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Online Supplement

Short-term exposure to sulphur dioxide (SO_2) and all-cause and respiratory mortality: a systematic review and meta-analysis

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Table A.1. PRISMA checklist.

#	Item	Guidance	On page #
Title			
1	Title	Identify the report as a systematic review, or systematic review and meta-analysis, as appropriate.	1
Abstract			
2	Structured summary	Provide a structured summary including, as applicable: • Background; • Objectives; • Data sources; • Study eligibility criteria, participants, and interventions; • Study appraisal and synthesis methods; • Results; • Limitations; conclusions and implications of key findings; • Systematic review registration number.	2-3
Introduction			
3	Rationale	Describe the rationale for the review in the context of what is already known.	4-5
4	Objectives	Provide an explicit Population-Intervention-Comparator-Outcome-Study Design (PICOS) or Population-Exposure-Comparator-Outcome-Study Design (PECOS) statement as appropriate, detailing the following in relation to the research questions being asked: • Participants • Interventions / Exposures (as appropriate) • Comparisons • Outcomes • Study design	5-6
Methods			
5	Protocol and registration	Indicate if a review protocol exists, if and where it can be accessed (e.g. web address), and registration information including registration number (if available).	1, 5, and Supplementary data 2
6	Eligibility criteria	Specify study characteristics (e.g. PICOS/PECOS, length of exposure) and report characteristics (e.g. years considered, language, publication status) used as criteria for eligibility, giving rationale.	6-7, and Table 1
7	Information sources	Describe all information sources (e.g. databases with dates of coverage, contact with study authors to identify additional studies) in the search, and date last searched.	7-8

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#	Item	Guidance	On page #
8	Search	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Table A.2 (Supplementary data 1)
9	Study selection	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	7-8
10	Data collection process	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	8
11	Data items	List and define all variables for which data were sought (e.g., PICOS/PECOS, funding sources) and any assumptions and simplifications made.	8
12	Risk of bias in individual studies	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	9-10, and Table A.3 (Supplementary data 1)
13	Summary measures	State the principal summary measures (e.g., risk ratio, difference in means).	10-11
14	Synthesis of results	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	10-13
15	Risk of bias across studies	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	13-16, and Supplementrary data 3
16	Additional analyses	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	11-12
Results			
17	Study selection	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, illustrated with a PRISMA flow diagram.	16-18, Figure 1, and Supplementary data 4
18	Study characteristics	For each study, present in a summary table the characteristics for which data were extracted (e.g., study size, PICOS/PECOS, follow-up period) and provide the citations.	Supplementary data 5
19	Risk of bias within studies	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	19, Figure A.1 (Supp. data 1), and Supp. Data 6

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#	Item	Guidance	On page #
20	Results of individual studies	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot (unless such a plot would be misleading)	Supplementary data 5, and Figures 2 to 5
21	Synthesis of results	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	19-21, and Table 2
22	Risk of bias across studies	Present results of any assessment of risk of bias across studies (see Item 15).	23-24, Figure A.2 (Supp. data 1), and Table 2
23	Additional analysis	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	21-24, and Tables A.4 to A.10 (Supp. Data 1)
Discussion			
24	Summary of evidence	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., researchers, users, and policy makers).	27-32
25	Limitations	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	32-33
26	Conclusions	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	33-34
Funding			
27	Funding	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	34-35

Environment International modified PRISMA report adapted from: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097. (Changes are minor, with text edits to accommodate the subject matter of the journal and formatting to fit page.).

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Table A.2. Search strategy for MEDLINE via PubMed.

	Search timeline: 01.Jan.1980 – 31.Dec.2018 [1]	**Abstracts**
#4	Search: (#1 AND #2 AND #3) AND (("1980/01/01"[Date - Publication] : "2018/12/06"[Date - Publication])) Sort by: Most Recent	311
#3	Search: ("short term"[TIAB] OR shortterm[TIAB] OR "short range"[TIAB] OR acute[TIAB] OR "acute disease"[MH]) AND (("1980/01/01"[Date - Publication] : "2018/12/06"[Date - Publication])) Sort by: Most Recent	1,194,266
#2	Search: (mortality[TIAB] OR mortalities[TIAB] OR death[TIAB] OR deaths[TIAB] OR dying[TIAB] OR fatal[TIAB] OR fatality[TIAB] OR lethal[TIAB] OR death[MH] OR mortality[MH]) AND (("1980/01/01"[Date - Publication] : "2018/12/06"[Date - Publication])) Sort by: Most Recent	1,611,713
#1	Search: (("sulfur dioxide"[TIAB] OR "sulfur oxides"[TIAB] OR SO2[TIAB] OR "sulfur dioxide"[MH] OR "sulfur oxides"[MH] OR SOx[TIAB])) AND (("1980/01/01"[Date - Publication] : "2018/12/06"[Date - Publication])) Sort by: Most Recent	14,106

[1] The search was updated in July 2020.

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Table A.3. Criteria for the risk of bias (RoB) assessment

Domain / Subdomain	Criterion for low RoB	Criterion for moderate RoB	Criterion for high RoB
1. Confounding			
Were all confounders considered adjusted for in the analysis?	Critical and additional confounders accounted for. For ETS: Temperature, Seasonality, Day of the week, Long-term trends, Holidays (not vacations), Influenza epidemics. For CCO: Temperature, Influenza epidemics.	Critical confounders accounted for. For ETS: Temperature, Seasonality, Day of the week, Long-term trends. For CCO: Temperature.	Less than all critical confounders accounted for, or confounders not reported.
Validity of measuring of confounding factors	The majority of critical and additional confounders are independent from the method for measuring (DoW, seasonality, long-term trends, holidays). Temperature is less subject to variations than air pollution, and does not need a particular monitoring network. Flu epidemics are in general well detected through epidemiological surveillance.	----	----
Control in analysis (Did the authors use an appropriate analysis method or study design that controlled for confounding domains?)	Use of poisson regression with GLM or GAM, or logistic regression in CCO designs.	----	Other procedures, or not reported.
2. Selection bias			
Selection of participants into the study (includes non-response)	As the outcome is mortality in a city (or region), it can be expected that all deads were reported and included in the study.	----	----

RoB, risk of bias; ETS, ecological time-series design; CCO, case-crossover design; DoW, day-of-week; GLM, generalized linear model; GAM, generalized additive model; ICD, international classification of diseases.

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Table A.3. *(continued)*

Domain / Subdomain	Criterion for low RoB	Criterion for moderate RoB	Criterion for high RoB
3. Exposure assessment			
Methods used for exposure assessment	Measurements of air pollutants were provided by one or more monitoring stations in the city.	Air pollution estimated through a validated prediction model, or using data from a station outside the city.	----
Exposure measurement methods comparable across the range of exposure	In time-series studies of short-term exposure, the methods for exposure measure are the same between groups.	----	----
Exposure contrast	In time-series studies of short-term exposure, between-subject (days) variance is always supposed to be larger than the within-subject variance. This can be seen in the description tables of averages and dispersion values.	----	----
4. Outcome measurement			
Blinding of outcome measurement	Mortality is not supposed to be influenced by the knowledge of the exposure.	----	----
Validity of outcome measurements	The validity is judged to be adequate in all-cause mortality.	The validity is judged to be not adequate in cause-specific mortality. However, the measurement is not related to the exposure.	---
Outcome measurement	The authors used the ICD; or the authors didn't use the ICD or other known standard, but for all-cause mortality this does not lead to bias	----	The authors didn't report the use of the ICD or other known standard for cause-specific mortality

RoB, risk of bias; ETS, ecological time-series design; CCO, case-crossover design; DoW, day-of-week; GLM, generalized linear model; GAM, generalized additive model; ICD, international classification of diseases.

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Table A.3 *(continued)*

Domain / Subdomain	Criterion for low RoB	Criterion for moderate RoB	Criterion for high RoB
5. Missing data			
Missing data of outcome measures	For mortality data extracted from death registries, missing data is not expected.	---	----
Missing data of exposures	The authors described adequate methods for imputation of missing data, or no missing data observed, or missing data lower than 5%.	----	No data on number of missing values, imputation methods, or number of missing data higher than 5%.
6. Selective reporting			
Authors reported a priori primary and secondary study aims	Paper reproting data analysis over a complete or original database.	Paper reporting a subset or re-analysis of data that were already published in a previous article, or that will be published later.	----

RoB, risk of bias; ETS, ecological time-series design; CCO, case-crossover design; DoW, day-of-week; GLM, generalized linear model; GAM, generalized additive model; ICD, international classification of diseases.

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Figure A.1. Summary of the risk of bias (RoB) assessment.

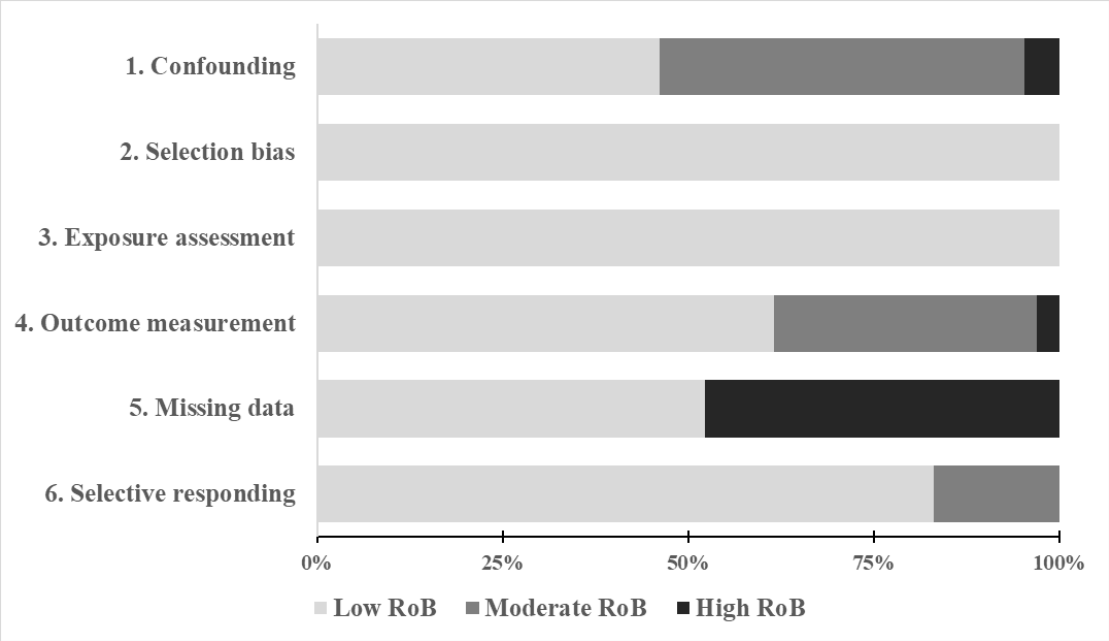

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Table A.4. Subgroup analysis by age, sex, and continent.

Pollutant	Outcome	Subgroup	Number of effect sizes	RR (95% CI)	p-value
SO_2 (24-hour average)	All-cause mortality	All ages	36	**1.0059 (1.0042-1.0075)**	**<0.01**
		Children	4	**1.0616 (1.0389-1.0849)**	
		Elderly	23	1.0042 (0.9989-1.0094)	
SO_2 (24-hour average)	All-cause mortality	Male	5	1.0060 (0.9958-1.0162)	0.36
		Female	5	1.0127 (0.9953-1.0304)	
SO_2 (24-hour average)	All-cause mortality	Europe	20	**1.0066 (1.0035-1.0098)**	0.49
		Asia	14	**1.0054 (1.0036-1.0073)**	
SO_2 (24-hour average)	Respiratory mortality	All ages	23	**1.0067 (1.0022-1.0113)**	0.09
		Elderly	10	**1.0153 (1.0050-1.0257)**	
SO_2 (24-hour average)	Respiratory mortality	Male	6	1.0115 (0.9829-1.0409)	0.99
		Female	6	1.0111 (0.9554-1.0701)	
SO_2 (24-hour average)	Respiratory mortality	Europe	15	1.0054 (0.9982-1.0127)	0.40
		Asia	8	**1.0084 (1.0054-1.0114)**	
SO_2 (1-hour max.)	All-cause mortality	All ages	4	1.0016 (0.9930-1.0102)	0.74
		Elderly	6	1.0005 (0.9953-1.0056)	

RR, pooled relative risks; 95% CI, 95% confidence interval; p-value, significance of the test for the difference between subgroups (interaction); statistically significant results in bold.

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Table A.5. Sensitivity analysis by lag[1].

Pollutant	Outcome	Number of effect sizes	RR (95% CI)	p-value	PI
SO_2 (24-hour average)	All-cause mortality	25	**1.0070 (1.0053-1.0088)**	**<0.0001**	**1.0026-1.0114**
SO_2 (24-hour average)	Respiratory mortality	14	**1.0070 (1.0006-1.0135)**	**0.0345**	0.9961-1.0180
SO_2 (1-hour max.)	All-cause mortality	4	1.0016 (0.9985-1.0046)	0.3137	0.9967-1.0064

RR, pooled relative risks; 95% CI, 95% confidence interval; p-value, significance of the association; PI, 80% prediction interval; statistically significant results in bold.

[1] Considering only lags 0-1, 0, and 1 days.

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Table A.6. Sensitivity analysis by study design.

Pollutant	Outcome	Study design	Number of effect sizes	RR (95% CI)	p-value
SO_2 (24-hour average)	All-cause mortality	ETS	29	**1.0063 (1.0049-1.0078)**	**<0.0001**
		CCO	7	**1.0033 (1.0025-1.0042)**	**<0.0001**
SO_2 (24-hour average)	Respiratory mortality	ETS	18	**1.0063 (1.0007-1.0120)**	**0.0308**
		CCO	5	**1.0059 (1.0008-1.0110)**	**0.0323**
SO_2 (1-hour max)	All-cause mortality	ETS	3	1.0015 (0.9902-1.0129)	0.6283
SO_2 (1-hour max)	Respiratory mortality	ETS	3	**1.0052 (1.0013-1.0091)**	**0.0287**

RR, pooled relative risks; 95% CI, 95% confidence interval; p-value, significance of the association; ETS, ecological time series design; CCO, case-crossover design; statistically significant results in bold.

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Table A.7. Sensitivity analysis comparing multicity versus single-city studies.

Pollutant	Outcome	Type of study	Number of effect sizes	RR (95% CI)	p-value
SO_2 (24-hour average)	All-cause mortality	Multicity	11	**1.0047 (1.0031-1.0063)**	0.25
		Single-city	25	**1.0067 (1.0034-1.0101)**	
SO_2 (24-hour average)	Respiratory mortality	Multicity	10	**1.0067 (1.0023-1.0112)**	0.72
		Single-city	13	1.0044 (0.9912-1.0178)	

RR, pooled relative risks; 95% CI, 95% confidence interval; P-value, significance of the test for the difference between subgroups (interaction); statistically significant results in bold.

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Table A.8. Sensitivity analysis by risk of bias (RoB) in individual studies.

Pollutant	Outcome	RoB domain	Number of effect sizes	RoB value	RR (95% CI)	p-value
SO_2 (24-hour average)	All-cause mortality	Missing	19	Low - moderate	**1.0048 (1.0023-1.0073)**	0.21
			17	High	**1.0067 (1.0047-1.0088)**	
SO_2 (24-hour average)	All-cause mortality	Confounding	33	Low - moderate	**1.0053 (1.0038-1.0068)**	0.06
			3	High	1.0105 (0.9993-1.0219)	
SO_2 (24-hour average)	Respiratory mortality	Missing	11	Low - moderate	**1.0094 (1.0039-1.0149)**	0.23
			12	High	1.0050 (0.9989-1.0111)	

RR, pooled relative risks; 95% CI, 95% confidence interval; p-value, significance of the test for the difference between subgroups (interaction); statistically significant results in bold.

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Table A.9. Unbiased relative risks and E-value.

Pollutant	**Outcome**	**E-value (95% CI)**	**RR_U**[1] (Song et al., 2017)
SO_2 (24-hour average)	All-cause mortality	1.2052 (1.1773-1.2292)	1.100
SO_2 (24-hour average)	Respiratory mortality	1.2213 (1.1253-1.2982)	1.210
SO_2 (1-hour max)	Respiratory mortality	1.1905 (1.0875-1.2665)	1.210

E-Value, a value that quantifies, for a single study, the minimum confounding bias capable of reducing the true effect to a chosen threshold; 95% CI, 95% confidence interval; RR_U, RR of the associations between air temperature, a potential unmeasured confounder, and all-cause and respiratory mortality.

[1] Song, X., Wang, S., Hu, Y., Yue, M., Zhang, T., Liu, Y., Tian, J., Shang, K., 2017. Impact of ambient temperature on morbidity and mortality: An overview of reviews. Sci. Total Environ. 586, 241–254. https://doi.org/10.1016/j.scitotenv.2017.01.212

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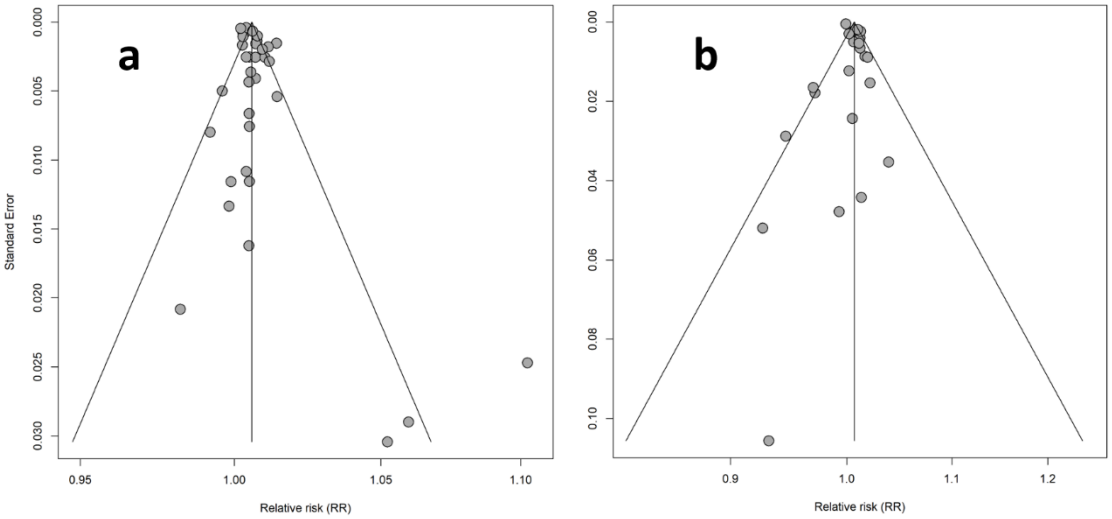
Figure A.2. Funnel plots to explore publication bias.



a) SO_2 (24-hour average) – All-cause mortality; b) SO_2 (24-hour average) – Respiratory mortality

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Table A.10. Co-pollutant analysis.

Pollutant	Outcome	Number of effect sizes	Single pollutant model	Co-pollutant model	
			RR (95% CI)	**RR (95% CI)**	**Adjusted by**
SO_2 (24-hour average)	All-cause mortality	8	**1.0053 (1.0031-1.0076)**	**1.0038 (1.0021-1.0054)**	PM
SO_2 (24-hour average)	All-cause mortality	3	1.0043 (0.9971-1.0115)	1.0043 (0.9964-1.0123)	O_3
SO_2 (24-hour average)	All-cause mortality	5	**1.0059 (1.0020-1.0099)**	1.0038 (0.9980-1.0095)	NO_2
SO_2 (24-hour average)	Respiratory mortality	4	**1.0088 (1.0032-1.0146)**	**1.0059 (1.0028-1.0090)**	PM

RR, pooled relative risks; 95% CI, 95% confidence interval; p-value, significance of the association; statistically significant results in bold.