| Question | Explanation |
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| SELECTION BIAS |  |
| 1. Are cases and controls a representative sample of the same source population?    * Yes    * No    * Insufficient information to answer | 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). Cases and controls should be a representative sample of the same source population (e.g. individuals living in the same geographical area). Each control should have an equal chance to be identified as a case (e.g. A public funded hospital may attract poorer people than in the general population, so factors that are linked to poverty may be artificially linked to the disease. This is difficult to demonstrate, but some elements can help to judge this:   * 1. Do all members of the source population have equal access to the hospital or health structure where the cases were identified and is the probability that they are diagnosed linked to relevant factors such as social class?   2. Use of different control groups can make results more robust if they show the same effect.   3. Nested case control studies, where a cohort of persons is followed up and all cases are included together with a random sample of controls, are probably the best way to address this issue. |
| 1. Are the same exclusion criteria used for both cases and controls?    * Yes    * No    * Insufficient information to answer | 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. |
| 1. Are participants and non-participants compared to establish their similarities and differences?    * Yes    * No    * Insufficient information to answer | 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. |
| 1. Are cases clearly defined and differentiated from controls?    * Yes    * No    * Insufficient information to answer | 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.* |
| 1. Is it clearly established that controls are non-cases?    * Yes    * No    * Insufficient information to answer | 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.* |
| DETECTION BIAS |  |
| 1. Are measures taken to prevent knowledge of primary exposure from influencing case ascertainment?    * Yes    * No    * Insufficient information to answer | 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. |
| 1. Is exposure status measured in a standard, valid and reliable way?    * Yes    * No → Is this likely to influence results?      + Yes      + No    * Insufficient information to answer | Exposure status should be ascertained in a way that limits recall bias. The fact that a person became a case will influence his/her answers. Ways to address this issue is the use of information that was collected independently, such as records or direct observation or measurement. Some exposures are more susceptible to this bias, especially when the study relies on information provided by the patient, such as information on diet. |
| CONFOUNDING |  |
| 1. Are the main potential confounders identified and taken into account in the design and analysis?    * Yes    * No    * Insufficient information to answer | 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 judgment 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. Confounding can be addressed either with statistical adjustment or matching. Problems often occur when confounding factors are not measured in a way that is sufficiently reliable. Some factors are very difficult to measure, such as social class, smoking (e.g. number of cigarettes), diet or sexual behavior. Even if the confounder is nominally taken into account, there remains an important risk of residual confounding.  One way to deal with confounding is matching, although matching in itself is not a quality criterion. Case control studies are often matched, either as a way to control for confounding or a way to increase the power of the study. Matching has a number of setbacks, however. If the matching factor is associated with the exposure then the power to demonstrate an effect is strongly reduced, as cases and controls have the same exposure status, and become non informative. Matching may also render the study non representative of the general population. Matching designs where the matching factor is geographical are particularly prone to these problems. |