard disease and COPD but not LRI or stoke in an influenza adjusted and unadjusted single pollutant model; association with all cause, cardiovascular and respiratory mortality and cardiovascular hospitalization in an influenza adjusted model; no association in influenza unadjusted or adjusted risk from hospitalizations from respiratory, acute respiratory disease or asthma	⊕○○○ (insufficient because the failure to include $PM_{2.5}$ in the analysis and the absence of two-pollutant modeling)
(Tolbert et al., 2007)	Atlanta, Georgia	1-hr maximum for an unstated number of monitoring sites	average 1-hr maximum 14.9 ppb (39.6 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	no change relative risk for emergency department visits for cardiovascular or respiratory disease per IQR 16 ppb (42.6 µg/m³) in single pollutant models with a 3 day (0-2) moving average lag	no change relative risk for emergency department visits for cardiovascular or respiratory disease per IQR 16 ppb (42.6 µg/m³) in single pollutant models with a 3 day (0-2) moving average lag	no statistically significant association with emergency room visits for cardiovascular or respiratory diseases in a single pollutant model at an 0-1 moving average lag period	⊕○○○ (insufficient because of bias from the use of a unstated number of monitoring sites and publication bias)

author	location	exposure monitoring	SO_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 - 2.0 ppb (5.3 µg/m³) winter - 3.0 ppb (8.0 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	no positive change in adjusted odds ratio for asthma ED visits any of seven different age groups per IQR of 3.0 ppb (8.0 µg/m³) for all seasons, summer months (Apr-Sept), or winter months (Oct - Mar) in a single pollution model for any of four lag periods	no positive change in adjusted odds ratio for asthma ED visits with any of seven different age groups per IQR of 3.0 ppb (8.0 µg/m³) for all seasons, summer months (Apr-Sept), or winter months (Oct - Mar) in a single pollution model for any of four lag periods	no statistically significant positive association with all season asthma ED visits in those aged 2 to ≥ 75 yrs of age or any of seven age stratified subgroups (2 - 4, 5 -14, 15 -24, 25 - 44 , 45 - 64, 65 - 74, or ≥ 75 years) for any of four lag periods; no associations following warm (Apr - Sept) or cold (Oct - Mar) season stratification; statistically significant negative associations seen for asthma visits in those 2 to ≥ 75 yrs of age in single pollutant model at all four lag periods for all seasons and the winter season	⊕○○○ (insufficient because of the exposure misclassification and the failure to perform two-pollutant modeling)
(Wood et al., 2010)	United Kingdom	annual mean from a geographical database built using emissions reporting from industrial sources and dispersion modeling together with regression analysis	annual mean 4.12 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 FEV_1 volume or KCO diffusion rate per 1 µg/m³ increase in SO_2 exposure using a single pollutant model that included all confounders	no change in FEV_1 volume or KCO diffusion rate per 1 µg/m³ increase in SO_2 exposure using a single pollutant model that included all confounders	no statistically significant association with changes in FEV_1 or KCO diffusion rate in COPD adults with at least one follow-up evaluation of lung function using a single pollutant model; a subgroup with four follow-up evaluations was similarly unaffected, no gender interactions observed that affected the negative associations	⊕○○○ (insufficient because the failure to include $PM_{2.5}$ in the analysis and the absence of two-pollutant modeling)

author	location	exposure monitoring	SO_2 concentration	study type (duration)	endpoint	co-pollutants	participants	ratio or risk	confidence interval	results	GRADE quality of evidence
(Yang et al., 2005)	Vancouver, British Columbia	daily average from five fixed monitoring sites	daily mean concentration 3.79 ppb (10.03 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 hospitalization per IQR of 2.8 ppb (7.4 µg/m³) increase in single and two-pollutant models for a moving average lag of up to 7 days single pollutant (6 day average lag) SO_2 only - 1.06 two pollutant (7 day average lag) SO_2/O_3 - 1.07	relative risk for COPD hospitalization per IQR of 2.8 ppb (7.4 µg/m³) increase in single and two-pollutant models for a moving average lag of up to 7 days single pollutant (6 day average lag) SO_2 only - 1.00 - 1.13 two pollutant (7 day average lag) SO_2/O_3 - 1.00 - 1.14	statistically significant association with COPD hospitalization in single pollutant model using a 6 day moving average lag but no average lags of 1, 2, 3, 4, 5, or 7days; significant association in a two pollutant model with O_3 but no association with PM_{10}, CO, or NO_2 for an 7 day average lag period; no association in pollutant models with PM_{10} & CO; no association in multi-pollutant model that included PM_{10}, CO, or NO_2 and O_3	⊕⊕◯◯ (low quality because no evaluation of $PM_{2.5}$ interactions)

author	location	exposure monitoring	SO_2 concentration	study type (duration)	endpoint	co-pollutants	participants	ratio or risk	confidence interval	results	GRADE quality of evidence
(Zhao et al., 2008c)	Taiyuan, China	weekly averages using indoor (classroom) and outdoor diffusion samplers placed at 10 schools	daily mean indoor schools - 264.8 µg/m³ outdoor schools - 712.8 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	odds ratio for asthmatic symptoms per 1 µg/m³ increase for nocturnal breathlessness in single pollutant model unadjusted multiple regression - indoor levels wheeze or whistling- 1.18 nocturnal breathlessness - 1.28 unadjusted hierarchical regression - indoor levels nocturnal breathlessness - 1.27 adjusted hierarchical regression - indoor levels wheeze or whistling- 1.55	odds ratio for asthmatic symptoms per 1 µg/m³ increase for nocturnal breathlessness in single pollutant model unadjusted multiple regression - indoor levels wheeze or whistling- 1.03 - 1.35 nocturnal breathlessness - 1.02 - 1.59 unadjusted hierarchical regression - indoor levels nocturnal breathlessness - 1.02 - 1.59 adjusted hierarchical regression - indoor levels wheeze or whistling- 1.06 - 2.27	statistically significant association with wheeze and nocturnal breathlessness in an unadjusted single pollutant model using indoor exposure measures and a multiple regression model; significant association with nocturnal breathlessness using an unadjusted single pollutant model, indoor levels and a hierarchical regression model, significant association with wheeze using a fully adjusted single pollutant model with indoor levels and a hierarchical regression model, no statistically significant association with cumulative asthma, daytime breathlessness, pet or pollen allergy, or respiratory infection using indoor or outdoor exposure levels and either regression model; no association with any symptom using outdoor levels and either the unadjusted multiple regression model or the unadjusted or adjusted hierarchical regression model	⊕○○○ (insufficient because the failure to include $PM_{2.5}$ and PM_{10} and the use of a cross-sectional design)

Birth Outcomes

author	location	exposure monitoring	SO_2 concentration	study type (duration)	endpoint	co-pollutants	participants	ratio or risk	confidence interval	results	GRADE quality of evidence
(Agay-Shay et al., 2013)	Tel Aviv, Israel	weakly averages from 10-13 fixed ambient monitoring stations were geocoded to residential location using inverse distance weighting	weakly mean 2.9 ppb (7.7 µg/m³)	cohort (8 years)	congenital heart defects including atrial septal defects, ventricular septal defects, or patent ductus arteriosus	association with $PM_{2.5}$, PM_{10}, SO_2, O_3, CO, & NO_2	males and females controls - 130,402 cases multiple congenital heart defects - 607 cases atrial septal defects - 567 cases ventricular septal defects 526 cases patent ductus arteriosus - 167 cases	no change in crude or adjusted odds ratio for multiple congenital heart defects, atrial septal defects, ventricular septal defects, or patent ductus arteriosus per 10 ppb (26.6 µg/m³) increase during weeks 3-8 of pregnancy using a single pollutant model	no change in crude or adjusted odds ratio for multiple congenital heart defects, atrial septal defects, ventricular septal defects, or patent ductus arteriosus per 10 ppb (26.6 µg/m³) increase during weeks 3-8 of pregnancy using a single pollutant model	no statistically significant positive association with multiple congenital heart defects, atrial septal defects, ventricular septal defects, or patent ductus arteriosus using a single pollutant model, significant negative association with multiple congenital heart defects using a single pollutant model	⊕⊕◯◯ (low quality because of the failure to perform two-pollutant modeling)
(Brauer et al., 2008)	Vancouver, British Columbia	mean during entire pregnancy using two techniques i) nearest of 22 fixed monitoring sites using assigned postal codes ii) inverse distance weighting (IDW) using three nearest fixed monitoring values	mean during pregnancy nearest - 5.7 µg/m³ IDW - 5.3 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 1 µg/m³ increase in single pollutant model small gestational age inverse distance weighting- 1.01	adjusted odds ratio per 1 µg/m³ increase in single pollutant model small gestational age inverse distance weighting 1.00 - 1.02	weak statistically significant association with small gestational age (SGA) with crude and adjusted model using IDW measurements but not nearest monitor for exposure estimation, no statistically significant association for low birth weight using crude or adjusted odds ratios using either exposure estimation method;	⊕⊕◯◯ (low quality because of the failure to perform two-pollutant modeling)

author	location	exposure monitoring	SO_2 concentration	study type (duration)	endpoint	co-pollutants	participants	ratio or risk	confidence interval	results	GRADE quality of evidence
(Dadvand et al., 2011)	Northeast England	measurements from the nearest of four fixed monitoring locations during weeks 3-8 of pregnancy, residential locations geocoded according to postal code; maximum distance to monitor was 16 km	weekly mean cases - 9.20 µg/m³ controls 9.00 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 tetralogy of Fallot)	association with PM_{10}, CO, O_3, SO_2, NO, & NO_2	male & female cases 2140 ontrols 14,256	no significant positive 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; five of the ten measures showed a negative association	no significant positive 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; five of the ten measures showed a negative association	no statistically significant association for the pooled heart disease incidence or specific heart disease cases using an adjusted single pollutant model; statistically significant negative association observed with the pooled cases along with the odds ratio for congenital malformations of cardiac chambers and septa, cardiac septa, aortic and mitral valves, as well as tetralogy of Fallot and ventricular septal defect	⊕○○○ (insufficient because the failure to include $PM_{2.5}$ in the analysis and the absence of two-pollutant modeling)
(Dales et al., 2006)	11 Canadian cities	daily average from an unstated number of fixed monitoring sites in each city	daily mean Calgary - 3.6 ppb (9.6 µg/m³) Edmonton - 2.7 ppb (7.2 µg/m³) Halifax - 10.1 ppb (26.9 µg/m³) Hamilton - 8.2 ppb (21.8 µg/m³) London - 3.7 ppb (9.8 µg/m³) Ottawa - 3.9 ppb (10.4 µg/m³) Saint John - 8.3 ppb (22.1 µg/m³) Toronto - 4.5 ppb (12.0 µg/m³) Vancouver - 4.6 ppb (12.2 µg/m³) Windsor - 7.6 ppb (20.1 µg/m³) Winnipeg - 1.2 ppb (3.2 µg/m³)	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 3.8 ppb (10.1 µg/m³) in single and multi-pollutant model on lag day 2 SO_2 only - 2.06 SO_2/CO, O_3, & NO_2 - 1.66 SO_2/PM_{10}, CO, O_3, & NO_2 - 1.41	pooled (random and fixed effects) percent increase in neonatal respiratory hospitalization per IQR of 3.8 ppb (10.1 µg/m³) in single and multi-pollutant model on lag day 2 SO_2 only - 1.04 - 3.08 SO_2/CO, O_3, & NO_2 - 0.63 - 2.69 SO_2/PM_{10}, CO, O_3, & NO_2 - 0.35 - 2.47	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}	⊕⊕⊕○ (moderate quality no adjustment necessary, but no evaluation of $PM_{2.5}$)

author	location	exposure monitoring	SO_2 concentration	study type (duration)	endpoint	co-pollutants	participants	ratio or risk	confidence interval	results	GRADE quality of evidence
(Darrow et al., 2009)	Atlanta, Georgia	mean daily concentration with either of three fixed monitoring locations by geocoding the residential location within 4 miles of nearest monitor	1-hr maximum 1-week mean 10.3 ppb (27.4 µg/m³) 4-week mean 10.5 ppb (27,9 µg/m³) 6-week mean 10.3 ppb (27.4 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 45,974 cases	no significant increase in risk ratio per IQR increase (3, 4, or 6 ppb) using a single pollutant model with either of the three exposure measurement periods	no significant increase in risk ratio per IQR increase (3, 4, or 6 ppb) using a single pollutant model with either of the three exposure measurement periods	no statistically significant increase in pre-term infants with any lag period (1, 4 or 6 weeks); no associations for infants born throughout the 5 county monitoring area without sorting for proximity to a monitoring site	⊕⊕○○ (low quality because of the failure to perform two-pollutant modeling)
(Darrow et al., 2011)	Atlanta, Georgia	population weighted spacial averages during the third trimester for census tracts using information from five 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}, $PM_{10\text{-}2.5}$ (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 for full term births per IQR increase of 3 ppb (7.9 µg/m³) change in a single pollutant model Hispanic - -11.1	mean change in birth weight for full term births per IQR increase of 3 ppb (7.9 µg/m³) change in a single pollutant model Hispanic - --22.1 - -0.0	weak statistically significant association with birth weight decline in Hispanic mothers but not non-Hispanic blacks or whites using exposure measures for the 3rd trimester in a single pollutant model; no association with birth weight declines for all races combined using exposures using exposures measures from each month of pregnancy or during the 1st month of gestation or the 3rd trimester	⊕⊕○○ (low quality because of the failure to perform two-pollutant modeling)

author	location	exposure monitoring	SO_2 concentration	study type (duration)	endpoint	co-pollutants	participants	ratio or risk	confidence interval	results	GRADE quality of evidence
(Dolk et al., 2010)	England	combination of background levels from an unstated number of monitoring sites and local levels based on dispersion modeling of roadway emissions that geocoded at the census level	annual average 7.86 µg/m³	cohort (9 years)	non-chromosomal and chromosomal congenital defects including tetralogy of Fallot, anomalies of cardiac chambers, transposition of great vessels, malformations of cardiac septa, atrioventricular septal defects, malformations of valves, hypoplastic left heart syndrome, great arteries and veins, coarctation of aorta, neural tube defects, hydrocephaly, cardiac defects, cleft lip with or without cleft palate, cleft palate, digestive system atresias, bilateral renal agenesis, cystic kidney disease, limb reduction, diaphragmatic hernia, omphalocele, gastroschisis, multiple anomalies, Downs syndrome	association with PM_{10}, SO_2, & NO_2	males and females non-chromosomal - 6136 cases chromosomal - 2949 cases	adjusted relative risk of congenital heart disease per 11.12 µg/m³ increase using a single pollutant model tetralogy of Fallot - 1.38	adjusted relative risk of congenital heart disease per 11.12 µg/m³ increase using a single pollutant model tetralogy of Fallot - 1.076 - 1.79	statistically significant association with tetralogy of Fallot using a single pollutant model; no association with anomalies of cardiac chambers, transposition of great vessels, malformations of cardiac septa, atrioventricular septal defects, malformations of valves, hypoplastic left heart syndrome, great arteries and veins, coarctation of aorta, neural tube defects, hydrocephaly, cardiac defects, cleft lip with or without cleft palate, cleft palate, digestive system atresias, bilateral renal agenesis, cystic kidney disease, limb reduction, diaphragmatic hernia, omphalocele, gastroschisis, multiple anomalies, Downs syndrome, no association with chromosomal or non-chromosomal anomalies	⊕○○○ (insufficient because the failure to include $PM_{2.5}$ in the analysis and the absence of two-pollutant modeling)

author	location	exposure monitoring	SO_2 concentration	study type (duration)	endpoint	co-pollutants	participants	ratio or risk	confidence interval	results	GRADE quality of evidence
(Farhi et al., 2014)	Israel	monthly averages using the measurement from 96 fixed monitoring sites along with ordinary kriging for residential geocoding and spatial resolution	monthly average first trimester - 2.81 ppb (7.47 µg/m³) second trimester - 2.74 ppb (5.23 µg/m³) third trimester - 2.74 ppb (5.23 µg/m³)	prospective cohort (8 years)	congenital malformations (circulatory system, ventricular septal defect, genital organs, cleft lip/palate, or chromosomal anomalies) in infants born spontaneously or needing assisted reproductive technology (ART)	association with PM_{10}, SO_2, O_3, and NOx	males and females spontaneous - 207,825 births assisted reproductive technology - 8905 births	no increase in adjusted odds ratio for congenital malformations in infants born spontaneously or using assisted reproductive technologies per 1 ppb (2.66 µg/m³) continuous increase or after a categorical comparison of the first and third exposure tertiles using a single pollutant model	no increase in adjusted odds ratio for congenital malformations in infants born spontaneously or using assisted reproductive technologies per 1 ppb (2.66 µg/m³) continuous increase or after a categorical comparison of the first and third exposure tertiles using a single pollutant model	no statistically significant positive association with congenital malformations of the circulatory system, ventricular septa, genital organs, lip/palate, or chromosomes in infants born spontaneously or using assisted reproductive technologies for exposures during the first, second or third trimester using a single pollutant model; statistically significant negative association with the first trimester exposures and all malformations and circulatory malformations in infants born spontaneously	⊕○○○ (insufficient because the failure to include $PM_{2.5}$ in the analysis and the absence of two-pollutant modeling)

author	location	exposure monitoring	SO_2 concentration	study type (duration)	endpoint	co-pollutants	participants	ratio or risk	confidence interval	results	GRADE quality of evidence
(Gianicolo et al., 2014)	Brindisi, Italy	weekly averages from 3 fixed monitoring stations	weakly mean congenital anomalies controls - 2.7 µg/m³ cases - 2.8 µg/m³ congenital heart defects controls - 2.8 µg/m³ cases - 2.9 µg/m³ ventricular septal defects controls - 2.9 µg/m³ cases -3.2 µg/m³	case control (10 years)	congenital anomalies, congenital heart defects and ventricular septal defects	association with total suspended particulates (TSP) and SO_2	males and females 0-28 days of age congenital anomalies 646 controls 168 cases congenital heart defects 273 controls 73 cases ventricular septal defects 150 controls 40 cases	odds ratio for congenital anomalies at the 90th percentile of the exposure distribution after a categorical comparison of the second tertile to the first tertiles using a single pollutant model for weeks 6-8 of gestation all congenital anomalies - 1.74 congenital heart defects - 3.21 ventricular septal defects - 4.57	odds ratio for congenital anomalies at the 90th percentile of the exposure distribution after a categorical comparison of the second tertile to the first tertiles using a single pollutant model for weeks 6-8 of gestation all congenital anomalies - 1.07 - 2.81 congenital heart defects - 1.42 - 7.25 ventricular septal defects - 1.31 - 15.96	statistically significant association with all congenital anomalies, congenital heart defects and ventricular septal defects for exposures at the 90th percentile during weeks 6-8 of gestation using a categorical comparison of the second tertile to the first tertile; no significant association comparing the first and third tertile; no statistically significant association with all congenital anomalies, congenital heart defects and ventricular septal defects using continuous exposure levels at the mean or 90th percentile	⊕○○○ (insufficient because the failure to include PM_{10} and $PM_{2.5}$ in the analysis and the absence of two-pollutant modeling)
(Hajat et al., 2007)	10 cites in United Kingdom	averages from a minimum of two monitoring sites per city except Middlesbrough and Newcastle which had a single site	mean daily concentration Birmingham - 17.5 µg/m³ Bristol - 17.8 µg/m³ Leeds - 17.0 µg/m³ Liverpool - 21.3 µg/m³ London - 21.3 µg/m³ Manchester - 15.1 µg/m³ Middleborough - 11.4 µg/m³ Newcastle - 14.9 µg/m³ Nottingham - 16.0 µg/m³ Sheffield - 16.5 µg/m³	time-series (10 years)	infant mortality	association with PM_{10}, SO_2, O_3, CO, NO, & NO_2	total male and female infant deaths in each city over the ten year period ranged 574 to 9037 in the ten cities	pooled relative risk per 10 increase in a single pollutant model on lag day average 02 all season - 1.02 summer months - 1.03	relative risk per 10 increase in a single pollutant model on lag day average 02 all season - 1.01 - 1.04 summer months - 1.00 - 1.06	statistically significant pooled 10-city association with infant mortality in a single pollutant model on average lag days 02 for the entire year and the summer period but not the winter period	⊕○○○ (insufficient because the failure to include $PM_{2.5}$ in the analysis and the absence of two-pollutant modeling)

author	location	exposure monitoring	SO_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 four fixed monitoring sites that were adjusted for residential to monitor distance	daily mean all seasons- 1.19 ppb (3.17 µg/m³) summer - 1.06 ppb (2.82 µg/m³) fall - 1.01 ppb (2.69 µg/m³) winter - 1.29 ppb (3.43 µg/m³) spring - 1.46 ppb (3.88 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 PM_{10}, SO_2, O_3, & NO_2	male & female fetuses 14,734 pregnancies	mean change in fetal ultrasound measurements between 13-26 weeks of gestation in crude or adjusted single pollutant model per IQR increase of 0.8 ppb (2.12 µg/m³) for any four different 30 day exposure periods single pollutant biparietal diameter/day 0-30 exposure (adjusted) - -0.68 abdominal circumference/day 61 - 90 exposure (crude) - -1.36 abdominal circumference/day 61 - 90 exposure (adjusted) - -1.67	mean change in fetal ultrasound measurements between 13-26 weeks of gestation in crude or adjusted single pollutant model per IQR increase of 0.8 ppb (2.12 µg/m³) for any four different 30 day exposure periods single pollutant biparietal diameter/day 0-30 exposure (adjusted) - -1.09 - 0.27 abdominal circumference/day 61 - 90 exposure (crude) - -2.63 - -0.09 abdominal circumference/day 61 - 90 exposure (adjusted) - -2.94 - -0.40	statistically significant association with ultrasonic measures of biparietal and abdominal diameter for women within 2 km of a monitoring site using a single pollutant model and one of four 30-day exposure measurement, no significant relationships with fetal femur length or head circumference for any exposure period, no associations with growth measure using a two pollutant model with PM_{10} or O_3 during the relevant exposure period; stratification of the single pollutant results by SES showed that the associations were confined to the highest two quartiles	⊕⊕◯◯ (low quality because the failure to include $PM_{2.5}$ in the analysis)

author	location	exposure monitoring	SO_2 concentration	study type (duration)	endpoint	co-pollutants	participants	ratio or risk	confidence interval	results	GRADE quality of evidence
(Hansen et al., 2009)	Brisbane, Australia	daily averages from 7 fixed monitoring stations	daily mean all seasons- 1.5 ppb (4.0 µg/m³) summer - 1.5 ppb (4.0 µg/m³) autumn - 1.6 ppb (4.3 µg/m³) winter - 1.4 ppb (3.7 µg/m³) spring - 1.4 ppb (3.7 µg/m³)	case control (8 years)	congenital cardiac defects (aortic artery and valve, atrial septal, pulmonary artery and valve, ventricular septal, conotruncal, and endocardial cushion and mitral valve defects), congenital cleft lip, cleft palate, and cleft lip/palate	association with PM_{10}, SO_2, O_3, CO, & NO_2	defects in males and females aortic artery and valve - 63 cases atrial septal - 127 cases pulmonary artery and valve - 64 cases ventricular septal - 222 cases conotruncal - 63 cases endocardial cushion and mitral valve defects - 33 cases cleft lip - 57 cases cleft palate - 100 cases cleft lip/palate - 145 cases	adjusted odds ratio for congenital anomalies for all births per 0.6 ppb (2.66 µg/m³) increase using a single pollutant model for weeks 3-8 of gestation cleft lip with or without cleft palate - 1.27	adjusted odds ratio for congenital anomalies for all births per 0.6 ppb (2.66 µg/m³) increase using a single pollutant model for weeks 3-8 of gestation cleft lip with or without cleft palate - 1.01 - 1.62	statistically significant association with cleft lip with or without a cleft palate using a single pollutant model; no positive association with cleft lip or cleft palate alone or with congenital cardiac defects following stratification according distance from the monitoring site (births ≤ 6km from site or ≤ 12 km from site), statistically significant negative association cardiac conotruncal defects for those births ≤ 6km from site	⊕○○○ (insufficient because the failure to include $PM_{2.5}$ in the analysis and the absence of two-pollutant modeling)
(Hou et al., 2014)	Tianjin, China	daily medians from the closest of ten fixed monitoring sites using geocoded residential and monitoring site locations	daily medians month of conception cases - 61 µg/m³ controls - 52 µg/m³ month after conception cases - 66 µg/m³ controls - 54 µg/m³	retrospective case control (69 months)	fetal death during the first trimester	association with total suspended particulate (TSP), PM_{10}, SO_2, and NO_2	females average age 29 years 959 cases 959 controls	odds ratio for fetal death per an unstated increase using a single pollutant model with different exposure periods month of conception - 12.22 month after conception - 17.46	odds ratio for fetal death per an unstated increase using a single pollutant model with different exposure periods month of conception - 2.18 - 69.59 month after conception - 3.01 - 101.24	statisitically significant association with fetal death using a single pollutant model and exposures during the month of conception or a month after conception; no association using exposure periods 1, 2, or 3 months prior to conception	⊕○○○ (insufficient because the failure to include $PM_{2.5}$ in the analysis and the absence of two-pollutant modeling)

author	location	exposure monitoring	SO_2 concentration	study type (duration)	endpoint	co-pollutants	participants	ratio or risk	confidence interval	results	GRADE quality of evidence
(Hwang et al., 2011)	Taiwan	geocoding and inverse distance weighting of mean monthly concentration from the nearest three of the 72 fixed monitoring sites located throughout the country	monthly mean 5.75 ppb (15.3 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	odds ratio for an IQR increase of 1 ppb (2.66 µg/m³) in an adjusted single or multi-pollutant models that considered different exposure periods by month, trimester, and whole pregnancy period single pollutant all births (first trimester) - 1.02 preterm births (first trimester) - 1.04 preterm births (entire pregnancy) - 1.03 three-pollutant models with CO & O_3 all births (first month) - 1.02 all births (second month) - 1.02 all births (third month) - 1.02 preterm births (first month) - 1.04 preterm births (second month) - 1.05 preterm births (third month) - 1.04 three-pollutant models with NO_2 & O_3 all births (first month) - 1.02 all births (second month) - 1.02 all births (third month) - 1.02 preterm births (first month) - 1.05 preterm births (second month) - 1.05 preterm births (third month) - 1.05	odds ratio for an IQR increase of 1 ppb (2.66 µg/m³) in an adjusted single or multi-pollutant models that considered different exposure periods by month, trimester, and whole pregnancy period single pollutant all births (first trimester) - 1.00 - 1.04 preterm births (first trimester) - 1.01 - 1.07 preterm births (entire pregnancy) - 1.00 - 1.06 three-pollutant models with CO & O_3 all births (first month) - 1.00 - 1.04 all births (second month) - 1.00 -1.04 all births (third month) - 1.00 - 1.03 preterm births (first month) - 1.01 - 1.07 preterm births (second month) - 1.01 - 1.07 preterm births (third month) - 1.01 - 1.06 three-pollutant models with NO_2 & O_3 all births (first month) - 1.00 - 1.04 all births (second month) - 1.00 - 1.04 all births (third month) - 1.00 -1.04 preterm births (first month) - 1.02 - .08 preterm births (second month) - 1.02 - 1.09 preterm births (third month) - 1.02 - 1.09	weak statistically significant associations with stillborn total and pre-term births (<37 weeks) using a single pollutant model with different exposure periods; statistically significant association with total and pre-term stillbirths using a three pollutant model with either CO & O_3 or NO_2 & O_3 using the first, second or third month of exposures as a metric; when no significant associations found using any measure of exposure with term births (≥37 weeks) using an adjusted single pollutant or three pollutant model	⊕○○○ (insufficient because the failure to include PM_{10} in the three pollutant modeling despite the high correlations observed between ambient SO_2 and PM_{10})

author	location	exposure monitoring	SO_2 concentration	study type (duration)	endpoint	co-pollutants	participants	ratio or risk	confidence interval	results	GRADE quality of evidence
(Lin et al., 2014)	Taiwan	measurement from 72 air pollution monitoring stations assigned to zip codes by inverse distance weighting	average concentration during the first trimester cases - 5.23 ppb (13.9 µg/m³) controls - 5.17 ppb (13.8 µg/m³)	case control (7 years)	limb defects (polydactyly, syndactyly, or reduction limb deformities) with pre-term and full term infants	association with PM_{10}, SO_2, O_3, CO, & NO_2	males and females 1687 cases 16,870 controls	adjusted odds ratio for limb defects (polydactyly, syndactyly, or reduction limb deformities) per 1 ppb (2.6 µg/m³) increase using a single or two-pollutant model single pollutant reduction limb deformities all infants (weeks 9-12) - 1.024 syndactyly females (1st trimester) - 1.026 females (weeks 1-4) - 1.023 females (weeks 5-8) - 1.025 females (weeks 9-12) - 1.022 syndactyly pre-term (1st trimester) - 1.051 pre-term (weeks 1-4) - 1.045 pre-term (weeks 5-8) - 1.043 pre-term (weeks 9-12) - 1.042 full term (weeks 5-8) - 1.015 two-pollutant model (all infants) reduction limb deformities (weeks 9-12) SO_2/O_3 - 1.024 SO_2/CO - 1.023 SO_2/NO_2 - 1.024 SO_2/PM_{10} - 1.023	adjusted odds ratio for limb defects (polydactyly, syndactyly, or reduction limb deformities) per 1 ppb (2.6 µg/m³) increase using a single pollutant model single pollutant reduction limb deformities all infants (weeks 9-12) - 1.000 - 1.048 syndactyly females (1st trimester) - 1.007 - 1.045 females (weeks 1-4) - 1.005 - 1.042 females (weeks 5-8) - 1.008 - 1.042 females (weeks 9-12) - 1.004 - 1.041 syndactyly pre-term (1st trimester) - 1.019 - 1.085 pre-term (weeks 1-4) - 1.013 - 1.078 pre-term (weeks 5-8) - 1.013 - 1.075 pre-term (weeks 9-12) - 1.015 - 1.071 full term (weeks 5-8) - 1.000 - 1.030 two-pollutant model (all infants) reduction limb deformities (weeks 9-12) SO_2/O_3 - 1.001 - 1.048 SO_2/CO - 1.000 - 1.047 SO_2/NO_2 - 1.000 - 1.048 SO_2/PM_{10} - 1.000 - 1.047	statistically significant association in all infant reduction deformities of the limbs for exposures during week 9-12 but not the entire first trimester or for weeks 1-4 or weeks 5-8 using a single pollutant model; significant association with syndactyly in female but not male infants for all four exposure measurement periods (entire first trimester, 1-4, 5-8, and 9-12 weeks) using a single pollutant model; significant association with syndactyly in pre-term for all four exposure measurement periods and full-term infants 5-8 and 9-12 week exposures using a single pollutant model; no association with all limb defects, polydactyly, or syndactyly in all infants for any exposure period; no association with all limb defects, polydactyly, or reduction deformities in males, all pre-term, or all full term infants for any exposure period; statistically significant association with reduction deformities in two pollutant models with PM_{10}, O_3, CO, or NO_2 for the 9-12 week exposures but not for remaining periods; no association all limb defects, polydactyly, or syndactyly using any pollutant model with any of four exposure periods	⊕⊕◯◯ (low quality because the failure to include $PM_{2.5}$ in the analysis and high probability of type 1 errors))

author	location	exposure monitoring	SO_2 concentration	study type (duration)	endpoint	co-pollutants	participants	ratio or risk	confidence interval	results	GRADE quality of evidence
(Mannisto et al., 2015)	United States	hourly averages estimated using CMAQ air shed model that considers national emission inventories along with meteorology and atmospheric photochemistry then corrected by inverse distance weighting using the values from an unstated number of fixed monitoring sites	hourly average 0 hour - 2.6 ppb (6.9 µg/m³) 1st hour - 2.6 ppb (6.9 µg/m³) 2nd hour - 2.5 ppb (6.6 µg/m³) 3rd hour - 2.5 ppb (6.6 µg/m³) 4th hour - 2.5 ppb (6.6 µg/m³)	cohort (7 years)	higher blood pressure category upon admission for delivery in women who are normotensive or have gestational hypertension, preeclampsia, chronic hypertension, or superimposed preeclampsia	association with $PM_{2.5}$, PM_{10}, SO_2, O_3, CO, NOx, EC, OC, nitrates, sulfates, dust particles, ammonium particles, 12 PAHs, and 14 VOCs	females average age 26.7 - 30.7 years normotensive - 138,470 cases gestational hypertension - 3935 cases preeclampsia - 5744 cases chronic hypertension - 2490 cases superimposed preeclampsia - 637 cases	adjusted odds ratio for a higher blood pressure category upon admission for delivery per 1 ppb (2.6 µg/m³) increase using a single pollutant model at various lag times normotensive 0 hour - 1.003 1st hour - 1.004 2nd hour - 1.003 3rd hour - 1.003 chronic hypertension 1st hour - 1.023 2nd hour - 1.027	adjusted odds ratio for a higher blood pressure category upon admission for delivery per 1 ppb (2.6 µg/m³) increase using a single pollutant model at various lag times normotensive 0 hour - 1.001 - 1.006 1st hour - 1.002 - 1.007 2nd hour - 1.001 - 1.006 3rd hour - 1.000 - 1.005 chronic hypertension 1st hour - 1.003 - 1.043 2nd hour - 1.005 - 1.049	statistically significant association with higher blood pressure in normotensive pregnant women upon admission for delivery using a single pollutant model with a lag of 0, 1, 2, or 3 but not 4 hours; significant association with higher blood pressure in pregnant women with chronic hypertension upon admission for delivery using a single pollutant model with a lag of 1 and 2 hours but not 0, 4, or 5 hours; no positive association in women with gestational hypertension, preeclampsia, or superimposed preeclampsia; significant negative association with a blood pressure decrease at a lag of 3 hours in women with superimposed preeclampsia	⊕⊕◯◯ (low quality because no multi-pollutant modeling)

author	location	exposure monitoring	SO_2 concentration	study type (duration)	endpoint	co-pollutants	participants	ratio or risk	confidence interval	results	GRADE quality of evidence
(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 2.10 ppb (5.59 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 change for birth weight < 2500 g at specific distances from monitoring site 10 km - 1.01	odds ratio per 10 µg/m³ change for birth weight < 2500 g at specific distances from monitoring site 10 km - 1.00 - 1.02	slight statistically significant increase in odds ratio for low birth weight (<2500 g) at distances of 10 km from the monitoring site; no statistically significant difference at 3 or 5 km; statistically significant percentage increase in birth weight during the first trimester at 5 and 10 km but not at 3 km; stratification against other race and ethnicity not performed to the equivocal results; two-pollutant modeling results not displayed because of the failure to find negative declines in most comparisons	⊕⊕◯◯ (low quality because exposure misclassification resulting from the use of the nearest monitor)
(Nordling et al., 2008)	Sweden (4 municipalities)	determination of home levels using local dispersion model that included emission estimates of oil consumption for home heating and sulfur content then linear back extrapolation of levels to earlier periods of life	source specific increase in annual mean concentration first year of life - 2.5 µg/m³	prospective cohort (48 month)	respiratory symptoms for wheeze (transient, late onset, or persistent), peak expiratory flow (PEF), and serum IgE antibodies for any food, any inhalant, pollens, or furred pets	association with outdoor PM_{10} and NO_2, and indoor SO_2	male and females (2 mo of age) 3515 infant volunteers	no change in adjusted odds ratio for transient, late onset, or persistent wheeze, PEF, or IgE antibodies to any food, any inhalant, pollens or furred pets per 3 µg/m³ (5-95% range) increment using a single pollutant model for indoor exposures	no change in adjusted odds ratio for transient, late onset, or persistent wheeze, PEF, or IgE antibodies to any food, any inhalant, pollens or furred pets per 3 µg/m³ (5-95% range) increment using a single pollutant model for indoor exposures	no statistically significant association of indoor levels with transient, late onset, or persistent wheeze in boys or girls up to four years of age in a single pollutant model; no association of indoor levels with peak expiratory flow in boys or girls; no association with IgE antibodies in both sexes to any food, any inhalant, pollen (birch, timothy, or mugwort, or furred (cats, horse, or dogs)	⊕◯◯◯ (insufficient because the failure to include $PM_{2.5}$ in the analysis and the absence of two-pollutant modeling)

author	location	exposure monitoring	SO_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 18.3 ppb (48.7 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	no increase in odds ratio for apnea or bradycardia per 20 ppb (53.2 µg/m³) for 2 day moving average lag in a single pollutant model	no increase in odds ratio for apnea or bradycardia per 20 ppb (53.2 µg/m³) for 2 day moving average lag in a single pollutant model	no statistically significant association with bradycardia or apnea in infants using a single pollutant model and a 2 day moving average lag; no statistically significant associations when the dependant variables were stratified by gestational age or birth weight	⊕⊕◯◯ (low quality because of the high probability of exposure misclassification)
(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 1st trimester - 5.8 ppb (15.4 µg/m³) 2nd trimester - 5.7 ppb (15.2 µg/m³) 3rd trimester - 5.5 ppb (14.6 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 134,798 births (single pollutant) 59,955 births (two pollutant)	no change in the risk percentage for SGA or VSGA fetal growth ratio per IQR of 3 ppb (8.0 µg/m³) in a single pollutant model at the first, second, or third trimester of gestational development	no change in the risk percentage for SGA or VSGA fetal growth ratio per IQR of 3 ppb (8.0 µg/m³) in a single pollutant model at the first, second, or third trimester of gestational development	no statistically significant associations in either of two gestational growth rate measures during all three trimesters in a single pollutant model; neither birth weight classified as either small for gestational age (SGA) with a growth ratio greater than or equal to 0.75 and less than 0.85 or very small for gestational age (VSGA) with a infant/normal birth weight ratio less than 0.75	⊕◯◯◯ (insufficient because the failure to include PM_{10} in the analysis and the absence of two-pollutant modeling)
(Slama et al., 2013)	Teplice, Czech Republic	monthly averages from a single fixed monitoring site	monthly averages not provided	cohort (11 years)	fecundability in a birth cohort	association with $PM_{2.5}$, SO_2, O_3, NO_2 and 8 PAHs	females 1916 pregnancies	no change in unadjusted, partially adjusted, or fully adjusted pregnancy ratio per 10 µg/m³ increase using a single pollutant model with either of the four monthly exposure lags	no change in unadjusted, partially adjusted, or fully adjusted pregnancy ratio per 10 µg/m³ increase using a single pollutant model with either of the four monthly exposure lags	no significant association with fetal death using an unadjusted or fully adjusted single pollutant model with lag periods of 0-30 days, 30-60 days, or 0-60 days before fertilization or 0-30 days after fertilization	⊕◯◯◯ (insufficient because the high probability of exposure misclassification and the failure to include PM_{10} in the analysis)

author	location	exposure monitoring	SO_2 concentration	study type (duration)	endpoint	co-pollutants	participants	ratio or risk	confidence interval	results	GRADE quality of evidence
(Son et al., 2008)	Seoul, Korea	pooled mean daily concentration from 27 fixed monitoring locations	mean daily concentration 5.60 ppb (14.9 µg/m³)	case-crossover and time-series (5 years)	postnatal mortality in first born infants	differential effects of PM_{10}, SO_2, O_3, CO & NO_2	males and females neonatal - 7839 deaths post neonatal - 1286 deaths	no significant change in relative risk for mortality in single pollutant model in either the time-series or case-crossover design using an unstated IQR increase and lag period	no significant change in relative risk for mortality in single pollutant model in either the time-series or case-crossover design using an unstated IQR increase and lag period	no significant associations observed for neonatal or post-neonatal mortality using either a time-series or case-crossover design with a single pollutant model and a lag period of either 1 or 7 days	⊕○○○ (insufficient because the failure to include $PM_{2.5}$ in the analysis and the absence of two-pollutant modeling)
(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 season of conception spring - 5.4 ppb (14.4 µg/m³) summer - 5.4 ppb (14.4 µg/m³) fall - 6.9 ppb (18.4 µg/m³) winter - 7.1 ppb (18.9 µg/m³)	retrospective cohort (18 years)	infant cardiovascular malformations (atrial septal defects, coarctation of aorta, hypoplastic left heart syndrome, patent ductus arteriosus, pulmonary valve stenosis, tetralogy of Fallot, transposition of the great arteries, muscular and perimembranous ventricular septal defect, conotruncal defect, and left and right ventricular outflow tract defect)	association with PM_{10}, SO_2, O_3, CO, & NO_2	male & female 3,338 cases	no change in risk ratios for any cardiovascular malformation per IQR increase of 4.0 ppb (10.6 µg/m³) using stringent or weak control for seasonal & temporal variation in a single pollutant model using the 5 week average exposure concentration	no change in risk ratios for any cardiovascular malformation per IQR increase of 4.0 ppb (10.6 µg/m³) using stringent or weak control for seasonal & temporal variation in a single pollutant model using the 5 week average exposure concentration	no statistically significant association with any of 12 different cardiovascular malformation in infants after at least 20 weeks gestation using a single pollutant model with strict or loose control of seasonal and temporal variations; 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 the high probability of exposure misclassification and the failure to include PM_{10} in the analysis)
(Tsai et al., 2006a)	Kaohsiung, Taiwan	daily average from six monitoring stations	daily mean concentration 11.24 ppb (29.90 µg/m³)	case-crossover (7 years)	post neonatal mortality	association with PM_{10}, SO_2, O_3, CO, & NO_2	male and female infants older than 28 days and less than a year mortality 207 deaths recorded	no change in adjusted odds ratio per IQR increase of 6.66 ppb (17.72 µg/m³) in a single pollutant model with 01 cumulative lag	no change in adjusted odds ratio per IQR increase of 6.66 ppb (17.72 µg/m³) in a single pollutant model with 01 cumulative lag	no statistically significant association with infant mortality in the first year of life using a single pollutant model a 2 day cumulative lag period	⊕○○○ (insufficient because the failure to include $PM_{2.5}$ in the analysis and the absence of two-pollutant modeling)

author	location	exposure monitoring	SO_2 concentration	study type (duration)	endpoint	co-pollutants	participants	ratio or risk	confidence interval	results	GRADE quality of evidence
(Woodruff et al., 2008)	96 counties in the United States	monthly monitoring data from an unknown number of sites linked by county to participants	median monthly conc. survivors - 2.81 ppb (7.47 µg/m³) all cause death - 3.14 ppb (8.35 µg/m³) respiratory causes - 3.01 ppb (8.01 µg/m³) SIDS - 2.81 ppb (7.47 µg/m³) SIDS & other ill defined - 3.13 ppb (8.33 µg/m³) other causes - 3.17 ppb (8.43 µg/m³)	case control (4 years)	infant mortality from sudden infant death syndrome (SIDS), respiratory causes, and other ill defined causes	association with PM_{10}, $PM_{2.5}$, O_3, SO_2 & CO	male & female up to a year of age 3,583,495 births 6639 deaths	no increase in fully adjusted odds ratio for any cause of death in either single or two pollutant models per IQR increase of 2.7 ppb (7.2 µg/m³)	no increase in fully adjusted odds ratio for any cause of death in either single or two pollutant models per IQR increase of 2.7 ppb (7.2 µg/m³)	no statistically significant increase in infant mortality from any cause including SIDS and other respiratory diseases using single or four pollutant models with PM, O_3, & CO	⊕⊕⊕○ (moderate quality no adjustment necessary, but number of monitoring sites not stated)

author	location	exposure monitoring	SO_2 concentration	study type (duration)	endpoint	co-pollutants	participants	ratio or risk	confidence interval	results	GRADE quality of evidence
(Xu et al., 2014)	Jacksonville, Florida	daily averages from the nearest of four fixed monitoring sites geocoded to residential location	daily averages full pregnancy - 6.08 ppb (16.17 µg/m³) 1st trimester - 5.98 ppb (15.91 µg/m³) 2nd trimester - 6.07 ppb (16.15 µg/m³)	retrospective cohort (3 years)	hypertensive disorders of pregnancy	association with $PM_{2.5}$, SO_2, CO, O_3, & NO_2	females 1037 cases 21,004 controls	adjusted odds ratio for hypertensive disorders of pregnancy per IQR increase in single pollutant model single pollutant model full pregnancy (IQR 2.55 ppb) - 1.01 - 1.25 1st trimester (IQR 3.73 ppb) - 1.03 - 1.26 two pollutant model SO_2/NO_2 full pregnancy (IQR 2.55 ppb) - 1.13 1st trimester (IQR 3.73 ppb) - 1.12 $SO_2/PM_{2.5}$ 1st trimester (IQR 3.73 ppb) - 1.12 SO_2/CO full pregnancy (IQR 2.55 ppb) - 1.11 1st trimester (IQR 3.73 ppb) - 1.11 SO_2/O_3 full pregnancy (IQR 2.55 ppb) - 1.13 1st trimester (IQR 3.73 ppb) - 1.16	adjusted odds ratio for hypertensive disorders of pregnancy per IQR increase in single pollutant model single pollutant model full pregnancy (IQR 2.55 ppb) - 1st trimester (IQR 3.73 ppb) - two pollutant model SO_2/NO_2 full pregnancy (IQR 2.55 ppb) - 1.02 - 1.26 1st trimester (IQR 3.73 ppb) - 1.01 - 1.24 $SO_2/PM_{2.5}$ 1st trimester (IQR 3.73 ppb) - 1.01 - 1.24 SO_2/CO full pregnancy (IQR 2.55 ppb) - 1.00 - 1.23 1st trimester (IQR 3.73 ppb) - 1.01 - 1.23 SO_2/O_3 full pregnancy (IQR 2.55 ppb) - 1.01 - 1.25 1st trimester (IQR 3.73 ppb) - 1.04 - 1.29	statistically significant association with hypertensive disorders of pregnancy in fully adjusted single pollutant model for the full pregnancy or during the 1st trimester; significant association with hypertensive disorders in two pollutant models with CO, O_3, & NO_2 for the full pregnancy and the 1st trimester and with $PM_{2.5}$ for the 1st trimester; no associations found in single or two pollutant models for exposures during the 2nd trimester; stratification by ethnicity, smoking status, and diabetic status showed associations in adjusted single pollutant models with non-Hispanic whites, non-smokers, and non-gestational diabetics for full pregnancy and 1st trimester; stratification by education and residential distance from a monitoring site showed associations in those with greater than a high school education and those living ≤ 10 km from a monitoring site for the 1 st trimester exposure measurements only	⊕⊕◯◯ (low quality because PM_{10} levels not measured)

Stroke and Hypertension

author	location	exposure monitoring	SO_2 concentration	study type (duration)	endpoint	co-pollutants	participants	ratio or risk	confidence interval	results	GRADE quality of evidence
(Brook and Kousha, 2015)	Calgary and Edmonton, Canada	daily averages from an unstated number of fixed monitoring sites	daily medians Calgary - 1.0 ppb (2.6 µg/m³) Edmonton - 0.9 ppb (2.4 µg/m³)	case-crossover (2 years)	emergency department visits for hypertension	association with $PM_{2.5}$, SO_2, O_3, and NO_2	males and females aged 0 to 100 6532 visits	pooled (fixed effects) odds ratio for hypertension stratified by sex and season per IQR increase of 0.78 ppb (2.07 µg/m³) in a single pollutant model on various lag days males (cold season) lag day 6 - 1.074 females (cold season) lag day 4 - 1.108 lag day 5 - 1.077 lag day 8 - 1068 females (warm season) lag day 2 - 1.080 lag day 8 - 1.052	pooled (fixed effects) odds ratio for hypertension stratified by sex and season per IQR increase of 0.78 ppb (2.07 µg/m³) in a single pollutant model on various lag days males (cold season) lag day 6 - 1.000 - 1.048 females (cold season) lag day 4 - 1.040 - 1.177 lag day 5 - 1.009 - 1.144 lag day 8 - 1005 - 1.131 females (warm season) lag day 2 - 1.022 - 1.138 lag day 8 - 1.000 - 1.110	statistically significant association with ED visits for hypertension in males during the cold season on lag day 6 but not lag days 0, 1, 2, 3, 4, 5, 7, or 8 using a single pollutant model; significant association in females in cold season on lag days 4, 5, and 8 but not the remaining 6 lag days; significant association in females during warm season on lag days 2 and 8 but not the remaining 7 lag days; no association with males during the warm season on any lag day	⊕○○○ (insufficient because of high likelihood of exposure misclassification and the failure to consider PM_{10} in two pollutant models)
(Chen et al., 2013)	8 cities in China	daily averages from 2-12 fixed monitoring units located in background sites within each city	daily mean Beijing - 41 µg/m³ Fuzhou - 16 µg/m³ Guangzhou - 50 µg/m³ Hong Kong - 18 µg/m³ Shanghai - 45 µg/m³ Shenyang - 55 µg/m³ Suzhou - 45 µg/m³ Tangshan - 84 µg/m³	time-series (12 years)	stroke mortality	association with PM_{10}, SO_2, & NO_2	males and females 4-26 deaths/day	pooled percent increase in stroke mortality per 10 µg/m³ increase using a 2 day (0-1) moving average lag SO_2 only - 0.88 SO_2/PM_{10} - 0.54	pooled percent increase in stroke mortality per 10 µg/m³ increase using a 2 day (0-1) moving average lag SO_2 only - 0.54 - 1.22 SO_2/PM_{10} - 0.06 - 1.01	statistically significant association with stroke in single pollutant model on lag days 0 and 1 and moving averages for 2 and 5 days but not on lag days 2,3, and 4; statistically significant association with stroke mortality in single pollutant and a two pollutant model with PM_{10} but not with NO_2 using 2 day moving average lag; associations observed with stoke in 7 of the 8 cites examined	⊕⊕○○ (low quality because collinearity from $PM_{2.5}$ not evaluated)

author	location	exposure monitoring	SO_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 4.94 ppb (13.14 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	no significant increase in biomarkers per IQR increase of 3.18 ppb (8.46 µg/m³) in single pollutant model	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	no statistically significant association with nine biochemical or physiological biomarkers (systolic BP, diastolic BP, total cholesterol, triglycerides, HDL cholesterol, fasting glucose, hemoglobin, interleukin 6, neutrophils) in a single pollutant model using a lag period of 1 year	⊕⊕○○ (low quality because of the failure to perform two-pollutant modeling)
(Corea et al., 2012)	Mantua, Italy	daily averages from 7 fixed monitoring sites	daily average exposures not stated	case-crossover (3 years)	hospitalization for cerebrovascular disease (transient ischemic attack and stroke)	association with PM_{10}, SO_2, O_3, CO, NO, NO_2, and benzene	males and females 781 cases	no change is odds ration for any cerebrovascular even or ischemic stroke in men or women per an unstated increase in SO_2 using a single pollutant model with an unstated lag period	no change is odds ration for any cerebrovascular even or ischemic stroke in men or women per an unstated increase in SO_2 using a single pollutant model with an unstated lag period	no statistically significant association with cerebrovascular disease or stroke hospital admissions in single pollutant model; no significant association found with 6 different stroke subtypes	⊕○○○ (insufficient because of poor methodological description and absence of two-pollutant modeling)
(Filho et al., 2008)	Sao Paulo, Brazil	daily average from thirteen fixed monitoring sites	daily average 13.8 µg/m³	time-series (31 months)	emergency room visits for cardiovascular disease (ischemic heart disease and hypertension) in type 2 diabetics and non-diabetics	association with PM_{10}, SO_2, O_3, CO, & NO_2	males and females (daily rates) diabetics - 0.6 visits/day non-diabetics - 16.8 visits/day	percent increase in cardiovascular ER visits per IQR 8.0 µg/m³ for diabetics and non-diabetics in single pollutant model at various lag periods (data depicted graphically) diabetics lag day 0 ≈ 20 avg lag 01 ≈ 25 avg lag 02 ≈ 25 non-diabetics lag day 0 ≈ 7 avg lag 01 ≈ 7 avg lag 02 ≈ 6 avg lag 03 ≈ 7	percent increase in cardiovascular ER visits per IQR 8.0 µg/m³ for diabetics and non-diabetics in single pollutant model at various lag periods (data depicted graphically) diabetics lag day 0 ≈ 4 - 37 avg lag 01 ≈ 5 - 44 avg lag 02 ≈ 2 - 47 non-diabetics lag day 0 ≈ 3 - 11 avg lag 01 ≈ 3 - 10 avg lag 02 ≈ 2 - 10 avg lag 03 ≈ 2 - 11	statistically significant association with cardiovascular emergency room visits for diabetics on lag day 0, 01, and 02 and non-diabetics on lag day 0, 01, 02 and 03, no statistically significant association on lag day 2 & cumulative lag 03 for diabetics and lag day 1 and cumulative lag 01 for non-diabetics	⊕○○○ (insufficient because no two-pollutant modeling and the failure to consider PM_{10} in two pollutant models)

author	location	exposure monitoring	SO_2 concentration	study type (duration)	endpoint	co-pollutants	participants	ratio or risk	confidence interval	results	GRADE quality of evidence
(Guo et al., 2010b)	Beijing, China	mean daily concentration at eight fixed monitoring locations	daily mean 47.3 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 using a single pollutant SO_2 only - 1.037	odds ratio per 10 µg/m³ increase on lag day 3 using a single pollutant SO_2 only - 1.004 - 1.071	statistically significant association with emergency department visits for hypertension in a single pollutant model on lag days 0 and 2 but not lag days 1, 3, 4, or 5; no statistically significant association in multi-pollutant models with PM_{10}, NO_2, or PM_{10}/NO_2 together on lag day 0	⊕⊕○○ (low quality because of exposure misclassification)
(Jalaludin et al., 2006)	Sydney, Australia	daily averages from 14 fixed monitoring sites	daily mean concentration 1.07 ppb (2.85 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 2.2 ppb (5.9 µg/m³) in single and two-pollutant models cardiovascular total (lag day 0) SO_2 only - 1.33 SO_2/O_3 ≈ 2.1 (depicted graphically) cardiac disease (lag day 0) SO_2 only - 1.62 ischemic heart disease (lag day 2) SO_2 only - 1.97	percent change in total cardiovascular emergency department visits per IQR 2.2 ppb (5.9 µg/m³) in single and two-pollutant models cardiovascular total (lag day 0) SO_2 only - 0.24 - 2.43 SO_2/O_3 ≈ 0.04 - 2.7 (depicted graphically) cardiac disease (lag day 0) SO_2 only - 0.33 -2.93 ischemic heart disease (lag day 2) SO_2 only - 0.07 - 3.91	statistically significant association with total cardiovascular ED visits on lag day 0 in single and two-pollutant models with O_3, but not with PM_{10}, $PM_{2.5}$, CO, or NO_2; statistically significant association with cardiac disease on lag day 0 and ischemic heart disease on lag day 2 in single pollutant model but not for stroke on any lag day: statistically significant positive association with all total cardiovascular, cardiac disease, and ischemic heart disease ED visits on lag day 0 for cool period but not warm periods, no statistically significant association with stroke visits for either season	⊕○○○ (insufficient because of publication, selection, and lag bias)

author	location	exposure monitoring	SO_2 concentration	study type (duration)	endpoint	co-pollutants	participants	ratio or risk	confidence interval	results	GRADE quality of evidence
(Liu et al., 2014)	Sault Ste. Marie, Ontario	daily average from a single fixed site monitor located near a steel mill (test site) or a college campus (control site)	daily median college site - 0.6 ppb (1.6 µg/m³) steel mill site - 1.2 ppb (3.2 µg/m³)	randomized crossover study (5 consecutive 8 hour days at each site with a 9 day wash-out period in between)	cardiovascular parameters (systolic blood pressure, diastolic blood pressure, pulse rate, pulse pressure, and flow mediated vasodilation) in normal individuals	association with ultarfine particulates (UFP), $PM_{2.5}$, SO_2, O_3, NO_2 and CO	males and females 18 to 55 years old 61 subjects	change in cardiovascular measurements following 30 minutes of exercise per IQR increase of 3.6 ppb (9.6 µg/m³) using a single pollutant model with no exposure lag pulse rate - 0.26	change in cardiovascular measurements following 30 minutes of exercise per IQR increase of 3.6 ppb (9.6 µg/m³) using a single pollutant model with no exposure lag pulse rate - 0.01 - 0.51	statisitically significant association with tan increase in pulse rate follwoing 30-minutes of exercise using a single pollutant model with no exposure lag; no significant difference in pulse rate increase for the test versus the control site; no statistically significant association with systolic blood pressure, diastolic blood pressure, pulse rate, pulse pressure, and flow mediated vasodilatation in normal subjects spending 8-hr near a steel mill versus a college campus using a singlue pollutant model with a same day or 1 day lag time	⊕○○○ (insufficient because of the exposure misclassification and the failure to perform two-pollutant modeling)

author	location	exposure monitoring	SO_2 concentration	study type (duration)	endpoint	co-pollutants	participants	ratio or risk	confidence interval	results	GRADE quality of evidence
(Mannisto et al., 2015)	United States	hourly averages estimated using CMAQ air shed model that considers national emission inventories along with meteorology and atmospheric photochemistry then corrected by inverse distance weighting using the values from an unstated number of fixed monitoring sites	hourly average 0 hour - 2.6 ppb (6.9 µg/m³) 1st hour - 2.6 ppb (6.9 µg/m³) 2nd hour - 2.5 ppb (6.6 µg/m³) 3rd hour - 2.5 ppb (6.6 µg/m³) 4th hour - 2.5 ppb (6.6 µg/m³)	cohort (7 years)	higher blood pressure category upon admission for delivery in women who are normotensive or have gestational hypertension, preeclampsia, chronic hypertension, or superimposed preeclampsia	association with $PM_{2.5}$, PM_{10}, SO_2, O_3, CO, NOx, EC, OC, nitrates, sulfates, dust particles, ammonium particles, 12 PAHs, and 14 VOCs	females average age 26.7 - 30.7 years normotensive - 138,470 cases gestational hypertension - 3935 cases preeclampsia - 5744 cases chronic hypertension - 2490 cases superimposed preeclampsia - 637 cases	adjusted odds ratio for a higher blood pressure category upon admission for delivery per 1 ppb (2.6 µg/m³) increase using a single pollutant model at various lag times normotensive 0 hour - 1.003 1st hour - 1.004 2nd hour - 1.003 3rd hour - 1.003 chronic hypertension 1st hour - 1.023 2nd hour - 1.027	adjusted odds ratio for a higher blood pressure category upon admission for delivery per 1 ppb (2.6 µg/m³) increase using a single pollutant model at various lag times normotensive 0 hour - 1.001 - 1.006 1st hour - 1.002 - 1.007 2nd hour - 1.001 - 1.006 3rd hour - 1.000 - 1.005 chronic hypertension 1st hour - 1.003 - 1.043 2nd hour - 1.005 - 1.049	statistically significant association with higher blood pressure in normotensive pregnant women upon admission for delivery using a single pollutant model with a lag of 0, 1, 2, or 3 but not 4 hours; significant association with higher blood pressure in pregnant women with chronic hypertension upon admission for delivery using a single pollutant model with a lag of 1 and 2 hours but not 0, 4, or 5 hours; no positive association in women with gestational hypertension, preeclampsia, or superimposed preeclampsia; significant negative association with a blood pressure decrease at a lag of 3 hours in women with superimposed preeclampsia	⊕⊕◯◯ (low quality because no multi-pollutant modeling)
(Spiezia et al., 2014)	Padua, Italy	monthly average form the nearest of two fixed monitoring sites	monthly exposure average not stated	case control (5 years)	hospital admission for thromboembolism	association with PM_{10}, SO_2, O_3, CO, NOx, benzene, benzo(a)pyrene, cadmium, nickel, lead, and arsenic	males and female > 18 years of age 17 cases 24 controls	no change in unadjusted or adjusted odds ratio for pulmonary embolism hospitalization per 2nd tertile increase of 2.01 µg/m³ using a single pollutant model	no change in unadjusted or adjusted odds ratio for pulmonary embolism hospitalization per 2nd tertile increase of 2.01 µg/m³ using a single pollutant model	no statistically significant association with admissions for pulmonary embolism in an unadjusted or adjusted single pollutant model	⊕◯◯◯ (insufficient because the exposure misclassification and absence of two pollutant modeling)

author	location	exposure monitoring	SO_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 2.6 ppb (6.9 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	change in relative risk percentage for ED visits for ischemic stroke per IQR 2.3 ppb (6.1 µg/m³) in a single pollutant model group age 20-64 years cold seasons & females (lag day 1) - 6.0 group age 65-100 years old cold season & all sexes (lag day 1) - 4.4 all seasons & females (lag day 1) - 4.6 warm seasons & males (lag day 0) - 9.1	change in relative risk percentage for ED visits for ischemic stroke per IQR 2.3 ppb (6.1 µg/m³) in a single pollutant model group age 20-64 years cold seasons & females (lag day 1) - 0.5 - 11.8 group age 65-100 years old cold season & all sexes (lag day 1) - 0.4 - 8.6 all seasons & females (lag day 1) - 0.4 - 9.0 warm seasons & males (lag day 0) - 2.2 - 16.4	significant association ED visits for ischemia in females but not males aged 20-64 years for the cold season but not all seasons or the warm season in a single pollutant model on lag day 1; statistically significant association for males and females aged 65- 100 years old during the cold season on lag day 1 and males during the warm season on lag day 0; significant association for all season females on lag 1 but not other seasons or lag days; no association in all season or cold season for males on lag day 1 and 2; no association warm or cold season for females on lag day 0 or 2	⊕○○○ (insufficient because of the exposure misclassification and the failure to perform two-pollutant modeling)
(Szyszkowicz et al., 2012c)	Edmonton, Canada	daily average concentration from three fixed monitoring sites	daily mean 2.6 ppb (6.9 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	increased odds ratio for hypertension ED visits per IQR of 2.3 ppb (6.1 µg/m³) in single pollutant model using single or cumulative 3-day lag periods up to seven days lag day 3 - 1.04	increased odds ratio for hypertension ED visits per IQR of 2.3 ppb (6.1 µg/m³) in single pollutant model using single or cumulative 3-day lag periods up to seven days lag day 3 - 1.00 - 1.08	statistically significant association with emergency dept visits for hypertension using a single pollutant model on lag day 3, no statistical significance on the other seven single lag days all eight 3-day cumulative lag periods	⊕○○○ (insufficient because of the exposure misclassification and the failure to perform two-pollutant modeling)

author	location	exposure monitoring	SO_2 concentration	study type (duration)	endpoint	co-pollutants	participants	ratio or risk	confidence interval	results	GRADE quality of evidence
(Szyszkowicz et al., 2012a)	Vancouver, Canada	daily averages from 4 to 11 fixed monitoring stations over the course of the study	daily average 2.5 ppb (6.6 µg/m³)	case-crossover (51 months)	emergency department visits for stroke or seizure	association with $PM_{2.5}$, PM_{10}, SO_2, O_3, CO, & NO_2	males and females aged 0 to 85 years stroke - 1002 cases seizure - 2120 cases	odds ratio for stoke or seizure ED visits per IQR increase of 1.9 ppb (5.1 µg/m³) in single and two pollutant models at various lag periods stroke (single pollutant) all subjects (lag day 3) - 1.12 female subjects (lag day 0) - 1.17 seizure (single pollutant) female subjects (lag day 1) - 1.15 female subjects (lag day 2) - 1.18 stroke (multi pollutant; lag day 3) all subjects (SO_2/O_3) - 1.16 all subjects (SO_2/CO) - 1.11 all subjects (SO_2/CO/O_3) - 1.11	odds ratio for stoke or seizure ED visits per IQR increase of 1.9 ppb (5.1 µg/m³) in single and two pollutant models at various lag periods stroke (single pollutant) all subjects (lag day 3) - 1.02 -1.23 female subjects (lag day 0) - 1.01 - 1.33 seizure (single pollutant) female subjects (lag day 1) - 1.02 - 1.28 female subjects (lag day 2) - 1.05 - 1.32 stroke (multi pollutant; lag day 3) all subjects (SO_2/O_3) - 1.05 - 1.29 all subjects (SO_2/CO) - 1.00 - 1.24 all subjects (SO_2/CO/O_3) - 1.00 - 1.24	statistically significant association with ED visits for stroke in all patients on lag day 3 and females on lag day 0 but not in any of other 7 lag periods examined using a single pollutant model, no significant associations with ED visits for stroke in males on any of eight lag days using a single pollutant model; association with ED visits for seizure with females on lag days 1 and 2 but not other lag periods using a single pollutant model; no significant associations with ED visits for seizure in all patients or males on any of eight lag days using a single pollutant model; significant association with visits for stroke in all patients using a two pollutant model with O_3 and CO and a three pollutant model with O_3 and CO together using a 3 day lag	⊕○○○ (insufficient because of the small number of cases and publication bias)

author	location	exposure monitoring	SO_2 concentration	study type (duration)	endpoint	co-pollutants	participants	ratio or risk	confidence interval	results	GRADE quality of evidence
(Xu et al., 2014)	Jacksonville, Florida	daily averages from the nearest of four fixed monitoring sites geocoded to residential location	daily averages full pregnancy - 6.08 ppb (16.17 µg/m³) 1st trimester - 5.98 ppb (15.91 µg/m³) 2nd trimester - 6.07 ppb (16.15 µg/m³)	retrospective cohort (3 years)	hypertensive disorders of pregnancy	association with $PM_{2.5}$, SO_2, CO, O_3, & NO_2	females 1037 cases 21,004 controls	adjusted odds ratio for hypertensive disorders of pregnancy per IQR increase in single pollutant model single pollutant model full pregnancy (IQR 2.55 ppb) - 1.01 - 1.25 1st trimester (IQR 3.73 ppb) - 1.03 - 1.26 two pollutant model SO_2/NO_2 full pregnancy (IQR 2.55 ppb) - 1.13 1st trimester (IQR 3.73 ppb) - 1.12 $SO_2/PM_{2.5}$ 1st trimester (IQR 3.73 ppb) - 1.12 SO_2/CO full pregnancy (IQR 2.55 ppb) - 1.11 1st trimester (IQR 3.73 ppb) - 1.11 SO_2/O_3 full pregnancy (IQR 2.55 ppb) - 1.13 1st trimester (IQR 3.73 ppb) - 1.16	adjusted odds ratio for hypertensive disorders of pregnancy per IQR increase in single pollutant model single pollutant model full pregnancy (IQR 2.55 ppb) - 1st trimester (IQR 3.73 ppb) - two pollutant model SO_2/NO_2 full pregnancy (IQR 2.55 ppb) - 1.02 - 1.26 1st trimester (IQR 3.73 ppb) - 1.01 - 1.24 $SO_2/PM_{2.5}$ 1st trimester (IQR 3.73 ppb) - 1.01 - 1.24 SO_2/CO full pregnancy (IQR 2.55 ppb) - 1.00 - 1.23 1st trimester (IQR 3.73 ppb) - 1.01 - 1.23 SO_2/O_3 full pregnancy (IQR 2.55 ppb) - 1.01 - 1.25 1st trimester (IQR 3.73 ppb) - 1.04 - 1.29	statistically significant association with hypertensive disorders of pregnancy in fully adjusted single pollutant model for the full pregnancy or during the 1st trimester; significant association with hypertensive disorders in two pollutant models with CO, O_3, & NO_2 for the full pregnancy and the 1st trimester and with $PM_{2.5}$ for the 1st trimester; no associations found in single or two pollutant models for exposures during the 2nd trimester; stratification by ethnicity, smoking status, and diabetic status showed associations in adjusted single pollutant models with non-Hispanic whites, non-smokers, and non-gestational diabetics for full pregnancy and 1st trimester; stratification by education and residential distance from a monitoring site showed associations in those with greater than a high school education and those living ≤ 10 km from a monitoring site for the 1st trimester exposure measurements only	⊕⊕◯◯ (low quality because PM_{10} levels not measured)

Myocardial Infarction

author	location	exposure monitoring	SO_2 concentration	study type (duration)	endpoint	co-pollutants	participants	ratio or risk	confidence interval	results	GRADE quality of evidence
(Berglind et al., 2009)	Augsburg, Germany Barcelona, Spain Helsinki, Finland Rome, Italy Stockholm, Sweden	daily average concentration in five European cites using an unstated number of fixed monitoring locations	daily median concentration Augsburg - 4.22 µg/m³ Barcelona - 11.00 µg/m³ Helsinki - 3.13 µg/m³ Rome - 3.98 µg/m³ Stockholm - 2.61 µg/m³	cohort study (up to 240 months)	mortality amongst survivors of myocardial infarction	association with PM_{10}, CO, O_3, SO_2, & NO_2	male & female 25,006 cohort 8,555 cases	pooled random effects change in the percentage of non-traumatic deaths per 2 µg/m³ change using a single pollutant model day lag 0 to 14 - 8.06	pooled random effects change in the percentage of non-traumatic deaths per 2 µg/m³ change using a single pollutant model day lag 0 to 14 4.38 - 11.90	statistically significant association with daily non-traumatic deaths with a 15 day lag period but not a 2-day or 5 day lag period when measurements pooled for 4 of the five cites examined; no association with deaths due to cardiovascular disease; statistical association with the group aged 35-65 yrs, but not in those 65-74, > 75 years, no association with groups followed up for a year longer or a year less	⊕⊕◯◯ (low quality because single pollutant modeling and high collinearity with other pollutants)
(Cheng et al., 2009)	Kaohsiung, Taiwan	mean daily concentration at six fixed monitoring locations	daily mean 9.33 ppb (24.82 µg/m³)	case-crossover (132 months)	hospitalization for myocardial infarction	association with PM_{10}, SO_2, O_3, CO, & NO_2	male & female cases 9.349	odds ratio per IQR of 5.16 ppb (13.72 µg/m³) in single and two-pollutant model single pollutant temp < 25 ˚C - 1.09 two pollutant (SO_2/O_3) temp ≥ 25 ˚C - 1.05 temp < 25 ˚C - 1.09	odds ratio per IQR of 5.16 ppb (13.72 µg/m³) in single and two-pollutant model single pollutant temp < 25 ˚C - 1.01 - 1.19 two pollutant (SO_2/O_3) temp ≥ 25 ˚C - 1.00 - 1.11 temp < 25 ˚C - 1.01 - 1.19	statistically significant associations observed in single pollutant model at ambient temperatures < 25 ˚C and in a two-pollutant model with O_3 at temperatures < 25 ˚C and ≥ 25 ˚C; not significant associations in two pollutant models with PM_{10}, NO_2, or CO	⊕⊕◯◯ (low quality because no evaluation of $PM_{2.5}$ interactions)

author	location	exposure monitoring	SO_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 4.36 ppb (11.60 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	no positive relationships with myocardial infarction admissions in single or two pollutant models with PM_{10}, NO_2, O_3, or CO with an IQR increase of 2.69 ppb (7.16 µg/m³ NO_2) at temperatures ≥ 23 ˚C or < 23 ˚C on lag day 0 plus the previous two days; some negative associations observed with two-pollutant models	no positive relationships with myocardial infarction admissions in single or two pollutant models with PM_{10}, NO_2, O_3, or CO with an IQR increase of 2.69 ppb (7.16 µg/m³ NO_2) at temperatures ≥ 23 ˚C or < 23 ˚C; some negative associations observed with two-pollutant models	no statistically significant positive change in the odds ratio for myocardial infarction in either of two temperature groups (≥ 23 ˚C or < 23 ˚C) using single or two -pollutant models with PM_{10}, NO_2, O_3, or CO; statistically significant negative associations observed with two-pollutant modeling using PM_{10}, NO_2, or CO	⊕○○○ (insufficient because of the failure to examine $PM_{2.5}$ interactions and imprecision indicated by the negative associations)
(Rich et al., 2010)	New Jersey	daily average from fourteen 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 increase in relative risk per IQR increase of 4.1 ppb (10.9 µg/m³) in a single or two pollutant model with a lag of 0 days	no increase in relative risk per IQR increase of 4.1 ppb (10.9 µg/m³) in a single or two pollutant model with a lag of 0 days	no statistically significant association with hospital admissions for transmural infarctions on lag day 0 with single or two pollutant model with $PM_{2.5}$	⊕○○○ (insufficient because the failure to include PM_{10} in the analysis)
(Silverman et al., 2010)	New York, New York	pooled mean daily concentration from 15 fixed monitoring locations	daily mean annual - 6.3 ppb (16.8 µg/m³) warm season - 4.2 ppb (11.2 µg/m³) cold season - 9.3 ppb (24.7 µg/m³)	time-series and case-crossover (60 months)	cardiac arrest (out of hospital)	differential effects of $PM_{2.5}$, SO_2, O_3, CO & NO_2	males and females in three age groups 8,216 cases	no change in annual, warm season, or cold season relative risk for cardiac arrest for an IQR increase of 6 ppb (16.0 µg/m³) in a single pollutant model a 2 day average lag	no change in annual, warm season, or cold season relative risk for cardiac arrest for an IQR increase of 6 ppb (16.0 µg/m³) in a single pollutant model a 2 day average lag	no significant associations for yearly, cold season, or warm season cardiac arrests using a single pollutant model with a time-series design	⊕○○○ (insufficient because of the failure to perform two-pollutant modeling and the high correlation with PM_{10} and $PM_{2.5}$)

author	location	exposure monitoring	SO_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 11 fixed monitoring sites	hourly mean Montreal - 4.8 ppb (12.8 µg/m³) Ottawa - 3.9 (10.4 µg/m³) Edmonton - 2.6 (6.9 µg/m³) Saint John - 7.7 (20.5 µg/m³) Halifax - 10.0 ppb (26.6 µg/m³) Toronto - 4.2 ppb (11.2 µg/m³) Vancouver - 2.6 ppb (6.9 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 (fixed and random effects) percent increase in emergency department visits per 5.1 ppb (13.6 µg/m³) in a single pollutant model for the summer season angina/infarction lag day 1 - 2.1	pooled (fixed and random effects) percent increase in emergency department visits per 5.1 ppb (13.6 µg/m³) in a single pollutant model for the summer season angina/infarction lag day 1 - 0.2 - 4.0	statistically significant association with ED visits for angina/infarction in a single pollutant model on lag day 2; no statistically significant associations ED visits for all other cardiac and respiratory conditions in a single pollutant model at any of three daily lag periods or any of six within day 3 hour lag periods; no associations with visits for any condition during the winter months	⊕⊕◯◯ (low quality because of absence of methodological details and the lack of two-pollutant models)

Inflammation

author	location	exposure monitoring	SO_2 concentration	study type (duration)	endpoint	co-pollutants	participants	ratio or risk	confidence interval	results	GRADE quality of evidence
(Hart et al., 2013)	Sweden	annual home level estimated using a local dispersion model that included emission estimates of oil consumption for home heating and sulfur content with a linear back extrapolation of levels to earlier periods of life	annual medians 5th year before - 1.7 µg/m³ 10th year before - 2.7 µg/m³ 20 the year before - 9.1 µg/m³ overall from birth - 7.7 µg/m³	case control (30 years)	rheumatoid arthritis in anti-citrullinated peptide antibody (ACPA) positive and negative individuals	association with PM_{10}, SO_2, and NO_2	males and females 18 - 70 years of age 1497 cases 2536 controls	partially (age and sex) and fully adjusted odds ratio per 8 µg/m³ increase for different exposure periods prior to onset partially adjusted 10th year before - 1.28 20th year before - 1.12 fully adjusted 20th year before - 1.08	partially (age and sex) and fully adjusted odds ratio per 8 µg/m³ increase for different exposure periods prior to onset partially adjusted 10th year before - 1.06 - 1.55 20th year before - 1.05 - 1.21 fully adjusted 20th year before - 1.00 - 1.16	statisitically significant association with all rheumatoid arthritis cases using a partially adjusted single pollutant model with a 10 or 20 year prior exposure metric but not a 5 year or total from birth metric; significant association in a fully adjusted single pollutant model using a 20 year prior exposure metric but not a 5 year, 10 year or total from birth metric; significant association antibody negative RA subjects for all partially and fully adjusted single pollutant models with a 10 or 20 year prior exposure metric but not a 5 year or total from birth metric;	⊕○○○ (insufficient because of the failure to perform two-pollutant modeling and likelihood of exposure misclassification)
(MacIntyre et al., 2011)	British Columbia	monthly average using inverse distance weighting to residential postal code using the measurement from 14 fixed monitoring sites	monthly average 5.1 µg/m³	prospective cohort (2 years)	physician diagnosis of for otitis media in children	association with $PM_{2.5}$, PM_{10}, SO_2, O_3, CO, NO, NO_2, wood smoke, and black carbon	males and females less than 2 years of age 41,506 births	no change in crude or adjusted relative risk for otitis media per 3.2 µg/m³ IQR increase using a single pollutant model	no change in crude or adjusted relative risk for otitis media per 3.2 µg/m³ IQR increase using a single pollutant model	no statistically significant association with physician diagnosed otitis media in children less than two years of age using a single pollutant model	⊕⊕○○ (low quality because publication bias of the narrow range of SO_2 concentrations)

author	location	exposure monitoring	SO_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 2.8 ppb (7.4 µg/m³)	time-series (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	absolute change serum biomarkers per IQR of 1.6 ppb (4.3 µg/m³) in multi-pollutant models serum fibrinogen concentration (mg/dL) men single pollutant lag day 4 - -5.5 lag day 5 - -3.9 lag day 0-6 avg - -7.1 men two pollutant model SO_2/O_3 lag day 4 - -5.1 white blood cell count men single pollutant lag day 6 - -115 lag day 7 - -151	absolute change serum biomarkers per IQR of 1.6 ppb (4.3 µg/m³) in multi-pollutant models serum fibrinogen concentration (mg/dL) men single pollutant lag day 4 - -9.1 - -2.0 lag day 5 - -7.4 - -0.5 lag day 0-6 avg - -12.3 - -2.0 men two pollutant model SO_2/O_3 lag day 4 - -9.5 - -0.7 white blood cell count men single pollutant lag day 6 - -222 - -8 lag day 7 - -258 - -45	statistically significant decrease in fibrinogen in males using a single pollutant model with a lag of 4 or 5 days or average one week lag but no association with the remaining lag periods; significant association with decreased white blood cell count with males in a single pollutant model on lag days 6 and 7 but not with the remaining 7 lag periods; no association with any biomarker changes in females using single or multi-pollutant models for any lag period; significant decrease in fibrinogen in males using a two pollutant model with O_3 but not with PM_{10},, NO_2, or CO on lag day 4; no association with decreased fibrinogen using three or four pollutant models with PM_{10},, NO_2, O_3, or CO on lag day 4	⊕⊕◯◯ (low quality because of absence of PM2.5 measurements)

author	location	exposure monitoring	SO_2 concentration	study type (duration)	endpoint	co-pollutants	participants	ratio or risk	confidence interval	results	GRADE quality of evidence
(Thompson et al., 2010)	Toronto, Ontario	hourly measurement from a single fixed monitoring site	seasonal average spring - 3.09 ppb (8.22 µg/m³) summer - 2.95 ppb (7.85 µg/m³) autumn - 3.61 ppb (9.60 µg/m³) winter - 4.60 ppb (1`2.24 µg/m³)	time-series (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	mean percentages for inflammatory biomarkers per unstated IQR increase in a single pollutant model fibrinogen 4 day (0-3) lag - 0.25 5 day (0-4) lag - 0.25 (depicted graphically)	mean percentages for inflammatory biomarkers per unstated IQR increase in a single pollutant model fibrinogen 4 day (0-3) lag - 0.06 - 0.43 5 day (0-4) lag - 0.02 - 0.46 (depicted graphically)	statistically significant positive association with blood fibrinogen levels in single pollutant model with a moving average lag period of 4 or 5 days but not for the remaining ten lag periods; no statistically significant association with blood interleukin-6 biomarker in single pollutant model for any of the 12 lag periods examines; no association with interleulin-6 levels collected during the winter, spring, summer, or fall seasons in single pollutant model	⊕○○○ (insufficient because of the failure to perform two-pollutant modeling and the high likelihood of exposure misclassification)

Central Nervous System

author	location	exposure monitoring	SO_2 concentration	study type (duration)	endpoint	co-pollutants	participants	ratio or risk	confidence interval	results	GRADE quality of evidence
(Dales et al., 2009)	Santiago, Chile	daily averages from seven fixed monitoring sites	daily concentration 9.32 ppb (24.79 µg/m³)	time-series (5 years)	hospitalization for headaches categorized as i) not otherwise specified, ii) migraine, and iii) specified cause (tension, cluster, vascular, post-traumatic, & drug-related)	association with $PM_{2.5}$, PM_{10}, SO_2, O_3, CO, & NO_2	males and females not otherwise specified - 1.168 cases/day migraine - 0.744 cases/day specified cause - 0.561 cases/day	pooled relative risk of headache hospitalization per IQR increase of 6.20 ppb (16.49 µg/m³) using a single pollutant model with 2 different lag periods not otherwise specified lag day 1 - 1.094 distributed lag 0-5 days - 1.108 migraine lag day 1 - 1.104 distributed lag 0-5 days - 1.133 specified cause lag day 1 -1.113 distributed lag 0-5 days - 1.125	pooled relative risk of headache hospitalization per IQR increase of 6.20 ppb (16.49 µg/m³) using a single pollutant model with 2 different lag periods not otherwise specified lag day 1 - 1.033 - 1.158 distributed lag 0-5 days - 1.014 - 1.202 migraine lag day 1 - 1.040 - 1.172 distributed lag 0-5 days - 1.049 - 1.217 specified cause lag day 1 -1.020 - 1.215 distributed lag 0-5 days - 1.017 - 1.233	statistically significant association with hospitalization for 3 types of headache (cause not specified, migraine, and specified cause) using a single pollutant model with either a single day or distributed 6 day lag period; significant association observed for caused not specified and migraine headaches using two pollutant models with either $PM_{2.5}$, PM_{10}, O3, and CO but not NO_2; significant association observed headaches with specified causes using two pollutant models with O3 & NO_2 but not $PM_{2.5}$, PM_{10}, or CO; stratification by age revealed associations for those ≤ 64 years of age, > 64 years of age for cause not specified and migraine headaches; stratification by sex found associations in males for cause not specified headache and females for migraine headache; stratification by season showed no association; stratification by age, sex or season showed no association with headaches with a specified cause	⊕⊕◯◯ (low quality because of the sex-related inconsistencies and the likelihood of case misidentification)

author	location	exposure monitoring	SO_2 concentration	study type (duration)	endpoint	co-pollutants	participants	ratio or risk	confidence interval	results	GRADE quality of evidence
(Szyszkowicz, 2011)	Edmonton, Alberta	mean daily concentration at an unstated number of fixed monitoring locations	daily mean 2.6 ppb (6.9 µg/m³)	case-crossover (120 months)	emergency department visits for clinical depression	association with control day separation, SO_2, CO & NO_2	female 15,556 cases	change in odds ratio for depression ED visits per an unstated IQR increase with a single pollutant model lag day 0 all seasons, female patients - 3.0 warm seasons, female patients - 4.5 lag day 2 all seasons, female patients - 3.5 warm season, female patients - 3.8	change in odds ratio for depression ED visits per an unstated IQR increase with a single pollutant model lag day 0 all seasons, female patients - 0.2 - 5.8 warm seasons, female patients - 0.1 - 9.1 lag day 2 all seasons, female patients - 0.7 - 6.3 warm season, female patients - 0.1 - 7.7	statistically significant association emergency department visits for depression in females for both seasons and the warm season using a single pollutant model on lag days o and 2 but not on lag day 1; no association with males or all patients for any lag period or any seasonal stratification	⊕○○○ (insufficient because of the unstated number of monitoring sites and failure to perform two-pollutant modeling)
(Szyszkowicz et al., 2009b)	7 Canadian cities Edmonton, Alberta Halifax, Nova Scotia Ottawa, Ontario Montreal, Quebec Toronto, Ontario Sunnybrook, Ontario Vancouver, British Columbia	mean daily concentration at an unstated number of fixed monitoring locations within seven cities	daily mean concentration Edmonton - 2.6 ppb (6.9 µg/m³) Halifax - 10.0 ppb (26.6 µg/m³) Ottawa - 4.8 ppb (12.8 µg/m³) Montreal - 3.9 ppb (10.4 µg/m³) Toronto - 4.2 ppb (11.2 µg/m³) Sunnybrook - 4.5 ppb (12.0 µg/m³) Vancouver - 2.5 ppb (6.6 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	pooled and adjusted percentage relative risk for depression ED visits per 4.6 ppb (12.2 µg/m³) change in a single pollutant model on lag day 0 warm season (Apr - Sept) - 5.9	pooled and adjusted percentage relative risk for depression ED visits per 4.6 ppb (12.2 µg/m³) change in a single pollutant model on lag day 0 warm season (Apr - Sept) - 1.1 - 11.0	statistically significant association depression ED vests in warm summer months using a single pollutant model on lag day 0, no association observed for all seasons and the cold months	⊕⊕○○ (low quality because of bias from single pollutant model)

author	location	exposure monitoring	SO_2 concentration	study type (duration)	endpoint	co-pollutants	participants	ratio or risk	confidence interval	results	GRADE quality of evidence
(Szyszkowicz et al., 2009a)	6 Canadian cities Edmonton, Alberta Halifax, Nova Scotia Ottawa, Ontario Toronto, Ontario Sunnybrook, Ontario Vancouver, British Columbia	mean daily concentration at an unstated number of fixed monitoring locations within six cities	daily mean concentration Edmonton - 2.6 ppb (6.9 µg/m³) Halifax - 10.0 ppb (26.6 µg/m³) Ottawa - 3.9 ppb (10.4 µg/m³) Toronto - 4.2 ppb (11.2 µg/m³) Sunnybrook - 4.5 ppb (12.0 µg/m³) Vancouver - 2.5 ppb (6.6 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	pooled percentage increase in relative risk for migraine ED visits per 2.3 ppb (6.1 µg/m³) change using a single pollutant model on lag day 0 warm seasons, female patients - 4.0	pooled percentage increase in relative risk for migraine ED visits per 2.3 ppb (6.1 µg/m³) change using a single pollutant model on lag day 0 warm seasons, female patients - 0.8 - 7.3	statistically significant association with ED visits for migraine in females during the warm season using a single pollutant model with the same day lag; no associations with visits for migraine in males or for males or females in all seasons combined or for the cold season for lag days 1 and 2; no association ED visits for headache following stratification by sex or season on any lag day	⊕⊕◯◯ (low quality because of bias from single pollutant model)

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