TECHNICAL COMMENTARY

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Behavioural disturbances & psychopathology

Introduction

Subtle deviations in various developmental trajectories during childhood and adolescence may foreshadow the later development of schizophrenia. Studies exploring these deviations (antecedents) are ideally based on representative, population-based samples that follow the cohort from birth through childhood and adolescence to adulthood. These studies can provide unique insights into the changes in developmental trajectories that may be associated with later development of schizophrenia.

Method

We have included only systematic reviews with detailed literature search, methodology, and inclusion/exclusion criteria that were published in full text, in English, from the year 2000. Reviews were identified by searching the databases MEDLINE, EMBASE, and PsycINFO. Reviews with pooled data are prioritized for inclusion. Reviews reporting fewer than 50% of items on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA[1]) checklist have been excluded from the library. The evidence was graded guided by the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group approach[2]. The resulting table represents an objective summary of the available evidence, although the conclusions are solely the opinion of staff of NeuRA (Neuroscience Research Australia).

Results

We found eight systematic reviews that met our inclusion criteria[3-10].

- Overall, moderate quality evidence suggests schizophrenia is be associated with a range of behavioural problems and psychopathology during childhood and early adolescence. These include ADHD, social anxiety, social maladjustment, deviant behaviour, self-reported delusions, hallucinations, and general psychopathology.
- Moderate quality evidence suggests the prevalence of psychotic experiences in children and adolescents is 9.83%. Prevalence is higher in cross-sectional studies than in longitudinal studies, and in studies using questionnaires rather than interviews to assess psychotic experiences. Children and adolescents who report psychotic experiences had a medium-sized increased risk of developing a psychotic disorder, or any other mental illness, in adulthood.
- The prevalence of hallucinatory experiences in children aged between 7 and 18 years is between 5% and 9%, and between 1% and 13% of these children experience persisting hallucinatory experiences. The odds of transitioning to a psychotic disorder are higher for children who have experienced hallucinatory experiences, than for children who have not experienced hallucinatory experiences.
- From age 3 years, 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. In adolescence, poor social functioning may be a specific predictor for a psychotic disorder.
- From age 3 to 6 years, higher levels of externalising 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 years in males. In this age group there is no evidence to suggest an increase in fighting, although results were not adjusted or analysed separately for males and females.
- From age 13 to 17 years higher levels of disagreeableness in males and disruptiveness in high-risk groups may be

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apparent with no increase in aggressiveness or negative attitudes.

- Antisocial-externalising 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.
- 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 children who exhibit behavioural features associated with later schizophrenia do not develop the disorder.

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Fusar-Poli P, Tantardini M, De Simone S, Ramella-Cravaro V, Oliver D, Kingdon J, Kotlicka-Antczak M, Valmaggia L, Lee J, Millan MJ, Galderisi S, Balottin U, Ricca V, McGuire P

Deconstructing vulnerability for psychosis: Meta-analysis of environmental risk factors for psychosis in subjects at ultra high-risk

European Psychiatry 2017; 40: 65-75

View review abstract online

Comparison	**Childhood and adolescent functioning, social skills, and affective symptoms in people with ultra high-risk (UHR) mental states, which are determined as; attenuated psychotic symptoms, brief and limited intermittent psychotic symptoms, and genetic risk and functional deterioration.**
Summary of evidence	**Moderate quality evidence (large samples, imprecise, inconsistent, direct) suggests large effects of poor social skills and more affective symptoms in the childhood and adolescence of people with UHR mental states. Moderate to low quality evidence (small samples) also suggests large effects of poor functioning.**
Social skills	
A significant, large effect of more social deficits in people with UHR mental states; 15 studies, N = 231,703, OR = 9.709, 95%CI 3.819 to 24.681, $p < 0.001$, $I^2 = 92\%$, $p < 0.001$ There was no evidence of publication bias.	
Affective comorbidities	
A significant, large effect of more prior affective comorbidities in people with UHR mental states; 10 studies, N = 835, OR = 9.555, 95%CI 3.969 to 23.003, $p < 0.001$, $I^2 = 80\%$, $p < 0.001$ Authors report possible publication bias.	
Functioning	
A significant, large effect of poor functioning in childhood in people with UHR mental states; 3 studies, N = 185, OR = 6.10, 95%CI 2.183 to 17.047, $p = 0.001$, $I^2 = 0\%$, $p = 0.741$ *A significant, large effect of poor functioning in early adolescence in people with UHR mental states;* 2 studies, N = 100, OR = 5.70, 95%CI 1.40 to 23.29, $p = 0.015$, $I^2 = 0\%$, $p = 0.355$ *A significant, large effect of poor functioning in late adolescence in people with UHR mental states;*	

2 studies, N = 100, OR = 6.46, 95%CI 1.58 to 26.45, p = 0.009, I^2 = 0%, p = 0.955 There was no evidence of publication bias.	
Consistency in results‡	Consistent for functioning, inconsistent for social deficits and affective comorbidities.
Precision in results§	Imprecise
Directness of results‖	Direct

Healy C, Brannigan R, Dooley N, Coughlan H, Clarke M, Kelleher I, Cannon, M.

Childhood and adolescent psychotic experiences and risk of mental disorder: a systematic review and meta-analysis

Psychological Medicine 2019; 49: 1589-99

View review abstract online

Comparison	**Psychotic experiences in childhood and adolescence and risk of developing schizophrenia.**
Summary of evidence	**Moderate quality evidence (large sample, inconsistent, imprecise, direct) suggests the prevalence of psychotic experiences is 9.83%. Prevalence was higher in cross-sectional studies than in longitudinal studies, and in studies using questionnaires rather than interviews to assess psychotic experiences. Children and adolescents who report psychotic experiences had a medium-sized increased risk of developing a psychotic disorder, or any other mental illness.**
Psychotic experiences	
12 community samples, N = 29,517, prevalence of psychotic experiences = 9.83% The prevalence in cross-sectional studies was higher than in longitudinal studies (16.11% vs. 7.41%). The prevalence in questionnaire-based studies was higher than in interview-based studies (11.83% vs. 9.12%). *Psychotic experiences were associated with a medium-sized increased risk of a psychotic disorder;* 5 longitudinal studies, N = 11,039, OR = 3.96, 95%CI 2.03 to 7.73, p < 0.05, I^2 = 70% *Psychotic experiences were also associated with an increased risk of any mental disorder;* 12 studies, OR = 3.08, 95%CI 2.26 to 4.21, p < 0.05, I^2 = 59% Results were similar in cross-sectional and longitudinal studies.	

Consistency in results	Inconsistent
Precision in results	Imprecise
Directness of results	Direct

Linscott R J, van Os J

An updated and conservative systematic review and meta-analysis of epidemiological evidence on psychotic experiences in children and adults: on the pathway from proneness to persistence to dimensional expression across mental disorders

Psychological Medicine 2013; 43: 1133-1149

View review abstract online

Comparison	**Psychotic experiences in childhood and adulthood.**
Summary of evidence	**Moderate quality evidence (large samples, inconsistent, unable to assess precision, direct) suggests overall annual incidence of psychotic experiences is 2.5% and prevalence is 7.2%. 20% of people reporting psychotic experiences report persistent experiences, although only 7.4% develop a psychotic disorder.**

Psychotic experiences

Estimates of the incidence and prevalence of psychotic experiences from 61 large cohorts:

Median annual incidence: 2.5%

Median prevalence: 7.2%

Of those who report psychotic experiences, around 20% report persistent psychotic experiences.

Of those with baseline psychotic experiences, 7.4% developed a psychotic disorder; no evidence that disorder outcomes were associated with baseline prevalence of psychotic disorders which may be due to low statistical power and/or differences in methods of classification of disorder across studies.

Rates were higher in samples comprising those that were; lower paid, ethnic, unmarried, young, misusing alcohol or cannabis, exposed to stressful life events, had a family history of mental illness. After removal of outliers, relationships were also observed with higher urbanicity, unemployment and lower education. Psychotic experiences were more commonly reported in studies using self-report methods than in studies using interview methods.

Consistency in results	Authors report high heterogeneity in overall incidence and

	prevalence rates.
Precision in results	Unable to assess
Directness of results	Direct

Matheson S, Vijayan H, Dickson H, Shepherd A, Carr V, Laurens K

Systematic meta-analysis of childhood social withdrawal in schizophrenia, and comparison with data from at-risk children aged 9-14 years

Journal of Psychiatric Research 2013; 47(8): 1061-8

View review abstract online

Comparison	**Childhood social withdrawal (9-14 years) in adults with schizophrenia vs. controls.**
Summary of evidence	**Moderate quality evidence (large samples, inconsistent, imprecise, direct) suggests a large effect of increased social withdrawal in the childhood of patients with schizophrenia.**
Social withdrawal	
A large effect of increased childhood social withdrawal in patients with schizophrenia vs. controls: 6 studies, N = 3,828, d = 1.035, 95%CI 0.304 to 1.766, p = 0.006, I^2 91%, p < 0.0001 Note: authors reported results of a primary study that also indicated a large effect of increased social withdrawal in children 9-14 years who were displaying psychotic-like-experiences, and other antecedents of schizophrenia (d = 0.743, p = 0.001). A medium size effect was reported in children with a family history of schizophrenia (d = 0.442, p = 0.051).	
Consistency in results	Inconsistent
Precision in results	Imprecise
Directness of results	Direct

Nourredine M, Gering A, Fourneret P, Rolland B, Falissard B, Cucherat M, Geoffray MM, Jurek L

Association of Attention-Deficit/Hyperactivity Disorder in Childhood and

Adolescence with the Risk of Subsequent Psychotic Disorder: A Systematic Review and Meta-analysis

JAMA Psychiatry 2021; 78(5): 519-29

View review abstract online

Comparison	**ADHD in childhood and subsequent psychotic disorder.**
Summary of evidence	**Moderate to high quality evidence (large sample, consistent, precise, direct) suggests a significant, large effect showed a diagnosis of ADHD in childhood was associated with an increase in the risk of subsequent psychotic disorder.**
ADHD	
A significant, large effect showed a diagnosis of ADHD in childhood was associated with an increase in the risk of subsequent psychotic disorder; 12 studies, N = 1.85, OR/HR = 4.74, 95%CI 4.11 to 5.46, I^2 = 43%, p = 0.11 There were no moderating effects of diagnosis (any psychotic disorder vs. schizophrenia), study design (cohort vs. case-control), country, adjusted vs. unadjusted ORs, sex, or study bias score.	
Consistency in results	Consistent
Precision in results	Imprecise
Directness of results	Direct

Rubino J, Sanjuan J, Florez-Salamanca L, Cuesta M

Examining the course of hallucinatory experiences in children and adolescents: A systematic review

Schizophrenia Research 2012; 138: 248-254

View review abstract online

Comparison	**Incidence and persistence of hallucinatory experiences in children in both clinical and community settings.** **Note: samples were subclinical, without any diagnosis at baseline.**
Summary of evidence	**Moderate quality evidence (large samples, unable to assess consistency or precision, direct) suggests the prevalence of**

	hallucinatory experiences in children aged between 7 and 18 years is between 5% and 9%, and between 1% and 13% of these children experience persisting hallucinatory experiences over time. The odds of transitioning to a psychotic disorder are higher for children experiencing hallucinatory experiences.
Hallucinatory experiences	
6 longitudinal studies (N = 9,573) were conducted in a community setting, comprising children and adolescents age 7 to 18 years, with 2 to 15 year follow up; Baseline prevalence of hallucinatory experiences: 4.9% to 9.0% Ongoing prevalence of hallucinatory experiences: 0.9% to 13.4%, with studies of longer duration reporting lowest prevalence over time. Discontinuation rates of hallucinations each year, during the follow-up period: 3.0% to 40.7%, with shorter studies reporting higher rates of discontinuation. 2 studies reported significant associations between baseline hallucinations and psychotic disorders at follow up: OR = 16.4 at 15 years, and OR = 5.1 for males and OR = 2.3 for females at 7 years. *5 longitudinal studies (N = 164) were conducted in a clinical setting, comprising children and adolescents age 5 to 20 years, with 1 to 17 year follow up:* 5 studies concluded that hallucinatory experiences had discontinued by follow-up for most of the cases. However, children with greater severity of the hallucinatory experiences and other psychological comorbidities showed an increased risk of symptom persistence.	
Consistency in results	Unable to assess; no measure of consistency is reported.
Precision in results	Unable to assess; no measure of precision is reported.
Directness of results	Direct

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

Comparison 1	**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.**

Summary of evidence	**Moderate quality evidence (large samples, unable to assess consistency or precision, direct) 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.**

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

<u>In infancy (ages 0–2)</u>

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* = -0.19, (no *p*-value or CI reported)

No psychiatric disorder comparison: N = 5,839, *d* = 0.66, (no p-value or CI)

<u>In preschool (ages 3-6)</u>

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)

No psychiatric disorder comparison: N = 5,590, *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).

<u>In childhood (ages 7 to 12)</u>

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)

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Other healthy children comparison: N = 4,955, *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 riskand 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) <u>In adolescence (ages 13 to 17)</u> 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 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) Non-psychotic disorder comparison High risk vs. high risk: N = 62, *d* = 0.94, *p* < 0 .02 (no CI) High risk vs. high + low risk: N = 59, *d* = 1.03, *p* < 0 .001 (no CI)	
Consistency in results	Unable to assess; no measure of consistency is reported.
Precision in results	Unable to assess; no measure of precision is reported.
Directness of results	Direct although authors state some measures of antisocial behaviour (e.g. teacher/parent report/interview) are not standardised and so may not be an accurate measurement tool.
Comparison 2	**Prospective and retrospective assessment of the association between antisocial and externalising behaviour 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 assess consistency or precision, direct) suggests that from age 3 to age 6, higher levels of externalising 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-externalising 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.**
Antisocial, externalising behaviours include aggression, bullying, disruptiveness, and noncompliance with adults	
Ages 5 to 12 years only Significant medium increase observed in antisocial/externalising behavior in children who later developed a schizophrenia spectrum illness compared to children who did not develop any psychiatric disorder; N = unclear, *d* = 0.55, range = 0.31 to 0.88, *p* = 0.0001 (no CI) Significant small increase observed in antisocial/externalising 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/externalising 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/externalising behaviour than for children without. In preschool (ages 3-6 years) 1 birth cohort study – results adjusted for sex 1 cohort study reported a significant, medium effect with more externalising 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 years)

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 externalising 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 externalising 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;

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)

<u>In adolescence (ages 13 - 17)</u>

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) 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* = ns (no *p*-value or CI)	
Consistency in results	Unable to assess; no measure of consistency is reported.
Precision in results	Unable to assess; no measure of precision is reported.
Directness of results	Direct although authors state some measures of antisocial behaviour (e.g. teacher/parent report/interview) are not standardised and so may not be an accurate measurement tool.
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 assess consistency or precision, direct) 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 – internalising behaviors include a preference for solitary activities, disengagement, inhibition, and social anxiety	
Pooled results <u>Age 4 – 9 years</u> 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 = unclear, *d* = 0.27, range = 0.08 to 0.32, *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 = unclear, *d* = 0.46, range = 0.41 to 0.51, *p* = 0.001 (no CI) <u>Age 11 years</u> 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;

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;

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;

N = unclear, range = -0.06 to 0.24, *p* = ns (no *d, p*-value or CI)

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 internalising 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

Margarete Ainsworth Building, Barker Street, Randwick NSW 2031. Phone: 02 9399 1000. Email: info@neura.edu.au

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)

<u>In childhood (ages 7 - 12)</u>

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 Internalising

Internalising at age 7: N = 279, *d* = 0.20, *p* = ns (no *p*-value or CI)

Internalising at age 9: N = 276, *d* = -0.13, *p* = ns (no *p*-value or CI)

Internalising at age 11: N = 269, *d* = 0.20, *p* = ns (no *p*-value or CI)

Social isolation at age 5-11: N = 314, *d* = 0.01, *p* = ns (no *p*-value or CI)

Mania comparison

Internalising at age 7: N = 50, *d* = 0.18, *p* = ns (no *p*-value or CI)

Internalising at age 9: N = 47, *d* = -0.10, *p* = ns (no *p*-value or CI)

Internalising at age 11: N = 46, *d* = 0.04, *p* = ns (no *p*-value or CI)

Social isolation at age 5-11: N = 56, *d* = -0.29, *p* = ns (no *p*-value or CI)

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;

Introversion - males at age 5-12: N = 32, *p* = ns (no *d, p*-value or CI)

Introversion - females at age 5-12: N = 46, *p* = ns (no *d, p*-value or CI)

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;

Disengagement at age 8-10: N = 25, *p* = ns (no *d, p*-value or CI)

Non-interaction at age 8-10: N = 25, *p* = ns (no *d, p*-value or CI)

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;

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)

<u>In adolescents (aged 13 – 17)</u>

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;

Pintner Inventory at age 13: N = 4740, *p* = 0.04 (no *d* or CI)

Teacher questionnaire at age 15: N = 4736, *d* = 0.23, *p* = 0.003 (no *d* or 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 = 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* = 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* = 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;

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

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* = 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 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)	
Consistency in results	Unable to assess; no measure of consistency is reported.
Precision in results	Unable to assess; no measure of precision is reported.
Directness of results	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

Welham J, Isohanni M, Jones P, McGrath J

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

Schizophrenia Bulletin 2009; 35(3): 603-623

View review abstract online

Comparison	**Prospective assessment of behavioural disturbances in childhood and adolescence and the later development of schizophrenia.**
Summary of evidence	**Moderate to high quality evidence (large samples, consistent, imprecise, direct) 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.**
Behavioural disturbances and psychopathology	
5 birth cohorts - no meta-analysis 1 British cohort (N = 4,746) 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 = 8,013) 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. The same cohort reported that at age 7, social maladjustment was also associated with later development of schizophrenia; Age 4; OR = 1.68, 95%CI = 1.14 to 2.46 Age 7; OR = 1.65, 95%CI = 1.13 to 2.41 1 New Zealand cohort (N = 3,801) 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 internalising problems in the past year (measured by Rutter Child Scales at age 5, 7, 9 & 11) and a trend towards more externalising 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.	
Consistency in results	Unable to assess; no measure of consistency is reported.
Precision in results	Unable to assess; no measure of precision is reported.
Directness of results	Direct

Explanation of acronyms

BSAG = Bristol Social Adjustment Guide, CBCL = Child Behavioral Checklist, CI = confidence interval, *d* = Cohens d, measure of standardised mean difference between groups, HR = hazard ratio, I^2 = degree of heterogeneity between study results, LR = positive likelihood ratios, 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, vs. = versus, 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 tath 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[11].

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† 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 randomised trial there is an assumption that both groups are comparable on this measure prior to treatment. Standardised mean differences are divided by the pooled standard deviation (or the standard deviation of one group when groups are homogenous) that allows results from different scales to be combined and compared. Each study's mean difference is then given a weighting depending on the size of the sample and the variability in the data. 0.2 represents a small effect, 0.5 a medium effect, and 0.8 and over represents a large treatment effect[11].

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, an RR of 1.25 translates to an increased risk of 25% relative to those not receiving treatment or not having been exposed to a risk factor. An RR or OR of 1.00 means there is no difference between groups. A medium effect is considered if RR > 2 or < 0.5 and a large effect if RR > 5 or < 0.2[12]. 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.

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

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

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 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 dependent variable, statistically controlling for the other independent variables. Standardised regression coefficients represent the change being in units of standard deviations to allow comparison across different scales.

‡ Inconsistency refers to differing estimates of treatment effect across studies (i.e. heterogeneity or variability in results) that is not explained by subgroup analyses and therefore reduces confidence in the effect estimate. I^2 is the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (chance) - 0% to 40%: heterogeneity might not be important, 30% to 60%: may represent moderate heterogeneity, 50% to 90%: may represent substantial heterogeneity and 75% to 100%: considerable heterogeneity. I^2 can be calculated from Q (chi-square) for the test of heterogeneity with the following formula[11];

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

§ 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[13].

‖ 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 that 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.

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