1 Standardization. ME1. Chapter 5.

The principle behind standardization is to calculate hypothetical crude rates for each compared group using an identical artificial distribution for the factor to be standardized; the artificial distribution is known as the *standard*.

Standardized rate (SR) $= \dfrac{\sum w_i R_i}{\sum w_i}$

R_i is the category-specific rate in category i w_i is the weight for category i, from the standard.
Note: weighting the sample by the sample distribution = crude rate.

Indirect

$$SR = \frac{\sum n_{i\cdot} \frac{y_i}{n_i}}{\sum n_i} = \frac{y_i}{n_i} = \text{crude rate}$$

$$SMR = \frac{\sum y_{1i}}{\sum n_{1i\cdot} \frac{y_{0i}}{n_{0i}}} = \frac{\text{observed}}{\text{expected}} = \frac{\frac{\sum y_{1i}}{\sum n_{1i}}}{\frac{\sum n_{1i\cdot} \frac{y_{0i}}{n_{0i}}}{\sum n_{1i}}}$$

R_{1i} is the exposed rate in category $i = \frac{y_{1i}}{n_{1i}}$. R_{0i} is the unexposed rate in category $i = \frac{y_{0i}}{n_{0i}}$.
SMR = ratio of two standardized rates that have been standardized (weighted) to the exposed distribution.

2 Lecture 19 and 20. Effect measure modification (EMM)

Effect modification The average causal effect of A on Y varies across levels of M. [HR13]
Effect-measure modification Measure of effect changes over values of some other variable. [Rot12]
Interaction
Biological joint operation of two or more causes to produce or prevent disease
Statistical observed heterogeneity of effect measures

2.1 Assessing modification

Stratum-specific measures of effect Association between exposure and outcome similar within subgroups formed by another factor?
Interaction tables designed to assess modification

2.1.1 Joint effects: In terms of interaction

Additive $IPD_{A+,B+} <> IPD_{A+,B-} + IPD_{A-,B+}$
Multiplicative $IPR_{A+,B+} <> IPR_{A+,B-} \times IPR_{A-,B+}$

2.1.2 Types of joint effect

Antagonistic	Not present	Synergy
observed < expected	observed = expected	observed >expected

2.1.3 Five types of joint effect

	1	2 (pt)	3	4 (pt)	5
Additive	sub		super		super
Multiplic.	sub		sub		super
Perfect	–	A	–	M	–
	Sub-A	Sub-M	Inter.	Super-A	Super-M

2.1.4 Antagonistic (ant) or Synergistic (syn)

Region	1	2 (pt)	3	4 (pt)	5
Additive	ant		syn		syn
Multiplic.	ant		ant		syn
Perfect	–	A	–	M	–
	Sub-A	Sub-M	Inter.	Super-A	Super-M

2.1.5 Joint effect summary

Departure from additivity Additive antagonistic, perfectly additive, additive synergistic
Departure from perfect multiplicativity Multiplicative antagonistic, Multiplicative synergistic

2.2 Modification and Confounding

Modification Crude estimate is weighted average of the stratum-specific
Modification ≠ Bias Crude measure has a meaningful interpretations the overall association across subgroups (if no confounding)
Confounding Stratum-specific effect estimates are similar to each other, but differ from crude.
Confounding = Bias Crude measure does not have a meaningful interpretation.

2.3 Key formulae

	Assumption
Expected	**Additive**
$IRD_{A+,B+} =$	$IRD_{A+,B-} + IRD_{A-,B+}$
$IRR_{A+,B+} =$	$IRR_{A+,B-} + IRR_{A-,B+}$ - 1
Expected	**Multiplicative**
$IRR_{A+,B+} =$	$IRR_{A+,B-} \times IRR_{A-,B+}$

3 Lecture 22. Selection bias

	Disease	
Exposure	yes	no
yes	pa	pb
no	pc	pd

OR_{obs}	RR_{obs}
$\frac{paApdD}{pbBpcC}$	$\frac{paA/(paA+pbB)}{pcC/(pcC+pdD)}$

OR unbiased when	Selection differs
by exposure only	pa=pb and pc=pd
by disease only	pa=pc and pb=pd

3.1 Types of selection bias

Refusal bias Non-responders or those declining study participation differ from respondents with respect to exposure
Assessment bias Differential attention given to exposure ascertainment in cases (or outcome ascertainment in exposed)
Healthy worker bias Occupational exposure; general population for comparison. People who can work are healthier than the general population.
Berkson's bias Hospital-based case control studies. Exposure increases the risk of hospitalization. More so among the cases than the noncases. The combination of exposure and disease increases the probability of hospitalization.

3.2 Avoid selection bias

1. High participation and response rates, 2. Complete and objective ascertainment, 3. Complete follow-up.

4 Lecture 22 and 23. Information bias

4.1 Sources of error

Random Affects precision. Quantified with confidence interval.
Systematic Affects validity. Explored with sensitivity analysis.

4.2 Sources of bias

Confounding Estimates of effect distorted by another factor
Information Mismeasurement of exposure, outcome, or covariates
Participant selection Study participation criteria, recruitment, and retention

4.3 Information bias terminology

Non-differential misclassification Under-ascertainment of outcome; Same in exposed & unexposed.

1. % of cases misclassified is the same for both exposed and unexposed	2. No bias for risk ratio (IPR)	3. No bias for the rate ratio (IRR)
4. But erodes precision (wider confidence intervals)	5. Assumes: prospective cohort design; no false positives (one-way misclassification) and rare outcome	

Differential misclassification: Under-ascertainment of outcome differs between exposed & unexposed.

1. % of cases misclassified is different for exposed and unexposed	2. Bias for risk ratio (IPR)
3. Bias for the rate ratio (IRR)	4. Direction of bias cannot be predicted without knowledge of mis-classification probabilities

Other 1. Misclassification of the exposure can occur
2. Misclassification of exposure and the outcome can be happening at the same time
3. Misclassification of a confounding variable can also occur

Applied to case-control studies When % of exposure misclassification is the same for cases and controls. Always biases the odds ratio (OR) towards the null. Assume binary exposure and misclassification probability ¡50%.

4.4 Quantifying misclassification

Report	Truth D+	D-	
R+	a (TP)	b (FP)	a+b
R-	c (FN)	d (TN)	c+d
	a+c	b+d	

Sensitivity (Se) a/(a+c) = Pr(R+ | D+)
Positive predictive value (PPV) a/(a+b) = Pr(D+ | R+)
Specificity (Sp) d/(b+d) = Pr(R- | D-)
Negative predictive value (NPV) d/(c+d) = Pr(D- | R-)
Prevalence of factor (exposure or outcome) Does not affect Se or Sp. **Does** affect PPV and NPV.

4.5 Sources of information bias, etc.

1. Cultural differences, Poorly worded questions, Faulty recall, Observer bias, Variation between observers, Errors in lab assays
2. Hallmarks of good studies (quantify bias a priority, use sensitivity analysis). Hallmark of bad study (ignore bias. say 'could bias null' in discussion)

5 Lecture 23. Estimation and testing

Estimation of effects: Strength of association between exposure and disease. **Precision** of estimate.

5.1 95% CI for effect measure (em)

General form of 95% CI EM ± 1.96 × se(EM)
ln scale for IPR, IRR, OR
95% lower limit $(LL_{IPR}) = exp(ln(IPR) - 1.96 \times se[ln(IPR)])$
95% upper limit $(UL_{IPR}) = exp(ln(IPR) + 1.96 \times se[ln(IPR)])$
Interpretation If we conducted this study and calculated the risk ratio and 95% confidence interval under the same conditions 100 times, we would expect 95 out of the 100 confidence intervals to contain the population(unobservable) risk ratio.
Incorrect The true risk ratio has a 95% chance of lying in a given confidence interval.

5.1.1 Risk

	Exposed	Unexposed	
Disease	a	b	M_1
No disease	c	d	M_0
	N_1	N_0	T

Odds ratio (OR) $= {}^{(a \times d)}/_{(b \times c)}$

$$SE[ln(OR)] = \sqrt{({}^1/_a + {}^1/_b + {}^1/_c + {}^1/_d)}$$

Risk ratio (IPR) $= \frac{{}^a/_{N_1}}{{}^b/_{N_0}}$

$$SE[ln(IPR)] = \sqrt{({}^1/_a - {}^1/_{N_1} + {}^1/_b - {}^1/_{N_0})}$$

risk difference (IPD) $= {}^a/_{N_1} - {}^b/_{N_0}$

$$SE(IPD) = \sqrt{\frac{a(N_1 - a)}{N_1^3} + \frac{b(N_0 - b)}{N_0^3}}$$

5.1.2 Incidence

	Exposed	Unexposed
Cases	a	b
Person-time	PT_1	PT_0

Incidence rate ratio (IRR) $= \frac{{}^a/_{PT_1}}{{}^b/_{PT_0}}$

$$SE[ln(IRR)] = \sqrt{({}^1/_a + {}^1/_b}$$

Incidence rate difference (IRD) $= {}^a/_{PT_1} - {}^b/_{PT_0}$

$$SE[(IRD)] = \sqrt{({}^a/_{(PT_1)^2} + {}^b/_{(PT_0)^2}}$$

5.1.3 Comparing confidence intervals

Confidence Limit Difference (CLD) $|UL_{IPD} - LL_{IPD}|$
Confidence Limit Ratio (CLR)

$$\frac{UL_{IPR}}{LL_{IPR}} = |ln(UL_{IPR}) - ln(LL_{IPR})|$$

5.1.4 Key messages

Strength of association point estimates (IPD, IPR, IRD, IRR, or OR)
Precision confidence intervals for IPD, IPR, IRD, IRR, or OR. Ratio measures (OR, IPR, IRR) calculate confidence interval for the natural log of the ratio.
Interpretation Involves concept of hypothetical replications. computed using formulae derived from sampling distributions.

5.2 Hypothesis tests and p-values

5.2.1 Hypothesis testing

p-value value is the probability of observing another test statistic at least as far from the null as the one we observed assuming the null is true.
reject the null hypothesis if the p-value is below a threshold (5%)
fail to reject the null hypothesis if the p-value is above a threshold (5%)

5.2.2 Key messages

Preference is given to estimation of effects (i.e. the OR, IRR, or IPR) and their precision (CI and CLR).

6 Lecture 24. Statistical power

Power important to design studies and some cases of failure to reject because of low sample size – not a case of 'no difference'.

	Truth (unobservable)	
Observed	**Assn in pop**	**No assn in pop**
Reject null	Correct (true +ve)	Type I error (false +ve)
Fail reject	Type II error (false -ve)	Correct (true -ve)

Type I error (alpha) Assume H_0 is true. Due to chance your sample is skewed toward disease risk is higher in exposed vs unexposed. Claim an association when none exists.
Type II error (beta) Assume H_0 is not true. Due to chance your sample is skewed in direction of same risk. Claim no association but there is one.

6.1 Sample size formulas

Sample size estimation Meet statistical needs of study to adequately **power** a hypothesis **test** and **precision** to **estimate** an association.
Depends on 1. research design, 2. alpha, 3. power, 4. effect size, 5. variability of outcome
Continuous outcome: diff in means

$$n = \frac{(Z_{\alpha/2} + Z_\beta)^2 \cdot (2\sigma^2)}{(\mu_1 - \mu_2)^2}$$

Binary outcome: diff of proportions

$$n = \frac{(Z_{\alpha/2} + Z_\beta)^2 \cdot [P_1(1 - P_1) + P_2(1 - P_2)]}{(P_1 - P_2)^2}$$

Continuous outcome: est of mean $n = \frac{Z^2_{\alpha/2} s^2}{d^2}$ Note: d = The desired precision level expressed as half of the maximum acceptable confidence interval width. Also, $Z_{\alpha/2}$=1.96 for α=0.05 and $Z_\beta)^2$=1.28 for 1-β=0.8.

Binary outcome: est of proportion $n = \frac{Z^2_{\alpha/2} p(1-p)}{d^2}$

7 Lecture 25 and 26. Screening

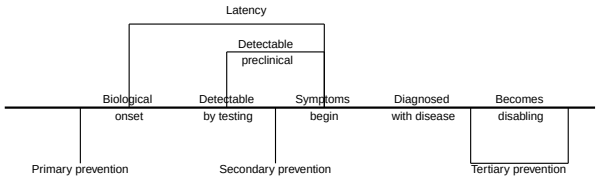
7.0.1 Screening

Examination of asymptomatic people in order to classify them as likely or unlikely to have the disease that is the object of screening.
Primary Avoid biological onset of disease
Secondary Minimize adverse outcomes through early detection and treatment of disease.
Tertiary Reduce complications of advanced disease
Asymptomatic People who have no clinical symptoms. (screening can benefit them with referral to diagnostic test.
False Positive Screen positive, negative in truth
False Negative Screen negative, positive in truth.

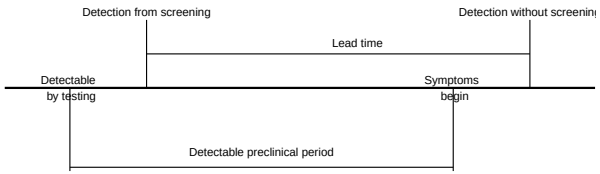
7.0.2 Diagnostic test

One or more diagnostic tests are used to establish that a person has or does not have the disease. Targets: people who screen positive, or are symptomatic.

7.1 Natural history of the disease



7.2 Lead time



7.3 Requirements for effective screening

1. Suitable disease Suficient population burden and suitable 'window of opportunity'.
2. Accurate test Reliable and Valid (sensitive and specific)
3. Effective treatment must be a treatment that favorably alters disease progression.
4. Benefits outweigh the harms
5. Reasonable cost

7.4 Sensitivity and Specificity

Trade-off Good cutpoint critical. With continuous measure need cutpoint. Maximize sensitivity and specificity of screen. $\uparrow$ Se $\Rightarrow \downarrow$ Sp and $\uparrow$ Sp $\Rightarrow \downarrow$ Se
High Se, Low Sp Good when: Dx test cheap, disease trt effective, little cost to false pos. **Bad** when: Dx test invasive\costly. Major emotional cost to screening +ve. Example: screen for HIV in donated blood.
Low Se, High Sp Good when: high emotional cost to screen +ve. Diagnostic tests are expensive\invasive. **Bad** when: trying to prevent transmission of disease. When trt is available and early detection will decrease mortality (missed opportunity). example: fatal disease with no treatment.
ROC curve Plot true positive rate (Se) vs false positive rate (1-Sp). 0.9 to 1.0 (Excellent), 0.8-0.9 (Good), 0.7-0.8 (Fair), 0.6-0.7(Poor), 0.5-0.6 (Fail)

7.5 Biases in screening

Lead time bias Diagnosis made earlier in screened group. Length of time from diagnosis to survival will look artifactually better in screened cases.
Length time bias Selection bias in which longer intervals are more likely to be chosen. Example: cancer and tumor growth. Higher proportion of tumors found in screened group and survival improvement an artifact of data.

7.6 Evaluation

Endpoint=Mortality, Endpoint $\neq$ Survival time.
RCT gold standard. controls for lead-time bias, length-time bias and over-diagnosis bias. requires large # of participants, long follow-up time. EXPENSIVE and TIME-CONSUMING. cohort studies have similar problems.

case-control When outcome is rare, screening tech. changes rapidly, speed required, disease detectable but preclinical.

Case person who died or developed relevant adverse outcome. Select regardless of stage of disease when first diagnosed.

Control Representative of the population that generated the cases with respect to the presence and/or level of screening activity. Don't exclude those with preclinical disease.

References

[HR13] MA Hernan and JM Robins. *Causal Inference*. Chapman & Hall, 2013.

[Rot12] Kenneth J Rothman. *Epidemiology: an introduction*. Oxford University Press, New York, NY, 2012.