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Addressing continuous data for participants excluded from trial analysis: a guide for systematic reviewers

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Abstract

Background: No methods directly address the impact of missing participant data for continuous outcomes in systematic reviews on risk of bias.

Methods: We conducted a consultative, iterative process to develop a framework for handling missing participant data for continuous outcomes. We considered sources reflecting real observed outcomes in participants followed-up in individual trials included in the systematic review, and developed a range of plausible strategies. We applied our approach to two systematic reviews.

Results: We used five sources of data for imputing the means for participants with missing data. To impute standard deviation (SD), we used the median SD from the control arms of all included trials. Using these sources, we developed four progressively more stringent imputation strategies. In the first example review, effect estimates diminished and lost significance as strategies became more stringent, suggesting rating down confidence in estimates of effect for risk of bias. In the second, effect estimates maintained statistical significance using even the most stringent strategy, suggesting missing data does not undermine confidence in results.

Conclusions: Our approach provides a useful, reasonable, and relatively simple, quantitative guidance for judging the impact of risk of bias as a result of missing participant data in systematic reviews of continuous outcomes.

Keywords: Missing participant data; Continuous outcomes; Risk of bias; Systematic reviews; Meta-analysis; Lost to follow-up

1. Introduction

More than 80% of the randomized controlled trials (RCTs) published in top general medical journals suffer from missing participant data [1]. If participants with missing data have different outcomes from those with available data, it may introduce bias in the results of the individual trials and of systematic reviews and meta-analyses using those results. For example, participants' experience of adverse outcomes or toxic effects from therapy may lead them to withdraw from the trial. Alternatively, participants could do very well, making them less interested in continuing the treatment and leading to their withdrawal from the trial.

The Cochrane Collaboration has proposed strategies for handling missing participant data for dichotomous outcomes in systematic reviews [2]. We proposed additional strategies that use plausible assumptions regarding outcomes of trial participants with missing data [3]. A systematic survey of

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What is new?

- Specific guidance for addressing missing participant data for continuous outcomes in meta-analyses and for judging the associated risk of bias is currently unavailable.
- We developed an approach consisting of four increasingly stringent data imputation strategies to address these two issues.
- Our approach provides a useful, reasonable, and relatively simple, quantitative guidance for judging the impact of risk of bias as a result of missing participant data in systematic reviews of continuous outcomes.

RCTs published in prestigious general medical journals found that applying these strategies could change the interpretation of results in up to 33% of the RCTs [1].

Individual trials with continuous outcomes sometimes analyze only participants with available data—complete case (or available case) analysis. Alternatively, individual trials commonly use single imputation techniques such as last observation carried forward (LOCF) and baseline observation carried forward (BOCF), and multiple imputation techniques. The LOCF technique replaces the missing value with the participant's last known value, whereas the BOCF technique replaces the missing value with the participant's baseline value. These single imputation techniques make an unlikely assumption that outcomes stay constant and ignore uncertainty in imputed estimates resulting in spuriously narrow confidence intervals (CIs) [4,5]. Multiple imputation technique incorporates missing data uncertainty by replacing missing values with a set of plausible values [6]. These imputation techniques are not applicable in systematic reviews unless individual participant data are available.

Addressing missing participant data for continuous outcomes in systematic reviews provides additional challenges to those of individual studies: Individual patient data are usually unavailable, there are a wide range of possible imputed values [2], and any approach should ideally address the measure of effect (such as the mean, mean difference, or standardized mean difference) and the associated measure of precision (such as the standard deviation [SD] or standard error).

Currently, no methods have been proposed for investigating the extent to which missing participant data for continuous outcomes may bias the results of systematic reviews. Other than rating down for loss to follow-up in the Cochrane Risk of Bias Tool [7], the Cochrane Collaboration handbook provides no guidance for systematic review authors to decide on the degree of concern warranted by missing participant data. To address this problem, we propose an approach for addressing the impact of missing participant data for continuous outcomes in systematic reviews.

1.1. Development of approach

We formed a group of nine members consisting of clinical epidemiologists, methodologists, and biostatisticians, with extensive experience in systematic reviews of continuous outcomes. Five members of the group had participated in a study of how to address missing participant data for dichotomous outcomes and its potential impact on the estimates of the effect of treatment in RCTs [1]. We reviewed the available literature on the topic including the Cochrane Handbook [1,2,7−9], and then conducted a consultative, iterative process to develop our approach.

We defined missing participant data as data unavailable to the investigator(s) or available to the investigator(s) but not included in published reports. For imputing means and SDs for participants with missing data, we considered a number of possible sources of data. All these sources reflect observed outcomes in participants followed-up (i.e., those with available outcome data) in individual trials included in the systematic review. We developed strategies to combine imputations for participants with missing data in the intervention and control arms with available results from patients with complete data. Our assumption for this approach is that the reasons for missing data, and the participants with missing data, were similar across studies. It then follows that systematic review authors should determine, as far as possible, reasons for missing data, and characteristics of populations with missing data (versus those with available data) in the intervention and control arms of the primary studies. Our goal was to suggest a range of plausible strategies that would be progressively more stringent in challenging the robustness of the pooled estimates of the intervention effect. In this article, we present our proposed approach, which we apply to two example meta-analyses [10,11].

1.2. Imputing measure of effect

We selected five sources of data reflecting observed mean scores in the participants followed-up (i.e., with available outcome data) in individual trials included in a meta-analysis:

A. The best mean score among the intervention arms of the included trials.
B. The best mean score among the control arms of the included trials.
C. The mean score from the control arm of the same trial.
D. The worst mean score among the intervention arms of the included trials.
E. The worst mean score among the control arms of the included trials.

The worst mean score represents the poorest outcome, and the best mean score represents the best outcome. These could be higher or lower scores depending on the outcome instrument used.

Using the five sources of data, we developed four progressively more stringent imputation strategies for participants with missing data in the intervention and control arms. Table 1 provides a matrix describing the following four strategies:

- Strategy 1 uses source C for those with missing data in both the intervention and control arm.
- Strategy 2 uses source D for those with missing data in the intervention arm, and source B for those with missing data in the control arm.
- Strategy 3 uses source E for those with missing data in the intervention arm, and source B for those with missing data in the control arm.
- Strategy 4 uses source E for those with missing data in the intervention arm, and source A for those with missing data in the control arm.

1.3. Imputing measures of precision

We considered three sources of SDs, in combination with our strategies for imputing means, for both the intervention and control arms, namely the smallest (likely most stringent), the median, and the largest SDs (likely the least stringent) among the control arms of all included trials. We tested these different sources and found only small differences in the impact on the pooled estimate and its CI. Given that the median SD is the most plausible, we propose its use among control arms of all included trials.

1.4. Combining observed and imputed data

We propose a three-step method for each imputation strategy. In the first step, for each arm in each trial, we combined the observed means and SDs of the participants with available data with the imputed means and SDs for participants with missing data using the following formulas:

$$1.\ \mathrm{M_{XTi}} = \frac{(\mathrm{M_{FTi}} \times n_{\mathrm{FTi}}) + (\mathrm{M_{LT}}i \times n_{\mathrm{LTi}})}{n_{\mathrm{FTi}} + n_{\mathrm{LTi}}}$$

$$2.\ \mathrm{M_{XCi}} = \frac{(\mathrm{M_{FCi}} \times n_{\mathrm{FCi}}) + (\mathrm{M_{LCi}} \times n_{\mathrm{LCi}})}{n_{\mathrm{FCi}} + n_{\mathrm{LCi}}}$$

$$3.\ \mathrm{SD_{XTi}} = \sqrt{\frac{(n_{\mathrm{FTi}} - 1)\mathrm{SD}^2_{\mathrm{FTi}} + (n_{\mathrm{LTi}} - 1)\mathrm{SD}^2_{\mathrm{LTi}}}{n_{\mathrm{FTi}} + n_{\mathrm{LTi}} - 2}}$$

$$4.\ \mathrm{SD_{XCi}} = \sqrt{\frac{(n_{\mathrm{FCi}} - 1)\mathrm{SD}^2_{\mathrm{FCi}} + (n_{\mathrm{LCi}} - 1)\mathrm{SD}^2_{\mathrm{LCi}}}{n_{\mathrm{FCi}} + n_{\mathrm{LCi}} - 2}}$$

$$5.\ n_{\mathrm{XTi}} = n_{\mathrm{FTi}} + n_{\mathrm{LTi}}$$

$$6.\ n_{\mathrm{XCi}} = n_{\mathrm{FCi}} + n_{\mathrm{LCi}}$$

Table 1. Matrix of assumptions for participants with missing data for continuous outcomes in intervention and control arms

Assumptions about the means of participants with missing data		Assumptions about the means of participants in intervention arm				
		Extreme ← Nonextreme → Extreme				
		Source A	***Source B***	***Source C***	***Source D***	***Source E***
Assumptions about the means of participants in control arm	Extreme ↕ Nonextreme ↕ Extreme					
	Source A					Strategy 4
	Source B				Strategy 2	Strategy 3
	Source C			Strategy 1		
	Source D					
	Source E					

Source A, best mean among intervention arms of included trials; Source B, best mean among the control arms of included trials; Source C, mean score from the control arm of the same trial; Source D, worst mean among the intervention arms of included trials; Source E, worst mean among control arms of included trials.

where "M" represents the mean, "SD" the standard deviation, "n" the sample size, "X" the combined estimates, "F" the followed-up group, "L" the lost to follow-up group, "T" the treatment group, "C" the control group, and "i" the trial.

In the second step, we used the combined mean and SD estimates from each arm to calculate a treatment effect (mean difference) for each study. In the third step, we performed a standard random-effects meta-analysis, where we assumed that the studies included are a random sample of a population of studies [12], to pool the newly calculated mean difference of all included studies.

We used Review Manager Version 5.1.6 (The Nordic Cochrane Center, The Cochrane Collaboration, Copenhagen, Denmark, 2011) and Microsoft Excel 2011 to complete our analyses.

1.5. Application of approach

We applied our approach to two systematic reviews. The first systematic review evaluated cognitive behavioral therapy versus minimal to no treatment or usual care for depression in patients receiving disability benefits [10]. Depressive symptoms were measured using the Beck Depression Inventory, in which higher scores represented a worse outcome and the minimal important difference is five units (Fig. 1). The systematic review included eight randomized trials and had a median missing participant data rate of 21% (range: 0−41%) [10]. The reasons for missing data were provided in three of the eight studies [13−15]. The reasons included personal circumstances, medical illness, time consuming, noncompliance, lack of treatment response, moved residence, refusal, and absent. We did not find important differences in reasons for missing participant data across study arms or studies, and no studies reported any significant differences in the characteristics of those followed versus those not followed. The complete case analysis showed a mean difference of −4.56 (95% CI: −7.35, −1.76). Strategy 1 resulted in some loss of effect but maintained statistical significance. Strategy 2 resulted in further loss of effect and a loss of statistical significance. Strategies 3 and 4 resulted in even further loss of effect and much larger *P*-values (Fig. 1).

The second systematic review evaluated the effectiveness of finasteride therapy versus placebo on improvement in scalp hair for men with androgenetic alopecia. The review included eight randomized trials and had a median missing participant data rate of 14% (range: 0−24%) [11]. The reasons for missing data were provided in five of the eight studies [16−20]. The reasons included lack of efficacy, relocation of residence, adverse events, protocol violations, withdrawal of consent, and other. Again, there were no important differences across studies or in the characteristics of those followed versus those not followed. The complete case analysis showed a mean hair count increase of 9.42% (95% CI: 7.95−10.90%), where greater hair count percentage represented a better outcome (Fig. 2). All four strategies resulted in some loss of effect (in descending order of approach) but maintained statistical significance at *P*-value lower than 0.001 (Fig. 2).

2. Discussion

We developed four increasingly stringent imputation strategies to take into account the missing participant data for continuous outcomes in meta-analyses. Our approach demonstrated varying impact on effects in the example systematic reviews. In the first review, effect estimates were diminished and lost significance as the strategies became more stringent. In the second review, effect estimates maintained statistical significance even using the most stringent strategy.

What are the implications of the results of our two examples on risk of bias associated with missing data? In the first example (Fig. 1), the results withstand only the least stringent assumptions regarding missing data. This suggests that the results are vulnerable to risk of bias; and by applying the GRADE/Cochrane handbook criteria for confidence in estimates of effect (quality of evidence) [21,22], one would rate down for risk of bias, even if the studies did not have other risk of bias issues (e.g., concealment or blinding).

In the second example (Fig. 2), the effect is maintained (although diminished) with even the most stringent assumption, and the CI remains relatively narrow with a low *P*-value (<0.001). The appropriate conclusion may be that the results are robust with respect to missing data. One might, however, want to consider the boundaries of what one could consider an important increase in percentage of hair count. For instance, if a guideline panel considered an increase of less than 10% unimportant, the panel might conclude that the missing data threatens the inference of an important treatment effect. Were that so, the panel might consider rating down their confidence in effect on the basis of possible risk of bias resulting from the missing data (i.e., a possibly important effect becomes unimportant under stringent assumptions regarding missing data).

Our examples appear to illustrate three properties, which likely explain the differences in results between the two examples. The first is the size of the effect and its precision; small effects with borderline significance are more likely to lose significance than larger, precise effects. The second is the proportion of missing participant data and the distribution between the treatment and control groups; the greater the percentage of participants with missing data, the greater the risk of losing significance. The third is that the more extreme the scores of imputation in the proposed strategies, the more likely the newly calculated effects will deviate from the complete case analysis results. Although these properties follow logically from

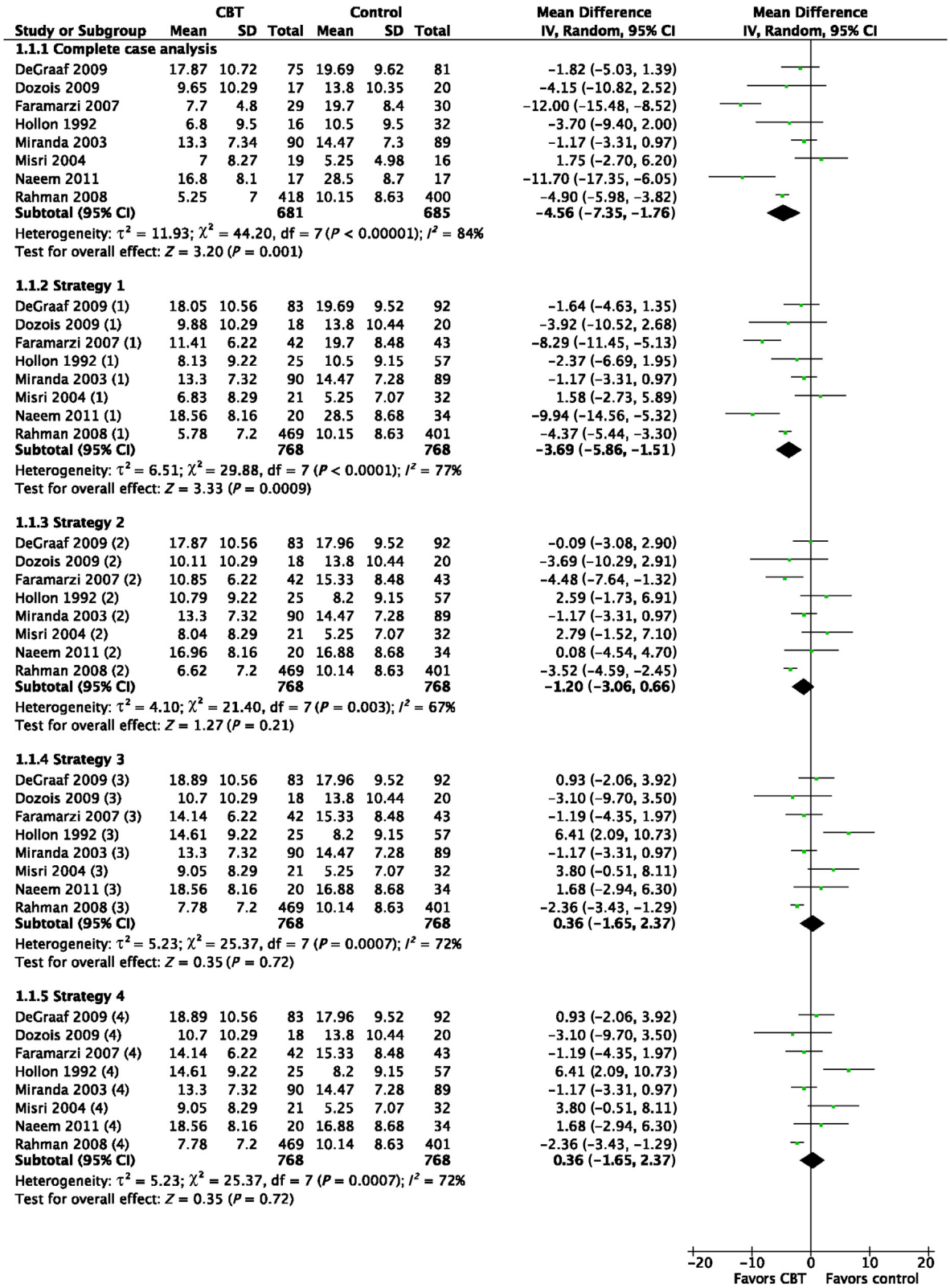

Fig. 1. Forest plots of the complete case analysis and sensitivity analyses using the four strategies for handling participants with missing data for continuous outcomes in a systematic review evaluating CBT for depression in patients receiving disability benefits. CBT, cognitive behavioral therapy; SD, standard deviation; CI, confidence interval.

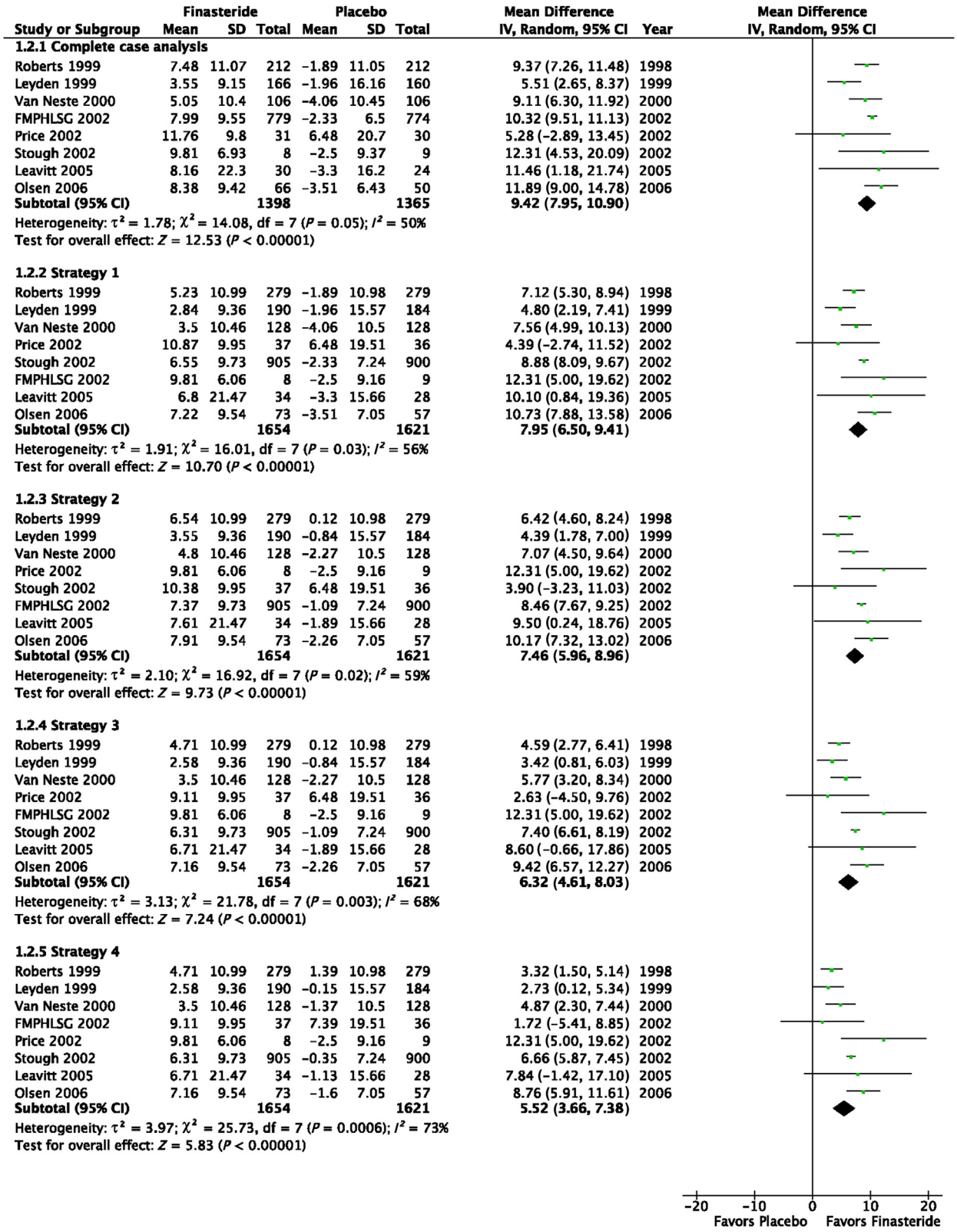

Fig. 2. Forest plots of the complete case analysis and sensitivity analyses using the four strategies for handling participants with missing data for continuous outcomes in a systematic review evaluating finasteride therapy for androgenetic alopecia. SD, standard deviation; CI, confidence interval.

first principles, further theoretical or empirical exploration would be desirable.

The strengths of our approach include the use of observed data from individual trials and meta-analyses, varying degrees of plausible scenarios to test the robustness of pooled estimates, and the application to completed systematic reviews with different magnitudes of effects and missing participant data rates. Our approach also addresses the implications of findings to inferences regarding risk of bias. The approach is compatible with the GRADE/Cochrane handbook guidance for addressing confidence in estimates [21,22]. Another strength is that the approach we offer is the first systematic, quantitative approach addressing a problem in which guidance, up to now, has been very limited.

We applied our approach to two particular examples; testing on a larger number would be desirable and might uncover problems or difficulties with our approach. Other limitations of our approach relate to some inevitable arbitrariness in the choices we have made. We suggest using the best and worst means of the control and intervention arms from all included trials for imputing means for participants with missing data. One could make the argument that using the best or worst means may not be plausible, particularly if these results come from very small trials. On the other hand, we are using real data that has actually been observed in clinical trials.

There is also some arbitrariness in the particular four strategies we made from the combinations of sources of mean values. At the extreme, one could test each of the potential 25 combinations. Furthermore, depending on the reasons for missing data, some assumptions may be more reasonable than others. Indeed, we suggest that if studies provide plausible reasons for missing data, investigators consider these in deciding on plausible imputation strategies. We anticipate, however, that for an approach to be widely adopted, it requires relative simplicity. If mechanisms underlying missingness are provided and are idiosyncratic, or there are important differences between those with available data and those with missing data that vary across studies, then confidence in the estimates derived from our approach decreases, and more sophisticated imputation strategies may be necessary. In our two example systematic reviews, 8 of the 16 studies reported reasons for missing data, no study reported idiosyncratic or unique reasons for missing participant data that would suggest this necessity, and no study reported important prognostic differences between those followed and those not followed. The reasons for missingness reported were typical of what is generally seen in RCTs. We suspect that the results in our two examples, which do not provide compelling reasons for modifying our approach as a result of different reasons for missingness or different prognostic characteristics of those missing across studies, will be typical of what systematic review authors will face.

Regarding the choice of SD one imputes for participants with missing data, reasonable options might include the median SD (our choice) or the smallest and largest SDs, or sensitivity analyses testing all three (which would require 12 sensitivity analyses simultaneously varying mean values and SDs). The median SD is the most plausible and offers desirable simplicity. Moreover, in the two examples to which we have applied our approach, the different SD options made very little difference to our results.

Systematic review authors applying our approach will face challenges when they confront trials that fail to adequately report missing participant data or do not report them at all. This failure can be classified into the following categories, namely (1) trialists do not report the frequency of missing participant data, (2) trialists report total missing participant data but not by trial arm, and (3) trialists report missing participant data to which they have applied imputation techniques and report only the analysis based on the imputed values.

For any trial in which authors do not report missing participant data rates, we suggest using the median missing participant data rate from the systematic review. Some may feel that this assumption is too stringent. We therefore propose performing a sensitivity analysis using a missing participant data rate of zero in both arms. If authors reported total missing participant data only, we suggest assuming that missing data was equally distributed in both arms.

If the individual trial handled missing participant data and reported imputed analyses only, we suggest using the imputed results for the meta-analysis. If the authors reported both the imputed analysis and the complete case analysis, we suggest applying our approach to the trial's complete case analysis. All of these suggestions assume that systematic review authors have attempted, and failed, to obtain the missing information directly from trialists.

A final consideration is that our approach is thus far restricted to systematic reviews in which each study has used the same measurement instrument producing continuous outcome data. Systematic review authors often face a group of trials that have used different instruments to measure a similar construct. Should others find our approach compelling, development of methods to extend the approach to systematic reviews pooling trials using multiple instruments would be important.

In summary, detailed guidance on how to determine the extent to which missing data in primary studies increases risk of bias in systematic reviews of continuous outcomes has thus far been unavailable. We suggest an approach that involves an initial complete case analysis with subsequent sensitivity analyses making progressively more stringent assumptions about results in patients with missing data; we have provided detailed guidance for conducting such analyses. To the extent that results change with the sensitivity analyses, risk of bias as a result of missing data increases. The explicit guidance we have provided represents a potentially

important step in addressing missing continuous outcome data in systematic reviews.

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References

[1] Akl EA, Briel M, You JJ, Sun X, Johnston BC, Busse JW, et al. LOST to follow-up Information in Trials (LOST−IT): potential impact on estimated treatment effects. BMJ 2012;344:e2809.

[2] Further issues in meta-analysis: intention to treat issues Available at http://www.cochrane-net.org/openlearning/html/mod14-4.htm. Accessed July 26, 2012.

[3] Akl EA, Johnston BC, Alonso-Coello A, Neumann I, Ebrahim S, Briel M, et al. Addressing dichotomous data for participants excluded from trial analysis: a guide for systematic reviewers. PLoS One 2013; 8:e57132.

[4] Molnar FJ, Hutton B, Fergusson D. Does analysis using "last observation carried forward" introduce bias in dementia research? CMAJ 2008;179(8):751−3.

[5] Ware JH. Interpreting incomplete data in studies of diet and weight loss. N Engl J Med 2003;348:2136−7.

[6] Rubin DB. Multiple imputation for nonresponse in surveys. New York, NY: John Wiley & Sons, Inc.; 1987.

[7] The Cochrane Collaboration. Chapter 8: Risk of bias. In: Higgins JPT, Green S, editors. Cochrane handbook for systematic reviews of interventions (Version 5.1.0). Oxford, UK: Cochrane Collaboration; 2011.

[8] Groenwold RHH, Donders RT, Roes KCB, Harrell FE Jr, Moons KGM. Dealing with missing outcome data in randomized trials and observational studies. Am J Epidemiol 2011;175:210−7.

[9] Higgins JPT, White IR, Wood AM. Imputation methods for missing outcome data in meta-analysis of clinical trials. Clin Trials 2008;5: 225−39.

[10] Ebrahim S, Montoya L, Truong W, Hsu S, Kamal el Din M, Carrasco-Labra A, et al. Effectiveness of cognitive behavioral therapy for depression in patients receiving disability benefits: a systematic review and individual patient meta-analysis. PLoS One 2012;7: e50202.

[11] Mella JM, Perret MC, Manzotti M, Catalano HN, Guyatt GH. Efficacy and safety of finasteride therapy for androgenetic alopecia: a systematic review. Arch Dermatol 2010;146:1141−50.

[12] Higgins J, Thompson S, Deeks J, Altman D. Statistical heterogeneity in systematic reviews of clinical trials: a critical appraisal of guidelines and practice. J Policy Health Serv Res Policy 2002; 7(1):51−61.

[13] de Graaf LE, Gerhards SAH, Arntz A, Riper H, Metsemakers JFM, Evers SMAA, et al. Clinical effectiveness of online computerised cognitive behavioural therapy without support for depression in primary care: randomised trial. Br J Psychiatry 2009;195: 73−80.

[14] Misri S, Reebye P, Corral M, Milis L. The use of paroxetine and cognitive-behavioral therapy in postpartum depression and anxiety: a randomized controlled trial. J Clin Psychiatry 2004;65:1236−41.

[15] Rahman A, Malik A, Sikandar S, Roberts C, Creed F. Cognitive behaviour therapy-based intervention by community health workers for mothers with depression and their infants in rural Pakistan: a cluster-randomised controlled trial. Lancet 2008;372:902−9.

[16] Finasteride Male Pattern Hair Loss Study Group. Long-term (5-year) multinational experience with finasteride 1 mg in the treatment of men with androgenetic alopecia. Eur J Dermatol 2002;12(1):38−49.

[17] Leavitt M, Perez-Meza D, Rao NA, Barusco M, Kaufman KD, Ziering C. Effects of finasteride (1 mg) on hair transplant. Dermatol Surg 2005;31:1268−76.

[18] Leyden J, Dunlap F, Miller B, Winters P, Lebwohl M, Hecker D, et al. Finasteride in the treatment of men with frontal male pattern hair loss. J Am Acad Dermatol 1999;40(6 Pt 1):930−7.

[19] Olsen EA, Hordinsky M, Whiting D, Stough D, Hobbs S, Ellis ML, et al, Dutasteride Alopecia Research Team. The importance of dual 5-reductase inhibition in the treatment of male pattern hair loss: results of a randomized placebo-controlled study of dutasteride versus finasteride. J Am Acad Dermatol 2006;55:1014−23.

[20] Roberts JL, Fiedler V, Imperato-McGinley J, Whiting D, Olsen E, Shupack J, et al. Clinical dose ranging studies with finasteride, a type 2 5alpha-reductase inhibitor, in men with male pattern hair loss. J Am Acad Dermatol 1999;41:555−63.

[21] Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, et al, for GRADE Working Group. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ 2008;336:924−6.

[22] The Cochrane Collaboration. Chapter 12: Interpreting results and drawing conclusions. In: Higgins JPT, Green S, editors. Cochrane handbook for systematic reviews of interventions (Version 5.1.0). Oxford, UK: Cochrane Collaboration; 2011.

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