Introduction to Epidemiology

TRAINING FOR HEALTH CARE PROVIDERS
How to interpret epidemiological studies on children’s health and the environment

Children’s Health and the Environment
CHEST Training Package for the Health Sector

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First author: Wojciech Hanke MD, PhD, Nofer Institute of Occupational Medicine
Are epidemiological studies needed in children’s health and the environment?

Quantitative risk assessment has greatly emphasized data from animal experiments because:

- epidemiological data involve uncertain measures of exposure compared with high-quality, well-controlled dosing of animals; and
- experimental models are free from biases such as confounding.

However, in reality the overall advantages of using human data far exceed the disadvantages.

Why we need epidemiological studies in CEH (1)
Quantitative risk assessment has put great emphasis on animal experimental data, as epidemiological data involve uncertain measures of exposures as compared with high-quality, well-controlled dosing of animals and that experimental model is free from biases such as confounding.

Introduction to Environmental Epidemiology edited by Evelyn O. Talbott and Gunther F. Craun, Lewis Publishers, 1995
Why are epidemiological studies needed in children’s health and the environment?

- First, the magnitude of error is likely to be greater using animal data because differences between species cause greater uncertainty than the sources of epidemiological studies.
- Second, the range of extrapolation is usually smaller for epidemiological studies, as the occupational or environmental studies from which data are available have much lower exposure than that in animal experiments.
- Third, epidemiological studies better represent the genetic diversity and variability in host factors in human populations than do animal studies.

However, in reality the net advantage of using human data is far greater than the disadvantages:

First, the magnitude of error is likely to be greater using animal data because interspecies differences incur greater uncertainty than the major sources of uncertainty in epidemiological studies (absorption rates, metabolic pathways, rates for activation or detoxification and elimination).

Second, range of extrapolation is usually smaller in case of epidemiological studies as available data on exposure from occupational or environmental studies are much lower than the doses used in animal experiments.

Third, genetic diversity and the variability in the host factors in human population is better represented in human studies than in animal ones. Because susceptibility to disease will differ according to these factors, the controlled experiment situation in which single strain in each of one or two species is tested has less generalizability than any human study.

*Introduction to Environmental Epidemiology edited by Evelyn O. Talbott and Gunther F. Craun, Lewis Publishers, 1995*
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Aspects that should be taken into account when interpreting epidemiological studies on children’s health and the environment

- What are the study questions?
- What is the study design?
- How has exposure been assessed?
- How have health effects been assessed?
- How has relative risk been estimated?
- Is the statistical power sufficient to answer the study questions?
- Might any bias influenced the results (information, selection and confounders)?
- Which causality criteria does the study fulfil?
- Is the study negative or just not informative?
What are the study questions?

- The study questions should be clearly specified.
- Usually they refer to the relationship between a specific type of exposure and specific health effects.
- If no study questions are specified, the reader cannot assess the quality of the report.
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<table>
<thead>
<tr>
<th>What is the study design? Value of cross-sectional and case–control studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Cross-sectional studies and case–control studies are the most popular study design</td>
</tr>
<tr>
<td>- The results obtained in both type of studies may be difficult to interpret, as they have several weak points</td>
</tr>
<tr>
<td>- The main disadvantage of cross-sectional studies is that they relate the health effects to current exposure in a selected population</td>
</tr>
<tr>
<td>- In case–control studies, the process of selecting cases and controls may influence the results, and estimating retrospective exposure may also provide biased results</td>
</tr>
</tbody>
</table>
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What is the study design? Advantages and disadvantages of prospective studies

- The most valuable studies are prospective cohort studies, because:
  - Assessment of exposure and health is of high quality
  - Health selection is controlled due to exposure
  - Several possible health outcomes can be detected provided that the battery of tests used in health surveillance is appropriately designed

- Prospective studies are usually very expensive and time-consuming, but this can sometimes be overcome by historical cohort studies
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Prospective studies – the National Children’s Study in the United States

- The National Children’s Study in the United States will follow more than 100,000 children from before birth and, in some cases, even before pregnancy.

- A representative sample of children will be followed from early life through adulthood, seeking information to prevent and treat such health problems as autism, birth defects, diabetes, heart disease and obesity.

- It is planned to be the largest study ever undertaken to assess the effects of the environment on the health of children and adults.
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**Was the control group properly selected? Cross-sectional studies**

- The ideal controls would be individuals similar in every respect to the group under study except for exposure to the agent of interest.
- External controls are selected from the general population or a particular segment.
- Internal controls are the residents of the same community who are not exposed to the agent of interest.
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Was the control group properly selected? Case–control study

- Hospital controls matched for relevant characteristics have often been used.
- Information on hospital cases can be obtained inexpensively and quickly.
- Hospital controls, however, might not properly represent the general population of cases.
- A random or stratified (by age and sex) sample of people living in the catchment area of the hospitals seems to be the best source of controls.

Hospital controls matched for relevant characteristics have often been used.

Information about hospital cases can be obtained inexpensively and quickly.

Hospital sources controls, however, might not be representative of the general population of cases.

A random or stratified (age, sex) sample of persons living in the area covered by the hospitals seems to be the best source of controls.
In prospective studies, exposure is measured at the start and periodically afterwards; the most appropriate methods can be used and checks to ensure good quality control can be incorporated into the study.

In cross-sectional studies, exposure is assessed based solely on current ad hoc measurements.

In case–control studies, the available records on past exposure are used; their quality has to be evaluated.
WHO; Lead poisoning and children

Deficits in psychological and classroom performance of children with elevated lead levels in dentine was among the first evidence that low levels of lead intoxication caused loss of intellectual capacity and changes behaviour.

Ref:


To measure the neuropsychological effects of unidentified childhood exposure to lead, the performance of 58 children with high and 100 with low dentine lead levels was compared. Dentine lead is a good measure of early lead exposure (at the time when dentine was formed, prenatally for the first teeth) – so in this case the cross-sectional design can capture the temporal structure of cause and effect. Children with lead levels scored significantly less well on the Wechsler Intelligence Scale for Children than those with low lead levels. This difference was also apparent on verbal subtests, on three other measures of auditory or speech processing and on a measure of attention. Analysis of variance showed that none of these differences could be explained by any of the 39 other variables studied. Also evaluated by a teachers’ questionnaire was the classroom behavior of all children (2146 in number) whose teeth were analyzed. The frequency of non-adaptive classroom behavior increased in a dose-related fashion to dentine lead level. Lead exposure, at doses below those producing symptoms severe enough to be diagnosed clinically, appears to be associated with neuropsychological deficits that may interfere with classroom performance.

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Case–control studies – assessment of exposure to pesticides

Some case–control studies have found an association between postnatal pesticide exposure and children’s cancer (acute lymphocytic leukaemia, non-Hodgkin lymphoma and brain tumours).

- In some studies, exposure assessment relied on self-reported pesticide use at home and in the garden.
- Confirmation from both parents increased confidence that the reported pesticides were really used.
- Some studies of the effects of prenatal exposure to pesticides also examined the critical windows of exposure.

A number of epidemiological studies have found a significant association between cancer and domestic exposure to pesticides. Evidence is increasing, but still limited because of the methodological weaknesses of the research.

In some case-control studies an association between postnatal pesticide exposure and paediatric cancer (acute lymphocytic leukaemia, non-Hodgkin lymphoma, brain tumours) have been found. However, most studies have relied on self-reported pesticide use in the home and garden or parental occupational exposure.

In some studies (Daniels et al. 2001) to improve the validity of exposure classification was considered whether only one parent or both parents reported exposure. Confirmation from both parents increased confidence that the reported pesticides were really used.

Daniels et al. 2001
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Case–control studies – using critical windows of exposure

Study population:
162 children (aged 0-14) newly diagnosed with leukemia and in United State (California) between 1995 and 1999
162 controls randomly selected from the birth registry

Information about exposure to pesticides:
Information about household pesticide use was collected retrospectively by interviewer

Can exposure be assessed better?

- Biological monitoring methods
- Recognizing the limitations of the measurements at the time of the study
- Standardized questionnaires, interviews and structured diaries
- Biomarkers of physiological effects
- Advantages of prospective studies

Biological monitoring methods (i.e. measuring agents which are accumulating in organisms or their metabolites) seem to be the most reliable measurements at the time of the study (area or individual samplings) provide information only about the level of current exposure? Questionnaires, interviews, and structured diaries if done in standardised way may offer information about the onset, duration and the level of exposure. Biomarkers of physiological effects are more and more often used but their utility has to be confirmed (e.g. protein adducts, DNA adducts). In carefully planned prospective study, exposure is measured at the start and periodically afterwards. The most appropriate methods can be used and checks to ensure good quality control can be incorporated into the study.
Health effects should be measured according to standardized procedures:

- Physiological measurements
- Questionnaires
- Use of regional and national registries
- Use of medical documentation

Health effects should be measured according to standardised procedures:

Physiological measurements (e.g. spirometry, IQ test, audiometry) are of the major value

Questionnaires – e.g. respiratory symptoms have a long history of application in paediatric environmental epidemiology and proved to be useful

Cancer cases can be derived from regional and national registers

Medical documentation can be very helpful in studies of reproductive health effects.
Assessing health effects
– prospective studies

- Diagnostic criteria are decided at the start of a study.
- Due precautions can be taken to ensure that diagnostic criteria are applied uniformly and in a standard way throughout the study.
- Any manifestations of the early stages of the diseases of interest can be recorded.
- People with disease are identified and categorized after their exposure has been categorized.
- Investigators categorizing disease in the population should not know the particular exposure category of any subject.

Decision on diagnostic criteria is taken at the start of a study.

Investigator has amply opportunity to specify these with precision and to take due precautions to ensure that they are applied in a uniform and standard way through the study.

Any manifestations of early stages of diseases of interest can be recorded.

Identification and categorisation of persons with disease in a prospective study takes place after they have been categorised with respect to exposure.

Investigators categorising the population with respect of disease should not be aware of the particular exposure category of any subject.
Assessing health effects – a cohort study on exposure to environmental tobacco smoke and the risk of sensitization to food allergens in children (IgE measurement)

<table>
<thead>
<tr>
<th>Exposure to tobacco smoke</th>
<th>Odds ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neither prenatally nor postnatally</td>
<td>1 (0.3-1.6)</td>
</tr>
<tr>
<td>Postnatally by father</td>
<td>0.7 (0.3-1.6)</td>
</tr>
<tr>
<td>Postnatally by mother and father</td>
<td>2.2 (0.9-5.9)</td>
</tr>
<tr>
<td>Prenatally and postnatally by mother and father</td>
<td>2.3 (1.1-4.6)</td>
</tr>
</tbody>
</table>

Cohort: 342 children - IgE measurements at the ages of 1, 2 and 3 years

Example of cohort study- association between tobacco smoke exposure and sensitization to food allergens- (Kulig 1999 )
Assessing health effects – cross-sectional and case-control studies

- The quality of the assessment of health effects in cross-sectional studies and case–control studies is similar to that in prospective studies.
- Uniform diagnostic criteria should be applied.

Quality of health assessment in cross-sectional studies and case-control studies is similar to prospective ones

Uniform diagnostic criteria should be applied if study is conducted by multiple centres (cross-sectional studies) or case and controls were recruited in more than one time periods
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Example of using medical data in studies of the effects of preconception or prenatal exposure

The following medical data have been taken into account in evaluating the effects of pesticide exposure before or during pregnancy on the pregnancy duration and outcome:

- Perinatal death
- Spontaneous abortion
- Premature birth
- Fetal growth retardation
- Congenital malformations
- Early childhood cancer

Exposure of either mother or father to pesticides before conception, or exposure of the mother during pregnancy, has been associated with an increased risk of fetal death, spontaneous abortion and early childhood cancer.

There is increasing evidence that *in utero* exposure increases the risk of growth retardation: small-for-gestational age baby, low birth weight, reduced length and small head circumference (see photo). Significant increases in the risk of congenital anomalies have also been reported. These include: eye defects, limb reduction, urogenital defects, hypospadias, cryptorchidism, orofacial clefts, central nervous system defects and heart defects.

**Refs:**

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Risk measures in epidemiology

Relative risk (RR)

- Relative risk measures how many times greater the risk of one population is than another. It is defined as the incidence among those exposed to a risk factor ($I_e$) divided by the incidence among those not exposed ($I_o$).

$$RR = \frac{I_e}{I_o}$$

- Relative risk measures the strength of an association. The greater the relative risk, the more likely that the risk factor is important in causation.

Relative risk is a measure of how many times greater is the risk of one population than another. It is defined as the incidence among those exposed to a risk factor ($I_e$), divided by the incidence among those nonexposed ($I_o$).

Relative risk is a measure of strength of an association. The greater the relative risk, the more likely that the risk factor is important in causation.
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<tr>
<th>Introduction to Epidemiology</th>
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</thead>
<tbody>
<tr>
<td><strong>Risk measures in epidemiology</strong></td>
</tr>
<tr>
<td><strong>– odds ratio (OR)</strong></td>
</tr>
<tr>
<td>• An approximate measure of relative risk can be obtained both from cross-sectional and case–control studies by comparing the odds favouring the occurrence of the disease in the two groups.</td>
</tr>
</tbody>
</table>

\[
\text{Odds ratio} = \frac{\text{number with the disease in the exposed group}}{\text{number without the disease in the exposed group}} \div \frac{\text{number with the disease in the unexposed group}}{\text{number without the disease in the unexposed group}}
\]
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Risk measures in epidemiology – interpreting relative risk and odds ratios

- An odds ratio or relative risk of 1 indicates that the rates of disease in the exposed and unexposed groups are identical (no association).
- Values greater than 1 indicate an increased risk among the people exposed.
- Values less than 1 indicates a decreased risk among the people exposed.
- Odds ratio or relative risk values are considered to be statistically significant when their confidence intervals do not include unity.

The values for OR or RR of 1 indicates rates of disease in the exposed and nonexposed groups are identical (i.e. no association).

Values greater than 1.0 indicates an increased risk among the exposed (i.e. harmful exposure effect).

Value less than 1.0 indicates a decreased risk among the exposed (i.e. protective exposure effect).

The values of RR or OR are considered to be significant ones when their confidence intervals do not include unity.
The ideal study would be infinitely large, but practical considerations limit the number of participants that can be included.

In epidemiological studies, increasing the study size is one of the ways to reduce the random error and increase the precision of the effect estimate.

Calculate the statistical power of the study before beginning the study.

The ideal study would be infinitely large, but practical considerations set limits on the number of participants that can be included.

In epidemiological studies, increasing the study size is one of the ways to reduce the random error and increase the precision of the effect estimate – what will be demonstrated by the narrower confidence intervals of estimated risk estimates.

Given these limits, it is desirable to find out, before commencing the study, whether it is large enough to be informative. One method is to calculate “power” of the study.
Statistical power is the likelihood that the study will yield a statistically significant finding when an effect of the postulated size exists. This depends on five factors:

- Cut-off values (alpha level below which the $P$-value from the study would be considered statistically significant; this value is almost always 0.05)
- Disease rate in the unexposed group in a cohort study or the exposure prevalence of controls in a case–control study
- Expected relative risk
- Relative size of the two groups
- Total number of study participants

Power is the likelihood that the study will yield a statistically significant finding when an effect of the postulated size exists. This depends on five factors:

- cut-off values (i.e. alpha level below which the $p$ value from the study would be considered statistically significant; this value is almost always 0.05)
- disease rate in the nonexposed group in a cohort study or the exposure prevalence of controls in a case-control study
- expected relative risk
- relative size of two groups
- total number of study participants
### Validity aspects of epidemiological studies

- Estimates derived from epidemiological studies may suffer from bias.
- Systematic error is distinguished from random error, since it would be present even in an infinitely large study.
- Correctly interpreting epidemiological studies requires recognizing and understanding the important potential sources of bias and assessing the magnitude and direction of potential bias.
- Three types of bias have been distinguished in epidemiological studies: information bias, selection bias and confounding.

Because of observational nature of most epidemiological studies, the estimates derived from epidemiological studies may suffer from bias (systematic deviation of results from truth).

Systematic error is distinguished from random error in that it would be present in even an infinitely large study, whereas increasing the study size can reduce random error.

To correctly interpret epidemiological studies, one must recognise and understand the important potential sources of bias and evaluate the magnitude and direction of potential biases.

Three types of bias have been distinguished in epidemiological studies (i.e. information bias, selection bias and confounding).
Information bias is due to errors in measuring (or classifying) the study variables.

Measurement error may be due to imperfect recall of subjects, may be introduced by improper calibration of measurement equipment, and by use of proxy variations as a substitute for the actual variable of interest.

Unlike some of the others types of bias, it usually cannot be eliminated by data analysis techniques.

Assessing the magnitude and direction of information bias requires identifying the sources of measurement (or classification) error.

To evaluate the magnitude and direction of information bias, the sources of measurement (or classification) error must be identified.
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How information bias works

- Assume a hypothetical case–control study of relationship between arsenic in drinking-water and lung cancer

- Perfectly classified data (true):

<table>
<thead>
<tr>
<th>Exposure to arsenic</th>
<th>Cases</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exposed</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Unexposed</td>
<td>25</td>
<td>100</td>
</tr>
</tbody>
</table>

- The correct (true) odds ratio: \( \frac{100 \times 100}{25 \times 100} = 4.0 \)

- Misclassified data:

<table>
<thead>
<tr>
<th>Exposure to arsenic</th>
<th>Cases</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exposed</td>
<td>50</td>
<td>50</td>
</tr>
<tr>
<td>Unexposed</td>
<td>75</td>
<td>150</td>
</tr>
</tbody>
</table>

- Odds ratio = \( \frac{50 \times 150}{75 \times 50} = 2.0 \)

50% of exposed subjects were misclassified into „unexposed” group. - all unexposed were correctly classified

OR obtained for the missclassified case-control study is much lower than the „true” one.
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Validity aspects – nondifferential information bias

- **Nondifferential information bias**: nondifferential misclassification of exposure generally (but not always) biases the relative risk estimates toward null.

- Nondifferential information bias tends to produce false-negative results.

*Nondifferential information bias* occurs when the likelihood of misclassification of exposure is the same in cases and controls or when the likelihood of misclassification of disease in question is the same in exposed and nonexposed persons.

Nondifferential misclassification of exposure generally (but not always) biases the relative risk estimates toward the null value.

Nondifferential information bias tends to produce “false negative” findings and is of particular concern in studies that find a negligible association between exposure and disease.
Validity aspects – differential information bias

- **Differential information bias**: occurs when the likelihood of misclassifying exposure differs in cases and controls or when the likelihood of misclassifying the disease of interest differs for exposed and unexposed people.

- This can bias the observed estimate of effect in either direction, either towards or away from null.
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Validity aspects – confounding

- A confounder is a risk (or protective) factor of the disease of interest that is associated with exposure in the source population and is not an intermediate step in the causal pathway between exposure and disease.

- If the confounder was not controlled when the study was designed, data analysis techniques should be used to control confounders (such as multivariate modelling techniques).

Confounder is a risk factor of disease in question, is associated with exposure in the source population and is not an intermediate step in the causal pathway between exposure and disease.

When the risks are compared in exposed and unexposed population, it might be assumed that in the absence of exposure, disease occurrence would be the same in both groups.

If this assumption is incorrect, the observed comparison between exposed and unexposed is confounded. That is, the estimate of effect reflects not only the effect of exposure but also the effects other factors that influence disease occurrence.
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**An example of a confounder**

- Consider a case-control study of the relation of exposure of pesticides and low birth weight.

- Assume the following:
  - Smoking is a risk factor for low birth weight and is associated with exposure to pesticides because:
  - Of the women not exposed to pesticides, 52% smoke regularly, whereas only 25% of the subjects exposed to pesticides smoke regularly.

- **Study population**

<table>
<thead>
<tr>
<th>Exposed to pesticides</th>
<th>+</th>
<th>Smoking</th>
<th>Š</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>+</td>
<td>148</td>
<td>25%</td>
<td>439</td>
<td>587</td>
</tr>
<tr>
<td>Š</td>
<td>710</td>
<td>52%</td>
<td>667</td>
<td>1377</td>
</tr>
<tr>
<td>Total</td>
<td>858</td>
<td>100%</td>
<td>1106</td>
<td>1964</td>
</tr>
</tbody>
</table>
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**A confounder at work**

- Odds ratios for low birth weight (LBW) in relation to pesticide exposure:
  - Smokers: OR = (100*340)/(370*48) = 1.91
    
    | Exposure to pesticides | LBW(+) | LBW(§) |
    |------------------------|--------|--------|
    | Exposed                | 100    | 48     |
    | Unexposed              | 370    | 340    |
    |                        | 470    | 388    |
  - Nonsmokers: OR = (210*450)/(217*229) = 1.91
    
    | Exposure to pesticides | LBW(+) | LBW(§) |
    |------------------------|--------|--------|
    | Exposed                | 210    | 229    |
    | Unexposed              | 217    | 450    |
    |                        | 427    | 679    |
  - Total group: OR = (310*790)/(587*277) = 1.50
    
    | Exposure to pesticides | LBW(+) | LBW(§) |
    |------------------------|--------|--------|
    | Exposed                | 310    | 277    |
    | Unexposed              | 587    | 790    |
    |                        | 897    | 1067   |

OR for LBW in relation to pesticide exposure or smokers and nonsmokers is similar OR=1.9

OR for all groups combined is lower - OR=1.5

It is the result of higher proportion of smokers (which have higher risk of LBW than non-smokers) in exposed group comparing to nonexposed group.

This is example of negative confounding. If not controlled can lead to false negative study results.
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<table>
<thead>
<tr>
<th>Were the study populations well selected?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Is there a selection bias?</td>
</tr>
</tbody>
</table>

Selection bias may occur when the samples of cases and controls provide a biased estimate of the distribution of exposure in the source population during a given period of time.

*How to control selection bias*

If a factor that affects the chance of being selected for the study can be identified (and measured), the analysis can adjust for this factor and selection bias can be removed.
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**Selection bias at work**

- Hypothetical true association between exposure to high-voltage transmission lines and childhood asthma

<table>
<thead>
<tr>
<th>Exposure</th>
<th>Asthma</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exposed</td>
<td>200</td>
<td>4800</td>
</tr>
<tr>
<td>Unexposed</td>
<td>300</td>
<td>7200</td>
</tr>
</tbody>
</table>

\[
OR = \frac{200 \times 7200}{300 \times 4800} = 1.0
\]

- Interpretation: exposure to high-voltage transmission lines is not a risk factor for asthma in the source population

- Results of biased sampling:

<table>
<thead>
<tr>
<th>Exposure</th>
<th>Asthma</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exposed</td>
<td>100</td>
<td>960</td>
</tr>
<tr>
<td>Unexposed</td>
<td>150</td>
<td>3600</td>
</tr>
</tbody>
</table>

\[
OR = \frac{100 \times 3600}{150 \times 960} = 2.5
\]

During the sampling the cases (both exposed and unexposed) and unexposed controls were sampled with probability 0.5 while exposed controls with probability 0.2

Biased OR = 2.5 is much higher than the true OR = 1.0.

Selection bias resulted in overestimation of OR value
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**Causality criteria**

- Temporal association (time sequence)
- Strength of the association
- Dose–response relationship
- Reversibility (stopping exposure stops the effects)
- Biological plausibility
- Consistency among studies (findings replicated)

Epidemiologist generally use a common set of criteria to help judge the evidence:

- **Temporal association (time sequence)** - does the cause precede the effect?
- **Strength of association** - Is the association between cause and effect strong and statistically significant (RRs, ORs)?
- **Dose–response relationship** - Is an increased exposure to a possible cause associated with increased effect?
- **Reversibility (cessation of exposure)** - Does the removal of a possible cause lead to a reduction in the risk of the disease?
- **Biologic plausibility** - Is the association consistent with other knowledge and evidence from animal studies?
- **Consistency among studies (replication of the findings)** - Have similar results been shown in other epidemiological studies?
A negative study must be large. “Not statistically significant” results obtained in small studies (with low statistical power) are uninformative.

The study must use methods allowing for detection of early manifestation of the disease.

Accurate exposure data must be provided. Reliable estimates of exposure should be made for “no effect” level.

Study methods must be valid (low probability of information/selection bias or confounding).
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Summary (1)

- The most valuable studies are prospective cohort studies. However, prospective studies are usually very expensive and time-consuming, so high-quality case-control and cross-sectional studies are needed.

- The ideal controls would be individuals similar in every respect to the group being studied except for exposure to the agent of interest.

- Diagnostic criteria should be applied in a uniform and standard way through the study.

- The ideal study would be infinitely large, but practical considerations limit the number of participants that can be included.
Correctly interpreting epidemiological studies requires recognizing and understanding the important potential sources of bias and assessing the magnitude and direction of potential bias (information bias, selection bias and confounding).

A set of criteria should be used for evaluating cause–effect relationships.

“Negative” findings should be interpreted very carefully.