Psychological Medicine (2012), **42**, 743–755. © Cambridge University Press 2011
doi:10.1017/S0033291711001693

ORIGINAL ARTICLE

Meta-analyses of cognitive and motor function in youth aged 16 years and younger who subsequently develop schizophrenia

H. Dickson[1]*, K. R. Laurens[1,2,3], A. E. Cullen[1] and S. Hodgins[1,4,5]

[1] *Department of Forensic and Neurodevelopmental Sciences, Institute of Psychiatry, King's College London, UK*
[2] *Research Unit for Schizophrenia Epidemiology, School of Psychiatry, University of New South Wales, Sydney, Australia*
[3] *Schizophrenia Research Institute, Sydney, Australia*
[4] *Département de Psychiatrie, Université de Montréal, Canada*
[5] *Department of Psychiatry, Heidelberg University, Germany*

Background. Previous reviews have reported cognitive and motor deficits in childhood and adolescence among individuals who later develop schizophrenia. However, these reviews focused exclusively on studies of individuals with affected relatives or on population/birth cohorts, incorporated studies with estimated measures of pre-morbid intelligence, or included investigations that examined symptomatic at-risk participants or participants 18 years or older. Thus, it remains unclear whether cognitive and motor deficits constitute robust antecedents of schizophrenia. Meta-analyses were conducted on published studies that examined cognitive or motor function in youth aged 16 years or younger who later developed schizophrenia or a schizophrenia spectrum disorder (SSD) and those who did not.

Method. Twenty-three studies fulfilled the following inclusion criteria: (1) written in English; (2) prospective investigations of birth or genetic high-risk cohorts, or follow-back investigations of population samples; (3) objective measures of cognitive or motor performance at age 16 or younger; (4) results provided for individuals who did and who did not develop schizophrenia/SSD later in life; and (5) sufficient data to calculate effect sizes. Four domains of function were examined: IQ; Motor Function; General Academic Achievement; and Mathematics Achievement.

Results. Meta-analyses showed that, by age 16, individuals who subsequently developed schizophrenia/SSD displayed significant deficits in IQ ($d = 0.51$) and motor function ($d = 0.56$), but not in general academic achievement ($d = 0.25$) or mathematics achievement ($d = 0.21$). Subsidiary analysis indicated that the IQ deficit was present by age 13.

Conclusions. These results demonstrate that deficits in IQ and motor performance precede the prodrome and the onset of illness.

Received 23 November 2010; Revised 29 July 2011; Accepted 4 August 2011; First published online 6 September 2011

Key words: Child, high-risk, intelligence, psychosis, school performance.

Introduction

Evidence has accumulated to indicate that schizophrenia is, in part, a neurodevelopmental disorder (Murray & Lewis, 1987; Weinberger, 1987) characterized by abnormal functioning during childhood and adolescence (Niemi *et al*. 2003; Schenkel & Silverstein, 2004). Converging evidence from prospective longitudinal studies of population cohorts, prospective studies of individuals at elevated risk of schizophrenia because they have a family history of the illness, and 'follow-back' studies of adults with schizophrenia suggest that cognitive and motor dysfunctions precede the onset of schizophrenia. However, past literature reviews of cognitive functioning among children who develop schizophrenia/schizophrenia spectrum disorders (SSD) in adulthood have been limited in several respects: (i) they have focused exclusively on individuals with affected relatives (Niemi *et al*. 2003; Keshavan *et al*. 2010) or on population and/or birth cohorts (MacCabe, 2008; Welham *et al*. 2009*a*); (ii) they have not followed samples into adulthood and assessed them for schizophrenia/SSD; or (iii) they have included studies with estimated measures of pre-morbid intellectual functioning assessed in adulthood

* Address for correspondence: H. Dickson, Department of Forensic and Neurodevelopmental Sciences (Box P023), Institute of Psychiatry, King's College London, De Crespigny Park, London SE5 8AF, UK.
(Email: hannah.dickson@kcl.ac.uk)

when the participant already had a diagnosis of schizophrenia (Schenkel & Silverstein, 2004). Thus, it remains unclear whether cognitive and motor deficits constitute robust antecedents of schizophrenia.

During childhood, individuals who subsequently developed schizophrenia or SSD, compared to those who did not, were characterized by lower IQ (Woodberry *et al*. 2008) and poorer motor function (Walker *et al*. 1994; Rosso *et al*. 2000; Cannon *et al*. 2002, 2006; Schiffman *et al*. 2004). Additional cognitive decline prior to the onset of the prodromal phase of schizophrenia has been reported (Fuller *et al*. 2002; Osler *et al*. 2007). Academic achievement has also distinguished children who later developed schizophrenia/SSD, although findings have differed according to subject and assessment type (Watt & Lubensky, 1976; Jones *et al*. 1994; Crow *et al*. 1995; Fuller *et al*. 2002; Bilder *et al*. 2006; MacCabe *et al*. 2007). Furthermore, five studies reported no differences in pre-morbid academic performance (Isohanni *et al*. 1998; Cannon *et al*. 1999; Isohanni *et al*. 1999; Helling *et al*. 2003; Ang & Tan, 2004), which may reflect differences in the education systems characterizing the study cohorts. Taken together, the extant literature suggests that individuals who develop schizophrenia present poorer cognitive abilities in childhood than those who never develop schizophrenia/SSD. To date, little is known about the age at which these deficits emerge or their specific nature.

Two previous, widely cited, meta-analyses evaluated IQ among individuals who subsequently developed schizophrenia, and both yielded medium-sized deficits (Aylward *et al*. 1984; Woodberry *et al*. 2008). The present meta-analysis differs from the more recent of these, by Woodberry and colleagues, in several ways. First, several studies that were included in that meta-analysis reported the results of IQ assessments completed at multiple ages spanning a broad age range of 3–19 years (Albee *et al*. 1964; Watt & Lubensky, 1976; Jones *et al*. 1994; Ott *et al*. 1998; Cannon *et al*. 2000, 2002; Seidman *et al*. 2006). An overall unweighted mean effect size was calculated for each of these studies spanning multiple assessments and a broad age range, thereby providing a less robust estimate of pre-morbid IQ than might be achieved by using a single assessment completed during childhood/adolescence. Second, the previous meta-analysis included studies of symptomatic, help-seeking individuals meeting inclusion criteria for treatment in an intervention programme for persons at ultra-high risk for psychosis (Brewer *et al*. 2005; Lencz *et al*. 2006), and studies examining IQ among young adults (Lubin *et al*. 1962; Zammit *et al*. 2004; Reichenberg *et al*. 2005; Kremen *et al*. 2006; Whyte *et al*. 2006). Given that intellectual deficits have been reported to increase in magnitude with the onset of psychosis (Rabinowitz *et al*. 2000; Gunnell *et al*. 2002; Caspi *et al*. 2003), the effect sizes of the difference between participants who did and who did not develop schizophrenia in these studies may reflect some early prodromal disease process rather than an antecedent of schizophrenia. Third, although the previous meta-analysis included subanalyses that examined IQ by narrower age bands, only three studies were included in the meta-analysis that assessed participants aged 13 years or younger. Finally, unlike both previous meta-analyses that focused solely on IQ (Aylward *et al*. 1984; Woodberry *et al*. 2008), the present meta-analysis includes examination of additional domains of academic achievement and motor functioning.

The aim of the present meta-analyses was to examine IQ, motor function and academic achievement in children and young adolescents (aged $\leqslant$16 years) who subsequently developed schizophrenia/SSD. A recent review of studies on individuals at ultra-high risk for psychosis indicated a typical age of onset of basic prodromal symptoms of greater than 16 years (Ruhrmann *et al*. 2010). By restricting the meta-analyses to studies of children aged 16 years or younger, the present meta-analyses aimed to determine whether deficits in IQ, motor function and academic achievement are present before the typical age of onset of the prodrome.

Method

Sample

Meta-analyses were conducted to identify the effect sizes of differences in scores obtained on cognitive and motor performance measures by individuals aged 16 years or younger who subsequently developed schizophrenia compared to those who did not. Articles were identified through literature searches conducted in PubMed/Medline and PsycINFO, using the keywords 'schizophrenia' and 'IQ' or 'intelligence' or 'motor' or 'school' or 'scholastic' and 'premorbid' or 'prospective' or 'cohort' or 'high risk'. References from articles and relevant literature reviews were also examined for possible inclusion in meta-analyses. Inclusion criteria were: (1) written in English; (2) published or unpublished prospective investigations of birth cohorts or genetic high-risk samples, or follow-back investigations of population samples; (3) objective measures of cognitive or motor function when participants were aged 16 or younger; (4) results provided for cohort members who did and who did not develop schizophrenia or an SSD later in life; and (5) sufficient data to calculate effect sizes.

https://doi.org/10.1017/S0033291711001693 Published online by Cambridge University Press

The initial literature search by the first author identified 2623 studies, of which 34 fulfilled the inclusion criteria. A co-author independently reviewed these studies to verify that inclusion criteria were met. Among the 34 studies, 10 contained samples that overlapped (Lane & Albee, 1963, 1968; Albee *et al*. 1964; Cannon *et al*. 2000, 2002, 2006; Niendam *et al*. 2003; Seidman *et al*. 2006). To avoid multiple entries on the same sample, only data from the study containing the largest number of participants were analysed (Albee *et al*. 1964; Cannon *et al*. 2000, 2002; Seidman *et al*. 2006). Ten studies reported assessments of participants at multiple ages ranging from 3 to 19 years (Watt & Lubensky, 1976; Jones *et al*. 1994; Crow *et al*. 1995; Ott *et al*. 1998; Cannon *et al*. 2000, 2002; Rosso *et al*. 2000; Ang & Tan, 2004; Bilder *et al*. 2006; Welham *et al*. 2009*b*). From these studies, only the results from a single assessment completed when participants were between 4 and 14 years old were included in the meta-analyses. Seven studies reported insufficient data to calculate an effect size (Ambelas, 1992; Crow *et al*. 1995; Cannon *et al*. 1999, 2006; Erlenmeyer-Kimling *et al*. 2000; Fuller *et al*. 2002; Walker *et al*. 2002). Additional data from authors were obtained for all but two studies (Ambelas, 1992; Walker *et al*. 2002), but data from two studies remained insufficiently detailed to satisfy the inclusion criteria (Erlenmeyer-Kimling *et al*. 2000; Fuller *et al*. 2002). Two other papers reported similar data (Isohanni *et al*. 1998, 1999); only data in the 1998 publication were included in the meta-analyses. Two studies that reported IQ scores for participants aged between 8 and 20 years were excluded (Bower *et al*. 1960; Sørensen *et al*. 2006). Another study, which presented results for performance IQ between members of a rubella-exposed birth cohort who subsequently developed schizophrenia and those who did not, was also excluded from the meta-analysis (Brown *et al*. 2001).

Meta-analyses were performed using the results from the 23 studies that fulfilled the inclusion criteria. The results were categorized into four domains of cognitive and motor function. Table 1 presents details of each study included in the meta-analyses, with a description of the sample, participant age at assessment, the test instrument used, and effect sizes denoting the difference in performance between the participants who subsequently developed schizophrenia/SSD compared to those who did not. Across all 23 studies, the age of the participants at the time of assessment ranged from 2 to 16 years. Twenty-one of the 23 studies included males and females whereas two examined only males (Ang & Tan, 2004; Osler *et al*. 2007). The comparison groups varied widely across studies, and were described as classmates, child psychiatric patients with no adult mental disorder, members of birth cohorts who did not develop schizophrenia/SSD, members of birth cohorts who did not develop any major mental disorder, and participants with or without a family history of schizophrenia/SSD.

Statistical analyses

Meta-analyses were conducted with Stata version 10 (Stata Corporation, USA) using a random effects model (Dersimonian & Laird, 1986) that assumes that the effects being investigated in a set of studies are a random sample drawn from a population of possible effect sizes. Meta-analyses were performed on difference scores for each domain of functioning, comparing participants who developed schizophrenia/SSD to those who did not. Difference scores were standardized by calculating Cohen's *d* effect sizes (Cohen, 1988) and interpreted according to effect size indices of 'small (0.2)', 'medium (0.5)' and 'large (0.8)' (Cohen, 1992). The summary effect sizes for each domain were the standardized mean differences (SMDs), weighted by the precision of the SMD. For each SMD, a *z* value and a significance level provided an indication of the two-sided statistical significance of the association at the 95% probability level. For the IQ domain, the effect size from one study was an extreme outlier (Woodberry *et al*. 2008), so the analysis was conducted with and without the inclusion of this study (Amminger *et al*. 2000).

The significance and the magnitude of heterogeneity across studies were calculated using the *Q* statistic and I^2 statistic. Where there was significant heterogeneity within a domain, and where there were sufficient studies to provide adequate statistical power (i.e. for IQ only), effect size moderators were examined. Three potential moderator variables were examined: comparison group, IQ assessment instrument, and disorder outcome. Comparison group (matched comparison group or unselected cohort) was included as it had been reported to be a significant source of heterogeneity in a previous meta-analysis on IQ (Woodberry *et al*. 2008). An instrument used to assess IQ (i.e. Wechsler Intelligence Scales or other test) was included as different types of IQ tests, particularly tests that are older, may provide variable estimates of IQ (Sattler, 2001). We also examined disease outcome (i.e. schizophrenia or SSD) based on the rationale that individuals who develop schizophrenia may differ from those who develop SSD. For each variable, a regression model was estimated using an unrestricted maximum likelihood model. Publication bias was assessed graphically and statistically using published methods (Begg & Mazumdar, 1994; Egger *et al*. 1997).

Table 1. *Study details and effect sizes for meta-analyses*

Study	Sample	Schizophrenia/SSD		Age at assessment (years)	Domain measure	Effect size[a]
		Present	Absent			
IQ						
Albee *et al*. (1964)	A follow-back study of adults from Cleveland, USA	154 Schizophrenia patients recruited from hospital in-patient unit	4166 Children in same school year	11–12	Cleveland classification IQ test	0.64[b]
Offord (1974)	A follow-back study of white adults from Pennsylvania, USA	116 Schizophrenia patients (including those with a diagnosis of mild to moderate retardation) recruited from in-patient unit: 51 males, 65 females	116 School classmates matched on ethnicity, sex and social class of origin: 51 males, 65 females	During first 9 years of school (exact age not given)	Group administered IQ test	0.69[b]
Watt & Lubensky (1976)	A follow-back study of adults from Massachusetts, USA	36 Schizophrenia patients recruited from hospital in-patient unit	36 School classmates matched on sex, ethnicity and social class of origin	4–12	Kuhlman–Anderson IQ test/Otis self-administration test	0.49[b]
Jones *et al*. (1994)	British birth cohort born 1946	30 Cohort members with a diagnosis of schizophrenia: 20 males, 10 females	4715 Cohort members without schizophrenia: 2457 males, 2259 females	11	Group administered IQ test	0.30[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	General ability IQ test	0.62[b]
Ott *et al*. (1998)	New York High-Risk Project	18 Study participants with a diagnosis of schizophrenia or SDD	189 Study participants from a similar school district with no mental disorder in adulthood	7–12	WISC-R IQ	0.78[b]
Cannon *et al*. (2000)	Birth cohort born 1959–1966 from Philadelphia, USA	57 Cohort members with a diagnosis of schizophrenia or SSD: 41 males, 16 females	5829 Cohort members with no mental disorder in adulthood: 2865 males, 2964 females	7	WISC	0.53[b]
Amminger *et al*. (2000)	A follow-back study of adults born 1960–1971 in Vienna	8 Child psychiatric patients with a diagnosis of schizophrenia or SSD in adulthood	13 Child psychiatric patients with no diagnosis in adulthood	$\leqslant$16	WISC	1.85[b]
Cannon *et al*. (2002)	Birth cohort born 1972–1973 from Dunedin, New Zealand	32 Cohort members with a diagnosis of SSD	579 Cohort members with no diagnosis of SSD, mania or anxiety/depression	11	WISC	0.44[b]

Seidman *et al*. (2006)	Birth cohort born 1959–1965 from New England, USA	31 Cohort members with a diagnosis of schizophrenia: 79.4% males, 20.6% females	61 Cohort members with no diagnosis of SSD, bipolar disorder, recurrent depressive disorder, suicide attempts or psychiatric hospitalizations in adulthood: 54.8% males, 45.2% females	7	WISC	0.65[b]
Osler *et al*. (2007)	Danish birth cohort of males born in 1953	87 Cohort members with a diagnosis of schizophrenia	6790 Cohort members who also completed a cognitive assessment at 18 years	12	Harnquist IQ test	0.14[b]
Welham *et al*. (2009*b*)[c]	Birth cohort born 1981–1984 from Brisbane, Australia	53 Cohort members with a diagnosis of non-affective psychosis.	3204 Cohort members without a diagnosis of non-affective psychosis in adulthood	14	Raven's Standard Progressive Matrices Test	0.35[b]
Sørensen *et al*. (2010)	Study participants drawn from Copenhagen Perinatal Cohort, individuals born 1959–1961	32 Study participants with a diagnosis of SSD	133 Study participants with no psychiatric diagnosis in adulthood	10–13	WISC	0.45[b]
Motor Function						
Walker *et al*. (1994)	A follow-back study of adults from Atlanta, USA	30 Schizophrenia patients recruited from hospital in-patient unit: 23 males, 7 females	21 Adults with no family history of mental disorders: 7 males, 14 females	2–15	Motor skills ratings (from childhood home videos)	0.39[b]
Rosso *et al*. (2000)	Birth cohort born 1959–1966 from Philadelphia, USA	66 Cohort members with a diagnosis of schizophrenia or SSD	6473 Cohort members with no mental disorder in adulthood	7	Motor coordination test	0.48[b]
Cannon *et al*. (2002)	Birth cohort born 1972–1973 from Dunedin, New Zealand	24 Cohort members with a diagnosis of SSD	579 Cohort members with no diagnosis of SSD, mania or anxiety/depression	9	Basic Ability Motor Test	0.73[b]
Schiffman *et al*. (2004)	Study participants drawn from Copenhagen Perinatal Cohort, comprising individuals born 1959–1961	32 Study participants with a diagnosis of schizophrenia	133 Study participants with no mental disorder in adulthood	11–13	Motor coordination scale.	0.69[b]
Academic Achievement: General						
Isohanni *et al*. (1998)	Northern Finland birth cohort 1966	84 Cohort members with a diagnosis of schizophrenia: 54 males, 30 females	10414 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 diagnoses other than schizophrenia	11	Year 4 examination results	0.02[b]
Ang & 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

Table 1 (*cont.*)

Study	Sample	Schizophrenia/SSD		Age at assessment (years)	Domain measure	Effect size[a]
		Present	Absent			
Bilder *et al*. (2006)	A follow-back study of adults from New York	59 Study participants with a diagnosis of schizophrenia or SDD recruited from an in-patient 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*. (2007)	Population-based historical cohort study of adults born 1973–1983 in Sweden	493 Cohort members with a diagnosis of schizophrenia: 318 males, 175 females	713876 Cohort members with no diagnosis: 364967 males, 348909 females	15–16	Swedish National Examination grade point average	0.52[b]
Academic Achievement: Mathematics						
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 Maths administered 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 in-patient unit	119 School classmates before/after each case	12	End of year teacher assigned grades	0.14[b]
Ang & 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

SSD, Schizophrenia spectrum disorder; WISC-R, Wechsler Intelligence Scale for Children – Revised.

[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 and a comparison group, except for the following: (i) IQ: for Offord (1974), the results were presented across gender, so data were collapsed and overall means and standard deviations were used; for Watt & Lubensky (1976), the effect size was computed from the sample size and *t* statistic; for Jones *et al*. (1994), effect sizes were taken from the Woodberry *et al*. (2008) meta-analysis; for Crow *et al*. (1995), effect size was estimated from the sample size and *f* statistic; for Welham *et al*. (2009*b*), effect size was calculated by converting β to *t* statistics (b/seB) with effect size derived from *t* statistic and sample size for both males and females. A mean weighted effect size was then calculated based on sample size by gender. (ii) Motor Function: for Rosso *et al*. (2000), the odds ratio was transformed into a Cohen's *d* using a method outlined by (Chinn, 2000). (iii) Academic Performance: Mathematics: for both Jones *et al*. (1994) and Helling *et al*. (2003), sample 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] Positive values indicate better performance in the comparison group.

[c] Sample size for males and females were taken from measures of attentional dysfunction because not available for Raven's Standard Progressive Matrices Test.

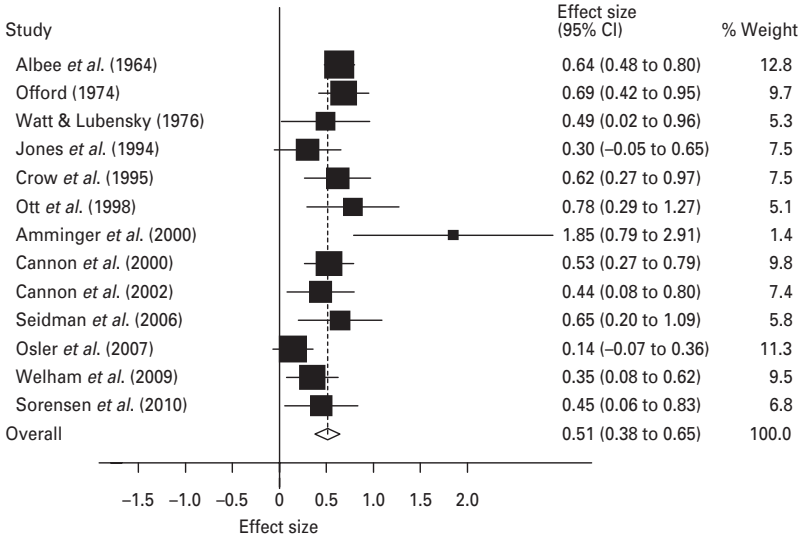

Fig. 1. Forest plot for IQ.

In domains with five studies or less, publication bias could not be explored (Sutton *et al*. 2000).

Results

IQ

A meta-analysis of the 13 studies included in the IQ domain indicated that youth aged 16 years or younger who subsequently developed schizophrenia/SSD obtained lower IQ scores than youth who did not develop these disorders. As illustrated in Fig. 1, a medium effect size was obtained [SMD 0.51, 95% confidence interval (CI) 0.38–0.65, $z=7.51$, $p<0.001$]. Significant heterogeneity was detected across studies ($Q=26.55$, df $=12$, $p<0.05/I^2=54.8\%$), but neither comparison group, IQ measure nor diagnostic outcome explained the heterogeneity. No publication bias was detected. After removing one study from the meta-analysis due to an effect size that was an outlier to the group (Amminger *et al*. 2000), the observed effect size remained of medium magnitude (SMD 0.49, 95% CI 0.37–0.61, $z=8.03$, $p<0.001$). Significant heterogeneity was detected ($Q=20.25$, df $=11$, $p<0.05/I^2=45.7\%$). Again, neither comparison group, IQ measure nor diagnostic outcome was associated with heterogeneity.

The meta-analysis was repeated after excluding two studies that assessed participants between the ages of 14 and 16 years (Amminger *et al*. 2000; Welham *et al*. 2009*b*). All participants in the remaining 11 studies were aged 13 years or younger. This analysis yielded an effect size that was similar in magnitude to that calculated for participants aged 16 years or younger (SMD 0.51, 95% CI 0.38–0.64, $z=7.69$, $p<0.001$). As before, significant heterogeneity was detected ($Q=19.11$, df $=10$, $p<0.05/I^2=47.7\%$). Again, heterogeneity was not associated with the type of comparison group, the measure of IQ or the outcome diagnosis of schizophrenia or SSD. No publication bias was detected.

Motor function

Of the four studies included in the motor function domain, the results from the meta-analysis showed that individuals aged 16 years or younger who subsequently developed schizophrenia/SSD, as compared to those who did not, displayed significant deficits in motor function (see Fig. 2) that were moderate in size (SMD 0.56, 95% CI 0.38–0.74, $z=6.25$ $p<0.001$). No significant heterogeneity was detected across studies ($Q=1.87$, df $=3$, $p=0.60/I^2=0.0\%$).

Academic Achievement

General

Five studies examined General Academic Achievement among youth aged 16 years or younger who subsequently developed schizophrenia/SSD, and the results indicated poorer overall academic achievement compared to youth who did not later develop schizophrenia/SSD (see Fig. 3). However, the effect size of the group difference was small and non-significant (SMD 0.25, 95% CI −0.03 to 0.53, $z=1.74$, $p=0.08$). Significant heterogeneity in the results was detected ($Q=40.72$, df $=4$, $p<0.001/I^2=90.2\%$), but could not be examined further given the limited number of studies comprising this domain.

https://doi.org/10.1017/S0033291711001693 Published online by Cambridge University Press

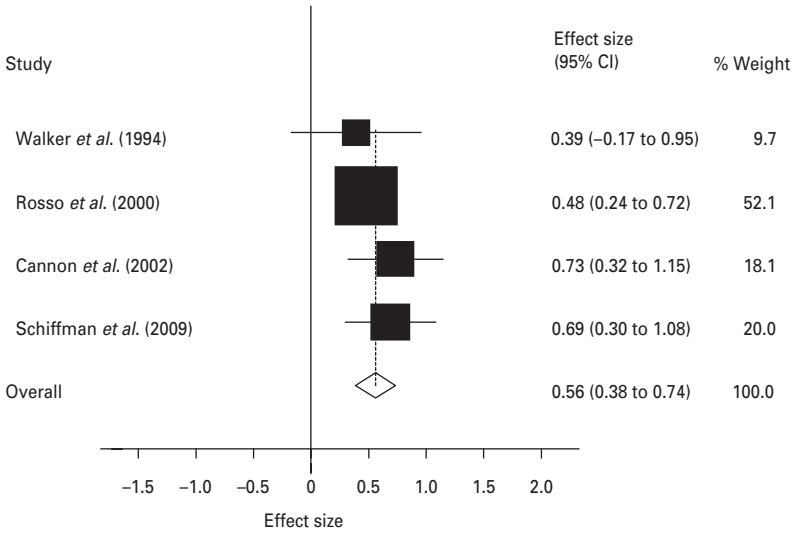

Fig. 2. Forest plot for motor function.

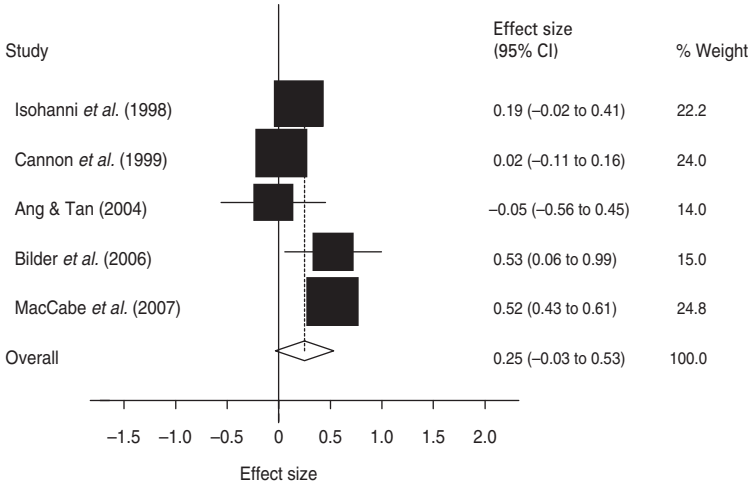

Fig. 3. Forest plot for Academic Achievement: General.

Mathematics

The results of the meta-analysis of four studies showed that youth aged 16 years and younger who later developed schizophrenia/SSD, as compared to those who did not, achieved more poorly on tests of mathematics. However, as indicated in Fig. 4, the effect size of the difference between the two groups was small and non-significant (SMD 0.21, 95% CI −0.09 to 0.51, $z=1.40$, $p=0.16$). Significant heterogeneity was detected ($Q=7.96$, df = 3, $p<0.05/I^2=62.3\%$), but could not be examined further because of an insufficient number of studies within the domain.

Discussion

To our knowledge, these are the first meta-analyses examining both cognitive and motor performance among youth aged 16 years or younger who later developed schizophrenia/SSD. The meta-analyses demonstrate that participants who subsequently developed schizophrenia/SSD displayed lower IQ and poorer motor function by age 16 than individuals who did not develop these disorders. Furthermore, there were sufficient studies to conduct a meta-analysis that showed that the deficit in IQ was present by age 13. By contrast, overall academic achievement and performance on tests of mathematics did not significantly distinguish those who subsequently developed schizophrenia/SSD from those who did not. These results extend previous findings by establishing that low IQ and impaired motor performance precede the prodrome and onset of illness.

Although significant heterogeneity was detected in the meta-analyses of IQ and the two domains of academic performance, the factors affecting heterogeneity

https://doi.org/10.1017/S0033291711001693 Published online by Cambridge University Press

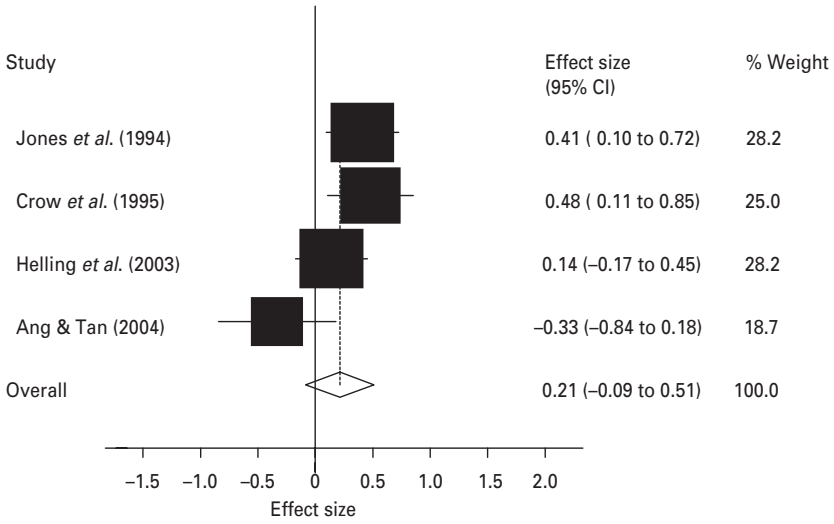

Fig. 4. Forest plot for Academic Achievement: Mathematics.

could be examined only for IQ. Analyses indicated that heterogeneity reported for the IQ results was not due to the type of comparison group used (matched comparison or unselected cohort), the test used to assess IQ (Wechsler or other) or diagnostic outcome (schizophrenia or SSD).

The present meta-analyses obtained the same medium effect size for the difference in IQ by age 16 and by age 13 ($d = 0.51$), between individuals who did and who did not develop schizophrenia/SSD later in life. The present IQ meta-analysis included results from five studies (Crow *et al*. 1995; Amminger *et al*. 2000; Osler *et al*. 2007; Welham *et al*. 2009*b*; Sørensen *et al*. 2010) that had not been included in previous meta-analyses (Aylward *et al*. 1984; Woodberry *et al*. 2008). Nevertheless, the effect sizes obtained in the present analyses by age 16 and by age 13 are similar in magnitude to that reported in a previous meta-analysis ($d = 0.54$) that included participants who were symptomatic or deemed to be at risk for psychosis (Woodberry *et al*. 2008). Thus, our meta-analyses indicate that, among individuals who later develop schizophrenia/SSD, a deficit in IQ is measurable by early to mid-adolescence.

Consistent with the findings of a previous meta-analysis (Woodberry *et al*. 2008), our current analysis indicated that the specific measure of IQ used did not account for significant heterogeneity in the results. Unlike the present meta-analysis, however, Woodberry *et al*. (2008) reported that the type of comparison group (i.e. unselected cohort *versus* matched comparison group) accounted for significant effect-size heterogeneity. Their finding was attributed primarily to the inclusion of one study of 18-year-old military conscripts that used an army classification battery to assess IQ (Lubin *et al*. 1962).

It was not possible to examine all potential moderator variables in the meta-analysis of IQ. This was because of the relatively small number of studies that met inclusion criteria and the limited data available from each study. Examining a larger number of potential moderators may increase the likelihood of drawing false positive conclusions (Thompson & Higgins, 2002). Given the evidence that the prevalence of schizophrenia is higher in males than in females (Aleman *et al*. 2003; McGrath *et al*. 2004), it is possible that gender differences may have contributed to the heterogeneity of the results in the IQ domain, as reported in one previous meta-analysis (Aylward *et al*. 1984), but not in another (Woodberry *et al*. 2008). Unfortunately, the data available for inclusion in the present study were insufficient to permit statistical analysis of gender differences. Five studies included in the present meta-analysis reported the prevalence of schizophrenia separately by gender, and all but one (Welham *et al*. 2009*b*) found higher rates among males than females (Offord, 1974; Jones *et al*. 1994; Cannon *et al*. 2000; Seidman *et al*. 2006). In these studies, the effect sizes of the differences in IQ of participants who did and who did not develop schizophrenia/SSD ranged from small to medium. Only two studies included in the present meta-analysis reported IQ scores separately for males and females (Offord, 1974; Welham *et al*. 2009*b*). These studies indicated that, among the participants who subsequently developed schizophrenia, the males obtained lower IQ scores than the females. However, we did not observe a larger effect size in a study that examined only males (Osler *et al*. 2007) than in studies that included both males and females.

It is unclear whether lower than average IQ is an antecedent specific to schizophrenia. Lower than

https://doi.org/10.1017/S0033291711001693 Published online by Cambridge University Press

average IQ has been reported to characterize children (Van Os *et al*. 1997; Koenen *et al*. 2009) and young adults, particularly males (Zammit *et al*. 2004; Mortensen *et al*. 2005; Tiihonen *et al*. 2005; Urfer-Parnas *et al*. 2009), who subsequently develop mental disorders other than schizophrenia. However, these findings are inconsistent and several studies have failed to identify IQ differences among children/adolescents who subsequently developed bipolar disorder (Cannon *et al*. 2002; Reichenberg *et al*. 2002; Zammit *et al*. 2004).

The present meta-analysis indicated that, by age 16, individuals who subsequently developed schizophrenia/SSD displayed poorer motor function than their peers who remained healthy. The lack of heterogeneity evidenced in this domain suggests that motor dysfunction is the most robust characteristic that distinguishes children/adolescents who subsequently develop schizophrenia. As noted previously, this is one of the most consistent findings in the literature on the antecedents of schizophrenia (Schenkel & Silverstein, 2004). Also consistent with these findings are the results of three studies that could not be included in the present meta-analysis of motor function because of lack of available data (Crow *et al*. 1995), or overlapping samples (Schiffman *et al*. 2004; Cannon *et al*. 2006). These studies all reported deficits in motor function among children/adolescents aged 7–13 years who developed schizophrenia/SSD in adulthood. However, one study (Walker *et al*. 1994) observed a reduction in motor dysfunction with increasing age among children who later developed schizophrenia, which may reflect the insensitivity of measures of motor function or age-related improvements in motor function similar to those reported among typically developing children. In addition, one prospective study of a birth cohort that repeatedly assessed children did not detect motor function deficits at every age among those who later developed schizophreniform disorder (Cannon *et al*. 2002). Given the relative paucity of prospective longitudinal studies that have assessed motor function through childhood and adolescence with repeated assessments, it is unclear whether motor dysfunction is present across all periods of development among individuals developing schizophrenia/SSD.

Whether or not children and adolescents developing schizophrenia/SSD do poorly in school is currently unclear. Two reviews found that repeating a school year and achieving poor grades were associated with an increased risk of developing SSD (MacCabe, 2008; Welham *et al*. 2009*a*). The results of the present meta-analyses indicated no significant difference in either overall academic achievement or performance on mathematics tests between individuals who did and did not later develop schizophrenia/SSD. This may be due, in part, to the inclusion of a study with a poorly matched comparison group (Ang & Tan, 2004). In that study, the individuals who subsequently developed psychosis showed deterioration in mathematics test scores from age 12 to age 16. In the present meta-analysis, all of the participants in the studies that assessed performance in mathematics were aged 11 or 12 years. Furthermore, a study excluded from the Mathematics domain due to age of participants also found significant differences in mathematics achievement between individuals aged 12–18 years who did and did not develop schizophrenia in adulthood (Watt & Lubensky, 1976). It is possible that individuals who later develop schizophrenia/SSD display a decline in performance on mathematics tests after age 12. Although significant heterogeneity was reported for both domains of academic performance, it could not be explored because of the limited number of studies meeting inclusion criteria. It is possible that the heterogeneity observed in the present meta-analysis and the inconsistent results across studies reflect differences in educational systems and measures of academic achievement that may preclude the examination of these domains in future meta-analyses.

Strengths and limitations

The present study is characterized by two principal strengths. One, the meta-analyses included only studies that had assessed performance in youth aged 16 years or younger. None of the 23 studies included in the meta-analyses reported that they had assessed prodromal symptoms at the same time as they assessed cognitive and/or motor performance. However, given the participants' age at the time of assessment, it is unlikely that the participants who subsequently developed schizophrenia/SSD had entered the prodromal phase of illness. Thus, the present results suggest that deficits in IQ and motor function emerge during childhood and early adolescence, prior to the onset of the prodrome. A second strength of the present meta-analyses was the examination of four domains of functioning: IQ, motor function, general academic achievement, and achievement in mathematics tests. Only the IQ domain had been examined previously using meta-analytic techniques. Despite using broad search terms to identify relevant studies, only 23 studies met final criteria for inclusion in the present meta-analyses. This was primarily due to the limited number of studies of cognitive and motor function in youth aged 16 years or younger who subsequently developed schizophrenia/SSD. More evidence is needed. Although the small number of

studies precluded the examination of the heterogeneity of results obtained in domains other than IQ, the strict criterion requiring that participants had been assessed by age 16 allowed us further understanding of the development of schizophrenia/SSD.

A potential caveat relates to the use of meta-analytic methods for comparisons of cognitive and motor function among children/adolescents of differing ages, which may fail to reflect the discontinuous nature of cognitive development (Harris, 1995). However, of the 23 studies included in the present meta-analyses, 18 assessed participants at 13 years or under, and only six studies examined participants with an age range of more than 3 years (Offord, 1974; Watt & Lubensky, 1976; Walker *et al*. 1994; Ott *et al*. 1998; Amminger *et al*. 2000; Sørensen *et al*. 2010). As only a few studies reported results separately for males and females, the meta-analyses could not contribute to the growing evidence on sex differences in the development of schizophrenia/SSD.

Conclusions

The meta-analyses provide evidence that among youth aged 16 years or younger, individuals who subsequently developed schizophrenia/SSD displayed lower IQ and poorer motor function than youth who did not develop illness. These results extend previous findings by showing that these deficits precede the onset of illness and of the prodrome. The results also endorse the view that schizophrenia, at least in part, represents a disorder of neurodevelopment. Stable cognitive and motor deficits in childhood and early adolescence are potential targets for interventions that may modulate illness development or reduce the extent of dysfunction present in individuals who develop schizophrenia/SSD.

Acknowledgements

We thank M. Cannon, A. Caspi, T. Crow, J. Done, L. Erlenmeyer-Kimling, R. Fuller, M. Isohanni, J. Jokelainen, P. Jones, J. MacCabe, T. Moffit and M. Osler for providing the data necessary to complete the meta-analyses, and D. Stahl for statistical advice.

H.D. was supported by a Ph.D. studentship from the NIHR BRC. K.R.L. was supported in part by an NIHR Career Development Fellowship.

Declaration of Interest

All authors are affiliated with the National Institute for Health Research (NIHR) Specialist Biomedical Research Centre (BRC) for Mental Health at the South London and Maudsley National Health Service (NHS) Foundation Trust and the Institute of Psychiatry, King's College London, UK.

References

Albee GW, Lane EA, Reuter JM (1964). Childhood intelligence of future schizophrenics and neighourhood peers. *Journal of Psychology* **58**, 141–144.

Aleman A, Kahn R, Selten J (2003). Sex differences in the risk of schizophrenia: evidence from meta-analysis. *Archives of General Psychiatry* **60**, 565–571.

Ambelas A (1992). Preschizophrenics: adding to the evidence, sharpening the focus. *British Journal of Psychiatry* **160**, 401–404.

Amminger GP, Schlögelhofer M, Lehner T, Ott SL, Friedrich MH, Aschauer HN (2000). Premorbid performance IQ deficits in schizophrenia. *Acta Psychiatrica Scandinavica* **102**, 414–422.

Ang Y-G, Tan H-Y (2004). Academic deterioration prior to first episode schizophrenia in young Singaporean males. *Psychiatry Research* **121**, 303–307.

Aylward E, Walker E, Bettes B (1984). Intelligence in schizophrenia: meta-analysis of the research. *Schizophrenia Bulletin* **10**, 430–459.

Begg CB, Mazumdar M (1994). Operating charactertistics of a rank correlation test for publication bias. *Biometrics* **50**, 1088–1101.

Bilder RM, Reiter G, Bates J, Lencz T, Szeszko P, Goldman RS, Robinson D, Lieberman JA, Kane JM (2006). Cognitive development in schizophrenia: follow-back from the first episode. *Journal of Clinical and Experimental Neuropsychology* **28**, 270–282.

Bower EM, Shellhamer TA, Daily JM (1960). School characteristics of male adolescents who later became schizophrenic. *American Journal of Orthopsychiatry* **30**, 712–729.

Brewer WJ, Francey SM, Wood SJ, Jackson HJ, Pantelis C, Phillips LJ, Yung AR, Anderson VA, McGorry PD (2005). Memory impairments identified in people at ultra-high risk for psychosis who later develop first-episode psychosis. *American Journal of Psychiatry* **162**, 71–78.

Brown AS, Cohen P, Harkavy-Friedman J, Babulas V, Malaspina D, Gorman JM, Susser ES (2001). Prenatal rubella, premorbid abnormalities, and adult schizophrenia. *Biological Psychiatry* **49**, 473–486.

Cannon M, Caspi A, Moffitt TE, Harrington H, Taylor A, Murray RM, Poulton R (2002). Evidence for early-childhood, pan-developmental impairment specific to schizophreniform disorder: results from a longitudinal birth cohort. *Archives of General Psychiatry* **59**, 449–456.

Cannon M, Jones P, Huttunen MO, Tanskanen A, Huttunen T, Rabe-Hesketh S, Murray RM (1999). School performance in Finnish children and later development of schizophrenia: a population-based longitudinal study. *Archives of General Psychiatry* **56**, 457–463.

Cannon M, Moffitt T, Caspi A, Murray R, Harrington H, Poulton R (2006). Neuropsychological performance at the age of 13 years and adult schizophreniform

disorder: prospective birth cohort study. *British Journal of Psychiatry* **189**, 463–464.

Cannon TD, Bearden CE, Hollister JM, Rosso IM, Sanchez LE, Hadley T (2000). Childhood cognitive functioning in schizophrenia patients and their unaffected siblings: a prospective cohort study. *Schizophrenia Bulletin* **26**, 379–393.

Caspi A, Reichenberg A, Weiser M, Rabinowitz J, Kaplan Z, Knobler H, Davidson-Sagi N, Davidson M (2003). Cognitive performance in schizophrenia patients assessed before and following the first psychotic episode. *Schizophrenia Research* **65**, 87–94.

Chinn S (2000). A simple method for converting an odds ratio to effect size for use in meta-analysis. *Statistics in Medicine* **19**, 3127–3131.

Cohen J (1988). *Statistical Power Analysis for the Behavioral Sciences*. Erlbaum: Hillsdale, NJ.

Cohen J (1992). A power primer. *Psychological Bulletin* **112**, 155–159.

Crow TJ, Done DJ, Sacker A (1995). Childhood precusors of psychosis as clues to evolutionary origins. *European Archives of Psychiatry and Clinical Neuroscience* **245**, 61–69.

Dersimonian R, Laird N (1986). Meta-analysis in clinical trials. *Controlled Clinical Trials* **7**, 177–188.

Egger M, Davey Smith G, Schneider M, Minder C (1997). Bias in meta-analysis detected by a simple, graphical test. *British Medical Journal* **315**, 629–634.

Erlenmeyer-Kimling L, Rock D, Roberts SA, Janal M, Kestenbaum C, Cornblatt B, Adamo UH, Gottesman II (2000). Attention, memory, and motor skills as childhood predictors of schizophrenia-related psychoses: the New York High-Risk Project. *American Journal of Psychiatry* **157**, 1416–1422.

Fuller R, Nopoulos P, Arndt S, O'Leary D, Ho B-C, Andreasen NC (2002). Longitudinal assessment of premorbid cognitive functioning in patients with schizophrenia through examination of standardized scholastic test performance. *American Journal of Psychiatry* **159**, 1183–1189.

Gunnell D, Harrison G, Rasmussen F, Fouskakis D, Tynelius PER (2002). Associations between premorbid intellectual performance, early-life exposures and early-onset schizophrenia: cohort study. *British Journal of Psychiatry* **181**, 298–305.

Harris CJ (1995). *Developmental Neuropsychiatry*. Oxford University Press: New York.

Helling I, Öhman A, Hultman CM (2003). School achievements and schizophrenia: a case control study. *Acta Psychiatrica Scandinavica* **108**, 381–386.

Isohanni I, Auml Rvelin M-R, Nieminen P, Jones P, Rantakallio P, Jokelainen J, Isohanni M (1998). School performance as a predictor of psychiatric hospitalization in adult life. A 28-year follow-up in the Northern Finland 1966 birth cohort. *Psychological Medicine* **28**, 967–974.

Isohanni I, Jarvelin M, Jones P, Jokelainen J, Isohanni M (1999). Can excellent school performance be a precusor of schizophrenia? A 28-year follow-up in the Northern Finland 1966 birth cohort. *Acta Psychiatrica Scandinavica* **100**, 17–26.

Jones P, Rodgers B, Murray R, Marmot M (1994). Child development risk factors for adult schizophrenia in the British 1946 birth cohort. *Lancet* **344**, 1398–1402.

Keshavan MS, Kulkarni SR, Bhojraj T, Francis A, Diwadkar V, Montrose DM, Seidman L, Sweeney J (2010). Premorbid cognitive deficits in young relatives of schizophrenia patients. *Frontiers in Human Neuroscience* **3**, 1–14.

Koenen KC, Moffitt TE, Roberts AL, Martin LT, Kubzansky L, Harrington H, Poulton R, Caspi A (2009). Childhood IQ and adult mental disorders: a test of the cognitive reserve hypothesis. *American Journal of Psychiatry* **166**, 50–57.

Kremen WS, Lyons MJ, Boake C, Xian H, Jacobson KC, Waterman B, Eisen SA, Goldberg J, Faraone SV, Tsuang MT (2006). A discordant twin study of premorbid cognitive ability in schizophrenia. *Journal of Clinical and Experimental Neuropsychology* **28**, 208–224.

Lane EA, Albee GW (1963). Childhood intellectual development of adult schizophrenics. *Journal of Abnormal and Social Psychology* **67**, 186–189.

Lane EA, Albee GW (1968). On childhood intellectual decline of adult schizophrenics: a reassessment of an earlier study. *Journal of Abnormal Psychology* **73**, 174–177.

Lencz T, Smith CW, McLaughlin D, Auther A, Nakayama E, Hovey L, Cornblatt BA (2006). Generalized and specific neurocognitive deficits in prodromal schizophrenia. *Biological Psychiatry* **59**, 863–871.

Lubin A, Gieseking CF, Williams HL (1962). Direct measurement of cognitive deficit in schizophrenia. *Journal of Consulting Psychology* **26**, 139–143.

MacCabe JH (2008). Population-based cohort studies on premorbid cognitive function in schizophrenia. *Epidemiologic Reviews* **30**, 77–83.

MacCabe JH, Lambe MP, Cnattingius S, Torrång A, Björk C, Sham PC, David AS, Murray RM, Hultman CM (2007). Scholastic achievement at age 16 and risk of schizophrenia and other psychoses: a national cohort study. *Psychological Medicine* **38**, 1133–1140.

McGrath J, Saha S, Welham J, El Saadi O, MacCauley C, Chant D (2004). A systematic review of the incidence of schizophrenia: the distribution of rates and the influence of sex, urbanicity, migrant status and methodology. *BMC Medicine* **2**, 13.

Mortensen EL, Sørensen HJ, Jensen HH, Reinisch JM, Mednick SA (2005). IQ and mental disorder in young men. *British Journal of Psychiatry* **187**, 407–415.

Murray RM, Lewis SW (1987). Is schizophrenia a neurodevelopmental disorder? *British Medical Journal* **295**, 681–682.

Niemi LT, Suvisaari JM, Tuulio-Henriksson A, Lönnqvist JK (2003). Childhood developmental abnormalities in schizophrenia: evidence from high-risk studies. *Schizophrenia Research* **60**, 239–258.

Niendam TA, Bearden CE, Rosso IM, Sanchez LE, Hadley T, Nuechterlein KH, Cannon TD (2003). A prospective study of childhood neurocognitive functioning in schizophrenic patients and their siblings. *American Journal of Psychiatry* **160**, 2060–2062.

Offord DR (1974). School performance of adult schizophrenics, their siblings and age mates. *British Journal of Psychiatry* **125**, 12–19.

Osler M, Lawlor DA, Nordentoft M (2007). Cognitive function in childhood and early adulthood and hospital admission for schizophrenia and bipolar disorders in Danish men born in 1953. *Schizophrenia Research* **92**, 132–141.

Ott SL, Spinelli S, Rock D, Roberts S, Amminger GP, Erlenmeyer-Kimling L (1998). The New York High-Risk Project: social and general intelligence in children at risk for schizophrenia. *Schizophrenia Research* **31**, 1–11.

Rabinowitz J, Reichenberg A, Weiser M, Mordechai M, Kaplan Z, Davidson M (2000). Cognitive and behavioural functioning in men with schizophrenia both before and shortly after first admission to hospital: cross-sectional analysis. *British Journal of Psychiatry* **177**, 26–32.

Reichenberg A, Weiser M, Rabinowitz J, Caspi A, Schmeidler J, Mark M, Kaplan Z, Davidson M (2002). A population-based cohort study of premorbid intellectual, language, and behavioral functioning in patients with schizophrenia, schizoaffective disorder, and nonpsychotic bipolar disorder. *American Journal of Psychiatry* **159**, 2027–2035.

Reichenberg A, Weiser M, Rapp MA, Rabinowitz J, Caspi A, Schmeidler J, Knobler HY, Lubin G, Nahon D, Harvey PD, Davidson M (2005). Elaboration on premorbid intellectual performance in schizophrenia: premorbid intellectual decline and risk for schizophrenia. *Archives of General Psychiatry* **62**, 1297–1304.

Rosso IM, Bearden CE, Hollister JM, Gasperoni TL, Sanchez LE, Hadley T, Cannon TD (2000). Childhood neuromotor dysfunction in schizophrenia patients and their unaffected siblings: a prospective cohort study. *Schizophrenia Bulletin* **26**, 367–378.

Ruhrmann S, Schultze-Lutter F, Klosterkötter J (2010). Probably at-risk, but certainly ill – advocating the introduction of a psychosis spectrum disorder in DSM-V. *Schizophrenia Research* **120**, 23–37.

Sattler J (2001). *Assessment of Children: Cognitive Applications*. Jerome M. Sattler, Publisher, Inc: San Diego, CA.

Schenkel LS, Silverstein SM (2004). Dimensions of premorbid functioning in schizophrenia: a review of neuromotor, cognitive, social, and behavioural domains. *Genetic, Social, and General Psychology Monographs* **130**, 241–270.

Schiffman J, Walker E, Ekstrom M, Schulsinger F, Sørensen H, Mednick S (2004). Childhood videotaped social and neuromotor precursors of schizophrenia: a prospective investigation. *American Journal of Psychiatry* **161**, 2021–2027.

Seidman LJ, Buka SL, Goldstein JM, Tsuang MT (2006). Intellectual decline in schizophrenia: evidence from a prospective birth cohort 28 year follow-up study. *Journal of Clinical and Experimental Neuropsychology* **28**, 225–242.

Sørensen HJ, Mortensen EL, Parnas J, Mednick SA (2006). Premorbid neurocognitive functioning in schizophrenia spectrum disorder. *Schizophrenia Bulletin* **32**, 578–583.

Sørensen HJ, Mortensen EL, Schiffman J, Ekstrøm M, Denenney D, Mednick SA (2010). Premorbid IQ and adult schizophrenia spectrum disorder: Verbal Performance subtests. *Psychiatry Research* **178**, 23–26.

Sutton AJ, Duval SJ, Tweedie RL, Abrams KR, Jones DR (2000). Empirical assessment of effect of publication bias on meta-analyses. *British Medical Journal* **320**, 1574–1577.

Thompson SG, Higgins JPT (2002). How should meta-regression analyses be undertaken and interpreted? *Statistics in Medicine* **21**, 1559–1573.

Tiihonen J, Haukka J, Henriksson M, Cannon M, Kieseppa T, Laaksonen I, Sinivuo J, Lonnqvist J (2005). Premorbid intellectual functioning in bipolar disorder and schizophrenia: results from a cohort study of male conscripts. *American Journal of Psychiatry* **162**, 1904–1910.

Urfer-Parnas A, Lykke Mortensen E, Sæbye D, Parnas J (2009). Pre-morbid IQ in mental disorders: a Danish draft-board study of 7486 psychiatric patients. *Psychological Medicine* **40**, 547–556.

Van Os J, Jones P, Lewis G, Wadsworth M, Murray R (1997). Developmental precursors of affective illness in a general population birth cohort. *Archives of General Psychiatry* **54**, 625–631.

Walker EF, Savoie T, Davis D (1994). Neuromotor precursors of schizophrenia. *Schizophrenia Bulletin* **20**, 441–451.

Walker NP, McConville PM, Hunter D, Deary IJ, Whalley LJ (2002). Childhood mental ability and lifetime psychiatric contact: a 66-year follow-up study of 1932 Scottish Mental Ability Survey. *Intelligence* **30**, 233–245.

Watt NF, Lubensky AW (1976). Childhood roots of schizophrenia. *Journal of Consulting and Clinical Psychology* **44**, 363–375.

Weinberger DR (1987). Implications of normal brain development for the pathogenesis of schizophrenia. *Archives of General Psychiatry* **44**, 660–669.

Welham J, Isohanni M, Jones P, McGrath J (2009*a*). The antecedents of schizophrenia: a review of birth cohort studies. *Schizophrenia Bulletin* **35**, 603–623.

Welham J, Scott J, Williams GM, Najman JM, Bor W, O'Callaghan M, McGrath J (2009*b*). The antecedents of non-affective psychosis in a birth-cohort, with a focus on measures related to cognitive ability, attentional dysfunction and speech problems. *Acta Psychiatrica Scandinavica* **121**, 273–279.

Whyte M-C, Brett C, Harrison LK, Byrne M, Miller P, Lawrie SM, Johnstone EC (2006). Neuropsychological performance over time in people at high risk of developing schizophrenia and controls. *Biological Psychiatry* **59**, 730–739.

Woodberry KA, Giuliano AJ, Seidman LJ (2008). Premorbid IQ in schizophrenia: a meta-analytic review. *American Journal of Psychiatry* **165**, 579–587.

Zammit S, Allebeck P, David AS, Dalman C, Hemmingsson T, Lundberg I, Lewis G (2004). A longitudinal study of premorbid IQ score and risk of developing schizophrenia, bipolar disorder, severe depression, and other nonaffective psychoses. *Archives of General Psychiatry* **61**, 354–360.