Meta-analysis of repeated measures study designs

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Outline

1. Introduction
2. Methods
3. Results
4. Discussion

Introduction

- Repeated measures studies are designed to record measurements or observations of a unit at a number of time-points in order to assess follow-up, trend or change over time.
- The analysis of this type of design is not straightforward.
- The temporal non-independence between measurements must be considered as the same individuals, or sites, are being measured at each time-point.

Introduction

- There are a number of approaches to the primary analysis of this type of data.
  A. Assessing the effect at one particular time-point only
  B. Calculating and assessing summary statistics of the individual measurements at each time-point, ignoring the temporal dependence
  C. Using more complex analyses such as multivariate analysis of variance or multilevel models.

Introduction

- Secondary analysis in the form of systematic reviews and meta-analyses have been commonly used to allow formal evaluation of the relevant evidence for a particular question of interest.
- Although standard techniques are available for the meta-analysis of most types of studies, there has been little guidance available to researchers for the meta-analysis of repeated measures.

Introduction

- Meta-analysis of IPD is considered the 'gold standard'
- When the IPD are available a one-or two-stage approach could be taken to the meta-analysis of repeated measures studies.
- The two-stage approach
  - Involves analysing each individual study and then combining the summary estimates as in a usual meta-analysis.

Introduction

- The one-stage approach
  - includes all the IPD in the synthesis model with study as an identifier.
  - However, it is often very difficult to obtain all of the IPD for a meta-analysis and properly account for study-specific issues such as design, missing data, covariates, biases and confounders.

Introduction

- The Cochrane Handbook's recommendations for the meta-analysis of repeated measures data,
  - The use of IPD and assessment of one particular time-point.
  - Calculate and combine a summary effect for each individual across time
  - Perform separate analyses at each time-point or select meta-analyse results for just the final time-point in each study.

Introduction

- Some considerations
  - How to deal with results that are not reported in the same format.
  - The choice of method will depend on the question of interest. (i.e. an outcome at a particular time-point or trend over time) and the data available from the primary studies.

Objective

- To outline and illustrate a number of possible approaches and reflect the most likely scenarios for meta-analysis of repeated measures studies.

Methods

- Meta-analysis methods and models
  - Meta-analysis models

$$y_i = \theta_i + \varepsilon_i; \quad \varepsilon_i \sim N(0, \sigma_i^2); \quad \theta_i \sim N(\mu, \tau^2)$$
$$\mathrm{var}(y_i) = \sigma_i^2 + \tau^2 \qquad (1)$$

Methods

- Meta-analysis methods and models
  - Bayesian random effect meta-analysis model

$$y_i \sim N(\theta_i, \sigma_i^2) \qquad \mu \sim N(0,100000)$$
$$\theta_i \sim N(\mu, \tau^2) \qquad \tau \sim N(0,100), \tau > 0 \quad (2)$$

Methods

- Methods of repeated measures meta-analysis
  1. Relevant time-point meta-analysis (RTM)
  2. First/final time-point meta-analysis (FTM)
  3. All time-points meta-analysis (ATM)
  4. Trend meta-analysis (TM)
  5. Change in time meta-analysis (CTM)

1. Relevant time-point meta-analysis (RTM)

- Aim: to assess evidence at one particular time-point
- Data required from primary studies
  - Summary effect (e.g.mean, slope estimate)
  - Some measure of variance at time-point of interest
- Assumptions/considerations
  - Only interested in that one particular time-point, not trend

2. First/final time-point meta-analysis (RTM)

- Aim: to assess evidence at first or final time-point for each study
- Data required from primary studies
  - Summary effect (e.g.mean, slope estimate)
  - Some measure of variance at first or final time-point
- Assumptions/considerations
  - Only interested in first or final time-point in each study
  - Limits interpretation as first or final time-points may be different in each study.

3. All time-points meta-analysis (ATM)

- Aim: to assess evidence at every time-point reported by the primary studies
- Data required from primary studies
  - Summary effect (e.g.mean, slope estimate)
  - Some measure of variance at each time-point
- Assumptions/considerations
  - Independent of time-points assumed.
  - Overlap of time-points in primary studies.

4. Trend meta-analysis (TM)

- Aim: to investigate any trend over time
- Data required from primary studies
  - Slope estimate and some measure of variance calculated within primary study
  - Summary effect (e.g. mean, slope estimate) and some measure of variance at each time-point
- Assumptions/considerations
  - Assuming the primary analyses are carried out correctly, this method maintains the temporal dependencies
  - Violates the assumption of independence between time-points

4. Trend meta-analysis (TM)

- Various approach can be taken depending on the form of the available data.
- If the primary studies have used multilevel modelling and report a slope estimate for trend, these can be combined using the random effects meta-analysis model.

$$y_i = \theta_i + \varepsilon_i; \quad \varepsilon_i \sim N(0, \sigma_i^2); \quad \theta_i \sim N(\mu, \tau^2)$$
$$\mathrm{var}(y_i) = \sigma_i^2 + \tau^2 \qquad (1)$$

4. Trend meta-analysis (TM)

- This analysis would maintain the time dependencies within each study.
- To carry out this analysis, Bayesian model given in (2)

$$y_i \sim N(\theta_i, \sigma_i^2) \quad \mu \sim N(0,100000)$$
$$\theta_i \sim N(\mu, \tau^2) \quad \tau \sim N(0,100), \tau > 0 \qquad (2)$$

- could be extended as follows

4. Trend meta-analysis (TM)

$$
\begin{aligned}
y_{it} &\sim N(\theta_{it}, \sigma_{it}^2) & \alpha_i &\sim N(0,100000) \\
\theta_{it} &= \alpha_i + \beta_i time_{it} & \mu &\sim N(0,100000) \\
\beta_i &\sim N(\mu, \tau^2) & \tau &\sim N(0,100), \tau > 0
\end{aligned}
\qquad (3)
$$

- This model allows inclusion of studies that do not contribute to the trend analysis, but do provide estimates at certain time-points.
- This 'borrowing of strength' is one advantage of the Bayesian approach to evidence synthesis.

5. Change in time meta-analysis

- Aim: to investigate the change between consecutive time-point
- Data required from primary studies
  - Summary effect (e.g. mean, slope estimate) and some measure of variance at each time-point
- Assumptions/considerations
  - Independence of time-point assumed
  - Overlap of time-points in primary studies

5. Change in time meta-analysis

- The data could be done in two ways.

1. The difference between each successive time-point is calculate and combined, or
2. The difference from baseline to each time-point is calculated.

Methods

- Illustrative meta-analysis
  - Pirozzo et al. report a Cochrane systematic review and meta-analysis of the impact of advice about low-fat diets on the weight reduction of obese or overweight individuals compared with other weight-loss interventions.

Methods

- Illustrative meta-analysis
  - Six RCTs were included in the meta-analysis.
  - The main outcome of interest was the difference in weight loss between subjects given low-fat diet advice and control subjects at 6,12 and 18 months
  - Only three of the six studies measured and reported weight loss at all three time-points.
  - One study only reported weight loss at 6 months and the remaining two studies only reported weight loss at 12 months.

Simulation study

- They simulated repeated measures IPD for meta-analysis to demonstrate the impact of assuming independence across time-points as the dependencies increase over time at the individual level.
- Three simple meta-analyses are simulated, each containing five studies with each study reporting some continuous measurements on 20 individuals at four time-points.

Simulation study

- A linear trend was assumed for each individual and data were simulated using a random effects model.
- These simulated datasets are meta-analysed in three ways:
  - By calculating the slope estimate from the pooled means at each time-point (using the ATM approach)
  - By calculating and combining the study-specific slope estimates based on the means at each time-point in each study (using the TM approach)
  - By carrying out an IPD analysis using a 3-level hierarchical model

Results

- RTM: relevant time point meta-analysis
  - The aim of this approach is to combine the available evidence at one particular time-point.
  - They define 6 months as the time-point of interest.
  - This choice has the immediate effect of excluding two of six studies from the meta-analysis as they did not report at 6 months.

RTM

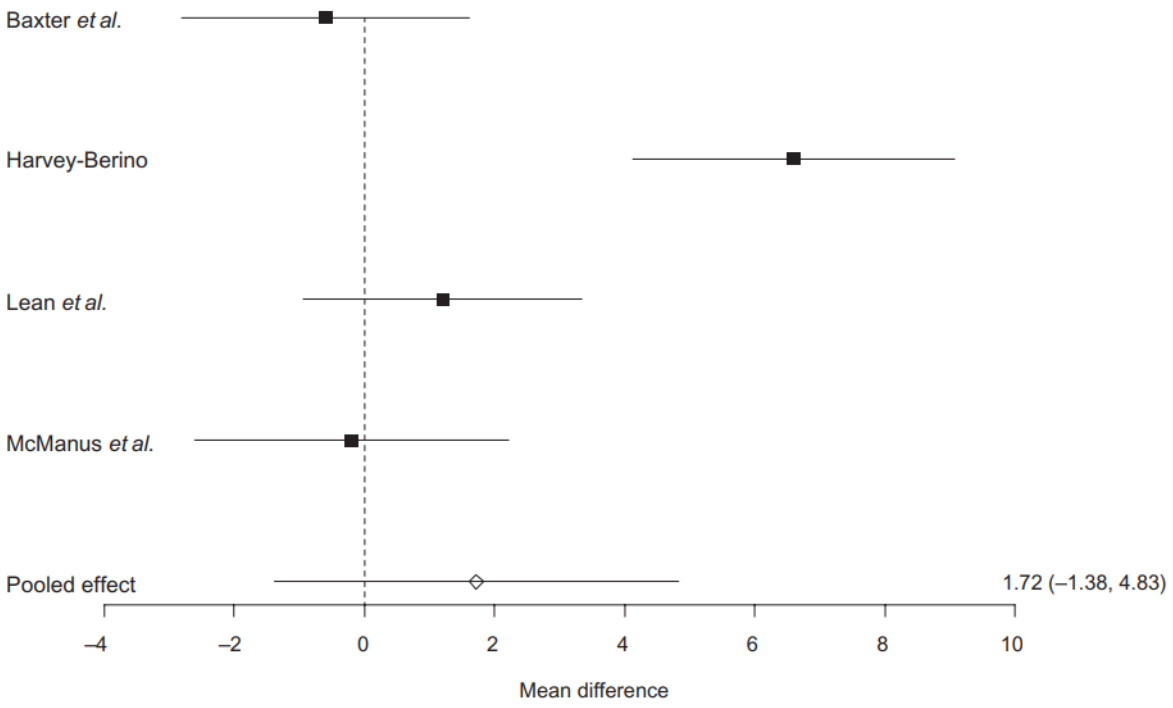


Figure 2 Observed and pooled estimates in *relevant time-point meta-analysis* (RTM).

Results

- FTM: final time point meta-analysis
  - Considered a meta-analysis of the final time-point with the Piroszzo et al.example.
  - Six months is the final time-point for one study
  - Twelve months for two studies and
  - Eighteen months for remaining three studies.

FTM

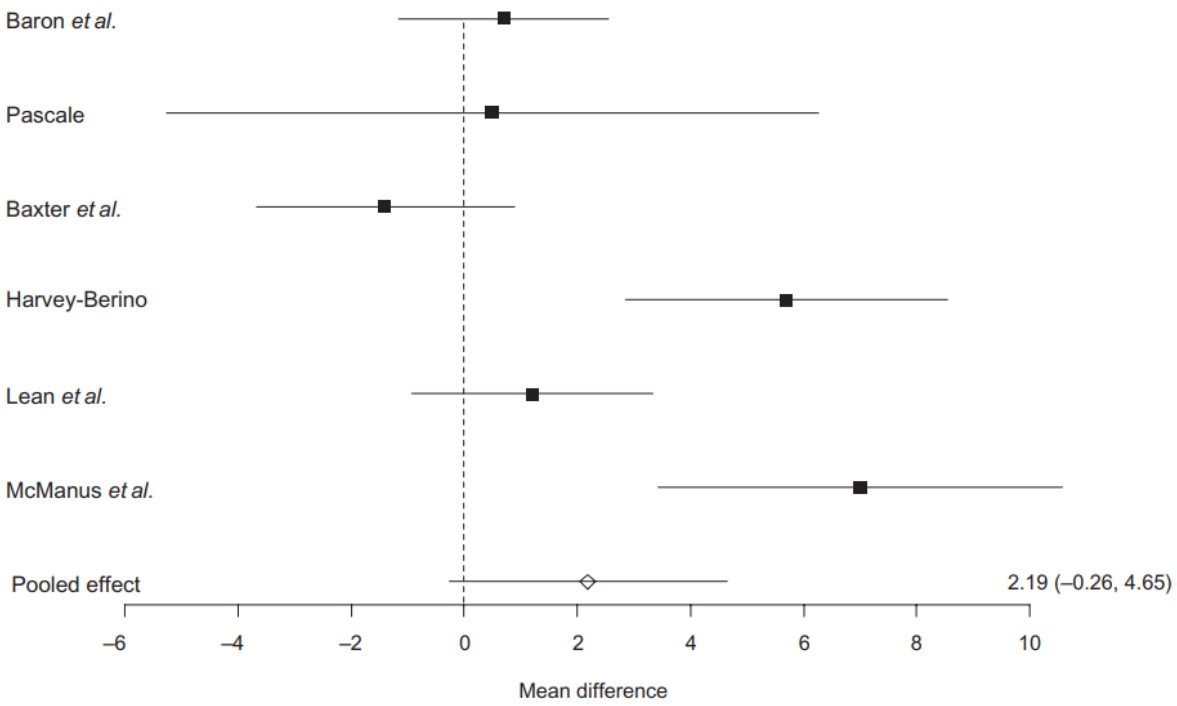
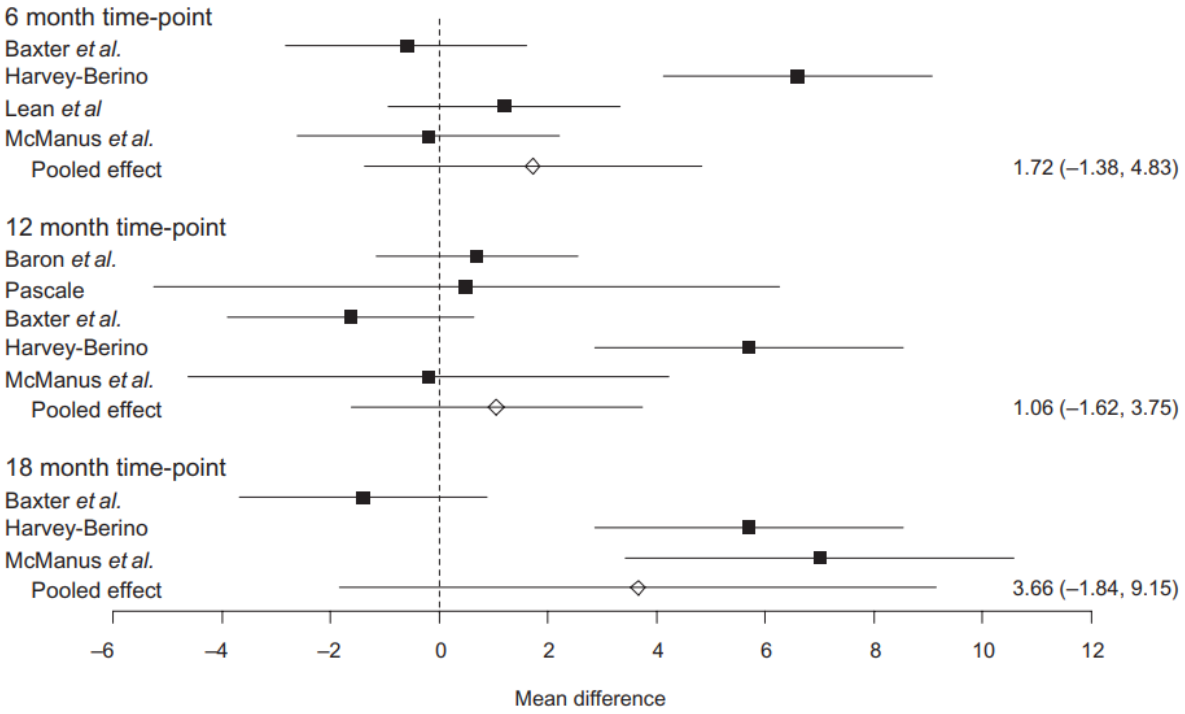


Figure 3 Observed, shrunken and pooled estimates in *final time-point meta-analysis* (FTM).

Results

- ATM: All time-point meta-analysis



	Bayesian pooled estimate	95%CrI
6 mo	1.72	-4.07,7.59
12 mo	1.04	-3.18,5.24
18 mo	3.63	-5.79,13.26

Figure 4 Observed and pooled estimates at (1) 6 months, (2) 12 months, and (3) 18 months follow-up for the all-time points meta-analysis (ATM).

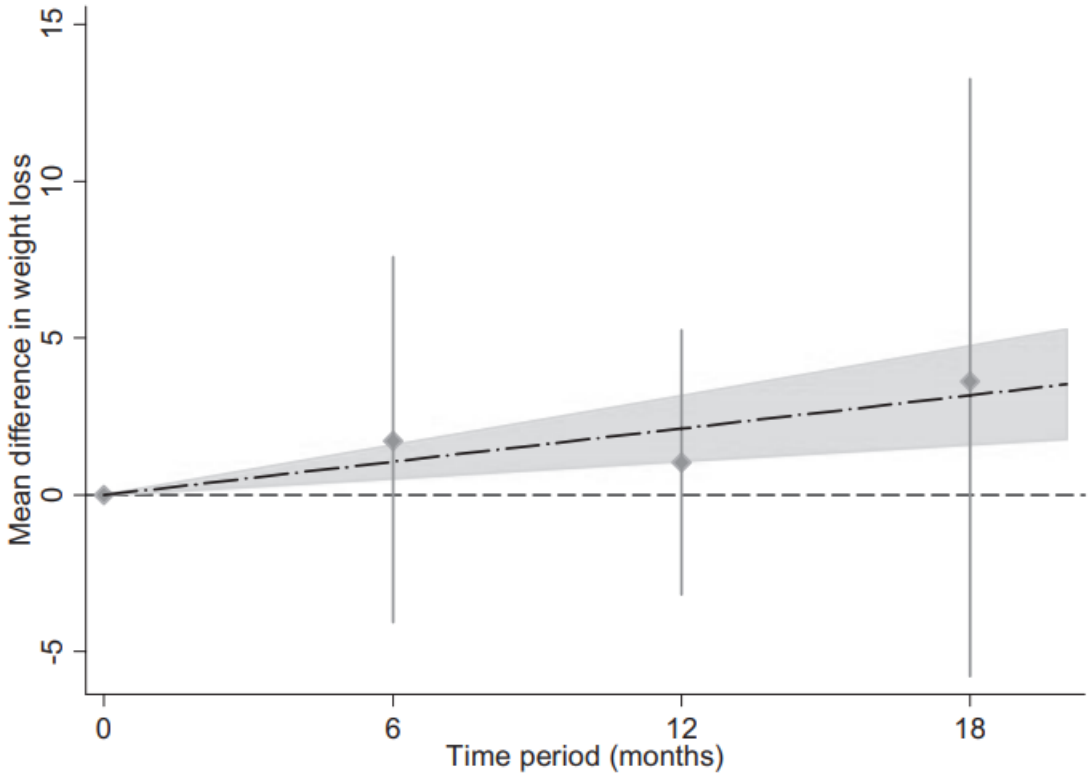


Figure 5 Pooled estimates at each time-point and associated regression slope from a Bayesian analysis of the data.

ATM

- If the intercept is allowed to be non-zero the slope estimate 95%CI from a frequentist analysis suggest that there is little evidence of a time trend: 0.17 (-0.13,0.47)
- The results of a Bayesian analysis are similar to this.

Result

- TM
  - The TM allows assessment of trend at the study level, as well as at the population level.
  - For the Pirozzo et al. meta-analysis, only the means and variances at each time-point are available

$$
\begin{aligned}
y_{it} &\sim N(\theta_{it}, \sigma_{it}^2) & \alpha_i &\sim N(0,100000) \\
\theta_{it} &= \alpha_i + \beta_i time_{it} & \mu &\sim N(0,100000) \\
\beta_i &\sim N(\mu, \tau^2) & \tau &\sim N(0,100), \tau > 0
\end{aligned}
\qquad (3)
$$

TM

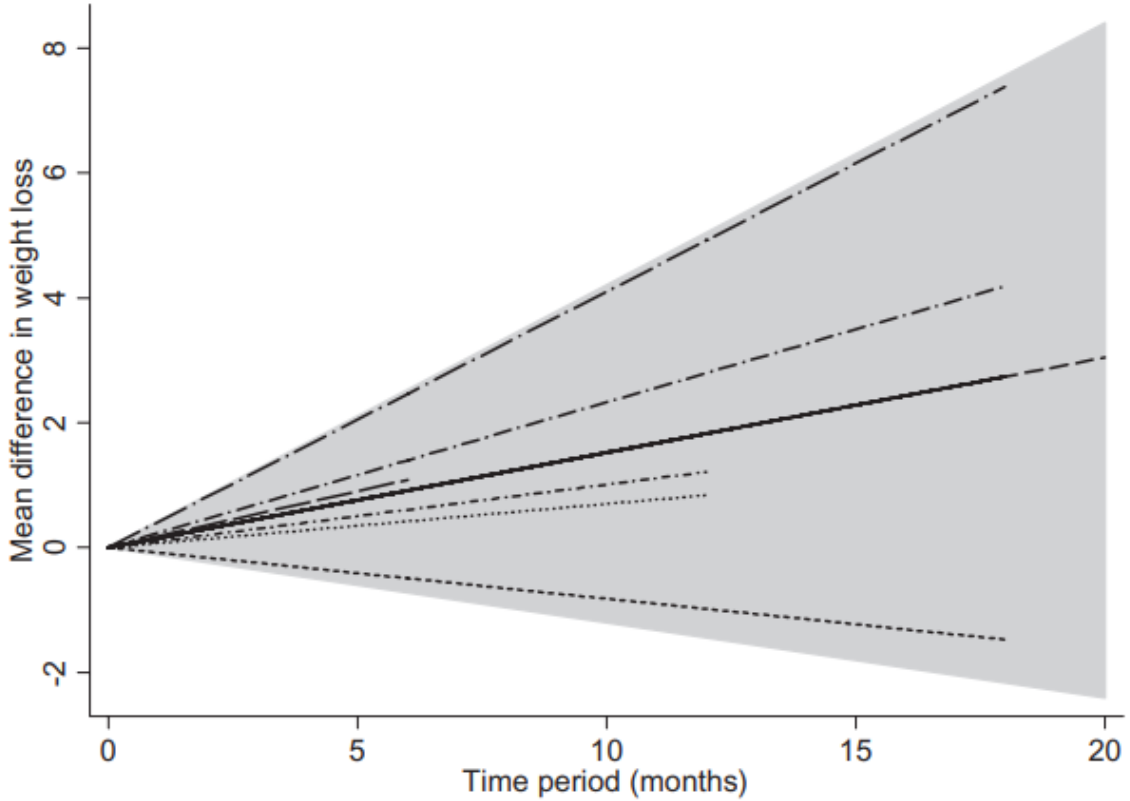


Figure 6 Study-specific (dashed) and pooled slope (bold) estimates with 95% CrI displayed. CrI, credibility interval.

Result

- CTM: change in time meta-analysis
  - The CTM focuses on the change between estimates at successive time-points.
  - Weight loss was defined in mean difference between control and treated subjects at 0 months to be zero.
  - Four different values were considered for the standard deviation at time zero (SD_0) in each primary study
    - SD_0 =0.001;
    - SD_0 = 1
    - SD_0= max (SD_t ; t= 1,….,3)
    - SD_0= 1.2max (SD_t ; t= 1,….,3)

Result

- CTM: change in time meta-analysis
  - Only three studies contributed to the analysis.

CTM

Table 2 Change in effect at different time-points for the Pirozzo *et al.* meta-analysis

Change-point	Median estimate (95% CrI)	I^2
1 ($t_1 - t_0$)	1.93 (–2.66, 6.53)	100%
2 ($t_2 - t_1$)	–0.68 (–1.25, –0.10)	81%
3 ($t_3 - t_2$)	2.41 (–1.56, 6.38)	100%

CrI, credibility interval.

Violating the independence assumption

- In the analysis of the Pirozzo et al. meta-analysis
  - The Bayesian slope estimate based on the pooled means at each time-point (from the ATM) is slightly larger and much more precise (0.18; 95%CrI: 0.09,0.26) than the Bayesian Slope estimated based on the pooled slopes across studies (calculated in the TM) (0.15; ; 95%CrI: 0.12,0.42)
  - This trend is also seen in the results of the simulation study.

Table 3 Application of different repeated measures Bayesian meta-analysis methods to the simulated datasets

Repeated measures meta-analysis method	Mean (standard deviation) slope estimate	Median (95% CrI) slope estimate	Estimate of between-study heterogeneity
Dataset 1			
Slope estimate based on results of ATM	1.36 (0.29)	1.36 (0.79, 1.93)	NA*
Slope estimate from TM	1.38 (0.44)	1.37 (0.58, 2.20)	0.15
Individual participant analysis	1.40 (0.44)	1.40 (0.55, 2.26)	0.42
Dataset 2			
Slope estimate based on results of ATM	1.33 (0.26)	1.33 (0.82, 1.84)	NA*
Slope estimate from TM	1.36 (0.41)	1.35 (0.61, 2.15)	0.15
Individual participant analysis	1.39 (0.43)	1.39 (0.57, 2.23)	0.31
Dataset 3			
Slope estimate based on results of ATM	1.31 (0.25)	1.31 (0.83, 1.80)	NA*
Slope estimate from TM	1.34 (0.39)	1.33 (0.63, 2.11)	0.15
Individual participant analysis	1.38 (0.42)	1.38 (0.58, 2.20)	0.30

ATM, all time-points meta-analysis; CrI, credibility interval; TM, trend meta-analysis.

*An estimate of between-study heterogeneity cannot be obtained with this analysis as the slope is calculated from the pooled means at each time-points (between-study heterogeneity at each time-point can, however, be obtained).

Violating the independence assumption

- It would be more appropriate to calculate a slope by pooling the study-specific slope estimates based on the mean measurements at each time-point within the individual studies, rather than pooling data across studies at each time-point and then calculating the slope estimate.

Sensitivity of prior distributions in Bayesian analysis

- For the TM approach described in this paper, the sensitivity of the prior distribution placed on τ^2 in equation (2) was assessed.

$$\begin{aligned} y_i &\sim N(\theta_i, \sigma_i^2) \quad \mu \sim N(0,100000) \\ \theta_i &\sim N(\mu, \tau^2) \quad \tau \sim N(0,100), \tau > 0 \end{aligned} \qquad (2)$$

Sensitivity of prior distributions in Bayesian analysis

- The following three alternative prior distributions were investigated

$$\frac{1}{\tau^2} \sim gamma(0.01, 0.01)$$

$$\frac{1}{\tau^2} \sim gamma(0.1, 0.1)$$

$$\tau \sim U(0, 100)$$

Sensitivity of prior distributions in Bayesian analysis

- Posterior mean of the pooled effect were unchanged.

- The larger estimates of on τ^2 in lead to wider posterior intervals around the pooled estimates for the half normal and uniform prior distributions.

Sensitivity of prior distributions in Bayesian analysis

- The sensitivity of the between-study heterogeneity estimate is expected given the relatively few data in this meta-analysis and the consequent influence of the prior.
- Nevertheless, the general conclusions are robust to changes in the prior distribution placed on τ^2 .

Discussion

- In this paper, the authors examined a number of approaches for the meta-analysis of repeated measures studies.
- These approaches differ in terms of type of result obtained and the data needed for analysis.
- These differences and the specific research question of the meta-analysis will ultimately lead to the choice of method to use.

Discussion

- In an ideal world, one would want to use the IPD from each study.
- Difficulties in obtaining the full IPD for a meta-analysis limit the applicability and generality of analyses.
- Often the data regarding the individuals is not available for a meta-analysis, so it is difficult to carry out the meta-analysis with the individual as the unit of analysis.

Discussion

- Hence, this assumption may often be violated, which may lead to deflated variance estimates and consequently biased pooled mean estimates.
- The aim of this paper was to compare methods, it was assumed that the data from studies for a meta-analysis are all reported in the same style.

Discussion

- In general, different studies might report different types of summary estimates, for example, some studies may model the time trend using one particular model, while another study may use a different model.
- Further work is required to examine how the different types of summary estimates from each repeated measures study could be meaning fully combined in a meta-analysis.

Thank You

Q&A