Cerebral Blood Flow & Metabolism - Magnetic Resonance Spectroscopy

Introduction

Magnetic resonance spectroscopy (MRS) is a specialised nuclear imaging technique which utilizes magnetic resonance imaging (MRI) technology to investigate biochemical alterations within tissues of interest. Different biochemicals have distinct peaks along a proton nuclear magnetic resonance (NMR) frequency spectrum and can be used to identify metabolites present in target tissues [1-6].

Two notable methods of MRS are $^{1}$H-MRS (proton-MRS) and $^{31}$P-MRS (phosphorus-MRS). Each technique is sensitive to different metabolic compounds. $^{1}$H-MRS can be used to measure N-acetylaspartate (NAA), an amino acid that is associated with the myelin sheath surrounding neurons, used as a marker of neural viability. Decreased levels of NAA are associated with neuronal death or axonal injury. $^{1}$H-MRS is also used to measure Creatine (Cr), a nitrogenous compound involved in energy metabolism; Glutamate (Glu), a neurotransmitter; and Glutamine (Gln), a synaptic metabolite of glutamate [1-3, 6].

Alternatively, $^{31}$P-MRS is used to visualise phospholipid levels, such as phosphomonoesters (PME) and phosphodiester (PDE) [4-6]. These phospholipids provide information about cellular energy metabolism, membrane synthesis, and neurodevelopment.

Research has identified that compounds such as NAA, Glu and phospholipids may be altered in schizophrenia. Functional activity has been investigated in patients with schizophrenia to identify regions of altered metabolic function compared to healthy controls. Reviews included in this table reflect evidence from whole brain investigations into biochemical activity in the frontal lobe, prefrontal cortex, temporal, occipital and parietal lobes, cerebellum, hippocampus, cingulate cortex, thalamus, striatum and basal ganglia, as well as regions containing cerebral white matter.

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. As part of a wider search for all topics included in the library, reviews on MRS for schizophrenia 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. The decision to include or exclude reviews was conducted in duplicate by two independent reviewers with any disagreements settled by discussion. All quality assessments and data extraction have been completed in duplicate by two reviewers who were not masked to review authors.

Review reporting assessment was guided by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist (formerly the QUOROM statement) which describes a preferred way to present a meta-analysis [7]. Reviews were assigned a low, medium or high possibility of reporting bias* depending on how many items were checked. For instance, a low possibility of bias would be assigned to reviews checking over 66% of items, a medium possibility between 33 and 66% and a high possibility would be given to reviews checking less than 33%. Reviews rated as having a high possibility of reporting bias 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 randomized controlled trials (RCT) may be downgraded to moderate, low or very 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 matter 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)[8]. The resulting table represents an objective summary of the available evidence, although the conclusions are solely the opinion of staff of the Schizophrenia Research Institute.

**Conclusions**

**Conclusions for NAA**

- Moderate to high quality evidence suggests NAA levels (measured as both NAA and NAA/Cr) are decreased both chronic and first-episode in the hippocampus and frontal lobe, particularly the prefrontal cortex and anterior cingulate cortex of schizophrenia patients. Moderate to low quality evidence suggests NAA levels are decreased in the cerebellum, parietal cortex, temporal cortex and thalamus in schizophrenia. In more chronic schizophrenia these differences were extended to also include the cerebellum and posterior cingulate.

- Moderate quality evidence suggests there are NAA reductions in the anterior cingulate and hippocampus of first degree relatives. People at high-risk of schizophrenia showed NAA reductions only in the thalamus.

**Conclusions for glutamate/glutamine**

- Moderate quality evidence suggests Glu and Gln levels are reduced in the dorsolateral prefrontal cortex (DLPFC) of first degree relatives

- Low to moderate quality evidence suggests Glu and Gln levels may be increased in the early stages of disorder and decrease as the disorder progresses or as a result of medication. These increases were observed in early schizophrenia in the anterior cingulate cortex, medial prefrontal
cortex, and thalamus. Decreases were observed in chronic schizophrenia in the anterior cingulate cortex and DLPFC. One study reported hippocampus increases in chronic schizophrenia.

Conclusions for phospholipids

• Moderate quality evidence suggests that PME levels are reduced and PDE levels are increased in the prefrontal cortex and temporal cortex of first episode psychosis

• Moderate quality evidence suggests that PME levels are reduced in the prefrontal cortex of schizophrenia patients

• Low to moderate quality evidence suggests PME levels may be reduced and PDE levels increased in the prefrontal cortex of individuals at high risk of psychosis
**Abbott, C., Bustillo, J.**

**What have we learned from proton magnetic resonance spectroscopy about schizophrenia? A critical update**


[View review abstract online](#)

<table>
<thead>
<tr>
<th>Comparison 1</th>
<th>Comparison of metabolic N-acetyl aspartate (NAA) and Creatine (Cr) activity (measured by $^1$H-MRS) in schizophrenia patients vs. healthy controls (NAA and Cr are reported as a ratio, NAA/Cr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Summary of evidence</td>
<td>Low to moderate quality evidence (small to moderate samples, direct, unable to assess precision or consistency) suggests decreased NAA/Cr levels in chronic schizophrenia only in the DLPFC, posterior cingulate, hippocampus, thalamus and cerebellum when compared to controls. Unclear if differences are statistically significant</td>
</tr>
</tbody>
</table>

**Cortical metabolic activity**

<table>
<thead>
<tr>
<th>Results reported for two observational studies investigating NAA/Cr levels</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 observational studies, N = 115</td>
</tr>
<tr>
<td>Three groups: Early schizophrenia (mean &lt; 2 years); chronic schizophrenia (mean &gt; 6 years); and controls</td>
</tr>
<tr>
<td><strong>DLPFC</strong></td>
</tr>
<tr>
<td>NAA/Cr levels were decreased in chronic schizophrenia only</td>
</tr>
<tr>
<td>No data reported</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Results reported for one observational study investigating NAA/Cr levels</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 observational study, N = 37</td>
</tr>
<tr>
<td><strong>Posterior cingulate cortex</strong></td>
</tr>
<tr>
<td>NAA/Cr levels were decreased in chronic schizophrenia</td>
</tr>
<tr>
<td>No data reported</td>
</tr>
</tbody>
</table>

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<tr>
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<tbody>
<tr>
<td>1 observational study, N = 37</td>
</tr>
<tr>
<td><strong>Medial temporal cortex/hippocampus</strong></td>
</tr>
</tbody>
</table>
## Cerebral Blood Flow & Metabolism - Magnetic Resonance Spectroscopy

<table>
<thead>
<tr>
<th>Metabolic Region</th>
<th>Results</th>
<th>N</th>
<th>Consistency</th>
<th>Directness</th>
<th>Comparison</th>
<th>Summary of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hippocampus</strong></td>
<td>Results reported for one observational study investigating NAA/Cr levels</td>
<td>30</td>
<td>No measure of heterogeneity reported</td>
<td>Direct measures and comparison of metabolic activity</td>
<td>Comparison of metabolic Glu and Gln activity (measured by $^1$H-MRS) in schizophrenia patients vs. healthy controls</td>
<td>Low to moderate quality evidence (small to moderate samples, direct, unable to assess precision or consistency) suggests Glu/Gln levels may be increased in the early stages of disorder and decrease as the disorder progresses or as a result of medication when compared to controls. Unclear if differences are</td>
</tr>
<tr>
<td><strong>Thalamus</strong></td>
<td>Results reported for one observational study investigating NAA/Cr levels</td>
<td>44</td>
<td>No confidence intervals reported</td>
<td>Direct measures and comparison of metabolic activity</td>
<td>Comparison of metabolic Glu and Gln activity (measured by $^1$H-MRS) in schizophrenia patients vs. healthy controls</td>
<td>Low to moderate quality evidence (small to moderate samples, direct, unable to assess precision or consistency) suggests Glu/Gln levels may be increased in the early stages of disorder and decrease as the disorder progresses or as a result of medication when compared to controls. Unclear if differences are</td>
</tr>
<tr>
<td><strong>Vermis and cerebellar cortex</strong></td>
<td>Results reported for one observational study investigating NAA/Cr levels</td>
<td>28</td>
<td>No confidence intervals reported</td>
<td>Direct measures and comparison of metabolic activity</td>
<td>Comparison of metabolic Glu and Gln activity (measured by $^1$H-MRS) in schizophrenia patients vs. healthy controls</td>
<td>Low to moderate quality evidence (small to moderate samples, direct, unable to assess precision or consistency) suggests Glu/Gln levels may be increased in the early stages of disorder and decrease as the disorder progresses or as a result of medication when compared to controls. Unclear if differences are</td>
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statistically significant. These increases were observed in early schizophrenia in the anterior cingulate cortex, medial prefrontal cortex, and thalamus. Decreases were observed in chronic schizophrenia in the anterior cingulate cortex and DLPFC. One study reported hippocampus increases in chronic schizophrenia.

<table>
<thead>
<tr>
<th>Cortical metabolic activity</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Results reported for two observational studies investigating Glu/Gln levels</em></td>
</tr>
<tr>
<td>2 observational studies, N = 102</td>
</tr>
<tr>
<td><strong>DLPFC</strong></td>
</tr>
<tr>
<td>One study reported decreased Glu/Gln levels in chronic schizophrenia</td>
</tr>
<tr>
<td>One study reported increased Glu levels in chronic patients with acute exacerbation</td>
</tr>
<tr>
<td>No data reported</td>
</tr>
</tbody>
</table>

| Results reported for two observational studies investigating Glu/Gln levels |
| 2 observational studies, N = 84 |
| **Anterior cingulate cortex** |
| In antipsychotic naive schizophrenia patients (mean illness duration 1.7 years), only Gln levels were increased |
| In chronic schizophrenia patients, decreased levels of Gln and Glu were reported |
| No data reported |

| Results reported for one observational study investigating Glu/Gln levels |
| 1 observational study, N = 20 |
| **Medial prefrontal cortex** |
| In adolescents with high genetic risk of schizophrenia, both Glu and Gln levels were increased |
| No data reported |

<table>
<thead>
<tr>
<th>Thalamus metabolic activity</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Results reported for two observational studies investigating Glu/Gln levels</em></td>
</tr>
<tr>
<td>2 observational studies, N = 102</td>
</tr>
<tr>
<td><strong>Thalamus</strong></td>
</tr>
<tr>
<td>Gln levels were increased in both antipsychotic naive schizophrenia patients (mean illness duration 1.7 years) and in chronic schizophrenia patients</td>
</tr>
<tr>
<td>No data reported</td>
</tr>
</tbody>
</table>
Hippocampus metabolic activity

Results reported for one observational study investigating Glu/Gln levels

1 observational study, N = 42

Hippocampus

One study reported increased Glu levels in chronic patients with acute exacerbation

No data reported

<table>
<thead>
<tr>
<th>Consistency in results</th>
<th>No measure of heterogeneity reported</th>
</tr>
</thead>
<tbody>
<tr>
<td>Precision in results</td>
<td>No confidence intervals reported</td>
</tr>
<tr>
<td>Directness of results</td>
<td>Direct measures and comparison of metabolic activity</td>
</tr>
</tbody>
</table>


Implications of lipid biology for the pathogenesis of schizophrenia

Australian and New Zealand Journal of Psychiatry, 36:3, p. 355 to 366

View review abstract online

Comparison 1

Comparison of prefrontal cortex phospholipid metabolites (measured by $^{31}$P MRS) in schizophrenia patients at varying illness stages vs. healthy controls

Summary of evidence

Moderate quality evidence (moderate to large samples, direct, unable to assess precision or consistency) suggests that PME levels are reduced in the prefrontal cortex of both first episode psychosis and schizophrenia patients and that increased PDE levels are present in the prefrontal cortex in only first episode psychosis patients when compared to controls. Unclear if differences are statistically significant.

Prefrontal cortex PME levels

Results reported for three observational studies in both drug naive first episode psychosis and newly diagnosed schizophrenia patients

3 observational studies, N = 78
### Cerebral Blood Flow & Metabolism - Magnetic Resonance Spectroscopy

#### Prefrontal cortex PDE levels

<table>
<thead>
<tr>
<th>Results reported for three observational studies in both drug naive first episode psychosis and newly diagnosed schizophrenia patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 observational studies, N = 78</td>
</tr>
<tr>
<td>3 of 3 studies reported increased PDE levels</td>
</tr>
<tr>
<td>No data reported</td>
</tr>
</tbody>
</table>

#### Temporal cortex PME levels

<table>
<thead>
<tr>
<th>Results reported for eleven observational studies in chronic schizophrenia patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>11 observational studies, N = 415</td>
</tr>
<tr>
<td>7 of 11 studies (222/415 patients) reported decreased PME levels</td>
</tr>
<tr>
<td>No data reported</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Consistency in results</th>
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</tr>
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<tbody>
<tr>
<td>Precision in results</td>
<td>No confidence intervals provided</td>
</tr>
<tr>
<td>Directness of results</td>
<td>Direct measures and comparison of lipid metabolism</td>
</tr>
<tr>
<td>Comparison 2</td>
<td>Comparison of temporal cortex phospholipid levels (measured by $^{31}$P MRS) in schizophrenia patients at varying illness stages vs. healthy controls</td>
</tr>
<tr>
<td>Summary of evidence</td>
<td>Moderate quality evidence (moderate size samples, direct, unable to assess precision or consistency) suggests that reduced PME and increased PDE levels are present in the temporal cortex of first episode psychosis patients when compared to controls. Unclear if differences are statistically significant. Data for chronic patients shows no difference in PME levels and inconsistent evidence for PDE levels.</td>
</tr>
</tbody>
</table>

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405 Liverpool Street, Darlinghurst, Sydney NSW 2010, Australia  
Tel: (02) 9295 8688  
Email: library@schizophreniaresearch.org.au  
Web: www.schizophreniaresearch.org.au  
To donate, phone the Institute or visit www.schizophreniaresearch.org.au
Results reported for three observational studies in drug naive first episode psychosis patients

3 observational studies, N = 84
3 of 3 studies reported decreased PME levels
No data reported

Results reported for eleven observational studies in chronic schizophrenia patients

7 observational studies, N = 246
No significant difference in PME levels
No data reported

Temporal cortex PDE levels

Results reported for three observational studies in drug naive first episode psychosis patients

3 observational studies, N = 84
3 of 3 studies reported increased PDE levels
No data reported

Results reported for ten observational studies in chronic schizophrenia patients

7 observational studies, N = 246
3 of 7 studies (130/246 patients) reported increased PDE levels
No data reported

Consistency in results
No measure of heterogeneity reported

Precision in results
No confidence intervals provided

Directness of results
Direct measures and comparison of lipid metabolism

Bruggar S, Davis JM, Leucht S, Stone JM.

Proton magnetic resonance spectroscopy and illness stage in schizophrenia – a systematic review and meta-analysis

Biological Psychiatry, 2011. 69: 495-503

View review abstract online
## Comparison

<table>
<thead>
<tr>
<th>Comparison</th>
</tr>
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<tbody>
<tr>
<td>Comparison of metabolic N-acetyl aspartate (NAA) activity measured by $^1$H-MRS in people at high risk of schizophrenia, first-episode schizophrenia and chronic schizophrenia patients vs. healthy controls</td>
</tr>
</tbody>
</table>

## Summary of evidence

<table>
<thead>
<tr>
<th>Summary of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moderate to high quality evidence (mostly consistent, precise where applicable, direct) suggests decreased NAA levels in first-episode and chronic schizophrenia in the frontal and temporal lobe, thalamus and cerebellum. People at high-risk of schizophrenia showed NAA reductions only in the thalamus.</td>
</tr>
</tbody>
</table>

## NAA metabolic activity

### Frontal lobe

41 (N = 1679) studies found significant medium reductions of NAA in the frontal lobe of people with chronic schizophrenia compared to controls

\[
d = -0.45, \text{95\%CI} -0.63 \text{ to } -0.26, \ p < 0.0001 \\
Q = 209.76, \ p < 0.0001, \ I^2 = 66\%
\]

19 studies (N = 804) found significant medium reductions of NAA in the frontal lobe of people with first-episode schizophrenia compared to controls

\[
d = -0.45, \text{95\%CI} -0.67 \text{ to } -0.23, \ p < 0.0001 \\
Q = 60.76, \ p = 0.001, \ I^2 = 49\%
\]

10 studies (N = 425) found no difference between people at high-risk of psychosis and controls

\[
d = 0.05, \text{95\%CI} -0.33 \text{ to } 0.43, \ p = 0.799 \\
Q = 50.71, \ p < 0.0001, \ I^2 = 68\%
\]

### Temporal lobe

22 studies (N = 1054) found significant large reductions of NAA in the temporal lobe of people with chronic schizophrenia compared to controls

\[
d = -0.60, \text{95\%CI} -0.85 \text{ to } -0.35, \ p < 0.0001 \\
Q = 110.73, \ p < 0.0001, \ I^2 = 69\%
\]

11 studies (N = 421) found significant medium reductions of NAA in the temporal lobe of people with first-episode schizophrenia compared to controls

\[
d = -0.53, \text{95\%CI} -0.69 \text{ to } -0.07, \ p = 0.0025 \\
Q = 48.11, \ p < 0.0001, \ I^2 = 62\%
\]

4 studies (N = 182) found no significant difference between people at high-risk of psychosis and controls, although there was a trend level small to medium size effect

\[
d = -0.38, \text{95\%CI} -0.79 \text{ to } 0.03, \ p = 0.07
\]
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Thalamus

12 studies (N = 546) found significant small to medium reductions of NAA in the thalamus of people with chronic schizophrenia compared to controls

\[ d = -0.32, 95\% CI -0.53 to -0.10, p = 0.004 \]

\[ Q = 25.67, p = 0.14, I^2 = 26\% \]

5 studies (N = 190) found significant medium reductions of NAA in the thalamus of people with first-episode schizophrenia compared to controls

\[ d = -0.40, 95\% CI -0.70 to -0.06, p = 0.02 \]

\[ Q = 9.05, p = 0.25, I^2 = 23\% \]

2 studies (N = 98) found significant medium to large reductions of NAA in the thalamus of people at high-risk of psychosis compared to controls

\[ d = -0.72, 95\% CI not reported, p = 0.0006 \]

\[ Q = 1.83, p = 0.39, I^2 = 0\% \]

Basal ganglia

11 studies (N = 381) found no difference between people with chronic schizophrenia and controls

\[ d = -0.07 95\% CI not reported, p = 0.498 \]

\[ Q = 13.58, p = 0.63, I^2 = 0\% \]

6 studies (N = 216) found significant medium reductions of NAA in the basal ganglia of people with first-episode schizophrenia compared to controls

\[ d = -0.09, 95\% CI not reported, p = 0.599 \]

\[ Q = 10.56, p = 0.23, I^2 = 24\% \]

Cerebellum

5 studies (N = 183) found significant medium reductions of NAA in the cerebellum in people with schizophrenia (all patients) compared to controls

\[ d = -0.50 95\% CI not reported, p = 0.01 \]

\[ Q = 7.72, p = 0.17, I^2 = 35\% \]

Occipital lobe

7 studies (N = 259) found no difference in people with schizophrenia (all patients) compared to controls

\[ d = 0.06 95\% CI not reported, p = 0.64 \]

\[ Q = 10.21, p = 0.42, I^2 = 2\% \]

Parietal lobe

5 studies (N = 175) found no difference in people with schizophrenia (all patients) compared to controls
## Cerebral Blood Flow & Metabolism - Magnetic Resonance Spectroscopy

<table>
<thead>
<tr>
<th>controls</th>
</tr>
</thead>
</table>
| $d = -0.08$ 95%CI not reported, $p = 0.62$  
| $Q = 2.83$, $p = 0.97$, $I^2 = 0\%$ |

<table>
<thead>
<tr>
<th>Consistency in results</th>
<th>Consistent for all except frontal lobe and temporal lobe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Precision in results</td>
<td>Precise where CI is reported</td>
</tr>
<tr>
<td>Directness of results</td>
<td>Direct</td>
</tr>
</tbody>
</table>

### Fenton, W.S, Hibbeln, J., Knable, M.  
**Essential Fatty Acids, Lipid Membrane Abnormalities, and the Diagnosis and Treatment of Schizophrenia**

**Biological Psychiatry 2000; 47:8-21**  
[View review abstract online](#)

### Comparison

Comparison of phospholipid metabolite levels (measured by $^{31}$P MRS) in schizophrenia patients at varying illness stages vs. healthy controls

### Summary of evidence

Low quality evidence (small sample sizes, direct, unable to assess precision or consistency) is unclear as to any difference in phospholipid levels in schizophrenia. Drug naive first episode schizophrenia may be associated with reduced PME and increased PDE levels, while medicated schizophrenia may be associated only with reduced PME levels when compared to controls. Unclear if differences are statistically significant

### Phospholipid levels

*Seven observational studies report on phospholipid levels in schizophrenia*

Two studies, $N = 43$, report reduced PME and increased PDE in drug naive first episode schizophrenia compared to healthy controls  
No data reported

Four studies, $N = 126$, report only reduced PME in medicated schizophrenia compared to control, no difference in PDE
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| No data reported                                                                 |
| Two studies, N not reported, report correlations between reduced PME and negative symptom profiles, as well as WCST performance |
| No data reported                                                                 |

| Consistency in results | No measure of consistency reported |
| Precision in results   | No measure of precision reported   |
| Directness of results  | Direct measures and comparison of phospholipid metabolite levels |

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Fusar-Poli, P., Perez, J., Broome, M., Borgwardt, S., Placentino, A., Caverzasi, E., Cortesi, M., Veggiotti, P., Politi, P., Barale, F., McGuire, P.

Neurofunctional correlates of vulnerability to psychosis: A systematic review and meta-analysis


| Comparison | Whole brain comparison of metabolite levels (measured by $^1$H-MRS) in individuals at high genetic risk of schizophrenia vs. healthy controls (NAA and Cr are reported as a ratio, NAA/Cr) |
| Summary of evidence | Moderate quality evidence (large sample size, direct, unable to assess precision and inconsistency) suggests reduced glutamatergic metabolite levels in the DLPFC, and reduced NAA/Cr in the anterior cingulate cortex and hippocampus of individuals at high genetic risk of schizophrenia (first degree relatives) when compared to controls not at risk. The medial temporal lobe shows no reductions in Gln or Glu. Unclear if differences are statistically significant |

**Metabolite levels**

*Results consider alterations in Glu, Gln, NAA and Cr in individuals with high genetic risk of developing schizophrenia*

Four observational studies, N = 268

*Frontal lobe (DLPFC)*

Reduced Glu/Gln in individuals at high risk of psychosis
Cerebral Blood Flow & Metabolism - Magnetic Resonance Spectroscopy

<table>
<thead>
<tr>
<th>Region</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anterior cingulate</td>
<td>Reduced NAA/Cr in individuals at high risk of psychosis No data reported</td>
</tr>
<tr>
<td>Medial temporal lobe</td>
<td>No difference in glutamatergic metabolite levels No data reported</td>
</tr>
<tr>
<td>Hippocampus</td>
<td>Reduced NAA/Cr in individuals at high risk of psychosis No data reported</td>
</tr>
</tbody>
</table>

Consistency in results: No measured of heterogeneity provided

Precision in results: No confidence intervals provided

Directness of results: Direct measures and comparison of metabolic activity

Comparison 2: Whole brain comparison of metabolite levels (measured by $^{31}$P-MRS) in individuals at high risk of schizophrenia vs. healthy controls

Summary of evidence: Moderate quality evidence (moderate size sample, direct, unable to assess precision and inconsistency) suggests reduced PME levels in the prefrontal cortex of individuals at high risk of psychosis. Also suggested increased PDE levels and disrupted membrane metabolism in the frontal lobes of this high risk group compared to controls not at risk. Unclear if differences are statistically significant

Phospholipid metabolite levels

Results consider alterations in PME and PDE in first degree relatives of schizophrenia patients

Three observational studies, N = 116

Prefrontal cortex

Reduced PME levels and reduced phospholipid synthesis in high risk individuals who later developed schizophrenia

Frontal lobe

Increased PDE levels in high risk individuals; disrupted membrane metabolism; increased phospholipid breakdown
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No data reported

<table>
<thead>
<tr>
<th>Consistency in results</th>
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**Kraguljac NV, Reid M, White D Jones R, den Hollander J, Lowman D, Lahti AC.**

Neurometabolites in schizophrenia and bipolar disorder – a systematic review and meta-analysis

*Psychiatry Research: Neuroimaging, 2012. 203: 111-25*

[View review abstract online](#)

**Comparison**
Whole brain comparison of metabolite levels (measured by $^1$H-MRS) in individuals with schizophrenia vs. healthy controls.

**Summary of evidence**
Moderate quality evidence (mostly inconsistent, precise, direct) suggests reduced NAA levels in the thalamus and frontal lobe, and reduced NAA/Cr in the thalamus, frontal lobe and hippocampus. No differences in Cr or Cho were found.

**Metabolite levels**

**Thalamus**
Significant medium reductions of NAA absolute levels, 8 studies $d = -0.62$, 95%CI $-1.12$ to $-0.13$, $p = 0.01$

Q not reported, $p = 0.001$, $I^2 = 73\%$

When first-episode (unmedicated) and chronic (medicated) schizophrenia were analysed separately, reduced NAA levels were found only for chronic schizophrenia ($d = -0.77$, $p < 0.01$), but not first-episode patients ($d = -0.13$, $p = 0.86$).

Significant medium size effect size shows lower NAA/Cr ratio, 9 studies, $d = -0.37$, 95%CI $-0.58$ to $-0.17$, $p < 0.01$, $I^2 = 6\%$.

There were no differences in:

Cr levels: 8 studies, $d = -0.03$, 95%CI $-0.29$ to $0.23$, $p = 0.81$, $I^2 = 0\%$. 
Cho levels: 8 studies, $d = -0.13$, 95%CI -0.41 to 0.16, $p = 0.38$, $I^2 = 18\%$.
Cho/Cr ratio: 6 studies, $d = -0.02$, 95%CI -0.34 to 0.30, $p = 0.91$, $I^2 = 42\%$.

**Frontal lobe**

Significant medium effect size shows reductions of NAA absolute levels, 11 studies, $d = -0.44$, 95%CI -0.65 to -0.23, $p < 0.001$

Q not reported, $p = 0.39$, $I^2 = 5\%$.

Significant small effect size shows lower NAA/Cr ratio, 16 studies, $d = -0.22$, 95%CI -0.39 to -0.06, $p < 0.01$, $I^2 = 0\%$

There were no differences in:

Cr levels: 10 studies, $d = 0.06$, 95%CI -0.16 to 0.28, $p = 0.58$, $I^2 = 11\%$.

Cho levels: 10 studies, $d = -0.06$, 95%CI -0.27 to 0.15, $p = 0.57$, $I^2 = 0\%$.

Cho/Cr ratio: 13 studies, $d = 0.09$, 95%CI -0.24 to 0.41, $p = 0.61$, $I^2 = 68\%$.

**Hippocampus**

Significant medium to large effect size shows lower NAA/Cr ratio, 8 studies, $d = -0.72$, 95%CI -1.20 to -0.25, $p < 0.01$, $I^2 = 74\%$.

Significant small effect size shows lower Cho/Cr ratio, 5 studies, $d = -0.28$, 95%CI -0.54 to -0.02, $p = 0.03$, $I^2 = 0\%$.

There were no differences in:

NAA levels: 7 studies, $d = -0.82$, 95%CI -1.69 to 0.05, $p = 0.06$, $I^2 = 92\%$.

Cr levels: 7 studies, $d = -0.12$, 95%CI -1.22 to 0.99, $p = 0.84$, $I^2 = 95\%$.

Cho levels: 7 studies, $d = -0.19$, 95%CI -1.09 to 0.71, $p = 0.68$, $I^2 = 93\%$.

**Anterior cingulate cortex**

There were no significant differences in:

NAA levels: 10 studies, $d = -0.22$, 95%CI -0.81 to 0.38, $p = 0.48$, $I^2 = 88\%$.

Cr levels: 10 studies, $d = -0.15$, 95%CI -0.41 to 0.10, $p = 0.23$, $I^2 = 37\%$.

Cho levels: 10 studies, $d = 0.05$, 95%CI -0.15 to 0.24, $p = 0.64$, $I^2 = 0\%$.

**DLPFC**

There were no significant differences in:

NAA levels: 6 studies, $d = -0.46$, 95%CI -1.09 to 0.17, $p = 0.15$, $I^2 = 85\%$. 


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Cr levels: 6 studies, $d = -0.13$, 95%CI -0.10 to 0.36, $p = 0.26$, $I^2 = 0\%$.

Cho levels: 6 studies, $d = 0.15$, 95%CI -0.44 to 0.74, $p = 0.62$, $I^2 = 84\%$.

NAA/Cr ratio: 3 studies, $d = 0.14$, 95%CI -0.72 to 1.00, $p = 0.75$, $I^2 = 86\%$.

Cho/Cr ratio: 2 studies, $d = -0.15$, 95%CI -0.73 to 0.42, $p = 0.60$, $I^2 = 58\%$.

**Basal ganglia**

There were no significant differences in:

- NAA levels: 6 studies, $d = -0.22$, 95%CI -0.48 to 0.05, $p = 0.11$, $I^2 = 0\%$.
- Cr levels: 6 studies, $d = -0.19$, 95%CI -0.59 to 0.21, $p = 0.35$, $I^2 = 53\%$.
- Cho levels: 6 studies, $d = 0.15$, 95%CI -0.37 to 0.68, $p = 0.57$, $I^2 = 84\%$.
- NAA/Cr ratio: 8 studies, $d = -0.16$, 95%CI -0.46 to 0.13, $p = 0.28$, $I^2 = 32\%$.
- Cho/Cr ratio: 6 studies, $d = -0.13$, 95%CI -0.22 to 0.48, $p = 0.47$, $I^2 = 37\%$.

**Temporal lobe**

Significant medium size effect size shows lower NAA/Cr ratio, 7 studies, $d = -0.64$, 95%CI -1.09 to -0.19, $p < 0.01$, $I^2 = 77\%$.

<table>
<thead>
<tr>
<th>Consistency in results</th>
<th>Mostly inconsistent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Precision in results</td>
<td>Mostly inconsistent</td>
</tr>
<tr>
<td>Directness of results</td>
<td>Direct measures and comparison of metabolic activity</td>
</tr>
</tbody>
</table>

**Sanches, R.F., Crippa, J.A., Hallak, J.E., Araujo, D., Zuardi, A.W.**

**Proton magnetic resonance spectroscopy of the frontal lobe in schizophrenics: a critical review of the methodology**

Revista do Hospital das Clinicas; Faculdade de Medicina Da Universidade de Sao Paulo 2004; 59(3):145-152

[View review abstract online](#)

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Comparison of NAA and Cr activity (measured by $^1$H-MRS) in the frontal lobes of schizophrenia patients vs. healthy controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Summary of evidence</td>
<td>Moderate quality evidence (large samples, direct, unable to fully assess precision or consistency) suggests NAA levels are</td>
</tr>
</tbody>
</table>
reduced in the frontal lobe, particularly the DLPFC, cingulate cortex and frontal pole in schizophrenia patients compared to healthy controls. Unclear if differences are statistically significant.

**Overall NAA levels in the frontal lobes**

- 26 observational studies, N = 1127
- 18/26 studies show decreased NAA in schizophrenia patients (N = 781)
- 8/26 studies show no significant difference in NAA levels (N = 346)
- No data reported

**NAA levels in DLPFC**

- 12 observational studies consider NAA levels in DLPFC, N = 586
- 8/12 studies show decreased NAA in schizophrenia patients (N = 346)
- No data reported

**NAA levels in cingulate cortex**

- 10 observational studies consider NAA levels in cingulate cortex, N = 434
- 8/10 studies show decreased NAA in schizophrenia patients (N = 301)
- No data reported

**NAA levels frontal pole**

- 9 observational studies consider NAA levels in frontal pole, N = 338
- 6/9 studies show decreased NAA in schizophrenia patients (N = 252)
- No data reported

<table>
<thead>
<tr>
<th>Consistency in results</th>
<th>No measure of heterogeneity reported, data appears inconsistent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Precision in results</td>
<td>No confidence intervals provided</td>
</tr>
<tr>
<td>Directness of results</td>
<td>Direct measures and comparison of NAA levels</td>
</tr>
</tbody>
</table>

**Steen RG, Hamer RM, Lieberman JA.**

**Measurement of brain metabolites by $^1$H magnetic resonance**
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**spectroscopy in patients with schizophrenia: a systematic review and meta-analysis**


[View review abstract online](#)

| Comparison 1 | Comparison of metabolic NAA activity (measured by $^1$H-MRS) in the hippocampus of schizophrenia patients vs. healthy controls
| | Compares the consistency of measuring NAA as a raw percentage to measuring as a ratio with control data |

| Summary of evidence | Moderate to high quality evidence (large samples, direct, precise inconsistent) suggests that a ratio of patient/control value is a valid method of comparing across studies. Both methods (raw percentage and LS ratio) obtained consistent ratios for reduced NAA levels (measured as both NAA and NAA/Cr) in the hippocampus in schizophrenia patients compared to controls |

<table>
<thead>
<tr>
<th>Meta-analysis of studies reporting NAA/Cr in the hippocampus</th>
</tr>
</thead>
<tbody>
<tr>
<td>8 observational studies, N = 305</td>
</tr>
<tr>
<td>Patient average hippocampus NAA/Cr 88.8% of control levels, SD = 8.7; p &lt;0.0001</td>
</tr>
<tr>
<td>Least squares (LS) mean difference NAA level in patients = 1.47U, 95%CI 1.39 to 1.54</td>
</tr>
<tr>
<td>LS mean difference NAA level in controls = 1.70U, 95%CI 1.63 to 1.77</td>
</tr>
<tr>
<td>LS ratio = 86.5%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Meta-analysis of studies reporting [NAA]</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 observational studies, N = 248</td>
</tr>
<tr>
<td>Patient average hippocampus NAA 85.8% of control levels, SD = 6.1; p &lt;0.0001</td>
</tr>
<tr>
<td>LS mean difference NAA level in patients = 15.37U, 95%CI 14.64 to 16.10</td>
</tr>
<tr>
<td>LS mean difference NAA level in controls = 18.18U, 95%CI 17.45 to 18.90</td>
</tr>
<tr>
<td>LS ratio = 84.5%</td>
</tr>
</tbody>
</table>

| Consistency in results | Significant heterogeneity reported, p <0.0001 |
| Precision in results | Precise, CIs reasonably stringent |
| Directness of results | Direct measures and comparison of of NAA levels |
# Comparison 2

Whole brain comparison of metabolic NAA activity (measured by $^1$H-MRS) in grey and white matter regions in schizophrenia patients vs. healthy controls

## Summary of evidence

Low to moderate quality evidence (sample size unclear, direct inconsistent, unable to assess precision) suggests that NAA may be decreased in the anterior cingulate, hippocampus, cerebellum, parietal cortex, frontal cortex (grey and white matter), temporal cortex (grey and white matter), and thalamus. Unclear if differences are statistically significant

## NAA levels in grey matter regions

<table>
<thead>
<tr>
<th>Region</th>
<th>Observational studies</th>
<th>Patient Average</th>
<th>NAA Level</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Anterior cingulate gyrus</strong></td>
<td>12</td>
<td>95.9%</td>
<td>Control</td>
</tr>
<tr>
<td><strong>Hippocampus</strong></td>
<td>17</td>
<td>88.9%</td>
<td>Control</td>
</tr>
<tr>
<td><strong>Basal ganglia</strong></td>
<td>6</td>
<td>98.5%</td>
<td>Control</td>
</tr>
<tr>
<td><strong>Lenticular nucleus (putamen + globus pallidus)</strong></td>
<td>2</td>
<td>104.5%</td>
<td>Control</td>
</tr>
<tr>
<td><strong>Caudate nucleus</strong></td>
<td>3</td>
<td>100.3%</td>
<td>Control</td>
</tr>
<tr>
<td><strong>Occipital cortex</strong></td>
<td>8</td>
<td>102.8%</td>
<td>Control</td>
</tr>
<tr>
<td><strong>Cerebellum</strong></td>
<td>3</td>
<td></td>
<td>Control</td>
</tr>
</tbody>
</table>
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<table>
<thead>
<tr>
<th>Region</th>
<th>Observational Studies</th>
<th>NAA Level</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Parietal cortex</strong></td>
<td>1</td>
<td>94.0%</td>
</tr>
<tr>
<td><strong>Frontal cortex</strong></td>
<td>25</td>
<td>94.2%</td>
</tr>
<tr>
<td><strong>Posterior cingulate cortex</strong></td>
<td>5</td>
<td>100.0%</td>
</tr>
<tr>
<td><strong>Putamen</strong></td>
<td>7</td>
<td>100.6%</td>
</tr>
<tr>
<td><strong>Striatum (caudate+putamen)</strong></td>
<td>1</td>
<td>112.6%</td>
</tr>
<tr>
<td><strong>Temporal cortex</strong></td>
<td>5</td>
<td>94.0%</td>
</tr>
<tr>
<td><strong>Thalamus</strong></td>
<td>19</td>
<td>96.5%</td>
</tr>
<tr>
<td><strong>NAA levels in white matter regions</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Centrum semiovale (cerebral white matter)</strong></td>
<td>5</td>
<td>100.2%</td>
</tr>
</tbody>
</table>
### Frontal lobe
18 observational studies consider NAA, N unclear
Patient average 94.8% of control levels

### Occipital lobe
1 observational study considers NAA, N unclear
Patient average 96.0% of control levels

### Parietal lobe
2 observational studies consider NAA, N unclear
Patient average 99.0% of control levels

### Temporal lobe
8 observational studies consider NAA, N unclear
Patient average 87.3% of control levels

#### Consistency in results
Significant heterogeneity reported, \( p < 0.0001 \)

#### Precision in results
No confidence intervals provided

#### Directness of results
Direct measures and comparison of NAA levels

#### Comparison 3
Comparison of metabolic N-acetyl aspartate (NAA) activity (measured by \(^1\text{H-MRS}\)) in the frontal lobe of schizophrenia patients vs. healthy controls

#### Summary of evidence
Moderate to high quality evidence (large sample size, precise, direct, inconsistent) suggests schizophrenia patients have NAA reductions in both grey and white matter in the frontal lobe when compared to controls. Unclear if differences are statistically significant

---

**Meta-analysis of studies reporting NAA grey matter levels in the frontal lobe**

16 observational studies consider NAA, N=848
Patient NAA < Control NAA; \( p < 0.0001 \)
Patient average frontal cortex 93.6% of control levels, SD = 11.3
Least squares (LS) mean difference NAA level in patients = 4.12U, 95%CI 4.03 to 4.21
LS mean difference NAA level in controls = 4.31U, 95%CI 4.23 to 4.39
LS ratio = 95.6%

Meta-analysis of studies reporting NAA white matter levels in the frontal lobe

24 observational studies consider NAA, N=518

Patient NAA < Control NAA, p<0.0001

Patient average frontal cortex 93.5% of control levels, SD = 6.2

Least squares (LS) mean difference NAA in patients = 5.98U, 95%CI 5.79 to 6.16

LS mean difference NAA level in controls = 6.48U, 95%CI 6.30 to 6.66

LS ratio = 92.3%

Consistency in results

Significant heterogeneity reported, p <0.0001

Precision in results

Precise, CIs reasonably stringent

Directness of results

Direct measures and comparison of NAA levels

Comparison 4

Comparison of metabolic N-acetyl aspartate (NAA) activity (measured by \(^1H\)-MRS) in the prefrontal cortex of first episode schizophrenia and chronic schizophrenia patients vs. healthy controls

Summary of evidence

Low to moderate quality evidence (moderate to large samples, direct measures, inconsistent, unable to assess precision) suggests NAA levels are reduced in the prefrontal cortex in both first episode and chronic schizophrenia compared to controls. Unclear if differences are statistically significant

NAA levels in first episode schizophrenia

Prefrontal cortex

4 observational studies consider NAA, N = 146

Patient average 82.3% of control levels, SD = 17.8

NAA levels in chronic schizophrenia

Prefrontal cortex

8 observational studies consider NAA, N = 333

Patient average 90.1% of control levels, SD = 5.4
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<table>
<thead>
<tr>
<th>Consistency in results</th>
<th>Significant heterogeneity reported, ( p &lt; 0.0001 )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Precision in results</td>
<td>No confidence intervals reported</td>
</tr>
<tr>
<td>Directness of results</td>
<td>Direct measures and comparison of NAA levels</td>
</tr>
</tbody>
</table>

Explanation of acronyms

CI = Confidence Interval, Cr = Creatine amino acid, DLPFC = dorsolateral prefrontal cortex, Gln = glutamine (glutamate synaptic metabolic), Glu = glutamate neurotransmitter, \(^1\)H-MRS = Proton Magnetic Resonance Spectroscopy, LS = Least Squares mean, N = number of participants, NAA = N-acetylaspartate amino acid, NAA/Cr = ratio of NAA and Cr, \( p \) = statistical probability of obtaining that result (\( p < 0.05 \) generally regarded as significant), \(^{31}\)P-MRS = Phosphorus Magnetic Resonance Spectroscopy, PDE = phosphodiester lipid, PME = phosphomonoester lipid, U = units
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Explanation of technical terms

* Bias has the potential to affect reviews of both RCT and observational studies. Forms of bias include: reporting bias which involves the selective reporting of results; publication bias - trials which 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 small.

† Different effect measures are reported by different reviews.

Weighted mean difference scores refer to mean differences between treatment and comparison groups after treatment (or occasionally pre to post treatment) and in a randomized trial there is an assumption that both groups are comparable on this measure prior to treatment. Standardized mean differences are divided by the pooled standard deviation (or the standard deviation of one group when groups are homogenous) which 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 moderate effect, and 0.8 and over represents a large effect [15].

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

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 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, a 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. A RR or OR of 1.00 means there is no difference between groups. A large effect is considered if RR > 2 or < 0.5 and a very large effect if RR > 5 or < 0.2[16]. 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.

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. Unstandardized (b) regression coefficients indicate the average change in the dependent variable associated with a 1 unit change in the independent variable,
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statistically controlling for the other independent variables. Standardized 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.

‡ 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 considerable heterogeneity and over this is 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[16].

¶ Indirectness of comparison occurs when a comparison of intervention A versus B is not available but A was compared with C and B was compared with C which allows indirect comparisons of the magnitude of effect of A versus B. Indirectness of population, comparator and or outcome can also occur when the available evidence regarding a particular population, intervention, comparator, or outcome is not available so is inferred from available evidence. These inferred treatment effect sizes are of lower quality than those gained from head-to-head comparisons of A and B.

Many thanks to Dr Melissa Green for reviewing the original version of this summary of evidence.

School of Psychiatry, University of New South Wales; Black Dog Institute, Prince of Wales Hospital, Sydney NSW
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References


