Duration of untreated psychosis and outcomes

Introduction

The duration of untreated psychosis (DUP) is generally determined as the time from the onset of psychotic symptoms to initiation of treatment or first clinical presentation, when diagnosis of a first episode of psychosis (FEP) may be made. FEP is distinct from diagnosis of a first episode of schizophrenia, which requires particular symptoms to be present for a defined period, whereas FEP can refer to a number of different psychotic disorders. It has been proposed that untreated psychosis may have an inherently “toxic” effect, contributing to psychological deterioration and possibly adverse neural processes with longer DUP being associated with poorer prognosis. DUP is also thought to be a predictor of the likelihood and extent of recovery in first-episode schizophrenia. Consequently, understanding the effects of DUP is particularly important because it is potentially modifiable, and thereby altering prognosis.

Method

We have included only systematic reviews (systematic literature search, detailed methodology with inclusion/exclusion criteria) published in full text, in English, from the year 2000 that report results separately for people with a diagnosis of schizophrenia, schizoaffective disorder, schizophreniform disorder or first-episode schizophrenia. Reviews were identified by searching the databases MEDLINE, EMBASE, CINAHL, Current Contents, PsycINFO and the Cochrane library. Hand searching reference lists of identified reviews was also conducted. When multiple copies of reviews were found, only the most recent version was included. Reviews with pooled data are prioritised for inclusion.

Review reporting assessment was guided by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist that describes a preferred way to present a meta-analysis. Reviews with less than 50% of items checked have been excluded from the library. The PRISMA flow diagram is a suggested way of providing information about studies included and excluded with reasons for exclusion. Where no flow diagram has been presented by individual reviews, but identified studies have been described in the text, reviews have been checked for this item. Note that early reviews may have been guided by less stringent reporting checklists than the PRISMA, and that some reviews may have been limited by journal guidelines.

Evidence was graded using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group approach where high quality evidence such as that gained from randomised controlled trials (RCTs) may be downgraded to moderate or low if review and study quality is limited, if there is inconsistency in results, indirect comparisons, imprecise or sparse data and high probability of reporting bias. It may also be downgraded if risks associated with the intervention or other matters under review are high. Conversely, low quality evidence such as that gained from observational studies may be upgraded if effect sizes are large, there is a dose dependent response or if results are reasonably consistent, precise and direct with low associated risks (see end of table for an explanation of these terms). The resulting table represents an objective summary of the available evidence, although the conclusions are solely the opinion of staff of NeuRA (Neuroscience Research Australia).

Results

We found eight systematic reviews that met our inclusion criteria.

- High quality evidence indicates longer DUP is associated with more social disability for up to 1 year, and moderate quality evidence suggests poorer social functioning in the longer-term (2+ years).
Duration of untreated psychosis and outcomes

- Moderate to high quality evidence indicates longer DUP is associated with increased negative symptoms for up to 8 years. Longer DUP may also be associated with more positive and general symptoms for over 2 years.
- Moderate quality evidence suggests longer DUP is also associated with more depression and anxiety; poorer overall functioning, quality of life, and response to treatment; and reduced likelihood of remission.
- Moderate to low quality evidence suggests brain structural anomalies in people with first-episode psychosis are not consistently associated with length of DUP.
Anderson KK, Rodrigues M, Mann K, Voineskos A, Mulsant BH, George TP, McKenzie KJ

Minimal evidence that untreated psychosis damages brain structures: A systematic review

Schizophrenia Research 2015; 162: 222-233

View review abstract online

<table>
<thead>
<tr>
<th>Comparison</th>
<th>DUP and brain structures in people with first-episode psychosis.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Summary of evidence</td>
<td>Moderate to low quality evidence (large samples, unable to assess consistency or precision, direct) suggests brain structural anomalies are not consistently associated with DUP.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>DUP and brain structure</th>
</tr>
</thead>
<tbody>
<tr>
<td>8 of 43 studies reported a statistically significant association between DUP in first-episode psychosis patients (medicated or not) and brain structure.</td>
</tr>
<tr>
<td>6% of 264 brain structures were found to have a statistically significant association with longer DUP. These were clustered in the parietal lobe (25% of examined structures), thalamus (17% of examined structures), basal ganglia (14% of examined structures), and the frontal lobe (13% of examined structures).</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Consistency in results‡</th>
<th>Unable to assess, no measure of consistence is reported.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Precision in results§</td>
<td>Unable to assess, not confidence intervals are reported.</td>
</tr>
<tr>
<td>Directness of results‖</td>
<td>Direct</td>
</tr>
</tbody>
</table>

Anderson KK, Flora N, Archie S, Morgan C, McKenzie K

Race, ethnicity, and the duration of untreated psychosis: a systematic review

Social Psychiatry Psychiatric Epidemiology 2014; 49: 1161-1174

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| Comparison | DUP in Black (African or Caribbean origin) or Asian vs. White people with first-episode psychosis. |
Duration of untreated psychosis and outcomes

**Summary of evidence**

Moderate quality evidence (large samples, precise, direct, inconsistent) suggests no differences in the duration of untreated psychosis between Black, Asian or White ethnic groups.

### Ethnic differences in DUP

*No significant differences in DUP between Black and White groups;*

- 6 studies, N = 1,930, SMD = 0.01, 95%CI -0.16 to 0.18, p > 0.05, $I^2 = 46.3\%$, $p = 0.097$

*No significant differences in DUP between Asian and White groups;*

- 3 studies, N = 1,004, SMD = -0.001, 95%CI -0.38 to 0.37, p > 0.05, $I^2 = 66.6\%$, $p = 0.050$

Authors report that country of study origin, definition of first episode of psychosis, measurement of ethnicity, and the tool used for measuring and defining the DUP did not explain the heterogeneity in study results.

### Consistency in results

Inconsistent

### Precision in results

Precise

### Directness of results

Direct

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**Boonstra N, Klaassen R, Sytema S, Marshall M, De Haan L, Wunderink L, Wiersma D**

**Duration of untreated psychosis and negative symptoms - A systematic review and meta-analysis of individual patient data**

Schizophrenia Research 2012; 142: 12-19

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### Comparison

Relationship between DUP (measured as time from onset of symptoms to initiation of treatment or contact with services) and negative symptoms.

- All studies reported diagnoses using DSM or ICD diagnostic criteria, and DUP and symptoms were measured using standardized assessment tools.

### Summary of evidence

Moderate to high quality evidence (consistent in the long term, direct, large sample, precise) indicates longer DUP is associated with increased negative symptoms for up to 8 years.

---

**Negative symptoms**
Duration of untreated psychosis and outcomes

**Significant association between longer DUP and increased negative symptoms;**

16 studies, N = 3,339, meta-analysis of individual patient data

1 to 2 years: Fisher's $z = 0.180$, 95%CI 0.086 to 0.274, $I^2 = 75.9\%$

5 to 8 years: Fisher's $z = 0.202$, 95%CI 0.137 to 0.267, $I^2 = 27.3\%$

<table>
<thead>
<tr>
<th>Consistency in results</th>
<th>Consistent in the long-term only.</th>
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</thead>
<tbody>
<tr>
<td>Precision in results</td>
<td>Precise</td>
</tr>
<tr>
<td>Directness of results</td>
<td>Direct</td>
</tr>
</tbody>
</table>

**Doyle R, Turner N, Fanning F, Brennan D, Renwick L, Lawlor E, Clarke M**

First-Episode Psychosis and Disengagement From Treatment: A Systematic Review

Psychiatric Services 2014; 65(50): 603-611

[View review abstract online](#)

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Relationship between DUP and engagement in treatment.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Summary of evidence</td>
<td>Low quality evidence (no measured provided) is uncertain as to the associations between DUP and engagement in treatment.</td>
</tr>
</tbody>
</table>

**Engagement in treatment**

10 studies indicated that approximately 30% of individuals with first-episode psychosis or schizophrenia disengage from services (range 20-40%).

Authors report that the variations in disengagement rates is due to the differences in study setting, type of service provided, and how each study measured disengagement.

The most consistent predictors of disengagement were; comorbid substance abuse/dependence and the involvement/support of family. Less consistent predictors were; greater symptom severity, duration of untreated psychosis, and reduced insight.

<table>
<thead>
<tr>
<th>Consistency in results</th>
<th>Unable to formally assess, appears inconsistent.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Precision in results</td>
<td>Unable to assess</td>
</tr>
<tr>
<td>Directness of results</td>
<td>Direct</td>
</tr>
</tbody>
</table>
## Duration of untreated psychosis and outcomes

**Farooq S, Large M, Nielssen O, Waheed W**

The relationship between the duration of untreated psychosis and outcome in low-and-middle income countries: A systematic review and meta-analysis

**Schizophrenia Research 2009; 109(1-3): 15-23**

View review abstract online

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Relationship between DUP and symptomatology, after treatment disability, cognitive function, and mortality, in low and middle income countries. All studies reported diagnoses using DSM or ICD diagnostic criteria, using corroborative information to measure DUP. None used a structured interview to assess the length of DUP.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Summary of evidence</td>
<td>High quality evidence (large sample, precise, consistent, direct) indicates longer DUP is associated with more social disability by 12 months. Moderate quality evidence (inconsistent) indicates longer DUP is associated with poorer response to treatment by 12 months.</td>
</tr>
</tbody>
</table>

### DUP and total symptoms from baseline to ~12 months post-treatment

*Medium significant association between longer DUP and less reduction in symptoms;* 5 studies, N = 446, r = −0.290, 95%CI −0.483 to −0.069, p < 0.011, Q = 25.2, I² = 84%

### DUP and social disability from baseline to ~12 months post-treatment

*Small to medium association between longer DUP and increased disability;* 4 studies, N = 1,030, r = 0.195, 95%CI 0.126 to 0.262, p < 0.000, Q = 1.245, I² = 0.00

### DUP and mortality rates from baseline to ~12 months post-treatment

1 study found patients with a DUP > 1 year had 6.7 times the mortality of those with DUP < 1 year.

<table>
<thead>
<tr>
<th>Consistency in results</th>
<th>Consistent for disability, inconsistent for symptoms.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Precision in results</td>
<td>Precise for symptoms and disability.</td>
</tr>
<tr>
<td>Directness of results</td>
<td>Direct</td>
</tr>
</tbody>
</table>

**Association between duration of untreated psychosis and outcome in cohorts of first-episode patients: a systematic review**

*Archives of General Psychiatry* 2005; 62(9): 975-83

View review abstract online

### Comparison

<table>
<thead>
<tr>
<th>Relationship between duration of untreated psychosis and outcomes.</th>
</tr>
</thead>
</table>

### Summary of evidence

Moderate quality evidence (medium to large samples, consistent, mostly imprecise, direct) suggests longer DUP is associated with higher ratings of depression, anxiety, negative symptoms, positive symptoms, and lower ratings of overall function, social function and quality of life, and a reduced likelihood of remission.

### Symptoms

Significant correlations were observed by 1 year for all symptom dimensions;

- **Total symptoms:** $N = 385$, $r = 0.282$, 95%CI 0.191 to 0.368, $p < 0.05$
- **Depression and anxiety:** $N = 376$, $r = 0.194$, 95%CI 0.094 to 0.291, $p < 0.05$
- **Negative symptoms:** $N = 779$, $r = 0.176$, 95%CI 0.106 to 0.244, $p < 0.05$
- **Positive symptoms:** $N = 777$, $r = 0.283$, 95%CI 0.216 to 0.347, $p < 0.05$

### Functioning and quality of life

Significant correlations were observed by 1 year for overall and social functioning and quality of life;

- **Overall functioning:** $N = 287$, $r = 0.277$, 95%CI 0.165 to 0.382, $p < 0.05$
- **Social functioning:** $N = 191$, $r = 0.234$, 95%CI 0.093 to 0.366, $p < 0.05$
- **Quality of life:** $N = 403$, $r = 0.251$, 95%CI 0.157 to 0.340, $p < 0.05$

Significant correlations were observed by 2 years for overall functioning and quality of life, but not social functioning;

- **Overall functioning:** $N = 68$, $r = 0.280$, 95%CI 0.045 to 0.486, $p < 0.05$
- **Quality of life:** $N = 164$, $r = 0.200$, 95%CI 0.048 to 0.343, $p < 0.05$
- **Social functioning:** $N = 55$, $r = 0.190$, 95%CI -0.079 to 0.433, $p > 0.05$

### Number of patients in remission
Duration of untreated psychosis and outcomes

Patients with long DUP were significantly less likely to achieve remission;

- At 6 months: N = 266, OR = 3.55, 95%CI 2.03 to 6.18
- At 12 months: N = 133, OR = 2.75, 95%CI 1.14 to 6.64
- At 24 months: N = 206, OR = 2.72, 95%CI 1.20 to 6.17
- At 269 months: N = 491, OR = 2.42, 95%CI 1.51 to 3.86

Authors state that after controlling for pre-morbid adjustment, the association between DUP and outcomes remained statistically significant. The relationship between DUP and positive symptoms seemed particularly robust.

<table>
<thead>
<tr>
<th>Consistency in results</th>
<th>Authors state data was reasonably consistent at 1 year.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Precision in results</td>
<td>Precise for correlation data only.</td>
</tr>
<tr>
<td>Directness of results</td>
<td>Direct</td>
</tr>
</tbody>
</table>

Penttila M, Jaaskelainen E, Hirvonen N, Isohanni M, Miettunen J

Duration of untreated psychosis as predictor of long-term outcome in schizophrenia: systematic review and meta-analysis

The British Journal of Psychiatry 2014; 205: 88-94

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Comparison

Relationship between DUP and long-term outcomes (≥ 2 years).
Mean length of DUP was 61.3 weeks and the percentage of participants with a diagnosis of schizophrenia was 60-100%.

Summary of evidence

Moderate quality evidence (large samples, inconsistent, precise, direct) suggests small effects of longer DUP being associated with poorer long-term outcomes for symptoms, remission and social functioning. There were no associations with the number of hospital admissions, employment or quality of life.

Symptoms and remission > 2 years after first contact with treatment
**Duration of untreated psychosis and outcomes**

**Significant, small effects suggest longer DUP is associated with poorer general symptomatic outcome, more severe positive and negative symptoms, and lesser likelihood of remission:**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Studies</th>
<th>N</th>
<th>r</th>
<th>95% CI</th>
<th>p</th>
<th>I²</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>General symptomatic outcome</td>
<td>15</td>
<td>1,878</td>
<td>-0.15</td>
<td>-0.22 to -0.09</td>
<td>&lt; 0.05</td>
<td>38.9%</td>
<td>0.061</td>
</tr>
<tr>
<td>Positive symptoms</td>
<td>18</td>
<td>2,079</td>
<td>-0.14</td>
<td>-0.22 to -0.07</td>
<td>&lt; 0.05</td>
<td>56.1%</td>
<td>0.002</td>
</tr>
<tr>
<td>Negative symptoms</td>
<td>18</td>
<td>2,079</td>
<td>-0.13</td>
<td>-0.21 to -0.05</td>
<td>&lt; 0.05</td>
<td>66.1%</td>
<td>0.019</td>
</tr>
<tr>
<td>Remission</td>
<td>10</td>
<td>1,656</td>
<td>-0.14</td>
<td>-0.23 to -0.06</td>
<td>&lt; 0.05</td>
<td>54.7%</td>
<td>0.019</td>
</tr>
</tbody>
</table>

No association was found between DUP and the number of hospital admissions:

- 11 studies, r = -0.09, N = 1,123, 95% CI -0.22 to 0.04, p > 0.05, I² = 75.8%, p < 0.001

Meta-regression revealed that longer follow-up resulted in stronger associations between DUP and negative symptoms (p = 0.035), and hospital admissions (p = 0.046).

Higher national income level resulted in stronger correlation between DUP and general symptomatic outcome (p = 0.008) and positive symptoms (p = 0.016).

Sex distribution, age at onset, length of DUP, the proportion of participants with schizophrenia, withdrawal percentage and study design did not affect the correlation between DUP and outcomes.

**Functioning, quality of life, employment > 2 years after first contact with treatment**

**Significant, small effects suggest longer DUP is associated with poorer long-term global outcomes and social functioning:**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Studies</th>
<th>N</th>
<th>r</th>
<th>95% CI</th>
<th>p</th>
<th>I²</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Global outcomes</td>
<td>19</td>
<td>2,190</td>
<td>-0.17</td>
<td>-0.26 to -0.07</td>
<td>&lt; 0.05</td>
<td>73.8%</td>
<td>0.001</td>
</tr>
<tr>
<td>Social functioning</td>
<td>14</td>
<td>1,822</td>
<td>-0.18</td>
<td>-0.27 to -0.09</td>
<td>&lt; 0.05</td>
<td>68.2%</td>
<td>0.0011</td>
</tr>
</tbody>
</table>

No association was found between DUP and employment or quality of life:

- Employment: 7 studies, N = 718, r = -0.05, 95% CI -0.16 to 0.06, p > 0.05, I² = 55.1%, p = 0.038
- Quality of life: 7 studies, N = 772, r = -0.10, 95% CI -0.22 to 0.01, p > 0.05, I² = 55.0%, p = 0.038

Meta-regression revealed longer follow-up resulted in stronger associations between DUP and global outcome (p = 0.035).

**Consistency in results** | Inconsistent
**Precision in results**  | Precise
**Directness of results**  | Direct

Perkins DO, Gu H, Boteva K, Lieberman JA

Relationship between duration of untreated psychosis and outcome in first-episode schizophrenia: a critical review and meta-analysis

American Journal of Psychiatry 2005; 162(10): 1785-804

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Relationship between DUP and response to antipsychotic treatment (3 months to 15 years).</th>
</tr>
</thead>
<tbody>
<tr>
<td>Summary of evidence</td>
<td>Moderate quality evidence (precise, large samples, direct, unable to assess consistency) suggests an association between shorter DUP and greater response to treatment.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Symptoms and functioning</th>
</tr>
</thead>
<tbody>
<tr>
<td>Small significant effects suggest shorter DUP is associated with greater response to treatment;</td>
</tr>
<tr>
<td>Global symptoms: 5 studies, N = 527, ( r = 0.29 ), 95%CI 0.20 to 0.36</td>
</tr>
<tr>
<td>Positive symptoms: 13 studies, N = 1359, ( r = 0.27 ), 95%CI 0.21 to 0.31</td>
</tr>
<tr>
<td>Negative symptoms: 14 studies, N = 1345, ( r = 0.23 ), 95%CI 0.17 to 0.27</td>
</tr>
<tr>
<td>Functioning: 7 studies, N = 646, ( r = 0.21 ), 95%CI 0.13 to 0.28</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Consistency in results</th>
<th>No measure of heterogeneity is provided.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Precision in results</td>
<td>Precise</td>
</tr>
<tr>
<td>Directness of results</td>
<td>Direct</td>
</tr>
</tbody>
</table>

Explanation of acronyms

CI = Confidence Interval, DUP = Duration of Untreated Psychosis, FEP = first-episode psychosis, GP = general practitioner, N = number of participants, \( p \) = statistical probability of obtaining that result (\( p < 0.05 \) generally regarded as significant), \( r \) = correlation coefficient, vs. = versus
Explanation of technical terms

* Bias has the potential to affect reviews of both RCT and studies. Forms of bias include; reporting bias – selective reporting of results; publication bias - trials that are not formally published tend to show less effect than published trials, further if there are statistically significant differences between groups in a trial, these trial results tend to get published before those of trials without significant differences; language bias – only including English language reports; funding bias - source of funding for the primary research with selective reporting of results within primary studies; outcome variable selection bias; database bias - including reports from some databases and not others; citation bias - preferential citation of authors. Trials can also be subject to bias when evaluators are not blind to treatment condition and selection bias of participants if trial samples are small11.

† Different effect measures are reported by different reviews.

Correlation coefficients (eg, r) indicate the strength of association or relationship between variables. They are an indication of prediction, but do not confirm causality due to possible and often unforeseen confounding variables. An r of 0.10 represents a weak association, 0.25 a medium association and 0.40 and over represents a strong association. Unstandardised (b) regression coefficients indicate the average change in the dependent variable associated with a 1 unit change in the dependent variable, statistically controlling for the other independent variables. Standardised regression coefficients represent the change being in units of standard deviations to allow comparison across different scales.

Prevalence refers to how many existing cases there are at a particular point in time. Incidence refers to how many new cases there are per population in a specified time period. Incidence is usually reported as the number of new cases per 100,000 people per year. Alternatively some studies present the number of new cases that have accumulated over several years against a person-years denominator. This denominator is the sum of individual units of time that the persons in the population are at risk of becoming a case. It takes into account the size of the underlying population sample and its age structure over the duration of observation.

Reliability and validity refers to how accurate the instrument is. Sensitivity is the proportion of actual positives that are correctly identified (100% sensitivity = correct identification of all actual positives) and specificity is the proportion of negatives that are correctly identified (100% specificity = not identifying anyone as positive if they are truly not).

Weighted mean difference scores refer to mean differences between treatment and comparison groups after treatment (or occasionally pre to post treatment) and in a randomised trial there is an assumption that both groups are comparable on this measure prior to treatment. Standardised mean differences are divided by the pooled standard deviation (or the standard deviation of one group when groups are homogenous) that allows results from different scales to be combined and compared. Each study’s mean difference is then given a weighting depending on the size of the sample and the variability in the data. 0.2 represents a small effect, 0.5 a medium effect, and 0.8 and over represents a large effect11.

Odds ratio (OR) or relative risk (RR) refers to the probability of a reduction (< 1) or an increase (> 1) in a particular outcome in a
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treatment group, or a group exposed to a risk factor, relative to the comparison group. For example, a RR of 0.75 translates to a reduction in risk of an outcome of 25% relative to those not receiving the treatment or not exposed to the risk factor. Conversely, an RR of 1.25 translates to an increased risk of 25% relative to those not receiving treatment or not having been exposed to a risk factor. An RR or OR of 1.00 means there is no difference between groups. A medium effect is considered if RR > 2 or < 0.5 and a large effect if RR > 5 or < 0.2\(^2\). InOR stands for logarithmic OR where a lnOR of 0 shows no difference between groups. Hazard ratios measure the effect of an explanatory variable on the hazard or risk of an event.

‡ Inconsistency refers to differing estimates of treatment effect across studies (i.e. heterogeneity or variability in results) which is not explained by subgroup analyses and therefore reduces confidence in the effect estimate. I\(^2\) is the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (chance) - 0% to 40%: heterogeneity might not be important, 30% to 60%: may represent moderate heterogeneity, 50% to 90%: may represent substantial heterogeneity and 75% to 100%: considerable heterogeneity. I\(^2\) can be calculated from Q (chi-square) for the test of heterogeneity with the following formula;

\[
I^2 = \left( \frac{Q - df}{Q} \right) 
\times 100\%
\]

§ Imprecision refers to wide confidence intervals indicating a lack of confidence in the effect estimate. Based on GRADE recommendations, a result for continuous
data (standardised mean differences, not weighted mean differences) is considered imprecise if the upper or lower confidence limit crosses an effect size of 0.5 in either direction, and for binary and correlation data, an effect size of 0.25. GRADE also recommends downgrading the evidence when sample size is smaller than 300 (for binary data) and 400 (for continuous data), although for some topics, this criteria should be relaxed\(^1\).
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References