

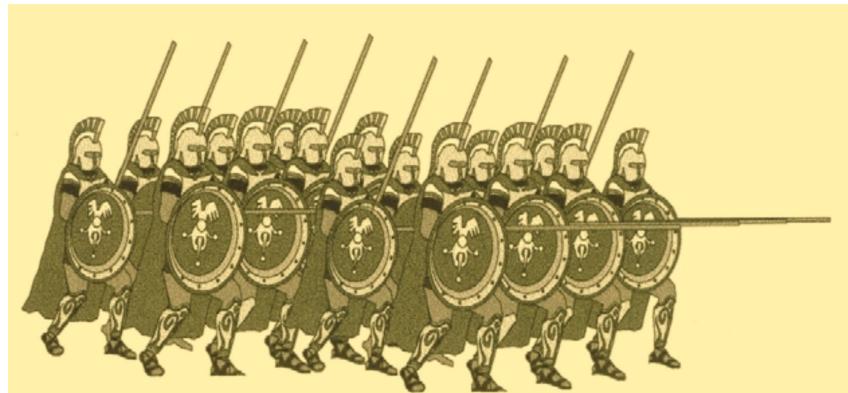
Cohort studies in depth

PHW250 B - Andrew Mertens



Quick review: cohort studies

- The term “cohort” has military roots.
- **Military:** A cohort was a 300–600-man unit in the Roman army.
- **Epidemiology:** A cohort study consists of bands or groups of persons marching forward in time from an exposure to one or more outcomes.

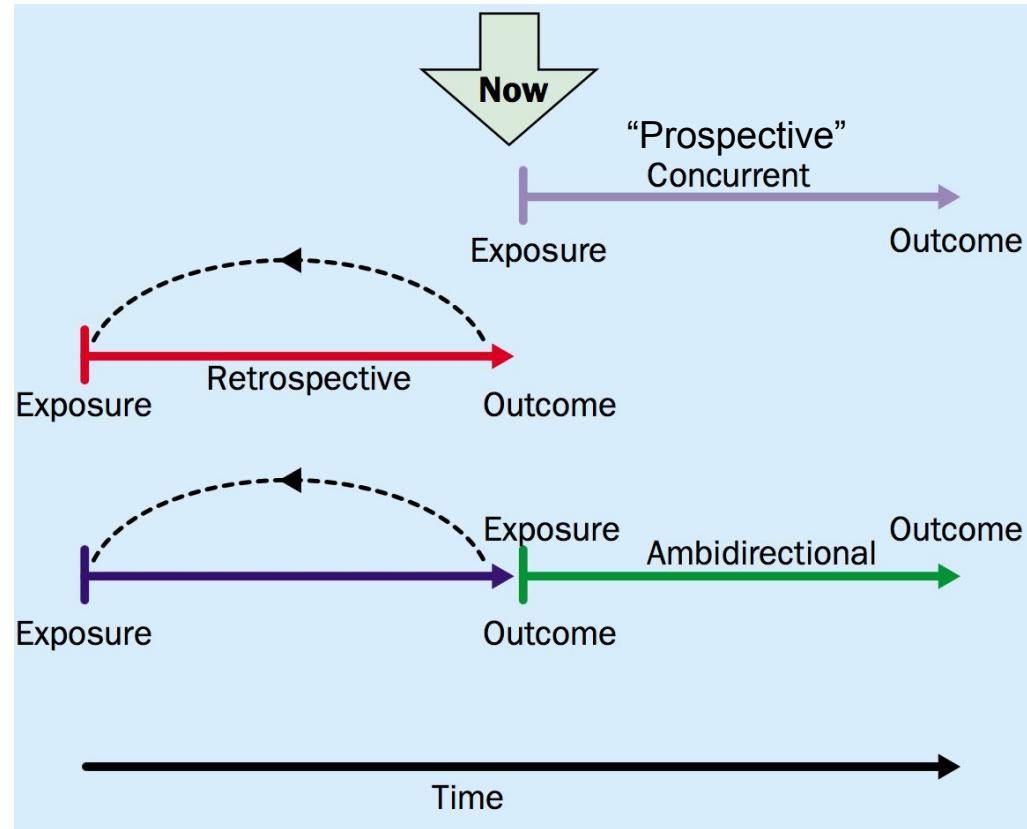


Quick review: types of cohort studies

The defining characteristic of all cohort studies is that they track people forward in time from exposure to outcome.

A cohort study moves in one direction, although gathering data might not.

Exposure □ outcome

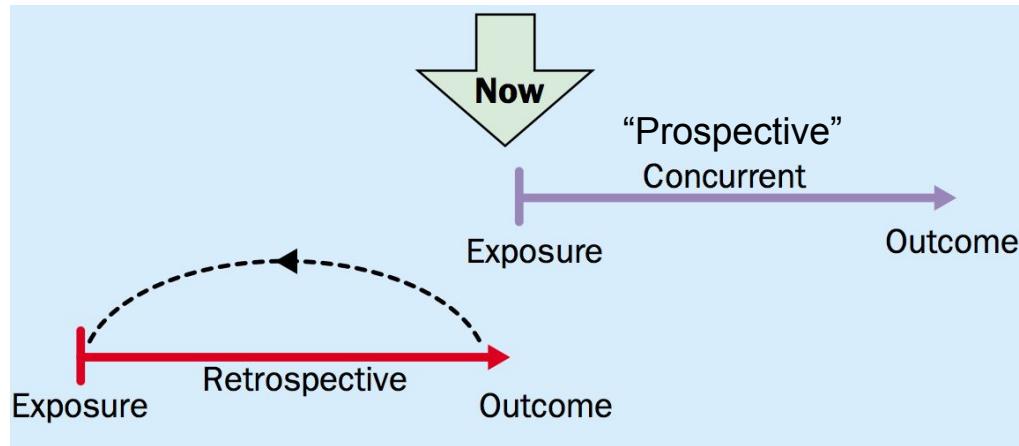


Quick review: types of cohort studies

Example: study of whether assisted reproductive technologies are associated with multiple births (e.g., twins)

Prospective: Track (a) women exposed to these technologies and (b) a similar group who conceived naturally. Monitor the frequency of multiple births.

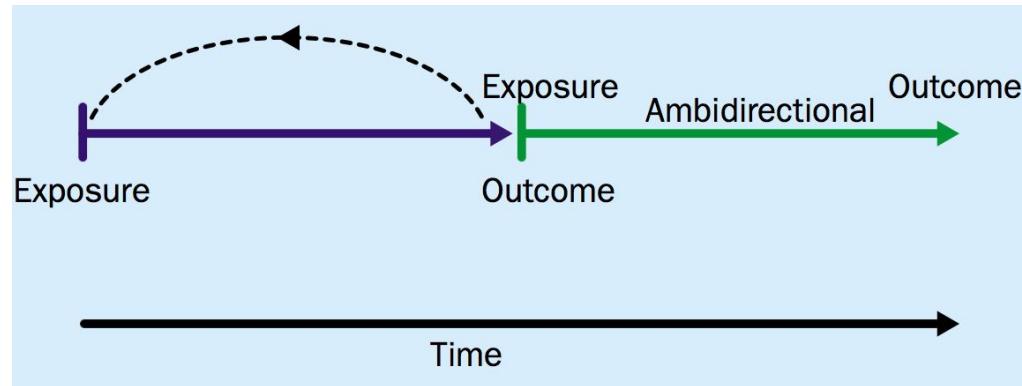
Retrospective: Use existing medical records and go back in time several years to identify women exposed and not exposed to these technologies. Then track them forward through records to note the birth outcomes.



Quick review: types of cohort studies

Example: Are assisted reproductive technologies associated with multiple births and with ovarian cancer in later life.

Ambidirectional: Look back through records for women who had multiple births and also start to follow these women into the future for ovarian cancer occurrence.



Quick review: types of populations

- **Closed population:**
 - There are no losses to follow-up
 - No migration in to the population
 - No competing risks
 - No change in exposure status over time
- **Open population:**
 - Migration in and out of the population may occur
 - Loss to follow-up may occur
 - Competing risks may occur
 - Exposure status may change over time

What measures of disease can be estimated in a cohort study?

- If there is **no loss to follow-up** and **no competing risks** (i.e. in a **closed population**) we can directly estimate
 - Cumulative incidence
 - Incidence density
 - Occurrence times
 - Prevalence

What measures of disease can be estimated in a cohort study?

- If there is **no loss to follow-up** and **no competing risks** (i.e. in a **closed population**) we can directly estimate
 - Cumulative incidence
 - Incidence density
 - Occurrence times
 - Prevalence
- If there is **loss to follow-up** and/or **competing risks** (i.e., in an **open population**) we do not know the final outcome status of some individuals in the study population, so:
 - Cumulative incidence: must use the Actuarial, Kaplan Meier, or Density methods
 - Incidence density: can still be calculated directly
 - Occurrence times: cannot be estimated directly
 - Prevalence: cannot be estimated directly
- This is the case in nearly all epidemiologic studies with the exception of efficacy trials with short follow-up periods.

Example of direct cumulative incidence calculation

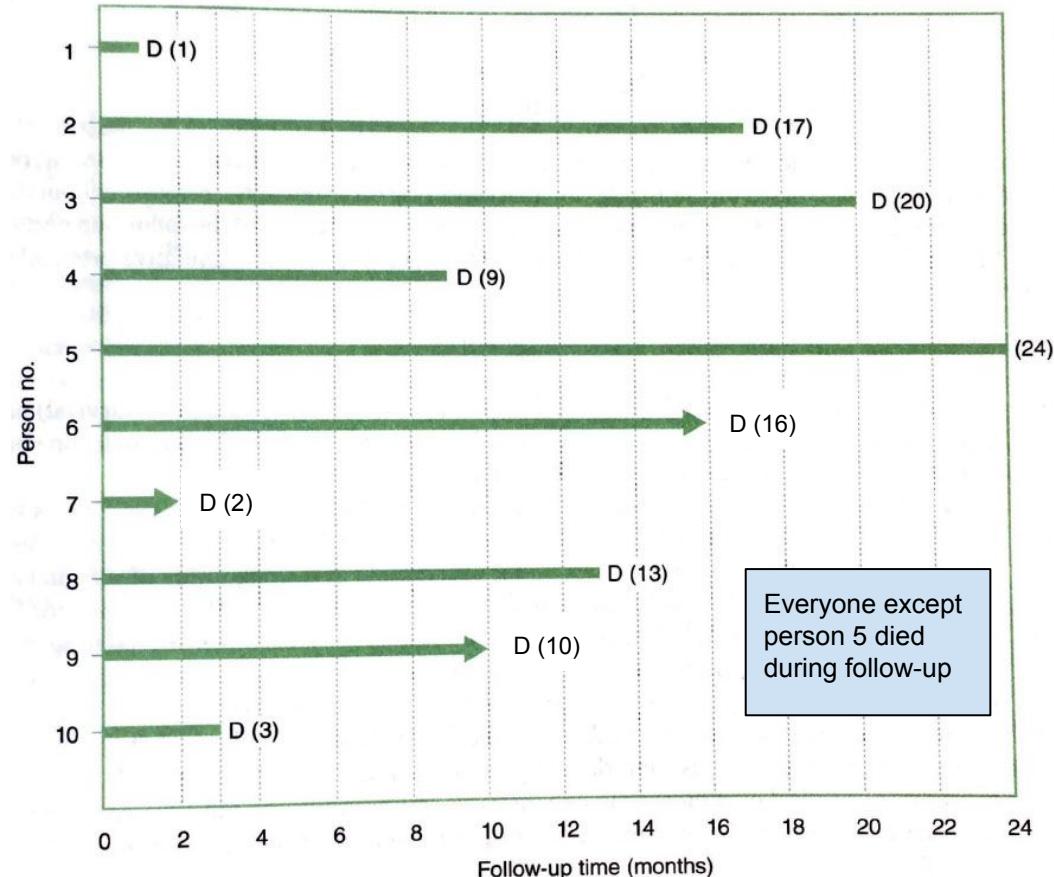
- No loss to follow-up or competing risks - we know the time of death for everyone in the population.
- Direct **cumulative incidence** from 0-24 months:

Number of deaths
Initial population at risk

$$= 9 / 10 = 0.9$$

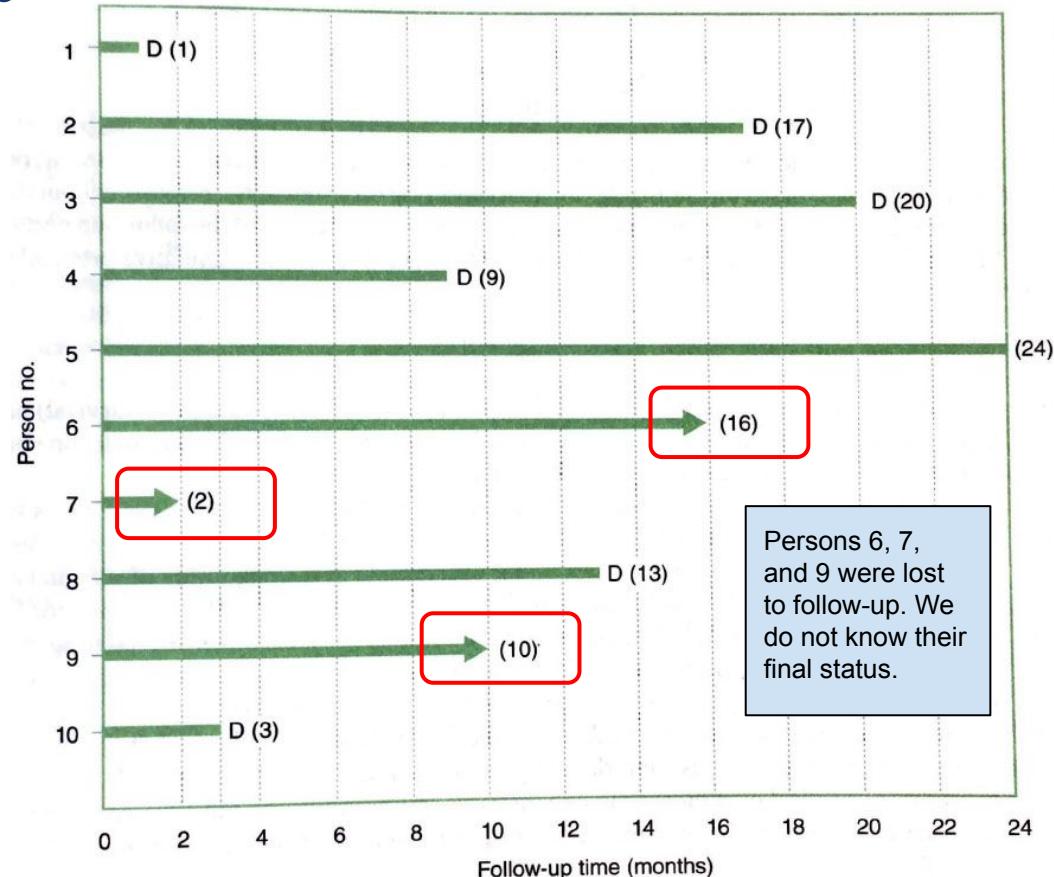
- Direct average time of occurrence among those who died during follow-up:

$$= (1+17+20+9+16+2+13+10+3)/9
= 10.1$$



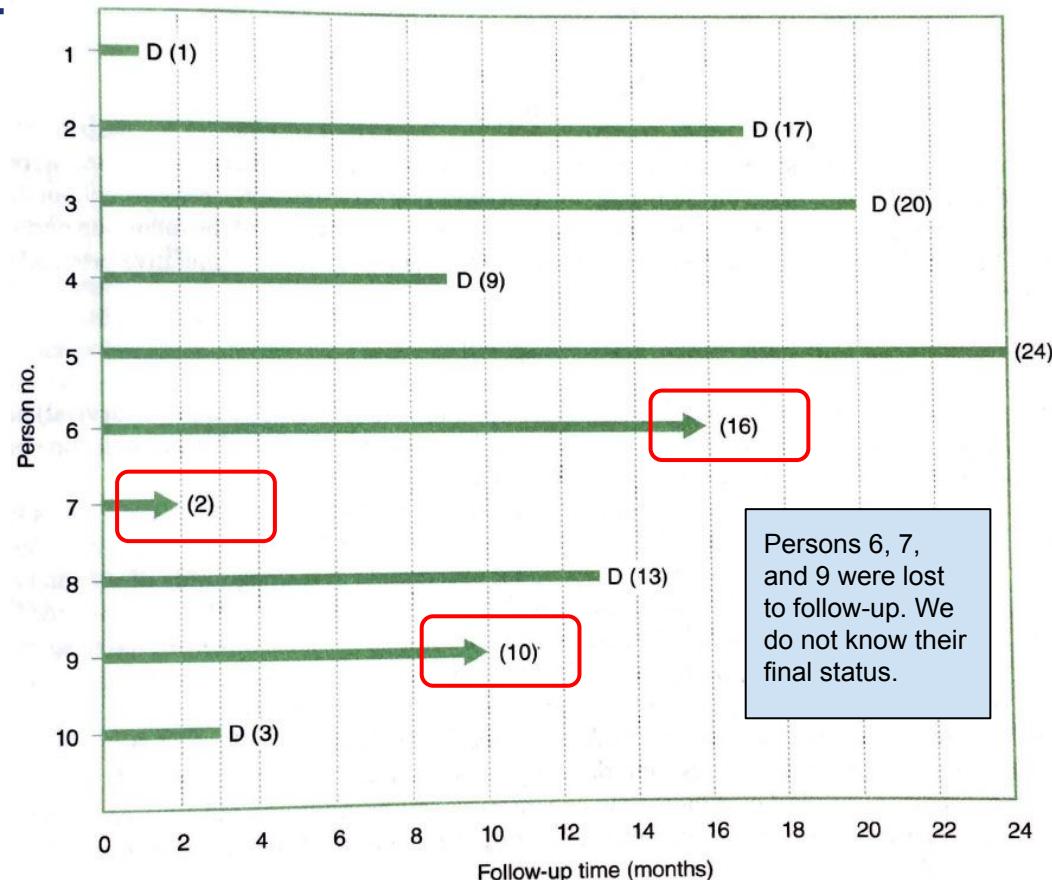
Example of loss to follow-up / competing risks

- We don't know the final death/survival status for 3 people in the population, so we can't directly calculate
- For example, person 6 could have died between months 16 and 24 or later, so we don't know if they should be in the numerator of the cumulative incidence.
 - The Kaplan-Meier, Actuarial, or density method.
- We also can't calculate average time to death because we don't know what values to use for persons 6, 7, and 9.



Advantages of estimating incidence density in cohort studies

- The denominator is person-time instead of individuals which allows for a more flexible classification into exposed and unexposed groups.
- A single person can contribute person-time to multiple exposure groups in a single cohort study.
- An individual whose exposure experience changes with time can contribute person-time to either the exposed or unexposed group.



Exposure classification in cohort studies

- Changes in exposure status at different points in follow-up can affect how we estimate measures of disease.
- The sequence of exposure and timing of exposure relative to age or disease onset could be important.
- Most epidemiologic studies assume that it is a numerical summary of exposure history determines the risk of disease. For example:
 - Current level of exposure
 - Average exposure
 - Cumulative exposure
 - Maximum exposure
- Often exposure is lagged, so that only exposure up to a certain time point before the time of disease measurement is classified as “exposed”.
- For chronic diseases, the time when exposure occurs may differ from the time when exposures have an effect.

Chronic exposures in cohort studies

- Accumulation of exposure experience may be a complex function of the intensity of the exposure and time
- **Example of a chronic exposure:** smoking and lung cancer
- Exposure could be defined by “pack-years”, the number of cigarette packs smoked per year
 - Composite of both duration and intensity of smoking
 - 20 pack-years =
 - Half a pack a day for 40 years
 - 1 pack a day for 20 years
 - 2 packs a day for 10 years
 - Using composite measures can conceal biological effects associated with intensity vs. duration
- Other factors to consider: age of smoking initiation, age of smoking cessation, timing of exposure relative to disease



Unexposed time for exposed subjects

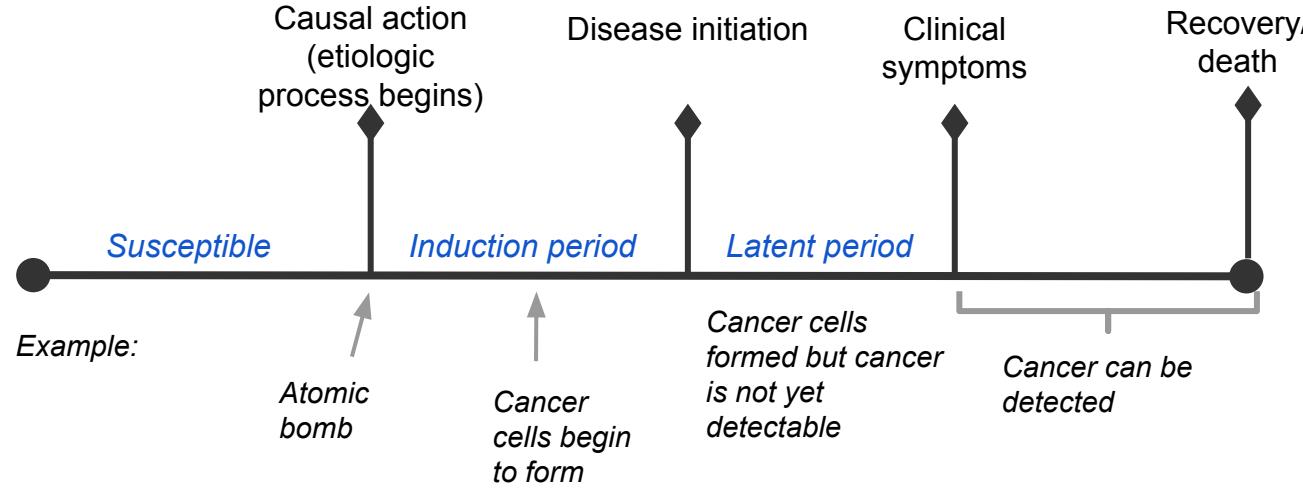
- In most cohort studies, individuals can be unexposed and exposed at different points during follow-up.
- How should exposure be classified in the analysis?
 - (1) Consider any time not related to the exposure as unexposed time
 - Ignores possible threshold effects
 - Ignores exposure accumulation or induction period
 - (2) Omit from the study the experience of exposed subjects that is not at risk of exposure effects
 - Requires a larger sample size
- Improper definition of the induction period may lead to misclassification.

Example of a brief exposure and chronic disease

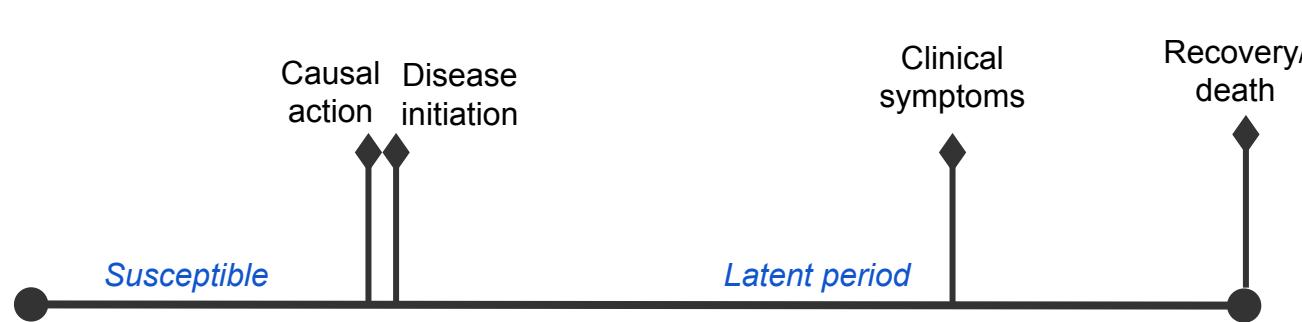
- Is radiation emitted from an atomic bomb associated with cancer risk?
- Exposure is nearly instantaneous, but the risk of disease does not increase immediately after exposure.
 - Some diseases occurring right after exposure can't have been caused by exposure, so are counted as having occurred during unexposed time.
- When we decide what time to include as exposed for an individual in the denominator of a rate, we are implicitly using a definition of the induction period.
- In this example, if we define follow-up time immediately after exposure as exposed, this implies a short induction period.
- The rate will be different with a short induction period than with a long induction period, so the choice of which time period to include in the denominator is important.



Example: atomic bomb & cancer



In this example, a certain induction period is assumed, and follow-up only begins at the point when disease initiation is hypothesized to have occurred.



When follow-up starts immediately after the causal action, a short induction period and a long latent period is implied. This increased the amount of time a person is considered exposed.

Induction period as unexposed time

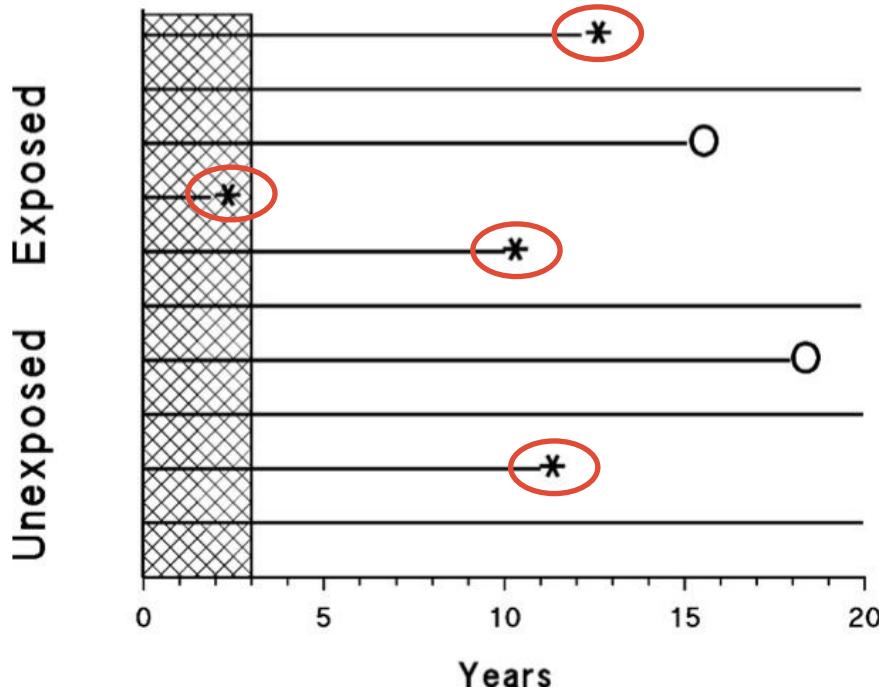
- Assume that the minimum time it takes for cancer to develop after radiation exposure is 3 years.
 - Any event occurring within the 3-year induction period counts towards the unexposed group.

3-year induction period:

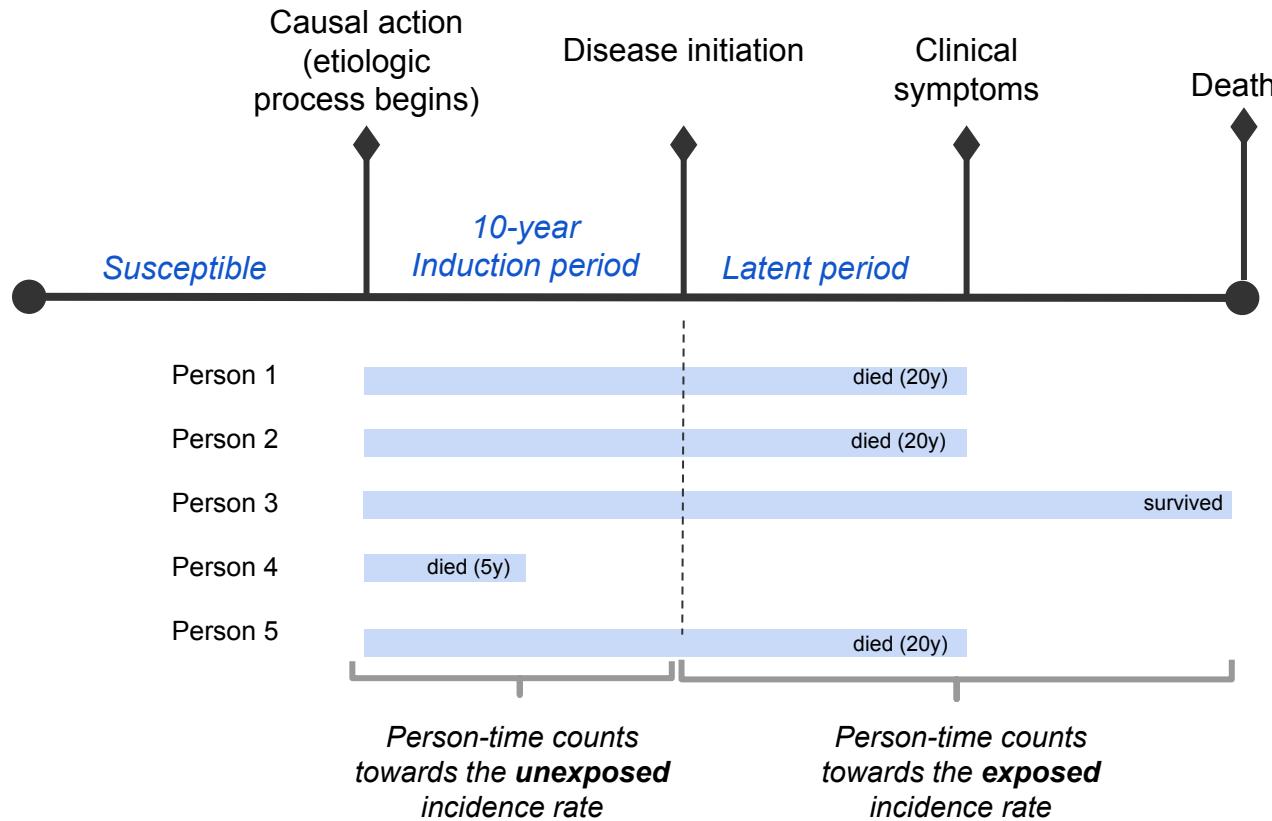
$$\frac{\text{Exposed} = \frac{2 \text{ events}}{45 \text{ years pt}}}{\text{Unexposed} = \frac{2 \text{ events}}{103 \text{ years pt}}} = 2.3 \text{ IRR}$$

No induction period:

$$\frac{\text{Exposed} = \frac{3 \text{ events}}{59 \text{ years pt}}}{\text{Unexposed} = \frac{1 \text{ events}}{89 \text{ years pt}}} = 4.6 \text{ IRR}$$



Induction period definition affects potential misclassification

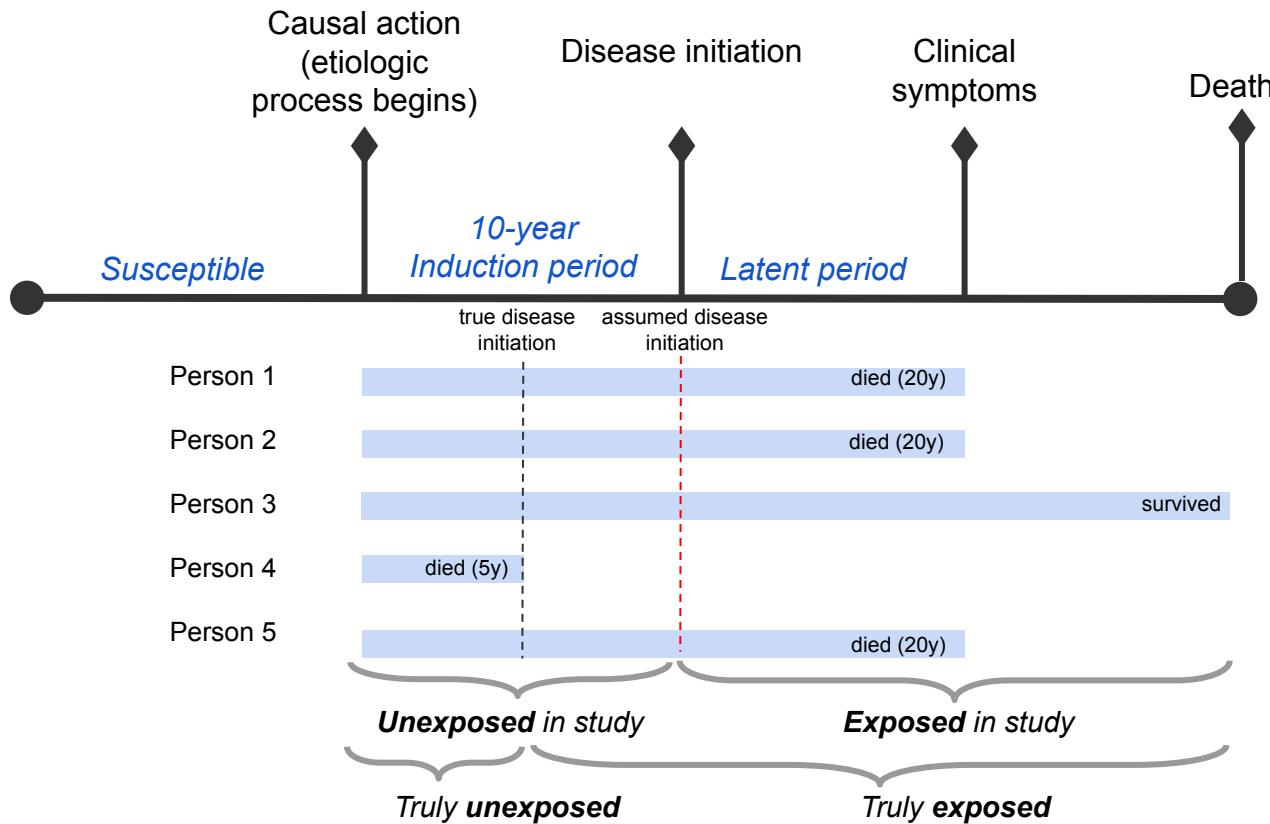


Rate among the **unexposed**
= $1/45$ person-years = 0.022

Rate among the **exposed**
= $3/50$ person-years = 0.06

IRR = $(3/50)/(1/45) = 2.7$

Induction period definition affects potential misclassification



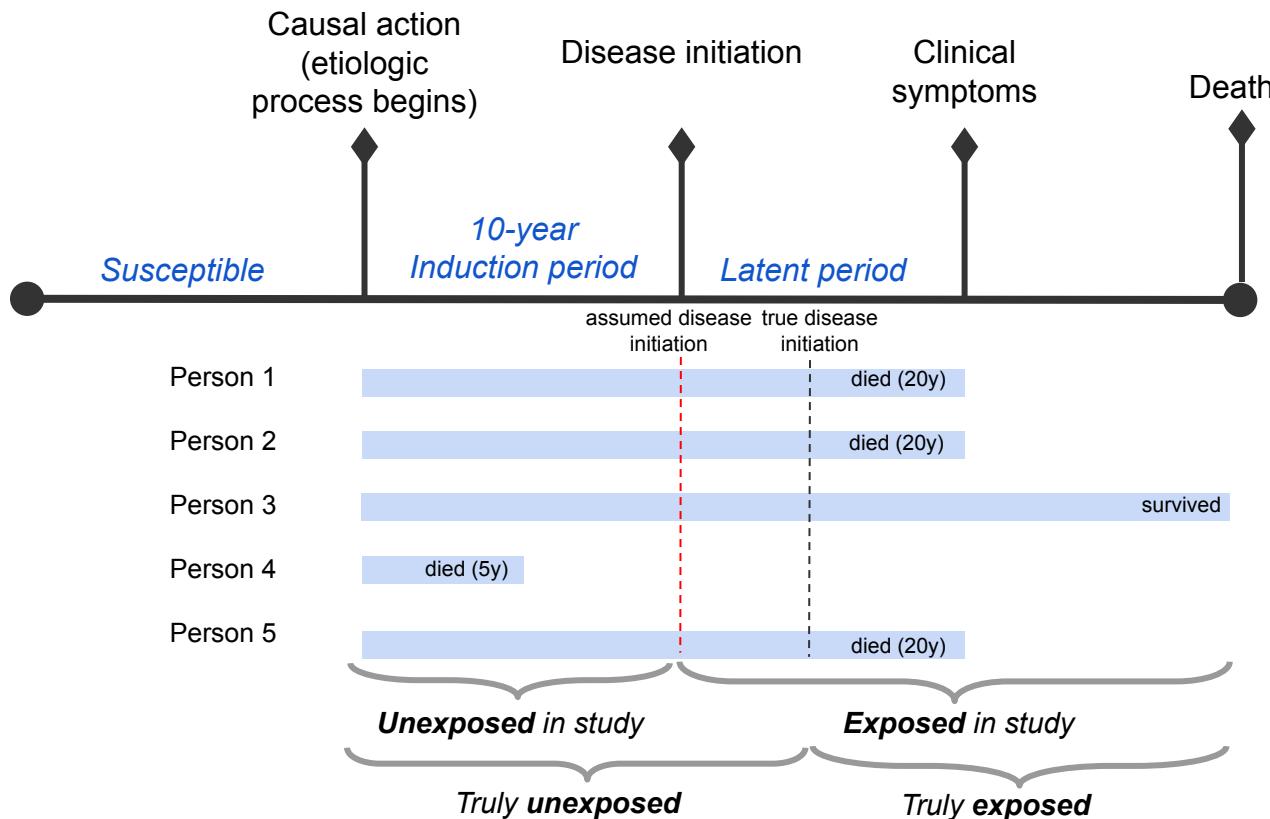
If the induction period was truly **shorter** than 10 years, then some person-time that were truly exposed would be misclassified as unexposed, which would bias measures of association away from the null.

Estimated IRR = 2.7 (from previous slide)

True unexposed rate
= $1/25 = 0.040$
True exposed rate
= $3/70 = 0.043$

True IRR = $(3/70)/(1/25) = 1.1$

Induction period definition affects potential misclassification



If the induction period was truly **longer** than 10 years, then some person-time that were truly unexposed would be misclassified as exposed, which would bias measures of association towards the null.

Estimated IRR = 2.7 (from previous slide)

True unexposed rate
= $1/65 = 0.015$
True exposed rate
= $3/30 = 0.010$

True IRR = $(3/30)/(1/65) = 6.5$

Summary of key points

- In most cohort studies, there is some loss to follow-up and some competing risks.
- As a result, to calculate cumulative incidence we must use the Actuarial, Kaplan Meier, or Density methods. We can calculate incidence density directly.
- Most cohort studies define a numerical summary of exposure history that is expected to determine the risk of disease.
 - The precise definition of the summary of exposure will affect measures of association as well as interpretation of the study.
- When exposure is time-varying, we can classify it by:
 - (1) Considering any time not related to the exposure as unexposed time
 - (2) Omitting from the study the experience of exposed subjects that is not at risk of exposure effects
- An incorrect definition of the induction period can lead to misclassification (bias).

Evaluating and reporting cohort studies

PHW250B

Assessment of cohort studies

How much selection bias was present?

- Were only people at risk of the outcome included?
- Was the exposure clear, specific, and measurable?
- Were the exposed and unexposed groups similar in all important respects except for the exposure?

What steps were taken to minimise information bias?

- Was the outcome clear, specific, and measurable?
- Was the outcome identified in the same way for both groups?
- Was determination of outcome made by an observer blinded as to treatment?

How complete was the follow-up of both groups?

- What efforts were made to limit loss to follow-up?
- Was loss to follow-up similar in both groups?

Were potential confounding factors sought and controlled for in the analysis?

- Did the investigators anticipate and gather information on potential confounding factors?
- What method(s) were used to assess and control for confounding?

STROBE Checklist for reporting cohort studies

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PLOS MEDICINE

Strengthening the Reporting of Observational Studies in Epidemiology (STROBE): Explanation and Elaboration

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Funding: The initial STROBE workshop was funded by the European Union (EU) and the European Society of Preventive Medicine (ESPM). Additional funding was received from the Medical Research Council (MRC) and the National Institutes of Health (NIH) through the Development Methodology Program. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Competing interests: The authors have declared that no competing interest exist.

Citation: Vandenhout JP, von Elm E, Altman DG, Gotzsche PC, Mulrow CD, et al. (2007) Strengthening the Reporting of Observational Studies in Epidemiology (STROBE): Explanation and Elaboration. PLoS Med 4(10):e297. doi:10.1371/journal.pmed.004297

Received: July 20, 2007
Accepted: August 25, 2007
Published: October 2, 2007

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Abbreviations: CI, confidence interval; IEL, relative excess risk difference; STROBE, Strengthening the Reporting of Observational Studies in Epidemiology.

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OPEN PLoS Medicine | www.plosmedicine.org 1628 October 2007 | Volume 4 | Issue 10 | e297

ABSTRACT

Much medical research is observational. The reporting of observational studies is often of insufficient quality, potentially hampering interpretation of the strengths and weaknesses of a study and the generalizability of its results. Taking into account empirical evidence and theoretical considerations, a group of methodologists, researchers, and editors developed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) recommendations to improve the quality of reporting of observational studies. The STROBE Statement consists of a checklist of items, which are to be used in abstract, introduction, methods, results and discussion sections of articles. Eighteen items are common to cohort studies, case-control studies and cross-sectional studies and four are specific to each of the three study designs. The STROBE Statement provides guidance to authors about how to improve the reporting of observational studies and facilitates critical appraisal and interpretation of studies by reviewers, journal editors and readers. The explanation and elaboration document is intended to enhance the user's understanding and use of the STROBE Statement. The meaning and rationale for each checklist item are presented. For each item, one or several published examples and, where possible, references to relevant empirical studies and methodological literature are provided. Examples of useful flow diagrams are also included. The STROBE Statement, this document, and the associated Web site (<http://www.strobe-statement.org/>) should be helpful resources to improve reporting of observational research.

- The checklist arose out of concerns that observational studies were poorly and inconsistently reported.
- Poor reporting makes it difficult to assess strengths and weaknesses of a study.
- A group of methodologists, researchers, and editors developed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) recommendations to improve the quality of reporting of observational studies.
- 22 item checklist
- 18 items are common to cohort studies, case-control studies and cross-sectional studies.
- 4 items are specific to each of the three study designs.

STROBE Statement—Checklist of items that should be included in reports of *cohort studies*

Item No	Recommendation
Title and abstract	<p>1 <u>(a) Indicate the study's design with a commonly used term in the title or the abstract</u></p> <p> (b) Provide in the abstract an informative and balanced summary of what was done and what was found</p>
Introduction	
Background/rationale	2 Explain the scientific background and rationale for the investigation being reported
Objectives	3 State specific objectives, including any prespecified hypotheses
Methods	
Study design	4 Present key elements of study design early in the paper
Setting	5 Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants	<p>6 <u>(a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up</u></p> <p> (b) For matched studies, give matching criteria and number of exposed and unexposed</p>
Variables	7 Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable

Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
Bias	9	Describe any efforts to address potential sources of bias
Study size	10	Explain how the study size was arrived at
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	12	<p>(a) Describe all statistical methods, including those used to control for confounding</p> <p>(b) Describe any methods used to examine subgroups and interactions</p> <p>(c) Explain how missing data were addressed</p> <p>(d) If applicable, explain how loss to follow-up was addressed</p> <p>(e) Describe any sensitivity analyses</p>

Results

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed (b) Give reasons for non-participation at each stage (c) Consider use of a flow diagram
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (b) Indicate number of participants with missing data for each variable of interest (c) Summarise follow-up time (eg, average and total amount)
Outcome data	15*	Report numbers of outcome events or summary measures over time
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (b) Report category boundaries when continuous variables were categorized (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period

Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion		
Key results	18	Summarise key results with reference to study objectives
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability	21	Discuss the generalisability (external validity) of the study results
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

Summary of key points

- You can use the list of question from the Grimes et al. 2002 article when evaluating the quality of a cohort study.
- We recommend that you use the STROBE reporting checklist when publishing results of a cohort study.
- The article by Vandenbrouke et al. 2007 article provides detailed examples of how to use the STROBE checklist with an example paper.