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# What is indirect comparison?

- **Indirect comparison** refers to a comparison of different healthcare interventions using data from separate studies, in contrast to a direct comparison within randomised controlled trials. Indirect comparison is often used because of a lack of, or insufficient, evidence from head-to-head comparative trials.
- **Naive indirect comparison** is a comparison of the results of individual arms from different trials as if they were from the same randomised trials. This method provides evidence equivalent to that of observational studies and should be avoided in the analysis of data from randomised trials.
- **Adjusted indirect comparison** (including mixed treatment comparison) is an indirect comparison of different treatments adjusted according to the results of their direct comparison with a common control, so that the strength of the randomised trials is preserved. Empirical evidence indicates that results of adjusted indirect comparison are usually, but not always, consistent with the results of direct comparison.
- Basic assumptions underlying indirect comparisons include a **homogeneity assumption** for standard meta-analysis, **similarity assumption** for adjusted indirect comparison and **consistency assumption** for the combination of direct and indirect evidence. It is essential to fully understand and appreciate these basic assumptions in order to use adjusted indirect and mixed treatment comparisons appropriately.

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## What is indirect comparison?

### Why use indirect comparison?

For many clinical indications, available treatments constantly increase over time. For example, a large number of different – old and new – drugs are available for the treatment of depressive and other mental disorders. Clinicians, patients and health policy-makers often need to decide which treatment is the most cost-effective.

Well-conducted randomised controlled trials provide the most valid estimates of the relative efficacy of competing healthcare interventions. However, many interventions have not been directly compared in randomised controlled trials. When there is no, or insufficient, evidence from direct comparison trials, it may be possible to use results of different trials to estimate the relative effects of different treatments.<sup>1</sup> In contrast to direct within-trial comparison, indirect comparison means a between-study comparison of different interventions (Figure 1).

### Methods for indirect comparison

Methods for indirect comparison can be classified into several categories: naive indirect comparison, informal indirect comparison, and formal adjusted indirect comparison.<sup>1</sup> To illustrate these methods, we use an example of risperidone versus haloperidol for schizophrenia, which includes three placebo controlled trials of risperidone, nine placebo controlled trials of haloperidol, and ten trials that directly compared risperidone and haloperidol (Table 1 and Figure 2).<sup>2</sup>

In a **naive indirect comparison**, results of individual arms from different trials are compared as if they were from the same randomised controlled trial. Because the advantage of the randomised trials is completely disregarded, evidence from this naive or unadjusted indirect comparison is equivalent to evidence from observational studies and has increased susceptibility to bias. The effect of a treatment may be over- or underestimated because of bias, resulting in flawed recommendations for clinical practice. Therefore, naive indirect comparison should not be used to analyse data from randomised controlled trials.<sup>1</sup>

In **informal indirect comparison**, neither relative effects nor statistical significance are formally calculated. For example, both risperidone and haloperidol were more effective than placebo in terms of clinical improvement (Table 1 and Figure 2).<sup>2</sup> An informal indirect comparison can be made by examining the point estimates and corresponding 95% confidence intervals (CIs) of the two odds ratios. The odds ratio of haloperidol versus placebo (0.18; 95% CI: 0.10, 0.34) suggested a greater treatment effect than the odds ratio of risperidone versus placebo (0.40; 95% CI: 0.26, 0.62), despite some overlap of the two CIs.<sup>2</sup>

Formal **adjusted indirect comparison** is an indirect comparison of competing interventions adjusted according to the results of their direct comparison with a common

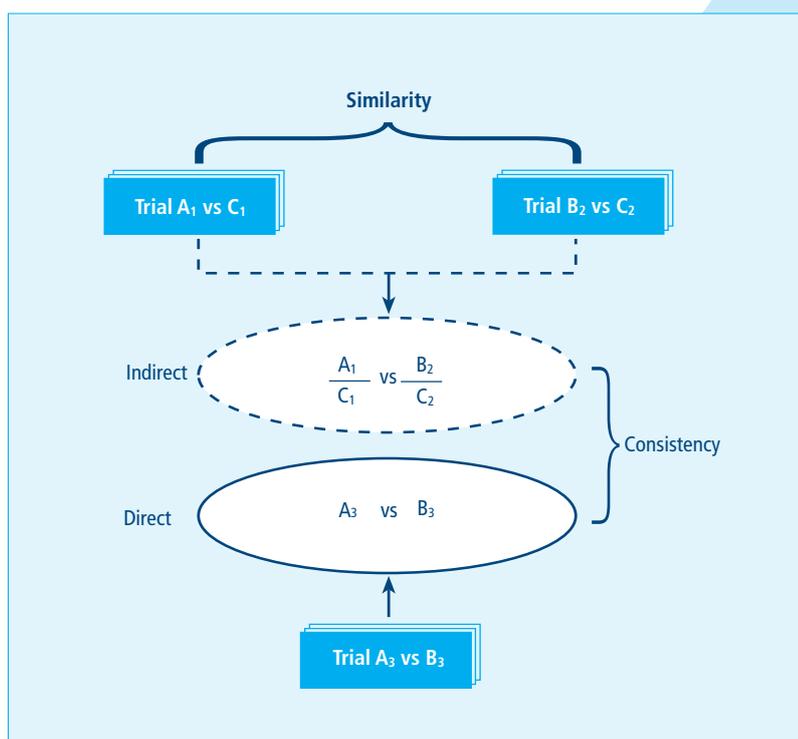


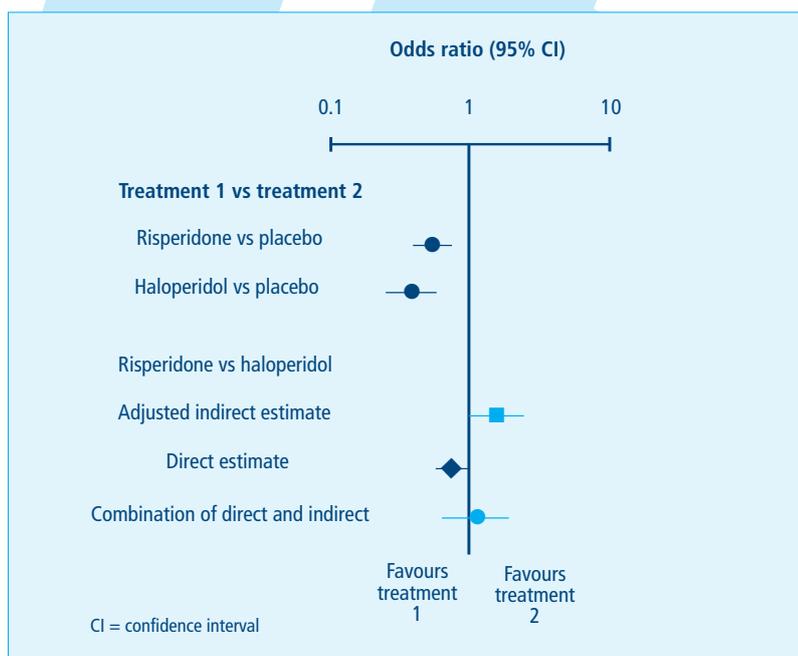
Figure 1. Direct and adjusted indirect comparison of treatments A and B

**Table 1. Meta-analyses of risperidone versus haloperidol for schizophrenia: number of patients without clinical improvement<sup>2</sup>**

Comparison	Number of trials	Log odds ratio (SE)	Odds ratio (95% CI)	I <sup>2</sup> %
<b>Placebo controlled trials</b>				
Risperidone vs placebo	3	-0.909 (0.218)	0.40 (0.26, 0.62)	37%
Haloperidol vs placebo	9	-1.707 (0.318)	0.18 (0.10, 0.34)	11%
<b>Risperidone vs haloperidol</b>				
Direct comparison	10	-0.262 (0.142)	0.77 (0.58, 1.02)	14%
Adjusted indirect comparison	3/9	0.798 (0.386)	2.22 (1.04, 4.72)	
Combination of direct and indirect estimates	10+(3/9)	0.207 (0.527)	1.23 (0.44, 3.45)	85%

NB Random-effects model was used in meta-analyses of trials and for the combination of the direct and indirect estimates. Odds ratio = EXP(log odds ratio).

CI: confidence interval; SE: standard error



**Figure 2. Results of different methods of comparing risperidone and haloperidol for schizophrenia. Outcome: not clinically improved<sup>2</sup>**

control. This means that the advantage of the randomised controlled trials can be at least partly preserved in the indirect comparison. Suppose that interventions A and C were compared in randomised trial 1 (with groups  $A_1$  and  $C_1$ ), and that interventions B and C were compared in trial 2 (with groups  $B_2$  and  $C_2$ ) (Figure 1). To overcome the potential problem of different prognostic factors between study participants in different trials,

Bucher and colleagues suggested a simple method of adjusted indirect comparison, in which the indirect comparison of A and B is adjusted according to the results of their direct comparisons with a common intervention - C.<sup>3</sup> This is illustrated in Figure 1.

Let  $\ln OR_{AC}$  denote log odds ratio of  $A_1$  versus  $C_1$  in trial 1, and  $\ln OR_{BC}$  denote log odds ratio of  $B_2$  versus  $C_2$  in trial 2. The log odds ratio of the adjusted indirect comparison of A and B ( $\ln OR'_{AB}$ ) can be estimated by:

$$\ln OR'_{AB} = \ln OR_{AC} - \ln OR_{BC}$$

and its standard error is:

$$SE(\ln OR'_{AB}) = \sqrt{SE(\ln OR_{AC})^2 + SE(\ln OR_{BC})^2}$$

Although an odds ratio is used in the above equations, this adjusted method of indirect comparison may also be used when the relative efficacy is measured by relative risk, risk difference and mean difference. Empirical evidence indicates that results of adjusted indirect comparison are usually, but not always, similar to those of direct comparison trials.<sup>4</sup>

More complex methods for adjusted indirect comparison, such as network meta-analysis and mixed treatment comparison, have also been developed to conduct adjusted indirect comparison of multiple healthcare

interventions, and to combine evidence from direct and indirect comparisons.<sup>5</sup>

Table 1 and Figure 2 show the results of an adjusted indirect comparison of risperidone and haloperidol, using the results of the two meta-analyses of placebo controlled trials.<sup>2</sup> The point estimate of log odds ratio by adjusted indirect comparison is:

$$\ln OR' = -0.909 - (-1.707) = 0.798$$

and its standard error is:

$$SE(\ln OR') = \sqrt{(0.218^2 + 0.318^2)} = 0.386$$

The results of the adjusted indirect comparison suggest that risperidone was less effective than haloperidol for schizophrenia (odds ratio 2.22; 95% CI: 1.04, 4.72).<sup>2</sup>

Risperidone and haloperidol were also compared in ten direct comparison trials (Table 1 and Figure 2).<sup>2</sup> According to data from head-to-head comparative trials, risperidone tended to be more effective than haloperidol (odds ratio 0.77; 95% CI: 0.58, 1.02), which conflicts with the results of the adjusted indirect comparison.<sup>2</sup> The discrepancy between the direct and indirect estimates is statistically significant ( $p=0.01$ ). The issue of inconsistent evidence will be discussed further in the section on basic assumptions.

The results of the direct comparison can be quantitatively combined with the indirect estimate (combined odds ratio 1.23; 95% CI: 0.44, 3.45) (Table 1 and Figure 2).<sup>2</sup> However, it is not clear whether the combined estimate is valid, given the significant discrepancy or inconsistency between the direct and indirect estimates.

## Basic assumptions underlying indirect comparisons

### Homogeneity assumption for standard meta-analysis

When multiple trials are available for a given comparison, the results from multiple trials can be pooled in meta-analyses before an adjusted indirect comparison is conducted. In standard meta-analysis, it is assumed that different trials estimate the same single effect

(fixed-effects model) or different effects are distributed around a typical value (random-effects model); that is, for a meta-analysis to be valid, results from different trials should be sufficiently homogeneous. Heterogeneity in results across studies can be statistically tested using the Chi<sup>2</sup> test and quantified using I<sup>2</sup>.<sup>6</sup> For example, the results of three placebo controlled trials of risperidone and the results of nine placebo controlled trials of haloperidol were combined in Table 1.<sup>2</sup> The underlying assumption was that these trials were sufficiently homogenous to be quantitatively combined.

### Similarity assumption for adjusted indirect comparison

For an adjusted indirect comparison to be valid, a similarity assumption is required in terms of moderators of relative treatment effect; that is, patients included should be sufficiently similar in the two sets of placebo controlled trials, so that the relative effect estimated by trials of A versus C is generalisable to patients in trials of B versus C, and the relative effect estimated by trials of B versus C is generalisable to patients in trials of A versus C.

Relative effects estimated in trials may also be associated with the methodological quality of the trials. Empirical evidence indicates that trials with poor quality may report greater treatment effects than good quality trials, particularly when outcomes are subjectively measured. It can be mathematically proven that the results of adjusted indirect comparison will be unbiased when the two sets of trials are similarly biased.<sup>2</sup>

Therefore, both clinical similarity and methodological similarity should be considered in adjusted indirect comparison. If the trial similarity assumption is not fulfilled, estimates from adjusted indirect comparisons will be invalid and misleading.

For the adjusted indirect comparison of risperidone and haloperidol (Table 1),<sup>2</sup> patient characteristics, dose of drug and treatment duration were similar between trials. However, the clinical improvement was defined differently between the two sets of placebo controlled trials. In placebo controlled trials of risperidone, it was predefined as a 20% or greater reduction in

the total score on the Positive and Negative Syndrome Scale or Brief Psychiatric Rating Scale, but in placebo controlled trials of haloperidol, it was rated by clinicians using the Clinical Global Impression or other scales.<sup>2</sup> Therefore, the results of adjusted indirect comparison should be interpreted cautiously.

### Consistency assumption for combining direct and indirect estimates

When both direct and indirect evidence is available, an assumption of evidence consistency is required to quantitatively combine the direct and indirect estimates. We can compare the direct estimate with the indirect estimate to examine whether the two estimates are consistent. For example, adjusted indirect comparison of risperidone and haloperidol provided inconsistent results compared with the results of direct comparison (Table 1 and Figure 2).<sup>2</sup> Although we can quantitatively combine the two estimates, the pooled estimate (odds ratio 1.23; 95% CI: 0.44, 3.45) may be invalid and misleading. It is important to investigate possible causes of discrepancy between the direct and indirect evidence, such as the play of chance, invalid indirect comparison, bias in head-to-head comparative trials, and clinically meaningful heterogeneity across trials.

When the direct comparison differs from the adjusted indirect comparison, we should usually give more credibility to evidence from head-to-head comparative trials. However, evidence from direct comparative trials may not always be valid. Some case studies indicated that adjusted indirect comparison may provide less biased results than head-to-head comparative trials under certain circumstances.<sup>2</sup>

## Appropriate use of indirect comparisons

A recent survey of published systematic reviews found that methodological problems in the use of indirect comparisons for evaluating healthcare interventions include the use of inappropriate or flawed methods, the lack of objective or validated methods to assess trial similarity, and inadequate comparison or inappropriate combination of direct and indirect evidence.<sup>7</sup> In particular, mixed treatment comparison has often been used to combine direct and indirect evidence without explicit assessment of evidence consistency. To use indirect and mixed treatment comparison appropriately, we need to adequately understand and fully appreciate the basic assumptions underlying valid indirect approaches. The assessment of the similarity of trials involved in adjusted indirect comparison and the assessment of evidence consistency in mixed treatment comparison should be more explicit and systematic.

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### Further reading

The references listed above are suggested as useful further reading.

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