



Introduction to occupational cancer epidemiology

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IARC Monograph evaluations

- Substances chosen on basis of two criteria:
 - human exposure
 - suspicion of cancer risk
- Working groups
 - selection of participants
 - functioning
- Evaluations
 - dimensions (human ca, animal ca, other)
 - overall evaluation
 - limitations (target organ, quantification)



IARC Evaluations Dimensions and Classes

Types of evidence

Human

Animal

Other

- mutagenicity
- genotoxicity
- metabolism
- etc.

Classes

- | | |
|----|---------------------------------|
| 1 | Carcinogenic to humans |
| 2A | Probably carcinogenic to humans |
| 2B | Possibly carcinogenic to humans |
| 3 | Not classifiable |
| 4 | Not carcinogenic to humans |



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Classes and criteria used by IARC Working Groups in evaluating human carcinogenicity based on the synthesis of epidemiological, animal and other evidence

Combinations which fit in this class				
Class		Human evidence	Animal evidence	Other evidence
1	Definite	S	Any	Any
		L	S	+
2A	Probable	L	S	+/-
		I or NA	S	+
2B	Possible	L	< S	Any
		I or NA	S	+/-
		I or NA	L	+
3	Not classifiable	I or NA	L	+/-
		Not elsewhere classified		
		I or NA	-	-
4	Not	-	-	Any

S: sufficient
 L: limited
 I: inadequate
 +: strongly positive
 +/-: less than strongly positive
 -: strongly negative
 NA: not available



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Number of IARC class 1 carcinogens by main source of exposure

<i>Exposure</i>	<i>Ag</i>	<i>Mix</i>	<i>EC</i>	<i>Tot</i>
Occupation	19	6	13	38
Environment	2	0	1	3
Biological agents	10	0	0	10
Medications	22	1	0	23
Radiation	12	0	0	12
Lifestyle factors	0	6	2	8

Ag, agents and groups of agents; Mix, mixtures; EC, exposure circumstances



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Occupational carcinogens (1)

Agent	Target organs	Susp. targets
<i>Physical agents</i>		
Ionizing radiation	Br, Leuk, Li, Lu, Th, Bone	Others
Solar radiation	NMS, Mel	
<i>Respirable dusts & fibers</i>		
Asbestos	Lu. Meso	Lar, GI
Talc cont. asbest. fibres	Lu, Meso	
Silica, crystalline	Lu	
Wood dust	Nose	



Occupational carcinogens (2)

Agent	Target organs	Suspected targets
<i>Metals & metal cmpds</i>		
Arsenic & arsenic cmpds	NMS, Lu	Li
Beryllium & beryllium comp.	Lu	
Cadmium & cadmium cmpds	Lu	
Chromium cmpds, hexavalent	Lu	Nose
Nickel & nickel cmpds	Lu, Nose	



Occupational carcinogens (3)

Agent	Target organs	Suspected targets
<i>Fuels & by-products of wood & fossil fuels</i>		
Benzene	Leuk	
Coal tars & pitches	NMS, Lu	Bl
Mineral oils, untreated & mildly treated	NMS	Lu, Bl, Nose
Shale oils or shale-derived lubricants	NMS	
Soots	NMS, Lu	Eso



Occupational carcinogens (4)

Agent	Target organs	Suspected targets
<i>Monomers</i>		
Vinyl chloride	AS	Li
1,3 Butadiene	Leuk	NHL
<i>Intermediates in plastics & rubber manufacturing</i>		
BCME & CMME	Lu	
<i>Aromatic amine dyes</i>		
4-Aminobiphenyl	Bl	
Benzidine	Bl	
2-Naphthylamine	Bl	



Occupational carcinogens (5)

Agent	Target organs	Suspected targets
<i>Pesticides & contaminants</i>		
Ethylene oxide	Leuk	
TCDD	All	
<i>Others</i>		
Formaldehyde	NP	Leuk
Mustard gas	Lar	Lu
Strong inorganic acid mists	Lar	Lu
Gallium arsenide	-	



Occupations and industries classified as entailing exposures with sufficient evidence of carcinogenicity

Aluminium production

Haematite mining
(undergr.)

Auramine (mft)

Iron and steel founding

Boot and shoe (mft, repair)

Isopropanol (mft)

Coal gasification

Magenta (mft)

Coke production

Painter

Furniture and cabinet
making

Rubber industry



The evaluation might not apply to all exposure circumstances within the
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industry and it might reflect the risks from past exposure conditions

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Selected probable occupational carcinogens (1)

Agent	Suspected targets
<i>Polyaromatic hydrocarbons</i>	
Benzo[a]pyrene	Lu, BI, NMS
Dibenz[a,h]anthracene	Lu, BI, NMS
<i>Fuels & by-products of wood & fossil fuels</i>	
Creosotes	NMS
Diesel engine exhaust	Lu, BI
<i>Intermediates in plastics & rubber manufacturing</i>	
MOCA	BI
Styrene-7,8-oxide	-



Selected probable occupational carcinogens (2)

Agent	Suspected targets
<i>Chlorinated hydrocarbons</i>	
Alpha-chlorinated toluenes	Lu
Polychlorinated biphenyls	Li
Tetrachloroethylene	Cer, Eso, NHL
Trichloroethylene	Li, Kid, NHL
<i>Monomers</i>	
Acrylamide	Pan
Epichlorohydrin	Lu, Br



Selected probable occupational carcinogens (3)

Substance or mixture	Suspected targets
<i>Aromatic amine dyes</i>	
Benzidine-based dyes	Bl
4-Chloro-ortho-toluidine	Bl
<i>Pesticides</i>	
Captafol	-
Ethylene dibromide	-
Non-arsenical insecticides	Br, Leuk, Lu, NHL
<i>Metals</i>	
Inorganic lead compounds	Lu



Occupations and industries classified as entailing exposures with limited evidence of carcinogenicity

Art glass manuft. Hairdresser or barber
Cobalt metal manuft Petroleum refining



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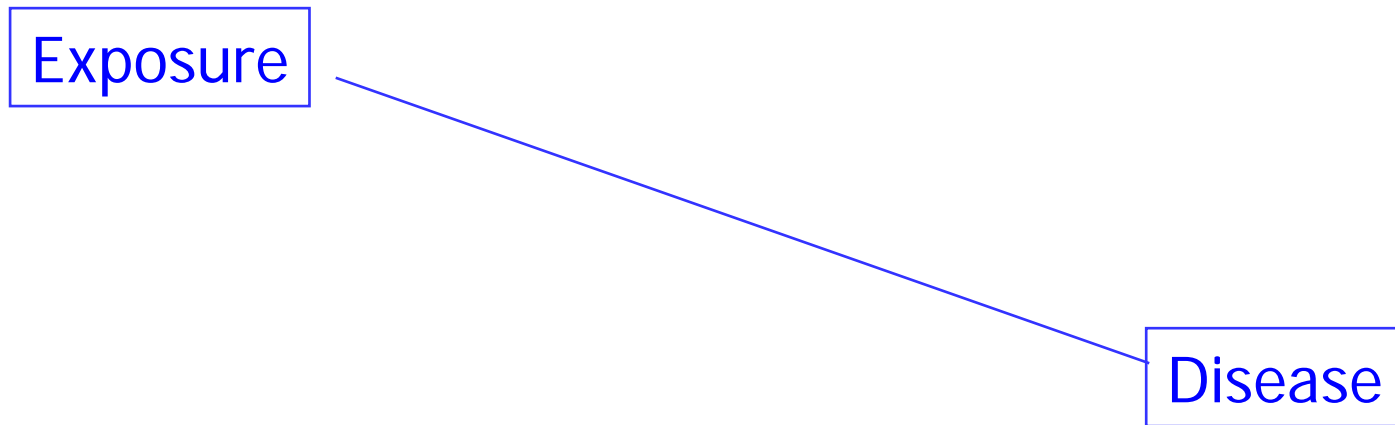
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Selected IARC class 2B occupational carcinogens

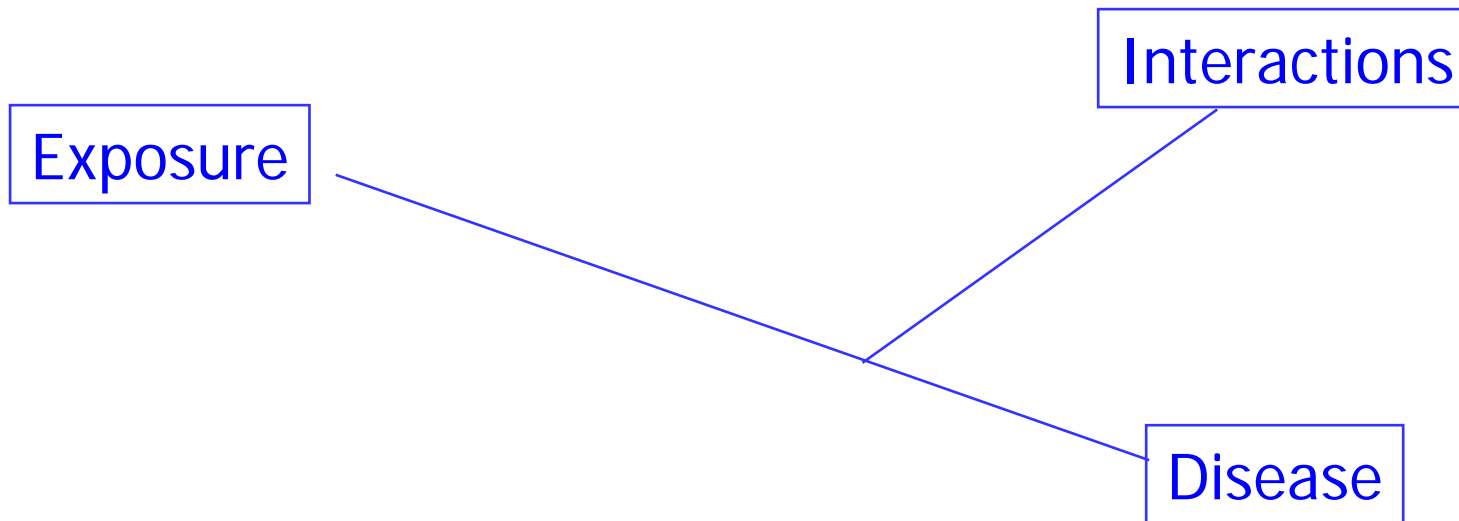
- Refractory ceramic fibres
- Nickel alloys
- Carbon black
- Gasoline engine exhaust
- Gasoline
- Bitumens
- Styrene
- Acrylonitrile
- Chloroform
- Dichloromethane
- Some pesticides
- Welding fumes



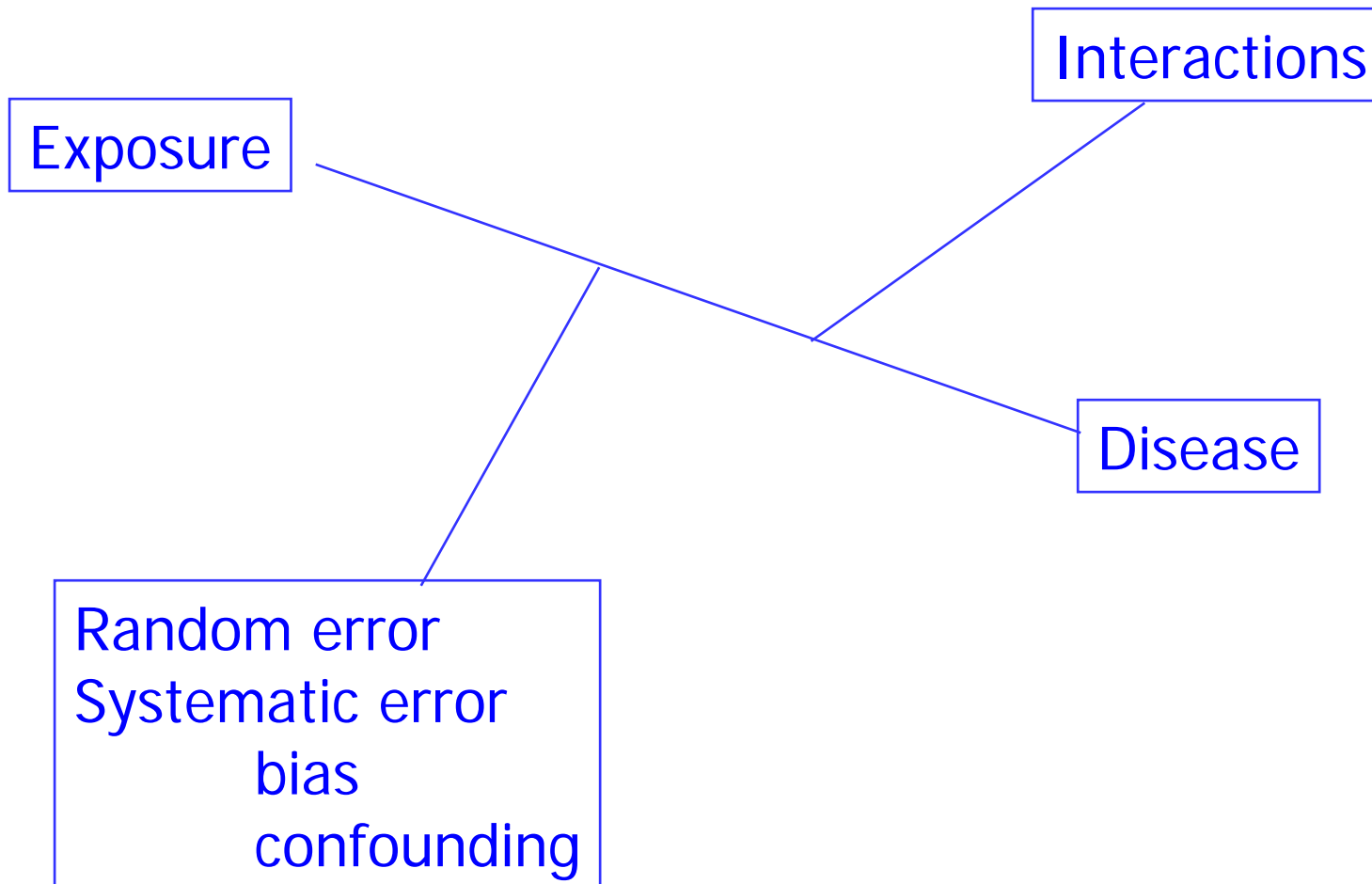
Identification of exposure-disease relations with epidemiology



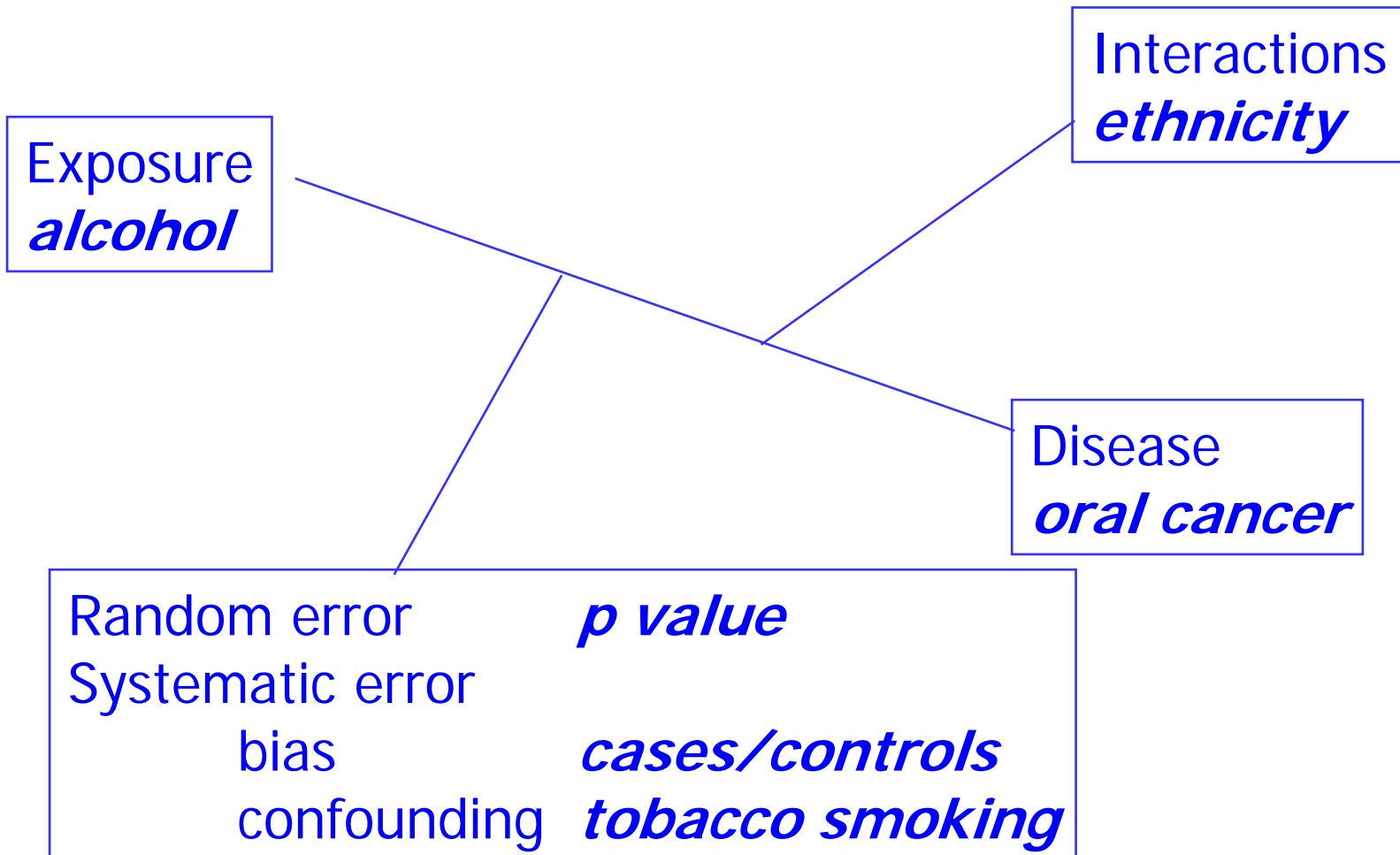
Interacting factors



Methodological problems



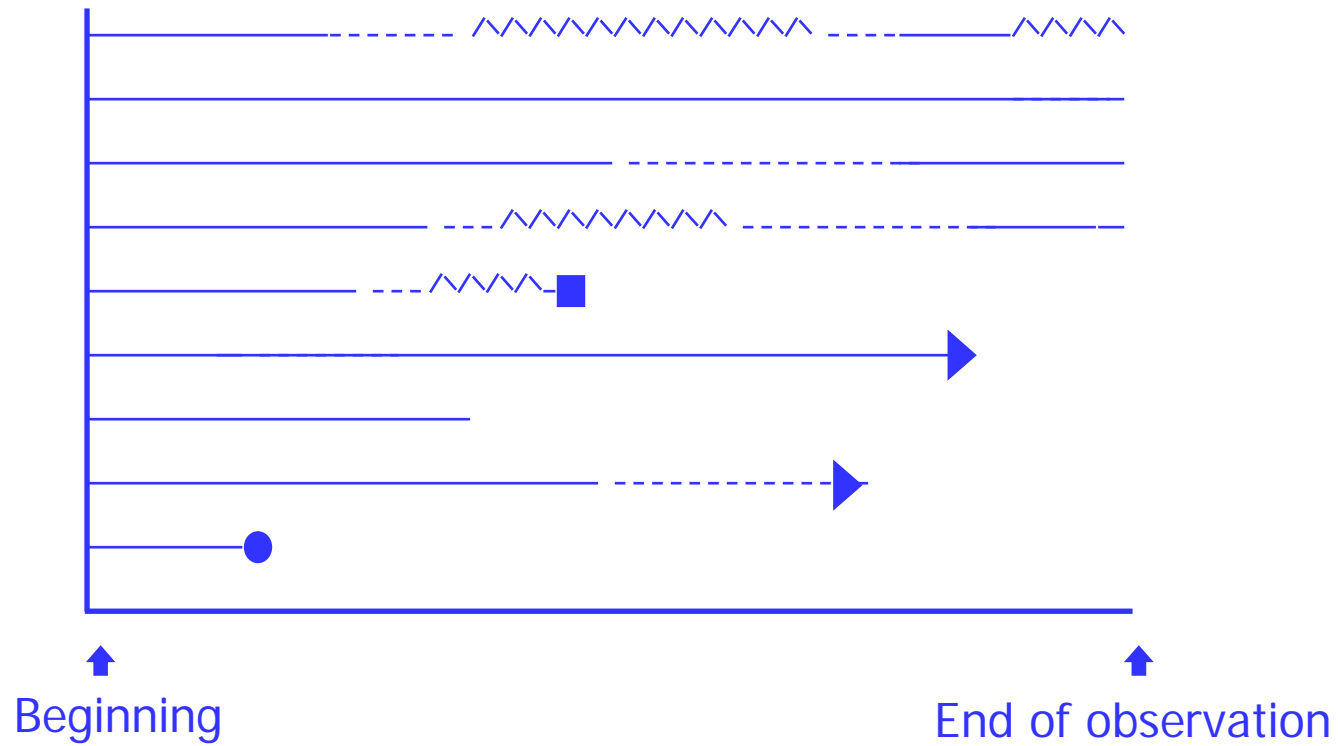
One example



Epidemiological study design

- All epidemiological studies are (or should be) based on a particular population (the source population) followed over a particular period of time (the risk period)
- The population-time experience is called **study base**
- The different study designs differ only in
 - definition of outcome
 - definition of the source population
 - collection of information





- death
- ▶ other death
- lost to follow up
- "non-diseased"
- - - symptoms
- ^^ severe disease



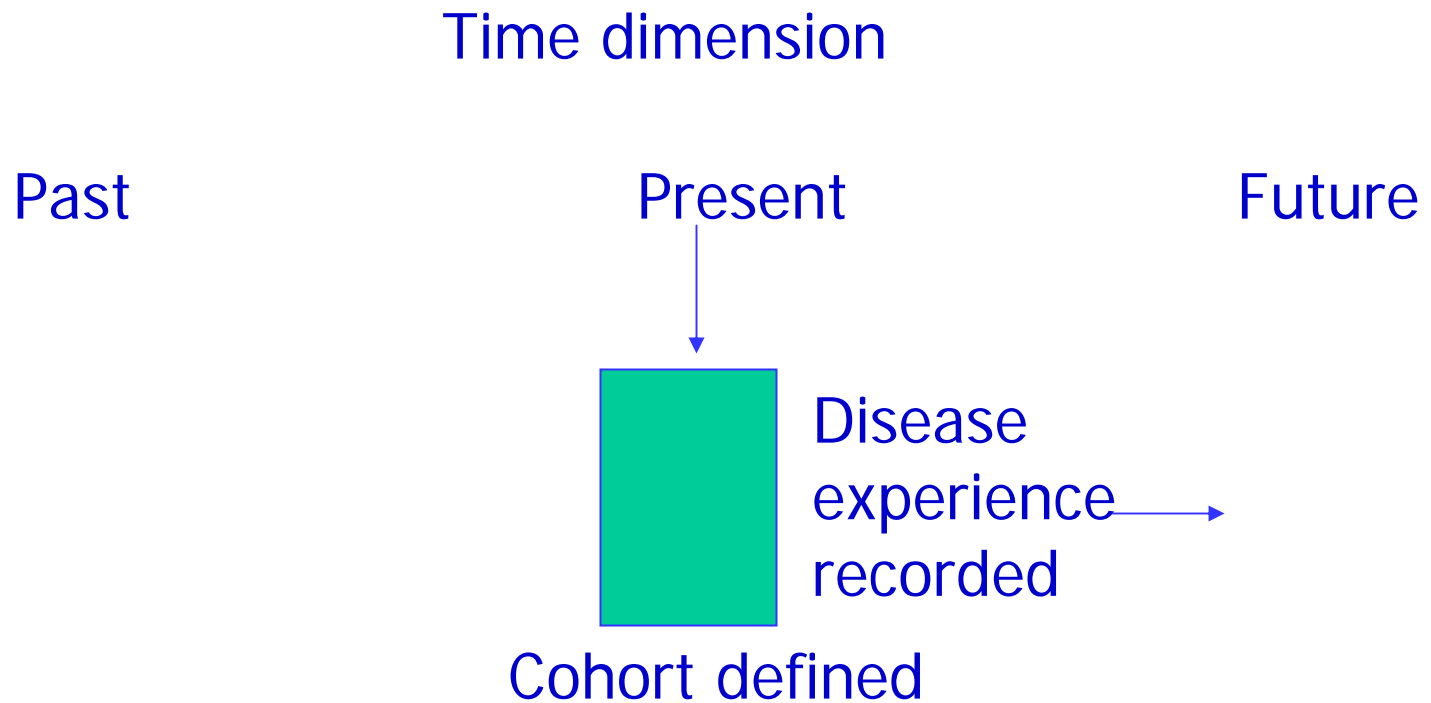
Cohort study

Information of risk factors is collected from exposed and unexposed individuals

The occurrence of disease is measured and compared in the two groups (follow-up)



Prospective cohort study



Historical cohort study

Time dimension

Past

Present

Future



Disease
experience
recorded



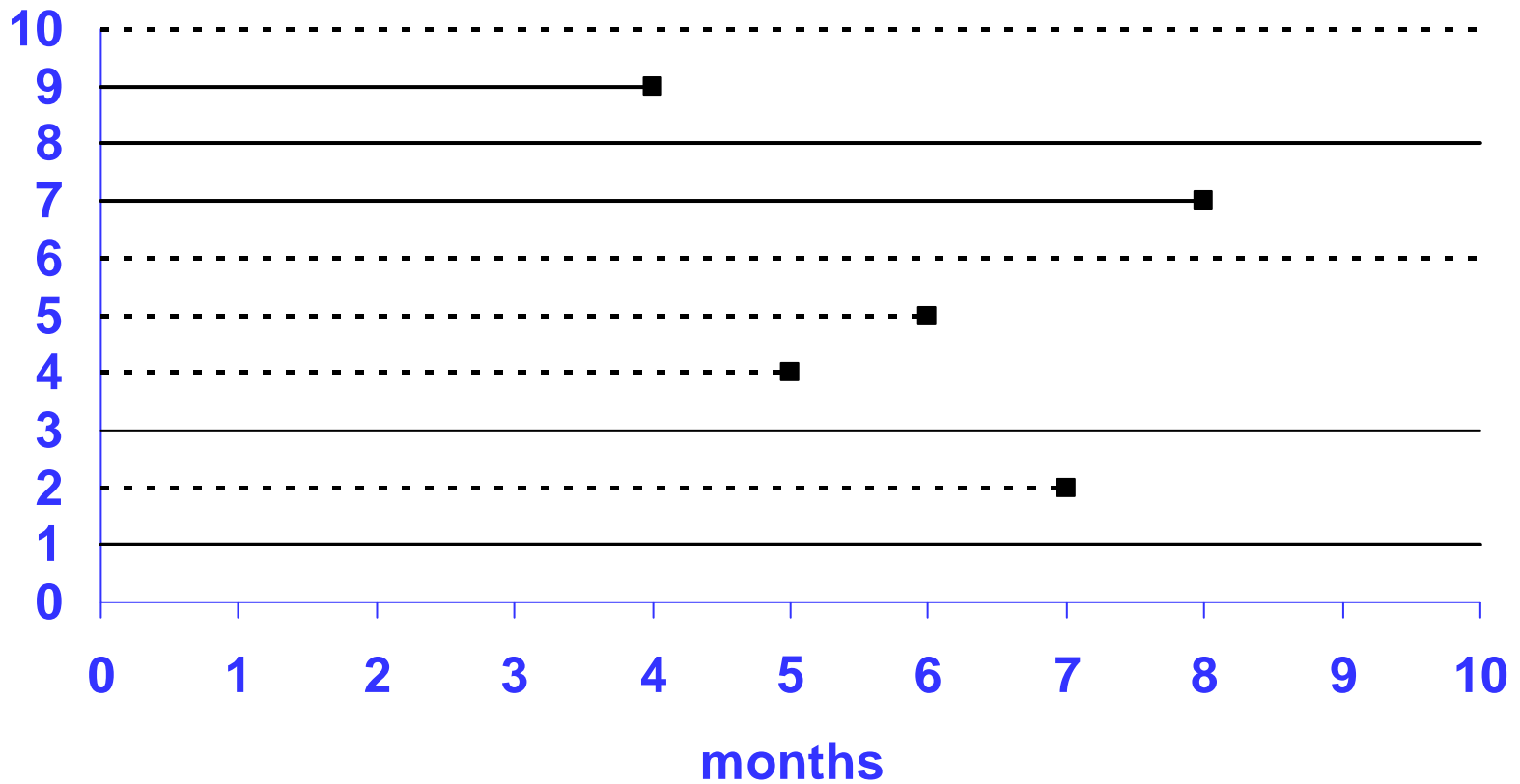
Cohort defined



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Cohort study of 10 individuals



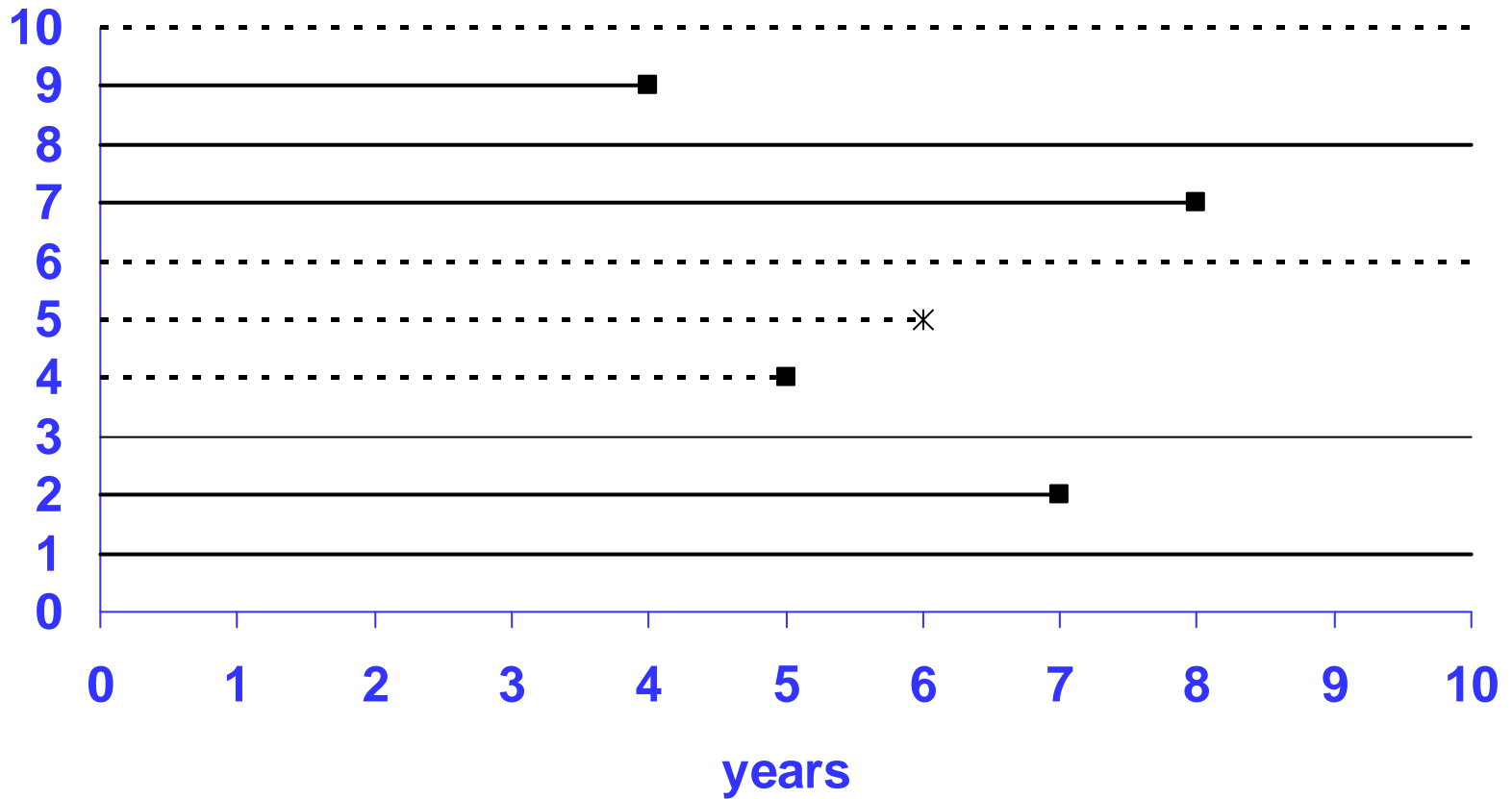
■ = death; exposed; — unexposed



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One case



■ = death; ● = death from cause of interest (case)



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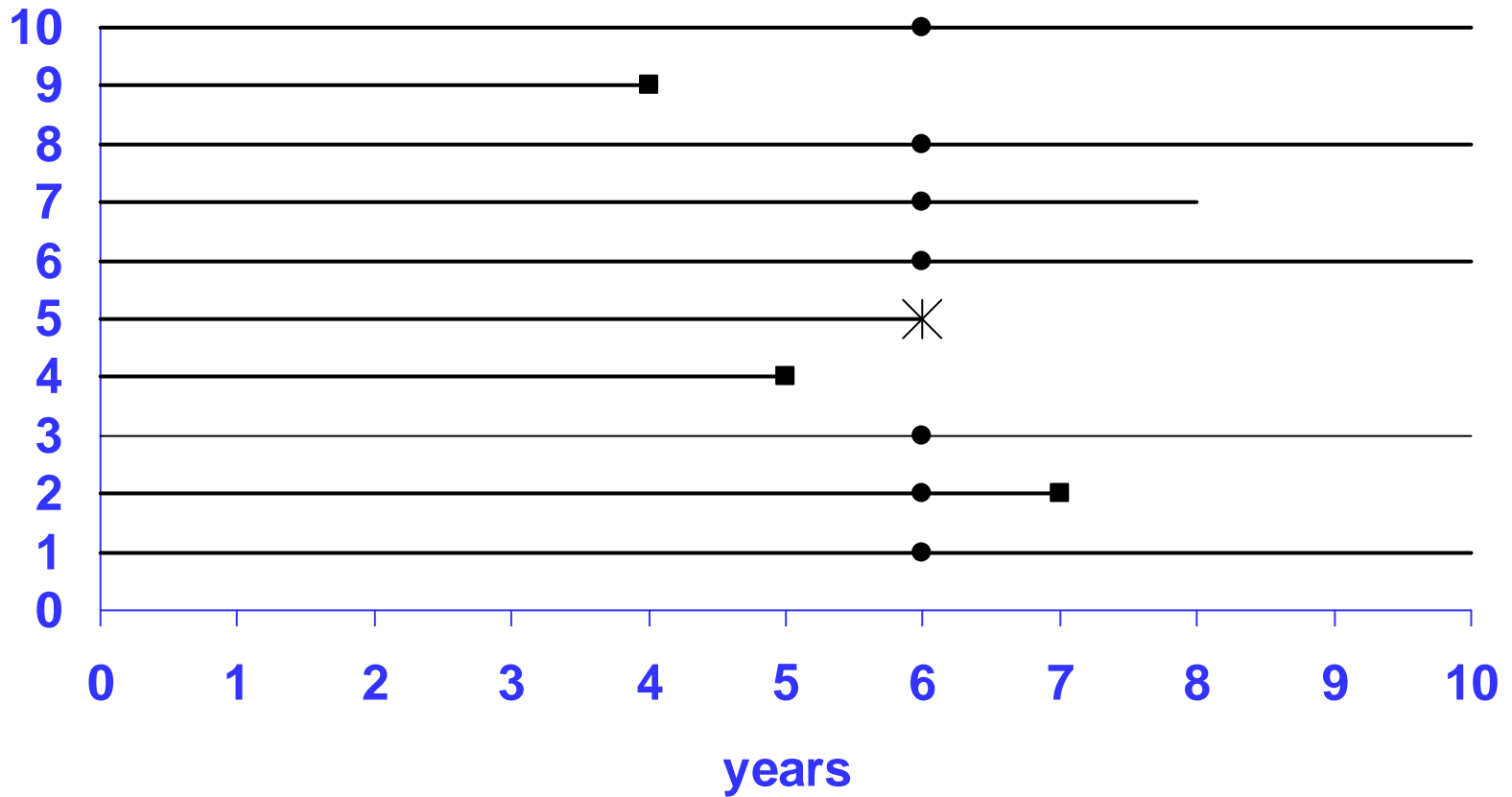
Case-control study

Comparison of distribution of exposure to risk factors between:

- Individuals with disease (CASES)
- Subset of individuals without disease from the same population (CONTROLS)
- Controls are selected among individuals free from disease at time of occurrence of cases



Selection of controls



■ = death; ✱ = case; ● = potential control



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Essence of case-control studies

A cohort study in which the experience of the cohort is sampled rather than completely measured

Gain in efficiency



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General-population case-control study

Cases (and controls) are selected from a population that is not a well established cohort

However, it is always possible to conceptualize the underlying 'cohort' (study base)



Selection of cases

All cases from a defined population
(underlying cohort)

- Geographical area
 - Population-based
- Patients from a hospital
 - Hospital-based
- Within a well-defined cohort
 - Nested case-control study (see below)



In practice ...

Cases are often a convenient series of patients

Also in this case, it is important to conceptualize the underlying population (e.g., patients afferent to the hospital)



Selection of controls

- They are a representative sample of the underlying population
- They would enter the series of cases if they had the disease
- Their choice depends on
 - selection of cases
 - practical issues



Selection of controls

- Population-based controls
 - random sample of population
- Hospital-based controls
 - cancer or non-cancer patients
 - visitors to patients
- Other controls
 - neighborhood controls
 - family members of cases



Matching

- Controls are paired to cases with respect to some variables
- Advantages
 - gain in statistical power
- Disadvantages
 - need to control in the analysis
 - matching factors cannot be studied
- **No need for matching**



Nested case-control study

- Basic information (including occurrence of outcome) is available for all cohort members
- Additional information is collected only for cases and controls
- Particularly suitable for molecular epidemiology
 - biological analyses done only on the cases and the subset of controls



Comparison of cohort and case-control studies

Cohort studies

1. Provide information about a range of effects related to a single exposure
2. Typically follow-up studies focus on one exposure
3. Evaluation of rare outcomes is problematic in follow-up studies

Case-control studies

1. Provide information about one effect that afflicts the cases selected (studies including multiple series of cases are an exception)
2. Provide information about a wide range of potentially relevant exposures
3. Evaluation of rare outcomes are well suited to case-control studies

Cohort studies

4. Efficient for the evaluation of rare exposures
5. Concern is in the follow-up
6. Exposure status is determined before the presence of disease. No possibility for the disease outcome to influence exposure classification
7. Large, expensive, take time

Case-control studies

4. Inefficient for the evaluation of exposures that are rare in the source population
5. Concern is in the avoidance of selection and information bias
6. Exposure information comes from the subject (or proxies) after disease onset. Knowledge of disease could affect exposure data. Greater possibility of bias
7. Smaller, less expensive, quick

Other study designs

- Cross-sectional study
 - a case-control study in which information on exposure and outcome refers to the same time (present)
 - prevalent cases
 - prone to reverse causality



Other study designs

- Case-only study
 - a case-control study in which two groups of cases are compared
 - reduced opportunity for selection bias
 - useful to study interactions, not main effect
- Case-cohort study
 - cases are compared to a subset of cohort members selected at the beginning of follow-up
 - efficient use of biological samples

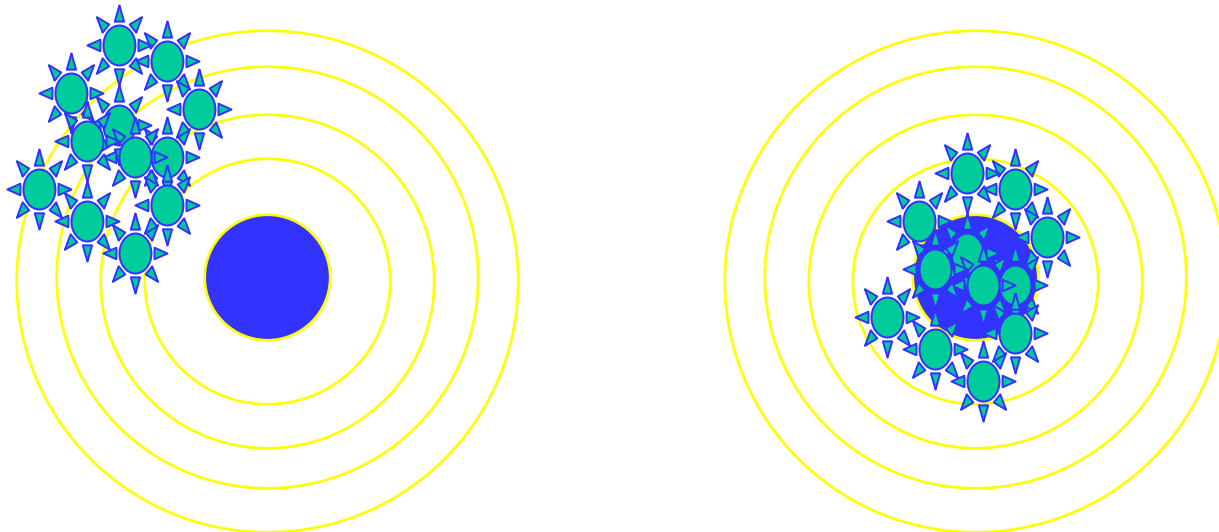


Ecological studies

- Unit of observation is a group
 - information on outcome or exposure available at group level
- Subject to ecological fallacy
 - due to intra-group heterogeneity in exposure and covariates



BIAS VS. CHANCE



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Random error and systematic error

- Random error can be controlled by increasing the number of observations
- Systematic error (bias)
 - selection bias
 - information bias
 - reporting bias
 - confounding

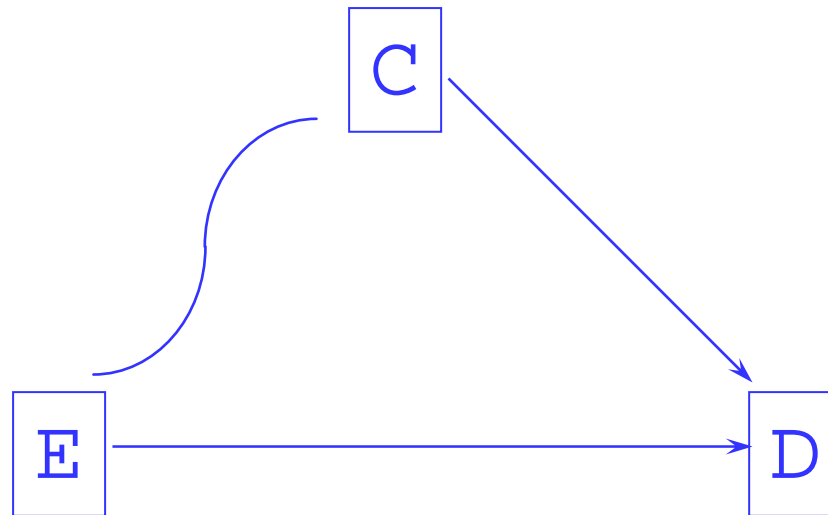


CONFOUNDING

The distortion of the exposure/outcome relation as a consequence of the association of another factor with both disease and exposure



CONFOUNDING



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Prevention of occupational cancer

Evidence from epidemiology

- Non-introduction of a carcinogenic agent
- Lack of increase in risk among exposed workers
- Disappearance of an occupation at risk
- Decrease in exposure levels at workplace
- Employment of low risk individuals
- Prevention of interacting factors



Non-introduction of a carcinogenic agent

- 4-aminobiphenyl
 - evidence of bladder cancer risk among US workers
 - Melick et al., 1971
 - never used in UK



Lack of evidence of increase in risk among exposed workers

- No increase in cancer risk among nuclear industry workers (IARC, 1994)
- Lack of scrotal cancer among chimney sweeps from Sweden (Gustavsson et al., 1987)
- ... power of the relevant studies!



IARC study of nuclear workers

- >95,000 workers from 7 facilities in 3 countries
- >95% with cumulative exposure < 100 mSv
- 3,976 cancer deaths, 146 from leukaemia
- RR for 100 mSv:
 - all cancers 1.00
 - non-leukaemia 0.99
 - leukaemia 1.16

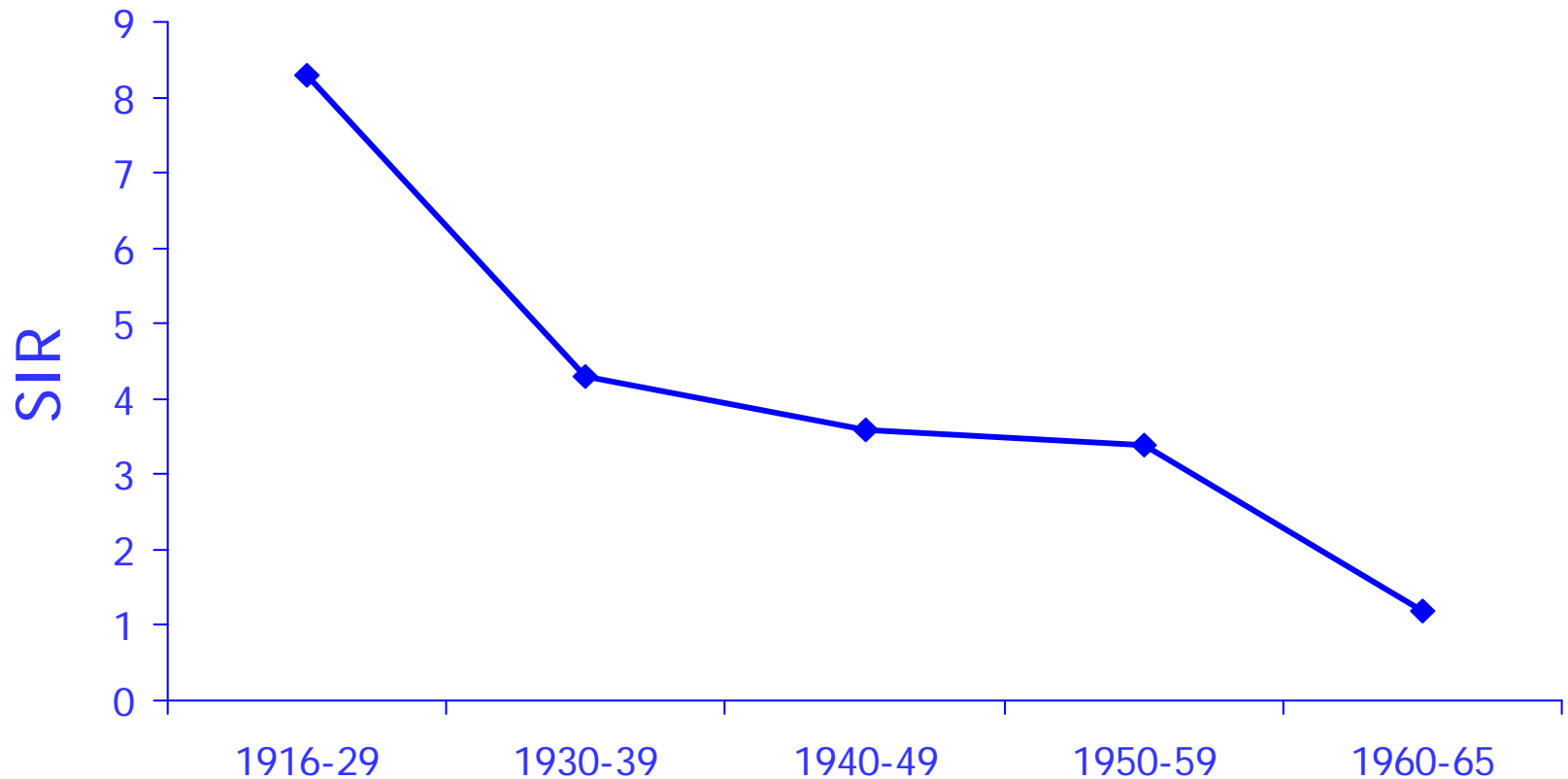


Disappearance of an occupation at risk

- Manufacture of mustard gas during war time
 - Wada et al., 1968; Miller et al., 1988; Easton et al., 1988
- Gas production from coal carbonization
 - Doll et al., 1972



Decrease in exposure levels at the workplace Lung cancer SIR among nickel refinery workers by year of hire



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Magnus et al., 1982

Outline

- Review of occupational carcinogens
- Study design in occupational epidemiology
- Evidence on prevention of occupational cancer

