Psychological Medicine

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Academic achievement and schizophrenia: a systematic meta-analysis

Hannah Dickson[1,*], Emily P. Hedges[1,2,*], Shin Y. Ma[1], Alexis E. Cullen[2], James H. MacCabe[2], Matthew J. Kempton[2], Johnny Downs[3] and Kristin R. Laurens[2,4,5]

[1]Department of Forensic and Neurodevelopmental Sciences, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, UK; [2]Department of Psychosis Studies, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, UK; [3]Department of Child and Adolescent Psychiatry, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, UK; [4]Queensland University of Technology (QUT), School of Psychology and Counselling, and Institute of Health and Biomedical Innovation, Brisbane, QLD, Australia and [5]School of Psychiatry, University of New South Wales, NSW, Australia

Abstract

Background. Cognitive impairments in childhood are associated with increased risk of schizophrenia in later life, but the extent to which poor academic achievement is associated with the disorder is unclear.

Methods. Major databases were searched for articles published in English up to 31 December 2019. We conducted random-effects meta-analyses to: (1) compare general academic and mathematics achievement in youth who later developed schizophrenia and those who did not; (2) to examine the association between education level achieved and adult-onset schizophrenia; and, (3) compare general academic achievement in youth at-risk for schizophrenia and typically developing peers. Meta-regression models examined the effects of type of academic assessment, educational system, age at assessment, measurement of educational level attained, school leaving age, and study quality on academic achievement and education level among individuals with schizophrenia.

Results. Meta-analyses, comprising data of over four million individuals, found that: (1) by age 16 years, those who later developed schizophrenia had poorer general academic (Cohen's $d = -0.29$, $p \leqslant 0.0001$) and mathematics achievement ($d = -0.23$, $p = 0.01$) than those who did not; (2) individuals with schizophrenia were less likely to enter higher education (odds ratio = 0.49, $p \leqslant 0.0001$); and, (3) youth reporting psychotic-like experiences and youth with a family history of schizophrenia had lower general academic achievement ($d = -0.54$, $p \leqslant 0.0001$; $d = -0.39$, $p \leqslant 0.0001$, respectively). Meta-regression analyses determined no effect modifiers.

Discussion. Despite significant heterogeneity across studies, various routinely collected indices of academic achievement can identify premorbid cognitive dysfunction among individuals who are vulnerable for schizophrenia, potentially aiding the early identification of risk in the population.

Introduction

Individuals with schizophrenia or schizophrenia spectrum disorders (SSD)[1†], and those experiencing their first episode of psychosis, are characterised by robust cognitive impairments spanning general intelligence (IQ), memory, processing speed, and executive functions (Sheffield, Karcher, & Barch, 2018). Similar, though less severe, cognitive impairments, alongside changes in social, emotional, and behavioural functioning, are also present before the onset of the first symptoms of the disorder (Laurens & Cullen, 2016; Sheffield et al., 2018). Using routinely collected data on academic achievement (such as performance in national exams) to identify the cognitive precursors of schizophrenia in the population may provide a feasible alternative to the administration of extensive cognitive batteries (Frey, 2019).

Two prior systematic reviews of antecedents of schizophrenia in population and birth cohort studies, now over a decade old, provided inconsistent evidence for poorer academic achievement among individuals who later developed schizophrenia relative to those who did not (MacCabe, 2008; Welham, Isohanni, Jones, & McGrath, 2009). More recently, our meta-analyses of data from prospective longitudinal studies of population cohorts, prospective studies of individuals with a family history of schizophrenia, and 'follow-back' studies of adults with schizophrenia reported that low IQ, but not poor general academic or mathematics achievement, precedes illness onset (Dickson, Laurens, Cullen, & Hodgins, 2012).

†The notes appear after the main text.

Review Article

*Joint first authors.

Cite this article: Dickson H, Hedges EP, Ma SY, Cullen AE, MacCabe JH, Kempton MJ, Downs J, Laurens KR (2020). Academic achievement and schizophrenia: a systematic meta-analysis. *Psychological Medicine* **50**, 1949–1965. https://doi.org/10.1017/S0033291720002354

Received: 18 December 2019
Revised: 12 June 2020
Accepted: 15 June 2020
First published online: 20 July 2020

Key words:
Academic attainment; adolescence; childhood; cognition; psychosis; scholastic achievement

Author for correspondence:
Hannah Dickson,
E-mail: hannah.dickson@kcl.ac.uk

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Inconsistency in findings across these three previous reviews might reflect differences in educational systems, the few studies available to inform the reviews, or that academic achievement is an indirect and less sensitive measure of cognitive function than standardised neurocognitive tests. Since the publication of our meta-analyses, there have been additional investigations demonstrating that poor academic achievement in childhood and adolescence is associated with the later development of schizophrenia (Lin et al., 2017; Sørensen et al., 2018). The first aim of the present study was thus to update our earlier meta-analyses comparing general academic and mathematics achievement in youth who later developed schizophrenia and those who did not. As in our earlier work, we included only studies of children aged 16 years or younger to minimise the likelihood of identifying a prodromal-related decline in academic achievement.

Alongside measures of academic achievement, other school-related risks and protective factors for schizophrenia have been reported. High educational attainment has been observed to be associated with protection against cognitive decline (Stern, 2002) and improved cognitive performance (Holthausen et al., 2002) among individuals with the disorder. Conversely, recent evidence shows that lower educational attainment is associated with subsequent schizophrenia, and, to a lesser extent, bipolar disorder, but not with adulthood depression (Lin et al., 2017; Tempelaar, Termorshuizen, MacCabe, Boks, & Kahn, 2017; Vreeker et al., 2016). Thus, the second aim of the study was to undertake a meta-analysis to examine the level of education attained in individuals with and without schizophrenia. As compulsory secondary schooling extends to age 18 years in some countries, for this analysis only, we did not restrict included studies to those of children aged ⩽16 years but required that studies used samples of individuals with adult-onset schizophrenia (i.e. ⩾18 years of age).

Research indicates that impaired cognitive function during childhood may index vulnerability to schizophrenia (Matheson, Shepherd, Laurens, & Carr, 2011). If poor academic achievement does precede illness onset and represents a readily identifiable risk marker for schizophrenia, we would expect to see evidence of poor academic achievement among at-risk youth. Indeed, a recent systematic review and meta-analysis found lower self-reported education level among help-seeking youth at ultra high-risk (UHR) for psychosis compared to healthy controls (Fusar-Poli et al., 2017). However, strategies identifying individuals based on UHR criteria identify only help-seeking adolescents or young adults who may be at imminent risk of developing psychosis and cannot provide information about whether low academic achievement is an antecedent of the disorder or an early prodromal disease process. It is currently not known whether poor academic achievement characterises children and adolescents identified as at-risk because they present with psychotic-like experiences (PLEs, an established risk marker for psychosis; Healy et al., 2019) or by virtue of having a family history of the disorder (Agnew-Blais & Seidman, 2013). The third aim of the study was thus to conduct additional meta-analyses to examine general academic achievement aged 16 years or younger in youth at-risk for schizophrenia compared to typically developing peers.

Methods

A series of meta-analyses were conducted assessing: (1a) general academic and (1b) mathematics achievement in youth aged 16 years and younger who later developed schizophrenia compared to those who did not; (2) level of educational attainment among adults with and without schizophrenia; and, (3a) general academic achievement in at-risk youth aged 16 years or younger who presented with PLEs or (3b) had a first-degree relative with schizophrenia, relative to youth without PLEs or family history, respectively.

Selection procedure

A systematic review protocol was registered with PROSPERO: CRD42017067438. The literature search followed PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines (Moher, Liberati, Tetzlaff, & Altman, 2009). Two authors (EH and SYM) independently searched MEDLINE, PsycINFO, and Embase to identify articles published up to December 2019. Articles were screened for eligibility in three stages. First, records were reviewed by title and abstract for possible inclusion. Next, the full-text of relevant studies was examined. Third, a manual search of reference lists from eligible articles was conducted to locate additional studies not identified in the database searches.

Search strategy and eligibility

Schizophrenia and schizophrenia spectrum disorders

General academic and mathematics achievement. The literature search, adopted from the original review (Dickson et al., 2012), identified articles published between January 2011 and December 2019 using the following search terms: 'schizophrenia' AND ('IQ' OR 'intelligence' OR 'motor' OR 'school' OR 'scholastic' OR 'academic') AND ('premorbid' OR 'prospective' OR 'cohort' OR 'high risk'). Inclusion criteria were: (1) written in English; (2) published or unpublished prospective birth cohort or genetic high-risk (i.e. family history) studies, or retrospective population sample studies; (3) an objective measure of cognitive functioning of youth aged 16 or younger; (4) results provided for participants who did and who did not develop schizophrenia in adulthood; and (5) sufficient data to determine effect sizes.

Educational level attained. An electronic database search was carried out, without date limitations, using the search terms 'schizophrenia' AND ('school' OR 'scholastic' OR 'education' OR 'academic') AND ('achievement' OR 'level' OR 'stage' OR 'years'). The inclusion criteria were: (1) written in English; (2) a sample of individuals with adult-onset diagnosis (aged 18 years or older) of schizophrenia and healthy control or general population comparison individuals; (3) summary data reported for educational level of both groups; and (4) sufficient data to calculate effect sizes.

Youth at-risk for schizophrenia and schizophrenia spectrum disorders

Two further literature searches were undertaken to identify published studies examining academic achievement in at-risk youth. Searches identified relevant articles using the key terms ('psychotic-like experiences' OR 'psychotic-like symptoms' OR 'subclinical psychotic symptoms' OR 'auditory hallucinations') or ['schizophrenia' AND ('family history' OR 'genetic risk' OR 'offspring' OR 'first-degree relatives'] AND ('school' OR 'scholastic' OR 'academic' OR 'education').

Inclusion criteria for both searches were: (1) published studies written in English; (2) objective measure of general academic

https://doi.org/10.1017/S0033291720002354 Published online by Cambridge University Press

achievement consisting of scores on at least two core academic subjects (e.g. literacy and mathematics) at age 16 years or younger. If the age range exceeded 16 years, studies were only included if at least two-thirds of participants were aged 16 years or younger (mean age + 1S.D. ⩽16 years); (3) scores recorded for youth reporting PLEs or having at least one first-degree relative with the disorder; (4) scores reported for a comparison group not at-risk for schizophrenia (i.e. not reporting PLEs in childhood or family history of the disorder, respectively); and (5) sufficient data to calculate effect sizes. No date limitations were applied.

Data extraction and risk of bias

Data were extracted from eligible studies using a structured coding form. Where additional data were needed, corresponding authors were contacted via email (Lin et al., 2017; Ramsay et al., 2018; Ranning et al., 2017; Stramecki et al., 2018; Vreeker et al., 2016). In the case of studies with overlapping samples, those with the greatest sample size were retained (Diaz, Velásquez, Susce, & de Leon, 2008; Gurpegui et al., 2005; Meesters et al., 2013), except where there was insufficient data to undertake meta-analysis (Kendler, Ohlsson, Mezuk, Sundquist, & Sundquist, 2016) and an alternative study was retained (MacCabe et al., 2008). Study quality was rated by two authors using the Newcastle-Ottawa Scale for cohort and case-control studies (NOS; Wells et al., 2011). Using a star rating scale, the tool assesses three categories of study quality: selection, comparability, and exposure/outcome. Total possible scores range from zero to nine stars. There is no threshold for determining 'good' and 'poor' quality studies but accumulating stars index increasing study quality.

Statistical analyses

Meta-analyses were conducted in Stata 15 statistical package (StataCorp., 2017) using the METAN command which implements (Bradburn, Deeks, & Altman, 1999) a random-effects model (DerSimonian & Laird, 1986). This model accounted for variation in the true effect, assuming that the observed effects within each study constituted a random sample from a larger population. For all meta-analyses examining general academic or mathematics achievement, effect sizes were calculated as the standardised mean difference (SMD, Cohen's d) and interpreted as 'small (0.2)', 'medium (0.5)' and 'large (0.8)' (Cohen, 1992). The summary effect size for the educational level meta-analysis was an odds ratio (OR), and interpreted as 'small (1.5)', 'moderate (2.5)', 'large (4.0)' and 'very large (10)' (Rosenthal, 1996). An OR value of 1.0, or 95% confidence interval (CI) crossing 1.0, indicated no difference between the groups. To determine the magnitude of final pooled effect sizes for OR<1.0, OR was converted to 1.0/OR (Chen, Cohen, & Chen, 2010). For each pooled effect size, at a 95% significance level, a z-value and p-value were computed to provide an indication of the two-sided statistical significance of the association. For meta-analyses comprising six or more studies (Sutton, Duval, Tweedie, Abrams, & Jones, 2000), small sample bias was assessed statistically utilising the Egger's Test.

Heterogeneity between studies was estimated using Cochran's Q (X^2 and p-value), and the degree of heterogeneity was measured by the I^2 statistic. I^2 values of 0–40% may be considered unimportant, 30–60% as moderate, 50–90% substantial, and 75–100% considerable (Higgins, Thompson, Deeks, & Altman, 2003). Heterogeneity was investigated using meta-regression for analyses with 10 studies or more implemented using the METAREG (Sharp, 1998) command in Stata 15. Four potential moderator variables were explored for general academic achievement: (i) type of academic assessment (i.e. national examination or other tests), based on the rationale that it may be less appropriate to compare the results of standardised academic achievement tests with those from national exams; (ii), the educational system of countries in which data were collected (i.e. Scandinavian/Nordic countries *v.* all other countries); (iii) the age at academic assessment (i.e. 7–12 years *v.* 13–16 years), as 12 years reflects the approximate age at which primary (elementary) school education concludes and we wished to determine any differences in academic underperformance between primary and secondary schooling; and (iv) NOS study quality score.

For the meta-analysis of educational level attained, in order to create equivalency across educational systems, we examined whether individuals with schizophrenia, compared to those without the disorder, were more or less likely to enter into higher education [i.e. continue education past secondary/high school (Bulgaria, France, India, Jamaica, Qatar, South Korea, Turkey, USA), past upper secondary or vocational (Denmark, Finland, Poland), past secondary senior (Netherlands), or complete greater than 12 years of education (Greece, Spain)]. Three potential effect size moderators were examined. One, in primary studies, educational level attained was measured either as a study outcome or as a socio-demographic characteristic of the sample. In the case of the former, these were objective measures of attainment, whereas the latter derived from self-reported attainment levels. Self-report may be less reliable than information derived from, or cross-referenced with, objective records; in comparison to objective measures, students self-report higher grades (Herman & Nelson, 2009). Two, we compared primary studies that utilised data from countries that have different ages for the end of compulsory education (i.e. 14–16 years *v.* 18 years). Evidence has highlighted the potential importance of secondary school attendance and attainment in influencing decisions to enter higher education. Three, we also examined the NOS study quality score.

Results

Schizophrenia and schizophrenia spectrum disorders

Search results – general academic and mathematics achievement

The literature search identified 2751 unique records, of which 27 full-text articles were assessed for eligibility (see online Supplementary Fig. S1 for screening procedure and search results). By adopting the search strategy from the original review (Dickson et al., 2012), which was not specific to academic achievement, the articles identified in the literature search included non-relevant studies of IQ and motor function which were therefore excluded during the first screening stage. One author was successfully contacted to provide summary statistics on general academic and mathematics achievement scores for youth aged 12 years who did and did not later develop schizophrenia (Lin et al., 2017). Six new published studies met inclusion criteria for the meta-analyses: six in the general academic achievement domain (Chong et al., 2009; Lin et al., 2017; Schulz, Sundin, Leask, & Done, 2014; Seidman et al., 2013; Sørensen et al., 2018; Ullman, Hornik-Lurie, & Reichenberg, 2017); and three in the mathematics achievement domain (Lin et al., 2017; Sørensen et al., 2018; Ullman et al., 2017). Table 1 outlines the details of each study, including

https://doi.org/10.1017/S0033291720002354 Published online by Cambridge University Press

sample characteristics, age at assessment, domain measure, and effect size of difference between youth who subsequently developed schizophrenia compared to those who did not. All studies contained mixed-gender samples, except for two that included only men (Ang & Tan, 2004; Chong et al., 2009). Assessments of academic achievement included results of standardised achievement tests and national examinations, as well as school tests administered at the end of the academic year. Participants were 7–16 years old at the time of the academic assessment.

General academic achievement

A meta-analysis of 11 studies, including six new studies since our previous meta-analysis (Dickson et al., 2012), indicated that individuals aged 16 years or younger who subsequently developed schizophrenia attained significantly lower general academic achievement scores than those who did not develop the disorder. Figure 1*a* illustrates the small effect size ($d = -0.29$, 95% CI −0.43 to −0.14, $z = 3.95$, $p < 0.0001$). Significant and substantial heterogeneity was identified ($Q = 120.77$, df = 10, $p < 0.001/I^2 = 91.7\%$). Meta-regression analyses indicated that heterogeneity was not associated with the type of academic assessment, educational system, age at assessment, nor study quality. No small sample bias was detected ($p = 0.80$).

Mathematics achievement

A meta-analysis of seven studies, including three new publications since our last meta-analysis (Dickson et al., 2012), showed that individuals aged 16 years or younger who later developed schizophrenia, compared to those who did not, performed worse on tests of mathematics. Figure 1*b* illustrates the small effect size differences ($d = -0.23$, 95% CI −0.41 to −0.05, $z = 2.46$, $p = 0.01$). The results highlighted significant and substantial heterogeneity across the studies ($Q = 63.54$, df = 6, $p < 0.001/I^2 = 91\%$). No small sample bias was observed ($p = 0.43$).

Educational level attained

The search yielded 13 088 unique studies (see online Supplementary Fig. S2 for screening procedure and search results) and 472 articles underwent full-text review. Three studies reported insufficient data to calculate an effect size: two were able to provide additional data (Stramecki et al., 2018; Vreeker et al., 2016), but one was unable (Ranning et al., 2017). Overall, 22 studies met inclusion criteria for the meta-analysis (see Table 2 for study details). Most studies obtained data on educational level attainment by self-report via structured interview or questionnaire, but four studies extracted data from population registers (Burgess, Curtis-Downes, & Gibson, 2013; Greve et al., 2017; Isohanni et al., 2001; Tempelaar et al., 2017). All studies had mixed-gender samples. The comparison group of one study included first- and second-degree relatives (Duarte, Mamani, Rosales, & Kymalainen, 2008). Online Supplementary Table S3 provides a description of stages of educational systems for the 15 countries of origin included within the analysis.

Results showed that individuals with schizophrenia, compared to those without the disorder, were significantly less likely to enter into higher (post-secondary) education. As illustrated in Fig. 2, a moderate effect size was found (OR 0.49, 95% CI 0.38–0.63, $z = 5.65$, $p < 0.0001$). Significant and substantial heterogeneity was identified across studies ($Q = 182.88$, df = 21, $p < 0.001/I^2 = 88.5\%$). For the meta-regression analysis of school leaving age, five studies were excluded because school leaving age could not be accurately determined (Bener, Al-Hamaq, & Dafeeah, 2014; Burgess et al., 2013; Cohen, Dembling, & Schorling, 2002; Duarte et al., 2008; Johnson-Greene et al., 1997). Meta-regression indicated that neither the measure of educational level used, school leave age, nor study quality were associated with heterogeneity. No significant small sample bias was detected ($p = 0.60$).

Youth at-risk for schizophrenia and schizophrenia spectrum disorders

Psychotic-like experiences

From 414 unique articles detected, full-text screening was carried out for seven studies (see online Supplementary Fig. S4 for screening procedure and search results). One study reported insufficient data to calculate an effect size and, upon contact, was unable to provide the necessary data (Ramsay et al., 2018). Table 1 provides details of the three studies included in the meta-analysis. Academic achievement scores were collected concurrently with symptoms and included the results of national exams and standardised achievement tests. The results demonstrated poorer overall academic achievement in youth with PLEs compared to youth without PLEs (see Fig. 3*a*). A moderate effect size was obtained ($d = -0.54$, 95% CI −0.77 to −0.30, $z = 4.41$, $p < 0.001$). No significant heterogeneity was detected ($Q = 2.09$, df = 2, $p = 0.35/I^2 = 3.6\%$).

Family history of schizophrenia

The literature search identified 1403 unique articles. Following the full-text screening of 19 articles, 15 were excluded for reasons detailed in online Supplementary Fig. S5. Two authors were contacted for additional information (Lin et al., 2017; Ranning et al., 2017), one provided data suitable for meta-analysis (Lin et al., 2017). Four studies met inclusion criteria and are described in Table 1. Assessments of academic achievement included standardised assessments or exams, and grades from the final year of compulsory school. The meta-analysis indicated that youth with at least one first-degree relative with schizophrenia, compared to those without, obtained lower general academic achievement scores. Figure 3*b* demonstrates the moderate effect size of group difference ($d = -0.39$, 95% CI −0.57 to −0.21, $z = 4.31$, $p < 0.0001$). Significant and substantial heterogeneity was detected across the studies ($Q = 26.99$, df = 3, $p < 0.001/I^2 = 88.9\%$).

Quality of included studies

For the updated general and mathematics achievement and educational level meta-analyses, total scores from NOS assessment ranged from three (Burgess et al., 2013; Rathor, Dave, Mehta, Oswal, & Gupta, 2008) to nine (Ang & Tan, 2004; Isohanni et al., 1998, 2001), with the most common score being seven. For the meta-analysis of individuals at-risk for schizophrenia, all studies achieved a total score of seven or eight (see online Supplementary Tables S6 and S7).

Discussion

These meta-analyses, comprising data from more than four million individuals, comprehensively explored whether individuals with a diagnosis of schizophrenia and children/adolescents at-risk for the disorder are characterised by academic underachievement. The findings demonstrated that, by age 16 years, children and adolescents who later develop the disorder presented with significantly poorer general academic and mathematics achievement

https://doi.org/10.1017/S0033291720002354 Published online by Cambridge University Press

Table 1. Study details and effect sizes for meta-analyses examining academic achievement in youth who subsequently developed schizophrenia or a schizophrenia spectrum disorder and in youth at-risk for schizophrenia or a schizophrenia spectrum disorder

Study	Sample	Schizophrenia/SSD		Age at exposure assessment (years)	Domain measure	Effect size[a]
		Present	Absent			
Schizophrenia and schizophrenia spectrum disorders						
General academic achievement		3902 Youth who later developed schizophrenia or SSD	851 748 Youth who did not develop schizophrenia or SSD			
Isohanni et al. (1998)	Northern Finland birth cohort 1966	84 Cohort members with a diagnosis of schizophrenia: 54 males, 30 females	10 414 Cohort members with no psychiatric hospital admission: 5245 males, 5169 females	16	School marks for all theoretical subjects	−0.19[b]
Cannon et al. (1999)	Helsinki birth cohort born 1951-1960	400 Cohort members with a diagnosis of schizophrenia or SSD	408 Cohort members with a diagnosis other than schizophrenia	11	Year 4 examination results	−0.02[b]
Ang and Tan (2004)	A follow-back study of military servicemen from Singapore	30 Military servicemen with a diagnosis of first-episode psychosis	30 Military servicemen without a past or current mental disorder	12	Primary school leaving examination (average score)	0.05
Bilder et al. (2006)	A follow-back study of adults from New York	59 Study participants with a diagnosis of schizophrenia or SSD recruited from an inpatient unit	26 Study participants recruited from newspaper advertisements. No mental disorder and matched for sex and age	10–11	Fifth-grade achievement test results	−0.53[b]
MacCabe et al. (2008)	Population-based historical cohort study of adults born 1973–1983 in Sweden	493 Cohort members with a diagnosis of schizophrenia: 318 males, 175 females	713 876 Cohort members with no diagnosis: 364 967 males, 348 909 females	15–16	Swedish National Examination grade point average	−0.52[b]
Chong et al. (2009)[c]	A retrospective cohort study of National Service male conscripts (aged 18–21 years) in Singapore between August 2004–2005	273 Cohort members with a single lifetime DSM-IV diagnosis of schizophrenia or SSD	5601 Cohort members with no DSM-IV diagnosis	12	Standardised National Primary School Leaving Examination	−0.33[b]
Seidman et al. (2013)[c]	Birth cohort born 1959–1965 from New England, USA	45 Cohort members with a diagnosis of schizophrenia or schizo-affective, depressed type (SAD)	101 Cohort members with no lifetime history of SSD, bipolar disorder, recurrent depressive disorder, suicide attempts or psychiatric hospitalisations	7	Reading, spelling and arithmetic subtests of WRAT	−0.80[b]
Schulz et al. (2014)[c]	British birth cohort: 1958 National Child Development Study (NCDS)	40 Cohort members with a diagnosis of schizophrenia	14 148 Cohort members with no diagnosis of schizophrenia	11	Reading comprehension test (35-item) and Arithmetic test (40-item)	−0.53[b]

(*Continued*)

https://doi.org/10.1017/S0033291720002354 Published online by Cambridge University Press

Table 1. (*Continued.*)

Study	Sample	Schizophrenia/SSD		Age at exposure assessment (years)	Domain measure	Effect size[a]
		Present	Absent			
Lin et al. (2017)[c]	Western Australia birth cohort 1980–2001	923 Cohort members with a diagnosis of schizophrenia	88 824 Cohort members with no diagnosis of schizophrenia	12	Western Australian Literacy and Numeracy Assessment	−0.05[b]
Ullman et al. (2017)[c]	Population-based cohort study of all eighth-graders at state school in Jerusalem Municipality from 1978 to 1988	85 Cohort members with a diagnosis of schizophrenia, schizotypal or delusional disorder	11 002 Cohort members without a psychiatric hospitalisation	13–14	Eighth-grade school marks	0.00[b]
Sørensen et al. (2018)[c]	Population-based case-cohort study of adults born 1987–1995 in Denmark	1470 Cohort members with a diagnosis of schizophrenia	7318 Subcohort non-cases with no diagnosis of schizophrenia	16	Grade Point Average	−0.37[b]
Mathematics achievement		2626 Youth who later developed schizophrenia or SSD	113 466 Youth who did not develop schizophrenia or SSD			
Jones et al. (1994)	British birth cohort born 1946	30 Cohort members with a diagnosis of schizophrenia: 20 males, 10 females	4716 Cohort members without schizophrenia: 2457 males, 2259 females	11	Group administered Maths test	−0.41[b]
Crow et al. (1995)	British birth cohort born 1958	29 Cohort members with a diagnosis of schizophrenia	1446 Cohort members with no psychiatric hospital admission	11	Group administered Maths test	−0.48[b]
Helling et al. (2003)	A follow-back study of adults born in Sweden	59 Study participants with a diagnosis of schizophrenia or SSD recruited from an inpatient unit	119 School classmates before/after each case	12	End of year teacher assigned grades	−0.14[b]
Ang and Tan (2004)	A follow-back study of military servicemen from Singapore	30 Military servicemen with a diagnosis of first-episode psychosis	30 Military servicemen without a past or current mental disorder	12	Primary school-leaving examination	0.33
Lin et al. (2017)[c]	Western Australia birth cohort 1980–2001	923 Cohort members with a diagnosis of schizophrenia	88 824 Cohort members with no diagnosis of schizophrenia	12	Western Australian Literary and Numeracy Assessment	−0.18[b]
Ullman et al. (2017)[c]	Population-based cohort of 1978–1988 eighth-graders at state school in Jerusalem Municipality	85 Cohort members with a diagnosis of schizophrenia, schizotypal or delusional disorder	11 013 Cohort members without a psychiatric hospitalisation	13–14	Eighth-grade school mathematics marks	0.00[b]
Sørensen et al. (2018)[c]	Population-based case-cohort study of adults born 1987–1995 in Denmark	1470 Cohort members with a diagnosis of schizophrenia	7318 Subcohort non-cases with no diagnosis of schizophrenia	16	Math grade point average	−0.47[b]

(*Continued*)

https://doi.org/10.1017/S0033291720002354 Published online by Cambridge University Press

Table 1. (*Continued.*)

Study	Sample	Schizophrenia/SSD		Age at exposure assessment (years)	Domain measure	Effect size[a]
		Present	Absent			
At-risk for schizophrenia and schizophrenia spectrum disorders						
Psychotic-like experiences		102 Youth presenting with psychotic-like experiences	668 Youth without psychotic-like experiences			
Bartels-Velthuis, van de Willige, Jenner, van Os, and Wiersma (2011)[d]	A study of children aged 7–8 years attending primary school in 2002–2003 in Groningen, The Netherlands	55 Children with auditory vocal hallucinations: 40 in the persistent group, 15 in the incident group	152 Children without auditory vocal hallucinations in the referent group	12–13	National Dutch end-of-primary-school test	−0.46[b]
Dickson et al. (2014)	Study participants aged 9–12 years recruited from 73 primary schools in greater London	32 Children presenting a triad of antecedents of schizophrenia including psychotic like-experiences; social, emotional and/or behavioural problems in the clinical range; and early speech and/or motor developmental delays/ abnormalities	45 Typically developing children with no family history or antecedents of schizophrenia	9–12	WIAT-II UK	−0.83[b]
Wu et al. (2014)	Study sample of school-aged children from the Colorado Learning Disabilities Research Center	15 Children with psychosis symptoms assessed by 4 items on the CBCL	471 Children without psychosis symptoms	8–18	Math subtest of the WRAT-R and Reading subtest of the PIAT-R	−0.38[b]
Family history of schizophrenia		4343 Youth with at least one first-degree relative with schizophrenia or SSD	1 527 058 Youth with no family history of schizophrenia or SSD			
Jundong et al. (2012)	Swedish population-based cohort study of individuals with final compulsory school grades from 1988 to 2006	3654 Offspring with at least one biological parent with schizophrenia	1 439 215 Offspring with biological parents without schizophrenia	15	Final year summary grades based on 16 best subject grades	−0.24[b]
Forsyth et al. (2013)	Study cohort of individuals born and studied in Helsinki, Finland between 2 January 1987 and 31 December 1993	373 Children with at least one parent with a diagnosis of schizophrenia: 202 males, 171 females	1070 Children born to mothers and fathers with no psychiatric diagnoses; 518 males, 552 females	15–16	Final year school marks for all mandatory subjects	−0.27[b]
Lin et al. (2017)	Western Australia birth cohort 1980–2001	303 Children whose mothers have a diagnosis of schizophrenia	86 728 Children with mothers who have no known mental illness	12	Western Australian Literacy and Numeracy Assessment	−0.48[b]
Dickson et al. (2014)[e]	Study participants aged 9–12 years recruited from 73 primary schools in greater London and	13 Children with at least one first-degree relative with schizophrenia	45 Typically developing children with no family history or	9–12	WIAT-II UK	−1.41[b]

(*Continued*)

https://doi.org/10.1017/S0033291720002354 Published online by Cambridge University Press

Table 1. (*Continued.*)

Study	Sample	Schizophrenia/SSD		Age at exposure assessment (years)	Domain measure	Effect size[a]
		Present	Absent			
	as relatives of South London and Maudsley NHS patients	or schizoaffective disorder	antecedents of schizophrenia			

SSD, Schizophrenia spectrum disorder; WRAT, Wide Range Achievement Test; WRAT-R, Wide Range Achievement Test – Revised; PIAT-R, Peabody Individual Achievement Test – Revised; CBCL, Child Behaviour Checklist; WIAT-II UK, Wechsler Individual Achievement Test – Second UK Edition.
[a]Effect sizes were estimated using Cohen's *d*, obtained using sample sizes, means and standard deviations for a group who later developed schizophrenia or an SSD, or a group at-risk for schizophrenia or an SSD, and a comparison group, except for the following: (1) Academic performance: Mathematics : for both Jones et al. (1994) and Helling et al. (2003), samples size and f statistics were used; and for Crow et al. (1995), *t* statistic was calculated from degrees of freedom and *p* value given in paper; effect size was then estimated from sample size and t statistic.
[b]Negative values indicate better performance in the comparison group.
[c]New studies included in meta-analysis.
[d](i) Persistent group: Hearing voices at 7–8 years old and at least occasionally during one other year over the 5-year follow-up period (up to 12–13 years old). (ii) Incident group: Not hearing voices at 7–8 years old but positive for auditory vocal hallucinations over the 5-year follow-up period (up to 12–13 years old). (iii) Referent group: Not hearing voices at 7–8 years old and the 5-year follow-up period (up to 12–13 years old).
[e]The sample included two children with at least two second-degree relatives with schizophrenia or schizoaffective disorder.

compared to individuals who did not develop schizophrenia. Individuals with schizophrenia were also less likely to enter higher education than individuals without the disorder. Furthermore, youth considered to be at-risk for schizophrenia because they reported PLEs or had an affected first-degree family member performed more poorly at school relative to their typically developing peers. Together, these findings suggest that poor academic achievement may represent a readily identifiable premorbid cognitive marker of vulnerability for later schizophrenia.

Although effect sizes were small in magnitude, our finding of poor general academic (d = -0.29) and mathematics achievement (d = -0.23) among individuals who later developed schizophrenia is inconsistent with the results of our previous meta-analyses (Dickson et al., 2012). This may be due to increased statistical power afforded by the additional studies (n = 6) in random-effects meta-analyses (Jackson & Turner, 2017). Some studies reported poor performance in children who developed schizophrenia relative to those who do not in specific academic subjects only (Bilder et al., 2006; Fuller et al., 2002; Lin et al., 2017; MacCabe et al., 2008). Our findings instead support a more generalised cognitive deficit preceding the diagnosis of schizophrenia (Sheffield et al., 2018). Meta-regression analyses comparing studies examining general academic achievement between 7–12 and 13–16 years indicated that age was not an effect modifier, suggesting that this underachievement may be measurable from middle childhood among individuals who go onto develop schizophrenia in adulthood. This observed deficit spanning 7–16 years (i.e. where lower academic achievement is present early and continues), contrasts with other research suggesting that poor academic achievement may be detectable only later in adolescence, closer to the putative prodromal period immediately preceding illness onset (Ang & Tan, 2004; Cannon et al., 1999; Fuller et al., 2002; Jones, Murray, Jones, Rodgers, & Marmot, 1994; Ullman, Levine, Reichenberg, & Rabinowitz, 2012). Our meta-analyses utilised cross-sectional data, and only longitudinal studies can truly determine whether a child who goes onto develop schizophrenia displays poor academic achievement at different ages and developmental stages (Dickson et al., 2018).

In the present study, we observed significant heterogeneity in both general and mathematics achievement domains, which has been suggested previously to reflect differences in educational systems (Dickson et al., 2012; MacCabe, 2008). Scandinavian and Nordic countries form a small set of educational systems that are each relatively culturally and linguistically homogenous that are reported to be among the best in the world (Gustafsson & Blömeke, 2018). In the present study, heterogeneity in the general academic achievement domain was not due to differences between studies originating from Scandinavian/Nordic countries and those from UK, USA, Australia, Israel, and Singapore although differences between the educational systems coded as 'other' may have obscured our results. Possibly, the heterogeneity reflects differences in the organisation and governance of school systems (Woessmann, 2016) and/or unobserved country-level heterogeneity such as cultural traits and the value placed on academic achievement (Gustafsson & Blömeke, 2018). We also found that assessment type (i.e. national exams *v.* standardised measures of academic achievement) was not an effect modifier. Standardised academic achievement tests like the Wide Range Achievement Test (WRAT; Wilkinson and Robertson, 2006) and Wechsler Individual Achievement Test (WIAT; Wechsler, 1992) are used in both educational and research settings to assess academic achievement in children and adolescents with and without special educational needs and correlate moderately with exam performance (Langberg et al., 2011). There is robust evidence that individuals with schizophrenia show premorbid cognitive impairments (Dickson et al., 2012; Sheffield et al., 2018), but it is not generally feasible to administer cognitive batteries that include measures of academic achievement at a population-level. It is increasingly recognised that schools have the potential to serve as a universal access point for the early detection of mental health difficulties (Levitt, Saka, Hunter Romanelli, & Hoagwood, 2007; McCormick, Thompson, Stoep, & McCauley, 2009). Our meta-analyses imply that it may be possible to use academic achievement, measured by performance in national examinations undertaken before pupils transition to secondary school, in conjunction with other known risk factors (Laurens & Cullen, 2016), to develop screening programmes aimed at identifying vulnerable pupils who may experience elevated risk for the later development of schizophrenia.

Consistent with findings from the meta-analyses of academic achievement, individuals with an adulthood diagnosis of schizophrenia were less likely to enter higher education compared to

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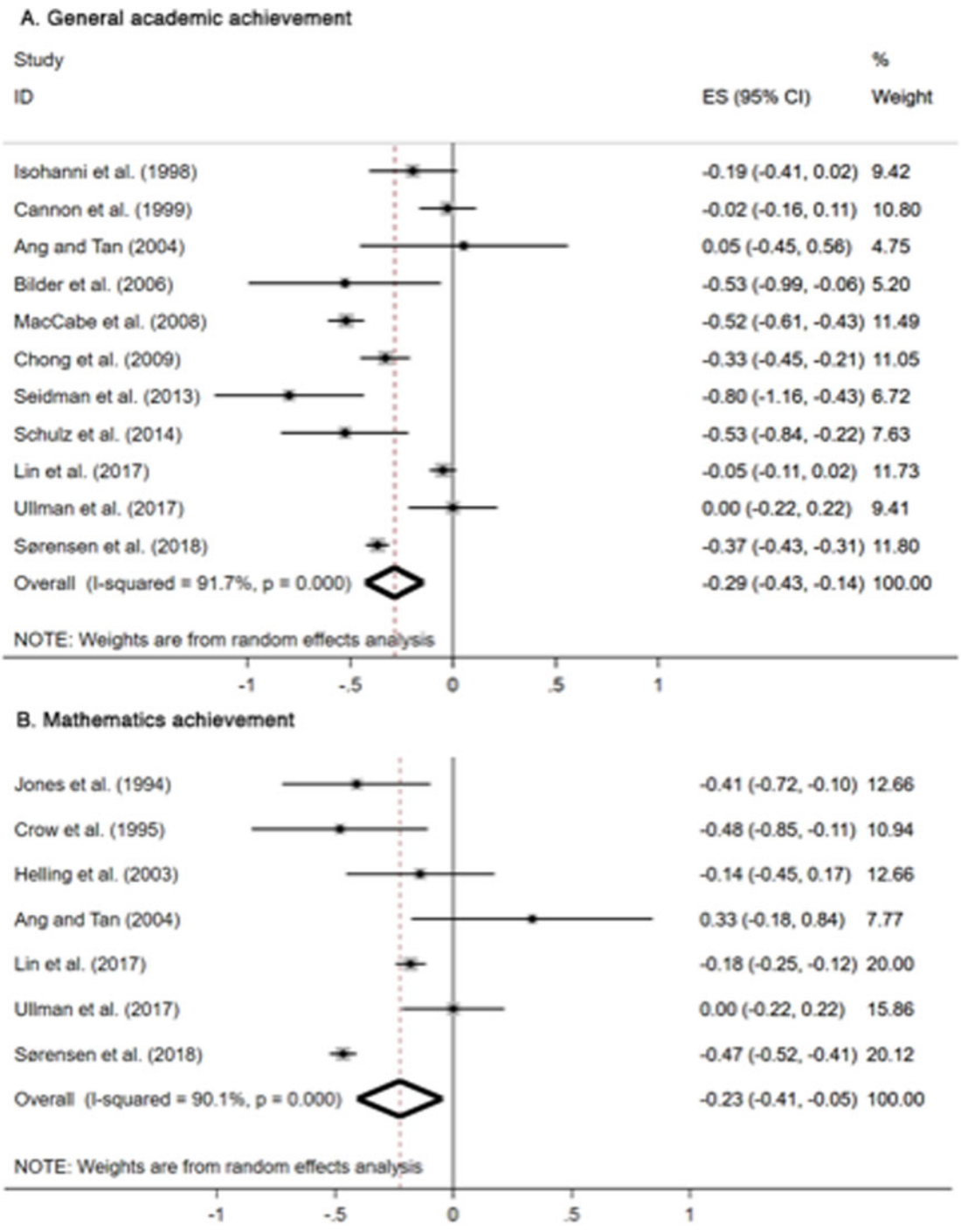


Fig. 1. Forest plots for general academic (*a*) and mathematics (*b*) achievement among youth aged 16 years or younger who subsequently developed schizophrenia or a schizophrenia spectrum disorder.

those without the disorder. As individuals generally enter higher education aged 18 years and older, our results may be associated with the emergence of prodromal symptoms, typically during late adolescence and early adulthood. Measures of educational level as a study outcome (objective measures *v.* self-reported socio-demographic variable), and compulsory school leaving age, were not found to effect modifiers. This was unexpected, as self-report methods are reported to less reliably measure academic achievement than routinely collected administrative information on exam performance (Herman & Nelson, 2009), and increases in the compulsory school leaving age have historically led to increases in enrolment in higher education (Messacar & Oreopoulos, 2013). Meta-regression analyses are typically under powered even with at least 10 studies available, and the lack of effect modification here may reflect the presence of type II errors (Hempel et al., 2013). Our present findings indicate that the attainment deficit is observed regardless of the measure used.

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Table 2. Study details and effect sizes for meta-analysis examining educational level attained in individuals with an adulthood diagnosis of schizophrenia or a schizophrenia spectrum disorder

		Schizophrenia/SSD				
Study	Sample	Present	Absent	Age range of sample (years)	Education level measure	Effect size[a]
Educational level attained		6 551 Individuals with schizophrenia or SSD	1 974 227 Individuals without schizophrenia or SSD			
Johnson-Greene et al. (1997)[b]	USA	19 Study participants with a diagnosis of schizophrenia or SSD	23 Healthy control individuals from the community	Does not specify	Self-reported information	1.06
Isohanni et al. (2001)	Northern Finland 1996 birth cohort	33 Cohort members with a diagnosis of schizophrenia with age at onset of 23 years or above	10 222 Cohort members with no psychiatric hospital treatment	31	National Registry of Educational Statistics in Finland	0.50[c]
Cohen et al. (2002)	1986 National Mortality Followback Survey, USA	130 participants with a diagnosis of schizophrenia or SSD on facility discharge record or death certificate	15 200 persons without a diagnosis of schizophrenia	N/A	Structured interviews with descendent families, or other knowledgeable informants	1.19
Mallett, Leff, Bhugra, Takei, and Corridan (2004)	Study participants drawn from services in Ealing and Camberwell, London	98 Individuals identified with schizophrenia	96 community controls with no prior contact with mental health services, matched by sex, age and ethnicity	17–62	Self-reported information by questionnaire	0.21[c]
Gurpegui et al. (2005)	Study participants drawn from outpatient facilities in Granada, Spain	250 Outpatients with a diagnosis of schizophrenia	290 Individuals without any psychotic mental illness	Does not specify	Does not specify	0.11[c]
Duarte et al. (2008)	Study participants recruited through Department of Mental Health sites in Boston, Los Angeles and Miami, USA	47 Patients with schizophrenia or schizoaffective disorder	57 Relatives of patients	19–86	Self-reported information	0.37[c]
Diaz et al. (2008)	Study participants drawn from services, churches, community organisations and the university in Kentucky, USA	258 Patients with schizophrenia or schizoaffective disorder	381 Controls not currently treated by a psychiatrist	⩾18	Does not specify	0.33[c]
Rathor et al. (2008)	Study participants drawn from Department of Psychiatry at New Civil Hospital and government medical college in Surat, India between 2004–2006	60 Patients with a diagnosis of schizophrenia	60 Controls with non-psychiatric illnesses	18–55	Does not specify	1.29
Akal and Dogan (2010)	Study participants were city centre residents in Sivas, Turkey in 2007	164 Patients with schizophrenia undergoing treatment at Cumhuriyet	164 Individuals with no mental disorders, matched by age, gender and residency	>16	Self-reported information by questionnaire	2.11

(*Continued*)

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Table 2. (*Continued.*)

Study	Sample	Schizophrenia/SSD		Age range of sample (years)	Education level measure	Effect size[a]
		Present	Absent			
		University, Faculty of Medicine				
Breton et al. (2011)	Study participants recruited through a psychiatric department of a French teaching hospital in Paris suburb	52 Outpatients with a diagnosis of schizophrenia	53 Healthy controls with no first-degree family history of bipolar or schizophrenia disorder	28–65	Does not specify	0.23[c]
Meesters et al. (2013)	Study participants recruited from outpatient services of GGZ inGeest, community centers and local newspaper advertising in catchment area of southern district of Amsterdam, Netherlands	67 Patients with a diagnosis of schizophrenia	69 Healthy controls with no history of psychiatric or substance-related disorders	⩾60	Demographic data collected during interviews	0.32[c]
Burgess et al. (2013)	Study sample drawn from individuals first attending psychiatric emergency, inpatient or outpatient services (between August – November 2008) across four hospitals, Jamaica	57 Patients with a diagnosis of schizophrenia	1 636 995 Individuals from National Data on the Labour force	18–80	Patients provided information during interviews and were compared with data from the Statistical Institute of Jamaica	0.50[c]
Bener et al. (2014)	Study participants drawn from outpatient clinics of Psychiatry hospital and the community, Qatar	233 Participants with a diagnosis of schizophrenia	466 Community controls, matched by age and gender	>20	Self-reported through interview	0.94[c]
García-Laredo, Maestú, Castellanos, Molina, and Peréz-Moreno (2015)	Study sample drawn from four hospital centres in Madrid, Spain	23 Patients with a diagnosis of paranoid schizophrenia	15 Individuals with no history of psychiatric illness or drug consumption	Does not specify	Does not specify	0.11[c]
Nugent, Chiappelli, Rowland, and Hong (2015)	Study sample recruited from outpatient clinics, media advertising and random digit dialling in Maryland, USA	30 Individuals with a diagnosis of schizophrenia	20 Healthy participants with no DSM-IV Axis 1 diagnoses or family history of psychosis, frequency-matched by age, sex and race	18–57	Does not specify	0.58[c]
Vreeker et al. (2016)	Study participants drawn from three Dutch studies: *Bi*polar Genetics, Dutch Genetic Risk and Outcome in Psychosis, and Cannabis Quest	944 Patients with a diagnosis of schizophrenia	1048 Unrelated community controls with no diagnosis of a psychotic disorder	>15	Self-reported information	0.45[c]

(*Continued*)

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Table 2. (*Continued.*)

Study	Sample	Schizophrenia/SSD		Age range of sample (years)	Education level measure	Effect size[a]
		Present	Absent			
Tempelaar et al. (2017)	Study participants drawn from Dutch Psychiatric Case Registry of the Middle Netherlands and national population database, Statistics Netherlands	1561 Patients with a diagnosis of schizophrenia or non-affective psychotic disorder	12 309 Randomly selected individuals with no psychiatric disorder, matched by birth year, gender, country of birth, residence and source of educational information	Does not specify	Statistics Netherlands	0.52[c]
Greve et al. (2017)	Study participants drawn from Danish Conscription Registry	1925 Parents with a diagnosis of schizophrenia or SSD	296 095 Parental controls with no diagnosis of schizophrenia, SSD or mood disorders	Does not specify	Statistics Denmark	0.64[c]
Fountoulakis, Panagiotidis, Gonda, Kimiskidis, and Nimatoudis (2018)	Study participants recruited from local hospitals and the community in Thessaloniki, Greece	133 Patients with a diagnosis of schizophrenia	122 Community controls with no history of, or family member with, any mental disorder	18–65	Does not specify	0.33[c]
Stramecki et al. (2018)	Study participants recruited from lower Silesian Center of Mental Health and Wroclaw and Pomeranian Medical Universities, Poland between 2016-2018	67 Patients with a diagnosis of schizophrenia spectrum disorders	62 Matched individuals with no previous psychiatric treatment, no past, present or family history of neurological and psychiatric disorders (except nicotine dependence)	18–65	Does not specify	4.19
Kim et al. (2019)	Study participants drawn from five community mental health centres in Gwangju, South Korea	292 Patients with schizophrenia, affective psychosis or other specified spectrum disorder	420 Control participants, matched by age and gender	⩽60	Does not specify	0.18[c]
Veleva, Stoimenova, and Valkova (2019)[b]	Study participants recruited by University Hospital Pleven, Bulgaria between 2015–2017	108 Patients with paranoid schizophrenia	60 Healthy control subjects	Does not specify	Does not specify	0.94[c]

SSD, Schizophrenia spectrum disorder; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, 4th Edition.
[a]Effect sizes were estimated using an odds ratio, obtained using the number of participants with higher education and total number of participants in each group of those who later developed schizophrenia or an SSD and a comparison group.
[b]Primary study inclusion criteria required participants to have at least two years of high school attendance (Johnson-Greene et al., 1997) or a minimum formal education of 8 years (Veleva et al., 2019).
[c]Values below 1.00 indicate better performance in the comparison group.

We found medium effect size differences in general academic achievement among 4445 at-risk youth aged 16 years and younger (PLEs: $d = -0.54$; affected first-degree relative: $d = -0.39$) compared to 1 527 726 youth not at-risk for the disorder. The magnitude of cognitive impairments is suggested to increase across illness stages in schizophrenia; that is, increasing in size across premorbid, prodromal, first-episode, and chronic stages (Mollon & Reichenberg, 2017; Sheffield et al., 2018). Although only a minority of youth with PLEs or a family history of schizophrenia will go onto develop schizophrenia (Mortensen, Pedersen, & Pedersen, 2009; Werbeloff et al., 2012), we observed larger effect size differences among at-risk youth relative to their typically developing peers than was obtained for the prospective assessments of youth who went onto develop schizophrenia relative to youth who did not. There are four possible explanations for these findings. One, given the small number of studies included in both at-risk meta-analyses, our results may reflect the inclusion of a study with a small sample size that utilised standardised measures of academic achievement and reported large effect sizes differences (Dickson et al., 2014). Two, children experiencing PLEs and children with a family history of schizophrenia are more likely to present with externalising and

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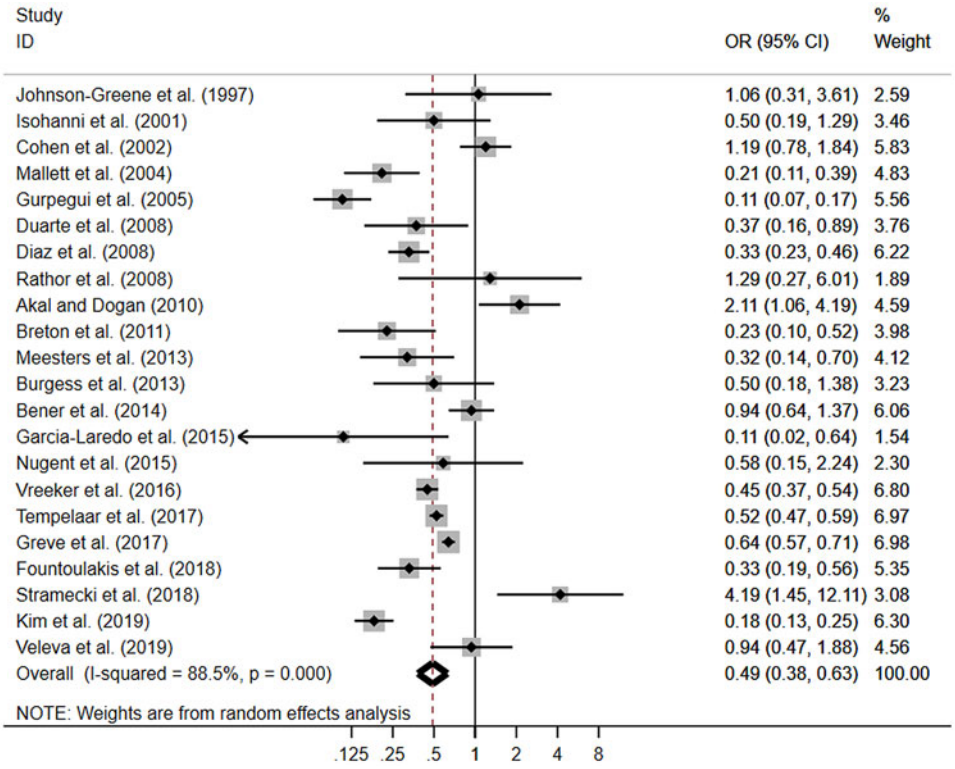


Fig. 2. Forest plot for educational level attained among individuals with an adulthood diagnosis of schizophrenia or a schizophrenia spectrum disorder.

internalising psychopathology (Lancefield, Raudino, Downs, & Laurens, 2016; Laurens et al., 2020; Sandstrom et al., 2019), which in turn has been reported to be associated with academic achievement and educational attainment (Masten et al., 2005; Melkevik, Nilsen, Evensen, Reneflot, & Mykletun, 2016). Three, some evidence suggests that type of comparison group (e.g. healthy selected controls *v.* unselected cohorts) maybe an effect modifier of the association between premorbid general intelligence and schizophrenia (Dickson et al., 2012; Woodberry, Giuliano, & Seidman, 2008); however, due to the small number of studies included in the at-risk meta-analyses, it was not possible to investigate this potential source of heterogeneity. Four, the effect of an unmeasured publication bias in which published negative findings from samples of at-risk youth are less likely relative to prospective longitudinal studies of individuals who later develop schizophrenia.

Our study comprehensively examined both academic achievement and education level attained among individuals with schizophrenia, and academic achievement in those at-risk for the disorder and, in doing so, examined over four million individuals, of whom 13 179 had a diagnosis of schizophrenia and 4445 were deemed to be at-risk. That we were able to examine a range of potential effect modifiers (i.e. educational system, assessment type, age, measurement of educational level, school leaving age, and study quality) was a further strength of the study. However, three limitations must be noted. One, our findings for meta-analyses examining academic achievement may reflect differences in marking systems employed in the countries included. For example, a peer-referencing system (i.e. comparing the performance of a pupil to peers) was used widely in schools in the USA and Sweden up to 1997, but a criterion-referencing system (i.e. performance that is measured against pre-determined criteria) is used to assess pupils' performance in UK primary schools. A peer-referencing system may be associated with grade inflation (Kendler et al., 2016). It was not possible to account for these changes to, and differences in, marking systems in the present study, so the impact on our results is not clear. Two, our search strategy highlighted the different ways in which educational attainment is reported as a sample descriptive variable and will have failed to identify some relevant studies reporting level of educational attainment. Nonetheless, the electronic database search identified over 13 000 articles, and it was not feasible to further broaden our search strategy. Three, our findings may be confounded by the age of onset of schizophrenia, as the typical age range of individuals in higher education overlaps with the peak period of onset of the disorder.

Conclusion

Our meta-analyses show that academic and educational underachievement precedes adult-onset schizophrenia. Youth at-risk for the disorder, compared to those who are not, are likewise characterised by poor academic achievement. Although we observed significant heterogeneity across studies, and effect sizes were small to moderate in magnitude only, future research could investigate whether it is feasible to develop a tool using academic achievement and other known antecedents of the disorder to help identify at-risk pupils and thereby facilitate their access to early treatment and preventative inventions well before the onset of schizophrenia.

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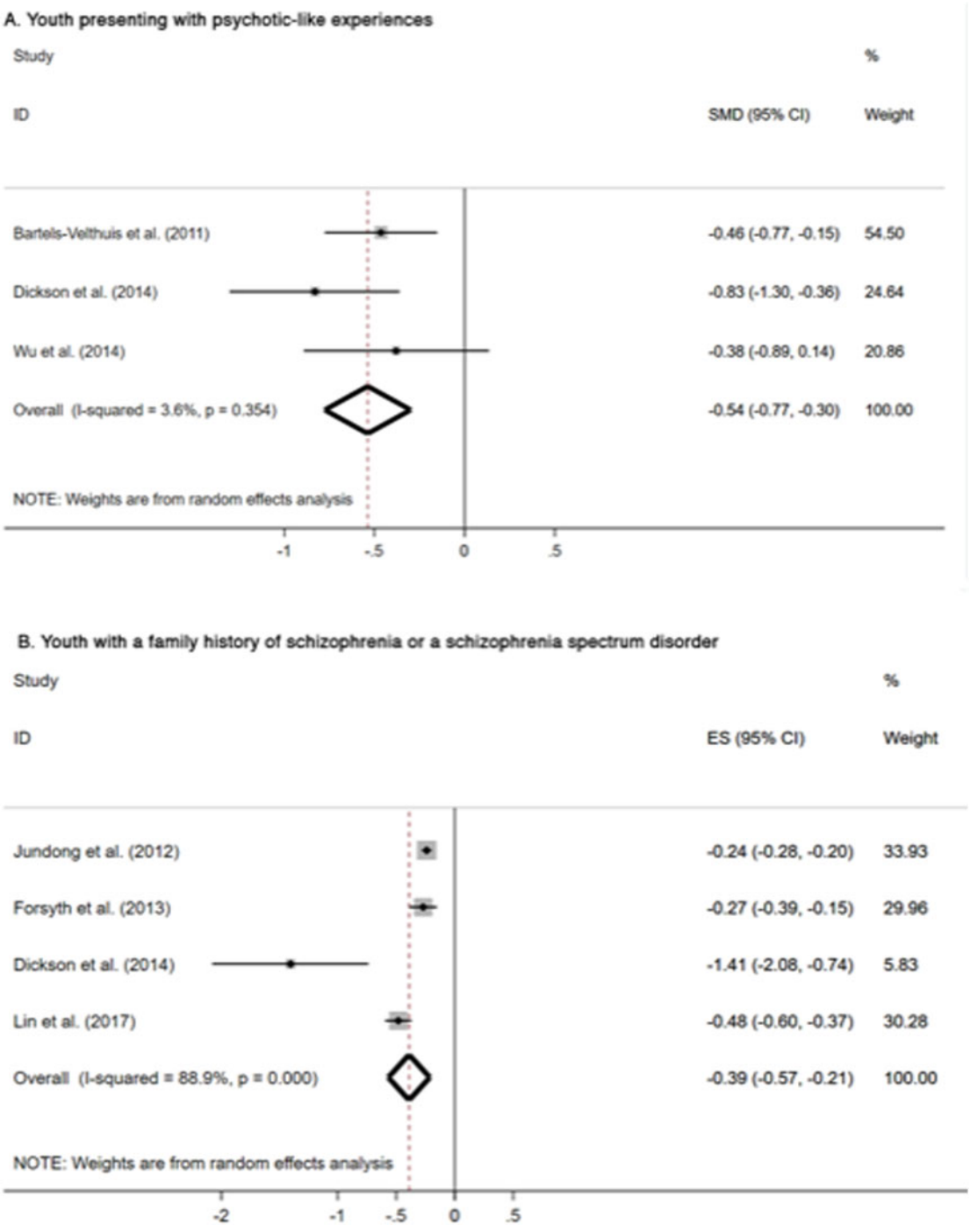


Fig. 3. Forest plot for general academic achievement among youth presenting with psychotic-like experiences (*a*) and youth with a family history of schizophrenia or a schizophrenia spectrum disorder (*b*).

Supplementary material. The supplementary material for this article can be found at https://doi.org/10.1017/S0033291720002354.

Acknowledgements. The authors would like to thank A. Lin, A. Vreeker, F. Stramecki, R. Kahn and M. Boks for providing the additional data necessary to complete the meta-analyses. HD, JHM and MJK are affiliated with the National Institute for Health Research (NIHR) Specialist Biomedical Research Centre for Mental Health at the South London and Maudsley NHS Foundation Trust and Institute of Psychiatry, Psychology & Neuroscience, King's College London, United Kingdom. AEC was supported by a Sir Henry Wellcome Postdoctoral Fellowship (107395/Z/15/Z) and a NARSAD Young Investigator Grant from the Brain & Behavior Research Foundation (28336). JD is supported by NIHR Clinician Science Fellowship award (CS-2018-18-ST2-014) and has received support from a Medical Research Council (MRC) Clinical Research Training Fellowship (MR/L017105/1) and Psychiatry Research Trust Peggy Pollak Research Fellowship in Developmental Psychiatry. KRL was supported by an Australian Research Council Future Fellowship (FT170100294).

Conflicts of interest. None.

Note

[1] Schizophrenia spectrum disorders include schizophrenia, schizoaffective disorder, and schizophreniform disorder and are hereafter referred to collectively as schizophrenia.

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