How do we know that smoking causes lung cancer?

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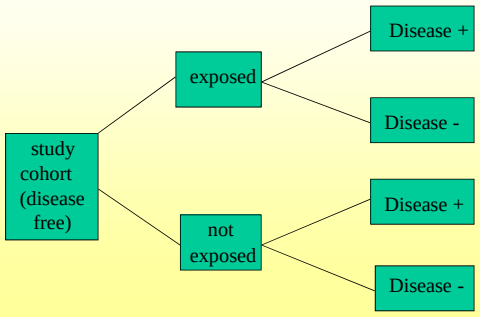
Objectives

- Cohort studies
  - Prospective and historical
  - Strengths and weaknesses
- Measuring risk
  - Absolute risk, relative risk
  - Attributable risk, population attributable fraction
- Causality
  - Criteria for causal inference
  - Using genetic epidemiology

Prospective cohort study: design



Conducting a cohort study: five steps

- Select cohort population
- Measure exposure
- Follow-up
- Measure disease outcome
- Estimate disease risk associated with exposure

Selection of exposed and non-exposed groups

- Common exposures eg smoking, diet
  - General population cohort
  - Internal comparisons of exposure status
- Rare exposures
  - Cohort defined by geography, environmental exposure/disaster
    - Montserrat volcano
  - Cohort defined by occupation eg asbestos workers
    - Internal comparison (other workers in same industry)
    - External comparison (workers in different industry)

Measuring exposure to risk factors

- Records
  - Hospital eg birth weight
  - Occupational eg dust exposure
- Environmental monitoring
  - dust mite, NO_2 levels in air
- Lifestyle questionnaire
  - smoking, diet, occupation
- Clinical/biochemical/molecular measurement
  - Body Mass Index, nutrient biomarker, genotype

Follow-up

- A challenge!
  - Chronic diseases have long latent period
- Optimising follow-up
  - stable population eg Isle of Wight, Framingham
  - motivated population eg health personnel
  - regular contact and tracing
  - important to minimise BIAS

Measuring outcome

- Records
  - Mortality
    - Death certificates
  - morbidity
    - Health care records
- Interview / examination
  - questionnaire (standardised / validated)
    - chronic bronchitis
    - asthma
  - clinical/biochemical
    - lung function, blood pressure, blood sugar

Categorising exposure for analysis

- "Natural" categorical variable
  - Smoker
    - Yes/No
    - Never/Ex/Current
- Categorical variable from continuous variable
  - body mass index
    - <20; 20-24.99; 25-29.99; ≥30
    - Quantiles
- More than two categories is more informative
  - "Dose-response"

Defining outcome for analysis

- Binary outcome: Yes/No
  - Death; asthma
    - Analyse risk
- Continuous outcomes eg lung function, bp
  - Define "disease" (Yes/No) using cut-off
    - Eg COPD: $FEV_1/FVC<70\%$
    - Analyse risk
  - Keep continuous outcome
    - Analyse difference in mean outcome between exposure groups

Comparing disease risk in exposed and non-exposed (1)

- Count number of new cases of disease in each exposure group
- Risk (incidence) of disease
  = number of new cases during defined period / total number at risk at start of period
- Relative risk (risk ratio) = risk in exposed / risk in non-exposed

Calculating the relative risk

	Develop disease		
	Yes	**No**	**Total**
Exposed			
Yes	a	b	a+b
No	c	d	c+d

Relative risk = $\frac{a/(a+b)}{c/(c+d)}$

Obesity and adult-onset asthma

- Nurses Health Study, USA
- 85, 911 participants aged 26-46 in 1991
- Body Mass index measured at baseline
- Followed up for 4 years
- Outcome measure: incident asthma

Arch Intern Med 1999; 159: 2582-8

Obesity and adult-onset asthma

	Develop asthma		
	Yes	**No**	**Total**
Obese			
Yes (BMI ≥30)	398	10,805	11,203
No	1,198	73,510	74,708

Relative risk = $\frac{398/11,203}{1,198/74,708}$ = **2.22 (1.98 - 2.48)**

Obesity and adult-onset asthma

BMI	**Adjusted RR (95% CI)**
< 20	0.9 (0.7 - 1.1)
20-22.4	1.00
22.5-24.9	1.1 (1.0 - 1.3)
25.0-27.4	1.6 (1.3 - 1.9)
27.5-29.9	1.7 (1.4 - 2.0)
≥30	2.7 (2.3 - 3.1)

Paracetamol and adult-onset asthma: Nurses Health Study

Frequency of use (days per month)	*Adjusted RR (95% CI)*	
None	1.0	
1-4	1.27	(0.96 to 1.66)
5-14	1.43	(0.99 to 2.07)
15-21	1.78	(1.04 to 3.04)
22+	1.53	(0.95 to 2.46)

P trend = 0.006

Leisure time physical activity and risk of death

- Copenhagen City Heart Study, Denmark
- 7,023 men and women aged 20-79
- Physical activity measured in 1976-8 and 1981-3
- 1424 men and 1301 women died during 17-year follow-up

AJE 2003; 158: 639-44

Physical activity and mortality risk

Level of activity at 2nd exam in those who had low activity at first exam	Men RR* (95% CI)	Women RR* (95% CI)
Low	1.00	1.00
Moderate/high	0.64 (0.50, 0.81)	0.74 (0.58, 0.95)

*Adjusted relative risk

Comparing disease risk in exposed and non-exposed (2)

- **Rate**

  = number of new cases during defined period
  total "person time at risk" during period

- **Relative rate** (rate ratio) = rate in exposed
  rate in non-exposed

Nut consumption and CHD

- Nurses Health Study, USA
- 1980-1994
  - 1,132, 229 person years of follow-up
- Dietary questionnaire at baseline
  - nut consumption
- 1255 new cases of coronary heart disease

Hu et al, BMJ 1998; 317: 1341-45

Nut consumption and CHD

Freq of eating nuts	**Cases**	**Person years**	**RR* (95% CI)**
Never	542	391,918	1.0
<2x/week	584	579,805	0.91 (0.81,1.03)
2-4x/week	85	102,175	0.78 (0.61,0.99)
≥5x/week	44	58,330	0.66 (0.47,0.93)

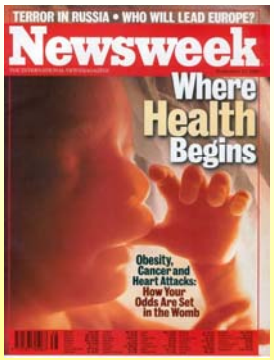
*adjusted Relative Rate

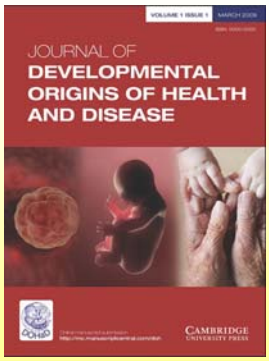
P trend 0.005

Prospective cohort studies

- Strengths
  - study rare exposure
  - study multiple effects of one exposure
  - demonstrate temporality
  - minimise bias in exposure measurement
  - measure incidence
- Limitations
  - inefficient for rare diseases
  - costly and time-consuming
  - potential bias from losses to follow-up

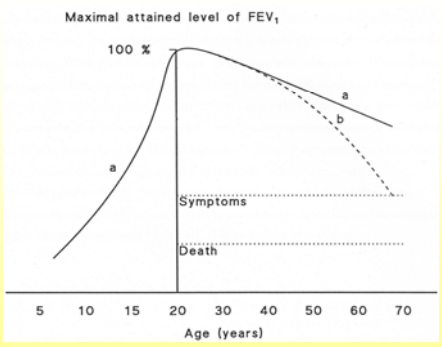
A revolutionary new idea….



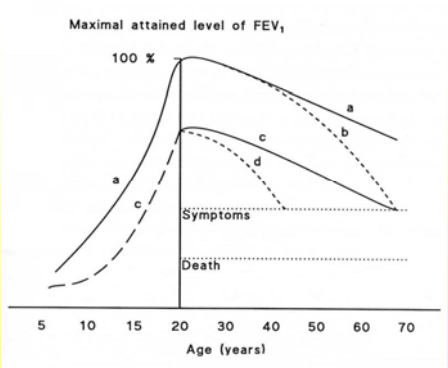


Historical cohort studies

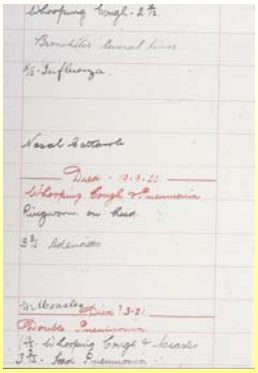
- How do they differ from prospective cohort studies?
  - Outcome of interest has already occurred when study begins, therefore efficient for diseases with long latent periods
- How do they differ from case control studies?
  - Individuals selected according to documented exposure status (historical records)



Speizer and Tager, Epidemiol Rev 1979;1: 124-42.



South Derbyshire: born 1917-1922

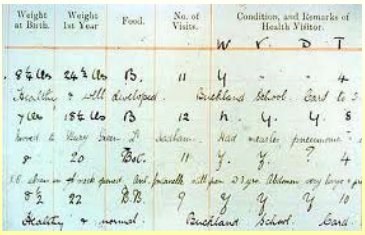


Mean FEV_1 (l), adj. for age and height, among D'shire men and women aged 67-74 (n=618)

	Mean FEV_1			
	Pneumonia <2yrs		**Diff in FEV_1 (95% CI)**	
	No	*Yes*		
Men	2.35	1.69	-0.65	(-1.02, -0.29)
(n)	(315)	(13)		
Women	1.70	1.52	-0.19	(-0.51, +0.14)
(n)	(279)	(7)		

Am J Respir Crit Care Med 1995; 151:1649-52

Hertfordshire: born 1920-1930

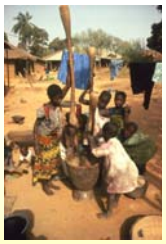


Mean FEV_1 (l), adjusted for age and height, among Herts men aged 59-67 (n=639)

	Infant bronchitis/pneumonia	
Birth wt (lbs)	*Absent*	*Present*
≤5.5	2.39 (22)	1.81 (4)
-6.5	2.40 (70)	2.23 (10)
-7.5	2.47 (163)	2.38 (25)
-8.5	2.53 (179)	2.33 (12)
-9.5	2.54 (103)	2.36 (5)
>9.5	2.57 (43)	2.36 (3)

BMJ 1991; 303:671-5

And so to Africa……



Guinea-Bissau, 1994; children who survived severe measles epidemic in 1979

Atopy according to measles history in 14-21year-olds in Bissau (n=262)

	Atopy %	OR* (95% CI)
Measles		
No (n=129)	25.6	1.0
Yes (n=133)	12.8	0.36 (0.17, 0.78)

* controlling for potential confounders

Lancet 1996; 347: 1792-6.

Why is it potentially misleading just to report the relative risk or odds ratio?

- The RR or OR only tells us about the aetiological, not public health, importance of an exposure
- The RR or OR alone may lead to “hype” by the media and unnecessary alarm for the public

How important are findings for Public Health?

- How many excess cases among exposed can be attributed to exposure?
  - Attributable risk
- What proportion of disease in the population can be attributed to exposure?
  - Population Attributable Fraction
- Gives an idea of scope for prevention if exposure removed (assuming causal relation)

Nurses' Health Study: Risk of primary PE by postmenopausal hormone use (1)

	Cases	Person-years	RR* (95% CI)
HRT use			
Never	27	320,339	1.0
Current	22	155,669	2.1 (1.2 to 3.8)

* adjusted relative rate

(Grodstein et al. Lancet 1996)

Nurses' Health Study: Risk of primary PE by postmenopausal hormone use (2)

HRT use	Cases	Person-years	Absolute rate
Never	27	320,339	8 /100,000 /yr
Current	22	155,669	14 /100,000 /yr

Attributable Risk = risk in exposed - risk in non-exposed
= 6 cases /100,000 women /year

The importance of reporting absolute and attributable risks

- Puts research findings (RRs and ORs) into perspective
  - For policy makers
    - Do we need to do anything about this risk factor?
    - "all policy decisions should be based on absolute measures of risk; relative risk is strictly for researchers only" (Geoffrey Rose, 1991)
  - For the public
    - Should we be worried about this risk factor?
- Enables fuller interpretation and better communication of risk

Does asthma begin in utero?

- Early presentation

- Prenatal risk factors
  - Maternal smoking in pregnancy
  - Antibiotic use in pregnancy
  - Infections in pregnancy
  - Complications of pregnancy
  - Mode of delivery
  - Gestational age at birth
  - Anthropometry at birth

Avon Longitudinal Study of Parents and Children (ALSPAC)

- Prospective study of 14,541 pregnancies
  - 14,062 live births
  - 13,988 survived to 1 year
- Eligible
  - EDD 1.4.91 - 31.12.92
  - resident in Bristol health districts
- Enrolled
  - as early as possible in pregnancy
  - 85-90% of those eligible

Data collected

- Maternal and child questionnaires
  - Prenatal nutrition
    - Biomarkers
    - FFQ in late pregnancy
  - Other prenatal/childhood exposures/confounders
- DNA on 10,000 mothers and 10,000 children
- Respiratory and atopic phenotypes
  - Early childhood wheezing phenotypes
  - Asthma, wheezing and atopic disease at 6 years
  - Skin test reactivity and total IgE at 7 years
  - Lung function and BR (methacholine) at 8-9 years

Paracetamol use in late pregnancy and prevalence of wheezing at 30-42 months

Frequency	n	%
Never	608/5134	11.8
Some days	561/3725	15.1
Most days/daily	26/88	29.5

Paracetamol use in late pregnancy and risk of wheezing at 30-42 months

(Thorax 2002; 57: 958-63)

Frequency	OR (95% CI)	Adj OR (95% CI)
Never	1.00	1.00
Some days	1.34 (1.18, 1.52)	1.12 (0.98, 1.28)
Most days/daily	3.17 (1.99, 5.05)	2.10 (1.30, 3.41)*

*P=0.003

Paracetamol in pregnancy and childhood wheezing: Interpretation


MIRROR (LONDON, UK) 30th October 2002

PREGNANT MUMS USING PAINKILLERS DOUBLE RISK OF ASTHMA IN BABIES DOC WARNS OF LINK

- BUT
  - Population Attributable Fraction = ~1%

Causal inference in observational studies

- Bradford Hill "criteria"
  - Size of effect
  - Dose response
  - Consistency
  - Biological plausibility
  - Temporality

Strengthening causal inference

- Gene by environment interaction
  - Modification of paracetamol effect by gene variants influencing toxicity: ↑ bio plausibility
    - nb human data lacking
- Glutathione-S-transferase
  - GSTT1, GSTM1, GSTP1
  - conjugates NAPQI with GSH
- Nrf2
  - Knockout mice sensitive to paracetamol toxicity
  - Disruption of Nrf2 leads to increased allergic inflammation in a mouse model of asthma

Paracetamol use in early pregnancy and asthma risk stratified by maternal Nrf2

	Adj OR*	**95% CI**	**P**
C:C (n=3754)	0.99	0.81 to 1.21	0.91
T:C/T:T (n=1137)	1.73	1.22 to 2.45	0.002
		Interaction	*0.02*

**Per category of exposure*

No interaction with child Nrf2 genotype

Risk of impaired lung function by maternal smoking and GSTM1

Overall: -0.043* (-0.069 to -0.016); P trend 0.0017

Child genotype

GSTM1 present: -0.017 (-0.06 to 0.027)

GSTM1 null: -0.061 (-0.10 to -0.02)

Maternal genotype

GSTM1 present: -0.019 (-0.07 to 0.033)

GSTM1 null: -0.054 (-0.10 to -0.005)

*Age/height-adjusted deficit (95% CI) in FEF_{25-75} (SDs) associated with smoking (per category increase)

Quiz!

Which study design would be optimal in order to study the following?:

	Case-control	Cohort
Rare disease		
Rare exposure		
Multiple exposures		
Multiple outcomes		
Natural history of disease		
Disease rate		

Quiz answers

Which study design would be optimal in order to study the following?:

	Case-control	Cohort
Rare disease	✓	x
Rare exposure	x	✓
Multiple exposures	✓	**(✓)**
Multiple outcomes	x	✓
Natural history of disease	x	✓
Disease rate	x	✓

Bored to death……..?

IJE 2010

- Follow-up of Whitehall civil servants
  - Higher cardiovascular mortality in those reporting ‘a great deal’ of boredom at baseline compared with those who were ‘not bored at all’

Essential reading Week 7

- Relevant to this lecture (cohort studies)
- Barker D, Cooper C, Rose G. Epidemiology in medical practice. Chapter 5.
- Doll R, Peto R. BMJ 1976; 2: 1525-36.
- (Doll R. Am J Respir Crit Care Med 2000; 162: 4-6.)
- **NB** Please read the above and the Introduction to the tutorial **BEFORE** the seminar.