Inverse probability weighting and meta analysis

CMED6020 – Session 7

Eric Lau (ehylau@hku.hk)

School of Public Health
The University of Hong Kong

8 Mar 2021

Session 7 learning objectives

After this session, students should be able to

- Appreciate the use of inverse probability weighting
- Apply inverse probability weighting for analysis of missing data
- Perform meta analysis to obtain overall estimate of an intervention effect from multiple studies

Introduction to inverse probability weighting

Missing data

- Is a common problem
- Potential reasons:
  - Dropout
  - Incomplete response
  - Censored
- Analysis based on available data only may result in biased result

Types of missing data

- Missing completely at random (MCAR)
  - Missingness is independent of all other variables
  - e.g. Accidental loss of data
- Missing at random (MAR)
  - Missingness is independent of unobserved variables
  - e.g. Loss of contact of recovered patients
- Missing not at random (MNAR)
  - Missingness is dependent on unobserved variables
  - e.g. Patients with treatment failure less likely to respond

Methods to handle missing data

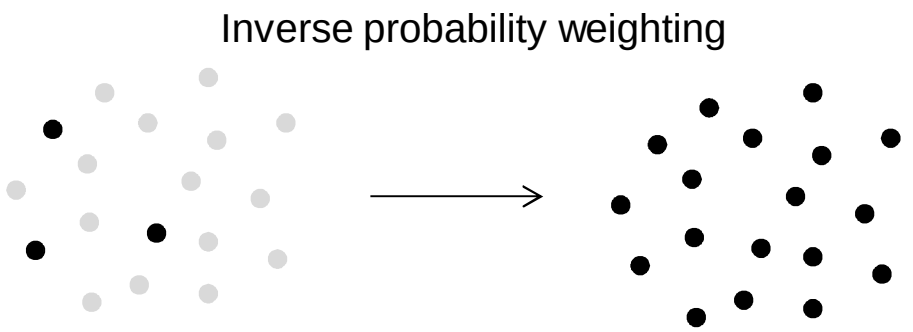
- Complete case analysis
  - May lose substantial information
  - Only valid for MCAR
- Nearest neighbour imputation
  - Impute missing value from most similar subject
  - Valid for MCAR
- Mean imputation
  - Impute missing values by the mean of the variable
  - Reduces variation in the data
  - May not maintain associations between variables
  - Valid for MCAR

Methods to handle missing data (cont'd)

- Regression imputation
  - Predict missing value from regression models (linear regression or other GLM)
  - Valid for MAR
- Multiple imputation (will be covered in CMED6040)
  - Single imputation treats imputed values as actual responses
  - Multiple imputation accounts for variability/uncertainty in the imputed data
  - Valid for MAR
- Inverse probability weighting
  - Estimate the probability of response based on some external knowledge
  - Weight the observed data using the inverse probability
  - Valid for MAR

Inverse probability weighting (IPW)

- Apply a weighting which is the inverse of the probability of being observed
- Example: if we know that a sample has a probability π of 20% being observed
  - weight the observed sample by 1/20% = 5



- High variance if some of the π are close to zero
- Can handle MAR by specifying π as a function of X (ie $\pi(X, \theta)$)

Example – estimating BMI

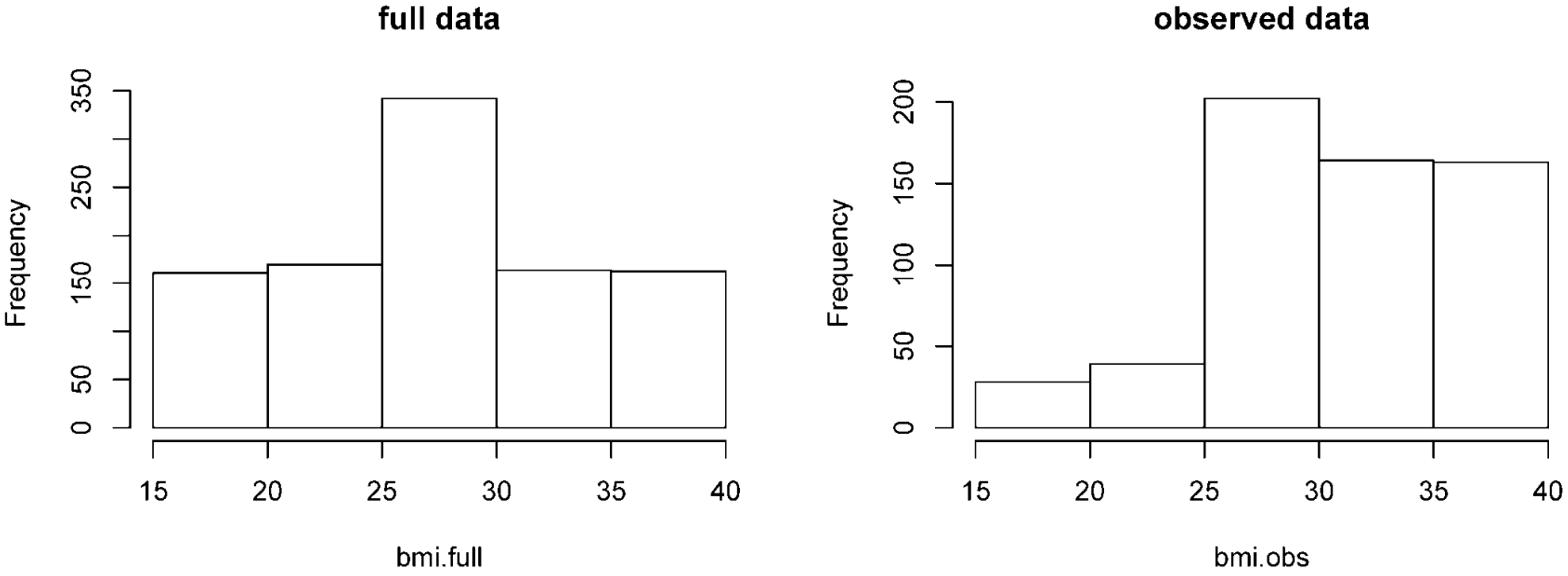
- Suppose we want to estimate the mean BMI in the population
- Suppose we have a target population where
  - Male has a uniformly distributed BMI from 25 to 40 kg/m^2
  - Female has a uniformly distributed BMI from 15 to 30 kg/m^2
  - We randomly recruited a sample of 500 persons for each sex
  - The true mean BMI is (40+25+15+30)/4 = 27.5 kg/m^2
- from previous experience, 80% of the female will not report their BMI
  - but all male are willing to report their BMI
- Missing at random
- How should we estimate the mean BMI based on the observed sample?

BMI – Simulating the data

```
> set.seed(123) # unify our results
> n <- 500
> bmi.m <- runif(n, 25,40)
> bmi.f <- runif(n, 15,30)
> bmi.full <- c(bmi.m, bmi.f)
> pi <- rep(c(1,0.2), each=n)
> obs <- rbinom(2*n,1,pi) # simulate the missing status
> bmi.obs <- bmi.full[obs==1]
```

BMI – Visualize the data

```
> par(mfrow=c(1,2))
> hist(bmi.obs, breaks=c(15,20,25,30,35,40))
> hist(bmi.full, breaks=c(15,20,25,30,35,40))
```



- The observed data has a very different BMI distribution due to missing response from female

Practice – estimate the mean BMI

- Suppose we have the observed data only
- With the knowledge of π (by sex), estimate the mean BMI using IPW

Practice – estimate the mean BMI

- Suppose we have the observed data only
- With the knowledge of π (by sex), estimate the mean BMI using IPW

```
> mean(bmi.obs) # this estimate is biased due to missing
   (completed case analysis)
[1] 30.84461
> pi.obs <- pi[obs==1]
> sum(bmi.obs/pi.obs)/(2*n)
[1] 27.05842
```

- Close to the true mean BMI (27.5 kg/m^2)

IPW estimator

- The IPW has the following general form:

$$\hat{\mu} = \frac{1}{n}\sum_{i=1}^{n}\frac{R_i Y_i}{\pi_i(X_i, \hat{\theta})}$$

- where R_i is an indicator that Y_i is being observed
- $\pi_i = \mathrm{P}(R_i = 1 | X_i)$, probability of being observed given X_i
- If R_i and Y_i are independent, then

$$E\left(\frac{1}{n}\sum_{i=1}^{n}\frac{R_i Y_i}{\pi_i}\right) = \frac{1}{n}\sum_{i=1}^{n}\frac{E(R_i Y_i)}{\pi_i} = \frac{1}{n}\sum_{i=1}^{n}\frac{E(R_i)E(Y_i)}{\pi_i} = \mu$$

($\mathrm{E}(R_i) = \pi_i$)

Propensity score analysis – MI example

- population: 400 men aged 40-70 admitted to hospital with suspected myocardial infarction
- outcome variable – 30-day mortality
- treatment: newer clot-busting drug vs standard therapy
- main confounding factors
  - age
  - pre-existing risk factor level (0-5, 5: highest risk)
  - admission severity score (0-10, 10: most severe)

MI example – deriving propensity score

```
> mi <- read.csv("examplemi.csv")
> ps.model <- glm(trt ~ age + risk + severity, data=mi,
   family=binomial)
> mi$ps <- predict(ps.model, type='response')
```

- One option is to use propensity score (inverse probability) weighting to estimate the treatment effect

Counterfactuals

- What would have happened if the patient received a different treatment (contrary to observed treatment taken)?
  - to estimate $E[Y_1-Y_0]$ for all patients
- Counterfactuals as ‘missing data’
- MI example:
  - For the same individual receiving the newer clot-busting drug, what would have happened if the standard therapy was received instead?
  - Propensity score *p* as the probability of being ‘observed’ receiving newer treatment
  - 1-*p* as the probability of being ‘observed’ receiving standard therapy

Propensity score weighting

- Propensity score (inverse probability) weighting
  - to estimate $E[Y_1-Y_0]$
  - observed outcome is actually conditioned on assigned treatment
    - ie, observed $E[Y_1|T=1]$ and $E[Y_0|T=0]$
  - estimate $E[Y_i]$ by $E[Y_i\delta(T=i)/P(T=i)]$, i=0, 1
    - δ: indicator function
  - treatment effect = $\frac{1}{N}\left(\sum_{trt=1}\frac{Y_{1i}}{p_{1i}}-\sum_{trt=0}\frac{Y_{0i}}{1-p_{1i}}\right)$
  - approximate variance for binary outcome:

$$\frac{1}{N^2}\left(\sum_{trt=1}\frac{1-p_{1i}}{p_{1i}}+\sum_{trt=0}\frac{1-p_{0i}}{1-p_{1i}}\right)$$

  - estimated effect for clot-busting therapy = -0.065, 95% CI = (-0.163, 0.033)

Your turn:
Try estimating the treatment effect by PS weighting method

Summary – IPW

- Handle data missing at random
- Use the inverse of the probability of being observed as weights
- In practice, may use logistic regression model to predict missingness
- Can be applied generally to the analytic model

Meta analysis

Systematic review

- “The application of strategies that limits bias in the assembly, critical appraisal, and synthesis of all relevant studies on a specific topic” (Porta, 2008)
- Assess both qualitative and quantitative aspects of the reviewed studies
- Always higher level of evidence than individual studies
- Considered as the highest level of evidence for systematic review of RCTs
  - if homogeneity is demonstrated

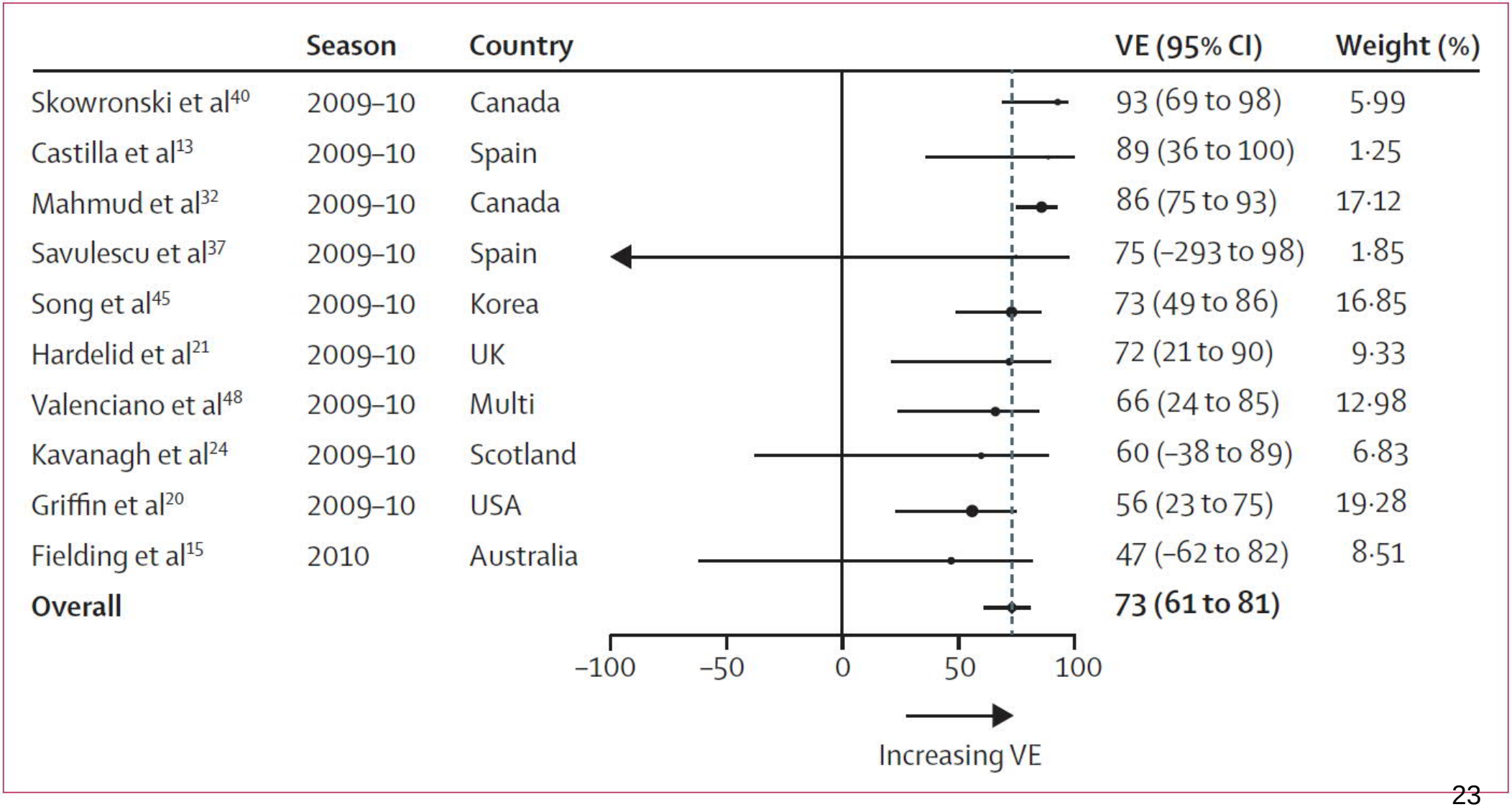
Porta MS, International Epidemiological Association. *A dictionary of epidemiology*. 5th ed. Oxford ; New York: Oxford University Press; 2008.

Meta analysis

- To estimate the pooled estimates from similar studies
  - With common exposures and outcomes
- Usually following a systematic review which identified a comprehensive list of relevant studies
  - Utilize a subset of suitable studies from the systematic review

Example of meta analysis

Vaccine effectiveness for H1N1pdm09 monovalent vaccine



Belongia et al. Lancet Infect Dis, 2016

Methods to obtain an overall estimate

- Fixed effects model
  - Assuming true effect of intervention is the same across studies
- Random effects model
  - Assuming the true intervention effect of each study comes from a larger population

Fixed effects model

- Model:

$$Y_i = \theta + \varepsilon_i$$

$$\varepsilon_i \sim N(0, v_i)$$

- Y_i is the outcome measure assumed to be normally distributed
  - e.g. log RR, log OR, mean difference
- Allows for different uncertainty for each study
- The overall estimate is a weighted average

$$\hat{\theta} = \sum_i w_i Y_i / \sum_i w_i$$

$$\text{var}(\hat{\theta}) = 1 / \sum_i w_i$$

Inverse variance weighting

- We like to assign more weight to studies with higher precision (larger sample size)
- The inverse of variance is roughly proportional to the sample size
- By setting $w_i = 1/v_i$, the variance of the overall estimate will be minimized
- Under the fixed effects model, the overall estimate is

$$\hat{\theta} = \sum_i \frac{Y_i}{v_i} \Big/ \sum_i \frac{1}{v_i}$$

$$\text{var}(\hat{\theta}) = 1 \Big/ \sum_i \frac{1}{v_i}$$

Fitting fixed effects model in R

rma(*yi, vi, sei, data, method="REML", …*) (in package: metafor)

- *yi*: outcome measures or effect size
- *vi*: corresponding sampling variance
- *sei*: corresponding sampling standard error
- *data*: specifies the data frame
- *method*: "FE" for fixed effects model, "REML" for random effects model (default)

Example – e-cigarette use and smoking cessation

- Aim: assess the association between e-cigarette use and cigarette smoking cessation among adult smokers interested in smoking
- 7 previous studies in 2013-2015
  - Reported adjusted ORs and their 95% CI
- Data: extracted from Kalkhoran et al., Lancet Respir Med, 2016
- Saved in “exampleecig.csv”

E-cigarette dataset

```
> ecig <- read.csv('d:/exampleecig.csv')
> ecig
       study   OR OR.lb OR.ub
1     Bullen 1.26  0.68  2.34
2 Vickerman 0.50  0.40  0.63
3  Borderud 0.50  0.30  0.80
4      Brown 1.61  1.19  2.18
5      Hajek 1.44  0.94  2.21
6     Pavlov 0.68  0.54  0.87
7    Pearson 0.77  0.59  1.00
```

Convert to appropriate measure for meta analysis

- Convert OR to log OR (assumed to be normal)

```
> ecig$logOR <- log(ecig$OR)
```

- Derive the standard error for log OR from the 95% CI

```
> ecig$se.logOR <- (log(ecig$OR.ub)-
   log(ecig$OR.lb))/(2*1.96)
```

- Carry out meta analysis using fix effects model

```
> require(metafor)
> ecig.fe <- rma(yi=logOR, sei=se.logOR, slab=study,
   method="FE", data=ecig)
```

Overall estimate for smoking cessation

```
> ecig.fe

Fixed-Effects Model (k = 7)


Test for Heterogeneity:

Q(df = 6) = 51.3890, p-val < .0001


Model Results:

estimate       se     zval     pval    ci.lb    ci.ub

 -0.2558   0.0591  -4.3273   <.0001  -0.3716  -0.1399      ***


> with(ecig.fe, exp(c(b, ci.lb, ci.ub)))

[1] 0.774310 0.689606 0.869418
```

- The overall estimate is 0.77 (95% CI = 0.69-0.87)

Heterogeneity

- Clinical diversity
  - Variability in participants, interventions and outcomes
- Methodological diversity
  - Variability in study design and risk of bias
- Statistical heterogeneity
  - Variability in the intervention effects across studies
  - Violate the assumption for fixed effects model
  - Random effects model allows the true effect to be different across studies

- Clinical / methodological diversity should be addressed in the systematic review
- Focus on statistical heterogeneity in the following slides

Cochrane Handbook for Systematic Reviews of Interventions, 2011

Metrics to measure heterogeneity

- Cochran's Q test

$$Q = \sum_i w_i (Y_i - \hat{\theta})^2 \sim \chi^2$$

  - H_0: no heterogeneity among studies
  - depends on no. of studies

- Higgins' I^2

$$I^2 = (Q - df)/Q \times 100$$

  - df = no. of studies - 1
  - Higher I^2 = higher heterogeneity
  - Rule of thumb: low: 0-30%, moderate: 30-60%, substantial: 50-90%

Heterogeneity among studies

```
> summary(ecig.fe)

Fixed-Effects Model (k = 7)

Test for Heterogeneity:
Q(df = 6) = 51.3890, p-val < .0001

> Q <- ecig.fe$QE
> I2 <- (Q-(ecig.fe$k-1))/Q * 100
> I2
[1] 88.32436
```

- Evidence of significant heterogeneity

Random effects model

- Model:

$$Y_i = \theta + \theta_i + \varepsilon_i$$

$$\theta_i \sim N(0, \tau^2)$$

$$\varepsilon_i \sim N(0, v_i)$$

- τ^2 describe the between-study variation
- Regards the studies coming from a larger ‘study population’
- The overall estimate is a weighted average

$$\hat{\theta} = \sum_i w_i Y_i / \sum_i w_i$$

$$\text{var}(\hat{\theta}) = 1 / \sum_i w_i$$

$$w_i = 1/(v_i + \tau^2)$$

Overall estimate for smoking cessation (random effects)

```
> ecig.re <- rma(yi=logOR, sei=se.logOR, slab=study,
   method="REML", data=ecig)
> ecig.re

Random-Effects Model (k = 7; tau^2 estimator: REML)

tau^2 (estimated amount of total heterogeneity): 0.2062 (SE =
   0.1398)
tau (square root of estimated tau^2 value):      0.4541
I^2 (total heterogeneity / total variability):   88.83%
H^2 (total variability / sampling variability):  8.95

Test for Heterogeneity:
Q(df = 6) = 51.3890, p-val < .0001
```

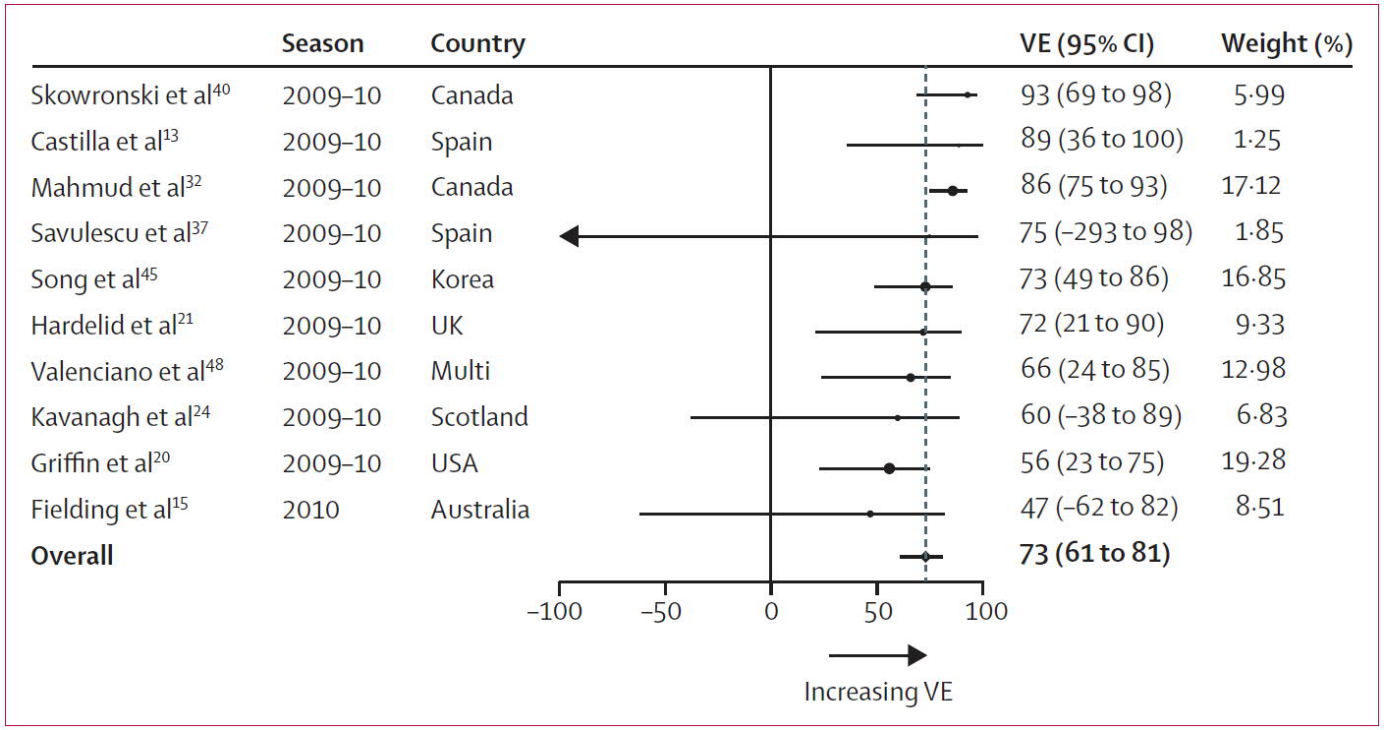
Overall estimate for smoking cessation (random effects)

```
Model Results:

estimate       se     zval     pval    ci.lb    ci.ub
 -0.1520   0.1863  -0.8161   0.4144  -0.5172   0.2131

---
Signif. codes:  0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1

> with(ecig.re, exp(c(b, ci.lb, ci.ub)))
[1] 0.8589488 0.5961948 1.2375035
```

- The overall estimate is 0.86 (95% CI = 0.60-1.24)
- Wider confidence interval

Forest plot

- Widely used to present results of meta analysis
- Display the effect size from individual studies
  - And the corresponding precision
- Display the overall estimate at the bottom



Belongia et al. Lancet Infect Dis, 2016

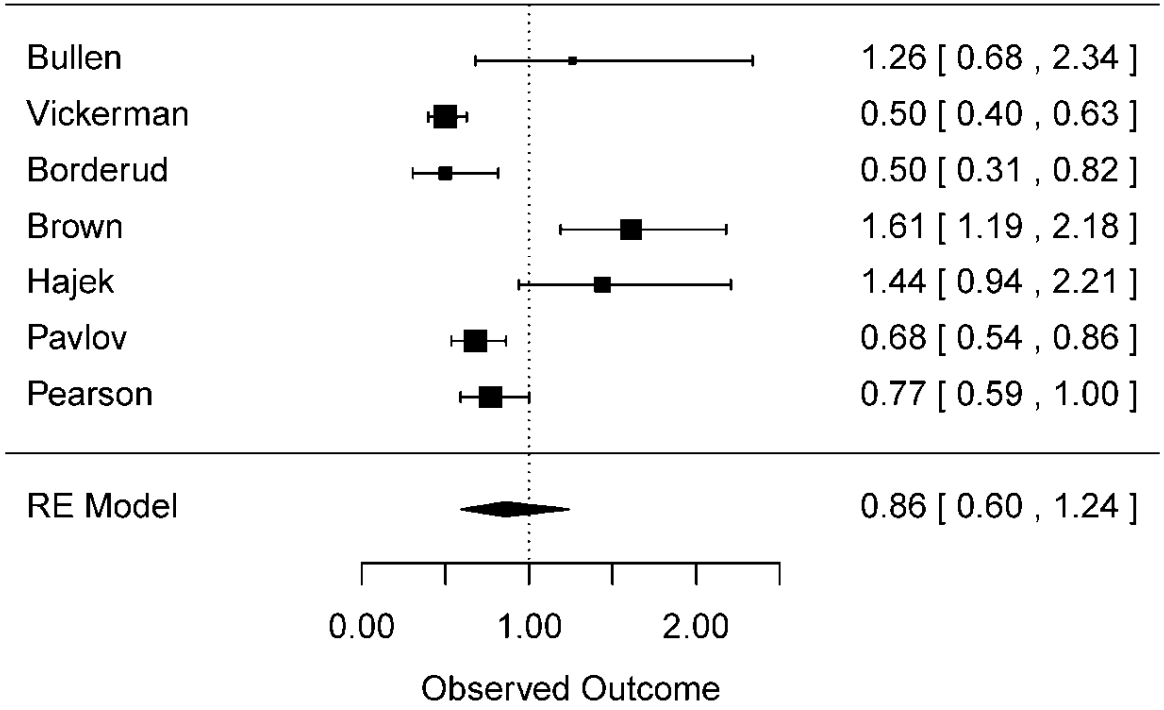
Forest plot in R

forest(x, *showweights=FALSE*, *transf*, *refline=0*, *order*, …) (in package: metafor)

- *x*: an “rma” object
- *showweights=TRUE* to show the weighting for each study
- *transf=exp* to take exponential transformation for the outcome measure
- *refline*: specifies the reference line
- *order*: specifies order in effect size: “obs”; sampling variance: “prec”

E-cigarette example forest plot

```
> forest(ecig.re, transf=exp, refline=1)
```

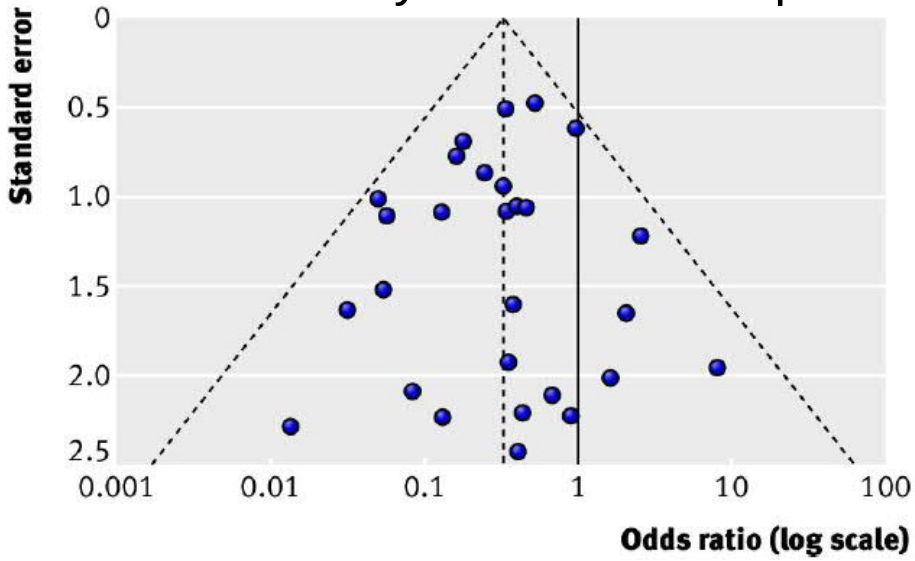


- No evidence that e-cigarette use is helpful to smoking cessation
- But large heterogeneity

Funnel plot

- Scatter plot of the effect estimates versus precision
- Vertical dotted line: overall estimate; diagonal: 95% CI
- A symmetric inverted funnel shape is expected if studies are of good methodological quality and no reporting bias exists
  - Larger studies likely to be near the top and closer to center line
- Asymmetry may arise from multiple reasons:
  - Reporting biases
  - Poor methodological quality
  - True heterogeneity
  - Chance
- Less useful for small no. of studies

A symmetric funnel plot:



Sterne et al., BMJ, 2011

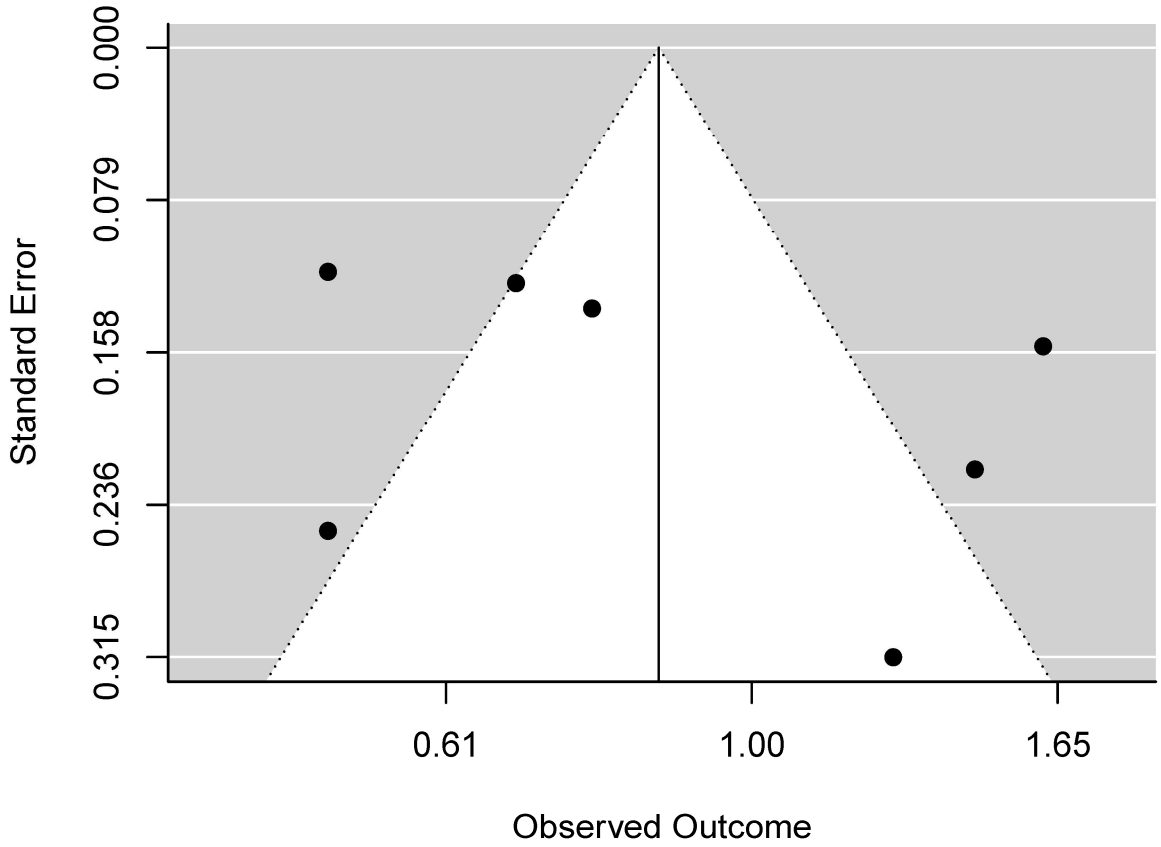
Funnel plot in R

funnel(x, *yaxis="sei"*, *atransf*, *refline …*) (in package: metafor)

- *x*: an "rma" object
- *yaxis*: specifies what is shown on the y-axis. "sei" for standard error, "vi" for variance, "ni" for sample size
- *atransf=exp* to take exponential transformation for x-axis (outcome measure)
- *refline*: specifies the reference line

E-cigarette example funnel plot

```
> funnel(ecig.re, atransf=exp)
```



- Not obvious asymmetry
- Large heterogeneity (also indicated by I^2)

Test of asymmetry in the funnel plot

- Egger's test
  - regtest() in package metafor
  - Low power with small number of studies (e.g. n < 10)
- Other tests: Begg's test, Harbord's test
- Specify the test before analysis

```
> regtest(ecig.re)
Regression Test for Funnel Plot Asymmetry

model:     mixed-effects meta-regression model
predictor: standard error

test for funnel plot asymmetry: z = 0.7469, p = 0.4552
```

- No strong evidence of asymmetry (but note: small sample size)

Remarks

- rma in R can also handle some type of original data (e.g. 2 x 2 table frequencies, observed no. of outcomes, etc)
  - All can be transformed into effect size and corresponding variances
- Meta-regression
  - Allow for potential moderator on the study effect size
  - R: can be specified in the ‘mod’ option in rma() function
- Trim and fill
  - In the presence of reporting bias, estimate the overall effect by filling the ‘missing’ studies
  - As a sensitivity analysis

Summary – meta analysis

- To obtain an overall estimates of an intervention from studies with similar interventions and outcomes
- Give higher weighting to studies with higher precision
- Need to assess study heterogeneity
- Refer to PRISMA / MOOSE for guidelines

Review

- We have discussed briefly how the inverse probability weighting can handle data missing at random
- We have discussed how to use meta analysis to obtain an overall estimate from multiple studies

Further reading

- The Cochrane Collaboration. Cochrane Handbook for Systematic Reviews of Interventions. 2011. http://handbook.cochrane.org/