ΟΙΚΟΝΟΜΙΚΟ ΠΑΝΕΠΙΣΤΗΜΙΟ ΑΘΗΝΩΝ
ATHENS UNIVERSITY OF ECONOMICS AND BUSINESS

ΣΧΟΛΗ ΕΠΙΣΤΗΜΩΝ & ΤΕΧΝΟΛΟΓΙΑΣ ΤΗΣ ΠΛΗΡΟΦΟΡΙΑΣ
SCHOOL OF INFORMATION SCIENCES & TECHNOLOGY

ΤΜΗΜΑ ΣΤΑΤΙΣΤΙΚΗΣ
DEPARTMENT OF STATISTICS

Ph.D. Open Day
AUEB
Stats Research Exposition

Dimitris Mavridis

Department of Primary Education
University of Ioannina

University of Ioannina

Introduction

Roughly,

- A third of the talk will be about my experience as a PhD student at the Department of Statistics (AUEB)
- A third of the talk will be about a research topic. That would be handling of missing data in meta-analysis models.
- Another third for possible questions

Tertiary Education

1996

Undergraduate studies
Department of Statistics,
Athens University
of Economics and Business

2000

MSc in Statistics
Department of Statistics,
Athens University
of Economics and Business

2003

PhD studies
Department of Statistics,
Athens University
of Economics and Business

2006

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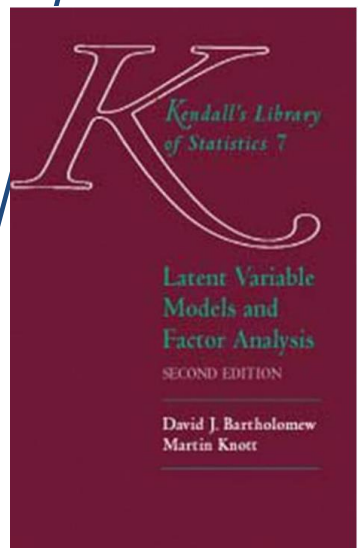
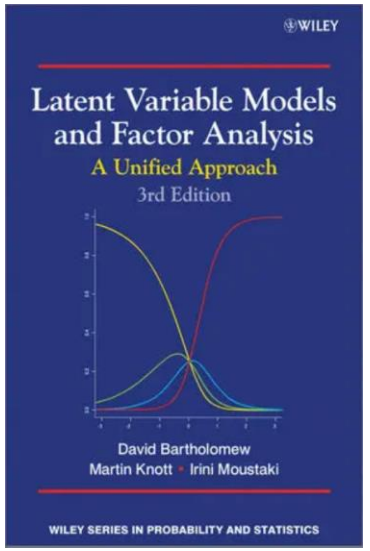
During Master studies…

- The Department invited D.J. Bartholomew from London School of Economics (LSE) to give a one-week workshop on latent variable models

- Covered a whole book and the topic amazed me

- In 2002 a new assistant professor in town working on this area
(Irini Moustaki)





D. J. Bartholomew

2 languages

Article Talk Read Edit View history Tools

From Wikipedia, the free encyclopedia

David John Bartholomew FBA (6 August 1931 – 16 October 2017) was a British statistician who was president of the Royal Statistical Society between 1993 and 1995.[1] He was professor of statistics at the London School of Economics between 1973 and 1996.[2]

Career [edit]

Bartholomew was born 6 August 1931, the son of Albert and Joyce Bartholomew in Oakley, Bedfordshire.[2][3] He was educated at Bedford Modern School[4] and University College London, where he earned his BSc and PhD.[1]

Bartholomew began his career as a scientist at the National Coal Board in 1955.[2] In 1957 he became a lecturer in statistics at the University of Keele,[2] before his appointment as a senior

D. J. Bartholomew
FBA

Born	6 August 1931 Oakley, Bedfordshire
Died	16 October 2017
Occupation(s)	Statistician, writer

Master Thesis

- Choose Irini Moustaki as my master thesis supervisor based on research interests alone
- Collaborated with Karl Joreskog
- My master thesis resulted in a publication
- Irini applied for an Heraclitus PhD scholarship (2002-2006)
- And “we” got it!

Karl Gustav Jöreskog

6 languages

Article Talk | Read Edit View history Tools

From Wikipedia, the free encyclopedia

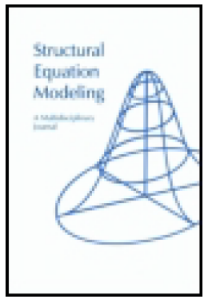
Karl Gustav Jöreskog (born 25 April 1935) is a Swedish statistician. Jöreskog is a professor emeritus at Uppsala University, and a co-author (with Dag Sörbom) of the LISREL statistical program. He is also a member of the Royal Swedish Academy of Sciences. Jöreskog received his bachelor's, master's, and doctoral degrees at Uppsala University. He is also a former student of Herman Wold. He was a statistician at Educational Testing Service (ETS) and a visiting professor at Princeton University.

Research [edit]

Jöreskog proposed a reliable numerical method for computing maximum-likelihood estimates in factor analysis; similarly reliable methods were also proposed by Gerhard Derflinger, Robert Jennrich, and Stephen M. Robinson at roughly the same time. Jöreskog's Fortran codes helped to popularize factor analysis around the world. While working at the Educational Testing Service and giving lectures at Princeton University, Jöreskog proposed a linear model for the analysis of covariance structures, a fundamental contribution to structural equation modeling (SEM).

Karl Gustav Jöreskog

Born	25 April 1935 (age 90) Åmål, Sweden
Nationality	Swedish
Citizenship	Sweden
Alma mater	Uppsala University
Occupation	Professor Emeritus in Uppsala University
Known for	Linear structural equation models LISREL software Maximum likelihood factor analysis
Scientific career	
Fields	Statistics Psychometrics
Institutions	Uppsala University Educational Testing Service
Doctoral advisor	Herman Wold
Doctoral students	Bengt O. Muthén



Structural Equation Modeling: A Multidisciplinary Journal

Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/hsem20

Factor Models for Ordinal Variables With Covariate Effects on the Manifest and Latent Variables: A Comparison of LISREL and IRT Approaches

Irini Moustaki , Karl G. Jöreskog & Dimitris Mavridis

PhD studies

- Started my PhD journey in 2003
- Worked on
  - goodness-of-fit tests for Latent Variable Models (LVM)
  - outlier detection in LVM using the Forward Search algorithm (developed by Marco Riani and David Atkinson)
- Research visit to the Department of Statistics at the London School of University (January – July 2005), worked with Professor Martin Knott

LSE THE LONDON SCHOOL OF ECONOMICS AND POLITICAL SCIENCE

I defended my thesis in December 2006

- Μαυρίδης Δημήτριος, (2007)
  Τίτλος διατριβής: "Goodness-of-Fit Measures and Outlier Detection in Latent Variable Models With Categorical and Mixed Data"
  Επιβλέπουσα: Ε. Μουστάκη, Αναπληρώτρια Καθηγήτρια
  Εξωτερικοί εξεταστές: Professor Martin Knott, London School of Economics, Professor Maria-Pia Victoria Feser, University of Geneva, Professor Marco Riani, University of Parma.
  Εσωτερικοί εξεταστές: Β. Βασδέκης, Επίκουρος Καθηγητής, Μ. Ζαζάνης, Καθηγητής, Ι. Ντζούφρας, Επίκουρος Καθηγητής

Επαγγελματική Απασχόληση: Αναπληρωτής Καθηγητής, Παιδαγωγικό Τμήμα Δημοτικής Εκπαίδευσης, Πανεπιστήμιο Ιωαννίνων

Publications during PhD

- **Mavridis D**, Moustaki I. Detecting Outliers in Factor Analysis Using the Forward Search Algorithm. *Multivariate Behavioral Research*. 2008;43(3):453-75.
- **Mavridis, D.,** and Moustaki, I. (2009), I. The forward search algorithm for detecting aberrant response patterns in factor analysis for binary data. *Journal of Computational and Graphical Statistics*, 18(4), 1016-1034.
- **Mavridis, D**.,Moustaki, I. and Knott, M. (2007). Goodness of fit measures for latent variable models for binary data. *Handbook of Latent Variable and Related Models*, Sik-Yum Lee (Editor), Elsevier.
- Moustaki, I., Joreskog, K. and **Mavridis, D.,** (2004). Factor models for ordinal variables with covariate effects on the manifest and latent variables: A comparison of LISREL and IRT approaches. *Structural Equation Modeling*, 11, 487-513.

What did I get during my PhD studies

- **Strong supervision and monitoring**
  - Accessible and supportive advisors, opportunity to present my work within the Department, regular feedback
- **Research excellence**
  - Focus on original high-impact research, a culture of collaboration (kudos to my fellow-PhDs Kostas Kalogeropoulos (LSE), Aristeidis Nikoloulopoulos (UEA), Anastasios Plataniotis (EY), Athanasios Petralias (Ministry of Finance)), working with several co-authors and presenting at conferences
- **Academic reputation**
  - A well-regarded Department with a staggering track record of producing successful graduates, well respected faculty members

What did I get during my PhD studies

- **Professional development**
  - Training in research methods, seeing other peoples' work, attending workshops
  - Had the opportunity to attend courses of several distinguished statisticians (David Freedman, Ioannis Karatzas, Karl Joreskog)
  - Many more during my years as an undergraduate and master student (Leslie Kish, Sir David Cox, C.R. Rao, David Bartholomew)
- **Networking**
  - Opportunities for collaborations within the Department and across Departments and Institutions

Other PhD trivia

- **Funding (lucky and grateful to get this one, unfortunately not taken for granted)**
  - Funds for sustaining myself and also travel grants, research visit to LSE.
- **Connections to industry, policy and clinical partners (not so strong back on the day)**

Academic Posts

- **2006-2009**
  Postdoctoral Research Associate in Forensic Statistics.
  School of Mathematics, University of Edinburgh.

THE UNIVERSITY of EDINBURGH

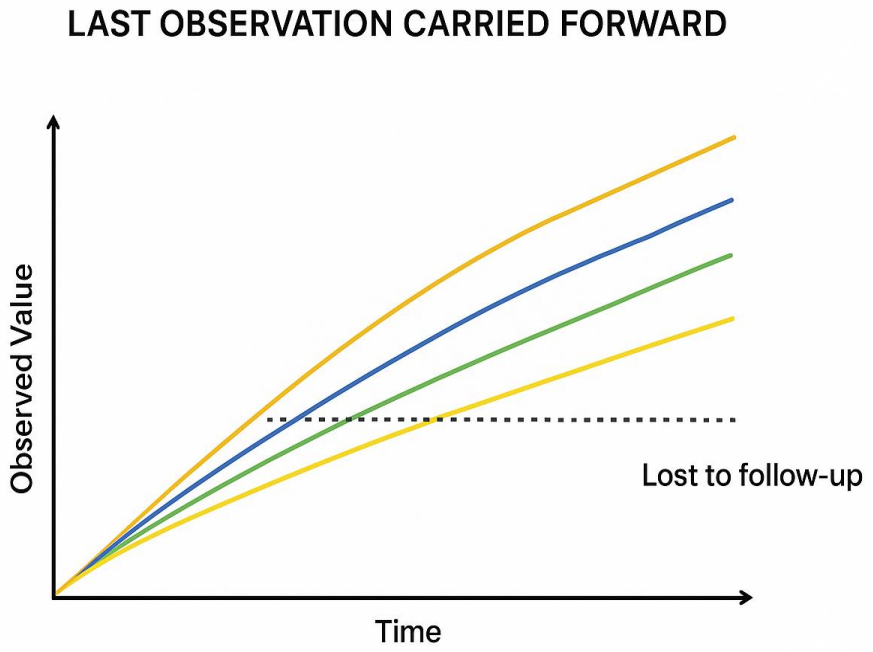
- **2010 – present**:
  Lecturer/Assistant/Associate Professor/Professor in Statistics
  Department of Primary Education, University of Ioannina.

University of Ioannina

- **2023 – present:**
  Editor-in-chief
  “Research Synthesis Methods” Journal

Research Synthesis Methods

Allowing for uncertainty due to missing and Last Observation Carried Forward (LOCF) imputed outcome data in meta-analysis



Some basics about this presentation

We are interested in research questions of the type

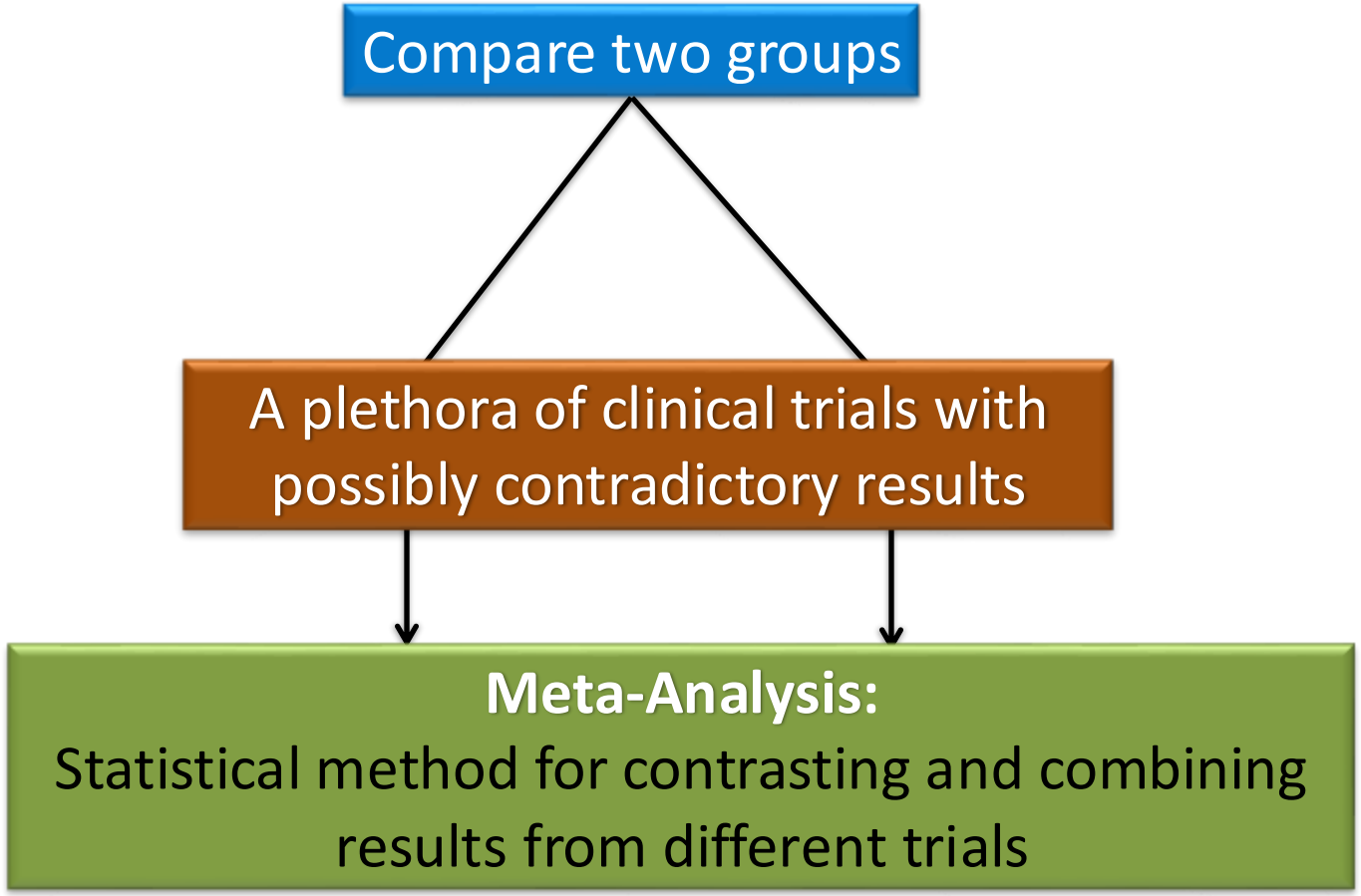
"Does this intervention work for improving this outcome in this population?" (intervention studies)

- We have:
  - an intervention arm/group and a control arm/group (could have more).
  - several studies addressing this research question and we want to synthesize quantitatively their findings
- In terms of data, typically, studies:
  - provide aggregate data
    (means, standard deviations, number of events, sample sizes per arm)
  - rr could give an effect size and its standard error.
- We do not have access to Individual Participant Data (IPD), that is the actual outcome and covariate values for each individual in each study. This is very common.
- We have missing data at the summary level .
  e.g., we have the mean value, the standard deviation, the sample size and the number of missing participants

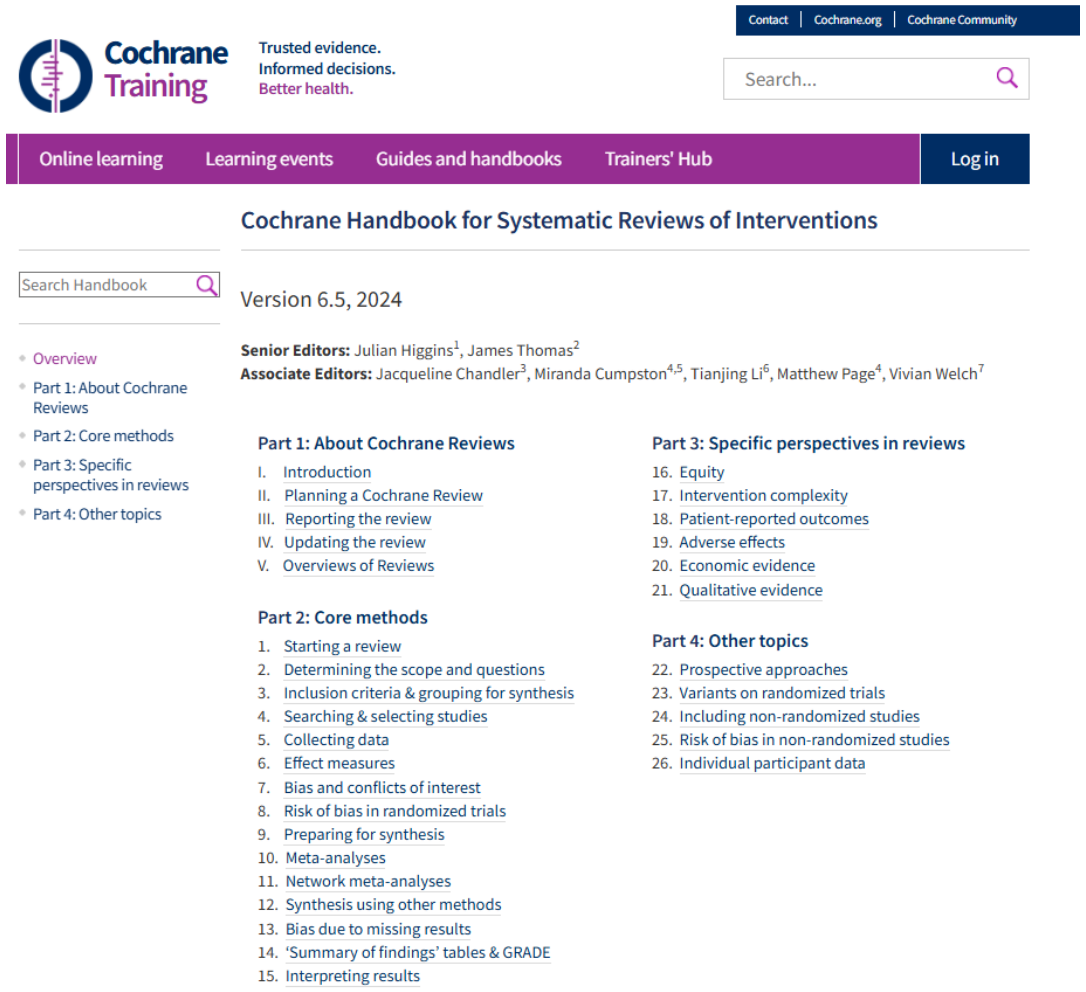
PICO criteria

P = POPULATION
I = INTERVENTION
C = COMPARISON
O = OUTCOME

What is a ‘Meta-Analysis’?



Cochrane Handbook for Systematic Review of Interventions

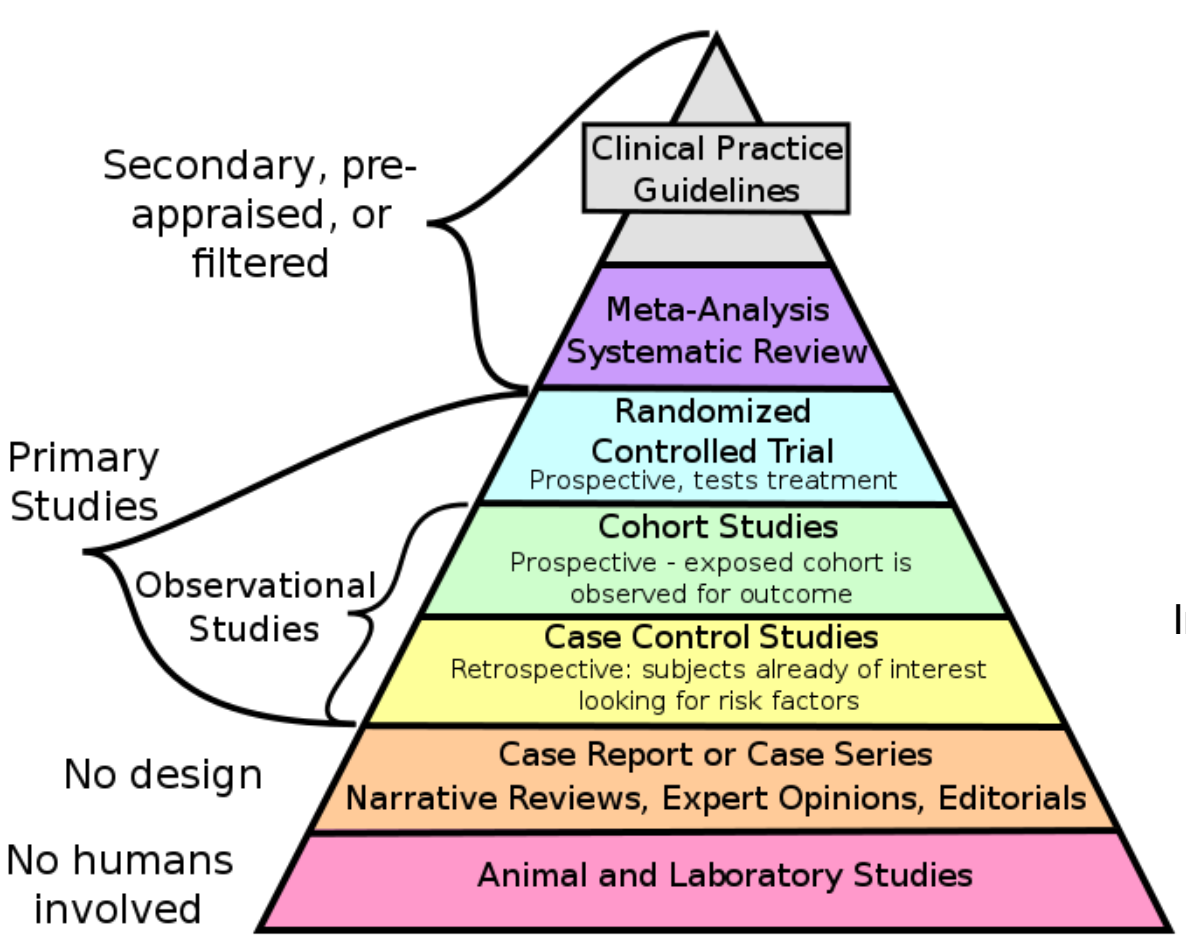


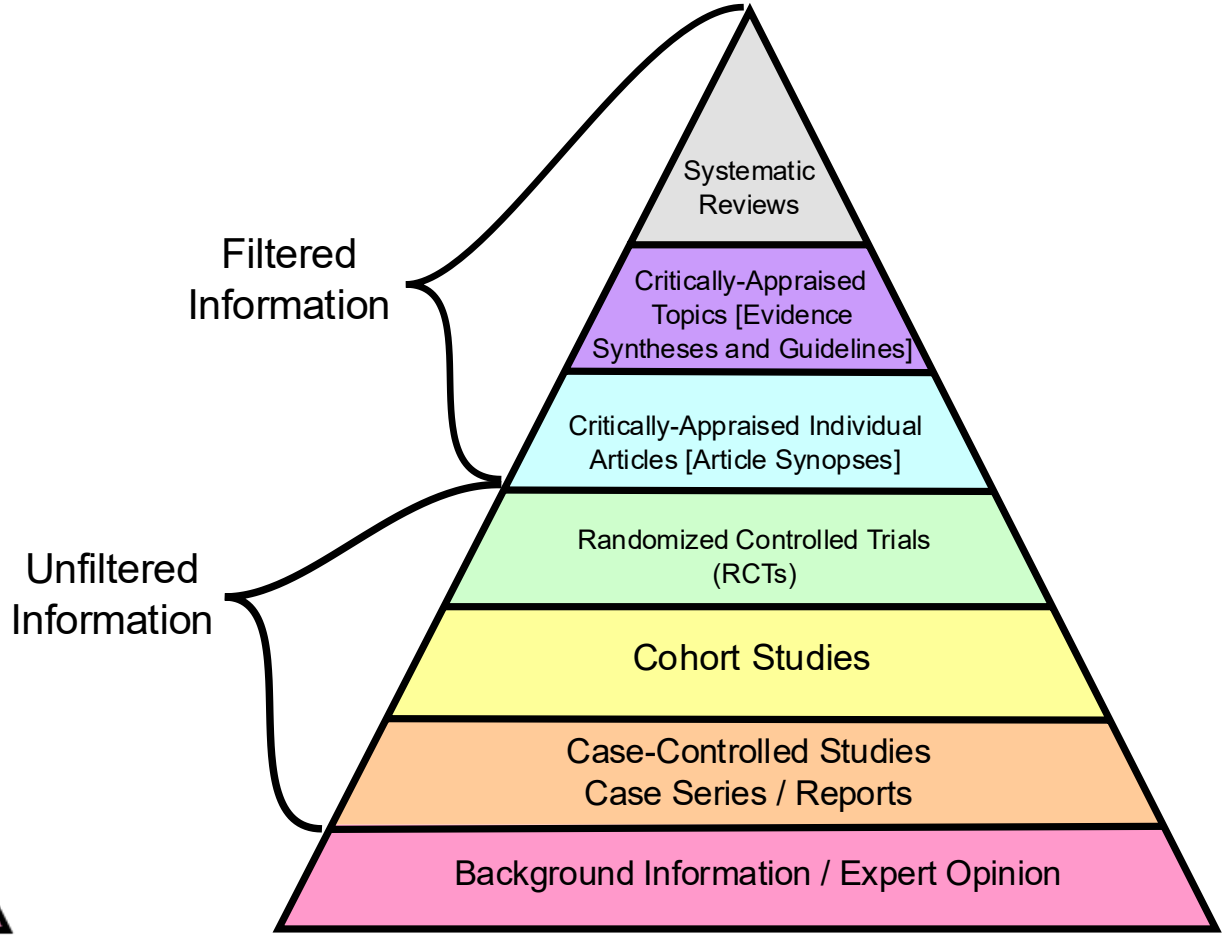
1. Forming the research question, inclusion and exclusion criteria (Part 2, chapters 1,2,3)
2. Search and selection of relevant studies (Part 2, chapter 4)
3. Data collection (Part 2,chapter 5)
4. Risk of Bias assessment (part 2, chapters 7,8,13)
5. Synthesis of results (Part 2, chapters 6,9,10 possibly 11,12)
6. Interpretation (Part 2, chapters 14, 15)

Available here: https://training.cochrane.org/handbook/current

Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). Cochrane Handbook for Systematic Reviews of Interventions version 6.5 (updated August 2024). Cochrane, 2024. Available from www.training.cochrane.org/handbook.

Hierarchy of Evidence





A well-known example

- Intravenous administration of streptokinase for patients with myocardial infarction (outcome: mortality)
- Since 1970 there were multiple RCTs (5000 in total), whose synthesis would have clearly shown the beneficial effect of streptokinase
- We had to wait for an extra decade and randomize an extra 30K patients before adopting administration of streptokinase in practice.
- Withholding a known beneficial care exposes participants to unnecessary risk and violates the principle of beneficence (do good, maximize benefit, minimize risk)

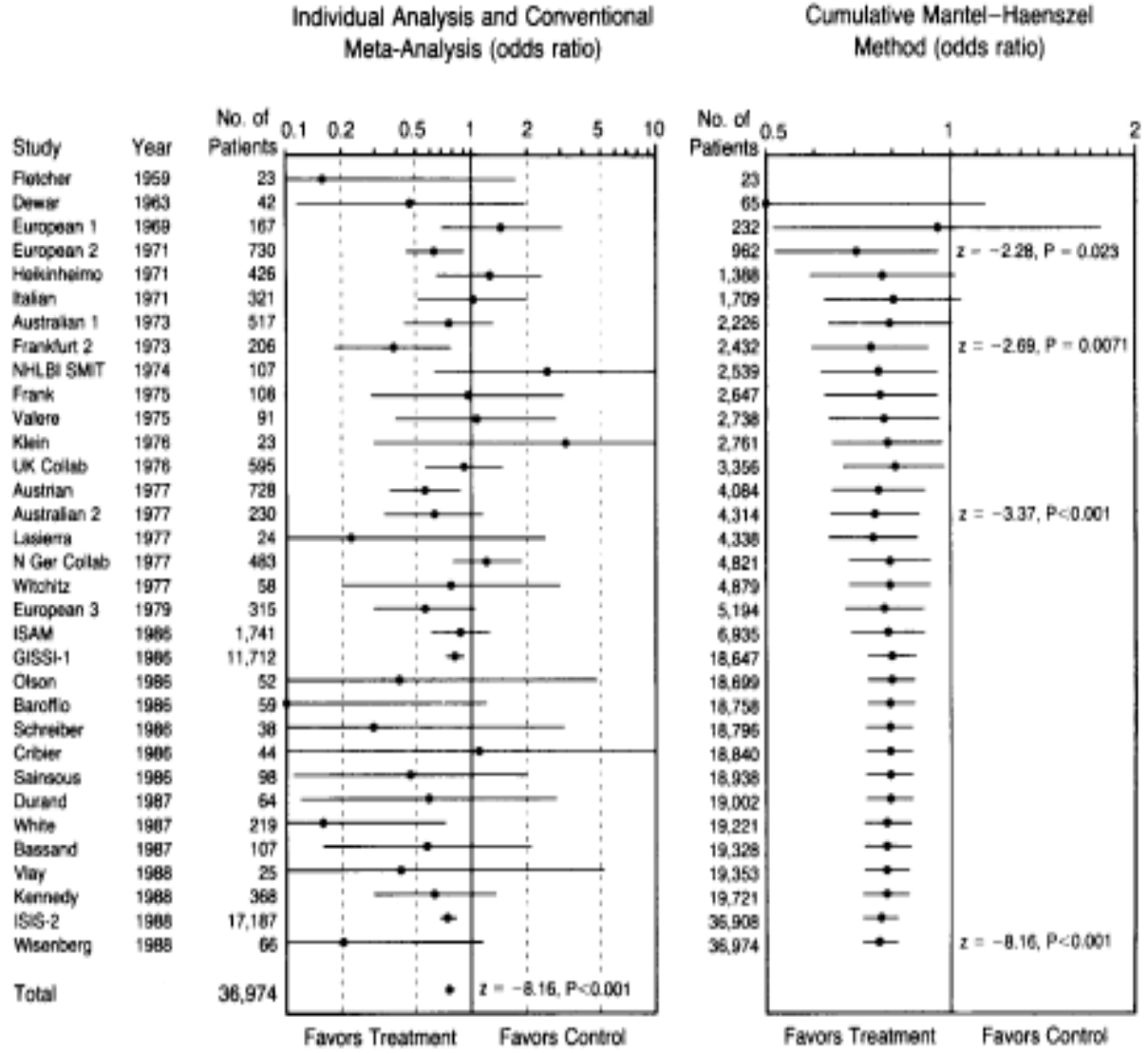


Figure 1. Conventional and Cumulative Meta-Analyses of 33 Trials of Intravenous Streptokinase for Acute Myocardial Infarction. The odds ratios and 95 percent confidence intervals for an effect of treatment on mortality are shown on a logarithmic scale. A bibliography of the published trial reports is available from the authors.

Lau J et al. 1992. Cumulative meta-analysis of therapeutic trials for myocardial infarction. New England Journal of Medicine 327(4): 248-254

Why missing outcome data matter

- Missing outcome data are common in RCTs
  - In mental health, the dropout rate may exceed 50%
- This creates two main problems at RCT level:
  - Loss in power and precision, because the sample size decreases
  - Bias (maybe)
- Systematic reviewers typically believe missing data have been adequately handled at the trial level
  - Wrong assumptions will lead to biased estimates
- There is no remedy for missing data - we can only do sensitivity analyses and see how much the results change under different assumptions
- **Any meta-analysis makes an untestable assumption about missing data – even if reviewers don't realize it!**

Assumptions about missing outcome data

Missing Completely At Random (MCAR)

The probability that data are missing does not depend on the outcome or other observed or unobserved factors that impact on the outcome

- e.g., in an RCT of antihypertensives that measures blood pressure (BP) data, some measurements are missing due to breakdown of an automatic sphygmomanometer

Missing At Random (MAR)

The probability that data are missing does not depend on the outcome or unobserved factors that impact on the outcome

- e.g., in an RCT of antihypertensives that measures blood pressure (BP) data, older participants are more likely to have their BP recorded. Missing data are MAR if at any age, individuals with low and high BP are equally likely to have their BP recorded

Missing Not At Random (MNAR) or Informatively Missing (IM)

The probability that data are missing depends on the outcome

- e.g., in an RCT of antipsychotics individuals with relapse are more likely to leave the study early in the placebo group

RCT: Haloperidol vs. placebo in schizophrenia (Beasley 1998)

	Success	Failure	Missing
Haloperidol	29	18	22
Placebo	20	14	34

- Outcome: clinical global improvement (yes/no)
- Missing rates are 32% for haloperidol and 50% for placebo
- **How do systematic reviewers analyze these data?**

RCT: Haloperidol vs. placebo in schizophrenia (Beasley 1998)

	Success	Failure	Missing
Haloperidol	29	18	22
Placebo	20	14	34

- **Success rates: 29/47=0.62 vs. 20/34=0.59 (Available Cases Analysis, ACA)**
- *Which is the assumption behind?*
  - *MAR!*
- **Success rates: 29/69=0.42 vs. 20/68=0.29**
- *Which is the assumption behind?*
  - *We assume that successes have no chance to dropout!*
- **ANY analysis makes assumptions which, if wrong, produces biased results!**

Mirtazapine vs. Placebo for depression

Change in depression symptoms measured on the HAMD21 scale

Study	Placebo				Mirtazapine			
	xp	sdp	n	m	xm	sdm	n	m
MIR 003-003	-11.5	8.3	24	21	-14	7.3	27	18

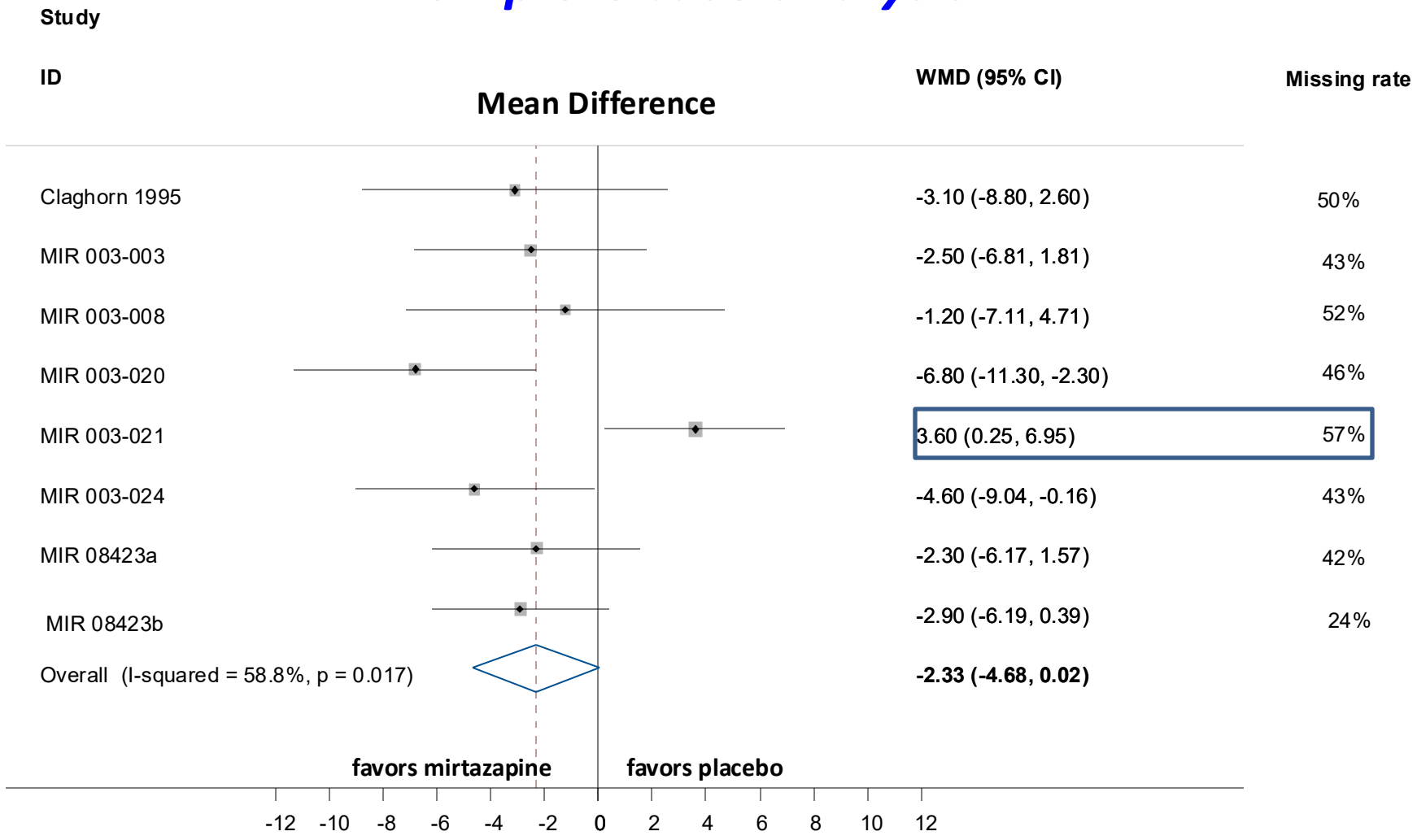
What is the sample size you would use to estimate the weight of the Mean Difference (MD) in this study?

- Option 1: the observed=24+27
  You assume MAR! Available Cases Analysis!
- Option 2: the randomized=24+27+21+18
  You impute the observe mean in all missing participants – it is wrong as it produces spuriously small standard errors!

Random effect meta-analysis of mean change in HAMD21 score.

Mirtazapine vs placebo.

Complete case analysis



Summary table of possible analyses (Cochrane Handbook)

Analysis	Outcome	Description of method/how it handles missing participants	Assumptions about missing outcome data	Adequacy for addressing missing data
Available cases	Binary; Continuous	Ignore them	A random sample of all participants	*Valid under missing at random (MAR)*
Worst (best)-case scenario	Binary	Imputes failures in the treatment group and successes in the control (or vice-versa)	Worse in the experimental group (better in the experimental group)	*Inflates sample size and erroneously increase precision/reduce standard errors too extreme downweighting.*
Mean imputation	Continuous	Imputes the mean value	The same as observed	
Other simple imputation	Binary; Continuous	Imputes specific number of successes/mean value	Explicit assumptions about them	
Last Observation Carried Forward	Continuous	Replace with the last observed value	Outcome does not change with time	
The suggested model	Binary; Continuous	Downweigh studies with high missing rates	The more the missing rate the less reliable is the estimate	***Accounts for uncertainty in the missing outcome data - Expert opinion can also be used.***

Many published papers in top medical journals suggest single imputation methods!

Many recent RCTs employ single imputation schemes such as LOCF!

A general approach

- We propose the Informative Missingness Parameter (IMP) as a general way to think about missing data
  - **Definition:** IM parameter relates a summary statistic in the missing group to the corresponding summary statistic in the observed group
  - **IMOR:** Informative Missing Odds Ratio; the odds of success in the missing group over the odds of success in the observed group
  - **IMDoM:** Informative Missing Difference of Means ; mean in the missing group minus the mean in the observed group

Pattern mixture models

i refers to study
j refers to arm
k refers to individual

$$Y = \left(Y^{obs}, Y^{miss}\right)'$$

$$R_{ijk} = \begin{cases} 1 & if\ outcome\ is\ reported \\ 0 & otherwise \end{cases}$$

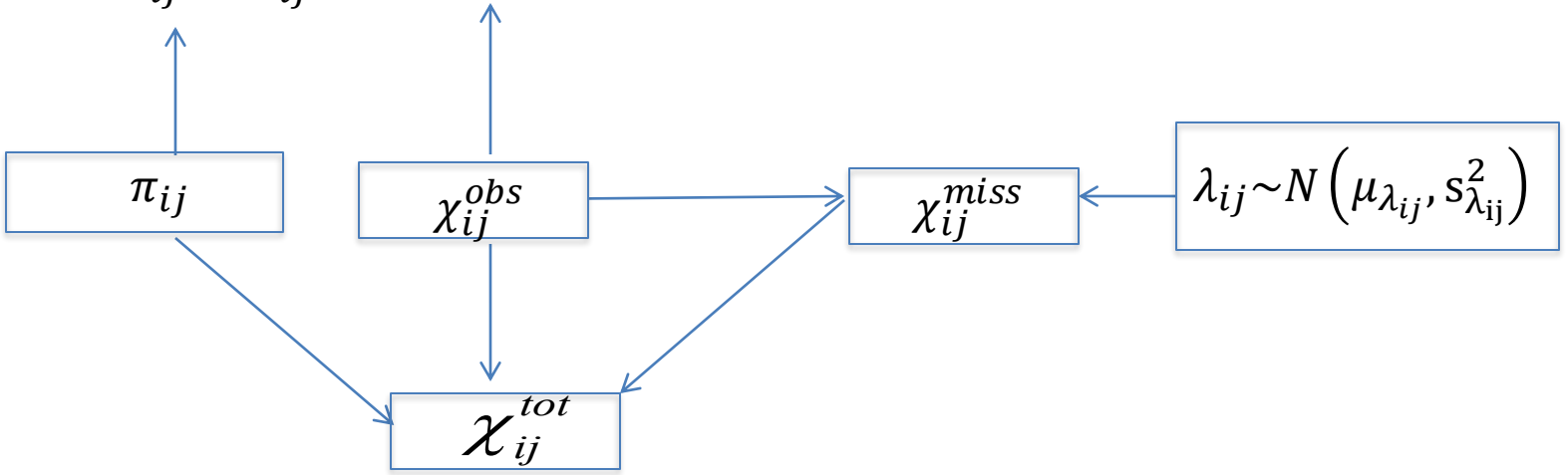
$$P\left(R_{ijk} = 1\right) = \pi_{ij}^{obs} \qquad P\left(R_{ijk} = 0\right) = \pi_{ij}^{miss} = 1 - \pi_{ij}^{obs}$$

$$E\left(Y_{ijk} \middle| R_{ijk} = 1\right) = \chi_{ij}^{obs} \qquad E\left(Y_{ijk} \middle| R_{ijk} = 0\right) = \chi_{ij}^{miss}$$

$$f(Y, R) = f(Y|R)f(R)$$

Model for arm j of study i pattern mixture model

$$p_{ij} = \frac{n_{ij}}{n_{ij} + m_{ij}} \qquad x_{ij}^{obs}, s_{ij}^{obs} \qquad g(x_{ij}^{miss}) = g(x_{ij}^{obs}) + \lambda_{ij}$$



$$x_{ij}^{tot} = p_{ij} x_{ij}^{obs} + (1 - p_{ij}) x_{ij}^{miss}$$

$$x_{ij}^{tot} = p_{ij} \chi_{ij}^{obs} + (1 - p_{ij})(g^{-1}(g(x_{ij}^{obs}) + \lambda_{ij})$$

studies i, arms j

Continuous outcome

Informative Missingness Difference in means

$$g(x_{ij}^{miss}) = g(x_{ij}^{obs}) + \lambda_{ij}$$

g is the identity function

$$\lambda_{ij} = x_{ij}^{miss} - x_{ij}^{obs}$$

IMP =λ= mean in missing – mean in observed

- **λ=1,** the mean in the missing participants exceed the mean in the observed participants by one unit
- **λ=-1,** the mean in the missing participant is one unit less compared to the mean of the observed participants
- **λ=0, the data is missing at random**

Mirtazapine vs. Placebo for depression

Study	Placebo				Mirtazapine			
	x	sd	n	m	x	sd	n	m
Claghorn 1995	-11.4	10.2	19	26	-14.5	8.8	26	19
MIR 003-003	-11.5	8.3	24	21	-14	7.3	27	18
MIR 003-008	-11.4	8	17	13	-13.2	8	12	18

We assume **IMP=1 for Placebo** (the symptoms increased in the missing participants) and **IMP=-1 for Mirtazapine** (missing participants left because of early response)

Study	Placebo		Mirtazapine		MD
	Missing mean	Total mean	Missing mean	Total mean	
Claghorn 1995	-10.4	-10.82	-15.5	-14.92	-4.10
MIR 003-003	-10.5	-11.03	-15	-14.40	-3.37
MIR 003-008	-10.4	-10.97	-14.2	-13.80	-2.83

Meta-analyze these! (you need their SEs)

Consider a study comparing Mirtazapine to Placebo in patients with depression and the outcome is measured using HAMD21 scale at 6 weeks.

In the mirtazapine group:

- *some participants provide the outcome (completers)*
- *others dropped out of the study without providing outcome data (non-completers).*

In the completers we observe a mean drop of 14 in HAMD21 compared to baseline and a 95% CI for the mean drop is (11,17).

Some participants dropped out of the study without providing outcome data (non-completers) and we want to guess their outcomes.

The table below gives some possible outcomes for a non-completer.

What proportion of the non-completers will have a reduction in HAMD21 scale falling in the categories described below?

	What proportion of the non-completers in the Mirtazapine group would have a reduction in HAMD21 in each of the following categories?								
	Interval of mean change for the non-completers (percentage improvements with respect to baseline score are given in parentheses)								
	More than 19	**Between 19 and 17**	**Between 17 and 15**	**Between 15 and 13**	**Between 13 and 11**	**Between 11 and 9**	**Between 9 and 7**	**Less than 7**	**Total**
Your answers	5	10	15	20	20	15	10	5	100%

White IR, Carpenter J, Evans S, Schroter S. Eliciting and using expert opinions about dropout bias in randomized controlled trials. Clin Trials. 2007;4(2):125-39. doi: 10.1177/1740774507077849.

$$\lambda \sim N(0, 2^2)$$

Estimating effect size β_i and $var(\beta_i)$
Taylor Series Approximation/Monte Carlo

$$\beta_i = f\left(x_{iT}^{tot}\right) - f\left(x_{iC}^{tot}\right)$$

$$x_{ij}^{tot} = p_{ij}\chi_{\mathrm{ij}}^{obs} + \left(1 - p_{ij}\right)\left(g^{-1}\left(g\left(x_{ij}^{obs}\right) + \lambda_{ij}\right)\right.$$

$E(\beta)$ and $Var(\beta)$ are straightforwardly calculated if *f* and *g* are identity functions

$$E(\beta_i) = x_{iT}^{obs} - x_{iC}^{obs} + (1 - p_{iT})\mu_{\lambda_{iT}} - (1 - p_{\mathrm{iC}})\mu_{\lambda_{ic}}$$

$$var(\beta_i) = \sum_{j=C,T}\left[\frac{p_{ij}(1-p_{ij})}{n_{ij}+m_{ij}}\left(\mu_{\lambda_{ij}}^2 + \sigma_{\lambda_{ij}}^2\right) + \frac{s_{ij}^2}{n_{ij}} + \sigma_{\lambda_{ij}}^2\left(1-p_{ij}\right)^2\right] - 2\rho_{\lambda_i}\sigma_{\lambda_{iC}}\sigma_{\lambda_{iT}}(1-p_{iT})\,(1-p_{iC})$$

Fictional example

Studies with same standard deviations and observed sample sizes per arm, but different missing rates

Study	Observed	Naïve SE (relative weight)	Randomized
1	100	0.07 (20%)	100
2	100	0.07 (20%)	120
3	100	0.07 (20%)	150
4	100	0.07 (20%)	200
5	100	0.07 (20%)	300

Would you give each study the same weight?

No, because uncertainty should be larger when you have more missing data!

- *The assumption (MAR or a specific form of IM) you will make to estimate IMP has more impact on study 5 rather than on study 2!*
- *The observed sample size is not the only source of uncertainty!*
- ***First source of extra uncertainty:** Proportion of missing data!*

Fictional example

Studies with same standard deviations and observed sample sizes per arm, but different missing rates

Study	Observed	Naïve SE (relative weight)	Randomized
1	100	0.07 (20%)	100
2	100	0.07 (20%)	120
3	100	0.07 (20%)	150
4	100	0.07 (20%)	200
5	100	0.07 (20%)	300

Would you give each study the same weight?

We want to assume that IMDOM=0

- *We can NEVER be sure that the mean in the missing is exactly the same as in the observed*
- *We have some uncertainty as to what exactly is the mean in the missing data*
- *This can be represented by uncertainty in IMDOM!*
- ***We assume IMDOM=0 with uncertainty interval (-1, 1)***
- ***Second source of extra uncertainty:*** *Uncertainty about the assumption and IM parameter*

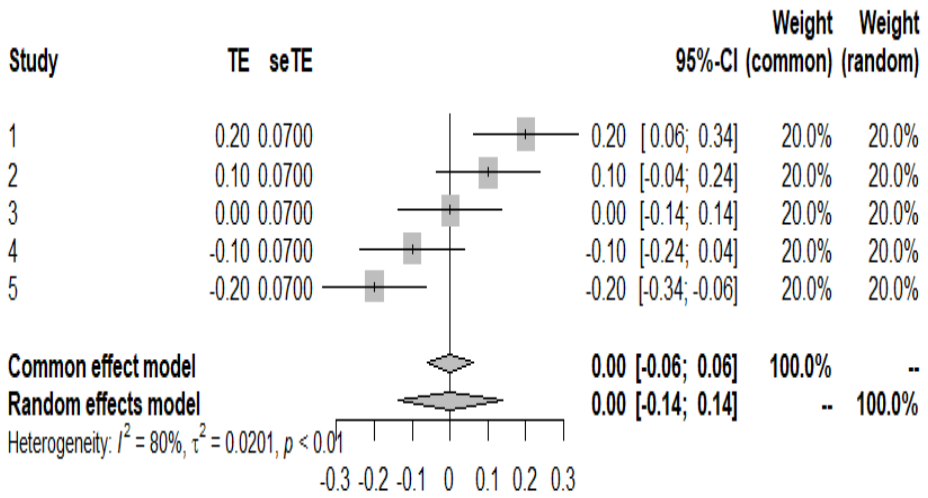
Fictional example

Studies with same standard deviations and observed sample sizes per arm, but different missing rates

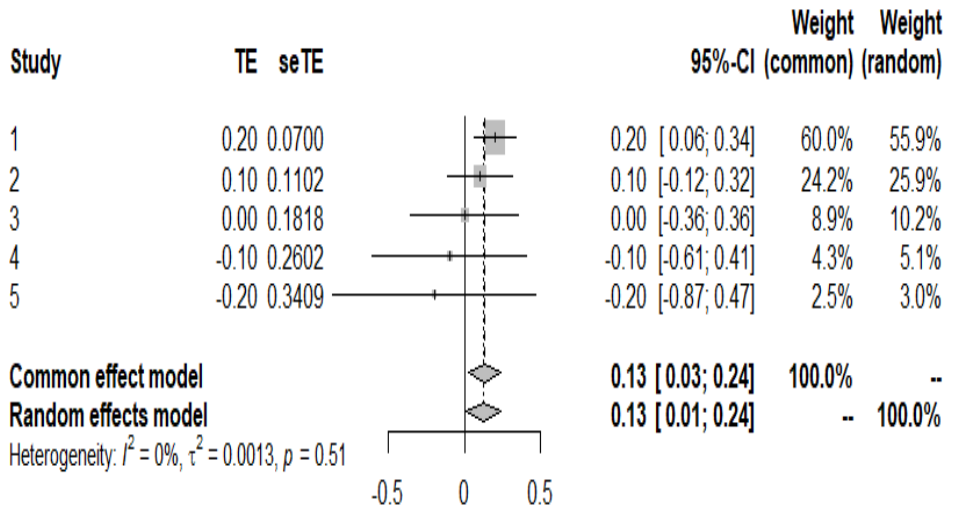
Study	Observed	Naïve SE (relative weight)	Randomized	**Corrected SE (relative weight)**
1	100	0.07 (20%)	100	0.07 (57%)
2	100	0.07 (20%)	120	0.11 (25%)
3	100	0.07 (20%)	150	0.17 (10%)
4	100	0.07 (20%)	200	0.24 (5%)
5	100	0.07 (20%)	300	0.32 (3%)

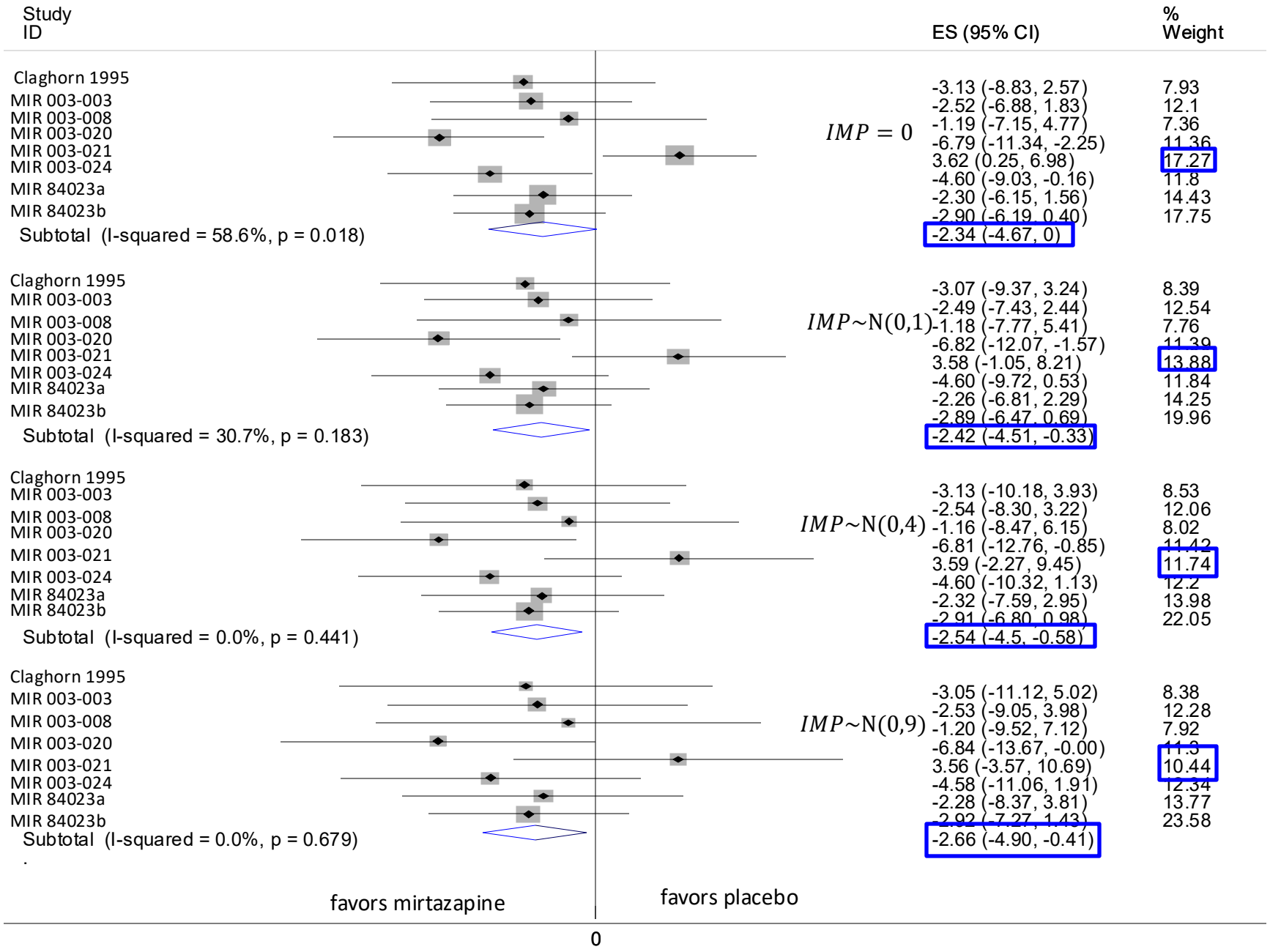
- We assume IMP=0 with uncertainty interval (-1, 1)
- Studies with more missing data get less weight!
  - *IM parameter*

Complete case analysis
$\lambda = 0$



$\lambda \sim N(0, 0.5^2)$

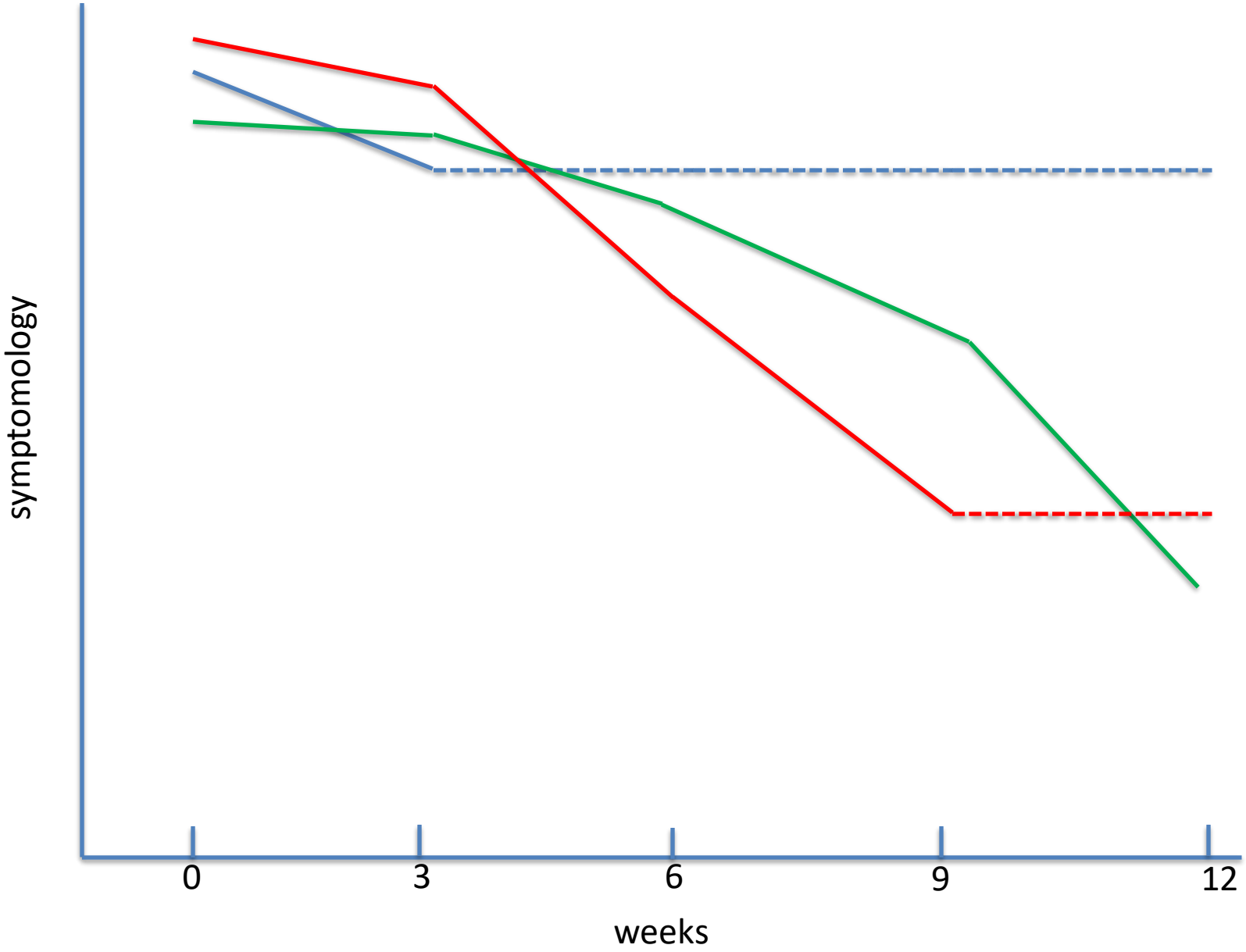



Study ID
ES (95% CI)
% Weight
Claghorn 1995
MIR 003-003
MIR 003-008
MIR 003-020
MIR 003-021
MIR 003-024
MIR 84023a
MIR 84023b
Subtotal (I-squared = 58.6%, p = 0.018)
-3.13 (-8.83, 2.57) 7.93
-2.52 (-6.88, 1.83) 12.1
-1.19 (-7.15, 4.77) 7.36
-6.79 (-11.34, -2.25) 11.36
3.62 (0.25, 6.98) 17.27
-4.60 (-9.03, -0.16) 11.8
-2.30 (-6.15, 1.56) 14.43
-2.90 (-6.19, 0.40) 17.75
-2.34 (-4.67, 0)
$IMP = 0$
Claghorn 1995
MIR 003-003
MIR 003-008
MIR 003-020
MIR 003-021
MIR 003-024
MIR 84023a
MIR 84023b
Subtotal (I-squared = 30.7%, p = 0.183)
-3.07 (-9.37, 3.24) 8.39
-2.49 (-7.43, 2.44) 12.54
-1.18 (-7.77, 5.41) 7.76
-6.82 (-12.07, -1.57) 11.39
3.58 (-1.05, 8.21) 13.88
-4.60 (-9.72, 0.53) 11.84
-2.26 (-6.81, 2.29) 14.25
-2.89 (-6.47, 0.69) 19.96
-2.42 (-4.51, -0.33)
$IMP \sim \mathrm{N}(0,1)$
Claghorn 1995
MIR 003-003
MIR 003-008
MIR 003-020
MIR 003-021
MIR 003-024
MIR 84023a
MIR 84023b
Subtotal (I-squared = 0.0%, p = 0.441)
-3.13 (-10.18, 3.93) 8.53
-2.54 (-8.30, 3.22) 12.06
-1.16 (-8.47, 6.15) 8.02
-6.81 (-12.76, -0.85) 11.42
3.59 (-2.27, 9.45) 11.74
-4.60 (-10.32, 1.13) 12.2
-2.32 (-7.59, 2.95) 13.98
-2.91 (-6.80, 0.98) 22.05
-2.54 (-4.5, -0.58)
$IMP \sim \mathrm{N}(0,4)$
Claghorn 1995
MIR 003-003
MIR 003-008
MIR 003-020
MIR 003-021
MIR 003-024
MIR 84023a
MIR 84023b
Subtotal (I-squared = 0.0%, p = 0.679)
-3.05 (-11.12, 5.02) 8.38
-2.53 (-9.05, 3.98) 12.28
-1.20 (-9.52, 7.12) 7.92
-6.84 (-13.67, -0.00) 11.9
3.56 (-3.57, 10.69) 10.44
-4.58 (-11.06, 1.91) 12.34
-2.28 (-8.37, 3.81) 13.77
-2.92 (-7.27, 1.43) 23.58
-2.66 (-4.90, -0.41)
$IMP \sim \mathrm{N}(0,9)$
favors mirtazapine
favors placebo
0

Why LOCF-imputed outcome data matter ?

Haloperidol vs. placebo in schizophrenia

r: success *f: failures* *m:missing*	Haloperidol			Placebo		
	rh	fh	mh	rp	fp	mp
Arvanitis	25	25	2	18	33	0
Beasley	29	18	22	20	14	34
Bechelli	12	17	1	2	28	1
Borison	3	9	0	0	12	0
Chouinard	10	11	0	3	19	0
Durost	11	8	0	1	14	0
Garry	7	18	1	4	21	1
Howard	8	9	0	3	10	0
Marder	19	45	2	14	50	2
Nishikawa 82	1	9	0	0	10	0
Nishikawa 84	11	23	3	0	13	0
Reschke	20	9	0	2	9	0
Selman	17	1	11	7	4	18
Serafetinides	4	10	0	0	13	1
Simpson	2	14	0	0	7	1
Spencer	11	1	0	1	11	0
Vichaiya	9	20	1	0	29	1

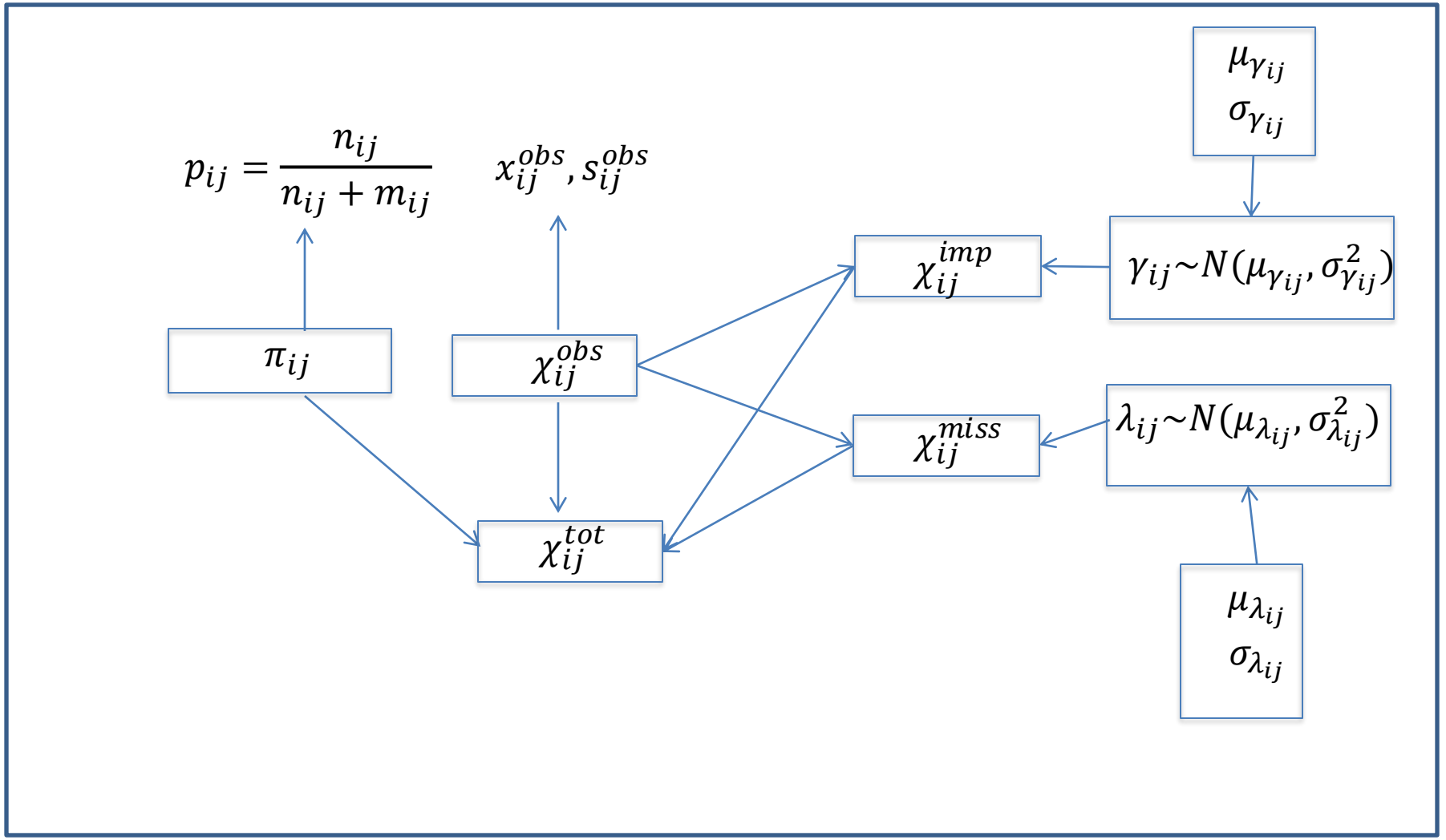

symptomology
0
3
6
9
12
weeks

The BILOCF parameter

- Bias in the LOCF imputed outcome value

BILOCF = true mean outcome – LOCF imputed mean

Model for arm j of study i pattern mixture model



Expert opinion to inform the BILOCF parameter

- *Participants randomized to fluoxetine were observed to have a mean score of 25 at the HAMD21 scale with 95% confidence interval [20-30] at 8 weeks after onset of the treatment (a reduction of 15 units compared to baseline). What is your prediction about their outcome at 12 weeks?*

IM and BILOCF parameters

Parameter	Interpretation
Informative Missingness (IM)	Difference in the mean outcome between missing participants and completers
Bias in the LOCF (BILOCF)	Difference between LOCF-imputed mean and its true value

When we adjust the weight of a study, we need to consider:

- *The observed data*
- *The missing rate*
- *Uncertainty in the IMP*
- *The imputation rate*
- *Uncertainty in the BILOCF parameter*

These parameters are unknown. We can inform them through:

- *Expert opinion*
- *Sensitivity analysis*
- *External data (e.g. if trials report both results from completers and completers+imputed outcomes)*

Reboxetine vs placebo for depression

Study	Treatment	IMP	MEAN IMP+COM	SD IMP+COM	COM	MEAN COM	SD COM	Missing
Study 1	reboxetine	4	12,60	10,30	22	10,10	8,20	0
	placebo	16	29,50	13,30	10	16,30	10,20	0
Study 2	reboxetine	7	17,18	4,75	17	16,59	4,73	2
	placebo	5	16,6	5,14	21	15,52	4,78	1

Conclusions

- We suggest models that can
  - account for the fact that the presence of missing and LOCF-imputed data introduce uncertainty in the study estimates
  - naturally downweight studies with lots of missing and imputed data
  - can model MAR or departures from MAR
- **metamiss2** command in STATA (R package forthcoming – Christos Christogiannis)

References

- **Mavridis D,** White IR. Dealing with missing outcome data in meta-analysis. Research Synthesis Methods. 2020;11(1):2-13. doi: 10.1002/jrsm.1349.
- White IR., **Mavridis D**. Dealing with missing data in meta-analysis, 3rd edition of *Systematic Reviews in Health Care: Meta- Analysis in Context*, BMJ publishing group
- **Mavridis D**, Salanti G, Furukawa TA, Cipriani A, Chaimani A, White IR. Allowing for uncertainty due to missing and LOCF imputed outcomes in meta-analysis. *Statistics in Medicine*. 2019;38(5):720-737. doi: 10.1002/sim.8009.
- Chaimani A, **Mavridis D**, Higgins JPT, Salanti G, White IR. Allowing for informative missingness in aggregate data meta-analysis with continuous or binary outcomes: Extensions to metamiss. *The Stata Journal* 2018;18(3) 716-740.
- **Mavridis D**, White IR, Higgins JP, Cipriani A, Salanti G. Allowing for uncertainty due to missing continuous outcome data in pairwise and network meta-analysis. *Statistics in Medicine* 2015;34(5):721-4.
- **Mavridis D**, Chaimani A, Efthimiou O, Salanti G. Missing outcome data in meta-analysis. *Evidence Based Mental Health* 2014
- https://www.youtube.com/watch?v=fY4sVM8H37w Cochrane Statistical Training. Talk with Christos Christogiannis who has developed a relative R package (soon to appear)