Practical methods for handling missing summary statistics in meta-analysis of continuous outcomes

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Acknowledgements

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• Researchers
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• Collaborators
  • Marshall Dozier, Academic Support Librarian, University of Edinburgh
  • Hazel Fraser, Cochrane Stroke Editorial Group
Outline

• Background to the issue
• Survey of Cochrane systematic review authors
• Systematic review of methods
  • Recovering missing SD value
  • Recovering missing mean value
• Real-world application of methods
• Conclusions and future work
Background

Number of people

Length of stay (days)

Average 12 days
Background

Number of people

Length of stay (days)

Median 9 days
Consequences

**Issue 1**
Some trial reports do not contain the summaries of outcome measures (mean and standard deviation) needed in a meta-analysis. Trials have to be left out of the meta-analysis.

**Issue 2**
For some outcomes, the usual approaches to combining the trial results in meta-analysis aren’t suitable and alternative methods need to be devised.
Polling Question 1
Aims

• Survey of Cochrane review authors to establish extent of problem

• Investigate (statistical) ways of recovering missing outcome summaries by using other information in the trial report
  • Systematic review of methods to recover missing standard deviation
  • Systematic review of methods to recover missing mean

• Test performance of methods using Cochrane review individual patient data
Survey of Cochrane Reviewers - Design

- Survey of authors of Cochrane review of stroke rehabilitation intervention
- Sent to lead and second authors (and contact author)
- Invited in covering email to complete survey within 1 month
- Survey in Google Forms
- Questionnaire linked to a specific published review
Survey of Cochrane Reviewers - Results

- 177 Cochrane stroke reviews; 70 of rehabilitation interventions
- Sent to 141 authors of 70 reviews
- 63 responses linked to 53 reviews (76%)
- 97% of reviewers who knew details of analysis aimed to extract continuous outcomes
- Of these, 38 (68%) encountered unreported mean or SD values
- 89% of these (34 of 38) still performed a meta-analysis
85% asked trial report authors for the missing information

How much did they get back?

- 50% less than half
- 25% half to three quarters
- 25% more than three quarters

76% left trial with missing information out of meta-analysis

- 41% extracted information from other sources (e.g., data from graphs in the research reports)
- 15% substituted similar values for missing information (e.g., Median or range)
- 15% changed method of analysing the data (e.g., dichotomise the outcome)
- 21% used another approach
- 26% imputed the missing measures
- 15% extracted information from other sources (e.g., data from graphs in the research reports)
Polling Question 2
Systematic Review – Missing Standard Deviation (SD)

• Update to previous review

• Methods for determining variance, SD or standard error where unreported
• Parallel group or crossover trials
• Single reviewer screened title and abstract; and full text to identify eligible articles
• Independent reviewer assessed full text to confirm eligibility
• Data sources (searched from 2002 to May 2016)
  • Searched MEDLINE, EMBASE, Web of Knowledge, PsycINFO, Global Health
  • Full text from Journals@Ovid (OVFT), YourJournals@Ovid, PsycARTICLES Full Text, Books@Ovid or via inter-library loan
  • Grey literature – Cochrane Colloquium abstract books, Cochrane Statistics Methods Group mailing list archive, emails to CSMG topic experts
Dealing with missing standard deviation and mean values in meta-analysis of continuous outcomes: a systematic review

Christopher J. Weir¹, Isabella Butcher¹, Valentina Assi¹, Stephanie C. Lewis³, Gordon D. Murray¹, Peter Langhorne² and Marian C. Brady³

Abstract

Background: Rigorous, informative meta-analyses rely on availability of appropriate summary statistics or individual participant data. For continuous outcomes, especially those with naturally skewed distributions, summary information on the mean or variability often goes unreported. While full reporting of original trial data is the ideal, we sought to identify methods for handling unreported mean or variability summary statistics in meta-analysis.

Methods: We undertook two systematic literature reviews to identify methodological approaches used to deal with
Systematic Review – Missing Standard Deviation (SD)

1. exp "meta analysis (topic)"/ or Meta-Analysis/ or exp Review Literature as Topic/ or Review Literature.mp.
2. (meta-analy$ or metaanaly$ or (meta adj analy$) or metanaly$).tw.
3. (systematic adj5 (review$1 or overview$1)).tw. or systematic review/
4. clinical trial/ or controlled clinical trial/ or Clinical Trials as Topic/ or (clinical adj3 trial$1).tw. or controlled clinical trial.mp.
5. randomized controlled trial/ or "randomized controlled trial (topic)"/ or (randomi#ed adj5 trial$1).tw.
6. *data analysis/ or *data extraction/ or *data synthesis/
7. *statistics as topic/ or *statistical parameters/ or *variance/ or *statistical analysis/ or "analysis of covariance"/ or "analysis of variance"/ or *attributable risk/ or *bootstrapping/ or *canonical analysis/ or *chi square test/ or *cohort analysis/ or *correlation analysis/ or *correspondence analysis/ or *effect size/ or *etiologic fraction/ or *fisher exact test/ or *frequency analysis/ or *friedman test/ or *geostatistical analysis/ or *inferenceal statistics/ or *instrumental variable analysis/ or *intention to treat analysis/ or *jackknife test/ or *kaplan meier method/ or *kappa statistics/ or *kolmogorov smirnov test/ or *kruskal wallis test/ or *latent structure analysis/ or *life table method/ or *log rank test/ or *loglinear model/ or *mantel haenszel test/ or *maximum likelihood method/ or *mcnemar test/ or *median test/ or *meta analysis/ or "meta analysis (topic)"/ or *monte carlo method/ or *most probable number method/ or *multilevel analysis/ or *multivariate analysis/ or *nonparametric test/ or *numbers needed to treat/ or *one tailed test/ or *ordination analysis/ or *parametric test/ or *post hoc analysis/ or *power analysis/ or "power of a test"/ or *principal coordinate analysis/ or *rank sum test/ or *rasch analysis/ or *redundancy analysis/ or *regression analysis/ or *risk benefit analysis/ or *sequential analysis/ or *sign test/ or *spatial analysis/ or *spatial autocorrelation analysis/ or *student t test/ or *temporal analysis/ or *two tailed test/ or *univariate analysis/ or *wilcoxon signed ranks test/ or *yates continuity correction/ or *youden index/
8. exp *statistical parameters/
9. (data adj5 (pool or pooled or pooling$)).tw.
10. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9
11. ((imput* adj4 (standard adj deviation$1)) or (imput* adj4 (standard adj error$1)) or (imput* adj4 variance$1)).tw.
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13. ((derive* adj2 (standard adj deviation$1)) or (derive* adj2 (standard adj error$1)) or (derive* adj2 variance$1)).tw.
14. (extracte* adj5 (standard adj deviation$1)).tw.
15. (heritability or genome-wide).tw.
16. hozo i.au. and variance.ti.
17. 11 or 12 or 13 or 14 or 16
18. 10 and 17
19. 18 not 15
Systematic Review – Missing Standard Deviation (SD)

Identification:
- Records identified through database searching (n = 876)
- Additional records identified through other sources (n = 13)

Records after duplicates removed (n = 631)

Records screened (n = 503)
- Pre-2002 records excluded (n = 128)

Records excluded (n = 265)
- Full-text articles excluded (n = 77)
  - Not relevant/no method described (n=53)
  - No method applied (n=24)

Full-text articles assessed for eligibility (n = 238)

Studies included in qualitative synthesis (n = 161)
- Known methods described / compared (n=146)
- New method described (n=15)
<table>
<thead>
<tr>
<th>Authors</th>
<th>Description</th>
<th>Statistics required</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abrams et al (2005)</td>
<td>Bayesian meta-analysis</td>
<td>Baseline, follow-up and change from baseline mean/SD</td>
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<tr>
<td>Hozo et al (2005)</td>
<td>Formulae provided</td>
<td>Min, Max, Median, N</td>
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<tr>
<td>Sung et al (2006)</td>
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<td>Variances in other studies</td>
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<tr>
<td>Walter and Yao (2007)</td>
<td>Look-up table</td>
<td>Min and Max (or Range), N</td>
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<td>Ma et al (2008)</td>
<td>Weighted average</td>
<td>Variances in other studies, N</td>
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<td>Nixon et al (2009)</td>
<td>Bayesian meta-analysis</td>
<td>Baseline SD, Follow-up SD</td>
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<td>Dakin et al (2010)</td>
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<td>SDs in other studies</td>
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<tr>
<td>Boucher (2012)</td>
<td>Emax model of SDs</td>
<td>Observed SDs over time (longitudinal study)</td>
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<td>Kwon and Reis (2015)</td>
<td>Approximate Bayesian computation</td>
<td>Available summary statistics</td>
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<tr>
<td>Choudhry et al (2016)</td>
<td>Meta-regression of variances</td>
<td>Variances in other studies</td>
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Systematic Review – Missing Mean

• Methods for determining mean where unreported
• Data sources (searched from 2005 to May 2016)
  • Searched EMBASE only
  • Full text from Journals@Ovid (OVFT), YourJournals@Ovid, PsycARTICLES Full Text, Books@Ovid or via inter-library loan
  • Grey literature – emails to CSMG topic experts
  • Cited reference searching of key paper:
Systematic Review – Missing Mean

Identification
- Records identified through database searching (n = 219)
- Additional records identified through Hozo cited reference searching (n = 950)
- Additional records identified from other sources (n = 2)

Records after duplicates removed (n = 1168)

Screening
- Records screened (n = 1124)
- Pre-2005 records excluded (n = 44)

Eligibility
- Full-text articles assessed for eligibility (n = 45)
- Records excluded (n = 1079)
  - Full-text articles excluded, with reasons (n = 41)
  - Not relevant / no method described (n = 26)
  - No method applied (n = 2)
  - Existing method applied (n = 13)

Included
- Studies included in qualitative synthesis (n = 4)
# Systematic Review – Missing Mean

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Case Study – Early Supported Discharge after Stroke

• Individual patient data from published Cochrane review

• 8 trials
• Total of 1055 patients
• Key secondary outcome: hospital length of stay
• Mean difference -9.4 days, 95% confidence interval (-16.3, -2.4)

• Assessed how successful methods were in recovering unreported SD or mean under scenarios where these were missing from 1 or more trials
  • Any bias compared to true result?
  • Did they reflect the uncertainty (precision) in the true result confidence interval?
Case Study – Missing SD

Missing SD in 1 Trial: Bias (days) in treatment effect estimate

Adelaide  Akershus  Belfast  London  Manchester  Newcastle  Oslo  Stockholm

Ma  Walter  Cochrane  Omit
Case Study – Missing SD

Missing SD in 1 Trial: Imprecision in treatment effect estimate
Case Study – Missing Mean

Missing Mean in 1 Trial: Bias (days) in treatment effect estimate

- Adelaide
- Akershus
- Belfast
- London
- Manchester
- Newcastle
- Oslo
- Stockholm

Legend:
- Hozo
- Bland
- Wan
- Omit
Case Study – Missing Mean

Missing Mean in 1 Trial: Imprecision in treatment effect estimate

Adelaide  Akershus  Belfast  London  Manchester  Newcastle  Oslo  Stockholm

Hozo  Bland  Wan  Omit
Conclusions

• Unreported mean and SD lead to trials being omitted from meta-analysis

• Numerous recent methods published
  • 15 for unreported SD (since 2002)
  • 5 for mean (since 2005)

• For SD
  • Method of Walter and Yao (2007) performed best
  • But needs minimum, maximum to be reported
  • Cochrane handbook method also performed well if upper, lower quartiles reported

• For mean
  • Wan (2014) method got closest to true value
  • Practically useful as includes values often reported
Polling Question 3
Final Thoughts

• Sometimes meta-analysis based on mean / SD not appropriate
  • Other methods (e.g. ratio of mean/ratio of geometric mean) do not depend on these

• No one method should be recommended
  • Need range of approaches in case the statistics required by “best” method not available

• Continue to promote high quality reporting of trials to address issue
  • But these methods always needed for historical studies
Questions and Comments?

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