Hugh Ramsay

PREDICTORS OF PSYCHOSIS RISK AND NEUROCOGNITIVE DEFICITS
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**Abstract**

Psychotic disorders usually become evident during adolescence and early adulthood and are commonly preceded by psychosis risk states. Young people at risk for developing psychosis may already have cognitive deficits.

This research examined factors associated with psychosis risk and adverse cognitive performance, particularly in those at risk for developing psychosis. We aimed to characterise genetic risk factors for psychosis risk and adverse cognitive performance. Additionally, early and later biological risk markers for adverse cognitive performance and psychosis risk were explored.

Two longitudinal birth cohorts, the Northern Finland Birth Cohort 1986 (NFBC 1986, n=6,985 at 16 years) and Avon Longitudinal Study of Parents and Children (ALSPAC, n=5,217 at 17 years), two NFBC 1986 sub-studies, the Oulu Brain and Mind 1 (n=182 for these analyses) and Oulu Brain and Mind 2 (n=471 for these analyses) studies, and two Irish case control studies, the Adolescent Brain Development (n=212) and Challenging Times (n=211) studies, were utilised. Predictors of interest were selected Single Nucleotide Polymorphisms (SNPs at COMT, BDNF and DRD2), prenatal exposure to maternal cigarette smoking (PEMCS) and adolescent metabolic measures.

Though not directly associated with psychotic experiences, the COMT-Val158Met Val-Val genotype interacted with experience of childhood trauma to predict more psychotic experiences. Two DRD2 SNPs were associated with poorer cognitive performance, though only in those with risk for psychotic disorders. PEMCS was associated with adult vocabulary and matrix reasoning performance in males, though not in males with adolescent psychotic experiences. Adolescent academic performance, but not psychotic experiences, were associated with metabolic measures, especially with ratios of omega-3 to total fatty acids.

These findings impact on prevention strategies for long-term adverse outcomes. Some risk factors differ for those with psychotic experiences compared to the general population, while others do not. SNPs at COMT and DRD2 may be more relevant in those with psychotic experiences. Interventions targeting these groups may be particularly beneficial. Smoking in pregnancy, however, is harmful to male cognitive performance across the population, suggesting elimination of this risk is more broadly relevant. Fatty acid-related metabolic measures may mark risk for cognitive deficits or may represent a developmental feature that is potentially open to intervention.

**Keywords:** BDNF, cognition, COMT, DRD2, metabolomics, prenatal exposure to maternal cigarette smoking, psychosis risk
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**Tiivistelmä**


Tässä tutkimuksessa selvitettiin tekijöitä, jotka liittyvät psykoosialttiuuteen ja heikkoon kognitiiviseen suoriutumiseen, etenkin nuorilla, jotka olivat psykoosiriskissä. Tutkimuksessa tarkasteltiin psykoosialttiuuteen ja heikkoon kognitiiviseen suoriutumiseen liittyviä genettiisiä tekijöitä. Lisäksi tutkittiin biologisia varhaisia ja myöhempiä psykoosialtiutta ja heikkoa kognitiivista suoriutumista ennustavia tekijöitä.


COMT-Val158Met geenin Val-Val genotyyppi ei ollut suoraan yhteydessä psykoositissyin kokemuksiin, mutta yhdessä lapsuuden traumaahtisten kokemuksen kanssa ennusti suurempaa psykoosioireiden määrää. Kaksi DRD2 SNP-varianttia assosioituiheen heikompaan kognitiiviseen suoriutumiseen, vaikka vaatiaan tutkiin tapahtumilla jotka olivat psykoosialtiita. Äidin raskaudenaikainen tupakointi ennusti suuremman pyörimysongelmatilanteen suoriutumista pojilla, tosin ei pojilla joilla oli nuoruusajan psykoosioireita. Metaboliset tekijät, erityisesti omega-3 rasvahapone suorakaiteen suhde kokonaisrasvahapon suorakaiteen yhteydessä koulumenestykseen.

Tutkimuksen tulosten perusteella voidaan mahdollisesti suunnitella ennaltaehkäiseviä toimia myöhempien haittojen ehkäisemiseksi. Jotkut tutkittujen riskitekijöistä assosioituvat eri tavalla kognitiivoon psykoosialtiillaan kuin yleisväestössä. COMT ja DRD2 geenien variantit psykoosialtiilla saattavat olla keskeisiä. Interventiot nuorille, joilla on näitä variantteja ja psykoosioireita, voisivat olla erityisesti hyödyllisiä. Äidin raskauden aikaisen tupakointi ennusti poikien kognitiivista suoriutumista. Äidin raskaudenaikaisen tupakoinnin vähentämisellä olisi suotuva vaikutus tässäkin suhteessa. Rasvahapopohjien liittyvät metaboliset suuret voivat olla riskikognitiivisille puutoksille tai ne voivat merkitä kehityskäytäviä piirteitä, jotka voisi mahdollistaa varhaisen ennaltaehkäisyn.

**Asiakunto:** BDNF, COMT, DRD2, kognitio, metabolismia, psykoosiriski, äidin raskaudenaikainen tupakointi
Acknowledgements

This work was carried out with the Department of Psychiatry, University of Oulu. It is based primarily on analysis of the Northern Finland Birth Cohort 1986 and its sub-studies. I wish to express my gratitude to several people, without whose help this thesis would not have been possible.

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I have been privileged to use data collected in Finland, Ireland and the United Kingdom. In examining this data and more besides, I am thankful to Professor Pirjo Mäki, Dr Tuula Hurtig, Professor Mika Ala-Korpela, and Dr Tanja Nordström in the University of Oulu. Outside of the University, Dr Graham Murray, Professor Tomas Paus, Dr Zdenka Pausova, Professor Tiina Paunio, and Professor Mary Cannon, have provided considerable assistance and advice, for which I am very grateful.

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My warmest thanks go to my parents, Patricia and Louis, who have always supported me whenever I have needed them. I am grateful for their constant support, confidence and love.

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Dublin, October 2017

Hugh Ramsay
Abbreviations

ABD    Adolescent Brain Development study
ADHD   Attention Deficit Hyperactivity Disorder
ALSPAC Avon Longitudinal Study of Parents and Children
ApoA1  Apolipoprotein A1
ApoB   Apolipoprotein B
BDNF   Brain-Derived Neurotrophic Factor
BLIPS  Brief Limited Intermittent Psychotic Symptoms
CAARMS Comprehensive Assessment of At-Risk Mental State
CDC    Center for Disease Control and Prevention
COMT   Catechol-O-Methyl Transferase
CRP    C-Reactive Protein
CSF    Cerebrospinal Fluid
CT     Challenging Times study
DHA    Docosahexaenoic Acid
DRD-2  Dopamine Receptor D-2
DSM-5  Diagnostic and Statistical Manual of Mental Disorders (5th Edition)
FHDR   Finnish Hospital Discharge Register
GCSE   General Certificate in Secondary Education
HDL    High-Density Lipoprotein
IDL    Intermediate-Density Lipoprotein
IL-1Ra  Interleukin-1 Receptor antagonist
K-SADS Schedule for Affective Disorders and Schizophrenia for School-aged children
LDL    Low-Density Lipoprotein
Mir-137 Micro Ribonucleic Acid-137
MUFA   Monounsaturated Fatty Acids
NFBC 1986 Northern Finland Birth Cohort 1986
NMDA   N-Methyl-D-Aspartate
NMR    Nuclear Magnetic Resonance
PAL    Paired Associates Learning
PEs    Psychotic experiences
PEMCS  Prenatal exposure to maternal cigarette smoking
PG     Phosphoglycerides
PL     Phospholipids
PUFA   Polyunsaturated Fatty Acids
<table>
<thead>
<tr>
<th>Acronym</th>
<th>Description</th>
</tr>
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<tbody>
<tr>
<td>RVP</td>
<td>Rapid Visual Information Processing</td>
</tr>
<tr>
<td>SCID</td>
<td>Structured Clinical Interview for DSM IV axis-I disorders</td>
</tr>
<tr>
<td>SDQ</td>
<td>Strengths and Difficulties Questionnaire</td>
</tr>
<tr>
<td>SFA</td>
<td>Saturated Fatty Acids</td>
</tr>
<tr>
<td>SIPS</td>
<td>Structured Interview for Prodromal Symptoms</td>
</tr>
<tr>
<td>SNP</td>
<td>Single Nucleotide Polymorphism</td>
</tr>
<tr>
<td>SOC</td>
<td>Stockings of Cambridge</td>
</tr>
<tr>
<td>SSRT</td>
<td>Stop Signal Reaction Time</td>
</tr>
<tr>
<td>sTNF-R1</td>
<td>soluble Tumour Necrosis Factor-Receptor 1</td>
</tr>
<tr>
<td>TG</td>
<td>Triglycerides</td>
</tr>
<tr>
<td>VLDL</td>
<td>Very Low-Density Lipoprotein</td>
</tr>
<tr>
<td>WAIS-3</td>
<td>Wechsler Adult Intelligence Scale</td>
</tr>
<tr>
<td>WASI</td>
<td>Wechsler Abbreviated Scale of Intelligence</td>
</tr>
<tr>
<td>WMS-R</td>
<td>Wechsler Memory Scale-Revised</td>
</tr>
<tr>
<td>YSR</td>
<td>Youth Self-Report</td>
</tr>
<tr>
<td>ZNF804A</td>
<td>Zinc Finger Protein 804A</td>
</tr>
</tbody>
</table>
Original publications

This thesis is based on the following publications, which are referred throughout the text by their Roman numerals:


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1 Introduction

Schizophrenia and other psychotic disorders generally emerge clinically in early adulthood following a developmental process evident in adolescence (Jones, 2013). Though psychotic disorders have variable courses, they are generally associated with a high degree of disability and disease burden (Whiteford, Ferrari, Degenhardt, Feigin, & Vos, 2015).

The neurodevelopmental period in adolescence prior to the emergence of frank psychosis offers an opportunity for secondary, or even primary, prevention. This period has been increasingly studied in both clinical and population samples (Cornblatt et al., 2003; Koutsouleris et al., 2015; McGorry et al., 1995). Among clinical samples, efforts have focused on those with “psychosis risk syndromes”, who display symptom or functional features along with help-seeking behaviours that indicate risk for later psychotic disorder (Fusar-Poli et al., 2013). Population studies have also examined risk for later psychotic disorders, considering the significance of “psychotic experiences” occurring throughout the population (Linscott & van Os, 2013).

Psychotic disorders are characterised by a range of specific and general neurocognitive deficits (Barch & Sheffield, 2014). These deficits are important because they are strongly associated with poorer functional outcomes (M. F. Green, Kern, & Heaton, 2004). Furthermore, many of these deficits are detectable in childhood and adolescence, prior to the onset of psychosis itself (Reichenberg et al., 2010). The detection of the cognitive deficits in adolescence and early adulthood therefore offers considerable potential to improve outcomes. This is particularly true where the development of these deficits is open to intervention.

Understanding the developmental origins of both psychosis risk and cognitive deficits offers the opportunity for potential intervention to prevent their development and the development of functional impairments with which they are associated. This process can be considerably furthered by better understanding of the genetic, early environmental and late environmental factors associated with psychosis risk and with cognitive deficits.

The studies presented in this thesis have focused on the identification of risk factors and risk markers for psychosis risk and cognitive deficits in adolescence and early adulthood. Psychosis risk will be considered both in terms of psychosis risk syndromes and population-level psychotic experiences. Broad and specific cognitive deficits will be considered alongside this. The thesis will explore four main risk factor questions. Firstly, can we identify genetic and environmental
factors that together contribute to psychosis risk? Secondly, can we identify genetic factors that are associated with cognitive deficits in those with psychosis risk? Thirdly, are there prenatal factors that are associated with cognition in early adulthood and how does this relate to risk for mental illness? Finally, this thesis considers whether adolescent biological markers can highlight risk for psychosis risk and cognitive deficits. The primary sources of data for these studies were the Adolescent Brain Development Study, the Challenging Times Study, the Northern Finland Birth Cohort 1986 and sub-studies within this cohort (the Oulu Brain and Mind 1 and 2 Studies), and the Avon Longitudinal Study of Parents and Children.
2 Review of the literature

2.1 Background

Psychotic disorders are complex neurodevelopmental disorders that are commonly preceded by a significant prodromal period mainly in adolescence and young adulthood (Cannon et al., 2008), which can be identified in clinical samples as “psychosis risk syndromes” and in the general population as “psychotic experiences”. These psychosis risk groups are associated with a variety of adverse clinical and functional outcomes in addition to progression to psychotic disorders. These outcomes include a range of static and dynamic cognitive deficits (Reichenberg et al., 2010). Increasingly, risk factors for psychosis risk and for associated cognitive deficits are being investigated. Indeed, there is evidence that risk factors for psychosis risk and for cognitive deficits in adolescence and early adulthood overlap. Further knowledge of how these risk factors contribute to both psychosis risk and cognitive deficits has the potential to inform strategies aimed at preventing long-term functional impairment.

2.2 Psychotic disorders and psychosis risk

While the meaning of the term psychosis has evolved since its first use in the 19th century, the adjective “psychotic” is now used primarily to refer to the presence of the symptoms of hallucinations and delusions (Bürgy, 2008). More broadly, other symptom clusters associated with schizophrenia may be regarded as psychotic, either as “positive” symptoms or “negative” symptoms (Andreasen & Olsen, 1982). Positive symptoms appear to reflect an excess or alteration of normal functions. In addition to hallucinations and delusions, these include disorganised thinking (evident in speech), and grossly disorganised or abnormal behaviour (American Psychiatric Association, 2013; Andreasen, Flaum, Swayze, Tyrrell, & Arndt, 1990). Negative symptoms reflect a loss of normal functions, such as reduced emotional expression, low motivation levels, poverty of speech, and social isolation (Andreasen & Olsen, 1982).

Psychosis has increasingly been conceptualised as existing on a continuum, termed the “extended psychosis phenotype” (Van Os & Linscott, 2012; Van Os & Reininghaus, 2016). This suggests that the fundamental processes underlying psychotic disorders exist on a continuum into the population in clinical and
subclinical phenotypes. The clinical phenotype includes psychotic disorders and clinical risk syndromes where the individual is help-seeking. The non-clinical phenotype includes family risk for psychosis and psychotic experiences in non-ill and non-help-seeking individuals (Van Os & Reininghaus, 2016).

2.2.1 Psychotic disorders

The classic clinical diagnosis associated with psychosis is schizophrenia but psychosis is recognised as a clinical feature of a range of disorders. Within the Diagnostic and Statistical Manual of Mental Disorders (5th Edition) (DSM-5), psychosis is naturally a feature of disorders in the chapter on “Schizophrenia Spectrum and Other Psychotic Disorders”, which also includes delusional disorder. However, it may also be present in disorders in other chapters across DSM-5, such as bipolar disorder, major depressive disorder and body dysmorphic disorder (American Psychiatric Association, 2013). Disorders with psychotic components differ in how the psychotic symptoms are relevant to diagnosis. Mental disorders in DSM-5 with psychotic features and their key features are listed in table 1.

Psychotic disorders are both common and serious. While schizophrenia itself has an estimated lifetime prevalence of almost 1% in the Finnish general population, this rises to 3% for all psychotic disorders, after including other primary psychotic disorders, affective psychoses, substance-induced psychosis and psychosis due to a medical condition (Perälä et al., 2007). Recent review has suggested that incidence varies considerably but that rates are higher in males (rate ratio = 1.4:1), in migrant groups, in urban settings, and possibly in developed nations and at higher latitudes (McGrath, Saha, Chant, & Welham, 2008).

The precise causes of schizophrenia remain unclear but a number of genetic and environmental factors are associated with increased risk. Genetic factors include family history and specific genetic conditions (Agerbo, Sullivan, & Vilhjálmsdóttir, 2015; Szatkiewicz et al., 2014), while environmental factors include early life exposures, such as birth complications and malnutrition in pregnancy (Liu, Keshavan, Tronick, & Seidman, 2015), and cannabis use in adolescence (Marconi, Di Forti, Lewis, Murray, & Vassos, 2016). Better understanding the precise causes of psychotic disorders has the potential to improve treatments and long-term outcomes.
### Table 1. DSM-5 psychotic disorders and disorders with the potential for psychotic features

<table>
<thead>
<tr>
<th>Disorder class and name</th>
<th>Relevant durations</th>
<th>Psychotic symptoms relevant to diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schizophrenia spectrum and other psychotic disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Delusional disorder</td>
<td>&gt;1 month</td>
<td>Delusions</td>
</tr>
<tr>
<td>Brief psychotic disorder</td>
<td>&lt;1 month</td>
<td>Delusions, hallucinations, disorganised speech, disorganised/catatonic behaviour</td>
</tr>
<tr>
<td>Schizophreniform disorder</td>
<td>1-6 months</td>
<td>Delusions, hallucinations, disorganised speech, disorganised/catatonic behaviour</td>
</tr>
<tr>
<td>Schizophrenia</td>
<td>Psychosis for &gt;1 month, disturbance for &gt;6 months</td>
<td>Delusions, hallucinations, disorganised speech, disorganised/catatonic behaviour, negative symptoms</td>
</tr>
<tr>
<td>Schizoaffective disorder</td>
<td>Mood episode criteria for &gt;50% of time; psychotic symptoms for &gt;2 weeks without mood episode criteria</td>
<td>Delusions, hallucinations</td>
</tr>
<tr>
<td>Substance-induced psychotic disorder</td>
<td>None</td>
<td>Delusions, hallucinations</td>
</tr>
<tr>
<td>Psychotic disorder due to another medical condition</td>
<td>None</td>
<td>Delusions, hallucinations</td>
</tr>
<tr>
<td>Bipolar and related disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bipolar 1 disorder with psychotic features</td>
<td>None</td>
<td>Delusions, hallucinations (within manic or depressive episode)</td>
</tr>
<tr>
<td>Depressive disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Major depressive disorder with psychotic features</td>
<td>None</td>
<td>Delusions, hallucinations (within depressive episode)</td>
</tr>
<tr>
<td>Obsessive compulsive and related disorders</td>
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<td></td>
</tr>
<tr>
<td>Obsessive compulsive disorder with absent insight/delusional beliefs</td>
<td>None</td>
<td>Obsessive compulsive disorder beliefs that reach delusional intensity</td>
</tr>
<tr>
<td>Body dysmorphic disorder with absent insight/delusional beliefs</td>
<td>None</td>
<td>Body dysmorphic disorder beliefs that reach delusional intensity</td>
</tr>
</tbody>
</table>

Schizophrenia and other psychotic disorders are commonly preceded by subtle social and cognitive impairments in childhood and low mood, anxiety and social withdrawal in adolescence (Howes & Murray, 2014). The mainstay of treatment
for psychotic disorders is anti-psychotic medication, which is believed to exert its effect through blockade of dopamine D2 receptors. This observation gave rise to the dopamine hypothesis, suggesting that psychosis emerges from dysfunction in the dopamine system (Davis, Kahn, Ko, & Davidson, 1991).

A second theory on the pathogenesis of schizophrenia is the neurodevelopmental hypothesis, suggesting that the illness is the clinical endpoint following from a combination of genetic risks and adverse conditions impacting on brain development from pregnancy into early adulthood. This hypothesis emerged from observation that schizophrenia is associated perinatal insult, subtle developmental findings in childhood and brain imaging abnormalities prior to illness onset (Howes & Murray, 2014). A number of these neurodevelopmental insults suggest an inflammatory component to psychosis. This inflammatory hypothesis is also supported by studies that have found that individuals with schizophrenia have higher concentrations of inflammatory cytokines than others (B. J. Miller, Buckley, Seabolt, Mellor, & Kirkpatrick, 2011). In addition to these observations, clues to the pathogenesis of schizophrenia and psychotic disorders have come from examination of body fluid inflammatory markers and metabolites. Untreated first episode psychosis has been associated with broad serum metabolic differences (Verma, Subramaniam, Liew, & Poon, 2009). More detailed metabolomics studies have found further metabolic abnormalities in cerebrospinal fluid (CSF) at illness onset (Holmes et al., 2006) and in serum during illness itself (Orešič et al., 2011), suggesting an illness process involving abnormalities in glucose and lipid metabolism. Metabolomics approaches examining fibroblast metabolites have also noted differences in reactivity to oxidative stress at the onset of psychosis, suggesting another possible component of dysfunction around illness onset (Fournier et al., 2014).

Long-term outcomes for schizophrenia have been regarded as poor. Recent research suggests a poorer outcome for patients with schizophrenia than with other disorders, though there is substantial variability in outcomes (Jobe & Harrow, 2005). Studies that have also included other psychotic disorders have also highlighted considerable variability, though with generally better outcomes for people with non-schizophrenia psychotic disorders (Harding, Brooks, Ashikaga, Strauss, & Breier, 1987). Identifying factors associated with this variability of outcomes is therefore important.
2.2.2 Risk for psychosis: psychosis risk syndromes and population-level psychotic experiences

While it has long been recognised that psychotic symptoms occur outside of psychotic disorders (Chopra & Beatson, 1986; Thakur, Hays, & Krishnan, 1999), such cases were assumed to be exceptions to the commonly understood separation of psychosis from neurosis in psychiatry. This assumption has been largely discarded over the past three decades (Johns & Van Os, 2001; Kelleher, Keeley, et al., 2012). The concepts of “psychosis risk syndromes” and “psychotic experiences” have challenged previously held assumptions around psychosis and its place in the diagnosis of mental disorders (Kelleher & Cannon, 2014). There has been increasing awareness of an extended psychosis phenotype that includes both clinical and non-clinical phenotypes (Van Os & Reininghaus, 2016). Clinical phenotypes include psychotic disorders but also situations where psychotic experiences not reaching the threshold for psychotic disorders are associated with help-seeking behaviour. Non-clinical phenotypes include family risk and trait markers, including psychotic experiences, which are not associated with help-seeking behaviour. Various terms used in this context are summarised in figure 1.

![Diagram](image_url)

Fig. 1. Summary of psychosis risk states
The earliest group identified as having high risk for psychotic disorder was individuals with a family history of psychotic disorders (Kendler et al., 1993). This knowledge regarding the importance of family history has led to the inclusion within the psychosis risk syndrome paradigm of individuals with a family history of psychotic disorder and a functional decline (Woods et al., 2009). In addition to being associated with schizophrenia and other psychotic disorders, family history of psychotic disorder is associated with population-level psychotic experiences (Sun et al., 2015), and non-psychotic mental disorders (Rasic, Hajek, Alda, & Uher, 2014) in offspring.

Awareness that people with a family history of psychotic disorder are at elevated risk for psychosis themselves has led to more recent efforts to identify those who will develop psychosis before illness onset. This research into “psychosis risk syndromes” also has its roots in the observation that frank psychosis is usually preceded by a potentially identifiable “prodromal stage” (Häfner et al., 1998). This led to the establishment of the first clinical services aiming to identify potentially prodromal individuals using operationalized definitions (Yung et al., 1996). Various terms have been used for this group: prodromal, ultra-high risk for psychosis, clinical high risk for psychosis, and basic symptoms (though this is somewhat different). The term “psychosis risk syndromes” includes three main groups: attenuated psychotic symptoms, brief limited intermittent psychotic symptoms (BLIPS), and trait vulnerability and decline in psychosocial functioning. These may be diagnosed using instruments such as the Comprehensive Assessment of At-Risk Mental State (CAARMS) (Yung et al., 2005) and the Structured Interview for Prodromal Symptoms (SIPS) (McGlashan et al., 2001). Among these groups, one third (36%) transit to psychosis by 3 years, though studies have noted an apparent decline in transition rates over time (Fusar-Poli, Bonoldi, et al., 2012). In addition to this psychosis risk, this group show high rates of comorbid diagnoses, including anxiety, depression and substance use disorders (Fusar-Poli, Nelson, Valmaggia, Yung, & McGuire, 2014), further suggesting a blurring of the historical divisions between psychosis and neurosis.

Alongside this clinical research on help-seeking individuals and those with family history of psychosis, population research has been examining the extended psychosis continuum in the general population. The terms “psychotic-like experiences” and “psychotic experiences” have been used in research of these phenomena. These terms include so-called attenuated psychotic symptoms. Examples of this are experiencing hallucinations with insight or feeling...
persecuted by someone but accepting this may not be real. Meta-analysis has suggested these are common at ages 9-12 years (17%) but decline in prevalence by 13-18 years (7.5%) (Kelleher, Connor, et al., 2012). Longer term follow-up suggests that while psychotic experiences are transitory in 80%, 20% show persistence and 7% develop a psychotic disorder (Kaymaz et al., 2012; Van Os & Reininghaus, 2016). In addition, this group shows higher rates of emotional, hyperkinetic and conduct disorders and psychotic experiences are especially prevalent among children with multiple disorders (Kelleher, Keeley, et al., 2012). It has become increasingly clear that psychosis is not a feature distinct from the rest of psychiatry, but rather a continuum associated with various levels of other mental distress and functioning.

2.3 Cognitive deficits in adolescence and early adulthood

Cognitive deficit or cognitive impairment is when a person has difficulty remembering, learning new things, concentrating, or making decisions that affect everyday life (Center for Disease Control and Prevention (CDC), 2011). When cognitive deficits arise during the developmental period, and are associated with significant deficits in adaptive functioning, they may be termed intellectual disability or intellectual developmental disorder (American Psychiatric Association, 2013). Neurocognition comprises cognitive processes involving linking and appraising information (Schmidt, Mueller, & Roder, 2011), including tasks such as processing speed, attention, verbal and visual learning and memory, problem-solving, reasoning and working memory (M. F. Green & Nuechterlein, 2004).

Cognitive deficits have been researched across the lifespan, from early childhood to old age. Those studied in early childhood tend to be in the context of child development broadly or intellectual developmental disorders (Harris, 2006), while those that arise in later adulthood are researched in the context of mild cognitive impairment and dementia (Albert et al., 2011). Deficits evident in adolescence and early adulthood have received less attention and have generally been considered in the context of neurodevelopmental mental disorders, particularly schizophrenia and its precursors (Lencz et al., 2006).

Psychotic disorders, psychosis risk syndromes and family history of psychosis are each associated with poorer cognitive performance (Bora et al., 2014). There is considerable evidence that cognitive function across domains is significantly impaired in schizophrenia and other psychotic disorders. A recent
A meta-analysis of cognitive performance of drug-naïve schizophrenia patients in Sweden found worse performance than healthy controls across all cognitive domains (Fatouros-Bergman, Cervenka, Flyckt, Edman, & Farde, 2014), using various tests. The greatest impairments were in verbal memory, speed of processing and working memory, in line with international evidence from anti-psychotic treated patients with schizophrenia (Schaefer, Giangrande, Weinberger, & Dickinson, 2013).

While these deficits are significant themselves, they also have broader implications in terms of outcomes. Specifically, poorer cognitive performance has been associated with adverse long-term functional (M. F. Green, 1996; M. F. Green, Kern, Braff, & Mintz, 2000) and symptomatic (M. F. Green & Nuechterlein, 2004) outcomes in those with psychotic disorders. Symptomatically, poorer cognitive functioning is particularly associated with negative symptoms but not with positive symptoms (Addington, Addington, & Maticka-Tyndale, 1991; Ventura, Hellemann, Thames, Koellner, & Nuechterlein, 2009). Deficits in cognitive function are associated with both theoretical functional capacity and real-world functioning (Bowie & Harvey, 2005; Milev, Ho, Arndt, & Andreasen, 2005). For example, Milev et al. found that verbal memory specifically predicted impairment in recreational activities, memory deficits (along with negative symptoms) specifically predicted impairment in relationships, while attention (and negative symptoms) specifically predicted work performance (Milev et al., 2005). This cognitive-functional relationship may, in fact, be mediated by the relationship between cognition and negative symptoms (Ventura et al., 2009).

Individuals with psychosis risk syndromes show neurocognitive deficits at an intermediate level between patients with schizophrenia and population controls (Fusar-Poli, Deste, et al., 2012; Giuliano et al., 2012; Hawkins et al., 2004; Niendam et al., 2007). These intermediate level difficulties in individuals with psychosis risk syndromes have also been observed in those with familial risk for psychosis (Bora et al., 2014). Within this clinical risk group, those who later develop psychotic disorders show significantly more verbal memory deficits than those who do not (Lencz et al., 2006; Seidman, Giuliano, & Walker, 2010) as well as more general deficits across domains (Bora et al., 2014; Giuliano et al., 2012). In addition to adverse clinical outcomes in those with psychosis risk syndromes, poorer cognitive performance has also been associated with functioning. For example, reduced processing speed predicts poor social outcome, while poorer
performance on tests for verbal memory predicts role outcome (Carrión et al., 2011).

There has been less research regarding cognitive deficits in non-help-seeking groups. A study with the Northern Finland Birth Cohort 1986 found no significant cognitive differences between (non help-seeking) young adults with familial and clinical risk and controls (Mukkala et al., 2011). However, using the psychotic experiences paradigm, adolescents in the population with these psychotic experiences perform more poorly in terms of processing speed and nonverbal working memory (Kelleher, Clarke, Rawdon, Murphy, & Cannon, 2013). These differences may reflect the age of the participants, the importance of help-seeking as a marker of risk within the psychosis risk syndrome paradigm or the tasks that were tested, for example processing speed was not specifically tested in the older Finnish group.

2.4 Risk factors for psychosis risk and cognitive deficits in adolescence and early adulthood

While there are significant differences between psychosis risk and cognitive deficits, both are reflective of brain developmental processes. As such, they are likely to share some risk factors and risk markers. Both psychosis risk and cognitive deficits are associated with genetic factors, early environmental factors and adolescent markers of risk (see table 2 for summary with details below).

Table 2. Risk factors and markers for psychosis risk and cognitive deficits in adolescence

<table>
<thead>
<tr>
<th>Risk factors</th>
<th>Psychosis risk</th>
<th>Adolescent cognitive deficits</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographic</td>
<td>Male sex</td>
<td>Male sex</td>
</tr>
<tr>
<td>Genetic</td>
<td>Family history of psychosis, schizophrenia, polygene risk score, COMT*, BDNF*</td>
<td>Parental intelligence, parental mental illness, MIR137$, BDNF*$</td>
</tr>
<tr>
<td>Early environmental</td>
<td>Perinatal complications</td>
<td>Less social support</td>
</tr>
<tr>
<td>Later environmental</td>
<td>Cannabis use, trauma</td>
<td>Family interaction factors, neglect and abuse (trauma)</td>
</tr>
</tbody>
</table>

*Interacting with other factors; $In the presence of mental disorders

COMT=Catechol-O-Methyl-transferase; BDNF=Brain-Derived Neurotrophic Factor; MIR-137=miRNA 137
2.4.1 Risk factors and markers for psychosis risk

Study into risk factors and markers in those with psychosis risk syndromes has been complicated by the presence of a risk syndrome depending on the “help-seeking” criterion, making it difficult to determine their true population prevalence. Examination of risk factors has therefore tended to focus on conversion to psychosis rather than the presence of the risk syndromes themselves. One Irish study found that 8% of 11-13 year-olds in the general population met criteria for a psychosis risk syndrome (Kelleher, Murtagh, et al., 2012). A Swiss study of 16-40 year-olds found that 13% of their population sample reported attenuated psychotic symptoms (the most common type of psychosis risk syndrome) (Schultze-Lutter, Michel, Ruhrmann, & Schimmelmann, 2014). This study found no differences in terms of age, gender, nationality or family history in this (non-help-seeking) population. However, in a help-seeking sample in the United States, there were relatively more males and high rates of history of major psychotic and affective disorders in first degree relatives (44%) (T. J. Miller, Zipursky, et al., 2003). These findings suggest that sample ascertainment is an important factor in examinations of psychosis risk syndromes.

These issues are less important in studies of psychotic experiences, which occur at the population-level (rather than clinic-level) by definition. Psychotic experiences share a range of familial, social, childhood experience and substance use risk factors with schizophrenia (Kelleher & Cannon, 2011). There is reasonably strong evidence for an association between psychotic experiences and genetic risk factors for schizophrenia. This is evident in familial clustering of these symptoms (Hanssen, Krabbendam, Vollema, Delespaul, & Van Os, 2006) and an analysis of the schizophrenia polygene risk score, which is associated with various levels of schizophrenia risk in addition to the diagnosis itself (Bigdeli et al., 2014; Tesli et al., 2014).

Two specific candidate genes, catechol-o-methyl-transferase (COMT) and brain-derived neurotrophic factor (BDNF), have been researched reasonably extensively regarding their associations with psychosis risk. The association between COMT and psychotic disorders arose initially from the observation of significantly higher rates of psychotic disorders in individuals with 22q11 deletion syndrome. COMT plays an important role in catecholamine metabolism in the central nervous system and its Val158Met polymorphism is associated with a 3-4 fold variation in enzymatic activity between the low activity Met/Met
genotype and the high activity Val/Val genotype (Weinshilboum, Otterness, & Szumlanski, 1999). This effect on enzymatic activity makes this polymorphism an ideal candidate to consider gene-environment interactions in relation to psychosis and its related phenotypes. Indeed, such gene environment interactions with psychotic disorders as the outcome have been noted with cannabis use in adolescence (Caspi et al., 2005; Henquet et al., 2009) and daily life stress (Peerbooms et al., 2012). Gene-environment interactions have also been noted in the case of psychotic experiences in the population, again in the context of cannabis use and stress (Stefanis, Henquet, et al., 2007; Vinkers et al., 2013).

BDNF is involved in neuronal development and cell survival in response to stress (Sofroniew, Howe, & Mobley, 2001). Dysfunction in the expression of BDNF has been observed in schizophrenia (Shoval & Weizman, 2005), while the BDNF Val66Met polymorphism has been shown to moderate the association between childhood abuse and population level psychotic experiences (Alemany et al., 2011).

There is therefore reasonably robust evidence for a broad association between genes of risk for schizophrenia and psychotic experiences. The evidence regarding specific genes, particularly COMT and BDNF, is weaker and would benefit from further replication.

There is also evidence that specific life events and exposures are associated with psychosis risk in the population. The strongest evidence for an association with psychotic experiences exists for exposure to perinatal complications (Zammit, Thomas, et al., 2009), cannabis use in adolescence (Harley et al., 2010; Miettunen et al., 2008) and childhood traumatic experiences (Kelleher et al., 2008). Unsurprisingly, these are also risk factors for psychotic disorders.

Biological markers, associated with psychotic disorders, have also been associated with various forms of psychosis risk. CSF studies have been particularly promising to date. For example, CSF disturbances seen in individuals with first-episode psychosis are also evident in a proportion of individuals with prodromal/clinical high risk for psychosis (Huang et al., 2007), while CSF endocannabinoid levels are altered in prodromal state (Koethe et al., 2009). Imaging studies have also noted biological differences in the clinical high risk stage with elevated striatal dopamine function (Howes, Montgomery, & Asselin, 2009) and abnormal lower thalamic glutamate in those at clinical high risk for psychosis (Stone et al., 2009). The evidence for these biological associations remains quite limited, suggesting a need for further replication and for research to
consider the nature of the associations (e.g. markers of risk, components of pathogenesis).

### 2.4.2 Risk factors and markers for cognitive deficits in adolescence and early adulthood

Risk factors relevant to cognitive deficits depend largely on the age that cognitive deficits are observed. Risk factors for neurodevelopmental processes and disorders are relevant in children, adolescents and young adults, while risk factors for neurodegenerative disorders are relevant in older adults. Learning more about cognitive development from adolescence into early adulthood, a period of particular importance in the development of executive function and social cognition (Blakemore & Choudhury, 2006), is particularly important in understanding the extended psychosis phenotype.

A range of risk factors have been associated with cognitive deficits in childhood and early adolescence. These include risk factors for intellectual disability (Chiurazzi, Pirozzi, Chiurazzi, & Pirozzi, 2016), detailed description of which is beyond the scope of this thesis. Examples of environmental risk factors that impact on cognitive development in childhood include childhood trauma (Bücker et al., 2012), family poverty (Yeung, Linver, & Brooks-Gunn, 2002), parental social supports (Melson, Ladd, & Hsu, 1993), parental mental illness (particularly depression) (NICHD Early Child Care Research Network, 1999) and parental neglect or abuse (Barnett, 1997). These risk factors have been hypothesised to impact child cognitive development in various ways. For example, childhood trauma may impact on development of specific aspects of executive functioning such as inhibitory control (Marshall et al., 2016), while poverty may impact by limiting family access to enriching environments (Yeung et al., 2002) and impacting on attachment (Pierrehumbert, Ramstein, Karmaniola, & Halfon, 1996).

Cognitive impairment is a core feature of schizophrenia and, to a lesser extent, other psychotic disorders (Reichenberg & Harvey, 2007). Three main process have been hypothesised to lead to cognitive impairment in schizophrenia-spectrum disorders: development deterioration, developmental deficit, developmental lag or a combination of these (Reichenberg et al., 2010). The developmental deterioration hypothesis predicts premorbid decline in cognitive performance. The developmental deficit hypothesis predicts a stable premorbid deficit. The developmental lag hypothesis predicts growth of cognitive abilities at
a rate that lags behind healthy groups. Current evidence favours a combination of developmental deficit and developmental lag (Reichenberg et al., 2010), consistent with the broader neurodevelopmental hypothesis for schizophrenia (Murray & Lewis, 1988). Consequently, it would be reasonable to expect that risk factors for cognitive deficits would be broadly neurodevelopmental and include genetic and environmental factors and biological risk markers.

**Genetic risk factors for cognitive deficits in adolescence and early adulthood**

Consistent with the neurodevelopmental hypothesis, there is evidence that cognitive impairments in relatives varies with genetic loading for schizophrenia, suggesting some shared genetic risk factors (Schulze-Rauschenbach et al., 2015). Specific genes have also been associated cognitive deficits. For example, risk alleles at MIR137 have been associated with an impaired cognition subtype in patients with schizophrenia (M. J. Green et al., 2012). However, it remains unclear if genetic risk for schizophrenia-spectrum disorders is shared with risk for cognitive impairment at a broader population level. Gene-environment interactions in association with cognitive phenotypes have also been detected, for example between the BDNF Val66Met polymorphism and cognitive functioning in the context of childhood abuse in adults with psychotic disorders (Aas et al., 2013).

There is a relative absence of research regarding genetic risk factors for cognitive deficits in those at risk for psychosis, as opposed to those with psychotic disorders. However, as outlined above, cognitive impairments in relatives varies with genetic loading for schizophrenia (Schulze-Rauschenbach et al., 2015) and the schizophrenia polygenic risk score has been associated with working memory (Hatzimanolis et al., 2015; Kauppi et al., 2015) as well as with sustained attention and vigilance (Hatzimanolis et al., 2015) in healthy individuals. While it has not been specifically studied in those with psychosis risk, there is little reason to consider the associations would be different in this population.

While research is lacking on specific genes, those involved in dopamine neurotransmission are putative candidates. Dopamine neurons projecting to the prefrontal cortex are involved in key aspects of normal cognitive function (Aalto, Brück, Laine, Nägren, & Rinne, 2005) and reduced dopaminergic neurotransmission appears to contribute to cognitive deficits in schizophrenia, particularly in executive function and working memory (Davis et al., 1991).
The dopamine D2 receptor (DRD2) gene is one potential candidate involved in dopamine neurotransmission. This codes for a G-protein coupled receptor that inhibits adenylyl cyclase activity involved in mesocorticolimbic pathways (Neville, Johnstone, & Walton, 2004). The receptor has also been implicated in schizophrenia (Allen et al., 2008; Betcheva et al., 2009; Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014) and is a target for antipsychotic drugs in the treatment of schizophrenia (Kapur, Zipursky, & Remington, 1999). Regarding cognition, DRD2 has been associated with abnormalities in functioning in the prefrontal cortex (Kellendonk et al., 2006) and with negative symptoms and poorer sustained attention performance (Chien et al., 2013).

Studies of DRD2 in those at risk for psychosis are lacking but two polymorphisms, rs6277 and rs1800497, have been associated with various cognitive tasks in healthy samples, including general cognitive ability, verbal learning and working memory (Berryhill, Wiener, Stephens, Lohoff, & Coslett, 2013; Bolton et al., 2010; Doll, Hutchison, & Frank, 2011). There is some reason to expect further findings among those at risk for psychosis, especially given imaging findings suggesting differences in the correlation between dopamine receptor density and activation in the right middle frontal gyrus between those at clinical risk for psychosis and controls (Fusar-Poli et al., 2010).

Environmental risk factors for cognitive deficits in adolescence and early adulthood

There are multiple environmental risk factors and markers of poorer cognitive performance in adolescence and early adulthood, including those arising in early life (Bradley et al., 1989; Bromley & Baker, 2017) and those present in adolescence (Hueston, Cryan, & Nolan, 2017). In addition to those discussed above, early environmental factors include exposures (to infection, toxins or brain hypoxia) in pregnancy or delivery (Frank, Augustyn, Knight, Pell, & Zuckerman, 2001) and after birth (Jurewicz & Hanke, 2008). Later environmental factors include an impoverished home environment (Bradley et al., 1989), parenting behaviours (Lugo-Gil & Tamis-LeMonda, 2008), exposure to trauma or neglect (Strathearn, Gray, & Wood, 2001), and exposure to harmful substances (Needleman, Schell, Bellinger, Leviton, & Allred, 1990) or significant infection (Berkman, Lescano, Gilman, Lopez, & Black, 2002). While many of these have evidence suggesting a causal relationship with aspects of neurodevelopment, it
remains unclear if they exert ongoing effects on cognitive development into adolescence and early adulthood.

A number of environmental factors have been associated with cognitive outcomes in patients with psychotic disorders. Cannabis use has been associated with relatively better cognitive performance in schizophrenia patients (Donoghue & Doody, 2012), possibly reflecting a different pathway to schizophrenia involving less cognitive damage. Childhood trauma has been associated with poorer cognition in those at clinical high risk for psychosis (Üçok et al., 2015). Evidence regarding other environmental risk factors in those at high risk for psychosis is lacking.

It is unclear if prenatal exposure to maternal cigarette smoking (PEMCS), for example, is an early environmental exposure that exerts on ongoing effect on cognition into early adulthood. PEMCS has been associated with a range of health problems (Oken, Levitan, & Gillman, 2008), including with adolescent and adult psychiatric and behaviour problems (Ekblad, Gissler, Lehtonen, & Korkeila, 2010; Kotimaa et al., 2003; Kovess et al., 2014; Räsänen et al., 1999; Tiesler & Heinrich, 2014; Zammit, Thomas, et al., 2009). However, psychiatric and behavioural associations for PEMCS are stronger for substance use disorders, behaviour disorders and attention deficit hyperactivity disorder. The associations of PEMCS in psychosis and its prodrome remain unclear.

PEMCS has also been associated with cognitive functioning in children (Braun, Daniels, Kalkbrenner, Zimmerman, & Nicholas, 2009; Cornelius et al., 2011; Cornelius, Ryan, Day, Goldschmidt, & Willford, 2001; Fried,Watkinson, & Gray, 2003; Lambe, Hultman, Tarräng, Maccabe, & Cnattingius, 2006; Lundberg et al., 2010; Mezzacappa, Buckner, & Earls, 2011; Mortensen, Michaelsen, Sanders, & Reinisch, 2005). However, not all research has supported this view (Huibregts et al., 2006; Kafouri et al., 2009). Indeed, substance use often occurs in the context of various other risk factors and markers. Studies examining its role must consider these important covariates (Lassen & Oei, 1998). A more recent study, accounting for many confounders, has suggested that PEMCS plays a larger role in academic achievement and general intellectual ability than in other domains (Clifford, Lang, & Chen, 2012). Another view is that PEMCS is more specifically associated with “hot” cognitive tasks that involve stress or frustration (Huibregts, Warren, De Sonneville, & Swaab-Barneveld, 2008; Zelazo, Müller, & Goswami, 2002), which would be consistent with observed associations between PEMCS and externalising behaviours (Gaysina et al., 2013; Hill, 2002).
Self-regulation difficulty in the context of PEMCS appears to be more pronounced in boys than in girls (Wiebe et al., 2015).

It is unclear if the effects of PEMCS on cognition persist into early adulthood in both males and females or if they are particularly pronounced in individuals with mental health symptoms in adolescence. There is limited evidence from male-only samples that the effect of PEMCS on general intelligence may persist to age 18 (Lundberg et al., 2010; Mortensen et al., 2005). Whether there are adult associations in females is unclear, with studies in children noting stronger and more consistent findings in male-only samples (Clifford et al., 2012) and sex-specific effects of prenatal nicotine exposure in animal studies (Slotkin et al., 2007; Z. Xu, Seidler, Ali, Slikker, & Slotkin, 2001). Further evidence for differences according to sex are found in differences in brain imaging findings between males and females (Paus et al., 2008; Toro et al., 2008) and higher rates of inattention and hyperactivity and other externalizing behaviours in males in response to PEMCS (Halperin, Trampush, Miller, Marks, & Newcorn, 2008).

There is reason to suspect that adolescent mental health factors may interact with PEMCS in predicting poorer cognitive outcomes. Firstly, as mentioned above, a range of adolescent mental health problems are associated with PEMCS that are also associated with cognitive performance. PEMCS has been associated with population-level psychotic experiences in adolescence (Zammit, Thomas, et al., 2009), as well as with hyperactivity and other externalizing behaviours (Kotimaa et al., 2003; Kovess et al., 2014), though not in all studies have reported associations (Obel et al., 2016). These three mental health problems are each associated with cognitive deficits across various domains (Bálint et al., 2009; Bridgett & Walker, 2006; Kelleher, Clarke, Rawdon, Murphy, & Cannon, 2012). It is therefore possible that associations between PEMCS and cognition are mediated by adolescent mental health, especially in the case of inattention and hyperactivity, or that these associations are particularly pronounced in those with adolescent mental health problems.

Adolescence could also be considered a period of vulnerability for cognitive development, particularly in the context of emerging mental disorders. Indeed, adolescence is a key vulnerability period in the development of schizophrenia as a neurodevelopmental disorder (Murray & Lewis, 1988; Rapoport, Addington, Frangou, & Psych, 2005). It is also a period of risk in terms of cognition due to gaps between emotional, behavioural and cognitive development (Steinberg, 2005). For example, such gaps can lead to cannabis use, which is associated with both adverse mental health outcomes and cognitive outcomes (Levine, Clemenza,
Emotional and behavioural problems themselves are associated with cognitive consequences (Steinberg, 2005). The mechanisms by which adolescent environmental risk factors impact on cognitive development and psychosis risk are only partly understood. Further clues may arise by clarifying the biological signatures associated with cognitive performance and psychosis risk.

**Biological markers of risk for cognitive deficits**

Metabolomics approaches offer one means to consider biological signatures of cognitive performance. Indeed, nuclear magnetic resonance (NMR) spectroscopy have provided insights regarding the development of diverse disease and risk states, such as such as obesity (Würtz et al., 2014), diabetes (Wang et al., 2015), cardiovascular events (Würtz et al., 2015), alcohol consumption (Würtz, Cook, Wang, Tiainen, & Tynkkynen, 2016) and physical activity (Kujala et al., 2013). NMR spectroscopy has also identified molecular patterns that appear to be associated with schizophrenia (Holmes et al., 2006) and mild cognitive impairment in older people (Tukiainen, Tynkkynen, Mäkinen, Jylänki, & Kangas, 2008). Such approaches may therefore provide insights into the development of adolescent cognitive performance and psychosis risk, either pointing to potential causal pathways or acting as markers of risk.

Indeed, there is emerging evidence that there are biomarkers associated with cognitive performance in the extended psychosis phenotype. Inflammatory markers have been particularly promising in this regard. For example, cognition has been inversely associated with levels of serum C-reactive protein (CRP) in individuals with acute psychosis (Johnsen et al., 2016) as well as with levels of interleukin-1 receptor antagonist (IL-1Ra) and soluble tumour necrosis factor receptor 1 (sTNF-R1) in schizophrenia patients (Hope et al., 2015). Metabolites involved in activation of the N-methyl-D-aspartate (NMDA) receptor have also been associated with cognitive and emotional reaction times in individuals with first episode psychosis (Scoriels et al., 2015). There is less evidence regarding biomarkers for cognition in individuals at risk for psychosis. Membrane fatty acids have been associated with poorer cognitive performance in individuals with psychosis risk syndromes (Kim et al., 2014). However, evidence regarding CSF or serum metabolites and cognition in those at risk for psychosis is lacking.
2.5 Theory synthesis

We now know more than ever before regarding the adverse outcomes associated with psychosis risk, whether clinical risk or population risk, and regarding adverse outcomes associated with poorer cognition in adolescence and early adulthood. However, there has been limited research to examine risk factors for psychosis risk and for cognitive deficits in the context of psychosis risk.

Identifying these risk factors and markers is of significant public health and clinical importance. From a public health perspective, identifying exposures or factors that are associated with negative outcomes, such as psychosis risk or cognitive deficits, allows for the possibility of prevention strategies to delay illness onset or even reduce incidence (Brenner, Madhusoodanan, Puttichanda, & Chandra, 2010). In the clinic, the identification of cognitive deficits and risk factors associated with these could inform early intervention strategies, such as types of cognitive remediation approaches (Revell, Neill, Harte, Khan, & Drake, 2015).

There is reason to expect overlap and interaction between risk factors for both psychosis risk and cognitive deficits. Both are signs of neurodevelopmental difficulty. Both can be impacted upon at various points during brain development.

Limited genetic associations have been made with psychosis risk. The COMT-Val158Met and BDNF-Val66Met polymorphism are well-researched polymorphisms that may be associated with psychosis risk based on existing hypotheses. Genetic associations with cognitive deficits are known but the interaction between genetic risks for psychosis and cognition are largely unknown. Polymorphisms at DRD2 are well-researched in relation to psychosis and cognition separately but evidence in the context of both psychosis risk and cognition is lacking, making these polymorphisms an ideal place to begin to consider the genetics of cognition in those with psychosis and psychosis risk. Similarly, many early and late environmental factors and markers associated with cognition are known but how these are related to adolescent mental health status is unclear. Examining smoking in pregnancy and adolescent metabolite levels, where there is some existing research in relation to cognition, represents a starting point in understanding the interplay of risk factors for psychosis risk and cognition.

While psychosis risk and cognitive deficits are important to identify as intermediate phenotypes to adverse long-term outcomes, they lack effective and specific treatments. The identification of risk factors for psychosis risk and
adverse cognition, particularly arising in those at risk for psychosis, has the potential to highlight events or contexts that are open to intervention, therefore preventing the development of psychotic experiences and adverse cognition in the first place. This thesis aims to fill this theoretical gap, examining genetic (and gene-environment) and environmental risk factors for psychotic experiences and adverse cognition. Such an investigation has the potential to inform prevention strategies prior to adverse intermediate outcomes, whether in pregnancy or during child and adolescent development.
3 Aims of the study

The extended psychosis phenotype, including clinical risk syndromes and population-level psychotic experiences, indexes risk for poor clinical and functional outcomes. When accompanied by cognitive deficits, these outcomes can be particularly severe. Therefore, the two broad objectives of this dissertation were to explore risk factors, genetic and environmental, for: (1) the extended psychosis phenotype and; (2) poorer cognitive performance, particularly as it occurs in the context of the extended psychosis phenotype. There has been considerable work identifying environmental risk factors for the extended psychosis phenotype (e.g. childhood trauma, cannabis use). However, there has been less examination of genetic risk factors and less again considering how psychosis risk interacts with risk factors for cognitive deficits.

This dissertation therefore narrowed the broad objective to examine risk factors for the extended psychosis phenotype and cognitive deficits in adolescence and early adulthood into four objectives: firstly, are specific genes associated with psychosis also associated with population-level psychotic experiences; secondly, are there specific genes that have been associated with psychosis that are also associated with cognitive deficits, including in young people at risk for psychosis; thirdly, are there early environmental risk factors/markers associated with cognitive deficits, that have a differential effect among those with psychosis risk; and fourthly, are there adolescent risk factors/markers that are shared for cognitive deficits in young people and psychosis risk?

The four broad objectives need to be made more specific, particularly by focusing on individual genes and environmental risk factors of interest. Based on the background literature, we decided to focus on the genes for COMT, BDNF and DRD2. Environmentally, we decided to examine one early and one adolescent risk factor/marker. This resulted in four specific hypotheses (addressed in four research papers as below) to be tested in this study:

HYPOTHESIS 1 (study I): Polymorphisms at COMT (Val158Met) and BDNF (Val66Met) are associated with psychotic experiences but this varies according to the presence or absence of experience of childhood trauma.

HYPOTHESIS 2 (study II): Polymorphisms at DRD2 predict poorer cognitive performance in young adults but poorer cognitive performance is significantly more marked in young adults with clinical and familial risk for psychosis.
HYPOTHESIS 3 (study III): Prenatal exposure to maternal cigarette smoking is associated with cognitive deficits in early adulthood and these risks differ according to adolescent mental health, including the presence of psychosis risk.

HYPOTHESIS 4 (study IV): Cognitive deficits and psychosis risk are associated with shared metabolic patterns and features in adolescence.
4 Materials and methods

The study methodology was primarily epidemiological with different sample designs used depending on the research question. The main outcomes were psychosis risk and cognitive deficits, with the exposures and covariates differing between the research questions.

4.1 Participants

The research questions of this study were considered through the analysis of two specific studies of adolescents, the Adolescent Brain Development (ABD) and Challenging Times (CT) studies, two birth cohorts, the Northern Finland Birth Cohort 1986 (NFBC 1986) and Avon Longitudinal Study of Parents and Children (ALSPAC), and sub-groups of the NFBC 1986, the Oulu Brain and Mind 1 and 2 studies. These studies took place in Finland, the United Kingdom and Ireland.

4.1.1 Specific studies of adolescents

The Adolescent Brain Development Study (Study I)

The Adolescent Brain Development (ABD) study took place in the counties of Dublin and Kildare in Ireland, which contains a mixture of urban and suburban housing types of different socioeconomic status. Full characteristics of the study have been described elsewhere (Kelleher, Murtagh, et al., 2012).

In brief, the study approached 27 primary schools (for children aged 4-13 years), of which sixteen agreed to participate (59%). Recruitment and attrition for the ABD and CT studies is presented in figure 2 below. The target population of the study were children aged 11-13 years who were in the two most senior classes of the Irish primary school system. Across these sixteen schools, 2,190 consent forms were distributed to parents with 1,131 (52%) agreeing for their children to participate. Among these 1,131 adolescents, 656 indicated interest in participating in an interview study and a random sample of 212 of these attended for interview. Those who attended did not differ from those who did not attend on psychopathology, measured using the Strengths and Difficulties Questionnaire (SDQ) (Goodman, Meltzer, & Bailey, 1998) and they were representative of the Irish population in terms of socioeconomic status and ethnic background. The
study received ethics approval from the Beaumont Hospital medical ethics committee. All participants provided informed assent and their parents provided written consent.

The Challenging Times Study (Study I)

The Challenging Times (CT) study took place in the geographical catchment area of a child and adolescent mental health team in north Dublin, Ireland, containing a population of 137,000. This area includes pockets of severe deprivation, alongside large suburban housing estates and more affluent areas of private housing and the overall population includes a higher proportion from lower socioeconomic backgrounds compared with the general population of Ireland. Full characteristics of the study have been described elsewhere (Harley et al., 2013; Lynch, Mills, Daly, & Fitzpatrick, 2006).
The study approached 12 secondary schools (for children aged 12-18 years) in the area, chosen based on a stratified random sampling procedure according to the approximate socioeconomic status of the school, and eight of these (67%) agreed to participate. In these schools, a total of 743 students aged 12-15 years were screened for psychopathology using the Strengths and Difficulties Questionnaire (SDQ) (Goodman et al., 1998) and the Children’s Depression Inventory (Kovacs, 1992). Among these, 140 children scored above the threshold of these instruments and were invited to attend for full psychiatric interview, with 117 attending (84%). A further 173 healthy control adolescents, matched on gender and school, were also invited to interview and 94 attended (54%). The total sample was therefore 211 adolescents. Ethics approval was given by the Mater Misericordiae University Hospital medical ethics committee and written informed consent was obtained from parents or guardians.

4.1.2 Northern Finland Birth Cohort 1986 (Studies II, III, IV)

The Northern Finland Birth Cohort 1986 (NFBC 1986) is a longitudinal birth cohort, covering 99% of births in the two northernmost provinces of Finland, Oulu and Lapland, who had an expected delivery date between July 1st 1985 and June 30th 1986. Details of the cohort have been described elsewhere (Järvelin, Hartikainen-Sorri, & Rantakallio, 1993). The cohort was surveyed prospectively during gestation and it has continued since. Of the original sample, 6,985 (74%) participated in the 16-year follow-up. The Ethics committee of the Northern Ostrobothnia Hospital District in Finland has approved the study and all participants and their parents provided written informed consent.

Oulu Brain and Mind 1 Study (Study II)

A subsample of the NFBC 1986, the Oulu Brain and Mind 1 study, was invited based on previously collected data to participate in a field study at age 21-25 years (mean age 23 years). This study took place during 2007-2010. Details of this sample have been described elsewhere (Veijola et al., 2013). Recruitment and attrition for the Oulu Brain and Mind 1 Study is presented in figure 3 below. In brief, participants were recruited based on the presence of familial risk for psychosis, symptomatic risk for psychosis, psychotic disorder diagnosis, and attention deficit hyperactivity disorder (ADHD) diagnosis, or they were recruited as controls. Familial risk for psychosis was defined as the presence of parental
psychoses, according to the Finnish Hospital Discharge Register (FHDR). Symptomatic risk for psychosis was defined according to performance on the Youth Self-Report (YSR) and PROD-screen questionnaires at age 16 years along with social function data at that age, or hospitalisation for a non-psychotic disorder using the FHDR. Psychotic disorder was defined according to the FHDR or the use of medication for psychosis according to the register of the national Social Insurance Institute. ADHD was defined according to previous field study data indicating the presence of definite ADHD at age 16-17 years. The control group were a random sample of the NFBC 1986 who did not belong to the above groups. Of those invited to attend, 78/272 (29%) of the familial risk group attended, 58/117 (50%) of the symptomatic risk group attended, 27/78 (35%) of the psychotic disorder group attended, 52/103 (51%) of the ADHD group attended, and 80/193 (41%) of the control group attended. This meant the total sample size was 295 individuals.

Assessment for psychosis risk syndromes and psychotic disorders was performed using the Structured Interview for Prodromal Syndromes (SIPS) (McGlashan et al., 2001) together with the Structured Clinical Interview for DSM IV axis-I disorders (SCID). Based on this assessment, a further 113 individuals were excluded: 31 individuals who were assessed as having psychotic disorder on SIPS, 37 individuals who were recruited as at symptomatic risk but showed no signs of clinical risk at assessment, and 45 individuals recruited with ADHD who did not show signs of any risk syndrome, reducing the final sample size to 182 individuals (see figure 2). All participants provided written informed consent.
A further subsample of the NFBC 1986, the Oulu Brain and Mind 2 study, was invited based on previously collected data to participate in a field study at age 25-27 years (mean age 26 years). This study took place during 2011-2013. Details of this sample have been described elsewhere (Lotfipour et al., 2014). In brief, participants were recruited based on exposure to smoking in pregnancy. The non-exposed group were matched to the exposed participants based on place of birth (urban vs. rural, Oulu region vs. Lapland region) and maternal education level. Among the extensive exclusion criteria were maternal use of alcohol in excess of 4 drinks per week during pregnancy, premature birth before 35 weeks, multiple births, serious childhood medical illnesses, neurological conditions, developmental conditions, diagnosis of psychosis and intellectual disability (IQ<70). Recruitment and attrition for the Oulu Brain and Mind 1 Study is
presented in figure 4 below. Full details are listed elsewhere (Lotfipour et al., 2014). Of the invited 1,396 eligible participants (698 exposed and 698 matched non-exposed), a total of 471 (34%) completed the full protocol (including magnetic resonance imaging). The Ethics committee of the Northern Ostrobothnia Hospital District in Finland has approved the study and all participants gave written informed consent.

Fig. 4. Recruitment and attrition for the Oulu Brain and Mind 2 study

4.1.3 The Avon Longitudinal Study of Parents and Children (ALSPAC) Cohort (Study IV)

The Avon Longitudinal Study of Parents and Children (ALSPAC) is a longitudinal birth cohort, consisting of 85% of eligible expectant mothers in Bristol, UK, and surrounding areas, who had an expected delivery date between April 1st 1991 and December 31st 1992. Details of the cohort have been described elsewhere (Golding, Pembrey, & Jones, 2001). Recruitment and attrition for the ALSPAC and NFBC 1986 in relation to metabolomics measures in presented in figure 5. In brief, this consisted of 14,062 live-born children, of whom 9,985 were invited and 5,253 attended to follow-up at age 15 years and 10,101 were invited and 5,217 attended to follow-up at age 17 years. The study received ethics approval from the ALSPAC Law and Ethics Committee, and all participants and their parents provided written informed consent.
Fig. 5. Recruitment and attrition for the NFBC 1986 and ALSPAC cohorts

4.2 Measures

The outcomes of interest for this study were psychosis risk and cognitive performance. The primary exposures of interest were genetic polymorphisms, prenatal exposure to maternal cigarette smoking and adolescent metabolic measures. The covariates considered varied by specific research question.

4.2.1 Outcome/exposure/covariate of interest: psychosis risk

Psychosis risk was the outcome of interest for the first research question and was one of the two outcomes of interest for the fourth research question. It was a covariate for the second and third research questions.
Psychosis risk assessment for the ABD and CT Studies (Study I)

Population-level psychotic experiences, assessed in the ABD and CT studies, were the outcome of interest for the first research question. In both studies, participants and their parents were interviewed using the Schedule for Affective Disorders and Schizophrenia for School-aged Children (K-SADS), Present and Lifetime versions, which is a well-validated semi-structured research diagnostic interview for the assessment of Axis I psychiatric disorders in children and adolescents (Kaufman, Birmaher, Brent, Rao, & Ryan, 1996). Both parents and children were asked the same question during separate interviews. The psychosis section of the K-SADS was used to assess the participants’ psychotic experiences. Following the interviews, there was a consensus meeting at which trained experts reviewed the extensive notes of potential psychotic phenomena. Blinded to participant diagnosis and all other information on the participants, this panel classified psychotic experiences as either present or absent. This measure of psychotic experiences was the outcome variable in the case of the first research question.

Psychosis risk assessment for the NFBC 1986 (Study III, Study IV)

Psychosis risk in adolescence, measured in the NFBC 1986, was one of two outcomes of interest for the fourth research question and a covariate of interest for the third research question.

All participants in the NFBC 1986 at age 16 years were asked to provide information regarding psychosis risk, measured using the PROD-screen questionnaire, which has been validated against the gold standard for psychosis risk, the Structured Interview for Psychosis risk Syndromes (SIPS) (Heinimaa et al., 2003). This screening questionnaire includes twenty-one questions measuring lower level psychosis risk. A factor analysis approach has previously identified three dimensions to the PROD-screen (Therman et al., 2011): positive, negative and general dimensions. Based on these dimensions, we classified individuals as having psychosis risk where they endorsed three or more of eleven positive items (1,791/4,662, 28%).
Psychosis risk assessment for the ALSPAC (Study IV)

Psychosis risk in adolescence, measured in the ALSPAC, was an outcome of interest for the fourth research question. ALSPAC participants were invited to follow-up at about age 17 years, at which point they were interviewed using the psychotic-like experiences (“PLIKS”) clinical interview, which was conducted by trained psychology graduates. Three main domains of positive psychotic symptoms were elicited: hallucinations, delusions, and thought interference and interviewers rated psychosis risk as absent, suspected or definitely psychotic. Individuals were classified as having psychosis risk where they showed one or more definite symptoms on interview (Zammit, Odd, et al., 2009). As a clinical interview undertaken by psychology graduates, the PLIKS interview has good face validity.

Psychosis risk assessment for the Oulu Brain and Mind 1 sample (Study II)

Psychosis risk was a key exposure and covariate of interest for the second research question, examined using the Oulu Brain and Mind 1 sample. In this case, psychosis risk was based on clinical risk as assessed at age 21-25 years, using the Structured Interview for Prodromal Syndromes (SIPS) (McGlashan et al., 2001), a well-validated measure of psychosis risk (T. J. Miller, McGlashan, et al., 2003) together with the Structured Clinical Interview for DSM IV axis-I disorders (SCID) (First, Gibbon, Spitzer, & Williams, 1996). The SIPS identifies three psychosis risk syndromes: attenuated psychotic symptoms; brief, limited and intermittent psychotic symptoms; and/or genetic risk with recent functional deterioration. Based on this interview and data on family history of parental psychotic disorder, individuals were classified into three groups: familial risk for psychosis group (n=61) with one parent or both with psychosis; clinical risk (prodromal syndrome) for psychosis group (n=47); and control group, a random sample of participating NFBC 1986 members (n=74). Fourteen individuals had both familial and clinical risk for psychosis and they were classified with the clinical risk group.
Psychosis risk was an exposure and potential mediator of interest for the third research question, examined using the Oulu Brain and Mind 2 sample. Psychosis risk in adolescence was assessed using the PROD-screen, as outlined above for the NFBC 1986. In this study, a conservative cut-off of 3 or more “specific items” on the PROD-screen was used to create a binary variable for population-level psychotic experiences (Heinimaa et al., 2003). These items included: difficulties thinking clearly or concentrating; experience of thoughts running wild or difficulty controlling speed of thoughts; difficulties understanding written text or speech; difficulty controlling one’s speech, behaviour or facial expression while communicating; feeling that events or behaviours of others specifically concern oneself; feeling euphoric or especially competent or important; visual problems; hearing problems, including hearing sounds or voices without source; difficulties with ordinary routine activities; feeling something strange is happening, feelings, thoughts or behaviours that could be considered peculiar; and feeling of being followed or influenced (Heinimaa et al., 2003). Based on this classification, 143/420 (34%) participants were judged to have psychosis risk.

4.2.2 Outcome of interest: cognitive performance

Cognitive performance was an outcome of interest for the second, third and fourth research questions, utilising data from the NFBC 1986, ALSPAC, and the Oulu Brain and Mind 1 and 2 samples.

Cognitive performance in the Oulu Brain and Mind 1 sample (Study II)

Cognitive performance from the Oulu Brain and Mind 1 sample was the primary outcome of interest for the second research question. This was measured at interview in young adulthood at age 21-25 years.

Cognitive assessments measured verbal and non-verbal intellectual ability, learning and memory, executive functioning, working memory, attention, decision-making and fine motor functioning (see table 3). The vocabulary and matrix reasoning sections of the Wechsler Adult Intelligence Scale (WAIS-3) (Wechsler, 1997) were used to measure intellectual ability. The Logical Memory component (immediate and delayed parts) of the Wechsler Memory Scale-
Revised (WMS-R) (Wechsler, 1987) and the Paired Associates Learning (PAL) test from the CANTAB battery (B. J. Sahakian et al., 1988) were used to measure learning and memory. Digit Span Backwards (Wechsler, 1997), Semantic Fluency (Benton & Hamsher, 1976) and Stockings of Cambridge (SOC) (Owen, Downes, Sahakian, Polkey, & Robbins, 1990) were used to measure executive functioning. Digit Span Forwards (Wechsler, 1997) and Rapid Visual Information Processing (RVP) (B. Sahakian, Jones, Levy, Gray, & Warburton, 1989) were used to measure working memory/attention. The Grooved Pegboard (Trites, 1989) was used to measure fine motor functioning. The CANTAB battery (including the PAL, SOC and RVP) has been validated to measure cognitive performance in individuals with schizophrenia (Levaux et al., 2007).

Raw scores of neurocognitive ability tests that were normally distributed were transformed to Z-scores using means and standard deviations derived from the control group. Paired associates learning (PAL) score was transformed using a square root transformation and this was converted into Z-scores.

Table 3. Cognitive assessments in the Oulu Brain and Mind 1 sample

<table>
<thead>
<tr>
<th>Domain</th>
<th>Test used</th>
</tr>
</thead>
<tbody>
<tr>
<td>Verbal intellectual ability</td>
<td>Vocabulary component of WAIS-3</td>
</tr>
<tr>
<td>Non-verbal intellectual ability</td>
<td>Matrix reasoning component of WAIS-3</td>
</tr>
<tr>
<td>Learning and memory</td>
<td>Logical memory component of WMS-R, Paired Associates Learning from CANTAB battery</td>
</tr>
<tr>
<td>Executive functioning</td>
<td>Digit span backwards, semantic fluency, Stockings of Cambridge from CANTAB battery</td>
</tr>
<tr>
<td>Working memory</td>
<td>Digit span forwards, Rapid Visual Information Processing</td>
</tr>
<tr>
<td>Fine motor functioning</td>
<td>Grooved pegboard</td>
</tr>
</tbody>
</table>

WAIS=Wechsler Adult Intelligence Scale, version 3; WMS-R=Wechsler Memory Scale, Revised

Under the assumption that the tests were examining latent neurocognitive factors, factor analysis with principal components factoring was then performed on variables with complete data available. Factor analysis was used in order to reduce the number of tests performed and the risk of false positive results. A principal components factor model was used because there was no predefined theory regarding the structure or number of variable dimensions. The factors were then varimax rotated to produce orthogonal factors that were not correlated to each other. This resulted in the identification of three main factors (presented in table 4 below).
Table 4. Loadings of baseline performance for individual tests to three main factors (n=181) in the Oulu Brain and Mind 1 sample

<table>
<thead>
<tr>
<th>Variable</th>
<th>Factor 1: Verbal</th>
<th>Factor 2: Psychomotor</th>
<th>Factor 3: Non-verbal</th>
<th>Uniqueness</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vocabulary</td>
<td>0.61</td>
<td>-0.39</td>
<td>0.28</td>
<td>0.41</td>
</tr>
<tr>
<td>Matrix reasoning</td>
<td>0.26</td>
<td>0.02</td>
<td>0.75</td>
<td>0.37</td>
</tr>
<tr>
<td>Logical memory</td>
<td>0.32</td>
<td>-0.29</td>
<td>0.57</td>
<td>0.49</td>
</tr>
<tr>
<td>PAL</td>
<td>-0.09</td>
<td>0.21</td>
<td>-0.71</td>
<td>0.44</td>
</tr>
<tr>
<td>DS-backwards</td>
<td>0.78</td>
<td>-0.08</td>
<td>0.26</td>
<td>0.31</td>
</tr>
<tr>
<td>Verbal fluency</td>
<td>0.46</td>
<td>-0.51</td>
<td>0.24</td>
<td>0.47</td>
</tr>
<tr>
<td>SOC</td>
<td>-0.09</td>
<td>-0.17</td>
<td>0.69</td>
<td>0.49</td>
</tr>
<tr>
<td>DS-forwards</td>
<td>0.88</td>
<td>-0.05</td>
<td>-0.05</td>
<td>0.23</td>
</tr>
<tr>
<td>PB-dominant</td>
<td>-0.13</td>
<td>0.91</td>
<td>-0.07</td>
<td>0.16</td>
</tr>
<tr>
<td>PB-non-dominant</td>
<td>-0.02</td>
<td>0.85</td>
<td>-0.11</td>
<td>0.27</td>
</tr>
</tbody>
</table>

PAL=Paired Associates Learning; DS=Digit-span; SOC=Stockings of Cambridge; PB=Pegboard

Cognitive performance in the Oulu Brain and Mind 2 sample (Study III)

Cognitive performance from the Oulu Brain and Mind 2 sample was the primary outcome of interest for the third research question. This was measured at interview in young adulthood at age 25-27 years.

Cognitive assessments measured verbal and non-verbal intellectual ability, learning and memory, working memory, attention, decision-making and fine motor skills (see table 5). Verbal skills were tested using the vocabulary component of the Wechsler Adult Intelligence Scale (WAIS-3), while non-verbal skills were tested using the Matrix Reasoning section of the WAIS-3 (Wechsler, 1997), as above. Learning and memory were assessed using the Paired Associates Learning (PAL) test as above (B. J. Sahakian et al., 1988). Executive functioning/cognitive flexibility was measured using Semantic Fluency (Benton & Hamsher, 1976). Fine motor-skills were measured with the Grooved Pegboard test (Trites, 1989). Processing speed was measured with time taken to complete the Stroop test (Strauss, Sherman, & Spreen, 2006). Response inhibition (impulse control) was tested using the modified Stop Signal Task (MSST) from the CANTAB battery, which has been well-validated previously (Lipszyc & Schachar, 2010), performed on an iPod Touch (Apple, Cupertino CA, USA) device. This test measures reaction time in response to a screen character. It measures various response parameters, including errors, successful stops and stop
signal reaction time (SSRT) (Lumsden, 2016). The outcome we utilized was the SSRT, after excluding outliers with SSRT<0.3s.

Raw scores of normally distributed tests were transformed to Z-scores with higher scores indicating better performance. Prior to conversion to Z-scores, non-normally distributed variables were transformed. The PAL test was transformed using a square root transformation.

Table 5. Cognitive assessments in the Oulu Brain and Mind 2 sample

<table>
<thead>
<tr>
<th>Cognitive domain</th>
<th>Cognitive test</th>
<th>Outcome measure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Verbal skills</td>
<td>Vocabulary component of WAIS-3</td>
<td>Z-transformed score</td>
</tr>
<tr>
<td>Non-verbal skills</td>
<td>Matrix reasoning component of WAIS-3</td>
<td>Z-transformed score</td>
</tr>
<tr>
<td>Learning and memory</td>
<td>Paired Associates Learning from CANTAB battery</td>
<td>Z-transformed inverse of total errors (adjusted)</td>
</tr>
<tr>
<td>Executive functioning/cognitive</td>
<td>Semantic Fluency</td>
<td>Z-transformed number of words named</td>
</tr>
<tr>
<td>flexibility</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fine motor skills</td>
<td>Grooved Pegboard test with dominant hand</td>
<td>Z-transformed inverse of time taken to complete</td>
</tr>
<tr>
<td>Processing speed</td>
<td>Stroop test</td>
<td>Z-transformed inverse of time taken to complete</td>
</tr>
<tr>
<td>Response inhibition/impulse control</td>
<td>Modified Stop Signal Test from CANTAB battery</td>
<td>Z-transformed inverse of stop signal reaction time</td>
</tr>
</tbody>
</table>

WAIS-3=Wechsler Adult Intelligence Scale, version 3; CANTAB=Cambridge Neuropsychological Test Automated Battery

Cognitive performance in the NFBC 1986 and ALSPAC (Study IV)

Cognitive performance was a primary outcome of interest for the fourth research question and this was measured using data from the NFBC 1986 and the ALSPAC. Academic performance at age 16 years was the cognitive outcome of interest for this research question using the NFBC 1986. The National Application Register for Upper Secondary Education provided information on academic performance based on nationally comparable grades of the final assessment of basic education (n=9162/9479). As we were interested in predictors of poorer performance, the results were categorised to compare those with performance >1 standard deviation below the mean with all other participants.

Cognitive performance from the ALSPAC was a primary outcome of interest for the fourth research question. This was measured at three time points in this study: general intelligence at age 15 years, academic performance at age 16 years.
and executive performance at age 17 years. ALSPAC participants were invited to follow-up at about age 15 years. During this follow-up, they completed the Wechsler Abbreviated Scale of Intelligence (WASI), a measure of general intelligence (n=5,260) (Hays, Reas, & Shaw, 2002). Academic performance was measured at age 16 years using overall points score, derived from the General Certificate in Secondary Education (GCSE) or equivalent exam. Data on academic performance was provided by the United Kingdom Department of Education. Participants were invited to follow-up at about age 17 years, at which point they completed the N-back and Probability Reversal tests. The N-back task measures working memory (K. M. Miller, Price, Okun, Montijo, & Bowers, 2009) and we utilised target identification accuracy on the 2-back task for this test. Probability Reversal measures ability to adapt to specific contingencies and we utilised latency in stage 2 for this test, which was log-transformed for normal distribution. As we were interested in predictors of poorer performance, the results of all these tests were categorised to compare those with performance >1 standard deviation below the mean with the remaining group with better performance.

4.2.3 Primary exposures of interest

The primary exposures of interest varied according to the research question. They included gene polymorphisms, trauma exposure, prenatal exposure to maternal cigarette smoking and metabolic measures.

Genetic measures and traumatic experiences in the ABD and CT studies (Study I)

The primary exposures of interest for research question 1 were polymorphisms at COMT (rs4680) and BDNF (rs6265), along with traumatic experiences. Participants provided saliva samples for genetic analysis. Of the 212 ABD participants who attended for interview, 168 (79%) provided genetic samples. In this group, there was insufficient DNA for analysis in 45 individuals, resulting in a final ABD sample of 123 for analysis. Of the 211 CT participants who attended for interview, 169 (80%) provided genetic samples. In this group there was insufficient DNA for analysis in 55 individuals, resulting in a final CT sample of 114 for analysis. In some individuals there was insufficient DNA for one polymorphism but not for the other, resulting in a final total sample of 226
participants for analysis of COMT-Val158Met (115 from ABD study and 111 from CT study) and 222 participants for analysis of BDNF-Val66Met (116 from ABD study and 106 from CT study).

The COMT rs4680 and BDNF rs6265 polymorphisms were genotyped from extracted DNA using Taqman® SNP genotyping assays on a 7900HT sequence detection system (Applied Biosystems). The call rate for the Taqman genotyping was >95% and the samples were in Hardy-Weinberg equilibrium (p>0.05). Based on the findings of previous studies, polymorphism genotypes were converted into binary variables for ease of analysis and interpretation. Based on research suggesting gene-environment associations between Val-Val and both transient psychotic experiences and schizotypal traits (Savitz, Van Der Merwe, Newman, Stein, & Ramesar, 2010; Stefanis, Henquet, et al., 2007), the COMT-Val158Met polymorphism was categorised as either Val-Val or Met-Met/Val-Met. Based on the previous finding of a gene environment association with psychotic experiences in Met carriers (Alemany et al., 2011), the BDNF-Val66Met polymorphism was categorised as either Val-Val or Met-Met/Val-Met.

In both studies, history of traumatic experiences was assessed at interview of both parent and child. The parent and child were both asked about instances of physical abuse, sexual abuse and exposure to domestic (interparental) violence. Based on previous study using the same data (Kelleher et al., 2008), where either the child or the parent reported these as present, this was classified as exposure to childhood trauma, a binary variable.

**Genetic measures in the Oulu Brain and Mind 1 sample (Study II)**

The primary exposures of interest for research question 2 were two polymorphisms at DRD2 and psychosis risk as defined with the SIPS for the Oulu Brain and Mind 1 sample (see above). The two candidate polymorphisms, rs1800497 and rs6277, were selected based on previous associations with schizophrenia and related phenotypes (Allen et al., 2008; Betcheva et al., 2009; Bolton et al., 2010; Parsons et al., 2007; Söderqvist, Matsson, Peyrard-Janvid, Kere, & Klingberg, 2013). Of the 182 eligible participants who provided samples, there was sufficient DNA for analysis for 158 individuals for rs1800497 and for 157 individuals for rs6277.

Genotyping was performed at the Institute for Molecular Medicine Finland with Sequenom Mass array technology (Sequenom, San Diego, California). The call rate for genotyping was >95% and the samples were in Hardy-Weinberg
equilibrium (P>0.05). Based on the findings of previous studies (Chien et al., 2013; Doll et al., 2011; Sakurai et al., 2013), the SNP rs6277 was analysed as a continuous variable with those with the TT genotype as the baseline group. Similarly, based on previous studies regarding the rs1800497 SNP (Berryhill et al., 2013; Bolton et al., 2010; Hirvonen et al., 2009; McAllister et al., 2005), those with any T allele (homozygous or heterozygous) were compared with the baseline CC group.

**Prenatal exposure to maternal cigarette smoking (PEMCS) in the Oulu Brain and Mind 2 sample (Study III)**

Prenatal exposure to maternal cigarette smoking (PEMCS) status was determined prospectively for all participants in the NFBC 1986. Mothers were asked about their smoking behaviour during antenatal clinic attendance. For the purpose of this study, smoking status was defined as continuing exposure to one or more cigarettes per day after the second month of pregnancy. The non-exposed group comprised offspring of mothers who had never smoked. In order to consider dose-response relationships, we used antenatal clinic information to classify smoking in pregnancy as 1-9 cigarettes or 10 or more cigarettes.

**Adolescent metabolic measures (Study IV)**

Adolescent metabolic markers were the exposures of interest for the fourth research question. This was measured in both the NFBC 1986 and ALSPAC. Nuclear Magnetic Resonance (NMR) spectroscopy has been extensively used in large-scale epidemiological studies to analyse patterns of metabolic measures in body fluids (Auro et al., 2014; Fischer et al., 2014; Mahendran et al., 2013; Würtz et al., 2015; Würtz et al., 2016). The precise methodology is described elsewhere (Soininen et al., 2009; Soininen, Kangas, Würtz, Suna, & Ala-Korpela, 2015).

In brief, the NFBC 1986 participants provided serum samples at age 16 years, while ALSPAC participants provided plasma samples at ages 15 and 17 years. These were stored at -80C prior to biomarker profiling, which involved using a high-throughput NMR spectroscopy metabolomics platform to quantify over 70 metabolic measures (Soininen et al., 2015). These metabolic measures represent a broad molecular signature of systemic metabolism, including lipoprotein lipids.
and subclasses, lipoprotein size, fatty acids, ratios of fatty acid subclasses to total fatty acids, amino acids, glycolysis-related metabolites, ketone bodies and others.

Of the original sample of the NFBC 1986, 6,985 (74%) participated in the 16-year follow-up and 5,606 (59%) provided serum samples at that age. In the case of the ALSPAC, 9,985 were invited to follow-up at age 15 years, 5,253 attended and 3,366 (34% of invitees) provided plasma samples for NMR-based metabolomics. A further 10,101 were invited to follow-up at age 17 years, of whom 5,217 attended and 3,176 (31% of invitees) provided plasma samples for NMR-based metabolomics.

Metabolic measures with skewed distribution were normalised by log-transformation. All metabolic measures were z-transformed to examine the effect of each 1 standard deviation increase on the cognitive outcome.

4.2.4 Other covariates of interest

A range of covariates of interest were considered for this study. Sex was considered in for all research questions while others varied according to the specific research question.

Covariates for assessing the association between COMT and BDNF polymorphisms and psychotic experiences in the context of childhood trauma in the ABD and CT studies (Study I)

The covariates considered in the first study were sex, school grade and cannabis use. School grade was a categorical variable with four levels, one for each grade. The first two grades were recruited for the ABD study and the second two grades for the CT study. This variable therefore included the effects of both age and study group. The ABD and CT studies also recorded history of cannabis use and participant sex and these were included as potential confounders.

Covariates for assessing the association between DRD2 polymorphisms and cognitive performance in the context of psychosis risk in the Oulu Brain and Mind 1 study (Study II)

The covariates considered for the second research question were sex and participant education level. Educational level was recorded on the day of assessment for the Oulu Brain and Mind 1 sample. For the purposes of analyses,
this was categorised into three classes: less than nine school years, more than nine school years without exit examination and completion of school exit examination (Veijola et al., 2013).

Covariates for assessing the effect of prenatal exposure to maternal cigarette smoking and cognitive deficits in the context of adolescent mental health in the Oulu Brain and Mind 2 study (Study III)

The covariates considered for the third research question were sex, prenatal exposure to maternal use of alcohol, birth weight, smoking status at assessment and adolescent mental health status. Prenatal exposure to maternal use of alcohol was determined prospectively for all participants in the NFBC 1986, by asking mothers about their alcohol use during antenatal clinic attendance. The Oulu Brain and Mind 2 excluded participants whose mothers had consumed in excess of 4 units of alcohol per week. Alcohol use was classified as either present or absent. Birth weight was recorded at birth in kilograms. Smoking status at assessment was determined on the same day that other testing (including cognitive testing) was performed. This was converted into a binary variable comparing any current smoking to no current smoking.

Three adolescent mental health factors were considered as covariates and potential mediators for the third research question. These were adolescent psychosis risk (explained above), adolescent inattention and hyperactivity and adolescent other externalising behaviours. In addition to the PROD-screen to assess for psychosis risk (see above), participants in the NFBC 1986 were asked to complete other questionnaires recording current mental health symptoms. The SWAN rating scale, a self-assessed measure, was used to measure inattention and hyperactivity at 16 years of age (Swanson et al., 2001). The SWAN scale measures problems in inattention and hyperactivity over the previous month. Results were z-transformed for ease of interpretation and inattention and hyperactivity was treated as a continuous variable. The Youth Self Report (YSR) (Achenbach, 1991), a self-assessed measure, was used to measure other externalizing behaviours, including aggressive behaviour, rule-breaking behaviour and intrusive behaviour, over the previous 6 months. The resulting scores were log-transformed for normal distribution and then z-transformed for ease of interpretation. As for inattention and hyperactivity, other externalising behaviours were treated as a continuous variable.
Covariates for assessing the association between metabolites and cognitive deficits and psychosis risk in the NFBC 1986 and ALSPAC (Study IV)

The covariates considered for the fourth research question were sex, socioeconomic status and body mass index. In the case of the NFBC 1986, the educational attainment of the mother was used as a proxy for the socioeconomic status of adolescents. At the birth of the participant, mothers were asked about their own level of educational attainment. This was classified into four groups: (1) 0-8 years of primary education; (2) 9-10 years of primary education; (3) vocational school or college for at least 6 months and; (4) commenced university education. In the case of the ALSPAC, socioeconomic status was controlled for using the social class of the mother based on occupation. Information on maternal occupation was collected at 7 points between 12 weeks gestation and 3 years 11 months and the most recent full information was utilised to determine social class. This was classified as six groups: professional, managerial and technical, skilled non-manual, skilled manual, partly skilled, and unskilled. The variables for socioeconomic status in both cohorts were treated as continuous variables for the purposes of analyses. Height and weight were measured during clinical examination for both samples and this was converted into body mass index.

4.3 Statistical analyses

Statistical approaches used varied with the research question. Descriptive statistics were primarily Chi-squared tests and t-tests. Univariate and multivariate logistic or linear regression was mostly used to answer the specific research questions. All statistical analyses, unless otherwise stated, were conducted using Stata version 11.0.

4.3.1 Study I: COMT-Val158Met and BDNF-Val66Met, childhood adversity and psychotic experiences

The first research question considered whether specific candidate genes interacted with childhood trauma in their association with adolescent psychotic experiences.

Chi-squared tests were used to compare those who participated in interview and provided genetic samples and those who participated but did not. Differences
between those with versus without psychotic experiences were assessed using chi-
squared tests or Fisher’s exact test as appropriate.

Prior to conducting the main analyses, a power analysis was performed to test
if there was sufficient sample size to detect small, medium and large effect sizes.
By convention, $f^2 \geq 0.02$ is a small effect size, $f^2 \geq 0.15$ is a medium effect size and
$f^2 \geq 0.35$ is a large effect size (Cohen, 1988). Power analyses were performed to
measure power to detect small, medium and large interaction between the
polymorphisms and childhood adversity in predicting psychotic experiences with
the sample sizes present at $P=0.05$ (Soper, 2014). Following this, post-hoc power
analysis was also used to determine the power to measure the observed
interactions (Soper, 2014).

Based on the hypothesis that $\text{COMT}$ and $\text{BDNF}$ genotypes can moderate the
influence of childhood trauma on psychotic experiences, we tested whether
psychotic experiences would be predicted by an interaction between a gene
(either $\text{COMT}^{\text{Val158Met}}$ or $\text{BDNF}^{\text{-Val66Met}}$) and an environment (childhood
trauma). To do this, we first fitted a logistic regression model with psychotic
experiences as the outcome of interest. Controlling for sex, school grade and
cannabis use, we compared two logistic regression models for each specific gene
($\text{COMT}^{\text{Val158Met}}$ or $\text{BDNF}^{\text{-Val66Met}}$). Model 1, showing the main effect of
childhood trauma and the specific gene (either $\text{COMT}^{\text{Val158Met}}$ or $\text{BDNF}^{\text{-Val66Met}}$), was compared with model 2, which contained an interaction term
between childhood trauma and the specific gene, using the likelihood ratio test.
Where these tests suggested a gene-environment interaction, we examined the
stratified associations between childhood trauma and psychotic experiences in
each genotype group, using odds ratios and 95% confidence intervals.

4.3.2 Study II: DRD2 and cognition in those with and without
psychosis risk

The second research question considered whether specific candidate genes
interacted with psychosis risk in their association with cognition in early
adulthood.

Chi-squared tests were used to assess if SNP group was directly associated
with psychosis risk group, education status and sex.

Cognitive performance was our main outcome of interest. As outlined above,
principal components factor analysis was used to reduce the number of cognitive
outcomes down to three main cognitive factors.
As above, prior to conducting the main analyses, a power analysis was performed to test if there was sufficient sample size to detect small, medium and large effect sizes. Power analyses were performed to measure power to detect small, medium and large interaction between the polymorphisms and psychosis risk in predicting cognitive performance with the sample sizes present at $P=0.05$ (Soper, 2014). Following this, post-hoc power analysis was also used to determine the power to measure the observed interactions (Soper, 2014).

Prior to conducting the main analyses, a power analysis was performed to test if there was sufficient sample size to detect a medium effect size. By convention, $f^2 \geq 0.02$ is a small effect size, $f^2 \geq 0.15$ is a medium effect size and $f^2 \geq 0.35$ is a large effect size (Cohen, 1988). Power analysis using G*Power software found that 485 individuals would be needed to detect a small effect size ($f^2=0.02$), 68 individuals would be needed for a medium effect size ($f^2=0.15$), and 32 individuals would be needed for a large effect size ($f^2=0.35$ at 80% power. The study therefore had power for medium to large, but not small, effect sizes.

Based on the hypothesis that psychosis risk can moderate the influence of $DRD2$ genotypes on cognitive performance in young adults, we tested whether performance on each cognitive factor would be predicted by an interaction between psychosis risk and a SNP (either rs6277 or rs1800497). To do this, we first fitted a linear regression model with performance on each cognitive factor as the outcome of interest. Controlling for sex and education, we measured the association between each specific SNP (either rs6277 or rs1800497) and cognitive performance. One SNP, rs6277, was treated as a continuous variable to examine if increasing numbers of $C$ alleles were associated with cognitive performance. In the case of the other SNP, rs1800497, those with 1-2 $T$ alleles were compared with those with no $T$ allele. Where an association was observed, a model that also included psychosis risk (without interaction) was compared with a model that included psychosis risk with an interaction term with the SNP, using the likelihood ratio test. Where a SNP was associated with a cognitive factor, the magnitude of this association was measured by determining the Cohen’s $f^2$ value for each subgroup to clarify if associations were similar across these groups.

4.3.3 Study III: Prenatal exposure to maternal cigarette smoking and cognition in the context of mental health risks

The third research question considered whether prenatal exposure to maternal cigarette smoking (PEMCS) was associated with cognitive performance in young
adults, and whether this association was moderated by adolescent mental health factors, including psychosis risk.

Chi-squared tests and independent t-tests were used to compare those with PEMCS to those not exposed in their demographic characteristics (sex, history of prenatal alcohol exposure, current smoking status, birth weight), their adolescent mental health status (psychosis risk, inattention and hyperactivity and other externalising behaviours) and their young adult cognitive performance.

Cognitive performance was our main outcome of interest. Based on theory suggesting differences in associations according to sex, separate analyses were performed for males and females. Prior to conducting the main analyses, a power analysis was performed to test if there was sufficient sample size to detect small, medium and large effect sizes, as outlined above. In this case, power analyses were performed to measure power to detect small, medium and large effects of PEMCS on cognition in males and females separately with the sample sizes present at $P=0.05$ (Soper, 2014). Following this, post-hoc power analysis was also used to determine the power to measure the observed associations (Soper, 2014).

The associations between exposure to PEMCS and the outcome variables, cognitive test z-scores (for vocabulary, matrix reasoning, verbal fluency, pegboard test, Stroop test, PAL and MSST), were measured using hierarchical linear regression. Step 1 examined the sex-specific associations between PEMCS and cognitive outcomes using univariate linear regression. Where a sex-specific association with a cognitive test was found, this was further tested for an interaction between sex and PEMCS using Chi-square test for interaction (see below) and for a dose-response relationship using a non-parametric test for trend (command=nptrend). We then progressed to step 2 with the observed associations in step 1. Step 2 repeated the sex-specific linear regression in step 1 but controlled for birth weight, prenatal exposure to alcohol and current smoking status (Jacobsen et al., 2005). Step 3 aimed to examine if observed associations were mediated by adolescent mental health factors. These were individually added to and compared with the model in step 2.

The results of these hierarchical regression models were used to determine if there was mediation by mental health status. Prior to interpreting these results, the basic requirements for mediation were considered (Baron & Kenny, 1986): (1) confirm that PEMCS predicts cognitive performance using regression; (2) confirm that PEMCS predicts the potential mediating variables using regression; (3) confirm that inclusion of the mediating variable in a regression model with PEMCS and cognitive performance reduces/eliminates the previous effect. Where
a change in association was noted with inclusion, we confirmed mediation statistically using the Sobel test (Sobel, 1986).

Finally, where an association was observed in step 1 and step 2, we measured for interaction between PEMCS and adolescent mental health status in predicting this. This involved comparing a model that included each of the adolescent mental health factors (psychosis risk, inattention and hyperactivity and other externalising behaviours) with a model with an interaction term between PEMCS and this factor, using Chi-squared test for interaction.

4.3.4 Study IV: Adolescent metabolic measures and cognition and psychosis risk

The fourth research question considered whether adolescent metabolic measures were associated with cognitive performance and psychosis risk, cross-sectionally or longitudinally.

The outcomes of interest were poorer cognitive performance, as outlined above, and psychosis risk. As for the above research questions, power calculations were performed to test if there was sufficient sample size to detect small, medium and large effect sizes. Specifically, power analyses were performed to measure power to detect small, medium and large effects of one serum metabolite (lipids in extremely large very-low-density-lipoprotein) on academic performance in the NFBC 1986 and ALSPAC at \( P=0.05 \) (Soper, 2014). Following this, post-hoc power analysis was also used to determine the power to measure the observed associations (Soper, 2014). Due to the correlated nature of the data, principal component analysis was used to evaluate the appropriate number of independent tests to correct for multiple testing. In each cohort, 90% of the variance in the 70 measures was explained by at most 12 principal components. The \( P \)-value for statistical significance was therefore corrected to account for 12 independent tests using the Bonferroni method, resulting in \( P<0.004 \) being considered statistically significant.

Cross-sectional and longitudinal relationships were both under consideration in this research question. The temporal relationship between exposures and outcomes and the cross-sectional and longitudinal associations under review are therefore presented in figure 6. For the cross-sectional analyses, a logistic regression model was fitted for each outcome measure (academic performance at age 16 years in the NFBC 1986, psychosis risk at age 16 in the NFBC 1986, WASI performance at age 15 for the ALSPAC, executive skills performance at
age 17 years for the ALSPAC, and psychosis risk at age 17 years for the ALSPAC), using metabolic measures as the explanatory variable and controlling for sex (model 1). The resulting odds ratios reflect the association between increasing standard deviations of metabolic measures and poorer cognitive performance/higher psychosis risk. Where an association was observed at P<0.004 in model 1, we sequentially adjusted for socioeconomic status (model 2) and body mass index (model 3).

Fig. 6. Overview of cross-sectional and longitudinal measurements

For the longitudinal analyses, cognitive performance and psychosis risk were also the outcomes of interest and metabolic measures were the explanatory variables. Logistic regression models were fitted for each outcome (academic performance at age 16 years, executive function at age 17 years, psychosis risk at age 17 years) with metabolic measures taken at age 15 years as the explanatory variables of interest and controlling for sex (model 1). Once again, where an association was observed at P<0.004, we then adjusted sequentially for socioeconomic status (model 2) and body mass index (model 3).
5 Results

5.1 Study I: COMT-Val158Met and BDNF-Val66Met, childhood adversity and psychotic experiences

5.1.1 Characteristics of the ABD and CT samples

Those who provided usable genetic samples were broadly similar to those who did not (see table 6), though a higher proportion of males and a lower proportion of those in the highest school grade provided usable genetic samples. Among the sample, 21/237 (9%) reported childhood trauma, which included witness of domestic violence (13, 5.5%), childhood physical abuse (9, 3.8%) and childhood sexual abuse (4, 1.7%), with some experiencing multiple forms of trauma.

Table 6. Comparison of those with genetic data to those without genetic data

<table>
<thead>
<tr>
<th>Groups</th>
<th>Genetic data</th>
<th>( \chi^2 )</th>
<th>Df</th>
<th>P-value~</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No (n=208) (%)</td>
<td>Yes (n=237) (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>78 (38)</td>
<td>128 (62)</td>
<td>11.25</td>
<td>1</td>
</tr>
<tr>
<td>Female</td>
<td>127 (54)</td>
<td>109 (46)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>School grade</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5th grade</td>
<td>41 (43)</td>
<td>55 (57)</td>
<td>10.83</td>
<td>3</td>
</tr>
<tr>
<td>6th grade</td>
<td>64 (48)</td>
<td>68 (52)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7th grade</td>
<td>47 (37)</td>
<td>79 (63)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8th grade</td>
<td>49 (60)</td>
<td>33 (40)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Social class</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Class I/II</td>
<td>77 (39)</td>
<td>118 (61)</td>
<td>2.61</td>
<td>2</td>
</tr>
<tr>
<td>Class III/IV/V</td>
<td>50 (38)</td>
<td>81 (62)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Class IIIN/IV/V</td>
<td>12 (27)</td>
<td>33 (73)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Psychotic experience</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>177 (47)</td>
<td>200 (53)</td>
<td>0.11</td>
<td>1</td>
</tr>
<tr>
<td>Yes</td>
<td>30 (45)</td>
<td>37 (55)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Traumatic experiences</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>193 (48)</td>
<td>216 (53)</td>
<td>1.01</td>
<td>1</td>
</tr>
<tr>
<td>Yes</td>
<td>13 (37)</td>
<td>21 (62)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cannabis use</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>131 (37)</td>
<td>226 (63)</td>
<td>1.95</td>
<td>1</td>
</tr>
<tr>
<td>Yes</td>
<td>10 (47)</td>
<td>9 (47)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Df=degrees of freedom; ~P-values based on chi-squared test or Fisher’s exact test as appropriate; Bold=P<0.05
Table 7 presents the group characteristics of those with and without psychotic experiences. There were no statistically significant differences between these groups by sex, childhood trauma, cannabis use, COMT-Val158Met genotype or BDNF-Val66Met genotype. Psychotic experiences were less common in the older age groups (9% at 13-14 years vs. 29% at 10-11 years).

**Table 7. Comparison of cases (with psychotic symptoms) and controls, according to demographic factors, trauma and COMT and BDNF genotype**

<table>
<thead>
<tr>
<th>Risk factor (total number)</th>
<th>Psychotic symptoms</th>
<th>X²</th>
<th>Df</th>
<th>P-value~</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No (n=200) (%)</td>
<td>Yes (n=37) (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Sex (n=237)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>105 (82)</td>
<td>23 (18)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Female</td>
<td>95 (87)</td>
<td>14 (13)</td>
<td>1.17</td>
<td>1</td>
</tr>
<tr>
<td><strong>Age (n=235)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10-11 years</td>
<td>39 (71)</td>
<td>16 (29)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>11-12 years</td>
<td>53 (78)</td>
<td>15 (22)</td>
<td>0.79</td>
<td>1</td>
</tr>
<tr>
<td>12-13 years</td>
<td>76 (96)</td>
<td>3 (4)</td>
<td>16.92</td>
<td>1</td>
</tr>
<tr>
<td>13-14 years</td>
<td>30 (91)</td>
<td>3 (9)</td>
<td>4.82</td>
<td>1</td>
</tr>
<tr>
<td><strong>Exposed to trauma (n=237)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>184 (85)</td>
<td>32 (15)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Yes</td>
<td>16 (76)</td>
<td>5 (24)</td>
<td>1.18</td>
<td>1</td>
</tr>
<tr>
<td><strong>COMT genotype (n=226)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Met-Met/ Val-Met</td>
<td>134 (83)</td>
<td>27 (17)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Val-Val</td>
<td>55 (85)</td>
<td>10 (15)</td>
<td>0.06</td>
<td>1</td>
</tr>
<tr>
<td><strong>BDNF genotype (n=222)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Val-Val</td>
<td>130 (86)</td>
<td>22 (14)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Met-Met/ Val-Met</td>
<td>59 (84)</td>
<td>11 (16)</td>
<td>0.06</td>
<td>1</td>
</tr>
<tr>
<td><strong>Cannabis use (n=235)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>191 (85)</td>
<td>35 (15)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Yes</td>
<td>7 (78)</td>
<td>1 (22)</td>
<td>0.30</td>
<td>1</td>
</tr>
</tbody>
</table>

Df=degrees of freedom; ~P-values based on Fisher’s exact test

### 5.1.2 Gene-environment interaction between COMT-Val158Met and BDNF-Val66Met and childhood trauma with respect to psychotic experiences

Power analyses suggested sufficient power to observe medium and large effects for interaction in relation to childhood trauma, genotypes and psychotic experiences, but not small effects. Table 8 presents the a priori and post-hoc power calculations for all four primary hypotheses.
Table 8. Power calculations (a-priori and post-hoc) for main research hypotheses

<table>
<thead>
<tr>
<th>Hypotheses</th>
<th>Number of predictors</th>
<th>Sample size</th>
<th>A priori power calculations</th>
<th>Post-hoc power calculations</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Small effect</td>
<td>Medium effect</td>
</tr>
<tr>
<td>H1: COMT</td>
<td>1 (6-5)</td>
<td>223</td>
<td>0.291</td>
<td>0.996</td>
</tr>
<tr>
<td>H1: BDNF</td>
<td>1 (6-5)</td>
<td>218</td>
<td>0.284</td>
<td>0.995</td>
</tr>
<tr>
<td>H2: rs6277</td>
<td>2 (7-5)</td>
<td>155</td>
<td>0.186</td>
<td>0.945</td>
</tr>
<tr>
<td>H2: rs1800497</td>
<td>2 (7-5)</td>
<td>156</td>
<td>0.188</td>
<td>0.947</td>
</tr>
<tr>
<td>H3: males</td>
<td>1 (2-1)</td>
<td>132</td>
<td>0.284</td>
<td>0.982</td>
</tr>
<tr>
<td>H3: females</td>
<td>1 (2-1)</td>
<td>185</td>
<td>0.388</td>
<td>0.998</td>
</tr>
<tr>
<td>H4: NFBC</td>
<td>1 (2-1)</td>
<td>5343</td>
<td>1.000</td>
<td>1.000</td>
</tr>
<tr>
<td>H4: ALSPAC</td>
<td>1 (2-1)</td>
<td>2897</td>
<td>0.999</td>
<td>1.000</td>
</tr>
</tbody>
</table>

Small effect where f²=0.02; medium effect where f²=0.15; large effect where f²=0.35

H1 (Hypothesis 1): interaction between polymorphism (COMT-Val158Met, BDNF-Val66Met) and childhood trauma in predicting psychotic experiences, controlling for sex, school year and cannabis use

H2 (Hypothesis 2): interaction between DRD2 polymorphisms and risk in predicting vocabulary performance, controlling for sex,

H3 (Hypothesis 3): association between prenatal exposure to maternal cigarette smoking (PEMCS) and vocabulary performance

H4 (Hypothesis 4): association between serum metabolite (lipids in extremely large very-low-density lipoprotein and academic performance, controlling for sex, in the Northern Finland Birth Cohort 1986 (NFBC 1986) and Avon Longitudinal Study of Parents and Children (ALSPAC)

Table 9 presents the associations between childhood trauma and genotypes and psychotic experiences, without and with interaction, after controlling for sex, school grade and cannabis use. Neither the COMT-Val158Met nor the BDNF-Val66Met genotypes were associated with psychotic experiences in the models without interaction. The COMT-Val158Met model with an interaction term for gene X childhood trauma was borderline superior to the model without an interaction term on the likelihood ratio test (P=0.057). The interaction term itself was also borderline significant (P=0.063), suggesting further stratified analysis would be appropriate. These findings were not evident for the BDNF models (see table 9), where the model with interaction was not superior to that without on the likelihood ratio test (P=0.958).
Table 9. Results from hierarchical binary logistic regression models

<table>
<thead>
<tr>
<th>Models</th>
<th>OR (95% CI)</th>
<th>P-value</th>
<th>OR (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>COMT models (n=223)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abuse</td>
<td>3.17 (0.85, 11.81)</td>
<td>0.130</td>
<td>1.33 (0.23, 7.62)</td>
<td>0.749</td>
</tr>
<tr>
<td>COMT Val158Met Val/Val genotype</td>
<td>1.07 (0.45, 2.53)</td>
<td>0.874</td>
<td>0.79 (0.31, 2.06)</td>
<td>0.636</td>
</tr>
<tr>
<td>COMT Val158Met X trauma</td>
<td>-</td>
<td>-</td>
<td>17.16 (0.86, 344.25)</td>
<td>0.063</td>
</tr>
<tr>
<td><strong>BDNF models (n=218)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trauma</td>
<td>3.25 (0.90, 11.78)</td>
<td>0.073</td>
<td>3.18 (0.67, 15.00)</td>
<td>0.145</td>
</tr>
<tr>
<td>BDNF Val66Met Met-Met/Val-Met genotype</td>
<td>0.98 (0.42, 2.31)</td>
<td>0.970</td>
<td>0.98 (0.39, 2.43)</td>
<td>0.958</td>
</tr>
<tr>
<td>BDNF Val66Met genotype X abuse</td>
<td>-</td>
<td>-</td>
<td>1.07 (0.08, 14.92)</td>
<td>0.958</td>
</tr>
</tbody>
</table>

All models controlled for sex, school year (categorical) and cannabis use

OR=odds ratios; 95% CI=95% confidence interval

Following this, the associations between childhood trauma and psychotic experiences were examined in each COMT-genotype sub-group (see table 10). Childhood trauma was associated with psychotic experiences in those with the COMT-Val-Val genotype (OR=7.43, 95% CI: 1.12-49.11), but not in the COMT-Met-Met/Val-Met genotype (OR=0.81, 95% CI: 0.17-3.88).

Table 10. Association between childhood trauma and psychotic experiences, stratified by COMT-Val158Met group

<table>
<thead>
<tr>
<th>COMT-Val158Met variant (n=226)</th>
<th>Frequency of psychotic experiences</th>
<th>OR (95% CI)</th>
<th>P-value*</th>
<th>Test for homogeneity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No trauma</td>
<td>Trauma</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Val-Val</td>
<td>7/59</td>
<td>3/6</td>
<td>7.43 (1.12, 49.11)</td>
<td>0.04</td>
</tr>
<tr>
<td>Met-Met/Val-Met</td>
<td>25/147</td>
<td>2/14</td>
<td>0.81 (0.17, 3.88)</td>
<td>1.00</td>
</tr>
</tbody>
</table>

OR=odds ratio; 95% CI=95% confidence interval
*P-value calculated based on Fisher’s exact test
5.2 Study II: DRD2 and cognition in those with and without psychosis risk

The SNPs were not directly associated with psychosis risk group, education status or sex (see Table 11).

Table 11. Association between DRD2 SNP minor alleles and risk groups for a psychotic disorder, and gender and education

<table>
<thead>
<tr>
<th>Variable groups</th>
<th>rs6277 C allele^</th>
<th>rs1800497 T allele#</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR (95% CI)</td>
<td>P-value</td>
</tr>
<tr>
<td>Psychosis Risk group (n=157-8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Controls</td>
<td>1.00</td>
<td>N/A</td>
</tr>
<tr>
<td>Familial risk</td>
<td>0.87 (0.33-2.27)</td>
<td>0.773</td>
</tr>
<tr>
<td>Clinical risk</td>
<td>1.25 (0.39-3.97)</td>
<td>0.710</td>
</tr>
<tr>
<td>Sex (n=157-8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>1.00</td>
<td>N/A</td>
</tr>
<tr>
<td>Female</td>
<td>1.84 (0.78-4.34)</td>
<td>0.167</td>
</tr>
<tr>
<td>Education (n=156-7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elementary</td>
<td>1.00</td>
<td>N/A</td>
</tr>
<tr>
<td>High school</td>
<td>0.54 (0.22-1.34)</td>
<td>0.183</td>
</tr>
</tbody>
</table>

OR=odds ratio; 95% CI=95% confidence interval; N/A=not applicable
^As continuous variable; #Comparing those with 1-2 T alleles with those with 0 T alleles

The second research question was whether specific candidate genes interacted with psychosis risk in their association with cognition in early adulthood. Power analyses suggested sufficient power to detect medium-to-large effects in terms of an interaction between psychosis risk and DRD2 genotype in predicting vocabulary performance, but not a small effect (see table 8 above). Firstly, the direct associations between the SNPs and cognitive factor performance were examined, controlling for sex and education level. The C allele of rs6277 was associated with better performance in the verbal factor (P=0.003) but no difference in performance in the nonverbal factor (P=0.463) or the psychomotor factor (P=0.064) in the entire sample (see table 12). The presence of any T allele for rs1800497 was associated with better performance in the psychomotor factor (P=0.038) but no difference in performance in the verbal factor (P=0.539) or the non-verbal factor (P=0.417) (see table 12).
Table 12. Association between polymorphisms and cognitive outcomes, controlling for gender and education level, in the entire sample of those at risk for psychosis and population controls

<table>
<thead>
<tr>
<th>Cognitive variable</th>
<th>rs6277 Beta</th>
<th>rs6277 Effect size</th>
<th>P-value</th>
<th>rs1800497 Beta</th>
<th>rs1800497 Effect size (Cohen’s f²)</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Verbal factor performance</td>
<td>0.327</td>
<td>1.03</td>
<td>0.003</td>
<td>-0.102</td>
<td>N/A</td>
<td>0.539</td>
</tr>
<tr>
<td>Psychomotor factor performance</td>
<td>0.208</td>
<td>N/A</td>
<td>0.064</td>
<td>0.332</td>
<td>+0.055</td>
<td>0.038</td>
</tr>
<tr>
<td>Non-verbal factor performance</td>
<td>0.083</td>
<td>N/A</td>
<td>0.463</td>
<td>0.138</td>
<td>N/A</td>
<td>0.417</td>
</tr>
</tbody>
</table>

As associations were observed between the C allele of rs6277 and verbal factor performance and between any T allele at rs1800497 and psychomotor factor performance, models without interaction between genotype and psychosis risk were compared with models with interaction. There was no statistically significant interaction between the C-allele of rs6277 and psychosis risk in predicting performance on the verbal factor (P=0.255 on Chi-squared test for interaction). However, as psychosis risk contained three groups and this made interaction analysis difficult to achieve, associations between the C-allele and verbal factor performance were examined, stratified by psychosis risk group (see table 13). This illustrates that the C-allele was associated with better verbal factor performance among those with familial risk (Cohen’s f²=2.226, P=0.011) and among those with clinical risk (Cohen’s f²=3.989, P=0.014) but not among the control group. The stratified mean cognitive factor scores for each rs6277 genotype, unadjusted for sex or education, are presented in table 14.

Table 13. Associations between rs6277 minor allele and verbal factor performance and rs1800497 minor allele and psychomotor factor performance, according to risk type for psychosis

<table>
<thead>
<tr>
<th>SNP and cognitive factor by risk group</th>
<th>Beta</th>
<th>Effect size (Cohen’s f²)</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>rs6277 and verbal performance factor</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Controls</td>
<td>0.081</td>
<td>+0.051</td>
<td>0.649</td>
</tr>
<tr>
<td>Familial risk</td>
<td>0.478</td>
<td>+2.226</td>
<td>0.011</td>
</tr>
<tr>
<td>Clinical risk</td>
<td>0.592</td>
<td>+3.989</td>
<td>0.014</td>
</tr>
<tr>
<td>rs1800497 and psychomotor factor performance</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Controls</td>
<td>-0.053</td>
<td>-0.121</td>
<td>0.822</td>
</tr>
<tr>
<td>Familial risk</td>
<td>0.838</td>
<td>+0.564</td>
<td>0.002</td>
</tr>
<tr>
<td>Clinical risk</td>
<td>0.351</td>
<td>+0.466</td>
<td>0.401</td>
</tr>
</tbody>
</table>

Bold=P<0.05

There was a statistically significant interaction between the presence of any T-allele at rs1800497 and psychosis risk in predicting performance on the
psychomotor factor ($P=0.049$ on Chi-squared test for interaction). The associations between any $T$-allele at rs1800497 and psychomotor factor performance, stratified by psychosis risk group, are presented in table 13. One or more $T$-allele at rs1800497 was associated with strongly poorer psychomotor factor performance among those with familial risk ($\text{Cohen’s } f^2=0.564, P=0.002$), but not among those with clinical risk or among controls (see table 13 for full details). The stratified mean cognitive factor scores for each rs1800497 genotype, unadjusted for sex or education, are presented in table 14.

Table 14. Mean performance scores by genotype, unadjusted for gender or education

<table>
<thead>
<tr>
<th>Risk group and SNP Variant (group number)</th>
<th>Verbal performance mean (95% CI)</th>
<th>Psychomotor performance mean (SD)</th>
<th>Non-verbal performance mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>rs6277 controls</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$TT$ (18)</td>
<td>0.34 (-1.35, 1.71)</td>
<td>0.04 (-0.96, 1.47)</td>
<td>0.18 (-1.16, 1.44)</td>
</tr>
<tr>
<td>$CT$ (34)</td>
<td>-0.20 (-2.49, 3.02)</td>
<td>-0.14 (-1.83, 4.07)</td>
<td>0.07 (-2.45, 2.10)</td>
</tr>
<tr>
<td>$CC$ (10)</td>
<td>0.19 (-0.96, 1.80)</td>
<td>0.02 (-1.83, 1.20)</td>
<td>-0.39 (-1.68, 1.33)</td>
</tr>
<tr>
<td>rs6277 familial risk</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$TT$ (19)</td>
<td>0.35 (-0.80, 3.27)</td>
<td>0.33 (-1.86, 2.15)</td>
<td>-0.20 (-2.07, 1.27)</td>
</tr>
<tr>
<td>$CT$ (27)</td>
<td>-0.40 (-2.16, 1.75)</td>
<td>-0.09 (-1.96, 2.82)</td>
<td>-0.20 (-2.15, 1.45)</td>
</tr>
<tr>
<td>$CC$ (10)</td>
<td>-0.07 (-1.50, 1.86)</td>
<td>-0.08 (-0.97, 1.07)</td>
<td>0.23 (-1.54, 1.17)</td>
</tr>
<tr>
<td>rs6277 clinical risk</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$TT$ (13)</td>
<td>0.55 (-0.73, 2.23)</td>
<td>0.22 (-0.88, 1.60)</td>
<td>0.58 (-0.82, 1.76)</td>
</tr>
<tr>
<td>$CT$ (20)</td>
<td>-0.10 (-1.32, 1.99)</td>
<td>0.24 (-1.36, 3.76)</td>
<td>-0.11 (-2.60, 1.59)</td>
</tr>
<tr>
<td>$CC$ (5)</td>
<td>-0.62 (-1.26, 0.31)</td>
<td>-0.52 (-0.96, 0.64)</td>
<td>0.86 (0.29, 1.58)</td>
</tr>
<tr>
<td>rs1800497 controls</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$CC$ (44)</td>
<td>0.12 (-1.84, 3.02)</td>
<td>-0.03 (-1.83, 4.07)</td>
<td>0.03 (-2.45, 2.10)</td>
</tr>
<tr>
<td>$CT$ (17)</td>
<td>-0.21 (-2.49, 1.71)</td>
<td>-0.13 (-1.83, 1.71)</td>
<td>-0.07 (-2.16, 1.02)</td>
</tr>
<tr>
<td>$TT$ (2)</td>
<td>0.03 (0.02, 0.04)</td>
<td>-0.44 (-0.82, -0.06)</td>
<td>1.02 (0.98, 1.07)</td>
</tr>
<tr>
<td>rs1800497 familial risk</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$CC$ (41)</td>
<td>-0.05 (-2.01, 3.27)</td>
<td>-0.18 (-1.96, 1.32)</td>
<td>-0.14 (-2.09, 1.45)</td>
</tr>
<tr>
<td>$CT$ (13)</td>
<td>-0.26 (-2.16, 0.98)</td>
<td>0.53 (-1.44, 2.82)</td>
<td>-0.12 (-2.15, 1.11)</td>
</tr>
<tr>
<td>$TT$ (2)</td>
<td>0.32 (-0.06, 0.70)</td>
<td>1.69 (1.63, 1.75)</td>
<td>0.15 (-0.44, 0.73)</td>
</tr>
<tr>
<td>rs1800497 clinical risk</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$CC$ (26)</td>
<td>0.05 (-1.32, 2.23)</td>
<td>0.03 (-1.36, 3.57)</td>
<td>0.17 (-2.80, 1.59)</td>
</tr>
<tr>
<td>$CT$ (11)</td>
<td>0.03 (-0.73, 1.80)</td>
<td>0.38 (-1.14, 3.76)</td>
<td>0.32 (-1.87, 1.51)</td>
</tr>
<tr>
<td>$TT$ (1)</td>
<td>0.49 (N/A)</td>
<td>0.25 (N/A)</td>
<td>1.76 (N/A)</td>
</tr>
</tbody>
</table>

SNP=single nucleotide polymorphism; 95% CI= 95% confidence interval
5.3 Study III: prenatal exposure to maternal cigarette smoking and cognition in the context of adolescent mental health

The third research question considered whether prenatal exposure to maternal cigarette smoking (PEMCS) was associated with young adult cognitive performance, particularly in the context of adolescent mental health, including psychosis risk.

The characteristics of those with PEMCS and those not exposed are presented in table 15. In brief, there were no differences between those with PEMCS and those not exposed in terms of sex or cognitive performance, though there was a trend towards poorer vocabulary performance in those with PEMCS (P=0.066). Those with PEMCS were more likely to be current smokers (P=0.004), to have had prenatal exposure to alcohol (P<0.001) and to have had a lower birth weight (P<0.001). They had higher inattention and hyperactivity scores (P<0.001) and higher other externalising behaviour score (P<0.001), while they had borderline more adolescent psychosis risk (P=0.064).

Table 15. Prenatal exposure to maternal cigarette smoking (PEMCS) and demographic characteristics, cognitive score and potential mediating factors

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No PEMCS</th>
<th>PEMCS</th>
<th>Test statistic*</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographic factors</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male sex</td>
<td>98/253 (39%)</td>
<td>95/218 (44%)</td>
<td>1.136</td>
<td>0.287</td>
</tr>
<tr>
<td>Smoking at 26-27 years</td>
<td>80/253 (32%)</td>
<td>97/218 (45%)</td>
<td>8.275</td>
<td>0.004</td>
</tr>
<tr>
<td>Prenatal alcohol exposure</td>
<td>19/249 (8%)</td>
<td>54/217 (25%)</td>
<td>26.129</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Birth weight (kg)</td>
<td>3.643</td>
<td>3.497</td>
<td>3.404</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cognitive z-scores</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vocabulary</td>
<td>0.079</td>
<td>-0.091</td>
<td>1.842</td>
<td>0.066</td>
</tr>
<tr>
<td>Matrix reasoning</td>
<td>0.054</td>
<td>-0.063</td>
<td>1.273</td>
<td>0.204</td>
</tr>
<tr>
<td>Verbal fluency</td>
<td>0.027</td>
<td>-0.031</td>
<td>0.628</td>
<td>0.530</td>
</tr>
<tr>
<td>Pegboard</td>
<td>0.036</td>
<td>-0.042</td>
<td>0.846</td>
<td>0.398</td>
</tr>
<tr>
<td>Stroop</td>
<td>0.011</td>
<td>-0.013</td>
<td>0.251</td>
<td>0.802</td>
</tr>
<tr>
<td>PAL</td>
<td>0.039</td>
<td>-0.052</td>
<td>0.979</td>
<td>0.328</td>
</tr>
<tr>
<td>MSST</td>
<td>-0.049</td>
<td>0.052</td>
<td>1.036</td>
<td>0.301</td>
</tr>
<tr>
<td>Adolescent mental health status</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inattention/hyperactivity (SWAN Z-score)</td>
<td>-0.170</td>
<td>0.203</td>
<td>3.720</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PEs</td>
<td>69/229 (30%)</td>
<td>74/191 (39%)</td>
<td>3.440</td>
<td>0.064</td>
</tr>
<tr>
<td>Other externalizing (YSR Z-score)</td>
<td>-0.185</td>
<td>0.208</td>
<td>4.072</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

PAL=Paired Associates Learning; MSST=Modified Stop Signal Test; SWAN=Strengths and Weaknesses of ADHD symptoms and normal behaviour; PEs=Psychotic Experiences; YSR=Youth Self Report
\*Test statistic is T-value or Chi-square value as appropriate; Bold=P<0.05
5.3.1 PEMCS and cognitive performance in males and females

Power analyses (see table 8) suggested sufficient power to detect medium-large effects but not small effects, though there was reasonable power (0.626) to detect the vocabulary associations observed in males. Full sex-specific associations are presented in table 16. There were no observed associations in females. PEMCS in males was associated with a small effect towards poorer performance in vocabulary ($f^2=0.05$, beta coefficient=-0.444, 95% CI: -0.783, -0.104) and matrix reasoning ($f^2=0.04$, beta coefficient=-0.379, 95% CI: -0.711, -0.047). Chi-squared tests for interaction provided evidence that sex and PEMCS interact in their association with vocabulary performance (Chi square=6.75, $P=0.009$) and provided weaker evidence that sex and PEMCS interact in their association with matrix reasoning (Chi-square=3.27, $P=0.071$). There was evidence for a dose-response trend in the relationship between PEMCS and matrix reasoning in males ($Z=2.89$, $P=0.004$) but insufficient evidence to support a dose-response trend for the relationship between PEMCS and vocabulary in males ($Z=1.60$, $P=0.109$).

Table 16. Prenatal exposure to maternal cigarette smoking and cognitive outcomes in adulthood (vocabulary, matrix reasoning, verbal fluency, pegboard test, Stroop test, PAL and MSST test), according to sex

<table>
<thead>
<tr>
<th>Cognitive test</th>
<th>Males (n=132)*</th>
<th>Females (n=181)$</th>
<th>Beta Coefficient (95% CI)</th>
<th>P-Value</th>
<th>Beta Coefficient (95% CI)</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vocabulary</td>
<td>-0.444 (-0.783, -0.104)</td>
<td>0.011</td>
<td>0.123 (-0.150, 0.396)</td>
<td>0.375</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Matrix reasoning</td>
<td>-0.379 (-0.711, -0.047)</td>
<td>0.026</td>
<td>0.026 (-0.265, 0.316)</td>
<td>0.863</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Verbal fluency</td>
<td>-0.256 (-0.615, 0.102)</td>
<td>0.160</td>
<td>-0.058 (-0.350, 0.233)</td>
<td>0.692</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pegboard</td>
<td>-0.068 (-0.339, 0.203)</td>
<td>0.621</td>
<td>-0.164 (-0.385, 0.057)</td>
<td>0.145</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stroop</td>
<td>-0.143 (-0.472, 0.186)</td>
<td>0.392</td>
<td>0.083 (-0.199, 0.366)</td>
<td>0.562</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PAL</td>
<td>-0.232 (-0.592, 0.128)</td>
<td>0.204</td>
<td>0.014 (-0.296, 0.324)</td>
<td>0.929</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MSST</td>
<td>-0.092 (-0.416, 0.234)</td>
<td>0.578</td>
<td>0.023 (-0.319, 0.364)</td>
<td>0.896</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

95% CI=95% confidence interval; PAL=Paired Associates Learning; MSST=Modified Stop Signal Test

*Except for MSST, where n=118; $Except for MSST, where n=166

We then progressed to step 2 with the observed associations between PEMCS and vocabulary and matrix reasoning in males observed in step 1. Controlling for prenatal exposure to alcohol, birth weight and current smoking status, PEMCS continued to show a similar association with vocabulary performance (coefficient=-0.456, 95% CI: -0.789, -0.122). Controlling for the same covariates, PEMCS continued to show a similar association with matrix reasoning.
(coefficient=−0.380, 95% CI: -0.715, -0.046). Full details are presented in table 17.

Table 17. Effect of potential mediating factors on the relationship between prenatal exposure to tobacco and vocabulary and matrix reasoning in males (n=132)

<table>
<thead>
<tr>
<th>Model</th>
<th>Vocabulary Coefficient (95% confidence interval)</th>
<th>P-value</th>
<th>Matrix reasoning Coefficient (95% confidence interval)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model 1*</td>
<td>-0.444 (-0.783, -0.104)</td>
<td>0.011</td>
<td>-0.379 (-0.711, -0.047)</td>
<td>0.026</td>
</tr>
<tr>
<td>Model 2$</td>
<td>-0.456 (-0.789, -0.122)</td>
<td>0.008</td>
<td>-0.380 (-0.715, -0.046)</td>
<td>0.026</td>
</tr>
<tr>
<td>Model 2 + psychosis risk</td>
<td>-0.460 (-0.794, -0.123)</td>
<td>0.007</td>
<td>-0.383 (-0.719, -0.048)</td>
<td>0.025</td>
</tr>
<tr>
<td>Model 2 + inattention and hyperactivity Z-score</td>
<td>-0.382 (-0.730, -0.034)</td>
<td>0.032</td>
<td>-0.300 (-0.648, 0.048)</td>
<td>0.091</td>
</tr>
<tr>
<td>Model 2 + other externalizing behaviour Z-score</td>
<td>-0.527 (-0.862, -0.192)</td>
<td>0.002</td>
<td>-0.395 (-0.737, -0.053)</td>
<td>0.024</td>
</tr>
</tbody>
</table>

*: Model 1 coefficient is association between prenatal exposure to tobacco and vocabulary or matrix reasoning in males
$: Model 2 coefficient is association between prenatal exposure to tobacco and vocabulary or matrix reasoning in males, controlling for prenatal exposure to alcohol in pregnancy, birth weight and current smoking status

5.3.2 Mediation by adolescent mental health status in boys

Step 3 of the analysis of PEMCS and cognition aimed to examine if observed associations in boys were mediated by adolescent mental health factors. These factors were individually added to and compared with the model in step 2 (see details in table 17). The three requirements for mediation are outlined in the methods section. Requirement (1) was met in the case of vocabulary and matrix reasoning in males, with poorer performance in those with PEMCS (see table 17 for details). Requirement (2) was broadly met in the case of all three mental health factors, with PEMCS showing a trend towards higher odds of psychosis risk in adolescence (P=0.089), and strong evidence for more inattention and hyperactivity in adolescence (P<0.001) and more other externalizing behaviours in adolescence (P<0.001). Requirement (3) involved a comparison of the results of steps 1 and 2 (above) with those of step 3 in the hierarchical multiple regression. These comparisons are presented in table 17.

There was minimal evidence regarding mediation by adolescent mental health status. There was no evidence that the association between PEMCS and either
vocabulary or matrix reasoning in males was mediated by either psychosis risk or other externalising behaviours. In the case of inattention and hyperactivity, there was evidence for partial mediation of the relationship with vocabulary (beta reduced from -0.456 to -0.383) and matrix reasoning (beta reduced from 0.380 to 0.300). However, Sobel test provided no evidence for mediation (vocabulary - 19.8% mediated, P=0.135; matrix reasoning – 22.6% mediated, P=0.137).

5.3.3 Interaction between PEMCS and adolescent mental health

In predicting vocabulary performance, there was no evidence for interaction between PEMCS and adolescent mental health factors, whether psychosis risk (P=0.798 for interaction), inattention and hyperactivity (P=0.231 for interaction), or other externalising behaviours (P=0.810 for interaction). Regarding matrix reasoning, there was no evidence for interaction between PEMCS and two of the mental health factors (P=0.919 for inattention and hyperactivity and P=0.810 for other externalizing behaviours). However, psychosis risk interacted with PEMCS in predicting matrix-reasoning performance (Chi-square=3.98, P=0.046). Specifically, PEMCS predicted poorer performance in matrix reasoning among those without psychosis risk in adolescence (beta = -0.606, 95% CI: -1.001, -0.205) but not among those with psychosis risk in adolescence (beta = -0.119, 95% CI: -0.624, 0.386).

5.4 Study IV: Adolescent metabolic measures and cognition and psychosis risk

The fourth research question considered whether adolescent metabolic measures marked risk for either cognitive performance or psychosis risk. The characteristics of participants in the NFBC 1986 and ALSPAC with regard to academic performance are presented in table 18. Higher academic performance was associated with female sex, more-educated or higher socioeconomic status mothers and lower body mass index.
### Table 18. Characteristics of the two cohorts

<table>
<thead>
<tr>
<th>Variable</th>
<th>NFBC 1986 academic scores</th>
<th>ALSPAC academic scores</th>
<th>P-value for difference (statistic)*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Higher</td>
<td>Lower</td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td>4,886</td>
</tr>
<tr>
<td>Male</td>
<td>3,536</td>
<td>1,110</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>(76%)</td>
<td>(24%)</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>3,988</td>
<td>428</td>
<td>&lt;0.001 (323.9)</td>
</tr>
<tr>
<td></td>
<td>(90%)</td>
<td>(10%)</td>
<td></td>
</tr>
<tr>
<td>Maternal education/social class</td>
<td></td>
<td></td>
<td>2,488</td>
</tr>
<tr>
<td>Least/classes III-M/IV/V</td>
<td>1,537</td>
<td>516</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>(75%)</td>
<td>(25%)</td>
<td></td>
</tr>
<tr>
<td>Middle/classes IV-NM</td>
<td>2,886</td>
<td>647</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(82%)</td>
<td>(18%)</td>
<td></td>
</tr>
<tr>
<td>Most/class I, II</td>
<td>2,123</td>
<td>151</td>
<td>&lt;0.001 (285.5)</td>
</tr>
<tr>
<td></td>
<td>(93%)</td>
<td>(7%)</td>
<td></td>
</tr>
<tr>
<td>Mean body mass index (SD)</td>
<td>21.1 (4.0)</td>
<td>21.4 (4.0)</td>
<td>0.044 (2.012)</td>
</tr>
</tbody>
</table>

NFBC 1986=Northern Finland Birth Cohort 1986; ALSPAC=Avon Longitudinal Study of Parents and Children

*Difference based on chi-squared test or t-test as appropriate with statistical value in brackets

### 5.4.1 Cross-sectional associations between metabolic measures and cognitive performance and psychosis risk

Power analyses suggested sufficient power to detect small to large cross-sectional effects in both the NFBC 1986 and ALSPAC samples (see table 8). A range of apolipoprotein and fatty acid-related metabolic measures were cross-sectionally associated with broad cognitive performance (see figures 7 and 8). In the NFBC 1986 sample, 18 metabolic measures were associated with academic performance at age 16, including lipids in lipoproteins, lipoprotein diameters, triglyceride measures and, particularly frequently, fatty acid ratios. Among these, LDL diameter, MUFA level, ratios of fatty acid subclasses (MUFA, PUFA, omega-6, omega-3, DHA, % unsaturation) to total fatty acids, citrate and creatinine remained associated with academic performance after controlling for maternal education and body mass index (see table 19). In the ALSPAC, nine metabolic measures were associated with general intelligence scores at age 15 years. Lipids...
in small HDL, LDL diameter, fatty acid levels (omega-3, DHA), and ratios of fatty acid subclasses (MUFA, omega-3, DHA) to total fatty acids showed continued significant (P<0.004) association after controlling for maternal social class and body mass index.

There were no statistically significant cross-sectional associations between any of the metabolic measures at age 17 years and Probability Reversal at age 17 years at the required P-value (P<0.004). Increasing standard deviations of the two DHA measures were associated with better performance on the N-back task. DHA level at age 17 years was associated in model 1 (OR=0.81, 95% CI: 0.70-0.93, P=0.004), borderline associated in model 2 (OR=0.79, 95% CI: 0.66-0.93, P=0.006) and associated in model 3 (OR=0.77, 95% CI: 0.65-0.92, P=0.003). Ratio of DHA to total fatty acids at age 17 years was associated with N-back performance in model 1 (OR=0.78, 95% CI: 0.68-0.90, P=0.001), model 2 (OR=0.76, 95% CI: 0.64-0.90, P=0.001), and model 3 (OR=0.76, 95% CI: 0.64-0.90, P=0.001).
Fig. 7. Cross sectional associations between metabolic measures and cognitive performance in late adolescence, adjusting for sex.
There were only weak cross-sectional associations between fatty acid levels and psychosis risk in the NFBC 1986 sample, and none were statistically significant at our threshold P-value (0.004) (see figures 9 and 10). In the ALSPAC sample, there were also weak cross-sectional associations between DHA levels and psychosis risk, though these did not reach our P-value threshold (see figure 10). Higher levels of one metabolic measure, acetate, were associated with lower risk for psychosis (OR=0.37, 95% CI: 0.16-0.57, P<0.001). However, though this association remained statistically significant on controlling for maternal social
class (OR=0.38, P=0.003), it was not statistically significant when BMI was added to the model (OR=0.42, P=0.008).

Fig. 9. Cross sectional associations between metabolic measures and psychosis risk in late adolescence, adjusting for sex
Fig. 10. Cross sectional associations between metabolic measures and psychosis risk in late adolescence, adjusting for sex
Table 19. Cross-sectional associations between metabolic measures and cognitive performance, controlling for covariates

<table>
<thead>
<tr>
<th>Metabolic measure</th>
<th>NFBC 1986 (n=5,510)</th>
<th>ALSPAC (n=3,022)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Model 1</td>
<td>Model 2</td>
</tr>
<tr>
<td>Lipids in small VLDL</td>
<td>1.13 (1.04, 1.22)</td>
<td>1.08 (0.99, 1.18)</td>
</tr>
<tr>
<td>Lipids in very large HDL</td>
<td>0.88 (0.81, 0.95)</td>
<td>0.92 (0.84, 1.00)</td>
</tr>
<tr>
<td>Lipids in small HDL</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>LDL diameter</td>
<td>0.85 (0.79, 0.93)</td>
<td>0.87 (0.80, 0.95)</td>
</tr>
<tr>
<td>HDL diameter</td>
<td>0.84 (0.78, 0.91)</td>
<td>0.89 (0.81, 0.97)</td>
</tr>
<tr>
<td>Serum TG</td>
<td>1.14 (1.05, 1.23)</td>
<td>1.08 (1.00, 1.18)</td>
</tr>
<tr>
<td>TG in VLDL</td>
<td>1.12 (1.04, 1.22)</td>
<td>1.07 (0.99, 1.17)</td>
</tr>
<tr>
<td>TG in LDL</td>
<td>1.15 (1.06, 1.25)</td>
<td>1.12 (1.02, 1.22)</td>
</tr>
<tr>
<td>PL in VLDL</td>
<td>1.12 (1.04, 1.21)</td>
<td>1.07 (0.99, 1.17)</td>
</tr>
<tr>
<td>MUFAs</td>
<td>1.18 (1.09, 1.27)</td>
<td>1.15 (1.05, 1.25)</td>
</tr>
<tr>
<td>Omega-3 FAs</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>DHA</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>MUFA/Total FA</td>
<td>1.24 (1.15, 1.34)</td>
<td>1.20 (1.11, 1.31)</td>
</tr>
<tr>
<td>PUFA/Total FA</td>
<td>0.80 (0.74, 0.86)</td>
<td>0.83 (0.76, 0.90)</td>
</tr>
<tr>
<td>Omega-6/Total FA</td>
<td>0.83 (0.77, 0.90)</td>
<td>0.87 (0.80, 0.94)</td>
</tr>
<tr>
<td>LA/Total FA</td>
<td>0.86 (0.80, 0.93)</td>
<td>0.89 (0.82, 0.97)</td>
</tr>
<tr>
<td>Omega-3/Total FA</td>
<td>0.80 (0.73, 0.87)</td>
<td>0.80 (0.73, 0.88)</td>
</tr>
<tr>
<td>DHA/Total FA</td>
<td>0.85 (0.79, 0.93)</td>
<td>0.87 (0.79, 0.95)</td>
</tr>
<tr>
<td>Unsaturated FA %</td>
<td>0.79 (0.73, 0.86)</td>
<td>0.82 (0.75, 0.89)</td>
</tr>
<tr>
<td>Citrate</td>
<td>0.82 (0.76, 0.89)</td>
<td>0.84 (0.77, 0.92)</td>
</tr>
<tr>
<td>Creatinine</td>
<td>0.87 (0.80, 0.95)</td>
<td>0.88 (0.81, 0.96)</td>
</tr>
</tbody>
</table>

VLDL=Very Low Density Lipoprotein; HDL=High Density Lipoprotein; LDL=Low Density Lipoprotein; TG=Triglycerides; PL=Phospholipids; FA=Fatty Acids; MUFA=Monounsaturated Fatty Acids; PUFA=Polyunsaturated Fatty Acids; DHA=Docosahexaenoic Acid

Bold=P<0.004
5.4.2 Longitudinal associations between metabolic measures and cognitive performance and psychosis risk

The longitudinal associations between metabolic measures and cognitive performance are presented in figures 11 and 12. In brief, there were cognitive associations with metabolic measures associated with apolipoproteins and fatty acids longitudinally. Nine measures at age 15 years were associated with academic performance at age 16 years (lipids in large HDL, LDL diameter, HDL diameter, MUFA, DHA, ratios of fatty acid subgroups to total fatty acids) (see table 20). Among these, four remained associated after controlling for maternal social class and body mass index: higher LDL diameter, MUFA level, ratios of MUFA and DHA to total fatty acids. Five fatty acid measures at age 15 years were associated with Probability Reversal performance at age 17 years (PUFA level, omega-6 level, linoleic acid level, omega-3 level and DHA level). All remained statistically significantly associated after controlling for maternal social class and body mass index. No metabolic measures at age 15 years were associated with N-back performance at 17 years and no metabolic measures at age 15 years were associated with psychosis risk at 17 years.
Fig. 11. Longitudinal associations between metabolic measures and cognitive performance in late adolescence, adjusting for sex.
Fig. 12. Longitudinal associations between metabolic measures and cognitive performance in late adolescence, adjusting for sex
Table 20. Longitudinal associations between metabolic measures and cognitive performance, controlling for covariates

<table>
<thead>
<tr>
<th>Metabolic measure</th>
<th>Academic scores (n=2,893)</th>
<th>PR latency (n=2,040)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Model 1</td>
<td>Model 2</td>
</tr>
<tr>
<td>Lipids in large HDL</td>
<td>0.75 (0.64, 0.89)</td>
<td>0.86 (0.70, 1.05)</td>
</tr>
<tr>
<td>LDL diameter</td>
<td>0.80 (0.68, 0.93)</td>
<td>0.70 (0.59, 0.84)</td>
</tr>
<tr>
<td>HDL diameter</td>
<td>0.76 (0.64, 0.89)</td>
<td>0.83 (0.68, 1.01)</td>
</tr>
<tr>
<td>MUFA</td>
<td>1.23 (1.07, 1.41)</td>
<td>1.36 (1.16, 1.60)</td>
</tr>
<tr>
<td>PUFA</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Omega-6</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Linoleic Acid</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Omega-3</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>DHA</td>
<td>0.76 (0.63, 0.92)</td>
<td>0.91 (0.73, 1.13)</td>
</tr>
<tr>
<td>MUFA/Total FA</td>
<td>1.35 (1.16, 1.56)</td>
<td>1.32 (1.11, 1.58)</td>
</tr>
<tr>
<td>PUFA/Total FA</td>
<td>0.79 (0.68, 0.91)</td>
<td>0.77 (0.65, 0.92)</td>
</tr>
<tr>
<td>Omega-3/Total FA</td>
<td>0.75 (0.63, 0.89)</td>
<td>0.84 (0.68, 1.03)</td>
</tr>
<tr>
<td>DHA/Total FA</td>
<td>0.70 (0.58, 0.84)</td>
<td>0.74 (0.59, 0.93)</td>
</tr>
</tbody>
</table>

HDL=High Density Lipoprotein; LDL=Low Density Lipoprotein; FA=Fatty Acids; MUFA=Monounsaturated Fatty Acids; PUFA=Polyunsaturated Fatty Acids; DHA=Docosahexaenoic Acid

Bold indicates P<0.004
6 Discussion

6.1 Theoretical implications

The results above have theoretical implications for their specific subject areas but also some shared theoretical implications for future research into risk factors for cognition and psychosis risk. The main findings for the individual studies are presented in table 21, including the relative strength of associations, strength of evidence against the null hypothesis, and the context of the findings. In brief, the strongest evidence was found for observed associations in study IV (specifically for metabolic measures and cognitive performance) and study III (PEMCS and cognitive performance in males). There was weaker evidence suggesting interactions between the T-allele of rs1800497 of DRD2 and psychosis risk in predicting psychomotor performance (study II). Evidence for interaction between the C-allele of rs6277 and psychosis risk in predicting verbal performance (study II) and between COMT-Val158Met and childhood trauma in predicting psychotic experiences (study I) have less robust evidence from results and should be interpreted more cautiously.
### Table 21. Comparison of evidence regarding the main findings of the studies

<table>
<thead>
<tr>
<th>Key findings for each study</th>
<th>N</th>
<th>Effect size</th>
<th>P-value</th>
<th>Other relevant evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Study 1</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Childhood trauma associated with psychotic experiences in those with COMT-Val158Met Val/Val genotype</td>
<td>65</td>
<td>OR=7.43</td>
<td>0.042</td>
<td>P=0.057 for interaction (n=266)</td>
</tr>
<tr>
<td><strong>Study 2</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C-allele of rs6277 associated with verbal performance in those with familial/clinical risk</td>
<td>56/38</td>
<td>0.480/</td>
<td>0.011/</td>
<td>P=0.255 for interaction (n=155)</td>
</tr>
<tr>
<td>T-allele of rs1800497 associated with psychomotor performance in those with familial risk</td>
<td>56</td>
<td>0.848</td>
<td>0.002</td>
<td>P=0.049 in test of interaction</td>
</tr>
<tr>
<td><strong>Study 3</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PEMCS associated with vocabulary/matrix reasoning in males</td>
<td>132</td>
<td>-0.444/</td>
<td>0.011/</td>
<td>P=0.009/0.071 in tests of interaction</td>
</tr>
<tr>
<td><strong>Study 4</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cross-sectional association between LDL diameter, ratios of MUFA/omega-3/DHA to total fatty acids and cognitive performance across two samples</td>
<td>5,510 + 3,022</td>
<td>See table</td>
<td>&lt;0.004</td>
<td>Replicated in 2 samples</td>
</tr>
<tr>
<td>Longitudinal association between LDL diameter, MUFA level, ratio of MUFA/DHA to total fatty acids and academic performance</td>
<td>2,893</td>
<td>See table</td>
<td>&lt;0.004</td>
<td>N/A</td>
</tr>
<tr>
<td>Longitudinal association between levels of PUFA, omega-6, linoleic acid, omega-3 and DHA and planning</td>
<td>2,040</td>
<td>See table</td>
<td>&lt;0.004</td>
<td>N/A</td>
</tr>
</tbody>
</table>

*Odds ratio; §Beta coefficient unless stated Beta coefficient unless stated
PEMCS=prenatal exposure to maternal cigarette smoking; LDL=low density lipoprotein; MUFA=monounsaturated fatty acids; DHA=Docosahexaenoic Acid; PUFA=polyunsaturated fatty acids
1Controlling for sex and school year; 2Controlling for alcohol in pregnancy, birth weight and current smoking status

### 6.1.1 Theoretical implications for candidate genes and psychotic experiences (Study I)

This study provides evidence that childhood trauma is associated with psychotic experiences in adolescents among those with a COMT-Val158Met Val-Val genotype but not in those with Val-Met or Met-Met genotypes.

These findings should be viewed in the context of existing theory regarding the genetic underpinnings of the extended psychosis phenotype. Among those with familial risk for psychosis, there may be high prevalence and low prevalence
genetic risks, interacting with environmental risk factors (Binbay et al., 2011). The genotype examined here (COMT-Val158Met) and the outcome variable (psychotic experiences) are both common. These findings may reflect the operation of a high prevalence genetic risk factor. However, the risk may only be operational along with a trigger environmental event.

The findings of associations between childhood trauma and psychotic experiences among those with the COMT-Val158Met Val-Val genotype but not others are consistent with existing evidence. A gene-environment interaction for the Val-allele of COMT-Val158Met and psychotic experiences has been reported in the case of cannabis (Vinkers et al., 2013). Similar to this study, the Val-allele has been associated with transient self-reported psychotic experiences under the stressful circumstances of army induction among Greek male conscripts (Stefanis, Henquet, et al., 2007). The Val-Val genotype has also been associated with more enduring schizotypal traits in the context of self-reported childhood trauma in an adult sample (Savitz et al., 2010). The findings reported here are therefore consistent with previous observations.

The findings of this study are consistent with higher psychosis reactivity to stress among those with Val alleles. It has been hypothesised that lower levels of background tonic dopamine, associated with higher COMT activity in Val carriers (Meyer-Lindenberg et al., 2005), may be associated with greater stress-induced phasic dopamine release in this group (Stefanis, Henquet, et al., 2007). This relatively hyper-dopaminergic state could facilitate abnormal salience to specific environmental stimuli, leading to erroneous interpretations in psychotic experiences (Kapur, 2003). This effect may also interact with another mechanism. The “neural diathesis-stress model” suggests that activation of the hypothalamus-pituitary-adrenal (HPA) axis by stress may trigger a cascade of events, including alterations in dopamine signalling (Walker, Mittal, & Tessner, 2008). This activation, alongside abnormal salience in those with the Val-Val genotype, may together increase risk for psychotic experiences. A further mechanism by which childhood trauma may be associated with psychotic experiences is DNA methylation (Klengel et al., 2013). For example, childhood abuse is associated with increased methylation of the glucocorticoid receptor promoter region, resulting in decreased expression (McGowan et al., 2009). Childhood trauma also has the potential to alter methylation at other genome sites. Methylation studies would be necessary to further explore this in the case of COMT-Val158Met and childhood trauma.
We found no association between BDNF genotype and psychotic experiences and no evidence for a gene-environment interaction between BDNF-Val66Met and childhood trauma in association with psychotic experiences. This study has therefore not replicated a previously observed interaction between the BDNF-Val66Met polymorphism and childhood abuse in predicting psychotic experiences in young adults (Alemany et al., 2011). This lack of replication may reflect that the interaction takes place over a longer time, i.e. that the interaction is not significant in adolescence itself but is more significant for those who show persistent psychotic experiences from adolescence into young adulthood. Psychotic experiences are more common in adolescence than in adulthood and their significance changes with time. Furthermore, BDNF is involved in neural plasticity and it may therefore moderate the effect of childhood trauma over a longer period of time. The different findings observed in this study may also reflect differences in the assessment of psychotic experiences (interview vs. questionnaire) or reflect the relatively small sample size in this sample.

6.1.2 Theoretical implications for candidate genes and psychosis risk for adult cognitive performance (Study II)

This study found differences in the associations between two polymorphisms at DRD2 and cognitive performance, depending on psychosis risk status, particularly in the case of the rs1800497 SNP. The presence of one or more T-alleles at rs1800497 was associated with poorer performance on a psychomotor factor only in those with familial risk for psychosis, but not among those at clinical risk for psychosis or population controls. This difference was also supported by testing for interaction. The C-allele at rs6277 was associated with better performance on a verbal cognitive factor in those with familial risk for psychosis or clinical risk for psychosis, but not among population controls. However, these observed differences were not evident in testing for interaction.

The presence of one or more copies of the rs1800497 T-allele was associated with poorer performance on a psychomotor factor, but only in the group with familial risk for psychosis. There are a number of possible explanations for this observation. Familial risk and genetic status manifestly exist prior to cognitive testing. This means that the direction of association is not from cognitive testing to familial risk for psychosis. It is possible that the T-allele has a causative role in affecting psychomotor function. There is evidence that the T-allele is associated with a preference for slower motor speed (Wiener, Lohoff, & Coslett, 2011) and
slower reaction time in visual working memory (Berryhill et al., 2013). The psychomotor factor in this study largely reflected performance on the pegboard test. It is interesting that associations were only observed in the family risk group. This may suggest that further underlying genetic risk factors are contributing to these deficits, along with the rs1800497 T-allele. One possible candidate is the COMT-Val158Met polymorphism, with some existing evidence suggesting differences in the association between rs1800497 and visual working memory according to COMT status (Berryhill et al., 2013). It remains to be seen if this is the case for psychomotor performance.

This study found that the C-allele at rs6277 was associated with better verbal factor performance, but only in those with risk (familial or clinical) for psychosis and not in controls. The explanation for these observations may differ between those with familial and clinical risk. While familial risk and genetic status predate cognitive testing, clinical risk status was ascertained at the same time as cognitive performance. In the case of those with clinical risk, it is therefore possible that, among those with the C-allele, poorer verbal performance may precede psychosis risk rather than the converse. Further longitudinal studies would be necessary to clarify this. It is also possible that the C-allele is affecting verbal performance in those with clinical and familial risk for psychosis. It is interesting that studies have associated the C-allele with poorer performance in executive function (Rodriguez-Jimenez et al., 2007) and working memory (H. Xu et al., 2007) in healthy samples. Though there were no associations in our healthy control group, it is perhaps surprising that the C-allele was associated with better verbal factor performance among those at risk for psychosis. This factor loaded performance in vocabulary, verbal fluency and digit span testing, covering significant working memory tasks in particular. Biologically, the CC genotype has been associated with decreased striatal binding at DRD2 (Hirvonen et al., 2009). The significance of the C-allele may differ in those at risk for psychosis, possibly reflecting interaction with another unidentified factor. One plausible biological mechanism is the observed differential response to stress among those with C alleles (White, Lawford, Morris, & Young, 2009). There is evidence that those at clinical high risk for psychosis experience more childhood trauma (Kraan, Velthorst, Smit, de Haan, & van der Gaag, 2015). It is therefore possible that higher rates of trauma in risk groups may interact with rs6277 genotype in impacting on development of verbal and working memory skills.

This study has observed interactions between SNPs, psychosis risk status and cognitive performance. To our knowledge, these have not been observed
elsewhere. Given increasing awareness of the importance of gene-environment (Uher, 2014) and gene-gene interactions (Buil et al., 2014), further study of interaction between genes and psychosis risk status could further inform understanding of the emergence of illness-associated deficits.

6.1.3 Theoretical implications for smoking in pregnancy as a risk factor for adult cognitive performance (Study III)

This study found that prenatal exposure to maternal cigarette smoking (PEMCS) was associated with poorer adult vocabulary and matrix reasoning performance in males but not in females. These associations in males were not significantly mediated by adolescent inattention and hyperactivity, other adolescent externalising behaviours or adolescent psychosis risk.

The findings here on cognition in males are consistent with existing evidence regarding very limited effects of PEMCS into adulthood and differences according to sex (Clifford et al., 2012). This study added to existing evidence by controlling for other important variables, such as socioeconomic status and use of other substances in pregnancy. PEMCS results in prenatal exposure to a variety of toxic compounds, including nicotine, along with reduced uterine blood flow with associated episodes of foetal hypoxia and malnutrition (Suzuki, Minei, & Johnson, 1980). However, significant brain development continues after birth, allowing multiple opportunities for adaptation to early insult, particularly if these insults are mild. This may explain the general lack of associations between PEMCS and cognition in our sample.

The persistence of associations between PEMCS and cognition into adulthood in males builds on previous observed associations in childhood and adolescence (Braun et al., 2009; Cornelius et al., 2001; Fried et al., 2003; Lambe et al., 2006). The results regarding differences between males and females in associations with cognitive performance also add to existing knowledge. While studies in children have suggested smaller effects of PEMCS on females than males (Clifford et al., 2012), the absence of on-going associations into adulthood in females has now been clearly shown. On the other hand, the results regarding the negative effects of PEMCS on aspects of male cognition replicate other adult male findings (Mortensen et al., 2005). Indeed, the magnitude of effect is also broadly similar to this study. Where this study found poorer performance by 0.44 standard deviations for vocabulary and 0.38 standard deviations for matrix reasoning, the previous study found that heavy smoking in pregnancy was
associated with reduced intelligence scores in young adult males of 0.41 standard deviations (Mortensen et al., 2005).

There are a number of potential mechanisms for the observed associations in males. One mechanism is suggested by the effect of PEMCS on behaviour during childhood and adolescence, with PEMCS associated with more conduct problems in males than females (Fergusson, Woodward, & Horwood, 1998; Wakschlag & Hans, 2002). This difference may reflect higher vulnerability in reward sensitivity and emotion regulation in response to PEMCS in boys (Wiebe et al., 2015). The differences in adults observed in this study may therefore reflect the long-term impact of these child differences on adult outcomes. Unmeasured factors, for example shared genetics or family environmental factors (Obel et al., 2016), may also impact on this difference. The latter has been suggested as a potential mediating factor in the relationship between PEMCS and cognitive outcomes (Zelazo et al., 2006).

Studying interactions in understanding how PEMCS may influence cognitive performance has the potential to help identify who may benefit most from intervention (Huijbregts et al., 2006). Although psychosis risk did not mediate the effect of PEMCS on adult cognition, it did interact with PEMCS in predicting performance in matrix reasoning. However, this finding was counter-intuitive, suggesting that PEMCS impacted on matrix reasoning in males without psychosis risk but not males with psychosis risk. This may reflect the exclusion of those later treated for serious mental illness from this study, resulting in the inclusion of only those with psychosis risk with particularly positive outcomes, a group that may therefore be particularly resilient. A further possibility is that the pathway to cognitive impairment in those with psychosis risk differs from the general population. Finally, it is possible that other risk factors overshadow the effect of PEMCS in those at risk for psychosis.

6.1.4 Theoretical implications for adolescent metabolic measures and cognition and psychosis risk (Study IV)

This study found that a number of metabolic measures are associated with cognitive performance but not with psychosis risk. Specifically, fatty acid metabolic measures and, to a lesser extent, apolipoprotein measures were associated with cognitive performance. Cross-sectional associations between LDL-diameter, ratio of MUFA to total fatty acids, ratio of omega-3 to total fatty acids, and ratio of DHA total fatty with general intelligence performance were
particularly strong as they were observed across both cohorts. The associations between LDL diameter, ratio of MUFA to total fatty acids and ratio of DHA to total fatty acids with general intelligence performance were also present longitudinally. There was also weaker evidence for other cross-sectional and longitudinal associations, including longitudinal associations between PUFA level, omega-6 level, linoleic acid level, omega-3 level and DHA level with executive function.

A range of fatty acid levels and ratios were associated on both cross-sectional and longitudinal analyses. The presence of cross-sectional and longitudinal associations across two cohorts adds significant weight to these results. While the observed associations in this study are not large, they are meaningful. There are a number of potential explanations for the findings. Firstly, the metabolic measures may play a causal role in adolescent cognitive development. However, using Bradford Hill’s criteria for causality, the evidence presented here is limited (Bradford Hill, 1965). Associations observed showed moderate strength and were consistent between studies. There were also some temporal associations. One plausible mechanism is omega-3 fatty acids could be impacting on general cognitive performance indirectly, via attention (Bos et al., 2015). The general pattern of associations was that higher ratios of polyunsaturated fatty acids were associated with better performance while higher ratios of monounsaturated fatty acids were associated with poorer performance. Long chain PUFAs are important in cell membrane structure and function. This role may be particularly important in adolescence, a time when psychiatric neurodevelopmental disorders associated with cognitive deficits (such as schizophrenia) begin to emerge.

A second possible explanation for the findings is that higher academic performance (or a factor for which academic performance is a proxy) may precede the metabolic findings. Thirdly, there may be lifestyle factors that are associated with academic performance and fatty acid ratios that are playing a causal role. Indeed, the pattern of fatty acids observed here has been noted in some other studies, particularly with regard to physical activity (Kujala et al., 2013). It may therefore be the case that we are observing a generally healthy metabolic profile associated with cognitive performance. Alternatively, we may be observing the effects of physical activity on cognitive performance, with the metabolic profile observed here being an intermediate step in that process or a marker of the process.

The findings regarding executive function are less consistent than those for general intelligence. There were cross-sectional, but not longitudinal, associations
for one test (N-back). There were longitudinal, but not cross-sectional, associations for the other test (Probability Reversal). Once again, fatty acid measures, particularly DHA, showed the most noteworthy effects. This may suggest that PUFA levels in mid-adolescence are particularly important in executive function. Given the variability in the findings, further replication is warranted.

One cross-sectional association was observed between acetate and psychosis risk in the ALSPAC. However, this finding was not evident in the NFBC sample or in the ALSPAC longitudinally. Other findings were weak and not consistent. However, it is interesting that fatty acid factors were again the main group with (weak) associations. There has been considerable interest in omega-3 supplements to prevent development of psychosis in those at clinical high risk for psychosis (Amminger et al., 2010; McGorry et al., 2016), while lower erythrocyte levels of DHA have been associated with poorer cognitive performance in those at clinical high risk for psychosis (Kim et al., 2014). One possible reason for differences in findings between the NFBC 1986 and the ALSPAC is differences in the measurement of psychosis risk. The PROD-screen is sensitive but not specific, with 28% of our sample endorsing 3 or more items. The PLIKS interview, on the other hand, was more specific for psychosis risk but the outcome was therefore rarer (only 5% of the ALSPAC group). Ideally studies would utilise the same measures to allow for potential replication.

6.1.5 General theoretical implications

The research presented in this study highlights some important general themes, including the need to consider that risks for cognition in those at psychosis risk may differ from the general population, the similarities and differences between risk factors for cognitive performance and psychosis risk, and the variety that exists within those judged “at risk” for psychosis.

The findings here suggest there are important differences in risk factors between those at risk for psychosis and the general population. Specific genes (e.g. DRD2) are more important for cognition in people at risk for psychosis. Alternatively, particular environmental exposures are less important for cognition in those at risk for psychosis. Further research is needed to explore differences in risk factors for those at risk for psychosis as these differences may be important in intervening in the earliest stages of illness.
Though some risk factors/markers are shared between cognition and psychosis risk, other risk factors/markers are not shared. This suggests that the neurodevelopmental process underpinning cognitive development differs from that of severe mental illness in important ways. Reducing risk factors for one of these will not necessarily reduce the prevalence of the other. In this study, \textit{DRD2} interacted with psychosis risk in predicting cognitive performance. It was a risk marker for cognitive performance only in this group with psychosis risk. Conversely, metabolic measures highlight risk for cognitive performance deficits but do not highlight the same level of risk for psychosis risk states. It appears that while some risk factors for adverse brain functional outcomes are shared, some are more specific to particular brain domains (cognition or tendency to psychosis).

This work further indicates that there are a variety of cognitive endophenotypes within the extended psychosis spectrum (Stefanis, Trikalinos, et al., 2007). We have observed differences within those at risk for psychosis according to specific genotypes. Specific \textit{COMT} genotypes interacted with traumatic experiences in childhood. Specific \textit{DRD2} genotypes were associated with differences in cognitive performance only in those at risk for psychosis. There are individuals with psychosis and psychosis risk with better cognitive performance as well as those with worse performance. For example, previous work in the Oulu Brain and Mind 1 sample, perhaps surprisingly, indicated that the risk groups did not differ in their neurocognitive performance from controls (Mukkala \textit{et al.}, 2011). This study highlights that variety within those at risk for psychosis may also be a factor in this. We have observed a group with poorer cognitive performance associated with \textit{DRD2} SNPs. There is also evidence for sub-groups with higher cognitive performance, for example in relation to the \textit{ZNF804A} gene in a sample with schizophrenia (Walters \textit{et al.}, 2010). Further exploration of cognitive endophenotypes within those at risk for psychosis could help to further classify psychosis and the pathway from risk to disorder and functional impairment.
6.2 Practical implications

The results of these studies have several implications, some specific to the individual research questions and some more general to the field. The practical implications of each study vary with the nature of the study and the strength of evidence from the results (see table 21 above). The strongest evidence was from study IV in the case of metabolic measures and cognition, with cross sectional and longitudinal findings across two large cohorts. There was also reasonably strong evidence for the association between PEMCS and general intelligence in young adult males (study III), and for the observed associations in study II for one of the DRD2 polymorphisms and psychomotor performance. The weakest evidence was for study I and for one of the polymorphisms and verbal performance in those with psychosis risk in study II. Comparing the strength of effect sizes observed in the studies is complicated by differences in the nature of the exposures and in the methods used. However, broadly speaking the weakest effect sizes were those observed between metabolic measures and cognition (study IV) and between PEMCS and cognition in young adult males study III), while the genetic associations showed stronger effect sizes. This is unsurprising given that metabolic measures studies were powered to detect smaller effect sizes.

6.2.1 Practical implications for candidate genes and psychotic experiences (Study I)

This study has identified a specific gene that may interact with an environmental exposure in association with psychotic experiences. Adolescent psychotic experiences index risk for a wide range of psychopathology, not limited to psychotic disorders (Fisher et al., 2013; Scott et al., 2009; Werbeloff et al., 2012; Wigman et al., 2012). These experiences are also associated with multi-morbid psychopathology (Kelleher, Keeley, et al., 2012) and with increased incidence of suicidal behaviour (Kelleher, Lynch, et al., 2012; Nishida et al., 2010; Saha et al., 2011). The finding that a specific polymorphism, COMT-Val158Met, is associated with psychotic experiences only alongside childhood trauma has practical implications. Psychiatrists do not routinely check COMT genotypes. Therefore, the finding highlights the importance of environmental exposures in the development of mental illness, even when they interact with a genetic risk. From a public health and child development perspective, the main implication is that efforts should be made to reduce childhood trauma and support children who
experience trauma. The findings here add to evidence that enquiring about psychotic experiences following trauma is appropriate (Kelleher, Keeley, et al., 2013). This may be particularly important where subtle signs of behaviour change, such as social withdrawal or functional decline, are evident. Further into the future, genetic testing at COMT-Val158Met may be helpful in identifying specific needs and risks for those who have experienced stress or trauma. For example, the presence of the COMT-Val158Met Val/Val genotype alongside trauma may warrant more assertive assessment for psychotic symptoms. In addition, a lower threshold of psychotic symptoms may be appropriate to commence treatment in the presence of the Val/Val genotype with trauma, for example commencing anti-psychotic medication where a person has a psychosis risk syndrome that appears to be deteriorating. However, currently there is insufficient evidence to perform such genotype testing.

6.2.2 Practical implications for candidate genes and psychosis risk for young adult cognition (Study II)

This study has identified one polymorphism at DRD2 that interacts with psychosis risk in association with cognitive performance in young adults and another that may interact with psychosis risk in association with cognitive performance in young adults. This finding has potential practical implications. Where psychosis risk is identified in the clinic, genetic assessment could inform predictions around functional prognosis. The findings of this study have identified one gene that can help this process but there are likely to be others. It remains too early to introduce such genetic testing into psychosis risk clinics but the findings here suggest there is potential for this in the future, particularly if further research replicates these findings and clarifies if there are treatment associations. However, as the cost of whole genome sequencing falls, candidate gene studies are not likely to be the approach taken. Calculation of polygene risk scores, which have shown associations with clinical and other outcomes in psychosis (McIntosh et al., 2013; Tesli et al., 2014), are more likely to be clinically useful.

6.2.3 Practical implications for smoking in pregnancy as a risk factor for adult cognitive performance (Study III)

This study has identified an early environmental exposure that is associated with adverse outcomes into early adulthood in the males. The findings have public
health implications, both in primary and secondary prevention. Primarily, smoking in pregnancy causes persistent harm into adulthood, harm that can be prevented by eliminating the behaviour. Further efforts should therefore be made to improve academic performance among males exposed to prenatal smoking.

6.2.4 Practical implications for adolescent metabolic measures and cognition and psychosis risk (Study IV)

This study found that adolescent metabolic measures, particularly fatty acid measures, were associated with cognitive performance in late adolescence. These findings currently have limited practical implications. However, with replication and further evidence for a causal association, the results could have a high practical value as they point towards lifestyle factors that may impact on healthy cognitive development.

6.2.5 General practical implications

The associations with psychosis risk and cognition observed in this study vary considerably in their type (genetic, environmental, biological markers), in their timing (at conception, during pregnancy or during adolescence) and in the strength of evidence for an association. They have practical implications both at the level of the clinic and at a public health level.

The genetic findings presented here are insufficiently strong to advocate for routine use of genetic testing in the clinic. However, they highlight that clinicians should consider screening more closely for psychotic experiences and psychosis risk where they identify childhood trauma. Assessment of young adults with psychosis risk should consider include cognitive function in their assessment, particularly as evidence accumulates that it has considerable prognostic importance (Seidman et al., 2010).

There are also public health implications, both in pregnancy and in childhood and adolescence. Further efforts are needed to reduce smoking in pregnancy (World Health Organization, 2013), in order to reduce the long-term morbidity associated with this preventable risk. Further efforts should also be made to reduce childhood trauma (Krug, Mercy, Dahlberg, & Zwi, 2002) and to support those exposed to these experiences.
6.3 Strengths and Limitations

6.3.1 COMT-Val158Met and BDNF-Val66Met, childhood adversity and psychotic experiences (Study I)

The study of COMT and BDNF has important strengths that add to its reliability and validity. Firstly, the ABD and CT studies used gold standard clinical interviews of both parent and child to ascertain psychotic experiences and childhood trauma, increasing study reliability. Furthermore, the assessments took place during childhood, relatively soon after the reported traumatic events, reducing recall bias and adding to study reliability. This is in contrast to much research in adults, where reported traumatic experiences were often many years before. A further strength of this study is that we have controlled for important potential confounders of a gene environment interaction, particularly cannabis use (Bendall, Jackson, Hulbert, & McGorry, 2008).

There were limitations that affected the reliability and validity of the study. Firstly, though the generalizability of the studies to other populations was improved by their recruitment from the general population of adolescents, it was limited by the relatively small sample size. Secondly, the reliability of the findings was limited by the borderline statistical significance for interaction between COMT genotype and childhood trauma. Chance is therefore a possible explanation for this interaction and the findings presented must be regarded as preliminary and in need of replication. Thirdly, psychotic experiences and trauma were assessed simultaneously, which could lead to some reporting bias and reduce reliability. It is also important because though traumatic events can precede psychotic experiences, psychotic experiences can also precede trauma, suggesting a bi-directional relationship (Kelleher, Keeley, et al., 2013). Data was not available to consider this issue here. A limitation that may affect validity was the sample ascertainment. The sampling methodologies resulted in recruitment of a relatively small number from larger surveys, opening up a risk of selection bias. However, those who participated in the ABD study had similar psychopathology scores on the SDQ to those who did not participate, while the CT study included a representative control group without significant SDQ psychopathology.
6.3.2 DRD2 and cognition in those with and without psychosis risk (Study II)

There are a number of study features that add to the reliability and validity of the study of the DRD2 polymorphisms and cognition. The sample was recruited from a birth cohort with prospective measurement of exposures and outcomes, reducing recall bias and increasing study reliability. The risk of confounding was reduced in this study because the sample was relatively homogenous in terms of age, cultural background and genetic context (Varilo & Peltonen, 2004). This further added to its reliability. The control group, who provided the reference ranges for neurocognitive scores, reflect a broader population than a healthy volunteer group. This adds to the real-world validity of the findings. Study validity was also increased due to the sample being representative of a subset of the general population. This was also the case for the family risk group, who were recruited from the general population rather than from relatives of clinic-attending groups. This reduces recruitment bias and adds to the validity of the findings.

There are limitations that may affect the reliability and validity of the study. Firstly, the generalizability of the finding regarding interaction is limited by the relatively small sample sizes and the higher attrition rates in some subgroups. Replication of findings would help to address this limitation. Secondly, the participation rate was quite low, leading to a risk of selection bias. The sample size was also relatively small, reducing study reliability, particularly for the genetic subgroups. For example the minor allele frequency for rs1800497 was quite low, though this was partly addressed by analysing minor alleles as a continuous variable. The psychosis clinical risk group was recruited from the population rather than being a help-seeking group, making them more difficult to compare with other psychosis clinical risk groups, who tend to be recruited from clinical centres. This reduces the validity of the findings for this group. Finally, the relatively genetically homogeneous nature of the population, though adding to the reliability of the findings, reduces generalizability and validity somewhat.

6.3.3 Smoking in pregnancy as a risk factor for adult cognitive performance (Study III)

Specific strengths add to the reliability and validity of findings in relation to smoking in pregnancy and adult cognition. Firstly, reliability was increased by careful consideration of confounding in the study design. In particular, the sample
was matched to reduce the possible confounding effects of parental socio-
-economic status or maternal education. Secondly, the sample has been followed
and data collected prospectively from birth, reducing recall bias and further
increasing reliability. This was particularly important in the case of factors that
occurred some years prior to this assessment, for example prenatal exposure to
maternal cigarette smoking and adolescent mental health factors, which are
particularly prone to recall bias (Coughlin, 1990). Thirdly, the sample included
large enough groups of both males and females to reliably test theories of sex-
specific effects. The validity of the study lies primarily in the fact that it was
drawn from a birth cohort. However, generalizability to other populations is
limited somewhat by inclusion and exclusion criteria, which resulted in a
generally healthier sample than the population in terms of both physical and
mental health, and by small differences in participation rates between those
exposed to smoking and those not exposed and between females and males. The
study was therefore representative of those who are generally healthier rather than
the entire population.

The reliability and validity of the study was limited in some ways. Firstly, the
sample size was too small to reliably detect small effects on cognitive domains in
males and females. However, our findings are consistent with previous studies.
Study of smaller effects requires study in a sample of 550 per group (Faul,
Erdfelder, Buchner, & Lang, 2009). As outlined above, the reliability was also
reduced somewhat by potential selection bias arising from small differences in
participation and attrition rates. Participants may have been healthier overall
(healthy participant bias), with findings therefore not reflecting the experience of
those with the worst outcomes. The exclusion criteria in this study reduce its
validity somewhat. The sample was relatively healthy in terms of mental health
and cognitive performance, making it more difficult to draw conclusions for other
groups. For example, we cannot comment on the role of PEMCS on intellectual
disability or cognitive performance in those with severe mental illnesses as those
with an IQ<70 and more severe mental illness were excluded.

6.3.4 Adolescent metabolic measures and cognition and psychosis
risk (Study IV)

The reliability and validity of findings in relation to adolescent metabolic
measures and cognition are strengthened by specific study strengths. The large
study numbers in both cohorts adds considerably to its reliability. Data on a large
range of factors was ascertained prospectively, addressing the risk of recall bias in longitudinal analyses and adding further to reliability. Using two cohorts from different genetic contexts and different social contexts, including with regard to diet reduced the chances of uncontrolled confounding and increased reliability. The validity of the results was increased significantly by both the use of two cohorts and the triangulation of cross-sectional and longitudinal analyses.

A number of limitations of this study impacted on reliability and validity. We could control for only a limited number of potential confounders, which may have reduced reliability. However, those chosen (maternal education, body mass index) at least partly address a wide variety of potential confounders such as diet and exercise levels. The main outcome of interest, academic performance, has limitations. It is a proxy for a broad range of cognitive processes (Rohde & Thompson, 2007), which may impact on its validity as a cognitive outcome. However, this could also be regarded as a strength, as academic achievement reflects a variety of personality and cognitive processes that are important for success into adulthood. In addition, this data was augmented with more specific measures of executive function, a key cognitive skill that advances rapidly during late adolescence.

6.3.5 Relative strengths and limitations between studies

As outlined above, each study had specific strengths and limitations. The studies of DRD2 and cognition (study II), PEMCS and cognition (study III) and metabolic measures (study IV) increased the reliability of their results by collecting much of their data prospectively. The study of COMT and BDNF and psychotic experiences (study I) and DRD2 and cognition (study II) increased outcome validity by including extensive clinical interviews, while the studies of PEMCS and cognition (study III) and metabolic measures (study IV) did this to a lesser extent. The study of metabolic measures (study IV) used two large population samples from different countries, which increased the generalizability of the findings.

There were differences in the limitations of the various studies. The studies of COMT and BDNF and psychotic experiences (studies I), DRD2 and cognition (study II) and PEMCS and cognition (study III) had relatively small numbers included and, to varying degrees, were not fully representative of the general population. This makes generalising the findings from these studies more difficult than is the case for the study of metabolic measures (study IV). Measurement of
mental health factors using questionnaires was less reliable in the study of PEMCS and cognition (study III) and in the NFBC component of the study of metabolic measures (study IV) than it was in the other studies.

6.4 Recommendations for future research

Future research into risk factors for cognitive deficits and psychosis risk is sorely needed. This study suggests that some risk factors for cognition may vary between the general population and those at risk for severe mental illness. Future research should further explore differences between these populations in terms of risk factors.

Future research should also examine how cognitive deficits and psychosis risk interact dynamically over the longer term.

6.4.1 COMT-Val158Met and BDNF-Val66Met, childhood adversity and psychotic experiences (Study I)

Future research could clarify if the associations with psychotic experiences observed here persist over a longer time period. Future research should also consider the treatment response of those with the Val-Val COMT-Val158Met genotype and traumatic experiences. For example, does this group respond better or worse to CBT for psychosis or to specific medications? Biological research could also help to better understand the molecular mechanisms of the observed gene-environment interaction. One candidate for research in this area is trauma-dependent DNA demethylation, which has been associated with increased stress-dependent gene transcription and long-term dysregulation of the stress hormone system (Klengel et al., 2013). Childhood trauma also has the potential to alter methylation at other sites on the genome. Further research on methylation and functional studies would be necessary to further explore this in the case of COMT and childhood trauma.

6.4.2 DRD2 and cognition in those with and without psychosis risk (Study II)

Further research is needed to understand why psychosis risk interacts with DRD2 SNPs in association with cognitive performance. The results of this study suggest that other factors, genetic and/or environmental, may be necessary for the
observed cognitive effects. Candidate risk factors include variation at COMT (Berryhill et al., 2013), which has been associated with visual working memory, or temperamental features.

6.4.3 Smoking in pregnancy as a risk factor for adult cognitive performance (Study III)

The results of this study suggest that future research should assume a more nuanced association between exposure to smoking in pregnancy and cognition. Future research could explore further potential mediating factors during development that may affect adult cognition, such as reward sensitivity and emotional regulation (Wiebe et al., 2015) or difficulties with “hot” cognition tasks (Huijbregts et al., 2008). The results here also suggest that risk factors for cognitive performance among those at risk for psychosis may differ in some ways from the general population. More specific studies of risk factors in this population may be warranted. This research is particularly important in those at risk for psychosis who progress to develop severe mental illness, where outcomes arising from cognitive deficits can be devastating.

6.4.4 Adolescent metabolic measures and cognition and psychosis risk (Study IV)

While this study has observed cross-sectional and longitudinal associations between metabolic markers and cognition, considerable gaps in understanding the significance of this remain. Future research should investigate for evidence regarding causality in the relationships. It could further consider the temporal association by examining it over a longer period of time. It could also consider potential biological mechanisms through animal models and studies. In addition to a causal association, future research should consider other mechanisms for the association between metabolic measures and cognition, for example whether the metabolic measures reflect another, causal, process. One potential candidate is exercise (Kujala et al., 2013), which has a similar metabolic profile. The metabolic profile associated with specific dietary patterns is harder to study but there is good reason to consider that diet will impact both metabolic profile and cognitive profile.
7 Conclusion

7.1 Main findings

This study had four main findings regarding risk factors for cognition and psychosis risk. Firstly, a common candidate gene polymorphism (COMT-Val158Met) interacts with childhood trauma in association with psychotic experiences in adolescence. Secondly, polymorphisms at a psychosis-related candidate gene (DRD2) interact with psychosis risk in association with cognition in young adults. Thirdly, an early life risk factor, prenatal exposure to maternal cigarette smoking, is associated with general intelligence in males but not females but this is not the case in those at risk for psychosis. Finally, metabolic measures are associated with cognitive performance but not psychosis risk in adolescence. These findings add to our understanding of the intersection of risk for cognitive deficits and psychosis risk.

7.2 Clinical implications

The results of this study have several clinical implications. Firstly, in reviews of those at risk for psychosis, a full assessment requires the consideration of cognitive deficits, including risk factors for cognitive deficits. These deficits are central to the evolution of long-term functional impairment in severe mental illness. The findings also highlight the importance of assessing for childhood trauma among adolescents with psychotic experiences. This may offer an opportunity for primary prevention of psychosis by intervening early to address the trauma. It may also serve as an indicator for enhanced treatment where trauma co-occurs with psychotic experiences, for example closer monitoring or more assertive treatment with evidence-based medication (Baldwin et al., 2014) or psychological therapies (Watts et al., 2013).

Secondly, in the education context, where cognitive deficits are evident in the male children of mothers who smoked in pregnancy, educators and clinicians should consider if supports with inattention and hyperactivity would help their overall development.

Finally, at a public health level, the findings regarding smoking in pregnancy further add to the obligation on clinicians to discourage this practice in order to prevent long-term adverse outcomes.
7.3 Implications for future research

Future research into risk factors for cognitive deficits and psychosis risk is sorely needed. This study suggests that some risk factors for cognition may vary between the general population and those at risk for severe mental illness. Future research should further explore differences between these populations in terms of risk factors.

More specifically, genetic research into associations with psychosis risk and cognition should further explore gene-environment and gene-gene interactions. Biological and animal studies would also be particularly helpful to better understand gene-environment interactions. The potential mechanisms underlying the association between smoking in pregnancy and adult cognition should be further explored, for example the association between smoking in pregnancy and reward sensitivity and emotional regulation. The potential mechanisms linking adolescent metabolic measures and cognition should also be further explored. Whether these are causal mechanisms or otherwise, better understanding them has the potential to improve cognitive development at a population level.
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PREDICTORS OF PSYCHOSIS RISK AND NEUROCOGNITIVE DEFICITS