World Health Organization

REGIONAL OFFICE FOR Europe

Long-term exposure to $PM_{2.5}$ and PM_{10} and all-cause and cause-specific mortality: a systematic review and meta-analysis protocol

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Update of WHO Global AQGs

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1. Introduction

The update of the WHO Global Air Quality Guidelines (AQGs) is a global project coordinated by the WHO Regional Office's European Centre for Environment and Health (ECEH) in Bonn (Germany), including participation from all WHO Regions and WHO headquarters.

The Guideline Development Group (GDG) for the AQGs at its first scoping meeting agreed to use, to the extent possible, existing systematic reviews, if those respond to the question of interest defined for the particular pollutant, averaging times and health outcome, and to update them to the latest date possible with additional primary studies. If required elements are missing in these existing systematic reviews (such as risk of bias assessment of individual studies on which causality determination is based or which are used for concentration-response function estimation, or proper reporting standards as those outlined in this document), these will have to be added a posteriori. Also, where specific evidence or data synthesis is lacking, the data of the primary studies will be extracted anew to be able to reach a conclusion about the magnitude and the direction of the effect and the confidence in it, based on a Grading of Recommendations Assessment, Development and Evaluation (GRADE) assessment. When no suitable systematic reviews can be identified for a specific question, new systematic reviews will be conducted by a group of experienced authors on the specific topic of the review (i.e. the systematic review team, SRT), ensuring proper methodological expertise and sufficient time commitment to meet the project timeline.

This document is based on a **draft protocol** for the conduct (and update) of systematic reviews for the WHO Global AQGs, and describes the rationale, objectives for the review, research question formulation, methods for its development (location, selection and extraction of data, risk of bias assessment of individual studies, data management and synthesis, and evaluation of the overall quality of the body of evidence) and requirements for reporting of the final product, to meet the quality standards required for use in WHO guidelines development. The development of this protocol has been largely based on standards set by the Cochrane Collaboration and adapted for application to observational studies (Higgins and Green, 2011) and the *Preferred Reporting Items for Systematic Review and Meta-analysis Protocols* (PRISMA-P) standards (Shamseer et al, 2015; Moher D et al, 2015).

The systematic review team has completed the protocol template where needed, and proposed modifications and changes where pertinent to develop a final version. The final protocol will be published in the International Prospective Register of Systematic Reviews (PROSPERO).

2. Administrative information

2.2.1 Type of systematic review

- Updated review.
- Review will be updated based on: Hoek G, Krishnan RM, Beelen R, Peters A, Ostro B, Brunekreef B, Kaufman JD. Long-term air pollution exposure and cardio-respiratory mortality: a review. Environmental Health 2013. 12:43.
- There is no published protocol for the 2013 review. We will follow the protocol outlined here to identify and extract information from studies. We will thus not use the quantitative information from the earlier review. We will use the review to identify studies.

2.2.2 The systematic review team

Table 1. Systematic review team members and tasks

Title of the review: Systematic review on long-term exposure to PM and all-cause and cause-specific mortality.			
Authors name and surname	**Affiliation and e-mail address**	**Role in review**	**Specific tasks conducted[1]**
Gerard Hoek[2]	IRAS, University Utrecht g.hoek@uu.nl	Guarantor author	Coordination, 2nd reviewer of identified studies, 2nd extractor of information from studies
Jie Chen	IRAS, University Utrecht j.chen1@uu.nl	Researcher	Search strategy, extraction of studies, review of identified studies, extract information from studies, synthesis of studies, completion GRADE evidence profile

[1]Example of specific tasks: "GH is the guarantor. JC drafted the protocol. All authors contributed to the development of the selection criteria, the risk of bias assessment strategy and data extraction criteria. JC developed the search strategy. GH provided statistical expertise. All authors read, provided feedback and approved the final protocol."

[2]mailing address of corresponding author: PO Box 80.178, 3508 TD, UTRECHT, The Netherlands

2.2.3 Timeline of the systematic review

Date of start (once protocol completed and agreement signed): 7 September 2017
Date of expected library of included studies: 30 September 2017
Date of expected data-extraction including risk of bias: 31 January 2018
Date of draft systematic review: 19 February 2018
Date of final update of review with any additional new studies published: 9 October 2018
Date of expected completion of the systematic review: 24 March 2019
Date of completion: 25 March 2019

2.2.4 Sources of funding and conflicts of interest

The following review will be funded by WHO as part of a Grant Agreement with the European Commission (DG Environment) to support the update of WHO Global Air Quality Guidelines. Additional funding support is provided to WHO by the Federal Ministry for the Environment, Nature Conservation, Building and Nuclear Safety (Germany) and by the Federal Office for the Environment (Switzerland).

As per specific WHO guidelines guidance, all authors involved in conducting or updating a systematic review for WHO (SRT members) have completed a declaration of interests form, and have declared no financial as well as non-financial conflicts of interest related to the topic of the specific review. Additionally, they may have performed systematic reviews on the same or a similar topic previously (WHO, 2014).

3. Rationale and objective

Air pollution is a major environmental hazard to human health and a leading cause of mortality and morbidity worldwide. WHO has published several volumes of AQGs to provide guidance to the public, especially to policy and other decision makers, on the health risks of air pollution. As new scientific evidence is generated, air quality guidelines need to be periodically revised and, where necessary, updated.

The overall objective of the update of WHO Global AQGs is to develop public health recommendations for ambient air quality in the form of guidelines (advice on limit concentrations in ambient air for various air pollutants to protect populations worldwide from major adverse health effects).

This specific protocol for systematic review will support the first objective of the updated guidelines: Provide updated evidence-based numerical concentration limits (i.e. guidelines) and, where possible, an indication of the shape of the concentration-response function (CRFs) for $PM_{2.5}$ and PM_{10}, for long term exposure and in relation to all-cause and cause-specific mortality.

4. Methods

4.1 Health outcomes selection and prioritization

In order to select the specific health outcomes that will be included in the different systematic reviews for the updated AQGs, the following decision framework was developed and applied by the GDG:

• Evidence on causality for a health outcome will be considered first, according to the latest determination (causal or likely causal) from the US Environmental Protection Agency (EPA), the International Agency for Research on Cancer (IARC), Health Canada (HC) or other integrated science assessments available.

• Using the precautionary principle, additional most severe health outcomes with suggestive causality can be included based on other considerations such as contribution to burden of disease (prevalence of disease, disability weight, etc), policy implications, expected increase in exposure to a pollutant in the future, etc.

• Causality determination will supersede severity of a health outcome but, in some cases, two (or more) different health outcomes may be systematically evaluated for the same pollutant (e.g. one with a definite or likely causal link to the pollutant, and another health outcome for which the evidence is suggestive but which is very severe or prevalent in the population).

Severity of disease is informed by considerations proposed by the joint European Respiratory Society and American Thoracic Society latest policy statement on health effects from air pollution (fatality, persistence of effect, susceptible groups, and medical/functional significance including loss of autonomy and reduced quality of life) (Thurston et al 2016).

• Finally, as health outcomes can be measured in various ways in studies, the specific health outcome measure/s will be identified to be used for quantitative health risk assessment. This will be based on evidence, the recommendation of the SRT and expert judgment of the GDG.

4.2 Development of PECOS questions and eligibility criteria

The formulation of adequate PECOS (Population, Exposure, Comparator, Outcome and Study) questions is a crucial first step in the process of developing guidelines, as these so known as foreground questions will form the basis of the search for the evidence that will inform the recommendations, and must therefore be framed in a way that enables systematic retrieval of the relevant literature that responds to the public health question/s of interest.

4.2.1 PECOS and health outcomes for long- term exposure to air pollutants

The following PECOS question has been developed by the GDG for the update of the WHO Global AQGs in relation to long-term exposure to $PM_{2.5}$ and PM_{10}:

"In any population, including subgroups of susceptible adults and children (P), what is the increase in risk (incidence/prevalence) of all-cause and cause-specific mortality (O) per unit increase (C) in $\mu g/m^3$ of long-term exposure (in the order of months to years) to ambient concentration of $PM_{2.5}$ and PM_{10} (E), observed in studies relevant for the health outcome and exposure duration of interest (S)? In these studies, what is the lowest concentration that produces a measurable increase in risk?"

Table 2. Inclusion and exclusion criteria for each PECOS domain in relation to long-term exposure and health effects to $PM_{2.5}$ and PM_{10}.

PECOS	Inclusion	Exclusion
Population	• General human population (including sub-groups at risk: children, pregnant women, elderly, or patients with particular conditions), of all ages, developed and developing areas, both urban and rural. No geographical restrictions. • Exposure to $PM_{2.5}$ and PM_{10} via inhalation through ambient air predominantly	• Exposure to $PM_{2.5}$ and PM_{10} in occupational settings or as a result of indoor exposure exclusively
Exposure	• Long-term exposure (in the order of months to years) to ambient air $PM_{2.5}$ and PM_{10} expressed in a concentration unit ($\mu g/m^3$). • Studies that have translated other particle metrics such as TSP into PM_{10} or $PM_{2.5}$ using local and time specific conversion factors will be identified.	• No exclusion criteria applied based on adjustment for co-pollutants.
Comparator	• Exposure to lower levels of $PM_{2.5}$ and PM_{10} in the same or in a control population	
Outcome	• Health outcomes selected in relation to long-term exposure include (ICD 10 codes, version 2016 in brackets): **all-cause mortality** (A00-Z99) and cause-specific mortality including **circulatory diseases** (I00-I99), **ischemic heart diseases** (IHD, I20-I25), **cerebrovascular diseases** (stroke, I60-I69), **respiratory diseases** (J00-J99), **chronic obstructive pulmonary diseases** (COPD, J40-J44, J47), **acute lower respiratory infection** (ALRI, J12-J18, J20-J22) and **lung cancer mortality** (C30-C39). • Non-accidental mortality will be considered equivalent to all-cause mortality (both definitions are used in studies) • Other definitions of cause-specific mortality will be identified provided they include the major diseases of these categories • Equivalent definitions using ICD-9 or other versions of ICD-10 will be included	
Study	• Human epidemiological studies including: o Prospective and retrospective cohort studies o Case-control and nested case-control studies o Systematic reviews of the above studies will be used to scan for references or as a basis for update • Published (or accepted for publication i.e. in press) journal articles in any language (abstract in English language). • If suitable articles are identified published in languages not known by the SRT, further	• Qualitative studies • Studies without individual level data i.e. fully ecological outcome, exposure and covariates data • Studies where no original data were analysed • Reviews and methodological papers • Non-human studies (*in vivo, in*

	assistance will be sought after (members of the GDG or external review team from different regions, colleagues, researcher networks, etc)	*vitro,* other) • Conference abstracts and papers, letters, notes, grey literature

SRT: Systematic review team

TSP: Total suspended particles

As a result, of the framework described in **Section 4.1**, the health outcomes presented in **Table 3** below have been selected for systematic review in relation to long-term air pollution exposure effects:

Table 3. Health outcomes selected for the update of the AQGs in relation to long-term exposure to ambient air pollutants.

Long-term exposure			
Pollutants	**Health outcome(s) used in latest WHO AQGs (2006)**	**Health outcome/s selected for updating WHO AQGs**	**Justification for health outcome selection**
$PM_{2.5}$ and PM_{10}	Total, cardiopulmonary and lung cancer mortality	• **All-cause mortality** • **Circulatory mortality (all, IHD, stroke)** • **Respiratory mortality (all, COPD, ALRI)** • **Lung cancer mortality**	**CAUSALITY DETERMINATION** **$PM_{2.5}$** • US EPA: mortality (causal for CV and respiratory mortality, 2009) • HC: mortality (causal for total and CV mortality, 2013) **PM (any, no size specified)** • HC: mortality (causal for total mortality in relation to PM, 2013) • IARC: lung cancer for PM (Group 1, 2013) • HC: mortality (likely causal for lung cancer mortality in relation to PM, 2013) **SUPPORTING CONSIDERATIONS** **$PM_{2.5}$** • Not expected to see effects on morbidity taking place at pollutant levels lower than those related to mortality **PM_{10}** • End user perspective: relevant globally as monitoring of PM_{10} is more common than $PM_{2.5}$ • Health outcome supported by evidence from PM and/or $PM_{2.5}$ **OTHER RELEVANT CAUSAL DETERMINATIONS** (to be described in guidelines background chapter) **$PM_{2.5}$** • US EPA: respiratory effects (likely, 2009) • HC: respiratory effects (likely, 2013)

HC: Health Canada science assessments; US EPA: United States Environmental Protection Agency; IARC: International Agency for Research on Cancer; IHD: Ischaemic Heart Disease; COPD: chronic obstructive pulmonary disease; ALRI: acute lower respiratory infections; CV: cardiovascular.

4.2.2. Listing of the confounding factors relevant to all or most studies eligible for the review

The relevant confounding factors will be identified both through the knowledge of subject matter by experts who are members of the review group, and through other reviews of the literature. Confounders that are typically taken into account include a) individual level variables such as age, sex, year of enrolment, race, smoking status (smoking history, smoking intensity, smoking duration, second hand smoke), diet intake, physical activity, body-mass index, educational level, employment status (occupational class), marital status, baseline illnesses, usage of medicine; b) area-level variables such as education level, mean income or deprivation index of the neighbourhood or municipality. The Risk of bias tool will be used to assess potential confounding bias.

4.3 Information sources and search strategy

Studies matching the PECOS questions will be searched comprehensively in the database MEDLINE using PubMed and the database EMBASE through EMBASE.com.

References of identified relevant articles (and reviews/guidelines) will be scanned to identify additional published data matching the PECOS question.

When the same study population is used in several publications, all studies will be identified and data extracted. For the meta-analysis one study will be selected which could be the most recent, see section 4.6

Data search will include studies from the start date of the databases up to 6 April 2018.

A literature search strategy using free text and MeSH terms/ Emtree terms will be developed for each search engine, considering pollutant, study design and health outcome. The strategy will be developed by JC, with input from the systematic review team, and reviewed by GH.

PubMed search strategy:

#	Searches
1	Mortality[Mesh]
2	mortality [Subheading]
3	Death[Mesh]
4	mortality[Title/Abstract] OR death[Title/Abstract]
5	OR/ 1-4
6	Particulate Matter[Mesh]
7	Particulate Matter[nm]
8	particulate matter[Title/Abstract] OR particulate air pollution[Title/Abstract] OR PM[Title/Abstract] OR PM10[Title/Abstract] OR PM2.5[Title/Abstract]OR particles[Title/Abstract]
9	OR/ 6-8
10	Cohort Studies[Mesh]
11	Case-Control Studies[Mesh]
12	cohort[Title/Abstract] OR follow up[Title/Abstract] OR Longitudinal[Title/Abstract] OR Prospective[Title/Abstract] OR Retrospective[Title/Abstract]
13	case-control[Title/Abstract]
14	OR/ 10-13
15	5 AND 9 AND 14
16	15 NOT "Clinical Trial"[pt]
17	16 NOT "animals"[Mesh:NoExp]
18	17 NOT "Treatment Outcome"[MeSH]
19	18 NOT "Air Pollution, Indoor"[Mesh] NOT "Occupational Exposure"[Mesh]
20	19 NOT "time series"[Title]

EMBASE.com search strategy:

#	Searches
1	'mortality'/exp
2	death'/exp
3	'death':ab,ti OR 'mortality':ab,ti
4	OR/ 1-3
5	'particulate matter'/exp
6	'particulate matter':ab,ti OR 'particulate air pollution':ab,ti OR pm:ab,ti OR pm10:ab,ti OR pm2.5:ab,ti OR particles:ab,ti
7	5 OR 6
8	'cohort analysis'/exp
9	'case control study'/exp
10	cohort:ab,ti OR 'follow up':ab,ti OR longitudinal:ab,ti OR prospective:ab,ti OR retrospective:ab,ti
11	OR/ 8-10
12	4 AND 7 AND 11
13	12 AND 'human'/de
14	13 NOT ('case report'/de OR 'clinical trial'/de OR 'medical record review'/de OR 'nonhuman'/de)
15	14 NOT ('occupational exposure'/exp/mj OR 'indoor air pollution'/exp/mj)
16	15 NOT 'time series':ti

4.4 Study records

4.4.1 Data management and selection process

Two reviewers (JC, GH) will independently screen titles and abstracts identified with the systematic search and identify those that can be excluded based on the eligibility criteria.

The remaining articles resulting from this selection will be assessed again by the same two reviewers independently based on the full-text to ensure that those meet all the eligibility criteria. Any disagreement on inclusion will be resolved by discussion. Additional information from study authors (where necessary) to resolve questions about eligibility will be obtained. Reasons for excluding articles at this stage will be recorded.

Full text screening and subsequent reviewers' agreement will result in a list of included studies for systematic review, that will be circulated with the whole SRT and the GDG to identify any additional potentially relevant missing studies (published or in press).

4.4.2 Data collection process

Data extraction will be conducted in duplicate by two independent authors (JC, GH). If disagreement occurs, this will be resolved by discussion.
A data extraction form developed in Excel will be used (see Appendix). If a single publication reports several health outcomes of interest, each outcome will take one record. If a single publication reports more than one effect estimates for a specific health outcome, multiple estimates from single pollutant models (the crude one, the most adjusted one, and the one the authors favoured) will be extracted. Additionally, we will extract estimates from two pollutant models, if available, and estimates for subgroups including age, sex and smoking status.

4.5 Data extraction

The following characteristics of the included studies will be extracted:

- citation details (e.g. title, authors, date of publication), type of design, study location (country/city),
- characteristics of the study population,
- follow up period(s),
- details on exposure (unit of measurement, concentration including 5-95th percentiles of population exposure, mean/ median and min - max, metric description e.g. annual mean, period of year of exposure assessment, e.g. either all-year or 'warm season',
- details on co-exposures,
- details on outcome assessment,
- details of confounders measured and confounders adjusted for,
- data to calculate the effect estimates and their confidence intervals,)

- methods and results of assessment of the shape of the exposure response function, including effect estimates for subsets of the data where the highest levels have been excluded from the analysis,
- conflicts of interest.

In the absence of complete descriptions of exposure assessment and outcomes, effect estimates, or other important information, reviewers will ask authors for this information. If no response, missing data will be calculated according to Higgins and Green (2011) and Wan et al (2014)

In addition to the items above, information on which the risk of bias is based will be extracted from the reports of the studies.

4.6 Risk of bias in individual studies

A risk of bias (RoB) assessment for all individual studies included in the systematic review will be conducted, and the constructs being assessed and a definition for each (domains) will be listed.

A new domain-based RoB assessment tool, developed by a group of experts convened by WHO, will be used for assessment. The RoB assessment tool will be adapted for long-term exposure by the reviewers and approved by WHO methodologists. RoB assessment will be conducted independently by one reviewer and checked for accuracy by a second reviewer. A WHO methods expert will support the application of the tools.

Reviewer judgment options (e.g. high, moderate, low), the number of assessors, experience of assessors (training, piloting, previous risk of bias assessment experience) will be reported. A 10% selection of studies will be reviewed by an independent assessor.

Planned methods to summarise risk of bias assessments across studies (how the individual assessment of studies will impact the overall judgment?) and a description of how risk of bias assessments will be incorporated into data synthesis (that is, subgroup or sensitivity analyses) and their potential influence on findings will be provided by the WHO expert group.

4.6 Data synthesis

The objective of this systematic review is to be quantitative, and provide a summary pooled estimate of the risk for an adverse health outcome per unit increase of exposure combining the results of the single studies that can be appropriately merged. In case three or more studies are identified for the same pollutant and health outcome, a meta-analysis will be performed. Because of differences in populations, pollution mixes across populations, we a priori decide that estimates will be pooled by means of a random effects meta-analysis (maximum likelihood approach). If there are less than 3 studies identified for the same pollutant and health outcome, the effect estimates will be described in the text. We will further evaluate the shape of the exposure response function by plotting the RR versus the mean concentration in a study or calculating the pooled RR for studies with an average or maximum concentration below certain values (e.g. 25, 20, 15 and 10 annual average for $PM_{2.5}$) only.

If no simple meta-analysis can be conducted, an expert may need to be consulted to identify appropriate statistical methods for analysing the data and to determine whether further modifications of effect size are required prior to performing a meta-analysis. If possible, expert methodologists will peer-review the statistical analyses conducted. Overall, statistical analysis will be performed according to the *Guidelines for Application of Meta-analysis in Environmental Epidemiology* (Blair et al, 1995), *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins and Green, 2011) or other authoritative meta-analysis guidance.

RRs will be used as the common effect measure of association across studies, and hazard ratios (HRs) may be considered equivalent to RRs. If ORs are reported in the study and the outcome prevalence is higher than 10%, they will be recalculated as RRs. As per Shah et al (2013), meta-analyses input data may be RR for a standardised increment in pollutant concentration (e.g. 10 $\mu g/m^3$), assuming a linear exposure-outcome relationship. As stated above, we will assess potential deviation from linearity, e.g. by stratifying by the mean PM concentrations. We will further collect assessments by the authors to assess linearity, e.g. spline analyses or information from the discussion sections.

Effects expressed as interquartile (or quintile or percentile differences) should be converted into effects per concentration unit increase. If the exposure metrics differs among studies, the data will be transformed to the same metric.

The STATA program package 'metan' will be used to produce forest plots and to undertake random/fixed-effects meta-analysis.

Statistical heterogeneity of effect estimates between studies (also inconsistency of study results) will be assessed using tau-squared, presented in the form of a prediction interval around the mean effect in a random effects meta-analysis (Borenstein et al, 2015). In addition, the Chi^2 test (Cochran's Q) with a significance level <0.1 and the I^2 value, where I^2 values of 25%, 50% and 75% are taken as of low, moderate and high degree of heterogeneity, respectively (Woodward, 2005). If considerable heterogeneity is present, an attempt will be made to explain the source of heterogeneity by subgroup analysis, meta regression, or sensitivity analysis. Subgroups at the study level will be geographical location (WHO Regions (EURO, WPRO, AFRO, SEARO, EMRO, PAHO)); type of population (general or disease group); sex (men/ women/ men + women); age groups; level of mean PM.

Sensitivity analysis will be conducted around the following issues, as applicable: 1) single pollutant model estimates versus 2-pollutant model estimates for PM (adjusted for coarse particles, adjusted for O3, adjusted for NO2); 2) subgroup analysis per risk of bias domain across studies; 3) excluding studies with declared conflicts of interest; 4) Excluding studies without individual level lifestyle confounders; 5) Excluding studies in patient populations ; 6) for unmeasured confounding using the E-Value (VanderWeele and Ding, 2017).

4.7 Meta-biases

Funnel plots (recommended when around 10 studies are included in the meta-analysis) with Egger test on asymmetry at alpha level 0.1 will be conducted for assessment of publication bias (Egger et al, 1997).

4.8 Confidence in cumulative evidence

The final result of the systematic reviews will be condensed in a GRADE Evidence Profile. This table will contain the PECOS question, the type and number of studies included, the number of participants in the studies, the effect sizes and their confidence intervals and the grading of the quality of the evidence and its starting level and reasons for upgrading or downgrading the quality.

The quality of evidence for all outcomes will be judged using an adaptation of the GRADE methodology (Balshem et al, 2011, Guyatt et al, 2011, Morgan et al, 2016). The quality of evidence will be assessed across the domains of risk of bias, consistency, directness, precision and publication bias. Studies that undergo meta-analyses will undergo GRADE assessment, but there might also other studies included in the systematic reviews that could not be used in the meta-analysis will be used for developing conclusions.

Based on guidance provided by the WHO Environmental Noise Guidelines for the European Region (Héroux et al, 2015), the Navigation Guide (Woodruff et al, 2011) and the US National Toxicology Program - Office of Health Assessment and Translation (OHAT) Handbook (OHAT, 2015), the GDG agreed that a working group on GRADE adaptation would be established and the final version shared with the SRT.

As a result of applying GRADE, the overall quality will be rated as:

- high (further research is very unlikely to change our confidence in the estimate of effect),
- moderate (further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate),
- low (further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate), or
- very low (very uncertain about the estimate of effect).

5. Reporting standards

The reporting of the systematic review will comply with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) standards (Moher et al., 2009) with slight adaptations since these were originally intended for health care intervention evaluation.

As such, the completed systematic review will include a clear formulation of the rationale and the objective of the review according to the protocol. At least a search strategy developed for MEDLINE/PubMed will be presented in an Appendix. In addition, a flow chart on studies included and excluded in every stage (from identification to screening, eligibility and inclusion) will be provided. Characteristics of included studies will be summarized (specifying country of the study and describing each of the PECOS elements), as well as information regarding excluded studies. The final review will describe the risk of bias assessment conducted within each individual study considered. The effects of the exposure/s of interest will be described according to the different exposure levels assessed in the review. For the main effect sizes there will be a qualification of the evidence that is summarised by these effect sizes. If this information is available, the effects of the exposures will be further described according to pre-specified population subgroups of interest such as elderly, children and diseased.

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