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|  | | Notes on Methodology Checklist 4: Case Control Studies | | |
| The studies covered by this checklist are designed to answer questions of the type “What are the factors that caused this event?”, and involve comparison of individuals with an outcome with other individuals from the same population who do not have the outcome. These studies start after the outcome of an event, and can be used to assess multiple causes of a single event. They are generally used to assess the causes of a new problem, but may also be useful for the evaluation of population based interventions such as screening. | | | | |
| **Section 1** | **Section 1** identifies the study, the reviewer, the guideline for which the paper is being considered as evidence, and the key question(s) it is expected to address. The reviewer is asked to consider a series of aspects of cohort study design and to make a judgement as to how well the current study meets this criterion. Each relates to an aspect of methodology that research has shown makes a significant difference to the conclusions of a study.  Case-control studies need to be very carefully designed, and the complexity of their design is often not appreciated by investigators, leading to many poor quality studies being conducted. The questions in this checklist are designed to identify the main features that should be present in a well designed study. There are few criteria that should, alone and unsupported, lead to rejection of a study. However, a study that fails to address or report on more than one or two of the questions addressed below should almost certainly be rejected.  If you would like more information on case-control studies, their characteristics and weaknesses then please refer to Greenhalgh T. How to read a paper: the basics of evidence-based medicine. 3rd edition. Oxford: Blackwell;2006. Section 3.5 Page 50.  Definitions for terms marked with a \* below can be found in the [Cochrane Handbook](http://www.cochrane.org/glossary).  *{Note that the “Response” column is for guidance only. You may opt for a different rating depending on how information is presented in any given review.}* | | | |
| **Statement 1.1** | **The study addresses an appropriate and clearly focused question** | | | |
|  | ***What does this statement mean?*** | | ***When does this statement apply?*** | ***Response:*** |
|  | Unless a clear and well defined question is specified in the report of the review, it will be difficult to assess how well it has met its objectives or how relevant it is to the question you are trying to answer on the basis of the conclusions. | | Always applies | **Yes** - if elements of the research question are present in the text.  **No** if there is no clear questioning the text.  **can’t say** - if you think there is insufficient detail to allow an assessment to be made. |
| **Statement 1.2** | **The cases and controls are taken from comparable populations** | | | |
|  | ***What does this statement mean?*** | | ***When does this statement apply?*** | ***Response:*** |
|  | Study participants may be selected from the target population (all individuals to which the results of the study could be applied), the source population (a defined subset of the target population from which participants are selected), or from a pool of eligible subjects (a clearly defined and counted group selected from the source population. **If the study does not include clear definitions of the source population it should be rejected.** | | always applies | **Yes** Where all populations are clearly defined.  **No** Where it is unclear on what bases the cases and controls were selected.  **can’t say** Where there is some discussion of which populations cases and controls were selected from, but no clarity about how each group was selected. |
| **Statement 1.3** | **The same exclusion criteria are used for both cases and controls** | | | |
|  | ***What does this statement mean?*** | | ***When does this statement apply?*** | ***Response:*** |
|  | All selection and exclusion criteria should be applied equally to cases and controls. Failure to do so may introduce a significant degree of bias into the results of the study. | | Always applies | **Yes** Where selection and exclusion criteria are explicitly stated for both cases and controls.  **No** Where there is evidence that selection and exclusion criteria were different for cases and controls.  **can’t say** Where selection and / or exclusion criteria, or their application, are not clearly specified. |
| **Statement 1.4** | **What percentage of each group (cases and controls) participated in the study?** | | | |
|  | ***What does this statement mean?*** | | ***When does this statement apply?*** | ***Response:*** |
|  | Differences between the eligible population and the participants are important, as they may influence the validity of the study. A participation rate can be calculated by dividing the number of study participants by the number of eligible subjects. It is more useful if calculated separately for cases and controls. If the participation rate is low, or there is a large difference between the two groups, the study results may well be invalid due to differences between participants and non-participants. In these circumstances, the study should be downgraded, and rejected if the differences are very large. | | Always applies | Percentage cases:  Percentage controls: |
| **Statement 1.5** | **Comparison is made between participants and non-participants to establish their similarities or differences** | | | |
|  | ***What does this statement mean?*** | | ***When does this statement apply?*** | ***Response:*** |
|  | Even if participation rates are comparable and acceptable, it is still possible that the participants selected to act as cases or controls may differ from other members of the source population in some significant way. A well conducted case-control study will look at samples of the non-participants among the source population to ensure that the participants are a truly representative sample. | | Always applies | **Yes** Where data is presented on the key characteristics of a sample of people from the source population that were not included in the study.  **No** Where no information on the characteristics of the source population is available.  **can’t say** Where the issues is discussed, but detailed information is not provided. |
| **Statement 1.6** | **Cases are clearly defined and differentiated from controls** | | | |
|  | ***What does this statement mean?*** | | ***When does this statement apply?*** | ***Response:*** |
|  | The method of selection of cases is of critical importance to the validity of the study. Investigators have to be certain that cases are truly cases, but must balance this with the need to ensure that the cases admitted into the study are representative of the eligible population. **The issues involved in case selection are complex, and should ideally be evaluated by someone with a good understanding of the design of case-control studies. If the study does not comment on how cases were selected, it is probably safest to reject it as a source of evidence.** | | Always applies | **Yes** Where methods used to define and identify cases are clearly described.  **No** Where there is no discussion of how cases were identified.  **can’t say** Where the methods used to define or identify cases are mentioned, but no details or justification are provided. |
| **Statement 1.7** | **It is clearly established that controls are non-cases** | | | |
|  | ***What does this statement mean?*** | | ***When does this statement apply?*** | ***Response:*** |
|  | Just as it is important to be sure that cases are true cases, it is important to be sure that controls do not have the outcome under investigation. Control subjects should be chosen so that information on exposure status can be obtained or assessed in a similar way to that used for the selection of cases. If the methods of control selection are not described, the study should be rejected. **If different methods of selection are used for cases and controls the study should be evaluated by someone with a good understanding of the design of case-control studies.** | | Always applies | **Yes** Where methods used to define and identify controls are clearly described.  **No** Where there is no discussion of how controls were identified.  **can’t say** Where the methods used to define or identify controls are mentioned, but no details or justification are provided. |
| **Statement 1.8** | **Measures will have been taken to prevent knowledge of primary exposure influencing case ascertainment** | | | |
|  | ***What does this statement mean?*** | | ***When does this statement apply?*** | ***Response:*** |
|  | If there is a possibility that case ascertainment can be influenced by knowledge of exposure status, assessment of any association is likely to be biased. A well conducted study should take this into account in the design of the study. | | Nearly always applies | **Yes** Where assessors are blinded to exposure status.  **No** Where no blinding of assessors takes place.  **can’t say** Where it is not possible to fully blind assessors (e.g. where assessors talk directly to participant or if the study is retrospective i.e. database or chart).  **not applicable.** Where studies are based on analysis of medical charts or databases. |
| **Statement 1.9** | **Exposure status is measured in a standard, valid and reliable way** | | | |
|  | ***What does this statement mean?*** | | ***When does this statement apply?*** | ***Response:*** |
|  | The primary outcome measures used should be clearly stated in the study. **If the outcome measures are not stated, or the study bases its main conclusions on secondary outcomes, the study should be rejected.** Where outcome measures require any degree of subjectivity, some evidence should be provided that the measures used are reliable and have been validated prior to their use in the study. | | Always applies | **Yes** Where outcome measures are clearly identified and are either objective or use a validated evaluation tool.  **No** Where outcome measures are subjective, and are not based on a validated tool.  **can’t say** Where outcome measures are not described in detail. |
| **Statement 1.10** | **The main potential confounders are identified and taken into account in the design and analysis** | | | |
|  | ***What does this statement mean?*** | | ***When does this statement apply?*** | ***Response:*** |
|  | Confounding is the distortion of a link between exposure and outcome by another factor that is associated with both exposure and outcome. The possible presence of confounding factors is one of the principal reasons why observational studies are not more highly rated as a source of evidence. The study should indicate which potential confounders have been considered, and how they have been allowed for in the analysis. Clinical judgement should be applied to consider whether all likely confounders have been considered. If the measures used to address confounding are considered inadequate, the study should be downgraded or rejected. **A study that does not address the possibility of confounding should be rejected.** | | Always applies | **Yes** Where confounders are discussed, identified, and allowed for in the analysis.  **No** Where confounding is not discussed  **can’t say** Where confounding is mentioned, but not discussed in detail. |
| **Statement 1.11** | **Confidence intervals are provided** | | | |
|  | ***What does this statement mean?*** | | ***When does this statement apply?*** | ***Response:*** |
|  | Confidence limits are the preferred method for indicating the precision of statistical results, and can be used to differentiate between an inconclusive study and a study that shows no effect. Studies that report a single value with no assessment of precision should be treated with extreme caution. | | Always applies | **Yes**  **No** |
| **Section 2** | **Section 2** relates to the overall assessment of the paper. It starts by rating the methodological quality of the study, based on your responses in Section 1 and using the following coding system: | | | |
| **Statement 2.1** | How well was the study done to minimise the risk of bias or confounding? | | | |

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|  | ++ | High quality (++): Majority of criteria met. Little or no risk of bias. Results unlikely to be changed by further research. |
|  | + | Acceptable (+): Most criteria met. Some flaws in the study with an associated risk of bias, Conclusions may change in the light of further studies. |
|  | 0 | Low quality (0): Either most criteria not met, or significant flaws relating to key aspects of study design. Conclusions likely to change in the light of further studies. |

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| **Statement 2.2** | Taking into account clinical considerations, your evaluation of the methodology used, and the statistical power of the study, do you think there is clear evidence of an association between exposure and outcome? | | |
|  | ***What does this statement mean?*** | | |
|  | This is your clinical judgement of the study | | |
| **Statement 2.3** | Are the results of this study directly applicable to the patient group targeted by this guideline? | | |
|  | ***What does this statement mean?*** | ***When does this statement apply?*** | ***Response:*** |
|  | Does this study make sense in the Scottish context**.** | Always. | **Yes**  **No** |
| **Statement 2.4** | **Notes.** Summarise the author’s conclusions. Add any comments on your own assessment of the study, and the extent to which it answers your question and mention any areas of uncertainty raised above. This section is very important and will appear on the evidence table. **PLEASE FILL IN**. | | |