Causation

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Intro epi

Measures of health

Measures of association

Study design

Error in epi research

Causation

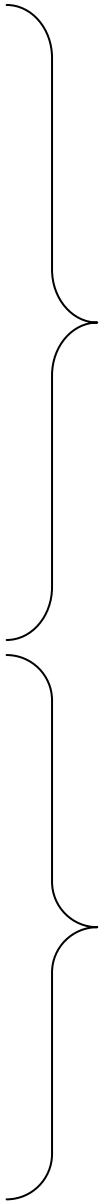
Sampling

Diagnostic tests

Outbreak investigation

Appraising the literature

Evidence based medicine



The basics …

Applied epi …

Roadmap

- The concept of cause
- Types of cause
- Causal web models
- Establishing the cause of disease
  - Koch's postulates
  - Evan's concept of causation
  - Hill's criteria
- Views on causal criteria

The concept of cause

- Always tempting to think that cause is a single condition or event that inevitably leads to a particular outcome

- In reality, ‘single cause outcomes’ tend to be the exception rather than the rule
  - presence or absence of disease depends on a complex interplay of factors

The concept of cause

- Aim of epidemiological research is to provide information that helps us to understand
  a) what factors are involved in causal pathways to disease
  b) the relative importance of each factor as a determinant of disease

The concept of cause

- Cause
  - an event, condition, or characteristic without which the disease would not have occurred (Rothman)
- Conditions
  1. Must precede the effect
  2. Can involve host or environmental factors
  3. Can be either

     positive ≡ the presence of an exposure

     negative ≡ the absence of exposure (e.g. vaccination)

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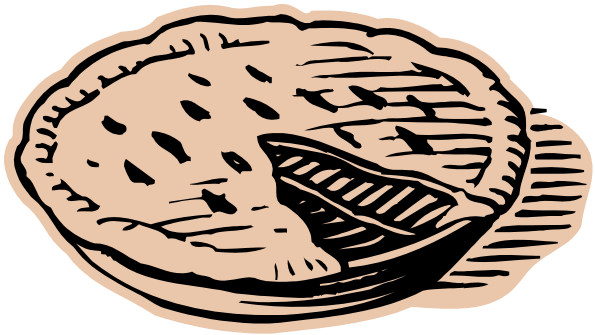
Types of cause

- Cause
  - easiest to think about causal factors as the pieces of a pie: once the pie is full, disease occurs
  - for some diseases (especially highly infectious diseases) it may be that exposure to the agent will cause disease – there is only one piece to the pie
  - for other diseases there may be many reasons why some exposed animals don't develop the disease yet others do – there a more than one pieces to the pie
    - e.g. mineral deficiencies may only show up in lactating animals and not dry stock

Types of cause

- Component causes
  - these are pieces of the pie
  - e.g. coronary heart disease in humans
    - high cholesterol
    - smoking
    - lack of exercise
    - genetics
    - concurrent diseases

Ken Rothman



Types of cause

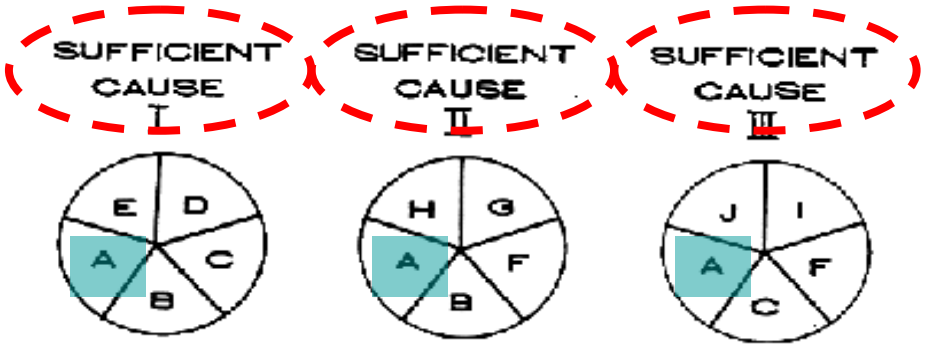
- Sufficient causes
  - the whole pie
  - a set of conditions without any one of which the disease would not have occurred
  - not usually a single factor, often several
    - e.g. respiratory disease in calves
    - Pasteurella spp., respiratory syncytial virus, and stress are all sufficient causes
    - respiratory disease tends to occur when two or more of these factors are present
    - two of the above factors are sufficient to cause respiratory disease

Types of cause

- Necessary cause
  - the most important piece of the pie
  - must be present for disease to occur
    - e.g. foodborne disease outbreak
    - chicken salad and cream desert have been identified as sufficient causes of Salmonella diarrhoea
    - Salmonella spp. is a necessary cause of diarrhoea

Types of cause

Sufficient cause: the whole pie



This illustration shows a disease that has 3 sufficient causal complexes, each having 5 component causes.

A is a necessary cause since it appears as a member of each sufficient cause.

B, C, and F are not necessary causes since they fail to appear in all 3 sufficient causes.

Types of cause

- Examples
  - although M. bovis is a necessary cause of TB it is not a sufficient cause since many animals harbour small foci of M. bovis without clinical disease
  - tobacco smoking is a sufficient cause of lung cancer, but so is exposure to other chemicals (e.g. radon or asbestos)
  - coronary heart disease in humans has no necessary cause, but rather a range of component causes which become sufficient when some or all occur together in individuals at levels that accumulate and interact to result in disease

Types of cause

- Uncle Joe is alive and well at age 95, having smoked 20 cigarettes a day since age 10 …
  - this doesn't show that smoking is not harmful
  - shows that smoking by itself is not a sufficient cause of death or disability before age 95
  - concluding that there is no causal link between smoking and ill health is like concluding that the existence of elderly war veterans of a war means that war does not kill people

Types of cause

- Note
  - component causes can act far apart in time
  - a component cause can involve the presence of a causative exposure or the lack of a preventive exposure
  - blocking the action of any component cause prevents the completion of the sufficient cause and therefore prevents the occurrence of disease by that pathway
  - completion of a sufficient cause is synonymous with occurrence (although not necessarily diagnosis) of disease

Types of cause

- Causes operate in different ways
  - predispose: age, sex, previous illness
  - enable: low income, poor nutrition, bad housing, inadequate medical care [getting to the edge]
  - precipitate: exposure to a specific disease agent [tipping you over]
  - reinforce: repeated exposure (e.g. repeated hard work) may aggravate an established disease or state
  - interact: the effect of two or more causes acting together is often greater than would be expected on the basis of summing the individual effects
    - smoking and exposure to asbestos → ↑ ↑ risk of lung cancer

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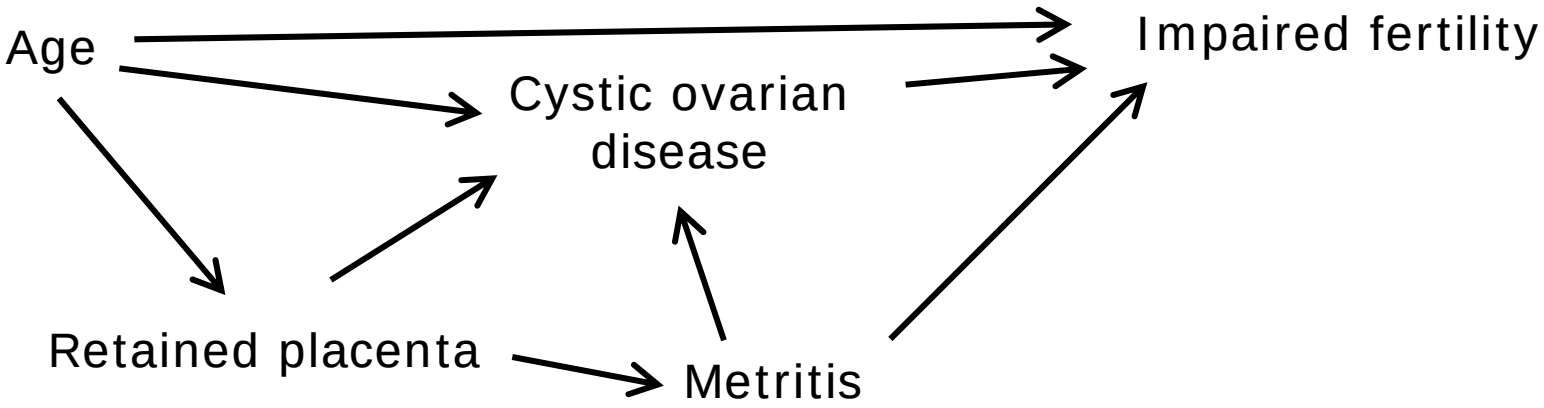
Causal web models

- Takes the sufficient and necessary causes of disease and displays them as a path diagram
- Direct causes:
  - no known intervening variable between the exposure factor and the disease
- Indirect causes:
  - effect of exposure is mediated through one or more intervening variables

Causal diagram of factors influencing fertility in dairy cattle.



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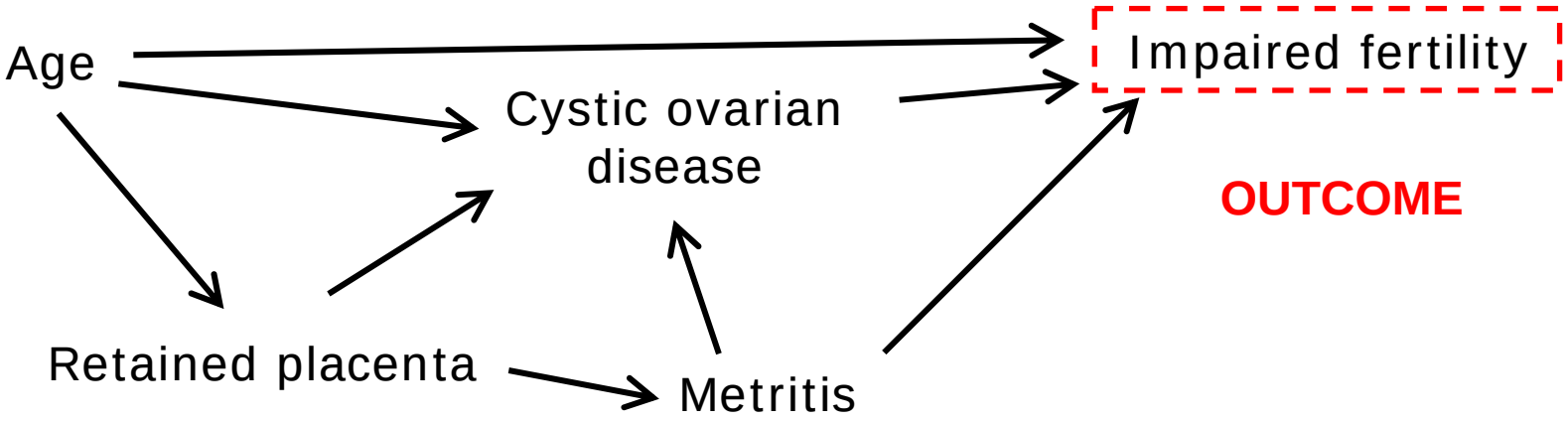

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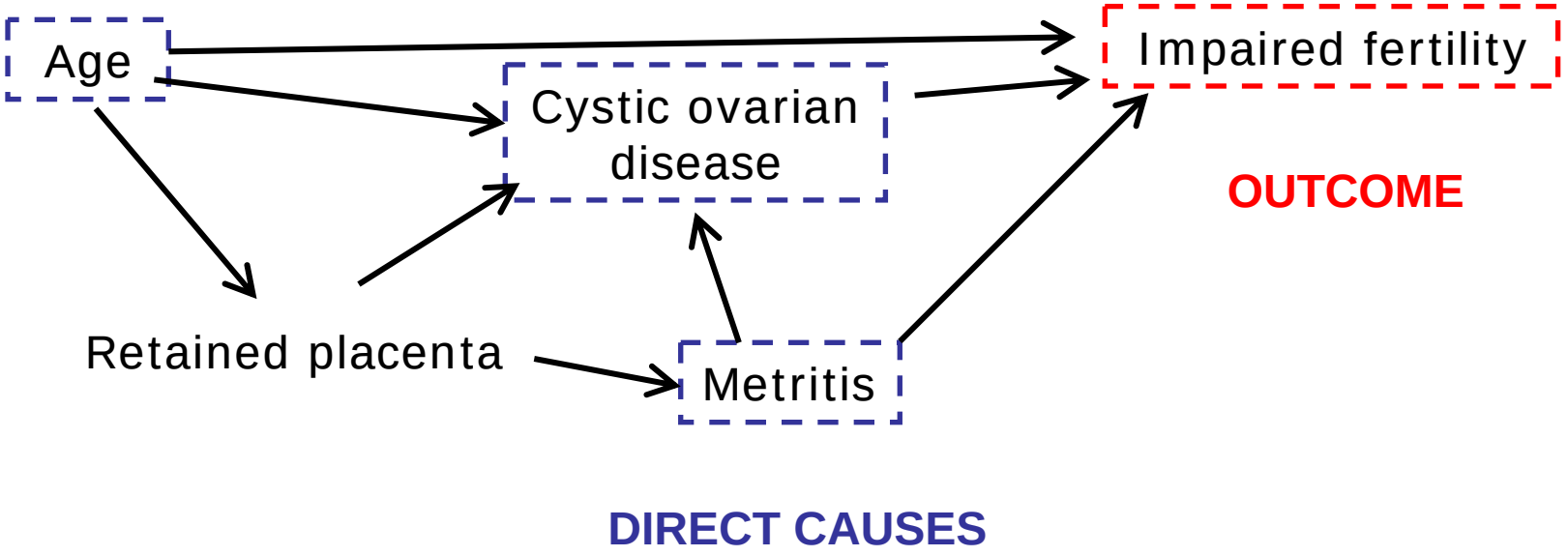

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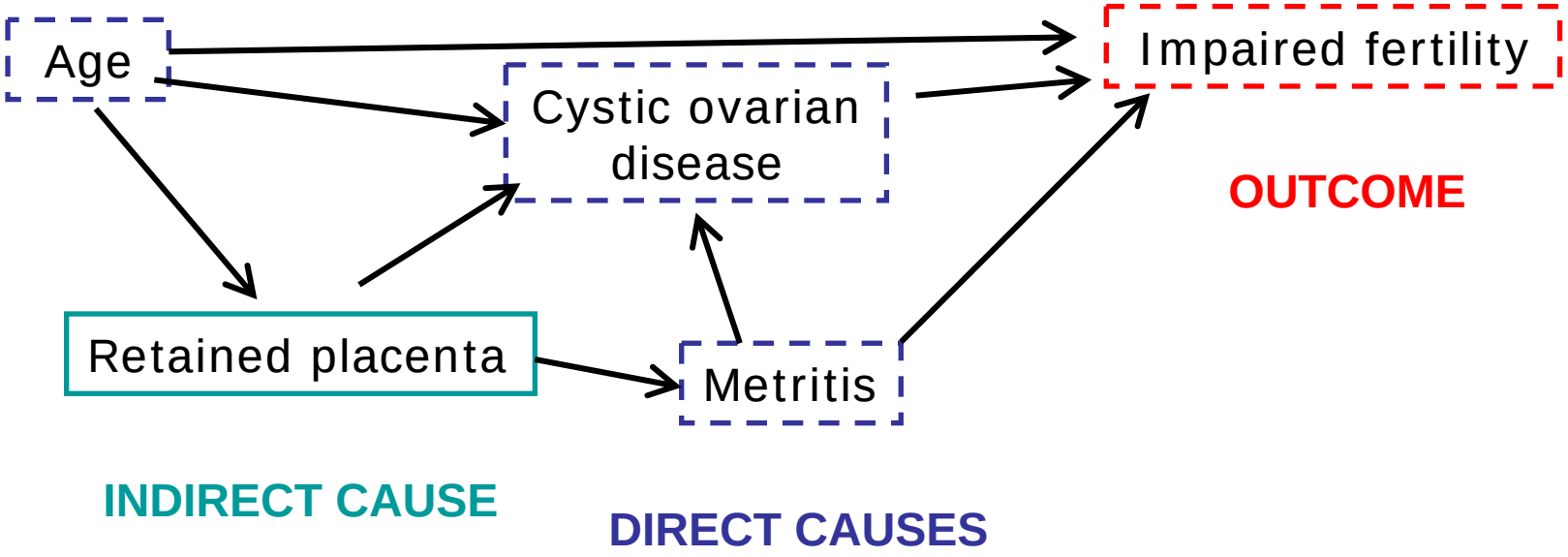
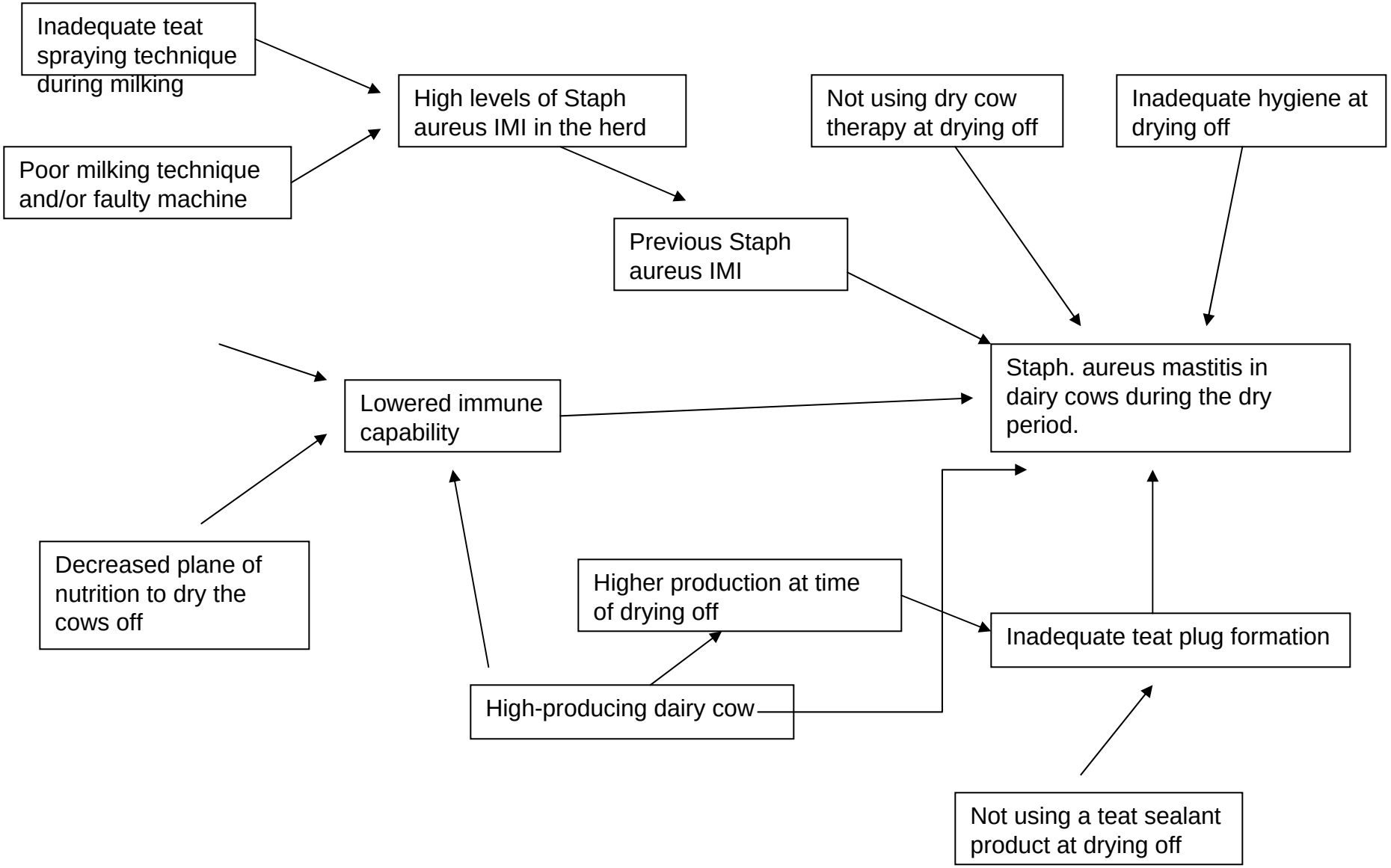
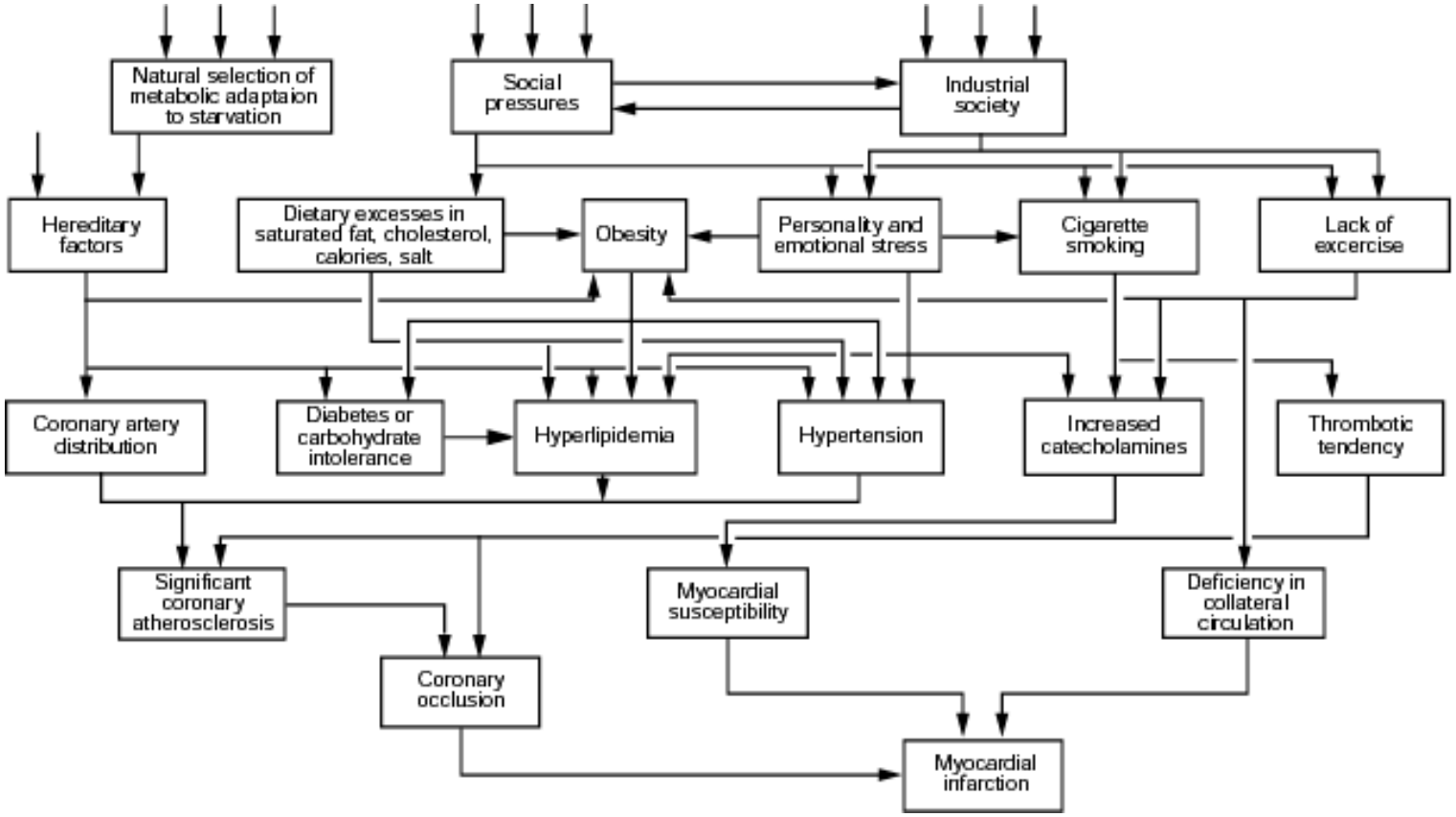


Causal diagram of factors influencing mastitis in dairy cattle.



Causal diagram – myocardial infarction in humans.



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  - Koch's postulates
  - Evan's concept of causation
  - Hill's criteria
- Views on causal criteria

Establishing the cause of disease

- Need to be careful to distinguish between those factors that cause disease *vs* those factors associated with the presence of disease

- A study conducted in the 1980s found that dairy herds milked by staff who wore shorts and aprons during milking were more likely to be positive for leptospirosis …

Epidemiology of leptospirosis in dairy farm workers in the Manawatu Part I: A cross-sectional serological survey and associated occupational factors.

C. G. Mackintosh*, Linda M. Schollum*, R. E. Harris‡, D. K. Blackmore*, A. F. Willis†, N. R. Cook†, J. C. J. Stoke†

N.Z.vet.J.28: 245-50

Shorts

The wearing of shorts appeared to constitute a risk factor. The attack rate for people who did not wear shorts was 10% compared with an attack rate of 40% for people who did wear shorts ($P<0.05$).

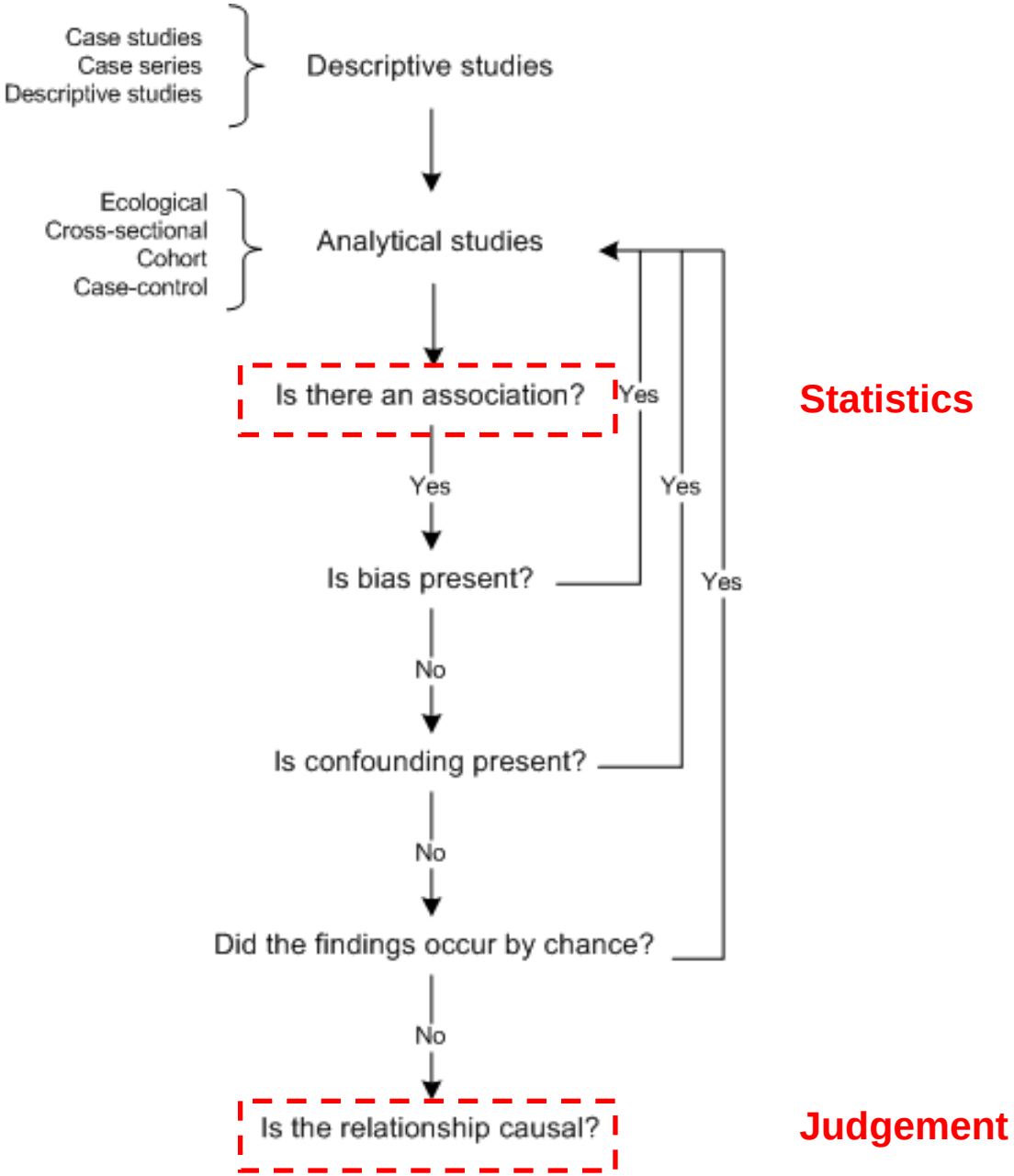
Aprons

Milkers wearing aprons appeared to be at a greater risk of contracting *hardjo* than non-wearers ($P<0.05$).

Establishing the cause of disease

- Interpretation …
  - do shorts and plastic aprons cause leptospirosis?
  - are shorts and plastic aprons associated with the presence of leptospirosis?

The epidemiological process …



Establishing the cause of disease

- Criteria for judging causation
  - Koch’s postulates
  - Evan's unified concept of causation
  - Hill’s criteria

Establishing the cause of disease

- Koch (1884) provided a framework for identifying causes of infectious disease
- Koch's postulates:
  - the agent has to be present in every case of the disease
  - the agent has to be isolated and grown in pure culture
  - the agent has to cause disease when inoculated into a susceptible animal and the agent must then be able to be recovered from that animal and identified

'Single cause' paradigm

Establishing the cause of disease

- Koch's postulates:
  - anthrax was the first disease demonstrated to meet these rules
  - really of value only when the specific cause is an overpowering infectious agent
- For many conditions (both infectious and non-infectious) Koch's postulates are inadequate:
  - e.g. respiratory disease in calves

Establishing the cause of disease

- Evan's unified concept of causation
  - a set of criteria for judging whether or not exposures cause disease
  - if an association is found between an exposure and the presence of disease it is important to determine if the exposure is causal
    - this is done by considering Evan's criteria

Establishing the cause of disease

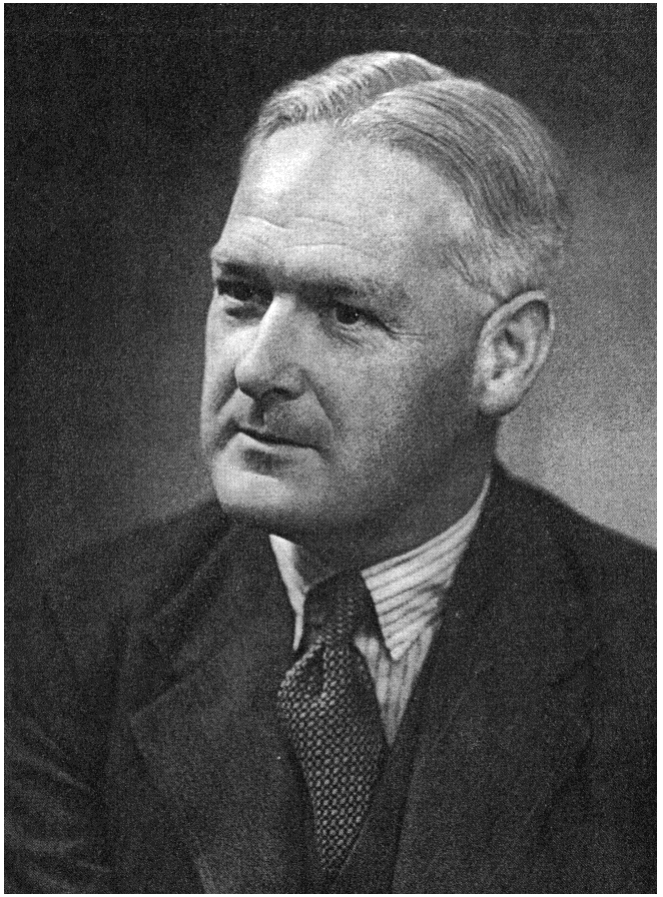
- Evan's unified concept of causation
  - the proportion of individuals with disease should be higher in those exposed to the putative cause than in those not exposed
  - exposure to the putative cause should be more common in cases than in those without the disease
  - the number of new cases should be higher in those exposed to the putative cause than in those not exposed, as shown in prospective studies

Establishing the cause of disease

- Evan's unified concept of causation (cont.)
  - temporally, the disease should follow exposure to the putative cause
  - there should be a measurable biologic spectrum of host responses
  - the disease should be reproducible experimentally
  - preventing or modifying the host response should decrease or eliminate the expression of disease
  - elimination of the putative cause should result in lower incidence of disease

Establishing the cause of disease

- Bradford Hill elaborated on Evan's criteria as part of work identifying smoking as a cause of lung cancer
- Now known as Hill's Guidelines for Causation (1965)



A. Bradford Hill (1897–1991)

Hill's criteria

- Purpose: guidelines to help determine if associations are causal
  - should not be used as rigid criteria to be followed slavishly
  - Hill stated that he did not intend for these 'viewpoints' to be used as 'hard and fast rules'

Hill's criteria

- Criteria for causation
  1. Strength of association
  2. Consistency
  3. Specificity
  4. Temporality
  5. Dose-response relationship
  6. Plausibility and coherence
  7. Experimental evidence
  8. Analogy

Hill's criteria (1)

- Strength of association
  - strong associations are more likely to be causal
  - indicated by risk ratio or rate ratio of greater than 2.0
    - relative risk of lung cancer in smokers vs non-smokers = 9
    - relative risk of CHD in smokers vs non-smokers = 2
  - cannot infer that weak association is not causal

Hill's criteria (1)

- Strength of association
  - strong associations are more likely to be causal because they are unlikely to be due entirely to bias and confounding
  - weak associations may be causal but it is harder to rule out bias and confounding
  - weak association does not eliminate causation
    - smoking and CHD
    - passive smoking and lung cancer
  - strong association but no causality
    - Down's syndrome and birth order

Hill's criteria (1)

- How strong is strong?

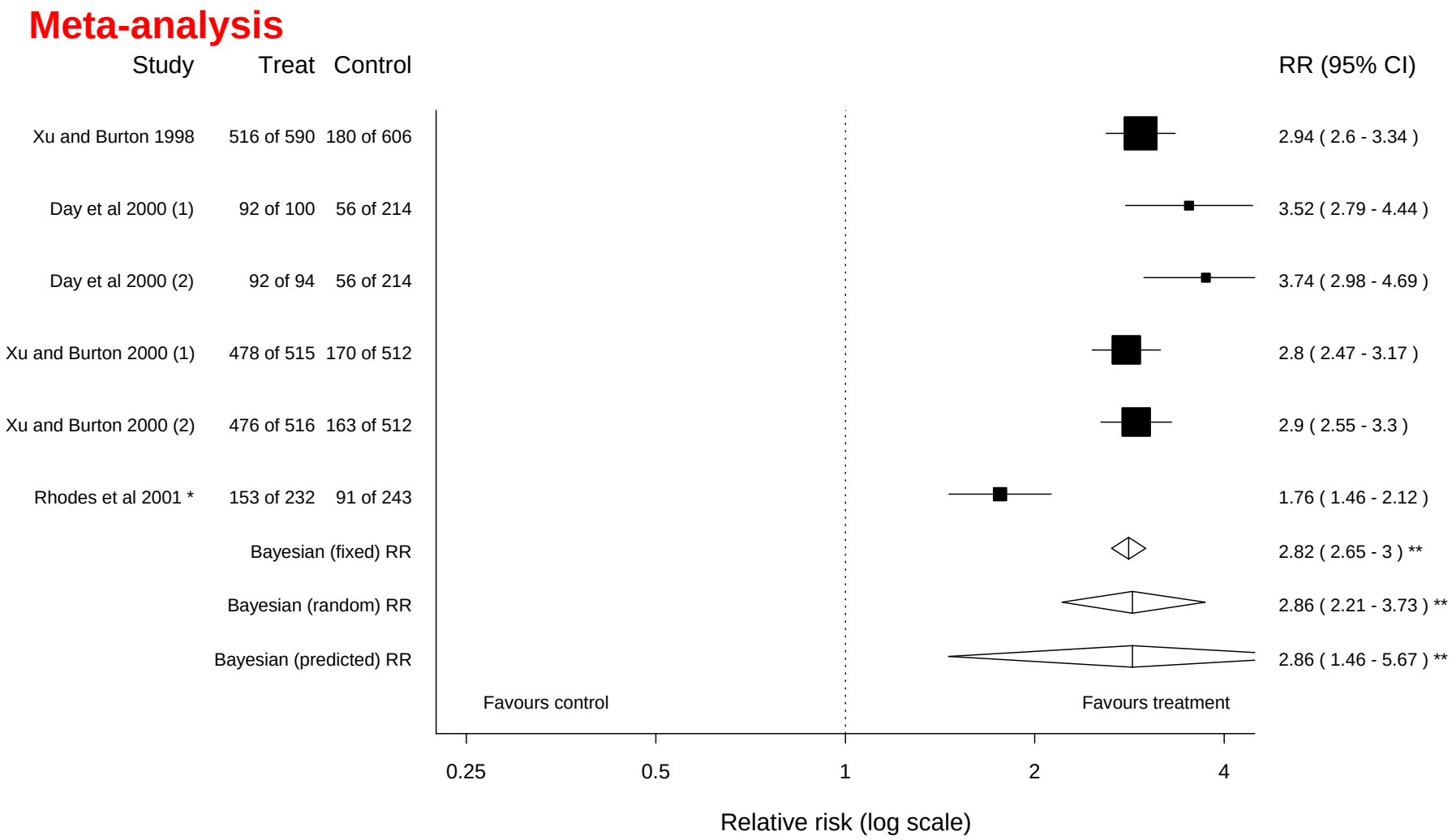
Relative risk	Interpretation
1.1 – 1.3	Weak
1.4 – 1.7	Modest
1.8 – 3.0	Moderate
3 – 8	Strong
8 – 16	Very strong
16 – 40	Dramatic
> 40	Overwhelming

Adapted from Schoenbach (1999)

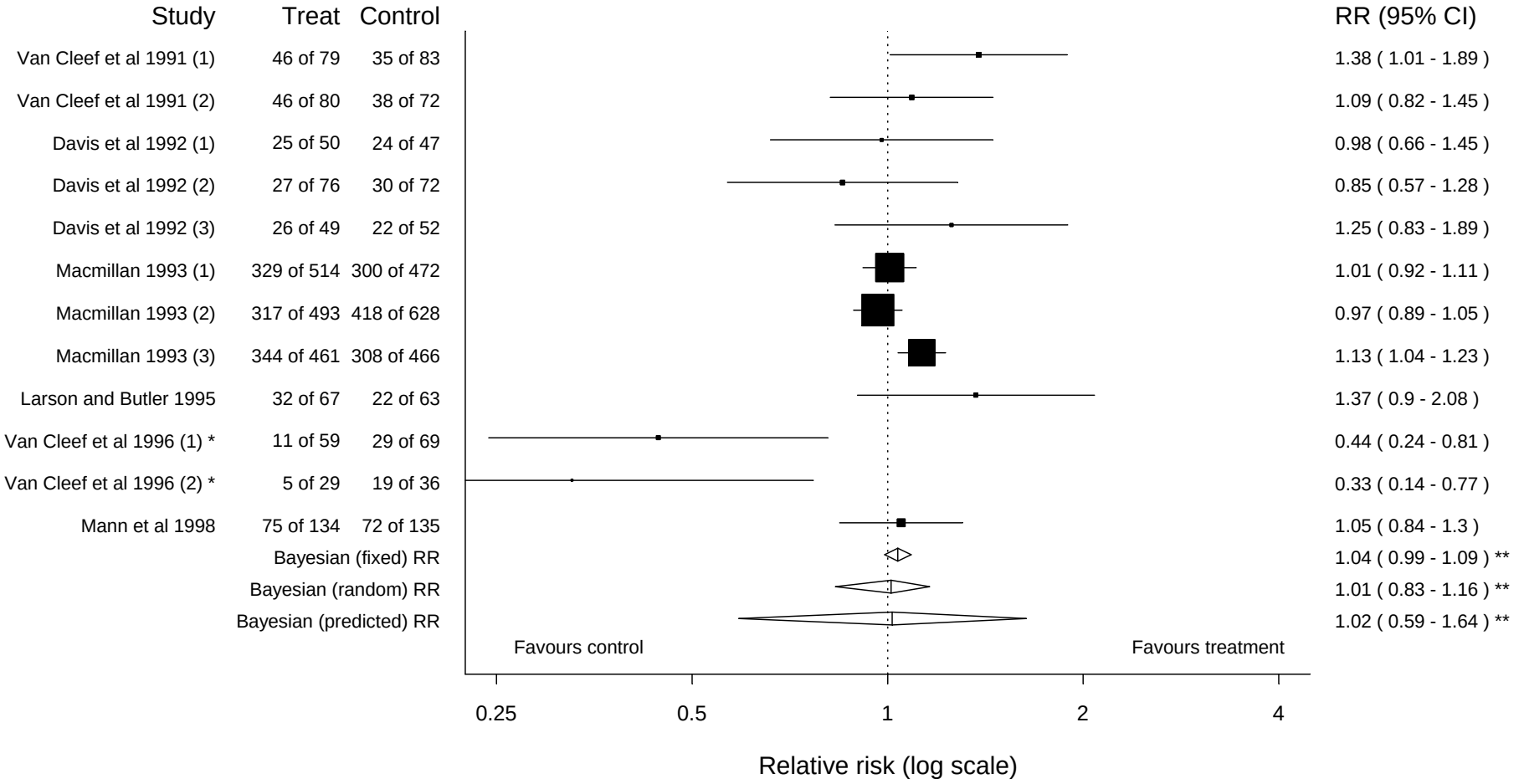
Hill's criteria (2)

- Consistency
  - has the cause and effect relationship been identified by a number of different researchers?
    - smoking has been associated with lung cancer in at least 29 retrospective and 7 prospective studies
  - sometimes there are good reasons why study results differ, for example, one study may have looked at low level exposures while another looked at high level exposures

Relative risks (and their 95% confidence interval) from six trials comparing the effect of CIDR treatment with untreated controls on submission rate.



Relative risks (and their 95% confidence interval) from 12 trials comparing the effect of post insemination CIDR treatment with untreated controls on conception rate.



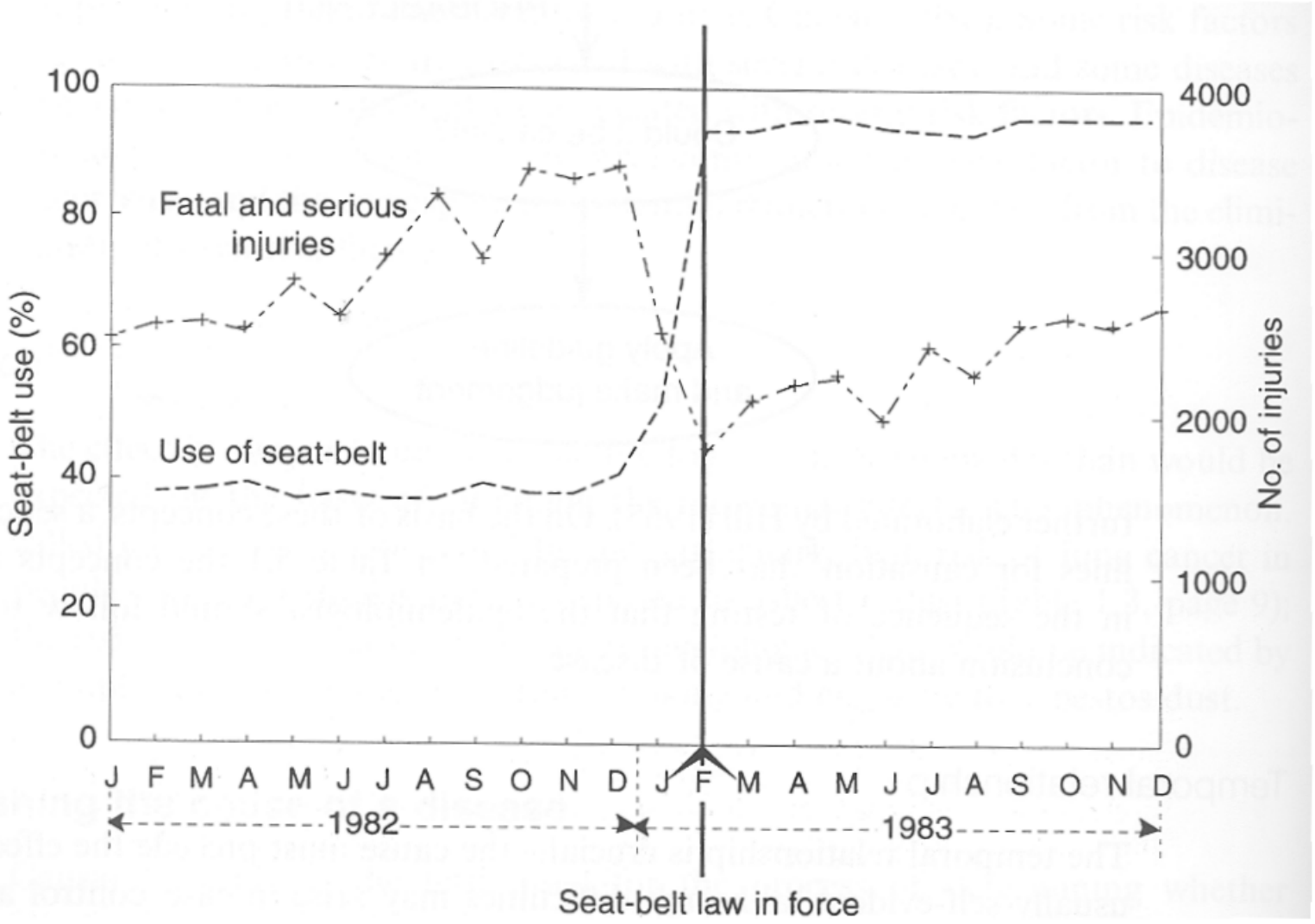
Hill's criteria (3)

- Specificity
  - a single exposure should cause a single disease
  - this is a hold-over from the concepts of causation that were developed for infectious diseases
  - many exceptions
    - smoking is associated with lung cancer as well as many other diseases
  - when present, specificity does provide evidence of causality, but its absence does not preclude causation

Hill's criteria (4)

- Temporality
  - cause must precede effect
  - if B comes after C, then B did not cause C
  - can be difficult to establish
    - long induction periods
    - long latent (sub-clinical) phase
  - what type of studies are less likely to confuse the issue of temporality?
    - prospective studies

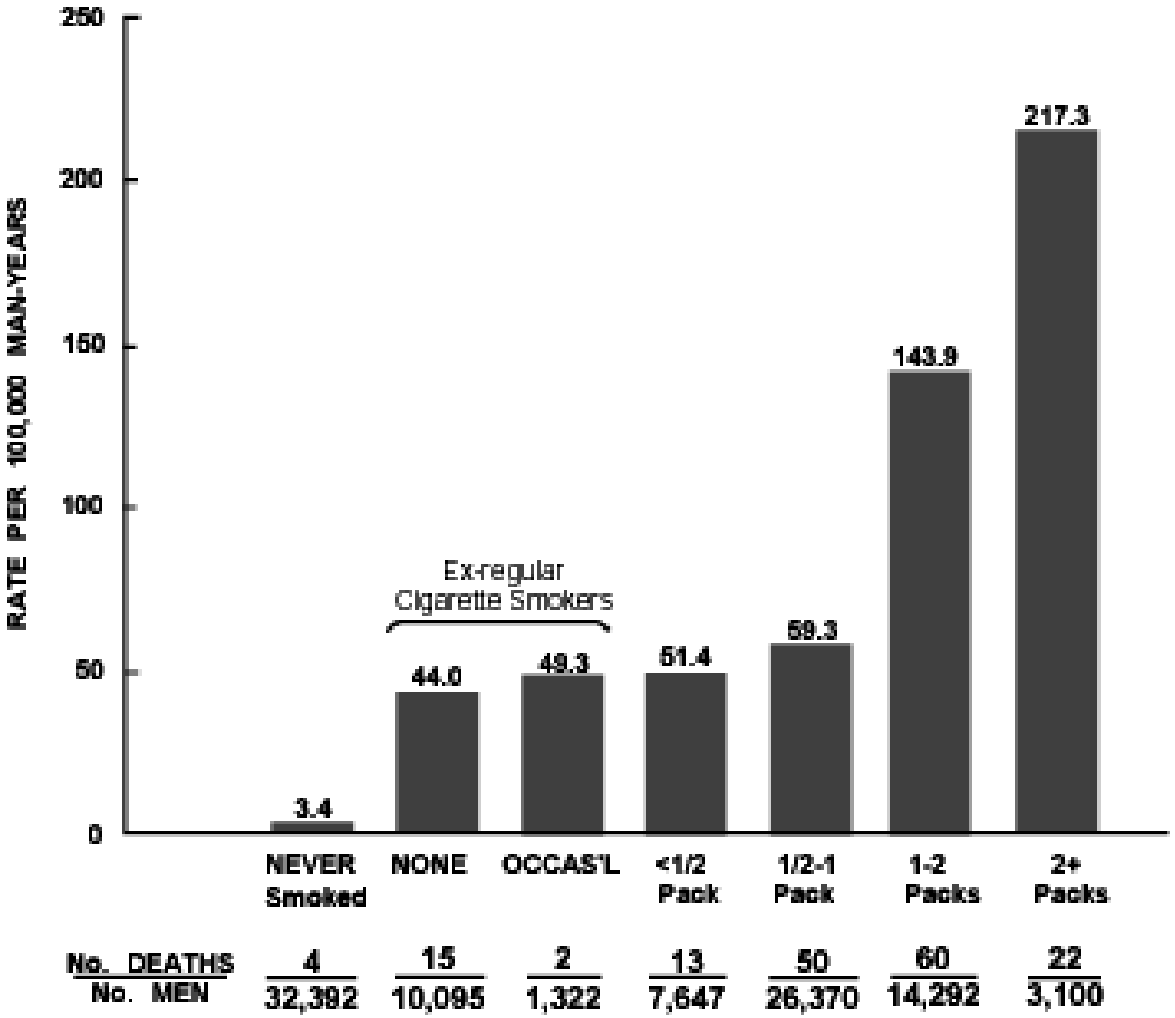
Frequency of seat belt use and injury occurrence in the United Kingdom 1982 – 1983.



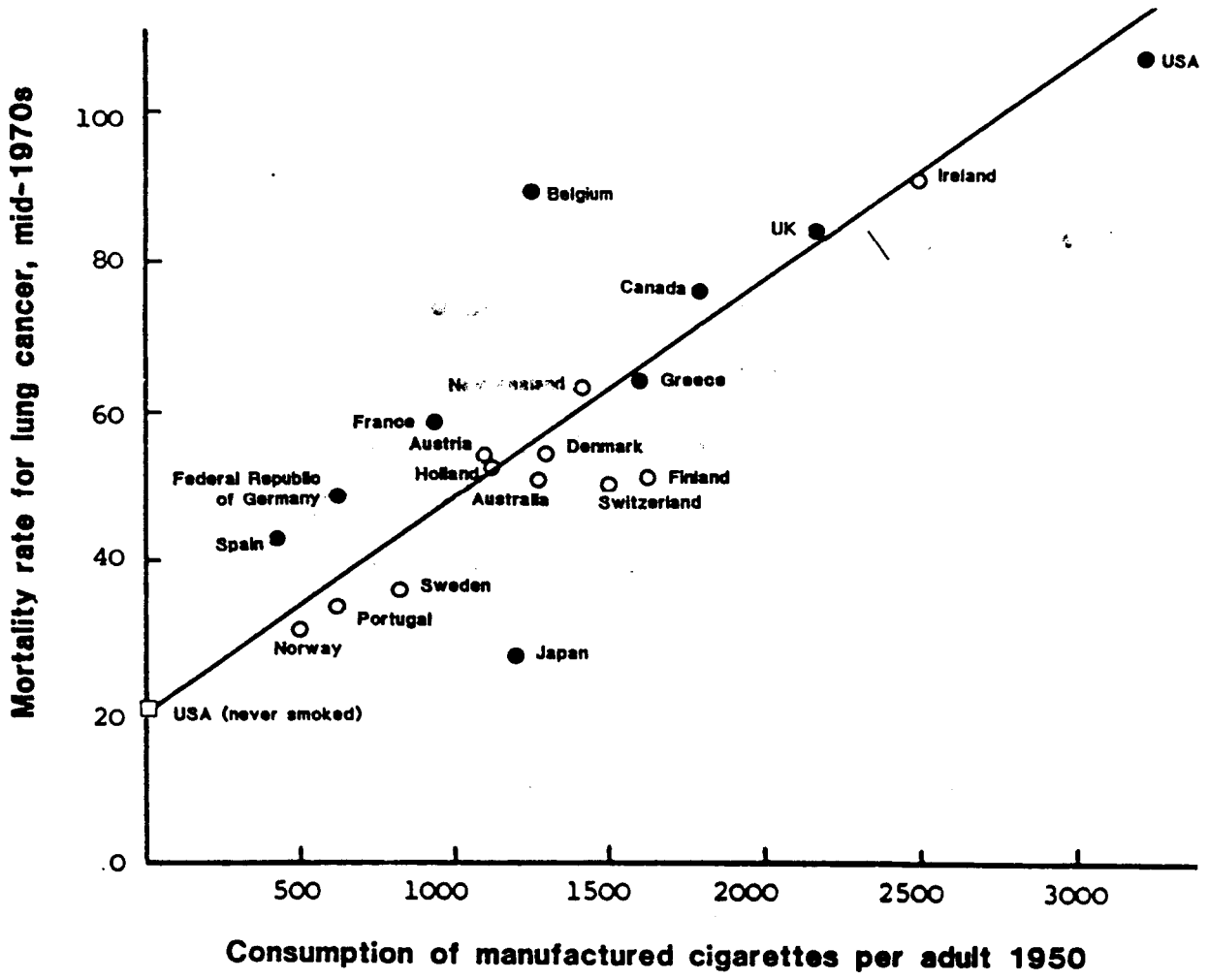
Hill's criteria (5)

- Dose-response relationship
  - as the level of exposure is increased, the rate of disease also increases
  - be aware that there may be also non-linear effects

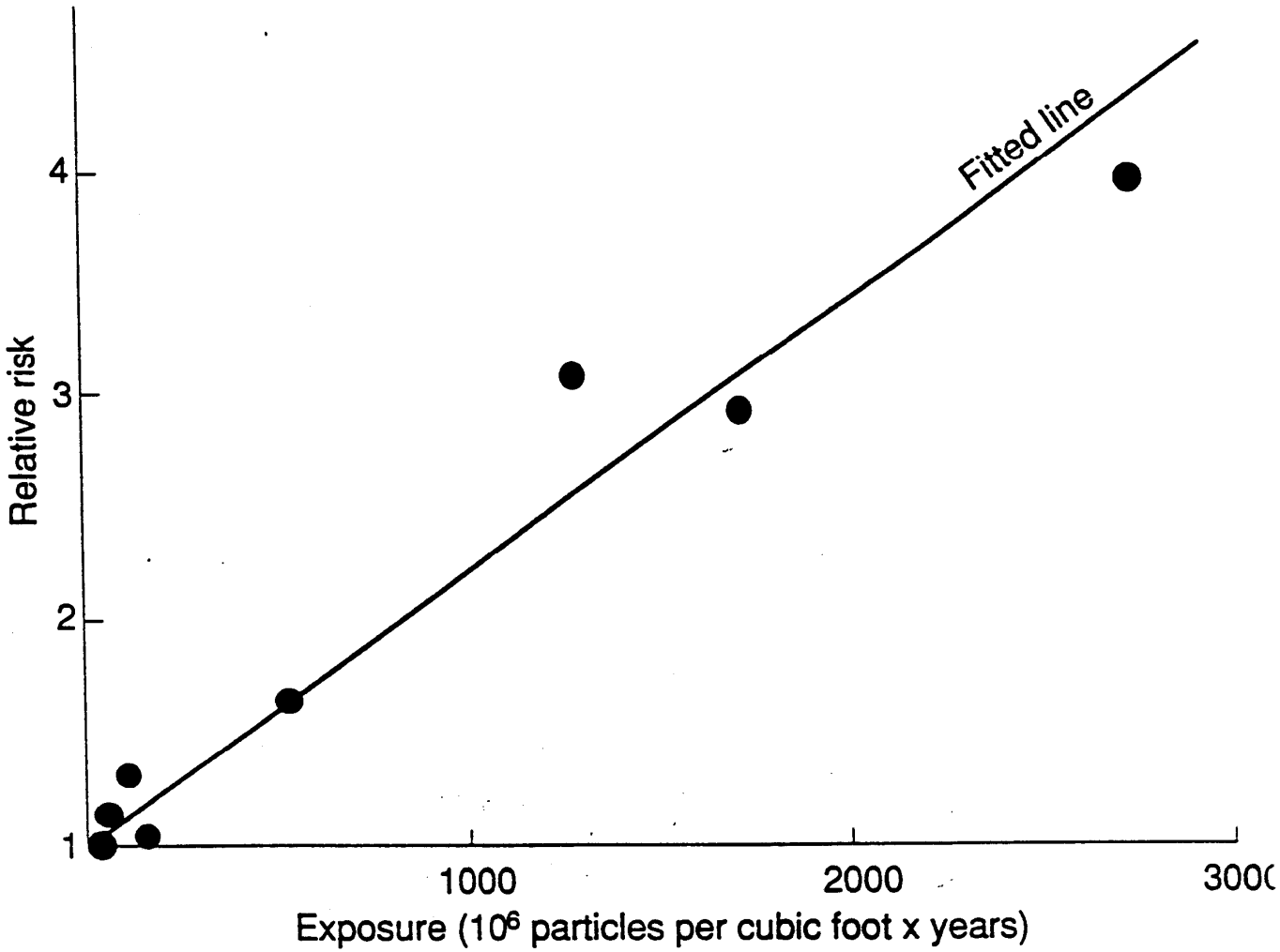
Age adjusted death rates for lung cancer as a function of approximate number of cigarettes smoked per day.



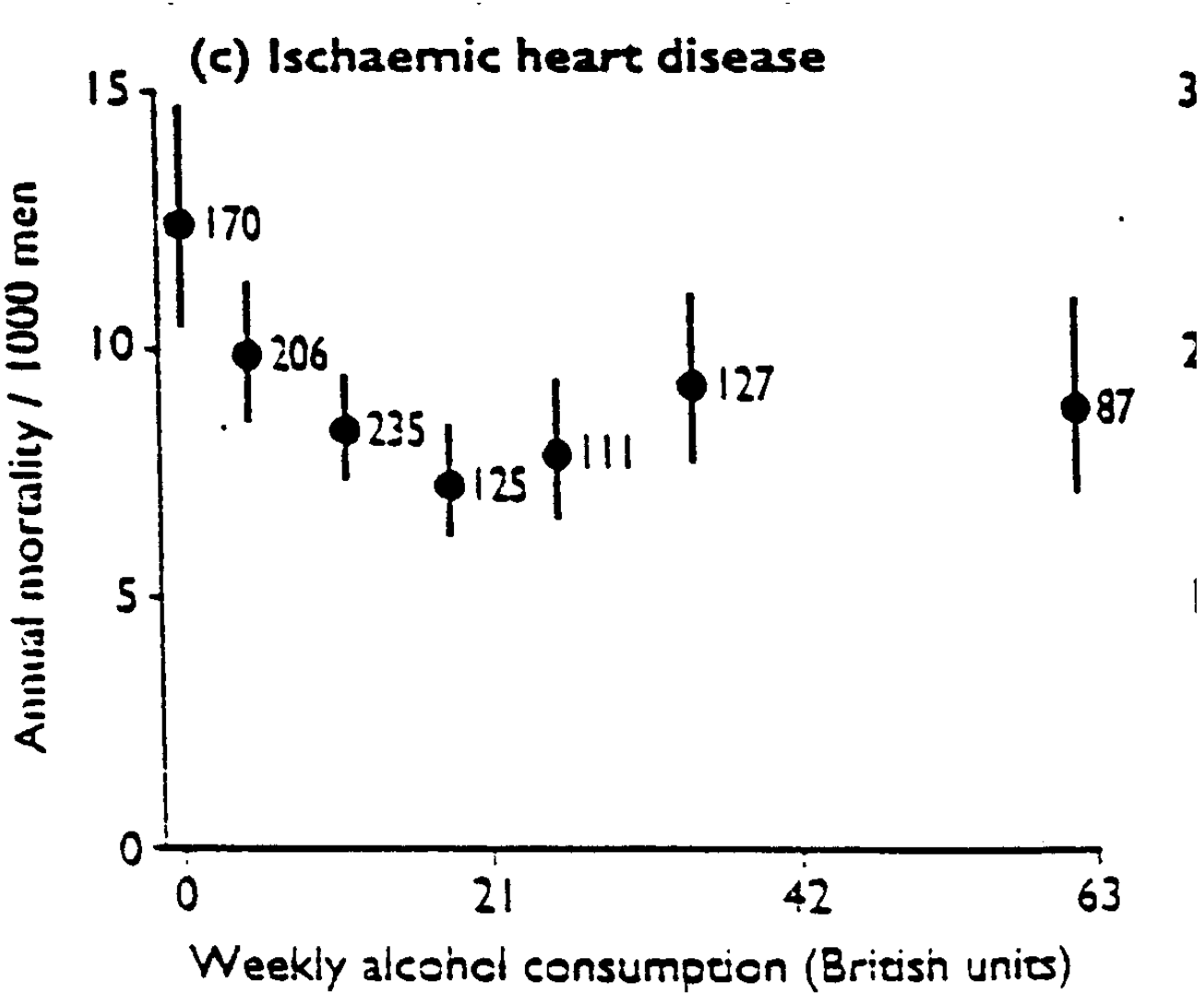
Correlation between consumption of manufactured cigarettes in 1950 and mortality rates from lung cancer in persons aged 35 - 44 in the mid-1970s.



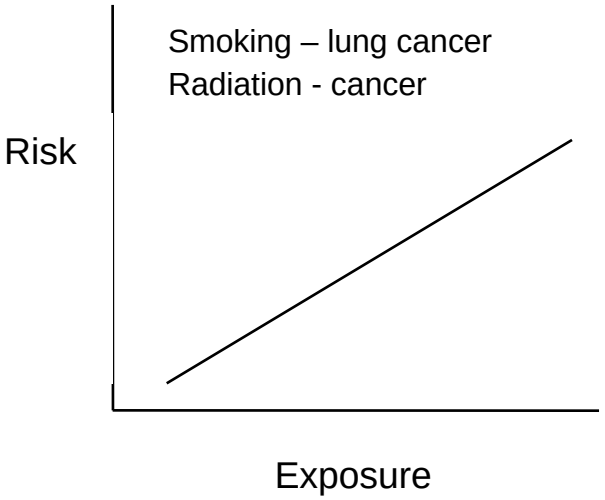
Relationship between asbestos exposure (particle-years) and relative risk of lung cancer.

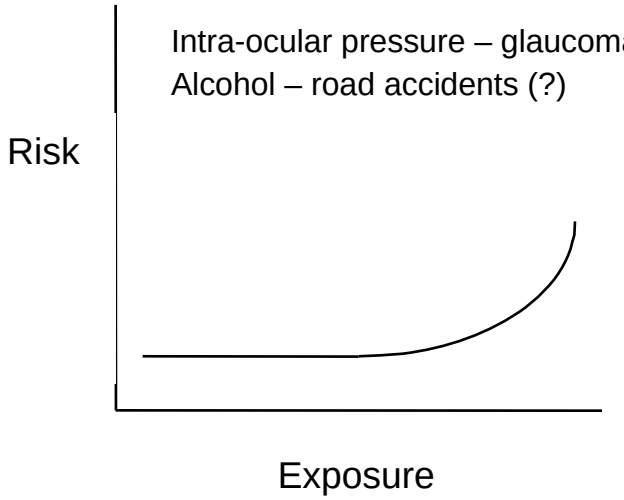


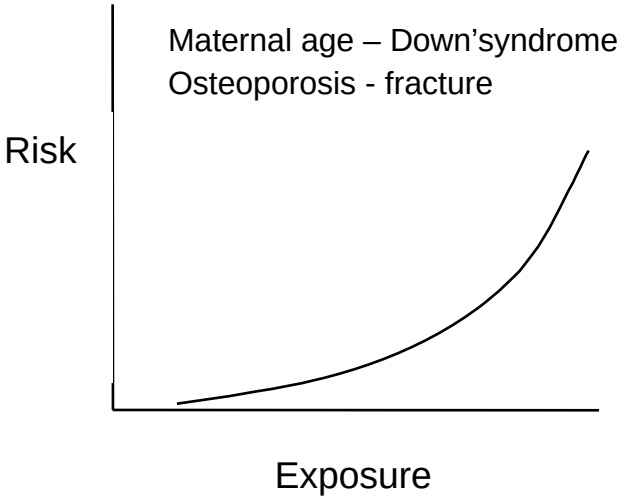
Annual mortality (per 1000 men) from ischaemic heart disease.

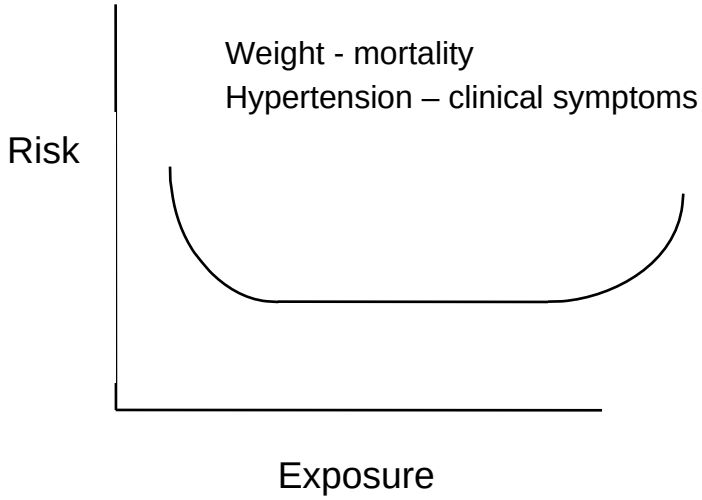


Risk as a function of exposure level.









Hill's criteria (6)

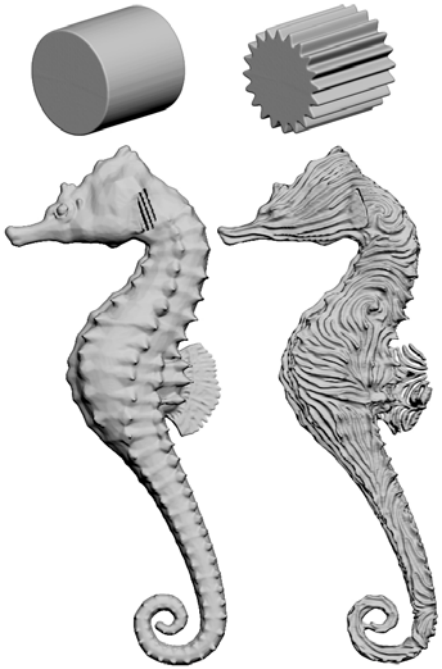
- Plausibility and coherence
  - does a causal interpretation fit with known facts of natural history and biology of disease, including distribution in time and space and laboratory experiments?
  - that is, does the association make 'biological sense'?
  - more willing to accept the case for a relationship that is consistent with current knowledge/belief
  - not objective
  - readier to accept arguments similar to others that we accept

Hill's criteria (7)

- Experimental evidence
  - investigator-initiated interventions that modify exposure through prevention, treatment, or removal should result in less disease
  - study designs, in order of usefulness:
    1. randomised, controlled trials
    2. cohort studies [some opportunity to minimise bias]
    3. case-control studies [subject to bias]
  - cross sectional studies not useful because they provide no direct evidence of the time sequence of events

Hill's criteria (8)

- Analogy
  - has a similar relationship been observed with another exposure and/ or disease?
    - BSE and scrapie - transmissible mink encephalopathy



Hill's criteria

- Judging the evidence
  - 'none of my viewpoints can bring indisputable evidence for or against the cause and effect hypothesis and none can be regarded as sine qua non[§] (Hill 1965)
  - causal inference less certain than logical deductions
  - bottom line: judgment

[§] sine qua non: an essential condition or element

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Views on causal criteria

- Scientific knowledge
  - always incomplete, whether it is observational or experimental
  - liable to be upset or modified by advancing knowledge
- Public health recommendations are possible without firm causal or preventive conclusions but are typically not made without some evidentiary support

- Don’t be a slave to the P value

Views on causal criteria

- Bovine spongiform encephalopathy in Great Britain
  - first case identified November 1986
  - a case-control study of the first 200 cases identified an association between the use of meat and bonemeal and BSE-positive farms
  - feeding meat and bone to cattle was banned in July 1988
  - to date, there have been ~ 190,000 confirmed cases of BSE
  - how many cases would there have been if the feed ban was delayed?

Summary

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