TECHNICAL COMMENTARY

Signs and Symptoms – Premorbid Social Dysfunction

Introduction
Subtle deviations in social developmental and functional behaviour during childhood and adolescence may foreshadow the later development of schizophrenia [1]. Studies exploring these social deviations (antecedents) are ideally based on representative, population-based samples that follow the cohort from birth through childhood and adolescence to adulthood. Identification of premorbid social dysfunction may provide unique insights into predictors [2] and the changes in developmental trajectories that may be associated with later development of schizophrenia [1, 2].

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 premorbid social dysfunction 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[3]. 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 randomised 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 or if there is a dose dependent response. We have also taken into account sample size and whether results are consistent, precise and direct with low associated risks (see end of table for an explanation of these terms)[4]. The resulting table represents an objective summary of the
Results

We found two systematic reviews that met our inclusion criteria [1, 2].
Click on review ID for a link to the review’s abstract.
See PRISMA checklists for assessment of reporting transparency.

Conclusions

• The evidence suggests that schizophrenia may be associated with a range of behavioural problems and psychopathology during childhood and early adolescence. These include social anxiety, social maladjustment, deviant behaviour, self-reported delusions, hallucinations and general psychopathology.

• Beginning around age 7 to 8, poor social functioning may be evident. This association may be seen earlier - from age 5 to 6 in high risk children (i.e. those with one or two parents with schizophrenia). In adolescence, poor social functioning may be a specific predictor for a psychotic disorder.

• From age 3 to 6, higher levels of externalizing behaviour may be evident which includes aggression, bullying, disruptiveness, and noncompliance with adults.

• Higher levels of over-reactive behaviours may be apparent from age 7 to 12 in males. In this age group there is no evidence to suggest an increase in fighting, although results were not adjusted or analyzed separately for males and females.

• From age 13 to 17 higher levels of disagreeableness in males and disruptiveness in high risk groups may be apparent with no increase in aggressiveness or negative attitudes.

• Antisocial-externalizing behaviour in preschool, childhood, and in high-risk adolescents may be a specific predictor of schizophrenia, although specificity does not extend to comparisons with mania.

• From age 3 to age 6, higher levels of social withdrawal may be apparent. This is not specific to schizophrenia as it is also related to later development of depression, anxiety, neurosis and mania.

• Behavioural disturbances may be predictive of the later development of schizophrenia. However, the behavioural antecedents of schizophrenia are subtle – individuals who later develop schizophrenia are not marked by extreme deviations in behaviours. Furthermore, most cohort members who exhibit a behavioural feature associated with later schizophrenia do not develop the disorder.
**TECHNICAL COMMENTARY**

**Signs and Symptoms – Premorbid Social Dysfunction**

*Tarbox SI, Pogue-Geile MF.*

**Development of social functioning in preschizophrenia children and adolescents: a systematic review.**

*Psychological Bulletin* 2008; 134(4):561-583

[View review abstract online](#)

<table>
<thead>
<tr>
<th>Comparison 1</th>
<th>Prospective and retrospective assessment of the association between social functioning in childhood and adolescence and the later development of schizophrenia, schizoaffective disorder or another schizophrenia spectrum illness.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Summary of evidence – see below for details</strong></td>
<td>Moderate quality evidence (large samples, observational) suggests that beginning around age 7 to 8, poor social functioning may be related to later development of a schizophrenia spectrum illness. This association may be apparent from age 5 to 6 in high risk children (those with one or two parents with schizophrenia) and in adolescence, poor social functioning may be a specific predictor for a schizophrenia spectrum illness.</td>
</tr>
</tbody>
</table>

**Undifferentiated social functioning – a broad range of social deficits which may include both social withdrawal and antisocial behaviour**

*In infancy (ages 0–2)*

1 birth cohort study – results adjusted for sex

No significant differences in undifferentiated social functioning between infants who later developed a schizophrenia spectrum illness and their non-psychotic siblings measured by ratings of either social over or under responding to the examiner and mother in a clinical setting. There were also no differences when compared to other infants who did not later develop any psychiatric illness.

- Non-psychotic siblings comparison: N = 91, $d^2 = -0.19$, (no $p$-value or CI reported)
- No psychiatric disorder comparison: N = 5839, $d = 0.66$, (no $p$-value or CI)

*In preschool (ages 3-6)*

1 birth cohort and 1 high risk study – results adjusted for sex

1 cohort study reported no significant differences in social over or under responding between preschoolers who later developed a schizophrenia spectrum illness and their non-psychotic siblings or other preschoolers who did not develop any psychiatric illness.

- Non-psychotic siblings comparison: N = 86, $d = 0.08$, (no $p$-value or CI)
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No psychiatric disorder comparison: N = 5590, d = 0.28, (no p-value or CI)

1 high risk study reported a significant, large effect with poorer physician-rated social adjustment in high risk preschoolers (one or both parents diagnosed with schizophrenia) who later developed a schizophrenia spectrum illness compared to high risk preschoolers who did not develop any of these disorders.

N = 92, d = 1.15, p < 0.05 (no CI)

In childhood (ages 7 to 12)

1 birth cohort and 1 high risk study – results adjusted for sex

1 cohort study reported no significant differences in social over or under responding between children who later developed a schizophrenia spectrum illness and their non-psychotic siblings. When compared with other children who did not develop any psychiatric illness there was a significant, medium effect with more over or under responding in children who later developed a schizophrenia spectrum illness.

Non-psychotic siblings comparison: N = 94, d = 0.57, p < 0.10, (no CI)

Other healthy children comparison: N = 4955, d = 0.51, p < 0.005 (no CI)

1 high risk study reported a significant, large effect with more withdrawn or antisocial behaviour (reported by parents, teachers, and/or the child) in high risk children who later developed a schizophrenia spectrum illness compared to both high risk children and to combined high risk and low risk children who did not develop any of these disorders.

High risk vs. high risk: N = 50, d = 1.12, p < 0.05 (no CI)

High risk vs. high + low risk: N = 100, d = 1.56, p < 0.001 (no CI)

In adolescence (ages 13 to 17)

1 high risk study – results adjusted for sex

1 high risk study reported a significant, large effect with more teacher rated passive or disruptive behaviour in high risk adolescents who later developed a schizophrenia spectrum illness compared to both high risk and high + low risk adolescents who did not develop any of these disorders or any other psychiatric disorder, as well as those who developed a non-psychotic disorder.

No schizophrenia illness comparison

High risk vs. high risk: N = 128, d = 1.12, p < 0.001 (no CI)

High risk vs. high + low risk: N = 215, d = 1.20, p < 0.001 (no CI)

No psychiatric disorder comparison

High risk vs. high risk: N = 96, d = 1.23, p < 0.001 (no CI)

High risk vs. high + low risk: N = 156, d = 1.35, p < 0.001 (no CI)
## Signs and Symptoms – Premorbid Social Dysfunction

### Meta-analysis results

**Ages 5 to 12 years only**

Significant medium increase observed in antisocial/externalizing behavior in children who later developed a schizophrenia spectrum illness compared to children who did not develop any psychiatric disorder.

### Antisocial, externalizing behaviours include aggression, bullying, disruptiveness, and noncompliance with adults

<table>
<thead>
<tr>
<th>Consistency ‡</th>
<th>Unable to assess as no pooled data</th>
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</thead>
<tbody>
<tr>
<td>Precision §</td>
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<tr>
<td>Directness ‖</td>
<td>Direct although authors state some measures of antisocial behaviour (e.g. teacher/parent report/interview) are not standardized and so may not be an accurate measurement tool</td>
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<tr>
<td>Comparison 2</td>
<td>Prospective and retrospective assessment of the association between antisocial and externalizing behaviour in childhood and adolescence and the later development of schizophrenia, schizoaffective disorder, or a schizophrenia spectrum illness</td>
</tr>
<tr>
<td>Summary of evidence – see below for details</td>
<td>Moderate quality evidence (large samples, observational, unable to fully assess evidence) suggests that from age 3 to age 6, higher levels of externalizing behaviour may be related to later development of schizophrenia schizoaffective disorder, or a schizophrenia spectrum illness. Higher levels of over-reactive behaviours may be apparent from age 7 to 12 in males only. In this age group, there is no increase in fighting and school misconduct although fighting results have not been adjusted for sex. There are also no differences in disagreeableness, however from age 13 to 17 higher levels of disagreeableness may be apparent in males. Disruptiveness in high risk groups may be apparent and no increase in aggressiveness or negative attitudes is apparent. Authors note that antisocial-externalizing behaviour in preschool, childhood, and in high-risk adolescents may be a specific predictor of schizophrenia, although specificity does not extend to comparisons with mania.</td>
</tr>
</tbody>
</table>
Signs and Symptoms – Premorbid Social Dysfunction

N = unclear, \( d = 0.55 \), range = 0.31 to 0.88, \( p = 0.0001 \) (no CI)

Significant small increase observed in antisocial/externalizing behavior in children who later developed a schizophrenia spectrum illness compared to children who did not develop any of these disorders

N = unclear, \( d = 0.35 \), range = 0.27 to 0.46, \( p = 0.008 \) (no CI)

Significant small increase in antisocial/externalizing behavior in children who later developed a schizophrenia spectrum illness compared to children who later developed depression, anxiety or neurosis, but not mania.

Depression, anxiety or neurosis comparison: \( d = 0.35 \), range = 0.21 to 0.46, \( p = 0.0001 \) (no N or CI)

Mania comparison: N = unclear, \( d = 0.07 \), range = 0.13 to 0.20, \( p = ns \) (no \( p \)-value or CI)

Authors state that the odds of being diagnosed with schizophrenia in adulthood (vs. no diagnosis, depression/anxiety, or neurosis) may be two to three times greater for children with antisocial/externalizing behaviour than for children without

**Individual study results**

*In preschool (ages 3-6)*

1 birth cohort study – results adjusted for sex

1 cohort study reported a significant, medium effect with more externalizing behaviour as reported by parents and teachers using the RCS in preschoolers who later developed a schizophrenia spectrum illness than in preschoolers who did not develop any psychiatric disorder, or who later developed depression or anxiety. There were no differences when compared with preschoolers who later developed mania

No psychiatric disorder comparison: N = 657, \( d = 0.41 \), \( p = 0.02 \) (no CI)

Depression or anxiety comparison: N = 297, \( d = 0.46 \), \( p < 0.02 \) (no CI)

Mania comparison: N = 54, \( d = 0.20 \), \( p = ns \) (no \( p \)-value or CI)

*In childhood (ages 7-12)*

3 birth cohort studies, 2 case-control studies, 1 high risk study

1 birth cohort study reported a significant, large effect with more over-reactive behaviour as reported by teachers using the BSAG in male (not female) children who later developed a schizophrenia spectrum illness than in male children who did not develop any psychiatric disorder or male children who later developed neurosis.

No psychiatric disorder comparison

Males at 7 years: N = 693, \( d = 0.92 \), \( p = 0.001 \) (no CI)

Females at 7 years: N = 725, \( d = 0.25 \), \( p = ns \) (no \( p \)-value or CI)

Males at 11 years: N = 690, \( d = 1.14 \), \( p = 0.001 \) (no CI)

Females at 11 years: N = 718, \( d = 0.42 \), \( p = ns \) (no \( p \)-value or CI)
Neurosis comparison

Males at 7 years: N = 48, d = 0.61, p < 0.05 (no CI)
Females at 7 years: N = 52, d = 0.00, p = ns (no p-value or CI)
Males at 11 years: N = 45, d = 1.05, p = 0.01 (no CI)
Females at 11 years: N = 55, d = -0.44, p = ns (no p-value or CI)

1 birth cohort study (adjusted for sex) reported a significant, medium effect with more externalizing behaviour as reported by teachers using the RCS in children aged 7 and 11 years who later developed a schizophrenia spectrum illness compared to children who did not develop any psychiatric disorder. No significant differences at age 9

7 years: N = 638, d = 0.45, p = 0.02 (no CI)
9 years: N = 656, d = 0.31, p < 0.10 (no CI)
11 years: N = 637, d = 0.56, p < 0.001 (no CI)

The same study reported a significant, medium effect with more externalizing behaviour as reported by parents and teachers using the RCS in 7 year old preschoolers who later developed a schizophrenia spectrum illness compared to preschoolers who developed depression or anxiety. No differences at 9 or 11 years. No difference with those who later developed mania

Depression/anxiety comparison

7 years N = 291, d = 0.43, p < 0.05 (no CI)
9 years N = 300, d = 0.21, p = ns (no p-value or CI)
11 years: N = 296, d = 0.35, p < 0.10 (no CI)

Mania comparison

7 years N = 51, d = 0.16, p = ns (no p-value or CI)
9 years: N = 53, d = 0.05, p = ns (no p-value or CI)
11 years: N = 49, d = -0.13, p = ns (no p-value or CI)

1 birth cohort study reported no differences in any fighting or high level of fighting as reported by teachers using the RCS between children who later developed a schizophrenia spectrum illness and children who did not develop any of these disorders

Any fighting: N = 759, d = 0.27, p = ns (no p-value or CI)
High level of fighting: N = 602, d = 0.46, p < 0.10 (no CI)

1 case-control study reported no differences in disagreeableness as reported in teacher notes between children who later developed a schizophrenia spectrum illness and children who did not develop any of these specific disorders
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Males: N = 32, p = ns (no d, p-value or CI)
Females: N = 46, p = ns (no d, p-value or CI)

1 case-control study (adjusted for sex) reported no differences in school misconduct as reported in school records between children who later developed a schizophrenia spectrum illness and children who did not develop any of these disorders.
N = 808, p = ns (no d, p-value or CI)

1 high risk study (adjusted for sex) reported a significant, medium effect with more behaviour problems as reported by parents in high and low risk children who later developed a schizophrenia spectrum illness than high and low risk children who did not develop any psychiatric disorder. No differences with high and low risk children (for affective/anxiety disorders) who later developed any non-psychotic disorder.

No psychiatric disorder comparison: N = 81, d = 0.69, p = 0.02 (no CI)
Any non-psychotic disorder comparison: N = 103, d = 0.31, p = ns (no d, p-value or CI)

In adolescence (ages 13 - 17)
1 birth cohort, 1 case-control and 1 high risk study
1 birth cohort study (adjusted for sex) reported no differences in aggressive behaviour or negative attitudes at age 13 as measured by the Pintner Inventory, or antisocial behaviour at age 15 as reported by teachers, between adolescents who later developed a schizophrenia spectrum illness and adolescents who did not develop any of these disorders.

Aggressive behaviour at 13 years: N = 4746, p = ns (no d, p-value or CI)
Negative attitudes at 13 years: N = 4746, p = ns (no d, p-value or CI)
Antisocial behaviour at 15 years: N = 4746, p = ns (no d, p-value or CI)

1 case-control study reported significantly more disagreeableness as reported by teachers in males (not females), aged 13 to 18 years who later developed a schizophrenia spectrum illness compared to males aged 13 to 18 who did not develop any of these disorders.
Males: N = 32, p = < 0.01 (no d or CI)
Females: N = 46, p = ns (no d, p-value or CI)

1 high risk study (adjusted for sex) reported a significant, medium effect with more disruptiveness as reported by teachers in high risk children who later developed a schizophrenia spectrum illness than high risk and high + low risk children who did not develop any psychiatric disorder, including a schizophrenia spectrum illness. No differences when compared to high risk children who later developed any non-psychotic disorder.

No psychiatric disorder comparison high risk vs. high risk: N = 102, d = 0.62, p = 0.005 (no CI)
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No psychiatric disorder comparison high risk vs. high + low risk: N = 160, \( d = 0.77 \), \( p = 0.001 \) (no CI)

No schizophrenia illness comparison high risk vs. high + low risk: N = 292, \( d = 0.57 \), \( p = 0.002 \) (no CI)

Non-psychotic disorder comparison: N = 126 \( d = 0.25 \), \( p = \text{ns} \) (no \( p \)-value or CI)

<table>
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<tr>
<th>Consistency</th>
<th>Heterogeneity measures not reported</th>
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<tr>
<td>Precision</td>
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</table>

Comparison 3
Prospective and retrospective assessment of the association between social withdrawal in childhood and adolescence and the later development of schizophrenia, schizoaffective disorder, or a schizophrenia spectrum illness

Summary of evidence
Moderate quality evidence (large samples, unable to fully assess evidence) suggests that from age 3 to age 6, higher levels of social withdrawal may be related to later development of schizophrenia schizoaffective disorder, or a schizophrenia spectrum illness. However this is not specific to schizophrenia, as it is also related to later development of depression, anxiety, neurosis and mania.

Social withdrawal – internalizing behaviors include a preference for solitary activities, disengagement, inhibition, and social anxiety

Meta-analysis results

Age 4 – 9

Significant, small increase observed in social withdrawal in children who later developed a schizophrenia spectrum illness compared to children who did not develop any psychiatric disorder (healthy controls)

\( N = \text{unclear, } d = 0.27, \text{ range } = 0.08 \text{ to } 0.32, \text{ } p = 0.001 \) (no CI)

Significant, small increase observed in social withdrawal in children who later developed a schizophrenia spectrum illness compared to children who did not develop these specific disorders

\( N = \text{unclear, } d = 0.46, \text{ range } = 0.41 \text{ to } 0.51, \text{ } p = 0.001 \) (no CI)

Age 11 years

Significant, medium increase observed in social withdrawal in children who later developed a schizophrenia spectrum illness compared to children who did not develop any psychiatric disorder (healthy controls)
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N = unclear, \( d = 0.56 \), range = 0.49 to 0.63, \( p = 0.0001 \) (no CI)

**In adolescence**

Significant, large increase observed in social withdrawal in children who later developed a schizophrenia spectrum illness compared to children who did not specifically develop these disorders

N = unclear, \( d = 0.81 \), range = 0.28 to 1.25, \( p = 0.0001 \) (no CI)

For high risk adolescents, no differences in social withdrawal compared to high risk adolescents who did not develop any psychiatric disorder (healthy controls)

N = unclear, \( d = 0.23 \), range = 0.17 to 0.28, \( p = 0.065 \) (no CI)

For high risk adolescents, a significant, small increase observed in social withdrawal compared to high risk adolescents who later developed any non-psychotic disorder

N = unclear, \( d = 0.26 \), range = 0.25 to 0.26, \( p = 0.036 \) (no CI)

No differences in social withdrawal in children or adolescents who later developed a schizophrenia spectrum illness compared to children who later developed depression, anxiety, neurosis or mania

Authors state that for children around age 11 with social withdrawal, the odds of being diagnosed with schizophrenia in adulthood (vs. no diagnosis) could be two to three times greater than the odds for children who are not withdrawn. For withdrawn adolescents, the odds of developing schizophrenia (vs. no schizophrenia diagnosis) may be four times greater than for non-withdrawn adolescents

**Individual study results**

**In preschool (ages 3-6)**

2 birth cohort and 1 case-control study

1 cohort study (adjusted for sex) reported a significant, small to medium effect with more solitary play as reported by mothers in preschoolers who later developed a schizophrenia spectrum illness than in preschoolers who did not develop any of these disorders

Age 4: \( N = 4746 \), \( d = 0.41 \), \( p = 0.05 \) (no CI)

Age 6: \( N = 4746 \), \( d = 0.51 \), \( p = 0.05 \) (no CI)

1 cohort study (adjusted for sex) reported no differences in internalizing as measured by parent and teacher rated RCS in preschoolers who later developed a schizophrenia spectrum illness compared to preschoolers who did not develop any psychiatric disorder or who later developed depression/anxiety or mania.

**No psychiatric disorder comparison:** \( N = 639 \), \( d = 0.34 \), \( p = ns \) (no \( p \)-value or CI)

**Depression/anxiety comparison:** \( N = 289 \), \( d = 0.12 \), \( p = ns \) (no \( p \)-value or CI)

**Mania comparison:** \( N = 53 \), \( d = -0.09 \), \( p = ns \) (no \( p \)-value or CI)
1 case-control study (adjusted for sex) reported no differences in disengagement or non-interaction as measured by home video in preschoolers who later developed a schizophrenia spectrum illness compared to their non-psychotic siblings

Disengagement: N = 25, \( p = \) ns (no \( d \), \( p \)-value or CI)
Non-interaction: N = 25, \( p = \) ns (no \( d \), \( p \)-value or CI)

*In childhood (ages 7 - 12)*

2 birth cohort, 2 case-control and 1 high risk study

1 cohort study reported a significant, medium effect with increased under-reaction at age 11, but not 7 as reported by teacher ratings on the BSAG in children who later developed a schizophrenia spectrum illness compared to children who did not develop any psychiatric disorder. No differences in comparison with children who later developed neurosis.

No psychiatric disorder comparison
- Age 7: male N = 693, \( d = 0.32 \), \( p = \) ns (no \( p \)-value or CI)
- Age 7: female N = 725, \( d = 0.23 \), \( p = \) ns (no \( p \)-value or CI)
- Age 11: male N = 690, \( d = 0.50 \), \( p = < 0.05 \) (no CI)
- Age 11: female N = 718, \( d = 0.74 \), \( p = < 0.01 \) (no \( p \)-value or CI)

Neurosis comparison
- Age 7: male N = 48, \( d = 0.29 \), \( p = \) ns (no \( p \)-value or CI)
- Age 7: female N = 52, \( d = 0.07 \), \( p = \) ns (no \( p \)-value or CI)
- Age 11: male N = 45, \( d = 0.30 \), \( p = \) ns (no \( p \)-value or CI)
- Age 11: female N = 55, \( d = 0.22 \), \( p = \) ns (no \( p \)-value or CI)

1 cohort study (adjusted for sex) reported a significant, medium effect with increased internalization at age 11, but not 7 or 9 as reported by parent and teacher ratings on the RCS in children who later developed a schizophrenia spectrum illness compared to children who did not develop any psychiatric disorder. No differences in social isolation or when compared to children who later developed depression, anxiety or mania.

No psychiatric disorder comparison
- Internalization at age 7: N = 616, \( d = 0.32 \), \( p = < 0.10 \) (no CI)
- Internalization at age 9: N = 597, \( d = 0.08 \), \( p = \) ns (no \( p \)-value or CI)
- Internalization at age 11: N = 594, \( d = 0.49 \), \( p = < 0.01 \) (no CI)

Social isolation at age 5-11: N = 678, \( d = 0.17 \), \( p = \) ns (no \( p \)-value or CI)

Depression/anxiety comparison Internalizing
- Internalizing at age 7: N = 279, \( d = 0.20 \), \( p = \) ns (no \( p \)-value or CI)
- Internalizing at age 9: N = 276, \( d = -0.13 \), \( p = \) ns (no \( p \)-value or CI)
**Signs and Symptoms – Premorbid Social Dysfunction**

<table>
<thead>
<tr>
<th>Measure</th>
<th>Sample Size</th>
<th>Effect Size (d)</th>
<th>p-Value</th>
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</thead>
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<tr>
<td>Internalizing at age 11</td>
<td>N = 269</td>
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<tr>
<td>Social isolation at age 5-11</td>
<td>N = 314</td>
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<tr>
<td>Mania comparison</td>
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<tr>
<td>Internalizing at age 7</td>
<td>N = 50</td>
<td>0.18</td>
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<tr>
<td>Internalizing at age 9</td>
<td>N = 47</td>
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<tr>
<td>Internalizing at age 11</td>
<td>N = 46</td>
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<tr>
<td>Social isolation at age 5-11</td>
<td>N = 56</td>
<td>-0.29</td>
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</table>

1 case-control study reported no differences in introversion as reported in teacher’s notes in children who later developed a schizophrenia spectrum illness compared to children who did not develop any of these disorders.

<table>
<thead>
<tr>
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<th>Sample Size</th>
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<td>Introversion - females at age 5-12</td>
<td>N = 46</td>
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1 case-control study (adjusted for sex) reported no differences in disengagement and non-interaction as rated by home video in children who later developed a schizophrenia spectrum illness compared to their non-psychotic siblings.

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<td>Non-interaction at age 8-10</td>
<td>N = 25</td>
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1 high risk study (adjusted for sex) reported a significant medium effect of lower sociability as measured by clinician rated peer interaction in high and low risk children who later developed a schizophrenia spectrum illness compared to high and low risk children who did not develop any psychiatric disorder and compared to those who developed a non-psychotic disorder.

<table>
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<tr>
<td>Non-psychotic disorder comparison, age 11-13</td>
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<td>&lt; 0.02</td>
</tr>
</tbody>
</table>

*In adolescents (aged 13 – 17)*

5 cohort, 2 case-control and 1 high-risk study

1 cohort study (adjusted for sex) reported a significant effect of lower sociability measured by the Pintner Inventory, and social anxiety as measured by teacher questionnaire in adolescents who later developed a schizophrenia spectrum illness compared to adolescents who did not develop any of these disorders.

<table>
<thead>
<tr>
<th>Measure</th>
<th>Sample Size</th>
<th>Effect Size (d)</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pintner Inventory at age 13</td>
<td>N = 4740</td>
<td>0.04</td>
<td>ns</td>
</tr>
<tr>
<td>Teacher questionnaire at age 15</td>
<td>N = 4736</td>
<td>0.23</td>
<td>0.003</td>
</tr>
</tbody>
</table>

No psychiatric disorder comparison, age 11-13: N = 100, d = 0.55, p = < 0.001 (no CI)

Non-psychotic disorder comparison, age 11-13: N = 54, d = 0.46, p = < 0.02 (no CI)
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1 cohort study reported a significant large effect with lower social adeptness/potency as measured by draft-board assessment in male adolescents who later developed a schizophrenia spectrum illness compared to male adolescents who did not develop any of these disorders.

Age 16-17: N = 10,233, \( d = 0.81, p = 0.001 \) (no CI)

1 cohort study reported a significant large effect with lower social adeptness/potency as measured by draft-board assessment in male adolescents who later developed a schizophrenia spectrum illness compared to male adolescents who did not develop any of these disorders.

Age 16-17: N = 1324, \( d = 1.25, p = 0.001 \) (no CI)

1 twin cohort study reported a significant large effect with lower social adeptness/potency as measured by draft-board assessment in male adolescents who later developed a schizophrenia spectrum illness compared to male adolescents who did not develop any of these disorders. No differences when comparing discordant twin pairs.

All twin pairs age 16-17: N = 2228, \( d = 0.83, p = 0.03 \) (no CI)

Discordant twin pairs age 16-17: N = 20, \( d = 0.40, p = \text{ns} \) (no \( p \)-value or CI)

1 cohort study reported a significant small effect with lower social adeptness/potency as measured by draft-board assessment in male adolescents who later developed a schizophrenia spectrum illness compared to male adolescents who did not develop any of these disorders. No differences when compared to male adolescents who later developed mania.

Age 16-17: N = 780, \( d = 0.28, p = 0.002 \) (no CI)

Age 16-17: N = 428, \( d = 0.24, p = \text{ns} \) (no \( p \)-value or CI)

1 case-control study (adjusted for sex) reported significantly less number of social activities as reported in high school yearbook in adolescents who later developed a schizophrenia spectrum illness compared to adolescents who did not develop any of these disorders. No differences when compared to neurosis (stats not reported).

Age 14-18: N = 40, \( p = 0.01 \) (no \( d \) or CI)

1 case-control study reported significantly more introversion as measured by teacher’s notes in female, not male adolescents who later developed a schizophrenia spectrum illness compared to female adolescents who did not develop any of these disorders.

Males aged 13-18: N = 32, \( p = \text{ns} \) (no \( d \), \( p \)-value or CI)

Females aged 13-18: N = 46, \( p = 0.025 \) (no \( d \) or CI)

1 high risk study (adjusted for sex) reported significantly more passivity as measured by teacher's notes.
questionnaire in high risk adolescents who later developed a schizophrenia spectrum illness compared to high or low risk adolescents who did not develop any of these disorders or any psychiatric disorder. There were no differences when the comparison was made between high risk adolescents only or when comparison was with adolescents who developed non-psychotic disorders.

No schizophrenia spectrum disorder comparison high risk vs. high + low risk: N = 292, d = 0.38 p = 0.041 (no CI)

No psychiatric disorder comparison high risk vs. high + low risk: N = 160, d = 0.49 p = 0.015 (no CI)

No psychiatric disorder comparison high risk vs. high risk: N = 102, d = 0.28 p = ns (no p-value or CI)

Non-psychotic disorders comparison high risk vs. high risk: N = 126, d = 0.26 p = ns (no p-value or CI)

The same study reported no differences in peer contact as measured by parent (mother) interview in high risk adolescents who later developed a schizophrenia spectrum illness compared to high or low risk adolescents who did not develop any of these disorders, any psychiatric disorder or any non-psychotic disorder.

No schizophrenia spectrum disorder comparison high risk vs. high + low risk: N = 292, d = 0.25 (no p-value or CI)

No psychiatric disorder comparison high risk vs. high + low risk: N = 160, d = 0.25 p = ns (no p-value or CI)

No psychiatric disorder comparison high risk vs. high risk: N = 102, d = 0.17 p = ns (no p-value or CI)

Non-psychotic disorders comparison high risk vs. high risk: N = 126, d = 0.25 p = ns (no p-value or CI)

<table>
<thead>
<tr>
<th>Consistency</th>
<th>Heterogeneity measures not reported</th>
</tr>
</thead>
<tbody>
<tr>
<td>Precision</td>
<td>CIs not reported</td>
</tr>
<tr>
<td>Directness</td>
<td>Direct although authors state some measures of social withdrawal (e.g. teacher/parent report/interview) are not standardized and so may not be an accurate measurement tool</td>
</tr>
</tbody>
</table>

Welham J, Isohanni M, Jones P, McGrath J.

The Antecedents of Schizophrenia: A Review of Birth Cohort Studies.

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<table>
<thead>
<tr>
<th>Comparison</th>
<th>Prospective assessment of behavioural disturbances in childhood and adolescence and the later development of schizophrenia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Summary of evidence – see below for details</td>
<td>Moderate to high quality evidence (very large samples, consistent, direct, imprecise) suggests that schizophrenia is associated with a range of behavioural problems and psychopathology during childhood and adolescence. These include social anxiety, social maladjustment, deviant behaviour, self-reported delusions, hallucinations and general psychopathology.</td>
</tr>
</tbody>
</table>

### Behavioural disturbances and psychopathology

5 birth cohorts - no meta-analysis

1 British cohort (N = 4746) reported an association of solitary play with later development of schizophrenia (measured by parental interview at age 4 and 6)

- Age 4; OR = 2.1, 95%CI = 0.9 to 4.7
- Age 6; OR = 2.5, 95%CI = 0.8 to 6.9

At age 13, the same cohort reported that social anxiety (measured by Pintner personality inventory) was associated with later development of schizophrenia. No associations were observed with aggression, emotional stability or negative attitudes. No statistics reported.

At age 15, the same cohort reported that teachers report anxiety (OR = 1.3, no CI or p-value reported) and lower IQ (p = 0.009, no CI or OR reported) were associated with later development of schizophrenia

1 British cohort (N = 12,537) reported that at age 7 and 11, social maladjustment (hostile and anxious towards other children and adults) was associated with later development of schizophrenia (p < 0.01, no other stats reported). In boys at age 7 and 11, over-reactive behaviours (anxiety for acceptance, hostility and inconsequential behaviour – measured by teacher rating on Bristol social adjustment guide) and poor concentration was associated with later development of schizophrenia.

By age 11, boys were also rated as depressed. In girls, by age 11, under-reactive behaviour (withdrawal) and depression was associated with later development of schizophrenia.

1 U.S. cohort (N = 8013) reported that deviant behaviour (measured by clinician) was associated with later development of schizophrenia, controlling for age, sex, race, parental education and socio-economic status. Rate of schizophrenia increased with the number of deviant behaviours.
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Age 4; OR = 1.68, 95%CI = 1.14 to 2.46
Age 7; OR = 1.65, 95%CI = 1.13 to 2.41

The same cohort reported that at age 7, social maladjustment was also associated with later development of schizophrenia

1 New Zealand cohort (N = 3801) reported that self-reported delusions and hallucinations (measured by structured diagnostic interview) at age 11 predicted schizophreniform disorder

Those reporting ‘strong’ symptoms; OR = 16.4, 95%CI = 3.9 to 67.8
Those reporting ‘weak’ symptoms; OR = 5.1, 95%CI = 1.7 to 18.3

The same cohort reported that those with schizophreniform disorder showed more internalizing problems in the past year (measured by Rutter Child Scales at age 5, 7, 9 & 11) and a trend towards more externalizing problems, adjusted for sex and socio-economic status. They also reported a higher likelihood of social rejection (measured by parental interview at age 5, 7, 9 & 11)

1 Australian cohort (N = 972) reported that general psychopathology (measured by Achenbach scales, CBCL and self-rated YSR at age 5 and 14) was associated with non-affective psychosis in males and at age 14 for females. Self-reported hallucinatory experiences at age 14 were associated with non-affective psychosis for both males and females

Note: Authors state that the behavioural antecedents of schizophrenia are subtle – individuals who later develop schizophrenia are not marked by extreme deviations in behaviours and most cohort members with a behavioural feature associated with later schizophrenia do not develop the disorder

Consistency | Unable to assess as no pooled data
Precision | Where CIs reported - imprecise
Directness | Direct

Explanation of acronyms

BSAG = Bristol Social Adjustment Guide, CBCL = Child Behavioral Checklist, CI = Confidence Interval, d = Cohen’s d and g = Hedges’ g = standardised mean differences (see below for interpretation of effect size), N = number of participants, OR = odds ratio, ns = not significant, p = statistical probability of obtaining that result (p < 0.05 generally regarded as significant), RCS = Rutter Child Scales, YSR = Youth Self Report
Explanation of technical terms

* Bias has the potential to affect reviews of both RCT and observational studies. Forms of bias include; reporting bias – 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[5].

† Different effect measures are reported by different reviews.

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 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).

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) 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. Less than 0.4 represents a small effect, around 0.5 a medium effect, and over 0.8 represents a large effect[5].

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 medium to large effect is considered if RR > 2 or < 0.5 and a large effect if RR > 5 or < 0.2[6]. lnOR 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 can provide an indirect indication of prediction, but do not confirm causality due to possible and often unforseen 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 independent 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.

‡ Inconsistency refers to differing estimates of 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[5]:

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

§ 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, these criteria should be relaxed[6].

‖ 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 and is therefore 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 Helen J. Stain for reviewing this summary of evidence
The Rural and Remote Mental Health (Orange, NSW) and the University of Newcastle, NSW
Signs and Symptoms – Premorbid Social Dysfunction

References