Meta-analysis methods used in systematic reviews of interrupted time series studies

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Systematic reviews
Used to inform health policy decision making

Natural disasters?
Organisational practice changes?
Media campaigns?
New laws?
Financial crisis?
Social distancing policies?
Before the mass media campaign  After the mass media campaign

INTERRUPTED TIME SERIES

Before the mass media campaign  
After the mass media campaign

Trend before the campaign
Trend after the campaign observed
Trend after the campaign had the campaign not been introduced  
i.e. the counterfactual

Number of HIV tests

Time (months)
INTERRUPTED TIME SERIES

Before the mass media campaign

After the mass media campaign

Change in slope

Immediate change in level

Number of HIV tests

Time (months)

0  10  20  30
META-ANALYSIS OF ITS 9 different studies
META-ANALYSIS OF ITS

9 different studies

[Graphs showing data over time for different studies, with axes labeled as 'Number of HIV tests' and 'Time (months)']

[Logo of Monash University]
META-ANALYSIS

Statistical synthesis of evidence from multiple studies to produce a combined effect estimate

• Two-stage approach

• One-stage approach
META-ANALYSIS

Statistical synthesis of evidence from multiple studies to produce a combined effect estimate

- Two-stage approach
- Effects calculated for each primary study
- Combined via meta-analysis

- One-stage approach
META-ANALYSIS
Statistical synthesis of evidence from multiple studies to produce a combined effect estimate

• Two-stage approach
• Effects calculated for each primary study
• Combined via meta-analysis

• One-stage approach
• Primary study data are analysed in one model, with an additional parameter to account for each study
A systematic review of methods to meta-analysis results of ITS studies

Objectives are to investigate:

1. Whether reviewers re-analyse primary ITS studies included in reviews, and if so, what re-analysis methods are used;
2. What meta-analysis methods are used;
3. What effect measures are used, and how completely the estimated combined effects are reported; and
4. What tools and domains are used to assess the risks of bias or methodological quality of the included ITS studies.
A systematic review of methods to meta-analysis results of ITS studies

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Systematic review - Methods

Inclusion criteria

1. a review that included at least two ITS studies/series which met the review authors’ definition of an ITS design; and

2. included at least one meta-analysis of ITS studies.
# Systematic review - Methods

## Data extraction

<table>
<thead>
<tr>
<th>Domain</th>
<th>Items</th>
</tr>
</thead>
<tbody>
<tr>
<td>Review characteristics</td>
<td>Author, journal, discipline, PICO elements</td>
</tr>
<tr>
<td>Outcome and studies included</td>
<td>Type of outcome</td>
</tr>
<tr>
<td></td>
<td>Number of ITS studies</td>
</tr>
<tr>
<td>Methods for combining ITS results</td>
<td>One-stage, two-stage meta-analysis</td>
</tr>
<tr>
<td></td>
<td>Re-analysis of primary studies</td>
</tr>
<tr>
<td></td>
<td>Accounting for autocorrelation etc</td>
</tr>
<tr>
<td>Results/Estimates</td>
<td>Type of effect measures</td>
</tr>
<tr>
<td></td>
<td>Level change, slope change, combination of level and slope (counterfactual)</td>
</tr>
<tr>
<td></td>
<td>Completeness of reporting (e.g. combined effect estimate confidence interval, measure of heterogeneity)</td>
</tr>
<tr>
<td>Risk of bias and/or assessment of study quality</td>
<td>Assessment of primary study risk of bias / methodological quality; Tool or domains used for assessment</td>
</tr>
</tbody>
</table>
Systematic review - Results

PRISMA 2009 Flow Diagram

Records identified from:
Databases (n = 4213)

Records removed before screening (n = 1536)

Records screened (n = 2677)

Records excluded (n = 2338)

Full-text articles assessed for eligibility (n = 339)

Records excluded (n = 285)

Studies included in review (n = 54)
Review of studies
n = 34

Primary studies with multiple series
n = 20

Data sources to be meta-analysed

ITS analysis

Analysis approaches

Meta-analysis

Pathway 1: Review of studies
n = 34

Pathway 2: Two-stage, Stage 1: Extraction of primary effects
n = 8

Pathway 3: Two-stage, Stage 2: Meta-analysis of reported effects from primary studies
n = 23

Pathway 4: Two-stage, Stage 1: Can’t determine
n = 2

Pathway 5: Two-stage, Stage 2: Meta-analysis of calculated effects
n = 2

Pathway 6: Two-stage, Stage 1: Reanalysis of individual series
n = 8

One-stage: Analysis of primary studies, accounting for each study source
n = 1

Two-stage, Stage 1: Reanalysis of primary studies
n = 1

Two-stage, Stage 2: Meta-analysis of calculated effects
n = 23

Two-stage, Stage 1: Extraction of primary effects
n = 8

Two-stage, Stage 2: Meta-analysis of calculated effects
n = 2

One-stage: Analysis of all series, accounting for the source of each individual series
n = 2

Two-stage, Stage 2: Meta-analysis of calculated effects
n = 18
Review of studies
n = 34

Primary studies with multiple series
n = 20

Data sources to be meta-analysed

ITS analysis

Meta-analysis

Analysis approaches

Pathway 1

Pathway 2

Pathway 3

Pathway 4

Pathway 5

Pathway 6

One-stage: Analysis of primary studies, accounting for each study source

Two-stage, Stage 1: Reanalysis of primary studies

Two-stage, Stage 2: Meta-analysis of calculated effects

n = 1

n = 23

n = 23

n = 2

n = 2

n = 18

Two-stage, Stage 1: Extraction of primary effects

Two-stage, Stage 2: Meta-analysis of reported effects from primary studies

Two-stage, Stage 1: Can’t determine

Two-stage, Stage 2: Meta-analysis

One-stage: Analysis of all series, accounting for the source of each individual series

Two-stage, Stage 1: Reanalysis of individual series

Two-stage, Stage 2: Meta-analysis of calculated effects
Review of studies  
\( n = 34 \)

Primary studies with multiple series  
\( n = 20 \)

**Data sources to be meta-analysed**

**ITS analysis**

**Pathway 1**
- One-stage: Analysis of primary studies, accounting for each study source
  - \( n = 1 \)

**Pathway 2**
- Two-stage, Stage 1: Reanalysis of primary studies
  - \( n = 1 \)
- Two-stage, Stage 2: Meta-analysis of calculated effects
  - \( n = 23 \)

**Pathway 3**
- Two-stage, Stage 1: Extraction of primary effects
  - \( n = 8 \)

**Pathway 4**
- Two-stage, Stage 2: Meta-analysis of reported effects from primary studies
  - \( n = 2 \)

**Pathway 5**
- Two-stage, Stage 1: Can't determine
  - \( n = 2 \)
- Two-stage, Stage 2: Meta-analysis
  - \( n = 18 \)

**Pathway 6**
- One-stage: Analysis of all series, accounting for the source of each individual series
  - \( n = 2 \)
- Two-stage, Stage 2: Meta-analysis of calculated effects
  - \( n = 2 \)

**Analysis approaches**
Review of studies
n = 34

Primary studies with multiple series
n = 20

Data sources to be meta-analysed

ITS analysis

Analysis approaches

Meta-analysis

Pathway 1

Pathway 2

Pathway 3

Pathway 4

Pathway 5

Pathway 6

One-stage: Analysis of primary studies, accounting for each study source

Two-stage, Stage 1:
Reanalysis of primary studies

Two-stage, Stage 2:
Meta-analysis of calculated effects

n = 1

n = 23

n = 8

n = 2

n = 2

One-stage:
Analysis of all series, accounting for the source of each individual series

Two-stage, Stage 1:
Reanalysis of individual series

Two-stage, Stage 2:
Meta-analysis of calculated effects

n = 1

n = 8

n = 2

n = 18
Review of studies  
*n = 34*

Primary studies with multiple series  
*n = 20*

Data sources to be meta-analysed

- One-stage: Analysis of primary studies, accounting for each study source
- Two-stage, Stage 1: Reanalysis of primary studies
- Two-stage, Stage 2: Extraction of primary effects
- Two-stage, Stage 2: Meta-analysis of reported effects from primary studies
- Two stage, Stage 1: Can’t determine
- One-stage: Analysis of all series, accounting for the source of each individual series
- Two-stage, Stage 1: Reanalysis of individual series
- Two-stage, Stage 2: Meta-analysis of calculated effects

Analysis approaches

- ITS analysis
- Meta-analysis
Review of studies
n = 34

Primary studies with multiple series
n = 20

Data sources to be meta-analysed

ITS analysis

Meta-analysis

Analysis approaches

Pathway 1: Review of studies

Pathway 2: Primary studies with multiple series

Pathway 3: Data sources to be meta-analysed

Pathway 4: ITS analysis

Pathway 5: Meta-analysis

Pathway 6: Number of ITS studies combined in meta-analysis
Median 5 studies, IQR: 3 – 7.5

Number of ITS series combined in a meta-analysis
Median 12 series, IQR: 6 – 26
Data sources to be meta-analysed

Review of studies
\( n = 34 \)

Primary studies with multiple series
\( n = 20 \)

Analysis approaches

ITS analysis

Meta-analysis

One-stage: Analysis of primary studies, accounting for each study source

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Two-stage, Stage 2: Meta-analysis

Pathway 1

Pathway 2

Pathway 3

Pathway 4

Pathway 5

Pathway 6

Provide a definition of ITS: 22/34 (65%)
Combined ITS with other designs: 15/34 (44%)
Assessed Risk of bias: 33/34 (97%)
Review of studies
n = 34

ITS analysis

One-stage: Analysis of primary studies, accounting for each study source

Two-stage, Stage 1: Extraction of primary effects

Two-stage, Stage 2: Meta-analysis of reported effects from primary studies

Two-stage, Stage 2: Meta-analysis of calculated effects

Meta-analysis

Two-stage, Stage 1: Reanalysis of primary studies

Two-stage, Stage 2: Meta-analysis of calculated effects

Primary studies with multiple series
n = 20

One-stage: Analysis of all series, accounting for the source of each individual series

Two-stage, Stage 1: Reanalysis of individual series

Two-stage, Stage 2: Meta-analysis of calculated effects

Analysis approaches

Two-stage meta-analysis
n = 51
51/54 (94%)
Review of studies
n = 34

Primary studies with multiple series
n = 20

Data sources
to be meta-analysed

ITS analysis

Meta-analysis

41/51 (80%) reviews perform their own analysis of the raw ITS data

The most commonly reported reason for re-analysis was to analyse as a time series
Review of studies
n = 34

Primary studies with multiple series
n = 20

Data sources to be meta-analysed

ITS analysis

One-stage: Analysis of primary studies, accounting for each study source

Two-stage, Stage 1: Reanalysis of primary studies

Two-stage, Stage 2: Extraction of primary effects

Two-stage, Stage 2: Meta-analysis of reported effects from primary studies

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Two-stage, Stage 1: Reanalysis of individual series

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Pathway 1

Pathway 2

Pathway 3

Pathway 4

Pathway 5

Pathway 6

Analysis approaches

Meta-analysis

Segmented time series regression: 35/41 (87%)
22% used ARIMA
25% could not determine IF or HOW autocorrelation was adjusted for

Can’t determine: 2/41 (5%)
**Review of studies**

- **n = 34**

**Primary studies with multiple series**

- **n = 20**

**Data sources to be meta-analysed**

**ITS analysis**

- **Pathway 1:**
  - One-stage: Analysis of primary studies, accounting for each study source

- **Pathway 2:**
  - Two-stage, Stage 1: Reanalysis of primary studies
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  - Two-stage, Stage 2: Meta-analysis

- **Pathway 5:**
  - One-stage: Analysis of all series, accounting for the source of each individual series

- **Pathway 6:**
  - Two-stage, Stage 1: Reanalysis of individual series
  - Two-stage, Stage 2: Meta-analysis of calculated effects

**Analysis approaches**

- **n = 8**
- **n = 2**

*Only 50% mentioned autocorrelation*
Review of studies
n = 34

Primary studies with multiple series
n = 20

Data sources to be meta-analysed

ITS analysis

Meta-analysis

Analysis approaches

Pathway 1
Pathway 2
Pathway 3
Pathway 4
Pathway 5
Pathway 6

Immediate level change: 42/51 (82%)
Slope change: 10/51 (19%)
Review of studies
n = 34

Primary studies with multiple series
n = 20

Data sources to be meta-analysed

ITS analysis

One-stage: Analysis of primary studies, accounting for each study source

Two-stage, Stage 1: Reanalysis of primary studies

Two-stage, Stage 1: Extraction of primary effects

Two-stage, Stage 1: Can't determine

One-stage: Analysis of all series, accounting for the source of each individual series

Two-stage, Stage 1: Reanalysis of individual series

Analysis approaches

Meta-analysis

Two-stage, Stage 2:

Meta-analysis of reported effects from primary studies

Two-stage, Stage 2: Meta-analysis

Two-stage, Stage 2:

Meta-analysis of calculated effects

Two-stage, Stage 2:

Meta-analysis of calculated effects

Meta-analysis method
Random effects: 35/51 (69%)
Can’t determine: 2/51 (4%)

Heterogeneity variance estimator
Dersimonian and Laird: 19/51 (37%)
Can’t determine: 14/51 (27%)

Confidence interval method
Wald type 18/51 (35%)
Can’t determine 15/51 (29%)
Review of studies
n = 34

Primary studies with multiple series
n = 20

Data sources to be meta-analysed

ITS analysis

Meta-analysis

Analysis approaches

Pathway 1

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Pathway 5

Pathway 6

One-stage: Analysis of primary studies, accounting for each study source

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Two-stage, Stage 1: Extraction of primary effects

Two-stage, Stage 2: Meta-analysis of calculated effects

Two-stage, Stage 1: Can’t determine

Two-stage, Stage 2: Meta-analysis

49/82 (60%) report a measure of heterogeneity
Review of studies

\[ n = 3 \]

Primary studies with multiple series

\[ n = 20 \]

Data sources to be meta-analysed

- ITS analysis
- Meta-analysis

Analysis approaches

Pathway 1: Analysis of primary studies, accounting for each study source

Two-stage, Stage 1: Reanalysis of primary studies
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\[ n = 3 \]
All meta-analysed immediate level change only
Only one mentioned autocorrelation
Systematic review - Discussion

• ITS studies ARE being meta-analysed!
  • Most often using two-stage meta-analysis approaches

• Reporting of included study designs must be improved

• Reporting of the statistical methods used to analyse the primary ITS studies must be improved
  • Regardless of whether the analysis was performed by the review authors or if they extracted the effect estimates from the primary studies

• Reporting of the meta-analysis methods should be improved
Systematic review - Discussion

- Strengths
  - We followed a pre-specified systematic review protocol
  - Searched several disciplines (public health, economics, psychology and education)
  - Detailed data extraction completed on all studies retrieved by our search

- Limitations
  - Reporting of definition of ITS studies
  - Identifying if ITS studies are included in the meta-analyses
  - We only captured the information reported in the reviews
Systematic review - Conclusions

- There is a necessity for improved reporting on the design and analysis characteristics of ITS studies that are included in meta-analyses.

- The meta-analysis methods used to combine results from the included studies should also be reported fully, including the effect estimator, methods of calculating confidence intervals and levels of between-study heterogeneity.
Thank-you!

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References


Questions?