







## Allowing for uncertainty due to missing outcome data in meta-analysis

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### **Scope of this webinar**

- To present a "new" method to deal with missing outcome data in aggregate data meta-analysis
- It is not about
  - missing studies (publication bias)
  - missing outcomes (selective outcome reporting)
  - missing statistics (standard deviations/errors)
- It is not about IPD meta-analysis

#### Outline

• Why are missing data a problem in meta-analysis?

- Examples
  - haloperidol in schizophrenia (dichotomous outcome)
  - mirtazapine in depression (continuous outcome)
- Very brief overview of currently used methods

• Proposed method based on Informative Missingness Parameters (IMP)

#### Why missing outcome data matter?

- Missing outcome data are common in RCT's
  - In mental health, the dropout rate may exceed 50%
- It creates two main problem at RCT level:
  - loss in power and precision
    - $\circ$  because the sample size decreases
  - bias (maybe)
    - $\circ$  any analysis must make an untestable assumption about missing data
    - $\circ$  wrong assumption  $\implies$  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

## **Fictional example**



Study	Observed	SMDNaïve SE (relative weight)		Randomized
1	100	0	0.07 (20%)	100
2	100	0.1	0.07 (20%)	120
3	100	0.2	0.07 (20%)	150
4	100	0.3	0.07 (20%)	200
5	100	0.4	0.07 (20%)	300

- Would you give each study the same weight in the meta-analysis?
  - a) Yes, because for all studies we have data for 100 participants
  - b) No, I will give the largest weight to study 5 because has the largest number of randomized participants
  - c) No, I will give the largest weight to study 1 because observed and randomized participants are the same
  - d) No, I will give the smallest weight to study 1 because the SMD is 0

# Meta-analysis with studies with missing outcome data

- There are methods to address missing outcome data at trial level (LOCF, multimple imputation, etc.)
  –NOT addressed here as you need IPD
- What do you do when you have aggregate data from studies with missing data?
  - any meta-analysis makes an untestable assumption about missing data even if reviewers don't realize it!

## **Missing data mechanisms**

• Missing completely at random (MCAR)

The probability that data are missing does not depend neither on observed nor on unobserved data

- In an RCT of antihypertensives that measures blood pressure (BP), some data are missing due to the 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

- In an RCT of antihypertensives that measures blood pressure (BP), 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)

#### The probability that data are missing depends on the outcome

 In an RCT of antipsychotics individuals with relapse are more likely to leave the study early in the placebo group

## Meta-analysis of studies with missing outcome data

Outcome is reponse to treatment in some standardized scale

- Example: Haloperidol vs. placebo in schizophrenia
- 17 trials in a Cochrane Review
- We use an inverse-variance-weighted random-effect analysis on the risk ratio scale
- Example: Mirtazapine vs. placebo in depression
- 8 trials taken from a recent network meta-analysis (Cipriani et al, 2018)
- We use an inverse-variance-weighted random-effect analysis on the standardized mean difference scale

	Success	Failure	Missing
Haloperidol	29	18	22
Placebo	20	14	34

- Outcome: clinical global improvement (yes/no)
- RR=1.05 (95% CI: 0.73-1.50)
- Missing rates are 32% for haloperidol and 50% for placebo

	Success	Failure	Missing
Haloperidol	29	18	22
Placebo	20	14	34

- What is the data missing mechanism?
  - a) MAR, because data are missing from both groups
  - b) Most probably MAR, because data are missing from both groups
  - c) Most probably MNAR, because this is the psychiatrists' opinion
  - d) We are clueless

	Success	Failure	Missing
Haloperidol	29	18	22
Placebo	20	14	34

- How would you analyze these data?
  - a) I would analyze only the completers
  - b) I would assume missing participants did not respond to treatment
  - c) I would assume the same risks in the missing participants as those in the observed
  - d) I would exclude the study from the meta-analysis
  - e) None of the above

	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)

#### RR=1.05 (95% CI: 0.73-1.50)

Which i	ANY analysis makes assumptions which, if wrong, produces
Succes	biased results!

RR=1.43 (95% CI: 0.90-2.27)

Which is the assumption behind? Successes have no chance to dropout!

#### Haloperidol vs. placebo in schizophrenia

	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	$\bigcirc$	2	9	$\bigcirc$
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

#### Haloperidol vs. placebo Available case analysis

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		/0
author	RR (95% CI)	Weight
Garry	1.75 (0.58, 5.24)	3.37
Durost	8.68 (1.26, 59.95)	1.09
Simpson	2.35 (0.13, 43.53)	0.48
Vichaiya	— 19.00 (1.16, 311.96)	0.52
Serafetinides	8.40 (0.50, 142.27)	0.51
Howard	2.04 (0.67, 6.21)	3.27
Reschke	3.79 (1.06, 13.60)	2.48
Selman	1.48 (0.94, 2.35)	19.11
Nishikawa_82	3.00 (0.14, 65.90)	0.42
Bechelli	6.21 (1.52, 25.35)	2.05
Nishikawa 84	9.20 (0.58, 145.76)	0.53
Borison	7.00 (0.40, 122.44)	0.49
Spencer	11.00 (1.67, 72.40)	1.14
Chouinard	3.49 (1.11, 10.95)	3.10
Marder	1.36 (0.75, 2.47)	11.37
Beasley	1.05 (0.73, 1.50)	31.22
Arvanitis	1.42 (0.89, 2.25)	18.86
$\phi$ verall (I-squared = 41.4%, p = 0.038)	1.57 (1.28, 1.92)	100.00
.1 .3 1 3 10 30 100		
nissing rate 41% Favors placebo Favors haloperidol		14

#### **Mirtazapine vs Placebo for depression** Change in depression symptoms measured on the HAMD21 scale

Study		Placebo				Mirtazapine		
	хр	sdp	n	m	xm	sdm	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
MIR 003-020	-6.2	6.5	24	19	-13	9	23	21
MIR 003-021	-17.4	5.3	21	29	-13.8	5.9	22	28
MIR 003-024	-11.1	9.9	27	23	-15.7	6.7	30	20
MIR 84023a	-11.9	8.6	33	24	-14.2	7.6	35	25
MIR 84023b	-11.8	8.3	48	18	-14.7	8.4	51	13

#### Mirtazapine vs Placebo for depression Complete case analysis



#### **Summary 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	
mean imputation	continuous	imputes the mean value	the same as observed	precision/reduce standard errors	
other simple imputation	binary continuous	imputes specific number of successes/mean value	explicit assumptions about them		
gamble- hollis	binary	downweight studies according to best/worst case scenarios	studies with large differences between best/worst case scenario are less reliable	too extreme downweighting	
The suggested model	binary continuous	downweight 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	

## A general approach

- We propose the informative missingness parameter (IMP) as a general way to think about missing data
- **Definition**: IMP 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): the mean in the missing group minus the mean in the observed group
- IMPs may different between intervention and control arm
- IMPs are not known, but we can suggest clinically plausible values

### **Characteristics of our approach**

- We don't impute missing data!
- We simply make assumptions about the outcome in the missing data and how it is related to the outcome in the observed data (we "update" the study outcome using the observed data)
- We employ a pattern-mixture model
- In the entire procedure we account for the fact that data is not fully observed
  - This is very important in order to obtain correct standard errors from studies! (see later...)

#### Pattern mixture model

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

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

$$R_{ijk} = \begin{cases} 1 \text{ if outcome is reported} \\ 0 \text{ if outcome is missing} \end{cases} P(R_{ijk} = 1) = \pi_{ij}^{obs}$$

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

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

#### Pattern mixture model Model for arm *j* of study *i*



#### **Continuous outcome** Informative missingness difference of means

$$g(\chi_{ij}^{miss}) = \lambda_{ij} + g(\chi_{ij}^{obs})$$
  
If g is the identity function  
$$\lambda_{ij} = \chi_{ij}^{miss} - \chi_{ij}^{obs}$$

#### IMP = $\lambda$ = mean in missing – mean in observed

- $\lambda=1$  the mean in the missing participants exceed the mean in the observed participants by one unit
- $\lambda$ =-1 the mean in the missing participant is one unit less compared to the mean of the observed participants
- $\lambda=0$  the data is missing at random

#### **Dichotomous outcome** Informative missingness odds ratio

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

If g is the identity function

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

IMP = $\lambda$ = log(odds) in missing – log(odds) in observed

 $IMOR=exp(\lambda)=\frac{odds of success in missing}{odds of success in observed}$ 

#### **Dichotomous outcome** Informative missingness odds ratio

# $IMOR = \frac{odds \text{ of success in missing}}{odds \text{ of success in observed}}$

• **IMOR=2** the odds of success is double in the missing participants rather than the observed

(e.g. maybe people leave the study because of early response!)

• **IMOR=0.5** the odds of success is half in the missing participants rather than the observed

(e.g. maybe people leave the study because of they are disappointed as they don't see any improvement!)

• IMOR=1 the data is missing at random

Note that in this case  $\lambda = log(IMOR)$ , hence  $\lambda = 0$  implies MAR

### **Assumptions about the IMP**

• Missing at random  $\lambda_{ij} = 0$ 

• Free 
$$\lambda_{ij} \sim N\left(\mu_{\lambda_{ij}}, \sigma_{\lambda_{ij}}^2\right)$$

- Study-specific  $\lambda_i \sim N(\mu_{\lambda_i}, \sigma_{\lambda_i}^2)$
- Correlated  $\lambda$ 's

$$\begin{pmatrix} \lambda_{iC} \\ \lambda_{iT} \end{pmatrix} \sim N \left( \begin{pmatrix} \mu_{\lambda_{iC}} \\ \mu_{\lambda_{iT}} \end{pmatrix}, \begin{pmatrix} \sigma_{\lambda_{iC}}^2 & \rho_{\lambda} \sigma_{\lambda_{iC}} \sigma_{\lambda_{iT}} \\ \rho_{\lambda} \sigma_{\lambda_{iC}} \sigma_{\lambda_{iT}} & \sigma_{\lambda_{iT}}^2 \end{pmatrix} \right)$$

# A two-stage approach

• At the first-stage we compute an adjusted effect size

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

– If the outcome is dichotomous (x is the risk of the event)

 $\circ \beta_i$  is the Risk Difference if f is the identity function

 $\circ \beta_i$  is the logarithm of Risk Ratio if f is the logarithmic function

 $\circ \beta_i$  is the logarithm of Odds Ratio if f is the logit function

– If the outcome is continuous (x is the mean outcome)

 $\circ \beta_i$  is the Mean Difference if *f* is the identity function

- $\beta_i$  is the Standardized Mean Difference if f is the identity function divided with the pooled standard deviation
- At the second-stage we compute an inverse-variance random effects meta-analysis

# Haloperidol vs placebo in schizophrenia

Ctudy/	Haloperidol			Placebo		
Study	rh	fh	mh	rp	fp	mp
Beasley	29	18	22	20	14	34
Selman	17	1	11	7	4	18
Marder	19	45	2	14	50	2

Let us assume:

IMOR=1 in Haloperidol (MAR)

IMOR=0.5 in Placebo (IM due to lack of effectiveness)

	Haloperidol (IMOR 1)			Placebo (IMOR 0.5)			
Study	Odds	Odds	Total	Odds	Odds	Total	OR
	observed	missing	odds	observed	missing	odds	
Beasley	1.61	1.61	1.61	1.43	0.72	1.01	1.60
Selman	17	17	17	1.75	0.88	1.13	15.04
Marder	0.42	0.42	0.42	0.28	0.14	0.27	1.56

Meta-analyze these!

(you need their SEs... see later) 27



# Work out the total means starting from IMDOM

• We ask a clinician (or several!) with experience in clinical trials in the field:

"Out of 100 patients randomized in drug X, 60 finished the study and had a mean score 3 whereas 40 patients did not finish. What do you guess would be the mean score in those who did not finish?"

-he answered "the mean score in those who did not finish is on average 4"

- What is the value of IMDOM?
  - a) IMDOM=7
  - b) IMDOM=4
  - c) IMDOM=3
  - d) IMDOM=1





IMDOM  $\lambda$ 

### Mirtazapine vs placebo for depression

Study	Placebo			Mirtazapine				
	хр	sdp	n	m	xm	sdm	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 **IMDOM=1** for Placebo (the symptoms decreased in the missing participants) and **IMDOM=-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... see later)

### **Fictional example**

Study	Observed	SMD	Naïve SE (relative weight)	Randomized
1	100	0	0.07 (20%)	100
2	100	0.1	0.07 (20%)	120
3	100	0.2	0.07 (20%)	150
4	100	0.3	0.07 (20%)	200
5	100	0.4	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 on how the outcome in the missing and observed participants is related ( $\lambda_{ij}$ ) 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 means and same standard deviations per arm and observed sample size, but different missingness.

Study	Observed	SMD	Naïve SE (relative weight)	Randomized
1	100	0	0.07 (20%)	100
2	100	0.1	0.07 (20%)	120
3	100	0.2	0.07 (20%)	150
4	100	0.3	0.07 (20%)	200
5	100	0.4	0.07 (20%)	300

Let us assume that there are no differences in the mean outcome between missing and observed participants

- 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!
- Let us assume assume IMDOM=0 with uncertainty interval (-1, 1) that is approximately translated to  $\lambda_{ij} \sim N(0, 0.5^2)$

Second source of extra uncertainty: Uncertainty about the assumption for IMP

# **IMOR/IMDOM** have uncertainty

#### IMDOM=0, (0.5, 0.0)

" the missing participants are likely to have on average the same score as the observed participant with uncertainty interval (0.5, 0.5)"

Equivalently we need to set values for IMDOM and sd(IMDOM)

 $\lambda_{ij} \sim N(0, 0.5^2)$ 

Similarly for IMOR...

IMOR=1, (0.6, 1.6)

" the missing participants are likely to have the same odds of success as the observed participant with uncertainty interval (0.6, 1.6)"

Equivalently we need to set values for IMOR and sd(logIMOR)

 $\lambda_{ij} \sim N(0, 0.25^2)$ 

#### **Fictional example**

Studies with means and same standard deviations per arm and observed sample size, but different missingness.

Study	Observed	SMD	Naïve SE (relative weight)Randomized		Corrected SE (relative weight)
1	100	0	0.07 (20%)	100	0.07 (59%)
2	100	0.1	0.07 (20%)	120	0.11 (24%)
3	100	0.2	0.07 (20%)	150	0.17 (10%)
4	100	0.3	0.07 (20%)	200	0.24 (5%)
5	100	0.4	0.07 (20%)	300	0.32 (3%)

We assume IMDOM=0 with uncertainty interval (-1, 1)

Studies with more missing data get less weight!


# Key thing: Estimation of SE of the effect size

- To estimate SE(logRR), SE(logOR) and SE(SMD) you need mathematical manipulations or simulations (rather cumbersome!)
- Likely, Stata will do the trick for you!
  - Using Monte Carlo
  - Using a Taylor series approximation

For all mathematical details see:

• For continuous outcomes

Mavridis D., White I., Higgins J., Cipriani A., Salanti G Allowing for uncertainty due to missing continuous missing outcome data in pairwise and network meta-analysis. *Statistics in Medicine* 2014, *34*, *721–741* 

• For dichotomous outcomes

White IR, Higgins JPT, Wood AM: Allowing for uncertainty due to missing data in metaanalysis-Part 1 : Two-stage methods. *Statistics in Medicine* 2008, 27, pp. 711-727

#### Mirtazapine vs placebo



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#### Most studies have zero missing values!

r: success		Haloperido	I	Placebo				
<b>m</b> :missing	rh	fh	mh	rp	fp	mp		
Arvanitis	25	25	2	18		0		
Beasley	29	18	22	20		34		
Bechelli	12	17	1			1		
Borison	3	9	0			0		
Chouinard	10	11	0		19	0		
Durost	11	8			14	0		
Garry	7	18			21	1		
Howard	8	9		3	10	0		
Marder	19	47		14	50	2		
Nishikawa 82	1			0	10	0		
Nishikawa 84	11		3	0	13	0		
Reschke	20		0	2	9	0		
Selman			11	7	4	18		
Serafetinides		0	0	0	13	1		
Simpson		14	0	0	7	1		
Spencer	11	1	0	1	11	0		
Vichaiya	9	20	1	0	29	1		

#### Haloperidol vs placebo

		%
author	RR (95% CI)	Weight
Garry	1.75 (0.58, 5.24)	3.37
Durost	8.68 (1.26, 59.95)	1.09
Simpson	2.35 (0.13, 43.53)	0.48
Vichaiya	— 19.00 (1.16, 311.96)	0.52
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Howard	2.04 (0.67, 6.21)	3.27
Reschke	3.79 (1.06, 13.60)	2.48
Selman	1.48 (0.94, 2.35)	19.11
Nishikawa_82	3.00 (0.14, 65.90)	0.42
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Nishikawa_84	9.20 (0.58, 145.76)	0.53
Borison	7.00 (0.40, 122.44)	0.49
Spencer	11.00 (1.67, 72.40)	1.14
Chouinard	3.49 (1.11, 10.95)	3.10
Marder	1.36 (0.75, 2.47)	11.37
Beasley	1.05 (0.73, 1.50)	31.22
Arvanitis	1.42 (0.89, 2.25)	18.86
Overall (I-squared = $41.4\%$ , p = $0.038$ )	1.57 (1.28, 1.92)	100.00
$\begin{array}{cccccccccccccccccccccccccccccccccccc$		
missing rate (11%)		
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#### Conclusions

- Many popular statistical techniques to account for missing data do not take uncertainty of the imputed values into account and get smaller standard errors and confidence intervals
- we suggest models that can
  - account for the fact that the presence of missing data introduce uncertainty in the study estimates
  - naturally downweight studies with lots of missing data
  - can model MAR or departures from MAR
- we need priors for IM parameters or conduct a sensitivity analysis
- We have extended the approach to network meta-analysis
- metamiss command in STATA (Ian White & Julian Higgins); metamiss2 command in STATA (Anna Chaimani and Ian White, forthcoming)
- We extend the method to account for data that have been imputed using single imputation techniques (e.g. LOCF)

#### **References**

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#### **Implementation in Stata**

#### The metamiss command

metamiss rE fE mE rC fC mC, imputation method [options]

aca	performs an available cases analysis
ica0	imputes missing values as failures
ical	imputes missing values as successes
icab	performs a best-case analysis
icaw	performs a worst-case analysis
icape	imputes missing values by using the observed probability in the experimental group
icapc	imputes missing values by using the observed probability in the control group
icap	imputes missing values by using the observed probability within groups
icaimor	<pre>imputes missing values by using the IMORs specified by imor() or logimor() and sdlogimor() within groups</pre>

#### The metamiss2 command

metamiss2 input\_variables, IPM\_definition [options]

impmean()	defines the mean(s) for the IMP parameter(s)
<pre>impsd()</pre>	defines the standard deviation(s) for the IMP parameters(s)
<pre>impcorr()</pre>	defines the correlation of the IMP parameters across groups
compare()	runs simultaneously two different analyses with different assumptions about the IMP parameter(s)
sensitivity	runs a sensitivity analysis on a range of different standard deviations for the IMP parameter

• Can be installed by typing (requires Stata 13 or later version):

net install metamiss2, from(http://www.mtm.uoi.gr)

#### Allowing for informative missingness in aggregate data metaanalysis with continuous or binary outcomes: extensions to metamiss

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#### Abstract

Missing outcome data can invalidate the results of randomized trials and their metaanalysis. However, addressing missing data is often a challenging issue since it requires untestable assumptions. The impact of missing outcome data on the meta-analysis summary effect can be explored by assuming a relationship between the outcome in the observed and the missing participants via an informative missingness parameter (IMP). The IMPs cannot be estimated from the observed data but they can be specified, with associated uncertainty, using evidence external to the meta-analysis, such as expert

# Installation of the Stata commands

If you have not already done so...

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1	***************************************	*****
2	* Allowing for uncertainty due to missing outcome data in meta-analysis	*
3	* Anna Chaimani & Dimitris Mavridis	*
4	* 18 June 2018, Cochrane SMG webinar	*
5	***************************************	*****
6		
7	*** 1.Installing the Stata commands ***	
8		
9	<pre>//if you have not already done so, please install the required Stata commands</pre>	
10	cap ssc install metan	
11	cap ssc install metamiss	
12	<pre>net install metamiss2, replace from(http://www.mtm.uoi.gr)</pre>	
13		
14	*** 2.Pairwise meta-analysis – binary data ***	
15		

✓ Load the dataset "haloperidol.dta"

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#### ✓ Look at the dataset

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13	<pre>net install metamiss2, replace from(http://www.mtm.uoi.gr)</pre>	
14		
15	<pre>*** 2.Pairwise meta-analysis - binary data ***</pre>	
16		
17	<pre>//load the dataset haloperidol.dta and look at the data</pre>	
18	li,clean	
19		
20	<pre>//generate the percentage of missing outcome data (PM) in each study</pre>	
21	<pre>gen PM=(mp+mh)/(rh+fh+mh+rp+fp+mp)*100</pre>	
22	li author year PM, clean	
23		

author	year	$\mathtt{rh}$	fh	mh	rp	fp	mp
Arvanitis	1997	25	25	2	18	33	0
Beasley	1996	29	18	22	20	14	34
Bechelli	1983	12	17	1	2	28	1
Borison	1992	3	9	0	0	12	0
Chouinard	1993	10	11	0	3	19	0
Durost	1964	11	8	0	1	14	0
Garry	1962	7	18	1	4	21	1
Howard	1974	8	9	0	3	10	0
Marder	1994	19	45	2	14	50	2
Nishikawa_82	1982	1	9	0	0	10	0
Nishikawa_84	1984	11	23	3	0	13	0
Reschke	1974	20	9	0	2	9	0
Selman	1976	17	1	11	7	4	18
Serafetinides	1972	4	10	0	0	13	1
Simpson	1967	2	14	0	0	7	1
Spencer	1992	11	1	0	1	11	0
Vichaiya	1971	9	20	1	0	29	1

✓ Find the percentage of missing outcome data in each study

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17	//load the dataset haloperidol.dta and look at the data	
18	li,clean	
19		
20	//generate the percentage of missing outcome data (PM) in each study	
21	<pre>gen PM=(mp+mh)/(rh+fh+mh+rp+fp+mp)*100</pre>	
22	li author year PM, clean	
23		
24	//run a meta-analysis using only the observed participants for each study (use th	ne random

✓ Find the percentage of missing outcome data in each study

author	year	PM
Arvanitis	1997	1.941748
Beasley	1996	40.875910
Bechelli	1983	3.278688
Borison	1992	0
Chouinard	1993	0
Durost	1964	0
Garry	1962	3.846154
Howard	1974	0
Marder	1994	3.030303
Nishikawa_82	1982	0
Nishikawa_84	1984	6.00000
Reschke	1974	0
Selman	1976	50.000000
Serafetinides	1972	3.571429
Simpson	1967	4.166667
Spencer	1992	0
Vichaiya	1971	3.333333

✓ Run a (random-effects meta-analysis) using only the observed participants (ACA)

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16		
17	<pre>//load the dataset haloperidol.dta and look at the data</pre>	
18	li,clean	
19		
20	<pre>//generate the percentage of missing outcome data (PM) in each study</pre>	
21	<pre>gen PM=(mp+mh)/(rh+fh+mh+rp+fp+mp)*100</pre>	
22	li author year PM, clean	
23		
24	<pre>/*run a meta-analysis using only the observed participants for each study</pre>	
25	(use the random effects model); that is the available-case analysis (ACA)*/	
26	<pre>metan rh fh rp fp, favours(Favors placebo # Favors haloperidol) ///</pre>	
27	xlabel(0.1, 0.3, 1, 3, 10, 30, 100) sortby(PM) lcols(author year PM) randomi tex	ts(130)
28		

author	year	РМ							RR (95% CI)	% Weight
Borison	1992	0							7.00 (0.40, 122.44)	1.30
Chouinard	1993	0							3.49 (1.11, 10.95)	6.10
Durost	1964	0				•		-	8.68 (1.26, 59.95)	2.65
Howard	1974	0		-	•				2.04 (0.67, 6.21)	6.33
Nishikawa_82	1982	0						-	3.00 (0.14, 65.90)	1.13
Reschke	1974	0				•			3.79 (1.06, 13.60)	5.20
Spencer	1992	0				•		_	11.00 (1.67, 72.40)	2.77
Arvanitis	1997	1.941748							1.42 (0.89, 2.25)	14.66
Marder	1994	3.030303							1.36 (0.75, 2.47)	12.40
Bechelli	1983	3.278688				•	_		6.21 (1.52, 25.35)	4.48
Vichaiya	1971	3.333333							▶ 19.00 (1.16, 311.96)	1.36
Serafetinides	1972	3.571429			i	•			8.40 (0.50, 142.27)	1.33
Garry	1962	3.846154		_	•				1.75 (0.58, 5.24)	6.46
Simpson	1967	4.166667							2.35 (0.13, 43.53)	1.26
Nishikawa_84	1984	6		_		•			9.20 (0.58, 145.76)	1.39
Beasley	1996	40.87591		-	<b>-</b>				1.05 (0.73, 1.50)	16.46
Selman	1976	50							1.48 (0.94, 2.35)	14.71
Overall (I-squa	red = 4	1.4%, p = 0.038)			$\diamond$				2.09 (1.49, 2.92)	100.00
NOTE: Weights	s are fro	m random effects ana	ysis							
			.1	і .3	1 1 1 3	10	і 30	1 100		
		F	avors placebo			Favors ha	loperic	ol		

✓ Run the same analysis using metamiss2 instead of metan



author	year	РМ							RR (95% CI)	% Weight
Borison	1992	0				۲			7.00 (0.40, 122.44)	1.30
Chouinard	1993	0				•			3.49 (1.11, 10.95)	6.10
Durost	1964	0				•		-	8.68 (1.26, 59.95)	2.65
Howard	1974	0		_	•				2.04 (0.67, 6.21)	6.33
Nishikawa_82	1982	0	_			]		_	3.00 (0.14, 65.90)	1.13
Reschke	1974	0				•			3.79 (1.06, 13.60)	5.20
Spencer	1992	0			+	•		_	11.00 (1.67, 72.40)	2.77
Arvanitis	1997	1.941748							1.42 (0.89, 2.25)	14.66
Marder	1994	3.030303		-					1.36 (0.75, 2.47)	12.40
Bechelli	1983	3.278688			-	•			6.21 (1.52, 25.35)	4.48
Vichaiya	1971	3.333333							- 19.00 (1.16, 311.96)	1.36
Serafetinides	1972	3.571429							8.40 (0.50, 142.27)	1.33
Garry	1962	3.846154			•				1.75 (0.58, 5.24)	6.46
Simpson	1967	4.166667							2.35 (0.13, 43.53)	1.26
Nishikawa_84	1984	6							9.20 (0.58, 145.76)	1.39
Beasley	1996	40.87591			<b>←</b>				1.05 (0.73, 1.50)	16.46
Selman	1976	50			<b>├</b>				1.48 (0.94, 2.35)	14.71
Overall (I-squa	ared = 4 s are fro	1.4%, p = 0.038) m random effects a	analysis		$\bigcirc$				2.09 (1.49, 2.92)	100.00
			1	3	 1   3	10	1 30	100		
			Favors placebo	.0	1 0	Favors I	naloperio	dol		

- ✓ Create a variable indicating the presence or absence of missing data for each study
- ✓ Run a subgroup analysis using this variable

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32							
33	11	run a	a sul	ogrou	p analys	is according to the presence or absence of missing data	
34	ge	n mis	ssing	g=(mh	!=0 mp!=	:0)	
35	la	bel (	defi	ne mi	ss 1 "Wi	th missing data" 0 "Without missing data"	
36	la	bel	value	es mi	ssing mi	.SS	
37	me	tami	ss2	rh fh	mh rp f	<pre>p mp, metanopt(favours(Favors placebo # Favors haloperido</pre>	l) ///
38	xl	abel	(0.1	, 0.3	, 1, 3,	10, 30, 100) by(missing) lcols(author year PM) ///	
39	so	rtby	(PM)	seco	nd(rando	om)) eform fixed	
40							
41	11	the o	odds	of r	esponse	in the missing participants are half the odds of response	in the

author	year	РМ		RR (95% CI)	% Weight (I-V)
With missing d	ata				
Arvanitis	1997	1.941748	<b>_</b>	1.42 (0.89, 2.25)	18.86
Marder	1994	3.030303		1.36 (0.75, 2.47)	11.37
Bechelli	1983	3.278688	· · · · · · · · · · · · · · · · · · ·	6.21 (1.52, 25.35)	2.05
Vichaiya	1971	3.333333	•	- 19.00 (1.16, 311.96)	0.52
Serafetinides	1972	3.571429	•	8.40 (0.50, 142.27)	0.51
Garry	1962	3.846154	_ <b>+</b> •	1.75 (0.58, 5.24)	3.37
Simpson	1967	4.166667		2.35 (0.13, 43.53)	0.48
Nishikawa_84	1984	6	•	9.20 (0.58, 145.76)	0.53
Beasley	1996	40.87591	<b></b>	1.05 (0.73, 1.50)	31.22
Selman	1976	50	<b></b>	1.48 (0.94, 2.35)	19.11
I-V Subtotal (I	-square	d = 34.7%, p = 0.130)		1.39 (1.12, 1.72)	88.00
D+L Subtotal			$\Diamond$	1.56 (1.13, 2.16)	
Without missin	g data				
Borison	1992	0	•	7.00 (0.40, 122.44)	0.49
Chouinard	1993	0		3.49 (1.11, 10.95)	3.10
Durost	1964	0		8.68 (1.26, 59.95)	1.09
Howard	1974	0		2.04 (0.67, 6.21)	3.27
Nishikawa_82	1982	0		3.00 (0.14, 65.90)	0.42
Reschke	1974	0		3.79 (1.06, 13.60)	2.48
Spencer	1992	0	•	11.00 (1.67, 72.40)	1.14
I-V Subtotal (I	-square	d = 0.0%, p = 0.764)		3.80 (2.13, 6.80)	12.00
D+L Subtotal				3.80 (2.13, 6.80)	
Heterogeneity	betwee	n groups: p = 0.001			
I-V Overall (I-s	squared	l = 41.4%, p = 0.038)	$\diamond$	1.57 (1.28, 1.92)	100.00
D+L Overall			$\diamond$	2.09 (1.49, 2.92)	
		II			
		.1 .3	3 1 3 10 30 100		
		Favors placebo	Favors haloperidol		

✓ Assume that the odds of response in the missing group are half the odds of response in the observed data for both arms



author	year	РМ							RR (95% CI)	% Weight
Borison	1992	0							7.00 (0.40, 122.44)	1.28
Chouinard	1993	0				•			3.49 (1.11, 10.95)	6.15
Durost	1964	0				•		-	8.68 (1.26, 59.95)	2.62
Howard	1974	0		-	•				2.04 (0.67, 6.21)	6.39
Nishikawa_82	1982	0	_					_	3.00 (0.14, 65.90)	1.10
Reschke	1974	0				•			3.79 (1.06, 13.60)	5.21
Spencer	1992	0				•		_	11.00 (1.67, 72.40)	2.74
Arvanitis	1997	1.941748			<b></b>				1.40 (0.88, 2.23)	15.56
Marder	1994	3.030303		-					1.36 (0.75, 2.47)	12.97
Bechelli	1983	3.278688				•	_		6.23 (1.52, 25.49)	4.47
Vichaiya	1971	3.333333					-		- 19.06 (1.16, 313.20)	1.33
Serafetinides	1972	3.571429			1				8.69 (0.51, 147.47)	1.30
Garry	1962	3.846154			•				1.75 (0.58, 5.27)	6.50
Simpson	1967	4.166667							2.49 (0.13, 46.33)	1.23
Nishikawa_84	1984	6		_		•			8.91 (0.56, 141.24)	1.36
Beasley	1996	40.87591		+	<b></b>				1.12 (0.74, 1.70)	16.53
Selman	1976	50							1.75 (0.97, 3.13)	13.25
Overall (I-squa	red = 3	5.0%, p = 0.077)							2.14 (1.54, 2.99)	100.00
NOTE: Weights	s are fro	m random effects an	alysis							
			.1	I .3	1 1 1 3	10	30	1 100		
			Favors placebo	-		Favors ha	loperid	ol		

✓ Run the same analysis using metamiss instead of metamiss2

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46	xlabel(0.1, 0.3, 1, 3, 10, 30, 100) lcols(author year PM) sortby(PM) texts(130))	
47		
48	<pre>//the same results are obtained when we run the same analysis with metamiss</pre>	
49	metamiss rh fh mh rp fp mp, logimor(-0.7) method(Taylor) randomi lcols(author yea	r PM) ///
50	favours(Favors placebo # Favors haloperidol) xlabel(0.1, 0.3, 1, 3, 10, 30, 100)	///
51	<pre>sortby(PM) texts(130)</pre>	
52		
53	/*the odds of response in missing participants are half the odds in the observed	participan
54	b) the odds of response in missing participants are twice the odds in the observed	d particip

author	year	РМ			_					RR (95% CI)	% Weight
Borison	1992	0								7.00 (0.40, 122.44)	1.28
Chouinard	1993	0				•	-			3.49 (1.11, 10.95)	6.15
Durost	1964	0				•	-			8.68 (1.26, 59.95)	2.62
Howard	1974	0		_	-					2.04 (0.67, 6.21)	6.39
Nishikawa_82	1982	0	-			•			-	3.00 (0.14, 65.90)	1.10
Reschke	1974	0				•				3.79 (1.06, 13.60)	5.21
Spencer	1992	0			<u> </u>		•		-	11.00 (1.67, 72.40)	2.74
Arvanitis	1997	1.941748								1.40 (0.88, 2.23)	15.56
Marder	1994	3.030303		-						1.36 (0.75, 2.47)	12.97
Bechelli	1983	3.278688				•		•		6.23 (1.52, 25.49)	4.47
Vichaiya	1971	3.333333								- 19.06 (1.16, 313.20)	1.33
Serafetinides	1972	3.571429			1		-			8.69 (0.51, 147.47)	1.30
Garry	1962	3.846154		_	•					1.75 (0.58, 5.27)	6.50
Simpson	1967	4.166667	-			}				2.49 (0.13, 46.33)	1.23
Nishikawa_84	1984	6		_		-				8.91 (0.56, 141.24)	1.36
Beasley	1996	40.87591		-	<b></b>					1.12 (0.74, 1.70)	16.53
Selman	1976	50			•	-				1.75 (0.97, 3.13)	13.25
Overall (I-squa	ared = 3	5.0%, p = 0.077)	<b>.</b> .			>				2.14 (1.54, 2.99)	100.00
NOTE: Weights	s are fro	om random effects ar	nalysis			1	I				
			.1	.3	1	3 1	0	30	100		
			Favors placebo	C		Favor	s halo	perid	ol		

 ✓ a) the odds of response in missing participants are half the odds in the observed participants for placebo arm and b) the odds of response in missing participants are twice the odds in the observed participants for haloperidol

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52	
53	/* a) the odds of response in missing participants are half the odds in the observed
54	participants for placebo arm and b) the odds of response in missing participants
55	are twice the odds in the observed participants for haloperidol*/
56	di log(2)
57	<pre>metamiss2 rh fh mh rp fp mp, impmean(0.7 -0.7) eform ///</pre>
58	<pre>metanopt(favours(Favors placebo # Favors haloperidol) xlabel(0.1, 0.3, 1, 3, 10, 30, 100) ///</pre>
59	<pre>lcols(author year PM) sortby(PM))</pre>
60	
61	//compare the results of this approach to the results obtain from another model. sav the avail

author	year	РМ			RR (95% Cl)	% Weight
Borison	1992	0			7.00 (0.40, 122.44)	1.09
Chouinard	1993	0		<u> </u>	3.49 (1.11, 10.95)	5.64
Durost	1964	0		•	8.68 (1.26, 59.95)	2.29
Howard	1974	0		_	2.04 (0.67, 6.21)	5.88
Nishikawa_82	1982	0			3.00 (0.14, 65.90)	0.94
Reschke	1974	0		<u> </u>	3.79 (1.06, 13.60)	4.72
Spencer	1992	0		•	11.00 (1.67, 72.40)	2.39
Arvanitis	1997	1.941748	_ <b>_</b>		1.43 (0.90, 2.28)	16.64
Marder	1994	3.030303			1.40 (0.77, 2.54)	13.27
Bechelli	1983	3.278688		•	6.39 (1.57, 26.10)	4.01
Vichaiya	1971	3.333333			- 19.64 (1.20, 322.29)	1.14
Serafetinides	1972	3.571429		•	8.69 (0.51, 147.47)	1.12
Garry	1962	3.846154		-	1.82 (0.61, 5.44)	6.04
Simpson	1967	4.166667			2.49 (0.13, 46.33)	1.05
Nishikawa_84	1984	6			9.57 (0.61, 151.34)	1.17
Beasley	1996	40.87591			1.32 (0.90, 1.95)	18.78
Selman	1976	50	┠╺╾		1.80 (1.02, 3.19)	13.83
Overall (I-squared	= 28.3%, e from ran	p = 0.133) dom effects analysis	$\diamond$		2.13 (1.57, 2.89)	100.00
			Favors placebo	Favors haloperidol		

✓ Compare the results of this analysis to the results obtained from another model, say the available cases analysis

10			A
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59	<pre>lcols(author year PM) sortby(PM))</pre>		
60			
61	/*compare the results of this approach to the results obtained from another mode	ι,	
62	say the available cases analysis, using the compare option*/		
63	<pre>metamiss2 rh fh mh rp fp mp, impmean(0.7 -0.7) compare(impmean(0)) eform ///</pre>		
64	metanopt(favours(Favors placebo # Favors haloperidol) xlabel(0.1, 0.3, 1, 3, 10,	30,	100) ///
65	<pre>lcols(author year PM) sortby(PM))</pre>		
66			
67	/*in both groups the odds of response in the missing data are the same with the	odds	of respo

Primary analysis 1.43 (0.90, 2.28) 16.64 1.32 (0.90, 1.95) 18.78 6.39 (1.57, 26.10) 4.01 7.00 (0.40, 122.44) 1.09 3.49 (1.11, 10.95) 5.64 8.68 (1.26, 59.95) 2.29 1.82 (0.61, 5.44) 6.04 1.82 (0.61, 5.44) 6.04 1.82 (0.61, 5.44) 6.04 1.82 (0.61, 5.41) 6.04 1.82 (0.61, 5.41) 1.17 3.00 (0.14, 65.90) 0.94 9.57 (0.61, 151.34) 1.17 2.30 (0.27, 2.54) 13.87 4.5 6.69 (0.51, 151.34) 1.17 3.79 (1.06, 13.00) 4.72 3.00 (1.23, 3.19) 13.83 8.69 (0.51, 147.47) 1.12 5.64 (1.20, 23.19) 13.83 8.69 (0.51, 147.47) 1.12 5.64 (1.20, 23.22.9) 100.00 11.00 (1.67, 72.40) 2.39 10.56 (0.73, 1.50) 16.48 9 1.42 (0.89, 2.25) 14.66 9 1.42 (0.89, 2.25) 14.66 9 1.42 (0.89, 2.25) 14.66 9 1.42 (0.89, 2.25) 14.66 9 1.42 (0.89, 2.25) 14.64 9 1.42 (0.89, 2.25) 14.66 1.05 (0.73, 1.50) 16.48 9 1.00 (0.75, 2.47) 12.24 1.30 (0.75, 2.47) 12.24 1.30 (0.75, 2.47) 12.40 1.30 (0.14, 6.5.90) 1.13 9.20 (0.58, 145.76) 1.39 9.20	Study ID	ES (95% CI)	% Weight
$\begin{array}{c} 1.43 (0.90, 2.28) & 16.64 \\ 3.2 (0.90, 1.95) & 18.78 \\ 6.39 (1.57, 26.10) & 4.01 \\ 7.00 (0.40, 122.44) & 1.09 \\ 3.49 (1.11, 10.95) & 5.64 \\ 8.68 (1.26, 59.95) & 2.29 \\ 1.82 (0.61, 5.44) & 6.04 \\ 2.04 (0.67, 6.21) & 5.88 \\ 0.0 & 1.40 (0.77, 2.54) & 13.27 \\ 3.00 (0.14, 65.90) & 0.94 \\ 1.80 (1.02, 3.19) & 13.83 \\ 1.5 & 5.7 (0.61, 151.34) & 1.17 \\ 2.3 & 3.00 (0.14, 65.90) & 0.94 \\ 1.80 (1.02, 3.19) & 13.83 \\ 1.5 & 5.6 \\ 7 & 7 & 7.40 \\ 2.49 (0.13, 46.33) & 1.06 \\ 6.9 (0.51, 147.47) & 1.12 \\ 2.49 (0.13, 46.33) & 1.05 \\ 6.7 & 7.40 \\ 2.39 & 19.64 (1.20, 322.29) & 1.14 \\ 3.0btotal (I-squared = 28.3\%, p = 0.133) \\ \hline \end{array}$	Primary analysis		
2       1.22 (0.90, 1.95)       18.78         3       1.32 (0.90, 1.95)       4.01         7.00 (0.40, 122.44)       1.09         3.49 (1.11, 10.95)       5.64         8       86 (1.26, 59.95)       2.29         1.82 (0.61, 5.44)       6.04         2.04 (0.67, 6.21)       5.84         1.40 (0.77, 2.54)       13.27         3.00 (0.14, (65.90)       0.94         1.22 (0.61, 151.34)       1.17         3.3       1.30 (1.02, 3.19)       13.83         4.5 (0.11, 157.34)       1.12         5.6 (0.11, 147.47)       1.12         2.49 (0.13, 46, 33)       1.05         11.00 (1.67, 72.40)       2.39         11.00 (1.67, 72.40)       2.39         11.00 (1.67, 72.40)       1.14         2.40 (0.76, 6.21)       1.46         9       5.6 (0.73, 1.50)       16.46         9       1.10 (1.67, 72.49)       1.00 (0.00         Secondary analysis       1.42 (0.89, 2.25)       14.66         9       1.05 (0.73, 1.50)       16.46         9       1.05 (0.73, 1.50)       16.46         1.21 (1.57, 2.89)       100.00         3.31 (1.50 (0.60, 1.22, 77))       12.40	1 🗕	1.43 (0.90, 2.28)	16.64
6.39 (1.57, 26.10) 4.01 7.00 (0.40, 122.44) 1.09 3.49 (1.11, 10.95) 5.64 8.68 (1.26, 59.95) 2.29 1.22 (0.61, 5.44) 6.04 2.04 (0.67, 6.21) 5.88 3.00 (0.14, 65.90) 0.94 3.00 (0.14, 65.90) 0.94 3.00 (0.14, 65.90) 0.94 3.00 (0.14, 65.90) 0.94 3.00 (0.14, 65.90) 1.13 3.79 (1.06, 13.60) 4.72 3.79 (1.06, 13.46.3) 1.05 1.06 (1.7, 72.40) 2.39 10.00 (1.7, 72.40) 2.39 10.00 (1.7, 72.40) 2.39 10.00 (0.7, 72.40) 1.14 2.13 (1.57, 2.89) 100.00 2.90 (0.4, 65.90) 14.66 1.06 (0.73, 1.50) 16.46 1.06 (0.76, 2.21) 6.33 1.42 (0.89, 2.25) 14.66 1.06 (0.76, 6.21) 6.33 1.42 (0.89, 2.25) 14.66 1.06 (0.76, 6.21) 6.33 1.36 (1.76, 5.247) 12.40 3.00 (0.14, 65.90) 1.13 3.90 (0.14, 65.90) 1.13 3.92 (0.58, 148.76) 1.39 9.20 (0.14, 65.90) 1.13 1.00 (1.16, 77, 72.40) 2.77 4.71 (1.00 (1.67, 72.40) 2.77 4.71 (1.00 (1.67, 72.40) 2.77 4.72 (1.06, 13.60) 2.20 1.72 (1.38, 1.45, 5.24) 1.36 1.36 (0.77, 2.47) 1.240 3.00 (0.14, 65.90) 1.13 9.20 (0.58, 148.76) 1.39 9.20 (0.58, 148.76) 1.36 2.09 (1.49, 2.92) 100.00 10TE: Weights are from random effects analysis	2	1.32 (0.90, 1.95)	18.78
7.00 (0.40, 122.44)       1.09         3.49 (1.11, 10.95)       5.64         8.68 (1.26, 59,95)       2.29         1.82 (0.61, 5.44)       6.04         2.04 (0.67, 6.21)       5.88         1.40 (0.77, 2.54)       13.27         3.00 (0.14, 65,90)       0.94         1.40 (0.77, 2.54)       13.27         3.05 (0.14, 65,90)       0.94         1.40 (0.77, 2.54)       13.23         3.05 (0.14, 65,90)       0.94         1.40 (0.77, 2.54)       13.23         3.05 (0.14, 65,90)       0.94         9.57 (0.61, 151.34)       1.17         3.73 (1.06, 13, 60)       4.72         1.80 (1.02, 3.19)       13.83         8.69 (0.51, 147, 47)       1.12         1.96 (1.20, 322.29)       1.14         2.49 (0.13, 46.33)       1.06         1.57 (0.58, 5.24)       6.46         9       1.05 (0.73, 1.50)       16.46         1.75 (0.58, 5.24)       6.46         1.75 (0.58, 5.24)       6.46         1.75 (0.58, 5.24)       6.46         1.75 (0.58, 5.24)       6.46         2.09 (0.14, 6.5.90)       1.33         3.09 (0.14, 6.5.90)       1.33         1.14       1.940	3	6.39 (1.57, 26.10)	4.01
3       3.49 (1.11, 10.95)       5.64         8       68       6.68 (1.26, 59.95)       2.29         1       1.40 (0.77, 2.54)       13.27         0       3.00 (0.14, 65.90)       0.94         9.57 (0.61, 151.34)       1.17         2       3.79 (1.06, 13.60)       4.72         3       1.40 (0.77, 2.54)       13.27         3.79 (1.06, 13.60)       4.72         3       1.80 (1.02, 3.19)       13.83         8.69 (0.51, 147, 47)       1.12         3       2.49 (0.13, 46.33)       1.05         7       11.00 (1.67, 72.40)       2.39         19.64 (1.20, 322.29)       1.1.46         8.69 (0.73, 1.50)       16.46         9       0.00 (0.40, 122.44)       1.30         13       1.55       6.10         13       1.150 (0.76, 2.27)       12.40         13       3.00 (0.14, 65.90)       2.165         14       1.17 (0.58, 15.24)       1.30         13       1.36 (0.75, 2.47)       12.40         13       3.00 (0.14, 65.90)       1.13         13       1.36 (0.75, 2.47)       1.34         14       1.15, 1.50       1.139         1.11	4	7.00 (0.40, 122.44)	1.09
8       868 (1.26, 59.95)       2.29         8       1.82 (0.61, 5.44)       6.04         2.04 (0.67, 6.21)       5.88         1       2.04 (0.67, 6.21)       5.88         1.40 (0.77, 2.54)       13.27         3.00 (0.14, 66, 500)       9.57 (0.61, 151.34)       1.17         3.79 (1.06, 13.60)       4.72         3.79 (1.06, 13.60)       4.72         3.79 (1.06, 13.60)       1.88 (9.05, 1.147, 47)       1.12         2.49 (0.15, 4.43.3)       1.05         6       11.00 (1.67, 72.40)       2.39         70 (0.04, 122, 319)       13.83         8       1.42 (0.89, 2.25)       14.66         9       1.64 (6.59.55)       1.64         9       1.05 (0.73, 1.50)       16.46         1.22       1.30 (1.04, 122, 41)       1.30         1.32       3.49 (1.11, 10.95)       6.10         1.75 (0.56, 5.24)       6.46         1.75 (0.58, 5.24)       6.46         1.75 (0.58, 1.47, 71)       1.24         1.30       3.09 (0.14, 6.5.90)       1.30         1.31       3.00 (0.14, 6.5.90)       1.31         1.32       3.79 (1.06, 13.60)       5.20         1.32       3.79 (1.06, 13.60) <td>5</td> <td>3.49 (1.11, 10.95)</td> <td>5.64</td>	5	3.49 (1.11, 10.95)	5.64
$\begin{array}{c} 1.82 (0.61, 5.44) & 6.04 \\ 2.04 (0.67, 6.21) & 5.88 \\ 1.40 (0.77, 2.54) & 13.27 \\ 3.00 (0.14, 65.90) & 0.94 \\ 9.957 (0.61, 151.34) & 1.17 \\ 3.79 (1.06, 13.60) & 4.72 \\ 3.79 (1.06, 13.60) & 4.72 \\ 1.80 (1.02, 3.19) & 13.83 \\ 8.69 (0.51, 147.47) & 1.12 \\ 2.49 (0.13, 46.33) & 1.06 \\ 10.01 (1.57, 2.40) & 2.39 \\ 19.64 (1.20, 322.29) & 1.14 \\ 2.13 (1.57, 2.89) & 100.00 \\ 3.40 (1.11, 10.95) & 6.10 \\ 1.55 (0.73, 1.50) & 16.46 \\ 6.21 (1.52, 25.5) & 14.66 \\ 1.05 (0.73, 1.50) & 16.46 \\ 6.21 (1.52, 25.5) & 14.66 \\ 1.05 (0.73, 1.50) & 16.46 \\ 6.21 (1.52, 25.5) & 14.66 \\ 6.21 (1.52, 25.5) & 14.66 \\ 1.05 (0.73, 1.50) & 16.46 \\ 1.05 (0.73, 1.50) & 16.46 \\ 1.05 (0.73, 1.50) & 16.46 \\ 1.05 (0.73, 1.50) & 16.46 \\ 1.05 (0.73, 1.50) & 16.46 \\ 1.05 (0.73, 1.50) & 10.46 \\ 1.05 (0.73, 1.50) & 10.46 \\ 1.05 (0.73, 1.50) & 10.46 \\ 1.05 (0.73, 1.50) & 10.46 \\ 1.05 (0.73, 1.50) & 10.46 \\ 1.05 (0.73, 1.50) & 10.46 \\ 1.05 (0.73, 1.50) & 10.46 \\ 1.05 (0.73, 1.50) & 10.46 \\ 1.05 (0.73, 1.50) & 10.46 \\ 1.05 (0.73, 1.50) & 10.46 \\ 1.05 (0.73, 1.50) & 10.46 \\ 1.05 (0.73, 1.50) & 10.46 \\ 1.05 (0.73, 1.50) & 10.46 \\ 1.05 (0.73, 1.50) & 10.46 \\ 1.05 (0.72, 2.40) & 2.77 \\ 1.30 (0.14, 65.90) & 1.13 \\ 1.30 (0.14, 65.90) & 1.13 \\ 1.30 (0.14, 65.90) & 1.13 \\ 1.30 (0.14, 5.29) & 1.06 \\ 2.09 (1.49, 2.92) & 100.00 \\ 1.00 (1.16, 311.96) & 2.77 \\ 19.00 (1.16, 311.96) & 2.77 \\ 19.00 (1.49, 2.92) & 100.00 \\ 10TE: Weights are from random effects analysis \\ \begin{array}{c} \\ \end{array}{}$	6	8.68 (1.26, 59.95)	2.29
$\begin{array}{c} 2.04 \ (0.67, 6.21) \\ 5.88 \\ 1.40 \ (0.77, 2.54) \\ 3.00 \ (0.14, 65.90) \\ 9.57 \ (0.61, 151.34) \\ 1.17 \\ 3.79 \ (1.06, 13.60) \\ 4.72 \\ 1.80 \ (1.02, 3.19) \\ 11.80 \ (1.22, 3.19) \\ 11.80 \ (1.57, 72.40) \\ 2.39 \\ 11.00 \ (1.57, 72.40) \\ 2.39 \\ 11.00 \ (1.57, 72.40) \\ 2.39 \\ 11.00 \ (1.57, 72.40) \\ 2.13 \ (1.57, 72.89) \\ 10.000 \\ 1.48 \ (1.20, 322.29) \\ 1.14 \\ 2.13 \ (1.57, 2.89) \\ 100.000 \\ 1.46 \ (6.21 \ (1.52, 2.55) \\ 4.48 \\ 7.00 \ (0.40, 122.44) \\ 1.30 \\ 3.49 \ (1.11, 1.095) \\ 6.10 \\ 8.68 \ (1.26, 59.95) \\ 2.65 \\ 1.75 \ (0.58, 5.24) \\ 1.46 \ (6.21 \ (1.52, 2.55) \\ 1.466 \\ 6.21 \ (1.52, 2.55) \\ 1.466 \\ 6.21 \ (1.52, 2.55) \\ 1.466 \\ 6.21 \ (1.52, 2.55) \\ 1.466 \\ 6.21 \ (1.52, 2.53) \\ 1.48 \ (0.67, 6.21) \\ 6.33 \\ 1.36 \ (0.75, 2.47) \\ 12.40 \\ 3.00 \ (0.14, 65.90) \\ 1.13 \\ 9.20 \ (0.58, 145.76) \\ 1.39 \\ 3.00 \ (0.14, 65.90) \\ 1.13 \\ 9.20 \ (0.58, 145.76) \\ 1.39 \\ 3.79 \ (1.06, 13.60) \\ 5.20 \\ 1.148 \ (0.94, 2.32) \\ 1.00 \ (1.46, 51.90) \\ 1.38 \\ 2.09 \ (1.49, 2.92) \\ 100.00 \\ 1.46 \ (2.92) \ (1.49, 2.92) \\ 100.00 \\ 1.46 \ (2.92) \ (1.49, 2.92) \\ 100.00 \\ 1.46 \ (2.92) \ (1.49, 2.92) \\ 100.00 \\ 1.46 \ (2.92) \ (1.49, 2.92) \\ 100.00 \\ 1.46 \ (2.92) \ (1.49, 2.92) \\ 100.00 \\ 1.46 \ (2.92) \ (1.49, 2.92) \\ 100.00 \\ 1.46 \ (2.92) \ (1.49, 2.92) \\ 100.00 \\ 1.46 \ (2.92) \ (1.49, 2.92) \\ 100.00 \\ 1.46 \ (2.92) \ (1.49, 2.92) \\ 100.00 \\ 1.46 \ (2.92) \ (1.49, 2.92) \\ 100.00 \\ 1.46 \ (2.92) \ (2.77 \ (2.40) \ (2.77 \$		1.82 (0.61, 5.44)	6.04
$\begin{array}{c} 1.40 (0.77, 2.54) \\ 3.00 (0.14, 65.90) \\ 9.57 (0.61, 151.34) \\ 1.77 \\ 3.79 (1.06, 13.60) \\ 4.72 \\ 3.00 (0.21, 465.90) \\ 9.57 (0.61, 151.34) \\ 1.77 \\ 3.79 (1.06, 13.60) \\ 4.72 \\ 2.49 (0.13, 46.33) \\ 1.80 (1.02, 3.19) \\ 1.80 (1.02, 3.19) \\ 1.80 (1.02, 3.19) \\ 1.80 (1.02, 3.19) \\ 1.80 (1.02, 3.19) \\ 1.80 (1.02, 3.19) \\ 1.80 (1.02, 3.19) \\ 1.80 (1.02, 3.19) \\ 1.80 (1.02, 3.19) \\ 1.80 (1.02, 3.19) \\ 1.80 (1.02, 3.19) \\ 1.80 (1.02, 3.19) \\ 1.80 (1.02, 3.19) \\ 1.96 (1.20, 3.22.29) \\ 1.14 \\ 2.13 (1.57, 2.89) \\ 100.00 \\ 1.46 (1.20, 3.22.29) \\ 1.14 \\ 2.13 (1.57, 2.89) \\ 100.00 \\ 1.46 (1.20, 3.22.29) \\ 1.14 \\ 2.13 (1.57, 2.89) \\ 100.00 \\ 1.46 (1.20, 3.22.29) \\ 1.14 \\ 2.13 (1.57, 2.89) \\ 100.00 \\ 1.46 (5.9.95) \\ 2.65 \\ 1.75 (0.58, 5.24) \\ 1.36 (0.75, 2.47) \\ 12.40 \\ 3.00 (0.14, 65.90) \\ 1.13 \\ 9.9 \\ 9.9 \\ 1.36 \\ 2.00 (1.58, 145.76) \\ 1.39 \\ 9.9 \\ 1.36 (0.75, 2.47) \\ 12.40 \\ 3.00 (0.14, 65.90) \\ 1.13 \\ 2.20 (0.58, 145.76) \\ 1.33 \\ 2.20 $	3	2.04 (0.67, 6.21)	5.88
0 0 1 1 2 3 3 4 5 6 7 7 Subtotal (I-squared = 28.3%, p = 0.133) Secondary analysis 8 9 7 Subtotal (I-squared = 28.3%, p = 0.133) Secondary analysis 8 9 7 Subtotal (I-squared = 28.3%, p = 0.133) Secondary analysis 8 9 1 4 5 5 6 9 7 5 6 9 7 7 7 7 7 7 7 7 7 7 7 7 7		1.40 (0.77, 2.54)	13.27
1       9.57 (0.61, 161.34)       1.17         2       3.79 (1.06, 13.60)       4.72         3       1.80 (1.02, 3.19)       13.83         4       2.49 (0.13, 46.33)       1.05         6       1.00 (1.67, 72.40)       2.39         7       1.10 (1.67, 72.40)       2.39         8.68 (0.51, 147.47)       1.12         2.49 (0.13, 46.33)       1.05         6       1.00 (1.67, 72.40)       2.39         7       7.3.150)       16.46         8       1.42 (0.89, 2.25)       14.66         9       0.00 (1.67, 72.40)       2.39         9       7.00 (0.40, 122.44)       1.30         9       0.00 (1.25, 25.35)       4.48         10       1.56 (0.73, 1.50)       16.46         6.21 (1.52, 25.35)       4.48         12       3.49 (1.11, 10.95)       6.10         13       3.49 (1.11, 10.95)       6.10         13       3.49 (1.11, 10.95)       6.10         13       3.49 (1.11, 10.95)       6.10         13       3.49 (1.11, 10.95)       6.10         13       3.49 (1.11, 10.95)       6.10         13       3.49 (1.11, 10.61, 13.09)       1.36      <	10	3.00 (0.14, 65.90)	0.94
2 3.79 (1.06, 13.60) 4.72 3 .79 (1.06, 13.60) 4.72 1.80 (1.02, 3.19) 13.83 4.55 6.69 (0.13, 46.33) 1.05 6.69 (0.13, 46.33) 1.05 7.5 8.09 (0.10, 17, 72.40) 2.39 100.00 8.00 (1.05, 0.73, 1.50) 16.46 9 1.42 (0.89, 2.25) 14.66 9 1.42 (0.89, 2.25) 14.66 1.05 (0.73, 1.50) 16.46 1.05 (0.73, 2.47) 12.40 3.49 (1.11, 10.95) 6.10 3.49 (1.11, 10.95) 6.10 3.39 (0.14, 65.90) 1.13 9.20 (0.58, 145.76) 1.39 9.20 (0.58, 145.76)	11	9.57 (0.61, 151.34)	1.17
$\begin{array}{c c c c c c c c c c c c c c c c c c c $		3.79 (1.06, 13.60)	4.72
44       8.69 (0.51, 147.47)       1.12         55       2.49 (0.13, 46.33)       1.05         60       11.00 (1.67, 72.40)       2.39         77       1.42 (0.89, 2.25)       14.66         80       1.42 (0.89, 2.25)       14.66         9       1.42 (0.89, 2.25)       14.66         1.05 (0.73, 1.50)       16.46         1.05 (0.73, 1.50)       16.46         1.10 (1.67, 72.40)       2.39         1.11 (1.52, 25.35)       4.48         700 (0.40, 122.44)       1.30         1.32       3.349 (1.11, 10.96)       6.10         1.33       8.69 (0.57, 4.71)       1.24         1.33       1.36 (0.75, 2.47)       1.24         1.33       1.36 (0.75, 2.47)       1.24         1.33       9.20 (0.58, 145.76)       1.33         1.34       0.94, 2.35)       14.71         1.35       9.20 (0.58, 145.76)       1.33         1.32       2.33 (0.114, 63.53)       1.26         1.32       2.33 (0.114, 63.53)       1.26         1.32       3.379 (1.06, 13.60)       5.20         1.48 (0.94, 2.35)       14.71         1.48 (0.94, 2.35)       14.71         1.36 (0.152, 77.240)	3	1.80 (1.02, 3.19)	13.83
55       2.49 (0.13, 46.33)       1.05         66       11.00 (1.67, 72.40)       2.39         7       19.64 (1.20, 322.29)       1.14         Subtotal (I-squared = 28.3%, p = 0.133)       105       1.42 (0.89, 2.25)       14.66         9       1.42 (0.89, 2.25)       14.66         9       1.05 (0.73, 1.50)       16.46         9       1.42 (0.89, 2.25)       14.86         10.95 (0.73, 1.50)       16.46         6.21 (1.52, 25.35)       4.48         7.00 (0.40, 122.44)       1.30         3.49 (1.11, 10.95)       6.10         8.68 (1.26, 59.95)       2.65         1.75 (0.58, 5.24)       6.46         2.04 (0.67, 6.21)       6.33         1.36 (0.75, 2.47)       12.40         3.00 (0.14, 65.90)       1.13         9.20 (0.58, 145.76)       1.39         9.20 (0.58, 145.76)       1.39         9.23 (0.13, 43.53)       1.26         11.42 (0.49, 2.35)       14.71         8.40 (0.50, 142.27)       1.33         2.35 (0.13, 43.53)       1.26         11.42 (0.49, 2.92)       100.00         10.00 (1.16, 311.96)       1.36         2.35 (0.13, 43.53)       1.26         1	4 •	8.69 (0.51, 147.47)	1.12
6       11.00 (1.67, 72.40)       2.39         7       19.64 (1.20, 322.29)       1.14         Subtotal (I-squared = 28.3%, p = 0.133)       1.42 (0.89, 2.25)       14.66         9       1.05 (0.73, 1.50)       16.46         9       1.05 (0.73, 1.50)       16.46         9       1.00 (1.67, 72.40)       2.39         1.01 (1.57, 2.89)       100.00         1.02 (0.67, 1.52)       14.66         1.05 (0.73, 1.50)       16.46         6.21 (1.52, 25.35)       4.48         7.00 (0.40, 122.44)       1.30         3.49 (1.11, 10.95)       6.10         8       8.68 (1.26, 59.95)       2.65         1.36 (0.75, 2.47)       12.40         3.00 (0.14, 65.90)       1.13         1.36 (0.75, 2.47)       12.40         3.00 (0.14, 65.90)       1.13         9.20 (0.58, 145.76)       1.39         3.79 (1.06, 13.60)       5.20         1.48 (0.94, 2.35)       14.71         8.40 (0.50, 142.27)       1.33         1.30       2.35 (0.13, 43.53)       1.26         1.1.00 (1.67, 72.40)       2.77         19.00 (1.16, 311.96)       1.36         2.09 (1.49, 2.92)       100.00         1	5 • •	2.49 (0.13, 46.33)	1.05
7 5 5 5 5 5 5 5 5 5 5 5 5 5	6	11.00 (1.67, 72.40)	2.39
Subtotal (I-squared = 28.3%, p = 0.133) Secondary analysis 8 9 9 100.00 Secondary analysis 8 9 1.42 (0.89, 2.25) 14.66 1.05 (0.73, 1.50) 16.46 6.21 (1.52, 25.35) 4.48 7.00 (0.40, 122.44) 1.30 3.49 (1.11, 10.95) 6.10 8.68 (1.26, 59.95) 2.65 1.75 (0.58, 5.24) 6.46 2.04 (0.67, 5.247) 12.40 3.00 (0.14, 65.90) 1.13 9.20 (0.58, 145.76) 1.39 3.79 (1.06, 13.60) 5.20 1.48 (0.94, 2.35) 14.71 8.40 (0.50, 142.27) 1.33 2.35 (0.13, 43.53) 1.26 11.00 (1.67, 72.40) 2.77 14 Subtotal (I-squared = 41.4%, p = 0.038) IOTE: Weights are from random effects analysis	7	19.64 (1.20, 322.29)	1.14
Secondary analysis 8 9 9 9 9 9 9 9 9 9 9 9 9 9	Subtotal (I-squared = 28.3%, p = 0.133)	2.13 (1.57, 2.89)	100.00
$ \begin{array}{c} 1 & 42 (0.89, 2.25) & 14.66 \\ 1.05 (0.73, 1.50) & 16.46 \\ 6.21 (1.52, 25.35) & 4.48 \\ 7.00 (0.40, 122.44) & 1.30 \\ 3.49 (1.11, 10.95) & 6.10 \\ 8.68 (1.26, 59.95) & 2.65 \\ 1.75 (0.58, 5.24) & 6.46 \\ 2.04 (0.67, 6.21) & 6.33 \\ 1.36 (0.75, 2.47) & 12.40 \\ 3.00 (0.14, 65.90) & 1.13 \\ 9.20 (0.58, 145.76) & 1.39 \\ 9.20 (0.58, 145.76) & 1.39 \\ 9.20 (0.58, 145.76) & 1.39 \\ 9.20 (0.58, 145.76) & 1.39 \\ 3.79 (1.06, 13.60) & 5.20 \\ 1.48 (0.94, 2.35) & 14.71 \\ 8.40 (0.50, 142.27) & 1.33 \\ 2.35 (0.13, 43.53) & 1.26 \\ 11.00 (1.67, 72.40) & 2.77 \\ 19.00 (1.16, 311.96) & 1.36 \\ 2.09 (1.49, 2.92) & 100.00 \end{array} $	Secondary analysis		
$\begin{array}{c} 9 \\ 9 \\ 20 \\ 20 \\ 21 \\ 22 \\ 22 \\ 23 \\ 24 \\ 25 \\ 24 \\ 25 \\ 24 \\ 25 \\ 24 \\ 25 \\ 26 \\ 24 \\ 25 \\ 26 \\ 26 \\ 26 \\ 20 \\ 20$	18	1.42 (0.89, 2.25)	14.66
$\begin{array}{c} 0 \\ 0 \\ 21 \\ 22 \\ 23 \\ 24 \\ 25 \\ 24 \\ 25 \\ 26 \\ 24 \\ 25 \\ 26 \\ 26 \\ 26 \\ 26 \\ 26 \\ 26 \\ 26$	9	1.05 (0.73, 1.50)	16.46
1       7.00 $(0.40, 122.44)$ 1.30         22       3.49 $(1.11, 10.95)$ 6.10         33       8.68 $(1.26, 59.95)$ 2.65         1.75 $(0.58, 5.24)$ 6.46         2.04 $(0.67, 6.21)$ 6.33         1.36 $(0.75, 2.47)$ 12.40         3.00 $(0.14, 65.90)$ 1.13         99       3.00 $(0.14, 65.90)$ 1.13         99       3.79 $(1.06, 13.60)$ 5.20         1.48 $(0.94, 2.35)$ 14.71         8.49 $(0.50, 142.27)$ 1.33         2.35 $(0.13, 43.53)$ 1.26         11.00 $(1.67, 72.40)$ 2.77         19.00 $(1.16, 311.96)$ 1.36         2.09 $(1.49, 2.92)$ 100.00	.0	<u> </u>	4.48
$\begin{array}{c} 3.49 (1.11, 10.95) & 6.10 \\ 8.68 (1.26, 59.95) & 2.65 \\ 1.75 (0.58, 5.24) & 6.46 \\ 2.04 (0.67, 6.21) & 6.33 \\ 1.36 (0.75, 2.47) & 12.40 \\ 3.00 (0.14, 65.90) & 1.13 \\ 9.20 (0.58, 145.76) & 1.39 \\ 3.79 (1.06, 13.60) & 5.20 \\ 1.48 (0.94, 2.35) & 14.71 \\ 8.40 (0.50, 142.27) & 1.33 \\ 2.35 (0.13, 43.53) & 1.26 \\ 11.00 (1.67, 72.40) & 2.77 \\ 19.00 (1.16, 311.96) & 1.36 \\ 2.09 (1.49, 2.92) & 100.00 \\ 100 \text{TE: Weights are from random effects analysis} \end{array}$		7.00 (0.40, 122.44)	1.30
3       8.68 (1.26, 59.95)       2.65         4       5       1.75 (0.58, 5.24)       6.46         2.04 (0.67, 6.21)       6.33         1.36 (0.75, 2.47)       12.40         3.00 (0.14, 65.90)       1.13         9       3.79 (1.06, 13.60)       5.20         1.48 (0.94, 2.35)       14.71         8.40 (0.50, 142.27)       1.33         2.35 (0.13, 43.53)       1.26         11.00 (1.67, 72.40)       2.77         4       19.00 (1.16, 311.96)       1.36         2.09 (1.49, 2.92)       100.00		3.49 (1.11, 10.95)	6.10
4       1.75 (0.58, 5.24)       6.46 $5$ $2.04$ (0.67, 6.21) $6.33$ $1.36$ (0.75, 2.47) $12.40$ $3.00$ (0.14, 65.90) $1.13$ $9$ $3.00$ (0.14, 65.90) $1.13$ $9.20$ (0.58, 145.76) $1.39$ $9.20$ (0.58, 145.76) $1.39$ $3.79$ (1.06, 13.60) $5.20$ $1.48$ (0.94, 2.35) $14.71$ $8.40$ (0.50, 142.27) $1.33$ $2.35$ (0.13, 43.53) $1.26$ $11.00$ (1.67, 72.40) $2.77$ $4$ $5.00$ (1.16, 311.96) $1.36$ $2.09$ (1.49, 2.92) $100.00$	3	8.68 (1.26, 59.95)	2.65
$\begin{array}{c} 2.04 \ (0.67, 6.21) & 6.33 \\ 1.36 \ (0.75, 2.47) & 12.40 \\ 3.00 \ (0.14, 65.90) & 1.13 \\ 9.20 \ (0.58, 145.76) & 1.39 \\ 9.20 \ (0.58, 145.76) & 1.39 \\ 9.20 \ (0.58, 145.76) & 1.39 \\ 9.20 \ (0.58, 145.76) & 1.39 \\ 9.20 \ (0.58, 145.76) & 1.39 \\ 9.20 \ (0.58, 145.76) & 1.39 \\ 9.20 \ (0.58, 145.76) & 1.39 \\ 9.20 \ (0.58, 145.76) & 1.39 \\ 9.20 \ (0.58, 145.76) & 1.39 \\ 9.20 \ (0.50, 142.27) & 1.33 \\ 2.35 \ (0.13, 43.53) & 1.26 \\ 11.00 \ (1.67, 72.40) & 2.77 \\ 19.00 \ (1.16, 311.96) & 1.36 \\ 2.09 \ (1.49, 2.92) & 100.00 \\ 100 \text{TE: Weights are from random effects analysis} \end{array}$	4	1.75 (0.58, 5.24)	6.46
66       1.36 (0.75, 2.47)       12.40         77       3.00 (0.14, 65.90)       1.13         99       99       9.20 (0.58, 145.76)       1.39         91       9.20 (0.58, 145.76)       1.39         92       1.48 (0.94, 2.35)       14.71         8.40 (0.50, 142.27)       1.33         92       2.35 (0.13, 43.53)       1.26         11.00 (1.67, 72.40)       2.77         19.00 (1.16, 311.96)       1.36         2.09 (1.49, 2.92)       100.00	5	2.04 (0.67, 6.21)	6.33
3.00 (0.14, 65.90)       1.13         3.00 (0.14, 65.90)       1.13         9       9.20 (0.58, 145.76)       1.39         3.79 (1.06, 13.60)       5.20         1.48 (0.94, 2.35)       14.71         8.40 (0.50, 142.27)       1.33         2.35 (0.13, 43.53)       1.26         11.00 (1.67, 72.40)       2.77         19.00 (1.16, 311.96)       1.36         2.09 (1.49, 2.92)       100.00		1.36 (0.75, 2.47)	12.40
1       9.20 (0.58, 145.76)       1.39         3.79 (1.06, 13.60)       5.20         1.48 (0.94, 2.35)       14.71         8.40 (0.50, 142.27)       1.33         2.35 (0.13, 43.53)       1.26         11.00 (1.67, 72.40)       2.77         19.00 (1.16, 311.96)       1.36         2.09 (1.49, 2.92)       100.00	7	3.00 (0.14, 65.90)	1.13
99       3.79 (1.06, 13.60)       5.20         11       14       14.71         12       1.48 (0.94, 2.35)       14.71         13       2.35 (0.13, 43.53)       1.26         11.00 (1.67, 72.40)       2.77         19.00 (1.16, 311.96)       1.36         2.09 (1.49, 2.92)       100.00	.8	9.20 (0.58, 145.76)	1.39
0       1.48 (0.94, 2.35)       14.71         11       1.48 (0.94, 2.35)       14.71         12       1.48 (0.94, 2.35)       1.33         13       2.35 (0.13, 43.53)       1.26         11.00 (1.67, 72.40)       2.77         19.00 (1.16, 311.96)       1.36         2.09 (1.49, 2.92)       100.00	9	3.79 (1.06, 13.60)	5.20
31       8.40 (0.50, 142.27)       1.33         32       2.35 (0.13, 43.53)       1.26         33       11.00 (1.67, 72.40)       2.77         34       9.00 (1.16, 311.96)       1.36         30 (0.TE: Weights are from random effects analysis       0.000		1.48 (0.94, 2.35)	14.71
32       2.35 (0.13, 43.53)       1.26         33       11.00 (1.67, 72.40)       2.77         34       19.00 (1.16, 311.96)       1.36         Subtotal (I-squared = 41.4%, p = 0.038)       100.00         NOTE: Weights are from random effects analysis       100.00	31	8.40 (0.50, 142.27)	1.33
33       11.00 (1.67, 72.40)       2.77         14       11.00 (1.67, 72.40)       2.77         Subtotal (I-squared = 41.4%, p = 0.038)       Image: squared = 41.4%, p = 0.038)       136         NOTE: Weights are from random effects analysis       Image: squared = 41.4%, p = 0.038)       100.00		2.35 (0.13, 43.53)	1.26
A4       19.00 (1.16, 311.96)       1.36         Subtotal (I-squared = 41.4%, p = 0.038)       2.09 (1.49, 2.92)       100.00         IOTE: Weights are from random effects analysis       100.00       100.00	3	11.00 (1.67, 72.40)	2.77
Subtotal (I-squared = 41.4%, p = 0.038)       Image: Construction of the construction	34	19.00 (1.16, 311 96)	1.36
NOTE: Weights are from random effects analysis	Subtotal (I-squared = $41.4\%$ , p = $0.038$ )	2.09 (1.49, 2.92)	100.00
	NOTE: Weights are from random effects analysis		

✓ Assume ACA in both groups (IMOR=1) but the IMOR is allowed to range from 1/2 to 2

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67 68 69 70	/*: re: di di	in bo spons log 0.7,	oth g se in (1) /1.90	group n the 6	s the odd observed	s of response in the missing data are the same with the o data (IMOR=1) but the IMOR is allowed to range from 1/2	dds of // to 2*/
71 72 73	me <sup>.</sup> me <sup>.</sup> lc	tamis tanop ols(a	ss2 ot(fa autho	rh fh avour or ye	mh rp fp s(Favors ar PM) so	<pre>mp, impmean(0) impsd(0.36) eform /// placebo # Favors haloperidol) xlabel(0.1, 0.3, 1, 3, 10, rtby(PM) texts(130))</pre>	30, 100) ///
74 75 76	/*; C01	assun mpare	me the	nat i e res	n the hal ults with	operidol group the IMOR=1 ranging from 1/4 to 4, whereas ACA*/	in placebo g

										%
author	year	PM							RR (95% CI)	Weight
Borison	1992	0				•			7.00 (0.40, 122.44)	1.30
Chouinard	1993	0							3.49 (1.11, 10.95)	6.14
Durost	1964	0			<u> </u>	•		-	8.68 (1.26, 59.95)	2.66
Howard	1974	0			•				2.04 (0.67, 6.21)	6.37
Nishikawa_82	1982	0						-	3.00 (0.14, 65.90)	1.13
Reschke	1974	0				•			3.79 (1.06, 13.60)	5.23
Spencer	1992	0				•			11.00 (1.67, 72.40)	2.78
Arvanitis	1997	1.941748		-	-				1.42 (0.89, 2.25)	14.90
Marder	1994	3.030303		_					1.36 (0.75, 2.47)	12.57
Bechelli	1983	3.278688			<u> </u>	•			6.21 (1.52, 25.36)	4.51
Vichaiya	1971	3.333333					•		▶ 19.00 (1.16, 312.00)	1.36
Serafetinides	1972	3.571429			- i	•			8.40 (0.50, 142.32)	1.33
Garry	1962	3.846154			•	_			1.75 (0.58, 5.24)	6.51
Simpson	1967	4.166667			•				2.35 (0.13, 43.57)	1.26
Nishikawa_84	1984	6							9.20 (0.58, 145.80)	1.39
Beasley	1996	40.87591		-	←				1.05 (0.70, 1.56)	16.09
Selman	1976	50							1.48 (0.91, 2.42)	14.47
Overall (I-squared = 39.3%, p = 0.049)					$\bigcirc$				2.09 (1.49, 2.93)	100.00
					Ĩ					
NOTE: Weights	s are fro	m random effects a	nalysis							
			.1	.3	1 3	10	30	100		
			Favors placebo			Favors ha	aloperid	ol		

✓ Assume that in the haloperidol group the IMOR=1 ranging from 1/4 to 4, whereas in placebo group IMOR=1/2 ranging from 1/8 to 2, compare the results with ACA

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74								
75	/*a	/*assume that in the haloperidol group the IMOR=1 ranging from 1/4 to 4,						
76	whe	whereas in placebo group IMOR=1/2 ranging from 1/8 to 2, compare the results with ACA*/						
77	di	log	(4)/:	1.96				
78	di	(0.7	/+0.]	7)/1.	96			
79	met	amis	ss2	rh fh	ı mh rp	fp mp	o, impmean(0 −0.7) impsd(0.71) compare(impmean(0) imps	d(0)) eform ///
80	met	anop	ot(fa	avour	`s(Favo	rs pla	acebo # Favors haloperidol)	30, 100) ///
81	lco	ls(a	autho	or ye	ear PM)	sortb	by(PM))	
82								
83	//r	run a	a sei	nsiti	⊥vity a	nalysi	is showing how the uncertainty in IMOR impacts the sum	mary effect wher
<u> </u>		•	^		ı	ſ.	end of do-	file

Study		%
ID	ES (95% CI)	Weight
Primary analysis		
1	1.42 (0.89, 2.25)	17.21
2	1.23 (0.73, 2.07)	15.71
3	6.31 (1.54, 25.80)	4.36
4	7.00 (0.40, 122.44)	1.21
5	3.49 (1.11, 10.95)	6.11
6	8.68 (1.26, 59.95)	2.51
7	1.78 (0.59, 5.35)	6.49
8	2.04 (0.67, 6.21)	6.36
9	1.38 (0.76, 2.50)	13.89
10	3.00 (0.14, 65.90)	1.04
11 •	9.20 (0.58, 145.90)	1.29
12	3.79 (1.06, 13.60)	5.13
13	1.78 (0.91, 3.47)	12.44
14	8.69 (0.51, 147.53)	1.23
15	2.49 (0.13, 46.38)	1.16
16	11.00 (1.67, 72.40)	2.63
17	→ 19.31 (1.18, 317.32)	1.26
Subtotal (I-squared = 27.0%, p = 0.146)	2.16 (1.57, 2.98)	100.00
Secondary analysis		
	1.42 (0.89, 2.25)	14.66
19	1.05 (0.73, 1.50)	16.46
20	6.21 (1.52, 25.35)	4.48
21	7.00 (0.40, 122.44)	1.30
22	3.49 (1.11, 10.95)	6.10
23	8 68 (1 26, 59 95)	2.65
24	1.75 (0.58, 5.24)	6.46
25	2.04 (0.67, 6.21)	6.33
26	1.36 (0.75, 2.47)	12.40
27	3 00 (0 14 65 90)	1 13
28	9 20 (0.58, 145 76)	1 39
29	3 79 (1 06, 13 60)	5 20
30	1 48 (0 94 2 35)	14 71
31	8 40 (0 50 142 27)	1 33
32	2 35 (0 13 43 53)	1.26
33	$11\ 00\ (1\ 67\ 72\ 40)$	2 77
34	- 19 00 (1 16 311 96)	1.36
Subtotal (I-squared = 41.4% $p = 0.038$ )	2 09 (1 49 2 92)	100.00
NOTE: Weighte are from rendem effects analysis	2.00 (1.10, 2.02)	
NOTE. Weights are from random effects analysis		
.00315 1	317	

 ✓ Run a sensitivity analysis showing how the uncertainty in IMOR impacts the summary effect when IMOR=1

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82		
83	/*run a sensitivity analysis showing how the uncertainty in IMOR impacts the	
84	<pre>summary effect when IMOR=1*/</pre>	
85	metamiss2 rh fh mh rp fp mp, sensitivity eform	
86		
87		
88	*** 3.Pairwise meta-analysis – continuous data ***	
89		
# Pairwise meta-analysis – binary data



DTA

✓ Load the dataset "mirtazapine.dta"



```
✓ Look at the dataset
```



id	study	ур	sdp	np	mp	Уm	sdm	nm	mm
1	Claghorn1995	-11.4	10.2	19	26	-14.5	8.8	26	19
2	MIR 003-003	-11.5	8.3	24	21	-14	7.3	27	18
3	MIR 003-008	-11.4	8	17	13	-13.2	8	12	18
4	MIR 003-020	-6.2	6.5	24	19	-13	9	23	21
5	MIR 003-021	-17.4	5.3	21	29	-13.8	5.9	22	28
6	MIR 003-024	-11.1	9.9	27	23	-15.7	6.7	30	20
7	MIR 84023a	-11.9	8.6	33	24	-14.2	7.6	35	25
8	MIR 84023b	-11.8	8.3	48	18	-14.7	8.4	51	13

✓ Find the percentage of missing data for each study

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89		
90	<pre>//load the dataset mirtazapine.dta and look at the data</pre>	
91	li,clean	
92		
93	//create again a variable PM that shows the percentage of missing data	-
94	<pre>gen PM=(mp+mm)/(mp+mm+np+nm)</pre>	
95	li study PM,clean	
96		
97	<pre>//run a meta-analysis using only the observed participants for each study (use t</pre>	he random effec

study	PM
Claghorn1995	• 5
MIR 003-003	.4333333
MIR 003-008	.5166667
MIR 003-020	.4597701
MIR 003-021	.57
MIR 003-024	.43
MIR 84023a	.4188034
MIR 84023b	.2384615

 Run a meta-analysis using only the observed participants for each study (use the random effects model); that is the available-case analysis (ACA)

•••		
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96		
97	/*run a meta-analysis using only the observed participants for each study	
98	(use the random effects model); that is the available-case analysis (ACA)*/	
99	<pre>metan nm ym sdm np yp sdp, nostandard lcols(study PM) xlab(-10,-5,0,5,10) ///</pre>	
100	<pre>favours(Favors mirtazapine # Favors placebo) texts(150) sortby(PM) randomi</pre>	
101		
102	<pre>//the above command is equivalent with the following</pre>	



✓ Run the same analysis with metamiss2 instead of metan

• •	•	🗃 missing data workshop commands vienna 2015.do	
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99 100 101 102	<pre>metan nm ym sdm np yp sdp, favours(Favors mirtazapine //the above command is equi</pre>	nostandard lcols(study PM) xlab(-10,-5,0,5,10) /// # Favors placebo) texts(150) sortby(PM) randomi ivalent with the following	
103 104	<pre>metamiss2 nm mm ym sdm np n favours(Favors mirtazapine</pre>	<pre>np yp sdp, md metanopt(lcols(study PM) xlab(-10,-5,0,5,10) /// # Favors placebo) sortbv(PM) texts(150))</pre>	
105 106	/*the mean change score in	the missing data is the same with the mean change score in the ob	bserv



The mean change score in the missing data is the same with the mean change score in the observed data for both arms, but with some uncertainty; the mean in the missing could be three units lower or three units higher compared to the observed, compare the results with ACA

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106	/*the mean change score in	the missing data is the same with the mean change sco	re in the
107	observed data for both arms	, but with some uncertainty; the mean in the missing	could be three
108	units lower or three units	higher compared to the observed, compare the results	with ACA*/
109	di 3/1.96		
110	metamiss2 nm mm ym sdm np m	<pre>p yp sdp, impmean(0) impsd(1.53) compare(impmean(0) i</pre>	mpsd(0)) ///
111	<pre>md metanopt(lcols(study PM)</pre>	sortby(PM) xlab(-10,-5,0,5,10) ///	
112	favours(Favors mirtazapine	<pre># Favors placebo))</pre>	
113			
114	//run a sensitivity analysi	s showing how the uncertainty in IMDOM impacts the su	mmary effect



 ✓ Run a sensitivity analysis showing how the uncertainty in IMDOM impacts the summary effect

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110	<pre>metamiss2 nm mm ym sdm np mp yp sdp, impmean(0) impsd(1.53) compare(impmean(0) i</pre>	Lmpsd(0)) ///
111	<pre>md metanopt(lcols(study PM) sortby(PM) xlab(-10,-5,0,5,10) ///</pre>	
112	favours(Favors mirtazapine # Favors placebo))	
113		
114	//run a sensitivity analysis showing how the uncertainty in IMDOM impacts the su	ımmary effect
115	metamiss2 nm mm ym sdm np mp yp sdp, md sensitivity	
116		
117		
118		



# Updates on www.mtm.uoi.gr



#### Multiple-Treatments Meta-Analysis A Framework for Evaluating and Ranking Multiple Healthcare Technologies

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IMMA ERC starting Grant	network meta-analysis. Stat Med 2015; 34: 721–741	
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