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An Epidemiological Investigation of Adolescents and Symptomatic High Risk for Psychosis

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An Epidemiological Investigation of Adolescents at Symptomatic High Risk for Psychosis

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PhD Thesis
February 2012
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This thesis is dedicated to my grandmother, Sally O'Mahony, in loving memory.
You taught me the most important principle of practising medicine – dignity. You were too humble, of course, to ever know.
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I realised (perilously late), from conversations with friends on the same academic track, that the most important factor in a happy PhD is the supervisor. I now extol to anyone considering postgraduate work the virtue of thoroughly gauging the views of others about your potential supervisor before joining a group. Sheer luck, however, rather than prescient forethought, led to me working with Mary Cannon (i.e., spotting an interesting newspaper article about a new Health Research Board-funded study). One PhD thesis later, I know that I have been incredibly lucky. The uncommon generosity, graciousness and respect Mary demonstrates to her junior colleagues say more about her than any of her papers in Archives. And, as karma would have it, these qualities also bring out the best in us as researchers.

Post-script: The above sentiment could not have been more strenuously tested than during the past year. Mary, thank you for stepping into battle for me (there is an iron fist in your velvet glove!). Bonds forged in the trenches are for a lifetime!

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"The more you know, the less you understand"

Lao Tzu
List of Abbreviations

ABD  Adolescent Brain Development
ADHD  Attention Deficit/Hyperactivity Disorder
ALSPAC  Avon Longitudinal Study of Parents and Children
APS  Attenuated Psychosis Syndrome
APSP  Attenuated Positive Symptoms Prodromal Syndrome
APSS  Adolescent Psychotic Symptom Screener
ARMS  At Risk Mental State
BACS:SC  Brief Assessment of Coding in Schizophrenia: Symbol Coding
BIPS  Brief Intermittent Prodromal Syndrome
BLIPS  Brief Limited Intermittent Psychotic Syndrome
BVMT-R  Brief Visuospatial Memory Test – Revised
CAARMS  Comprehensive Assessment of At Risk Mental States
CGAS  Children’s Global Assessment Scale
CI  Confidence Interval
CPT-IP  Continuous Performance Test – Identical Pairs
CT  Challenging Times
DALYS  Disability-Adjusted Life Years
DSM  Diagnostic and Statistical Manual of Mental Disorders
GRD  Genetic Risk and Deterioration
HVLT-R  Hopkins Verbal Learning Test – Revised
K-SADS  Schedule for Affective Disorders and Schizophrenia for School-aged Children
LNS  Letter Number Span
MATRICS  Measurement And Treatment Research to Improve Cognition in Schizophrenia
MDD       Major Depressive Disorder
NAB       Neuropsychological Assessment Battery
NAPLS     North American Prodromal Longitudinal Study
NC        Normal control
NIMH      National Institute of Mental Health
ODD       Oppositional Defiant Disorder
OR        Odds Ratio
PE        Psychotic Experience
PLE       Psychotic-Like Experience
PS        Prodromal Syndrome
SDQ       Strengths and Difficulties Questionnaire
SES       Socio Economic Status
SIPS      Structured Interview for Prodromal Syndromes
SOPS      Scale of Prodromal Syndromes
TMT-A     Trail Making Test Part A
TMT-B     Trail Making Test Part B
WHO       World Health Organization
WMS-R     Wechsler Memory Scale - Revised
Publications arising in whole or in part from this thesis


Summary

Background: Epidemiological research has shown that hallucinations and delusions, the classic symptoms of psychosis, are far more prevalent in the population than actual psychotic disorder. These symptoms are especially prevalent in childhood and adolescence. Longitudinal research has demonstrated that psychotic symptoms in adolescence increase risk for psychotic disorder in adulthood. There has been little research, however, on the immediate clinicopathological significance of psychotic symptoms in adolescence and on the prevalence of prodromal risk syndromes in the community.

Aims:
Aim 1: To assess the prevalence of psychotic symptoms and the association of psychotic symptoms with age and with DSM-IV Axis-1 psychopathology
Aim 2: To assess the relationship between psychotic symptoms and suicidal behaviour
Aim 3: To assess the neurocognitive profile of adolescents who report psychotic symptoms
Aim 4: To assess the prevalence of prodromal risk syndromes in the population and assess associations with non-psychotic psychopathology and global functioning

Method: Data from three population studies were used: Study 1 involved a school-based survey of 1,131 11-to 13-year olds for psychotic symptoms,
assessed using the Adolescent Psychotic Symptom Screener, and for emotional and behavioural symptoms of psychopathology, assessed using the Strengths and Difficulties Questionnaire. Studies 2 and 3 involved in-depth diagnostic interview assessments of psychotic symptoms and lifetime Axis-1 disorders in two community samples of 11-to 15-year olds, involving 423 adolescents in total. Psychotic symptoms, Axis-1 psychiatric disorders and suicidal behaviour were assessed using the Schedule for Affective Disorders and Schizophrenia (K-SADS). Global functioning was assessed using the Children’s Global Assessment Scale. Neurocognition was assessed using the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) consensus battery. Prodromal risk syndromes were assessed using the criteria of prodromal syndromes from the Structured Interview for Prodromal Syndromes.

Results:

A majority of community-based adolescents who reported psychotic symptoms had at least one lifetime diagnosable Axis-1 disorder on clinical interview: Study 2, Odds ratio (OR)=3.57, 95% confidence interval (CI95)=1.87-6.84, p<0.001; Study 3: OR=11.94, CI95=3.14-45.41, p<0.01. Psychotic symptoms (i) were associated with a wide range of non-psychotic Axis-1 disorders, (ii) were reported more commonly by younger adolescents, (iii) were increasingly associated with psychopathology with age and (iv) indexed high risk for multiple co-occurring diagnoses.
Psychotic symptoms were associated with a 10-fold increased risk for any suicidal behaviour (ideation, plans or acts) in both interview studies (Study 2, OR=10.2, 95%CI=3.3-32.3, P<0.001; Study 3, OR=10.5, 95% CI=3.1-35.2, P<0.001). Among all adolescents with suicidal ideation, those who also reported psychotic symptoms had a nearly 20-fold increased risk for suicide plans and suicide acts compared to adolescents with suicidal ideation who did not report psychotic symptoms (OR=19.6, 95% CI=1.8-216.1).

In tests of neurocognition, adolescents with psychotic symptoms performed significantly more poorly on three processing speed tasks – Trail Making Test-A (F=3.3, p<0.05), Trail Making Test-B (F=3.1, p<0.05) and digit symbol coding task (F=7.0, p<0.001) – as well as on a non-verbal working memory (spatial span) task (F=3.2, p<0.05).

Up to 8% of the sample met clinical criteria for a prodromal risk syndrome. The risk syndrome group had a higher prevalence of co-occurring non-psychotic Axis-1 psychiatric disorders (OR=4.77, CI95=1.81 – 12.52; p<0.01) and poorer global functioning (F=24.5, df=1, p<0.0001) compared to controls.

Conclusions: The majority of adolescents who report psychotic symptoms have at least one lifetime diagnosable Axis-1 disorder and demonstrate poorer neurocognitive performance than controls. Prodromal risk syndromes are relatively common in the community, which has implications for the proposed DSM-V diagnosis of Attenuated Psychosis Syndrome. Psychotic symptoms are important risk markers for severe multiple Axis-1 disorders and suicidal
behaviour and should be routinely assessed in child and adolescent psychiatric clinics.
Contributors

A number of individuals contributed to the collection of the data used in this thesis:

**ABD Clinical Interviews:**
- Ian Kelleher
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Aileen Murtagh

Statistical analyses:
Ian Kelleher
Chapter 1: Introduction (Part 1)

Existing evidence on the relationship between psychotic disorder and psychotic symptoms in the community

1.1 Background

Hallucinations and delusions have, since the 19th Century, been regarded as the classic symptoms of psychosis. Recently, however, our ideas about hallucinations and delusions are being challenged by findings from epidemiology. Simply put, hallucinations and delusions are more common than we think (Polanczyk et al., 2010, van Os et al., 2009, Wiles et al., 2006, Yung et al., 2009a). Research in this area is often traced to John Strauss who, in 1969, questioned the view that the symptoms of patients with psychosis differed qualitatively from other psychiatric patients and argued that hallucinations and delusions, while dichotomously diagnosed as present or absent in clinical samples, are in fact part of a continuum of experience varying continuously along dimensions of, for example, conviction, preoccupation and implausibility (Strauss, 1969).

This argument returned to the fore at the start of the 21st Century. Van Os et al. argued that hallucinations and delusions existed as points on continua not just in clinical populations but also in the general population (van Os et al., 2000). In a random community sample of more than 7,000 adults, they found that 17.5%
reported hallucinations and/or delusions. This, they argued, suggested that a psychosis phenotype extends beyond the clinical concept of schizophrenia and related disorders. In the absence of illness, psychotic symptoms are also referred to as psychotic experiences (PEs) or psychotic-like experiences (PLEs) and this population is said to express a 'non-clinical psychosis phenotype'.

The Dunedin birth cohort study also demonstrated a high prevalence of psychotic symptoms in the general population, with 26% of adults reporting at least one hallucination or delusion at age 26. Importantly, this study also provided important longitudinal data which demonstrated that psychotic symptoms confer increased risk for later psychotic disorder (Poulton et al., 2000). Children aged 11 who reported psychotic symptoms were at a 5- to 16-fold increased risk of schizophreniform disorder at age 26. This finding was replicated by researchers in an Australian sample, who showed that self-reported auditory hallucinations at age 14 years were associated with increased risk for psychotic disorder at age 21 (Welham et al., 2009). These findings have led to a swell of interest in studying psychotic symptoms as a means of understanding the roots or origins of psychosis. A wide range of risk factors for schizophrenia have now been investigated in individuals who report psychotic symptoms and some striking similarities have emerged between the non-clinical and clinical populations (see Table 1.1)
1.2 Psychotic symptoms: familiality and heritability

Hanssen and colleagues investigated psychotic symptoms among 257 members of the general population and reported familial clustering of the symptoms, in line with findings in family and adoption studies in schizophrenia (Hanssen et al., 2006). Furthermore, Polanczyk and colleagues (2010) have shown familial covariation of psychotic symptoms with maternal schizophrenia-spectrum disorder, as well as with family psychiatric hospitalisations and family suicide attempts. Twin studies have also established that psychotic symptoms are heritable, with studies showing greater concordance for psychotic symptoms among monozygotic compared to dizygotic twins (Lataster et al., 2009, Polanczyk et al., 2010).

1.3 Schizophrenia-related social risk factors

An elevated incidence of schizophrenia has been consistently demonstrated amongst migrant and ethnic minority groups, particularly African-Caribbeans in the UK (Boydell et al., 2001, Fearon et al., 2006). Johns and colleagues found a similar pattern among individuals who report psychotic symptoms, with persons of African-Caribbean descent 2.5 times more likely to admit to hallucinations than the white British population (Johns et al., 2002). Similarly, Laurens and colleagues found that psychotic symptoms were more commonly reported by British children of African-Caribbean ethnicity than by white British children (Laurens et al., 2008). While they did not find a significant association with migration status, a larger representative Australian study of more than 10,000 people showed that migrants from non-English speaking backgrounds were
more likely to report psychotic symptoms on interview (Scott et al., 2006). Further social risk factors for schizophrenia, including unemployment, lower socioeconomic background and being unwed or divorced, were also replicated in this large Australian sample. Similarly, a higher rate of urbanicity, one of the most frequently reported findings in schizophrenia (Kelly et al., 2010, Krabbendam and van Os, 2005, Pedersen and Mortensen, 2001) has also been demonstrated in association with psychotic symptoms (Scott et al., 2006).

1.4 Schizophrenia-related adverse childhood experiences risk factors

In line with findings in schizophrenia (Bechdolf et al., 2010, Morgan and Fisher, 2007, Read et al., 2005), psychotic symptoms have been found to be more common in adolescents who have had traumatic experiences, including physical abuse and unwanted sexual experiences (Arseneault et al., 2011, Bartels-Velthuis et al., 2012, Janssen et al., 2004, Lataster et al., 2006). Similarly, an association has been reported between peer victimisation and risk of psychotic symptoms, with higher rates of symptoms reported by victims of bullying (Campbell and Morrison, 2007, Mackie et al., 2011, Schreier et al., 2009), but also, conversely, by perpetrators of bullying (Nishida et al., 2008). Mothers of children with psychotic symptoms have also been demonstrated to show increased levels of negative expressed emotion, though no difference has been shown in terms of maternal warmth (Polanczyk et al., 2010).
1.5 **Schizophrenia-related substance use risk factors**

The well established relationship between psychotic disorder and cannabis use (Arseneault *et al.*, 2002, Arseneault *et al.*, 2004, Di Forti *et al.*, 2009, Moore *et al.*, 2007, Zammit *et al.*, 2002) has been replicated in adolescents with psychotic symptoms (Cougnard *et al.*, 2007, Harley *et al.*, 2009, Kuepper *et al.*, 2011, Miettunen *et al.*, 2008). Henquet and colleagues showed that the risk for psychotic symptoms among adolescents and young adults increased in a dose-response manner relative to the frequency of cannabis use over a four-year period (Henquet *et al.*, 2005). Harley and colleagues demonstrated a synergistic interaction between cannabis use and traumatic childhood events, with exposure to both variables associated with a greater risk of psychotic symptoms than the summed risk that each variable accounted for individually (Harley *et al.*, 2009). In addition to cannabis use, both alcohol dependence and tobacco use have also been shown to be more common among individuals who report psychotic symptoms (Johns *et al.*, 2004, Wiles *et al.*, 2006).

1.6 **Schizophrenia-related obstetric and developmental deficits**

Adverse prenatal and perinatal events, including maternal infection and obstetric complications, are well-documented in schizophrenia (Cannon *et al.*, 2002b, Clarke *et al.*, 2006, Lewis and Murray, 1987, Owen *et al.*, 1988, Wright *et al.*, 1995). Similar findings have been reported for young people who report psychotic symptoms. In the ALSPAC longitudinal study, maternal infection and obstetric complications were both shown to significantly increase the risk of psychotic symptoms later in childhood (Zammit *et al.*, 2009). Neuromotor
deficits have also been demonstrated among adolescents who report psychotic symptoms (Blanchard et al., 2010, Cannon et al., 2002a). Mittal and colleagues, for example, demonstrated that dyskinetic movements were more common in young people with psychotic symptoms compared to controls (Mittal et al., 2011). Associations with advanced paternal age and with winter and spring births, however, have failed to be replicated in individuals with psychotic symptoms (Polanczyk et al., 2010, Zammit et al., 2008).

1.7 Schizophrenia-related deficits in IQ, cognition and language

Lower IQ scores have, as in schizophrenia (Zammit et al., 2004), been demonstrated in the non-clinical psychosis population (Cannon et al., 2002a, Horwood et al., 2008, Johns et al., 2004). To date, however, there have been few studies of cognition for the non-clinical phenotype. Deficits in receptive, though not expressive, language have been reported (Blanchard et al., 2010, Cannon et al., 2002a). Blanchard and colleagues have also demonstrated poorer performance by adolescents with psychotic symptoms on the Trail-making test part B, though deficits were not found in a number of other neurocognitive tasks implicated in schizophrenia. Poorer performance in tests of verbal fluency have also been shown in men who report psychotic symptoms (Krabbendam et al., 2005).
Table 1.1: Aetiological and risk factor continuity between clinical and non-clinical psychosis phenotypes

<table>
<thead>
<tr>
<th>Category</th>
<th>Risk factor</th>
<th>Schizophrenia (Clinical phenotype)</th>
<th>Psychotic symptoms (Nonclinical phenotype)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genetics/Transmission</td>
<td>Familial</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td>Heritable</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Social</td>
<td>Urbanicity</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td>Migration</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td>Ethnic minority</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td>Low socio-economic background</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td>Unemployed</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td>Unmarried/Divorced</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adverse childhood experiences</td>
<td>Traumatic childhood physical or sexual experiences</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td>Bullying/Victimisation</td>
<td>+</td>
<td>+</td>
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<tr>
<td></td>
<td>Parental domestic violence</td>
<td>+</td>
<td>+</td>
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<tr>
<td></td>
<td>Maternal expressed emotion: negativity</td>
<td>+</td>
<td>+</td>
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<tr>
<td></td>
<td>+ Positive findings</td>
<td>- Negative findings</td>
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<td>--------------------------------</td>
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<td></td>
</tr>
<tr>
<td><strong>Maternal expressed emotion: warmth</strong></td>
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<tr>
<td>Substance use</td>
<td></td>
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<tr>
<td>Cannabis use</td>
<td>+</td>
<td>+</td>
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<tr>
<td>Tobacco use</td>
<td>+</td>
<td>+</td>
<td></td>
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<tr>
<td>Alcohol dependence</td>
<td>+</td>
<td>+</td>
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<tr>
<td>Obstetric and Developmental deficits</td>
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<tr>
<td>Obstetric complications</td>
<td>+</td>
<td>+</td>
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</tr>
<tr>
<td>Maternal infection</td>
<td>+</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Neuromotor deficits</td>
<td>+</td>
<td>+</td>
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<tr>
<td>Winter/spring birth</td>
<td>+</td>
<td>-</td>
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<tr>
<td>Paternal age</td>
<td>+</td>
<td>-</td>
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<tr>
<td>Cognition and Language</td>
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<tr>
<td>Verbal fluency</td>
<td>+</td>
<td>+</td>
<td></td>
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<tr>
<td>Receptive language</td>
<td>+</td>
<td>+</td>
<td></td>
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<tr>
<td>Expressive language</td>
<td>+</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Trail-Making Test B</td>
<td>+</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Intelligence</td>
<td>+</td>
<td>+</td>
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</tbody>
</table>

+ Positive findings

- Negative findings
1.10 Implications

The past decade of research summarised above illustrates an important continuum between the clinical and non-clinical psychosis phenotypes in the general population. Psychotic symptoms have been shown to be familial, heritable, confer increased risk for schizophrenia-spectrum disorder and covary with maternal psychotic disorder. Furthermore, these symptoms have been found to share an extensive range of social, environmental, motor, cognitive, linguistic and intellectual risk factors with schizophrenia.
Chapter 2: Introduction (Part 2):

Systematic review and meta-analysis of population-based studies on the prevalence of psychotic symptoms in children and adolescents

2.1 Introduction

A review of the general population prevalence of psychotic symptoms by van Os and colleagues up to 2007 reported a median prevalence of 5% (van Os et al., 2009). However, this meta-analysis was based primarily on adult studies. There has been no systematic review to date on the prevalence of psychotic symptoms specifically in childhood or adolescence. This issue was addressed in the current thesis by carrying out a systematic review and meta-analysis of studies reporting prevalence rates for psychotic symptoms in the general population among children and adolescents up to age 18.

2.2 Method

2.2.1 Search Strategy

A systematic review was conducted on all published literature on the prevalence of psychotic symptoms in children and adolescents. We searched through electronic databases PUBMED, OVID MEDLINE, PsychINFO and EMBASE from their inception to June 2011 with the following search terms: young people, adolescents, teenagers, child / children, psychotic symptoms, psychosis, paranoia, delusions, hallucinations, grandiosity, unusual beliefs/ideations,
positive and negative symptoms, prevalence and psychotic-like experiences. We searched using the format [(Young people OR adolescents OR teenagers OR child) AND (prevalence) AND (psychotic symptoms OR psychosis OR paranoia OR delusions OR hallucinations OR grandiosity OR unusual beliefs/ideations OR positive symptoms OR negative symptoms OR psychotic-like experiences)]. We also searched references within papers to identify other possible studies.

2.2.3 Inclusion Criteria

Methods used to assess the prevalence of psychotic symptoms in studies to date include interviews and questionnaire surveys. The latter approach has involved a number of different questionnaires that have had a great deal of variance in terms of the number of questions asked (from 1 to 92 items). Furthermore, endorsement rates of more than 90% for ‘at least one psychotic symptom’ have been reported in questionnaire studies (Wigman et al., 2011), raising concerns about the validity of these items. Questionnaires have largely been unvalidated against clinical interview in terms of sensitivity and specificity and the inclusion of questionnaire studies risks overestimating the true prevalence of psychotic symptoms in the population. We recently showed, however, that some items on self-report questionnaire perform well in terms of identifying individuals with genuine psychotic symptoms when compared with gold standard clinical interview, while others perform poorly (Kelleher et al., 2011). In particular, we found that a question on auditory hallucinations – “Have you ever heard voices or sounds that no one else can hear?” – demonstrated
very good sensitivity, specificity and positive and negative predictive value not just for auditory hallucinations but for psychotic symptoms in general. Laurens et al. have also recently demonstrated, using item response theory analysis in a large population sample of children, that the same auditory hallucinations question demonstrates the strongest psychometric properties for assessing the continuum of psychotic symptoms compared to other questions (Laurens et al., 2011). For this reason, in addition to including psychotic symptom prevalence rates from interview studies, we included reports that used the same question as in our initial validation report (Kelleher et al., 2011), or a question with a similar wording, in order to calculate a meta-analytic median prevalence of psychotic symptoms in studies of children and adolescents.

2.2.4 Exclusion Criteria

We excluded papers for the following reasons (a) did not report prevalence rates or data from which rates could be calculated, (b) did not report rates for individuals under 18 years or allow calculation of rates for this age group, (c) reported psychotic symptoms that were sleep related, substance use related or organic in origin only or (d) reported on clinical samples – that is inpatient/outpatient or help-seeking groups.

2.2.5 Study selection and data extraction

Four individuals (Ian Kelleher, Dearbhla Connor, Nina Devlin and Michelle Harley) independently conducted the searches and examined all titles and
abstracts and assessed the relevance and appropriateness of the studies for the question under review (see Figure 2.1). Full texts of potentially relevant papers were obtained. Where necessary, authors were contacted for further information. From each paper collected, two individuals (Ian Kelleher and Mary Clarke) extracted data on the age range of participants and the reported rates of psychotic symptoms. Where samples overlapped (e.g., publications on preliminary data), papers that reported on the largest overall sample size were used.

2.2.6 Data Analysis

Eligible studies were divided into two groups according to whether participants were aged 9 to 12 years (the child population) or aged 13 to 18 years (the adolescent population). Where studies cut across these age ranges, the mean age of participants was used to assign the study to the 'childhood' or the 'adolescence' group. We adopted the approach advocated by Saha et al. and also used in a previous psychotic symptom meta-analysis conducted by van Os et al. to summarise rate data, reporting median prevalences for both age groups (Saha et al., 2008, van Os et al., 2009).

2.3 Results

Our literature search yielded 3,597 papers. Titles and, as necessary, abstracts were read to determine articles of interest to the research question, yielding 199 papers. Of these, 26 (13%) had data on psychotic symptom prevalence in
community samples of young people. Seven of these studies were excluded because they involved questionnaire surveys that did not contain a question of similar wording to the question chosen for the research protocol or because it was not possible to calculate the endorsement rate for such a question. A total of 19 studies met criteria for inclusion - 5 interview studies (Horwood et al., 2008, Kelleher et al., 2008, Kelleher et al., In Press, Polanczyk et al., 2010, Poulton et al., 2000) and 14 self report questionnaire studies (Barragan et al., 2011, De Loore et al., 2011, Dhossche et al., 2002, Kelleher et al., In Press, Kinoshita et al., 2011, Lataster et al., 2006, Laurens et al., 2011, Scott et al., 2009a, Scott et al., 2009b, Wigman et al., 2011, Yoshizumi et al., 2004, Yung et al., 2009a) (see Table 2.1). Prevalence rates were extracted from each study. The median prevalence of psychotic symptoms was 17% for the child population (ages 9 to 12 years), and 7.5% for the adolescent population (ages 13 to 18 years).
Figure 2.1: Flow chart for studies included in meta-analysis
Table 2.1: Summary table of the prevalence rates of psychotic symptoms in the 19 community studies included in the systematic review

<table>
<thead>
<tr>
<th>Country of study</th>
<th>Source</th>
<th>Age (Years)</th>
<th>Method of Assessment</th>
<th>Observed Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spain</td>
<td>Barragan et al., 2011</td>
<td>12 to 18</td>
<td>Questionnaire</td>
<td>31.7%</td>
</tr>
<tr>
<td>Netherlands</td>
<td>De Loore et al., 2011</td>
<td>13 to 14</td>
<td>Questionnaire</td>
<td>5%</td>
</tr>
<tr>
<td>Netherlands</td>
<td>Dhossche et al., 2002</td>
<td>11 to 18</td>
<td>Questionnaire</td>
<td>4.7%</td>
</tr>
<tr>
<td>UK</td>
<td>Horwood et al., 2008</td>
<td>12</td>
<td>Interview</td>
<td>13.7%</td>
</tr>
<tr>
<td>Ireland</td>
<td>Kelleher et al., 2008</td>
<td>13 to 15</td>
<td>Interview</td>
<td>6.6%</td>
</tr>
<tr>
<td>Ireland</td>
<td>Kelleher et al., In Press</td>
<td>11 to 13</td>
<td>Interview</td>
<td>22.6%</td>
</tr>
<tr>
<td>Ireland</td>
<td>(a)</td>
<td>11 to 13</td>
<td>Questionnaire</td>
<td>21.2%</td>
</tr>
<tr>
<td>Ireland</td>
<td>(b)</td>
<td>11 to 13</td>
<td>Questionnaire</td>
<td>7.1%</td>
</tr>
<tr>
<td>Japan</td>
<td>Kinoshita et al., 2011</td>
<td>12 to 18</td>
<td>Questionnaire</td>
<td>9.6%</td>
</tr>
<tr>
<td>Country</td>
<td>Authors</td>
<td>Age Range</td>
<td>Method</td>
<td>Prevalence</td>
</tr>
<tr>
<td>--------------</td>
<td>--------------------------</td>
<td>-----------</td>
<td>--------------</td>
<td>------------</td>
</tr>
<tr>
<td>Netherlands</td>
<td>Lataster et al., 2006</td>
<td>13 to 14</td>
<td>Questionnaire</td>
<td>7%</td>
</tr>
<tr>
<td>UK</td>
<td>Laurens et al., 2011</td>
<td>9 to 12</td>
<td>Questionnaire</td>
<td>35.3%</td>
</tr>
<tr>
<td>UK</td>
<td>Polanczyk et al., 2010</td>
<td>12</td>
<td>Interview</td>
<td>19.6%</td>
</tr>
<tr>
<td>New Zealand</td>
<td>Poulton et al., 2000</td>
<td>11</td>
<td>Interview</td>
<td>14.7%</td>
</tr>
<tr>
<td>Australia</td>
<td>Scott et al., 2009a</td>
<td>13 to 17</td>
<td>Questionnaire</td>
<td>7.5%</td>
</tr>
<tr>
<td>Australia</td>
<td>Scott et al., 2009b</td>
<td>14</td>
<td>Questionnaire</td>
<td>10.6%</td>
</tr>
<tr>
<td>Netherlands</td>
<td>Wigman et al., 2011</td>
<td>12 to 16</td>
<td>Questionnaire</td>
<td>22.2%</td>
</tr>
<tr>
<td></td>
<td>(a)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Netherlands</td>
<td>(b)</td>
<td>10 to 12</td>
<td>Questionnaire</td>
<td>9%</td>
</tr>
<tr>
<td>Japan</td>
<td>Yoshizumi et al., 2004</td>
<td>11 to 12</td>
<td>Questionnaire</td>
<td>9.2%</td>
</tr>
<tr>
<td>Australia</td>
<td>Yung et al., 2009</td>
<td>13 to 17</td>
<td>Questionnaire</td>
<td>27.9%</td>
</tr>
</tbody>
</table>
2.4 Discussion

This is the first systematic review to report on the prevalence of psychotic symptoms specifically in children and adolescents. A median of 17% of the childhood sample (9 to 12 years) reported psychotic symptoms, and 7.5% of the adolescent sample (13 to 18 years) reported psychotic symptoms. This compares to a median prevalence of 5% reported by van Os and colleagues in a meta analysis of mainly adult studies of psychotic symptoms (van Os et al., 2009), which supports the idea that psychotic symptoms are more prevalent in childhood compared to adulthood. This is also in line with longitudinal research, which has shown a decline in the incidence of psychotic symptoms in young people followed over time (Bartels-Velthuis et al., 2011, De Loore et al., 2011, Dominguez et al., 2011, Laurens et al., 2011, Mackie et al., 2011).

This meta-analysis has a number of strengths: firstly, an 'a priori' design was used whereby the research question and inclusion criteria were formulated before the conduct of the review. Secondly, four independent researchers carried out the data searches and two independent researchers extracted the specific data. The use of a validated psychotic symptom assessment question used in all of the questionnaire studies helps us to control for quality of assessment across studies.

Hallucinations and delusions have typically been viewed as symptoms of psychosis and, in keeping with this, population research to date has largely
considered these symptoms to represent a distributed risk for psychosis in the population (Polanczyk et al., 2010, van Os et al., 2009). However, the relatively high prevalence of these symptoms would suggest a lack of specificity in terms of risk for psychosis. A number of recent studies have suggested that psychotic symptoms may predict a wider range of psychopathology than adulthood psychosis. Varghese et al., for example, reported an increased prevalence of psychotic symptoms among individuals who screened positive for depressive and anxiety disorders on the Composite International Diagnostic Interview (Varghese et al., 2011). Furthermore, Rossler et al. have recently shown that psychotic symptoms at age 19 or 20 years predict a wide range of (non-psychotic) mental disorders in follow up studies 30 years later (Rossler et al., 2011).

Conclusion
Psychotic symptoms are common in childhood and adolescence, with a median of 17% of 9 to 12 year olds and 7.5% of 13 to 18 year olds reporting symptoms. While an increased risk for psychosis is well established for young people who report psychotic symptoms (Poulton et al., 2000, Welham et al., 2009), more recent research has suggested that these symptoms may be important in relation to a wide variety of non-psychotic psychopathology (Rossler et al., 2011, Varghese et al., 2011). Further work is necessary to test the relationship between psychotic symptoms and non-psychotic psychopathology.
Chapter 3: Aims of this work

3.1 Psychotic symptoms and Axis-1 psychopathology

Aim 1: To assess the prevalence of psychotic symptoms and the association of psychotic symptoms with age and with Axis-1 psychopathology

While psychotic symptoms have typically been viewed as a marker of risk for psychotic disorder, more recently, several research groups have reported that individuals who report psychotic symptoms are also more likely to report symptoms of non-psychotic psychopathology, especially symptoms of depression (Nishida et al., 2008, Scott et al., 2009b, Varghese et al., 2011). Yung et al., for example, reported that individuals who had a diagnosed depressive disorder endorsed an increased number of psychotic symptoms on the Community Assessment of Psychic Experiences (CAPE) questionnaire compared to controls (Yung et al., 2007a). Bartels-Velthuis et al. found that young adolescents who disclosed psychotic symptoms were approximately 3 to 5 times more likely to score in the clinical psychopathology range on the parent-completed Child Behaviour Checklist (Bartels-Velthuis et al., 2011). Community based studies to date, however, have relied mainly upon questionnaires to assess psychotic symptoms and have involved limited data on non-psychotic psychopathology. In addition, although the meta-analysis above suggests that psychotic symptoms are more common in younger compared to older children, there is a lack of information on whether there are differences in the clinical significance of psychotic symptoms across different stages of adolescence. In an attempt to
improve our understanding of the clinical significance of psychotic symptoms in the general population, data from one large population survey and two in-depth clinical interview studies of psychotic symptoms were used in the current thesis. The aims of this work were (i) to investigate whether psychotic symptoms predicted non-psychotic clinical diagnoses and, if so, which disorders (ii) to investigate whether psychotic symptoms predicted more clinically severe disorder, in terms of having multiple diagnosable disorders and (iii) to investigate whether the significance of psychotic symptoms varied as a function of age.
3.2  *Psychotic symptoms and suicidal behaviour*

**Aim 2:** To assess the relationship between psychotic symptoms and suicidal behaviour

Suicidal behaviour is one of the most important causes of mortality worldwide. According to WHO (2008) estimates, there are approximately one million deaths by suicide annually and reducing suicide is a national health priority for many countries, including Ireland. The causes of suicidal behaviour, however, remain poorly understood (Batty *et al.*, 2010). An increased prevalence of suicidal behaviour in psychosis is well established. In fact, when Eugen Bleuler first defined schizophrenia in 1911, he recognized the 'suicidal drive' as 'the most serious of schizophrenic symptoms' (Bleuler, 1911). Psychosis patients have recently been shown to be at a 12-fold increased risk of completed suicide compared to the general population (Dutta *et al.*, 2010). However, psychosis is only known to play a role in a small absolute number of cases of suicidal behaviour.

Recent evidence from both clinical and population research has pointed to psychotic symptoms as potentially important markers of risk for suicide. In an emergency psychiatry patient sample, Penagaluri *et al.* noted that patients who reported subclinical hallucinations had more severe suicidal ideation (Penagaluri *et al.*, 2010). Similarly, following a review of medical records of patients with suicidal behaviour, which showed a high rate of hallucinations in particular in early adolescence, Hysinger *et al.* stressed the need for
further research on the role of psychotic symptoms in suicidal behaviour (Hysinger et al., 2011). In population-based research, two recent questionnaire surveys have linked psychotic symptoms and suicidal behaviour. Nishida et al. found that adolescents who endorsed a questionnaire item about hallucinations were 3-times more likely to also endorse an item related to suicidal ideation (Nishida et al., 2010). Saha et al., on the other hand, found that individuals who endorsed questionnaire items about delusions were 2 to 4 times more likely to endorse questionnaire items on suicidal behaviour (Saha et al., 2011). There have been no epidemiological studies to date, however, that have reported data on psychotic symptoms and suicidality in individuals who have received a clinical assessment for suicidal behaviour.
3.3 **Psychotic symptoms and neurocognition**

**Aim 3:** To assess the neurocognitive profile of adolescents who report psychotic symptoms

Neurocognitive impairments are among the most replicated findings in schizophrenia (Fioravanti *et al.*, 2005). Deficits have been demonstrated across a wide range of cognitive domains (Heinrichs and Zakzanis, 1998). Recently, however, debate has emerged over the primacy of certain neurocognitive deficits over others. Addressing this question is crucial because neurocognitive deficits inform us about the pathophysiology of the underlying disease and, therein, provide important direction for research on treatment. The importance of this has been reflected in the recent galvanisation of efforts from government, industry and academia to produce a consensus cognitive battery for the purposes of research into treatment of psychosis – the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) battery, developed under the aegis of the US National Institute of Mental Health (*Kern et al.*, 2008, *Nuechterlein et al.*, 2008).

A number of researchers have recently argued that impairments in processing speed represent the core neurocognitive deficit of psychosis (*Carrion et al.*, 2011, *Dickinson*, 2008, *Dickinson et al.*, 2007, *Rodriguez-Sanchez et al.*, 2007). Deficits in processing speed, that is, the speed with which cognitive operations can be performed, have not only been shown in
patients with chronic schizophrenia (Dickinson et al., 2007) but have also been demonstrated in first episode psychosis (Mesholam-Gately et al., 2009) and in the psychosis prodrome (Seidman et al., 2010). In an attempt to test the primacy of processing speed deficits over other neurocognitive deficits in schizophrenia, Rodriguez-Sanchez et al. conducted a multivariate analysis of neurocognitive performance in a sample of early psychosis patients (Rodriguez-Sanchez et al., 2007). The authors demonstrated impairments across a wide variety of tests. However, they found that differences for all other cognitive domains were no longer significant once they adjusted for the effect of processing speed, supporting the centrality of this deficit to psychosis. Dickinson et al. argued that a particular type of processing speed task, digit symbol coding, taps into the impairment that is at the core of cognitive dysfunction in psychosis (Dickinson et al., 2007). In a meta-analysis of 40 studies, they found that the effect size of the impairment on this task significantly exceeded the effect sizes of tasks commonly used to measure more specific cognitive domains, including episodic memory, executive function and working memory. In a subsequent meta-analysis, Knowles et al. reported that a number of variables moderated the effect size of symbol coding task deficits, most notably anti-psychotic medication (Knowles et al., 2010), thus raising questions about how intrinsic processing speed impairment is to the pathology itself as opposed to downstream factors associated with the illness. A solution to this methodological problem is to examine the association between neurocognition and psychosis in a population sample who have not yet had contact with mental health services and who, thus, have not been exposed to treatment effects, including
antipsychotic medication. Young people with psychotic symptoms, while part of a psychosis continuum, are distal from psychotic illness and, thus, potential confounds such as disease chronicity and medication. This approach can, thus, facilitate investigation of the earliest cognitive risk factors underlying psychosis risk.
3.4 **Prodromal risk syndromes in the population**

**Aim 4:** To assess the prevalence of prodromal risk syndromes in the population and assess associations with non-psychotic psychopathology and global functioning.

The onset of psychosis is usually preceded by a prodromal period prior to full-blown illness. Intervention at this early stage offers the hope of disease prevention. The concept of prodromal intervention as currently conceived emerged from research at the University of Melbourne in the 1990s. Yung, McGorry and colleagues developed a set of 'ultra high risk' (UHR) criteria for help-seeking individuals who presented to the clinic, which they demonstrated could predict a very high transition rate to psychosis (approximately 40%) over a 12-month period. Individuals meeting UHR criteria are said to have an 'at risk mental state' (ARMS). These criteria were used to formulate the Comprehensive Assessment of At Risk Mental States (CAARMS), a clinical instrument for the assessment of ARMS based upon defined criteria involving (i) attenuated psychotic symptoms, (ii) frank psychotic symptoms of brief duration or (iii) genetic risk combined with functional deterioration (McGorry *et al.*, 2002, Yung *et al.*, 1996, Yung *et al.*, 2003). Researchers at Yale University developed the Structured Interview for Prodromal Syndromes (SIPS) with a similar goal and demonstrated that, in line with Australian findings, individuals who met criteria for these 'prodromal risk syndromes' were at very high risk for psychosis (Addington *et al.*, 2007, Cannon *et al.*, 2008, McGlashan *et al.*, 2001). In Europe, a set of 'basic
symptoms’, such as problems in dividing attention, thought blockages and disturbances in receptive and expressive language, have been used to successfully predict high risk for psychosis, either alone or in combination with UHR criteria (Klosterkotter et al., 2005, Klosterkotter et al., 1997, Ruhrmann et al., 2010b, Salokangas et al., 2011). The largest study to date examining transition from prodromal risk syndrome to psychosis has been the collaborative North American Prodrome Longitudinal Study (NAPLS), which reported that up to 40% of individuals who met risk syndrome criteria converted to psychosis over 2.5 years (Cannon et al., 2008, Woods et al., 2009).

Such has been the impact of risk syndrome research that a new diagnosis – ‘Attenuated Psychosis Syndrome’ – has been proposed for the next version of the Diagnostic and Statistical Manual of Mental Disorders (DSM-V) (see Table 4.1). The goal of a new diagnosis is to provide a diagnostic category that facilitates identification, treatment and research. This proposal, however, has sparked a great deal of debate amongst leading researchers in the field (Carpenter and van Os, 2011, Corcoran et al., 2010, Drake and Lewis, 2010, McGorry, 2010, Ruhrmann et al., 2010a, Woods et al., 2010, Yung et al., 2010). One important issue is the lack of population studies – while a great deal of research has been conducted on psychotic symptoms in the general population to date (Poulton et al., 2000, van Os et al., 2009, Yung et al., 2009b), population researchers have not conducted the in-depth clinical assessments that have characterized the work of researchers at UHR clinics. On the other hand, UHR researchers have, to date, focused almost
exclusively on help-seeking (i.e., self-presenting) individuals, without venturing into the community. A more complete understanding of prodromal risk syndromes requires that the detailed work carried out in UHR clinics be combined with a community-based, epidemiological approach. One preliminary report that has begun to address this issue involved telephone SIPS interviews with a sample of 16 to 35 year olds from the general population (Schimmelmann et al., 2011). The researchers reported that just one participant fulfilled criteria for a prodromal risk syndrome. However, this study was limited by the small sample size (n=58) and the lack of information on the validity of telephone interviews compared to face-to-face assessment. With this in mind, further aims of the present work were to (i) test whether prodromal risk syndromes/at risk mental states could be identified among young adolescents in the general population and (ii) characterize these individuals in terms of psychopathology and general functioning.
Chapter 4: Methodology

4.1 Survey study: Associations between psychotic symptoms and psychopathology

4.1.1 Study 1: the Adolescent Brain Development (ABD) survey study

The ABD study was established to assess the prevalence and clinicopathological significance of psychotic symptoms in community-based adolescents. The survey study took place in a two-stage format. The study team visited schools and gave a short information session about brain development in childhood and adolescence to 5th and 6th classes (i.e., pupils in the two most senior classes, aged 11-13 years). Consent forms for the study were distributed for the children to take home to their parents. This was an 'opt in' study, with written parental consent required for adolescents to take part. On the form parents were asked to tick one box to indicate consent for their child to complete the questionnaire in the classroom. Parents were also asked to tick a second box and leave contact details if they would like to hear about the second stage of the study involving an interview and further testing. The study team returned to the school one week later to collect the completed forms and administer the questionnaire in the classrooms. The questionnaire took just a few minutes for each child to complete. They completed the questionnaires in the classrooms in small groups with the researcher present. For the sake of confidentiality, pupils were asked to complete the questionnaire without allowing anyone else to see their
answers, but could ask a researcher for clarification of any question that they did not understand.

Sixteen schools in Dublin, Ireland and surrounding areas, took part in this study. In total 2190 consent forms were distributed and 1131 (52%) parents gave signed consent for their child to complete the survey in school. A total of 88.9% of participants were Irish-born participants (compared to 90.3% of 0 to 14 year olds nationally in the 2006 national census).

4.1.2 Exposure and Outcome measures

Using the Adolescent Psychotic Symptom Screener (APSS – see Appendix for copy), we have previously shown that a question on auditory hallucinations (“Have you ever heard voices or sounds that no one else can hear?”) demonstrates very good positive and negative predictive validity not just for clinical interview-verifiable auditory hallucinations but for psychotic symptoms in general (Kelleher et al., 2011). This question was used in both survey studies to assess for psychotic symptoms (exposure measure).

The Strengths and Difficulties Questionnaire (SDQ) was used as the measure of general psychopathology in both samples (Goodman et al., 2000) (see Appendix for copy). The SDQ is a well-validated brief screening instrument, which asks about 25 attributes divided into subscales. The emotional disorders section assesses for anxiety, depressive and obsessive compulsive disorders, the conduct disorders section assesses for conduct and oppositional defiant disorders, and the hyperkinetic disorders section
assesses for attention deficit/hyperactivity disorders. A ‘total difficulties’ score is also generated by summing the psychopathology subscales, which predicts the presence of any psychiatric disorder. The SDQ has been validated both in terms of its ability to distinguish between clinic and community samples (Goodman, 1997) and as a screening device to detect children with a mental health disorder (Goodman et al., 2000). More recently, the SDQ has been shown not only to predict psychopathology at the same point in time but also to predict disorder status three years later (Goodman and Goodman, 2009).

4.1.3 Statistical Analyses for ABD survey study

Statistical analyses were conducted using STATA version 11.0 for Windows. First, analysis of variance was used to test the association between endorsement of the auditory hallucinations question and SDQ total difficulties score. Second, the samples were divided into quartiles based on their SDQ total difficulties scores and logistic regression was used to test the odds of reporting psychotic symptoms in each quartile of (increasing) psychopathology. To test for a statistically significant increase (or decrease) in the prevalence of psychotic symptoms across the quartiles of SDQ-rated psychopathology, the STATA command nptrend was used, which is an extension of the Wilcoxon rank-sum test and performs a nonparametric test for trend across ordered groups. Logistic regression was also used to compare the prevalence of auditory hallucinations among the 5% who scored highest on the SDQ total difficulties, which is often taken as a ‘severe’ psychopathology group, with the 5% who scored lowest on the SDQ total
difficulties. Finally, we stratified by the number of SDQ-rated disorder domains (emotional, conduct and hyperkinetic disorders) and used logistic regression to determine whether psychotic symptoms predicted comorbidity across these domains and, therein, more severe psychopathology.

4.2 Interview studies: Associations between psychotic symptoms, psychopathology and suicidal behaviour

4.2.1 Study 2: the Adolescent Brain Development interview study

Participants in the ABD clinical interview study were drawn from the larger survey study of 11 to 13 year olds reported above. Of the 1131 adolescents who took part in the survey study, 656 (58%) indicated an interest in taking part in the interview study and a sample of 212 of these attended for interview. Among the first 20% of the sample who attended for interview we enriched at a rate of 2:1 for adolescents with a score of 2 or more on the APSS psychotic symptoms questionnaire. For the majority (80%), however, the sample was a random sample representative of the overall larger surveyed sample. A frequency weight was applied in STATA for all statistical analyses to account for enrichment at a rate of 2:1 in the first 20% of interviewed participants.

In order to test whether the interview sample were representative of the total population, we compared our interview sample with national demographic statistics and with data from the larger survey sample. The SES of participants approximated national figures: 34.6% of participants were
categorized as SES groups 1-2 (compared to 32.1% of the national population) and 65.4% as SES groups 3-7 (compared to 67.9% of the national population). Participants were also representative of the overall national ethnic profile from the 2006 national census, including 88.9% Irish-born participants (compared to 90.3% of 0 to 14 year olds nationally). Furthermore, adolescents who attended for interview were no more likely to have an abnormal or borderline-abnormal score on the SDQ ($\chi^2=1.22$ (df=1) $p=0.27$) and did not differ significantly in their scores on the APSS compared to the non-interviewed sample (interviewed group mean=1.8 (SE=0.12), non-interviewed group mean=1.9 (SE=0.19); $t=0.26$, df=1130, $p=0.79$).

4.2.2 Study 3: the Challenging Times interview study

The Challenging Times (CT) study was established to investigate the prevalence of psychiatric disorders and suicidal behaviour among Irish adolescents aged 13 to 15 years. The study was carried out in the geographical catchment area of a Child and Adolescent Mental Health Team in North Dublin with a population of 137,000. The participating schools were selected using a stratified random sampling technique according to the approximate socioeconomic class of the school in order to approximate to the geographical area population. A total of 743 pupils in eight mainstream schools were screened for psychiatric symptoms using the SDQ (Goodman et al., 2000), and with the Children's Depression Inventory (Kovacs, 1985), which assesses cognitive, affective and behavioural signs of depression. Written informed consent was obtained from the parent or guardian of participants. One hundred and forty adolescents scored above threshold on
these instruments, indicating high risk of having mental health problems, and all of these adolescents were invited to interview, of whom 117 (83.6%) agreed to attend for full psychiatric interview. A comparison group of 173 adolescents, matched for gender and school were also invited to attend, of whom 94 (54%) agreed. A frequency weight was applied to participants in the CT study to account for enrichment for psychopathology so that reported rates represent the general population rather than a psychopathology-enriched sample. Higher SES individuals were slightly over-represented in the CT study compared to the population norm, with 39.9% of participants categorized as SES groups 1-2 and 60.1% as SES groups 3-7. Data were not collected on participant nationalities.

4.2.3 Exposure and Outcome Measures – Axis-1 psychopathology

The interview instrument used in both studies was the Schedule for Affective Disorders and Schizophrenia for School-aged Children, Present and Lifetime versions (K-SADS-PL) (Kaufman et al., 1996). The K-SADS is a well-validated semi-structured research diagnostic interview for the assessment of all Axis-1 psychiatric disorders in children and adolescents. Children and parents were interviewed separately, both answering the same questions about the child. In the early adolescence study, interviews were conducted by two psychiatrists and four psychologists and in the mid adolescence study, interviews were conducted by one psychiatrist and two psychologists, all trained in the use of the K-SADS. The Psychosis section of the K-SADS was used to assess the participants' psychotic symptoms (hallucinations and
delusions). All interviewers recorded extensive notes of potential psychotic phenomena in this section of the interview and a clinical consensus meeting was held following the interviews to classify these phenomena as psychotic symptoms (or not), blind to diagnoses and all other information on the participants. The exposure measure was the presence or absence of psychotic symptoms and the outcome measure was a DSM diagnosable lifetime affective, anxiety or behavioural disorder.

4.2.4 Statistical analyses

Statistical analyses were conducted using STATA version 11.0 for Windows. Univariate and multivariate regression analyses were used to measure the relationship between psychopathology and psychotic symptoms. First, the prevalence of psychotic symptoms is reported in diagnosable affective, behavioural and anxiety disorders, together with odds ratios and 95% confidence intervals. Second, I stratify by the presence of multiple psychopathology (that is, having 2 or more diagnosable Axis-1 diagnoses) in order to determine the prevalence of psychotic symptoms in increasingly severe (multiple) disorders and report odds ratios and 95% confidence intervals for the association with psychotic symptoms. To test for a statistically significant increase (or decrease) in the prevalence of auditory hallucinations in line with the number of diagnosable Axis-1 disorders, the STATA command nptrend was used.
4.2.5 Exposure and outcome Measures – Suicidal behaviour

The exposure measure was psychotic symptoms, as assessed by the K-SADS. The outcome measure was a history of suicidal behaviour. Suicidal behaviour refers to a continuum from suicidal ideation to suicidal plans to suicidal acts (Nock et al., 2008). Suicidal behaviour was assessed as part of the K-SADS interview. The suicidal behaviour section begins with the interviewer asking about whether the individual has ever experienced recurrent thoughts of death, before moving on to ask a series of questions to assess suicidal ideation, suicidal plans and suicidal acts. Interviews were conducted with parents and children separately and parental and children's reports of suicidal behaviour were both used in the analyses.

4.2.6 Statistical analyses

Logistic regression analyses were used to examine the association between the outcome measure, suicidal behaviour, and the exposure, psychotic symptoms. First, I report univariate associations in terms of odds ratios, along with 95% confidence intervals (95%CI) and p-values for the association of psychotic symptoms with suicidal behaviour in the general population. Second, in order to control for the effect of co-morbid psychiatric illness, I report a regression analysis stratified by the presence of psychiatric disorder. Third, in order to assess whether psychotic symptoms predict more severe forms of suicidal behaviour (suicide plans and acts) in groups at higher risk of suicidal behaviour, I report regression analyses stratified by the
presence of (i) depressive disorders, (ii) behavioural disorders (attention deficit/hyperactivity disorder, oppositional defiant disorder and conduct disorder) and (iii) suicidal ideation. All analyses were carried out using STATA version 11.0 for Windows.

4.3 Neurocognitive assessment

4.3.1 Participants and Methods

The neurocognitive assessment was carried out in years 2 and 3 of the ABD study, which included approximately 80% of the total sample (n=165). A neurocognitive assessment was not conducted as part of the CT study. The MATRICS neurocognitive battery was used (Kern et al., 2008, Nuechterlein et al., 2008) with the Wide Range Achievement Test 4 (WRAT-4) (Wilkinson and Robertson, 2005) used as a brief assessment of general scholastic ability/IQ. Holmen and colleagues have previously reported administering the MATRICS in an adolescent sample (ages 12 to 18 years) with early onset schizophrenia and showed it to be a sensitive marker of cognitive dysfunction in this age group (Holmen et al., 2010). The MATRICS covers seven putative domains in ten tests. Because of time constraints, the social cognition task was excluded from our panel of tests. The following six domains were covered using the nine MATRICS tasks below, with one additional task – the Trail Making Test-Part B (TMT-B).
4.3.2 Tasks

Trail making test- Parts A and B (TMT): pencil and paper task which requires the participant to draw a line connecting, in consecutive order, numbers arranged randomly on a page (Part A), followed by both numbers and letters arranged randomly on a page (Part B); outcome: total time for completion.

Brief Assessment of Cognition in Schizophrenia-Symbol coding (BACS-SC): a pencil and paper task which requires participants to write numbers that correspond to nonsense symbols as rapidly as possible in 90 seconds; outcome: number of symbols coded correctly.

Category fluency (Fluency): verbal fluency for animals in 60 seconds; outcome: number of correct words spoken.

Hopkins Verbal Learning Test-Revised (HVLT-R): participants heard a list of 12 words and were asked to repeat these in a series of three trials; outcome: number of correct responses summed over three trials.

Letter Number Span (LNS) (verbal memory): participants heard sets of letters and numbers, which they were required to repeat after mentally reordering numerically and alphabetically; outcome: total number correctly spoken.

Wechsler Memory Scale-Spatial Span (WMS-SS) (non-verbal memory): requires participants to remember and repeat which of a series of blocks the
test administrator points to, first forward then backward; outcome: sum of raw scores for both conditions.

Mazes (Neuropsychological Assessment Battery): pencil and paper test where participants attempted seven mazes of increasing difficulty; outcome: scores were based on the speed with which participants completed the seven mazes.

Brief Visuospatial Memory Test-Revised (BVMT-R): participants were shown a page displaying six geometric figures for ten seconds over three trials and asked to draw these figures on a sheet of paper after each trial. Outcome: points were awarded for the accuracy of the drawings over the three trials.

Continuous Performance Test-Identical Pairs (CPT-IP): participants were required to monitor numbers as they flashed on screen and press a button whenever two numbers in a row were identical; outcome: summed mean $d'$ value, which is an index of signal/noise discrimination, across 2-, 3-, and 4-digit conditions.

4.3.3 Statistical Analyses

Statistical analyses were conducted using STATA version 11.0 for Windows. Means and standard deviations are reported for adolescents with and without psychotic symptoms. Standardized Z-scores were calculated for each participant across each of the tasks and analysis of covariance (ANCOVA) was used to examine neurocognitive performance on the MATRICS in
adolescents with psychotic symptoms compared to the rest of the population sample, controlling for sex and number of years of education.
4.4 **Prodromal Risk Syndromes**

### 4.4.1 Participants and Methods

The Psychosis Section of the K-SADS interview was altered to include questions covering the five positive symptom sections (P1 to P5) of the Structured Interview for Prodromal Syndromes (SIPS). This was to assess additional information necessary to diagnose prodromal risk syndromes according to the criteria of prodromal syndromes defined by the SIPS interview. Questions were also added about the onset and frequency of and attributions for symptoms, as well as questions about whether or not symptoms caused distress to the interviewee, in order to gain information related to the proposed DSM-V diagnosis of 'Attenuated Psychosis Syndrome' (see Table 4.1 for criteria). The K-SADS interview finished with an assessment of the young person's functioning using the Children's Global Assessment Scale, which is a validated measure of global functioning adapted from the Global Assessment Scale for adults (Shaffer et al., 1983).

Three certified SIPS raters (Ian Kelleher, Aileen Murtagh and Mary Cannon), trained by a senior clinician from the Yale PRIME Prodrome Research Clinic (Barbara Walsh), reviewed all interviews and applied the criteria of prodromal syndromes (COPS) in order to confirm risk syndrome diagnoses. Diagnostic criteria are included in the Appendix but, briefly, there were 3 possible risk syndrome diagnoses:
Attenuated positive symptoms prodromal syndrome (APSP) is characterized by the following: (i) positive psychotic symptoms that are rated as three (moderate), four (moderately severe) or five (severe but not psychotic) on the P1 to P5 scales, (ii) symptoms began, or worsened by one or more scale points, within the past 12 months and (iii) symptoms occurred at least one a week in the past month.

Brief intermittent psychotic symptoms prodromal syndrome (BIPS) is characterized by the following: (i) positive symptom(s) rated six (i.e., frankly psychotic), (ii) symptom(s) have reached a psychotic level of intensity within the past three months and (iii) symptom(s) have been present for at least several minutes per day at a frequency of at least once per month.

Genetic risk and deterioration prodromal syndrome (GRD) is characterized by the following: (i) the participant meets criteria for current schizotypal personality disorder or has a first degree relative with a psychotic disorder, and (ii) a drop of at least 30% in the Global Assessment of Functioning score over the past month as compared to 12 months ago.

We also estimated the prevalence of prodromal risk syndromes/at risk mental states according to CAARMS criteria (see Appendix for full CAARMS criteria). In addition to criteria on positive psychotic symptoms, the most recent edition of the CAARMS added a criterion of a 30% decline in social/occupational functioning. CAARMS risk syndrome prevalences are reported with and without this criterion in the results.
Table 4.1: Criteria for the proposed ‘Attenuated Psychosis Syndrome’ for DSM-V

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>a)</td>
<td>Characteristic symptoms: at least one of the following in attenuated form with intact reality testing, but of sufficient severity and/or frequency that it is not discounted or ignored</td>
</tr>
<tr>
<td>(i)</td>
<td>delusions</td>
</tr>
<tr>
<td>(ii)</td>
<td>hallucinations</td>
</tr>
<tr>
<td>(iii)</td>
<td>disorganized speech</td>
</tr>
<tr>
<td>b)</td>
<td>Frequency/Currency: symptoms meeting criterion A must be present in the past month and occur at an average frequency of at least once per week in past month</td>
</tr>
<tr>
<td>c)</td>
<td>Progression: symptoms meeting criterion A must have begun in or significantly worsened in the past year</td>
</tr>
<tr>
<td>d)</td>
<td>Distress/Disability/Treatment Seeking: symptoms meeting criterion A are sufficiently distressing and disabling to the patient and/or parent/guardian to lead them to seek help</td>
</tr>
<tr>
<td>e)</td>
<td>Symptoms meeting criterion A are not better explained by any DSM-5 diagnosis, including substance-related disorder</td>
</tr>
<tr>
<td>f)</td>
<td>Clinical criteria for any DSM-V psychotic disorder have never been met</td>
</tr>
</tbody>
</table>
4.4.2 Statistical Analyses

Statistical analyses were conducted using STATA version 11.0 for Windows. A prevalence figure is reported for prodromal risk syndromes in the interviewed sample. Logistic regression was used to examine the relationship between risk syndromes and Axis-1 diagnoses. Analysis of variance was used to examine the association between risk syndrome status and functioning on the Children’s Global Assessment Scale.

4.5 Ethical approval

Ethical approval for the ABD study was received from the Beaumont Hospital Medical Ethics Committee and for the CT study from the Mater Misericordiae University Hospital Medical Ethics Committee. Following complete description of the study to participants and their parents, informed consent (parents) and assent (children less than 18 years) were received. A consultant child and adolescent psychiatrist was available to give guidance for cases that raised clinical concerns (Dr Michelle Harley for the ABD study; Prof Carol Fitzpatrick for the CT study), such as where suicidal behavior was reported, and participants were offered referrals to child and adolescent mental health services whenever appropriate. Parents and children were given contact details for the research teams, who were available to answer any questions or concerns that arose during or after participation in the studies.
Chapter 5: Results

Psychotic symptoms and Axis-1 psychopathology

5.1 Results of ABD Survey Study

5.1.1 Psychotic symptoms and SDQ-rated psychopathology

Psychotic symptoms were reported by 21% (n=239) of the early adolescence sample in the survey study, based on endorsement of the auditory hallucinations question. Increasing ‘total difficulties’ scores on the SDQ were associated with increasing odds of reporting psychotic symptoms (F=94.72, p<0.001). Adolescents who scored within the top quartile for SDQ-measured psychopathology were 6.5 times more likely to report psychotic symptoms compared to those in the lowest quartile (test for trend, Z = 8.60, p<0.001) (see Table 5.1). In fact, among adolescents with the top 5% most severe SDQ total difficulties scores, 48.1% reported psychotic symptoms, in contrast to just 2.9% of adolescents with the lowest 5% SDQ total difficulties score (OR=31.10, CI95=6.91-140.02, p<0.001). Psychotic symptoms were not confined to any one disorder – rather they were reported at an increased prevalence across each of the SDQ-rated emotional, conduct and hyperkinetic disorders (see Table 5.2).

5.1.2 Comorbid psychopathology

In order to investigate whether psychotic symptoms were more common in adolescents who had SDQ-rated comorbidity across the three disorder domains (i.e., abnormal on 2 or more of the emotional disorders, conduct
disorders and hyperkinetic disorders domains), the prevalence of psychotic symptoms was calculated among adolescents who screened positive for psychopathology on 1, 2 or all 3 of the disorder domains compared to adolescents with no disorder. The prevalence of psychotic symptoms among those who did not demonstrate psychopathology on any of the 3 domains was 15%, but for psychopathology on 1 domain the prevalence of psychotic symptoms was 33% (OR=2.71, CI95=1.85-3.98, p<0.001), for psychopathology on 2 domains the prevalence of psychotic symptoms was 43% (OR=4.85, CI95=2.69-8.74, p<0.001) and for psychopathology on all 3 domains the prevalence of psychotic symptoms was 54% (OR=8.59, CI95=2.00-36.92, p<0.001) (test for trend: Z = 7.83, p<0.001) (see Figure 5.1).
Table 5.1: Odds of experiencing psychotic symptoms according to SDQ psychopathology scores in quartiles (a) unadjusted and (b) adjusted for sex in the ABD survey study

<table>
<thead>
<tr>
<th>Quartile</th>
<th>N</th>
<th>% with psychotic symptoms</th>
<th>Early adolescence survey study</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>OR (CI95)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(a)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(b)</td>
</tr>
<tr>
<td>1</td>
<td>313</td>
<td>7.7%</td>
<td>1</td>
</tr>
<tr>
<td>2</td>
<td>322</td>
<td>18%</td>
<td>2.31 (1.42-3.76)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1.91 (1.10-3.32)</td>
</tr>
<tr>
<td>3</td>
<td>221</td>
<td>22.2%</td>
<td>3.00 (1.81-4.97)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2.59 (1.45-4.60)</td>
</tr>
<tr>
<td>4</td>
<td>276</td>
<td>38.2%</td>
<td>6.50 (4.09-10.33)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>5.50 (3.25-9.30)</td>
</tr>
</tbody>
</table>

Test for trend across quartiles: \( Z=8.60, \ p<0.001 \)

ABD, Adolescent Brain Development; SDQ, Strengths and Difficulties Questionnaire
Table 5.2: Odds of experiencing psychotic symptoms among adolescents with SDQ-rated emotional, hyperkinetic and conduct disorders (a) unadjusted and (b) adjusted for sex in the ABD survey study

<table>
<thead>
<tr>
<th></th>
<th>% with psychotic symptoms</th>
<th>Early adolescence survey study</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>OR (CI95)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(a)</td>
</tr>
<tr>
<td>Emotional disorders</td>
<td>44%</td>
<td>3.44 (2.33-5.10)</td>
</tr>
<tr>
<td>Hyperkinetic disorders</td>
<td>35%</td>
<td>2.34 (1.62-3.37)</td>
</tr>
<tr>
<td>Conduct disorders</td>
<td>36%</td>
<td>2.38 (1.63-3.48)</td>
</tr>
</tbody>
</table>

ABD, Adolescent Brain Development; SDQ, Strengths and Difficulties Questionnaire
Results of ABD and CT Interview Studies

5.2 Psychotic symptoms and Psychopathology

5.2.1 Diagnoses of Axis-1 disorders

Thirty one percent of the ABD interview study sample had a lifetime diagnosable affective, anxiety or behavioural disorder. The lifetime disorders included depressive disorders, including major depressive disorder (MDD) and adjustment disorder with depressed mood (15%); behavioural disorders, including attention deficit/hyperactivity disorder (ADHD), oppositional defiant disorder and conduct disorder (9%); and anxiety disorders, including, generalized anxiety disorder, social phobia, separation anxiety disorder and obsessive compulsive disorder (14%).

Thirty four percent of the CT interview study sample had a lifetime diagnosable affective, anxiety or behavioural disorder. The lifetime disorders included depressive disorders, including MDD and adjustment disorder with depressed mood (18%); behavioural disorders, including ADHD, oppositional defiant disorder and conduct disorder (9%); and anxiety disorders, including generalized anxiety disorder, social phobia, separation anxiety disorder, obsessive compulsive disorder and panic disorder (11%).
5.2.3 Association between psychotic symptoms and Axis-1 diagnoses in the ABD study

A total of 22.6% (n=53) of the ABD sample reported psychotic symptoms, primarily auditory hallucinations. The prevalence of psychotic symptoms was higher among males ($\chi^2=7.03$, p<0.01). Of all adolescents who reported psychotic symptoms, 57% had a lifetime diagnosable Axis-1 disorder (OR=3.73, CI95=1.97-7.07, p<0.001) and 30.2% had a current diagnosable Axis-1 disorder (OR=3.46, CI95=1.64-7.31, p<0.01). Adolescents with a lifetime diagnosable affective disorder were 5-times more likely to report psychotic symptoms compared to the rest of the sample, while adolescents with a lifetime diagnosable behavioural disorder were 3-times more likely to report psychotic symptoms (see Table 5.3)

5.2.4 Association between psychotic symptoms and Axis-1 diagnoses in the CT study

In the mid-adolescence sample, 7% of participants reported psychotic symptoms, primarily auditory hallucinations. There was a trend for psychotic symptoms to be more prevalent among males ($\chi^2=3.62$, p=0.057). Of all adolescents who reported psychotic symptoms, 79% had a lifetime diagnosable Axis-1 disorder (OR=8.19, CI95=2.2-30.4, p<0.01) and 43% had a current diagnosable Axis-1 disorder (OR=4.27, CI95=1.38-13.21, p=0.01). Adolescents with a lifetime diagnosable affective disorder were more than 10-times as likely to report psychotic symptoms compared to the rest of the
sample, while adolescents with a lifetime diagnosable behavioural disorder were 5-times as likely to report psychotic symptoms (see Table 5.3).

5.2.5 Multiple psychopathology in the ABD and CT interview studies

Multiple psychopathology (that is, a history of more than one Axis-1 diagnosis) was present in 15% (n=35) of the ABD sample interviewed. A dose-response relationship was observed between the number of Axis-1 diagnoses an adolescent had and their risk of reporting psychotic symptoms (Z = 3.67, p < 0.001). In the ABD study, 29% of participants with one diagnosable Axis-1 disorder reported psychotic symptoms, compared to 38% of participants with two diagnosable disorders and 55% of adolescents with three or more diagnosable disorders (see Table 5.4 and Figure 5.1). Multiple psychopathology was present in 10% (n=21) of the CT sample interviewed. A dose-response relationship was also observed between the number of Axis-1 diagnoses an adolescent had and their risk of reporting psychotic symptoms in this sample (Z = 4.29, p < 0.001). Eight percent of participants with one diagnosable Axis-1 disorder reported psychotic symptoms, compared to 31% of participants with two diagnosable disorders and 40% of participants with three or more diagnosable disorders (see Table 5.4 and Figure 5.1).
Table 5.3: Odds of experiencing psychotic symptoms among adolescents with lifetime DSM IV Axis-1 diagnoses diagnosed by clinical interview (a) unadjusted and (b) adjusted for sex in the ABD interview study and the CT interview study

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>% with psychotic symptoms</th>
<th>ABD interview study OR (CI95) (a)</th>
<th>% with psychotic symptoms</th>
<th>CT interview study OR (CI95) (a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any lifetime Axis-1 disorder</td>
<td>40%</td>
<td>2.89 (1.54-5.41)</td>
<td>19%</td>
<td>11.15 (2.99-41.65)</td>
</tr>
<tr>
<td>Affective disorders</td>
<td>51%</td>
<td>4.93 (2.31-10.51)</td>
<td>24%</td>
<td>10.67 (3.33-34.19)</td>
</tr>
<tr>
<td>Behavioural disorders</td>
<td>50%</td>
<td>3.95 (1.55-10.10)</td>
<td>22%</td>
<td>5.14 (1.43-18.51)</td>
</tr>
<tr>
<td>Anxiety disorders</td>
<td>23%</td>
<td>0.99 (0.48-2.06)</td>
<td>9%</td>
<td>1.45 (0.30-6.95)</td>
</tr>
</tbody>
</table>
Table 5.4: Odds of experiencing psychotic symptoms in adolescents with one, two or three or more comorbid DSM-IV Axis-1 disorders diagnosed by clinical interview, (a) unadjusted and (b) adjusted for sex, in the ABD interview study and the CT interview study

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>% with psychotic symptoms</th>
<th>ABD interview study</th>
<th>% with psychotic symptoms</th>
<th>CT interview study</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>OR (CI95)</td>
<td>(a)</td>
<td>(b)</td>
</tr>
<tr>
<td>One disorder only</td>
<td>29%</td>
<td>2.25 (1.06-4.75)</td>
<td>8%</td>
<td>3.86 (0.83-17.88)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2.27 (1.06-4.87)</td>
<td>4.12 (0.88-19.38)</td>
<td></td>
</tr>
<tr>
<td>Two disorders only</td>
<td>38%</td>
<td>3.23 (1.27-8.27)</td>
<td>31%</td>
<td>20.15 (4.24-95.59)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3.18 (1.22-8.29)</td>
<td>18.33 (3.77-89.15)</td>
<td></td>
</tr>
<tr>
<td>Three or more disorders</td>
<td>55%</td>
<td>6.47 (1.82-22.98)</td>
<td>40%</td>
<td>29.56 (3.53-247.17)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>6.31 (1.73-23.05)</td>
<td>36.18 (3.94-332.06)</td>
<td></td>
</tr>
<tr>
<td>Test for trend</td>
<td>Z = 3.67, p &lt; 0.001</td>
<td></td>
<td>Z = 4.29, p &lt; 0.001</td>
<td></td>
</tr>
</tbody>
</table>
Figure 5.1: Prevalence of psychotic symptoms by comorbid diagnoses in the ABD survey sample (green line), ABD interview sample (blue line) and CT interview sample (red line)
5.3 Psychotic symptoms and suicidal behaviour

5.3.1 Prevalence of suicidal behaviour and association with psychotic symptoms

Findings on the association between psychotic symptoms and suicidal behaviour are shown in Table 5.5. Seven percent of the ABD sample reported suicidal behaviour. Specifically, 6.8% (n=16) reported suicidal ideation, 3.7% (n=5) reported specific suicide plans and just one participant reported a suicidal act (0.4%). Adolescents who reported psychotic symptoms demonstrated a greater than 10-fold increased risk of suicidal behaviour.

Thirteen percent of the CT sample reported suicidal behaviour. Specifically, 13.2% (n=28) reported suicidal ideation, 5% (n=11) reported specific suicide plans and 3.3% (n=7) reported a suicidal act. Adolescents who reported psychotic symptoms demonstrated a greater than 10-fold increased risk of suicidal behaviour (see Table 5.5).

5.3.2 Stratification by psychiatric disorder

A diagnosable psychiatric disorder was also associated with increased risk for suicidal behaviour (ABD study: OR=3.09, CI95=1.08-8.83, p<0.05; CT study: OR=7.6, CI95=3.17-18.06, p<0.001). Therefore, in order to examine the relationship between psychotic symptoms and suicidal behaviour in this higher risk group, and in order to allow extrapolation to clinical populations, we conducted secondary analyses limited to adolescents with a history of
diagnosable psychiatric disorder. Results are shown in Table 5.5. In the ABD study, adolescents with a diagnosable psychiatric disorder plus psychotic symptoms were at a greater than 5-fold increased risk of suicidal behaviour compared to adolescents with a diagnosable psychiatric disorder but no psychotic symptoms. In the CT study, adolescents with a diagnosable psychiatric disorder plus psychotic symptoms were at a greater than 5-fold increased risk of suicidal behaviour compared to adolescents with a diagnosable psychiatric disorder but no psychotic symptoms.

5.3.3 Stratification by suicidal behaviour severity: suicide plans and acts

Because suicidal behaviour varies in severity, with ideation on one end and other forms – suicide plans and acts – further along the continuum of severity, we conducted a further set of analyses to assess the risk for more severe behaviour - suicide plans and acts. As the ABD study contained a younger age group (mean age 11.5 years) and did not enrich for suicidal behaviour, there were few cases of severe suicidal behaviour; however, the CT data, with its older population and enrichment for suicidal behaviour, facilitated this analysis. Adolescents with a diagnosis of a depressive disorder or a behavioural disorder and adolescents with suicidal ideation were all more likely to have suicide plans or acts. In order to test whether psychotic symptoms helped to differentiate adolescents in these diagnostic groups who had suicide plans or acts from those who did not, we conducted a number of stratified analyses. Among adolescents with (i) depressive disorders and (ii) behavioural disorders, adolescents who reported psychotic
symptoms were at greatly increased risk for suicidal plans and acts compared to adolescents with the same diagnoses who did not report psychotic symptoms (see Table 5.6). Among adolescents with suicidal ideation, psychotic symptoms were associated with a 20-fold increased risk for suicide plans and acts. Strikingly a majority of adolescents with suicidal plans or acts reported psychotic symptoms when they were directly questioned about this in both the ABD (80%) and CT (55%) studies.
Table 5.5: Psychotic symptoms and odds of suicidal behaviour in 2 population samples ages 11-13 years (ABD study) and 13-15 years (CT study) (a) unadjusted and (b) adjusted for sex

<table>
<thead>
<tr>
<th>Population Sample</th>
<th>All suicidal behaviour</th>
<th>( P )</th>
<th>All suicidal behaviour</th>
<th>( p )</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(a)</td>
<td></td>
<td>(b)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>OR (CI95)</td>
<td></td>
<td>OR (CI95)</td>
<td></td>
</tr>
<tr>
<td>ABD study population sample (n=212)</td>
<td>9.01 (2.97-27.33)</td>
<td>0.000</td>
<td>10.23 (3.25-32.26)</td>
<td>0.000</td>
</tr>
<tr>
<td>CT study population sample (n=211)</td>
<td>8.52 (2.21-32.91)</td>
<td>0.002</td>
<td>10.50 (3.14-35.17)</td>
<td>0.000</td>
</tr>
<tr>
<td>ABD study sample with diagnosable psychiatric disorder (n=78)</td>
<td>5.27 (1.25-22.23)</td>
<td>0.023</td>
<td>5.13 (1.15-22.81)</td>
<td>0.032</td>
</tr>
<tr>
<td>CT study sample with a diagnosable psychiatric disorder (n=72)</td>
<td>4.37 (1.14-16.79)</td>
<td>0.031</td>
<td>5.31 (1.29-21.84)</td>
<td>0.021</td>
</tr>
</tbody>
</table>
Table 5.6: Prevalence and odds of suicide plans and acts among stratified samples of mid adolescence (CT) study (a) unadjusted and (b) adjusted for sex

<table>
<thead>
<tr>
<th></th>
<th>Prevalence of suicide plans or acts – no psychotic symptoms</th>
<th>Prevalence of suicide plans or acts – psychotic symptoms</th>
<th>OR (CI95)</th>
<th>OR (CI95)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CT sample with depressive disorder (n=37)</td>
<td>16%</td>
<td>67%</td>
<td>10.4 (1.9 to 56.0)</td>
<td>13.7 (2.1 to 89.6)</td>
</tr>
<tr>
<td>CT sample with behavioural disorder (n=18)</td>
<td>0%</td>
<td>75%</td>
<td>∞</td>
<td>∞</td>
</tr>
<tr>
<td>CT sample with suicidal ideation (n=28)</td>
<td>24%</td>
<td>86%</td>
<td>19.2 (1.8 to 200.0)</td>
<td>19.6 (1.8 to 216.1)</td>
</tr>
</tbody>
</table>

∞ odds ratio not calculable because 0 participants in comparison group
5.4 Psychotic symptoms and Neurocognition

Adolescents with psychotic symptoms did not differ in general scholastic ability/IQ as measured with the WRAT-4 (F=0.02, df=1, p=0.89). In tests of neurocognitive function, adolescents with psychotic symptoms performed significantly more poorly on three tests of processing speed: TMT-A (F=3.33, p<0.05), TMT-B (F=3.06, p<0.05) and BACS symbol coding (F=7.03, p<0.001). Adolescents with psychotic symptoms also performed more poorly in their non-verbal working memory: WMS spatial span task (F=3.17, P<0.05). Differences on the HVLT-R were just outside statistical significance at the level of p=0.05. See Table 5.7 and Figure 5.2 for details.
Table 5.7: Neurocognitive performance on the MATRICS battery, adjusted for sex and years of education

<table>
<thead>
<tr>
<th>Test (Putative neurocognitive domain)</th>
<th>Males (n=85) Mean (sd)</th>
<th>Females (n=80) Mean (sd)</th>
<th>F (p value)</th>
<th>Psychotic symptoms group (n=42) Mean (sd)</th>
<th>Comparison group (n=123) Mean (sd)</th>
<th>F (p value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TMT-A* (Processing speed)</td>
<td>44.9 (13.3)</td>
<td>41.8 (12.1)</td>
<td>2.47 (0.12)</td>
<td>45.5 (14.0)</td>
<td>42.6 (12.3)</td>
<td>3.33 (&lt;0.05)</td>
</tr>
<tr>
<td>TMT-B* (Processing speed)</td>
<td>74.3 (29.0)</td>
<td>68.3 (28.8)</td>
<td>1.46 (0.23)</td>
<td>83.4 (32.3)</td>
<td>67.4 (26.8)</td>
<td>3.06 (&lt;0.05)</td>
</tr>
<tr>
<td>BACS:SC (Processing speed)</td>
<td>45.5 (9.4)</td>
<td>50.3 (8.6)</td>
<td>11.66 (&lt;0.001)</td>
<td>44.4 (10.2)</td>
<td>49.1 (8.7)</td>
<td>7.03 (&lt;0.001)</td>
</tr>
<tr>
<td>Category Fluency (Processing speed)</td>
<td>20.2 (5.4)</td>
<td>20.1 (4.9)</td>
<td>0.01 (0.91)</td>
<td>19.8 (5.2)</td>
<td>20.3 (5.2)</td>
<td>1.20 (0.31)</td>
</tr>
<tr>
<td>HVLT-R (Verbal learning/memory)</td>
<td>24.6 (4.2)</td>
<td>26.0 (4.5)</td>
<td>3.71 (0.06)</td>
<td>24.3 (5.3)</td>
<td>25.6 (4.0)</td>
<td>2.59 (0.05)</td>
</tr>
<tr>
<td>WMS spatial span (Working memory: nonverbal)</td>
<td>14.7 (3.1)</td>
<td>15.9 (3.1)</td>
<td>6.89 (&lt;0.01)</td>
<td>14.9 (3.7)</td>
<td>15.4 (2.9)</td>
<td>3.17 (&lt;0.05)</td>
</tr>
<tr>
<td>LNS (Working memory: verbal)</td>
<td>13.1 (2.8)</td>
<td>13.5 (2.9)</td>
<td>0.84 (0.36)</td>
<td>13.4 (2.9)</td>
<td>13.3 (2.8)</td>
<td>0.37 (0.78)</td>
</tr>
<tr>
<td>NAB: Mazes (Reasoning and problem solving)</td>
<td>16.5 (5.1)</td>
<td>14.9 (5.0)</td>
<td>3.97 (&lt;0.05)</td>
<td>15.2 (5.1)</td>
<td>15.9 (5.1)</td>
<td>2.38 (0.07)</td>
</tr>
<tr>
<td>BVMT-R (Visual learning)</td>
<td>25.1 (7.9)</td>
<td>27.5 (6.6)</td>
<td>4.56 (&lt;0.05)</td>
<td>26.9 (7.0)</td>
<td>26.1 (7.5)</td>
<td>2.24 (0.09)</td>
</tr>
<tr>
<td>CPT-IP (Attention/Vigilance)</td>
<td>5.0 (4.8)</td>
<td>5.4 (1.7)</td>
<td>0.24 (0.63)</td>
<td>4.5 (2.8)</td>
<td>5.3 (4.0)</td>
<td>0.27 (0.85)</td>
</tr>
</tbody>
</table>

*Higher score = poorer performance. Abbreviations: sd, standard deviation; TMT, Trail Making Test (Part A and Part B); BACS:SC, Brief Assessment of Coding in Schizophrenia: Symbol Coding; HVLT-R, Hopkins Verbal Learning Test – Revised; WMS, Wechsler Memory Scale; LNS, Letter Number Span; NAB, Neuropsychological Assessment Battery; BVMT-R, Brief Visuospatial Memory Test – Revised; CPT, Continuous Performance Test – Identical Pairs
Figure 5.2: Mean differences in Z-scores between adolescents with and without psychotic symptoms on the MATRICS neurocognitive battery.

5.5 Prodromal Risk Syndromes

5.5.1 Prevalence of risk syndromes

Applying SIPS criteria to adolescents who reported psychotic symptoms, 8.1% (n=19) of the total sample met criteria for a current prodromal risk syndrome. Specifically, 7.7% met criteria for an attenuated positive symptoms prodromal syndrome (APSP) and 3.5% met criteria for a brief intermittent psychotic symptoms prodromal syndrome (BIPS). One additional participant met criteria for APSP in remission. Three participants had a first degree relative with a psychotic disorder but none of these participants had experienced a significant decline in functioning within the past year and so no participant met criteria for GRD. There was no significant effect of age or socioeconomic status on risk syndrome status. However, significantly more males than females fulfilled criteria for a risk syndrome ($\chi^2=4.17$, p=0.04).

Applying the CAARMS criteria, 7.7% of the sample met criteria for an at risk mental state without applying a criterion of a 30% decrease in functioning in the last year. Just 0.9% (n=2) of participants would have met criteria for an at risk mental state, however, were a 30% decrease in functioning used as an obligate criterion (using the Children’s Global Assessment Scale as the measure of functioning).
5.5.2 Attenuated Psychosis Syndrome

The proposed DSM-V diagnosis of attenuated psychosis syndrome (see Table 4.1) differs from APSP in Criterion D, that is, the requirement that, in addition to attenuated psychotic symptoms, there is also distress and disability. The majority of adolescents who fulfilled criteria for APSP, in fact, did report being distressed by their symptoms (89%). Similarly, in terms of disability, adolescents who fulfilled criteria for APSP also demonstrated significantly impaired functioning compared to controls, as measured by the Children's Global Assessment Scale (F=24.5, df=1, p<0.0001).

5.5.3 Prodromal Risk Syndromes and Psychiatric Comorbidity

A total of 63% of the adolescents who met criteria for a prodromal risk syndrome also met criteria for at least one lifetime Axis-1 diagnosis (OR=4.77, CI95=1.81 – 12.52; p<0.01) (see Table 5.8). The most common lifetime Axis 1 diagnosis was major depressive disorder (MDD) (26%). Thirty seven percent of adolescents with risk syndromes met criteria for a depressive disorder, 32% met criteria for an anxiety disorder and 21% met criteria for a behavioural disorder. Furthermore, 30% reported current or past suicidal ideation and 20% reported a history of self harm.
Table 5.8: Lifetime Axis 1 diagnoses and suicidal behaviour in patients with prodromal risk syndromes and in controls

<table>
<thead>
<tr>
<th>Lifetime Axis 1 diagnosis</th>
<th>Prodromal risk syndrome (n=19)</th>
<th>Controls (n=193)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any diagnosis</td>
<td>63%</td>
<td>28%</td>
</tr>
<tr>
<td>Affective disorders</td>
<td>37%</td>
<td>13%</td>
</tr>
<tr>
<td>Major Depressive Disorder</td>
<td>26%</td>
<td>5%</td>
</tr>
<tr>
<td>Dysthymic disorder</td>
<td>0</td>
<td>0.5%</td>
</tr>
<tr>
<td>Adjustment disorder with depressed mood</td>
<td>16%</td>
<td>8.4%</td>
</tr>
<tr>
<td>Behavioural Disorders</td>
<td>21%</td>
<td>7%</td>
</tr>
<tr>
<td>Attention Deficit/Hyperactivity Disorder</td>
<td>16%</td>
<td>4%</td>
</tr>
<tr>
<td>Oppositional Defiant Disorder</td>
<td>5%</td>
<td>4%</td>
</tr>
<tr>
<td>Conduct Disorder</td>
<td>0</td>
<td>1%</td>
</tr>
<tr>
<td>Anxiety Disorders</td>
<td>16%</td>
<td>13%</td>
</tr>
<tr>
<td>Generalized Anxiety Disorder</td>
<td>0</td>
<td>6%</td>
</tr>
<tr>
<td>Separation anxiety disorder</td>
<td>5%</td>
<td>5%</td>
</tr>
<tr>
<td>Avoidant disorder</td>
<td>5%</td>
<td>2%</td>
</tr>
<tr>
<td>Obsessive Compulsive Disorder</td>
<td>5%</td>
<td>2%</td>
</tr>
<tr>
<td>Social phobia</td>
<td>5%</td>
<td>5%</td>
</tr>
<tr>
<td>Suicidal ideation</td>
<td>30%</td>
<td>5%</td>
</tr>
<tr>
<td>Self-harm</td>
<td>20%</td>
<td>6%</td>
</tr>
</tbody>
</table>
Chapter 6: Discussion

6.1 Psychotic symptoms and Axis-1 psychopathology

Using one large population-based survey study and two in-depth clinical interview studies, a number of significant findings have emerged. First, psychotic symptoms are prevalent in a wide range of non-psychotic psychopathologies. Second, while psychotic symptoms are not pathognomonic of illness, the majority of young people in the community who report psychotic symptoms do have a diagnosable psychiatric disorder. Third, psychotic symptoms index particularly high risk for multiple pathology, that is having more than 1 DSM diagnosis. Fourth, psychotic symptoms are reported more commonly in early compared to middle adolescence. Fifth, psychotic symptoms become increasingly predictive of diagnosable psychopathology with increasing age.

While some research has shown that the majority of psychotic symptoms in childhood are transient, with symptoms that persist over time thought to be of more clinical significance (van Os et al., 2009), in the current study the majority of adolescents who reported psychotic symptoms had at least one diagnosable Axis-1 psychiatric disorder, regardless of the issue of psychotic symptom persistence. Increased risk for psychopathology was not related to a particular diagnosis or even one group of disorders; rather, a variety of Axis-1 disorders were associated with psychotic symptoms. Interestingly,
however, psychotic symptoms demonstrated a particularly strong relationship with more severe psychopathology, with prevalence of psychotic symptoms increasing in a dose-response fashion with the number of diagnosable disorders. In the CT study, for example, 40% of adolescents with three or more comorbid disorders reported psychotic symptoms, compared to just 8% of adolescents with only one disorder.

Psychotic symptoms were more common in the early adolescence samples (21% to 23%) compared to middle adolescence (7%). This is in line with the meta-analytic findings in the current thesis of a decline in prevalence of psychotic symptoms from childhood into adolescence. However, associations between psychotic symptoms and diagnosable disorder were stronger in the older sample compared to the younger samples. While 57% of the early adolescence (ABD study) sample who reported psychotic symptoms had a diagnosable psychiatric disorder, nearly 80% of the mid adolescence (CT study) sample who reported psychotic symptoms had at least 1 diagnosable disorder. In a study of younger children, aged 7 to 8, Bartels-Velthuis and colleagues found that auditory hallucinations were associated with only a minor increase in risk for parent-reported behavioural and emotional symptoms (Bartels-Velthuis et al., 2010) but that at age 12 to 13 years psychotic symptoms predicted an approximately 3- to 5-fold increased risk of scoring in the clinical range of the Child Behaviour Checklist (Bartels-Velthuis et al., 2011). Hallucinatory and delusional
experiences, then, may fall somewhat within the normal spectrum of experience in early childhood but might be expected to discontinue in the course of development. Psychotic symptoms in adolescence, the current findings suggest, become increasingly associated with psychopathology – in particular with severe, multiple co-occurring disorders.

There are a number of possible explanations as to how psychotic symptoms act as a marker for a wide range of psychopathology. One possibility is that the same risk factors may predispose to both psychotic symptoms and psychiatric illness. In fact, Breetvelt et al. have recently demonstrated that many risk factors that have typically been considered risk factors for psychosis are risk factors for a wider range of (non-psychotic) psychopathology (Breetvelt et al., 2010). It is also possible that mental distress caused by psychotic symptoms contributes to, for example, depressive thoughts or behavioural symptoms. It may also be the case, however, that psychotic symptoms do not contribute to psychopathology per se but, rather, emerge in vulnerable individuals who experience non-psychotic psychopathology and therein act as a marker, rather than an aetiological factor, for non-psychotic psychopathology.

The limited structural and functional magnetic resonance imaging (MRI) research on psychotic symptoms to date suggests that adolescents with psychotic symptoms exhibit a profile of subtle neurodevelopmental
differences that shares features with a number of psychiatric disorders (Jacobson et al., 2010). A recent meta-analysis of brain volume abnormalities in major depressive disorder, for example, showed that the greatest changes occur in two regions important in emotion processing and stress regulation – the cingulum and orbitofrontal cortex (Koolschijn et al., 2009), both of which we have recently shown to be abnormal in adolescents with psychotic symptoms (Jacobson et al., 2010). Using functional MRI and digital tractography, Jacobson et al. also demonstrated reduced activity within the right frontal and bilateral temporal cortices during response inhibition tasks and overall reduced integrity of fronto-temporal pathways in adolescents with psychotic symptoms, supporting a profile of a relative disinhibition/pro-impulsivity phenotype. These neurobiological findings mirror the clinical findings of increased affective and behavioural disorders in the current thesis.

**Strengths and limitations**

There are a number of strengths to the current work, most notably the use of three studies, each of which shows the same pattern of results. While the larger survey study allowed testing for relationships between psychotic symptoms and psychopathology in terms of a symptomatic continuum, the downside of this approach is that clinical implications, in the absence of actual diagnoses, can be hard to draw. However, the use of two clinical interview studies allows us to draw clear clinical implications by exploring the
relationship between psychotic symptoms and actual psychiatric diagnoses. The use of multiple studies also allowed an examination of the relationship between psychotic symptoms and psychopathology from early through middle adolescence. In addition, the use of community samples is particularly valuable because findings are generalisable to the population. A limitation is that the issue of temporality cannot be resolved, i.e., which came first: psychotic symptoms or psychopathology, or, indeed, did both arise together. However, this does not detract from the clinical utility of understanding the contemporaneous relationship between psychotic symptoms and non-psychotic psychopathology. Subgroup analyses within studies means that there are small groups and confidence intervals, as a result, are wide in some cases. However, the same pattern of results was found across all three studies showing that the findings are robust.
6.2 *Psychotic Symptoms and Suicidal Behaviour*

The results of two Independent epidemiological studies showed that psychotic symptoms index large increases in risk for (i) suicidal behaviour in the general adolescent population, (ii) suicidal behaviour in adolescents with psychiatric disorders and (iii) more severe forms of suicidal behaviour (suicidal plans and acts) among adolescents with depressive disorders, behavioural disorders and suicidal ideation. In fact, in both studies, psychotic symptoms were reported by the majority of adolescents who reported having formulated specific suicide plans or previous suicidal acts. This is a particularly important fact given that suicide plans and history of parasuicide have been shown to be among the most predictive risk factors for completed suicide (Powell *et al.*, 2000, Suominen *et al.*, 2004).

There are a number of possible explanations as to the mechanisms underlying the strong relationship between psychotic symptoms and suicidal behaviour. The most obvious is that hallucinations may direct the individual to harm or kill themselves. In fact, a post-hoc analysis of the type of psychotic symptoms reported by adolescents with suicidal behaviour demonstrated that all included auditory hallucinations. However, only one of the participants in either of the studies reported command hallucinations to harm or kill themselves. It is possible, however, that psychotic symptoms may impact on suicidal behaviour via indirect cognitive mechanisms. Changes in the subjective sense of self, for example, are amongst the
earliest recognizable symptoms of psychosis (Klosterkotter et al., 1997, Yung et al., 1996) and a sense of disintegration and fragmentation of the self resulting from intrusive voices has long been linked to suicidal thinking (Bleuler, 1911, Frosh, 1983). Similar effects may occur in the extended psychosis phenotype – Bleuler’s concept of the ‘suicidal drive’ might not be just the most severe symptom of schizophrenia (Bleuler, 1911) but the most severe symptom of a much broader psychosis phenotype made up of individuals in the general population who experience psychotic symptoms.

Common causes shared between psychotic symptoms and suicidal behaviour may be part of the mechanism underlying the striking relationship between the two variables. Individuals with mental disorders who experience psychotic symptoms, for example, may be more unwell in general than individuals with mental disorders who do not experience psychotic symptoms. This is supported by the finding in the current thesis that adolescents with a psychiatric disorder who reported psychotic symptoms were significantly more likely to have a second co-occurring disorder. These symptoms, then, may be an important marker of deteriorating mental health in a way that indexes high risk for suicidal behaviour. Jacobson et al. recently showed volumetric differences in the cingulum and orbitofrontal cortex in a sample of adolescents with psychotic symptoms (Jacobson et al., 2010), two centres that are known to play important roles in emotion processing and stress regulation (Koolschijn et al., 2009). Abnormalities in
the orbitofrontal cortex have also recently been highlighted as an area of interest in magnetic resonance imaging (MRI) studies of suicidal patients (Monkul et al., 2007). Furthermore, the clinical findings of the current thesis showed that depressive and behavioural symptoms and disorders were prevalent among young people with psychotic symptoms. In terms of suicidal behaviour, the combination of depressive and impulsive traits poses a high risk phenotype.

For clinicians, these findings highlight the importance of a thorough assessment of psychotic symptoms in patients presenting with suicidal behaviour. Young people rarely volunteer information on psychotic symptoms unless questioned directly about such experiences. The experience from ABD study interviews, however, is that adolescents are usually willing to talk openly about their experiences in response to direct but sensitive questioning. This is especially important in child mental health clinics, where psychosis can sometimes be seen as an ‘adult psychiatry’ issue and therefore not fully explored. For researchers, these findings highlight a complex novel aspect in the study of the aetiology of suicidal behaviour.

While the current report includes participants in early and middle adolescence, suicidal behaviour in childhood and adolescence predicts suicidal behaviour throughout the lifecourse. Reinherz and colleagues, for
example, showed that adolescents who reported suicidal ideation were, at
age 30, 15-times more likely to report suicidal ideation and 12-times more
likely to have attempted suicide (Reinherz et al., 2006). Therefore the
association between suicidal behaviour and psychotic symptoms in
adolescence is likely to continue into adulthood. Whether or not psychotic
symptoms are as prevalent in individuals who demonstrate suicidal
behaviour in adulthood, however, remains to be investigated.

Strengths of the current work include that assessments involved in-depth
clinical interview and that it was possible to test interactions between
psychotic symptoms and psychiatric disorders in predicting suicidal
behaviour. In addition, findings were replicated across two independent
studies. The age ranges of participants was also complementary across the
two studies, demonstrating the relationship between psychotic symptoms
and suicidal behaviour from early through to middle adolescence (ages 11 to
15 years). As with the psychopathology results above, subgroup analyses for
suicidal behaviour involved relatively small groups and, because of this,
confidence intervals are wide. Both studies, however, showed the same
strong relationship between psychotic symptoms and suicidal behaviour,
demonstrating that this is a robust finding. Further research on the
relationship between psychotic symptoms and suicidal behaviour, however,
will be valuable. Further work is also needed to investigate the relationship
between psychotic symptoms and suicidal behaviour in later adolescence and into adulthood.
Adolescents with psychotic symptoms demonstrated processing speed deficits using the TMT-A, the TMT-B and the BACS digit symbol coding tasks, and (non-verbal) working memory deficits on the WMS spatial span task. Processing speed has been suggested to be the core neurocognitive deficit of psychosis (Dickinson, 2008, Dickinson et al., 2007). The results of the current study reflect findings in a treatment-naive, extended psychosis phenotype and support the hypothesis that a deficit in processing speed is at the core of neurocognitive dysfunction in psychosis. Working memory deficits were also apparent in this sample, demonstrating the centrality of this deficit to the broad psychosis phenotype, though these deficits were less pronounced than those of processing speed.

This is the first study to report on symbol coding in a population sample with psychotic symptoms, with strong findings of impairment demonstrated on this task. This is in keeping with findings from Dickinson et al., who have argued that symbol coding deficits in particular reflect slowed information processing that is the central feature of cognitive dysfunction in psychosis (Dickinson et al., 2007). Interestingly, in a longitudinal study, Niendam and colleagues showed a number of neurocognitive deficits at age 7-years in both individuals who would go on to develop schizophrenia and in their siblings (Niendam et al., 2003); however, only symbol coding scores differentiated those who would later develop schizophrenia from their
unaffected siblings. Adolescents with psychotic symptoms also demonstrated deficits in TMT-A and TMT-B performance in the current study. This is in line with a previous cohort study, which demonstrated that childhood performance on processing speed tasks (TMT and verbal fluency tasks), uniquely among tests of neurocognition, predicted adulthood schizophrenia (Cannon et al., 2006). This finding is also in keeping with a previous report on a small sample of adolescents with psychotic symptoms (n=17), which showed poorer performance on the TMT-B (Blanchard et al., 2010).

The significance of processing speed deficits to 'real world' measures of function has recently been highlighted. Using the Specific Level of Function Scale, an observer-rated assessment of a patient's behaviour and functioning, Bowie and colleagues found that processing speed tasks, uniquely in a battery of neurocognitive tests, predicted functioning in all three domains of functioning, including interpersonal relationships, community involvement and work skills, among a sample of more than 200 schizophrenia patients (Bowie et al., 2008). More recently, among a sample of patients at ultra high risk for psychosis, Carrion and colleagues showed that both social and role functioning related specifically to processing speed (a combined symbol coding and TMT score) and argued that processing speed represents a rate-limiting step in the formation of good social and role functioning (Carrion et al., 2011). The community findings in the current
study suggest that deficits in processing speed may represent an early neurocognitive marker of psychosis vulnerability, present not only in psychosis patients but even in community-based young adolescents with psychotic symptoms.

In contrast to many neurocognitive tasks that might be attributed to specific neural networks or specific anatomical regions, processing speed tasks have been argued to measure a 'systems' based process, reflecting speeded integration and coordination between distributed brain networks (Dickinson, 2008). Recent empirical support for this has come from digital tractography imaging of white matter microstructural organization in both healthy and brain injured individuals. Turken et al., for example, showed that processing speed is closely related to the structural integrity of major white matter tracts that run along the anterior-posterior axis of the brain, allowing fronto-posterior network interactions, including the superior longitudinal fasciculus, occipito-frontal fasciculus and inferior longitudinal fasciculus (Turken et al., 2008). The findings of the current study, then, are in line with the dysconnection hypothesis of schizophrenia, which asserts that impaired communication within the brains of schizophrenia patients occurs when there is focal disruption that adversely affects the entire network (Friston and Frith, 1995, Weinberger et al., 1992). This is in keeping with neuroimaging findings, described above, which showed impaired connectivity in a community sample of adolescents with psychotic symptoms (Jacobson et al.,
2010). Processing speed deficits, then, may point to aberrant functional connectivity within and between whole-brain neural systems, rather than indexing impairment in discrete neural networks.

This is the largest population-based neurocognitive assessment of young people with psychotic symptom to date. In addition, this is the first epidemiological study in children to use the MATRICS battery. The use of a standardized neurocognitive battery in the current study will facilitate comparison with other studies. None of the adolescents in the current study had a diagnosis of a psychotic disorder and none had ever used antipsychotic medication, outruling disease chronicity or treatment effects (Knowles et al., 2010) in the relationship between psychotic symptoms and neurocognitive performance. Further neurocognitive work in this population will help to elucidate the underlying pathophysiology associated with risk for psychosis.
6.4 *Prodromal Syndromes*

Up to 8% of the ABD sample fulfilled criteria for diagnosis of a current prodromal risk syndrome. The findings of the current work suggest that there are many prospectively identifiable individuals with prodromal risk syndromes in the community who have not presented to clinical services. What proportion of these individuals would ultimately present to services is unknown. However, while the overwhelming majority of cases of new onset psychosis have been established to be preceded by a prodromal period (Jackson *et al.*, 1995, Schultze-Lutter *et al.*, 2010, Yung and McGorry, 1996), only a minority of cases of the population-wide incidence of psychosis emerge in patients from prodrome risk syndrome clinics, which suggests that many such individuals will not clinically present prior to illness onset.

Attenuated positive symptoms prodromal syndrome (APSP), as described, differs from the proposed DSM-V diagnosis of 'Attenuated Psychosis Syndrome' in Criterion D ("distress/disability/treatment seeking"). However, the majority of adolescents meeting criteria for APSP reported distress as a result of their symptoms and this group demonstrated significantly poorer functioning on the Children's Global Assessment Scale. BIPS diagnoses, which usually constitute a relatively small proportion of patients seen in prodromal risk syndrome clinics, were present in 40% of all risk syndromes in the current study. Interestingly, in the clinic, risk for psychosis has been
demonstrated to be particularly high for patients with BIPS, with a faster onset of psychosis compared to young people with APSP (Nelson et al., 2011). It is possible that fewer BIPS patients will present clinically during the prodrome and are more likely to present for the first time during first episode psychosis due to what appears to be a shorter prodromal period. It is also possible that, because the symptoms are ‘brief’ and ‘intermittent’, that patients believe their symptoms have resolved and are, as a result, less likely to seek help. Further research will be necessary to understand this difference between the clinic and the community.

Non-psychotic psychiatric disorders were present in a large majority of adolescents with prodromal risk syndromes, consistent with research on clinically-presenting individuals (Addington et al., 2011). Rosen et al., for example, reported that in a sample of clinically presenting individuals who met criteria for a prodromal risk syndrome, 76% had at least one diagnosable lifetime Axis 1 disorder (Rosen et al., 2006). Svirskis et al., similarly, reported that over 90% of help-seeking individuals who met criteria for a prodromal risk syndrome had at least one comorbid disorder (Svirskis et al., 2005). Depressive disorders were the most common diagnosis in both studies, as in the current report. Lencz et al., using the same diagnostic instrument as the current study to assess for Axis-1 psychopathology in a sample of putatively prodromal help seekers, found MDD to be the most
common diagnosis, followed by attention deficit/hyperactivity disorder, in keeping with the current community findings (Lencz et al., 2004).

There are a number of implications of this research in relation to the proposed DSM-V diagnosis of attenuated psychosis syndrome. Findings from the current study that might support this diagnosis include that (i) a large majority of the individuals identified are distressed by their symptoms; (ii) this group demonstrates significantly poorer global functioning; and (iii) the majority of these adolescents have other diagnosable psychopathology that suggests that they as a population are truly in need of care. On the other hand, the findings of the current study also raise a number of concerns or limitations with regard to creation of an ‘attenuated psychosis syndrome’ diagnosis, including that (i) the proposed diagnostic criteria are applicable to a relatively large proportion of adolescents, meaning that, following publication of DSM-V, many young people could suddenly be imposed with a stigmatizing diagnosis that they did not previously have; (ii) we do not know the relative risk for psychosis among this group since longitudinal community research has not been conducted. Given the high prevalence of the syndrome, however, it is unlikely to approach the level of risk observed in help-seeking samples reported on to date; thus, we risk greatly increasing the rate of false positives; (iii) since the majority of these individuals already have psychiatric disorders, there would not, in most cases, appear to be a major financial barrier to receiving psychiatric treatment in healthcare
systems that require a formal diagnosis for insurance purposes; (iv) the proportion of adolescents who fulfil criteria for a risk syndrome varies greatly depending on how 'disability' is interpreted in terms of the degree of functional decline, something that is not currently specified in the proposed criteria; and (v) 'attenuated psychosis syndrome' may be a misnomer for a syndrome that is, in fact, associated with a wide range of (non-psychotic) disorders.

It is important to note that none of the participants in the current study, despite meeting criteria for prodromal risk syndromes, had presented to a prodrome or other healthcare clinic and so none of the participants can be considered 'help seekers' in the same way as individuals who have been reported on to date in clinic-based research. Why some individuals who meet risk syndrome criteria present to clinics while others do not is unclear and will require further research. There are many possible reasons for this. As already speculated, given the high proportion of BIPS in the current community study compared to the proportion of BIPS in clinic-based studies, it is possible that young people with BIPS are less likely to present to the clinic. The young age of participants in the current study may also be a contributing factor. Although, in our experience, even at this age, young people are very aware that these experiences are unusual, it is possible that younger individuals are less likely to attend their doctor or other health professional compared to older teenagers and young adults. Education
around psychotic symptoms and psychosis risk syndromes may also be a factor. Addington et al., for example, showed that, following an extensive community education program, referrals to prodrome services increased (Addington et al., 2008). Thus, a lack of community education and confusion about ‘where to turn for help’ with these unusual experiences may play a role in non-presentation. There may be multiple other differences between help-seeking and non-help seeking individuals with prodromal risk syndromes. Further cross-sectional and longitudinal research comparing clinical and community samples will be necessary to address this question.
Chapter 7: Conclusions

Hallucinations and delusions, while classically known as symptoms of psychosis, are common in a wide range of non-psychotic psychiatric disorders in young people. These symptoms appear to become increasingly associated with diagnosable psychopathology with age. Psychotic symptoms demonstrated a particularly strong relationship with more severe psychopathology, indexing a large increase in risk for comorbid diagnoses. The immediate clinical implications of these findings are that (i) psychotic symptoms, which are to a large extent seen as an ‘adult psychiatry’ issue, are in fact very prevalent in childhood and adolescence and should be carefully assessed in child and adolescent psychiatric clinics, and (ii) when psychotic symptoms are present, they index risk for more severe psychopathology, necessitating a consideration of the possibility of multiple diagnoses and, following from this, the potential importance of multiple therapeutic targets or approaches. For researchers, these findings highlight psychotic symptoms as a complex novel aspect in the study of the aetiology of severe mental illness, of which schizophrenia is only one.

The results of the studies reported here also demonstrate that psychotic symptoms index greatly increased risk for suicidal behaviour, both in adolescents in the general population and in adolescents with diagnosable psychiatric disorder, and that the presence of psychotic symptoms greatly increases the risk for more severe suicidal behaviour among adolescents.
with suicidal ideation and with depressive and behavioural disorders. Both interview studies showed that, when directly questioned, the majority of adolescents with suicidal plans and acts reported psychotic symptoms, in particular auditory hallucinations. The immediate clinical relevance of these findings is that patients presenting at risk for suicidal behaviour should receive a thorough assessment of psychotic symptoms, and not just a screening to rule out psychotic disorder. Since approximately half of patients who complete suicide have contact with primary care providers in the month preceding their death (Luoma et al., 2002), it is important that clinicians are aware of the significance of psychotic symptoms in non-psychotic patients in terms of risk for suicidal behaviour. Among patients presenting with mood or behavioural disorders or with suicidal ideation, these results suggest that disclosure of psychotic symptoms, particularly hallucinations (regardless of their phenomenological content), indicates a greatly increased risk for more severe suicidal behaviour.

In terms of neurocognitive function, adolescents with psychotic symptoms demonstrated impairments on processing speed tasks and in non-verbal working memory. This group likely demonstrates some of the earliest cognitive impairments associated with a psychosis phenotype. Our findings support the idea that impairment in processing speed and, to a lesser extent, working memory, is at the core of neurocognitive dysfunction in psychosis. This adds to the evidence that a systems-based dysfunction may be the core
cognitive feature of psychosis, as opposed to cognitive features that suggest that the pathology emerges from localised or region-specific deficits.

Up to 8% of 11 to 13 year olds met formal criteria for a prodromal risk syndrome (compared to 23% who reported psychotic symptoms). Adolescents with prodromal risk syndromes demonstrated poorer global functioning and high rates of non-psychotic psychopathology, consistent with findings on clinically presenting risk syndrome patients. The long term outcomes for these ‘community risk syndromes’ has yet to be determined and will require further research. However, the decline in rates of conversion to psychosis at risk syndrome clinics over the past number of years highlights the fact that, even in clinically presenting individuals, outcomes are not clear cut (Addington et al., 2011, Yung et al., 2007b). Follow up research will be necessary to determine the degree of risk for clinical psychosis associated with prodromal risk syndromes in the community.
References


Fronto-limbic brain structures in suicidal and non-suicidal female patients with major depressive disorder. Mol Psychiatry 12, 360-6.


symptoms in a nonclinical population at age 12 years. *Arch Gen Psychiatry* 66, 527-36.


Appendices
Appendix A: The Adolescent Psychotic Symptom Screener (APSS)

Please tick one box for each question

<table>
<thead>
<tr>
<th>Question</th>
<th>No, Never</th>
<th>Maybe</th>
<th>Yes, definitely</th>
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<tbody>
<tr>
<td>Some people believe that their thoughts can be read by another person. Have other people ever read your mind?</td>
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<tr>
<td>Have you ever had messages sent just to you through TV or radio?</td>
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<td>Have you ever felt that you were under the control of some special power?</td>
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<td>Have you ever heard voices or sounds that no one else can hear?</td>
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<td>Have you ever seen things that other people could not see?</td>
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<tr>
<td>Have you ever felt that you have extra-special powers?</td>
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<tr>
<td>Have you ever thought that people are following you or spying on you?</td>
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</table>

Thank you very much for your help!
## Appendix B: Strengths and Difficulties Questionnaire

**Please tick one box for each question**

<table>
<thead>
<tr>
<th></th>
<th>No, Never</th>
<th>Maybe</th>
<th>Yes, definitely</th>
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<tbody>
<tr>
<td>I try to be nice to other people. I care about their feelings</td>
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<td>I am restless, I cannot stay still for long</td>
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<td>I get a lot of headaches, stomach-aches or sickness</td>
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<td>I usually share with others, for example CD’s, games, food</td>
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<td>I get very angry and often lose my temper</td>
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<td>I would rather be alone than with people of my age</td>
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<td>I usually do as I am told</td>
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<td>I worry a lot</td>
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<td>I am helpful if someone is hurt, upset or feeling ill</td>
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<td>I am constantly fidgeting or squirming</td>
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<td>I have one good friend or more</td>
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<td>I fight a lot, I can make other people do what I want</td>
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<td>I am often unhappy, depressed or tearful</td>
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<td>Other people my age generally like me</td>
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<td>I am easily distracted, I find it difficult to concentrate</td>
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<td>I am nervous in new situations. I easily lose confidence</td>
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<td>I am kind to younger children</td>
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<td>I am often accused of lying or cheating</td>
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<td>Other children or young people pick on me or bully me</td>
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<tr>
<td>I often offer to help others (parents, teachers, children)</td>
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<tr>
<td>I think before I do things</td>
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<tr>
<td>I take things that are not mine from home, school or elsewhere</td>
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<td>I get along better with adults than with people my own age</td>
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<td>I have many fears, I am easily scared</td>
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<tr>
<td>I finish the work I’m doing. My attention is good</td>
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Thank you very much for your help!
Appendix C: Clinical classification of psychotic symptoms in the ABD study

Essentially a strong psychotic symptom refers to experiencing hallucinations and/or delusions. Not all such phenomena are of equal clinical significance, however. The following characteristics help to separate hallucinations and delusions of potential clinical significance from hallucinations and delusions that are of limited or no clinical significance.

**Hallucinations:**

Auditory hallucinations may involve voices or other sounds. A formed hallucination involves hearing one or more voices saying at least one word and is classed as a strong psychotic symptom in general (see notes below for notable exceptions). Common formed auditory hallucinations, classed as strong psychotic symptoms, include

- Voice commenting on behaviour
- Voice giving commands
- Voices conversing

Unformed auditory hallucinations may involve whispering voices, voices at normal volume or shouting voices where the words cannot clearly be distinguished by the individual. These are classed as strong psychotic symptoms in general
Auditory hallucinations may also include non-vocal sounds, such as music playing
or animal noises but these are generally classed as weak psychotic symptoms. E.g.,
hearing music playing for a short period of time when none is playing would be
classed a weak psychotic symptom unless it is distressing or disorganizing, when it
would be classed a strong psychotic symptom. Experiences that are very common
such as occasionally hearing footsteps or knocking, are not classed as psychotic
symptoms unless these experiences are associated with delusional ideation.

**Visual hallucinations** are classically thought to be associated with organic pathology
but are not uncommon types of psychotic symptoms in the general population. They
often occur in individuals who also experience auditory hallucinations. Common
visual hallucinations, which are rated as strong psychotic symptoms, include seeing
- People
- Faces
- Ghosts
- Aliens

**Tactile hallucinations** are common but most could be considered trivial and would
not be classed as psychotic symptoms. For example, most people report experiencing
their mobile telephone vibrating when it had not really done so or occasionally
feeling something brush lightly against their skin when nothing was there. These
experiences would not be classed as psychotic symptoms unless they involved
delusional attributions (e.g., believing it was a ghost that was brushing against them).
Isolated tactile hallucinations that would be classed as psychotic symptoms are
unusual but may occur occasionally (e.g., recurring feeling of forceful physical touch
when nobody was there), but would generally be rated as weak psychotic symptoms in the absence of delusional attributions.

Olfactory and gustatory hallucinations are not uncommon but are rarely significant enough to warrant classification as a strong psychotic symptom. Occasional experiences of smells or tastes which are not distressing are not classed as psychotic symptoms. Some individuals may report recurrent experiences of clearly smelling a particular food (often one the individual desires) which they have found odd; this type of experience would be rated as a weak psychotic symptom.

Note on rating formed hallucinations

Exceptions, which are not considered psychotic symptoms, include experiences that are very common if not universal, including the experience of hearing one’s own name when no one has called it, unless such experiences are associated with delusional beliefs (e.g., a ghost is calling my name).

Brief experiences of gedankenlautwerden (the experience of hearing one’s own thoughts aloud even though the individual did not speak them) are common in childhood and early adolescence and are classed as weak psychotic symptoms as long as they are brief in duration (a few words or one sentence), are not associated with delusional ideation and are not experienced as significantly distressing or disorganising. Frequency of gedankenlautwerden varies, but does not in-and-of-itself impact on rating.

Note on illusions
Common illusions such as occasionally hearing the doorbell or the telephone while the TV or radio are playing, or seeing a coat from the corner of one's eye and briefly believing it to be a person, are not classed as psychotic symptoms. However, more elaborate illusions, for example thinking that a face in a picture or poster had been moving, would be classed as a weak psychotic symptom.

Note on hypnagogic and hypnopompic hallucinations

Hypnagogic and hypnopompic hallucinations are generally not classed as psychotic symptoms. However, it is important to distinguish between hypnopompic/hypnagogic and simply being in bed – if the individual is not actually in the process of waking up or falling asleep then the hallucination should not be dismissed as hypnopompic/hypnagogic; it is often at night time that individuals are alone and hallucinatory experiences may be more likely to occur and these experiences are classed the same as any other psychotic symptom.

Hallucinations that occur only when the individual is tired (but not falling asleep or awakening) and are brief in duration would be classed as weak psychotic symptoms (e.g., a vague but identifiable image of a person moving past the doorway). Prolonged hallucinations would be classed as strong psychotic symptoms even if the individual is tired.

Note on hallucinations versus pseudohallucinations

Insight into the hallucination (a 'pseudohallucination') does not preclude it from being classed as a strong (or weak) psychotic symptom.
Note on hallucinations and daydreaming

Very brief hallucinations that occur only when daydreaming would generally be classed as weak psychotic symptoms.

Note on illness and intoxication

Hallucinations that occur as the result of an organic illness (e.g., a fever) are not classed as psychotic symptoms. Whether or not to include psychotic symptoms that are associated with drug use is unclear; we would generally include psychotic symptoms that occur other than during acute intoxication.

Delusions:

Significant delusions most commonly occur in individuals who also experience hallucinations and often relate to the content of the hallucination, though they may also occur in individuals with no hallucinations. The following are experiences that are commonly encountered.

- A vague feeling of unease associated with the occasional feeling that someone may be watching the individual would be classed as a weak psychotic symptom. More frequent or more concrete ideas about being watched, such as being able to suggest a certain person or organisation as being responsible or the belief that cameras have been set up to watch the individual, would be classed as a strong psychotic symptom.

- Recurrent, unfounded or very exaggerated ideas that others (generally more than one person or group) are saying negative things about the individual would be classed as a strong psychotic symptom. Care must be taken, however, to
distinguish paranoia from self-consciousness (e.g., about clothes or physical appearance), which is not classed as a psychotic symptom.

- Bizarre attributions for experiences (e.g., the belief that ghosts/deceased relatives/aliens are the cause of the experience) are not uncommon. A belief that ghosts/spirits can influence events is in-keeping with many cultures/subcultures and would not be considered a psychotic symptom. However, the belief that ghosts are directly communicating with the individual in question (for example, the ghost of a dead relative) would be considered a strong psychotic symptom.

- Subcultural beliefs about that the world may be coming to an end are not uncommon among young people and are often in-keeping with ideas from books or film. These would generally be classed as weak psychotic symptoms unless they are of a psychotic level of intensity (unshakable conviction), when they would be classed as strong psychotic symptoms.

- A belief that one can read minds or that one’s mind has been read is usually somewhat in-keeping with subcultural beliefs about psychics and is generally classed as a weak psychotic symptom at most. In some circumstances, however, it would be classed as a strong psychotic symptom, for example, if it was associated with paranoia, such as the individual believed that others had singled out him/her and were aiming to read their mind for a particular (usually nefarious) reason.

- A vague unsubstantiated but persistent feeling that something strange is going on or that the individual feels he or she might be ‘going crazy’ despite no specific or concrete examples of hallucinations or delusions would be classed as a weak psychotic symptom.
• Note: magical thinking, such as a belief that one had predicted the future, is very common and is generally classed as a weak psychotic symptom at most, unless, for example, it is distressing or disorganising.

Note on severity of hallucinations and delusions

The significance of the severity of the hallucination or delusion is unclear at present. However, there are a range of severities in the experiences that can be considered strong psychotic symptoms.
Appendix D: Clinical classification of prodromal risk syndromes: Criteria of the Scale of Prodromal Syndromes

The Scale of Prodromal Syndromes (SOPS) criteria facilitate diagnosis of three ‘risk syndromes’ for psychosis: (i) attenuated positive symptoms prodromal syndrome (APSP), (ii) brief intermittent psychotic symptoms prodromal syndrome (BIPS), and (iii) genetic risk and deterioration prodromal syndrome (GRD). These diagnoses are operationalized based principally on positive symptoms assessed in clinical interview. The SIPS assesses five subtypes of positive symptoms on five scales: P1 to P5. P1: Unusual thought content/delusional ideas; P2: Suspiciousness/Persecutory ideas; P3: Grandiose ideas; P4: Perceptual abnormalities/hallucinations; P5: Disorganized communication. Each of these scales can be scored from 0 to 6 for each participant as follows:

0 = Absent
1 = Questionably present
2 = Mild
3 = Moderate
4 = Moderately severe
5 = Severe but not psychotic
6 = Severe and psychotic

Questions about psychotic symptomatology from the SOPS that were not adequately assessed by the K-SADS were added to the instrument for the purposes of assessing prodromal syndromes in the current study.
Each of the scales P1 to P5 includes a severity scale that guides the clinical rating.

**P1: Unusual thought content/Delusional ideas Severity scale**

- 0 = Absent
- 1 = Questionably present
  - ‘Mind tricks’ that are puzzling. Sense that something is different.
- 2 = Mild
  - Over interested in fantasy life. Unusually valued ideas/beliefs. Some superstitions beyond what might be expected by the average person within cultural norms.
- 3 = Moderate
  - Unanticipated mental events/non-persecutory ideas of reference/mind tricks/magical thinking that are not easily dismissed and may be irritating and worrisome. A sense that these experiences or compelling new beliefs are becoming meaningful because they will not go away.
- 4 = Moderately severe
  - Notion that experiences may be coming from outside the self or that ideas/beliefs may be real, but scepticism remains intact. Does not usually affect functioning.
- 5 = Severe but not psychotic
  - Belief in reality of ‘mind tricks’/mental events/external control/magical thinking is compelling but doubt can be induced by contrary evidence and other’s opinions. May affect functioning.
- 6 = Severe and psychotic
— Delusional conviction (with no doubt) at least intermittently. Usually interferes with thinking, social relations, or behaviour.

P2: Suspiciousness/Persecutory ideas Severity scale

• 0 = Absent

• 1 = Questionably present
  — Wariness.

• 2 = Mild
  — Doubts about safety. Hypervigilance without clear source of danger.

• 3 = Moderate
  — Notions that people are hostile, untrustworthy, and/or harbour ill will easily. Sense that hypervigilance may be necessary. Mistrustful. Recurrent (yet unfounded or exaggerated at times) sense that people are thinking or saying negative things about person. May appear mistrustful with interviewer.

• 4 = Moderately severe
  — Clear or compelling thoughts of being watched or singled out. Sense that people intend to harm. Beliefs easily dismissed. Presentation may appear guarded. Reluctant or irritable in response to questioning.

• 5 = Severe but not psychotic
  — Loosely organized beliefs about danger or hostile intention. Scepticism and perspective can be elicited with non-confirming evidence or opinion. Behaviour is affected to some degree. Guarded presentation may interfere with ability to gather information in the interview.
• 6 = Severe and psychotic
  – Delusional paranoid conviction (with no doubt) at least intermittently.
    Likely to affect functioning.

P3: Grandiose ideas Severity scale

• 0 = Absent

• 1 = Questionably present
  – Private thoughts of being generally superior in intellect or talent.

• 2 = Mild
  – Thoughts of being particularly talented, highly understanding, or gifted in one or more areas. Thoughts kept mostly private.

• 3 = Moderate
  – Notions of being unusually gifted, powerful, or special. May be expansive. Promotes significantly unrealistic plans, but easily reoriented.

• 4 = Moderately severe
  – Loosely organized beliefs of power, wealth, talent or abilities.
    Unrealistic goals that may affect plans and functioning.

• 5 = Severe but not psychotic
  – Persistent beliefs of having superior intellect, attractiveness, power or fame. Scepticism about belief can be elicited. Often influences behaviour or actions.

• 6 = Severe and psychotic
  – Delusions of grandiosity with conviction (no doubt) at least intermittently. Influences behaviour and beliefs.
P4: Perceptual abnormalities/Hallucinations Severity scale

- **0 = Absent**
- **1 = Questionably present**
  - Minor but noticeable perceptual sensitivity (e.g., heightened, dulled, distorted etc.).
- **2 = Mild**
  - Unexpected, unformed perceptual experiences/changes that are puzzling but are not considered to be significant.
- **3 = Moderate**
  - Repeated unformed images (e.g., shadows, trails, sounds etc.), illusions or persistent perceptual distortions that may be worrisome or experienced as unusual.
- **4 = Moderately severe**
  - Recurrent illusions or momentary hallucinations that are recognized as not real yet can be frightening or captivating, and may affect behaviour slightly. Not sure of source of experiences.
- **5 = Severe but not psychotic**
  - Hallucinations that occasionally affect thinking or behaviour that are experienced as possibly external to self or possibly real. Scepticism can be induced.
- **6 = Severe and psychotic**
  - Recurrent hallucinations perceived as real and distinct from the person’s thoughts. Clearly influence thinking, feeling, and/or behaviour. Scepticism cannot be induced.
P5: Disorganized communication Severity scale

- 0 = Absent
- 1 = Questionably present
  - Some words or phrases that don’t make sense.
- 2 = Mild
  - Occasionally vague, confused, muddled, inconsistent communications. May go off track briefly.
- 3 = Moderate
  - Occasional incorrect words, irrelevant topics. Frequently going off track but responds easily to clarifying questions. Stereotyped or over-elaborate speech.
- 4 = Moderately severe
  - Speech is clearly circumstantial (i.e., eventually getting to the point). Some difficulty in directing sentences toward a goal. Person is able to be redirected through questioning and structure.
- 5 = Severe but not psychotic
  - Communications are tangential (i.e., never getting to the point). Some loosening of associations under pressure. Can respond accurately to brief questions.
- 6 = Severe and psychotic
  - Communication is loose or irrelevant and unintelligible when under minimal pressure or when the content of the communication is complex. Not responsive to structuring of the conversation.
A diagnosis of APSP is operationalized where (i) at least one of the SOPS P1 to P5 scales is scored three (moderate), four (moderately severe) or five (severe but not psychotic), (ii) symptom(s) have begun, or worsened by one or more scale points, within the past 12 months and (iii) symptom(s) have occurred at an average frequency of at least once per week in the past month.

A diagnosis of BIPS is operationalized where (i) the SOPS P1 to P5 scales (which relate to positive psychotic symptoms) rate a six (that is, psychotic), (ii) the symptom(s) have reached a psychotic level of intensity within the past three months and (iii) the symptom(s) have been present for at least several minutes per day at a frequency of at least once per month.

GRD is diagnosed where there has been a drop of at least 30% in the Global Assessment of Functioning score over the past month as compared to 12 months ago and one or both of the following criteria are also fulfilled: (i) the individual meets criteria for current schizotypal personality disorder and/or (ii) the individual has a first degree relative with a psychotic disorder. In reality, given the complex issues around diagnosing young people (aged 11-13 years) with a personality disorder, a diagnosis of GRD could only be given in the present study if, in addition to the stipulated functional decline, the individual had a first degree relative with a psychotic disorder.
Appendix E: Clinical Assessment of At Risk Mental States (CAARMS) criteria

Prodromal syndrome diagnostic categories include (i) vulnerability group, (ii) attenuated psychosis group and (iii) brief limited intermittent psychotic symptoms (BLIPS group)

1. Vulnerability Group criteria
1a) Family history of psychosis in a first degree relative or schizotypal personality disorder in the identified patient

Plus

1b) 30% drop in social/occupational functioning (measured on the Social and Occupational Functioning Assessment Scale – SOFAS) compared to premorbid level, sustained for a month, occurred within past 12 months or a SOFAS score of 50 or less for past 12 months or longer

2. Attenuated Psychosis Group criteria
2a) Psychotic symptoms of subthreshold intensity, specifically a global rating scale score of 3-5 on Unusual Thought Content subscale, 3-5 on Non-Bizarre Ideas subscale, 3-4 on Perceptual Abnormalities subscale and/or 4-5 on Disorganised Speech subscales of the CAARMS

Plus
2b) Frequency Scale Score of 3-6 on Unusual Thought Content, Non-Bizarre Ideas, Perceptual Abnormalities and/or Disorganised Speech subscales of the CAARMS for at least a week

2c) Subthreshold frequency: Global Rating Scale score of 6 on Unusual Thought Content, 6 on Non-Bizarre Ideas, 5-6 on Perceptual Abnormalities and/or 6 on Disorganised Speech subscales of the CAARMS

Plus

2d) Frequency scale score of 3 on Unusual Thought Content, Non-Bizarre Ideas, Perceptual Abnormalities and/or Disorganised Speech subscales of CAARMS

Plus (for both categories)

2e) Symptoms present in past year

Plus (for both categories)

2f) 30% drop in SOFAS score from premorbid level, sustained for a whole month, occurred within past 12 months or SOFAS score of 50 or less for past 12 months or longer

3. BLIPS Group criteria

3a Global Rating Scale score of 6 on Unusual Thought Content subscale, 6 on Non-Bizarre Ideas, 5 or 6 on Perceptual Abnormalities subscale and/or 6 on Disorganised Speech subscales of the CAARMS

Plus

3b) Frequency Scale score of 4-6 on Unusual Thought Content, Non-Bizarre Ideas, Perceptual Abnormalities and/or Disorganised Speech subscales

Plus
3c) Each episode of symptoms is present for less than one week and symptoms spontaneously remit on every occasion

Plus

3d) Symptoms occurred during last year

Plus

3e) 30% drop in SOFAS score from premorbid level, sustained for a month, occurred within past 12 months or SOFAS score of 50 or less for past 12 months or longer

Note: in the current study the social/occupational functioning measure was the Children’s Global Assessment Scale and not Social and Occupational Functioning Assessment Scale. The criterion of a 30% decline in social/occupational functioning was added to the most recent edition of the CAARMS but was not a criterion for prodromal syndromes in previously published research. We report prevalences for CAARMS prodromal syndromes (i) without and (ii) with this new criterion.