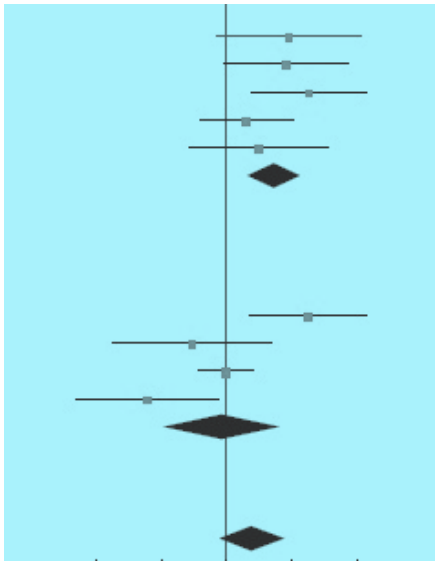


An introduction to numerical methods for meta-analysis and meta-regression

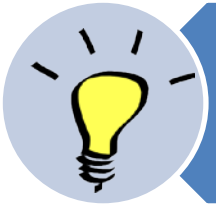
Dr Jonathan Williman
Biostatistics and Computational Biology, University of Otago Christchurch

Dr James Foulds
Psychological Medicine, University of Otago Christchurch

What is meta-analysis?

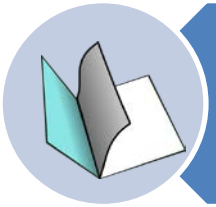
- a way to combine results from different studies, using statistical methods

- Improves estimate of treatment effect, or other parameters of interest

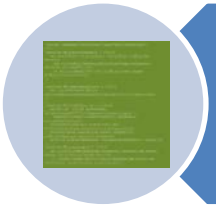


Define the research question and write a protocol

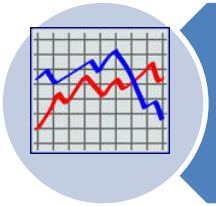
Conduct literature search (preferably 2 independent authors)



Extract data from studies



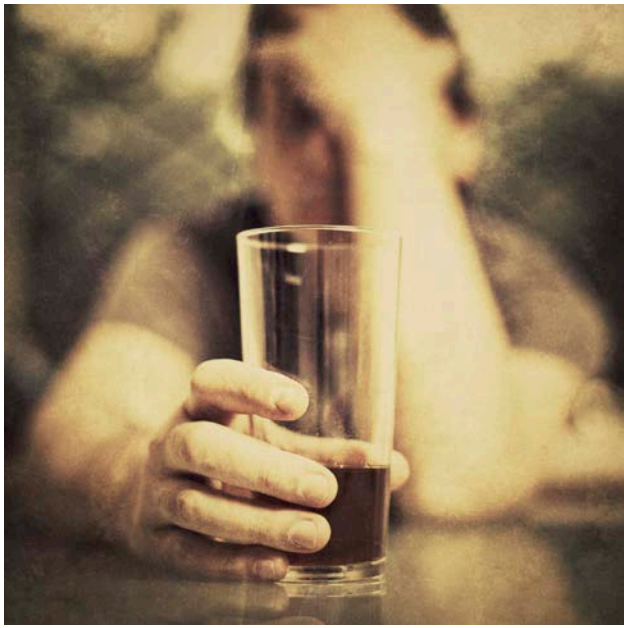
Analyse data using meta-analysis model



Summarise and interpret data

Motivating example: depression and alcohol disorders

- Depression common in heavy drinkers
- Depression improves when patients enter addiction treatment
- Common belief that most of the depression is alcohol-induced therefore antidepressants not needed



Synthesising data via meta-analysis

- By how much does depression improve?
- What is the effect of antidepressants?
- What study characteristics are associated with greater improvement in depression during treatment?

PRISMA

TITLE		
Title	1	Identify the report as a systematic review, meta-analysis, or both.
ABSTRACT		
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.
INTRODUCTION		
Rationale	3	Describe the rationale for the review in the context of what is already known.
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).
METHODS		
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.

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Moher D, Liberati A, Tetzlaff J, Altman DG, et al. (2009) Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed.1000097
http://www.plosmedicine.org/article/info:doi/10.1371/journal.pmed.1000097

PRISMA

RESULTS		
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome-level assessment (see Item 12).
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group and (b) effect estimates and confidence intervals, ideally with a forest plot.
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).
DISCUSSION		
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., health care providers, users, and policy makers).
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review level (e.g., incomplete retrieval of identified research, reporting bias).
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.
FUNDING		
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.

doi:10.1371/journal.pmed.1000097.t001

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Moher D, Liberati A, Tetzlaff J, Altman DG, et al. (2009) Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed.1000097
http://www.plosmedicine.org/article/info:doi/10.1371/journal.pmed.1000097

Inclusion criteria

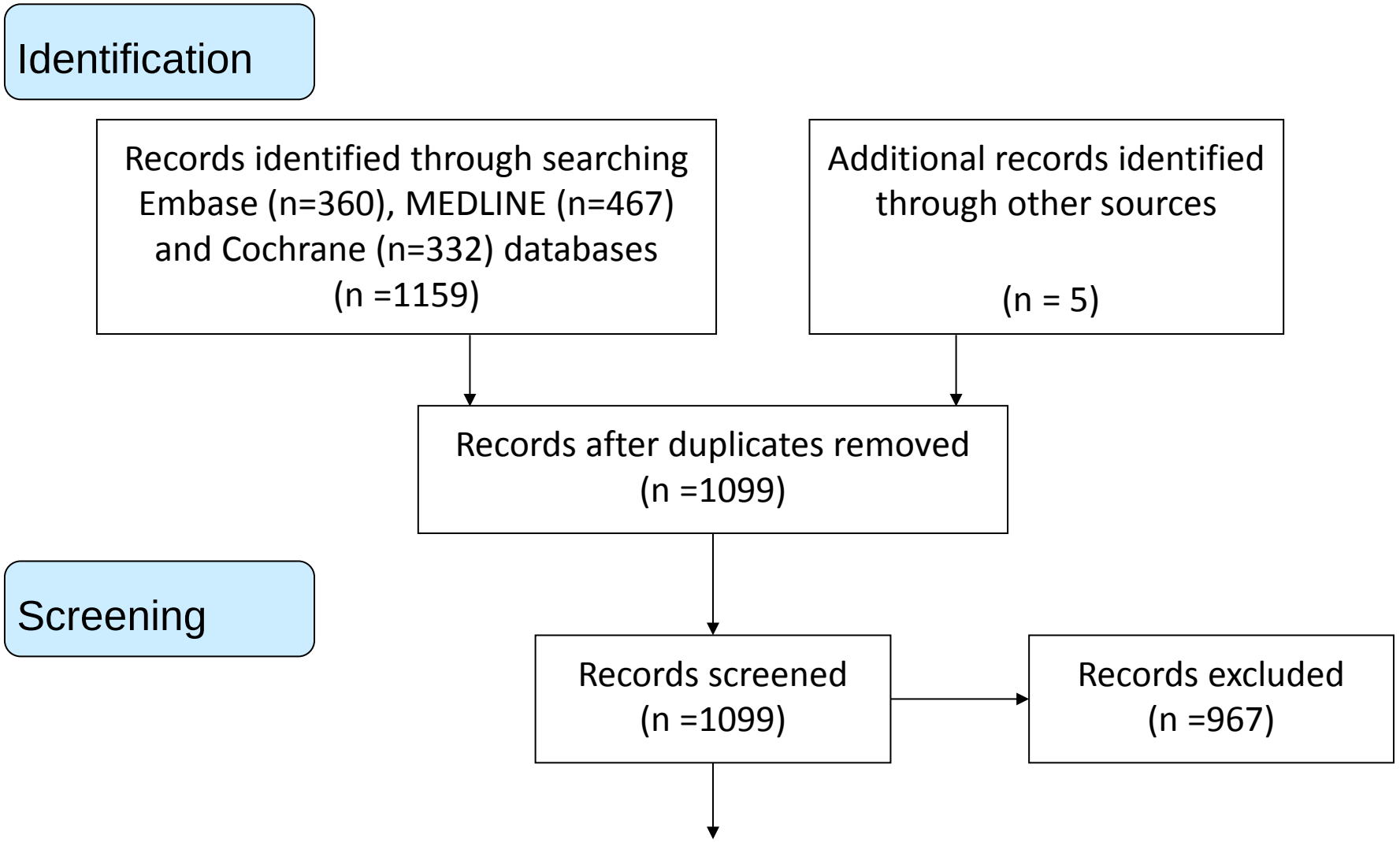
Studies were chosen according to the following criteria:

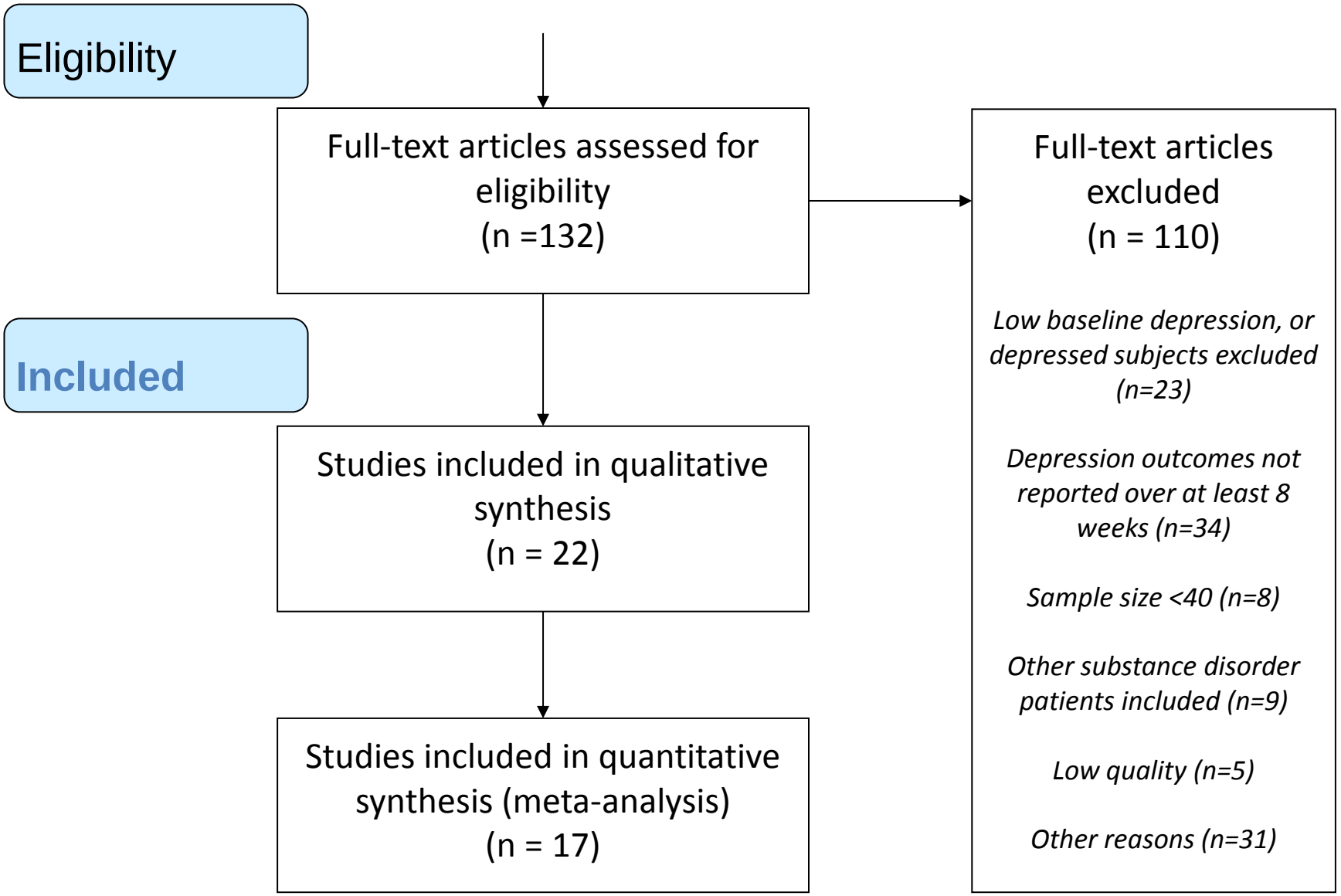
1. Studies with longitudinal data on alcohol use and depression over 8+ weeks in treatment-seeking populations, n≥40.
2. Change in mean score on a validated depression scale was reported.
3. Subjects had a currently active alcohol use disorder.
4. Mean baseline depression score ≥ 10 on the Hamilton Depression Rating Scale

Search strategy

- MEDLINE, Embase and Cochrane databases, searched on 21 June 2013.
- Search items were alcohol drinking; alcohol-induced disorder; alcohol-related disorder; alcoholics; alcoholism AND depression; antidepressive agents
- English-language publications on subjects aged 18+ from 1980 onwards were considered.

PRISMA flow chart




Eligibility
Full-text articles assessed for eligibility
(n =132)
Full-text articles excluded
(n = 110)
Low baseline depression, or depressed subjects excluded (n=23)
Depression outcomes not reported over at least 8 weeks (n=34)
Sample size <40 (n=8)
Other substance disorder patients included (n=9)
Low quality (n=5)
Other reasons (n=31)
Included
Studies included in qualitative synthesis
(n = 22)
Studies included in quantitative synthesis (meta-analysis)
(n = 17)

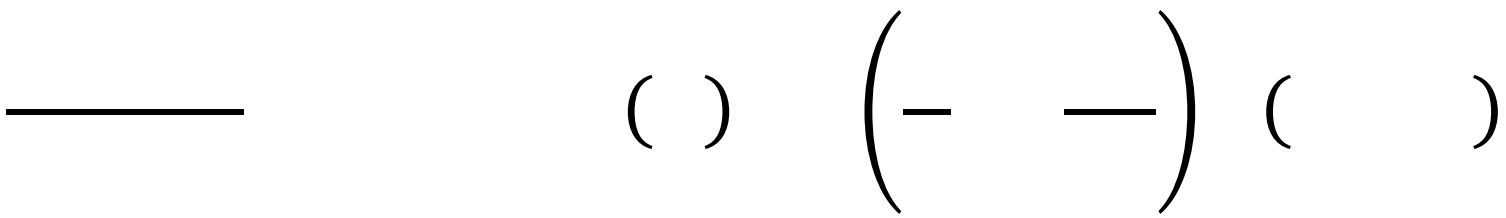
Decide on your summary statistic

	Binary	Count	Continuous	Survival
Group contrasts	log(RR), log(OR), RD	log(IRR), IRD	Mean difference (raw or standardised)	log(HR), log(OR)
Univariable	Proportion	Incident rate	Mean change (raw or standardised)	
Association	log(OR), phi		Correlation coefficient	

Example

Use of multiple depression scales
(BDI, HAM-D, MADRS)

Standardised mean change (Cohen's d)

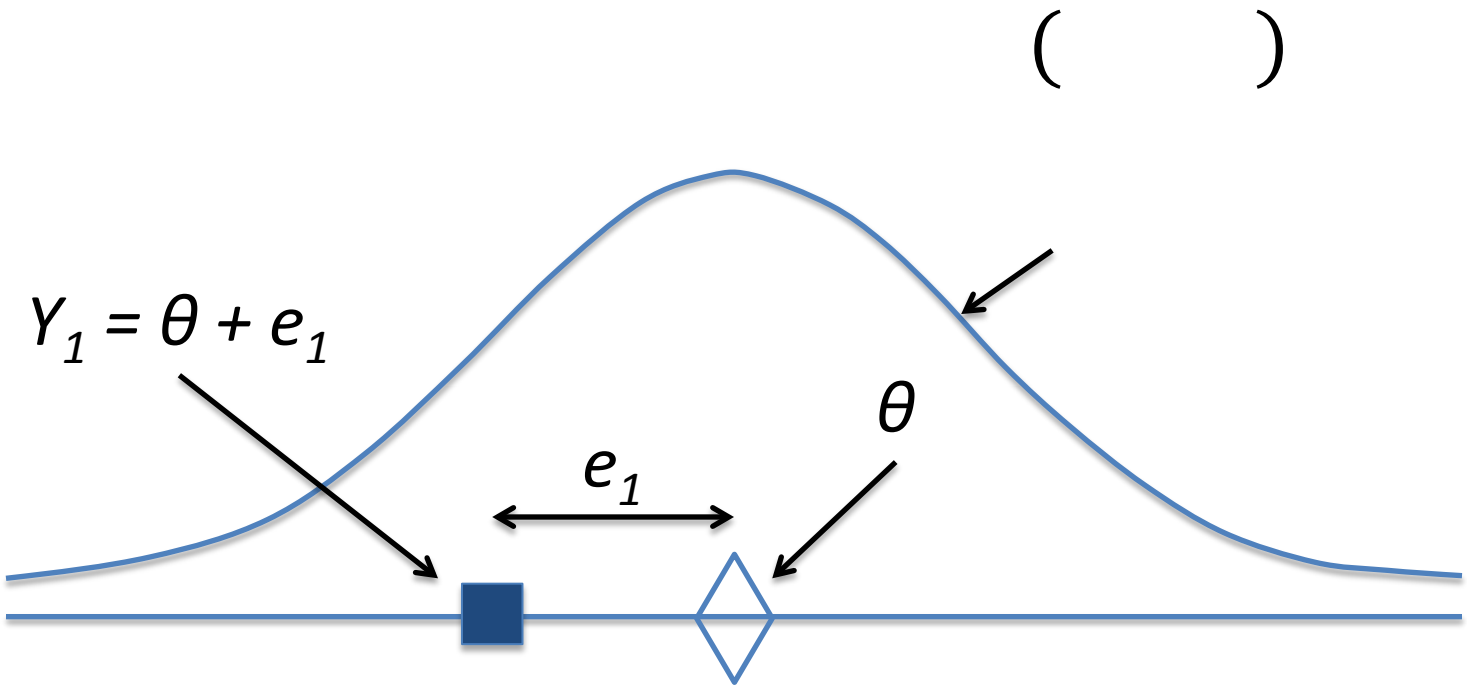


- *NB S_{within} usually taken from sample baseline sd*
- *Var(d) requires known correlation (r) between baseline (Y1) and follow-up (Y2) measures.*

Extracting data

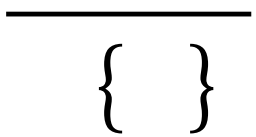
- Ideally, publication reports raw counts or means (SDs), or summary effect size estimate (SE).
- Where SE is not reported, can derive it from CI, *f* or *t* statistics, or p-values.
- For repeated measures need correlation (*r*), or SD of change scores. Very often this is not reported.
- May need to extract data from figures (imprecise).
- Can impute missing values from similar studies, or conduct sensitivity analysis.

Pooling study data – fixed effects



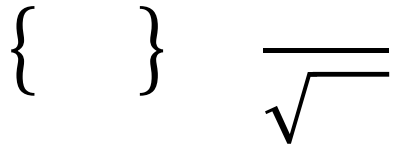
- Assumption that all studies are estimating a single common effect size.
- Large studies tend to dominate the analysis

Fixed effects model
Inverse variance method



1. Calculate ‘inverse variance’ weight for each study

2. Pool effects by taking weighted mean



3. Calculate SE for pooled estimate

Measuring and interpreting heterogeneity

- Measuring consistency between studies.

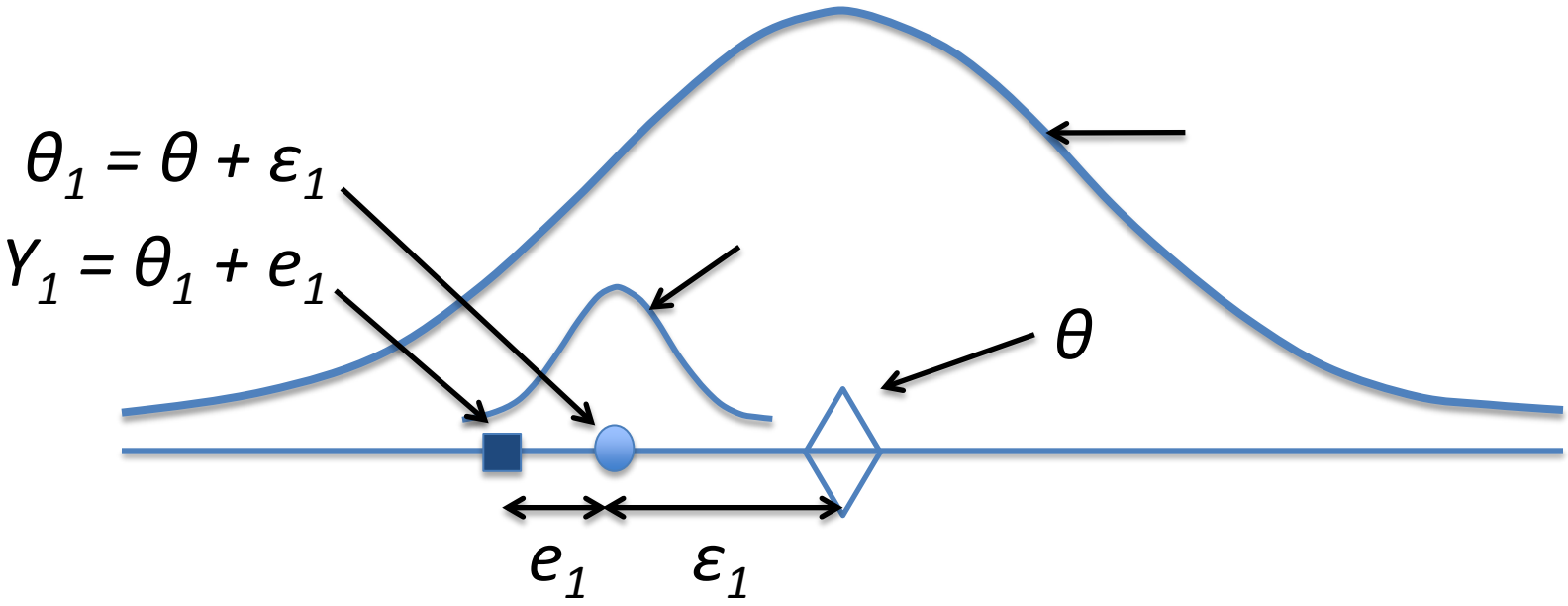
( )

- Estimating the proportion of variance attributable to heterogeneity

$$\left\{ \quad \frac{\qquad}{\qquad} \quad \right\}$$

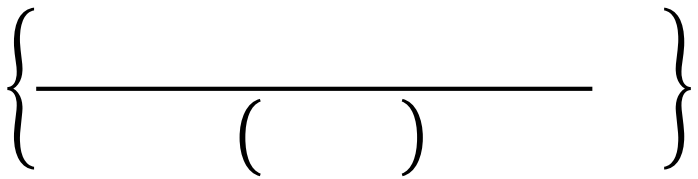
Pooling study data – random effects

( ), ( )



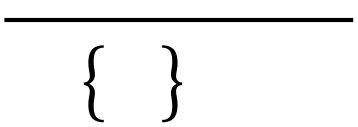
- Effect sizes are considered normally distributed due to (unmeasured) between study differences.
- Studies more evenly weighted

Random effects model
DerSimonian and Laird method

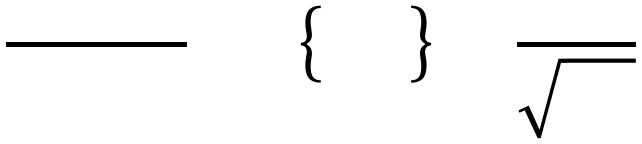


1. Calculate study weights and Q statistic as above

2. Calculate unexplained between-trial variance ( )



3. Calculate new ‘adjusted’ study weights



4. Pool summary statistic as before.

Meta-regression

- Attempts to identify significant study-level predictors associated with effect estimate
- Easily run as mixed effects model. Predictors typically treated as fixed effects and studies as a random effect
- Readily extended to multilevel scenario: ie treatment arms within studies and potentially individual subjects within treatment arms

Meta-regression using random effects model

Basic model: **$Y=X\beta + Z\gamma + \varepsilon$** **Var (Y) = ZGZ'+R**

Where Y=vector of outcome variables
X=matrix of fixed effects; β=fixed effect parameters
Z=matrix of random effects; γ=random effects parameters
ε = error vector

$$\mathrm{Var}\begin{bmatrix}\boldsymbol{\gamma}\\ \boldsymbol{\varepsilon}\end{bmatrix} = \begin{bmatrix}\mathbf{G} & \mathbf{0}\\ \mathbf{0} & \mathbf{R}\end{bmatrix} \qquad \mathrm{E}\begin{bmatrix}\boldsymbol{\gamma}\\ \boldsymbol{\varepsilon}\end{bmatrix} = \begin{bmatrix}\mathbf{0}\\ \mathbf{0}\end{bmatrix}$$

- covariance structures specified using G and R matrices
  (G = between-subject covariance structure, R = within-subject covariance)
- Components of R (within-study variance) known
- intercept-only model is used to estimate the pooled estimate of effect size
- model easily extends to meta-regression (by adding fixed effects) and multilevel scenarios (eg subjects nested within treatment arms within studies) via more complex specifications of G and R
- Likelihood-based methods (ML or REML) to find model parameters.

Sample data set

Study name	Effect size	SE	variance
Cornelius 1997	0.48	0.2857	0.0816
McGrath 1996	0.46	0.2449	0.0600
Moak 2003	0.63	0.2296	0.0527
Pettinati 2010	0.16	0.1786	0.0319
Roy-Byrne 2000	0.25	0.2704	0.0731
Gual 2003	0.63	0.2245	0.0504
Hernandez-Avila 2004	-0.27	0.3163	0.1001
Kranzler 2006	-0.01	0.1020	0.0104
Pettinati 2001	-0.61	0.2806	0.0787

Code example: simple random effects meta-analysis

```
PROC MIXED DATA=meta;
CLASS study_name;
MODEL effect_size= / cl solution;
RANDOM study_name;
REPEATED / group=study_name;
PARMS
(0.5)
(0.0816)(0.0600)(0.0527)(0.0319)(0.0731)
(0.0504)(0.1001)(0.0104)(0.0504)
/eqcons=2 to 10;
RUN;
```

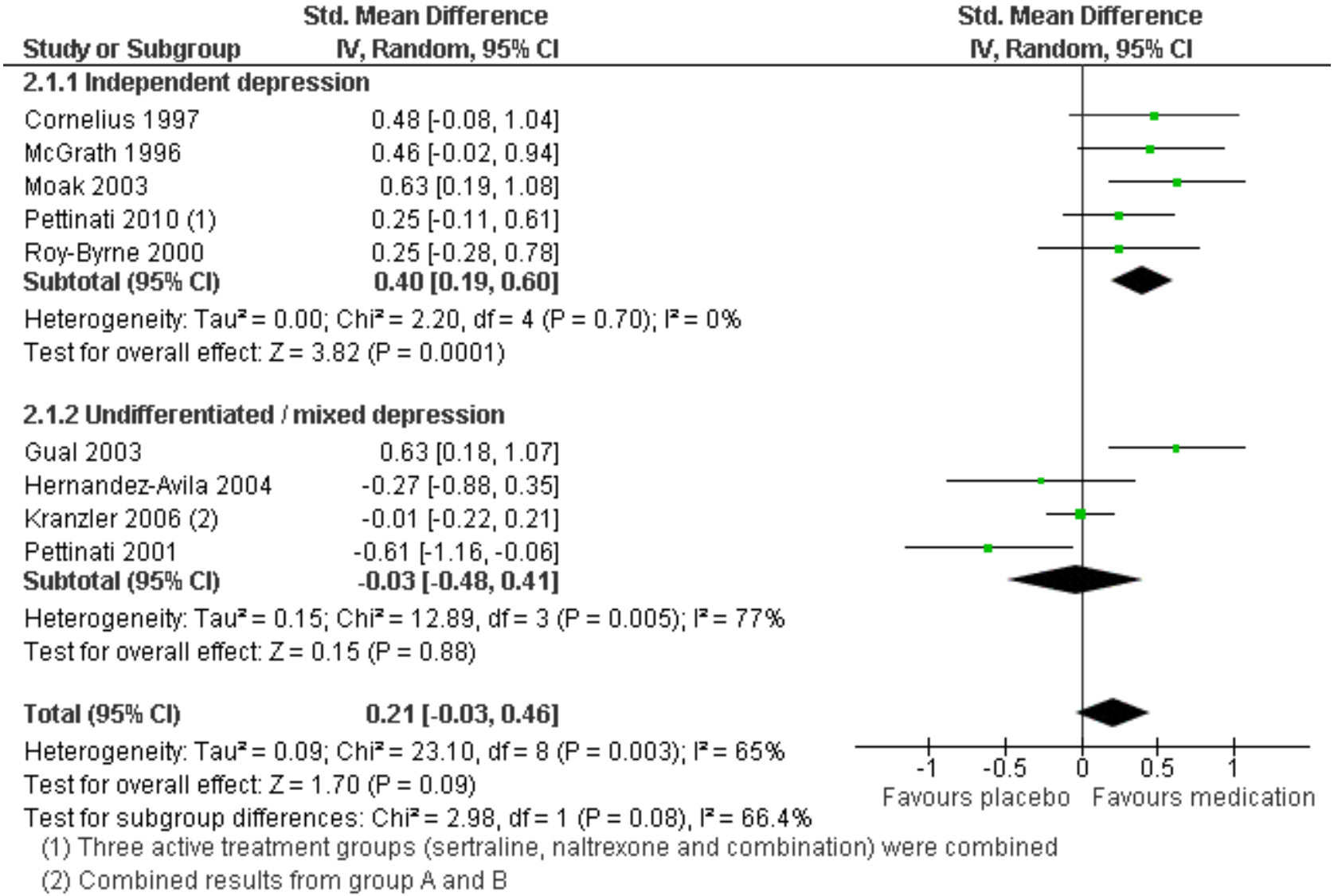
Interpreting SAS output for PROC MIXED

- Main output of interest is the solution for the intercept

Solution for Fixed Effects							
Effect	**Estimate**	**SE**	**DF**	**t**	**Pr > |t|**	**Lower 95% CL**	**Upper 95% CL**
Intercept	0.197	0.124	8	1.59	0.15	-0.089	0.484

- Can check specification of the model by outputting G, R and V matrices

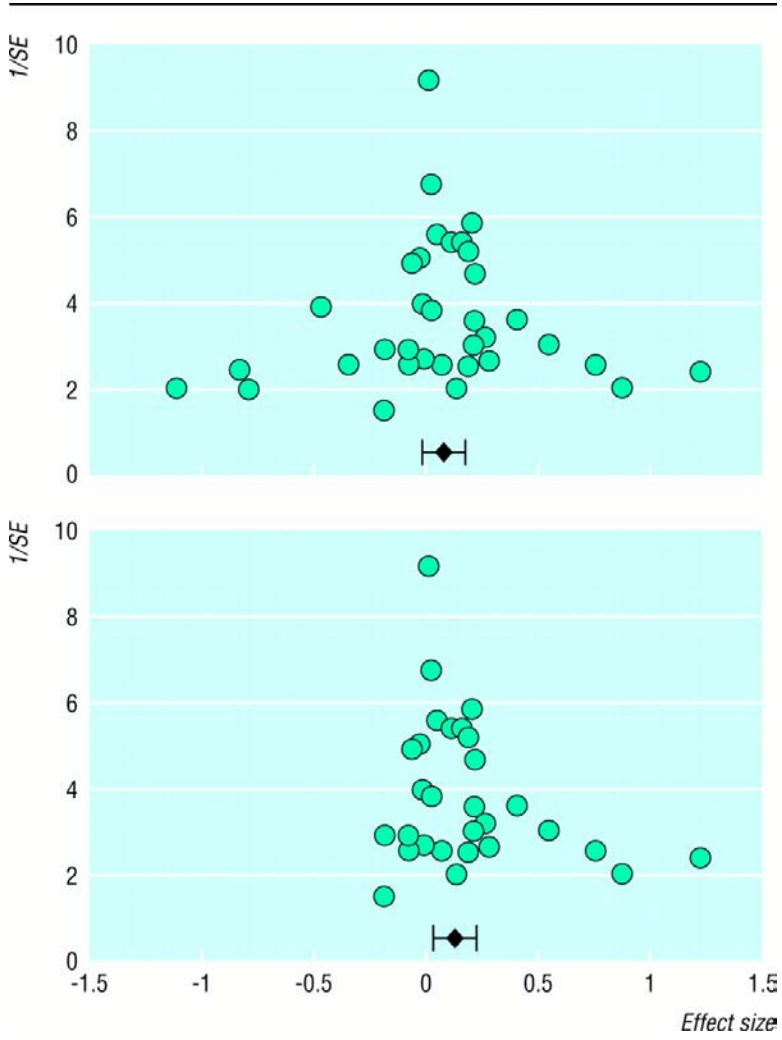
Presenting results with forest plot



(1) Three active treatment groups (sertraline, naltrexone and combination) were combined

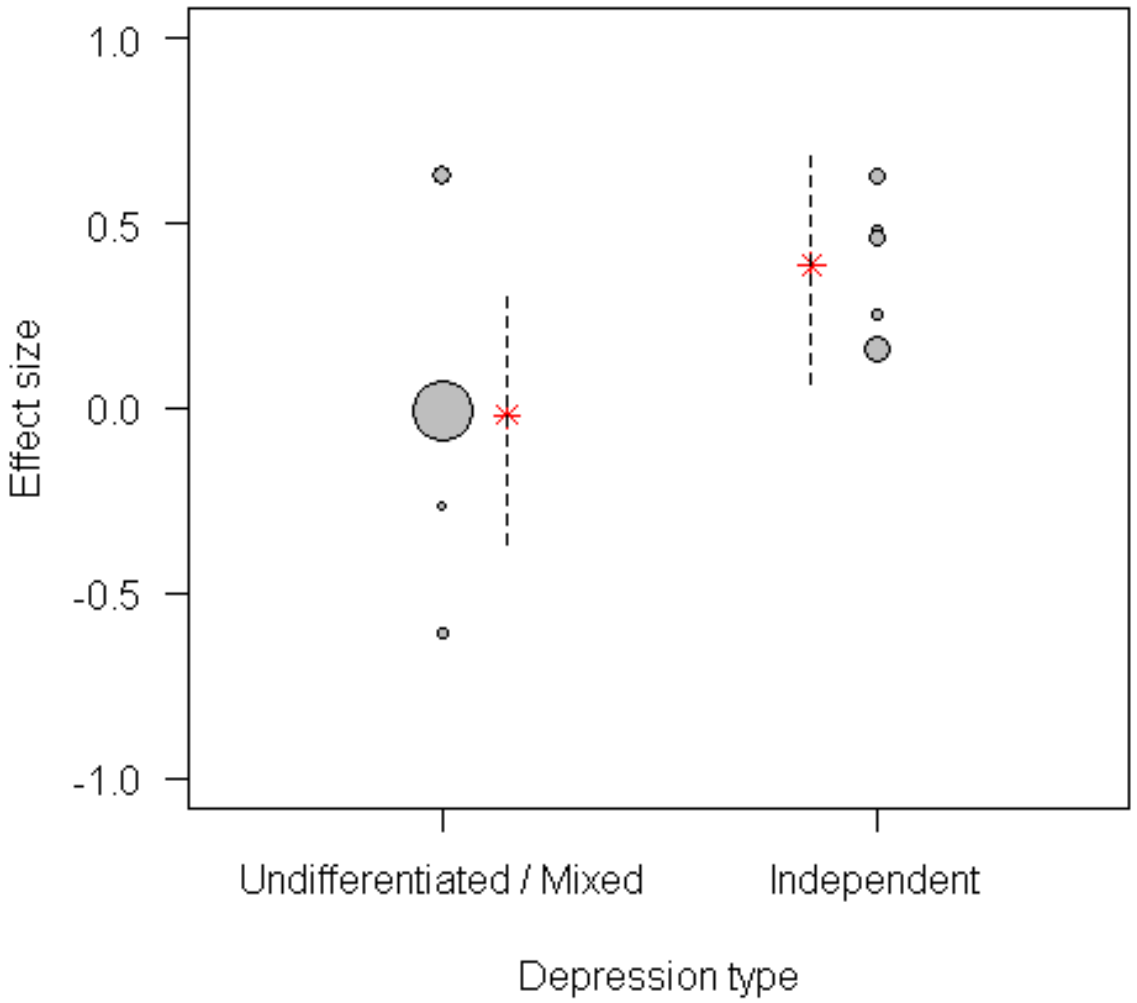
(2) Combined results from group A and B

Typical funnel plot generated from 35 simulated studies (top) and same data with five missing studies showing a typical manifestation of publication bias (bottom).



Sutton A J et al. BMJ 2000;320:1574-1577

Presenting results with bubble plot



Meta-regression: limitations

- Observational, exploratory technique: hypothesis generating rather than confirmatory
- Usually few studies therefore low power
- Less precise than looking at predictors at an individual subject level
- Potential for data dredging. Predictors should be identified *a priori*