EPIDEMIOLOGY

The study of the distributions (rates) and determinants (causes) of diseases and injuries in human populations.

Cholera epidemic and water sources in London, 1854*

Water supplier	*Houses*	*Cholera deaths*	*Rate per 10,000 houses*
Southward & Vauxhall Co.	40,046	1253	315
Lambeth Co.	26,107	98	37
Others	256,423	1422	59

*Gardner M. *Arch Environ Health* 1988;43:102-8

Types of epidemiologic studies

- Case series
- Cross-sectional
- Prospective cohort
- Retrospective cohort
- Case-control
- Case-crossover (variant of case-control)

Case series

Report of case cluster, usually rare disease

Example: Angiosarcoma of the liver in workers in polyvinylchoride manufacturing plant (Creech and Johnson, 1974)

Advantages of case series reports

- May identify new occupational or environmental hazard (e.g., vinyl chloride and angiosarcoma, asbestos and mesothelioma)
- Can lead to intervention

Limitations of case series reports

- Only anecdotal information (reporting bias?)
- May be spurious cluster ("Texas sharpshooter phenomenon")

Prospective cohort studies

Follow-up of exposed and non-exposed cohorts, with comparisons of disease rates of changes in physiological function

Prospective cohort study of spontaneous abortion among women semi-conductor industry workers*

		Spontaneous abortions		
Exposure	*No. of pregnancies*	*Number*	*Percent*	*RR (95%CI)*
Ethylene glycol ethers	3	3	100.0	2.0 (1.5-2.8)
Fluorides	14	8	57.1	1.1 (0.7-2.0)
Neither	38	19	50.0	1.0 [ref]

*Eskenazi B, et al. (1995) *Am J Ind Med* 28:833-46.

Longitudinal study of lung function change in Shanghai textile workers*

- Study groups: Cotton factory workers exposed to endotoxin (n=408) and silk factory reference workers (n=417)
- Follow-up 1981-2001
- Outcomes: Longitudinal decline in lung function (FEV1), cross-shift and annually, and respiratory symptoms

*Wang X, et al. (2008) *Am J Respir Crit Care Med* 177:316-20

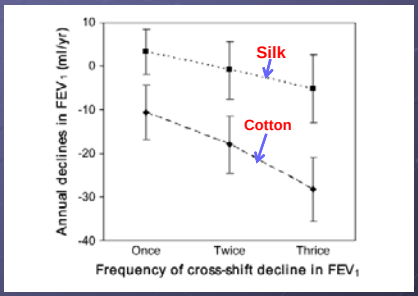
TABLE 2. MEANS (SD) OF ΔFEV_1 IN THREE SURVEYS AMONG COTTON AND SILK GROUPS

	Cotton			Silk		
	N	ΔFEV_1 (*ml*)	ΔFEV_1 (%)	n	ΔFEV_1 (*ml*)	ΔFEV_1 (%)
1981	391	−57.9 (154.9)*	−1.98 (5.49)*	376	−5.6 (131.9)	−0.02 (4.82)
1986	284	−47.8 (135.3)†	−1.77 (6.62)†	307	−26.1 (115.9)	−0.87 (4.22)
1992	222	−54.2 (120.9)‡	−1.87 (4.42)§	225	−20.2 (98.9)	−0.69 (3.78)
1996	119	−66.6 (141.5)	−2.15 (5.51)	0	—	—

Definition of abbreviation: ΔFEV_1 = cross-shift change in FEV_1.
Calculations are based on all available data at each survey.
* $P < 0.0001$.
† $P = 0.04$.
‡ $P = 0.001$.
§ $P = 0.003$ in comparison with silk workers.

*Wang X, et al. (2008) *Am J Respir Crit Care Med* 177:316-20

Annual decline in FEV1 over 15 years in relation to frequency of cross-shift change: Shanghai textile workers*



*Wang X, et al. (2008) *Am J Respir Crit Care Med* 177:316-20

Advantages of prospective cohort studies

- Logic similar to experiment
- Well suited to short-term health outcomes
- Eliminates prevalent cases at outset of follow-up

Limitations of prospective cohort studies

- Not practical for most studies of chronic diseases (need very large cohort and long follow-up)
- Practical difficulties updating exposure data prospectively

Historical cohort studies

- Enumeration of cohort at a point in the past
- Follow-up to the present for health outcome incidence

Cause-specific mortality among 5777 male workers in the French hard-metal industry, 1968-1991*

Cause of death	Observed	Expected†	Obs/Exp
All causes	591	644.6	0.92
Circulatory diseases	139	158.3	0.88
Respiratory diseases	22	29.21	0.75
Cancers (all sites)	209	203.1	1.03
lung cancer	61	47.22	1.29
pleural cancer	3	1.39	2.16
larynx cancer	7	12.80	0.55
esophagus cancer	19	15.30	1.24
oral cancer	23	19.51	1.18
bladder cancer	4	5.43	0.74

* Moulin, et al., Am J Epidemiol 1998; 148:241-8

† Expected based on rates for French men

Lung cancer among U.S. steelworkers*

Job category/ Duration (yrs)	Obs	Exp	Obs / Exp
All coke plants/ ≥ 5	29	13.6	2.1
Non-coke oven/ ≥ 5	1	5.3	0.2
All coke oven / ≥5	27	7.6	3.6
Coke oven, never topside /<5	6	4.1	1.5
Coke oven, topside / <5	6	2.1	2.9
Coke oven, topside / ≥5	15	1.5	10.0

Lloyd W, *J Occup Med* 1971;13:53-68

Advantages of historical cohort studies

- Permits study of rare, chronic diseases (follow-up over historical time)
- Exposure data collection simplified relative to prospective follow-up

Limitations of historical cohort studies

- Incomplete cohort enumeration common problem
- Historical exposure data often sparse or absent
- Data on potential non-occupational confounders seldom available

Case-control design

Comparison of past exposures of persons with index disease (cases) with exposures of persons free of index disease at times when cases occurred (controls)

Case-control studies

- Nested within defined occupational cohort
- Community – (registry-) based

Nested case-control study of lung cancer and diesel exhaust among US underground non-metal miners*

Cumulative REC exposure (µg/m3-yrs)**	Cases	Controls	OR (95% CI)***
0-<81	29	92	1.0 [ref]
81->325	29	52	2.5 (1.0-6.0)
325-<878	29	69	2.4 (1.0-5.8)
≥878	29	51	5.1 (1.9-13.9)

*Silverman DT et al. *J Natl Cancer Inst* 2012:104:1-14

**Respirable elemental carbon, lagged 15 years
***Odds ratio (95% confidence interval), adjusted for age, smoking, history of non-cancer resp. disease

Multiple risk factor evaluation in multi-country European population-based case-control study of Parkinson's disease *

Risk factor	OR (95% CI)
Ever smoked	0.5 (0.4-0.6)
River or well water source	1.2 (1.0-1.4)
Knocked unconscious >1 time	2.5 (1.8-3.6)
Solvents**	0.9 (0.7-1.1)
Pesticides**	1.4 (1.1-1.9)
Iron**	1.1 (0.8-1.6)
Manganese**	0.9 (0.6-1.3)

*Dick FD, et al. *Occup Environ Med* 2007;64:673-80
**High vs. none

Advantages of case-control design

- Permits studies of rare disease
- Can have multiple case groups and common control group ("case-cohort" design)
- Obtaining data on confounders more feasible than in cohort studies

Limitations of case-control design

- Reliance on questionnaire data for exposures in community-based studies
- Selection of controls may be biased
- Unequal participation rates and data quality may differ for cases and controls

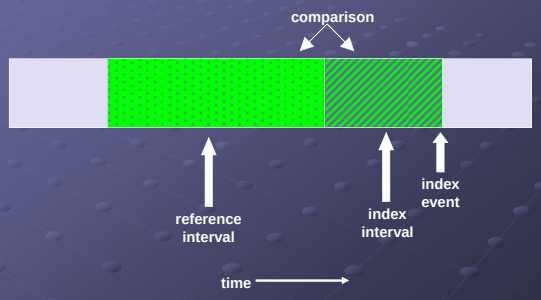
Case-crossover design

- "Case only" study, i.e., cases serve as their own controls (special type of matched case-control study)
- Comparisons of exposures during cases' "index" intervals with exposures during "reference" intervals

Index and reference intervals in case-crossover design

- Index interval: time period preceding disease (or injury) onset when exposures may have etiologic relevance
- Reference interval: time interval of typical exposure, usually preceding disease onset
  - Unidirectional (before index interval)
  - Bidirectional (before and after index interval)

Case-crossover design: unidirectional reference interval



Case-crossover design: bidirectional reference interval

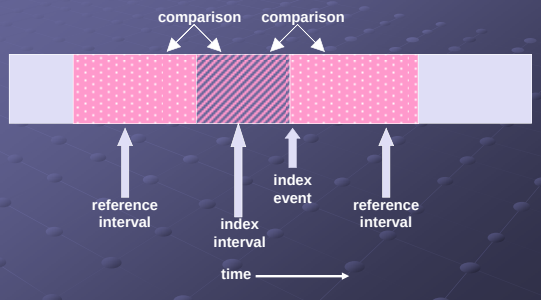


Table 2 Transient exposures and relative risks of occupational acute traumatic hand injury, northeastern USA, 1997–2000

Exposure	One or more exposures: No. of subjects exposed at time of injury	Average no. of hours exposed in month prior to injury‡	No. of subjects exposed in month prior to injury	RR*	95% CI*
Unusual performing equip/materials	161	4.5	276	11.0	9.4 to 12.8
Wearing gloves	216	53.1	771	0.4	0.3 to 0.5
Different work method	107	2.2	202	10.5	8.7 to 12.7
Doing an unusual task	127	3.9	356	6.7	5.7 to 8.0
Being distracted	147	5.6	558	5.3	4.6 to 6.1
Being rushed	290	29.2	769	2.4	2.1 to 2.7
Feeling ill	25	2.4	263	1.9	1.3 to 2.8

*RR, relative risk; CI, confidence interval.
‡The estimated average individual hours of exposure includes subjects who report zero hours of each exposure and takes into account individual differences in hours worked including overtime.

Source: Sorock G, et al. *Occup Environ Med* 2005;61:305-11

Advantages of case-crossover design (relative to conventional case-control design)

- Suitable for studies of acute onset outcomes
- Logical/convenient choice of controls
  (e.g., Who would controls be in a study of acute injuries? How would they be identified)
- Better control of confounding by fixed variables (e.g., medical history, genetics)

Cross-sectional design

Comparison of prevalence of disease by exposure level

- One time cross-sectional study
- Repeated measures survey
  (i.e., becomes cohort study)

Respiratory symptoms and endotoxin exposure in Dutch wastewater workers*

Endotoxin level (EU/mg/m3)	No. subjects	Lower resp. and skin symptoms	Flu-like symptoms	Upper resp. symptoms
<50 (ref)	141	1.0+	1.0	1.0
51 – 200	63	1.1 (0.5 – 2.4)	1.2 (0.6 – 2.3)	1.6 (0.9 – 3.0)
>200	12	1.8 (0.6 – 5.2)	2.0 (0.8 – 4.9)	1.8 (0.8 – 3.8)

*Source: Smit LAM, et al. *Am J Ind Med* 2005;48:30-9.
+Prevalence ratio adjusted for age, sex, smoking

Advantages of cross-sectional studies

- Very suitable for studying symptoms, physiological variation (e.g., lung function)
- Direct contact with workers permits additional data collection (confounders, use of PPE, etc.)

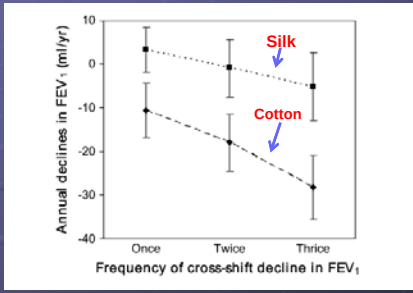
Limitations of cross-sectional studies

- Generally limited to active workers – workers who left may be most affected
- Possible selection bias (e.g., migration between jobs influenced by health status.

Repeated Measures Design

- Baseline measurements of exposure and health status (initial cross-sectional study)
- Repeated assessments of changes in health status in relation to changes in exposure

Annual decline in FEV1 over 15 years in relation to frequency of cross-shift change: Shanghai textile workers*



*Wang X, et al. (2008) *Am J Respir Crit Care Med* 177:316-20

Validity and precision definitions

- **Bias: difference between what study attempts to measure with what it actually measures (i.e., systematic error)**
- **Validity: extent to which bias is minimized**
- **Precision: The statistical stability of a measured value (e.g., relative risk)—the larger the study, the more precise it is**

Confounding

- Definition: mixing of effects of exposure of interest with effects of extraneous factors
- Criteria:
  - independent risk factor for health outcome of interest
  - associated with exposure under study
  - not intermediate in exposure/outcome pathway

Examples of confounding

- Demographic factors: age, gender, ethnicity
- Lifestyle exposures: smoking, diet, alcohol
- Personal characteristics: medical history
- Co-occurring occupational or environmental exposures (e.g., solvent mixtures)

Methods to control confounding

- Direct statistical adjustment when confounder data are available
- Stratification by confounder status
- Restriction of study to persons with single level of confounder (e.g., only non-smokers)
- Indirect assessments
  - Examine risks for other conditions related to confounder
  - Hypothetical calculation of confounder effects

Lung cancer in non-smoking uranium miners*

	Cumulative exposure (WLM)			
Years since	1-200		>200	
first exposure	Obs	RR	Obs	RR
<20	0	0	4	20
≥20	0	0	10	25

*Roscoe RJ, et al. *JAMA* 1989;262:629-33

Selection bias

- Biased* choice of exposed or non-exposed groups in a cohort or cross-sectional study,
- Or, biased** choice of cases or controls in a case-control study

*Exposure groups should be selected without prior knowledge or expectation of health status

**Cases and controls should be selected irrespective of exposure status

Healthy worker effect

- Definition: typically lower mortality (or morbidity) in an occupational group than in the population-at-large (which includes persons too ill or disabled to work)
- Causes of HWE:
  - "Healthy" workers selected for employment (primary selection)
  - Adequate health needed to stay employed (secondary selection)

Healthy worker effect: aspects of selection bias *and* confounding

- Selection bias: selection of inappropriate comparison group (e.g., national population)
- Confounding: the index and comparison groups have different distributions of disease determinants (e.g., health status)

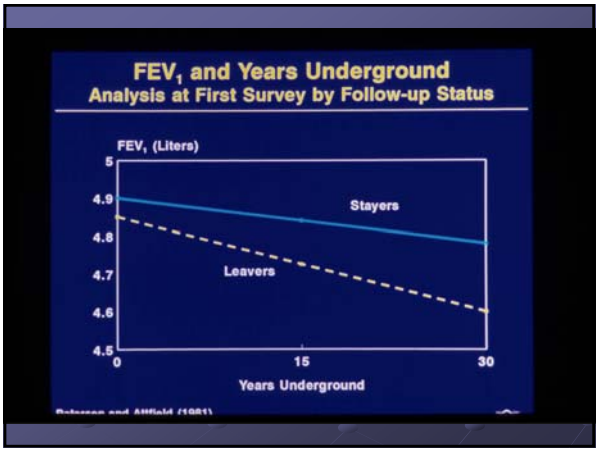
Cause-specific mortality among white male U.S. crude oil production workers, 1946-94*

Cause of death	Obs	SMR+
All causes	4361	0.73
Arteriosclerosis heart disease	1489	0.74
Stroke	282	0.74
Non-malignant respiratory disease	299	0.68
Diabetes mellitus	36	0.41
All cancers	1080	0.83
Lung cancer	347	0.80

*Divine and Hartman (2000) *Occup Environ Med* 57:411-7
+ Standardized mortality ratio, based on rates in U.S. white males, 1946-94

Healthy worker survivor effect

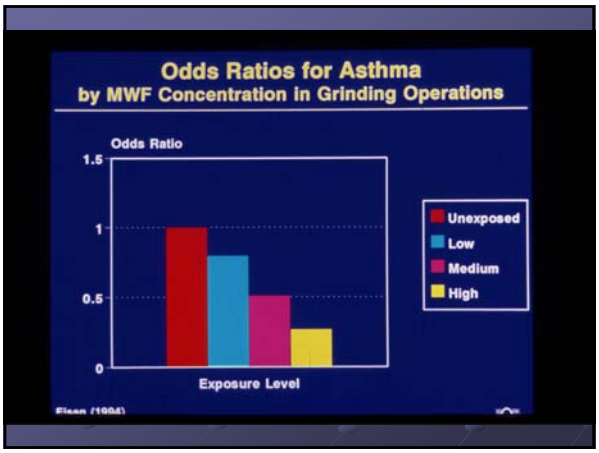
- **Definition**: Depletion of workforce due to loss of affected ("susceptible") workers
- **Net effect**: diminished ability to detect exposure/disease associations
- **Causes**:
  - Affected workers leave employment
  - Affected workers preferentially move from higher to lower exposed jobs



Respiratory symptoms as predictors of leaving employment from Turkish cotton mills within one year of hire*

	1 month		3 months		6 months		12 months	
	leavers	*stayers*	*leavers*	*stayers*	*leavers*	*stayers*	*leavers*	*stayers*
Work-related lower resp sx	0/16 (0%)	5/157 (3%)	6/24 (25.%)	6/125 (5%)	3/17 (18%)	17/111 (15%)	0/17 (0%)	4/93 (4%)
Work-related upper resp sx	4/16 (25%)	50/157 (32%)	12/24 (50%)	49/125 (39%)	7/17 (41%)	49/111 (44%)	4/17 (24%)	32/93 (34%)

*Bakirici N, et al. (2006) *Occup Environ Med* 63:126-130.



Longitudinal change in lung function in Boston firefighters*

Year	No. firefighters	Annual decline FVC (ml)	Annual decline FEV_1 (ml)
1971	1768	----	----
1972	1430	77	68
1974	1146	40	30

NB: Expected annual declines of FVC, FEV_1 ~25-30 ml

*Musk, et al. Am J Public Health 1977;67:626-9