Effect modification and confounding

Intended Learning Outcomes

By the end of the session, you are expected to be able to:

1. Define concept of effect modification (interaction) and confounding
2. List and explain the steps required to identify effect modification in a dataset
3. Be able to interpret results tables and identify evidence of effect modification
4. Summarise how confounding may affect results, and ways to deal with confounding in observational studies
5. Define the concept of residual confounding in contrast to the general concept of confounding
6. Evaluate confounding in published observational studies

Influences on health

- Rare to have simple exposure and outcome with no other influences
- Health status and risk of most diseases is subject to multiple influences (e.g. CHD)
- One-variable-at-a-time approach (2x2 table)
- Public health & intervention
- Associations may vary according to other factors

Alternative explanations for your results

- Chance
  Bias (yesterday)

- Strive to avoid at design stage
- Control or adjust at analysis stage

- Effect modification

- Identify at design stage
- Carefully describe and discuss at analysis stage

- Confounding

- Strive to avoid at design stage
- Control or adjust at analysis stage

Biological Interaction

Last's Dictionary of Epidemiology (4th Ed)

Biological interaction is the interdependent operation of two or more causes to produce, prevent or control disease

$$\text{Factor 1} + \text{Factor 2} \longrightarrow \text{Outcome}$$

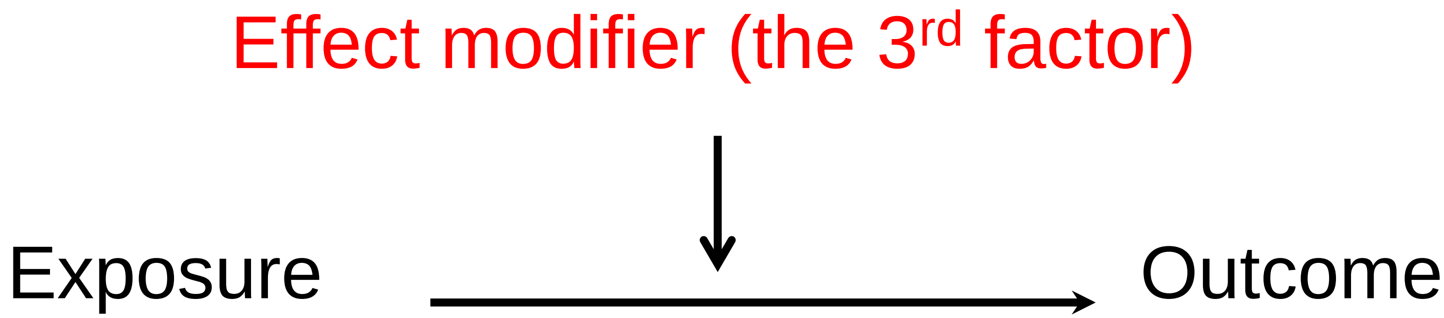
Examples of biological interaction

1. **Antibiotic tetracycline and tooth discolouration**
   - Tetracycline is associated with discoloration of teeth but mainly among children <8 years
   - effect of antibiotic (exposure) on tooth colour (outcome) is modified by age (effect modifier)

2. **Measles and vaccination**
   - Exposure to measles virus is associated with measles infection if not vaccinated or has not had measles
   - Here immune status = effect modifier

Statistical interaction

when the association between exposure and outcome of interest varies according to the level of a third factor (the effect modifier)

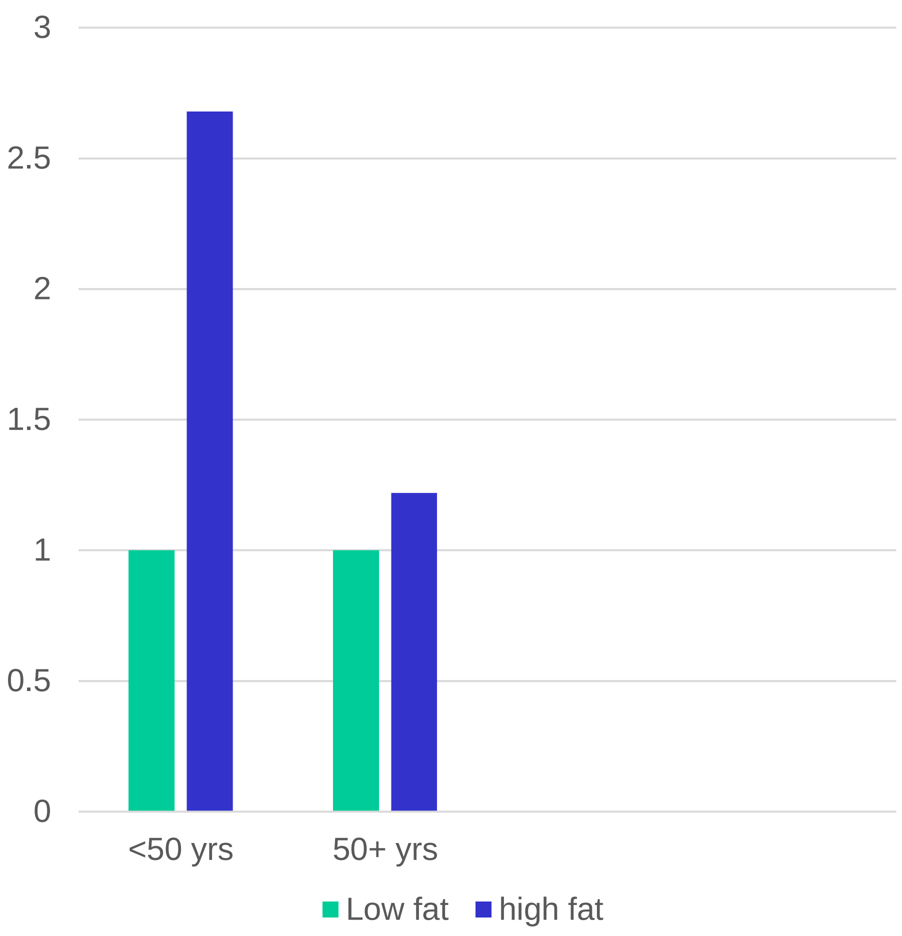


Note: may not imply biological interaction

Examples of statistical interaction

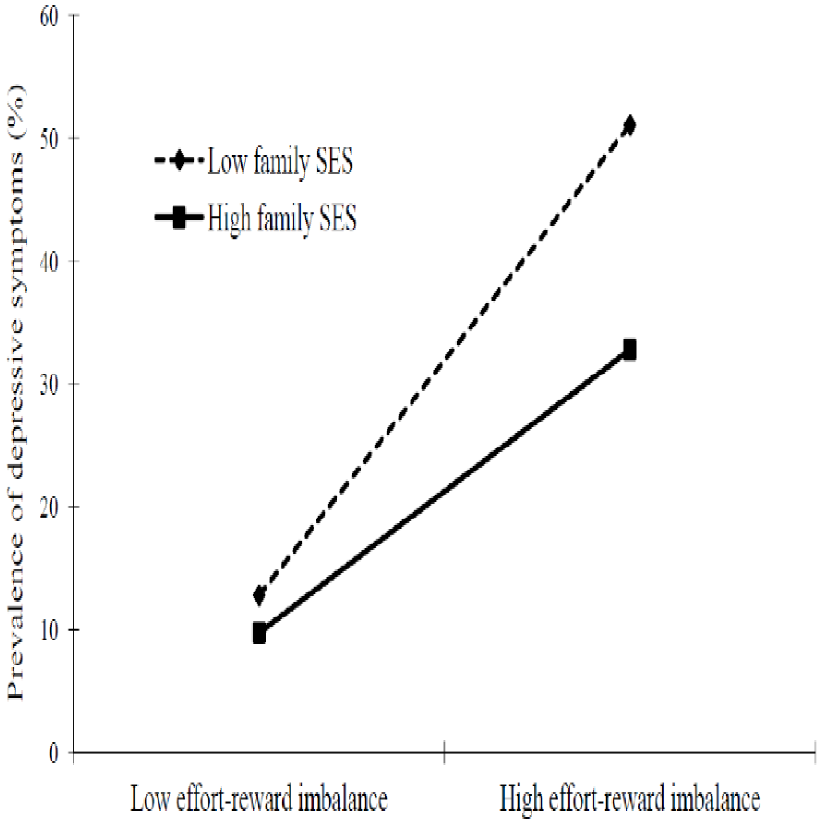
Energy from total fat and coronary heart disease (CHD)

Energy from total fat is associated with CHD among younger women (HR=2.68, 95%CI 1.40,5.12) but not among older women (HR=1.22, 95%CI 0.86,1.71) (Source: [Jakobsen et al. Am J Epidemiol. 2004](#))



Effort Reward Imbalance (ERI) and depressive symptoms among children (China)

School-related stress (ERI school questionnaire) is associated with depressive symptoms among low SES children compared to high SES children (Source: Guo et al. Int J Environ Res Public Health. 2014)



Measuring effect of association

- Absolute risk or rate (differences)
- Relative risk or rate (ratios)

Additive and multiplicative models

Absolute risk = Additive model (acts in additive way)

- When the <u>absolute difference in risk or rate</u> between those with and without the exposure varies according to a third variable

Relative risk = Multiplicative model (acts in a multiplicative way)

- When the <u>risk ratio, rate ratio or odds ratio</u> for an association between exposure and disease varies according to a third variable

Generally interested in interactions on a relative scale

How can we determine whether interaction is present?

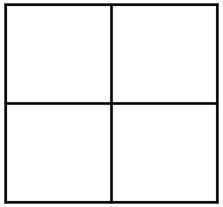
Adopt a statistical approach – two options

1. Assess homogeneity of effects

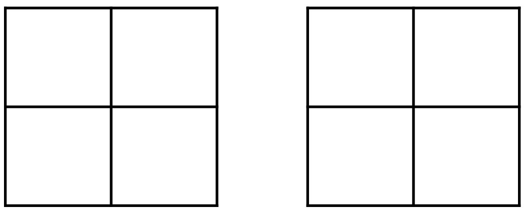
2. Compare observed and expected effects

Option 1 – Assessing homogeneity of effects

Crude



Stratum 1 *Stratum 2*



Crude 2 x 2 table
Calculate crude measure of effect

Stratify by 3^{rd} variable

Calculate measure of effect
for each stratum (values of 3^{rd} variable)

Test whether stratum specific measures of effect are similar (p-value from homogeneity test)

Not sig.

Investigate other possible influences of 3^{rd} variable (later in the session)

Sig. p-value

Evidence of effect modification
(Stratified NOT pooled estimates reported)

Assessing homogeneity of effects. Example 1

Absolue risk of disease according to exposure and factor A

Exposure	Factor A	No factor A
Yes	Risk = 0.9	0.3
No	0.4	0.2

Additive model (absolute risk difference)

- Factor A = 0.9 - 0.4 = 0.5
- No factor A = 0.3 – 0.2 = 0.1

Evidence of interaction

Multiplicative model (risk ratios)

- Factor A = 0.9/0.4 = 2.25
- No factor A = 0.3/0.2 = 1.5

Evidence of interaction

Assessing homogeneity of effects. Example 2

- Case-control study of history of blood pressure (BP) and myocardial infarction (MI)
- Crude OR for association between BP & MI =1.4
- Age-specific stratum estimates

  <=60 years OR = 0.97

  >60 years OR =1.87
- Evidence of effect modification on the multiplicative (relative) scale
- Test for homogeneity, p-value = 0.01

How can we determine whether interaction is present?

Two options

1. Assess homogeneity of effects

2. Compare observed and expected effects

Comparison of observed & expected effects. Example 1.

Risk of obesity according to presence / absence of 2 variables

Exposure	**Factor A** **(the 3rd factor)**	
	Yes	No
Yes	0.9	0.3
No	0.4	0.2

Measure of effect = risk difference
Model = Additive model

What is the background risk? 0.2
Observed excess risk:

- due to only exposure 0.3 - 0.2 = 0.1
- due to only factor A 0.4 - 0.2 = 0.2
- due to both 0.9 - 0.2 = **0.7**

Joint **observed** effect

Combined independent effects

Expected excess risk due to both 0.1 + 0.2 = **0.3**

On additive scale, there is evidence of effect modification because joint observed effect ≠ expected effect

Comparison of observed & expected effects. Example 1 (cont)

Risk of obesity according to the presence or absence of 2 variables

Exposure	**Factor A**	
	Yes	No
Yes	0.9	0.3
No	0.4	0.2

Measure of effect = risk ratio
Model = multiplicative model

NOTE: The effect of A is greater in the presence of exposure, and vice versa.

What is the background risk? 0.2

Observed risk ratio (RR)

- due to only exposure 0.3 / 0.2 = 1.5
- due to only factor A 0.4 / 0.2 = 2.0
- due to both 0.9 / 0.2 = **4.5**

Joint **observed** effect

Combined indep. effects

Expected risk ratio due to both 1.5 x 2.0 = **3.0**

Interaction term

Suggests effect modification with regard to <u>risk ratio</u>

Because joint observed RR ≠ expected RR (Obs RR = exp RR x **1.5**)

Reciprocal nature of effect modification

- For any given outcome and two predictor variables, it is a purely arbitrary decision which predictor variable will be the exposure, and which the potential effect modifier.

- Effect modification is reciprocal. In any of examples, the exposure and other factor (or variable) could have be labelled the other way round, and the same effect would still have been seen.

Positive and negative interaction

Synergism or positive interaction (interaction term > 1)

- Presence (or higher values) of Factor A strengthens the association between exposure and disease
- the combined effect is **greater** than the sum (or product) of the parts

Antagonism or negative interaction (interaction term < 1)

- Presence (or higher values) of Factor A weakens the association between exposure and disease.
- the combined effect is **less** than the sum (or product) of the parts

Ischemic heart disease mortality rates, smoking and age in British doctors study

Age (years)	*Annual death rate per 100,000 men*	
	Non-smokers	*Heavy smokers*
<45	7	104
45-54	118	393
55-64	531	1025
All <65	166	427

Source: Table V of Doll & Peto 1976, BMJ 2, 1525-1536
http://www.bmj.com/content/2/6051/1525

Ischemic heart disease mortality rates, smoking and age in British doctors study

Age (years)	*Annual death rate per 100,000 men*		*Odds ratio (heavy vs non-smokers)*
	Non-smokers	*Heavy smokers*	
<45	7	104	104/7 =14.9
45-54	118	393	393/118 = 3.3
55-64	531	1025	1025/531 = 1.9
All <65	166	427	2.7
Odds ratio (55-64 vs <45)	531/7 = 75.9	1025/104 = 9.9	

Summary of results

Association between smoking and CHD	OR	Conclusion
Crude assoc.	2.7	Odds of CHD 2.7 times higher among smokers compared to non-smokers
Stratified anal.		
<45	14.9	Among those aged <45, odds of CHD 14.9 times higher among smokers than non-smokers
45-54	3.3	Among those aged 45-54, odds of CHD 3.3 times higher among smokers than non-smokers
55-64	1.9	Among those aged 55-64, odds of CHD 1.9 times higher among smokers than non-smokers
Test of homogeneity	$p < 0.001$	Evidence against null hypothesis → heterogeneity → interaction between smoking and age in the association with CHD

What is confounding?

$\boxed{\text{Latin verb: confundere = to mix up, to confuse}}$

A situation in which the effects of two processes are not separated.

The distortion of the apparent effect of an exposure on risk, brought about by the association with other factors that can influence the outcome. (Last's Dict. Epi., 4th ed, 2001)

Potential alternative explanation(s)

- **CONFOUNDING** (confusing one thing with another) arises when there are **important differences between groups** being compared. The differences are **associated with the variable or factor of interest, and with the health outcome of interest**.
- Confounding must be considered in the evaluation of epidemiological associations.
- A **confounding variable** (**confounding factor**, or **confounder**) is a **third variable** that correlates (positively or negatively) with both the exposure and outcome**.**

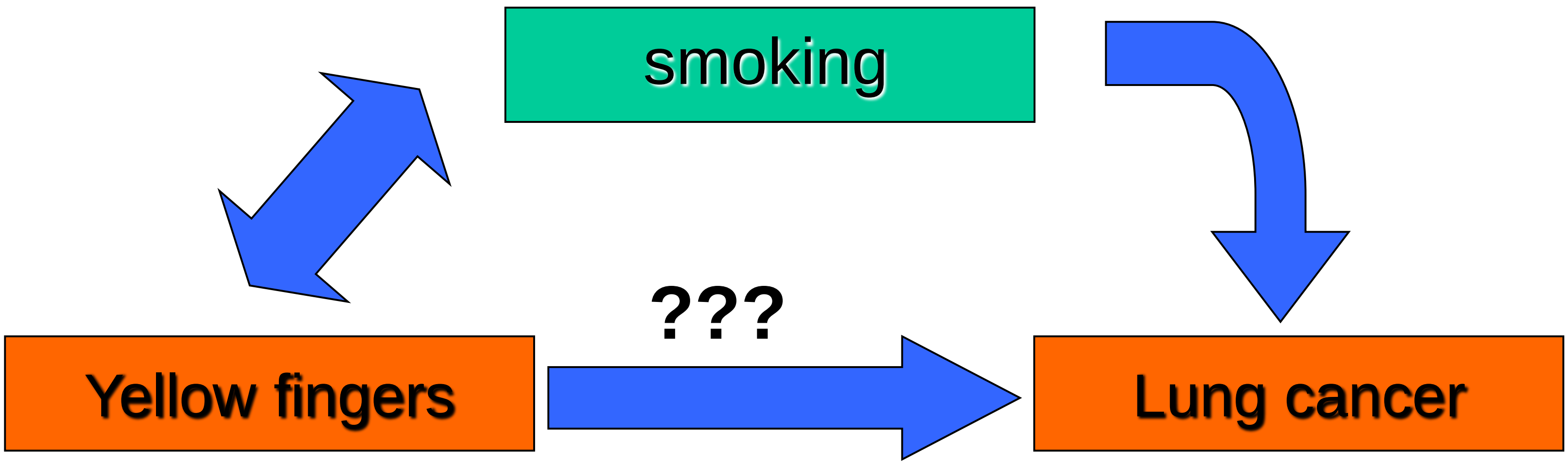
Statistical definition of a ‘confounder’

To be a confounder, a variable must:

- be related to exposure;
- be related to outcome;
- and <u>not</u> lie on the causal pathway between exposure and outcome

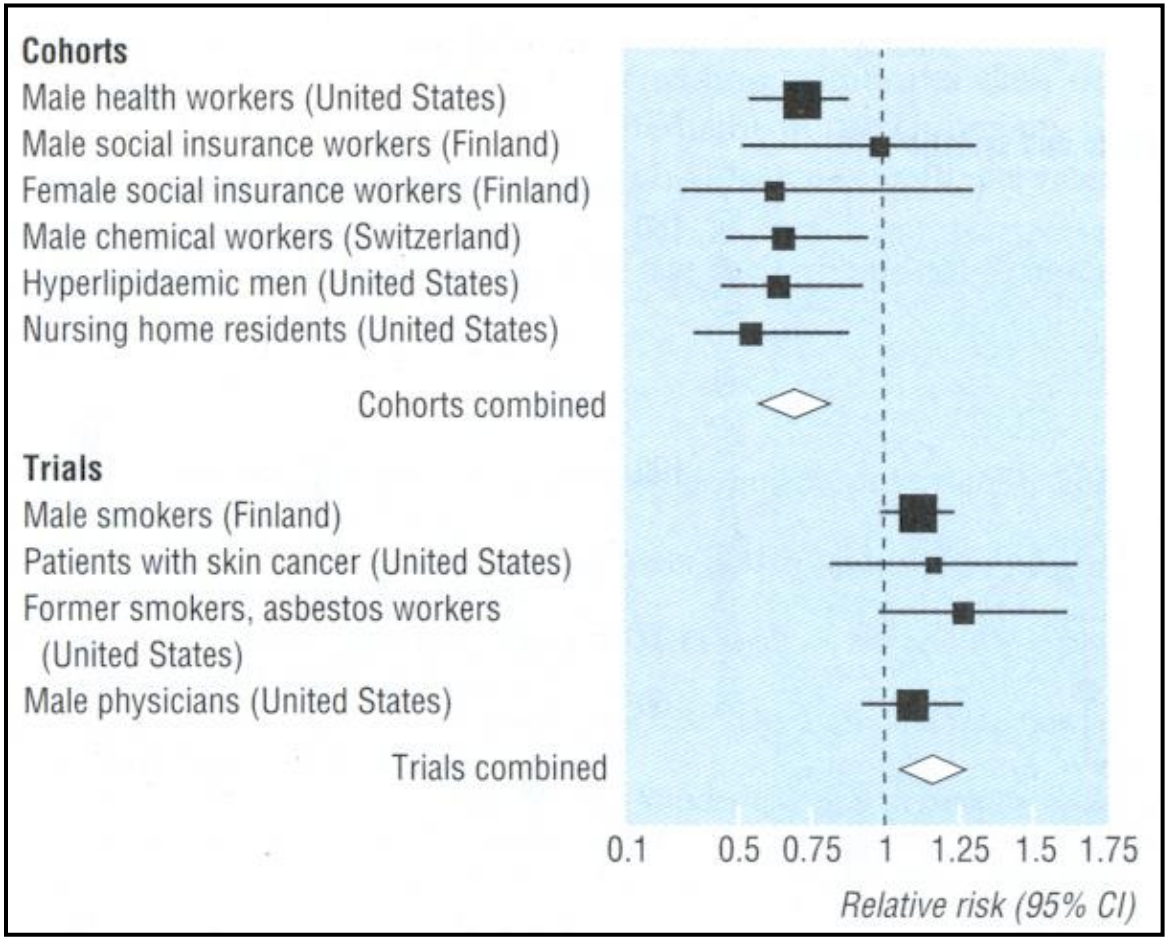
mediation

The confounding triangle: 2 exposures and an outcome



Davey Smith and Phillips BMJ 1992

β-carotene intake and cardiovascular mortality



Example of spurious findings produced by confounding

Egger et al BMJ 1998

The critic's view

"The disparity between observational studies and RCTs…is probably explained by a failure to appreciate the complex and important differences between adults with high vitamin concentrations and those with lower. High intake of antioxidant vitamins might not be causally related to cardiovascular and other diseases, but rather serves as a proxy indicator of a host of [protective] factors."

Lawlor et al Lancet 2004

Difference between systematic error and confounding

- Systematic error, as the name implies, is intrinsic to study design and methods – the result of weaknesses in scientific approach
- Confounding is intrinsic to the population and units of observation e.g. people, places, being studied – it is not a study artefact, it is ‘out there’

Dealing with confounding

Two ways to deal with confounding:

At the **design stage** or at the **analysis stage**

In both cases:

Confounding must be addressed at the design stage of a study. If **potential confounding factors** are not measured, the study will be weak, even uninterpretable.

1. Minimising by design

- **randomisation** e.g. drug trial
- **restriction** e.g. exclude ever-smokers
- **matching** e.g. case-control study

Minimising by design

Randomised controlled trials (RCT) have strongest protection against differences in the groups being compared

Confounding factors (measured and unmeasured) tend to be evenly distributed across groups

RCTs are the **gold standard** design to establish a causal relationship between cause and effect, but are not always feasible.

It is not ethical to randomise interventions thought to be harmful.

2. Controlling in analysis

- stratification
- standardisation
- multivariable analysis (adjustment)

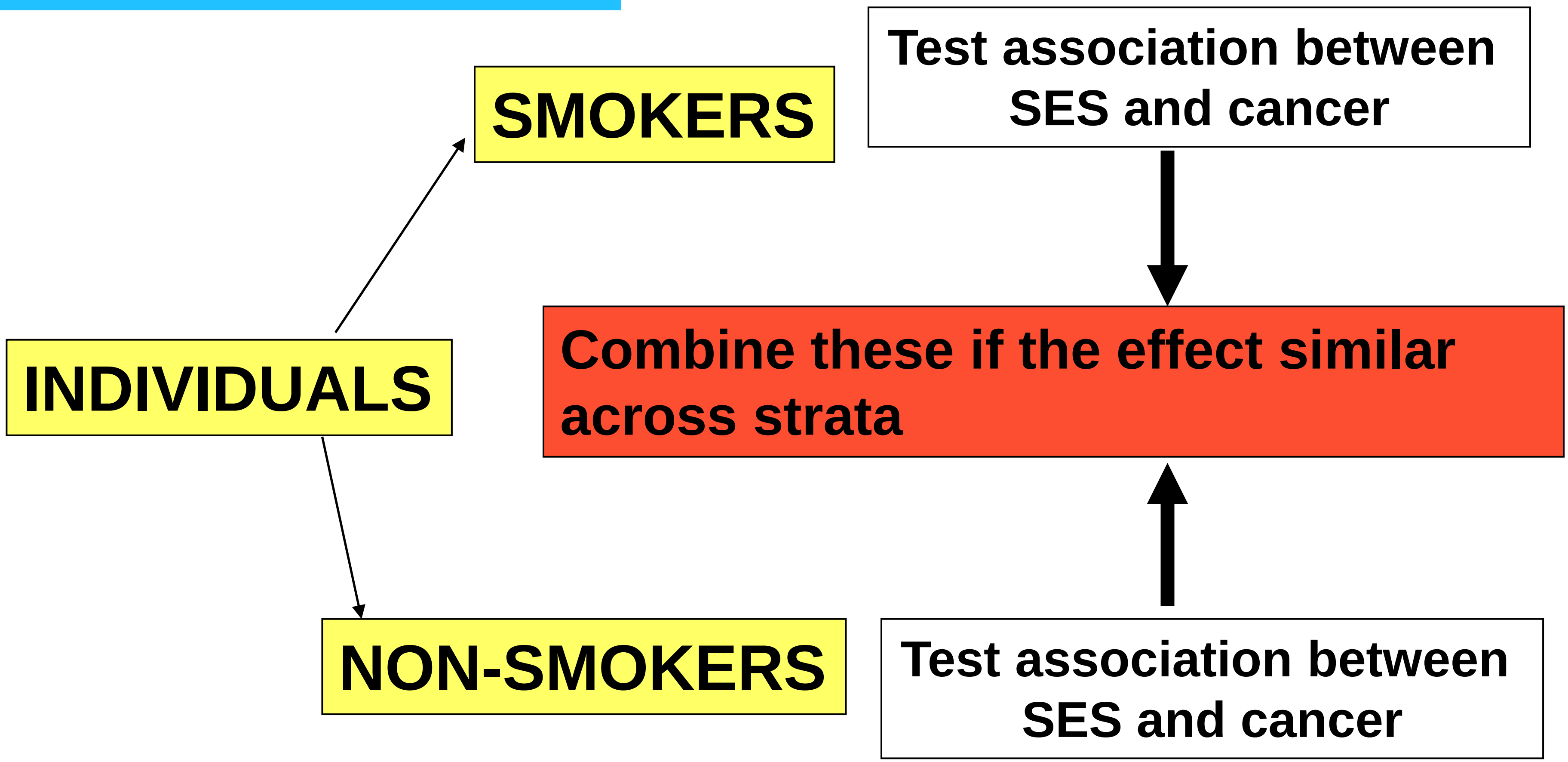
Controlling in analysis: stratification

Data analysed and results presented according to subgroups of related characteristics.

Confounding is indicated if an association between exposure and outcome is seen in the whole sample but not in the subgroups

e.g. examine the effect of SES in smokers and non-smokers

Study evaluating the association between SES and stomach cancer



Summary of results

Association between **SES and cancer**	OR	P-value	Conclusion
Crude assoc.	1.63	<0.001	Odds of cancer 1.63 times higher if low SES
Stratified anal.			
Smokers	1.44	<0.001	Odds of cancer 1.44 times higher if low SES
Non-smokers	1.40	0.006	Odds of cancer 1.40 times higher if low SES
Adjusted for smoking	1.43	<0.001	SES-cancer effect is confounded by smoking. OR=1.43 for low SES rather than 1.63

Multivariable analysis

Probably the most common method

The only feasible way to deal with several potential confounding factors at the same time

Unmeasured confounding factors or measurement error in confounding factors may lead to leftover confounding (residual confounding)

Multivariable analysis to test confounding

Is A a confounding factor for the effect of B on O?

- calculate a crude estimate of the effect of B on O e.g. age- and sex-adjusted HR, OR or RR
- repeat the analysis controlling for potential confounder A (age-, sex- and confounder-A adjusted HR, OR or RR)
- Compare the two estimates, if different, A is a confounder

Standardisation

- When comparing different populations, or different time periods, there is always the danger that age structure of the compared populations differ.
- Risk of most diseases increases with age.
- <u>Age</u> acts as a <u>confounder</u>.

Age standardised death rates: example

Cancer death rates are much lower in Mexico than in the UK.

One explanation is that risk factors are much less common in Mexico

Another explanation is the difference in cancer mortality is not genuine.

Cancer rates are higher in older people. The higher the proportion of older persons in a population, the higher the crude cancer mortality rate, even if age-specific death rates are the same.

Hypothetical example: cancer mortality rate (MR) in three populations with symmetrical, young and old population structures

Age group	*Symmetrical*		*Young*		*Old*	
	%	*MR*	*%*	*MR*	*%*	*MR*
25-44	33%	10	50%	10	20%	10
45-64	33%	100	30%	100	30%	100
65+	33%	500	20%	500	50%	500
Total	100%	203	100%	135	100%	282

Direct standardisation

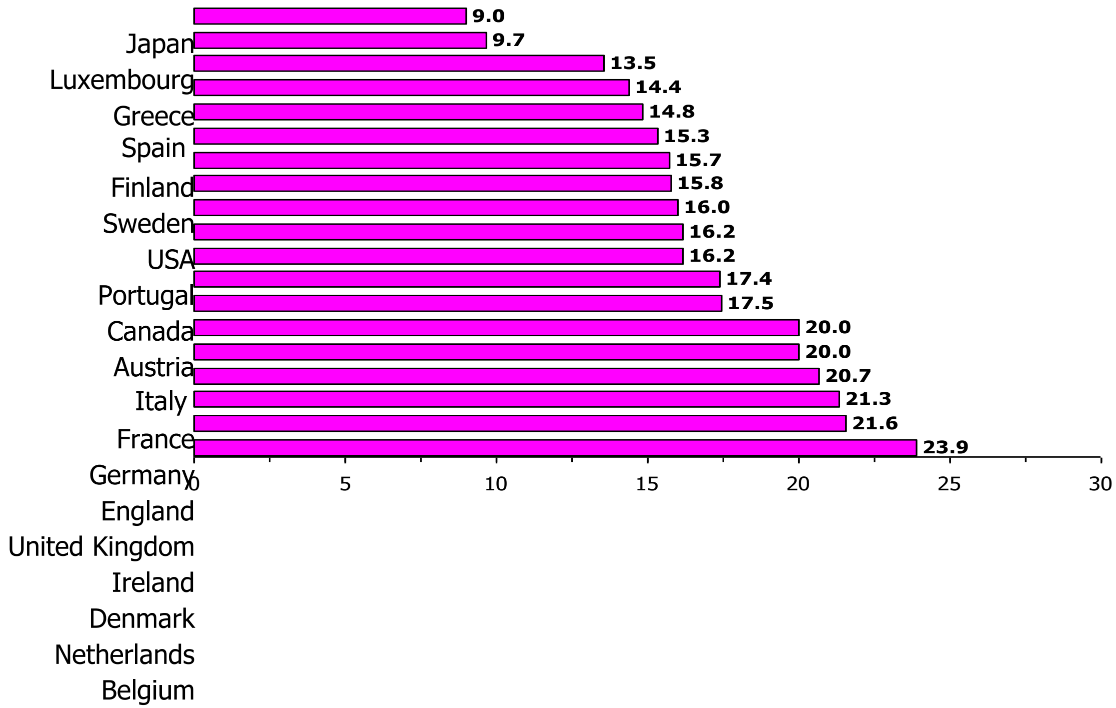
- Standardisation is based on a standard age structure, that of the whole sample or of some external population

- Calculate a weighted average of the age-specific death rates in each sub-group (country, region, social class, etc.), using as weights the proportions of the entire sample in age bands, e.g. age 30-34.9
- The adjusted (weighted) rate in each sub-group is comparable because it is the rate that would be observed if the age structure was the same in each group.

Age	2000 US Standard Million	2000 US Standard Population (Census P25-1130)	European Standard Million	World Standard Million
00 years	13,818	3,794,901	16,000	24,000
01-04 years	55,317	15,191,619	64,000	96,000
05-09 years	72,533	19,919,840	70,000	100,000
10-14 years	73,032	20,056,779	70,000	90,000
15-19 years	72,169	19,819,518	70,000	90,000
20-24 years	66,478	18,257,225	70,000	80,000
25-29 years	64,529	17,722,067	70,000	80,000
30-34 years	71,044	19,511,370	70,000	60,000
35-39 years	80,762	22,179,956	70,000	60,000
40-44 years	81,851	22,479,229	70,000	60,000
45-49 years	72,118	19,805,793	70,000	60,000
50-54 years	62,716	17,224,359	70,000	50,000
55-59 years	48,454	13,307,234	60,000	40,000
60-64 years	38,793	10,654,272	50,000	40,000
65-69 years	34,264	9,409,940	40,000	30,000
70-74 years	31,773	8,725,574	30,000	20,000
75-79 years	26,999	7,414,559	20,000	10,000
80-84 years	17,842	4,900,234	10,000	5,000
85+ years	15,508	4,259,173	10,000	5,000
Total	1,000,000	274,633,642	1,000,000	1,000,000

http://seer.cancer.gov/stdpopulations/stdpop.19ages.html

Directly standardised death rates from breast cancer Selected countries 1998*, Females aged under 65



Age standardised death rate per 100,000 population

Rates are calculated using the European Standard Population to take account of differences in age structure.

* Data for 1998 except for Belgium 1995.

Brstcerv.ppt (02/2000)

Source: WHO Annual of Statistics, HFA Indicators (ICD 174)

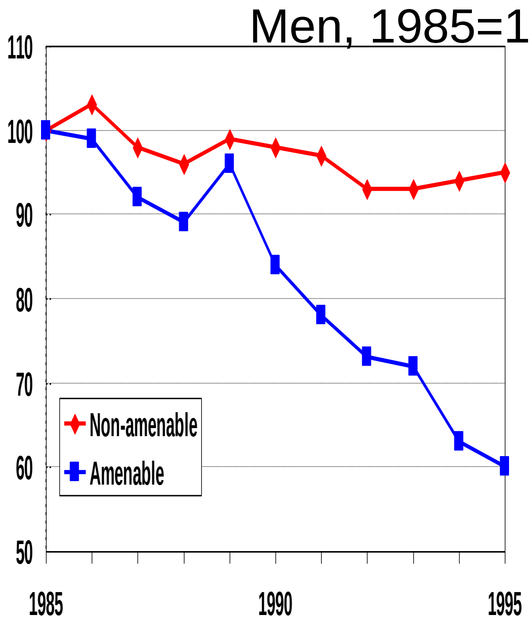
Indirect standardisation

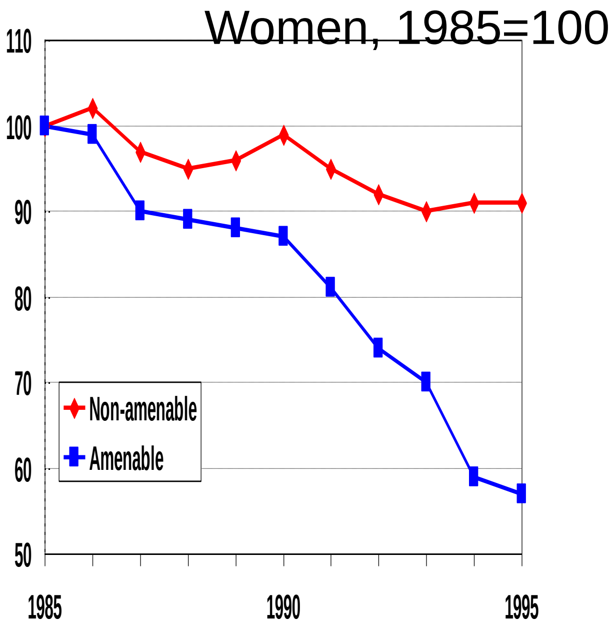
- Standardisation is based on age-specific disease rates in the reference population (group), weighted by the age structure of the study population
- Calculate the expected number of deaths in the group of interest that would be obtained if it experienced the same age-specific rates as the reference group
- The adjusted (weighted) number of deaths in the group of interest is compared to the observed number:

Standardised mortality ratio (SMR)

$$= \frac{\text{Observed deaths} * 100\ \%}{\text{Expected deaths}}$$

Mortality from amenable and non-amenable causes Czech Republic 1985-1995





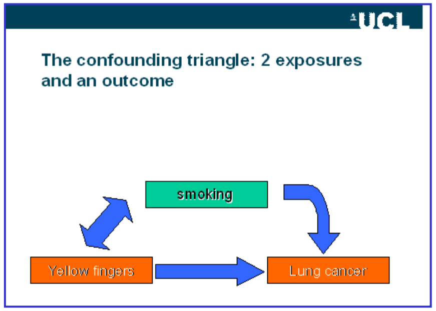
Blazek & Dzurova, 2000

Further reading for those wanting to know more about age standardisation

M Bartley, Health inequalities, 2nd edition pp 48-60, 70-73

R Bhopal, Concepts of epidemiology, 2002 pp194-9

Confounding - summary



- Condition for confounding – risk factor and confounding factor are correlated with each other, and both are correlated with outcome
- Confounding leads to spurious findings
- Confounding should be considered at the design stage of all studies. It can be minimised by design
  - **randomisation**
  - **matching**
- Or in analysis, if the necessary measurements are available
  - **stratification**
  - **multivariable adjustment**

Residual confounding

- **Last 4th ed, 2001**

Confounding that persists after unsuccessful attempts to adjust for it. The sources of residual confounding are insufficiently detailed information, improper categorization, and misclassification of one or more confounding variables. It is a variable-specific concept.

"we only rarely have the information needed to fully adjust for confounding"

Olsen and Basso AJE 1999

Calculating attenuation

If a risk estimate is unaffected by controlling (adjusting) for potential confounders then it is **robust**

If the risk estimate is largely abolished by adjustment it is **not an independent risk factor**

The extent to which an effect is reduced is called the **attenuation**

$$\textbf{Attenuation} = \frac{\textbf{RRunadj} - \textbf{RRadj}}{\textbf{RRunadj} - 1} \times 100\%$$

Confounding – yes or no?

A rule of thumb: if an effect is attenuated by 10% or more, then confounding is probably important

Hazard ratio for diabetes per doubling of serum CRP at age 49 with sequential adjustments. 13 year follow-up

Model (279 cases, total N=4291)	HR	95% CI	P
Age, sex, CRP>10 mg/L	1.40	(1.29-1.51)	<0.0001
+ occupational status	1.39	(1.28-1.50)	<0.0001
+ prevalent CHD, infectious symptoms	1.39	(1.28-1.50)	<0.0001
+ BMI categories, waist circumference	1.22	(1.11-1.33)	<0.0001
+ systolic BP, diastolic BP, BP treatment	1.20	(1.10-1.32)	<0.0001
+ serum HDL-cholesterol, TG	1.17	(1.07-1.28)	0.001

Whitehall II study

CRP-T2D effect attenuated by 53% on adjustment

Brunner et al PLoS Med 2008

Confounding vs. interaction

Confounding

- Alternative explanation
- Distorts the “truth”
- Efforts to remove it to get nearer to the “truth”
- When present, stratum specific effects are similar to each other but different from the overall crude effect.

Effect modification

- One factor modifies effect of another factor
- It is genuine, not artefact
- Property of the relationship between factors
- We should detect and describe it but not remove it.

Difference between interaction and confounding

- **Confounding**: **stratum-specific effects** of the risk factor of interest will be smaller (usually) but they **will be similar**

- **Interaction/effect modification:** also examined by stratification. As the label '**effect modification**' indicates, the **stratum-specific effects will be different**. If very different, this is called strong interaction.

Steps in testing an association

1. Is there an association?
2. If yes, is it due to confounding?
3. If not, is the association similar in strata formed on the basis of potential effect modifiers?

4a. If yes, there is no effect modification/interaction

4b. If no, effect modification/interaction is present

Conclusions: association does not mean causation

Associations are often observed: when alternative explanations (chance, bias, confounding) have been considered and rejected, the association may be causal

Strength of association (effect size), replication and biological plausibility are further considerations

Note that the precise biological mechanisms linking smoking and lung cancer were not known 40 years ago, however the evidence on other dimensions of the link was powerful

These issues will be explored in the session on causality