6. Evidence synthesis and network meta-analysis

Gianluca Baio

Department of Statistical Science | University College London

g.baio@ucl.ac.uk
https://gianluca.statistica.it/
https://egon.stats.ucl.ac.uk/research/statistics-health-economics/
https://github.com/giabaio
https://github.com/StatisticsHealthEconomics
@gianlubaio

Bayesian Methods in Health Economics, Lausanne

Summary

- Motivation for Network Meta Analysis (NMA)
  - Example: Smoking cessation
- Fixed effects meta-analysis
- Random effects meta-analysis

References

Doing Meta-Analysis in R Book website Code

Evidence Synthesis for Decision Making in Healthcare Book website

Bayesian Cost-Effectiveness Analysis with the R package BCEA Book website (Springer) Book website

Data Analysis Using Regression and Multilevel/Hierarchical Models Book website (CUP) Book website

NICE DSU Evidence Synthesis Technical Support Document Series

Introduction

- Unusual for a policy question to be informed by a single study
  – Must use all available and relevant evidence

Multiparameter evidence synthesis

Learning about more than one quantity from combination of direct and indirect evidence.

- Example: Network Meta Analysis (NMA)

Simplest example

- New treatment C: been trialled against old treatment B, but not to A
- For health economic evaluation need to compare A/B/C together
- ➔ Learn about C/A effect from C/B and B/A trial data

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  – Since can also “mix” direct and indirect data on same comparison...

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⚠ Common in UK health technology assessment, but require some statistical skills!

Smoking cessation trial

Data

Comparison	A: No intervention	B: Self-help	C: Individual counselling	D: Group counselling
	79 / 702	77 / 694		
AB	18 / 671	21 / 535		
	8 / 116	19 / 149		
AC	75 / 731		363 / 714	
	2 / 106		9 / 205	
	58 / 549		237 / 1561	
	0 / 33		9 / 48	
	3 / 100		31 / 98	
	1 / 31		26 / 95	
	6 / 39		17 / 77	
	64 / 642		107 / 761	
	5 / 62		8 / 90	
	20 / 234		34 / 237	

Outcome

- Successfully quit smoking by 6-12 months
- Number of success / number of participants

Set up

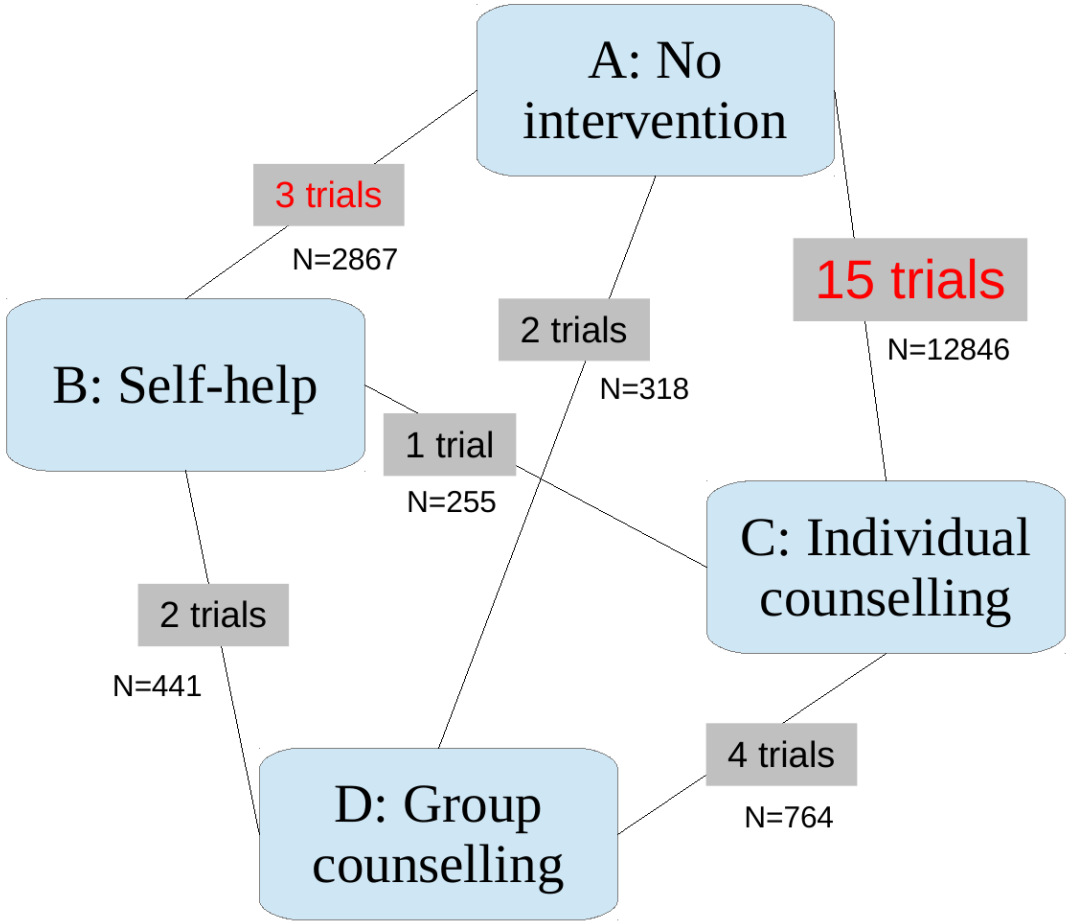
- 24 trials in total
- Network of comparisons involving 4 interventions
- Not all interventions tested against all others!

Objective

- Estimate the overall effectiveness of the interventions
- Potentially add cost-effectiveness analysis

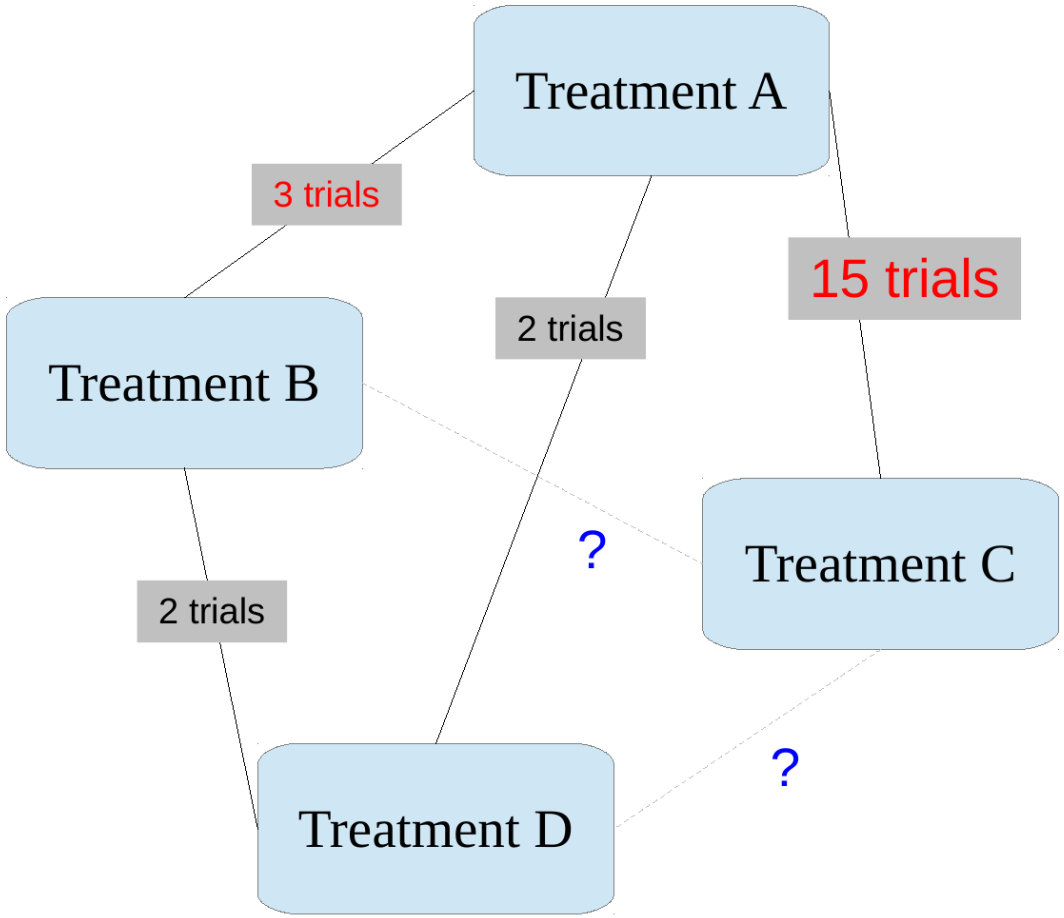
Smoking cessation trial

Network of comparisons



- All comparisons have at least one trial with direct data
- We wish to enhance direct with indirect evidence
- e.g. A-D comparison (only 2 direct trials) improved by including A-C, C-D trials (15 + 4)

Network of comparisons



- In other applications, might want to learn about comparisons with no direct trial evidence
- e.g. how much better than current treatment C is new treatment D?

Fixed effects network meta-analysis

- Log odds of response in each arm modelled as effect of study s plus effect of treatment t ($s = 1, \ldots, NS$, different values of t in each s)

$$r_{st} \sim \text{Binomial}(p_{st}, n_{st})$$
$$\text{logit}(p_{st}) = \mu_s + \delta_{st}$$
$$\delta_{st} \sim d_t - d_{t_{s0}}$$

Fixed effects network meta-analysis

- Log odds of response in each arm modelled as effect of study s plus effect of treatment t ($s = 1, \ldots, NS$, different values of t in each s)

$$
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\text{logit}(p_{st}) &= \mu_s + \delta_{st} \\
\delta_{st} &\sim d_t - d_{t_{s0}}
\end{aligned}
$$

- **Study effects** μ_s: log odds in baseline group of study s, considered independent between studies

- **Treatment effects**

  δ_{st}: compared to study s baseline $t_{s_{s0}}$

  d_t: compared to overall baseline treatment $t = 1$ (e.g. placebo) $\Rightarrow d_1 := 0$

  – This essentially means that the effect of treatment $t = 1$ versus the effect of the baseline treatment (again $t = 1$) is... nothing $(= 0)$!

- "Fixed" effects: d_t are identical in each study s

Smoking cessation example

- logORs d_B, d_C, d_D (compared to "baseline" treatment A) are directly identifiable from A-B, A-C, A-D trials

But: can deduce indirect comparisons from these basic parameters (with assumptions...)

- logOR of C compared to B is $d_C - d_B$
- logOR of D compared to B is $d_D - d_B$
- logOR of D compared to D is $d_D - d_C$

NB This assumes **consistency** between indirect and (potential) direct evidence!

Estimating effects of indirect comparisons

- Consider $t = B$
- By definition: $\text{logit}(p_{st}) = \log\left(\frac{p_{st}}{1-p_{st}}\right) =$ log odds of the event (quit smoking), if you are in group B
- Similarly, $\text{logit}(p_{sA}) = \log\left(\frac{p_{sA}}{1-p_{sA}}\right) =$ log odds of the event (quit smoking), if you are in group A $(\Rightarrow t = 1)$
- By definition: $\text{OR}_{BA} = \frac{\text{odds}_B}{\text{odds}_A} \Rightarrow \text{logOR}_{BA} = \log \text{odds}_B - \log \text{odds}_A = \text{logit}(p_{sB}) - \text{logit}(p_{sA})$
- So

$$\begin{aligned}
\text{logOR}_{BA} &= \text{logit}(p_{sB}) - \text{logit}(p_{sA}) \\
&= [\mu_s + \delta_{sB}] - [\mu_s + \delta_{sA}] \\
&= [\mu_s + (d_B - d_A)] - [\mu_s + (d_A - d_A)] \\
&= d_B - d_A \\
&= d_B \qquad (\text{because } d_A = d_1 := 0)
\end{aligned}$$

Manipulating data

Nested indices (see Practical & Solutions)

Outcome | Sample sizes | Treatment index | Using nested indices

```
> # Shows the first 2 rows...
> head(smoke.list$r,2)
```

```
     [,1] [,2] [,3] [,4]
[1,]   79   77   NA   NA
[2,]   18   21   NA   NA
```

```
> # ...and the last 4 rows of the data for the number of quitters in each arm
> tail(smoke.list$r,4)
```

```
      [,1] [,2] [,3] [,4]
[21,]   NA   11   12   29
[22,]   NA    7   NA   32
[23,]   NA   NA   12   20
[24,]   NA   NA    9    3
```

```
> # In study 1, treatments 3 (=C) and 4 (=D) are not present so the data show 'NA'
> # Similarly, in study 21, treatment 1 (=A) was not involved, so there's a 'NA'
```

Manipulating data

Nested indices (see Practical & Solutions)

Outcome | **Sample sizes** | Treatment index | Using nested indices

```
> # Similarly, shows the first 2 rows...
> head(smoke.list$n,2)
```

```
     [,1] [,2] [,3] [,4]
[1,]  702  694   NA   NA
[2,]  671  535   NA   NA
```

```
> # ...and the last 4 rows of the data for the total sample size in each arm
> tail(smoke.list$n,4)
```

```
      [,1] [,2] [,3] [,4]
[21,]   NA   78   85  170
[22,]   NA   66   NA  127
[23,]   NA   NA   76   74
[24,]   NA   NA   55   26
```

Manipulating data

Nested indices (see Practical & Solutions)

Outcome | Sample sizes | **Treatment index** | Using nested indices

```
> # Here shows the first 2 and last 4 rows of the matrix indicating the treatment included in the comparison
> head(smoke.list$t,2)
```

```
     t1 t2 t3
[1,]  1  2 NA
[2,]  1  2 NA
```

```
> tail(smoke.list$t,4)
```

```
      t1 t2 t3
[21,]  2  3  4
[22,]  2  4 NA
[23,]  3  4 NA
[24,]  3  4 NA
```

```
> # So in study number 1, the comparison is between intervention 1 (=A) and intervention 2 (=B)
> # while in study number 21, the comparison is among interventions 2 (=B), 3 (=C) and 4(=D)
```

Nested indices (see Practical & Solutions)


```
> # What are the treatment involved in study 21?
> smoke.list$t[21,]
```

```
t1 t2 t3
 2  3  4
```

```
> # What is the number of quitters in study 21 and in the second treatment arm of that study?
> smoke.list$r[21,smoke.list$t[21,2]]
```

```
[1] 12
```

```
> # What is the sample size in study 21 and in the second treatment arm of that study?
> smoke.list$n[21,smoke.list$t[21,2]]
```

```
[1] 85
```

Coding NMA in BUGS

Just write out the equations-ish... 😉

- **NB**: `t[s,a]` indicates the treatment associated with study `s` and its arm `a`
- Vague priors for effects / baseline are typically OK
  - But **not** when the number of comparisons is very small!

```
for(s in 1:NS) {
  for (a in 1:na[s])  {
    r[s,t[s,a]] ~ dbin(p[s,t[s,a]], n[s,t[s,a]])
    logit(p[s,t[s,a]]) <- mu[s] + delta[s,t[s,a]]
  }
# delta are effects compared to arm 1 of each study s
  delta[s,t[s,1]] <- 0
  for (a in 2:na[s])  {
    delta[s,t[s,a]] <- d[t[s,a]] - d[t[s,1]]
  }
}
for (i in 1:NS){
# vague prior for baseline log-odds
  mu[i] ~ dnorm(0,0.0001)
}
# effect compared to treatment 1 (e.g. placebo)
d[1] <- 0
# vague prior
for (i in 2:NT) {
  d[i] ~ dnorm(0, 0.0001)
}
```

Presenting treatment effects

For each treatment $2, \ldots, NT$ compared to treatment 1 (the reference/baseline: eg "no intervention"/"status quo", or placebo), can back-transform the logORs

```
for (t in 2:NT) {
  or[t] <- exp(d[t])  # odds ratios
}
```

Presenting treatment effects

For each treatment $2, \ldots, NT$ compared to treatment 1 (the reference/baseline: eg "no intervention"/"status quo", or placebo), can back-transform the logORs

```
for (t in 2:NT) {
  or[t] <- exp(d[t])  # odds ratios
}
```

Then can compute the odds ratio for every other treatment pair `c, k` – even if no direct comparison exist

- $\text{OR}_{ck} = \text{OR}_{c1} / \text{OR}_{k1}$

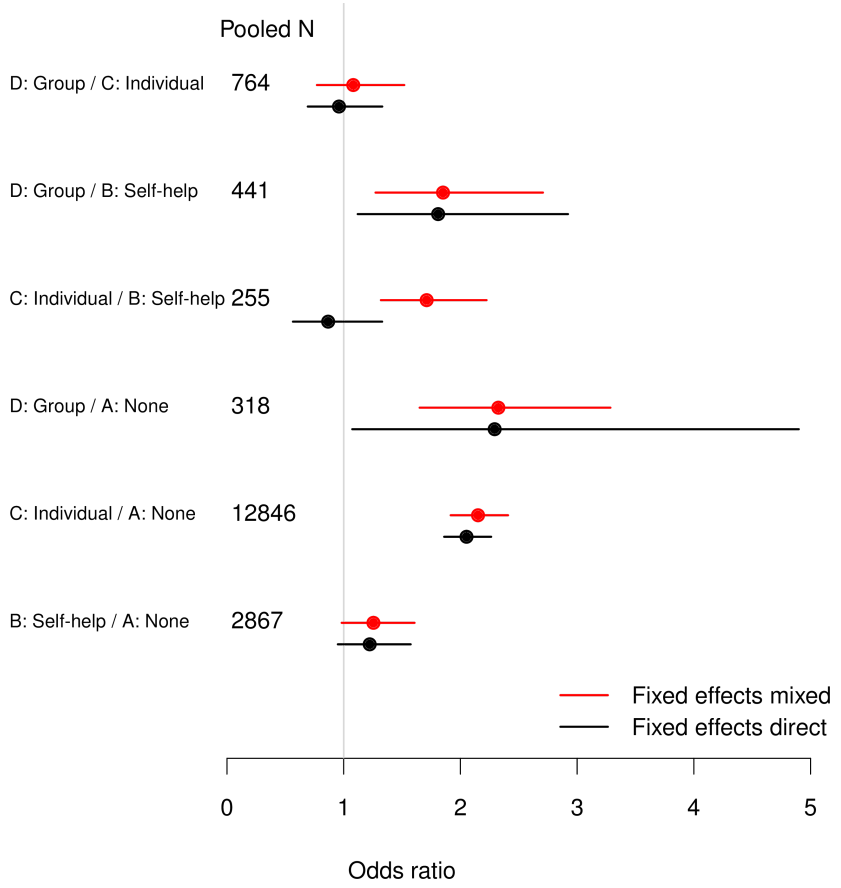
```
for (c in 1:(NT-1)) {
  for (k in (c+1):NT) {
    or[c,k] <- exp(d[c] - d[k])
    or[k,c] <- 1/or[c,k]
  }
}
```

Comparing direct and mixed evidence

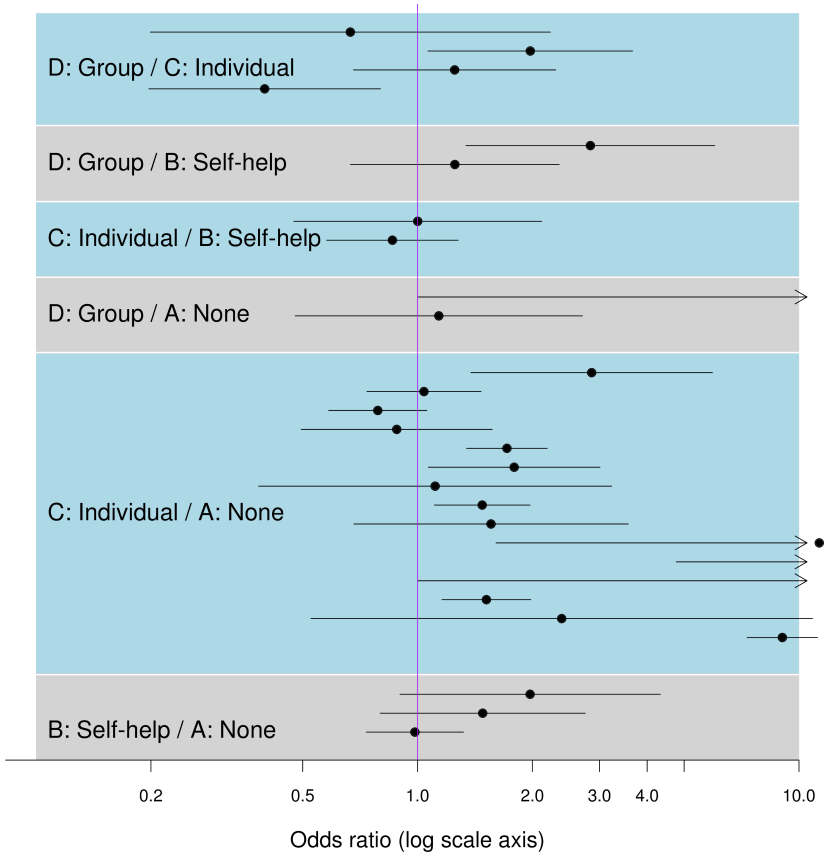
Direct-only odds ratios (CIs) from classical analysis of pooled individual data

- Precision of D/A estimate improved by indirect C/A and C/D data
- Strong direct data for other comparisons, so not improved much by indirect evidence
- C/B estimate from one direct study $\Rightarrow$ pulled towards much bigger indirect C/A and B/A data

  – evidence of heterogeneity...



Heterogeneity between individual studies



- Classical odds ratio (CIs) for all individual trials, sorted by pairwise comparison
- Heterogeneity between ORs within most comparisons
- Consider "random" effects models...

Random effects NMA

Replace fixed effects δ_{ts} of treatment t in study s

$$
\begin{aligned}
r_{st} &\sim \text{Binomial}(p_{st}, n_{st}) \\
\text{logit}(p_{st}) &= \mu_s + \delta_{st} \\
\delta_{st} &\sim d_t - d_{t_{s0}}
\end{aligned}
$$

with a random effect varying between studies s with a Normal distribution with mean defined by the fixed effect

$$
\begin{aligned}
r_{st} &\sim \text{Binomial}(p_{st}, n_{st}) \\
\text{logit}(p_{st}) &= \mu_s + \delta_{st} \\
\delta_{st} &\sim \text{Normal}(\mu^{\delta}_{st}, \sigma^2_{st}) \\
\mu^{\delta}_{st} &\sim d_t - d_{t_{s0}}
\end{aligned}
$$

still with $\delta_{st} = 0$ for $t =$ baseline arm of s

Coding this in BUGS

Equations translate relatively straight to BUGS model, again:

```
for (a in 2:na[s]) {
  delta[s,t[s,a]] <- d[t[s,a]] - d[t[s,1]]
}
```

is replaced by:

```
for (a in 2:na[s]) {
  delta[s,t[s,a]] ~ dnorm(md[s,t[s,a]], taud[s,t[s,a]])
  md[s,t[s,a]] <- d[t[s,a]] - d[t[s,1]]
  taud[s,t[s,a]] <- tau
}
d[1] <- 0
# Priors on the mean same as fixed effects
for (i in 2:NT) {
  d[i] ~ dnorm(0, 0.0001)
}
```

But: a couple of complicating features...

Constraints on random effects variances

- In a NMA, we have
  - NT different treatments
  - $(NT-1)$ different pooled effects, relative to treatment 1 (the baseline / reference) Only 1 effect in standard meta-analysis
- $(NT-1)$ different random effects distributions to estimate?
  - Not feasible unless many studies of every single treatment
  - $\Rightarrow$**identifiability** constraints needed

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  - $\sigma^2_{st} = \sigma^2$
  - unless expect differing amounts of heterogeneity for different treatment effects (Lu and Ades, 2004 and Lu and Ades, 2006)

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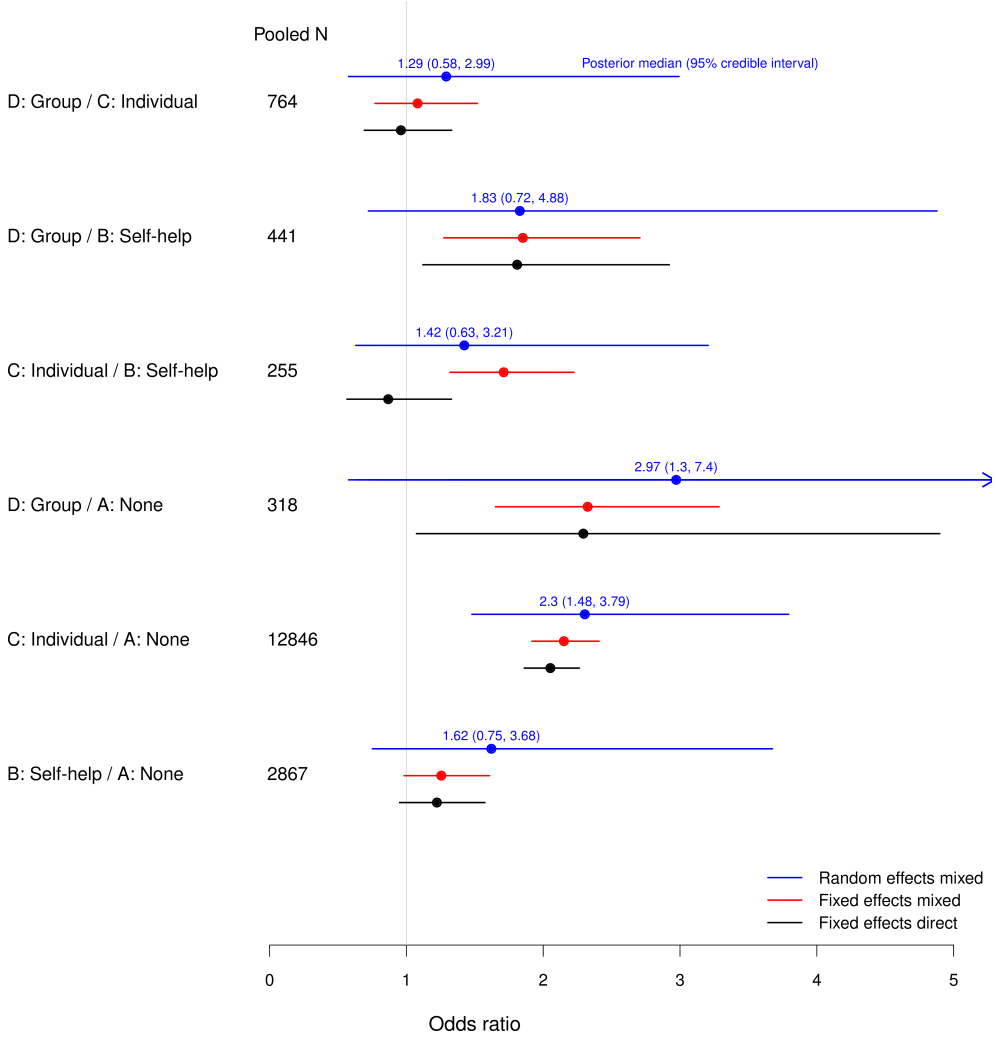
Prior for σ^2: Uniform from 0 to a large upper limit (eg 10 if on the log scale) is often used, especially to align with standard meta-analysis

- **But**: Beware of sensitivity to this – particularly if only few studies are considered...

Random effects models

- Wider CIs after accounting for heterogeneity
- C/B: compromise between direct and indirect evidence
- D/A: smallest trials, still a lot of uncertainty



Use in cost-effectiveness analysis

Example

External data on Expected Life-Years Gained if quit smoking:

- around 15 years (sd $\approx$ 4): model as $L \sim \text{Normal}(\text{mean} = 15, \text{sd} = 4)$
- and code this as `L ~ dnorm(15, 0.0625)` in BUGS

Example

External data on Expected Life-Years Gained if quit smoking:

- around 15 years (sd $\approx$ 4): model as $L \sim$ Normal(mean $= 15$, sd $= 4$)
- and code this as `L ~ dnorm(15, 0.0625)` in BUGS

Model L by Prob(quit) to get E[LYG] under each intervention

	A: No intervention	B: Self-help	C: Individual counselling	D: Group counselling
Posterior Pr(quit)	7% (5,8)	11% (8,15)	15% (11,19)	19% (14,26)
e: Expected LYG	1.0 (0.4, 2.4)	1.6 (0.5, 4.5)	2.1 (0.8, 5.1)	2.8 (0.8, 7.4)
c: Cost	0	200	6000	600

and compare to cost of each intervention:

Willing to pay k	$<$300	300–400	$>$400
Intervention with optimal net benefit $ek - c$	No intervention	Self help	Group counselling

Further issues...

- Different type of outcomes
  - Binary data (Binomial models, as here)
  - Counts of events/person-years at risk (Poisson models)
  - Mean + sd of continuous outcomes (Normal models)

  ... in each arm of the study
- Individual patient data alongside data aggregated by arms
- Meta-regression: explain heterogeneity between studies using study-level characteristics as covariates
- Detecting / handling conflicts between direct / indirect evidence

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Further tools

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Next lecture