CHAPTER 24

Multiple Outcomes or Time-Points within a Study

INTRODUCTION

The second case of a complex data structure is the case where a study reports data on more than one outcome, or more than one time-point, where the different outcomes (or time-points) are based on the same participants.

For example, suppose that five studies assessed the impact of tutoring on student performance. All studies followed the same design, with students randomly assigned to either of two groups (tutoring or control) for a semester, after which they were tested for proficiency in reading and math. The effect was reported separately for the reading and the math scores, but within each study *both outcomes were based on the same students*.

Or, consider the same situation with the following difference. This time, assume that each study tests only for reading but does so at two time-points (immediately after the intervention and again six months later). The effect was reported separately for each time-point but *both measures were based on the same students*.

For our purposes the two situations (multiple outcomes for the same subjects or multiple time-points for the same subjects) are identical, and we shall treat them as such in this discussion. We shall use the term *outcomes* throughout this chapter, but the reader can substitute *time-points* in every instance.

If our goal was to compute a summary effect for the impact of the intervention on reading, and *separately* for the impact of the intervention on math scores, we would simply perform two separate meta-analyses, one using the data for reading and the other using the data for math. The issues we address in this chapter are how to

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proceed when we want to incorporate both outcomes in the same analysis. Specifically,

- We want to compute a summary effect for the intervention on *Basic skills*, which combines the data from reading and math.
- Or, we want to investigate the *difference* in effect size for reading versus math.

In either case, the issue we need to address is that the data for reading and math are not independent of each other and therefore the errors are correlated.

COMBINING ACROSS OUTCOMES OR TIME-POINTS

The data for the five fictional studies are shown in Table 24.1. In study 1, for example, the effect size for reading was 0.30 with a variance of 0.05, and the effect size for math was 0.10 with a variance of 0.05.

While it might seem that we could treat each line of data as a separate study and perform a meta-analysis with ten *studies*, this is problematic for two reasons. One problem is that in computing the summary effect across studies this approach will assign more weight to studies with two outcomes than to studies with one outcome. (While this problem does not exist in our set of studies, it would be a problem if the number of outcomes varied from study to study.)

The second, and more fundamental problem, is that this approach leads to an improper estimate of the precision of the summary effect. This is because it treats the separate outcomes as providing independent information, when in fact the math and reading scores come from the same set of students and therefore are not independent of each other. If the outcomes are positively correlated (which is almost always the case with effects that we would want to combine), this approach underestimates the error (and overestimates the precision) of the summary effect.

Table 24.1 Multiple outcomes – five fictional studies.

Study	Outcome	ES	Variance
Study 1	Reading	0.300	0.050
	Math	0.100	0.050
Study 2	Reading	0.200	0.020
	Math	0.100	0.020
Study 3	Reading	0.400	0.050
	Math	0.200	0.050
Study 4	Reading	0.200	0.010
	Math	0.100	0.010
Study 5	Reading	0.400	0.060
	Math	0.300	0.060

Table 24.2 Creating a synthetic variable as the mean of two outcomes.

Study	Outcome	Effect size	Variance	Mean	Variance
Study 1	Math Reading	0.30 0.10	0.05 0.05	0.20	**?**

Note. If the correlation between outcomes is negative, this approach will overestimate the error (and underestimate the precision) of the summary effect. The solutions presented below will work for this case as well, but in the discussion we assume that we are dealing with a positive correlation.

To address these problems, rather than treating each outcome as a separate unit in the analysis, we'll compute the mean of the outcomes for each study, and use this synthetic score as the unit of analysis. In Table 24.2 we show this schematically for study 1.

We start with summary data for two outcomes (math and reading), and compute an effect size and variance for each. If the data are continuous (means and standard deviations on the exam) the effect size might be Hedges' g. If the data are binary (number of students passing the course) the effect size might be a log risk ratio. And so on. Then, we compute a synthetic effect size for *Basic skills* which incorporates both the math and reading effects. The method used to compute this effect size and its variance is explained below.

Since every study will be represented by one score in the meta-analysis regardless of the number of outcomes included in the mean, this approach solves the problem of more weight being assigned to studies with more outcomes. This approach also allows us to address the problem of non-independent information, since the formula for the variance of the synthetic variable will take into account the correlation among the outcomes.

Computing a combined effect across outcomes

Our notation will be to use Y_1, Y_2 etc. for effect sizes from different outcomes or time points within a study, and Y_j to refer to the j^{th} of these. Strictly, we should use Y_{ij}, for the j^{th} outcome (or time-point) in the i^{th} study. However, we drop the i subscript for convenience. The effect size for *Basic skills* is computed as the mean of the reading and math scores,

$$\overline{Y} = \frac{1}{2}\left(Y_1 + Y_2\right). \tag{24.1}$$

This is what we would use as the effect estimate from this study in a meta-analysis. Using formulas described in Box 24.1, the variance of this mean is

$$V_{\overline{Y}} = \frac{1}{4}\left(V_{Y_1} + V_{Y_2} + 2r\sqrt{V_{Y_1}}\sqrt{V_{Y_2}}\right) \tag{24.2}$$

BOX 24.1 COMPUTING THE VARIANCE OF A COMPOSITE OR A DIFFERENCE

1. The variance of the sum of two correlated variables

If we know that the variance of Y_1 is V_1 and the variance of Y_2 is V_2, then

$$\operatorname{var}(Y_1 + Y_2) = V_1 + V_2 + 2r\sqrt{V_1}\sqrt{V_2},$$

where r is the correlation coefficient that describes the extent to which Y_1 and Y_2 co-vary. If Y_1 and Y_2 are inextricably linked (so that a change in one determines completely the change in the other), then $r = 1$, and the variance of the sum is roughly twice the sum of the variances. At the other extreme, if Y_1 and Y_2 are unrelated, then $r = 0$ and the variance is just the sum of the individual variances. This is because when the variables are unrelated, knowing both gives us twice as much information, and so the variance is halved compared with the earlier case.

2. The impact of a scaling factor on the variance

If we know the variance of X, then the variance of a scalar (say c) multiplied by X is given by

$$\operatorname{var}(cX) = \mathrm{c}^2 \times \operatorname{var}(X).$$

3. The variance of the mean of two correlated variables

Combining 1 with 2, we can see that the variance of the mean of Y_1 and Y_2 is

$$\operatorname{var}\left(\frac{1}{2}(Y_1 + Y_2)\right) = \left(\frac{1}{2}\right)^2 \operatorname{var}(Y_1 + Y_2) = \frac{1}{4}\left(V_1 + V_2 + 2r\sqrt{V_1}\sqrt{V_2}\right).$$

4. The variance of the sum of several correlated variables

If we know Y_i has variance V_i for several variables $i = 1, \ldots, m$, then the formula in 1 extends as follows:

$$\operatorname{var}\left(\sum_{i=1}^{m} Y_i\right) = \sum_{i=1}^{m} V_i {}_{1} + \sum_{i \neq j}\left(r_{ij}\sqrt{V_i}\sqrt{V_j}\right)$$

where r_{ij} is the correlation between Y_i and Y_j.

5. The variance of the mean of several correlated variables

Combining 4 with 2, we can see that the variance of the mean of several variables is

$$\operatorname{var}\left(\frac{1}{m}\sum_{i=1}^{m} Y_i\right) = \left(\frac{1}{m}\right)^2 \operatorname{var}\left(\sum_{i=1}^{m} Y_i {}_{2}\right) = \left(\frac{1}{m}\right)^2 \left(\sum_{i=1}^{m} V_i {}_{1} + \sum_{i \neq j}\left(r_{ij}\sqrt{V_i}\sqrt{V_j}\right)\right).$$

6. The variance of the difference between two correlated variables

If we know that the variance of Y_1 is V_1 and the variance of Y_2 is V_2, then

$$\operatorname{var}(Y_1 - Y_2) = V_1 + V_2 - 2r\sqrt{V_1}\sqrt{V_2},$$

BOX 24.1 CONTINUED

where r is the correlation coefficient that describes the extent to which Y_1 and Y_2 co-vary. If Y_1 and Y_2 are inextricably linked (so that a change in one determines completely the change in the other), then $r = 1$, and the variance of the difference is close to zero. At the other extreme, if Y_1 and Y_2 are unrelated, then $r = 0$ and the variance is the sum of the individual variances. If the correlation is $r = 0.5$ then the variance is approximately the average of the two variances.

where r is the correlation between the two outcomes. If both variances V_{Y_1} and V_{Y_2} are equal (say to V), then (24.2) simplifies to

$$V_{\overline{Y}} = \frac{1}{2}V(1+r). \tag{24.3}$$

In the running example, in study 1 the effect sizes for math and reading are 0.30 and 0.10, the variance for each is 0.02. Suppose we know that the correlation between them is 0.50. The composite score for *Basic skills* ($\overline{Y}$) is computed as

$$\overline{Y} = \frac{1}{2}(0.30 + 0.10) = 0.2000,$$

with variance (based on (24.2))

$$V_{\overline{Y}} = \frac{1}{4}\left(0.05 + 0.05 + 2 \times 0.50 \times \sqrt{0.05} \times \sqrt{0.05}\right) = 0.0375,$$

or, equivalently (using (24.3)),

$$V_{\overline{Y}} = \frac{1}{2} \times 0.05 \times (1 + 0.50) = 0.0375.$$

Using this formula we can see that if the correlation between outcomes was zero, the variance of the composite would be 0.025 (which is half as large as either outcome alone) because the second outcome provides entirely independent information. If the correlation was 1.0 the variance of the composite would be 0.050 (the same as either outcome alone) because all information provided by the second outcome is redundant. In our example, where the correlation is 0.50 (*some* of the information is redundant) the variance of the composite falls between these extremes. When we were working with independent subgroups (earlier in this chapter) the correlation was zero, and therefore the variance of the composite was 0.025.

These formulas are used to create Table 24.2, where the variance for each composite is based on formula (24.2) and the weight is simply the reciprocal of the variance.

At this point we can proceed to the meta-analysis using these five (synthetic) scores. To compute a summary effect and other statistics using the fixed-effect model, we apply the formulas starting with (11.3). Using values from the line labeled *Sum* in Table 24.3,

Table 24.3 Multiple outcomes – summary effect.

Study	Outcome	ES	Variance	ES	Correlation	Variance	Weight	ES*WT
Study 1	Reading Math	0.300 0.100	0.050 0.050	0.200	0.500	0.038	26.667	5.333
Study 2	Reading Math	0.200 0.100	0.020 0.020	0.150	0.600	0.016	62.500	9.375
Study 3	Reading Math	0.400 0.200	0.050 0.050	0.300	0.600	0.040	25.000	7.500
Study 4	Reading Math	0.200 0.100	0.010 0.010	0.150	0.400	0.007	142.857	21.429
Study 5	Reading Math	0.400 0.300	0.060 0.060	0.350	0.800	0.054	18.519	6.481
Sum							275.542	50.118

$$M = \frac{50.118}{275.542} = 0.1819,$$

with variance

$$V_M = \frac{1}{275.542} = 0.0036.$$

The average difference between the tutored and control groups on *Basic skills* is 0.1819 with variance 0.0036 and standard error 0.060. The 95% confidence interval for the average effect is 0.064 to 0.300. The Z-value for a test of the null is 3.019 with a two-sided p-value of 0.003.

Working with more than two outcomes per study

These formulas can be extended to accommodate any number of outcomes. If m represents the number of outcomes within a study, then the composite effect size for that study would be computed as

$$\overline{Y} = \frac{1}{m}\left(\sum_{j}^{m} Y_j\right), \tag{24.4}$$

and the variance of the composite is given by

$$V_{\overline{Y}} = \left(\frac{1}{m}\right)^2 \mathrm{var}\left(\sum_{j=1}^{m} Y_i\right) = \left(\frac{1}{m}\right)^2\left(\sum_{j=1}^{m} V_i + \sum_{j\neq k}\left(r_{jk}\sqrt{V_j}\sqrt{V_k}\right)\right) \tag{24.5}$$

as derived in Box 24.1. If the variances are all equal to V and the correlations are all equal to r, then (24.5) simplifies to

$$V_{\overline{Y}} = \frac{1}{m} V(1 + (m-1)r). \tag{24.6}$$