

Chapter 7: Systematic reviews of etiology and risk

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7.1 Introduction to etiological evidence and systematic reviews

In the epidemiological literature, terms such as risk, risk factors, and cause are inconsistently and imprecisely used, and as a result are often misinterpreted leading to incorrect research and policy recommendations. (Kraemer, Kazdin et al. 1997) Risk refers to the probability of an outcome within a population of subjects (e.g. risk of lung cancer among people exposed to asbestos) (Kraemer, Kazdin et al. 1997) and etiology refers to the cause or the causes (origin) of a certain disease. It is important to distinguish between etiology and risk factors. A risk factor refers to an individual characteristic or exposure that is associated with an increased likelihood of an outcome occurring. For example, are children in sub-Saharan Africa who are exposed to *Plasmodium falciparum* malaria at an increased risk of developing mental disorders? (Akpulu, Ae-Ngibise et al. 2012) Whereas a protective factor refers to a characteristic or exposure that is associated with the reduced likelihood of an adverse outcome. For example, are people who perform regular higher levels of physical activity less likely to develop lung cancer than those who perform little or no physical activity? (Cancer Australia 2014)

Risk factors are commonly referred to as modifiable, which means they may be controlled or modified in some way, or they may represent a characteristic over which an individual has no control, and therefore categorized as non-modifiable. Exposure to cigarette smoke (either actively or passively), elevated arsenic concentrations, or asbestos in the work or home environment are examples of exposure to modifiable factors – all can ultimately be avoided in most circumstances. Conversely, having a family history of the disease is also known to increase the likelihood of lung cancer development in an individual, (Cancer Australia 2014) and despite any efforts, these non-modifiable risk factors, though less common, are difficult to control or modify.

Systematic reviews of etiology and risk factors assess the relationship (association) between certain factors (whether genetic or environmental for example) and the development of a disease or condition or other health outcome. Systematic reviews underpin evidence-based healthcare. The process of conducting a systematic review is a scientific exercise, and as the results will influence health care decisions, it is required to have the same rigor expected of all research. The quality of a systematic review depends on the extent to which the methods minimize the risk of error and bias. There is currently no universally accepted methodology for conducting systematic reviews of etiology and risk. Systematic review and meta-analysis of studies related to etiology and risk can provide useful information for healthcare professionals and policymakers on the risk factors (and preventive or protective factors) of disease and where factors, other than direct intervention with therapy and treatment, may influence or impact on health outcomes. Systematic review of etiological studies is important in the public health domain for informing health care planning, resource allocation and strategies for disease prevention.

This chapter outlines and describes JBI's approach and guidance for synthesizing evidence related to etiology and risk and contributes to the emerging field of systematic review methodologies. The systematic review of studies to answer questions of etiology and risk still adheres to the same basic principles of systematic review of other types of data. An *a priori* protocol must precede and inform the conduct of the systematic review, comprehensive searching must be performed, and critical appraisal of retrieved studies must be carried out followed by data abstraction, analysis and synthesis. These steps will be further discussed in the following sections of this chapter. Additionally, reviewers should refer to two statements/checklists: one for transparent reporting of a systematic review of various research study designs (preferred reporting items for systematic reviews and meta-analyses (PRISMA)) (Moher, Liberati et al. 2009) and one for Meta-Analyses Of Observational Studies in Epidemiology (MOOSE), which provides a checklist or guidance to report meta-analyses of observational studies in epidemiology, including background, search strategy, methods, results, discussion, and conclusion. (Stroup, Berlin et al. 2000)

A note on causation

British epidemiologist Sir Austin Bradford Hill proposed in 1965 a list of nine “viewpoints”, or “circumstances” or “aspects” that should be considered when exploring the likelihood of inferring causation from examined associations: strength of the association; consistency of the observed association; specificity of the association; temporal relationship of the association; biological gradient (dose-response); biological plausibility; coherence (cause-effect interpretation of data should not conflict with generally known facts regarding natural history and biology of the disease; experimental evidence; analogy). (Hill 1965) Sir Bradford Hill explicitly stated that none of the nine viewpoints can be used as “indisputable evidence” for or against the causal hypothesis and that these aspects are used to explore more or less likely alternative explanations to the proposed causal explanation for the observed association.¹⁶

A comprehensive modern discussion about causality (including a critical examination of Hill's viewpoints) was provided by Rothman et al (2008). (Rothman, Greenland et al. 2008) It was contended that temporality is a *sine qua non* for causal explanations of observed associations; however, there is no other criterion other than temporality that is necessary or sufficient criterion for determining whether an observed association is causal. (Rothman, Greenland et al. 2008)

7.2 Study designs for etiology and risk

Commonly, epidemiological or observational studies are utilized to investigate etiology and risk. Observational studies aid in studying causal associations between an exposure and disease/health outcome (for example associations between occupational risk factors and lung cancer, or the adverse effects of a treatment in healthcare), although distinguishing true causality generally requires experimental research. Observational studies do not involve manipulation on the part of the researcher. These studies rely on the natural or 'ecological' events of exposures and disease, where the researcher simply observes certain characteristics of the sample population as they occur "naturally", and records the relevant data.(The Joanna Briggs Institute b 2014) In this way they can be distinguished from experimental or quasi-experimental studies (such as RCTs and controlled clinical trials) where there is researcher manipulation of the independent variable (the potential cause or the exposure).(The Joanna Briggs Institute b 2014)

7.2.1 Observational Study Designs

Observational study designs include prospective and retrospective cohort studies, case-control studies, cross-sectional studies, case series and case reports, and can be broken down into the broad categories of analytical studies and descriptive studies. Generally, descriptive studies describe the occurrence /presence of an outcome or exposure, whereas analytical studies describe the relationship between the exposure and an outcome. Due to the nature of observational study designs compared with experimental designs, they are more at risk of the influence of confounding factors and different sources of bias that are unavoidable, which will be discussed further below. Similar to the MOOSE statement,(Stroup, Berlin et al. 2000) reviewers should also refer to the Strengthening the reporting of observational studies in epidemiology (STROBE) statement, which is a checklist of items that need to be addressed in studies reporting on cohort, case-control, and cross sectional study designs and provides guidance on how to report observational research.(von Elm, Altman et al. 2007)

7.2.1.1 Cohort Studies

Cohort studies are the 'gold standard' of observational study designs and prospective cohort studies appear the highest on evidence hierarchies of observational study designs. (Thiese 2014) These longitudinal studies are typically used to analyse relationships between exposures and disease by comparing the outcomes between two groups over time, where individuals in one group are exposed to a common event or characteristic, such as a risk factor, and the other group are not. Sampling in cohort studies is based on the presence or absence of an exposure or characteristic, and participants are followed over time to observe development of any disease or health outcomes. A prospective cohort study begins with the exposure of interest, and participants are followed forward through time to observe any outcomes that may occur. Conversely, a retrospective cohort study generally begins after the outcomes of interest have already been recorded; a researcher may sift through patient records or data that is already available and groups patients according to exposures, and identifies any differences in outcomes. Cohort studies enable observations of a large number of people over a long period of time.

7.2.1.2 Case-control studies

Case-control studies select participants based on presence of disease or a specific condition, and look for prior exposures that may have led to the disease or outcome developing. In this study design, those with the disease/outcome (cases) are matched with comparable individuals who do not have the disease (controls), and both groups are studied to determine if any differences in characteristics or past exposures exist. Case control studies have an advantage over cohort studies, particularly when investigating rare diseases, because of fewer costs associated with recruiting participants (usually less). In addition, the issue of 'drop out' or 'loss to follow up' of participants as seen in cohort studies does not arise in case-control studies.

7.2.1.3 Cross-sectional studies (Analytical)

Cross-sectional studies are used to provide a snapshot of disease and other variables in a defined population at one point in time. Data can be used to infer relationships between a disease and other variables, however as the data is gathered simultaneously, chronological sequences of exposures and outcomes cannot be determined. Some cross-sectional studies are purely descriptive, in that they just describe the number of cases or number of events in a particular population at a point in time or over a period of time.

7.2.2. Descriptive study designs

Descriptive studies aim to collect information about a given individual or group and can be used to provide data on the distribution of disease. Examples of descriptive study designs are case reports and case series. In health care, these types of studies are typically used to describe the occurrence of disease or a risk factor. Case reports and case series are often used to report novel occurrences of a disease or a unique finding, and they can be particularly informative for rare or emerging diseases. There are guidelines to report case reports in terms of completeness, transparency and data analysis (The CARE Guidelines: Consensus-based Clinical Case Reporting Guideline Development),(Gagnier, Kienle et al. 2014) which the reviewers should refer to when including and reporting case reports in their systematic review reports.

7.3 The systematic review protocol and report

This section outlines the requirements and methods for systematic review protocols and systematic review reports addressing etiology and risk.

7.3.1 Title of the systematic review

The title should be clear, explicit and reflect the core elements of the question. It should be as informative and descriptive as is reasonable reflecting the scope and type of systematic review to be undertaken. The title should not be phrased as a question or conclusion and there should be congruency between the title, review objectives/questions and inclusion criteria. The title should include the phrase "A systematic review protocol" in a review protocol and "A systematic review" in a review report.

Although a range of mnemonics have been described for different types of review (and research) questions, if, for example the review aims to examine etiology of disease or risk of a health outcome, this should, as much as possible, be stated clearly in the title of the document. If specific exposure/s and/or patient outcomes are to be examined these should also be included in the title. For example: "Long-term topical corticosteroid use and risk of skin cancer: a systematic review protocol".(Ratib, Burden-Teh et al. 2016) This example provides potential readers of the review with a clear indication of the population, the exposure (corticosteroid use), and the outcome (incidence of skin cancer) of interest, as well as that it is a systematic review protocol.

7.3.2 Abstract

This section forms a structured abstract of the main features of the systematic review. It must be no longer than 500 words and should contain no abbreviations or references. The abstract must accurately reflect and summarize the systematic review with the main focus on the results of the review.

The abstract should report the essential elements of the review using the following sub-headings in this order:

- **Objective:** State an overarching review objective structured using the key components of the inclusion criteria (approximately one to two sentences).
- **Background:** Briefly describe what is already known on the topic and what this review will add to the evidence-base (approximately two to three sentences).
- **Inclusion criteria:** Summarize the inclusion criteria as it relates to the type of review being conducted. Present the information in one or two sentences – **NOT** under individual subheadings.
- **Methods:** List the key information sources searched (those that provided the majority of included studies), any limits placed on the scope of the search (e.g. language), and the date range, or the date of the last search. If the recommended JBI approach to critical appraisal, study selection, data extraction and data synthesis was used, simply state it as such (without naming the actual tool). Otherwise, briefly describe any notable deviations to the methodological approach taken (e.g. criteria used to exclude studies on the basis of methodological quality etc.).
- **Results:** The bulk of the abstract should be reserved to convey the main results of the review. As a general rule, report the number and type of included studies and participants, as well as any pertinent study characteristics. Summarize the overall quality of the included studies and notable aspects of rigor for qualitative reviews). Report the number of findings and categories and final synthesized findings. Depending how many are presented in the review, the synthesized findings may be presented here or abridged summarized statements.
- **Conclusions:** Provide a conclusion based on a general interpretation of the results considering, for example, the methodological quality of the included studies and any limitations of the review. Briefly convey key implications for practice and/or research.

7.3.3 Objective and review question

The objective(s) of the review should be clearly stated. This should be followed by the specific review question(s). The overarching objectives of reviews of etiology and risk are to determine whether and to what degree a relationship exists between two or more quantifiable variables. Accordingly, the review question should outline the exposure, the population or groups at risk and the disease, symptom or health outcome of interest. The specific context/location (which may include any contextual factors such as geographical, or cultural elements relevant to the topic), and the duration of the exposure (e.g. pregnancy) may also be important to articulate if relevant.

An example of an objective for a systematic review of etiology and risk is:

- The objective of this review is to assess the epidemiological association between consumption of alcohol (as exposure of interest or risk factor) and lung cancer (as the outcome of interest).

A question that will align with this review objective is:

- Does the consumption of alcohol increase the incidence of lung cancer?

The exposure and outcome may be positively associated or the relationship may be negative e.g. as one increases the other decreases.

7.3.4 Background

The background section of the review protocol and systematic review should be comprehensive and consider the main elements of the topic under review. Many reviewers will find that the background provided with the protocol needs modification or extension following the conduct of the review proper. The background should detail any definitions important to the review. The information in the background section must be sufficient to put the review inclusion criteria into context and also highlight the importance and relevance of the topic for the reader and a clear basis for the rationale to pursue the review topic. The background section should conclude with a statement that a preliminary search for previous systematic reviews on the topic was conducted (state the sources searched e.g. [JBI Evidence Synthesis](#), Cochrane Library, CINAHL, PubMed, PROSPERO). If there is a previous systematic review on the topic, it should be specified how the proposed review differs. All JBI systematic reviews should contain a sentence clearly stating:

"The objectives, inclusion criteria and methods of analysis for this review were specified in advance and documented in an a priori protocol. Ref" (Reference should be to the appropriate citation in the [JBI Evidence Synthesis](#), and provide registration number in PROSPERO where applicable).

This sentence should appear as the final line of the background/introduction section of the review report and complies with the recommendations for reporting of systematic reviews detailed in the PRISMA guidelines.

7.3.5 Inclusion criteria

Specific inclusion criteria ensure that the included studies will meet these criteria and they represent an important and transparent plan for to the selection of studies for the review. The inclusion criteria are also critical when formulating a comprehensive search strategy to locate studies.

Authors will realize that the traditional PICO format (Population, Intervention, Comparator, Outcomes) commonly encountered and well aligned to systematic reviews(The Joanna Briggs Institute a 2014) assessing the effectiveness of interventions or therapies in health care does not readily align with questions relating to etiology and risk. Rather, a systematic review of etiology should include the following components, easily referred to as PEO:

- Population (types of participants)
- Exposure of interest (independent variable)
- Outcome (dependent variable)

7.3.5.1 Population (types of participants)

The types of participants should be appropriate for the review objective and question(s). The reasons for the inclusion of a participant group should be supported by information in the background and the rationale for the review. Specific criteria for inclusion or exclusion of participants should be explained in this section. The inclusion and exclusion criteria need to reflect sound clinical and scientific reasoning and the need for an adequate degree of homogeneity amongst the samples in the studies.

7.3.5.2 Exposure of interest (Independent variable)

This refers to a particular risk factor or several risk factors (or protective factors) of interest. It should be clearly reported in this section what the exposure or risk factor (or protective factor) is, and how it may be measured/identified including the nature of the exposure and its intensity and/or the duration of exposure, if relevant. The exposure of interest may be modifiable, and relate to lifestyle habits such as alcohol consumption, smoking or may relate to the environment and occupation such as asbestos and air pollution or conversely, may be non-modifiable, such as family history of the disease.

7.3.5.3 Outcome (dependent variable)

It should be clearly reported in this section what the outcome (disease or condition) is, and how it may be measured/identified. Commonly, the outcome of reviews of etiology and risk is often the incidence or observed rate of a disease or condition. Outcomes should be presented in a non-directional expression; for example, the outcome should simply be stated as the incidence of lung cancer, not an increase in lung cancer, as the evidence may suggest that the exposure has no effect and does not increase risk (neutral factor) or may decrease the risk (protective factors). The review protocol should specify the important outcomes of interest relevant to the health issue and relevant to key stakeholders like the knowledge users, consumers, policy makers, consumers and the like.

7.3.5.4 Types of studies

Epidemiological observational studies of etiology relate individual characteristics, personal behaviours, environmental conditions, and treatments as 'exposures' that may modify risk of disease. These reviews will predominantly include observational studies such as prospective and retrospective cohort studies, case control studies and analytical cross-sectional studies. Randomized controlled trials may also report on the risk associated with an exposure and can be included. Prospective cohort studies usually provide stronger evidence than case-control studies when addressing etiological questions or issues.

7.3.6 Methods

This section of the review report is reserved for the methods used to conduct the review and should be presented under the relevant subheadings, including any deviations from the method outlined in the *a priori* protocol. In empty reviews for example, this section should not refer to methods that were not performed.

Directly below the Methods heading provide the following information:

- State and appropriately cite the JBI methodology that was employed in the conduct of the review and synthesis.
- Refer to and cite the *a priori* protocol that was published, or accepted for publication (e.g. 'in press'), in the [JBI Evidence Synthesis](#).
- If the protocol has been registered with PROSPERO, provide registration information including registration number (e.g. PROSPERO CRD42015425226).

7.3.6.1 Search strategy

This section should state how the reviewers plan to search for relevant papers in a protocol and how they conducted the final search in a review report, clearly detailing how the review authors located the studies included in their review. Details of the databases and sources searched must be provided along with search strategies and the search dates. Databases and sources searched should be appropriate for the review question and include specification from the outset of the platform used to search a particular database. A JBI review should search for studies published by commercial and academic publishers as well as non-commercially published studies (grey literature). An example of a source of grey literature is Open Grey. Any limits applied to the search, for example limiting the range of years searched, should be justified and any language restrictions stated (e.g. only studies published in English will be considered for inclusion).

In the JBI review report, a detailed search strategy for all of the major databases searched should be appended and relevant details and dates of searching through other sources. The documentation of search strategies is a key element of the scientific validity of a systematic review. It enables readers to look at and evaluate the steps taken, decisions made to consider the comprehensiveness and exhaustiveness of the search strategy for each included database.

7.3.6.2 Sources to search

Appropriate databases to search should be included, the most common being Medline (PubMed) and EMBASE. Details should include specification from the outset of the platform used to search a particular database. Etiology and risk data are commonly reported within the published, peer-reviewed literature and accordingly the standard JBI three-step search strategy can be applied to locating this type of evidence. The search strategy should use both subject heading and text word searches. Initial search terms should be updated after searching the reference lists of relevant articles. The timeframe chosen for the search should be justified and any language restrictions stated (e.g. only studies published in English will be considered for inclusion).

A JBI review should consider papers both published and unpublished (grey) literature. Grey literature can often provide useful studies and estimates for reviews of etiology and risk factors.

Some examples include:

- Disease and health association websites. (e.g. American Diabetes Association)
- Bibliographic databases: Disease and allied health research database (e.g. Medline, EMBASE, PsycINFO, CINAHL, British Nursing Index (BNI), Web of Science, and Cochrane library. PhD theses etc.)
- Conference abstracts or proceedings (e.g. BIOSIS databases, American Society of Clinical Oncology (ASCO), Biological Abstracts/RRM, British Library Inside, British Library Direct Plus, ISI Proceedings)
- Web searching (e.g. Google Scholar, Science.gov, scricus.com)
- Administrative sources (clinical records, insurance data)
- Vital statistics data, government reports, Centers for Disease control and prevention data, population consensus and surveys.
- Medical books, grey literature and reports from experts.

7.3.6.3 Assessment of methodological quality

Assessment of methodological quality, or critical appraisal, is a process conducted in systematic reviews to establish the internal validity and risk of bias of studies that meet the review inclusion criteria. The JBI has developed a number of tools for assessing the quality of various quantitative study designs that are appropriate to use in systematic reviews assessing questions of etiology & risk. (See Appendix II).

The protocol should indicate which tool is going to be used that match the included study designs when determining methodological quality of papers to include in the review. JBI appraisal tools should be used preferentially; if not clear reasoning should be provided. Critical appraisal tools should be cited in the protocol and should be appended if the tools are modified in any way. Critical appraisal must be conducted by two reviewers independently of each other. The reviewers should then meet to discuss the results of their critical appraisal for their final appraisal. If the two reviewers disagree on the final critical appraisal and this cannot be resolved through discussion, a third reviewer may be required.

When detailing the 'Methods' of the review report, the section on appraisal should detail the approach to critical appraisal, not the assessment results, and should be consistent with the protocol. The approach to critical appraisal process should include information on what constitutes acceptable levels of information for appraisal and whether the decision to include or exclude studies following critical appraisal is based on meeting a predetermined proportion of criteria or weighing criteria differently. The authors of the review should state *a priori* in the review protocol the criteria used to determine the inclusion or exclusion of poor quality studies. The authors have to make explicit and agree on criteria to determine whether a study is of good, moderate or poor quality, and based on these criteria or a combination of criteria, the authors can decide whether to include only good quality studies or all studies irrespective of the quality. However, the importance of these criteria (e.g. selection, measurement bias, confounding) will vary with study type and problems specific to the review question.

The report should detail the criteria that were considered when determining the methodological quality of papers considered for inclusion in the review. In the systematic review, appraisal questions should be presented with the results, or appended.

7.3.6.3.1 Confounding and confounders

Confounding occurs when another factor other than primary factor of interest or being investigated, can directly influence the outcome being measured. To be classed as a confounding factor, it should not be a factor that appears in the casual pathway between and exposure and the outcome. Confounding bias is defined as “bias of the estimated effect of an exposure on an outcome due to the presence of common causes of the exposure and the outcome”.(Miquel 2014) (p.55) A confounder or confounding variable is a variable that can be used to decrease confounding bias when properly adjusted for.(Miquel 2014) (p.55)

Criteria for confounders are:(Rothman, Greenland et al. 2008) (p.132-134)

1. A confounding factor must be an extraneous risk factor for the disease; i.e. the confounder is a risk factor for the disease and the factor's association with disease arises from a causal pathway other than the one under study.
2. A confounding factor must be associated with the exposure under study in the source population (the population at risk from which the cases are derived).
3. A confounding factor must not be affected by the exposure or the disease. In particular, it cannot be an intermediate step in the causal path between the exposure and the disease. (For example, in the case of increased risk of lung cancer from high levels of red meat consumption, the confounding factor could possibly be the 'cooking method')(Cancer Australia 2014)

Confounding can be controlled in the design and analysis phases in the case of observational studies. The two approaches used for the control of confounding in the analysis of data are stratification and statistical modelling. In stratification, study participants are split into strata that are different groups based on levels of the potential confounding variable, for example age. Although this approach is a simple method, this approach is limited by the fact that only a certain a number of potential factors could be stratified. Hence, it is not a common approach to control for confounding in observational studies in the analysis phase. (Kahlert, Gribsholt et al. 2017) Statistical modelling (such as multiple logistic regression, conditional logistic regression, Cox proportional hazards regression, multivariable regression analysis) is used to estimate the strength of the relationship of interest while controlling for all of the potential confounders.(Webb and Bain 2011)

7.3.6.3.2 Types of bias in studies of etiology and risk

Bias is a particular concern when assessing the methodological quality of studies of etiology and risk. Bias refers to systematic errors in any type of study that result in an incorrect estimate of the association between putative risk or predictive factors and the study outcome(s). The taxonomy of bias is well covered in the Cochrane Handbook (Higgins and Green 2011) and in the Agency for Healthcare Research and Quality Methods Guide for Comparative Effectiveness Reviews. (Viswanathan, Ansari et al. 2008) If bias is suspected or reported, it is important to try and detect the direction of the bias, i.e. is it towards a change in the effect estimate of risk or not. Table 1 below shows the common types of bias that affect studies of etiology and risk.

Table 1: Common types of bias affecting studies of etiology and risk

T y p e o f b i a s	Definition	Check for
S e l e c t i o n B i a s	Systematic errors that result from procedures used to select study participants, from factors that influence participation in the study, or the ways in which data are collected or analyzed	<p>Sample</p> <p>e.g. inappropriate definition of the eligible population or use of an inappropriate sampling frame; oversampling of healthy volunteers; exclusion of those who cannot or do not access health care services /those from a CALD background/those who are illiterate; changes to population over time; attrition (general or greater in one group than another)/non-response related to survivorship and severity of illness or length of illness; institutional bias e.g. hospital patients are different from community living patients.</p> <p>Classification</p> <p>e.g. uneven diagnostic procedures; changes in procedures over time; observer bias; competing risks (e.g. attribution of cause of death); changes in guidelines/institutional policy outside the researchers' control and publication bias.</p>
I n f o r m a t i o n b i a s	Flawed measuring of independent and/or dependent variables/s that results in differential quality of information.	Inadequate detection; missing variables; misclassification; Hawthorne effect ; ecological fallacy; prestige/social desirability bias; recall bias; interviewer bias; reporting bias and missing data.

7.3.6.4 Data extraction

This section in the review report should include details of the types of data extracted from the included studies. Standardized data extraction tools allow the extraction of the same types of data across the included studies and are required for JBI systematic reviews. The protocol should detail what data the reviewers plan to extract from the included studies and the data extraction tool should be appended to the protocol.

The data extracted should include specific details about the participants, exposure of interest and outcomes of significance to the review question. Irrespective of the focus of the systematic review, additional data should be extracted, such as study methods, covariates and the sample size for each study included in the review. The methods of collection of exposure and outcome data (i.e. number of cigarettes or ppm of asbestos fibres or dust), which commonly include questionnaires, registries or interviews should also be stated.

Relative risk and other measures of association should be extracted, preferably those adjusted for the maximum number of covariates. Unadjusted results should be included only where no other data is provided. Epidemiological studies investigating the same association between an exposure and disease /condition provide different effect measures that may be too dissimilar to combine, which presents a challenge when combining studies in a meta-analysis. Each different study may report different measures of association, or estimates of effect, which most commonly include relative risks (RR), odds ratios (OR), hazard ratios (HR), standardized incidence ratios (SIR) or a standardized mortality ratios (SMR). An absolute risk reflects the observed or calculated probability of an outcome (disease) in a population exposed to a specific risk factor. A relative risk, which is the most common metric of risk, is simply the ratio of absolute risk in the group exposed to the risk factor of interest, to the absolute risk in a group (control) that is not exposed to the risk factor. An OR uses the odds of developing a disease in both groups to calculate a relative measure between two groups rather than the risk.

Where an absolute risk of the exposed group is presented relative to available existing data for a population group, this is referred to as a standardized ratio. Depending on whether incidence or mortality data is used will depend on whether the SIR or SMR is reported. Standardized mortality ratio refers to the ratio of observed and expected mortality, based on the age-sex-calendar period specific rates. Usually SMR greater than 1 implies higher than expected deaths and SMR less than 1 implies lower than expected deaths. Standardized incidence ratio is the ratio of the observed number of cases to the expected number of cases, based on the age-sex specific rates. A range of corrections, transformations and assumptions can be used to account for difference in the different types of data presented.

The following details are suggested at a minimum for extraction.

Study details

Author - This is an alphabetic or character code which is usually the first few characters of the primary study author's name. This serves as an easy way to identify the study in the bibliography

Year – the year of publication

Journal – the journal in which the article was published

Study method/characteristics

Study design – briefly describing the type of study design. For e.g. if it is a cohort study or a cross-sectional study.

Setting - may refer to hospital or community. May also refer to rural/urban etc.

Participants - – Includes age, sex, country/location, sample size, diagnosis and other relevant characteristics

Recruitment procedures utilized

Follow-up or study duration – any details on the duration of the study or follow-up of the participants

Exposure(s) of interest (Independent variable) – type, frequency, intensity, duration

Dependent variable (outcome)

Outcomes – the primary outcome measured and where relevant includes associated secondary outcomes.

Outcome measurements – describe the scales or tools used to measure the outcomes. For e.g. a standardized pain scale to measure pain.

Data analysis methods including statistical technique (e.g. regression), adjustment for confounding factors, etc.

Study results

Appropriate measures for effect size such as:

- Risk ratio
- Relative risk ratio
- Odds ratio

P value & 95% Confidence Intervals

Reviewer comments

7.3.6.5 Data synthesis

The protocol should detail how the reviewers plan to synthesize data extracted from included studies. The types of data it is anticipated will be synthesized should be consistent with the methods used for data collection and the included study designs. The review report should detail how the reviewers synthesized the data extracted from included studies and how it was applied consistently across all included studies.

As with all systematic reviews, there are various approaches to present the results, including a narrative, graphical or tabular summary, or meta-analysis (refer to the appropriate section below). (Munn, Tufanaru et al. 2014) There are some special considerations when conducting meta-analysis for questions related to etiology & risk.

7.3.6.5.1 Meta-analysis of observational research

A meta-analysis is a statistical procedure that combines the findings from multiple primary studies into a single overall summary estimate. A meta-analysis can be conducted to improve statistical power to detect a treatment effect, to estimate a summary average effect, to identify sub-groups associated with a negative outcome or a beneficial effect, and to explore differences in the size or direction of the treatment effect associated with study-specific variables. Interpretation of summary effect sizes from meta-analyses of epidemiological studies addressing etiological issues is difficult because of the differences in the factors controlled for in multivariate analyses from individual studies, and also because of poor reporting in the original studies with lack of adequate or complete details. For more information and guidance on meta-analysis, refer to Chapter 3 of this manual.

An overall effect size is reported in a meta-analysis. It is computed for each study and the findings are pooled together to draw overall inferences. There are many different types of effect size and it is possible to convert one effect size into another, so each really just offers a differently scaled measure of the strength of an effect or a relationship. Reviewers should be aware that there are different guidelines for the interpretation of practical significance of the effect sizes such as ORs and RRs.(Tufanaru C, Huang WJ et al. 2012) One proposed guide for interpretation of effect sizes suggests that a value of 2 for a risk estimate (such as a relative risk RR or an odds ratio OR) is considered the minimum significant value from a practical point of view; a value of 3 is considered moderate significant; a value of 4 is considered to indicate strong significance from a practical point of view.(Tufanaru C, Huang WJ et al. 2012)

Frequently primary published studies investigating risk of an exposure will design the study and present the available data at different levels of the exposure, or in different categories to reflect a 'dose-response' relationship between the exposure and outcome variable. Difficulties will naturally arise if different studies have used different exposure categories and have presented this data in a variety of different ways. A dose response relationship between an exposure and the outcome is most commonly investigated to strengthen the support for causal inference or causation.(Greenland and Longnecker 1992, Bekkering, Harris et al. 2008) Individual studies may present results in a stratified manner, either across different exposure groups or in different quantiles. For example, considering the risk of alcohol intake and lung cancer, the data may be presented as different exposure groups such as in glasses/week or in grams of alcohol. Irrespective of this, methods are available to combine the results of individual studies presenting such 'trend' data. Dependent on the type of data presented from such a dose response investigation, accepted methods exist to summarize the data to a consistent risk estimate which can then be subsequently used in meta-analysis.

Bekkering et al in a study on the usability of results in a meta-analysis reported that majority of usable results reported were odds, risk, or hazard ratios that compared one or more exposure categories with a baseline category.(Bekkering, Harris et al. 2008) They further suggest some advantages in reporting results in ORs, RRs and HRs, which include checking informally for nonlinear exposure effects, and easier interpretation of the magnitude of the association.(Bekkering, Harris et al. 2008) In case of nonlinear associations, there is a risk for conclusions from dose-response meta-analysis being misleading and it is suggested that linearity assumptions be checked for each study, when conducting dose-response meta-analysis.(Greenland and Longnecker 1992, Bekkering, Harris et al. 2008) Bekkering et al,(Bekkering, Harris et al. 2008) Chene and Thompson,(Chene and Thompson 1996) Greenland and Longnecker,(Greenland and Longnecker 1992) Hamling et al,(Hamling, Lee et al. 2008) and Orsini et al (Orsini, Bellocco et al. 2006) describe methods for conducting linear and non-linear dose-response meta-analyses. Essentially, for linear dose-response meta-analysis, the method involves estimation of a linear dose-response curve for each study when combining studies with different exposure category definitions. Further, it requires the numbers of cases and noncases (outcomes) and persons/person-years (person-time) and the effect estimates (RR or OR) with confidence intervals for at least three quantitative exposure categories.(Aromataris, Hopp L et al. 2011)

A note on heterogeneity (refer to [Chapter 3](#) for more details)

Despite the impediment to meta-analysis that heterogeneity of the published data presents, be it for methodological, clinical or statistical reasons, meta-analysis of observational studies to inform etiology and risk is almost always possible and can offer a valid means to explore heterogeneity and its impact within a data set. A combined analysis of individual studies, beyond the outright aim of increased precision due to increased sample size, may be desirable as it allows the exploration of potential confounders and interactions and other modifying effects that may explain the heterogeneity among the included studies. It is suggested that the decision to conduct meta-analysis should not be just based on statistical considerations regarding heterogeneity but should be based on the review question, the characteristics of the studies, and the interpretability of the results.

7.3.6.5.2 The narrative synthesis of data

The results of all systematic reviews require some degree of narrative. Where a meta-analysis has been performed, that narrative may focus on synthesis of the characteristics of studies and their quality to explain and interpret the calculated effect estimates. In instances where meta-analysis has not been possible, the review authors will have to resort to narrative synthesis of the results of the included studies also. Narrative synthesis relies primarily on the use of words and text (tables are often included also, See Section 2.8.3) to summarise and explain the findings of a synthesis process. Its form may vary from the simple recounting and description of study characteristics, context, quality, and findings. The textual description of studies (individual or group of studies) and the thematic analysis methods are briefly presented below. Further exploration as well as worked examples for these approaches is provided by Lucas & co.(Lucas, Baird et al. 2007)

- Textual descriptions of individual studies. Summaries of individual studies can be structured to provide details of the setting, participants, exposure, and outcomes, along with any other factors of interest (e.g. the income level of the users, age of users, previous experiences, attrition, length of follow-up, sample size);
- Textual descriptions of groups of studies. Based on relevant criteria (e.g. types of participants) included studies can be sub-grouped. Subsequently, commentaries summarizing key aspects of the studies in relation to the sub-group within which they were included are produced. In a final step, the scope, differences and similarities among studies are used to draw conclusions across the studies.

Where a narrative synthesis is undertaken to describe the included studies and their conclusions, it is important to discern how the evidence was weighted and whether conclusions were biased. It is recommended that the characteristics of the studies and the data extracted are emphasised and tables, graphs, and other diagrams are made use of to compare data.(Lockwood and White 2012) The narrative summary will present quantitative data extracted from individual studies, as well as, where available, point estimates (a value that represents a best estimate of effects) and interval estimates (an estimated range of effects, presented as a 95% confidence interval).

Because a potentially large amount of data can be conveyed in a narrative summary, consistency can be ensured in the results section if all reviewers agree beforehand on a structure for the reporting of results. If a structure is not followed, the report of results may appear incomplete or unreliable.(Lockwood and White 2012) However, if included studies do not provide the relevant information to comply with a structure, it should be made clear in the summary. A textual combination of data is often used when the included studies are dissimilar in terms of patients, methods, or data.

7.3.6.5.3 The tabular synthesis of data

Tabulating the data begins with grouping the studies in discrete categories (e.g. based on types of participants, exposures, outcomes, country of origin, duration of the exposure, number of participants in each group, context, results and comments). When the analysis of the tables reveals the presence of dominant groups or clusters of characteristics groups of studies can be formed by which the subsequent synthesis can be organized; this technique is particularly useful when there are larger number of papers. Based on the type of data reported, a common results rubric can be tabulated as well (e.g. absolute difference, relative risk, odds ratio, favours exposure vs. favours no exposure column); this approach can serve as a first step in comparing the effects observed across the included studies.

Bellow you will find some suggested steps for tabulating information from studies included in a systematic review.(Khan, Kunz et al. 2003)

Suggested steps:

- Place features related to populations, exposures and outcomes in columns.
- Consider what subgroups of populations there are among included studies.
- Consider what subtypes of exposures there are.
- Consider the outcomes and their importance.
- Consider if studies need to be sub-classified according to study designs and quality.
- Populate the cells in the table with information from studies along rows in subgroups.
- Sort studies according to a feature that helps to understand their results (e.g. a characteristic of a population or exposure, rank order of quality, year of publication, etc.).

7.3.7 Results

The findings of the review should flow logically from the review objective/question i.e. they must ultimately answer the question! Findings should be extracted using JBI SUMARI and a narrative, tabular, graphical or meta-analysis should constitute part of this section. Reporting of results, as suggested by previous research, can include graphical summaries of study estimates and any combined estimate, a table listing descriptive information for each study, results of sensitivity testing and any subgroup analysis, and an indication of statistical uncertainty of findings.

This section should allow the reader to clearly follow how the included studies were identified and selected for inclusion in the review. In addition, the number of papers excluded should also be stated. There should be a narrative description of the process accompanied by a [flowchart of the review process](#) (from the PRISMA statement) detailing the flow from the search, through study selection, duplicates, full text retrieval, and any additions from 3rd search, appraisal, extraction and synthesis.

7.3.7.1 Description of studies

This section of the results should include an overall description of the included studies (with reference to the table in the appendices), with the main aim to provide some context to the results section and sufficient detail for the reader to determine if the included studies are similar enough to combine in meta-analysis. Specific items/points of interest from individual studies may also be highlighted here. Additional details may include the assessment of methodological quality, characteristics of the participants, location and types of exposures and outcomes. These can be presented in a narrative form, in a table or in both formats when studies vary in orientation and focus.

7.3.7.2 Methodological quality

This section should focus on methodological quality as determined by the relevant critical appraisal checklist. There should be a narrative summary of the overall methodological quality of the included studies, which can be supported (optional) by a table showing the results of the critical appraisal. Where only few studies are identified, or there are specific items of interest from included studies, these should be addressed in the narrative also, particularly where studies were deficient, or particularly good, i.e. with clear narrative regarding risk of bias/rigor of included studies. Use of N/A should also be justified in the text.

7.3.7.3 Findings of the review

This section should be organized in a meaningful way based on the review objectives and questions and types of exposures and outcomes and types of studies. This section should provide comprehensive information regarding the results of all performed meta-analyses and additional analyses such as sensitivity analysis and sub-group analysis. Point estimates and interval estimates (confidence intervals) should be reported. Before presenting any meta-analysis results, the conduct of meta-analyses should be justified; reviewers should explicitly provide commentaries regarding the clinical, methodological, and statistical heterogeneity of the studies included in meta-analyses and the appropriateness of conducting meta-analyses. Summary results from meta-analyses should be reported as summary point estimates and interval estimates. The meta-analysis forest plots for all performed meta-analyses should be presented in this section. A narrative summary should complement the forest plots and provide additional commentaries and explanations for all performed meta-analyses (Munn et al 2014).

Reviewers should report the funnel plot for publication bias if such assessment was appropriate and performed. Reviewers should include the results of assessment of risk of publication bias, including the results of statistical tests for publication bias, if such tests were used.

Even if meta-analysis is performed, a narrative summary should be included to supplement the technical details provided on the process and results of meta-analysis and to provide synthesis of data not captured in statistical meta-analysis.

If meta-analysis is not performed, a narrative summary should be included. The narrative summary should provide an overall summary of the findings of the included studies and their biases, strengths and limitations. The essence of narrative summary is that the results are summarized in words and in tables without any statistical meta-analysis. Textual commentaries and tables are used in order to summarize the results from the included studies and to provide context information for these results, thus facilitating understanding of the summarized results.

7.3.8 Discussion

This section should discuss the results of the synthesis as well as any limitations of the primary studies included in the review and of the review itself (i.e. language, access, timeframe, study design, etc.). The results should be discussed in the context of current literature, practice and policy.

The aim of this section is to explain and discuss the main findings – including the strength of the evidence, for each main outcome. It should address the issues arising from the conduct of the review including limitations and issues arising from the findings of the review (such as search limitations). The discussion does seek to establish a line of argument based on the findings regarding the exposure and its association with the outcomes identified in the protocol. The application and relevance of the findings to relevant stakeholders (e.g. healthcare providers, patients and policy makers) should also be discussed in this section.

Points to consider this section include:

- Where any problems identified undertaking the search (perhaps there is little primary research on this topic or perhaps it is poorly indexed by the databases that were searched or perhaps the search was insufficient)?
- What limitations were found in the included primary research (e.g. were there inconsistencies or errors in reporting)?
- How do the review findings fit with what is currently known on the topic (from issues highlighted in the Background section)?
- Are the findings generalizable to other populations of participants/healthcare settings etc.?

Suggested layout of Discussion section:

Paragraph 1 – Begin your discussion with the:

- Amount and weight of available evidence
- Any particular feature/s associated with future risk of disease/harm/outcome
- Limitations to establish the reliability of results of the included studies (e.g. biases, data issues)

Paragraph 2 – set in context.

- Set the results in context of other knowledge on the topic, i.e. compare your work with previous systematic reviews or current opinions and guidelines.

Paragraph 3 – outline strengths and weaknesses of the meta-analytic methods used.

- Strengths: e.g. multiple reviewers reduced inclusion bias; which moderating variables were identified and how they were managed e.g. study design; determined that the effect estimate was sufficiently large in practical as well as statistical terms; determined precision of the effect; determined heterogeneity of the participants to enable generalisation of findings; conducted sensitivity analyses to assess any changes in the pooled effect estimator.
- Weaknesses: bias e.g. included only English language publications, unable to access suitable grey literature; possibility of missing (explanatory) variable/s, some issues with interpretation of findings.

Paragraph 4 – discuss limitations to establish the reliability of result/s.

- Of your review (bias)

7.3.9 Conclusion and Recommendations

This section should begin with an overall conclusion based on the results. The conclusions drawn should match with the review objective/question.

The conclusion section of a systematic review should provide a general interpretation of the findings in the context of other evidence and provide a detailed discussion of issues arising from the findings of the review and demonstrate the significance of the review findings to practice and research. Areas that may be addressed include:

- A summary of the major findings of the review;
- Issues related to the quality of the research within the area of interest;
- Other issues of relevance; and
- Potential limitations of the systematic review.

Recommendations for practice

It should be stated how the findings of the review impact on public health issues and clinical practice in the area. If there is sufficient evidence to make specific recommendations for practice, then the appropriate JBI Grades of Recommendation should be assigned to each recommendation based on the study design that led to the recommendation.

Recommendations for research

This section should include clear, specific recommendations for future research based on gaps in knowledge identified from the results of the review. Recommendations for research should avoid generalised statements calling for further research, but should be linked to specific issues.

7.3.10 Appendices

Here are several required appendices for a JBI review:

- Appendix I: Search strategy
 - A detailed and complete search strategy for all of the major databases and other sites and sources searched must be appended. Major databases that were searched must be identified, including the search platform used where necessary. All search filters with logic employed should be displayed, including the number of records returned.
- Appendix II: Table of included studies
 - A table of included studies is crucial to allow a snapshot of the studies included in the review.
- Appendix III: List of excluded studies
 - At a minimum, a list of studies excluded at the full text selection stage, if any, must be appended and reasons for exclusion should be provided for each study.

7.4 Chapter references

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Appendix 7.1 Critical appraisal checklist for cohort studies

JBI Critical Appraisal Checklist for Cohort Studies

Reviewer_____Date_____

Author _____Year_____Record Number _____

	Y es	No	Uncl ear	Not applicable
1. Were the two groups similar and recruited from the same population?				
1. Were the exposures measured similarly to assign people to both exposed and unexposed groups?				
1. Was the exposure measured in a valid and reliable way?				
1. Were confounding factors identified?				
1. Were strategies to deal with confounding factors stated?				
1. Were the groups/participants free of the outcome at the start of the study (or at the moment of exposure)?				
1. Were the outcomes measured in a valid and reliable way?				
1. Was the follow up time reported and sufficient to be long enough for outcomes to occur?				
1. Was follow up complete, and if not, were the reasons to loss to follow up described and explored?				
1. Were strategies to address incomplete follow up utilized?				
1. Was appropriate statistical analysis used?				

Overall appraisal: Include Exclude Seek further info

Comments (Including reason for exclusion)

Explanation of cohort studies critical appraisal

How to cite: Moola S, Munn Z, Tufanaru C, Aromataris E, Sears K, Sfetcu R, Currie M, Lisy K, Qureshi R, Mattis P, Mu P. Chapter 7: Systematic reviews of etiology and risk. In: Aromataris E, Munn Z (Editors). JBI Manual for Evidence Synthesis. JBI, 2020. Available from <https://synthesismanual.jbi.global>. <https://doi.org/10.46658/JBIMES-20-08>

Cohort studies Critical Appraisal Tool

Answers: Yes, No, Unclear or Not/Applicable

1. Were the two groups similar and recruited from the same population?

Check the paper carefully for descriptions of participants to determine if patients within and across groups have similar characteristics in relation to exposure (e.g. risk factor under investigation). The two groups selected for comparison should be as similar as possible in all characteristics except for their exposure status, relevant to the study in question. The authors should provide clear inclusion and exclusion criteria that they developed prior to recruitment of the study participants.

2. Were the exposures measured similarly to assign people to both exposed and unexposed groups?

A high quality study at the level of cohort design should mention or describe how the exposures were measured. The exposure measures should be clearly defined and described in detail. This will enable reviewers to assess whether or not the participants received the exposure of interest.

3. Was the exposure measured in a valid and reliable way?

The study should clearly describe the method of measurement of exposure. Assessing validity requires that a 'gold standard' is available to which the measure can be compared. The validity of exposure measurement usually relates to whether a current measure is appropriate or whether a measure of past exposure is needed.

Reliability refers to the processes included in an epidemiological study to check repeatability of measurements of the exposures. These usually include intra-observer reliability and inter-observer reliability.

4. Were confounding factors identified?

Confounding has occurred where the estimated intervention exposure effect is biased by the presence of some difference between the comparison groups (apart from the exposure investigated/of interest). Typical confounders include baseline characteristics, prognostic factors, or concomitant exposures (e.g. smoking). A confounder is a difference between the comparison groups and it influences the direction of the study results. A high quality study at the level of cohort design will identify the potential confounders and measure them (where possible). This is difficult for studies where behavioral, attitudinal or lifestyle factors may impact on the results.

5. Were strategies to deal with confounding factors stated?

Strategies to deal with effects of confounding factors may be dealt within the study design or in data analysis. By matching or stratifying sampling of participants, effects of confounding factors can be adjusted for. When dealing with adjustment in data analysis, assess the statistics used in the study. Most will be some form of multivariate regression analysis to account for the confounding factors measured. Look out for a description of statistical methods as regression methods such as logistic regression are usually employed to deal with confounding factors/variables of interest.

6. Were the groups/participants free of the outcome at the start of the study (or at the moment of exposure)?

The participants should be free of the outcomes of interest at the start of the study. Refer to the 'methods' section in the paper for this information, which is usually found in descriptions of participant/sample recruitment, definitions of variables, and/or inclusion/exclusion criteria.

7. Were the outcomes measured in a valid and reliable way?

Read the methods section of the paper. If for e.g. lung cancer is assessed based on existing definitions or diagnostic criteria, then the answer to this question is likely to be yes. If lung cancer is assessed using observer reported, or self-reported scales, the risk of over- or under-reporting is increased, and objectivity is compromised. Importantly, determine if the measurement tools used were validated instruments as this has a significant impact on outcome assessment validity.

Having established the objectivity of the outcome measurement (e.g. lung cancer) instrument, it's important to establish how the measurement was conducted. Were those involved in collecting data trained or educated in the use of the instrument/s? (e.g. radiographers). If there was more than one data collector, were they similar in terms of level of education, clinical or research experience, or level of responsibility in the piece of research being appraised?

8. Was the follow up time reported and sufficient to be long enough for outcomes to occur?

The appropriate length of time for follow up will vary with the nature and characteristics of the population of interest and/or the intervention, disease or exposure. To estimate an appropriate duration of follow up, read across multiple papers and take note of the range for duration of follow up. The opinions of experts in clinical practice or clinical research may also assist in determining an appropriate duration of follow up. For example, a longer timeframe may be needed to examine the association between occupational exposure to asbestos and the risk of lung cancer. It is important, particularly in cohort studies that follow up is long enough to enable the outcomes. However, it should be remembered that the research question and outcomes being examined would probably dictate the follow up time

9. Was follow up complete, and if not, were the reasons to loss to follow up described and explored?

It is important in a cohort study that a greater percentage of people are followed up. As a general guideline, at least 80% of patients should be followed up. Generally a dropout rate of 5% or less is considered insignificant. A rate of 20% or greater is considered to significantly impact on the validity of the study. However, in observational studies conducted over a lengthy period of time a higher dropout rate is to be expected. A decision on whether to include or exclude a study because of a high dropout rate is a matter of judgement based on the reasons why people dropped out, and whether dropout rates were comparable in the exposed and unexposed groups.

Reporting of efforts to follow up participants that dropped out may be regarded as an indicator of a well conducted study. Look for clear and justifiable description of why people were left out, excluded, dropped out etc. If there is no clear description or a statement in this regards, this will be a 'No'.

10. Were strategies to address incomplete follow up utilized?

Some people may withdraw due to change in employment or some may die; however, it is important that their outcomes are assessed. Selection bias may occur as a result of incomplete follow up. Therefore, participants with unequal follow up periods must be taken into account in the analysis, which should be adjusted to allow for differences in length of follow up periods. This is usually done by calculating rates which use person-years at risk, i.e. considering time in the denominator.

11. Was appropriate statistical analysis used?

As with any consideration of statistical analysis, consideration should be given to whether there was a more appropriate alternate statistical method that could have been used. The methods section of cohort studies should be detailed enough for reviewers to identify which analytical techniques were used (in particular, regression or stratification) and how specific confounders were measured.

For studies utilizing regression analysis, it is useful to identify if the study identified which variables were included and how they related to the outcome. If stratification was the analytical approach used, were the strata of analysis defined by the specified variables? Additionally, it is also important to assess the appropriateness of the analytical strategy in terms of the assumptions associated with the approach as differing methods of analysis are based on differing assumptions about the data and how it will respond.

Appendix 7.2 Critical appraisal checklist for case-control studies

JBI Critical Appraisal Checklist for Case Control Studies

Reviewer_____Date_____

Author _____Year_____Record Number_____

	Y es	No	Uncl ear	Not applicable
1. Were the groups comparable other than the presence of disease in cases or the absence of disease in controls?				
1. Were cases and controls matched appropriately?				
1. Were the same criteria used for identification of cases and controls?				
1. Was exposure measured in a standard, valid and reliable way?				
1. Was exposure measured in the same way for cases and controls?				
1. Were confounding factors identified?				
1. Were strategies to deal with confounding factors stated?				
1. Were outcomes assessed in a standard, valid and reliable way for cases and controls?				
1. Was the exposure period of interest long enough to be meaningful?				
1. Was appropriate statistical analysis used?				

Overall appraisal: Include Exclude Seek further info

Comments (Including reason for exclusion)

Explanation of case control studies critical appraisal

How to cite: Moola S, Munn Z, Tufanaru C, Aromataris E, Sears K, Sfetcu R, Currie M, Lisy K, Qureshi R, Mattis P, Mu P. Chapter 7: Systematic reviews of etiology and risk. In: Aromataris E, Munn Z (Editors). *JBI Manual for Evidence Synthesis*. JBI, 2020. Available from <https://synthesismanual.jbi.global>. <https://doi.org/10.46658/JBIMES-20-08>

Case Control Studies Critical Appraisal Tool

Answers: Yes, No, Unclear or Not/Applicable

1. Were the groups comparable other than presence of disease in cases or absence of disease in controls?

The control group should be representative of the source population that produced the cases. This is usually done by individual matching; wherein controls are selected for each case on the basis of similarity with respect to certain characteristics other than the exposure of interest. Frequency or group matching is an alternative method. Selection bias may result if the groups are not comparable.

2. Were cases and controls matched appropriately?

As in item 1, the study should include clear definitions of the source population. Sources from which cases and controls were recruited should be carefully looked at. For example, cancer registries may be used to recruit participants in a study examining risk factors for lung cancer, which typify population-based case control studies. Study participants may be selected from the target population, the source population, or from a pool of eligible participants (such as in hospital-based case control studies).

3. Were the same criteria used for identification of cases and controls?

It is useful to determine if patients were included in the study based on either a specified diagnosis or definition. This is more likely to decrease the risk of bias. Characteristics are another useful approach to matching groups, and studies that did not use specified diagnostic methods or definitions should provide evidence on matching by key characteristics. A case should be defined clearly. It is also important that controls must fulfil all the eligibility criteria defined for the cases except for those relating to diagnosis of the disease.

4. Was exposure measured in a standard, valid and reliable way?

The study should clearly describe the method of measurement of exposure. Assessing validity requires that a 'gold standard' is available to which the measure can be compared. The validity of exposure measurement usually relates to whether a current measure is appropriate or whether a measure of past exposure is needed.

Case control studies may investigate many different 'exposures' that may or may not be associated with the condition. In these cases, reviewers should use the main exposure of interest for their review to answer this question when using this tool at the study level.

Reliability refers to the processes included in an epidemiological study to check repeatability of measurements of the exposures. These usually include intra-observer reliability and inter-observer reliability.

5. Was exposure measured in the same way for cases and controls?

As in item 4, the study should clearly describe the method of measurement of exposure. The exposure measures should be clearly defined and described in detail. Assessment of exposure or risk factors should have been carried out according to same procedures or protocols for both cases and controls.

6. Were confounding factors identified?

Confounding has occurred where the estimated intervention exposure effect is biased by the presence of some difference between the comparison groups (apart from the exposure investigated/of interest). Typical confounders include baseline characteristics, prognostic factors, or concomitant exposures (e.g. smoking). A confounder is a difference between the comparison groups and it influences the direction of the study results. A high quality study at the level of case control design will identify the potential confounders and measure them (where possible). This is difficult for studies where behavioral, attitudinal or lifestyle factors may impact on the results.

7. Were strategies to deal with confounding factors stated?

Strategies to deal with effects of confounding factors may be dealt within the study design or in data analysis. By matching or stratifying sampling of participants, effects of confounding factors can be adjusted for. When dealing with adjustment in data analysis, assess the statistics used in the study. Most will be some form of multivariate regression analysis to account for the confounding factors measured. Look out for a description of statistical methods as regression methods such as logistic regression are usually employed to deal with confounding factors/ variables of interest.

8. Were outcomes assessed in a standard, valid and reliable way for cases and controls?

Read the methods section of the paper. If for e.g. lung cancer is assessed based on existing definitions or diagnostic criteria, then the answer to this question is likely to be yes. If lung cancer is assessed using observer reported, or self-reported scales, the risk of over- or under-reporting is increased, and objectivity is compromised. Importantly, determine if the measurement tools used were validated instruments as this has a significant impact on outcome assessment validity.

Having established the objectivity of the outcome measurement (e.g. lung cancer) instrument, it's important to establish how the measurement was conducted. Were those involved in collecting data trained or educated in the use of the instrument/s? (e.g. radiographers). If there was more than one data collector, were they similar in terms of level of education, clinical or research experience, or level of responsibility in the piece of research being appraised?

9. Was the exposure period of interest long enough to be meaningful?

It is particularly important in a case control study that the exposure time was sufficient enough to show an association between the exposure and the outcome. It may be that the exposure period may be too short or too long to influence the outcome.

10. Was appropriate statistical analysis used?

As with any consideration of statistical analysis, consideration should be given to whether there was a more appropriate alternate statistical method that could have been used. The methods section should be detailed enough for reviewers to identify which analytical techniques were used (in particular, regression or stratification) and how specific confounders were measured.

For studies utilizing regression analysis, it is useful to identify if the study identified which variables were included and how they related to the outcome. If stratification was the analytical approach used, were the strata of analysis defined by the specified variables? Additionally, it is also important to assess the appropriateness of the analytical strategy in terms of the assumptions associated with the approach as differing methods of analysis are based on differing assumptions about the data and how it will respond.

Appendix 7.3 Critical appraisal checklists for case series

JBICritical Appraisal Checklist for Case Series

Reviewer_____Date_____

-
-

Author _____Year_____Record
Number _____

	Y es	No	Uncl ear	Not applicable
1. Were there clear criteria for inclusion in the case series?				
1. Was the condition measured in a standard, reliable way for all participants included in the case series?				
1. Were valid methods used for identification of the condition for all participants included in the case series?				
1. Did the case series have consecutive inclusion of participants?				
1. Did the case series have complete inclusion of participants?				
1. Was there clear reporting of the demographics of the participants in the study?				
1. Was there clear reporting of clinical information of the participants?				
1. Were the outcomes or follow up results of cases clearly reported?				
1. Was there clear reporting of the presenting site(s)/clinic(s) demographic information?				
1. Was statistical analysis appropriate?				

Overall appraisal: Include Exclude Seek further info

Comments (Including reason for exclusion)

Introduction to the Case Series Critical Appraisal Tool

How to cite: Moola S, Munn Z, Tufanaru C, Aromataris E, Sears K, Sfetcu R, Currie M, Lisy K, Qureshi R, Mattis P, Mu P. Chapter 7: Systematic reviews of etiology and risk. In: Aromataris E, Munn Z (Editors). *JBI Manual for Evidence Synthesis*. JBI, 2020. Available from <https://synthesismanual.jbi.global>. <https://doi.org/10.46658/JBIMES-20-08>

The definition of a case series varies across the medical literature, which has resulted in inconsistent use of this term (Appendix 1).¹⁻³ The gamut of case studies is wide, with some studies claiming to be a case series realistically being nothing more than a collection of case reports, with others more akin to cohort studies or even quasi-experimental before and after studies. This has created difficulty in assigning 'case series' a position in the hierarchy of evidence and identifying and appropriate critical appraisal tool.^{1, 2}

Dekkers et al. define a case series as a study in which 'only patients with the outcome are sampled (either those who have an exposure or those who are selected without regard to exposure), which does not permit calculation of an absolute risk.'^{1p.39} The outcome could be a disease or a disease related outcome. This is contrasted to cohort studies where sampling is based on exposure (or characteristic), and case- control studies where there is a comparison group without the disease.

The completeness of a case series contributes to its reliability.¹ Studies that indicate a consecutive and complete inclusion are more reliable than those that do not. For example, a case series that states 'we included all patients (24) with osteosarcoma who presented to our clinic between March 2005 and June 2006' is more reliable than a study that simply states 'we report a case series of 24 people with osteosarcoma.'

For the purposes of this checklist, we agree with the principles outlined in the Dekker et al. paper, and define case series as studies where only patients with a certain disease or disease-related outcome are sampled. Some of the items below relate to risk of bias, whilst others relate to ensuring adequate reporting and statistical analysis. A response of 'no' to any of the questions below negatively impacts the quality of a case series.

Tool Guidance

Answers: Yes, No, Unclear or Not/Applicable

1. Were there clear criteria for inclusion in the case series?

The authors should provide clear inclusion (and exclusion criteria where appropriate) for the study participants. The inclusion/exclusion criteria should be specified (e.g., risk, stage of disease progression) with sufficient detail and all the necessary information critical to the study.

2. Was the condition measured in a standard, reliable way for all participants included in the case series?

The study should clearly describe the method of measurement of the condition. This should be done in a standard (i.e. same way for all patients) and reliable (i.e. repeatable and reproducible results) way.

3. Were valid methods used for identification of the condition for all participants included in the case series?

Many health problems are not easily diagnosed or defined and some measures may not be capable of including or excluding appropriate levels or stages of the health problem. If the outcomes were assessed based on existing definitions or diagnostic criteria, then the answer to this question is likely to be yes. If the outcomes were assessed using observer reported, or self-reported scales, the risk of over- or under-reporting is increased, and objectivity is compromised. Importantly, determine if the measurement tools used were validated instruments as this has a significant impact on outcome assessment validity.

4. Did the case series have consecutive inclusion of participants?

Studies that indicate a consecutive inclusion are more reliable than those that do not. For example, a case series that states 'we included all patients (24) with osteosarcoma who presented to our clinic between March 2005 and June 2006' is more reliable than a study that simply states 'we report a case series of 24 people with osteosarcoma.'

5. Did the case series have complete inclusion of participants?

The completeness of a case series contributes to its reliability (1). Studies that indicate a complete inclusion are more reliable than those that do not. As stated above, a case series that states 'we included all patients (24) with osteosarcoma who presented to our clinic between March 2005 and June 2006' is more reliable than a study that simply states 'we report a case series of 24 people with osteosarcoma.'

6. Was there clear reporting of the demographics of the participants in the study?

The case series should clearly describe relevant participant's demographics such as the following information where relevant: participant's age, sex, education, geographic region, ethnicity, time period, education.

7. Was there clear reporting of clinical information of the participants?

There should be clear reporting of clinical information of the participants such as the following information where relevant: disease status, comorbidities, stage of disease, previous interventions/treatment, results of diagnostic tests, etc.

8. Were the outcomes or follow-up results of cases clearly reported?

The results of any intervention or treatment should be clearly reported in the case series. A good case study should clearly describe the clinical condition post-intervention in terms of the presence or lack of symptoms. The outcomes of management/treatment when presented as images or figures can help in conveying the information to the reader/clinician. It is important that adverse events are clearly documented and described, particularly a new or unique condition is being treated or when a new drug or treatment is used. In addition, unanticipated events, if any that may yield new or useful information should be identified and clearly described.

9. Was there clear reporting of the presenting site(s)/clinic(s) demographic information?

Certain diseases or conditions vary in prevalence across different geographic regions and populations (e.g. women vs. men, sociodemographic variables between countries). The study sample should be described in sufficient detail so that other researchers can determine if it is comparable to the population of interest to them.

10. Was statistical analysis appropriate?

As with any consideration of statistical analysis, consideration should be given to whether there was a more appropriate alternate statistical method that could have been used. The methods section of studies should be detailed enough for reviewers to identify which analytical techniques were used and whether these were suitable.

References

- 1 Dekkers OM, Egger M, Altman DG, Vandenbroucke JP. Distinguishing case series from cohort studies. *Annals of Internal Medicine*. 2012;156(1 Part 1):37-40.
- 2 Esene IN, Ngu J, El Zoghby M, Solaroglu I, Sikod AM, Kotb A et al. Case series and descriptive cohort studies in neurosurgery: the confusion and solution. *Child's Nervous System*. 2014;30(8):1321-32.
- 3 Abu-Zidan FM, Abbas AK, Hefny AF. Clinical "case series": a concept analysis. *African Health Sciences*. 2012;12(4):557-62.
- 4 Straus SE, Richardson WS, Glasziou P, Haynes RB. Evidence-based medicine: How to practice and teach EBM. 3rd Edition ed: Elsevier 2005.

Appendix 1: Case series definitions:

'A report on a series of patients with an outcome of interest. No control group is involved.'(4) (p 279)

'A case series is a descriptive study involving a group of patients who all have the same disease or condition: the aim is to describe common and differing characteristics of a particular group of individuals' (Oxford Handbook of medical statistics)

'A group or series of case reports involving patients who were given similar treatment. Reports of case series usually contain detailed information about the individual patients. This includes demographic information (for example, age, gender, ethnic origin) and information on diagnosis, treatment, response to treatment, and follow-up after treatment.' Law K, Howick J. OCEBM Table of Evidence Glossary. 2013 [cited 2014 10th January]; Available from: <http://www.cebm.net/index.aspx?o=1116>

'A **case series** (also known as a clinical **series**) is a type of medical research study that tracks subjects with a known exposure, such as patients who have received a similar treatment, or examines their medical records for exposure and outcome.' Wikipedia

'A study which makes observations on a series of individuals, usually all receiving the same intervention, with no control group. Comments: At this stage it is unclear whether case series should be included in Cochrane systematic reviews, but we have left them in the list so that working groups can consider whether there are circumstances in which it would be appropriate to include them, and to assess risk of bias. A particular reason for including case series might be where they provide evidence relating to adverse effects of an intervention. Potential examples of risk of bias might be that if a case series does not [attempt to] recruit consecutive participants, this might introduce a risk of selection bias, while some case series could be at risk of detection bias, if the circumstances in which adverse effects are reported (or elicited) are not standardised.' <http://bmj.bmjjournals.com/research-projects/cochrane-risk-bias-tool>

Appendix 7.4 Critical appraisal checklist for case reports

JBI Critical Appraisal Checklist for Case Reports

Reviewer _____ Date _____

Author _____ Year _____ Record Number _____

	Yes	No	Unclear	Not applicable
1. Were patient's demographic characteristics clearly described?				
1. Was the patient's history clearly described and presented as a timeline?				
1. Was the current clinical condition of the patient on presentation clearly described?				
1. Were diagnostic tests or assessment methods and the results clearly described?				
1. Was the intervention(s) or treatment procedure(s) clearly described?				
1. Was the post-intervention clinical condition clearly described?				
1. Were adverse events (harms) or unanticipated events identified and described?				
1. Does the case report provide takeaway lessons?				

Overall appraisal: Include Exclude Seek further info

Comments (Including reason for exclusion)

Explanation of case reports critical appraisal

How to cite: Moola S, Munn Z, Tufanaru C, Aromataris E, Sears K, Sfetcu R, Currie M, Lisy K, Qureshi R, Mattis P, Mu P. Chapter 7: Systematic reviews of etiology and risk. In: Aromataris E, Munn Z (Editors). *JBI Manual for Evidence Synthesis*. JBI, 2020. Available from <https://synthesismanual.jbi.global>. <https://doi.org/10.46658/JBIMES-20-08>

Case Reports Critical Appraisal Tool

Answers: Yes, No, Unclear or Not/Applicable

1. Were patient's demographic characteristics clearly described?

Does the case report clearly describe patient's age, sex, race, medical history, diagnosis, prognosis, previous treatments, past and current diagnostic test results, and medications? The setting and context may also be described.

2. Was the patient's history clearly described and presented as a timeline?

A good case report will clearly describe the history of the patient, their medical, family and psychosocial history including relevant genetic information, as well as relevant past interventions and their outcomes. (CARE Checklist 2013)

3. Was the current clinical condition of the patient on presentation clearly described?

The current clinical condition of the patient should be described in detail including the uniqueness of the condition/disease, symptoms, frequency and severity. The case report should also be able to present whether differential diagnoses was considered.

4. Were diagnostic tests or methods and the results clearly described?

A reader of the case report should be provided sufficient information to understand how the patient was assessed. It is important that all appropriate tests are ordered to confirm a diagnosis and therefore the case report should provide a clear description of various diagnostic tests used (whether a gold standard or alternative diagnostic tests). Photographs or illustrations of diagnostic procedures, radiographs, or treatment procedures are usually presented when appropriate to convey a clear message to readers.

5. Was the intervention(s) or treatment procedure(s) clearly described?

It is important to clearly describe treatment or intervention procedures as other clinicians will be reading the paper and therefore may enable clear understanding of the treatment protocol. The report should describe the treatment/intervention protocol in detail; for e.g. in pharmacological management of dental anxiety - the type of drug, route of administration, drug dosage and frequency, and any side effects.

6. Was the post-intervention clinical condition clearly described?

A good case report should clearly describe the clinical condition post-intervention in terms of the presence or lack thereof symptoms. The outcomes of management/treatment when presented as images or figures would help in conveying the information to the reader/clinician.

7. Were adverse events (harms) or unanticipated events identified and described?

With any treatment/intervention/drug, there are bound to be some adverse events and in some cases, they may be severe. It is important that adverse events are clearly documented and described, particularly when a new or unique condition is being treated or when a new drug or treatment is used. In addition, unanticipated events, if any that may yield new or useful information should be identified and clearly described.

8. Does the case report provide takeaway lessons?

Case reports should summarize key lessons learned from a case in terms of the background of the condition/disease and clinical practice guidance for clinicians when presented with similar cases.

References:

Gagnier JJ, Kienle G, Altman DG, Moher D, Sox H, Riley D, CARE Group. The CARE Guidelines: ConsensusBased Clinical Case Reporting Guideline Development. Headache: The Journal of Head and Face Pain, 2013;53(10):1541-1547.

Appendix 7.5 Critical appraisal checklist for analytical cross-sectional studies

JBI Critical Appraisal Checklist for Analytical Cross Sectional Studies

Reviewer_____Date_____

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Author _____Year_____Record
Number _____

	Yes	No	Unclear	Not applicable
1. Were the criteria for inclusion in the sample clearly defined?				
1. Were the study subjects and the setting described in detail?				
1. Was the exposure measured in a valid and reliable way?				
1. Were objective, standard criteria used for measurement of the condition?				
1. Were confounding factors identified?				
1. Were strategies to deal with confounding factors stated?				
1. Were the outcomes measured in a valid and reliable way?				
1. Was appropriate statistical analysis used?				

Overall appraisal: Include Exclude Seek further info

Comments (Including reason for exclusion)

Explanation of analytical cross sectional studies critical appraisal

How to cite: Moola S, Munn Z, Tufanaru C, Aromataris E, Sears K, Sfetcu R, Currie M, Lisy K, Qureshi R, Mattis P, Mu P. Chapter 7: Systematic reviews of etiology and risk. In: Aromataris E, Munn Z (Editors). *JBIM Manual for Evidence Synthesis*. JBI, 2020. Available from <https://synthesismanual.jbi.global>. <https://doi.org/10.46658/JBIMES-20-08>

Analytical cross sectional studies Critical Appraisal Tool

Answers: Yes, No, Unclear or Not/Applicable

1. Were the criteria for inclusion in the sample clearly defined?

The authors should provide clear inclusion and exclusion criteria that they developed prior to recruitment of the study participants. The inclusion/exclusion criteria should be specified (e.g., risk, stage of disease progression) with sufficient detail and all the necessary information critical to the study.

2. Were the study subjects and the setting described in detail?

The study sample should be described in sufficient detail so that other researchers can determine if it is comparable to the population of interest to them. The authors should provide a clear description of the population from which the study participants were selected or recruited, including demographics, location, and time period.

3. Was the exposure measured in a valid and reliable way?

The study should clearly describe the method of measurement of exposure. Assessing validity requires that a 'gold standard' is available to which the measure can be compared. The validity of exposure measurement usually relates to whether a current measure is appropriate or whether a measure of past exposure is needed.

Reliability refers to the processes included in an epidemiological study to check repeatability of measurements of the exposures. These usually include intra-observer reliability and inter-observer reliability.

4. Were objective, standard criteria used for measurement of the condition?

It is useful to determine if patients were included in the study based on either a specified diagnosis or definition. This is more likely to decrease the risk of bias. Characteristics are another useful approach to matching groups, and studies that did not use specified diagnostic methods or definitions should provide evidence on matching by key characteristics.

5. Were confounding factors identified?

Confounding has occurred where the estimated intervention exposure effect is biased by the presence of some difference between the comparison groups (apart from the exposure investigated/of interest). Typical confounders include baseline characteristics, prognostic factors, or concomitant exposures (e.g. smoking). A confounder is a difference between the comparison groups and it influences the direction of the study results. A high quality study at the level of cohort design will identify the potential confounders and measure them (where possible). This is difficult for studies where behavioral, attitudinal or lifestyle factors may impact on the results.

6. Were strategies to deal with confounding factors stated?

Strategies to deal with effects of confounding factors may be dealt within the study design or in data analysis. By matching or stratifying sampling of participants, effects of confounding factors can be adjusted for. When dealing with adjustment in data analysis, assess the statistics used in the study. Most will be some form of multivariate regression analysis to account for the confounding factors measured.

7. Were the outcomes measured in a valid and reliable way?

Read the methods section of the paper. If for e.g. lung cancer is assessed based on existing definitions or diagnostic criteria, then the answer to this question is likely to be yes. If lung cancer is assessed using observer reported, or self-reported scales, the risk of over- or under-reporting is increased, and objectivity is compromised. Importantly, determine if the measurement tools used were validated instruments as this has a significant impact on outcome assessment validity.

Having established the objectivity of the outcome measurement (e.g. lung cancer) instrument, it's important to establish how the measurement was conducted. Were those involved in collecting data trained or educated in the use of the instrument/s? (e.g. radiographers). If there was more than one data collector, were they similar in terms of level of education, clinical or research experience, or level of responsibility in the piece of research being appraised?

8. Was appropriate statistical analysis used?

As with any consideration of statistical analysis, consideration should be given to whether there was a more appropriate alternate statistical method that could have been used. The methods section should be detailed enough for reviewers to identify which analytical techniques were used (in particular, regression or stratification) and how specific confounders were measured.

For studies utilizing regression analysis, it is useful to identify if the study identified which variables were included and how they related to the outcome. If stratification was the analytical approach used, were the strata of analysis defined by the specified variables? Additionally, it is also important to assess the appropriateness of the analytical strategy in terms of the assumptions associated with the approach as differing methods of analysis are based on differing assumptions about the data and how it will respond.