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Meta-analysis with missing data

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Abstract. A new command, `metamiss`, performs meta-analysis with binary outcomes when some or all studies have missing data. Missing values can be imputed as successes, as failures, according to observed event rates, or by a combination of these according to reported reasons for the data being missing. Alternatively, the user can specify the value of, or a prior distribution for, the informative missingness odds ratio.

Keywords: st0157, metamiss, meta-analysis, missing data, informative missingness odds ratio

1 Introduction

Just as missing outcome data present a threat to the validity of any research study, so they present a threat to the validity of any meta-analysis of research studies. Typically, analyses assume that the data are missing completely at random or missing at random (MAR) (Little and Rubin 2002). If the data are not MAR (i.e., they are informatively missing) but are analyzed as if they were missing completely at random or MAR, then nonresponse bias typically occurs. The threat of bias carries over to meta-analysis, where the problem can be compounded by nonresponse bias applied in a similar way in different studies.

Many methods for dealing with missing outcome data require detailed data for each participant. Dealing with missing outcome data in a meta-analysis raises particular problems because limited information is typically available in published reports. Although a meta-analyst would ideally seek any important but unreported data from the authors of the original studies, this approach is not always successful, and it is uncommon to have access to more than group-level summary data at best. We therefore address the meta-analysis of summary data, focusing on the case of an incomplete binary outcome.

A central concept is the informative missingness odds ratio (IMOR), defined as the odds ratio between the missingness, M, and the true outcome, Y, within groups (White, Higgins, and Wood 2008). A value of 1 indicates MAR, while IMOR $= 0$ means that missing values are all failures, and IMOR $= \infty$ means that missing values are all successes. We allow the IMOR to differ across groups and across subgroups of individuals defined by reasons for missingness, or to be specified with uncertainty.

We will describe `metamiss` in the context of a meta-analysis of randomized controlled trials comparing an "experimental group" with a "control group", but it could be used

in any meta-analysis of two-group comparisons. `metamiss` only prepares the data for each study, and then it calls `metan` to perform the meta-analysis. It allows two main types of methods: imputation methods and Bayesian methods.

First, `metamiss` offers imputation methods as described in Higgins, White, and Wood (2008). Missing values can be imputed as failures or as successes; using the same rate as in the control group, the same rate as in the experimental group, or the same rate as in their own group; or using IMORs. When reasons for missingness are known, a mixture of the methods can be used.

Second, `metamiss` offers Bayesian methods that allow for user-specified uncertainty about the missingness mechanism (Rubin 1977; Forster and Smith 1998; White, Higgins, and Wood 2008). These use the prior $\text{logIMOR}_{ij} \sim N(m_{ij}, s_{ij}^2)$ in group $j = E, C$ of study i, with $\text{corr}(\text{logIMOR}_{iE}, \text{logIMOR}_{iC}) = r$.

The approach of Gamble and Hollis (2005) is also implemented. In this approach, two extreme analyses are performed for each study, regarding all missing values as successes in one group and failures in the other. The two 95% confidence intervals are then combined (together with intermediate values), and a modified standard error is taken as one quarter the width of this combined confidence interval. This method appears to overpenalize studies with missing data (White, Higgins, and Wood 2008), but it is included here for comparison.

2 metamiss command

2.1 Syntax

`metamiss` requires six variables (*rE*, *fE*, *mE*, *rC*, *fC*, and *mC*), which specify the number of successes, failures, and missing values in each randomized group. There are four syntaxes described below.

Simple imputation

`metamiss` *rE fE mE rC fC mC*, *imputation_method* [*imor_option* *imputation_options* *meta_options*]

where

imputation_method is one of the imputation methods listed in section 2.2, specified without an argument.

imor_option is either `imor(`# | *varname* [# | *varname*]`)` or `logimor(`# | *varname* [# | *varname*]`)` (see section 2.3).

imputation_options are any of the options described in section 2.4.

meta_options are any of the meta-analysis options listed in section 2.6, as well as any valid option for `metan`, including `random`, `by()`, and `xlabel()` (see section 2.6).

Imputation using reasons

`metamiss` *rE fE mE rC fC mC*, *imputation_method1 impuation_method2* [*imputation_method3 ...*] [*imor_option imputation_options meta_options*]

where

imputation_method1, *imputation_method2*, etc., are any imputation method listed in section 2.2 except `icab` and `icaw`, specified with arguments to indicate numbers of missing values to be imputed by each method.

imor_option, *imputation_options*, and *meta_options* are the same as documented in *Simple Imputation*.

Bayesian analysis using priors

`metamiss` *rE fE mE rC fC mC*, `sdlogimor(`# | *varname* [# | *varname*]`)` [*imor_option bayes_options meta_options*]

where

imor_option and *meta_options* are the same as documented in *Simple Imputation*.

bayes_options are any of the options described in section 2.5.

Gamble–Hollis analysis

`metamiss` *rE fE mE rC fC mC*, `gamblehollis` [*meta_options*]

where

`gamblehollis` specifies to use the Gamble–Hollis analysis.

meta_options are the same as documented in *Simple Imputation*.

2.2 imputation_method

For simple imputation, specify one of the following options without arguments. For imputation using reasons, specify two or more of the following options with arguments. The abbreviations ACA, ICA-0, etc., are explained by Higgins, White, and Wood (2008).

`aca`[`(`#| *varname* [#| *varname*]`)`] performs an available cases analysis (ACA).

`ica0`[`(`#| *varname* [#| *varname*]`)`] imputes missing values as zeros (ICA-0).

`ica1`[`(`#| *varname* [#| *varname*]`)`] imputes missing values as ones (ICA-1).

`icab` performs a best-case analysis (ICA-b), which imputes missing values as ones in the experimental group and zeros in the control group—equivalent to `ica0(0 1) ica1(1 0)`. If *rE* and *rC* count adverse events, not beneficial events, then `icab` will yield a worst-case analysis.

`icaw` performs a worst-case analysis (ICA-w), which imputes missing values as zeros in the experimental group and ones in the control group—equivalent to `ica0(1 0) ica1(0 1)`. If *rE* and *rC* count beneficial events, not adverse events, then `icaw` will yield a best-case analysis.

`icape`[`(`#| *varname* [#| *varname*]`)`] imputes missing values by using the observed probability in the experimental group (ICA-pE).

`icapc`[`(`#| *varname* [#| *varname*]`)`] imputes missing values by using the observed probability in the control group (ICA-pC).

`icap`[`(`#| *varname* [#| *varname*]`)`] imputes missing values by using the observed probability within groups (ICA-p).

`icaimor`[`(`#| *varname* [#| *varname*]`)`] imputes missing values by using the IMORs specified by `imor()` or `logimor()` within groups (ICA-IMORs).

The default is `icaimor` if `imor()` or `logimor()` is specified; if no IMOR option is specified, the default is `aca`.

Specifying arguments

Used with arguments, these options specify the numbers of missing values to be imputed by each method. For example, `ica0(mfE mfC) icap(mpE mpC)` indicates that `mfE` individuals in group E and `mfC` individuals in group C are imputed using ICA-0, while `mpE` individuals in group E and `mpC` individuals in group C are imputed using ICA-p. If the second argument is omitted, it is taken to be zero. If, for some group, the total over all reasons does not equal the number of missing observations (e.g., if `mfE` + `mpE` does not equal `mE`), then the missing observations are shared between imputation types in the given ratio. If the total over all reasons is zero for some group, then the missing observations are shared between imputation types in the ratio formed by summing overall numbers of individuals for each reason across all studies. If the total is zero for all studies in one or both groups, then an error is returned. Numerical values can also be given: e.g., `ica0(50 50) icap(50 50)` indicates that 50% of missing values in each group are imputed using ICA-0 and the rest are imputed using ICA-p.

2.3 imor_option

`imor(`*#* | *varname* [*#* | *varname*]`)` sets the IMORs or (if the Bayesian method is being used) the prior medians of the IMORs. If one value is given, it applies to both groups; if two values are given, they apply to the experimental and control groups, respectively. Both values default to 1. Only one of `imor()` or `logimor()` can be specified.

`logimor(`*#* | *varname* [*#* | *varname*]`)` does the same as `imor()` but on the log scale. Thus `imor(1 1)` is the same as `logimor(0 0)`. Only one of `imor()` or `logimor()` can be specified.

2.4 imputation_options

`w1` specifies that standard errors be computed, treating the imputed values as if they were observed. This is included for didactic purposes and should not be used in real analyses. Only one of `w1`, `w2`, `w3`, or `w4` can be specified.

`w2` specifies that standard errors from the ACA be used. This is useful in separating sensitivity to changes in point estimates from sensitivity to changes in standard errors. Only one of `w1`, `w2`, `w3`, or `w4` can be specified.

`w3` specifies that standard errors be computed by scaling the imputed data down to the number of available cases in each group and treating these data as if they were observed. Only one of `w1`, `w2`, `w3`, or `w4` can be specified.

`w4`, the default, specifies that standard errors be computed algebraically, conditional on the IMORs. Conditioning on the IMORs is not strictly correct for schemes including ICA-pE or ICA-pC, but the conditional standard errors appear to be more realistic than the unconditional standard errors in this setting (Higgins, White, and Wood 2008). Only one of `w1`, `w2`, `w3`, or `w4` can be specified.

`listnum` lists the reason counts for each study implied by the imputation method option.

`listall` lists the reason counts for each study after scaling to match the number of missing values and imputing missing values for studies with no reasons.

`listp` lists the imputed probabilities for each study.

2.5 bayes_options

`sdlogimor(`*#* | *varname* [*#* | *varname*]`)` sets the prior standard deviation for log IMORs for the experimental and control groups, respectively. Both values default to 0.

`corrlogimor(`*#* | *varname*`)` sets the prior correlation between log IMORs in the experimental and control groups. The default is `corrlogimor(0)`.

`method(gh | mc | taylor)` determines the method used to integrate over the distribution of the IMORs. `method(gh)` uses two-dimensional Gauss–Hermite quadrature and is

the recommended method (and the default). `method(mc)` performs a full Bayesian analysis by sampling directly from the posterior. This is time consuming, so dots display progress, and you can request more than one of the measures `or`, `rr`, and `rd`. `method(taylor)` uses a Taylor-series approximation, as in section 4 of Forster and Smith (1998), and is faster than the default but typically inaccurate for `sdlogimor()` larger than one or two.

`nip(#)` specifies the number of integration points under `method(gh)`. The default is `nip(10)`.

`reps(#)` specifies the number of Monte Carlo draws under `method(mc)`. The default is `reps(100)`.

`missprior(## [ ## ])` and `respprior(##)` apply when `method(mc)` is used, but they are unlikely to be much used. They specify the parameters of the beta priors for $P(M)$ and $P(Y \mid M = 0)$: the parameters for the first group are given by the first two numbers, and the parameters for the second group are given by the next two numbers or are the same as for the first group. The defaults are both beta$(1, 1)$.

`nodots` suppresses the dots that are displayed to mark the number of Monte Carlo draws completed.

2.6 meta_options

`or`, `rr`, and `rd` specify the measures to be analyzed. Usually, only one measure can be specified; the default is `rr`. However, when using `method(mc)`, all three measures can be obtained for no extra effort, so any combination is allowed. When more than one measure is specified, the formal meta-analysis is not performed, but measures and their standard errors are saved (see section 2.7).

`log` has the results reported on the log risk-ratio (RR) or log odds-ratio scale.

`id(`*varname*`)` specifies a study identifier for the results table and forest plot.

Most other options allowed with `metan` are also allowed, including `by()`, `random`, and `nograph`.

2.7 Saved results

`metamiss` saves results in the same way as `metan`: `_ES`, `_selogES`, etc. The sample size, `_SS`, excludes the missing values, but an additional variable, `_SSmiss`, gives the total number of missing values. When `method(mc)` is run, the `log` option is assumed for the measures `or` and `rr`, and the following variables are saved for each measure (`logor`, `logrr`, or `rd`): the ACA estimate, `ESTRAW_`*measure*; the ACA variance, `VARRAW_`*measure*; the corrected estimate, `ESTSTAR_`*measure*; and the corrected variance, `VARSTAR_`*measure*. If these variables already exist, then they are overwritten.

3 Examples

3.1 Data

We apply the above methods to a meta-analysis of randomized controlled trials comparing haloperidol to placebo in the treatment of schizophrenia. A Cochrane review of haloperidol forms the basis of our data (Joy, Adams, and Lawrie 2006). Further details of our analysis are given in Higgins, White, and Wood (2008).

The main data consist of the variables `author` (the author); `r1`, `f1`, and `m1` (the counts of successes, failures, and missing observations in the intervention group); and `r2`, `f2`, and `m2` (the corresponding counts in the control group).

3.2 Available cases analysis

The following analysis illustrates `metamiss` output, but the same results could in fact have been obtained by using `metan r1 f1 r2 f2, fixedi`:

```
. use haloperidol
. metamiss r1 f1 m1 r2 f2 m2, aca id(author) fixed nograph
**********************************************************************
******** METAMISS: meta-analysis allowing for missing data ********
********              Available cases analysis            ********
**********************************************************************
Measure: RR.
Zero cells detected: adding 1/2 to 6 studies.
(Calling metan with options: label(namevar=author) fixed eform nograph ...)
           Study     |     ES    [95% Conf. Interval]     % Weight
---------------------+-------------------------------------------------
Arvanitis            |  1.417       0.891     2.252         18.86
Beasley              |  1.049       0.732     1.504         31.22
Bechelli             |  6.207       1.520    25.353          2.05
Borison              |  7.000       0.400   122.442          0.49
Chouinard            |  3.492       1.113    10.955          3.10
Durost               |  8.684       1.258    59.946          1.09
Garry                |  1.750       0.585     5.238          3.37
Howard               |  2.039       0.670     6.208          3.27
Marder               |  1.357       0.747     2.466         11.37
Nishikawa_82         |  3.000       0.137    65.903          0.42
Nishikawa_84         |  9.200       0.581   145.759          0.53
Reschke              |  3.793       1.058    13.604          2.48
Selman               |  1.484       0.936     2.352         19.11
Serafetinides        |  8.400       0.496   142.271          0.51
Simpson              |  2.353       0.127    43.529          0.48
Spencer              | 11.000       1.671    72.396          1.14
Vichaiya             | 19.000       1.157   311.957          0.52
---------------------+-------------------------------------------------
I-V pooled ES        |  1.567       1.281     1.916        100.00
---------------------+-------------------------------------------------
  Heterogeneity chi-squared =  27.29 (d.f. = 16) p = 0.038
  I-squared (variation in ES attributable to heterogeneity) =  41.4%
  Test of ES=1 : z=   4.37 p = 0.000
```

The effect size (ES) refers to the RR in this output. For brevity, future listings include only the four largest studies: Arvanitis, Beasley, Marder, and Selman, with 2%, 41%, 3%, and 42% missing data, respectively. Interest therefore focuses on changes in inferences for the Beasley and Selman studies.

3.3 Imputation methods

We illustrate imputing all missing values as zeros, using the weighting scheme `w4`, which correctly allows for uncertainty (although in `ica0`, `w1` gives the same answers):

```
. metamiss r1 f1 m1 r2 f2 m2, ica0 w4 id(author) fixed nograph
*********************************************************************
******** METAMISS: meta-analysis allowing for missing data ********
********                  Simple imputation                ********
*********************************************************************
Measure: RR.
Method: ICA-0 (impute zeros).
Weighting scheme: w4.
Zero cells detected: adding 1/2 to 6 studies.
(Calling metan with options: label(namevar=author) fixed eform nograph ...)
           Study     |     ES    [95% Conf. Interval]     % Weight
---------------------+-------------------------------------------------
Arvanitis            |  1.362       0.854     2.172         24.38
Beasley              |  1.429       0.901     2.266         25.01
  (output omitted)
Marder               |  1.357       0.745     2.473         14.75
  (output omitted)
Selman               |  2.429       1.189     4.960         10.42
  (output omitted)
---------------------+-------------------------------------------------
I-V pooled ES        |  1.898       1.507     2.390        100.00
---------------------+-------------------------------------------------
  Heterogeneity chi-squared =  21.56 (d.f. = 16) p = 0.158
  I-squared (variation in ES attributable to heterogeneity) =  25.8%
  Test of ES=1 : z=   5.45 p = 0.000
```

The Beasley and Selman trials have more missing data in the control group, so imputing failures increases their estimated RR, and the pooled RR also increases.

3.4 Impute using known IMORs

Now we assume that the IMOR is 0.5 in each group, that is, that the odds of success in missing data are half the odds of success in observed data.

```
. metamiss r1 f1 m1 r2 f2 m2, icaimor imor(1/2 1/2) w4 id(author) fixed nograph
************************************************************
******** METAMISS: meta-analysis allowing for missing data ********
********                  Simple imputation                ********
************************************************************
Measure: RR.
Method: ICA-IMOR (impute using IMORs 1/2 1/2).
Weighting scheme: w4.
Zero cells detected: adding 1/2 to 6 studies.
(Calling metan with options: label(namevar=author) fixed eform nograph ...)
          Study     |     ES    [95% Conf. Interval]     % Weight
--------------------+-------------------------------------------------
Arvanitis           |  1.399       0.878     2.227         22.12
Beasley             |  1.120       0.737     1.700         27.47
  (output omitted)
Marder              |  1.358       0.746     2.473         13.34
  (output omitted)
Selman              |  1.743       0.973     3.121         14.11
  (output omitted)
--------------------+-------------------------------------------------
I-V pooled ES       |  1.699       1.365     2.115        100.00
--------------------+-------------------------------------------------
  Heterogeneity chi-squared =  24.63 (d.f. = 16) p = 0.077
  I-squared (variation in ES attributable to heterogeneity) =  35.0%
  Test of ES=1 : z=   4.75 p = 0.000
```

The assumption is intermediate between ACA and ICA-0, and so is the result.

3.5 Impute using reasons for missingness

Most studies indicated the distribution of reasons for missing outcomes. We assigned imputation methods as follows:

- For reasons such as "lack of efficacy" or "relapse", we imputed failures (ICA-0).
- For reasons such as "positive response", we imputed successes (ICA-1).
- For reasons such as "adverse event", "withdrawal of consent", or "noncompliance", we considered that the patient had not received the intervention, and we imputed according to the control group rate ICA-pC, implicitly assuming lack of selection bias.
- For reasons such as "loss to follow-up", we assumed MAR and imputed according to the group-specific rate ICA-p.

Counts for these four groups are given by the variables `df1`, `ds1`, `dc1`, and `dg1` for the intervention group, and `df2`, `ds2`, `dc2`, and `dg2` for the control group.

In some trials, the reasons for missingness were given for a different subset of participants, for example, when clinical outcome and dropout were reported for different

time points. In such a case, `metamiss` applies the proportion in each reason-group to the missing population in that trial. In trials that did not report any reasons for missingness, the overall proportion of reasons from all other trials is used.

```
. metamiss r1 f1 m1 r2 f2 m2, ica0(df1 df2) ica1(ds1 ds2) icapc(dc1 dc2)
> icap(dg1 dg2) w4 id(author) fixed nograph
**********************************************************************
******** METAMISS: meta-analysis allowing for missing data ********
********             Imputation using reasons              ********
**********************************************************************
Measure: RR.
Method: ICA-r combining ICA-0 ICA-1 ICA-pC ICA-p.
Weighting scheme: w4.
Zero cells detected: adding 1/2 to 6 studies.
(Calling metan with options: label(namevar=author) fixed eform nograph ...)
          Study     |     ES    [95% Conf. Interval]     % Weight
--------------------+-------------------------------------------------
Arvanitis           |  1.381       0.867     2.201         21.37
Beasley             |  1.349       0.892     2.041         27.10
  (output omitted)
Marder              |  1.368       0.751     2.491         12.91
  (output omitted)
Selman              |  1.767       1.037     3.010         16.36
  (output omitted)
--------------------+-------------------------------------------------
I-V pooled ES       |  1.785       1.439     2.214        100.00
--------------------+-------------------------------------------------
  Heterogeneity chi-squared =  21.86 (d.f. = 16) p = 0.148
  I-squared (variation in ES attributable to heterogeneity) =  26.8%
  Test of ES=1 : z=   5.27 p = 0.000
```

3.6 Impute using uncertain IMORs

Finally, we allow for uncertainty about the IMORs. In the analysis below, we take a $N(0, 4)$ prior for the log IMORs in each group, with the log IMORs in the two groups being a priori uncorrelated.

```
. metamiss r1 f1 m1 r2 f2 m2, sdlogimor(2) logimor(0) w4 id(author) fixed
> nograph
*********************************************************************
******** METAMISS: meta-analysis allowing for missing data ********
********           Bayesian analysis using priors          ********
*********************************************************************
Measure: RR.
Zero cells detected: adding 1/2 to 6 studies.
Priors used:  Group 1: N(0,2^2). Group 2: N(0,2^2). Correlation: 0.
Method: Gauss-Hermite quadrature (10 integration points).
(Calling metan with options: label(namevar=author) fixed eform nograph ...)
           Study     |     ES    [95% Conf. Interval]     % Weight
---------------------+-------------------------------------------------
Arvanitis            |  1.416       0.889     2.257         30.37
Beasley              |  1.085       0.506     2.324         11.36
  (output omitted)
Marder               |  1.350       0.737     2.472         18.04
  (output omitted)
Selman               |  1.596       0.671     3.799          8.77
  (output omitted)
---------------------+-------------------------------------------------
I-V pooled ES        |  1.867       1.444     2.413        100.00
---------------------+-------------------------------------------------
  Heterogeneity chi-squared =  20.93 (d.f. = 16) p = 0.181
  I-squared (variation in ES attributable to heterogeneity) =  23.6%
  Test of ES=1 : z=   4.76 p = 0.000
```

Note how the weight assigned to the Beasley and Selman studies is greatly reduced. Because these studies have estimates below the pooled mean, the pooled mean increases.

4 Details

4.1 Zero cell counts

Like `metan`, `metamiss` adds one half to all four cells in a 2×2 table for a particular study if any of those cells contains zero. However, this behavior is modified under methods that impute with certainty (ICA-0, ICA-1, ICA-b, and ICA-w): the certain imputation is performed before `metamiss` decides whether to add one half. As a result, apparently similar options such as `ica1` and `logimor(99)` differ slightly in the haloperidol data, because the `logimor(99)` analysis adds one half to six studies with `r2` $= 0$, whereas the `ica1` analysis does this only for three studies with `r2` + `m2` $= 0$.

(*Continued on next page*)

4.2 Formula

For the imputation methods, in a given group of a given study, let r, f, and m be the number of observed successes, failures, and missing observations; let $\widehat{\pi} = r/(r+f)$ be the observed success fraction; and let $N = r + f + m$ be the total count. Let k index reason-groups with counts m_k and IMOR θ_k, so that, for example, a group imputed by ICA-0 has $\theta_k = 0$. Then the estimated success fraction is

$$\widehat{\pi}^* = \frac{1}{N}\left(r + \sum_k \frac{m_k \theta_k \widehat{\pi}}{1 - \widehat{\pi} + \theta_k \widehat{\pi}}\right)$$

with the variance obtained by a Taylor-series expansion (Higgins, White, and Wood 2008).

For the Bayesian methods, let δ_j be the log IMOR in group j. Then

$$\widehat{\pi}^*_j(\delta_j) = \frac{1}{N_j}\left(r_j + \frac{m_j e^{\delta_j}\widehat{\pi}_j}{1 - \widehat{\pi}_j + e^{\delta_j}\widehat{\pi}_j}\right)$$

and, for example, the log risk ratio is obtained by finding the expectation of

$$\log\widehat{\pi}^*_E(\delta_E) - \log\widehat{\pi}^*_C(\delta_C)$$

over the prior $p(\delta_E, \delta_C)$ by numerical integration. The variance is obtained by combining the variance conditional on $p(\delta_E, \delta_C)$ with the variance over $p(\delta_E, \delta_C)$ (White, Higgins, and Wood 2008).

5 Discussion

We believe that ACA is a suitable starting point for a sensitivity analysis that might encompass, for example, `imor(1/2 1/2)`, `imor(1/2 2)`, `sdlogimor(2) corrlogimor(1)`, and `sdlogimor(2) corrlogimor(0)` (Higgins, White, and Wood 2008; White, Higgins, and Wood 2008). However, a "best" analysis might use reasons for missingness together with subject matter knowledge to assign suitable IMORs. Future work will explore how to integrate the two approaches.

6 References

Forster, J. J., and P. W. F. Smith. 1998. Model-based inference for categorical survey data subject to non-ignorable non-response. *Journal of the Royal Statistical Society, Series B (Statistical Methodology)* 60: 57–70.

Gamble, C., and S. Hollis. 2005. Uncertainty method improved on best–worst case analysis in a binary meta-analysis. *Journal of Clinical Epidemiology* 58: 579–588.

Higgins, J. P. T., I. R. White, and A. M. Wood. 2008. Imputation methods for missing outcome data in meta-analysis of clinical trials. *Clinical Trials* 5: 225–239.

Joy, C. B., C. E. Adams, and S. M. Lawrie. 2006. Haloperidol versus placebo for schizophrenia. *Cochrane Database of Systematic Reviews* 4: CD003082.

Little, R. J. A., and D. B. Rubin. 2002. *Statistical Analysis with Missing Data*. 2nd ed. Hoboken, NJ: Wiley.

Rubin, D. B. 1977. Formalizing subjective notions about the effect of nonrespondents in sample surveys. *Journal of the American Statistical Association* 72: 538–543.

White, I. R., J. P. T. Higgins, and A. M. Wood. 2008. Allowing for uncertainty due to missing data in meta-analysis - Part 1: Two-stage methods. *Statistics in Medicine* 27: 711–727.

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